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Developments in cardiac implantable electronic device therapy: How can we improve clinical implementation?

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Developments in cardiac implantable electronic device therapy: How can we improve clinical implementation?

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Editorial: Developments in cardiac implantable electronic device therapy: how can we improve clinical implementation?

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KEYWORDS

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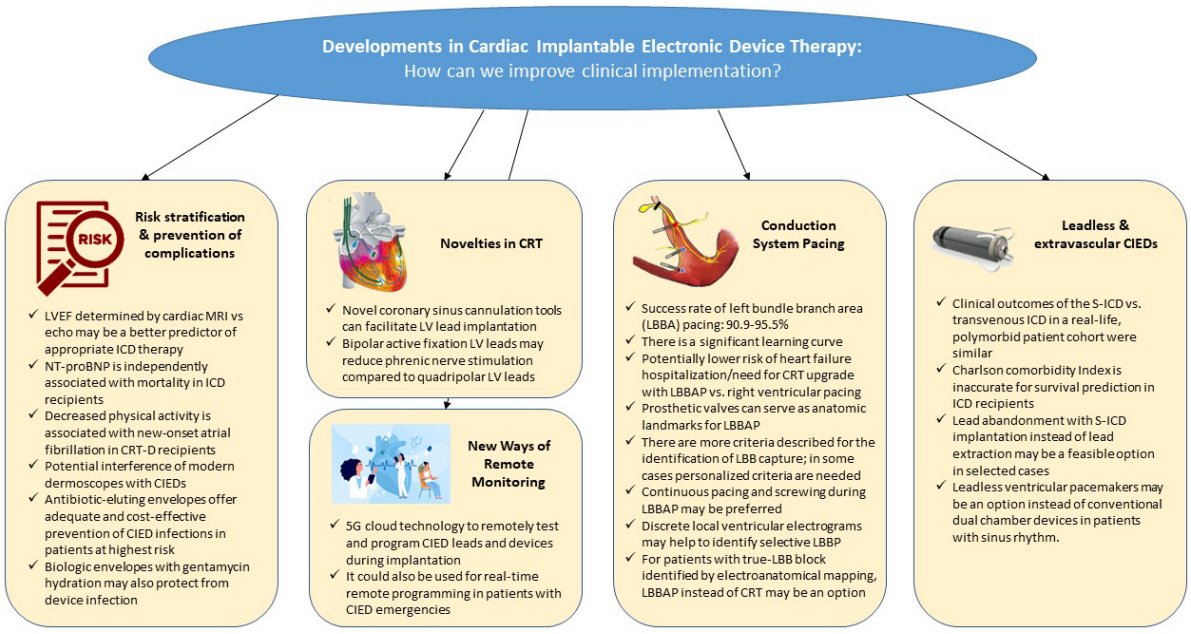
Editorial on the Research Topic
Developments in cardiac implantable electronic device therapy: How can we improve clinical implementation?



GRAPHICAL ABSTRACT
CIED, cardiac implantable electronic devices; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; EA, electroanatomical; ICD, implantable cardioverter defibrillator; LBB, left bundle branch; LBBAP, left bundle branch area pacing; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MRI, cardiac magnetic resonance imaging; S-ICD, subcutaneous defibrillator.

Introduction

Since their introduction, cardiac pacemakers and later implantable cardioverter-defibrillators (ICDs) have advanced remarkably. By the early 2000s, one might have thought that significant changes in this field could no longer be expected. However, the next revolution in the development of cardiac implantable electronic device (CIED) therapy was just waiting in front of the door. It started with the introduction of extravascular and leadless devices and has led to conduction system pacing (CSP), which awaits more experience, evidence, and improved tools to further improve its clinical implementation. The current research topic (RT) presents valuable papers to physicians with an interest in novel clinical and scientific aspects of CIED therapy.

Risk stratification and prevention of complications in patients receiving a transvenous cardiac implantable electronic device

The first section of this series is focused on risk stratification and reduction of complications in patients receiving a transvenous CIEDs. Both echocardiography and cardiac magnetic resonance imaging (MRI) may be used to assess left ventricular ejection fraction (LVEF) before implantation of a primary prophylactic ICD. Marcos-Garcés et al. explored the role of these two imaging modalities in 52 patients receiving an ICD following ST-elevation myocardial infarction at a single center in Spain. Their study suggests that, compared with assessment by echocardiography, LVEF determined by cardiac MRI may be a better predictor for appropriate ICD therapy.

Natriuretic peptides are powerful biomarkers in cardiovascular disease. Plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) are essential for the diagnosis of heart failure and a strong predictor of mortality in this context (1, 2). Risk stratification of patients receiving an ICD may help identify optimal candidates. Deng et al. explored the association of NT-proBNP with all-cause mortality and time to first appropriate shock in a cohort of 500 patients undergoing *de novo* implantation of a transvenous single- or dual-chamber ICD at a single center in Beijing, China. In analyses adjusted for clinical covariates and potential confounders, higher levels of NT-proBNP were independently associated with mortality, but not with time to first appropriate shock.

An accelerometer sensor of contemporary CIEDs may be used to derive surrogate data on physical activity. Using data from a prospective, multicenter registry in China, Sun et al. assessed the relationship between physical activity and new-onset atrial fibrillation and other outcomes in 1,015 patients undergoing implantation of an ICD or cardiac resynchronization therapy defibrillator (CRT-D). They found that decreased physical activity as indicated on the accelerometer sensor was independently associated with new-onset atrial fibrillation and fatal outcomes following CRT-D implantation.

Static magnetic fields may interfere with CIEDs. Modern dermoscopes used for detailed inspection of skin lesions and diagnosis of some skin cancers often contain a built-in magnet. Sławinski et al. characterized and compared the magnetic fields created by built-in magnets of several commercially available dermoscopes in a pre-clinical setting. Although more data are needed, their study emphasizes the need to create awareness of potential interference of modern dermoscopes with CIEDs.

Antibacterial envelopes were developed to reduce the risk of infection in patients undergoing implantation of a cardiac implantable electronic device. Traykov and Blomström-Lundqvist reviewed the pertinent literature on risk stratification in CIED infection and assessed the efficacy and cost-effectiveness of antibiotic-eluting envelopes in patients at highest risk for device infection. In the pivotal Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT), adjunctive use of an absorbable, non-biologic, antibiotic-eluting envelope reduced the risk of major cardiac implantable electronic device infection by 40% (3). Furthermore, there are biologic envelopes made from a non-crosslinked extracellular matrix that are hydrated prior to implantation. The addition of antibiotics to the hydration solution may confer incremental protection from device infection. Combining data from two observational studies conducted at 40 sites in the United States and Greece, Deering et al. studied physician hydration preferences in 1,102 patients receiving a CIED and a biologic envelope. Their results suggest that the addition of gentamycin to the hydration solution may be especially advantageous and that perioperative intravenous antibiotic prophylaxis is indispensable despite use of an envelope.

Novelities in cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) was proven to reduce both hospitalization rates and mortality in multiple trials. During CRT implantation, one of the most challenging steps is coronary sinus (CS) cannulation and LV lead implantation. In a case series, Duan et al. report their experience using a novel venogram balloon catheter ("Lee's venogram balloon catheter"). They describe five cases of CRT upgrade, of which four are challenging due to special anatomical characteristics, with a low fluoroscopy and total procedure duration (mean 5 ± 3 min and 57 ± 13 min) and propose a shorter learning curve. This promising tool warrants further evaluation in a larger, prospective patient cohort.

Phrenic nerve stimulation (PNS), especially in patients with difficult CS anatomies, is a common problem during CRT. In a single-center study by Schiedat et al. the usage of bipolar active fixation leads (Medtronic Attain Stability 20066) has been evaluated in direct comparison to quadripolar LV leads. In the cohort of 81 patients, no difference in implantation success or CRT-response was observed, but PNS was significantly lower in patients with bipolar active fixation leads (13% vs. 0%; $p < 0.05$). Although single-center and retrospective, this is the first study suggesting that LV active fixation leads might not only be used in case of large target veins, but also in CRT candidates at high risk for PNS.

Leadless and extravascular cardiac implantable electronic devices

As the Achilles' heel of modern CIED therapy seems to be the intracardiac and intravascular presence of leads, major improvements have been observed in the last decade to avoid mechanical lead fractures and to minimize CIED-related infection risks. Although there are no randomized studies showing superiority of the new subcutaneous defibrillators (S-ICD) or leadless pacemakers (LMP) over conventional technologies, several studies prove the non-inferiority of these.

A real-life comparison of patients who underwent S-ICD or conventional ICD implantations revealed no differences in a composite clinical endpoint including survival, freedom of hospitalization, and device-associated events. The decision to implant S-ICD showed a trend towards patients with more complex diseases, measured by the Charlson comorbidity Index (CCI). Compared with previous studies, the observed mortality of patients with similar CCI was much lower in the study of Kattih et al., which raises the question of whether to use the CCI to predict patient mortality in patients needing an ICD.

An Italian multicenter study by Russo et al. investigated patients with non-functional ICD leads, where the decision to extract the ICD lead and implant a new conventional ICD system (62 patients) or abandon the lead and implant an S-ICD (43 patients) was left to the clinician. There was no difference observed in major or minor complications in the two patient groups, although in four patients the lead extraction failed, and a crossover to S-ICD strategy was performed.

Another Italian multicenter study investigated the use of single chamber LPM in 73 "non-AF" patients with sinus node disfunction or sinus rhythm and atrioventricular block. There were no major differences in the perioperative or late complications and in the combined clinical endpoint of syncope, pacemaker syndrome, cardiac hospitalization, and all-cause death compared with permanent atrial fibrillation patients receiving LPM. Although the non-AF patients had a higher percentage of ventricular pacing (52 ± 36 vs. $40 \pm 29\%$; $p = 0.002$) there were no patients reported with pacemaker syndrome. This highlights the option to choose LMP instead of a conventional dual chamber pacemaker in patients with sinus rhythm.

All these results provide clinicians with more options to treat patients with specific conditions. However, there is still a lack of randomized trials on S-ICD or LPM which would confirm the superiority of these new technologies with higher costs.

Conduction system pacing

One of the most relevant changes of the last years in device therapy is the break-in of CSP into the daily clinical practice. However, some concerns limiting its faster and wider spread should be acknowledged: technically challenging implantation, reduced success rate, elevated pacing thresholds, and lack of data on long-term outcomes. The papers submitted to the RT nicely represent that the leading technique for CSP is no longer the His bundle, but the left bundle branch (area) pacing (LBB(A)P). Wang et al. found in their single center, observational comparative study of 689 consecutive bradycardia patients that procedure and fluoroscopy time is higher when performing LBBAP compared to conventional right ventricular pacing (RVP). However, they also found that these parameters could be significantly reduced by increasing procedure volume, reflecting a learning curve effect of this finding. Nonetheless, their overall implantation success rate was high (92.6%) and comparable with that reported by Li et al. from a multicenter collaboration (95.5%). This latter group also demonstrated lower occurrences of HF hospitalization or upgrading to biventricular pacing in patients with LBBAP compared to patients with RVP. Notably, this benefit was predominantly observed in patients with ventricular pacing >40% or with baseline LVEF <60%. Slightly lower implantation success rate (90.9%) was reported in 22 patients undergoing LBBAP following prosthetic cardiac valves by Wei et al. Further important lessons were learnt from this publication regarding the anatomic landmarks of optimal LBBAP.

A systematic review summarizing the criteria for differentiating left bundle branch pacing and left ventricular septal pacing by Zhu et al. serves as a valuable practical guide to physicians who are learning this technique. We can see that there is unfortunately no one-size-fits-all concept; personalized criteria are needed in some cases. For note, further novel criteria have also been published since this review (for example the V6-V1 interpeak interval) (4), which may further help the reliable identification of left bundle branch capture. Shen et al. contribute their case report to the experts who recommend a continuous pacing and screwing during LBBAP instead of the interrupted method. Beyond the advantage of the continuous monitoring of the current of injury, further concepts also support this method (i.e., detection of screw-in-beats, better mechanical penetration of the lead body, etc.) (5). To use this method also with lumenless leads, a dedicated tool connecting the lead to the analyzer/EP-system during screwing, is still awaited from the industry. In a research article, Shen et al. drew attention to the optimal setting of the high-pass filter to identify the morphology of the discrete local ventricular components in the intracardiac EGM as a marker of selective LBBP. The relevance of the detection of the discrete local ventricular EGM in LBBP needs further confirmation.

Most recently, LBBAP also appeared as an alternative to classical CRT. Hua et al. presents an interesting concept for choosing between these two modalities based on the electroanatomical mapping of the left ventricle. They describe this method feasible in 71 CRT recipients to differentiate between true left bundle branch block (candidates for LBBP) and pseudo-left bundle branch block (candidates for conventional CRT). Whether this method will spread in clinical practice requires further research. Zheng et al. also report LBBAP as an alternative in a unique case of a patient with a giant atrium with standstill and inability of atrial capture. This rare situation also highlights that CSP may be a good option in case of narrow QRS and bradypacing indication.

New ways of remote management

Remote monitoring of CIED patients has not only evolved as a technology to unburden daily clinical routine from growing patient contacts but has also shown to lower HF worsening rates during the COVID-19 pandemic (6). Xiong et al. expand the idea of remote monitoring to remotely control and reprogram a device in real-time using a 5G-cloud technology system. In their case series, they present three everyday emergency settings that require immediate CIED interrogation and potential reprogramming. Long et al. describe their experience with the 5G-cloud technology during two dual-chamber pacemaker and one CRT-P implantation which enabled to conduct remote parameter testing and programming by a device specialist without entering the cath lab. Although remote device programming offers promising innovative approaches as demonstrated in these case reports, further prospective evaluation—predominantly due to safety issues—is warranted.

Author contributions

The authors confirm being the only contributors to this work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CLINICAL TRIAL
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Clinical Outcomes in Patients With Left Bundle Branch Area Pacing vs. Right Ventricular Pacing for Atrioventricular Block

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Background: Left bundle branch area pacing (LBBAP) is a novel pacing modality with stable pacing parameters and a narrow-paced QRS duration. We compared heart failure (HF) hospitalization events and echocardiographic measures between LBBAP and right ventricular pacing (RVP) in patients with atrioventricular block (AVB).

Methods and Results: This multicenter observational study prospectively recruited consecutive AVB patients requiring ventricular pacing in five centers if they received LBBAP or RVP and had left ventricular ejection fraction (LVEF) >50%. Data on electrocardiogram, pacing parameters, echocardiographic measurements, device complications, and clinical outcomes were collected at baseline and during follow-up. The primary outcome was first episode hospitalization for HF or upgrade to biventricular pacing. LBBAP was successful in 235 of 246 patients (95.5%), while 120 patients received RVP. During a mean of 11.4 ± 2.7 months of follow-up, the ventricular pacing burden was comparable (83.9 ± 35.1 vs. 85.7 ± 30.0%), while the mean LVEF differed significantly (62.6 ± 4.6 vs. 57.8 ± 11.4%) between the LBBAP and RVP groups. Patients with LBBAP had significantly lower occurrences of HF hospitalization and upgrading to biventricular pacing than patients with RVP (2.6 vs. 10.8%, $P < 0.001$), and differences in primary outcome between LBBAP and RVP were mainly observed in patients with ventricular pacing >40% or with baseline LVEF <60%. The primary outcome was independently associated with LBBAP (adjusted HR 0.14, 95% CI: 0.04–0.55), previous myocardial infarction (adjusted HR 6.82, 95% CI: 1.23–37.5), and baseline LVEF (adjusted HR 0.91, 95% CI: 0.86–0.96).

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Conclusion: Permanent LBBAP might reduce the risk of HF hospitalization or upgrade to biventricular pacing compared with RVP in AVB patients requiring a high burden of ventricular pacing.

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Keywords: atrioventricular block, left bundle branch area pacing, heart failure hospitalization, upgrade to biventricular pacing, right ventricular pacing

INTRODUCTION

Some patients with advanced atrioventricular block (AVB) may be at high risk of pacing-induced heart failure (HF) because conventional right ventricular pacing (RVP) can result in left ventricular mechanical dyssynchrony and impaired cardiac function (1). A previous study (2) reported that the risk of HF death was increased by 8% at every 10% increase in RVP burden. Biventricular pacing (BiVP) may prevent adverse left ventricular (LV) remodeling and a reduction in LV ejection fraction (LVEF) in bradycardia patients with normal systolic function (3) and reduce the progressive risk of HF in AVB patients with impaired cardiac function (4) compared with RVP. However, BiVP is not a routine treatment for AVB with preserved cardiac function due to the complicated procedure and expensive device. His bundle pacing can achieve normal paced QRS duration (QRSd) and ventricular mechanical synchrony (5). However, His bundle pacing is also not routinely used because of a low success rate, high risk of lead dislodgement, or raising threshold (5).

Left bundle branch area pacing (LBBAP) has emerged recently (6) as a new physiological pacing approach. LBBAP can achieve almost normal paced QRSd with a low and stable pacing threshold, good R wave sensing, and short procedure duration comparable to RVP (7–10). LBBAP can also correct bundle branch block (BBB) in bradycardia patients (11) and improve LV systolic function in patients with HF (12). However, most current studies focus on the feasibility, safety, pacing parameters, electrocardiogram, or echocardiographic features of LBBAP during short-term follow-up. The comparison of the long-term clinical effect on HF hospitalization events between LBBAP and RVP has not been reported in patients with AVB requiring a high burden of ventricular pacing (VP). This multicenter study aimed to prospectively observe HF hospitalization events between LBBAP and RVP in patients with AVB.

Methods

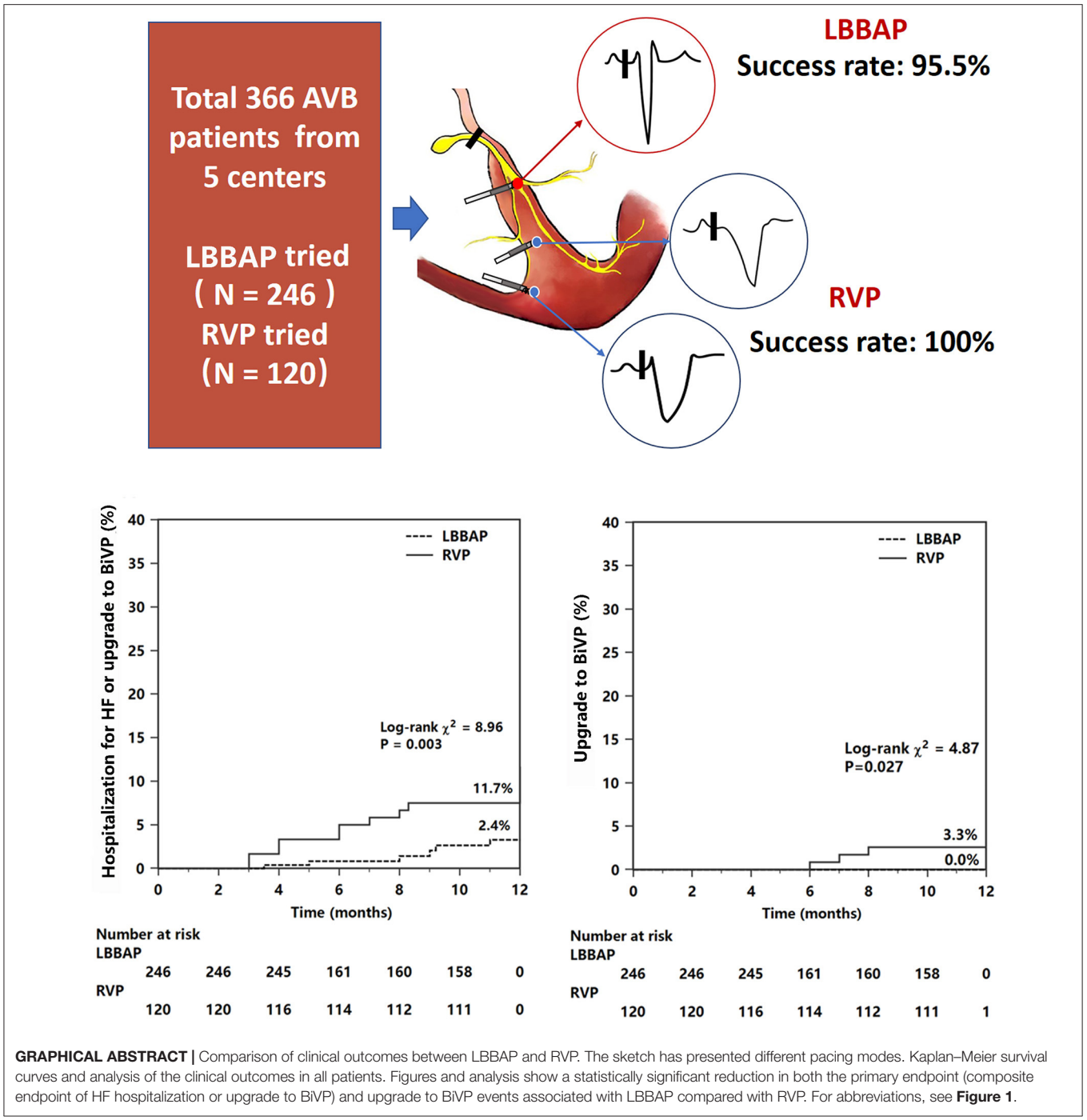
This study was conducted at Fuwai Hospital, National Center for Cardiovascular Diseases, Beijing; Anzhen Hospital, Beijing; Sun Yat-sen Memorial Hospital, Guangzhou; the First Affiliated Hospital of Zhengzhou University; and the Second Hospital of Hebei Medical University. This prospective observational study was approved by the Institutional Review Board of all five hospitals in this study. All consecutive patients with AVB requiring ventricular pacing according to current guidelines were enrolled from 2019 if they signed written informed consent for an agreement of the implantation procedure and study analysis. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Study Population

Patients with AVB recruited in this study were over 18 years old and had LVEF >50% at baseline. The pacing strategies were determined by operators as per the clinical practice at each hospital. The LBBAP group included all patients who attempted the LBBAP procedure, while the RVP group included patients undergoing RV apex or septum pacing. Patients were excluded if they (1) were younger than 18 years; (2) underwent pacemaker replacement or upgrading with existing leads; (3) had severe valvular diseases, congenital heart disease, or hypertrophic cardiomyopathy; (4) were diagnosed with acquired AVB after surgery for hypertrophic cardiomyopathy or other congenital heart diseases; (5) were diagnosed with persistent atrial fibrillation; and (6) were unavailable to be regularly followed up at the clinic visit for various reasons or to provide written informed consent (**Figure 1**).

LBBAP Procedure

The LBBAP procedure has been previously described in detail (8). During the later period of the study, we simplified the implant procedure of the LBBAP ventricular pacing lead. Briefly, the Select Secure pacing lead of model 3830 (Medtronic, Inc., Minneapolis, MN, USA) was delivered through the C315 sheath (Medtronic, Inc.) after left axillary vein access. In the right anterior oblique 30° position, the sheath with a 3830 pacing lead was directly inserted into the right ventricle through the tricuspid annulus. The tip of the 3830 pacing lead was advanced slightly outside the sheath to touch the septum myocardium at an area 1.5∼2.0 cm away from the tricuspid annulus. Unipolar pacing was performed at an output of 2.0 V/0.4 ms to identify a potential screwing site according to the following criteria: (1) a paced morphology of the QS complex with a notch in the bottom in lead V1 and (2) R wave amplitudes >5 mV. After screwing the lead deep into the septum, unipolar pacing was performed to assess the paced QRS morphology, the R wave amplitude, and pacing impedance. The stimulus-to-peak LV activation time (S-pLVAT) was measured at both low (2.0 V/0.4 ms) and high (5.0 V/0.4 ms) outputs in lead V_{4-6}. Ring pacing was tested to evaluate the lead depth in the interventricular septum. Measures of impedance and R wave amplitudes are helpful to prevent lead penetration into the LV. If LBBAP could not be successful after five attempts, the lead was screwed into the interventricular septum to achieve deep LV septal pacing. The RV lead was implanted



GRAPHICAL ABSTRACT | Comparison of clinical outcomes between LBBAP and RVP. The sketch has presented different pacing modes. Kaplan–Meier survival curves and analysis of the clinical outcomes in all patients. Figures and analysis show a statistically significant reduction in both the primary endpoint (composite endpoint of HF hospitalization or upgrade to BiVP) and upgrade to BiVP events associated with LBBAP compared with RVP. For abbreviations, see **Figure 1**.

at the RV apex or septum by a shaping stylet to achieve stable pacing parameters.

Successful LBBAP was confirmed per the previously published criteria (8, 9, 11): (a) paced QRS morphology presented with an RBBB pattern and (b) S-pLVAT shortened abruptly and remained shortest and constant at different testing outputs. Selective LBBP was identified if a discrete component was presented between the spike and the QRS onset on intracardiac electrogram at a low output (usually at 0.5 V/0.4 ms), or left bundle branch potential could be recorded, or a transition in QRS morphology of V1 from "Qr" or "QR" type to "rsR" type with decreasing unipolar output could be observed. Sixty beats per minute with bipolar pacing mode was set in all of the patients. The pacing output was set as 3.0 V/0.4 ms at the first 3 months of follow-up. If the threshold remained stable at the 3-month follow-up, the automatic ventricular capture management algorithms might be turned on, or the pacing output would be set at 2.0–2.5 V/0.4 ms based on

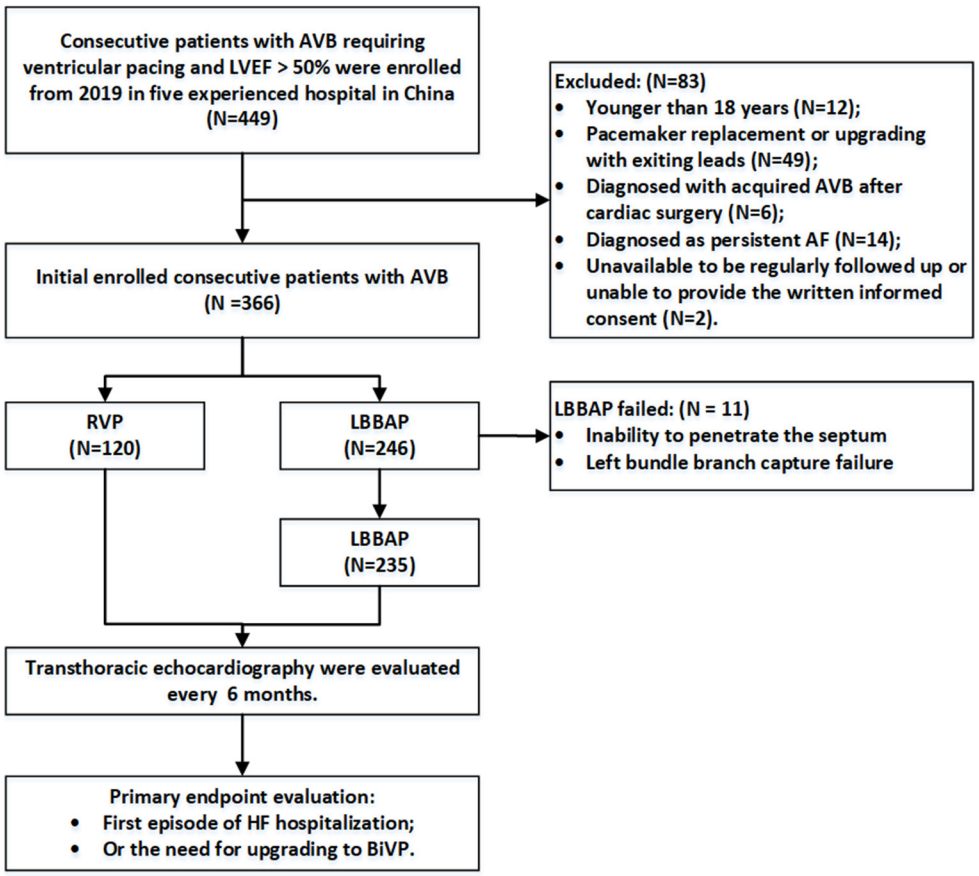


FIGURE 1 | Flowchart of the study population enrollment. AVB, atrioventricular block; RVP, right ventricular pacing; LBBAP, left bundle branch area pacing; AF, atrial fibrillation; HF, heart failure; BiVP, biventricular pacing.

pacing thresholds. For patients with complete heart block, the atrioventricular delay was set as 150/120 ms after the procedure of both LBBAP and RVP. For patients with intermittent AVB, atrioventricular delay programming strategies were different between LBBAP and RVP. In patients with RVP, automatic atrioventricular delay optimization algorithms were routinely turned on to minimize the use of RVP. In patients with LBBAP, the atrioventricular delay was set 30 ms longer than the intrinsic atrioventricular interval if the patient had a normal intrinsic QRS duration. If patients had baseline bundle branch block, the atrioventricular delay was set 30 ms shorter than the intrinsic atrioventricular interval to achieve possible correction of electrical dyssynchronization.

Clinical Outcomes and Follow-Up

The clinic visit follow-up was performed every 6 months after pacemaker implantation in each hospital. Echocardiographic evaluations were conducted at baseline, 6 months, and 1 year after the procedure by using Vivid E9 systems (GE Vingmed Ultrasound AS, Horten, Norway). Left ventricular end-diastolic diameter (LVEDD) and LVEF were evaluated by the core lab that was blinded to the pacing parameter settings, and in cases of disagreement, a senior echocardiographer was invited to read the original data to reach an agreement. Biplane Simpson's method in two-dimensional transthoracic echocardiography was used for the evaluation of LVEF.

The primary outcome was defined as a combined endpoint including the first episode of HF hospitalization or the need for upgrading to BiVP. The independent event committee adjudicated all events. HF hospitalization was identified if the patient presented to outpatients or emergency department visits or inpatient hospitalization with symptoms and signs consistent with HF and required diuretics and other therapy (vasodilation, etc.). The indications for requiring an upgrade to BiVP were according to current guidelines (13), including HF and AVB with reduced LVEF (<40%) after guideline-directed medical treatment for at least 3 months. The pacing parameters and ventricular pacing burden and 12-lead ECG were all recorded at baseline and at each follow-up visit. Lead-related complications were routinely tracked.

Statistical Analysis

The statistical analyses were performed by SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad

TABLE 1 | Baseline characteristics of AVB patients.

Variables	LBBAP group ($N = 246$)	RVP group ($N = 120$)	*P*
Age, years	63.3 ± 15	62.1 ± 17.2	0.575
Female, %	85 (34.6)	39 (32.5)	0.052
Paroxysmal atrial fibrillation, %	72 (29.3)	19 (15.8)	0.005
Hypertension, %	132 (53.7)	65 (54.2)	0.927
Diabetes, %	50 (20.3)	25 (20.8)	0.910
Coronary arterial disease, %	31 (12.6)	20 (16.7)	0.292
MI history, %	11 (4.5)	4 (3.3)	0.606
Dilated cardiomyopathy, %	6 (2.4)	0 (0.0)	0.085
Valvular heart disease, %	19 (7.7)	12 (10)	0.463
Baseline QRSd	115.9 ± 26.7	117.9 ± 27.9	0.514
Conduction disorders			
Marked first-degree AVB, %	20 (8.1)	8 (6.7)	0.621
Second-degree AVB, %	59 (24.0)	27 (22.5)	0.753
High-grade AVB, %	47 (18.9)	24 (20.0)	0.839
Third-degree AVB, %	120 (48.8)	61 (50.8)	0.712
AVB with sinus node dysfunction, %	71 (28.9)	30 (25.0)	0.438
Left bundle branch block, %	37 (17.9)	15 (14.2)	0.402
Right bundle branch block, %	59 (28.5)	33 (31.1)	0.629
Echo data			
Baseline LVEDD, mm	49.4 ± 6.6	49.6 ± 5.9	0.787
Baseline LVEF, %	61.7 ± 7.4	61.5 ± 6.4	0.738
NT-proBNP, pg/ml	261.5 (89.3, 864.3)	424.2 (100.1, 976.7)	0.301

MI, myocardial infarction; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

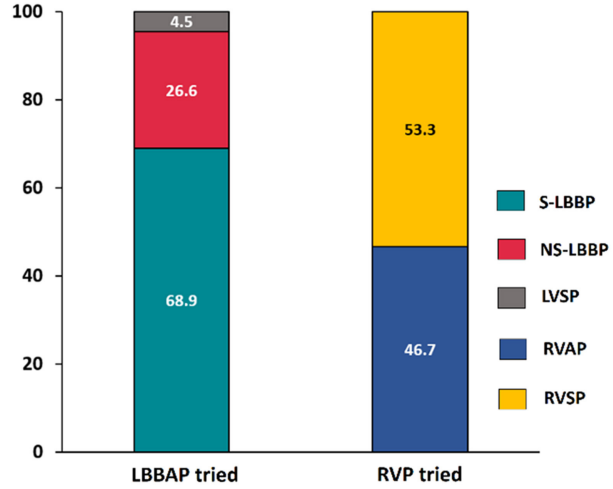


FIGURE 2 | Comparison of success rate between LBBAP and RVP. LBBAP, left bundle branch area pacing; S-LBBP, selective left bundle branch pacing; NS-LBBP, non-selective left bundle branch pacing; LVSP, left ventricular septal pacing; RVAP, right ventricular apical pacing; RVSP, right ventricular septal pacing.

Software, Inc., San Diego, CA). Continuous variables were summarized using the means and standard deviation or median and interquartile range and compared with two-tailed Student's *t*-tests or Wilcoxon rank sum test. Nominal data are presented as frequencies and percentages and were compared by using the chi-square test or Fisher's exact test. Kaplan–Meier curves and univariate and multivariate Cox proportional hazard models were used to analyze the primary outcomes, and time censoring was determined by time to primary outcomes or time to last follow-up. All statistical tests were two-tailed. A P value of <0.05 was considered significant.

RESULTS

Baseline Clinical Characteristics and Implant Outcomes of Patients

A total of 366 consecutive patients were included. LBBAP was attempted in 246 patients, while 120 patients received RVP. As shown in **Table 1**, patients between the two groups had similar mean age, sex distribution, AVB grades, BBB types, and other clinical characteristics except for the prevalence of paroxysmal atrial fibrillation (29.3 vs. 15.8%, $P = 0.005$). Baseline LVEF was also comparable between the LBBAP (61.7 ± 7.4)% and RVP (61.5 ± 6.4)% groups.

Permanent LBBAP was successful in 235 of 246 patients (95.5%), with selective LBBP in 162 (68.9%) patients. As shown in **Figure 2**, deep LV septal pacing was performed in 11 patients. The reasons for LBBAP failure included the inability to penetrate the septum in five patients and failure to capture the left bundle branch in six patients. In the RVP group, there were 56 (46.7%) apical pacing and 64 (53.3%) septal pacing.

Pacing Parameters and Procedure Complications During Follow-Up

The mean follow-up duration was 11.4 ± 2.7 months. **Table 2** shows the pacing parameters and complications during the procedure and follow-up. Compared with RVP, LBBAP showed better sensing R wave amplitude, lower pacing impedance, and similar pacing threshold and significantly narrower QRSd during the procedure and at the 6-month follow-up. The ventricular pacing percentage was comparable between these two groups (83.9 ± 35.1 vs. 85.7 ± 30.0%, $P = 0.614$). At the 1-year follow-up, the pacing threshold and sensing R wave amplitude were comparable between the two groups. The lower pacing impedance and narrower QRSd (112.3 ± 16.3 vs. 152.9 ± 40.8 ms, $P < 0.001$) remained in the LBBAP group.

The complications in the LBBAP group were similar to those in the RVP group. Even though five patients (2.1%) suffered septal perforation during the procedure, the perforation did not cause any symptoms. Only one septal perforation occurred 2 h after the procedure and resulted in dislodgement and ventricular capture failure. After repositioning the pacing lead, most patients underwent successful LBBAP with uneventful recovery. Lead perforations or dislodgement was not found following hospital discharge. In the RVP group, apical perforation occurred in one patient, ventricular lead dislocation occurred in three

TABLE 2 | Pacing characteristics during the procedure and follow-up.

Variables	LBBAP (*N* = 235)	RVP (*N* = 120)	*P*
Dual-chamber pacemaker	235 (100)	120 (100)	1.000
During the procedure			
Sense, mV	12.4 ± 11.2	9.6 ± 5.7	0.013
Threshold, V/0.4 ms	0.67 ± 0.23	0.66 ± 0.24	0.762
Impedance, Ω	757.2 ± 164.0	853.6 ± 258.5	<0.001
Paced QRSd, ms	114.2 ± 13.8	158.5 ± 25.5	<0.001
6-month follow-up			
Sense, mV	14.9 ± 5.4	11.7 ± 5.6	<0.001
Threshold, V/0.4 ms	0.73 ± 0.25	0.65 ± 0.67	0.122
Impedance, Ω	577.1 ± 145.7	647.8 ± 184.0	<0.001
Paced QRSd, ms	112.5 ± 15.3	153.5 ± 32.6	<0.001
VP, %	83.9 ± 35.1	85.7 ± 30.0	0.614
1-year follow-up	***N* = 173**	***N* = 109**	
Sense, mV	14.8 ± 4.8	13.0 ± 3.6	0.213
Threshold, V/0.4 ms	0.8 ± 0.3	0.7 ± 0.2	0.180
Impedance, Ω	621.3 ± 149.0	771.2 ± 184.4	0.002
Paced QRSd, ms	112.3 ± 16.3	152.9 ± 40.8	<0.001
Complications			
Septal perforation during the procedure	5 (2.1)	0 (0.0)	0.172
Septal or apical perforation after procedure	1 (0.4)	1 (0.8)	0.668
Dislocation during follow-up	1 (0.4)	3 (2.5)	0.114

VP, ventricular pacing percentage.

TABLE 3 | Echocardiographic measures at baseline and during follow-up.

Variables	LBBAP (*N* = 235)	RVP (*N* = 120)	*P*
Baseline			
LVEDD, mm	49.4 ± 6.6	49.6 ± 5.9	0.787
LVEF, %	61.7 ± 7.4	61.5 ± 6.4	0.738
6-month follow-up			
LVEDD, mm	48.4 ± 6.5	49.4 ± 6.5	0.435
LVEF, %	61.2 ± 6.7	58.6 ± 9.4*	0.045
One-year follow-up			
LVEDD, mm	46.6 ± 5.2*	51.7 ± 7.5*	0.005
LVEF, %	62.6 ± 4.6	57.8 ± 11.4*	0.004

**Compared with baseline status, P < 0.05.*
LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

TABLE 4 | Clinical outcomes evaluation.

Variables	LBBAP (*N* = 235)	RVP (*N* = 120)	*P*
HF hospitalization, *N* (%)	6 (2.6)	13 (10.8)	<0.001
Upgrade to BiVP, *N* (%)	0 (0.0)	4 (3.3)	0.011

HF, heart failure; BiVP, biventricular pacing.

patients during follow-up, and all patients underwent uneventful lead revision.

Comparison of Echocardiographic Measures

Compared with baseline, patients with LBBAP had stable LVEF and slightly decreased LVEDD at the 1-year follow-up (**Table 3**). In contrast, patients with RVP had gradually decreased LVEF and significantly increased LVEDD from baseline to 6 months and at 1-year follow-up. The comparison between RVP and LBBAP at 1-year follow-up showed a significant difference in LVEF (62.6 ± 4.6 vs. 57.8 ± 11.4%, $P = 0.004$) and LVEDD (46.6 ± 5.2 vs. 51.7 ± 7.5 mm, $P = 0.005$).

Clinical Outcomes

The primary composite endpoint of HF hospitalization and upgrading to BiVP was 2.6% in the LBBAP group and 10.8% in the RVP group ($P < 0.001$, **Table 4**). Among patients who suffered HF hospitalization, upgrading to BiVP occurred in four patients in the RVP group during three to nine months of follow-up compared with zero patients in the LBBAP group. The Kaplan–Meier analysis showed a trend toward higher HF hospitalization ($P = 0.003$) and a higher occurrence of an upgrade to BiVP ($P = 0.027$) in the RVP group than in the LBBAP group (**Figure 3**). In **Table 5**, the univariate and multivariate Cox analyses showed that the LBBAP pacing modality was an independent predictor for a reduced risk of the primary composite outcome (adjusted HR 0.14, 95% CI: 0.04–0.55, $P = 0.005$). HF hospitalization and upgrading to BiVP were also associated with a history of previous myocardial infarction (adjusted HR 6.82, 95% CI: 1.23–37.75, $P = 0.028$) and LVEF at baseline (adjusted HR 0.91, 95% CI: 0.86–0.96, $P = 0.001$).

The results of the subgroup analysis are shown in **Figure 4**. The significant reduction in composite HF hospitalization events associated with LBBAP was confirmed in patients with VP burden >40% (2.0 vs. 12.0%, $P = 0.005$) (**Figure 4A**) but not in patients with VP burden ≤40% (**Figure 4B**). The difference in composite HF events did not statistically differ between RVP and LBBAP in patients with LVEF >60% (**Figure 4C**). However, in patients with baseline LVEF <60% ($n = 150$), the RVP group had significantly higher composite HF events than the LBBAP group (14.6 vs. 3.2%, $P = 0.034$) (**Figure 4D**). In patients with baseline organic cardiac disease (coronary artery disease, old myocardial infarction, mild dilated cardiomyopathy, or valvular heart disease) or atrial fibrillation, the primary HF events differed significantly between the LBBAP and RVP groups (1.8 vs. 11.6%, $P = 0.034$, **Figure 4E**). The trend toward a reduction in the primary outcome in patients with LBBAP compared with RVP did not reach statistical significance (2.3 vs. 10.4%, $P = 0.056$, **Figure 4F**) in patients without baseline organic cardiac disease or atrial fibrillation.

DISCUSSION

This multicenter prospective study demonstrated that permanent LBBAP presented stable pacing parameters and procedural complications similar to RVP during a 1-year follow-up. In patients with normal cardiac function and a high burden of

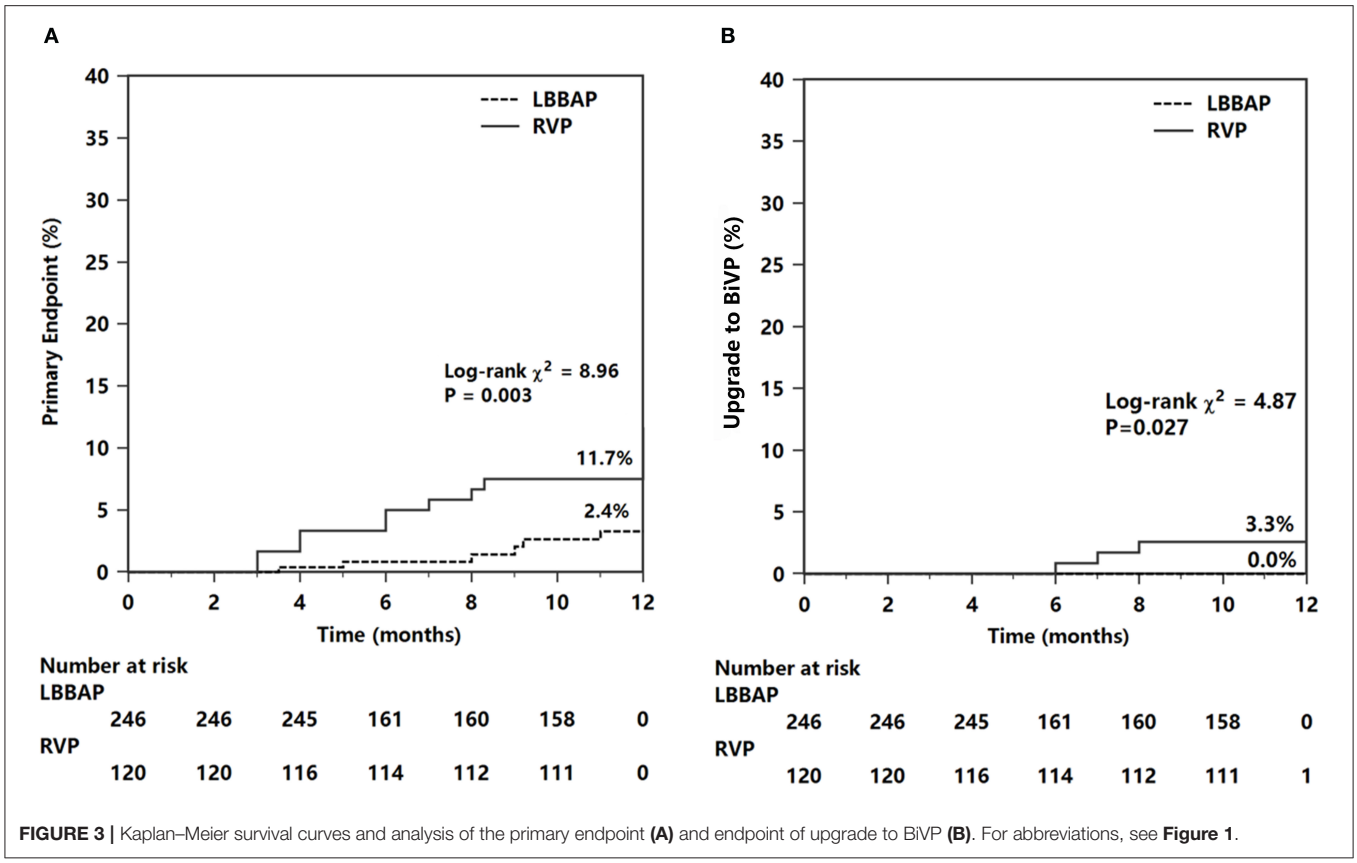


FIGURE 3 | Kaplan–Meier survival curves and analysis of the primary endpoint **(A)** and endpoint of upgrade to BiVP **(B)**. For abbreviations, see **Figure 1**.

TABLE 5 | Univariate and multivariate Cox analyses for the composite outcome of HFH or upgrading to BiVP.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	Adjusted HR	95% CI	*P*
LBBAP vs. RVP	0.25	0.09–0.71	0.009	0.14	0.04–0.55	0.005
Female	0.64	0.25–1.62	0.686			
Age, years	0.99	0.96–1.02	0.455			
Atrial fibrillation	1.46	0.51–4.15	0.479			
Coronary arterial disease	1.39	0.40–4.84	0.605			
MI history	3.52	0.80–15.39	0.095	6.82	1.23–37.75	0.028
Dilated cardiomyopathy	4.06	0.54–30.60	0.174			
Valvular heart disease	0.04	0.01–81.65	0.415			
HCM (post Morrow)	1.97	0.26–14.79	0.514			
Baseline QRSd	1.01	0.99–1.02	0.582			
Baseline LVEF	0.93	0.90–0.97	<0.001	0.91	0.86–0.96	0.001
VP	1.02	1.00–1.05	0.087			

LBBAP, left bundle branch area pacing; RVP, right ventricular pacing; CAD, coronary atrial disease; MI, myocardial infarction; DCM, dilated cardiomyopathy; VHD, valvular heart disease; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; VP, ventricular pacing percentage.

VP, LBBAP achieved preserved LVEF and reduced LVEDD, while RVP resulted in reduced LVEF and enlarged LVEDD. Patients with LBBAP had a significant reduction in HF hospitalization events (including upgrading to BiVP) compared with conventional RVP (central illustration). The effect of LBBAP was seen predominantly in patients with VP >40%, patients with LVEF ≤60%, or patients with baseline organic cardiac disease or AF. LBBAP was an independent predictor for a reduced risk of HF hospitalization after adjustment for other risk factors.

The detrimental effect of traditional RVP has been associated with an increased risk for HF hospitalization and mortality in patients with a high VP burden (14). A recent study (15) indicated that an RVP > 20% is an independent risk factor for

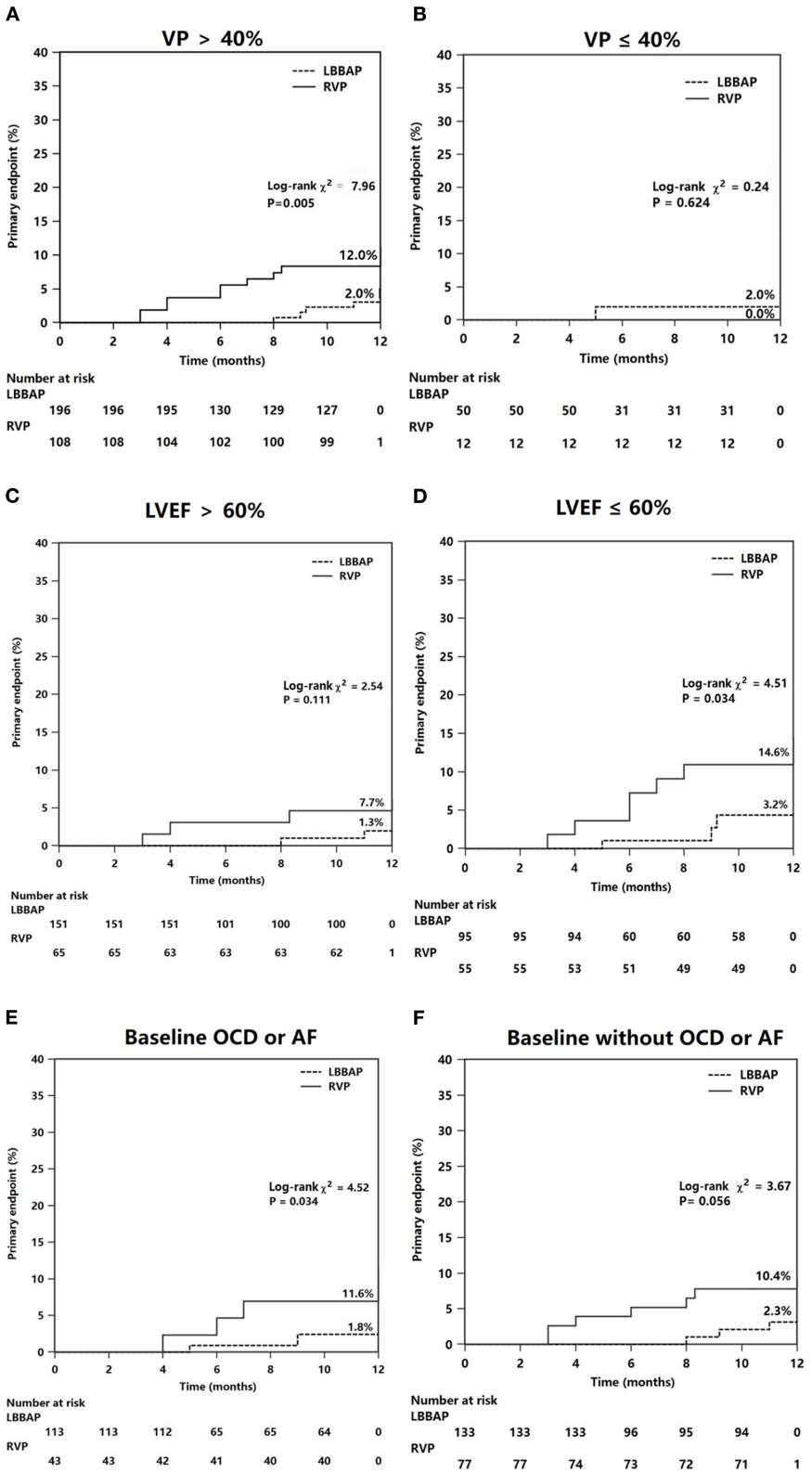


FIGURE 4 | Subgroup Kaplan–Meier survival curves and analysis of the primary endpoints. The composite heart failure events was analyzed according to different groups of VP **(A,B)**, LVEF **(C,D)**, and status of OCD or AF at baseline **(E,F)**. VP, ventricular pacing (percentage); OCD, organic cardiac disease; AF, atrial fibrillation.

pacing-induced cardiomyopathy in AVB patients with baseline preserved LV function during a mean follow-up of 4.3 years. His bundle pacing is effective in preventing ventricular dyssynchrony and can reduce the risk of death, HF hospitalization, or upgrading to BiVP by 35% in patients with a VP burden of >20% (16). Consistent with previous studies (15), we found that HF hospitalization or upgrading to BiVP was common in patients with VP > 40%, baseline 50% < LVEF ≤ 60%, or baseline organic cardiac disease or AF. Pacing-induced HF hospitalization has been reported to occur within the first 6 months (17). The high RVP% in our study (85.7%) might be the main contributor to the occurrence of HF hospitalization events. In addition, damage to the myocardium (previous myocardial infarction) and mildly reduced baseline cardiac function (50% < LVEF ≤ 60%) might be the underlying reasons for the increased risk of HF hospitalization.

LBBAP can pace the conduction system beyond pathological or disease-vulnerable regions to produce nearly physiological ventricular capture. In recent studies, LBBAP generally achieves paced QRSd within 130 ms, mostly between 110 and 120 ms (7–11, 18–20). This study verified the narrower-paced QRSd by LBBAP at the 1-year follow-up in patients with a high VP burden. Because the capture thresholds of His bundle pacing might be unstable and increase during long-term follow-up (21), the long-term stability of low pacing thresholds of LBBAP has been questioned. A previous study (22) reported comparable R wave amplitudes and pacing thresholds between LBBAP and RVP at the 6-month follow-up. Our study confirmed the low and stable pacing thresholds of LBBAP at the 1-year follow-up and similar sensing amplitudes to those of RVP in patients with AVB and a high burden of VP. Although our previous study showed similar success rates of LBBAP (91.3%) to His bundle pacing (87.2%) (23), successful LBBAP appears to be easily achieved with increasing procedure experience. Huang et al. (24) reported a high success rate of LBBAP (97.8%) in their single-center experience, while a comparable success rate of LBBAP (93%) was reported by Vijayaraman et al. (9). The success rate of LBBAP in the present study (95.5%) was slightly higher than that (90.9%) in our previous study (8) due to increasing procedure volume and experience.

LBBAP could achieve LV synchrony and preserve LV function in bradycardia patients with normal cardiac function (8). A recent study (25) evaluated the systolic dyssynchrony index and the standard deviation of time-to-peak contraction velocity in LV 12 segments among native-conduction mode, LBBAP, and RVP situations and found that the LV synchrony of LBBAP is similar to that of native-conduction mode and superior to that of RV septal pacing. LBBAP could correct left bundle branch block (LBBB) and deliver cardiac resynchronization therapy (CRT) to effectively improve LV function and reduce HF symptoms in patients with HF and LBBB (18). In several small sample sizes of studies with mid-term follow-up (12, 26, 27), the effect of LBBAP on LV systolic function and CRT response appears to be superior to that of BiVP-delivered CRT. In addition, successful LBBAP can shorten QRS duration in bradycardia patients with right bundle branch block (RBBB) (9, 11, 28).

To our knowledge, this is the first study comparing LV function and clinical outcomes between LBBAP and RVP in AVB patients with high VP burden and baseline narrow QRSd. The significant difference in LVEF and LVEDD between the LBBAP and RVP groups at 1-year follow-up verified the beneficial effect of LBBAP on cardiac function. Although patients with normal cardiac function usually have few clinical outcomes after receiving RVP, our study still observed a significant difference in HF hospitalization events between LBBAP and RVP. A high burden of VP > 40% has been recognized as a risk factor for HF events during long-term follow-up. Our subgroup results further indicated that LBBAP might provide an additional benefit of cardiac function in patients with VP > 40%, baseline decreased LVEF (<60%), or baseline organic cardiac disease or atrial fibrillation. This is also the first study reporting the occurrence of HF hospitalization in patients with a high burden of LBBAP. Six patients in the LBBAP group presented HF symptoms and relatively reduced LVEF (>50 and <60%), and they recovered well after receiving medical treatment, including oral diuretics and beta-blockers. No patients in the LBBAP group presented with indications for upgrading to BiVP. Our results together with previous studies indicate that LBBAP might effectively reduce the risk of HF hospitalization compared with RVP in patients with normal LV function and a high burden of VP.

STUDY LIMITATION

The main limitation of this study is the observational study design. The clinical homogeneity of patients could not be guaranteed between LBBAP and RVP. However, the higher prevalence of atrial fibrillation in the LBBAP group further demonstrated the potential benefit of LBBAP compared with RVP. Second, the relatively small sample size and the high percentage of RVAP in the RVP group might contribute to the difference in the clinical outcomes between RVP and LBBAP. Third, the clinical outcomes of all-cause death or cardiovascular death during longer follow-up may provide more solid evidence for the superiority of LBBAP. Therefore, future prospective randomized clinical trials with a large sample size are needed in patients with a high burden of VP.

CONCLUSION

The results of this multicenter observational study indicate that LBBAP might be a preferable pacing modality to reduce potential HF events in patients requiring a high burden of VP compared with traditional RVP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Fuwai Hospital, Beijing; Institutional Review Board of Anzhen Hospital, Beijing; Institutional Review Board ofSun Yat-sen Memorial

Hospital, Guangzhou; Institutional Review Board of the First Affiliated Hospital of Zhengzhou University, Zhengzhou and Institutional Review Board of the Second Hospital of Hebei Medical University, Hebei, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XF, XL, YC, and YW conceptualized and designed the research. XF, XL, JZ, CQ, HL, KP, ZW, ZL, and RX were responsible for the acquisition, analysis, and interpretation of data. XF had obtained funding and supervised the work. XF and XL drafted the manuscript. YY, YC, and YW critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Lead Abandonment and Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) Implantation in a Cohort of Patients With ICD Lead Malfunction

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Background: When an implantable-cardioverter defibrillator (ICD) lead becomes non-functional, a recommendation currently exists for either lead abandonment or removal. Lead abandonment and subcutaneous ICD (S-ICD) implantation may represent an additional option for patients who do not require pacing. The aim of this study was to investigate the outcomes of a strategy of lead abandonment and S-ICD implantation in the setting of lead malfunction.

Methods: We analyzed all consecutive patients who underwent S-ICD implantation after abandonment of malfunctioning leads and compared their outcomes with those of patients who underwent extraction and subsequent reimplantation of a single-chamber transvenous ICD (T-ICD).

Results: Forty-three patients underwent S-ICD implantation after abandonment of malfunctioning leads, while 62 patients underwent extraction and subsequent reimplantation of a new T-ICD. The two groups were comparable. In the extraction group, no major complications occurred during extraction, while the procedure failed and an S-ICD was implanted in 4 patients. During a median follow-up of 21 months, 3 major complications or deaths occurred in the S-ICD group and 11 in the T-ICD group (HR 1.07; 95% CI 0.29–3.94; $P = 0.912$). Minor complications were 4 in the S-ICD group and 5 in the T-ICD group (HR 2.13; 95% CI 0.49–9.24; $P = 0.238$).

Conclusions: In the event of ICD lead malfunction, extraction avoids the potential long-term risks of abandoned leads. Nonetheless the strategy of lead abandonment

and S-ICD implantation was feasible and safe, with no significant increase in adverse outcomes, and may represent an option in selected clinical settings. Further studies are needed to fully understand the potential risks of lead abandonment.

Clinical Trial Registration: URL: ClinicalTrials.gov Identifier: NCT02275637

Keywords: implantable defibrillator, subcutaneous, lead extraction, lead abandonment, lead malfunction

INTRODUCTION

Implantable cardioverter-defibrillators (ICDs) are an effective therapy for sudden cardiac death prevention (1). However, complications with ICD therapy exist and are mainly associated with the use of transvenous leads in the heart and vascular system (2, 3). In the case of lead malfunction, it may be removed or left *in situ*, and the decision should be based on the expected risks and benefits (4). The risks of removal include venous or cardiac perforation, and depend on many factors, such as the duration of the lead implant, the patient's age and condition, and the experience of the operator. The benefits of removal include the avoidance of possible infections requiring later and more difficult extraction, and the creation of an access to allow implantation of a new lead. Currently, in the setting of lead malfunction, a class IIa recommendation exists for either lead abandonment or removal (4); this is based on single-center observational studies that have compared the two strategies, followed by transvenous ICD (T-ICD) reimplantation (5, 6). An entirely subcutaneous ICD (S-ICD) (Emblem^{TM}, Boston Scientific Inc., Natick, MA, USA) has been developed to prevent all possible complications associated with the insertion and long-term presence of transvenous leads in the heart and the vascular system (7, 8). Since with S-ICD no leads are inserted into the cardiovascular system, it may represent a preferred option for patients with limited venous access or those who are at high risk of infection (9). Thus, a strategy of S-ICD implantation after the abandonment of malfunctioning leads may represent an additional option for patients who do not require pacing.

The aim of the present study was to compare outcomes of a strategy of lead abandonment and S-ICD implantation in the setting of lead malfunction, with those of patients who underwent transvenous extraction with subsequent reimplantation of a single-chamber T-ICD.

METHODS

Study Design

Patients undergoing implantation of an ICD were prospectively enrolled at the cardiovascular centers that participate in the Rhythm Detect registry (NCT02275637). The Institutional Review Boards approved the study, and all patients provided written informed consent for data storage and analysis. For the present analysis, we identified all patients, from 2015 to 2018 at 12 Italian centers, who underwent S-ICD (Boston Scientific Inc., Natick, MA, USA) implantation after the abandonment of malfunctioning leads and compared their outcomes with those of patients who underwent transvenous extraction with subsequent reimplantation of a single-chamber T-ICD. Baseline assessment comprised collection of demographic data, medical history (including data from the extraction and subsequent implantation procedures), clinical examination, 12-lead electrocardiogram, echocardiography and estimation of NYHA functional class. The extraction and implantation procedures, as well as perioperative and postoperative clinical management, were performed in accordance with the clinical practice of each center. In patients who received an S-ICD, an ECG morphology tool was used to verify the quality of device sensing before implantation. Devices were implanted and acute defibrillation tests were performed according to the local clinical practice. Defibrillation testing through induction of ventricular fibrillation was performed under deep sedation or general anesthesia. Information on clinical outcomes, such as hospitalizations and deaths, was collected during hospital visits or, if patients missed scheduled visits, via telephone calls.

Study End-Points

In the present analysis, the study database was searched for all procedure- or device-related adverse events, defined as untoward events resulting from the presence or performance of the system implanted. Specifically, those events resulting in prolonged hospitalization or surgical intervention for system revision were considered to be major complications. The primary endpoint was the combination of major complications and all-cause deaths. All adverse events not requiring surgical intervention (including inappropriate shocks) or hospitalization were classified as minor complications. The end-points were analyzed according to the intention-to-treat principle. On-treatment analysis was also performed.

Statistical Analysis

Descriptive statistics are reported as means ± SD for normally distributed continuous variables or medians with 25th to 75th percentiles in the case of skewed distribution. Normality of distribution was tested by means of the non-parametric Kolmogorov-Smirnov test. Categorical variables are reported as percentages. Differences between mean data were compared by means of a t-test for Gaussian variables, and Mann–Whitney non-parametric test for non-Gaussian variables. Differences in proportions were compared by means of chi-square analysis or Fisher's exact test, as appropriate. Survival analysis was performed by means of the Kaplan-Meier method, and the log-rank test was applied to evaluate differences between survival trends. For all time-to-event estimations, patients were censored on death or at their last follow-up visit. A P value < 0.05 was considered significant for all tests. All statistical analyses

TABLE 1 | Demographics and baseline clinical parameters.

Parameter	All patients $n = 105$	Lead abandonment and S-ICD $n = 43$	Lead extraction and T-ICD $n = 62$	*p*-value
Male gender, *n* (%)	80 (76)	36 (84)	44 (71)	0.131
Age, years	55 ± 17	55 ± 16	54 ± 18	0.749
Body Mass Index	25 ± 5	26 ± 4	24 ± 5	0.084
LV ejection fraction, %	46 ± 15	43 ± 15	48 ± 14	0.096
NYHA Class III-IV, *n* (%)	13 (12)	6 (14)	7 (11)	0.684
Ischemic/Non-ischemic Cardiomyopathy, *n* (%)	60 (57)	27 (63)	33 (53)	0.330
Hypertrophic Cardiomyopathy, *n* (%)	9 (9)	3 (7)	6 (10)	0.734
Congenital/ARVD, *n* (%)	13 (12)	5 (12)	8 (13)	0.845
Channelopathies/Other, *n* (%)	23 (22)	8 (18)	15 (24)	0.496
Chronic kidney disease, *n* (%)	20 (19)	12 (28)	8 (13)	0.054
Diabetes, *n* (%)	15 (14)	6 (14)	9 (15)	0.974
Previous dual-chamber ICD, *n* (%)	24 (23)	13 (30)	11 (18)	0.133
Previous biventricular ICD, *n* (%)	3 (3)	1 (2)	2 (3)	1.000
Number of previous leads,	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.5	0.249
Time from first implant, years	4 ± 3	5 ± 3	4 ± 2	0.021

NYHA, New York Heart Association; LV, Left ventricular; ARVD, Arrhythmogenic Right Ventricular Dysplasia; ICD, Implantable Cardioverter Defibrillator.

were performed by means of STATISTICA software, version 7.1 (StatSoft, Inc, Tulsa, OK, USA).

RESULTS

Study Population

From 2015 to 2018, a total of 43 patients underwent S-ICD implantation after the abandonment of malfunctioning leads at the study centers. In the same period, transvenous extraction of malfunctioning leads and subsequent reimplantation of a single-chamber T-ICD was attempted in 62 patients. **Table 1** shows the baseline clinical variables in the two groups. Age, left ventricular systolic function, functional status and etiology were comparable between the groups. Chronic kidney disease was non-significantly more frequent in patients with abandoned leads and S-ICD ($p = 0.054$). A multi-lead (dual-chamber or biventricular) ICD had previously been implanted in 33% of patients who subsequently received an S-ICD and in 21% of those who underwent extraction and received a single-chamber ICD ($p = 0.181$, **Table 1**). The implant duration (time from the first ICD implantation) was significantly longer in patients with lead abandonment and S-ICD implantation (5 ± 3 vs. 4 ± 2 years, $p = 0.021$).

S-ICD Implantation Procedure

The surface ECG screening procedure identified at least 1 suitable vector in all patients; at least two vectors were appropriate in 37 (86%), and three vectors in 15 (35%). The S-ICD generator was positioned in a standard subcutaneous pocket in 8 (19%) patients, while an intermuscular approach was adopted in the remaining 81%. The lead was positioned by means of a 2-incision technique (avoiding the superior parasternal incision) in 38 (88%) patients. Defibrillation testing was performed in 31 S-ICD patients (72%) and was effective in all cases at 80J and in 30 (96.7%) cases at 65J. In the remaining patients, defibrillation testing was not performed because of concerns over reported clinical instability (3 patients), lack of inducibility of ventricular fibrillation (3 patients), or physician preference (6 patients). On hospital discharge, sensing from the primary vector was programmed in 26 (60%) patients, from the secondary vector in 15 (35%) and from the alternative vector in 2 (5%).

Lead Extraction and Transvenous ICD Implantation

A total of 75 leads (1.2 ± 0.5 leads per patient) were extracted from 62 patients. Leads were extracted by means of locking stylets in 1 (2%) patient, mechanical non-powered sheaths (Byrd Dilator Polypropylene Sheaths©, Cook Medical, Bloomington, IN, USA) in 57 (92%) and powered sheaths (multiple manufacturers) in 4 (6%). Complete procedural success was obtained in 56 (90%) patients. Partial success (<4 cm lead fragment remained in the body) was reported in 1 (2%) patient and radiological failure (>4 cm lead fragment remained in the body) was reported in 5 (8%) patients. In 4 of these 5 patients, the decision was taken to implant an S-ICD; these 4 patients were analyzed in the lead extraction group, according to the intention-to-treat principle, and in the lead abandonment and S-ICD group, according to the on-treatment principle. No major complications occurred during extraction. Pocket hematomas were reported in two patients. In one case, it resolved without specific therapy; in the other, it required evacuation and was associated with a vagal crisis rapidly resolved with fluid infusion and atropine.

Follow-Up

During a median follow-up of 21 months (25th to75th percentiles, 7 to 39), 3 patients died (1 in the S-ICD group and

TABLE 2 | Major complications reported during follow-up.

Major complications	Number	Resolution	Details
Lead abandonment and S-ICD			
Early depletion	1	Device replacement	
Need for bradycardia pacing	1	Leadless pacemaker implantation	*Atrioventricular block*
Lead extraction and T-ICD			
Early depletion	2	Device replacement (2)	
Surgical revision	1	Extraction	*Previous extraction failure*
Lead dislodgement	1	Lead repositioning	
Need for resynchronization therapy	3	System upgrade (3)	*The previous ICDs were single- (2) and dual-chamber ICD (1)*
Systemic infection	1	Resolved with in-hospital antibiotic therapy	

TABLE 3 | Minor complications reported during follow-up.

Minor complications	Number	Resolution	Details
Lead abandonment and S-ICD			
Pocket hematoma	2	Resolved with no specific therapy (1) Hematoma requiring evacuation (1)	
Inappropriate shock	2	Device reprogramming (2)	
Lead extraction and T-ICD			
Pocket hematoma	2	Resolved with no specific therapy (2)	
Inappropriate shock	2	Device reprogramming (2)	
Ineffective therapy	1	Device reprogramming	*Hemodynamically stable ventricular tachycardia accelerated into fibrillation*

1 in the T-ICD group from chronic heart failure, and 1 in the T-ICD group from non-cardiac reasons). One patient with T-ICD underwent urgent heart transplantation. No sudden cardiac deaths occurred. Additional major complications were reported in 10 patients (**Table 2**). All complications were successfully resolved. Moreover, 9 additional events were managed non-invasively, and were defined as minor complications (**Table 3**). The Kaplan-Meier estimates of time to the primary endpoint were compared between the groups according to the intention-to-treat principle (hazard ratio, 1.07; 95% CI, 0.29 to 3.94; $p = 0.912$) (**Figure 1**). Similar findings were obtained with the analysis of time to first major complication (hazard ratio, 0.85; 95% CI, 0.19 to 3.74; $p = 0.834$). In the on-treatment analysis,

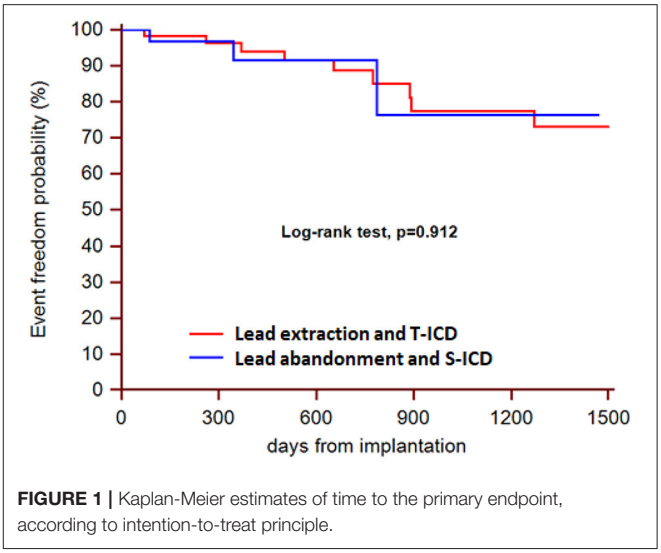

FIGURE 1 | Kaplan-Meier estimates of time to the primary endpoint, according to intention-to-treat principle.

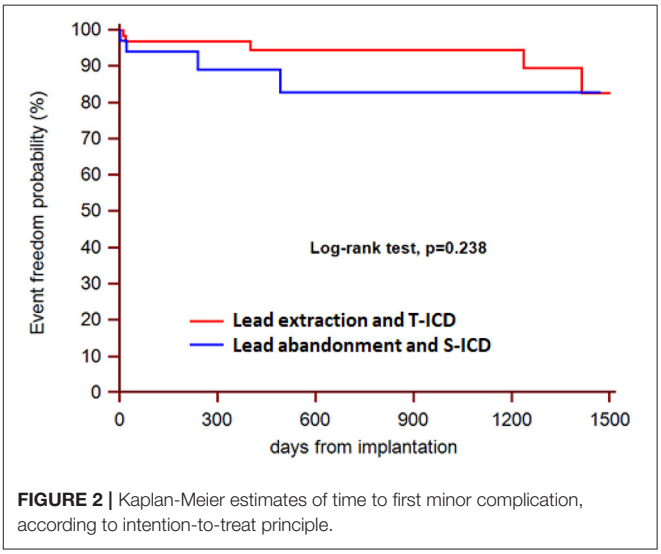

FIGURE 2 | Kaplan-Meier estimates of time to first minor complication, according to intention-to-treat principle.

estimates of time to the primary endpoint were compared between the 47 patients who actually had abandoned leads and received S-ICD and the 58 patients who underwent successful lead extraction and T-ICD implantation (hazard ratio, 1.35; 95% CI, 0.39 to 4.69; $p = 0.590$). The Kaplan-Meier analysis of minor complications according to the intention-to-treat principle is reported in **Figure 2** (hazard ratio, 2.13; 95% CI, 0.49 to 9.24; $p = 0.238$). The on-treatment analysis yielded similar findings (hazard ratio, 1.79; 95% CI, 0.44 to 7.36; $p = 0.365$).

DISCUSSION

Despite the proven effectiveness of ICD therapy in preventing sudden cardiac death, the transvenous lead still constitutes the weakest link in the chain. According to the literature, the annual rate of transvenous ICD lead failure may reach 20% in 10-year-old leads (10), and in recent years an unexpectedly high failure

rate, related to structural issues, has been reported for some specific lead types (11, 12).

In the event of lead failure, either extraction and reimplantation or abandonment and the addition of a new lead may be considered. The advantages and disadvantages of both strategies need to be weighed carefully. In patients who do not require pacing, a third possible solution could be to implant an S-ICD and to leave the malfunctioning T-ICD lead in place. This approach avoids the risks of lead removal and those related to the insertion of additional transvenous leads. In our experience, the strategy of lead abandonment and S-ICD implantation appeared to be feasible and safe, with no increase in adverse outcomes.

Although the two groups in analysis were similar, the lead abandonment and S-ICD implantation strategy seemed to be preferred by the study centers in patients with a higher risk profile, i.e. with comorbidities, such as chronic kidney disease, with longer implant durations and with more leads in place. This is in line with the results of a European survey that investigated operators' views on the management of malfunctioning leads (13). Indeed, the variables associated with the decision to extract or abandon a lead included the lead-dwelling time and the total number of leads.

The S-ICD implantation procedure was found to be safe, with no complications reported, in agreement with previous and larger reports on *de-novo* S-ICD implantation (7, 8, 14). As previously described with regard to *de-novo* S-ICD implantation procedures in Europe (15), in most of our patients the generator was positioned in an intermuscular pocket and the lead was implanted by means of a 2-incision technique (16). Our findings extend those of our previous study on the use of S-ICD in patients undergoing ICD extraction, in which we recorded a reduction in complications when intermuscular generator positioning was adopted (17). Defibrillation testing was effective at 65J in 96.7% and at 80 J in 100% of patients; comparable success rates have been reported for *de-novo* implantation procedures (18). This confirms the effectiveness of the defibrillation wave generated by the S-ICD system, even in the presence of abandoned defibrillation coils.

In the present study, we also observed a high rate of success of the transvenous lead extraction procedure in the extraction/reimplantation group, with few radiological failures and only minor complications. These findings are in line with the results of the European Lead Extraction ConTRolled (ELECTRa) study, in which transvenous lead extraction generally proved safe and effective when performed at high-volume centers and by experienced operators (19). However, the procedure remains potentially associated with life-threatening operative and postoperative complications. Thus, the availability of an alternative approach may be extremely valuable, when extraction is not mandated in order to eradicate an infection. Interestingly, after a failed extraction attempt in 4 patients, the decision was taken to abandon the leads and to implant an S-ICD. Plausibly, the decision to interrupt the extraction procedure was prompted by the availability of an alternative solution.

In this analysis, the rates of complications during follow-up were comparable between the groups. This finding agrees with the results of studies that compared the performance of S-ICD and T-ICD after *de-novo* implantation (20) and with those of our previous study comparing S-ICD with T-ICD implantation after T-ICD explantation because of infection or for other reasons (17). The present analysis also complements a previous comparison between patients undergoing S-ICD implantation after extraction of a T-ICD and patients receiving a *de-novo* S-ICD (21), which documented similar complication rates.

Our results showed that there was no increased risk of complications, such as ineffective or inappropriate shocks or infections, related to abandoned leads. Although a recent publication (22) showed that 9% of abandoned ICD leads needed to be extracted at a median follow up of 4.4 $\pm$ 3.1 years, mostly due to infection. This is relevant not only in comparison with the patients who underwent extraction in this series, but also, and especially, if a strategy consisting of placement of an additional lead and T-ICD use is considered after lead abandonment (23). Indeed, Wollmann et al. (24) found a 3-year adverse event rate of 30% in patients who underwent implantation of an additional lead. An abandoned lead may interfere with the active transvenous lead and result in inappropriate shocks. Moreover, the presence of multiple leads is associated with higher risk of infection (25), and ICD-related infections carry significant risks of mortality and morbidity (26). Additional implications of lead abandonment and the placement of additional leads are the increased risk of venous thrombosis (27) and additional difficulties in the case of future extraction (28). Moreover, according to a recently published ELECTRa study sub-analysis, in the case of mandatory extraction (i.e. for infection), the presence of previously abandoned leads is associated with increased procedural complexity, clinical failure, and major complication rates (29). Our study revealed the practice of re-evaluating the need for pacing. Indeed, single-chamber ICDs and S-ICDs were frequently adopted after removal of dual-chamber or biventricular ICDs. Nevertheless, adopting this approach requires caution, in order to avoid the need for subsequent upgrades. Indeed, in our series, a leadless pacemaker was implanted in one S-ICD patient after verification of the need for bradycardia pacing. Similarly, the need for resynchronization therapy was identified during follow-up in 3 patients in the T-ICD group, and an additional procedure was required in order to upgrade the system.

According to the data from the ELECTRa study (19), lead malfunction is becoming a more frequent indication for lead extraction than it was in the past (30). Currently, a class IIa recommendation exists for either lead abandonment or removal, followed by T-ICD reimplantation (4). Extraction avoids the potential long-term risks of abandoned leads and allows magnetic resonance imaging to be performed. Indeed, although growing aggregate of data seems to question this (31), the presence of abandoned leads remains an absolute contraindication for magnetic resonance imaging. Nonetheless, in this series, the strategy of lead abandonment and S-ICD implantation avoided the possible complications associated with the extraction procedure, and appeared to be feasible and safe, with no significant increase in adverse outcomes in patients

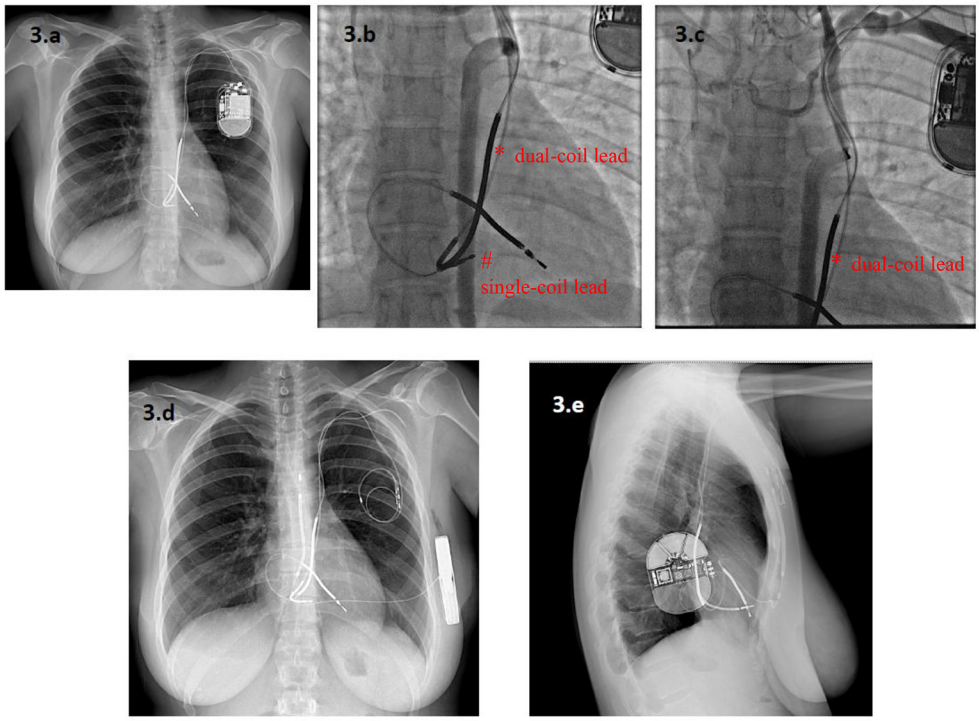

FIGURE 3 | A 33-year-old woman with a Long QT Syndrome received a single-chamber T-ICD and a dual-coil lead via a persistent left superior vena cava (PLSVC) after a cardiac arrest. A new single-coil ICD lead was added **five** years later owing to malfunction of the first one, which was abandoned **(a)**. After seven years, the second ICD lead also malfunctioned. Angiography showed complete occlusion of the PLSVC, with a variant venous circulation from an accessory hemiazygos vein. The dual-coil ICD lead (*) and the single-coil lead (#) are visible in **(b,c)**. In this setting, lead extraction was considered to be at very high risk of venous laceration, while implantation of a new lead from the right side was deemed inappropriate because of the patient's young age. Finally, an S-ICD was implanted and both leads were abandoned **(d,e)**. * dual-coil lead # single-coil lead.

not requiring pacing. In current clinical practice (15), an S-ICD is preferred in younger patients and in those with a life expectancy longer than 10 years, who will probably survive their ICD leads (10). This may also apply to patients who experience ICD lead malfunction. Indeed, lead malfunction occurs most frequently in younger patients, both because they are more active and because a longer lead-dwelling time results in more prolonged lead stress (32). If the use of the S-ICD therefore appears justified in the event of lead malfunction, when pacing is not required, the actual need to extract malfunctioning leads may remain an open question, also in the light of the positive outcomes reported with the use of S-ICD after transvenous ICD extraction (17). In clinical practice, the risk profile of the patient, the number of leads, the time from the first implant are variables that may guide the management, as well as performing venography and discussing with patient before making a decision (**Figure 3**).

Limitations

Our findings might be affected by a bias, owing to the retrospective study design. However, we included all consecutive patients who underwent S-ICD implantation after the abandonment of malfunctioning leads and all patients who underwent extraction and subsequent reimplantation of a single-chamber T-ICD in our analysis. The non-randomized comparison of the study represents an additional limitation. Indeed, a bias could derive from the differences between groups and specifically from factors influencing the operator's decision to extract or abandon a lead. In addition the small cohort size and the limited length of follow-up limit the statistical power and may have concealed differences between the groups. Indeed, a recent long-term analysis from a nationwide cohort study showed that the cumulative risk of interventions on abandoned ICD leads increased from 5.5% after 2.5 years to 15.2% after 10 years of abandonment (22). However our study represents the first experience of SICD implantation after abandonment of malfunctioning transvenous lead it and could pave the way for future larger studies.

Conclusions

Although guidelines indicate the same class of recommendation both for lead abandonment and for removal followed by T-ICD reimplantation in the case of ICD lead malfunction, extraction is usually preferred in order to avoid the potential risks of abandoned leads. Nonetheless, in this study, the strategy of lead abandonment followed by S-ICD implantation proved feasible and safe, with no significant increase in adverse outcomes in patients who did not require pacing. This approach may constitute an option in selected clinical settings (e.g. high risk, failed extractions, etc.) in order to avoid the risks of lead removal.

Longer follow-up studies are needed in order to fully understand the potential clinical value of this strategy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethic Committee of Fondazione IRCCS POLICLINICO SAN MATTEO, Pavia, Italy. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

VR and SVi: concept/design and data collection. GT, GB, AD, PS, LO, GP, LC, and LS: data analysis/interpretation and data collection. FM, RR, and GN: drafting article. ML and SVa: critical revision of article. MGB, MB, and EB: approval of article. All authors contributed to the article and approved the submitted version.

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Feasibility and Safety of Permanent Left Bundle Branch Pacing in Patients With Conduction Disorders Following Prosthetic Cardiac Valves

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Background: The feasibility and safety of left bundle branch pacing (LBBP) in patients with conduction diseases following prosthetic valves (PVs) have not been well described.

Methods: Permanent LBBP was attempted in patients with PVs. Procedural success and intracardiac electrical measurements were recorded at implant. Pacing threshold, complications, and echocardiographic data were assessed at implant and follow-up visit.

Results: Twenty-two consecutive patients with atrioventricular (AV) conduction disturbances (10 with AV nodal block and 12 with infranodal block) underwent LBBP. The PVs included aortic valve replacement (AVR) in six patients, mitral valve repair or replacement (MVR) with tricuspid valve ring (TVR) in four patients, AVR with TVR in one patient, AVR with MVR plus TVR in three patients, transcatheter aortic valve replacement (TAVR) in five patients, and MVR alone in three patients. LBBP succeeded in 20 of 22 (90.9%) patients. LBB potential was observed in 15 of 22 (68.2%) patients, including 10 of 15 (66.7%) patients with AVR/TAVR and five of seven (71.4%) patients without AVR/TAVR. AVR and TVR served as good anatomic landmarks for facilitating the LBBP. The final sites of LBBP were 17.9 ± 1.4 mm inferior to the AVR and 23.0 ± 3.2 mm distal and septal to the TVR. The paced QRS duration was 124.5 ± 13.8 ms, while the baseline QRS duration was 120.0 ± 32.5 ms ($P = 0.346$). Pacing threshold and R-wave amplitude at implant were 0.60 ± 0.16 V at 0.5 ms and 11.9 ± 5.5 mV and remained stable at the mean follow-up of 16.1 ± 10.8 months. No significant exacerbation of tricuspid valve regurgitation was observed compared to baseline.

Conclusion: Permanent LBBP could be feasibly and safely obtained in the majority of patients with PVs. The location of the PV might serve as a landmark for guiding the final site of the LBBP. Stable pacing parameters were observed during the follow-up.

Keywords: left bundle branch pacing, prosthetic valves, physiological pacing, conduction system, pacing

INTRODUCTION

Traditional right ventricular (RV) apical pacing has been widely used for about 50 years. However, long-term RV apical pacing is associated with increased risk for atrial fibrillation, heart failure, and mortality due to ventricular electrical and mechanical asynchrony (1, 2). Pacing at alternative RV sites, such as the septal or outflow tract pacing, has not been shown to be superior to RV apical pacing (3, 4). His bundle pacing (HBP) is a more physiologic form of pacing and has demonstrated a reduced risk of pacing-induced cardiomyopathy, heart failure hospitalization, and mortality compared with RV pacing (5–7). However, several factors, such as higher capture threshold, low R-wave amplitude, and longer learning curve, have limited the wider adoption of this technique in routine practice. Left bundle branch pacing (LBBP), a novel pacing strategy, has been considered to be a feasible and safe approach with low and stable pacing threshold and narrow QRS duration (8, 9).

Conduction system disease is not uncommon after prosthetic valve (PV) surgery. Recently, His–Purkinje conduction system pacing in patients with transcatheter aortic valve replacement (TAVR) has been reported (10). However, the feasibility and success rate of LBBP in patients with other PV surgery have not been well described. The aim of this study was to report the feasibility and safety of LBBP in patients undergoing pacemaker (PM) implantation for atrioventricular (AV) conduction diseases after PV surgery.

METHODS

Patient Population

All patients who received an implantable PM after PV surgery for AV conduction diseases and underwent attempts at LBBP between January 2018 and December 2019 were retrospectively included in a single-center study. Patients were excluded from the study if they underwent pulse generator changes or cardiac resynchronization therapy (CRT) or implantable cardioverter defibrillator (ICD) implantation. This study was approved by the institutional review board.

Preprocedural Management

All patients underwent a transthoracic echocardiography to access ventricular structure before the procedure. For patients under warfarin, uninterrupted administration was performed. All patients signed an informed consent prior to the procedure.

Implantation Procedure

Intracardiac electrograms from the pacing lead and 12-lead ECG were continuously recorded in an electrophysiology recording system (LabSystem PRO, Bard Electrophysiology, Lowell, MA, USA).

LBBP was performed using the 3,830 pacing lead (SelectSecure, Medtronic, Minneapolis, MN, USA), which was delivered through a fixed-curve sheath (C315 His, Medtronic, Minneapolis, MN, USA) inserted *via* the left subclavian or axillary vein. The distal His location was identified at the right anterior oblique (RAO) 30°position, and the fluoroscopic view was used as a reference. Subsequently, the sheath with the lead was further advanced to the anterior lower site of the distal His position and rotated in a counterclockwise fashion to place the lead tip in a perpendicular orientation toward the interventricular septum (IVS). A "W" pattern by unipolar pacing in lead V_1 was selected as the initial implantation site. As the lead tip was gradually screwed into the IVS, a rightward shift of the second notch in the "W" -shaped pacing morphology was recorded. Once the right bundle branch block (RBBB) pattern in lead V_1 was observed, the rotation of the lead was stopped. The depth of the lead within the IVS was accessed by contrast injection *via* the sheath at the left anterior oblique (LAO) 45°fluoroscopic view. Left bundle branch (LBB) potential was usually recorded in patients without left bundle branch block (LBBB). Selective LBBP was defined as follows: (1) There was an isoelectric interval between pacing spike and ECG QRS complex; (2) The pacing spike–QRS interval was almost identical with the LBB potential–QRS interval; (3) A local ventricular intracardiac electrogram (EGM) was present as a discrete component. Nonselective LBBP was defined as the following criteria: (1) There was no isoelectric interval between pacing spike and ECG QRS complex; (2) The local ventricular EGM showed direct capture of local myocardium by the pacing stimulus.

Data Collection and Follow-Up

Baseline characteristics and type of AV conduction diseases (AV nodal or infranodal) were documented. The type of AV conduction diseases was based on the intracardiac recording. The atrial deflection was not followed by a His potential, while the ventricular deflection was preceded by the His potential, which was defined as AV nodal block (**Figure 1**). The atrial deflection was followed by a conducted His potential, and ventricular deflection was not preceded by the His potential, which was characterized as infranodal block. Baseline echocardiographic parameters, such as the IVS thickness, left ventricular (LV) end-diastolic diameter, left ventricular ejection fraction (LVEF), and the degree of tricuspid regurgitation (TR) at baseline, were noted. Feasibility and LBBP parameters including the LBB capture threshold, R-wave amplitude, and pacing impedance were recorded. Presence of LBB potential, paced QRS duration, and the stimulus to peak left ventricular activation time (LVAT) were also recorded. The stim-LVAT was defined as the pacing stimulus to the peak of R-wave in lead V5 or V6. After discharge from the hospital, patients were scheduled for follow-up visit at 1, 3, 6, and 12 months in the device clinic. Pacing parameters were also recorded, and complications such as loss of capture, lead dislodgment, and significant increases in pacing threshold were tracked during the follow-up visit. Furthermore, multiple echocardiographic views were performed to quantify TR and to assess if there was any obstruction of tricuspid leaflet motion induced by the septal pacing lead. TR was categorized as none, mild, moderate, and severe. The severity of TR after LBBP lead implantation was compared to baseline echocardiography.

Statistical Analysis

Continuous variables are given as mean ± standard deviation. The chi-square or Fisher exact test was used for categorical

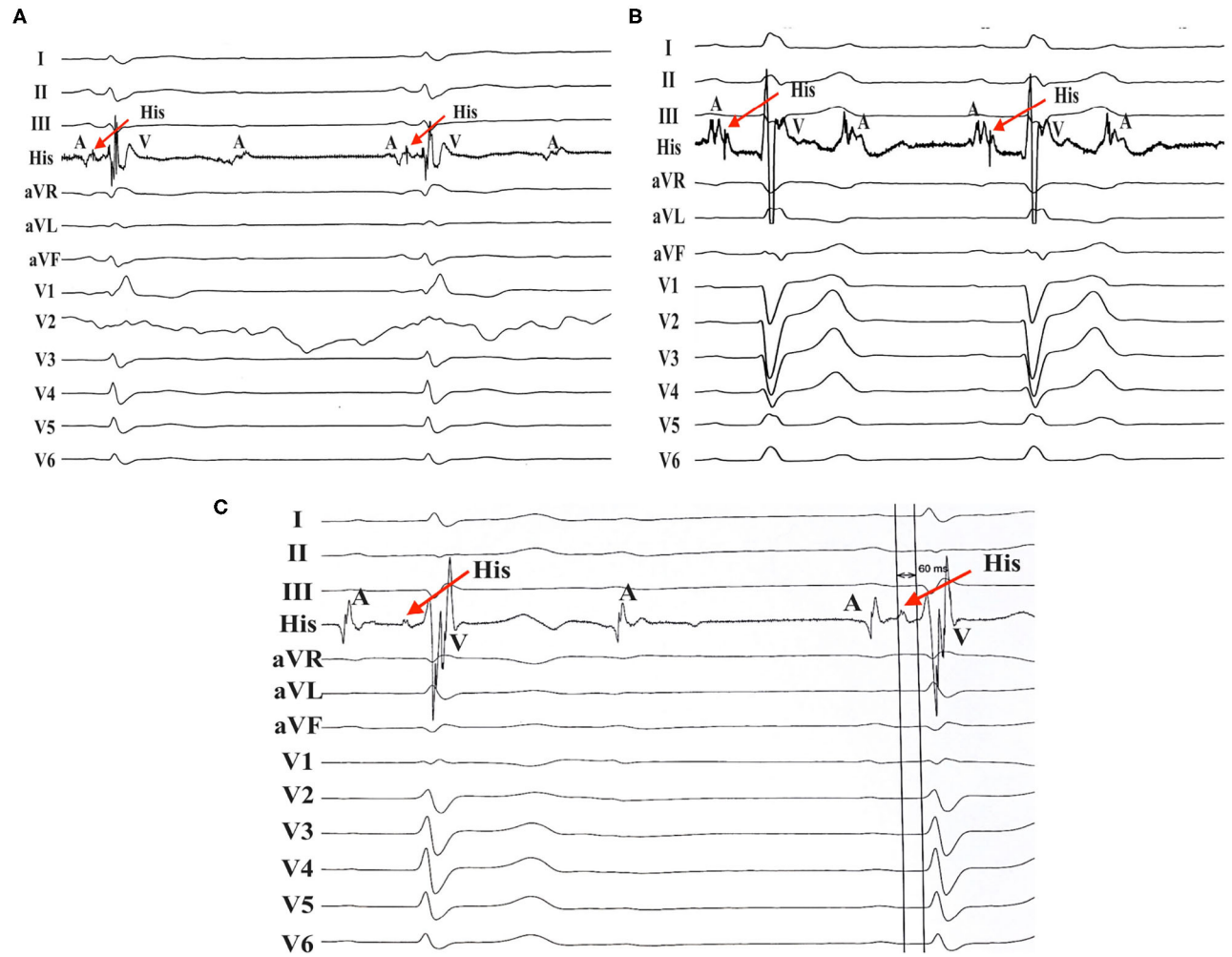

FIGURE 1 | AV nodal block in patients with RBBB/LBBB. **(A)** Patient no. 8 with RBBB developed AV nodal block. **(B)** AV nodal block was found in patient no. 13 with LBBB. **(C)** Patient no. 17 with RBBB also developed AV nodal block with an His-ventricular (HV) interval of 60 ms. AV, atrioventricular; RBBB, right bundle branch block; LBBB, left bundle branch block.

variables. Normally distributed continuous variables were analyzed using independent-sample *t*-test. Two-tailed paired *t*-test was performed for continuous paired variables. All statistical analyses were performed using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 22 consecutive patients (14 males, 61.7 ± 13.5 years) who had undergone an attempt at LBBP were included during the study period. Four (18.2%) patients had hypertension, three (13.6%) patients had coronary disease, and six (27.3%) patients had atrial fibrillation. The mean LVEF at baseline was 61.0 ± 10.8%, with underlying LV dysfunction in 9.1% of patients. All patients had AV conduction diseases, with high-grade or complete AV nodal block in 10 patients and infranodal block in 12 patients. Baseline QRS duration was 120.0 ± 32.6 ms, with right bundle branch block (RBBB) in nine patients and left bundle branch block (LBBB) in five patients. Baseline characteristics and procedural results of each patient are described in **Table 1**.

Implantation Results

The PVs included aortic valve replacement (AVR) in six patients, mitral valve repair or replacement (MVR) with tricuspid valve ring (TVR) in four patients, AVR with TVR in one patient, AVR with MVR plus TVR in three patients, TAVR in five patients, and MVR alone in three patients. Types of aortic valves implanted were the Sapien valve (Edwards Lifesciences, Irvine, CA, USA) in one patient, J-valve (Jiecheng Medical, Soochow, China) in one patient, and Venus-A valve (Venus Medtech, Hangzhou, China)

TABLE 1 | Baseline characteristics and procedural results.

Patient	Age	Gender	Valve type	Site of block	AF	CMP	LVEF	Baseline QRSd (ms)	BBB	Paced QRSd (ms)	Septal thickness (mm)
1	52	Female	AVR+MVR+TVR	AVN	Yes		62	92		116	8
2	54	Female	AVR	Infranodal			67	130	cRBBB	144	13
3	83	Male	TAVR	Infranodal			68	95		92	9
4	66	Female	AVR	Infranodal			70	84	iRBBB	106	9
5	49	Male	MVR	AVN			59	108		100	9
6	36	Male	AVR	Infranodal			75	156	cRBBB	128	10
7	72	Female	MVR+TVR	AVN			62	76		126	10
8	52	Male	MVR+TVR	AVN			45	164	cRBBB	120	11
9	40	Female	AVR+TVR	AVN			67	82	iRBBB	134	11
10	86	Female	AVR	AVN			70	88		130	12
11	55	Male	MVR	AVN			47	103		128	12
12	66	Female	MVR	AVN			69	98		132	10
13	62	Male	MVR+TVR	AVN	Yes	Yes	40	132	LBBB	133	8
14	61	Male	AVR	Infranodal			68	156	cRBBB	126	10
15	82	Male	TAVR	Infranodal			52	190	LBBB	146	12.7
16	61	Male	AVR+MVR+TVR	Infranodal	Yes		60	142	cRBBB	128	10
17	45	Male	MVR+TVR	AVN	Yes		55	138	cRBBB	142	11.7
18	57	Male	AVR	Infranodal			64	106		123	9
19	71	Male	TAVR	Infranodal			65	140	LBBB	128	13
20	61	Male	TAVR	Infranodal	Yes	Yes	38	148	LBBB	148	10
21	76	Female	TAVR	Infranodal			78	149	LBBB	138	10
22	70	Male	AVR+MVR+TVR	Infranodal	Yes		62	160	cRBBB	112	11

AF, atrial fibrillation; AVN, atrioventricular nodal; AVR, aortic valve replacement; BBB, bundle branch block; CMP, cardiomyopathy; cRBBB, complete right bundle branch block; iRBBB, incomplete right bundle branch block; LBBB, left bundle branch block; LBBP, left bundle branch pacing; LVEF, left ventricular ejection fraction; MVR, mitral valve replacement or repair; TAVR, transcatheter aortic valve replacement; TVR tricuspid valve ring.

in three patients. Twelve of 15 (80%) patients with AVR/TAVR developed infranodal block, while infranodal block was not found in patients without AVR/TAVR. Seventeen patients received a dual-chamber PM, whereas a single-chamber PM was implanted in five patients. LBBP was successfully obtained in 20 of 22 (90.9%) patients. In two patients (patients no. 2 and no. 15), we were unable to place the lead in the LV septum and the lead tip remained on the right side of the septum. AVR and TVR acted as good anatomic landmarks for guiding the LBBB lead implantation in our study. The final sites of LBBP were 17.9 ± 1.4 mm inferior to the AVR and 23.0 ± 3.2 mm distal and septal to the TVR. Contrast septal angiography was performed to confirm the depth of the lead in the septum in 15 of 22 (68.2%) patients in LAO fluoroscopic view. The mean length of the lead in the septum from the RV to LV wall along the course of the lead was 1.2 ± 0.36 cm.

Electrophysiologic Characteristics

LBB potential was observed in 15 of 22 (68.2%) patients. Of these 15 patients, LBB potential was recorded in 10 of 15 (66.7%) patients with AVR/TAVR and five of seven (71.4%) patients without AVR/TAVR. No LBB potential was found in four patients with LBBB and three patients with temporary PM dependency due to complete block without escape rhythm. A typical ECG morphology of right BBB was recorded during the lead implantation for LBBP in 20 patients (**Figure 2**). In two patients with failed LBBP, the paced QRS duration was 144 ms and 146 ms without RBBB pattern. Possible explanation may be related to the local hypertrophic myocardium. The final paced QRS duration was 124.5 ± 13.8 ms, while the baseline QRS duration was 120.0 ± 32.6 ms ($p = 0.346$). The mean stim-LVAT was 70.6 ± 8.1 ms. LBBP was successfully achieved in four of five patients with LBBB. Successful correction of LBBB and narrowing QRS duration were recorded in these four patients (**Figure 3**).

Complications and Follow-Up

No procedure-related complications occurred during the implantation procedure. Pocket hematoma or infection, loss of capture, lead dislodgment, or septal perforation was not observed during the mean follow-up of 16.1 ± 10.8 months (ranged from 3 to 33 months). Pacing threshold, R-wave amplitude, and lead impedance at implant and follow-up were described in **Table 2**. Lead parameters, including pacing threshold, R-wave amplitude, and lead impedance, were stable during the follow-up period. Of our series, 15 out of 22 patients fulfilled the 12 months of follow-up, and echocardiographic data were noted. No significant differences in LV end-diastolic diameter (47.8 ± 7.5 mm vs. 44.1 ± 4.5 mm, $p = 0.12$) and LVEF (63.3 ± 8.2% vs. 62.6 ± 3.4%, $p = 0.83$) were found compared with those at baseline. The degree

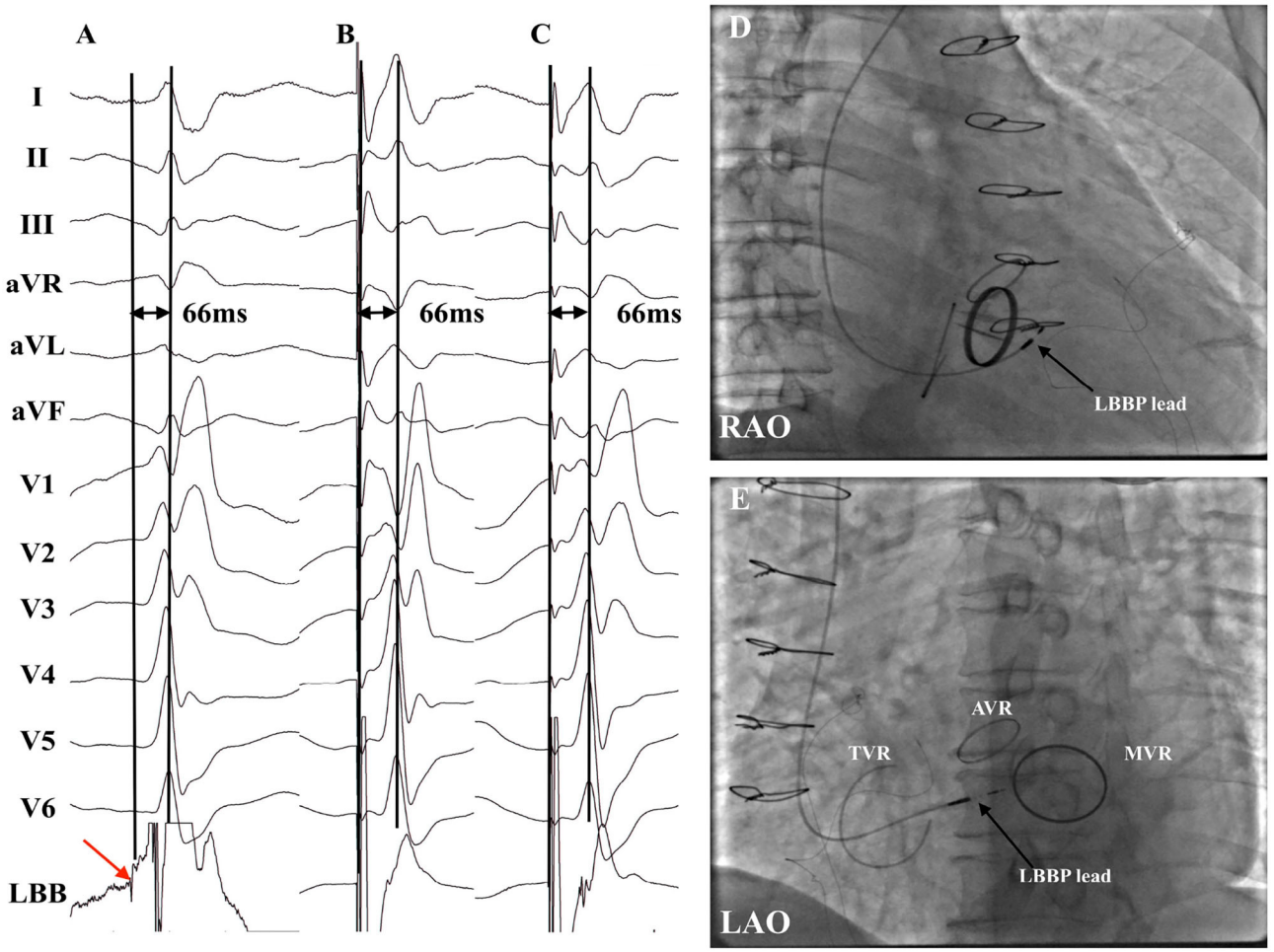

FIGURE 2 | Successful LBBP in a patient with AVR with MVR plus TVR (patient no. 16). **(A)** LBB potential was recorded with the intrinsic LVAT being 66 ms. **(B)** Pacing at 3 V demonstrated nonselective LBBP with the stim-LVAT of 66 ms. **(C)** Selective LBBP was achieved under the low output at 0.5 V with the identical stim-LVAT of 66 ms. **(D,E)** Fluoroscopic images of LBBP in RAO view **(D)** and LAO view **(E)** revealed that the LBBP lead tip was distal and septal to the TVR and inferior to the AVR. AVR, aortic valve replacement; LAO, left anterior oblique; LBB, left bundle branch; LBBP, left bundle branch pacing; LVAT, left ventricular activation time; MVR, mitral valve replacement or repair; PV, prosthetic valve; RAO, right anterior oblique; TVR, tricuspid valve ring.

of TR noted was detailed as follows: none in three (20%), mild in 10 (66.7%), and moderate in two (13.3%) patients. No significant exacerbation of TR was observed compared to baseline. The obvious restriction of leaflet motion by the LBBP lead was not found in any patient.

DISCUSSION

In the present study, we investigated the feasibility and safety of treating patients with PV-induced AV conduction disorders by pacing the LBB. The major findings of this study are described as follows. First, permanent LBBP was safe and feasible in most patients with PVs referred for PM implantation. Second, the location of the PVs could act as an anatomic landmark and facilitated the LBBP lead implantation. Moreover, a low and stable pacing threshold was observed during the mean follow-up of 16.1 ± 10.8 months.

AV conduction disturbance is a common adverse event in patients undergoing PV surgery. The incidence of PM implantation among patients receiving surgical or transcatheter PV replacement has been reported to be between 4 and 17.2% (11–13). As documented in our study, AV block at the level of the AV node was commonly observed in patients with MVR/TVR, while patients with AVR/TAVR tended to develop infranodal block, which is consistent with a previous study (14). RV apical pacing is the traditional treatment for patients complicated with AV conduction disturbances after PV surgery. However, long-term RV apical pacing may induce ventricular electrical and mechanical asynchrony and therefore increase the risk for heart failure and mortality rate, especially for these patients with AV conduction diseases after PV

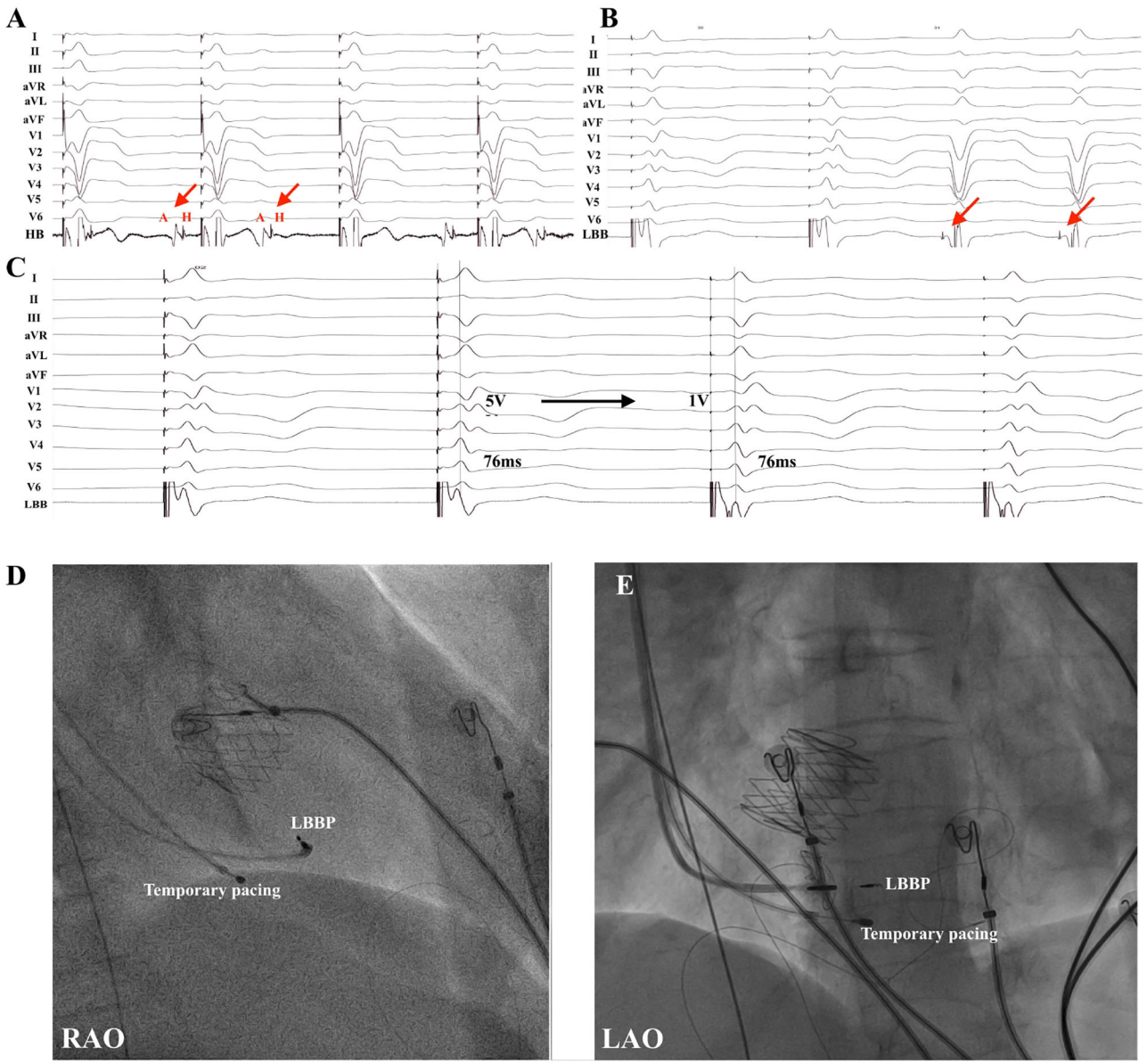

FIGURE 3 | LBBP in a patient with TAVR (patient no. 19). **(A)** Example of a 71-year-old male who underwent TAVR and developed infranodal block. **(B)** Intrinsic rhythm with LBBB occurred after cessation of temporary right ventricular pacing and LBB potential (red arrow) was noted. **(C)** Pacing at 5 V resulted in correction of LBBB with nonselective LBBP with local myocardial fusion and stim-LVAT of 76 ms. Selective LBBP with discrete local ventricular myocardial electrogram was shown during pacing at 1 V with the same stim-LVAT of 76 ms. Note the subtle change in QRS morphology in lead V1 and intracardiac electrograms. **(D,E)** Fluoroscopic views of LBBP in a patient with TAVR were presented in RAO **(D)** and LAO **(E)** projections. HB, His bundle; LAO, left anterior oblique; LBB, left bundle branch; LBBB, left bundle branch block; LBBP, left bundle branch pacing; LVAT, left ventricular activation time; RAO, right anterior oblique; TAVR, transcatheter aortic valve replacement.

surgery who have a need for significant ventricular pacing (15, 16).

HBP in patients with AV conduction diseases has been considered to be a more physiological form of ventricular activation (5, 17). However, HBP could not recruit the bundle branches and narrow the QRS width due to failure of pacing beyond the site of conduction block in some patients with PVs, especially in patients undergoing TAVR surgery. Furthermore, HBP may lead to an increase in pacing threshold and lead revision (18, 19). Sharma et al. (14) reported that permanent HBP was achieved in 93% of patients with PVs. However, the success rate for HBP was as low as 50% in TAVR patients. De Pooter et al. (20) described the feasibility of HBP in patients with conduction diseases following TAVR. Their results suggested that HBP with LBBB correction was only recorded in 69% of patients with TAVR surgery. LBBB correction threshold was 1.9 ± 1.1 V

TABLE 2 | Pacing parameters at implant and follow-up.

	Pacing parameters					
	Implant	**1 month($n = 22$)**	**3 months ($n = 22$)**	**6 months($n = 20$)**	**12 months ($n = 15$)**	**24 months($n = 8$)**
Ventricular pacing burden (%)	-	97.75 ± 9.42	98.42 ± 8.52	98.21 ± 7.53	97.64 ± 8.12	98.65 ± 6.45
Threshold at 0.5 ms (V)	0.60 ± 0.16	0.68 ± 0.44	0.76 ± 0.41	0.71 ± 0.17	0.86 ± 0.36	0.91 ± 0.30
R-wave amplitude (mV)	11.9 ± 5.5	16.5 ± 4.0	15.1 ± 6.8	15.8 ± 3.5	16.2 ± 2.3	14.9 ± 5.5
Impedance (Ω)	749 ± 117	523 ± 104	516 ± 92	477 ± 65	503 ± 68	515 ± 70

Values are described as mean ± SD.

at 1.0 ms. Sen et al. (21) reported that LBBB could be successfully corrected by HBP in a patient with TAVR. However, the capture threshold was as high as 5 V at 1 ms at the follow-up of 1 month after the procedure. Vijayaraman et al. (10) recently investigated the success rate of His–Purkinje conduction system pacing in 65 patients with TAVR. They described that HBP was successful in 63% of patients, and LBBP was successful in 93% of patients. LBBP was associated with higher success rates and lower pacing thresholds compared with HBP. It can be explained by a more significant involvement at the level of a more distal conduction system in TAVR patients (22). In our study, all patients with TAVR developed infranodal disease, which is consistent with the abovementioned studies. Therefore, TAVR patients generally tend to develop infranodal block, and lower success in HBP achievement may be expected in this patient population.

LBBP is a novel pacing modality aimed at pacing the conduction system beyond the site of conduction block in most patients with His–Purkinje disease (23). Several studies have reported that LBBP can offer a favorable ventricular mechanical synchrony by the rapid recruitment of left His–Purkinje system, which is similar to HBP (24, 25). Therefore, a more distal recruitment of conduction system in LBBP may provide significant advantage in success rate compared with HBP. Guo et al. (26) reported LBBP in 20 patients with PVs. In their study, LBBP was successfully achieved in four patients with TAVR with a short-term follow-up period of 10.4 ± 5.9 months. In our study, among patients undergoing TAVR, the success rate for LBBP was 80% with a low and stable threshold during the follow-up period of 16.1 ± 10.8 months. We failed to deploy the lead tip to the side of the septum in one patient with TAVR because of local hypertrophic myocardium. Therefore, LBBP may be considered a promising pacing technique especially in patients with TAVR.

HBP in patients with TVR may be challenging because the valve may obstruct the access to His bundle region, which makes a successful HBP difficult. Furthermore, HBP may result in high pacing threshold in some cases (27). Guo et al. (26) also described successful LBBP in four patients with TVR. However, tricuspid valve regurgitation after LBBP procedure was not evaluated in their study. In our study, seven patients with TVR were enrolled for analysis. Successful LBBP was performed in all of them, and no significant worsening of tricuspid valve regurgitation was noted in these patients during the follow-up visit. Therefore, LBBP is feasible and safe in patients with TVR. However, the PV may still limit the ability to steer the sheath, and the significantly enlarged right atrium in some patients is another challenge that needs to be overcome during the procedure. Application of adjustable sheath or prefabricating the sheath during the procedure is a useful way to ensure a successful procedure. Furthermore, the presence of TVR can serve as a radiographic marker and facilitate the location of LBBP. In this study, the average distance from the final site of LBBP was 23.0 ± 3.2 mm distal and septal to the TVR.

LBBP has been considered the physiological pacing modality to date. Hou et al. (24) confirmed the feasibility and favorable cardiac synchrony of LBBP. In their study, LBBP was successfully achieved in 90% of patients. LBB potential was recorded in 61% of patients. Vijayaraman et al. (9) prospectively evaluated the effectiveness of LBBP in bradycardia or heart failure patients. LBBP was successful in 93 of 100 patients, and LBB potential was found in 63 patients. Li et al. (8) also reported a similar success rate in LBBP. In the present study, a majority (90.9%) of patients with PVs successfully received LBBP. LBB potential was observed in 68.2% of patients. During the follow-up period, the pacing threshold was low, with no loss of capture or lead dislodgment observed. Furthermore, no significant differences in echocardiographic parameters between the baseline and follow-up visit were found despite high pacing burden with LBBP. Therefore, LBBP can be applied safely and feasibly in different patient populations, even in patients with PVs.

Study Limitations

The study was limited by its retrospective single-center design and relatively small sample size. Further randomized studies with a large sample may be needed to confirm our findings. Only 13.6% had coronary disease, and success rates may not be as high in patients with prior septal infracts.

CONCLUSION

Permanent LBBP is feasible and safe in patients with PVs. The location of AVR and TVR may serve as landmarks for guiding the final site of the LBBP. A low and stable capture threshold can be obtained during the follow-up visit.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethic committee of Guangdong Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Association Between Changes in Physical Activity and New-Onset Atrial Fibrillation After ICD/CRT-D Implantation

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Background: Changes in physical activity (PA) after implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy defibrillators (CRT-D) implantation were unknown. The association of PA changes with new-onset atrial fibrillation (AF), cardiac death and all-cause mortality was unclear in patients at high risk of sudden cardiac death.

Methods: Patients receiving ICD/CRT-D implantation from SUMMIT registry were retrospectively analyzed. Changes in PA were considered from baseline status to 1 year after implantation. New-onset AF was defined as the first atrial high-rate episode ≥1% of the daily AF burden detected after implantation.

Results: Over a mean follow-up of 50.3 months, 124 new-onset AF events (36.2%), 61 cardiac deaths (17.8%), and 87 all-cause deaths (25.4%) were observed in 343 patients with ICD/CRT-D implantation. PA at 1 year after implantation was increased compared with PA at baseline (11.97 ± 5.83% vs. 10.82 ± 5.43%, $P = 0.008$), and PA at 1 year was improved in 210 patients (61.2%). Per 1% decrease in PA was associated with 12.4, 18.3, and 14.3% higher risks of new-onset AF, cardiac death and all-cause mortality, regardless of different baseline characteristics. Patients with decreased PA had 2-fold risks of new-onset AF (hazard ratio [HR] = 1.972, 95% confidence interval [CI]: 1.352–2.877, $P < 0.001$) as high as those with unchanged/increased PA. Decreased PA was an independent risk factor for cardiac death (HR = 3.358, 95% CI: 1.880–5.996, $P < 0.001$) and all-cause mortality (HR = 2.803, 95% CI:1.732–4.535, $P < 0.001$).

Conclusion: PA decrease after ICD/CRT-D implantation is associated with a higher incidence of new-onset AF, resulting in worsened outcomes in cardiac death and all-cause mortality.

Keywords: atrial fibrillation, changes in physical activity, cardiac death, all-cause mortality, implantable cadioverter defibrillators

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia with an increasing prevalence (1). It was reported the prevenance of AF in patients with implantable cardioverter defibrillators (ICDs) was as high as 25% (2). AF is associated with higher risks of ischemic stroke, cardiovascular events, hospitalizations, and all-cause mortality (3, 4). In patients receiving ICD or cardiac resynchronization therapy defibrillator (CRT-D) implantation, new-onset AF was also associated with a greater number of ICD shocks for ventricular arrhythmia, inappropriate shocks, hospitalizations for heart failure (HF), and increased mortality (5–8). Thus, it is essential to predict the incidence of new-onset AF and initiate anticoagulation and rate control management to improve the long-term clinical outcomes after ICD/CRT-D implantation.

Physical activity (PA) can predict the outcomes of different diseases (9–12). PA can be measured via questionnaires to reflect an individual's functional status over the preceding years or months (13). Moreover, accelerometer-derived PA can be detected within the first 30–60 days to reflect the baseline PA status (14). Low levels of baseline PA were associated with higher incidences of hospitalizations for HF, cardiac death, and all-cause mortality after ICD/CRT-D implantation (11, 14). Baseline PA can also predict new-onset AF among the general population or patients with HF (15–18). Chelu et al. found PA decreased and mortality increased significantly after a newly persistent AF episode in patients with ICD (19). It was indicated that longitudinal decrease in PA was associated with a higher incidence of new-onset AF, resulting in worsened long-term outcomes.

To date, few studies have assessed changes in PA after ICD/CRT-D implantation. In the present study, early changes in PA from baseline to 1 year after implantation were evaluated in patients with ICD/CRT-D implantation. Dual-chamber ICDs can provide quantitative and continuous daily PA and AF burden data using a remote home monitoring system, enabling accurate detection of PA changes and new-onset AF (15). This study aimed to investigate the association of changes in PA with the incidence of new-onset AF, as well as explore the effects of PA decreases on long-term cardiac death and all-cause mortality among patients at high risk of sudden cardiac death.

METHODS

The Biotronik Home Monitoring System Safety and Efficacy in Cardiac Implantable Electronic Device-implanted Patients (SUMMIT) registry is a prospective, observational, and multicentre study in China. We performed a retrospective analysis using the archived home monitoring transmission data from SUMMIT registry and evaluated the association of changes in PA with the incidence of new-onset AF, long-term cardiac death, and all-cause mortality. The present study, which conformed to the Declaration of Helsinki, was approved by all participating institutions. All patients provided written informed consent before entering this study.

Study Participants

Patients who underwent ICD/CRT-D implantation between May 2010 and May 2015 were included when the following criteria were met: (1) ICD or CRT-D was implanted in accordance with the current guideline's recommendations; (2) continuous home monitoring transmission started immediately after implantation; (3) data related to AF daily burden and PA were available; (4) patients were aged ≥18 years at implantation; and (5) life expectancy was >1 year after device implantation. Patients were excluded when (1) AF, atrial flutter (AFL) or atrial tachycardia (AT) was diagnosed using ICD-10 codes (ICD-10: I48, I49.9) before enrolment; (2) patients were lost to follow-up; (3) remote monitoring transmission data was missing or incomplete; or (4) patients were diagnosed with a malignant tumor or scheduled for heart transplantation.

Measurement of AF Daily Burden and PA

The Biotronik remote home monitoring system can transmit and store data from implantable devices to service centers every day. Data on daily AF burden and PA were collected for each patient. Daily AF burden was expressed as a percentage of the time with atrial high-rate episodes (AHREs) > 180 beats in a 24-h period, where 1% indicated a total of 14.4 min of AHREs per day, which is the minimum daily AF burden. Similar measurement algorithms were previously shown to have a sensitivity and specificity of 95% for AHREs and AF burden detection (20, 21).

Continuous PA was recorded using a Biotronik accelerometer sensor. PA was defined as a percentage of total daily duration recorded when rates were higher than basic rates, where 10% indicated 2.4 h of daily PA, with a resolution of 2 s. PA at baseline was the average daily value detected during the first 30–60 days after ICD/CRT-D implantation, as recommended by previous studies (14), and PA at 1 year was detected during the first 30 days at 1 year after ICD/CRT-D implantation.

Study Endpoints and Follow-Up

The primary endpoint was new-onset AF. New-onset AF was defined as the first AHRE ≥1% of the daily AF burden, whether symptomatic or not, detected after ICD/CRT-D implantation (15, 20).

The secondary endpoints were cardiac death (ICD-10: I00 to I09, I11, and I20 to I51) and all-cause mortality. The date and cause of death was based on the death certificate. Routine follow-ups were conducted via telephone or clinics. If data transmission was disrupted, the clinical research coordinator immediately confirmed the patient's conditions by contacting the family members.

Abbreviations: AADs, antiarrhythmic drugs; ACEI/ARB, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; AF, atrial fibrillation; AHRE, atrial high-rate episode; BMI, body mass index; CCBs, calcium channel blockers; CI, confidence interval; HR, hazard ratio; CRT-D, cardiac resynchronization therapy defibrillators; DCM, hypertrophic cardiomyopathy; DM, diabetes mellitus; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA class, New York Heart Association class; PA, physical activity; PCI, percutaneous coronary intervention.

Data Collection

Baseline data for the enrolled patients were derived from medical records during hospitalization, including age at implantation, sex, body mass index (BMI), ICD or CRT-D implantation, New York Heart Association (NYHA) class, echocardiographic characteristics (left ventricular ejection fraction [LVEF] and left ventricular end diastolic diameter [LVEDD]), comorbidities [hypertension, diabetes mellitus [DM], stroke, dilated cardiomyopathy [DCM], hypertrophic cardiomyopathy [HCM], ischemic cardiomyopathy [ICM], valvular disease, prior myocardial infarction [MI], percutaneous coronary intervention [PCI], and pre-implant syncope], and medication (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [ACEIs/ARBs], diuretics, aldosterone antagonists, calcium channel blockers [CCBs], statins, beta-blockers, amiodarone and antiplatelets).

Grouping

Changes in PA were considered from baseline to 1 year after ICD/CRT-D implantation. All enrolled patients were divided into three groups based on the tertiles of changes in PA, including PA decreased group (Tertile 1, $n = 114$, mean $= -2.85\%$, range [-12.9 to -0.4%]), PA unchanged group (Tertile 2, $n = 114$, mean $= 0.98\%$, range [-0.4–2.2%]), and PA increased group (Tertile 3, $n = 115$, mean $= 5.29\%$, range [2.3–18.0%]).

Statistical Methods

Continuous variables are presented as means ± standard deviations (SDs), and categorical variables are presented as frequencies and percentages. Clinical characteristics were compared across decreased PA, unchanged PA, and increased PA groups using one-way analysis of variance for continuous variables and a chi-square test for categorical variables. Clinical outcomes, including new-onset AF, long-term cardiac death, and all-cause mortality, were calculated and compared using chi-square test.

Considering the competing risks, cumulative incidence function and Fine and Gray model were used in the survival analysis of detected new-onset AF between different groups of PA performance. Kaplan-Meier survival curves and cox proportional hazards regression models were performed to evaluate the association of changes in PA with cardiac death and all-cause mortality. In the multivariate analysis, model 1 was adjusted for age at implantation and sex. Model 2 was adjusted for additional confounders, including BMI, LVEF, LVEDD, ICD or CRT-D implantation, NYHA class, hypertension, DM, DCM, ICM, prior MI, PCI, and ACEI/ARB, diuretics, and aldosterone antagonist usage. Model 3 was adjusted for the above-mentioned confounders and baseline PA.

Subgroup analysis was performed to explore the effects of changes in PA on the incidence of new-onset AF in patients with different baseline characteristics using Fine & Gray model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to show the impact. *P*-values <0.05 were considered statistically significant. Statistical analyses were conducted using SPSS Statistics version 23.0 (IBM Corp., Armonk, NY) and R version 4.0.3 (Bunny-Wunnies Freak Out, The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

A total of 1,015 patients with ICD/CRT-D implantation were retrospectively analyzed. Patients were excluded due to lack of data on AF daily burden ($n = 520$), unavailable or incomplete monitoring data ($n = 75$), <1 year survival after device implantation ($n = 40$), and diagnosis of AF and/or AFL before enrolment ($n = 37$, 36 AF cases and 1 AFL case). Finally, a total of 343 patients were included in the study.

Overall, PA at 1 year after ICD/CRT-D implantation was significantly higher than PA at baseline (11.97 ± 5.83 vs. 10.82 ± 5.43%, $P = 0.008$). PA was improved at 1 year in 210 patients (61.2%), compared with baseline PA. Changes in PA across PA decreased, PA unchanged, and PA increased groups were -2.85 ± 2.63, 0.98 ± 0.79, and $5.29 \pm 2.93\%$, respectively. The average age at implantation was 62.53 ± 13.54 years, and male patients were dominant in the cohort study (77.6%). The mean LVEF and LVEDD were $39.08 \pm 14.57\%$ and 62.07 ± 13.37 mm, respectively. About half of the patients (51.0%) underwent CRT-D implantation. Significant differences between the groups were observed for baseline PA ($P < 0.001$) and PA at 1 year ($P < 0.001$), in addition to sex ($P = 0.042$), and PCI ($P = 0.039$). No significant differences were observed for other baseline characteristics. **Table 1** illustrates the comparison of baseline characteristics across three groups.

Clinical Outcomes

The average follow-up time was 50.28 ± 17.75 months. A total of 124 new-onset AF events (36.2%) were detected. The incidence of new-onset AF was significantly higher in the PA decreased group than in PA unchanged and PA increased groups (45.6 vs. 33.3 vs. 29.6%, $P = 0.031$). For the secondary endpoints, 61 (17.8%) cardiac deaths and 87 (25.4%) all-cause mortality events occurred. In 124 patients who experienced new-onset AF, 44 death events (35.5%) were observed, which was significantly higher than the incidence of mortality (43/219,19.6%) in the remaining 219 patients who did not experience new-onset AF. Patients in PA decreased group had higher risks of cardiac death (24.6 vs. 15.8 vs. 13.0%, $P = 0.059$) and all-cause mortality (32.5 vs. 21.9 vs. 21.7%, $P = 0.103$) than those in PA unchanged and PA increased groups. **Figure 1** illustrates the differences in clinical outcomes across three groups.

Univariate Survival Analysis for PA Changes and Clinical Outcomes

Cumulative incidence function and Kaplan-Meier survival curves were plotted to compare the cumulative incidences of new-onset AF, long-term cardiac death, and all-cause mortality between the PA decreased and unchanged/increased groups. Univariate analysis demonstrated that patients had significantly higher incidences of new-onset AF ($P = 0.013$), cardiac death ($P = 0.007$), and all-cause mortality ($P = 0.010$) in PA decreased group, compared to PA unchanged/increased group (**Figure 2**).

TABLE 1 | Baseline characteristics.

	Total $N = 343$	PA decreased group (PA changes tertile 1, $n = 114$)	PA unchanged group (PA changes tertile 2, $n = 114$)	PA increased group (PA changes tertile 3, $n = 115$)	*P*-value
Physical performance					
PA at baseline, %	10.82 ± 5.43	12.59 ± 5.54	9.98 ± 5.02	9.90 ± 5.33	<0.001
PA at 1 year, %	11.97 ± 5.83	9.74 ± 5.38	10.96 ± 5.08	15.18 ± 5.58	<0.001
Changes in PA, %	1.15 ± 4.06	−2.85 ± 2.63	0.98 ± 0.79	5.29 ± 2.93	–
Demographic characteristics					
Age at implantation, years	62.53 ± 13.54	63.56 ± 12.94	62.63 ± 14.14	61.41 ± 13.55	0.484
Sex, male%	266 (77.6%)	93 (81.6%)	93 (81.6%)	80 (69.6%)	0.042
BMI, Kg/m^2	23.62 ± 2.84	23.91 ± 2.80	23.74 ± 2.80	23.20 ± 2.90	0.146
CRT-D implantation	175 (51.0%)	59 (51.8%)	58 (50.9%)	58 (50.4%)	0.980
NYHA class III-IV	209 (60.9%)	69 (60.5%)	71 (62.3%)	69 (60.0%)	0.934
Echocardiological characteristics					
LVEF, %	39.08 ± 14.57	39.75 ± 13.89	38.63 ± 15.51	38.87 ± 14.38	0.830
LVEDD, mm	62.07 ± 13.37	63.15 ± 13.06	62.71 ± 14.70	60.39 ± 12.21	0.252
Comorbidity					
Hypertension	121 (35.3%)	48 (42.1%)	40 (35.1%)	33 (28.7%)	0.105
DM	48 (14.0%)	20 (17.5%)	18 (15.8%)	10 (8.7%)	0.124
Stroke	8 (2.3%)	4 (3.5%)	2 (1.8%)	2 (1.7%)	0.595
DCM	100 (29.2%)	33 (28.9%)	33 (28.9%)	34 (29.6%)	0.993
HCM	12 (3.5%)	6 (5.3%)	4 (3.5%)	2 (1.7%)	0.349
ICM	131 (38.2%)	47 (41.2%)	40 (35.1%)	44 (38.3%)	0.634
Valvular disease	9 (2.6%)	4 (3.5%)	5 (4.4%)	0 (0.0%)	0.089
Prior MI	52 (15.2%)	21 (18.4%)	13 (11.4%)	18 (15.7%)	0.330
PCI	38 (11.1%)	19 (16.7%)	7 (6.1%)	12 (10.4%)	0.039
Pre-implant syncope	58 (16.9%)	13 (11.4%)	22 (19.3%)	23 (20.0%)	0.157
Medication					
ACEIs/ARBs	141 (41.1%)	48 (42.1%)	45 (39.5%)	48 (41.7%)	0.909
Diuretics	110 (32.1%)	38 (33.3%)	32 (28.1%)	40 (34.8%)	0.520
Aldosterone antagonists	150 (43.7%)	44 (38.6%)	51 (44.7%)	55 (47.8%)	0.358
CCBs	38 (11.1%)	12 (0.5%)	11 (9.6%)	15 (13.0%)	0.697
Statins	77 (22.4%)	26 (22.8%)	22 (19.3%)	29 (25.2%)	0.559
Betablockers	201 (58.6%)	66 (57.9%)	70 (61.4%)	65 (56.5%)	0.742
Amiodarone	95 (27.7%)	30 (26.3%)	27 (23.7%)	38 (33.0%)	0.264
Antiplatelets	78 (22.7%)	26 (22.8%)	29 (25.4%)	23 (20.0%)	0.617

ACEI/ARB, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; CRT-D, cardiac resynchronization therapy defibrillators; DCM, hypertrophic cardiomyopathy; DM, diabetes mellitus; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA class, New York Heart Association class; PA, physical activity.

Association of Changes in PA With New-Onset AF

Changes in PA were inversely associated with the incidence of new-onset AF in patients who underwent ICD/CRT-D implantation (**Table 2**). In Fine and Gray model 1, which was adjusted for age at implantation and sex, changes in PA were inversely associated with the incidence of new-onset AF (HR = 1.073, 95%CI: 1.027–1.121, $P = 0.002$), and PA decreased group was associated with a higher incidence of new-onset AF (HR = 1.558, 95% CI: 1.091–2.227 $P = 0.015$) than PA unchanged/increased group. After adjusting for additional confounders, including BMI, LVEF, LVEDD, ICD or CRT-D implantation, NYHA class, hypertension, DM, DCM, ICM, prior MI, PCI, ACEI/ARB, diuretics, and aldosterone antagonist usage in model 2, and the above-mentioned factors and baseline PA in model 3, PA decrease remained an independent risk factor of new-onset AF. Per 1% decrease in PA at 1 year could result in 12.4% higher risks of new-onset AF (HR = 1.124, 95%CI: 1.069–1.182, $P < 0.001$), and patients with decreased PA had 2-fold risks of new-onset AF (HR = 1.972, 95%CI: 1.352–2.877, $P < 0.001$) as high as those with unchanged/increased PA.

Association of Changes in PA With Cardiac Death and All-Cause Mortality

Regarding the long-term cardiac death and all-cause mortality, PA decrease was shown as independent risk predictors (**Table 2**).

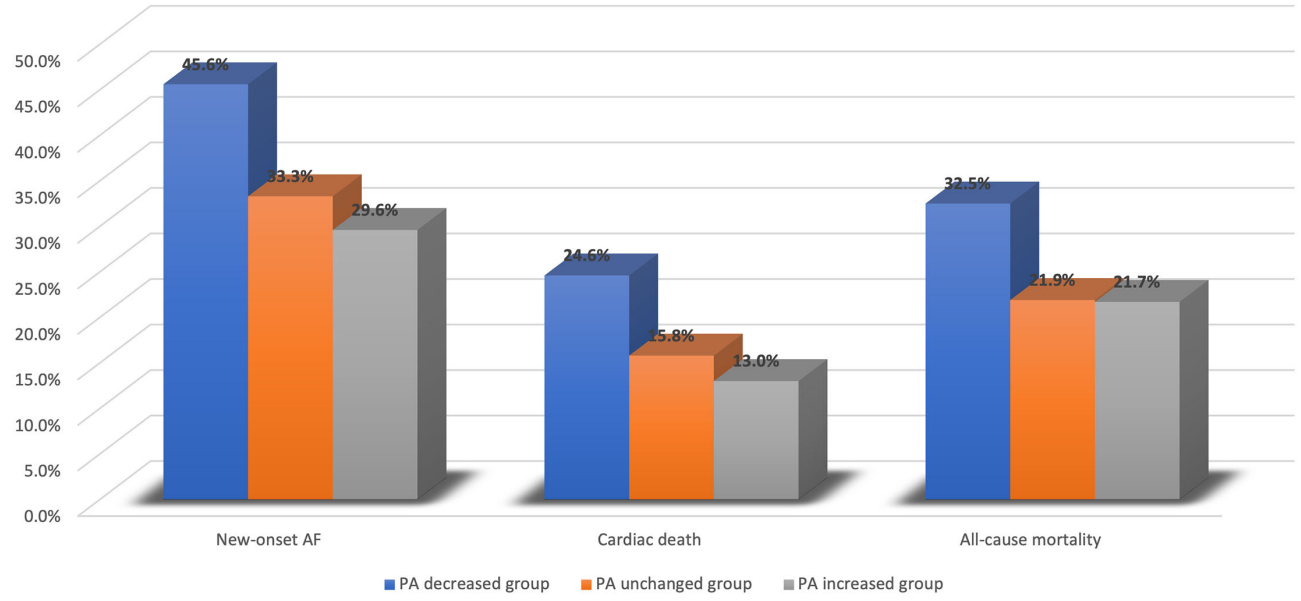

FIGURE 1 | Clinical outcomes across PA decreased group, PA unchanged group, and PA increased group. AF, atrial fibrillation; PA, physical activity.

Decreased PA was associated with higher risks of cardiac death (HR = 1.980, 95% CI: 1.191–3.292, $P = 0.008$) and all-cause mortality (HR = 1.714, 95% CI: 1.117–2.631, $P = 0.014$), compared to unchanged/increased PA, in multivariate Cox regression model 1, adjusted for age at implantation and sex. After adjusted for age at implantation, sex, BMI, LVEF, LVEDD, ICD or CRT-D implantation, NYHA class, hypertension, DM, DCM, ICM, prior MI, PCI, prior AF and ACEI/ARB, diuretics, and aldosterone antagonist usage, changes in PA remained an independent predictor for cardiac death and all-cause mortality in model 2. After further adjusting for baseline PA in model 3, the results remained consistent for cardiac death and all-cause mortality. Per 1% decrease in PA contributed to 18.3% and 14.3% higher risks in cardiac death (HR = 1.183, 95%CI: 1.093–1.280, $P < 0.001$) and all-cause mortality (HR = 1.143, 95%CI: 1.071–1.221, $P < 0.001$), respectively. Compared to patients with unchanged/increased PA, the risks of cardiac death (HR = 3.358, 95%CI: 1.880–5.996, $P < 0.001$) and all-cause mortality (HR = 2.803, 95%CI: 1.732–4.535, $P < 0.001$) increased 2.4 times and 1.8 times, respectively, in patients with decreased PA.

Subgroup Analysis Based on Different Baseline Characteristics

Subgroup analysis was performed using Fine and Gray model 3 to evaluate the association of new-onset AF with changes in PA based on different baseline characteristics, including baseline PA (low level <10.2% or high level ≥10.2%), age at implantation (<60 years old or ≥60 years old), BMI (<24 kg/m^2 or ≥24 kg/m^2), device type (ICD or CRT-D), and LVEF (<35% or ≥35%) (**Table 3**). Changes in PA, as a continuous variable, were inversely associated with the incidence of new-onset AF among groups with different baseline characteristics, except for patients with low levels of baseline PA (HR = 1.053, 95%CI: 0.973–1.139, $P = 0.200$).

Effects of Changes in PA at Different Baseline PA Levels

Considering the potential effects of PA at baseline on new-onset AF, the effects of changes in PA was evaluated among patients with high PA at baseline (PA at baseline >10.2%) and low PA at baseline (PA at baseline <10.2%) using cumulative incidence function (**Figure 3**). Patients with low levels of baseline PA had higher incidence of new-onset AF than those with high levels of baseline PA ($P = 0.117$) although it was not statistically significant. In patients with high baseline PA levels, decreased PA resulted in significant higher incidence of new-onset AF, compared to unchanged/increased PA ($P < 0.001$). However, no significant difference was shown between the PA decreased group and PA unchanged/increased group among patients with low baseline PA levels ($P = 0.761$).

DISCUSSION

In a cohort study of 343 patients, time-varying changes in PA and new-onset AF were detected using continuous remote monitoring system. Overall, PA at 1 year after ICD/CRT-D implantation was significantly higher than PA at baseline, and PA at 1 year was improved in 210 patients (61.2%). Early changes in PA from baseline to 1 year after implantation were inversely associated with the incidence of new-onset AF, especially among patients with high levels of baseline PA. Additionally, PA decrease at 1 year after implantation remained an independent risk factor of long-term cardiac death and all-cause mortality at 4.2 years.

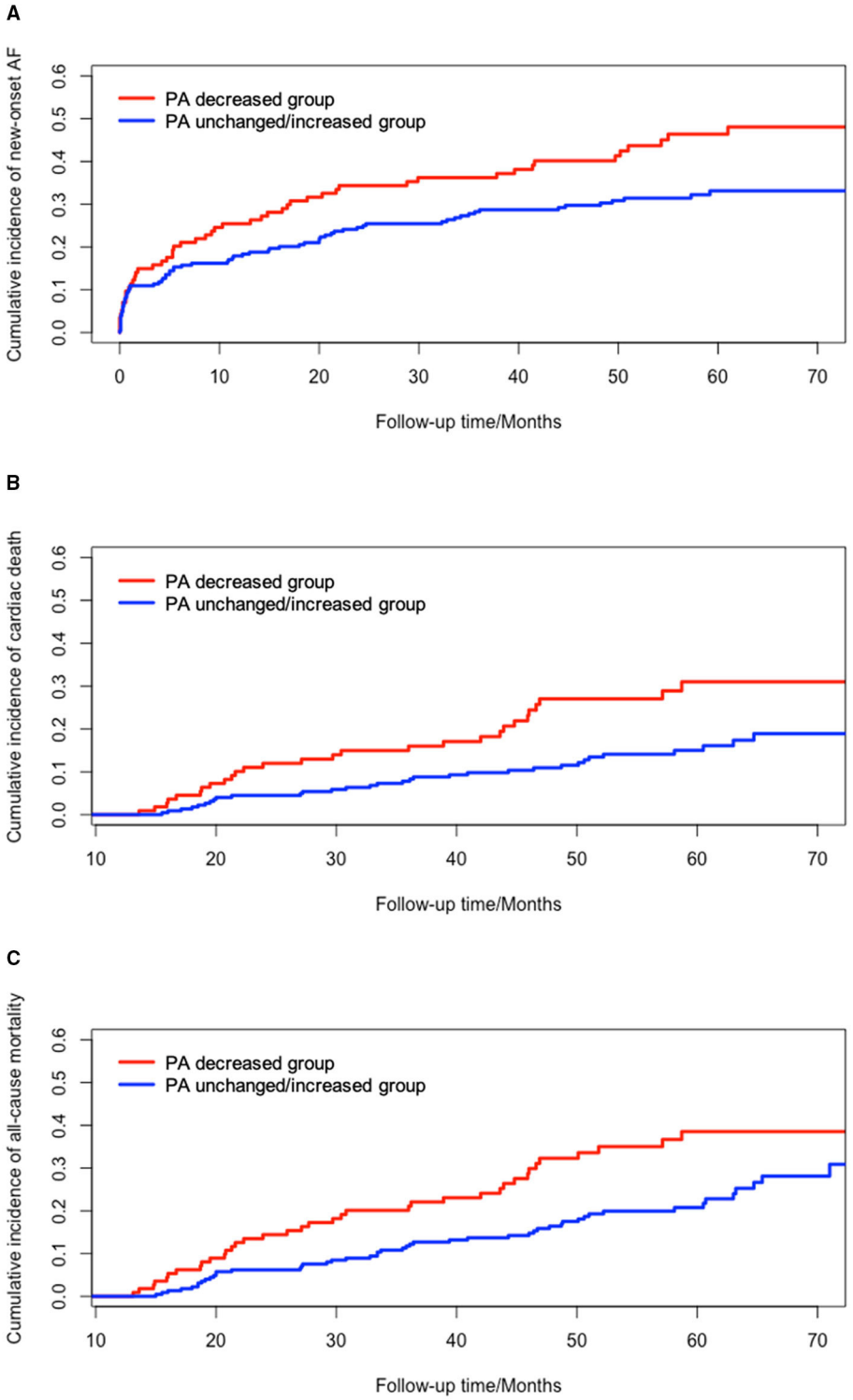

FIGURE 2 | Univariate survival analysis of changes in PA and clinical outcomes. **(A)** cumulative incidence of new-onset AF between PA decreased group and PA unchanged/increased group ($P = 0.013$); **(B)** cumulative incidence of cardiac death between PA decreased group and PA unchanged/increased group ($P = 0.007$); **(C)** cumulative incidence of all-cause mortality between PA decreased group and PA unchanged/increased group ($P = 0.010$). AF, atrial fibrillation; PA, physical activity.

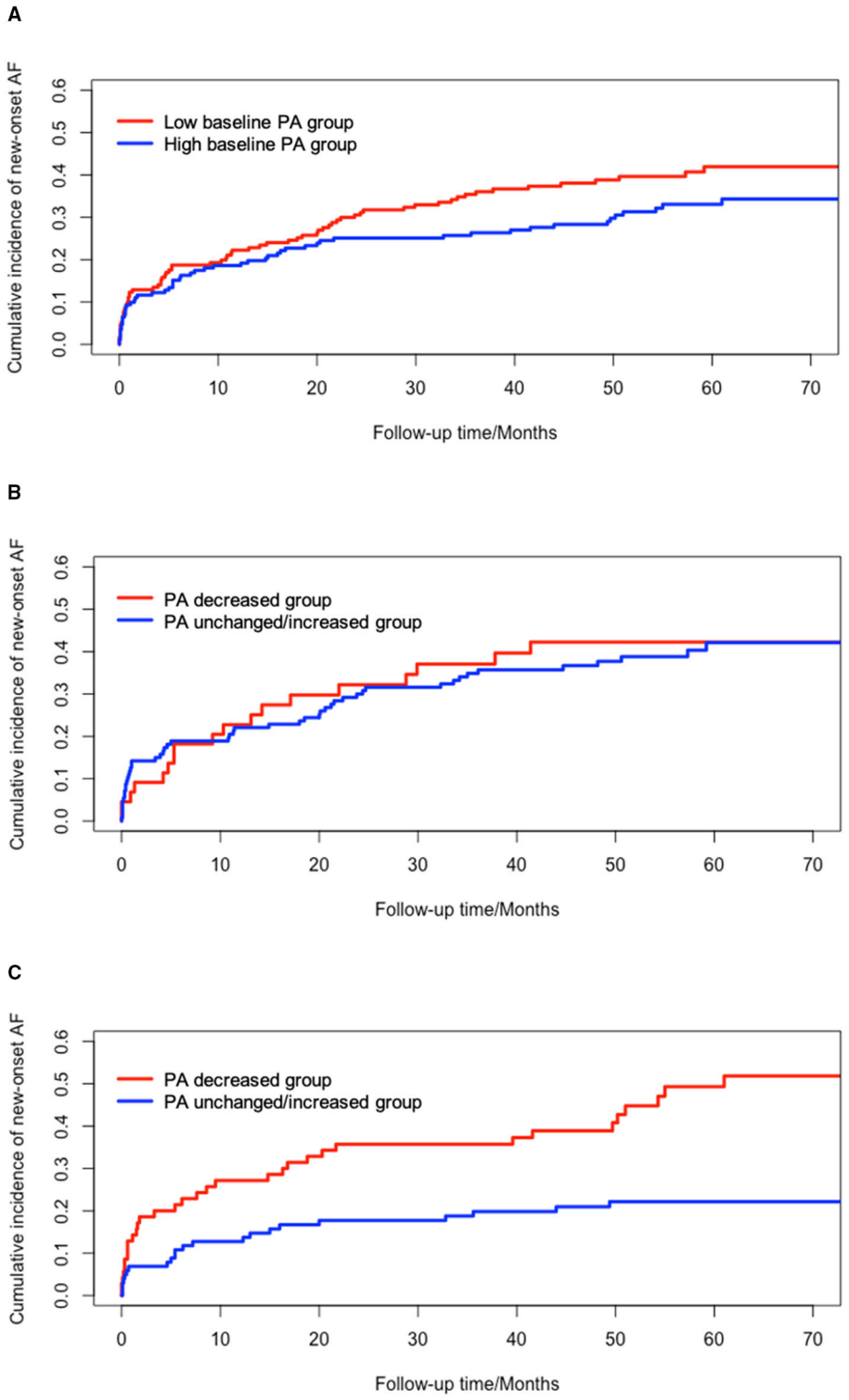

FIGURE 3 | Univariate survival analysis of new-onset AF based on different levels of PA at baseline. **(A)** cumulative incidence of new-onset AF between low baseline PA and high baseline PA group ($P = 0.117$); **(B)** cumulative incidence of new-onset AF in low baseline PA group ($P = 0.761$); **(C)** cumulative incidence of new-onset AF in high baseline PA group (Log-rank, $P < 0.001$). AF, atrial fibrillation; PA, physical activity.

TABLE 2 | Changes in PA associated with clinical outcomes.

	Model 1		Model 2		Model 3	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
New-onset AF						
Changes in PA (per 1%/decrease)*	1.073 (1.027–1.121)	0.002	1.088 (1.039–1.138)	<0.001	1.124 (1.069–1.182)	<0.001
PA decreased vs. unchanged/increased	1.558 (1.091–2.227)	0.015	1.679 (1.165–2.419)	0.005	1.972 (1.352–2.877)	<0.001
Cardiac death						
Changes in PA (per 1%/decrease)*	1.093 (1.026–1.166)	0.006	1.106 (1.034–1.183)	0.004	1.183 (1.093–1.280)	<0.001
PA decreased vs. unchanged/increased	1.980 (1.191–3.292)	0.008	2.278 (1.332–3.894)	0.003	3.358 (1.880–5.996)	<0.001
All-cause mortality						
Changes in PA (per 1%/decrease)*	1.064 (1.007–1.131)	0.027	1.079 (1.018–1.143)	0.010	1.143 (1.071–1.221)	<0.001
PA decreased vs. unchanged/increased	1.714 (1.117–2.631)	0.014	1.932 (1.236–3.020)	0.004	2.803 (1.732–4.535)	<0.001

Fine and Gray for new-onset AF or Cox regression model 1 for cardiac death/all-cause mortality was adjusted for age at implantation and sex. Model 2 was adjusted for additional confounders, including BMI, LVEF, LVEDD, ICD or CRT-D implantation, NYHA class, hypertension, DM, DCM, ICM, prior MI, PCI, ACEI/ARB, diuretics, and aldosterone antagonist usage. Model 3 was adjusted for the above mentioned variables and baseline PA. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; HR, hazard ratio; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA class, New York Heart Association class; PA, physical activity; PCI, percutaneous coronary intervention.

**Changes in PA was analyzed as a continuous variable and expressed as per 1% decrease in PA changes.*

TABLE 3 | Subgroup analysis of new-onset AF based on different characteristics.

Changes in PA*	**No. of incident events (n)**	**No. of group participants(N)**	**Model 3**	
(Per 1%/decrease)			**HR (95% CI)**	***P*-value**
Low baseline PA (<10.2%)	69 (40.4%)	171	1.053 (0.973–1.139)	0.200
High baseline PA (≥10.2%)	55 (32.0%)	172	1.133 (1.064–1.207)	<0.001
Age at implantation <60 years old	54 (38.0%)	142	1.074 (1.005–1.149)	0.036
Age at implantation ≥60 years old	70 (34.8%)	201	1.153 (1.068–1.245)	<0.001
BMI < 24 Kg/m^2	70 (36.5%)	192	1.111 (1.033–1.195)	0.005
BMI ≥ 24 Kg/m^2	54 (35.8%)	151	1.124 (1.048–1.206)	0.001
CRT-D implantation	67 (38.3%)	175	1.094 (1.028–1.165)	0.005
ICD implantation	57 (33.9%)	168	1.165 (1.067–1.273)	0.001
LVEF < 35%	63 (37.1%)	170	1.133 (1.061-1.210)	<0.001
LVEF ≥ 35%	61 (35.3%)	173	1.104 (1.016–1.201)	0.020

Fine and Gray Model 3 was adjusted for age at implantation, sex, BMI, LVEF, LVEDD, ICD or CRT-D implantation, NYHA class, hypertension, DM, DCM, ICM, prior MI, PCI, ACEI/ARB, diuretics, and aldosterone antagonist usage and baseline PA. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; HR, hazard ratio; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA class, New York Heart Association class; PA, physical activity; PCI, percutaneous coronary intervention.

**Changes in PA was analyzed as a continuous variable and expressed as per 1% decrease in PA changes.*

Some studies have clarified the association of activity performance with AF episodes, hospitalisations, and death among different populations (13, 15–18). The ARIC and MESA studies and a prospective case-control study conducted by Calvo et al. discovered that vigorous PA was associated with a lower risk of incident AF in the general population (16–18). The EORP-AF pilot survey demonstrated that low PA levels were associated with higher risks of cardiovascular death and all-cause mortality in patients with AF, indicating that efforts to increase PA might improve outcomes among AF patients (13). However, PA was measured by patients' self-reported questionnaires, which only indicated the activity level over the preceding years or months, and incident AF episodes were detected using intermittent electrocardiograms. In the IMPLANTED registry (15), objective accelerometer-derived PA and continuous monitoring of AHREs were obtained using remote monitoring system in HF patients who received ICD implantation. It was observed that low baseline PA levels can predict the incidence of AHREs, death, or HF hospitalisations, although the detected AHREs might not be newly AF episodes. For the underlying mechanism between physical performance and AF episodes, vigorous PA probably contributed to weight loss, which has known cardioprotective effects for AF episodes. The CARDIO-FIT Study, Henry Ford Exercise Testing Project, and HUNT3 study reported that high levels of cardiorespiratory fitness (CRF) measured using exercise stress tests were associated with a significantly reduced number

of AF episodes among overweight and obese populations over a long-term follow-up (4–8 years) (22–24). However, those above-mentioned studies only focused on baseline PA performance and the individual time-varying PA changes were not discussed.

Regarding the changes in PA, the longitudinal changes in PA over an entire lifespan were expressed as the total energy expenditure by Westerterp KR et al., which showed that PA gradually increased from an early age to adulthood but decreased in old age (25). Vamos M et al. reported that significant short-term decrease in device-measured PA was associated with a high incidence of hospitalisations for HF in CRT-D recipients (26). Decrease in PA was adopted during a 20-day windows period prior to OptiVol alerts, which was proved to be an independent predictor of the following hospitalization for HF (26). The DISCERN AF study demonstrated an association between AF burden and activity level changes in patients after AF ablation. PA began to decrease after the AF daily burden exceeded 500 min (34.7%) and dropped after 1,000 min (69.4%) (27). Although the inverse relationship between AF burden and activity level changes was not shown at an individual level, it was suggested that individual time-varying PA may be a valuable prognostic predictor for the incidence of new-onset AF. Different from these two studies, the present study measured time-varying changes in PA after ICD/CRT-D implantation for each patient, using a continuous, accurate, and rapid monitoring system. We observed that PA at 1 year after device implantation was generally higher than baseline PA (11.97 ± 5.83 vs. $10.82 \pm 5.43\%$, $P = 0.008$), and PA increase was observed in 210 patients (61.2%) with an average value of $3.44 \pm 3.00\%$. This finding was consistent with previous published studies, which showed that PA at 3 and 6 months after CRT implantation were generally higher than baseline PA of patients with HF (28). Regarding the mechanism of PA changes after device implantation, the improvement of PA was likely due to the clinical effects of device implantation or lifestyle modification on activity (28, 29). However, worsening PA might reflect that symptomatic or ongoing AF with heavy AHRE burdens exerted limitations on activity tolerance (25).

The present study focused on new-onset AF events during the whole monitoring period, which were detected by ICD/CRT-D devices. A 36.2% incidence of new-onset AF (AF daily burden $\geq$14 min) over a follow-up period of 4.2 years was reported, which was comparable to the incidence of newly AHREs (30.1%) detected among patients with HF (15). After adjusting for considerable demographic and echocardiographic characteristics, comorbidities, medication, and baseline PA, PA decrease was demonstrated as a strong independent risk factor of new-onset AF. Additionally, changes in PA remained inversely associated with the incidence of new-onset AF among different groups with various baseline characteristics, except for patients with low levels of baseline PA. The possible explanation might be that less patients at low baseline PA levels had decreased PA, especially when the sample size was not large enough. Low baseline PA could also predict the incident new-onset AF events, probably hiding the association between PA changes and new-onset AF. In the clinical complication, the occurrence of new-onset AF should be considered when PA decreases after implantation, especially for those with good performance of PA at baseline. ECG, anticoagulation, and rate control treatment were required to confirm and manage AF, when necessary. Among patients at high risk of sudden cardiac death, initiating AF management might help to decrease the risks of ICD shocks for ventricular arrhythmias and inappropriate shocks (5). Moreover, patients with PA decrease at 1 year after device implantation had 2–3 times higher risk of long-term cardiac death and all-cause mortality than those with PA increases. Time-varying PA after device implantation was valuable to reflect the clinical response and therapeutic efficacy of device implantation (28). Only focusing baseline PA performance was not enough. This study highlighted the importance of monitoring the time-varying PA changes for improving long-term outcomes. Besides this, it is suggested that exercise rehabilitation might improve long-term clinical outcomes in patients receiving ICD/CRT-D implantation, especially for patients with a high level of PA at baseline.

LIMITATION

There are several limitations in the present study. First, the sample size was small, which might limit the analysis of PA changes in low baseline group; Second, the study participants were patients with high risks of sudden cardiac death, so further studies are needed to determine if the association of early changes in PA with new-onset AF can be generalized to other patient populations. Third, due to the limitation of the home monitoring system, AHREs with <1% of total AF burden over a 24-h period cannot be detected. However, the measurement algorithms in this analysis were previously shown to have a sensitivity and specificity of 95% for AHREs and AF burden detection (21).

CONCLUSION

PA decrease at 1 year was associated with a higher risk of new-onset AF, regardless of baseline characteristics. Moreover, PA decrease was an independent predictor for long-term cardiac death and all-cause mortality in patients at high risk of sudden cardiac death.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fuwai Hospital (the chief institute) and all other participating organizations (Zhongshan Hospital Fudan University, Nanjing Drum Tower Hospital, Shanghai First People's Hospital et al.). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XS and SZhao performed the conception or design of the work. XS, KC, WH, YS, WX, FW, XF, YD, ZL, and SZhang contributed to the acquisition, analysis, and interpretation of data for the work. XS drafted the manuscript. SZhao critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Comparison of Procedure and Fluoroscopy Time Between Left Bundle Branch Area Pacing and Right Ventricular Pacing for Bradycardia: The Learning Curve for the Novel Pacing Strategy

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Background: Left bundle branch area pacing (LBBAP) is a novel physiological pacing approach.

Objective: To assess learning curve for LBBAP and compare the procedure and fluoroscopy time between LBBAP and right ventricular pacing (RVP).

Methods: Consecutive bradycardia patients who underwent LBBAP or RVP were prospectively recruited from June 2018 to June 2020. The procedure and fluoroscopy time for ventricular lead placement, pacing parameters, and periprocedural complications were recorded. Restricted cubic splines were used to fit learning curves for LBBAP.

Results: Left bundle branch area pacing was successful in 376 of 406 (92.6%) patients while 313 patients received RVP. Learning curve for LBBAP illustrated initial (1–50 cases), improved (51–150 cases), and stable stages (151–406 cases) with gradually increased success rates (88.0 vs. 90.0 vs. 94.5%, $P = 0.106$), steeply decreased median procedure (26.5 vs. 14.0 vs. 9.0 min, $P < 0.001$) and fluoroscopy time (16.0 vs. 6.0 vs. 4.0 min, $P < 0.001$), and shortened stimulus to left ventricular activation time (Sti-LVAT; 78.7 vs. 78.1 vs. 71.2 ms, $P < 0.001$). LBBAP at the stable stage showed longer but close median procedure (9.0 vs. 6.9 min, $P < 0.001$) and fluoroscopy time (4.0 vs. 2.8 min, $P < 0.001$) compared with RVP.

Conclusion: The procedure and fluoroscopy time of LBBAP could be reduced significantly with increasing procedure volume and close to that of RVP for an experienced operator.

Keywords: left bundle branch area pacing, right ventricular pacing, learning curve, procedure duration, fluoroscopy time

INTRODUCTION

Traditional right ventricular pacing (RVP) has been extensively used in clinical practice for more than 50 years. However, RV apex pacing (RVAP) can produce a deleterious effect on cardiac function and consequently increase the risk of heart failure and atrial fibrillation, especially in patients with a high burden of ventricular pacing (1). Pacing the right ventricular septum (RVSP) or outflow tract does not present superiority to RVAP (2, 3). Biventricular pacing can maintain interventricular electromechanical synchrony and has been proposed as an alternative to RVP in patients with heart failure and atrioventricular block (AVB) (4).

His bundle pacing (HBP) has been the most physiological pacing modality since 2000 (5). However, routine application of HBP has been limited in specific subgroups due to the high capture threshold, low sensing amplitude, potential risk of loss of capture, and a steep learning curve (6). Left bundle branch area pacing (LBBAP), first reported by Huang et al. (7) has emerged as a promising physiological pacing modality with stable low threshold and other pacing parameters. Recently, the middle- and long-term feasibility and safety of LBBAP have been demonstrated in patients with symptomatic bradycardia or advanced heart failure (8, 9). Compared with HBP, LBBAP could achieve a similar paced QRS duration (pQRSd), success rate, and better pacing parameters with significantly shorter procedure duration and fluoroscopy time (10). Compared with RVAP or RVSP, LBBAP presents a significantly narrower pQRSd, similar pacing parameters, and significantly longer procedure and fluoroscopy time (8, 11, 12). However, most studies reported their experience of the LBBAP procedure at the initial stage. Few studies focused on learning curves for LBBAP. Whether the procedure duration of LBBAP after a series of cases with currently available implantation tools could be comparable to RVP has not been investigated. Therefore, the present study aimed to (1) fit learning curves for LBBAP indicated by procedure and fluoroscopy time; (2) compare the procedure and fluoroscopy time, electrophysiological parameters, and periprocedural complications between LBBAP at different learning stages and RVP.

METHODS

Study Populations

We prospectively enrolled consecutive patients who attempted LBBAP or RVP procedures in our working group at Fuwai Hospital from June 2018 to June 2020. All patients had symptomatic bradycardia and were indicated for pacemaker implantation according to the current American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines (13). Patients were excluded if they were younger than 18 years or indicated for cardiac resynchronization therapy (CRT) or implantable cardioverter-defibrillator, or underwent pacemaker replacement or upgrade with existing lead, or the procedures were not performed by our group. All participants provided written informed consent, and the institutional review board of Fuwai hospital approved this study.

Procedures

All procedures were performed under local anesthesia. Preventive antibiotics were administered intravenously half an hour before the procedure. Venous access was usually obtained via the left axillary vein, sometimes via the right axillary vein due to various reasons.

LBBAP: All LBBAP procedures were performed by an experienced operator in RVP and HBP. Our previous study has described the LBBAP procedure by using the single-lead technique in the initial stage (14). Briefly, we first mapped the His bundle electrogram from the lead tip and then moved the tip 1.5–2 cm toward the RV apex with the tricuspid annulus as a landmark. And then the ideal screwing site was identified by pace mapping. After nearly 20 procedures, His mapping was discarded, and the 3830 lead was directly advanced to the RV septal area 1.5–2 cm from tricuspid annulus, and then pace mapping was used to find the target-screwing site. The lead tip was quickly screwed into the septum with approximately 5–6 clockwise rotations. As the lead was screwed deeper, detailed pacing tests were performed frequently. The surface 12-lead electrocardiogram (ECG), the intracardiac electrogram (IEGM), and fluoroscopy imaging were simultaneously monitored during the procedure, and left bundle branch (LBB) potential was recorded. Pacing stimulus to left ventricular activation time (Sti-LVAT) in lead V5 was measured at low (at 2V/0.4 ms) and high (at 5V/0.4 ms) outputs. Our method without His mapping was similar to the simplified nine-partition method (15, 16) and was performed in all the rest patients. The criteria of successful LBBAP were defined per previously published criteria (17). If successful LBBAP could not be achieved after five attempts or fluoroscopy duration exceeded 20 min, LVSP was then preferred to achieve a relatively narrow QRSd, with the lead positioned in the mid-LV septum. An electrophysiology recording system (Bard/Boston Scientific, Lowell, MA, USA) was used to monitor and record the IEGM in 90.6% of patients, while a surface 12-lead ECG was used alone in 9.4% of all patients with LBBAP.

RVP: All RVP procedures were performed by two experienced operators. The active-fixation pacing lead was positioned at the RV septum. Fluoroscopic radiographs from 45° left anterior oblique (LAO) were applied to confirm the RV lead position.

Data Collection and Device Programming

Baseline clinical data were collected, such as demographic characteristics, medical histories, pacing indications, ECG, and echocardiographic evaluation parameters. For LBBAP, the procedure and fluoroscopy time counting began when the C315 HIS sheath was advanced and ended when the LBBAP or LVSP was achieved. For RVP, the procedure and fluoroscopy time were defined as the duration from the beginning of delivery sheath to the end of successful placement of the ventricular lead. Pacing parameters (capture threshold, impedance, and sensing amplitude) were recorded. ECG parameters were measured at a sweep speed of 100 mm/s on electrophysiology recording systems, such as LBB potential to ventricle interval (P-V interval), Sti-LVAT, pQRSd, QRS axis deviation, and QRS transition zone. Periprocedural complications were documented, such as lead

dislodgement and revision, lead perforation, pacing system infection, and other device-related complications.

Depending on the intrinsic atrioventricular (AV) conduction interval and conduction system disease, individualized AV delay was programmed. Automatic AV search algorithm was routinely turned on in patients with intact AV conduction to avoid unnecessary ventricular pacing.

Statistical Analysis

Continuous variables are presented as mean ± SD or median with interquartile range according to the normal distribution of data. The means or medians are compared using the Student's *t*-test or analysis of variance or the Kruskal–Wallis H test. Categorical variables are expressed as frequency or percentage and compared using chi-square or Fisher exact test. We used restricted cubic splines (RCS) with four knots at the 5th, 35th, 65th, and 95th centiles to flexibly model and visualize the correlations between procedure and fluoroscopy time and numbers of procedures. Based on the learning curve, all LBBAP procedures were divided into three groups: initial (1–50 cases), improved (51–150 cases), and stable stages (151–406 cases). A two-tailed $P < 0.05$ was considered statistically significant. Statistical analysis was performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Clinical Characteristics

A total of 406 patients who received LBBAP procedures during the study period were included. The mean age was 64.9 ± 14.3 years old, and male patients accounted for 48.5%. Indications for pacemaker implantation included sinus node dysfunction (SND) in 39.7% of patients and AVB in 60.3% of patients. Baseline Baseline left or right bundle branch block (LBBB or RBBB) was present in 10.5 and 23.4% of patients. Other baseline clinical features are summarized in **Table 1**.

TABLE 1 | Baseline clinical and demographic features of patients attempting LBBAP.

Variables	LBBAP ($n = 406$)
Age	64.9 ± 14.3
Male	197(48.5%)
Hypertension	244(60.1%)
Diabetes	79 (19.5%)
Atrial fibrillation	178(43.8%)
Paroxysmal	104(58.4%)
Persistent	74 (41.6%)
CAD	76 (18.7%)
Valvular heart disease	35 (8.6%)
Hypertrophic cardiomyopathy	10 (2.5%)
Baseline electrocardiogram	
Heart rate	54.7 ± 17.5
QRS duration	112 ± 24.1
Left bundle branch block	43 (10.5%)
Right bundle branch block	95 (23.4%)
Pacing indications	
AVB	245(60.3%)
SND	161(39.7%)
Baseline Echocardiography	
LAD	40.2 ± 8.45
LVEDD	48.6 ± 6.91
LVEF	61.2 ± 7.27
IVS	9.82 ± 1.93
Type of device	
Double-chamber PM	341(84.0%)
Single-chamber PM	65 (16.0%)

Data are presented as mean ± SD for continuous variables and number and percentages for categorical variables.
LBBAP, left bundle branch area pacing; CAD, coronary artery disease; AVB, atrioventricular block; SND, sinus node dysfunction; LAD, left atrium diameter; LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; IVS, interventricular septum; PM, pacemaker.

Implantation Outcomes and Learning Curves of LBBAP

Figure 1 shows trends in procedural performance reflected by procedure duration, fluoroscopy time, and Sti-LVAT at high output. We first divided all patients into eight groups (every 50 cases in one group) across the study period. The median procedure duration and fluoroscopy time of each group were listed (**Figures 1A,C**). In the first 50 cases, the median procedure time and fluoroscopy time for ventricular lead implantation were 26.5 and 16.0 min, respectively. The median time was markedly decreased in the following 100 procedures (from 51 to 150). Since the 151st procedure, the median procedure and fluoroscopy time reached a relatively low plateau and ranged from 8.3 to 9.5 min and 4.0 to 4.5 min. **Figures 1B,D** visualizes the association between the procedure or fluoroscopy time and numbers of LBBAP procedures. Both the predicted procedure duration and fluoroscopy time dropped off sharply until around the 150th case and became relatively stable afterward (Both *P* for nonlinearity < 0.001). The steepest part of learning curves appeared to be over the first 50 cases. The procedure and fluoroscopy time were improved over the following 100 cases (from 51 to 150) and stabilized after 150 cases (from 151 to 406).

The changing trends of Sti-LVAT at the high output are shown in **Figures 1E,F**. During the first 150 procedures, the mean Sti-LVAT was stable at 77.7–78.7 ms. After 150 procedures, the mean Sti-LVAT was markedly shortened and plateaued at 70.4–72.1 ms. **Figure 1F** shows the predicted Sti-LVAT curve (*P* for nonlinearity = 0.003).

ECG and Pacing Parameters at Different LBBAP Stages

Based on learning curves of LBBAP, three step-by-step stages were identified: initial stage ($n = 50$, procedure 1–50), improved stage ($n = 100$, procedure 51–150), and stable stage ($n = 256$, procedure 151–406). As shown in **Table 2**, the success rate of LBBAP was 92.6% in overall patients, and gradually increased along three stages (88.0 vs. 90.0 vs. 94.5%, $P = 0.106$). The mean Sti-LVAT at the stable stage was the shortest at the high output (71.2 ± 11.6 ms) and low output (74.3 ± 16.2 ms). The mean LBB capture threshold and the mean pQRSd did not

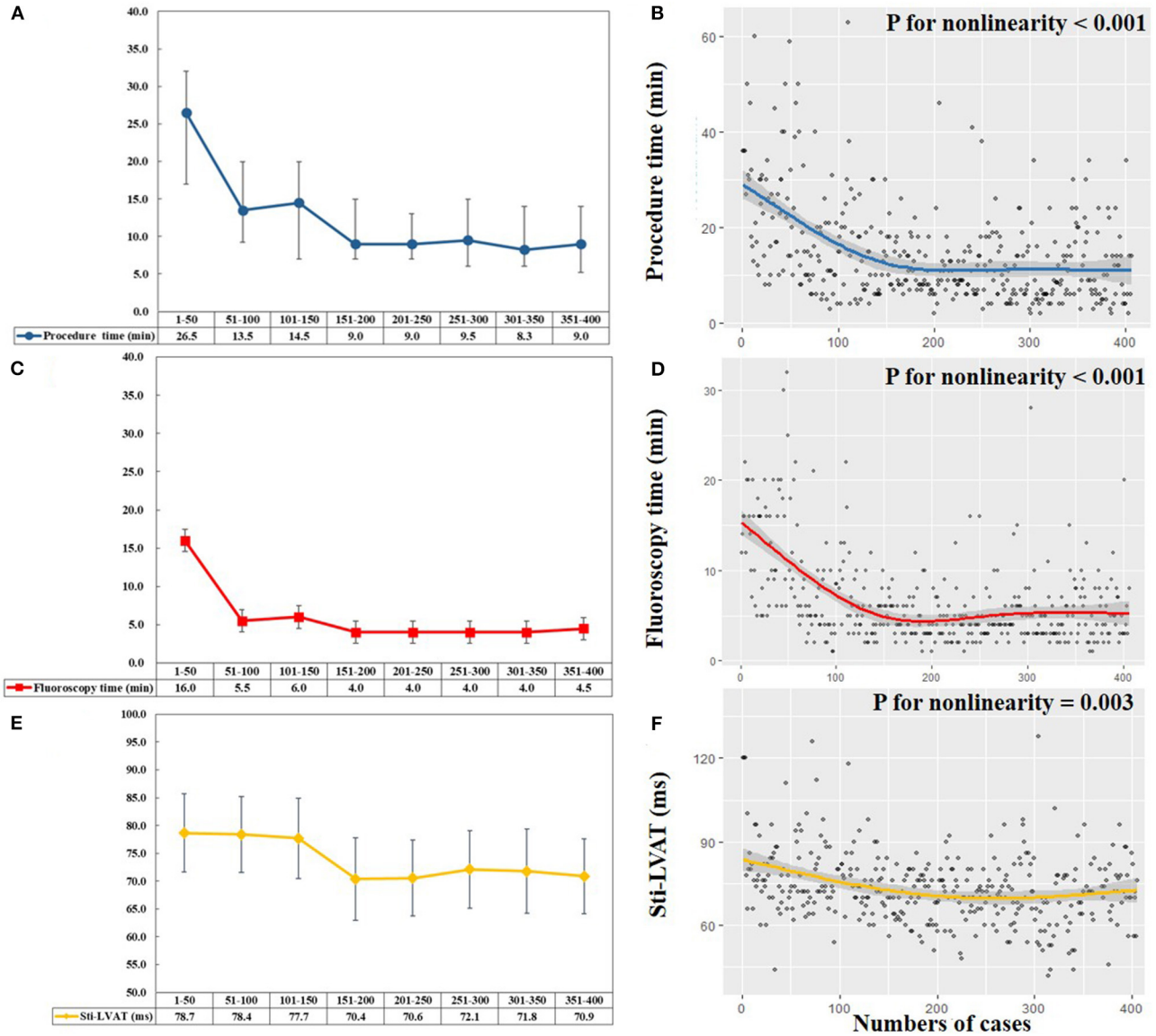

FIGURE 1 | Learning curves of left bundle branch area pacing (LBBAP). **(A,C)** Median procedure time (blue line) and fluoroscopy time (red line) of per 50 consecutive patients attempting LBBAP. (**B,D)** Scatterplots and predicted learning curves of LBBAP indicated by procedure time (blue line) and fluoroscopy time (red line). The curves rapidly decreased until the 150th procedure and then reached a plateau, with the procedure time of 9 min and fluoroscopy time of 5 min (both *P* for nonlinearity < 0.001). **(E)** Mean Sti-LVAT (yellow line) at the high output (5 V/0.4 ms) of per 50 consecutive patients attempting LBBAP. **(F)** Scatterplot and predicted learning curve of LBBAP indicated by Sti-LVAT (yellow line). The curve plateaued after approximately 200 procedures (*P* for nonlinearity = 0.003). Sti-LVAT, Stimulus to left ventricular activation time.

differ among the three stages ($P > 0.05$). The mean numbers of attempts were significantly different among the three stages (2.1 ± 0.7 vs. 1.7 ± 0.8 vs. 1.2 ± 0.5, $P < 0.001$). With accumulated experience, we attempted once to achieve successful LBBAP in 80% of cases in the stable stage, twice in 10% of cases, and three times or more in the rest of cases. The median procedure (26.5 vs. 14.0 vs. 9.0 min, $P < 0.001$) and fluoroscopy time (16.0 vs. 6.0 vs. 4.0 min, $P < 0.001$) rapidly decreased from initial to stable stages.

Comparison Between LBBAP and RVP

A total of 313 patients received RVP during the same period. LBBAP was more frequently performed in patients with AVB (60.3 vs. 27.5%, $P < 0.001$; **Table 3**). Periprocedural complications did not differ between LBBAP and RVP ($P = 0.658$). One ventricular septal perforation and one lead dislodgement occurred soon after the LBBAP procedure at the initial stage. Both patients patients had no symptoms except for having features of pacing failure. Two lead dislodgements

TABLE 2 | Pacing and procedural parameters in patients attempting LBBAP.

Variables	Overall (n = 406)	Initial stage (n = 50)	Improved stage (n = 100)	Stable stage (n = 256)	P-value
IEGM, n (%)	368 (90.6%)	46 (92%)	94 (94%)	228 (89.1%)	0.205
Successful LBBAP, n (%)	376 (92.6%)	44 (88.0%)	90 (90.0%)	242 (94.5%)	0.106
LBB potential, n (%)*	256 (68.1%)	31 (70.5%)	74 (82.2%)	151 (62.4%)	0.040
P-V interval, ms	27.7 ± 4.7	29.6 ± 6.7	27.1 ± 4.9	27.7 ± 4.2	0.78
Sti-LVAT at 5V/0.4 ms, ms	73.9 ± 13.4	78.7 ± 16.4	78.1 ± 14.2	71.2 ± 11.6	<0.001
Sti-LVAT at 2V/0.4 ms, ms	76.7 ± 15.4	83.4 ± 13.5	79.2 ± 14.2	74.3 ± 16.2	<0.001
Anodal capture at 2V/0.4 ms, n (%)*	366 (97.3%)	42 (95.5%)	87 (96.7%)	237 (97.9%)	0.879
Ring capture threshold, V/0.4 ms	1.04 ± 0.65	0.96 ± 0.53	1.06 ± 0.75	1.04 ± 0.64	0.696
Paced QRSd, ms	114 ± 10.7	117 ± 11.5	114 ± 9.5	114 ± 10.4	0.303
LBB capture threshold, V/0.4 ms	0.64 ± 0.21	0.65 ± 0.17	0.65 ± 0.21	0.64 ± 0.23	0.874
Impedance, Ω	783 ± 154	762 ± 144	773 ± 166	791 ± 157	0.420
R wave amplitude, mV	11.7 ± 6.1	11.5 ± 4.9	12.3 ± 9.3	11.4 ± 4.9	0.476
QRS axis*					0.548
Normal axis, n(%)	265 (70.5%)	23 (52.3%)	70 (77.8%)	172 (71.1%)	
Left axis deviation, n(%)	85 (22.6%)	11(25.0%)	16 (17.8%)	58 (24.0%)	
Right axis deviation, n(%)	26 (6.9%)	10 (22.7%)	4 (4.4%)	12 (5.0%)	
QRS transition zone#	3 (2, 3)	2 (2, 3)	3 (2, 3)	3 (2, 4)	0.248
Numbers of attempts	1.4±0.6	2.1±0.7	1.7±0.8	1.2±0.5	<0.001
Procedure time, min	11.0 (7.0, 18.8)	26.5 (17.0, 32.0)	14.0 (8.0, 20.0)	9.0 (6.0, 14.0)	<0.001
Fluoroscopy time, min	5.0 (3.0, 8.0)	16.0 (9.0, 18.0)	6.0 (4.0, 9.0)	4.0 (3.0, 6.0)	<0.001

Data are presented as mean ± standard deviation or median (Q1, Q3) for continuous variables and frequency and percentages for categorical variables.
IEGM, intracardiac electrogram; LBBAP, left bundle branch area pacing; LBB, left bundle branch; P-V interval, interval from LBB potential to ventricle; Sti-LVAT, pacing stimulus to left ventricular activation time; QRSd, QRS duration.
**divided by successful LBBAP cases.*
 # each number represents the corresponding precordial lead.

happened in the RVP group. All lead revisions were successful without further clinical symptoms or signs.

Figure 2 shows comparisons of procedural and pacing parameters between LBBAP at three stages and RVP. As compared with RVP, LBBAP at stable stage presented statistically longer procedure duration (9.0 vs. 6.7 min, $P < 0.001$) and fluoroscopy time (4.0 vs. 2.8 min, $P < 0.001$). However, RVP produced significantly wider pQRSd compared with that in three stages of successful LBBAP (160 ± 24.1 vs. 117 ± 11.5 vs. 114 ± 9.5 vs. 114 ± 10.4 ms, $P < 0.001$). Similar pacing parameters were observed between LBBAP at three stages and RVP (**Figures 2 C,D,F**).

DISCUSSION

This single-center study firstly demonstrated learning curves of LBBAP indicated by procedure duration and fluoroscopy time and made a comparison between LBBAP at three stages and RVP. The main findings of our study are as follows: (1) for operators who are adept at pacemaker implantation, the steepest part of learning curves for LBBAP was over the first 50 cases. The procedure and fluoroscopy time could be improved further over the following 100 cases and plateaued after 150 cases; (2) using the currently available implantation tools, the success rate of LBBAP could be 94.5% or more at the stable stage, and the fluoroscopy time for the ventricular lead placement could be as short as 4.0 min; (3) although LBBAP presented statistically significantly longer procedure and fluoroscopy time than RVP did, the absolute values were very close to that of RVP. Considering the advantages of LBBAP compared with RVP, our results indicate that LBBAP might be considered as the first choice in patients with a high burden of ventricular pacing to avoid the potential risk of cardiac dysfunction induced by RVP.

Procedure and Fluoroscopy Time of LBBAP and the Learning Curve

Left bundle branch area pacing has been recently used as an alternative physiological pacing modality to HBP in some centers. Previous studies have reported fluctuated procedure and fluoroscopy time at different performing phases (8–11, 14, 18–20). The different definitions of procedure and fluoroscopy time might lead to significantly varied records. The procedure and fluoroscopy time in our study were defined as the duration of ventricular lead placement because the implant of atrial lead may confound the comparison between LBBAP and RVP. Chen et al. firstly reported a mean fluoroscopy time of 4.82 ± 3.37 min for the LBBAP procedure (21) and then presented a mean procedure duration of 18.0 ± 8.8 min and a mean fluoroscopy time of 3.9 ± 2.7 min for LBBAP implantation (18). Su et al. recently reported the largest single-center cohort study of LBBAP with a mean fluoroscopy time of 5.1 ± 4.6 min for lead placement and a mean procedure time of 86.4 ± 43.5 min (9). The median

TABLE 3 | Comparison of clinical characteristics and periprocedural complications between LBBAP and RVP.

Variables	LBBAP ($n = 406$)	RVP ($n = 313$)	*P*-value
Age	64.9 ± 14.3	67.5 ± 12.2	0.573
Male	197 (48.5%)	150 (47.9%)	0.940
Pacing indications			<0.001
AVB	245 (60.3%)	86 (27.5%)	
SND	161 (39.7%)	227 (72.5%)	
Type of device			<0.001
Double-chamber PM	341 (84.0%)	297 (94.9%)	
Single-chamber PM	65 (16.0%)	16 (5.1%)	
Periprocedural complications			
Lead revision	2	2	0.658
Lead dislodgement	1	2	
Lead perforation	1	0	
Pericardial effusion	0	0	1
Pacing system infection	0	0	1
Pocket hematoma	0	0	1
Pneumothorax/hemothorax	0	0	1

Data are presented as mean ± standard deviation for continuous variables and frequency and percentages for categorical variables.
LBBAP, left bundle branch area pacing; RVP, right ventricular pacing; AVB, atrioventricular block; SND, sinus node dysfunction; PM, pacemaker.

fluoroscopy time at the stable stage (4 [3.0, 6.0] min) in our study was consistent with previous results (3.9-5.1 min) (9, 18).

Different techniques applied to achieve LBBAP could also affect the procedure time. Huang et al. reported the "dual lead technique" with a mean fluoroscopy time ranging from 5.1 ± 4.6 min to 6.9 ± 2.5 min (9, 22), which was utilizing two 3830 pacing leads with one lead located in the His bundle region as a landmark and another lead seeking the optimal LBBAP pacing site (17). The "nine-partition method" by using single lead has also significantly decreased the mean fluoroscopy time from 12.9 ± 12.9 min to 6.3 ± 3.0 min (15, 16). Like most doctors in China, our group routinely used the single lead technique, which is similar to the nine-partition method, to identify the screwing site of LBBAP lead by using the tricuspid valve annulus as an anatomic marker. Early in the initial stage, we also performed His potential mapping to help to locate the screwing site of the LBBAP lead. Therefore, the prolonged procedure and fluoroscopy time at the initial stage were attributed to His locating, repeated pacing test and fluoroscopy verification of the lead position, and three to five attempts for successful LBBAP. Later in the initial stage, we discarded His locating and directly placed the 3830 lead to the target area just based on the anatomic marker (tricuspid valve annulus). At the stable stage, the whole procedure could be achieved in the right anterior oblique 30° position with one attempt in 80% of patients, which significantly shortened the procedure and fluoroscopy time. Our results could be only interpreted in bradycardia patients with relatively normal cardiac structure because patients indicated for CRT or with congenital heart disease were excluded from our study. The LBBAP procedure might be technically challenging in patients with significantly enlarged right atrium or left ventricle.

Left bundle branch area pacing results in rapid electrical propagation along the conduction system fibers and presents the shortest and constant Sti-LVAT at high and low outputs (14). In our study, LBB potential was less recorded during the stable stage while the mean Sti-LVAT decreased over time. The shortened Sti-LVAT was due to more selective-LBBAP cases achieved with accumulated experience in performing LBBAP. During the stable stage, LBBAP was mainly performed in patients with AVB while patients with SND commonly underwent RVP. LBB potential was less commonly recorded in patients with AVB than patients with SND (76.3 vs. 92.5%) according to Huang et al. (9) and could not be recorded in patients with LBBB without His corrective pacing (23). Moreover, 10.9% of patients during the stable stage underwent the LBBAP procedure without IEGM recording because the device implant in our center was not always performed in a catheter room equipped with a multichannel electrophysiology recording system. The nine-partition method was mainly introduced to perform LBBAP without an electrophysiology recording system (16). LBB potential may not be essential for LBB capture. The previous study has reported that the pQRSd, Sti-LVAT, and LBB capture threshold demonstrate no significant difference between patients with or without LBB potential (24).

The learning curve for LBBAP in our study was fitted based on performance data of one operator because this novel pacing modality has not been widely extended to many doctors in our hospital. The operator performing the LBBAP procedure in our study had implanted more than 600 active-fixation ventricular leads and nearly 60 successful HBP leads. The procedure and fluoroscopy time could be greatly influenced by the experience of the operator. We speculated that operators with high volume experience of HBP might be more skilled in performing LBBAP with shorter procedure and fluoroscopy time when compared with beginners without experience of HBP. The learning curve might be steeper for beginners, but smoother for an experienced operator in HBP. The significant decrease in LBBAP attempts in our study also supported the close association between learning curves and accumulated experience of the operator. Our results may provide novel insights into the routine application of LBBAP for bradycardia patients requiring ventricular pacing.

Comparison Between RVP and LBBAP

Despite the potential risk of developing cardiac dysfunction, traditional RVP is still the most widely used pacing technique (13). In our study, the procedure and fluoroscopy time between LBBAP at the stable stage and RVP differed statistically significant. However, the absolute difference in the procedure (2.3 min) and fluoroscopy time (1.2 min) might not be clinically significant for ventricular lead implantation. Frequent pacing tests and limited implantation tools might account for the slightly longer time. LBBAP could achieve narrow pQRSd, left ventricular synchrony, and similar pacing parameters to RVP (8, 11, 12). Consistent with previous studies (8, 9, 20), few procedural complications during LBBAP were comparable to RVP. Considering the advantages and disadvantages of the two

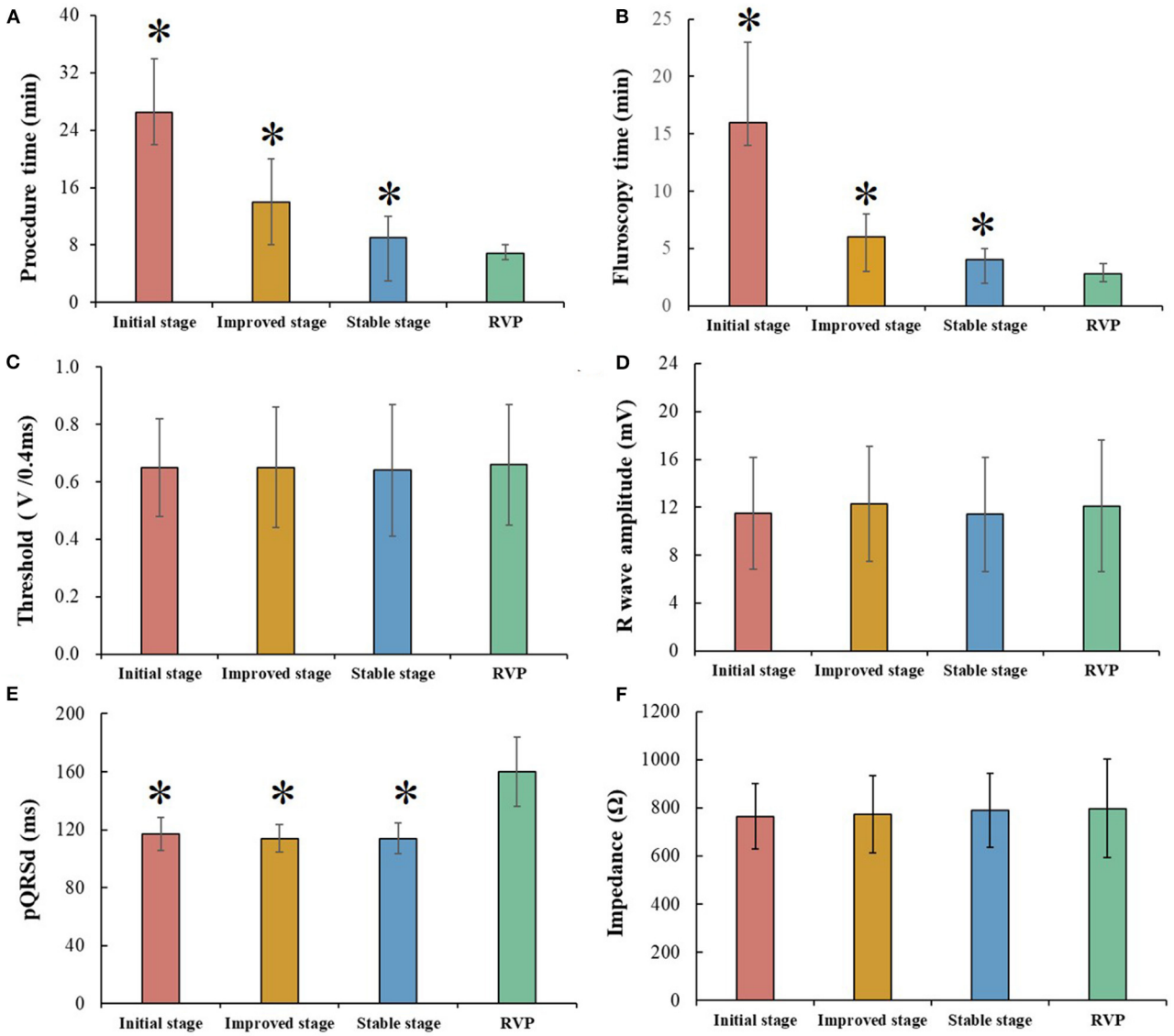

FIGURE 2 | Comparison between different left bundle branch area pacing (LBBAP) stages and right ventricular pacing (RVP). (**A,B)** Procedure time and fluoroscopy time gradually decreased among three LBBAP stages but still longer than that of RVP. (**C,D,F)** Pacing parameters, including, capture threshold, R wave amplitude, and impedance, were comparable among three LBBAP stages and RVP. (**E)** LBBAP produced a narrower pQRSd than RVP; *$P < 0.05$ compared with RVP.

pacing modalities, LBBAP might be preferred in patients with a high burden of ventricular pacing. However, multicenter large-scale randomized controlled trials are needed to provide evidence for the priority of LBBAP compared with RVP.

LIMITATIONS

Several limitations should be noted. Firstly, different techniques may present various learning curves. Our study described the learning curve of an operator by using the single lead technique for LBBAP. The implant technique was slightly changed in our study with performing His potential mapping in the first less than 20 patients early in the initial stage. However, it should be a neglectable bias because all the rest of the patients underwent the same procedure without His mapping. The improved procedure and fluoroscopy time, illustrated by the fitted learning curve, were associated with accumulated procedure experience instead of changing implant techniques over time. Besides, the learning curve for LBBAP in our study was fitted based on the data of one operator. Because the main point of our study was to explore whether the procedure and fluoroscopy time of LBBAP could be compared with that of RVP or not, the data from an experienced operator in LBBAP should be more convincing than data from several beginners. Furthermore, the number of LBBAP attempts, a sensitive indicator of the experience of operators, decreased significantly over time in our study. The procedure time decreased significantly accompanied by fewer attempts.

Finally, safety is also a critical concern for a new technique. The complication events in the LBBAP group were low and only two lead-related complications occurred at the initial stage in the present study. A large sample and multicenter study might be needed to investigate the change of the complication rates in different stages of LBBAP.

CONCLUSION

Procedure and fluoroscopy time of LBBAP could be reduced rapidly after 50 cases and plateaued over 150 procedures, while the Sti-LVAT could be shortened further until reaching a plateau after approximately 150 procedures. Compared with RVP, LBBAP can produce a narrower pQRSd and comparable pacing parameters with acceptable procedure and fluoroscopy time.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fuwai Hospital, National Center for Cardiovascular Diseases. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZW and HZ contributed to design of the study and performed the statistical analysis. XL organized the database. HZ wrote the first draft of the manuscript. XF wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Electromagnetic Field Associated With Dermoscope Magnets May Affect the Safety of Cardiac Implanted Electronic Devices Patients

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Dermoscopy is currently used as an auxiliary tool in general dermatology. Since some commercially available dermoscopes have built-in magnets, electromagnetic interference (EMI) may occur when examining cardiac implantable electronic devices (CIED) patients. The aim of the study was to create maps of electromagnetic fields defining a safe distance in terms of EMI. The study was performed in laboratory conditions using measuring equipment specially designed for this purpose. The following dermoscopes have been tested: Illuco IDS-1100, Visiomed Luminis, Visiomed Luminis 2, Heine NC2 with and without a contact plate, DermLite DL4, and DermLite Handyscope. Measurements were made for the following set of lift-off distances: 5, 10, 20, 30, 40, 50, and 150 mm. Each 2D scan consisted of 10-line scans shifted from each other by 10 mm. The strength of the magnetic field decreased with the distance from the faceplate. The distribution of the magnetic field differed depending on the position of the magnets. The highest magnetic field was recorded in the center of the Heine NC2 faceplate (up to 8 mT). In most cases, at a distance of 10 mm, the magnetic field strength was measured below 1 mT, with the exception of Heine NC2 and Heine NC2 with a contact plate. All tested dermoscopes generated a magnetic field of <1 mT at the distance of 20 mm. The use of dermoscopes with built-in magnets may affect the functioning of CIEDs, and the impact may vary depending on the type of dermoscope.

Keywords: dermoscopy, electromagnetic field, cardiac implantable electronic devices, pacemaker, implantable cardioverter-defibrillator

INTRODUCTION

Dermoscopy, apart from its traditional application in the diagnostics of skin neoplasia, is currently used as an auxiliary tool in general dermatology, and the dermoscope is compared to the dermatologist's stethoscope (1). In parallel with the increasing use of dermoscopy, due to the more frequent incidence of skin cancer, the number of patients treated with cardiac implantable

electronic devices (CIEDs) is also increasing. CIEDs include cardiac pacemakers, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices.

Since some commercially available dermoscopes have built-in magnets, possible electromagnetic interference (EMI) may occur when examining a CIED patient, including sensing disturbances (undersensing or oversensing), asynchronous pacing, increased pacing rate, pacing inhibition, and running the mode switch function. Atrial oversensing may trigger false positive mode switch to an asynchronous mode in dual chamber pacemakers or ICDs. This causes loss of synchrony of atrial and ventricular contractions and associated symptoms such as palpitations, dizziness and a deterioration in exercise tolerance. Atrial oversensing may also trigger inadequate ventricular pacing (2). In contrast, ventricular oversensing can inhibit pacing, a potentially life-threatening condition in a pacemaker-dependent patients (3). In patients with implanted ICD, ventricular oversensing may lead to inadequate therapy (anti-tachycardia pacing or high voltage shock). Inappropriate ICD therapies can be potentially proarrhythmic and harmful, and are associated with worse prognosis (4).

EMIs can also trigger a magnet-like response in the ICD, temporarily or permanently suspending therapy in the event of a threatening ventricular tachyarrhythmia. In addition, on rare occasions, the CIED may switch to a backup mode of operation known as "power-on reset" when the device returns to a back-up pacing mode and enables therapy for ventricular tachyarrhythmia in the ICD (5). So far, only one study has assessed the safety of dermoscopy in the context of EMI, but only for a few of handheld dermoscopes available on the market (6). Additionally, no information was provided on the distribution of electromagnetic fields depending on the position of the magnets in individual dermoscopes.

The aim of the study was to evaluate various types of dermoscopes in laboratory conditions and to create maps of electromagnetic fields defining a safe distance in terms of EMI.

MATERIALS AND METHODS

The study was performed from October 1, 2020 to December 18, 2020 in laboratory conditions using measuring equipment specially designed for this purpose. As the study did not include humans, the approval from the Ethics Committee was waived. The measurements were performed by an engineer specializing in magnetic measurements (ZU), assisted by a specialist in cardiac electrotherapy (GS) and a dermatologist who uses a dermoscope in her daily practice (MS).

Dermoscopes with magnets available in Poland, which were provided by two manufacturers, were used for the tests. We tested the following dermoscopes: Illuco IDS-1100 (Illuco Corporation, South Korea), Visiomed Luminis (Canfield Scientific, USA), Visiomed Luminis 2 (Canfield Scientific, USA), Heine NC2 with and without a contact plate (HEINE Optotechnik GmbH & Co. KG, Germany), DermLite DL4 (3Gen Inc., USA), and DermLite Handyscope (3Gen Inc., USA). The MPR-H2 (MagLabs s.c, USA) magnetometer was used to measure the magnetic field generated by a dermoscope. The main part of the magnetometer is a probe consisting of several Hall sensors, but for the purpose of this study only one of them was used to measure the magnetic field. Using a magnetometer, the magnetic field was measured, which is perpendicular to the faceplate of the dermoscope. The probe was additionally equipped with a sensor (encoder) to measure the probe displacement through the magnetic field. The distance (x direction) was measured with a resolution of 1.12 mm. The magnetometer allowed to measure the magnetic flux density in two ranges: 2 mT with a resolution of 1 μT and 20 mT with a resolution of 10 μT. The first range was used when the output power of the magnetometer did not exceed 2 mT. A measurement platform was created that allowed to maintain a constant distance between the magnetometer and the faceplate. This distance was called the lift-off distance. Two-dimensional (2D) magnetic field scans were performed for each dermoscope at different lift-off distances. The measurements were made for the following lift-off distances: 0, 5, 10, 20, 30, 40, 50, and 150 mm. Each 2D scan consisted of 10-line scans shifted from each other by 10 mm. Therefore, the resolution of the scans performed is different for the x direction (1.12 mm) and for the y direction (10 mm). The obtained data was collected and saved using a virtual instrument created in the LabVIEW environment. The raw data was then processed using Python 3.0 libraries. The planned endpoint of the study was to demonstrate a safe distance that would allow dermoscope examination of a patient with an implanted CIED.

RESULTS

The strength of the magnetic field decreased with the distance from the faceplate (**Figure 1**, **Table 1**). The magnetic field distribution measured at the faceplate differed depending on the arrangement of magnets in a given device (**Figures 2**, **3**). For most devices magnets are arranged on the circumference of the faceplate. Magnetization of the magnets is generally directed perpendicularly to the faceplate. As a result, the highest value of the magnetic flux density is usually not observed in the center but on the periphery of the faceplate. This is confirmed by the results presented in **Figure 2**, in particular for Visiomed Luminis, Visiomed Luminis 2, Dermlite DL4, and Illuco IDS-1100. The highest magnetic field was recorded for the Heine NC2 (up to 7.8 mT) directly above its two magnets. The circumferential field distribution is not visible with the Dermlite Handyscope. The reason for this is the long distance (several cm) of the magnets that attach this device to a smartphone, from the faceplate. At this distance, the magnetic flux is diffused and its density significantly decreases. The Visiomed Luminis and DermLite Handyscope were characterized by the lowest density of the generated magnetic flux and as the only two they did not exceed the value of 1 mT (at the distance of 0 mm), which is indicated by CIEDs manufacturers as the threshold value for activating the magnetic switch in CIEDs. In most cases, the magnetic field strength at a distance of 10 mm was below 1 mT, except for the Heine NC2 and Heine NC2 with a contact plate. All tested dermoscopes generated a magnetic field of <1 mT at a distance of 20 mm. The safe lift-off distances for the magnetic flux density

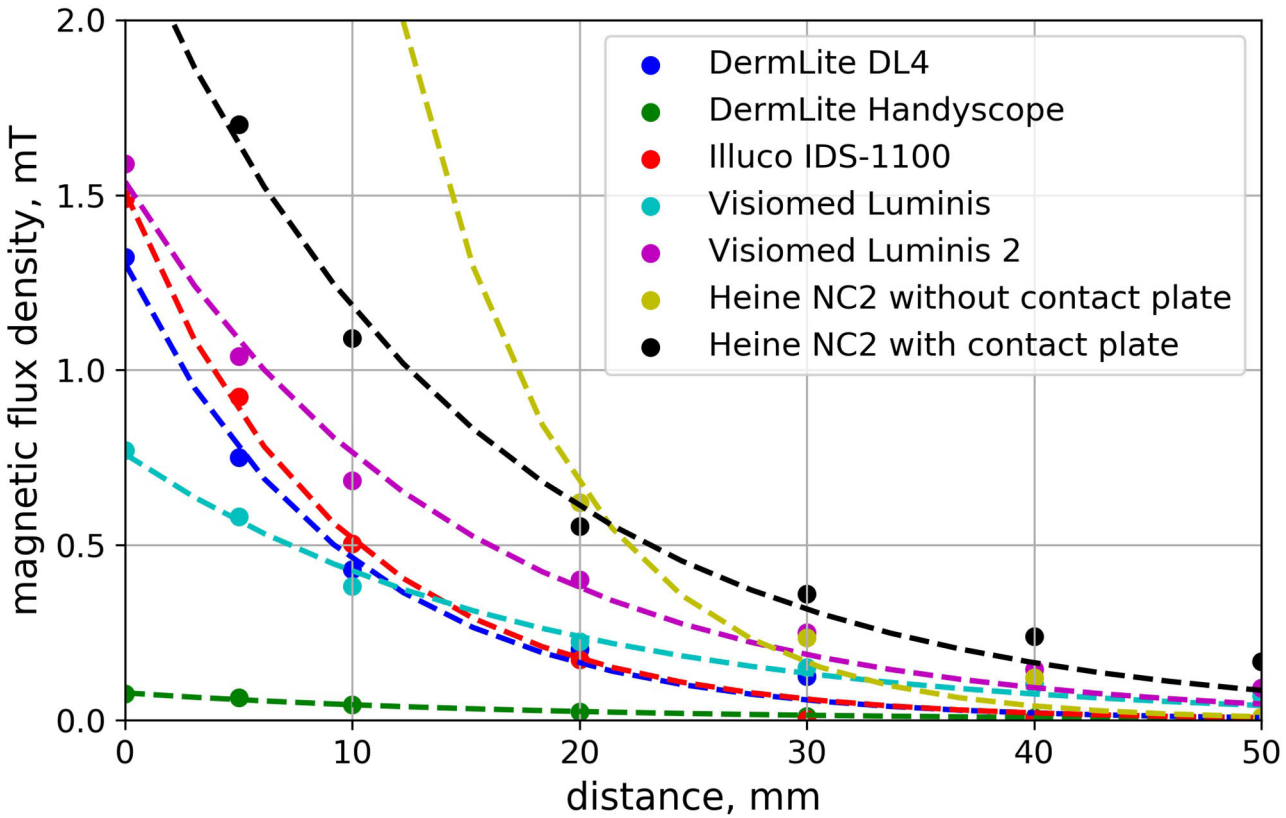

FIGURE 1 | Dependence of the magnetic flux density on the distance from the dermoscope faceplate. Each curve was determined for a path that starts at the point over a faceplate corresponding to the maximum absolute value of measured magnetic flux density.

TABLE 1 | The strength of the magnetic field depending on the type of dermoscope and distance from the faceplate.

Dermoscope \ Distance [mm]	0	5	10	20	30	40	50	150
Dermlite DL4	1.322	0.750	0.431	0.202	0.124	0.006	0.002	−0.003
Dermlite handyscope	0.075	0.064	0.044	0.023	0.011	0.007	0.005	0.014
Illuco IDS-1100	1.490	0.924	0.505	0.173	0.001	0.004	−0.004	0.003
Visiomed Luminis	0.772	0.580	0.383	0.225	0.150	0.102	0.069	0.011
Visiomed Luminis 2	1.589	1.040	0.684	0.402	0.250	0.145	0.092	0.009
Heine NC2 without contact plate	7.765	7.766	2.741	0.621	0.236	0.121	0.009	0.001
Heine NC2 with contact plate	2.283	1.701	1.091	0.554	0.361	0.239	0.167	0.015

Values of the magnetic flux density in the table are expressed in mT.

of 0.5, 1.0, and 1.5 mT differed between the tested dermoscopes (**Table 2**). Therefore, on the basis of the obtained results, the distance ensuring the highest probability of safe examination of a patient with an implanted CIED (assuming a lower EMI threshold—i.e., 1.0 mT and regardless of the type of dermoscope) is 17 mm from the implanted CIED.

DISCUSSION

As the indications for treatment with CIEDs expand, the number of these devices continues to increase. In Western Europe, in 2005–2011, the number of implanted pacemakers increased from 82.9/100,000 to 93.8/100,000, and CRT from 6.0/100,000 to 14.0/100,000 (7). The number of patients treated with ICD has also increased significantly. Between 1993 and 2009, the number of ICD implantations in the United States increased from 6.1/100,000 to 46.2/100,000 (8). At the same time, the incidence of skin cancer and skin melanoma is increasing, therefore, it is very likely that patients with implanted CIED may require examination with a dermoscope (9). There are also reports in the literature of malignant skin neoplasms developing around the implanted CIED, including

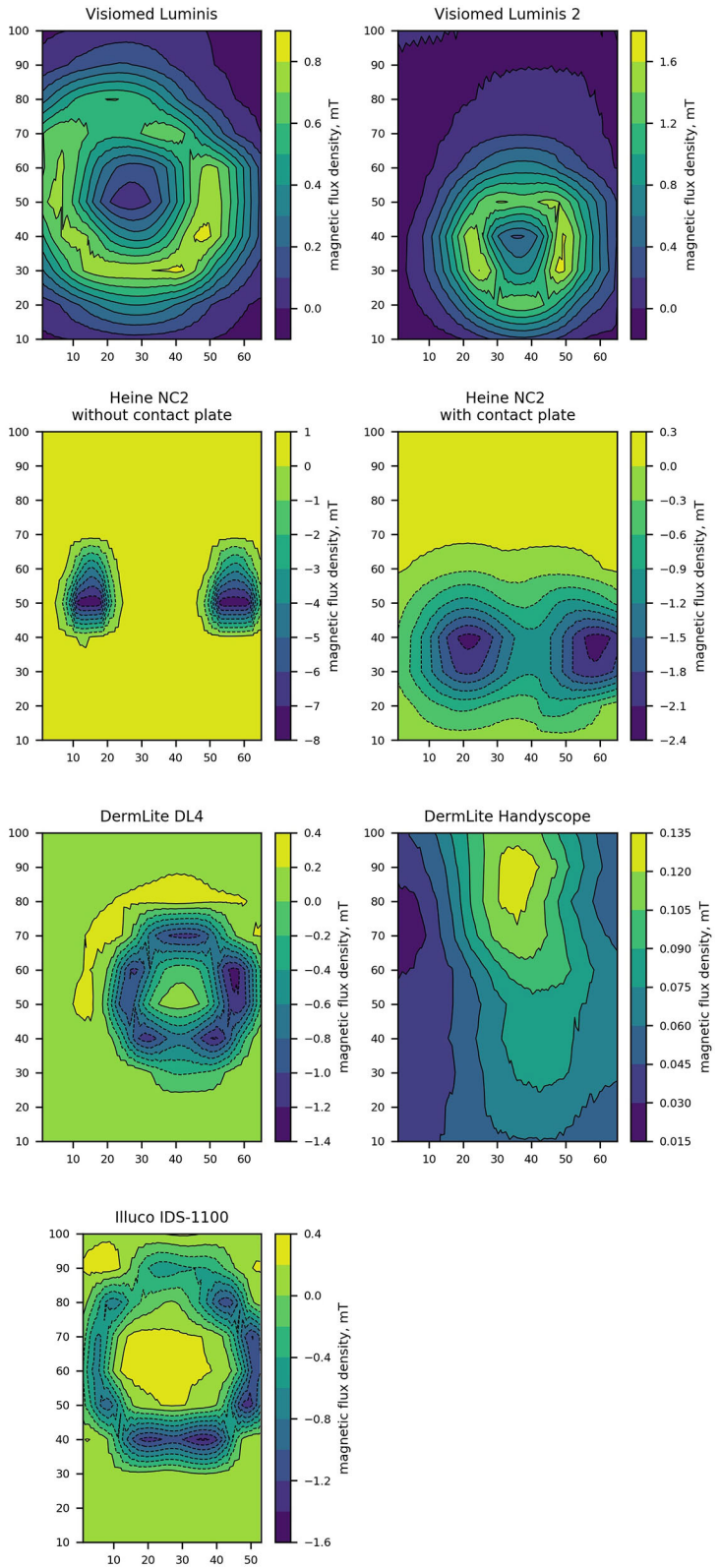

FIGURE 2 | Contour plots representing the perpendicular component of magnetic flux density measured directly over a dermoscope faceplate of the tested dermoscopes models. Dimensions of contour plots are expressed in milimeters.

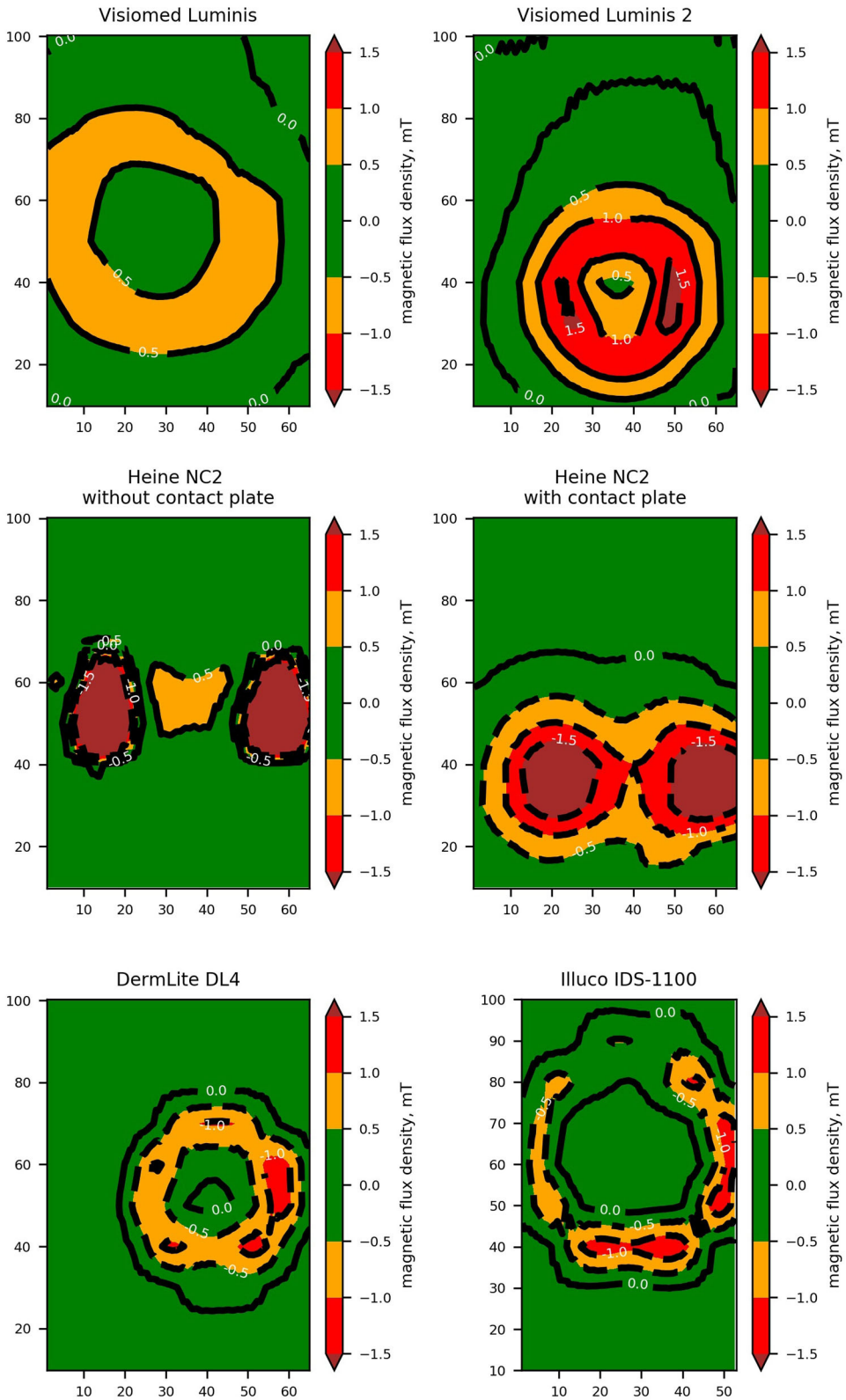

FIGURE 3 | High contrast contour plots representing the perpendicular component of magnetic flux density measured directly over a dermoscope faceplate. Both axes of the contour plots are labeled with a dimension expressed in milimeters. Areas where the magnetic field exceeds thresholds of 0.5, 1.0, and 1.5 mT are highlighted.

TABLE 2 | The distance from the dermoscope faceplate in a vertical plane at which the magnetic flux density of 0.5, 1.0, and 1.5 was measured.

Dermoscope \ Magnetic flux density	1.5 mT	1.0 mT	0.5 mT
DermLite DL4	N/A	3 mm	9 mm
DermLite Handyscope	N/A	N/A	N/A
Illuco IDS-1100	N/A	4 mm	10 mm
Visiomed Luminis	N/A	N/A	7 mm
Visiomed Luminis 2	N/A	6 mm	16 mm
Heine NC2	14 mm	17 mm	22 mm
Heine NC2 with contact plate	6 mm	13 mm	23 mm

The values of magnetic flux density provided by manufacturers which may affect the functioning of the CIED are 1.0 mT (in Medtronic, Boston Scientific, Abbott devices) and 1.5 mT (Biotronik).
N/A, not applicable.

melanoma, basal cell carcinoma, leiomyosarcoma, and atypical fibroxanthoma (10–12).

Some dermoscopes have built-in magnets, e.g., to facilitate the process of connecting and disconnecting the contact plate or compatible electronic devices which are required for their use, such as smartphones or tablets. The electromagnetic field generated by these magnets may interfere with the operation of the CIED, which may pose a risk to pacemaker-dependent patients (pacing inhibition) and to ICD patients (inhibition of ventricular tachyarrhythmia detection). CIEDs contain a magnetic switch (reed switch) which is activated by a sufficiently strong magnetic field. The reed switch consists of two metal magnetic strips in a glass capsule. It was designed to prevent the adverse effects of the magnetic field. The most common configuration is to separate these strips (open-switch) from successive contacts of the strips (closed-switch) after exposure to a strong magnetic field. This changes the voltage detected by the amplifier in the CIED, which causes the device to switch to the specified program (13). According to information provided by CIED manufacturers, the reed switch (starts to close at a field strength of 1.0 mT (in Medtronic, Boston Scientific, Abbott devices) or 1.5 mT (Biotronik), which means that stronger static magnetic fields may affect the functioning of the CIED (14).

With regard to dermoscopes with integrated magnets, so far only Rishpon et al. (6) assessed in laboratory conditions their potential impact on the performance of CIEDs. The authors tested the following devices: DermLite DL4 and DL4w [3Gen], VEOS HD1 and HD2 [Canfield Scientific Inc], and NC1 and NC2 [Heine Optotechnik]. In their study, the authors used the gauss (G), which is a unit of measurement of magnetic flux density (1 G = 0.1 mT). According to the study the magnetic field strength at the faceplate varied between 2.22 and 9.98 G (respectively, 0.222 and 0.998 mT). At the distance of 0.5 cm it varied between 0.82 and 2.4 G (respectively, 0.082 and 0.024 mT); at 1.0 cm between 0.5 and 1.04 G (respectively, 0.05 and 0.104 mT), and 0 G for all devices at 15 cm. The values obtained by the authors in this study for DermLite DL4 dermoscope and Heine NC2 were significantly lower in comparison to the results obtained in our study. The differences may be explained by a different methodology, i.e., the lack of contour maps of the electromagnetic field above the surface of the dermoscope and relying solely on the measurements in its central part—which, as we confirmed in our study, does not always correspond to a place with maximum magnetic flux density. In our study, the maximum magnetic flux density was 7.8 mT for the Heine NC2 dermoscope without a contact plate. However, in most of the measurements it exceeded the safety threshold values provided by CIED manufacturers. Importantly, based on our research, no dermoscope exceeded the magnetic flux density of 10 mT, i.e., the threshold activating the AutoDetect function in CIED designed to detect a strong magnetic field and allowing for the safe performance of an MRI examination. Activating this function would be particularly dangerous as it would prevent detection of ventricular arrhythmias (15).

Among the three currently used dermoscopy techniques (standard contact dermoscopy, polarized contact dermoscopy, and polarized non-contact dermoscopy), only contact dermoscopy requires direct contact with the patient's skin. In contrast, non-contact dermoscopes with built-in cross-polarized filters do not require direct skin contact and have been suggested to be safer for patients with CIEDs (6). Similarly to Rishpon et al. (6), we found that a distance of only a few millimeters from a CIED can significantly reduce the strength of the magnetic field. In addition, we showed significant differences in the magnetic field in the spatial presentation for individual models of dermoscopes, which results from the different arrangement of magnets in these devices. It is necessary to remember about these differences when examining skin lesions not only directly over the implanted CIEDs, but also in the close vicinity of the CIEDs. In our study, among the investigated dermoscopes with embedded magnets, the DermLite Handyscope had the best safety profile, but it should be emphasized that using it requires a connection to a smartphone or tablet, which in certain conditions may electromagnetically interfere with the CIEDs. This may be the subject of a future study in which different modern devices connected to the dermoscope should be used, taking into account different scenarios, e.g., active Wi-Fi connection, data transfer via Bluetooth, etc.

Many medical devices and procedures can interfere with the functioning of CIEDs. These include magnetic resonance imaging, left ventricular assist devices, radiotherapy, electrical cardioversion, radiofrequency ablation, electrocoagulation, percutaneous nerve electrostimulation, lithotripsy, and electroconvulsive therapy (16). The potential risk of electromagnetic disturbances during dermatological procedures was also included in the guidelines published by the British Society of Dermatological Surgery (17). It is recommended that procedures performed within 5 cm from the CIED take place in the presence of a cardiologist and with a programmer for a given CIED in case of any problems. There are also single reports confirming safety of smartwatches and their chargers, smartphones (18), electric cars (19), induction ovens, and body scanners among patients with implanted CIEDs. More disturbing data came from a study by Lee et al. (20) assessing the safety of portable headphones in patients with CIEDs. In this study headphones generated a magnetic field stronger than 20

mT. This resulted in disturbances in the functioning of CIED in as many as 30% of patients.

Despite the fact that dermoscopes may influence CIED functioning, it is important to balance the benefits and risks of performing dermoscopic examination in this group of patients. In fact, dermoscopy is a method used mainly for diagnostics of potentially life-threatening skin tumors, while to date we have not found any case reports describing documented CIED functioning disturbances that occurred during dermoscopic examination. From the other side, such potential risk cannot be neglected, which has been clearly shown in our study. Increasing the awareness between both clinicians and patients seems to be crucial. Medical professionals using dermoscopes in daily practice should be aware of the presence of magnets in devices they use and their possible interactions with CIED. Before using a dermoscope with a magnet, the question about previous CIED implantation should be asked routinely. Patients undergoing CIED implantation should be educated by cardiologists about the potential risk associated with dermoscopes magnets and report the fact of having an implanted CIED to the examining dermatologist. It is important to underline the fact that having an implanted CIED does not disqualify the patient from a dermoscopic examination. Use of another model without embedded magnets is completely safe and does not affect CIED in any way. If the physician possesses only the device with embedded magnets, it would be advisable not to cross the safety distance which depends not only on the dermoscopic device but also on CIED type. In case of need to examine the skin just over the CIED, patient referral to another specialist for examination with a safe dermoscopic device would be recommended.

LIMITATIONS OF THE STUDY

The main limitation of the study is its laboratory setting, without human subjects with CIEDs and not validated or tested in cardiac devices. However, due to the scarce data in the literature, the assessment of the hypothetical risk of EMI among patients with implanted CIEDs is an important preliminary study confirming the need for further studies in the field. Another limitation is the fact that we did not have an opportunity to confirm the measurements on multiple devices of the same model of dermoscope, what would be one of the issues to be addressed in future studies.

CONCLUSIONS

In conclusion, it should be emphasized that the use of dermoscopes with built-in magnets may affect the functioning of the CIED, with significant differences between individual devices. Physicians who use dermoscopes in their daily practice should be aware of the presence of magnets in these devices and be aware of the possible consequences this may have in patients with pacemakers, ICDs and CRT devices. Another aspect is the use of dermoscopes with built-in magnets in conjunction with smartphones and tablets, and their possible impact on the functioning of CIED, which requires further studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

GS, MSł, ZU, MSo, MK, AL-S, and EL conceived and planned the experiments. GS, MSł, and ZU carried out the experiments. GS, MSł, ZU, MSo, MK, AL-S, EL, RN, and GR contributed to the interpretation of the results. GS, MSł, and ZU took the lead in writing the manuscript. All authors provided critical feedback and helped to shape the research, analysis, and manuscript.

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Long-Term Performance Comparison of Bipolar Active vs. Quadripolar Passive Fixation Leads in Cardiac Resynchronisation Therapy

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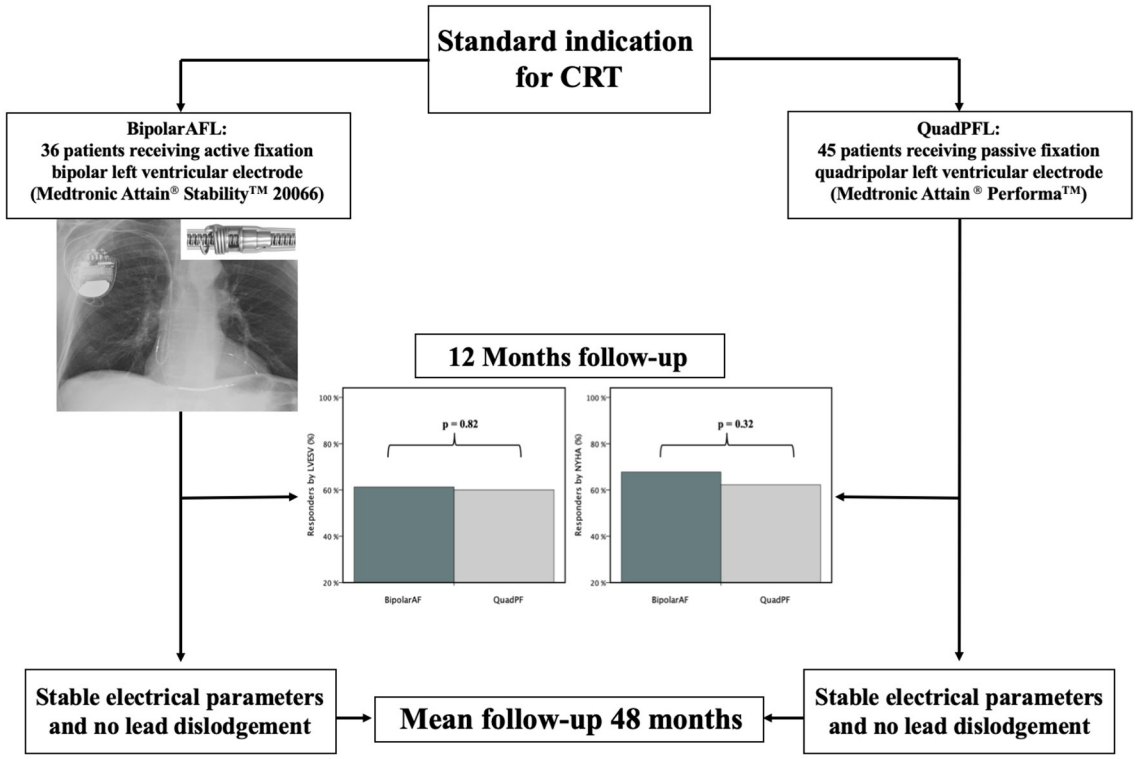
Background: Bipolar active fixation (BipolarAFL) and quadripolar passive fixation left-ventricular leads (QuadPFL) have been designed to reduce the risk of phrenic nerve stimulation (PNS), enable targeted left-ventricular pacing, and overcome problems of difficult coronary venous anatomy and lead dislodgment. This study sought to report the long-term safety and performance of a BipolarAFL, Medtronic Attain Stability 20066, compared to QuadPFL.

Methods: We performed a single-operator retrospective analysis of 81 patients receiving cardiac resynchronization therapy (CRT) (36 BipolarAFL, 45 QuadPFL). Immediate implant data and electrical and clinical data during follow-up (FU) were analyzed.

Results: BipolarAFL has been chosen in patients with significantly larger estimated vein diameter (at the lead tip: 7.2 ± 4.1 Fr vs. 4.1 ± 2.3 Fr, $p < 0.001$) without significant time difference until the final lead position was achieved (BipolarAFL: 20.9 ± 10.5 min, vs. QuadPFL: 18.9 ± 8.9 min, $p = 0.35$). At 12 month FU no difference in response rate to CRT was recorded between BipolarAFL and QuadPFL according to left ventricular end-systolic volume (61.1 vs. 60.0%, $p = 0.82$) and New York Heart Association (66.7 vs. 62.2%, $p = 0.32$). At median FU of 48 months (IQR: 44–54), no lead dislodgment occurred in both groups but a significantly higher proportion of PNS was recorded in QuadPFL (13 vs. 0%, $p < 0.05$). Electrical parameters were stable during FU in both groups without significant differences.

Conclusion: BipolarAFL can be implanted with ease in challenging coronary venous anatomy, shows excellent electrical performance and no difference in clinical outcome compared to QuadPFL.

Keywords: cardiac resynchronisation therapy, active fixation, left ventricular lead, lead dislodgement, biventricular pacing



GRAPHICAL ABSTRACT | Study design and important results.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a well-established therapy for patients with heart failure, reduced left ventricular-ejection fraction (LV-EF), and prolonged QRS duration. Response to CRT therapy, achieving desired LV lead placement, and LV pacing site remain a challenge until today (1, 2). With different coronary venous anatomy and size, manufacturers tried to overcome the problem of nerve stimulation (PNS), lead stability, and pacing at the desired position by manufacturing different sizes, shapes, and adding more poles. This was with limited success (3). With the Attain Stability 20066 (Medtronic, Tilburg, the Netherlands), a bipolar active fixation LV lead (BipolarAFL) has been introduced to help solve these problems. The 20066 is a 4 Fr bipolar steroid eluting lead with a small exposed side helix that is rotated clockwise into the vein wall until fixated (**Figure 1**). The lead has already been described in more detail elsewhere (4). First short-to-medium-term results showed good feasibility and promising clinical performance (5). Attain Performa Models 4,298, 4,398, and 4,598 (Medtronic, Tilburg, the Netherlands) is a well-established series of quadripolar passive fixation electrodes (QuadPFL) with four steroid eluting pacing electrodes (6). In this paper, we report our implant experience with BipolarAFL in comparison to QuadPFL, compare clinical outcome at 12 months between both leads and report long-term electrical results and rates of lead stability and dislodgment.

Abbreviations: BipolarAFL, Bipolar active fixation left ventricular lead; CRT, Cardiac resynchronization therapy; Fr, French; FU, Follow-up; IQR, Interquartile range; LV, Left ventricle; LV-EF, Left ventricular ejection fraction; LVEDV, Left ventricular end-diastolic volume; LVESV, Left ventricular end-systolic volume; NYHA, New York Heart Association; PCT, Pacing capture threshold; PNS, Phrenic nerve stimulation; QuadPFL, Quadripolar passive fixation left ventricular lead.

METHODS

Study Population

We performed a retrospective analysis of patients receiving a Medtronic CRT device with either a BipolarAFL or QuadPFL. The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local ethics committee. Patients with standard indications for CRT therapy were included in the study. Inclusion criteria were CRT implant indication in patients with impaired LV function (LV-EF $\leq$ 35%) and bundle branch block (BBB) according to European Society of Cardiology/European Heart Rhythm Association guidelines (7, 8). Patients were included regardless of whether they were undergoing a first-device implantation procedure or received the LV electrode as part of an upgrade from an implantable cardiac defibrillator without a prior LV lead.

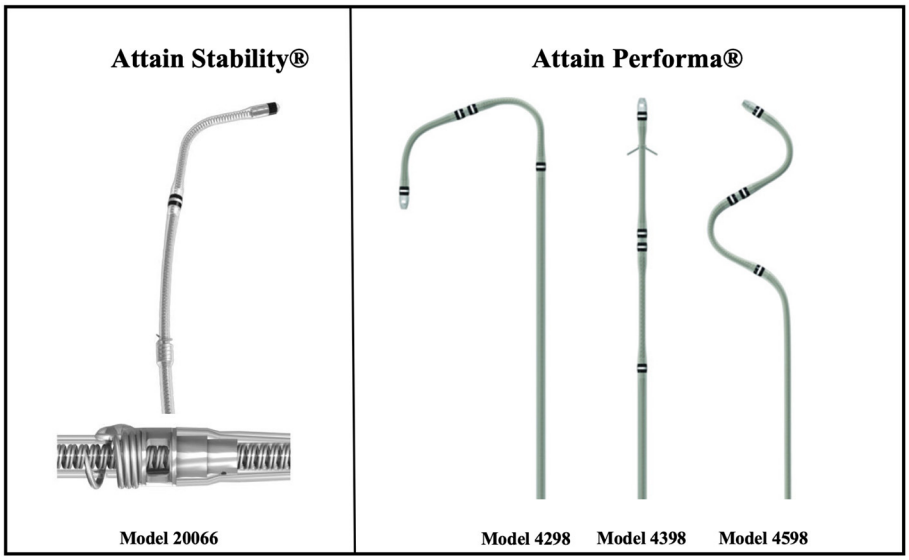


FIGURE 1 | Bipolar active fixation lead (Medtronic Attain® Stability™ 20066) with side helix and quadripolar passive fixation leads (Medtronic Performa® 4298, 4398, and 4598).

Before Implant

A total of 81 consecutive patients were included in a single center (University Hospital Bergmannsheil Bochum) in Germany. This center is specialized in CRT implantations for more than 15 years with more than 200 annual cases. It is the largest cardiovascular hospital in a city with a population of almost half a million people. Every patient received a 12-lead ECG at rest, New York Heart Association (NYHA)-class evaluation, two-dimensional transthoracic echocardiography, and medical history was collected.

Echocardiography

Echocardiographic images were obtained by an echocardiography specialist using a transthoracic echocardiographic system (GE Vivid E9, GE Vingmed Ultrasound, Horten, Norway). The following parameters were obtained at baseline and after 12 months according to the American Society of Echocardiography guidelines: left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and LV-EF.

LV-EF was measured by the Simpson biplane method determined from the cine loops acquired in a two-dimensional model with measurement of end-diastolic and late systolic volumes in five consecutive cardiac cycles in the apical axis at focused LV views. Analysis was undertaken during postprocessing with the software EchoPAC (EchoPAC 13, GE Medical, Milwaukee, USA).

Implant Procedure

Implantation of all three leads *via* either subclavian or cephalic vein was planned in patients with first device implantation with the right atrial lead placed in the right atrial appendage and the right ventricular lead in mid-septal position. LV lead was aimed in the basal or mid, posterolateral or lateral position after coronary venogram. The choice of LV lead was at the discretion of the implanting physician. Criteria to choose BipolarAFL included implantation from right side, aim to pace at a certain region with larger vein diameter or challenging venous anatomy according to physicians experience. All implants were performed by a single, very experienced physician (more than 12 years of implant experience at that time with an average of more than 100 annual cases). Implantation was performed under conscious sedation. For BipolarAFL, a tug test has been performed to check proper fixation. The lead position was checked and documented by fluoroscopy at 20° right anterior oblique and 20° left anterior oblique during the procedure and by x-ray the day after implantation. Vein sizes were estimated in millimeters using a catheter lab analyzation tool (Philips Xcelera, Eindhoven, the Netherlands) according to fluoroscopy at the tip, helix, and great cardiac vein. For better comparison vein size 36 mm proximal from the tip of QuadPFL has been documented as vein size at imaginary helix. To compare the vein size to lead size and have an internationally known standard size, the vein size has been converted into French (Fr). Vein angle has been measured by postprocessing as well. These measurements have been performed by three different cardiologists, blinded to the study, and the mean of the three measurements was used for further analysis.

During the procedure, all possible biventricular pacing configurations were programmed and tested for PNS with 8 V at 0.5 ms, and the threshold was tested at 0.5 ms. If pacing configurations were possible, the configuration with the longest RV to LV delay was programmed with

TABLE 1 | Baseline data.

	Bipolar active fixation lead ($n = 36$)	Quadripolar passive fixation lead ($n = 45$)	p-value
Age at implant (years)	71.8 ± 9.6	72 ± 7.6	0.71
Sex, male, *n* (%)	27 (75%)	34 (75.6%)	0.22
BMI (kg/m^2)	29.1 ± 3.9	27.1 ± 4.2	0.16
BSA	2.0 ± 0.2	2.0 ± 0.2	0.41
Ischemic cardiomyopathy, *n* (%)	22 (61.1%)	25 (55.6%)	0.36
Myocardial infarction, *n* (%)	14 (28.8%)	21 (46.7%)	0.43
Hypertension, *n* (%)	26 (72.2%)	33 (73.3%)	0.25
Diabetes, *n* (%)	14 (38.9%)	17 (37.8%)	0.87
Chronic kidney disease, *n* (%)	13 (36.1%)	16 (28.9%)	0.09
History of stroke/TIA, *n* (%)	4 (11.1%)	6 (13.3%)	0.33
Atrial fibrillation, *n* (%)	15 (41.9%)	23 (51.1%)	0.77
Beta-Blocker, *n* (%)	35 (97.2%)	43 (95.6%)	0.75
ACE-Inhibitor/ARBs	34 (94.4%)	43 (95.6%)	0.82
MRA	32 (88.9%)	41 (91.1%)	0.72
NYHA class	2.6 ± 0.8	2.8 ± 0.6	0.21
Left bundle branch block, *n* (%)	35 (97.2%)	41 (91.1%)	0.30
QRS duration (ms)	166.4 ± 38.2	170.8 ± 26.1	0.38
Left ventricular ejection fraction (%)	29.6 ± 10.2	28.3 ± 8.3	0.54
Left ventricular end-systolic volume (ml)	120 ± 36	123.6 ± 29.2	0.15
Left ventricular end-diastolic volume (ml)	165.7 ± 54.4	168.1 ± 58.6	0.21
CRT-D implant, *n* (%)	33 (91.7%)	40 (88.8%)	0.77
Device upgrade, *n* (%)	10 (27.8%)	11 (24.4%)	0.61

a pacing amplitude safety margin of 1.0 V above the threshold at 0.5 ms. For QuadPFL biventricular pacing with LV pacing from a single site was programmed. The day after implant, the benefit of chosen biventricular pacing configuration was tested by echocardiography and atrioventricular optimization has been done together with an echocardiography specialist.

Follow-Up

Device follow-up (FU) was performed 3 and 6 months after implant and every 6 months following. NYHA-class evaluation, 12-lead ECG, and two-dimensional transthoracic echocardiography assessment were performed at 12-month FU. Decrease of LVESV $\geq$ 15% was considered as reverse remodeling and response to CRT. Improvement of at least one NYHA class was considered as a clinical response to CRT.

Statistical Analysis

All statistical analysis was performed using IBM SPSS Statistics version 24.0.0 on mac.

Continuous variables were stated as mean ± SD and compared with unpaired t-test/ANOVA for normally distributed variables and Mann–Whitney U-test for nonnormally distributed variables. Paired data were compared by paired t-test. Frequencies and percentages were reported for categorical data and compared by the chi-squared test or Fisher's exact test. Median (interquartile range) was reported for non-normally distributed data. All statistical analyses were two-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Demographics and Implant Procedure Bipolar Active Fixation Left Ventricular Lead

A total of 37 BipolarAFL implants were attempted between January 2014 and April 2015 with a success rate of 97.3% ($n = 36$). In one case implantation was not successful due to high thresholds at the desired position and too small vessel diameter at the tip to apply torque. The patient received a QuadPFL. The desired position was achieved in all other BipolarAFL cases and defibrillator therapy was used in 33 (91.7%) cases. Patient demographic data are summarized in **Table 1**. There were 26 (72.2%) first implants and 10 (27.8%) ipsilateral upgrade procedures. Right-side access was used in six (13.9%) cases. The estimated angle of the target vein was lower than 90° in 12 (33.3%) cases (**Figure 2**). Repositioning of BipolarAFL until the achievement of final position was necessary during 12 (33.3%) procedures. A single attempt of repositioning was necessary in nine (25%) cases, two attempts in one (2.8%), and three attempts in two (5.6%) cases. Meantime to access coronary sinus was 6.6 ± 4.3 and 20.9 ± 10.5 min until the lead was fixated at the final position. Estimated vein size at final helix position was larger than 7 Fr in 28 (78%) cases (**Figure 3**). The final position of the helix and tip is illustrated in **Figure 4**. There were no early dislodgements.

Implant Procedure Quadripolar Passive Fixation Left Ventricular Lead and Comparison to Bipolar Active Fixation Lead

A total of 46 QuadPFL implants were attempted between January 2014 and April 2015 with a success rate of 98%. In one case, the diameter of the target vein was too small to achieve wedge position and a standard bipolar lead was implanted instead. The desired position was achieved in all other patients with the final position of tip illustrated in **Figure 4**. Right-side access was used in three (4.4%) cases with no significant difference compared to BipolarAFL ($p = 0.15$). The estimated angle of the target vein was lower than 90° in eight (17.8%) cases (**Figure 2**), being significantly less than in BipolarAFL ($p < 0.05$). Repositioning of QuadPFL until achievement of final position was necessary during 10 (22.2%) procedures, not being significantly different to BipolarAFL (22.2 vs. 33.3%, $p = 0.23$). Meantime to access

coronary sinus (6.6 ± 3.4 min) was not significantly different compared to BipolarAFL (6.2 vs. 6.6 min, $p = 0.78$) and neither was time until the achievement of final position (18.9 ± 8.9 min) compared to BipolarAFL (18.9 vs. 20.9 min, $p = 0.35$). Estimated vein size at imaginary helix position (36 mm from the tip of QuadPFL) was significantly smaller compared to estimated vein size at the helix in BipolarAFL (5.8 ± 3.6 Fr vs. 8.8 ± 3.4 Fr, $p < 0.01$) and at the tip compared to BipolarAFL (4.1 ± 2.3 Fr vs. 7.2 ± 4.1 Fr, $p < 0.001$; **Figure 3**). Tip of QuadPFL was compared to BipolarAFL significantly more often placed in a more anterior ($n = 6$, 13.3% vs. $n = 1$, 2.9%, $p < 0.05$) and apical ($n = 12$, 26.7% vs. $n = 2$, 5.9%, $p < 0.05$) position (**Figure 4**).

Clinical Follow-Up

All patients completed 12 months FU. Clinical FU data are summarized in **Table 2**. Heart failure-associated hospitalizations occurred in two BipolarAFL (5.7%) and two QuadPFL (4.6%) patients and were not significantly different ($p = 0.81$).

During 12 months FU reverse remodeling in terms of LVESV reduction was significant compared to baseline for both groups (BipolarAFL: −22.2 ± 26.2 ml, $p < 0.001$; QuadPFL: −29.6 ± 31.4, $p < 0.001$) but not significantly different between the groups ($p = 0.48$). Absolute LV-EF improvement was significant in both groups compared to baseline (BipolarAFL: +10.1 ± 7.9%, $p < 0.001$; QuadPFL: +8.1 ± 8.2, $p < 0.001$) but not significantly different between both groups ($p = 0.89$). There was no difference in response rate according to LVESV with 61.1% response rate in BipolarAFL and 60% in QuadPFL ($p = 0.82$) (**Figure 5**).

Improvement of NYHA class was significant for both groups compared to baseline (BipolarAFL: −1.2 ± 1.1 NYHA class, $p < 0.01$; QuadPFL: −1.0 ± 1.0 NYHA class, $p < 0.01$), but was not significantly different between both ($p = 0.42$). Response rate according to NYHA was not different with 66.7% response rate in BipolarAFL and 62.2% in QuadPFL ($p = 0.32$) (**Figure 5**). Shortening of QRS duration was significant in both groups during FU (BipolarAFL: −20.8 ± 8.5 ms, $p < 0.01$; QuadPFL: −21.3 ± 8.2 ms, $p < 0.01$), but was not significantly different between both groups ($p = 0.68$). There has not been a significant change of medication during clinical FU.

Electrical Performance During Follow-Up in BipolarAFL

The median FU time was 48 months (IQR: 44–54 months). A comparison of x-ray after implant and at 12 months showed no movement of electrode or dislodgement in BipolarAFL. During further FU there was no dislodgement either. The final bipolar pacing capture thresholds (PCT) at 0.5 ms were 1.2 ± 0.6 V at implant, 1.2 ± 0.8 V at 3 months, 1.0 ± 0.6 V at 6 months, 1.0 ± 0.6 V at 12 months, 1.0 ± 0.5 V at 24 months, 1.0 ± 0.6 V at 36 months, and 1.1 ± 0.5 V at 48 months. There were no significant changes during the time (implant vs. 48 months $p = 0.41$). Bipolar pacing impedance during FU were 572 ±149 Ohms at implant, 542 ± 157 Ohms at 3 months, 512 ± 109 Ohms at 6 months, 508 ± 159 Ohms at 12 months, 538 ± 99 Ohms at 24 months, 535 ± 121 Ohms at 36 months, and 514 ± 141 Ohms at 48 months. There were no significant changes during the time (implant vs. 48 months $p = 0.18$). Sensing was good at implant 12.4 ± 6.4 mV and stable during FU with 12.5 ± 5.9 mV at 3 months, 12.4 ± 6.0 mV at 6 months, 12.5 ± 5.6 mV at 12 months, 12.5 ± 5.5 mV at 24 months, 12.4 ± 5.5 mV at 36 months, and 12.5 ± 5.4 mV at 48 months. There were no significant changes during the time (implant vs. 48 months $p = 0.78$). PNS did not occur at 8.0 V in chosen pacing configuration during FU. The mean of biventricular pacing was 99.2 ± 3.5% during the observational period.

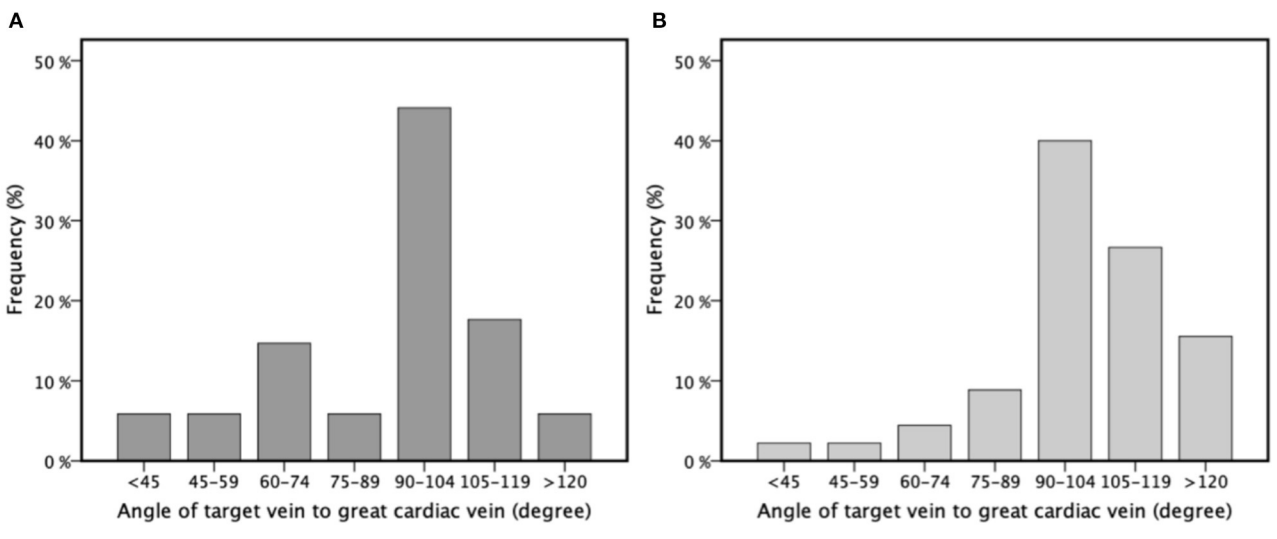


FIGURE 2 | The angle of target vein to the great cardiac vein for bipolar active fixation left ventricular lead **(A)** and quadripolar passive fixation left ventricular lead **(B)** divided into different categories for better visualization presented in percentages of frequency (%) by a bar chart.

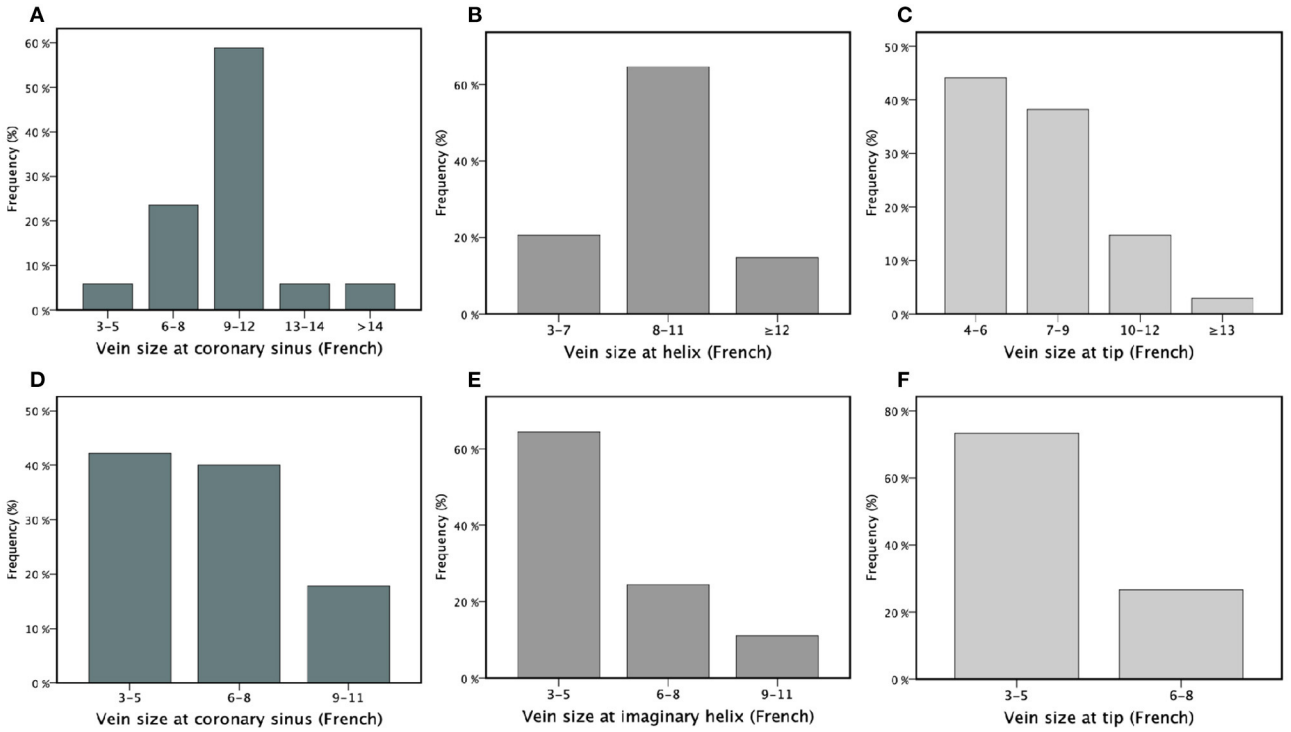


FIGURE 3 | Estimated vein size for bipolar active fixation lead at coronary sinus **(A)**, the helix of the electrode **(B)** and the tip of electrode **(C)** and estimated vein size for quadripolar passive fixation group at coronary sinus **(D)**, imaginary helix position **(E)** of the electrode (36 mm from the tip) and the tip of electrode **(F)** presented in different categories of size in French (x-axis) analyzed in percentages (%) by a bar chart.

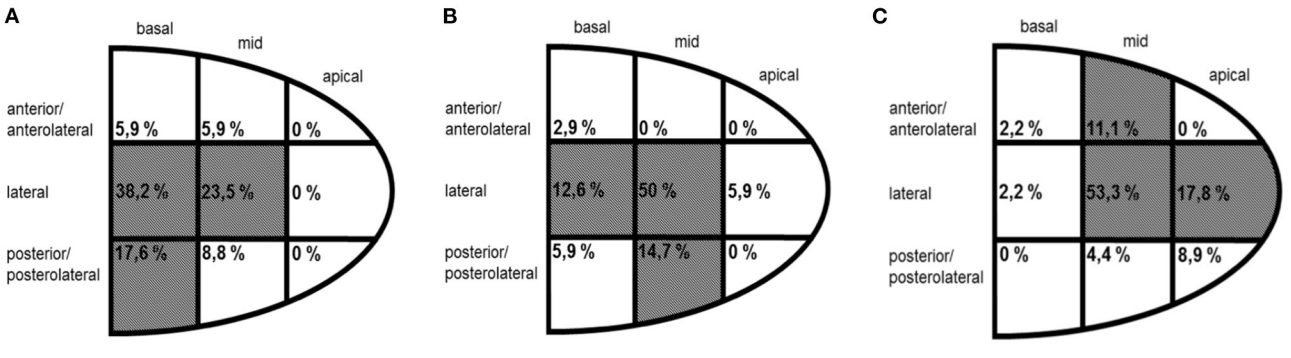


FIGURE 4 | Location of the helix **(A)** and tip **(B)** of bipolar active fixation electrode and the tip of quadripolar passive fixation electrode **(C)** according to fluoroscopy shown in percentages (%) by region of the final position.

Comparison of BipolarAFL and QuadPFL Long-Term Electrical Performance

In QuadPFL there were no lead dislodgments during FU either. At desired pacing area, final programmed PCTs at 0.5 ms were stable during FU (1.4 ± 0.8 V at implant vs. 1.2 ± 0.7 V at 48 months, $p = 0.34$) and not significantly different in average during total FU time compared to BipolarAFL (QuadPFL: 1.3 ± 0.8 V vs. BipolarAFL: 1.1 ± 0.6 V, $p = 0.23$). Pacing impedance was stable in QuadPFL during FU (610 ± 199 Ohms at implant vs. 601 ± 205 Ohms at 48 months FU, $p = 0.51$) and not significantly different in average during FU compared to BipolarAFL (QuadPFL: 603 ± 200 Ohms vs. 531 ± 139 Ohms, $p = 0.34$). PNS at 8 V and even 5 V occurred during FU in six (13%) patients but was resolved with a change of bipolar pacing configuration. This was significantly more often compared to BipolarAFL ($p < 0.05$). The mean of biventricular pacing was 98.9 ± 2.8% during the observational period. This was not significantly different compared to BipolarAFL ($p = 0.53$).

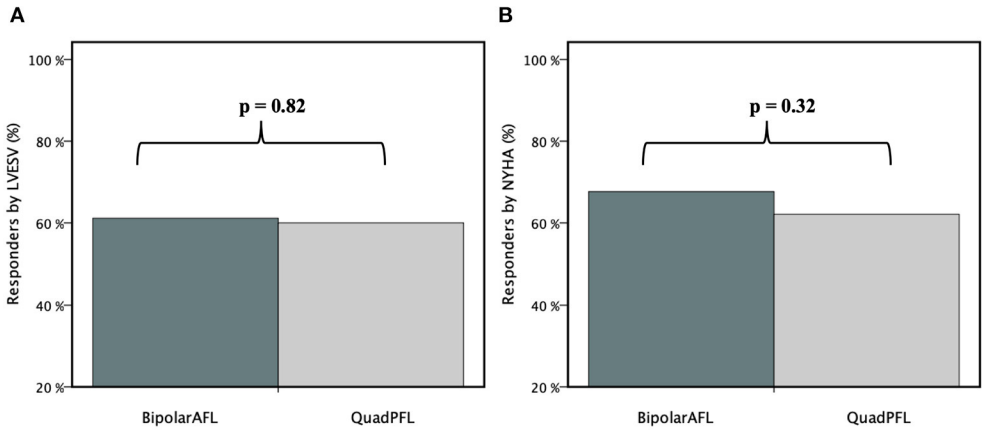


FIGURE 5 | Percentage of responders (%) according to LVESV **(A)** and NYHA **(B)** compared between bipolar active fixation (BipolarAFL) and quadripolar passive fixation (QuadPFL) group by bar graph.

TABLE 2 | Clinical data during follow-up (baseline and 12-month follow-up).

	Bipolar active fixation lead ($n = 36$)	Quadripolar passive fixation lead ($n = 45$)	*p* value
Delta QRSd (ms)	−20.8 ± 8.5	−21.3 ± 8.2	0.68
Delta LVESV (ml)	−22.2 ± 26.2	−29.6 ± 31.4	0.48
Delta LVESV (%)	−20.1 ± 20.8	−21.8 ± 22.0	0.73
Delta LV-EF absolute change (%)	+10.1 ± 7.9	+8.1 ± 8.2	0.89
Delta LV-EF relative change (%)	+29.4 ± 42.4	+24.7 ± 42.4	0.81
Delta NYHA class	−1.2 ± 1.1	−1.0 ± 1.0	0.42
Responder according to LVESV, *n* (%)	22 (61.1 %)	27 (60 %)	0.82
Responder according to NYHA, *n* (%)	24 (66.7%)	28 (62.2%)	0.32

DISCUSSION

The development of quadripolar leads and improved lead design has helped to reduce problems of PNS, high thresholds, and lead stability (9, 10). With the possibility of pacing at a desired area clinical outcome, the rate of hospitalization and mortality has improved as well (11, 12). Attain Performa is a well-established quadripolar lead for which these benefits have been described (13). A problem that remained and evolved to be the main problem in LV lead implant failure, is difficult coronary venous anatomy as reported in a meta-analysis by Gamble et al. (3). Our data suggest that BipolarAFL is helpful in these cases with difficulties like implantation from the right side, large coronary veins and target veins with a less steep angle, where achieving a stable wedge position with QuadPFL could be difficult. Implantation of BipolarAFL was done with ease, repositioning was possible if necessary and procedure times were comparable to QuadPFL. This is in line with data reported by Ziacchi et al. (5). A very small vein diameter however can make it difficult to screw the side helix into the vein wall as reported by us and Johar and Luqman (14). This, however, seems to be the only anatomy in which BipolarAFL is not helpful.

In this study, there were no lead dislodgments during FU in both groups. For passive fixation, quadripolar LV electrodes Erath et al. reported significantly lower rates of dislodgment requiring replacement in a meta-analysis compared to passive fixation bipolar leads, with rates however still ranging between 1 and 9% (10, 15, 16). For 20066 BipolarAFL, no cases of dislodgement after discharge have been reported so far and early dislodgment can be prevented by performing a push-test (5).

A big advantage of quadripolar leads is pacing at a mid/basal part of the vein with the tip being wedged distally. As illustrated in **Figure 4**, we were able to place the tip of BipolarAFL in a mid/basal part for most cases and less often in an apical and anterior position compared to QuadPFL. This is important as Kutyifa et al. demonstrated higher mortality in apical and anterior placed leads (17). Active fixation leads can be an advantage compared to passive fixation leads where insufficient wall contact of pacing poles or high PCT can prevent pacing at the desired area and therefore lead to pacing in more apical or anterior areas.

To determine prognosis, LV reverse remodeling is probably the most important marker (18). Reverse remodeling and response to CRT according to LVESV in our study conforms with larger trials with quadripolar electrodes (19). Clinical data have been collected at 12 months FU as reverse remodeling continues in most patients for 6–12 months and not further afterward (20). Electrical performance of BipolarAFL was good and stable in this long-term FU with chronically low PCTs and in line with previous reported short-to-medium-term FU data (4, 5, 14). The main difference to these studies is the longer electrical FU, which has not been reported before. PNS did occur more frequently in QuadPFL but with the change of bipolar pacing configuration, this could be resolved.

With quadripolar leads, this seems to be more of an issue if modern technology like multisite pacing is desired. Extraction was not necessary during our FU for either type of lead. But even for BipolarAS, cases of easy extractability have been reported (21, 22).

LIMITATIONS

The limitation of our study was the single-center, single-operator, non-randomized, and retrospective study design with a limited sample size. Therefore, proper analysis of lead dislodgment is limited. CRT implants after April 2015 have not been included as the goal was to have comparable groups in the long-term with similar FU duration.

As with all studies involving echocardiography, intra- and interobserver variability is a known issue. As the choice which led to implant was made at implanting physicians' discretion, it remains unclear whether passive fixation leads would have shown high stability in difficult coronary venous anatomy as well. Reported data suggest otherwise, with lead dislodgment rates between 1 and 9% for quadripolar passive fixations leads, but this remains uncertain for our cohort (15). Confounding is an issue as the lead has been chosen at the operator's discretion according to venous anatomy.

By now a quadripolar active fixation electrode (Metronic Attain Stability Quadripolar 4798) has been introduced and showed promising results in initial reports and short-term FU (23). A combination of active fixation, quadripolar lead design, and modern pacing technologies, such as multisite pacing, should be examined as they could lead to improvement in LV reverse remodeling and CRT response in a long-term FU. This technology however has not been available at the time of initiation of our study. Additionally, technologies such as His-bundle pacing or left-bundle branch pacing are other modern alternatives in selected patients where implantation of LV lead is difficult.

CONCLUSION

Bipolar active fixation lead (Medtronic Attain Stability 20066) is a safe and easy implantable LV lead, even in situations with a high risk of lead dislodgement (implantation from the right side, large coronary vein diameter, or less steep target vein angle). It was not associated with the measurable difference in clinical outcome compared to quadripolar passive fixation leads. During this long-term FU reported with a median of 48 months, BipolarAFL enabled pacing at the desired area with no dislodgement, was stable with excellent electrical parameters, and showed a low incidence of PNS. Further prospective, randomized studies with a larger cohort and combination with modern pacing options would be interesting.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the Ruhr University Bochum. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FS, AM, and AK: design of study. FS, HB, DS, AA, PP, and CH: data acquisition. FS, HB, DS, and CH: data analysis. CH, AM, and AK: data interpretation. FS and HB: writing manuscript. AM and AK: revision of manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: AK received speakers honoraria from Medtronic.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Single-Chamber Leadless Cardiac Pacemaker in Patients Without Atrial Fibrillation: Findings From Campania Leadless Registry

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Introduction: Little is known about the clinical performance of single-chamber leadless pacemaker (LLPM) in patients without atrial fibrillation (AF) as pacing indication. The aim of this study was to describe the clinical characteristics of patients who underwent single chamber LLPM implantation at three tertiary referral centers and to compare the safety and effectiveness of the single-chamber LLPM among patients with or without AF.

Materials and Methods: All the consecutive patients who underwent LLPM implantation at three referral centers were analyzed. The indications to LLPM in a real-world setting were described. The study population was divided into two groups according to AF as pacing indication. We assessed the procedure-related complications; moreover, we compared syncope, cardiac hospitalization, pacemaker syndrome, and all-cause death recurrence during the follow-up between patients with and without AF as pacing indication.

Results: A total of 140 consecutive patients (mean age, 76.7 ± 11.24 years, men 64.3%) were included in the study. The indication to implantation of LLPM was permanent AF with slow ventricular response (*n*: 67; 47.8%), sinus node dysfunction (*n*: 25; 17.8%), third atrioventricular block (AVB) (*n*: 20; 14.2%), second-degree AVB (*n*: 18; 12.8%), and first degree AVB (*n*: 10; 7.1%). A total of 7 patients (5%) experienced perioperative complications with no differences between the AF vs. non-AF groups. During a mean follow-up of 606.5 ± 265.9 days, 10 patients (7.7%) died and 7 patients (5.4%) were reported for cardiac hospitalization; 5 patients (3.8%) experienced syncope; no patients showed pacemaker syndrome. No significant differences in the clinical events between the groups were shown. The Kaplan–Meier analysis for the combined endpoints did not show significant differences between the AF and non-AF groups [hazard ratio (HR): 0.94, 95% CI: 0.41–2.16; $p = 0.88$].

Conclusion: Our real-world data suggest that LLPM may be considered a safe and reasonable treatment in patients without AF in need of pacing. Further studies are needed to confirm these preliminary results.

Keywords: leadless pacemaker, atrial fibrillation, sinus node dysfunction, atrioventricular block, effectiveness, safety, complications, syncope

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INTRODUCTION

The leadless pacemaker (LLPM) is a miniaturized, self-contained cardiac pacemaker that emerged as a meaningful alternative to a transvenous pacemaker for single-ventricular pacing in patients at high-infectious risk or with upper limbs venous occlusion or anatomical constraints (1). Permanent atrial fibrillation (AF) with a slow ventricular rate is the most common indication for single chamber LLPM (2); however, nearly one-third of patients selected to receive this therapy were for indications not associated with AF (3). The outcome of LLPM in the real-world setting was associated with a low risk of complications and good electrical performance up to 1 year after implantation compared to a transvenous pacemaker (4). Actually, there are a few data about the clinical performance of LLPM in patients with pacing indication not associated with AF (3) and no data are still available in a real-world setting. The aim of this study was to compare the safety and effectiveness of single-chamber LLPM among patients with or without AF as a pacing indication in a real-world setting.

MATERIALS AND METHODS

The Campania Leadless Registry is an observational real-world multicenter registry that included all the consecutive patients who underwent LLPM implantation from July 2017 to December 2020 at three tertiary referral hospitals in Campania Region—Italy (Monaldi Hospital of Naples, University of Campania "*Luigi Vanvitelli*" of Naples and Umberto I Hospital of Nocera Inferiore). All the patients received Micra transcatheter pacemaker system (Medtronic, Minneapolis, Minnesota, USA) because it was the only available LLPM in Italy at the time of this study. All the procedures were performed by expert electrophysiologists who were trained at a special training laboratory with a hands-on simulator. At implantation, anthropometric, anamnestic, clinical, and intraoperative pacemaker parameters were collected. At each follow-up visit, performed at 1- and 4-weeks post-implantation and every 6 months thereafter, clinical status, pacemaker electric parameters, the occurrence of syncope, cardiac hospitalization, pacemaker syndrome, and survival were assessed. In case of missed follow-up, the patient was contacted by phone; after two unsuccessful phone contact attempts, information on the life status of the patients was collected from the regional healthcare information platform. Informed consent was obtained from all the participants before inclusion in the database. The database and this analysis were approved by the local institutional review committee (ID: 120717).

Outcomes

The outcomes of interest were the LLPM intraoperative data, the perioperative complications, the occurrence of syncope, cardiac hospitalization, pacemaker syndrome, and all-cause death. The implant duration was defined as the time between the femoral vein cannulation and decannulation after implantation of LLPM. The perioperative complications were defined as adverse events that occurred intraoperatively or within 30 days post-operatively. The occurrence of syncope was based on self-reported data. The cardiac hospitalization and all-cause mortality were collected from the regional healthcare information platform. The pacemaker syndrome was defined as the development of either congestive signs or symptoms associated with retrograde conduction during single-chamber pacing or a $\geq$20 mm Hg reduction of the systolic blood pressure, associated with reproducible symptoms of weakness, lightheadedness, or syncope.

Statistical Analysis

Categorical data were expressed as number and percentage, while continuous variables either as a median and interquartile range (IQR) or mean and SD based on their distribution assessed both by the Kolmogorov–Smirnov and the Shapiro–Wilk tests. Between the group differences, for categorical variables, were assessed by the chi-squared test, as the sample size was > 50 subjects, with the application of Yates correction where appropriate. Either the parametric Student's *t*-test or the non-parametric Mann–Whitney *U* test and Wilcoxon signed-rank test were instead used to compare continuous variables, according to their distribution. The Kaplan–Meier analysis was further performed to assess the risk of combined endpoints (syncope, cardiac hospitalization, and mortality) between the two subgroups. A two-sided probability $p < 0.05$ was considered statistically significant. All the analyses were performed using the SPSS statistical software (version 24.0, SPSS Chicago, Illinois, USA) and the STATA 14.0 software (StataCorp LLP, College Station, Texas, USA).

RESULTS

Study Population

A total of 140 consecutive patients (mean age 76.7 $\pm$ 11.24 years, men 64.3%) who underwent LLPM at our referral centers were included in the study. The indication to LLPM implantation was permanent AF with slow-ventricular response (*n*: 67; 47.8%), sinus node dysfunction (*n*: 25; 17.8%), third atrioventricular block (AVB) (*n*: 20; 14.2%), second-degree AVB (*n*: 18; 12.8%), and first-degree AVB (*n*: 10; 7.1%). A total of 96 (68.1%) and 61 (43.6%) patients experienced a history of presyncope and syncope, respectively. The study cohort was further split into two subgroups based on the permanent AF as primary-pacing indication. All the baseline clinical characteristics of the study population are given in **Table 1**.

The non-AF group showed the lower prevalence of hypertension (60.3 vs. 80.5%; $p = 0.009$), anemia (4.1 vs. 19.4%; $p = 0.005$), and higher prevalence of patients who underwent infectious leads extraction (17.8 vs. 4.5%; $p = 0.014$) and dialysis (12.3 vs. 3%; $p = 0.004$) compared with the AF group.

LLPM Implantation Procedure

All the patients underwent a successful implantation procedure according to the standard technique (1). The mean procedure duration time was 45.21 $\pm$ 18.59 min and the mean fluoroscopy time was 9.05 $\pm$ 6.23 min. The non-AF group showed a

TABLE 1 | Baseline characteristics of study population.

	Overall population *n*: 140	AF group *n*: 67	No-AF group *n*: 73	*P*
Age, years	76.7 ± 11.24	78.1 ± 10.8	75.5 ± 11.2	*0.16*
Male, *n* (%)	90 (64.3)	41 (61.2)	49 (67.1)	*0.47*
Hypertension, *n* (%)	98 (70)	54 (80.5)	44 (60.3)	*0.0095*
Diabetes, *n* (%)	43 (30.7)	19 (28.3)	24 (32.9)	*0.56*
COPD, *n* (%)	22 (15.7)	7 (10.4)	15 (20.5)	*0.10*
Dyslipidemia, *n* (%)	70 (50)	34 (50.7)	36 (49.3)	*0.87*
CKD, *n* (%)	28 (20)	9 (13.4)	16 (21.9)	*0.2*
Dialysis, *n* (%)	11 (7.8)	2 (3.0)	9 (12.3)	*0.0042*
Anemia, n, (%)	16 (11.4)	13 (19.4)	3 (4.1)	*0.0046*
Malignancy, *n* (%)	18 (12.8)	10 (14.9)	8 (10.9)	*0.48*
DCM, *n* (%)	30 (21.4)	14 (20.9)	16 (21.9)	*0.88*
CAD, *n* (%)	41 (29.3)	16 (23.9)	25 (34.2)	*0.18*
Pre-syncope, *n* (%)	96 (68.6)	51 (76.1)	45 (61.6)	*0.06*
Syncope, *n* (%)	61 (43.6)	19 (28.3)	42 (57.5)	*0.0005*
Infectious Leads extraction, *n* (%)	16 (11.4)	3 (4.5)	13 (17.8)	*0.0138*

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DCM, dilated cardiomyopathy; CAD, coronary artery disease.

slightly longer procedure time compared with the AF group (49.24 ± 21.56 vs. 43.10 ± 13.23; $p = 0.046$). No differences in LLPM electrical parameters were reported between the two groups (**Table 2**). A total of 7 patients (5%) experienced perioperative complications with no differences between the two groups (**Table 3**). No procedure-related complications led to perioperative death.

Follow-Up

The follow-up data were gathered to 130 patients (77.4 ± 10.9 years; 63.8% males). **Figure 1** shows the study flow chart and the causes of loss to follow-up. The mean follow-up was 606.5 ± 265.9 days with no significant difference between the AF vs. non-AF groups (620.3 ± 259.1 vs. 591.1 ± 274.7 days; $p = 0.5$). The clinical characteristics and pharmacological therapies were stable over time. The pacing mode was a ventricular demand pacing (VVI) at 50 bpm in 79 patients (69.8%) and a rate responsive VVI (VVIR) at 50 bpm in 41 patients (31.5%). The non-AF group showed a higher percentage of ventricular pacing (52 ± 36 vs. 40 ± 29%; $p = 0.002$). The LLPM electrical parameters remained stable over time and did not differ between the two groups (**Table 4**). During the follow-up, 10 patients (7.7%) died; 7 patients (5.4%) reported cardiac hospitalization; 5 patients (3.8%) experienced syncope; no patients showed pacemaker syndrome. No significant differences in the outcome of interest were shown between the groups. The Kaplan–Meier analysis for the combined endpoints did not show significant differences between the AF and non-AF groups (HR: 0.94, 95% CI 0.41–2.16; $p = 0.88$) (**Figure 2**).

DISCUSSION

The results of our multicenter registry showed that more than half of patients with LLPM had a pacing indication not associated with permanent AF. Moreover, there was no difference in LLPM procedure-related complications, when stratified according to the primary pacing indication (AF vs. non-AF); non-AF patients who received LLPM were more likely on dialysis or following infectious leads extraction; no significant difference in syncope recurrence, cardiac hospitalization, and all-cause mortality was shown between the two groups during the follow-up.

Recently, we observed a gradual small increase in single-chamber LLPM implantation rate in patients who do not need resynchronization therapy, more likely in those presenting with AF or a high-anticipated risk of infection (5). This tendency might be explained by the fewer major complications at 1-year follow-up compared with patients with transvenous systems, mainly attributed to a lack of dislodgement and a lower rate of system revision (6, 7).

Despite the operator learning curve, we reported a low number of major intraoperative complications, in particular pericardial effusion, with no remarkable difference from those described by the Micra Transcatheter Pacing (IDE) Trial (1) and the Micra Transcatheter Pacing System Post-Approval Registry (8).

Regarding the pacing indication, 53% of our study population received single-chamber LLPM for sick sinus syndrome or AVB; the extensive use of LLPM in our clinical practice might be related to the high prevalence of risk factors for the cardiac implantable electronic device (CIED) infection among our population, such as diabetes, chronic kidney disease, malignancy, systemic anticoagulation, and prior CIED infection (9, 10).

In patients with sinus node dysfunction and AVB, dual-chamber pacing is recommended over the single-chamber pacing; however, in those in which frequent ventricular pacing is not expected or with significant comorbidities impacting on patients' outcome, single-chamber ventricular pacing is reasonable (11).

TABLE 2 | Intraoperative data and electrical parameters.

	Overall population *n*: *140*	AF group *n*: *67*	No-AF group *n*: *73*	*P*
Implant duration, minutes	45.21 ± 18.59	43.10 ± 13.23	49.24 ± 21.56	*0.0465*
Fluoroscopy time, minutes	9.05 ± 6.23	9.09 ± 5.16	9.24 ± 7.11	*0.89*
R wave amplitude, mV	12.08 ± 4.93	11.32 ± 4.75	12.19 ± 4.84	*0.29*
Ventricular threshold, V	1.25 ± 0.75	1.45 ± 0.63	1.12 ± 1.24	*0.05*
Ventricular impedance, Ohm	792.4 ± 214.4	788.22 ± 228.78	784.58 ± 201.65	*0.92*

TABLE 3 | Perioperative complications.

	Overall population *n*: *140*	AF group *n*: *67*	No-AF group *n*: *73*	*P*
Pericardial effusion, *n* (%)	2 (1.4)	0 (0)	2 (2.6)	*0.19*
Inguinal hematoma, *n* (%)	1 (0.7)	1 (1.5)	0 (0)	*0.29*
Femoral Pseudoaneurysm, *n* (%)	1 (0.7)	1 (1.5)	0 (0)	*0.28*
Device dislocation, *n* (%)	1 (0.7)	0 (0)	1 (1.3)	*0.36*
High ventricular threshold, *n* (%)	2 (1.4)	1 (1.5)	1 (1.3)	*0.92*

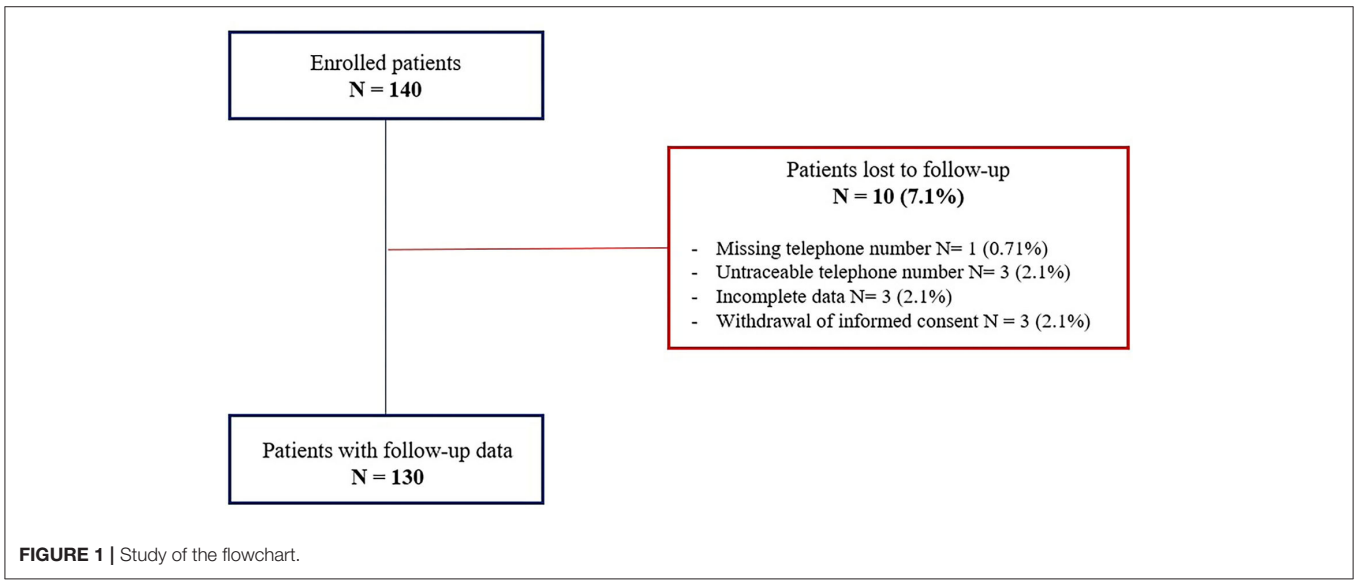

FIGURE 1 | Study of the flowchart.

The single-chamber pacing does not impact the mortality or major cardiovascular events in elderly patients with AVB (12) or with sinus node dysfunction (13); however, it shows an increased risk of AF, and patients with higher percentages of ventricular pacing experienced an increased risk of the heart failure, regardless of pacing mode (14).

In this study, no significant difference in syncope events, cardiac hospitalizations, and all-cause mortality have been shown between LLPM patients with and without AF as primary pacing indication, despite the non-AF group showing a higher percentage of ventricular pacing.

Our real-world data confirm the evidence by Piccini et al. (3) which showed no significant difference in a composite outcome including heart failure, pacemaker syndrome, and syncope events between patients with and without AF indication or history in the IDE trial. Our findings suggest the hypothesis that, in the absence of technical issues, the LLPM could be considered a safe and reasonable treatment in patients without AF in need of cardiac pacing. This approach may constitute an option

TABLE 4 | Electrical parameters and clinical events at follow-up.

	Overall population *n: 130*	AF group *n: 61*	No AF group *n: 69*	*P*
Electrical parameters				
R wave amplitude, mV	13.75 ± 5.04	11.8 ± 5.2	10.9 ± 4.8	*0.32*
Ventricular threshold, V	1.2 ± 0.4	0.53 ± 0.45	0.55 ± 0.37	*0.79*
Ventricular impedance, Ohm	716.9 ± 187.4	707.9 ± 168	711 ± 187	*0.92*
Ventricular pacing (%)	40 ± 29	31 ± 16	52 ± 36	*0.002*
Clinical events				
Syncope, *n* (%)	5 (3.8)	2 (3.3)	3 (4.3)	*0.71*
Cardiac hospitalization, *n* (%)	7 (5.4)	3 (4.9)	4 (5.8)	*0.82*
All-cause death, *n* (%)	10 (7.7)	5 (8.2)	5 (7.2)	*0.83*

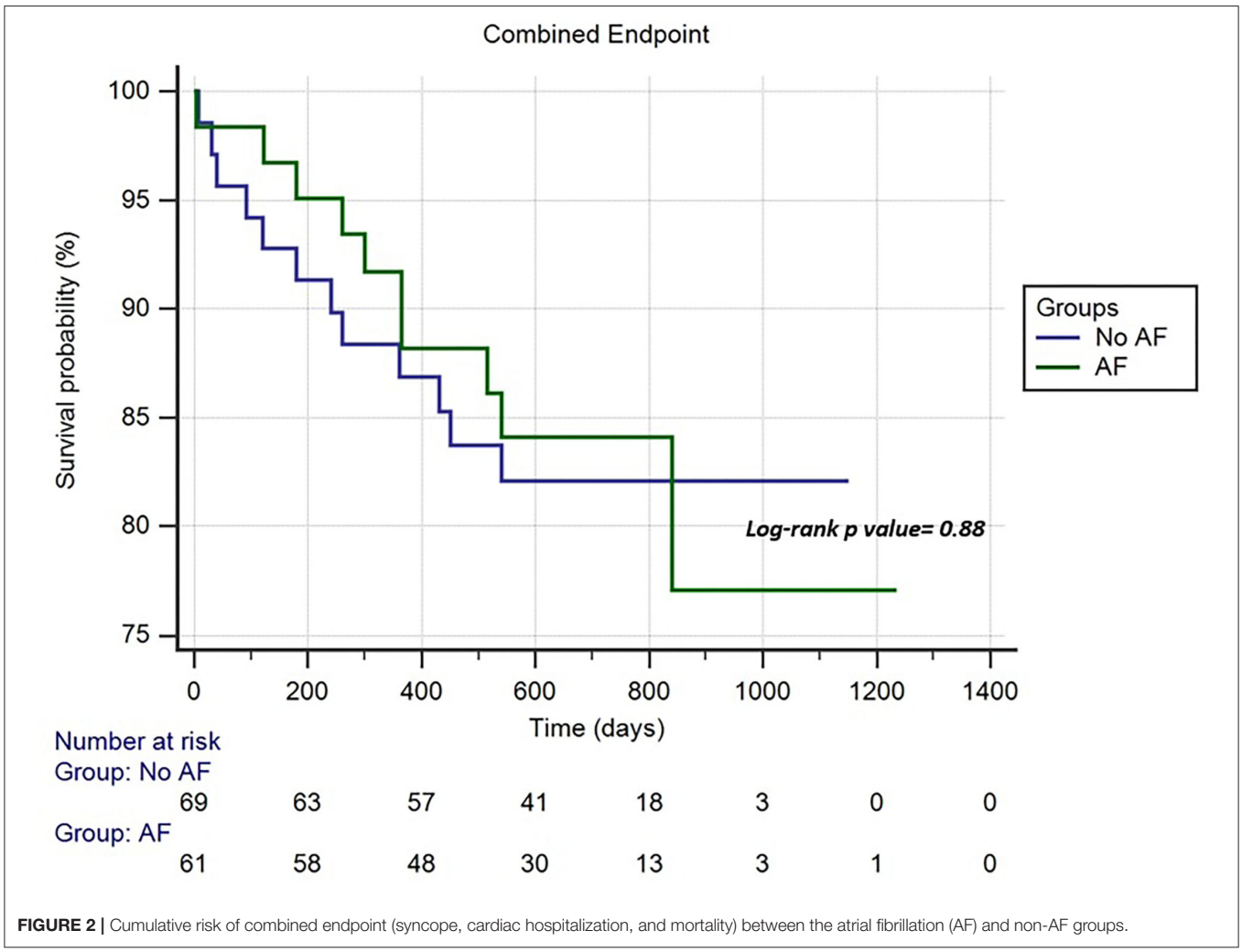

FIGURE 2 | Cumulative risk of combined endpoint (syncope, cardiac hospitalization, and mortality) between the atrial fibrillation (AF) and non-AF groups.

in the selected clinical settings (e.g., high risk, infectious lead extractions, etc.) in order to avoid the risks of *de-novo* dual chambers pacemaker implantation. The LLPM with automated, enhanced accelerometer-based algorithms (15) that provide atrioventricular synchronous pacing should be used for longer follow-up studies, in order to fully understand the potential clinical value of this strategy. Actually, the use of LLPM is still considerably limited by reimbursement issues and the availability of the device in many European countries.

Limitations

Our findings might be affected by several biases. The retrospective design and the non-randomized comparison between the groups limit the strength of our results.

Moreover, the small cohort size, the differences in the baseline clinical characteristics between the groups, and the limited length of follow-up limits represent the additional limitations.

CONCLUSION

More than half of the patients who underwent LLPM in a real-world setting had a pacing indication not associated with permanent AF; this subgroup did not show significant differences in intraoperative major complications and terms of syncope recurrence, cardiac hospitalization, and all-cause mortality compared to those with AF. Our results suggest that LLPM may be considered a safe and reasonable treatment in patients without AF in need of pacing. Further studies are necessary to confirm our preliminary results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Monaldi Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VR and AD designed the study. SD, AR, GM, AP, and VG collected the data. AB, BS, and EA perfomed statistical analysis. VR, PG, and GN wrote the manuscript. All authors read and revised the manuscript.

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ORIGINAL RESEARCH
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N-Terminal Pro-B-Type Natriuretic Peptide in Risk Stratification of Heart Failure Patients With Implantable Cardioverter-Defibrillator

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Background: The prognostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in heart failure (HF) is well-established. However, whether it could facilitate the risk stratification of HF patients with implantable cardioverter-defibrillator (ICD) is still unclear.

Objective: To determine the associations between baseline NT-proBNP and outcomes of all-cause mortality and first appropriate shock due to sustained ventricular tachycardia/ventricular fibrillation (VT/VF) in ICD recipients.

Methods and results: N-terminal pro-B-type natriuretic peptide was measured before ICD implant in 500 patients (mean age 60.2 ± 12.0 years; 415 (83.0%) men; 231 (46.2%) Non-ischemic dilated cardiomyopathy (DCM); 136 (27.2%) primary prevention). The median NT-proBNP was 854.3 pg/ml (interquartile range [IQR]: 402.0 to 1,817.8 pg/ml). We categorized NT-proBNP levels into quartiles and used a restricted cubic spline to evaluate its nonlinear association with outcomes. The incidence rates of mortality and first appropriate shock were 5.6 and 9.1%, respectively. After adjusting for confounding factors, multivariable Cox regression showed a rise in NT-proBNP was associated with an increased risk of all-cause mortality. Compared with the lowest quartile, the hazard ratios (HRs) with 95% *CI* across increasing quartiles were 1.77 (0.71, 4.43), 3.98 (1.71, 9.25), and 5.90 (2.43, 14.30) for NT-proBNP (p for trend < 0.001). A restricted cubic spline demonstrated a similar pattern with an inflection point found at 3,231.4 pg/ml, beyond which the increase in NT-proBNP was not associated with increased mortality (p for nonlinearity < 0.001). Fine-Gray regression was used to evaluate the association between NT-proBNP and first appropriate shock accounting for the competing risk of death. In the unadjusted, partial, and fully adjusted analysis, however, no significant association could be found regardless of NT-proBNP as a categorical variable or log-transformed continuous variable (all $p > 0.05$). No nonlinearity was found, either ($p = 0.666$). Interactions between NT-proBNP and predefined factors were not found (all $p > 0.1$).

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Conclusion: In HF patients with ICD, the rise in NT-proBNP is independently associated with increased mortality until it reaches the inflection point. However, its association with the first appropriate shock was not found. Patients with higher NT-proBNP levels might derive less benefit from ICD implant.

Keywords: N-terminal pro-B-type natriuretic peptide, heart failure, implantable cardioverter-defibrillator, all-cause mortality, appropriate defibrillator shock, restricted cubic spline

INTRODUCTION

Sudden cardiac death (SCD) represents a heavy health burden accounting for 15–20% of all deaths around the world (1, 2). Although advances in resuscitation and defibrillation have been made throughout these years, more than 80% of individuals experiencing SCD still could not survive hospital discharge (3, 4). Most SCD events occur in the community-based population without a prior history of structural heart disease, making it difficult to predict (5). Therefore, preventive strategies have been focusing on the high-risk population, such as those with severe heart disease. An implantable cardioverter-defibrillator (ICD) therapy is the widely accepted effective modality to reduce SCD in current guidelines (6, 7). Nevertheless, the selection of patients is mainly based on New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF) (6, 7). A large number of ICD recipients, especially those with Non-ischemic etiology, do not receive appropriate therapy in the long-term follow-up (8–14). Therefore, there is an urgent need to find an additional indicator to identify patients more likely to benefit from ICD therapy.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a hormone secreted primarily by the ventricular myocardium in response to increased wall stress due to volume expansion and/or pressure overload in heart failure (HF) patients (15). It is an established biomarker of HF diagnosis and prognosis (15, 16). Moreover, it is recognized as a surrogate indicator for all-cause mortality, HF hospitalization, and HF death (16). In addition, it is associated with myocardial fibrosis (17), which is a well-established arrhythmogenic substrate (18–20). Prior studies have proven that it is associated with an increased risk of SCD both in the general population and patients with heart disease (21–27). This makes it a promising biomarker for risk stratification in patients with ICD. However, because it might increase the occurrence of both SCD and pump failure death, it must be systematically evaluated before it can be applied in the decision-making process of ICD implantation.

The purpose of the present study was to explore the role of NT-proBNP in the risk stratification of HF patients with ICD. To address this hypothesis, we tested its relationship with outcomes of all-cause mortality and first appropriate shock in a population of ischemic or Non-ischemic dilated cardiomyopathy (DCM).

Study Patients

In total, 689 consecutive patients with ischemic or Non-ischemic dilated cardiomyopathy disease implanted with ICD (single or dual chamber) between January 1, 2013 and September 1, 2020 were enrolled. Ischemic cardiomyopathy (ICM) was defined as left ventricular systolic dysfunction with marked coronary stenosis (28). Non-ischemic DCM was defined as ventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions and marked stenosis (29). The exclusion criteria were (1) age <18 years ($n = 2$), (2) had previous pacemaker or ICD ($n = 38$), (3) did not fulfill at least one interrogation follow-up ($n = 67$), (4) failed to fulfill the current guideline indication for implantation (6, 7) ($n = 25$), (5) had missing NT-proBNP ($n = 35$), and (6) hospitalized for acute HF within a week ($n = 22$). **Figure 1** shows the flowchart of the selection of the study population. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Fuwai Hospital. All patients gave informed consent.

Data Collection and Device Programming

Information about demographic characteristics, physical examination, comorbidities, NYHA functional class, and medication history was collected from electronic medical records, which were obtained by trained clinicians at admission. ECGs were obtained by experienced physicians. Blood samples from the participants were taken in the fasting state. NT-proBNP levels were measured within 3 days before ICD implant, using an electrochemiluminescence immunoassay (Roche, Basel, Switzerland) with a limit of quantification (LoQ) of 50 pg/ml by experienced operators.

Although devices were programmed at the discretion of treating physicians, shocks were delivered in the ventricular tachycardia/ventricular fibrillation (VT/VF) zone if the arrhythmia was not terminated by anti-tachycardia pacing or initially applied in the VF zone. Device interrogation results were adjudicated by experienced electrophysiologists. Appropriate therapies were defined as therapies delivered for VT/VF.

Outcomes

The primary endpoint was all-cause mortality. The survival status was confirmed with medical death records or telephone calls to the patients' relatives or themselves until June 2021. The secondary endpoint was the first appropriate ICD shock. Patients were required to complete device interrogation every 6–12 months or unintended visits after sensing therapies by ICD until June 2021. The dates for the censoring of survival status and interrogation information were not necessarily the same. The appropriate shock was the only type of ICD therapy selected for

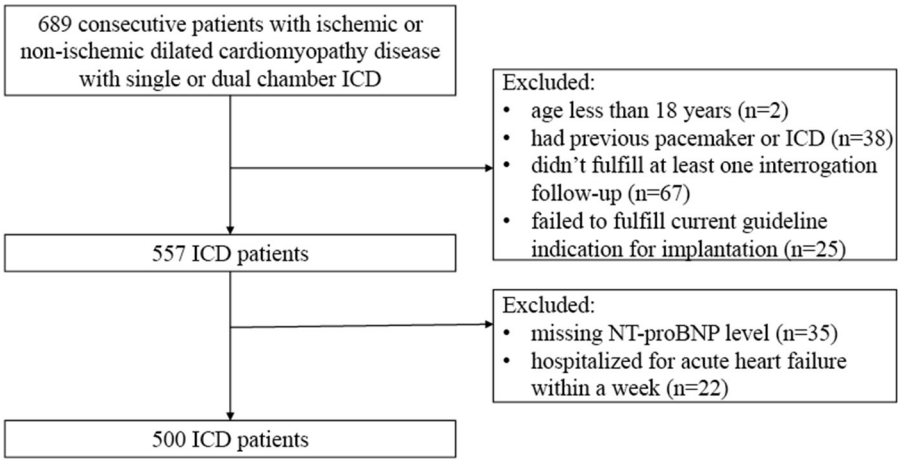

FIGURE 1 | Flowchart on patient inclusion and exclusion.

the secondary endpoint because it was set only to treat the rapid sustained VT or VF (28).

Statistics

Continuous data are expressed as mean ± SD or the median with the interquartile range (IQR) as appropriate; categorical data are presented as frequencies and percentages. Patients were divided into four groups according to baseline NT-proBNP quartiles. In addition, NT-proBNP was $\log_{10}$-transformed for its skewed distribution. Baseline characteristics of the groups were compared with one-way ANOVA for normally distributed continuous variables, the Kruskal–Wallis test for Non-normally distributed continuous variables, and the χ^2 test for categorical variables. Univariable predictors significant at the $p < 0.10$ level were entered into the subsequent multivariable model. Kaplan–Meier curves were constructed for all-cause mortality, and cumulative incidence curves were constructed for the first appropriate shock. The log-rank test and Fine–Gray test were used to investigate the unadjusted differences of primary and secondary endpoints between groups, respectively. Multivariable Cox proportional hazards models were used to assess the association between NT-proBNP quartiles and all-cause mortality. A Fine–Gray subdistribution hazard model accounting for the competing risk of death was used to assess the association between NT-proBNP quartiles and first appropriate shock. To eliminate the collinearity between LVEF and left ventricular end-diastolic dimension (LVEDD), only LVEF was kept in the multivariable model. The proportional-hazard assumption was assessed with Schoenfeld residuals, and no violations were found. The lowest NT-proBNP quartile was served as the reference group. Tests for trends were calculated by including each corresponding quartile as a continuous numeric variable in the models. Event rates were reported per 100 person-years.

Furthermore, we used a restricted cubic spline with 3 knots according to the Akaike information criterion (AIC) to flexibly model the potential nonlinear effects of NT-proBNP with the outcomes of all-cause mortality and first appropriate shock after adjusting for confounding factors significant in univariable analyses. Nonlinearity was tested by the Wald statistics. If this was detected, we calculated the inflection point by a recursive algorithm to calculate the places where the second derivative of the fitted spline equaled to zero.

Several interactions between NT-proBNP quartiles and baseline characteristics were considered. These included age, gender, body mass index (BMI), primary/secondary prevention indication, ICM/DCM, NYHA functional class, presence of atrial fibrillation (AF), creatinine, and LVEF (≤35% or >35%). Interactions between variables were considered significant at the value of $p \leq 0.1$.

Additional sensitivity analyses to evaluate the robustness of our results were also conducted. (1) We replaced LVEF with LVEDD in the multivariable model. (2) We further adjusted for all covariates presented in **Table 1** using stepwise selection by AIC rule with the forced entry of NT-proBNP quartiles.

All analyses were performed using Stata 16.1/IC (StataCorp, College Station, TX) and R 4.1.1 (R Core Development Team, Vienna, Austria), such as the "rm," "mstat," "cmprs," and "survival" packages. A two-sided $p \leq 0.05$ was considered statistically significant if not otherwise specified.

RESULTS

Finally, a total of 500 patients were included. The baseline characteristics of patients according to the NT-proBNP quartiles are presented in **Table 1**. The study population was predominantly male (83.0%). The mean age was 60.2 ± 12.0 years. Median NT-proBNP was 854.3 pg/ml (IQR: 402.0 to 1,817.8 pg/ml). Patients with higher NT-proBNP were more likely to be older, Non-smokers, and have more prevalent DCM, diabetes, and AF (all $p < 0.05$). These patients were more likely to have lower BMI, higher NYHA functional class, lower LVEF,

TABLE 1 | Clinical characteristics of all patients in terms of baseline NT-proBNP quartiles.

Characteristics	All Patients ($n = 500$)	Quartile 1 ($n = 125$)	Quartile 2 ($n = 125$)	Quartile 3 ($n = 125$)	Quartile 4 ($n = 125$)	*P*-value
NT-proBNP (pg/mL)	854.2 [402.0; 1,817.8]	219.2 [122.7; 299.5]	625.3 [515.4; 717.3]	1,198.0 [1,029.7; 1,467.0]	3,121.0 [2,296.0; 4,609.7]	<0.001
log-transformed NT-proBNP	2.92 ± 0.49	2.27 ± 0.28	2.78 ± 0.09	3.09 ± 0.10	3.53 ± 0.19	<0.001
Age (years)	60.2 ± 12.0	57.6 ± 12.5	59.3 ± 11.5	60.7 ± 11.9	63.1 ± 11.7	0.003
Male sex	415 (83.0%)	111 (88.8%)	105 (84.0%)	101 (80.8%)	98 (78.4%)	0.146
Non-ischemic etiology	231 (46.2%)	44 (35.2%)	58 (46.4%)	60 (48.0%)	69 (55.2%)	0.016
BMI (kg/m^2)	25.1 ± 3.5	25.7 ± 3.1	25.9 ± 3.5	24.9 ± 3.4	24.0 ± 3.7	<0.001
Current smoking	263 (52.6%)	74 (59.2%)	72 (57.6%)	63 (50.4%)	54 (43.2%)	0.044
Secondary prevention	364 (72.8%)	97 (77.6%)	97 (77.6%)	89 (71.2%)	81 (64.8%)	0.068
Frequent PVCs	234 (46.8%)	55 (44.0%)	50 (40.0%)	62 (49.6%)	67 (53.6%)	0.143
NSVT	147 (29.4%)	42 (33.6%)	28 (22.4%)	34 (27.2%)	43 (34.4%)	0.121
Dual-chamber ICD	182 (36.4%)	38 (30.4%)	50 (40.0%)	48 (38.4%)	46 (36.8%)	0.412
NYHA class						
I/II	295 (59.0%)	95 (76.0%)	85 (68.0%)	69 (55.2%)	46 (36.8%)	<0.001
III/IV	205 (41.0%)	30 (24.0%)	40 (32.0%)	56 (44.8%)	79 (63.2%)	<0.001
Echocardiogram						
LVEDD (mm)	64.1 ± 9.25	61.1 ± 8.59	63.2 ± 9.29	65.0 ± 8.74	67.0 ± 9.40	<0.001
LVEF (%)	37.4 ± 11.1	42.8 ± 12.0	40.1 ± 11.8	35.3 ± 8.14	31.3 ± 8.12	<0.001
Comorbidities						
AF	136 (27.2%)	19 (15.2%)	26 (20.8%)	37 (29.6%)	54 (43.2%)	<0.001
Hypertension	232 (46.4%)	56 (44.8%)	57 (45.6%)	56 (44.8%)	63 (50.4%)	0.779
Diabetes	120 (24.0%)	27 (21.6%)	24 (19.2%)	27 (21.6%)	42 (33.6%)	0.034
Laboratory tests						
Hemoglobin (g/L)	143 ± 18.6	144 ± 14.2	145 ± 15.7	144 ± 21.2	138 ± 21.4	0.008
Creatinine (μmol/L)	97.5 ± 27.8	89.0 ± 21.0	95.4 ± 23.7	95.6 ± 30.9	110 ± 30.1	<0.001
BUN (mmol/L)	7.50 ± 2.95	6.52 ± 2.39	7.19 ± 2.48	7.46 ± 3.19	8.82 ± 3.20	<0.001
Sodium (mmol/L)	140.0 ± 2.5	140.4 ± 2.0	140.0 ± 2.3	139.7 ± 2.7	140.0 ± 2.8	0.168
Medications						
ACEI/ARB	383 (76.6%)	95 (76.0%)	101 (80.8%)	91 (72.8%)	96 (76.8%)	0.519
Sacubitril/valsartan	33 (6.60%)	12 (9.60%)	9 (7.20%)	6 (4.80%)	6 (4.80%)	0.360
Beta-blockers	428 (85.6%)	114 (91.2%)	105 (84.0%)	105 (84.0%)	104 (83.2%)	0.232
Amiodarone	297 (59.4%)	68 (54.4%)	76 (60.8%)	81 (64.8%)	72 (57.6%)	0.380
Diuretics	383 (76.6%)	77 (61.6%)	94 (75.2%)	104 (83.2%)	108 (86.4%)	<0.001
MRA	364 (72.8%)	92 (73.6%)	90 (72.0%)	90 (72.0%)	92 (73.6%)	0.984
Digitalis	107 (21.4%)	19 (15.2%)	23 (18.4%)	27 (21.6%)	38 (30.4%)	0.023
Statin	296 (59.2%)	82 (65.6%)	71 (56.8%)	74 (59.2%)	69 (55.2%)	0.355

Quartile 1: NT-proBNP ≤ 401.9 pg/ml, Quartile 2: 402.0 ≤ 854.2 pg/ml, Quartile 3: 854.3 ≤ 1,817.7 pg/mL, Quartile 4: ≥ 1,817.8 pg/ml.
Values are presented as mean ± SD, median, and interquartile range (IQR), or frequency (%).
ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; BUN, blood urea nitrogen; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; NSVT, Non-sustained ventricular tachycardia; PVC, premature ventricular contractions.

larger LVEDD, higher blood urea nitrogen and creatinine, and receive diuretics and digoxin treatment at baseline (all $p < 0.05$).

Over a median survival follow-up of 4.1 (IQR 2.8–5.7) years, 106 patients died (incidence 5.61 per 100 person-years; 95% *CI* 4.59–6.78 per 100 person-years). The median interrogation follow-up was 1.7 (IQR 0.8–3.5) years, and 89 patients had their first appropriate shock due to the sustained VT/VF (incidence 9.09 per 100 person-years; 95% *CI* 7.30–11.19 per 100 person-years). The incidence rates of the two outcomes according to NT-proBNP quartiles are shown in **Figure 2**.

Relationship Between NT-proBNP and All-Cause Mortality

Survival curves according to NT-proBNP quartiles are shown in **Figure 3A**. Patients in the 1st and 2nd quartiles had similar survival ($p = 0.211$), whereas patients in the 3rd and 4th quartiles had significantly worse survival than those in the 1st quartile (*HR* = 4.52, 95% *CI*: 1.99–10.25, $P < 0.001$; *HR* = 8.37, 95% *CI*: 3.80–18.42, $p < 0.001$, respectively). After adjusting for confounding factors, such as age, smoking, prevention indication, ICD/DCM, NYHA functional class, BMI, diabetes,

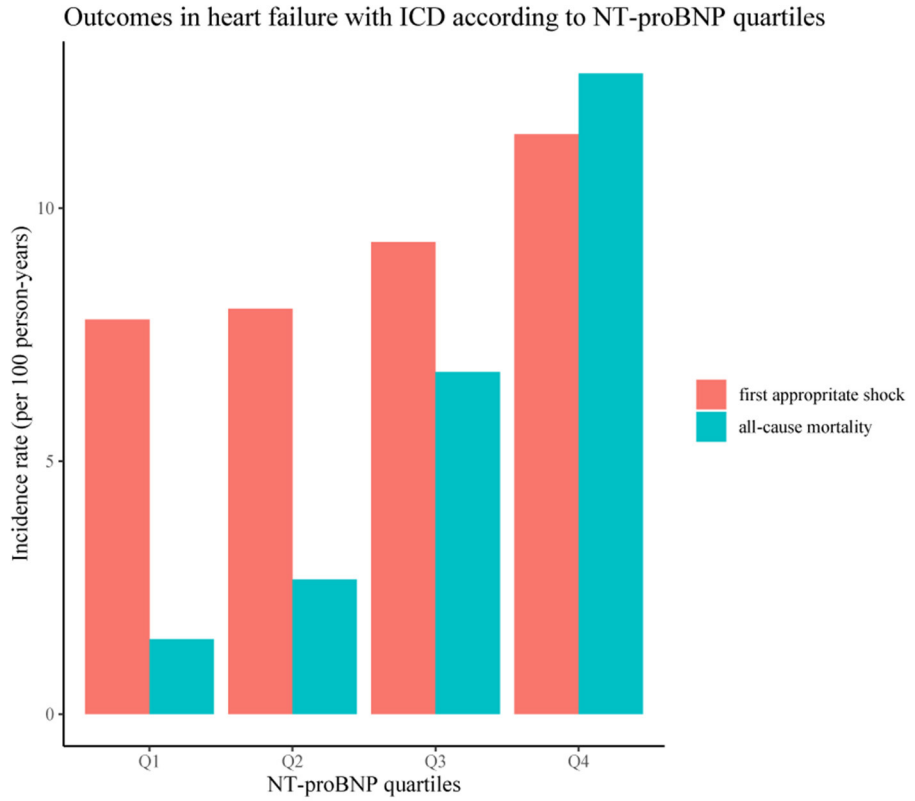

FIGURE 2 | Outcomes in heart failure (HF) with implantable cardioverter-defibrillator (ICD) according to N-terminal pro-brain natriuretic peptide (NT–proBNP) quartiles.

AF, hemoglobin, creatinine, LVEF, and the use of diuretics and digoxin, compared with that in the lowest quartile, the hazard ratios (*HR*s) with 95% *CI* across increasing quartiles were 1.77 (0.71, 4.43), 3.98 (1.71, 9.25), and 5.90 (2.43, 14.30) for NT-proBNP, as shown in **Table 2**. A similar association was also found after adjusting for LVEDD and further adjusting for other variables in **Table 1**. The interactions between NT-proBNP and age, gender, BMI, prevention indication, ICM/DCM, NYHA functional class, AF, creatinine, and LVEF were not statistically significant (all $p > 0.1$).

The restricted cubic spline shown in **Figure 4** displays the association between NT-proBNP and all-cause mortality (p for nonlinearity < 0.001). The risk of all-cause mortality increased rapidly until it reached the inflection point, which was equal to 3,231.4 pg/ml. Above this point, the curve was relatively flat, which meant that the risk would not increase afterward.

Relationship Between NT-proBNP and First Appropriate Shock

Cumulative incidence curves according to NT-proBNP quartiles in **Figure 3B** did not show a difference in time to the first appropriate shock ($p = 0.885$). In the multivariable competing risk analyses shown in **Table 2,** NT-proBNP, regardless of whether it was coded as a categorical variable or log-transformed as a continuous variable, did not show a significant association with the first appropriate shock after adjusting for variables significant in univariable analyses (all $p > 0.05$). Even after further adjusting for other variables using the AIC rule, it was not significant ($p > 0.05$). Additionally, we examined the potential nonlinear association between NT-proBNP and first appropriate shock using the restricted cubic spline, while no such association was found (p for nonlinearity $= 0.666$). The interactions between NT-proBNP and predefined factors were also not significant (all $p > 0.1$). Sensitivity analyses by adjusting LVEDD showed similar results. Instead, LVEDD itself was found to be a significant predictor (per 5 mm increase, subdistribution HR $= 1.13$, 95% *CI:* 1.01–1.26, P $= 0.035$). Overall, we did not observe the association between NT-proBNP levels and the first appropriate shock.

DISCUSSION

The prognostic importance of NT-proBNP has been broadly studied in patients with HF, but remains largely unexplored in HF patients with ICD. In our study, we found that patients with higher NT-proBNP levels had a lower survival probability, however, did not have a higher risk of appropriate shock. Therefore, these patients might derive less benefit from an ICD implant. Our study validated the prognostic importance of NT-proBNP associated with all-cause mortality in previous studies. Nonetheless, our findings raised key questions about the utility of NT-proBNP in the risk stratification of SCD.

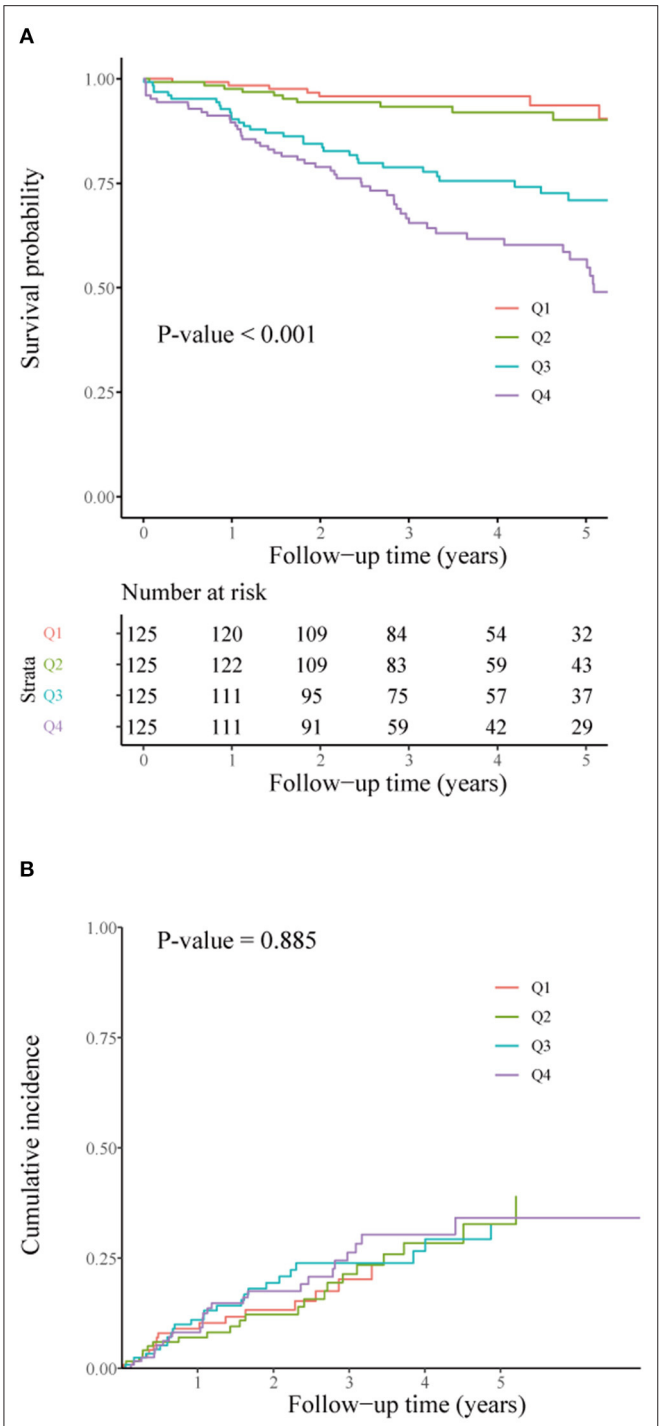

FIGURE 3 | Survival curves for all-cause mortality **(A)** and cumulative incidence curves for first appropriate shock **(B)** according to NT-proBNP quartiles (Q1–Q4). NT-proBNP quartiles were defined as Q1, NT-proBNP ≤ 401.9 pg/ml; Q2, NT-proBNP 402.0 ≤ 854.2 pg/ml; Q3, NT-proBNP 854.3 ≤ 1,817.7 pg/ml; Q4, NT-proBNP ≥ 1,817.8 pg/ml.

According to current guidelines (6, 7), a lot of HF patients implanted with ICDs would not receive appropriate ICD shock in the long-term follow-up (8–11). Consequently, there is an urgent need to find a new risk stratification marker in addition to LVEF and NYHA. Since published data have shown that NT-proBNP has a close relationship with all-cause mortality (15, 16), pump failure death (15, 16), and sudden death in a variety of populations (21–27), it is also expected to be a promising marker for HF with ICD.

As expected, we demonstrated that NT-proBNP conferred an increased risk of all-cause mortality. Nonetheless, particular attention must be paid that our population was comprised of patients with ICD, in which death due to cardiac arrest was greatly prevented (6, 7). Therefore, it could be speculated that the predominant modes of death were pump failure in our setting. In this regard, our finding was consistent with previous studies showing that higher NT-proBNP was associated with an increased risk of HF death (24, 25, 27, 30). To the best of our knowledge, our study is the first to characterize NT-proBNP levels with all-cause mortality using a smooth spline in patients with ICD patients. The spline illustrated the relationship between NT-proBNP and all-cause mortality as a logarithmic curve. This was also in line with our finding that log-transformed NT-proBNP was a significant predictor in the multivariable models. Therefore, it justifies the convention that NT-proBNP should be log-transformed in the data analysis process (18, 22, 24, 27). Furthermore, our results showed that once the NT-proBNP level surpassed the inflection point, the risk of all-cause mortality would not increase further. This might reflect the ceiling effect of NT-proBNP. Unfortunately, most previous studies failed to find this effect (24, 25, 27, 30). Of note, our inflection point might not be suitable for other populations. Nonetheless, it shows a phenomenon that an extremely high NT-proBNP value does not necessarily translate into an extremely high risk of death. This might be explained by the fact that even when the NT-proBNP level is high, it could be considerably reduced when treatments are further intensified in stable patients (15, 31–33). However, we cannot rule out that this finding represented the play of chance. It needs to be replicated in the future.

In contrast with published studies, we failed to demonstrate the connection between NT-proBNP and SCD, which was substituted by appropriate shock in our study. In fact, according to the definition of SCD (34), precise adjudication of SCD was almost impossible except for evidence found at autopsy. In this regard, the endpoint we used might be more accurate to reflect the actual rate of sudden death from a cardiac cause. On the other hand, since NT-proBNP is a surrogate for intracardiac volumes and filling pressures (15, 20, 35), echocardiographic parameters might reflect this nature more directly. Among these, LVEDD was proved to have a positive relationship with increased intracardiac pressures and also to be positively correlated with NT-proBNP (36). A case-cohort study of 418 patients with SCD and 329 controls based on the general population suggested that moderate or severe left ventricular dilation was an independent predictor of SCD (37). Given the strong relationship between NT-proBNP and LVEDD, inference can only be considered robust when two variables are put together in the multivariable model. Otherwise, it might lead to a biased result. However, most studies failed to adjust for LVEDD in their analyses (22, 23, 26,

TABLE 2 | Unadjusted and adjusted hazard ratios (*HR*s) and subdistribution HRs of outcomes.

Outcome	Events, no.	Incidence rate, per 100 person-years	Model 1		Model 2*		Model 3†		Model 4‡	
			unadjusted HR/sdHR# (95% CI)	*P* value	adjusted HR/sdHR# (95% CI)	*P* value	adjusted HR/sdHR# (95% CI)	*P* value	fully adjusted HR/sdHR# (95% CI)	*P* value
All-cause mortality										
NT-proBNP quartile										
1	7	1.48	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
2	14	2.66	1.79 (0.72, 4.43)	0.211	1.77 (0.71, 4.43)	0.223	1.77 (0.71, 4.42)	0.221	1.60 (0.64, 3.99)	0.313
3	32	6.76	4.52 (1.99, 10.25)	<0.001	3.98 (1.71, 9.25)	0.001	4.17 (1.80, 9.63)	<0.001	3.99 (1.74, 9.12)	0.001
4	53	12.66	8.37 (3.80, 18.42)	<0.001	5.90 (2.43, 14.30)	<0.001	6.33 (2.64, 15.14)	<0.001	6.61 (2.92, 14.98)	<0.001
P for trend§				<0.001		<0.001		<0.001		<0.001
P for nonlinearity				<0.001		<0.001		<0.001		<0.0001
log10(NT-proBNP)			5.46 (3.46, 8.61)	<0.001	4.16 (2.32, 7.48)	<0.001	4.40 (2.47, 7.82)	<0.001	5.10 (3.03, 8.57)	<0.001
First appropriate shock										
NT-proBNP quartile										
1	17	7.80	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
2	22	8.01	1.10 (0.58–2.07)	0.769	1.03 (0.54–1.97)	0.938	1.02 (0.53–1.95)	0.952	1.12 (0.59–2.12)	0.738
3	25	9.33	1.23 (0.66–2.29)	0.507	1.10 (0.56–2.14)	0.783	1.14 (0.59–2.19)	0.696	1.28 (0.68–2.43)	0.452
4	25	11.46	1.27 (0.68–2.35)	0.449	1.13 (0.53–2.37)	0.757	1.18 (0.57–2.42)	0.661	1.27 (0.65–2.47)	0.483
P for trend§				0.404		0.729		0.604		0.434
P for nonlinearity				0.751		0.666		0.774		0.771
log10(NT-proBNP)			1.25 (0.80–1.95)	0.334	1.12 (0.64–1.96)	0.688	1.15 (0.67–1.99)	0.608	1.21 (0.74–1.98)	0.443

**Model 2 was adjusted for age, smoking, prevention indication, ICD/DCM, NYHA class, BMI, diabetes, AF, hemoglobin, creatinine, LVEF, and use of diuretics and digoxin.*
†Model 3 was adjusted for age, smoking, prevention indication, ICD/DCM, NYHA class, BMI, diabetes, AF, hemoglobin, creatinine, LVEDD, and use of diuretics and digoxin.
‡ Model 4 was fully adjusted, such as all variables in model 3 and sex, device type, NSVT, PVC, hypertension, BUN, LVEF, use of ACEI/ARB, sacubitril/valsartan, Beta-blockers, MRA, and use of amiodarone and statin. Stepwise regression by AIC rule with the forced entry of NT-proBNP was used.
§P for linear trend was calculated by including each corresponding quartile as a continuous numeric variable.
#The HR and subdistribution HRs were used for the Cox and Fine-Gray models, respectively.
sdHR, subdistribution hazard ratio; other abbreviations as in ***Table 1****.*

27, 38). Furthermore, although NT-proBNP showed significant associations with SCD (22, 38), a cause-and-effect relationship might not exist. A variety of studies have demonstrated that NT-proBNP has a stronger relationship with all-cause mortality and pump failure death than SCD (23–25, 27) by showing a higher *HR*. Clinical models, including NT-proBNP, to predict pump failure death also showed better discrimination ability than to predict SCD (24, 38). These findings indicate that NT-proBNP might not have a direct effect on SCD. Conversely, it might be just a marker of HF progression (39). As a result, the Danish study to assess the efficacy of ICDs in patients with non-ischemic systolic heart failure on mortality (DANISH) trial found that only patients in the subgroup of NT-proBNP <1,177 pg/ml had an increased benefit of ICD implant (10). Instead, we found that LVEDD was a predictor of SCD, consistent with a previous meta-analysis that included four relevant studies (40). This finding further indicates that NT-proBNP might not be a proper predictor for SCD. In conclusion, a single NT-proBNP level should not be used as a risk stratification tool for SCD.

Our finding was contrary to an analysis of 342 patients with primary prevention ICD after a median follow-up of 35 months (20). The authors found that NT-proBNP was not associated with its combined outcomes including death from any cause while it was positively associated with appropriate ICD therapies. An earlier study also revealed that NT-proBNP was associated with both appropriate ICD therapies and total mortality (19). In contrast, our finding was consistent with the risk prediction model developed by Bergau et al. (41), in which NT-proBNP was a predictor of all-cause mortality, while it was not a predictor of ICD shock (42). Disparities between these studies might be explained by their population, conduction, and slightly different definitions of endpoints. Most importantly, these studies failed to handle the Non-normality of NT-proBNP properly, where the first two simply dichotomized it while the third treated it as a continuous normal distribution variable. In this regard, their conclusions were less reliable than ours.

Our study has some limitations. First, the mean follow-up duration of shock status was less than that of survival status. It might undermine the power of our analysis. However, it is comparable with other studies (19, 23) dedicated to solving this hypothesis. Moreover, the follow-up period does not have an influence on the *HR* in the proportional hazards model in the

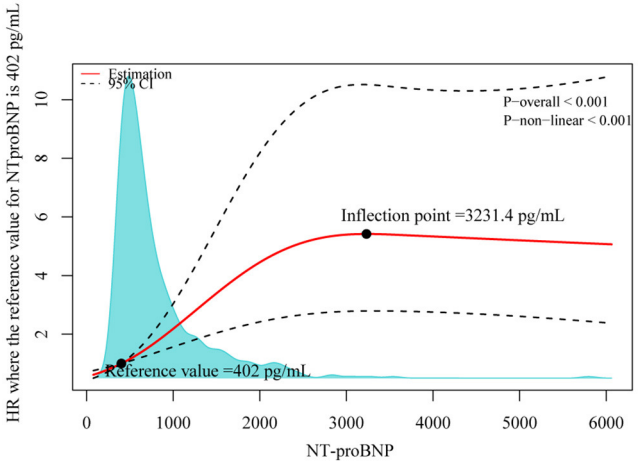

FIGURE 4 | Distributions of NT-proBNP in the overall population and adjusted hazard ratios (*HR*s) of all-cause mortality according to NT-proBNP levels. This plot demonstrates the nonlinear relationship between baseline NT-proBNP levels and the risk of all-cause mortality. A single inflection point was found at 3,231.4 pg/ml. Increases in NT-proBNP from 0 to 3,231.4 pg/ml were associated with a rapid increase in mortality risk but further increases in NT-proBNP >3,231.4 pg/mL were not associated with an increased risk (p for nonlinearity < 0.001). The dotted line indicates the corresponding 95% *CI*s. The 25th percentile of NT-proBNP (402.0 pg/ml) was set as a reference. A density plot is also drawn to show the distribution of NT-proBNP.

absence of time-varying variables (43). Second, we only explored the baseline effect of NT-proBNP instead of repetitive levels. Dynamic changes in NT-proBNP levels and echocardiography parameters might provide incremental information on prognosis (30–33, 44). For example, an improvement in LVEF was associated with reduced ICD therapy and lower mortality (44). However, due to the retrospective nature of our study, it is hard to strictly choose unified timepoints to define serial change. Nonetheless, our study demonstrated that a single baseline NT-proBNP level was a predictor of death, which is easier to interpret and use in clinical setting. Third, our endpoint did not include anti-tachycardic pacing, which might also be triggered by fatal arrhythmic events. In fact, the inclusion of anti-tachycardic pacing is not proper because it was mainly designed for treating hemodynamically stable, slower rate ventricular tachyarrhythmia. As a result, only appropriate shock was included as the endpoint.

CONCLUSION

We conducted a thorough exploration of the association of NT-proBNP with all-cause mortality as well as the first appropriate shock by restricted cubic spline analysis. We found increasing NT-proBNP levels were related to an increased risk of death with a ceiling effect at 3,231.4 pg/ml, but not related to the first appropriate shock. Therefore, patients with higher NT-proBNP might derive less benefit from ICD implant. It still needs further investigation to confirm our results.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Fuwai Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WH, YD, SZ, H-XN, X-HC, MG, and CC contributed to conception and design of the study. YD, N-XZ, XL, M-SC, S-JC, and HH organized the database. YD and M-SC performed the statistical analysis. YD wrote the first draft of the manuscript. WH revised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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Antibiotic-Eluting Envelopes for the Prevention of Cardiac Implantable Electronic Device Infections: Rationale, Efficacy, and Cost-Effectiveness

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Infections related to cardiac implantable electronic devices (CIED) are associated with significant morbidity and mortality. Despite optimal use of antimicrobials and other preventive strategies, the incidence of CIED infections is increasing over time leading to considerable costs to the healthcare systems. Recently, antibiotic-eluting envelopes (AEEs) have been introduced as a promising technology to prevent CIED infections. This review will address the current evidence on stratification of CIED infection risk, present the rationale behind AEE, and summarize the currently available evidence for CIED infection prevention as well as demonstrate the cost-effectiveness of this novel technology.

Keywords: cardiac implantable electronic device, infection, pacemaker, cardiac resynchronization therapy, implantable cardioverter defibrillator, antibiotic eluting envelope, cost-effectiveness

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INTRODUCTION

Since the initial experience with electronic pacemakers in the late 1950s and the introduction of implantable cardioverter-defibrillators in the 1980s, cardiac implantable electronic devices (CIEDs) have become routine therapy of numerous arrhythmias and conduction disturbances. The numbers and complexity of CIED implantations continue to rise worldwide (1), especially with the introduction of cardiac resynchronization pacemakers (CRT-P) and defibrillators (CRT-D) (2) which has been accompanied by an increasing rate of complications. Device infection is an important factor for increased morbidity and mortality among CIED recipients (3). The rate of CIED infections has been shown to increase over the years (1, 4). Among the possible causes are increasing complexity of implanted devices, increasing comorbidities, and longer life expectancy with the need for multiple generator replacements and lead revisions.

Although various preventive strategies have been proposed to reduce these serious and costly CIED complications (5) there is a significant discrepancy in the implementation of the different preventive strategies worldwide (6). The rules of antisepsis and preoperative antibiotic prophylaxis have been shown to be highly effective and are recommended by consensus papers and guidelines (5, 7). The introduction of subcutaneous ICDs and leadless pacemakers may also contribute to a reduction of CIED infections but are applicable only in a selected patient population. The implantation of antibiotic-eluting envelopes (AEE) currently presents a promising strategy to prevent CIED infections in patients at risk for device infections including those not suitable for the currently available leadless or subcutaneous technology. As such, AEE use has been recommended by recent guidelines and consensus statements (5, 7).

The aim of this review is to summarize the currently available data on risk stratification of CIED infections, present the rationale behind AEE, and summarize the available evidence on the benefit of AEEs for the prevention of CIED infection including its cost-effectiveness.

EPIDEMIOLOGY AND MICROBIOLOGY OF CIED INFECTIONS

Device-related infections, ranging from 1 to 7% depending on the type and complexity of the implantation (2, 8, 9), are among the most devastating complications of CIED implantations resulting in significant morbidity and mortality (3, 10). Data from the US National Inpatient Sample Database encompassing 4,144,683 device-related procedures from 2000 until 2012 demonstrated a significant rise in the infection rates over time from 1.45% to 3.41% with the highest increase for CRT-P/D devices (1). This contrasts with recent randomized studies reporting much lower infection rates in the range of 0.6–1.3% (3, 9, 11). In addition, very recent real-life, nonrandomized data demonstrates infection rates comparable to that reported in the randomized trials (12, 13). A study by Lee et al. reported 7.2% in-hospital mortality and 25.3% mortality at 1 year (3) among 387 patients following lead extraction for CIED infection. In contrast, more recent retrospective data from a single center study demonstrate lower 30-day mortality rates following transvenous lead extraction (due to CIED infection in 93% of the studied population) (14). The trend for increased mortality despite successful infection eradication was preserved at 3 years as reported by Sohail et al. (10).

There are two basic mechanisms of CIED infections: contamination during implantation (15) and bloodstream infection (16). The most common manifestation of CIED infection is pocket infection (9, 16). In the most typical clinical scenario (due to contamination) the pocket infection develops in the first 12 months following implantation although skin erosion late after implantation can also be seen (16, 17). The infection spreads along the leads and eventually causes systemic infection resulting in device-related endocarditis. Bacteremia due to remote infectious foci (e.g., as a result of contaminated vascular catheters, surgical site infection, septic thrombophlebitis, etc.) leads to direct lead seeding which later progresses to systemic infection usually leaving the pocket intact.

The microbiology of CIED infections includes mainly Gram-positive bacteria (70–90% of the isolates) some of which are normally non-pathogenic. The latter are most commonly coagulase-negative staphylococci (mainly *Staphylococcus epidermidis*). *Staphylococcus aureus* is another commonly isolated bacterium in cases of pocket infection (especially in early cases); it is also the most common cause of bacteremia (18–22). Methicillin-resistant staphylococci have been reported to be the underlying cause in almost half of all staphylococcal CIED infections (18). Gram-negative bacilli account for about 9% of the infections while fungi are rare (22).

IDENTIFYING HIGH-RISK PATIENTS

The highest benefit from any preventive measure is projected to the population at highest risk. Therefore, estimating infection risk in each patient is of utmost importance to identify the CIED recipients where more aggressive preventive measures should be taken to reduce infection rate. Risk factors associated with higher CIED infection risk can be grouped into patient-related, procedure-related, and device-related (**Table 1**). Among the numerous patient-related factors, end-stage renal disease, prior CIED infection, advanced age, and preprocedural fever are associated with the highest infection risk (5, 23, 24). Procedural factors associated with greatest risk are early (<30 days) reintervention, procedure duration >1 h, pocket hematoma, and system revision/lead revision, upgrade or generator replacement (5, 23). Importantly, there is randomized data on the impact of hematoma formation on the CIED infection rate. The BRUISE CONTROL INFECTION study included 659 patients with CIED infection from the original study population and demonstrated that development of hematoma was associated with a more than 7-fold increased risk of infection (HR 7.7, 95% CI 2.9–20.5) within 1 year follow-up (27). Another very recent study analyzed the WRAP-IT population ($N = 6{,}800$ participants) and demonstrated a 2.2% incidence of hematoma 30 days after the implantation (26). The risk for CIED infection in patients with hematoma was 11-fold higher (HR 11.3, 95% CI 5.5–23.2) vs. uncomplicated cases. Device-related factors mainly include system size and complexity. Of these, implantation of CRT devices, the presence of more than two leads, and high energy devices are associated with increased infection risk, which has been corroborated by many studies. In one large Danish registry including 97,750 patients, 1,827 developed CIED infection. There was a significantly increased infection risk in patients with complex devices with hazard ratios (HR) of 1.26, 1.67, and 2.22 for ICD, CRT-P, and CRT-D systems (multivariate analysis, $P < 0.002$ for all entries), respectively, compared to conventional pacemakers (28). Higher infection rates were also reported in an observational study of patients implanted with ICD and CRT-D vs. pacemakers (29). Moreover, randomized data from the PADIT study demonstrated the importance of the procedure type as a risk factor for CIED infection (25). In that analysis, implantation of CRT and ICD as well as revisions/upgrades were associated with an increased risk for CIED infection OR 1.77 (1.09–2.87), 2.73 (1.72–4.31), and 4.01 (2.62–6.13), respectively ($P < 0.02$), for all comparisons. A very recent analysis of the randomized WRAP-IT trial provides firm evidence on the risk for CIED infection after a secondary procedure (30). Among risk factors, device type (CRT-P/D vs. ICD), number of previous procedures, history of atrial arrhythmia, geography (outside North America and Europe), procedure duration, periprocedural antithrombotic therapy, and device implant location were important risk factors.

Development of risk score systems to stratify CIED recipients may be a promising tool for better identification of patients at low and high risk. One of the first attempts to create and implement a risk scoring system was by Mittal et al. who identified 7 clinical variables included in a risk score system ranging from 0 to 25 by using retrospective observational data from 2,981 patients

TABLE 1 | Major risk factors for CIED infections.

Risk factors	Odds ratio
Patient-related factors	
End stage renal disease	8.73
Prior CIED infection	7.84
Age ≥ 75 years	5.93
Fever prior to implantation	4.27
Immunosuppression	3.44
Renal failure	1.45*-3.02
COPD	2.95
NYHA class ≥ 2	2.47
Skin disorder	2.46
Immune compromise	2.28*
Malignancy	2.23
Diabetes mellitus	2.08
Heparin bridging	1.87
Congestive heart failure	1.65
Oral anticoagulation	1.59
Device related factors	
Epicardial leads	8.09
Abdominal pocket	4.01
CRT	2.73*
Two or more leads	2.02
ICD	1.77*
Dual chamber device	1.45
Procedure-related factors	
Reintervention < 30 days	16.29
Procedure duration > 1 h	13.96
Haematoma	11.3[§]-4.95
Revision or upgrade	6.46-4.01
Lead repositioning	6.37
Replacement	4.93
Two or more prior procedures	3.43*
Inexperienced operator	2.85
Temporary pacing	2.31
Prior procedure	1.51*

CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease, CRT, cardiac resynchronization therapy; h, hour; ICD, implantable cardioverter defibrillator.

References marked with asterisks are randomized controlled trials.

Figures taken from previously published non-randomized data by Polyzos et al. (23), Sławek-Szmyt et al. (24) AND to randomized data from Birnie et al. [*] (25) and Tarakji et al. [§] (26).

(29). The infection risk increased significantly from the low-risk group (score 0–7, 1% infection rate) to the medium-risk group (score 8–14, 3.4% infection rate) and to the high-risk group (score ≥15, 11.1% infection rate). Another scoring system, including 10 clinical variables has been proposed by Sharriff et al. (31). It was later modified and was recently demonstrated to identify high CIED infection risk in 1,391 patients undergoing first-time implantation. (32). In this retrospective study Shariff score ≥ 4 was associated with more than three-fold increased risk of CIED infection–RR 3.20 (1.29–12.59), $P = 0.029$. Kolek et al. also proposed a scoring system consisting of several clinical variables known to be associated with CIED infection risk (33, 34). The recently developed PADIT risk score system (25) identified five independent predictors: prior procedure (P), age (A), depressed renal function (D), immunocompromised (I), and procedure type (T). The score, ranging from 0 to 15 points, was used to group patients into low (0–4 points), intermediate (5–6 points), and high (≥7 points) risk groups with hospitalization rates due to CIED infection of 0.51, 1.42, and 3.41%, respectively. The predictive value of the PADIT risk score has recently been validated in a large real-world dataset comprising 54,042 procedures where each unit increase in PADIT risk score was associated with 28% increase in infection risk (35). Very recently Boriani et al. have also introduced a scoring system (RI-AIAC score) based on real-life registry data including 2,675 patients (13). They have identified three major clinical characteristics associated with increased CIED infection risk and have created a 5-point scoring system. The latter was tested for predictive ability in the study population and was compared against the PADIT, Shariff and Kolek scores in that regard. Results demonstrated a modest predictive ability of RI-AIAC score with a C-index of 0.64 (0.52–0.75) and of PADIT score with a C-index of 0.64 (0.53–0.76) while the other two risk scores were not able to predict infectious outcome in this population.

ANTIBIOTIC ELUTING ENVELOPES: TECHNOLOGY

Early versions of AEEs consisted of non-absorbable polypropylene mesh, but this design was associated with significant pocket fibrosis and was therefore abandoned. There are currently two absorbable CIED envelope devices on the market. One of them (CanGaroo-G™, Aziyo Biologics, Silver Spring Inc, MD, US) is made from a decellularized and non-crosslinked extracellular matrix produced from porcine intestinal submucosa. That device does not possess antibiotic-eluting properties *per se* but can be impregnated with gentamycin prior to implantation (36). This ensures a peaking early antibiotic release and a stable level of the antibacterial agent for up to a week (36). Animal data has shown the lack of bacterial growth in device pockets inoculated with six different microbial species and exposed to gentamycin-impregnated AEEs. In this experiment, local gentamycin concentrations remained stable up to 7 days (37). The other commercially available envelope (TYRX™; Medtronic, Inc. Monmouth Junction, NJ, US) is made of a synthetic mesh of glycolide, caprolactone, and trimethylene carbonate absorbed in the body over a nine-week period. Both envelopes can stabilize the CIED in the pocket and reduce migration and erosion. However, only TYRX™ provides true antibiotic elution and will be discussed further on. The synthetic mesh is coated with an absorbable polyacrylate polymer that carries minocycline and rifampin and delivers them locally in the tissues over seven days. Both antimicrobials are active against Staphylococcus spp. (38). Rifampin has been shown to be active against *Staphylococcus epidermidis* in the

biofilm where many other antibiotics are ineffective (39). The combination of minocycline and rifampin has been shown to have additive antibacterial effects on resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) (40). *In vitro* studies have shown the antimicrobial activity of TYRX™ against many bacteria such as MRSA and methicillin-sensitive *Staphylococcus aureus* and *Staphylococcus epidermidis* as well as *Escherichia coli (41).* In an animal model of CIED implantation, TYRX™ effectively reduced infection after bacterial inoculation of the pocket (42). This AEE comes in two sizes: medium (designed for pacemaker implantations) containing 8.0 mg rifampin and 5.1 mg minocycline and large (designed for ICD implantation) with 11.9 mg rifampin and 7.6 mg minocycline (41).

EVIDENCE FOR THE BENEFIT OF ANTIBIOTIC ENVELOPES

The initial studies assessing efficacy of AEE were conducted with the older and nonabsorbable polymer design. One of the first publications including 624 patients undergoing PM, ICD, or CRT-D implantation showed low overall incidence of CIED infections: 0.48% [95% CI 0.17–1.40 (43). The lack of an active comparator makes it difficult to draw firm conclusions on AEE efficacy. A subsequent observational study demonstrated lower infection rates with AEE−0.4 vs. 3% in the control group (OR 0.13, 95% CI 0.02–0.95, $P = 0.04$) (33). This difference persisted in the propensity-matched cohort (OR 0.09, 95% CI 0.01–0.73, $P = 0.02$). The same group conducted another single center retrospective cohort study with similar outcome (34). After a minimum follow-up of 300 days, CIED infection rates were 0% for the TYRX™ group, 0.3% for the nonabsorbable AEE group, and 3.1% in the control group ($P = 0.03$ and 0.002 vs. controls, respectively). There was no difference in the infection rates between the two AEE groups. A larger retrospective observational study included 2,890 patients undergoing CIED implantation of whom 275 received an AEE (29). Propensity-matched analysis demonstrated a significantly lower infection rate at 6 months in the patients implanted with AEE 1.1 vs. 3.6% in the standard-of-care group ($P = 0.048$). The reduction in CIED infections was more expressed in the higher-risk population. In a single center observational study Shariff et al. also demonstrated significantly lower infection rates in AEE recipients−0 vs. 1.7% in the patients at similar risk not receiving the AEE ($P = 0.006$) (31). In contrast, one small retrospective study reported higher rates of major infections in AEE recipients: 5.4 vs. 1.1% in the standard-of-care group ($P = 0.048$) (44). However, the patients receiving AEE in this study had higher rates of chronic corticosteroid use, higher rates of replacement or revision, and were more frequently implanted with systems requiring >2 intra-cardiac leads. The Citadel and Centurion studies represent two multicenter prospective non-randomized registries enrolling patients undergoing CIED replacement or upgrade of an ICD (Citadel) or CRT (Centurion) with the use of a non-absorbable AEE (45). Among the studied population major CIED infection occurred in five patients (0.4%), significantly lower than the benchmark infection rate of 2.2% for these high-risk groups ($P = 0.0023$). A very recent two-center observational cohort study included 1,943 patients with CRT undergoing reoperation for replacement, upgrade, or revision who were followed up for a maximum of 2 years (46). An AEE was implanted in 736 patients (38%) with significantly more risk factors for CIED infection. The risk for CIED infection necessitating system extraction was reduced by 48% in the patients receiving an AEE (HR 0.52, 95% CI 0.30–0.90, $P = 0.021$).

The only randomized trial assessing the benefit of AEE in patients undergoing device implantations is the WRAP-IT trial, which included 6,983 patients randomized to AEE vs. standard of care (41). The primary endpoint was a major CIED infection in the 12 months following the operation. Patients included were those with increased risk of CIED infection: 1. Implantation of a *de novo* CRT-D; 2. Generator replacement or an upgrade of a previous implanted PM, CRT-P, ICD, or CRT-D; and 3. Pocket revision of an existing PM, CRT-P, ICD, or CRT-D. Certain patients with very high risk were excluded (e.g., those with previous pocket intervention in the previous 365 days, patients on dialysis on chronic immunosuppressive therapy, or those with previous CIED infection within 12 months). The study demonstrated a 40% reduction in major infections occurring in 0.7% of patients receiving TYRX™ vs. 1.2% in controls (HR 0.60, 95% CI 0.36–0.98, $P = 0.04$) (9). The positive outcome was entirely driven by the lower rate of pocket infections which comprised 75% of all major events–0.4 vs. 1% in the control group (HR 0.39, 95% CI 0.21–0.72). Subgroup analysis demonstrated a significant reduction in major CIED infection in patients receiving high-power devices (ICD and CRT-D) (HR 0.51, 95% CI 0.29–0.90); no difference was observed in the group receiving low-power devices (CRT-P and PM) (HR 1.02, 95% CI 0.236–2.02). The benefit of TYRX™ was sustained during longer term follow-up (mean 21 ± 8.3 months) with a persistent reduction in CIED infections to 1.3% in the AEE group vs. 1.9% in the control group (HR 0.64, 95% CI 0.41–0.99) (47). Further analyses of the WRAP-IT population demonstrated a more than 11-fold higher risk of major CIED infection in patients with pocket hematoma and without the AEE (26). In patients who received the AEE and later developed pocket hematoma the risk was 82% lower (HR 0.18; 95% CI 0.04–0.85%, $P = 0.03$) and the infection rate was comparable to those without hematoma.

In a recent meta-analysis summarizing six major observational and randomized studies comprising 11,897 patients (5,844 receiving the envelope) the AEE was associated with a 66% relative risk reduction of major CIED infections in high-risk patients (RR 0.34; 95% CI 0.14–0.86, $P = 0.02$) (48). A subgroup analysis including only high-risk patients demonstrated that the AEE use was associated with a 74% reduction in the relative risk for major CIED infection (RR 0.26, 95% CI 0.08–0.85, $P = 0.03$) and that there was no difference in the risk when the studies enrolling any risk patients were analyzed (RR 0.53, 95% CI 0.06–4,52, $P = 0.56$). A summary of all the available evidence on efficacy of AEE is presented on **Table 2**.

TABLE 2 | Summary of the studies on efficacy of antibiotic-eluting envelopes.

Authors	Year	Study design	Number of patients, AEE group/ comparator group	Envelope type	Follow-up duration	Patient population	Main results	Devices
Bloom et al. (43)	2011	Retrospective	624/no comparator	Non-absorbable	1.9 ± 2.4 months	Consecutive initial implantation or revision/replacement procedures	Low overall incidence of CIED infections: 0.48%	PM, CRT-D, ICD
Kolek et al. (33)	2013	Observational	260/639	Non-absorbable	Minimum 90 days	Prospectively determined criteria for AE implantation	Significant benefit of AEE (OR 0.13, 95% CI 0.02-0.95, $P = 0.04$)	PM, CRT-D, ICD
Mittal et al. (29)	2014	Retrospective	275/275 (propensity matched controls)	Non-absorbable	Minimum 6 months	Single centre study on initial implantations, generator replacement or system upgrade	Lower infection rates in the AEE group vs controls: 1.1% vs. 3.6% ($P < 0.048$).	PM, CRT-D, ICD
Kolek et al. (34)	2015	Retrospective	488/636	Non-absorbable and absorbable	Minimum 300 days	$\geq$ 2 risk factors for CIED infection: DM, CKD, OAC, chronic steroid use, prior CIED infection, $\geq$ 3 trsv leads, early pocket reentry	Lower infection rates in both AEE groups vs controls: 0% and 0.3% vs. 3.1% ($P < 0.03$)	PM, CRT-D, ICD
Shariff et al. (31)	2015	Retrospective	365/1,111	Non-absorbable	Minimum 6 months	Initial CIED implantation, generator replacement or system upgrade	Lower infection rate in AEE groups vs standard-care group: 0% vs. 1.7% ($P = 0.006$)	PM, CRT-D, ICD
Hassoun et al. (44)	2017	Retrospective	92/92	Non-absorbable	Mean follow-up 9 months	CIED implantation at a single centre	Higher rate of major CIED infection in AEE group vs standard-of-care group: 5.4% vs. 1.1% ($P = 0.048$). Higher rates of revision/replacement (51.1% vs. 8.7%, $P = 0.001$); implantation of systems with >2 leads (42.4% vs. 29.3%, $P = 0.03$) and of chronic corticosteroid use in AE group vs controls.	PM, CRT-D, ICD
Henrikson et al. (45)	2017	Prospective	1,129/no active comparator	Non-absorbable	Minimum 12 months	Device upgrades, lead revisions or pulse generator replacements and high risk CIED infection patients	Major CIED infections less frequent in a high-risk AE group (0.4%) vs expected benchmark infection rate (2.2%) ($P = 0.0023$).	ICD/CRT-P/D
Tarakji et al. (9)	2019	RCT	3,495/3,488	Absorbable	12 months	High-risk patients undergoing CIED replacement, system upgrade, pocket or lead revision or initial implantation (some device types)	Major CIED infection Incidence 0.7% in AEE recipients vs. 1.2% in controls; 40% RRR (HR 0.60, 95% CI 0.36-0.98, $P = 0.04$). Effect mainly driven by reduction of pocket infections.	PM, CRT-D, ICD
Frausing et al. (46)	2021	Retrospective	736/1,207	Absorbable	12 months	Reoperations due to replacement, upgrade or revision	CIED infection incidence 2.3% in AEE recipients vs. 4.1% in controls. (adjusted HR 0.52, 95% CI 0.30-0.90, $P = 0.021$).	CRT-P/D

AEE, antibiotic-eluting envelope; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DM, diabetes mellitus; HR, hazards ratio; ICD, implantable cardioverter defibrillator; OAC, oral anticoagulation therapy; PM, pacemaker; RCT, Randomized controlled trial; RRR, relative risk reduction; trsv, transvenous.

COST-EFFECTIVENESS

Despite the proven clinical benefit of the AEE, its utilization is associated with an extra cost which might lead to an additional financial burden on the healthcare systems. Economic perspectives of any medical procedure should be subject to a thorough cost-effectiveness analysis (CEA) that serves to assist in decision-making. A widely accepted measure of cost-effectiveness is the incremental cost-effectiveness ratio (ICER) that is most commonly expressed as the cost invested for quality adjusted life years (QALY) gained by implementing the new intervention compared to standard care (49). The decision to reimburse any form of treatment is usually multifactorial and considers numerous factors specific for each country or healthcare system (49). However, decision-making bodies do impose a threshold value for cost effectiveness—the so-called willingness to pay threshold. The World Health Organization has proposed benchmarks based on the gross domestic product per capita in each country (50). According to a joint statement published in 2014 by the American College of Cardiology and the American Heart Association, ICER per QALY gained of <$50 000 was determined to be highly cost-effective, between $50 000 and $150 000 was considered of intermediate cost-effectiveness, and ICER > $150 000 was not considered cost-effective (51). The willingness-to-pay threshold accepted by the UK National Institute of Clinical Excellence is £20 000–30 000, the official threshold accepted in Italy is €25 000–40 000 and ICER < €41 500 per QALY in Germany is considered cost-effective (52).

Cost effectiveness of the AEE has been studied in an early observational study encompassing all ICD and CRT procedures at a single center and calculating additional hospital costs associated with CIED infections (31). At 6 months, the costs associated with CIED infections management exceeded the costs of using AEE as a standard of care by $ 23 863. Another CEA performed in the setting of the UK public healthcare system was based on data from six observational studies of AEE (53). The analysis with a 12-month horizon including the calculated relative risk of 0.163 associated with AEE implantation (84% relative risk reduction) suggested that TYRX™ use was dominant compared to standard of care in ICD and CRT-D and cost effective for CRT-P (ICER £21 768). The AEE was not cost-effective in the patients receiving anti-bradycardia pacemakers (ICER £46 548) suggesting that the economic benefits of AEE are only valid for specific types of devices. Further analysis of this data showed that there is an infection rate threshold for each specific type of devices only above which TYRX™ remains cost-effective. Overall, this study reported that the number needed to treat (NNT) to prevent one device extraction due to CIED infection was 37 while 22 patients needed to be treated for the prevention of one infection-related hospitalization.

Cost-effective analyses have been performed on the WRAP-IT population as well (**Figure 1**). A recent CEA in the US healthcare system over a lifetime horizon demonstrated that TYRX™ had an incremental cost effectiveness (55). The use of AEE resulted in 6.925 QALYs at a cost of $37 598 while the standard of care was associated with 6.919 QALYs costing $ 36 929. ICER of TYRX™ was calculated at $112 603 per QALY compared to standard of care. The willingness-to-pay threshold used in the analysis was $150 000 demonstrating overall cost-effectiveness of the AEE. Model iterations with varying infection rates in the standard of care arm demonstrated that TYRX™ is cost saving when the infection rate was ≥4.0% and highly cost-effective with an ICER below $50 000 with infection rates ≥2.0%. The AEE remained cost-effective (ICER <$ 150 000) with an infection rate of ≥1.0% while economic benefits were lost with infection rates <1.0%. Subgroup analysis showed that TYRX™ use in patients with prior CIED infections are cost-saving, while high cost-effectiveness was demonstrated in immunocompromised patients, those with high-power devices, two or more previous procedures, as well as those in revision or upgrade of low-power devices. The use of TYRX™ demonstrated intermediate cost-effectiveness in revision/upgrade or single previous procedure in high-power devices or multiple procedures in low-power devices as well as in patients with a history of renal failure. AEE was not cost-effective in cases of CRT-D *de novo* implants and in cases of single previous procedures in low-power devices. In this study, the NNT to prevent one CIED infection was calculated at 200, probably due to the low infection rates in the studied population.

Another very recent CEA was performed on the WRAP-IT population in the setting of the healthcare systems of several European countries—Italy, Germany and England (54). Based on a decision tree with a lifetime horizon, this analysis uses model inputs from the WRAP-IT (e.g., mortality data, health-related quality of life, probability of CIED infection, etc.) and PADIT trials (probability of CIED infection). In this study, ICER was calculated for each type of CIED in each of the studied countries. Additional analysis of cost-effectiveness based on the PADIT risk score was also included. The willingness-to-pay thresholds considered were €40 000 per QALY in Italy, €50 000 per QALY in Germany, and £30 000 (€35 564) in England. Base-case scenario analysis demonstrated that TYRX™ was cost-effective in each of the three countries in patients with immunosuppressive therapy, those with a previous CIED infection, the ones undergoing generator replacement with lead modification (apart from CRT-P in England), and those having had two or more previous CIEDs and who received a high-power device. The AEE was found to be more cost-effective in patients with higher PADIT risk scores. TYRX™ was shown to be economically efficient in patients with PADIT risk scores ≥ 6 for all device types in all countries. The AEE was not cost-effective for any device type in Italy and England as well as for CRT-D in Germany when the PADIT risk score was estimated at ≥5. Further analyses including risk sharing with the manufacturer demonstrated low direct costs for the healthcare system and thus improving cost-effectiveness.

Contrary to these findings, in the Canadian healthcare system, TYRX™ was recently shown to not be cost-effective for any type of devices in the base-case scenario (56). The calculated ICER per infection prevented was $274 416, which exceeds the willingness-to-pay threshold. When modeling the infection rate in the sensitivity analysis (standard value of 1.2%), the authors found the AEE to be cost-effective at much higher infection rates (>6%). The observed discrepancies with previous publications

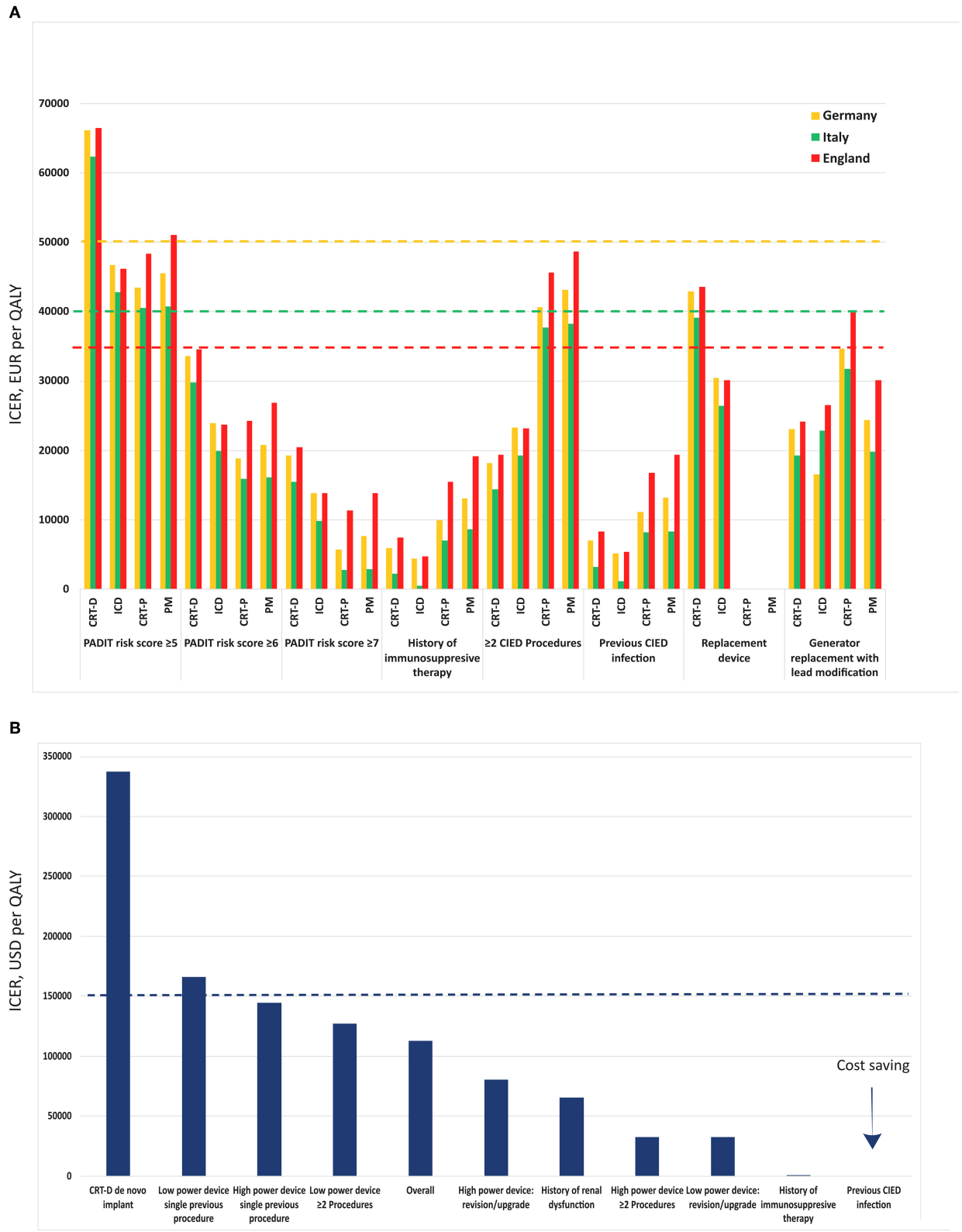

FIGURE 1 | Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) among different subgroups and based on the population from WRAP-IT trial. Results are shown for Europe **(A)** as reported by Boriani et al. (54) and in US **(B)** as reported by Wilkoff et al. (55). The dashed lines represent the willingness to pay threshold for each country. The values for UK have been recalculated in Euro to facilitate comparability. CIED–cardiac implantable electronic device, CRT-D–cardiac resynchronization defibrillator, CRT-P–cardiac resynchronization pacemaker, ICD–implantable cardioverter defibrillator, PM–pacemaker.

are likely multifactorial with methodology of the study likely playing a role.

CONCLUSION

Cardiac implantable electronic device infections are a major concern in terms of morbidity, mortality, and healthcare costs. Despite the presence of well-defined preventive strategies including antimicrobial agents, the rate of CIED infections continue to rise. Following firm evidence from a large randomized study, supported by confirmative registry data, the AEE has proven to be a major step toward adequate and cost-effective prevention of CIED infections in patients at highest risk of CIED infection.

AUTHOR CONTRIBUTIONS

VT drafted the manuscript. CB-L provided critical revision of the manuscript. Both authors contributed to the article and approved the submitted version.

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CASE REPORT
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Left Bundle Branch Area Pacing in a Giant Atrium With Atrial Standstill: A Case Report and Literature Review

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Atrial standstill (AS) is a rare condition defined by the lack of atrial electrical and mechanical activities. It is usually clinically manifested as symptomatic bradycardia, which requires permanent pacemaker (PPM) implantation. Traditional right ventricular apical pacing causes electrical and mechanical dyssynchrony resulting in left ventricular dysfunction, heart failure, and arrhythmias. As a novel physiological pacing strategy, left bundle branch area pacing (LBBaP) has demonstrated effectiveness and safety in recent years, but its application in exceptional conditions is rarely reported. We report the case of a 47-year-old female, who was diagnosed with AS complicated with a giant atrium, and successfully received a single-chamber PPM with LBBaP.

Keywords: left bundle branch area pacing, physiological pacing, atrial standstill, giant atrium, permanent pacemaker

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INTRODUCTION

Atrial standstill (AS) is a rare type of arrhythmia characterized by the loss of electrical and mechanical activities of the atrium (1, 2). Electrocardiogram (ECG) typically shows no visible P waves or atrial fibrillatory waves and a borderline or ventricular escape rhythm. It is clinically characterized by symptomatic bradycardia that requires permanent pacemaker (PPM) therapy. Since AS is always combined with atrial enlargement and tricuspid regurgitation, ventricular lead implantation is a challenge. A single-chamber PPM with its ventricular active lead positioned in the right ventricular apex was traditionally performed in a few previous cases (3, 4). As a physiological pacing strategy, left bundle branch area pacing (LBBaP) was recently proposed. It activates the normal cardiac conduction, thereby providing synchronized contraction of the ventricles (5). However, AS with a giant atrium is a challenge to the placement of the ventricular lead, especially for LBBaP, as similar cases are rarely reported.

CASE REPORT

A 47-year-old female patient was admitted with recurrent syncope for 2 days. Bedside ECG on admission discovered no visible P waves or atrial fibrillatory waves, ventricular escape rhythm with ventricular rate 40–45 bpm, and torsade de pointes. Bedside echocardiography indicated an enlarged heart dominated by the atrium, where the right atrium (RA) size was 8.9 cm × 5.6 cm, the left atrium (LA) size was 7.2 cm × 5.6 cm, the left ventricular end diastolic diameter was 5.1 cm, the left ventricular ejection fraction (LVEF) was 50%, and there was extensive tricuspid regurgitation (**Figure 1a**). Moreover, only E waves were observed in the early diastolic period, but no A wave

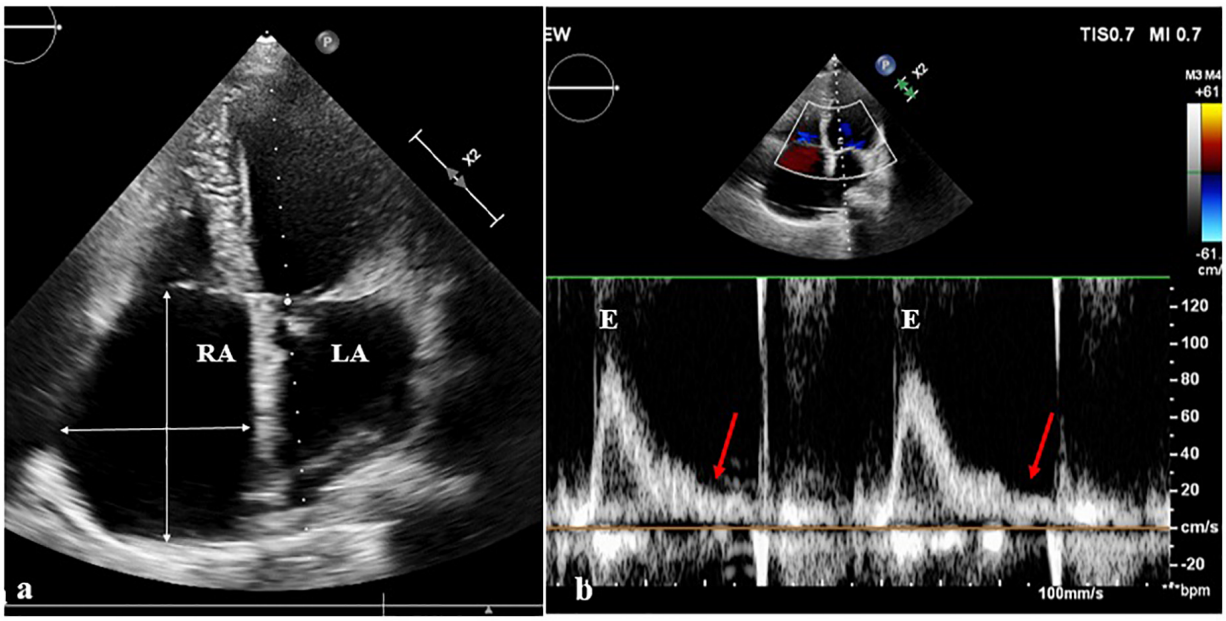

FIGURE 1 | Echocardiography images. **(a)** On the echocardiography, both atrium were observably enlarged, the right atrium (RA) size was 8.9 cm × 5.6 cm, and the left atrium (LA) size was 7.2 cm × 5.6 cm. **(b)** In the mitral inflow pulse by Doppler recording, only E wave was observed in the early diastolic period, but no A wave was observed in the late diastolic period.

was detected in the late diastolic period in the mitral inflow pulse by Doppler recording (**Figure 1b**). A temporary pacemaker was immediately implanted. However, it was difficult for the temporary pacemaker lead to enter the right ventricle. The patient was instructed to take deep breaths and cough repeatedly. After repeated attempts, the lead was successfully placed into the apex of the right ventricle under the guidance of bedside echocardiography, and the pacing rate was set to 80 bpm. Subcutaneous injection of low molecular weight heparin was administered to prevent blood clots and intravenous infusion of cefazolin sodium was administered to prevent infection. The next day, ECG monitoring indicated ventricular pacing dysfunction, and the lead dislocation of the temporary pacemaker was considered. On the second day, a PPM was implanted. Intraoperative X-ray fluoroscopy showed that the temporary pacemaker lead was dislocated and coiled in the right atrial lumen (**Figures 2a,b**). Electrophysiology study indicated that no atrial action potential could be recorded in multiple regions of the RA, including right atrial appendage, middle atrial septum, the bottom of the interatrial septum, and low lateral region. Furthermore, there was a lack of atrial capture in several parts of the RA during high output at 5.0 V/0.5 ms, and consequently, atrial activity was considered to be paralyzed electrically (**Figure 3a**). The decisions to implant a single-chamber PPM and to attempt the LBBaP were made. First, a loach guide wire was delivered to the right ventricular outflow tract, and the His sheath (C315-His, Medtronic, Minneapolis, MN, United States) was delivered to the tricuspid annulus along the guide wire. The unshaped His sheath was difficult to be positioned in place. Through the sheath shaping technology, we put the inner core back into the His sheath, shaped the middle area of the second bend by hand, and adjusted the curvature of the His sheath. Subsequently, the sheath tube was sent to the tricuspid annulus, and an active fixation lead (3830, Medtronic, United States) was sent along the sheath to the right ventricular septum to select an acceptable initial fixation site with an obvious current of injury (**Figures 4A,B**). A right bundle branch block (RBBB) pattern was clearly observed during ventricular pacing when the lead was screwed into the interventricular septum, which indicated LBBaP (**Figures 3b,c**), with a stable stimulus to left ventricular activation time (Stim-LVAT) of 68 ms (a sensing of 11.8 mV, a pacing threshold of 0.9 V at a 0.5 ms pulse width and an impedance of 1,002 Ω). After the implantation of the pacemaker (ADSR01, Medtronic, Minneapolis, MN, United States), the temporary pacemaker leads were removed under fluoroscopy. The histology of myocardial biopsy showed hyaline degeneration within the collagen fibers, and the existence of blurred stripes in some myocardial fibers with mucoid degeneration among parallel collagenous fibers (**Figure 5**). A postoperative ECG showed that ventricular pacing was stable (VVI mode, pacing rate of 60 bpm). Benazepril 5 mg qd was given to improve cardiac remodeling, and apixaban 2.5 mg bid was given to prevent embolism. Ventricular tachycardia did not occur during the postoperative hospitalization. In the postoperative follow-up, the ventricular pacing burden was 96.2%. Pacemaker parameters remained stable with ventricular sensing of 12.5 mV and ventricular pacing threshold of 0.75 V at 0.4 ms. The patient has since remained free of syncope and not experienced cardiac insufficiency.

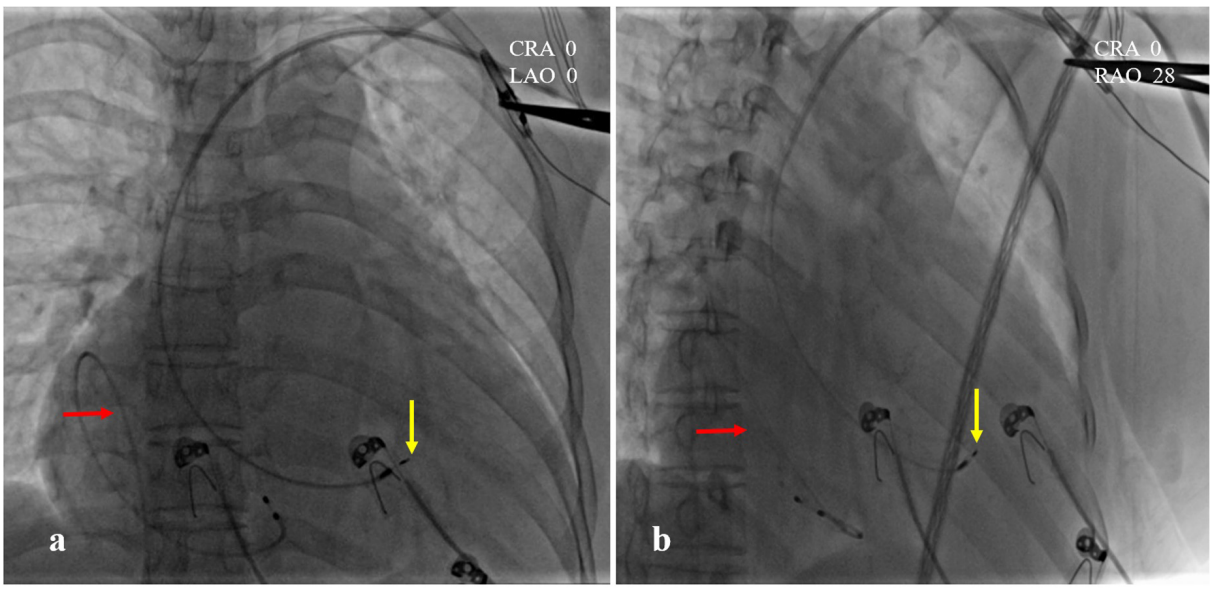

FIGURE 2 | Intraoperative X-ray fluoroscopy images. **(a)** CRA 0, LAO 0; **(b)** CRA 0, RAO 28. The temporary pacemaker lead was coiled in the right atrial lumen (red arrow). The position of left bundle branch area pacing (LBBaP) was at the distal end of the ventricle, 1.5 cm approximately beyond HIS (yellow arrow).

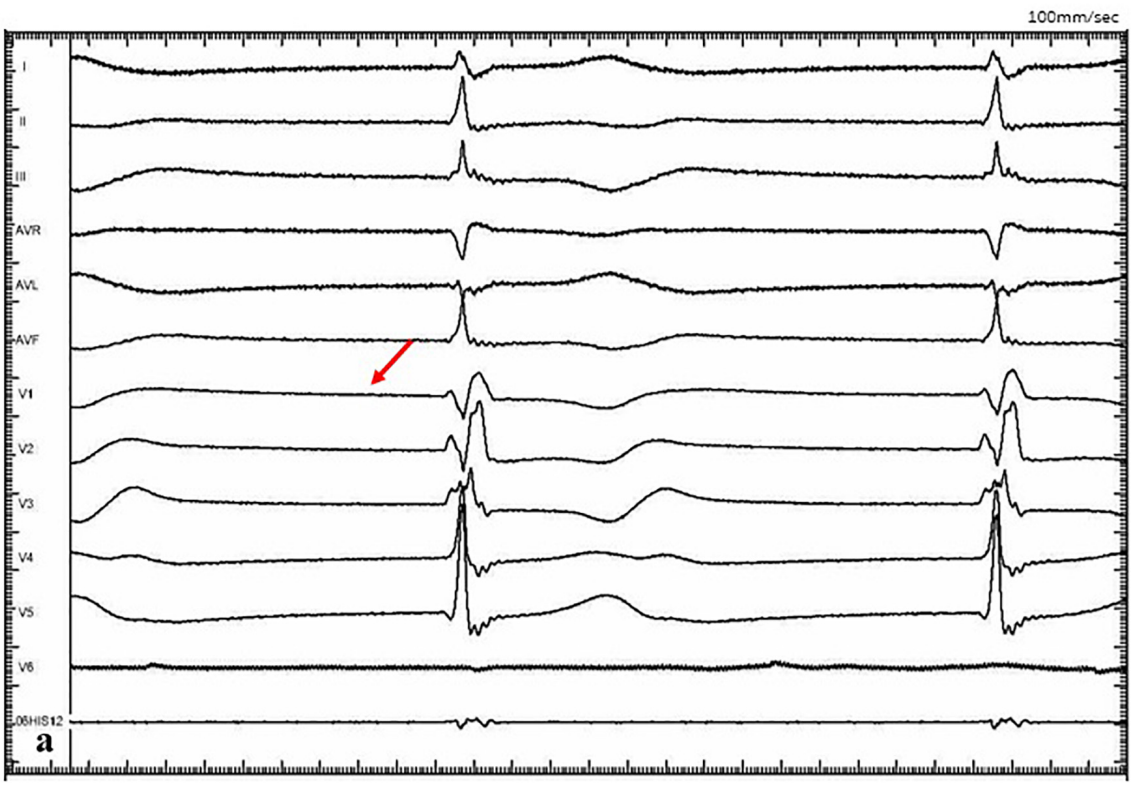

FIGURE 3 | (Continued)

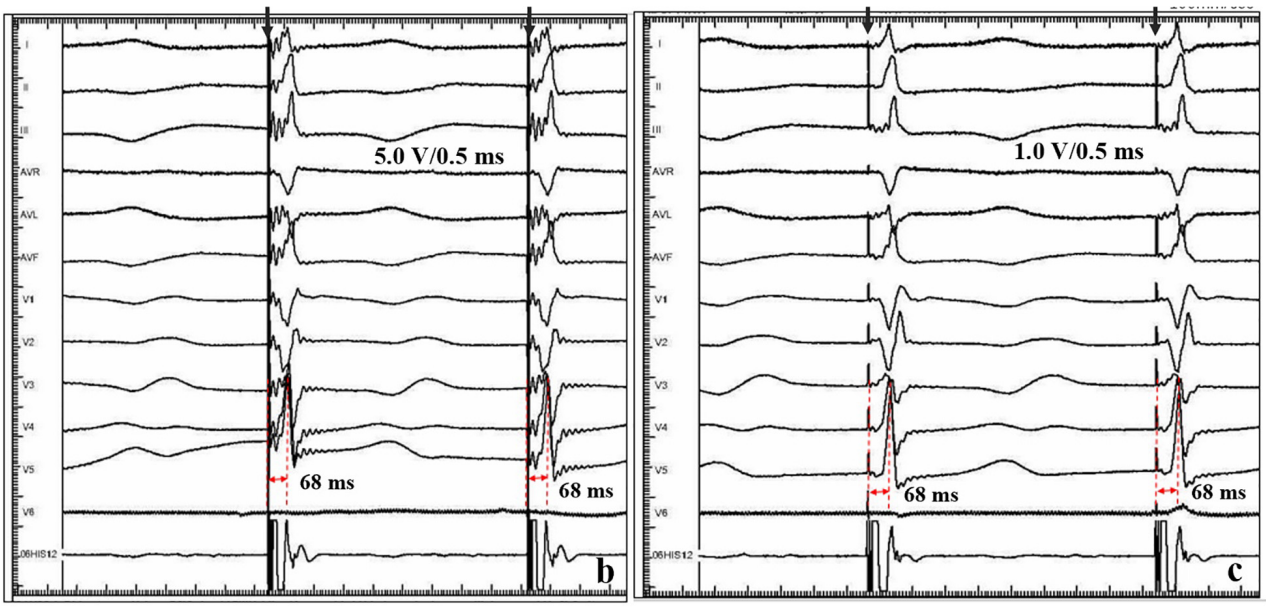

FIGURE 3 | Intracardiac electrograms. **(a)** There was no atrial action potential (red arrow) in RA. **(b)** Ventricular pacing at 5.0 V/0.5 ms output, and Sti-LVAT was 68 ms. **(c)** Ventricular pacing at 1.0 V/0.5 ms output, and Sti-LVAT was 68 ms.

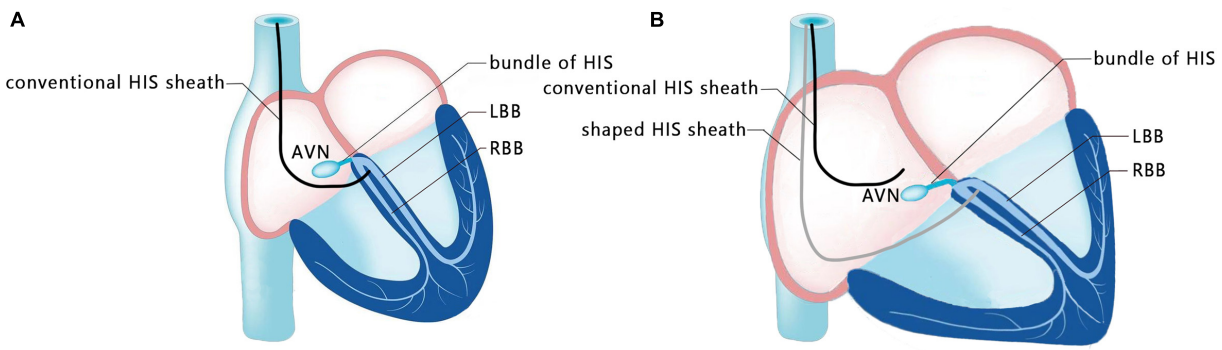

FIGURE 4 | Schematic diagram of shaping the sheath. **(A)** Conventional HIS sheath in patients with a normal size atrium. **(B)** Shaped HIS sheath in patients with an enlarged atrium.

DISCUSSION

Atrial standstill is a rare condition defined by the lack of atrial electrical and mechanical activities, which may be intermittent or permanent, partial or total, and congenital or secondary. The congenital pathogenesis is mostly related to gene mutations including the reported mutations of *EMD*, *SCN5A*, and *MYL4* (6–9). The secondary causes are more commonly observed in patients with Emery-Dreifuss muscular dystrophy (10), cardiac sarcoidosis (11), acute myocarditis (12), acute myocardial infarction (13), hyperkalemia, drug poisoning (e.g., digoxin or quinidine), and surgical myocardial injury. The clinical manifestations of AS include dizziness, syncope (3), heart failure, arterial embolism, and stroke (14, 15). The mechanism of embolism is considered similar to that of atrial fibrillation. The loss of atrial regular contractile activity may lead to atrial thrombosis, which can cause arterial embolism. At present, there are no relevant guidelines and consensus to provide a treatment standard for AS. In this case, a long-term anticoagulant (apixaban) was given based on the benefits demonstrated by the relevant reports, and with the consent of the patient.

AS may manifest as partial or total atrial paralysis. It often appears early at the site of the high and mid-lateral RA, progresses to the entire RA, and then to the LA (16, 17). Bogossian et al. (18) reported a case of right atrial tachycardia despite silent RA with a remaining pacing site in the bottom of the interatrial septum. Demiralp et al. (19) reported a case of a partial AS with mechanical activity only documented at the left atrial appendage. For a few patients who had residual local electrical activity in the atrium, implanting atrial leads at appropriate

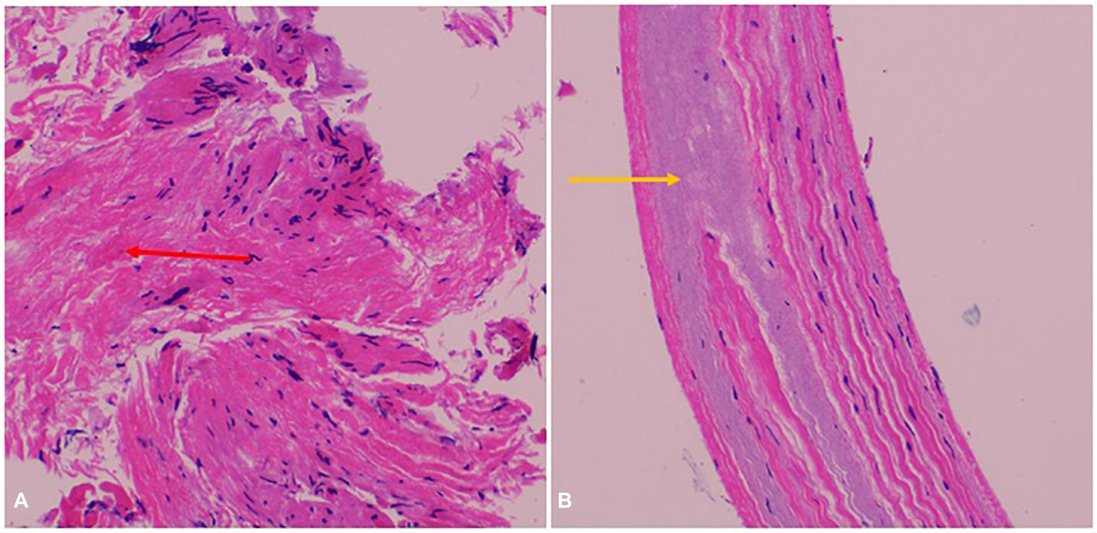

FIGURE 5 | Myocardial biopsy pathological result. **(A)** Hyaline degeneration within the collagen fibers (red arrow). **(B)** Blurred stripes in some myocardial fibers with mucoid degeneration among parallel collagenous fibers (yellow arrow).

sites can be used to select double-chamber pacemakers. Suzuki et al. (20) reported a case of AS with the atrial lead implanted in the coronary sinus. Considering the possibility of atrial disease progression, close follow-up is still recommended. Single-chamber PPM has been used in most previous cases. The torsade de pointes in this patient was considered to be secondary to QT interval prolongation in bradycardia, so we implanted a temporary pacemaker to increase the pacing rate to 80 bpm. After excluding other causes of torsade de pointes, a pacemaker was selected instead of an implantable cardiac defibrillator. We performed a single-chamber PPM implantation (VVI mode). During the postoperative hospitalization, ventricular tachycardia completely disappeared.

Cardiac pacing is the only effective treatment for symptomatic bradyarrhythmia. Traditional right ventricular apical pacing causes electrical and mechanical dyssynchrony resulting in left ventricular dysfunction, heart failure, and arrhythmias. Physiological pacing activates the normal cardiac conduction, thereby providing synchronized contractions of the ventricles. LBBaP technique is a novel pacing strategy evolving from His bundle pacing (HBP), including selective left bundle branch pacing (LBBP) and non-selective LBBP. The active lead is twisted through the septum from the right ventricular septum to the left fascicular branch area under the intima of the left ventricular septum, and the pacing captures the left Purkinje network to circumvent the blocked site and maintains the electrical synchronization of the left ventricle (21–24). LBBaP paces beyond the site of block and results in a low pacing threshold with a high success rate in patients with infranodal atrioventricular block. Relevant studies have reported a success rate of 81–93% (24–26). Huang et al. (27) reported the first case of LBBaP. The left bundle branch block (LBBB) could not be corrected at 10 V/0.5 ms output by HBP. The tip end of the electrode wire was then sent to the distal end of the ventricle, and as a result, the LBBB could be corrected by 0.5 V/0.5 ms output. The pacing threshold was low and stable, and above all, heart failure symptoms improved significantly during follow-up. Since then, the characteristics of LBBaP have been continuously explored. An *in vivo* canine model illustrated the electrophysiological parameters and anatomical evaluation of LBBP, and showed the improvement of hemodynamics (28). LBBaP was confirmed to maintain left ventricular synchronization by nuclide examination (29). Several clinical studies have also confirmed the benefits of LBBaP. Notably, a multicenter observational study verified that LBBaP improved cardiac function and reduced the hospitalization rate of heart failure patients. It also showed better clinical outcomes than right ventricular pacing (RVP) in patients with atrioventricular block, requiring a heavy burden of ventricular pacing (30). For patients with heart failure, current studies showed that LBBaP was associated with remarkable improvements in cardiac function, mechanical synchronization, and mechanical efficiency and may be a promising alternative to cardiac resynchronization therapy (31–35). In addition, many clinical studies have demonstrated the safety of LBBaP. A single-center study indicated that the total incidence of procedure-related complications of LBBP was 1.63% (36). Another single-center study showed that the complications and cardiac outcomes were not significantly different between LBBP and RVP after mid-long-term follow-up (37).

Huang et al. (21) expounded the operation specification of LBBP for the first time, and more admissible judgment criteria were provided in the subsequent studies. Su et al. (38) indicated that the current of injury is meanful to judge the LBB capture, pacing threshold and electrode perforation. Huang et al. (39) established the standard model for judging the capture of LBB. Direct LBB capture was defined as retrograde HIS potential on the HPV

lead and/or anterograde left conduction system potentials on the multielectrode catheter during LBBP. An abrupt decrease in Stim-LVAT of ≥10 ms and demonstration of selective LBBP could be used as simple criteria to confirm LBB capture. In this present case, we recognized this as an LBBaP by the following evidences: ① paced morphology is a RBBB shape; ② the Sti-LVAT remains 68 ms at high and low outputs; ③ paced morphology was not a typical RBBB shape and the dissociation was not definite enough at 1.0 V/0.5 ms output. Because of AS and ventricular escape rhythm without normal AV conduction in this case, the intracardiac electrograms did not show the internal rhythm and the LBB potential. Retrograde His potential or anterograde left conduction system potentials are a golden criterion of direct LBB captured, but it is not practical and adaptable in clinical practice, especially in complex conditions like in our case. Zhang et al. (40) explored a simplified approach ("9-partition method") to perform LBBaP under fluoroscopy. This provides a means of operation in the absence of multi-channel electrophysiology instruments. For special anatomical structures, techniques such as the "sheath in sheath" (His bundle sheath covering the left ventricular delivery system) (25, 34, 41) can also be used to further increase the supporting force of the sheath and to contribute to the fixation of leads in the target area. In this case, we shaped the middle area of the second bend of the His sheath by hand, and adjusted the curvature to reach the acceptable initial site. In recent years, the use of newly developed implant tools and related auxiliary means have helped clinicians to implant pacemaker systems into patients with special anatomical structures.

In summary, when PPM treatment is essential in AS with a giant atrium, LBBaP is a promising pacing strategy and the technique should not be waived prematurely. In this case, LBBaP was successfully achieved by HIS sheath shaping, and the intraoperative and postoperative parameters were satisfactory and stable. Further follow-up observation is indispensable to assess the stability, safety, and clinical prognosis. This clinical experience in such exceptional circumstances justifies further investigation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JinZ and QJ contributed to the conception of the study. JinZ wrote the manuscript. QY, JiaZ, and QC helped to analyze the patient data and curate the data. QJ helped to perform the analysis with constructive discussions. All authors contributed to the article and approved the submitted version.

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Realtime Remote Programming in Patients Carrying Cardiac Implantable Electronic Devices Requiring Emergent Reprogramming

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To protect cardiac implantable electronic device (CIED) patients with arrhythmia or possible device malfunction, it is important for health care professionals to provide emergent device evaluation and reprogramming. This case series illustrated the clinical application of realtime remote programming in CIED patients requiring emergent in-person evaluation and reprogramming (ChiCTR2100046883 chictr.org). All remote sessions were performed safely and efficiently by remote electrophysiologists without being in the physical presence of a patient. The implementation of realtime remote programming not only largely reduces the response time to urgent events but also greatly helps to minimize personnel exposure to COVID-19 infection.

Keywords: cardiac implantable electronic device, remote programming, emergent programming, telemedicine, COVID-19, follow-up, in-office evaluation

INTRODUCTION

Telemedicine, crossing geographic, social, and cultural barriers, has emerged as an important tool for the postimplantation management of patients with cardiac implantable electronic devices (CIEDs). Although remote monitoring (RM) has been classified as I a recommendation for routine use in CIED patients, annual in-office evaluations are also required (1). Limited resources and a seriously imbalanced distribution of follow-up clinics are common hurdles for in-office CIED evaluations (2). The outbreak of the COVID-19 pandemic further induced a drastic reduction in the frequency of in-office evaluations (3). Therefore, the adoption of a prompt response to a patient with a device needing emergent reprogramming remains crucial. From this perspective, we tested an alternative service model using realtime remote programming of CIEDs that would allow for the expeditious and safe testing and programming of dysfunctional cardiac devices without the need for proficient onsite specialists.

METHODS

We employed a 5G-cloud follow up platform that allows CIEDs to be evaluated and reprogrammed in realtime from a remote location via an internet connection or a mobile wireless network (**Figure 1**). The 5G-cloud follow up platform comprised a 5G remote support terminal (China Telecom Corporation Limited Shanghai Branch, Shanghai, China) that was externally connected

to the programmer (A Merlin Patient Care System Programmer Model 3650, St. Jude Medical Inc., Saint Paul, Minnesota, USA), a PAD (tablet personal computer) installed with a 5G-cloud follow-up application (China Telecom Corporation Limited Shanghai Branch, Shanghai, China), and a remote service system deployed on cloud servers (China Telecom Cloud, China). Patients were enrolled in the observational trial (ChiCTR2100046883) designed to evaluate the clinical use of cloud follow-up in CIED patients. The study was approved by local ethics committees, and all patients gave informed consent.

The real-time programming session has rigorous security protocols to protect patient safety and cybersecurity. First, the onsite medical staff, after obtaining written informed consent from the CIED patient, began the cloud follow-up session by contacting the remote device specialist via an audio-visual device, and introduced the patient to the remote device specialist. This kind of communication method enabled the remote device specialist to keep in contact with the onsite medical staff and the patient during the whole follow-up session. The onsite medical staff was in charge of precheck of the system, turning on the programmer and applying the programmer wand to the patient's device. Second, a two-step verification was used to log into the 5G-cloud follow-up application on a PAD by the authorized device specialist: Step 1: log into the designated account using a password, and Step 2: use the access password for the second verification to establish remote connection for

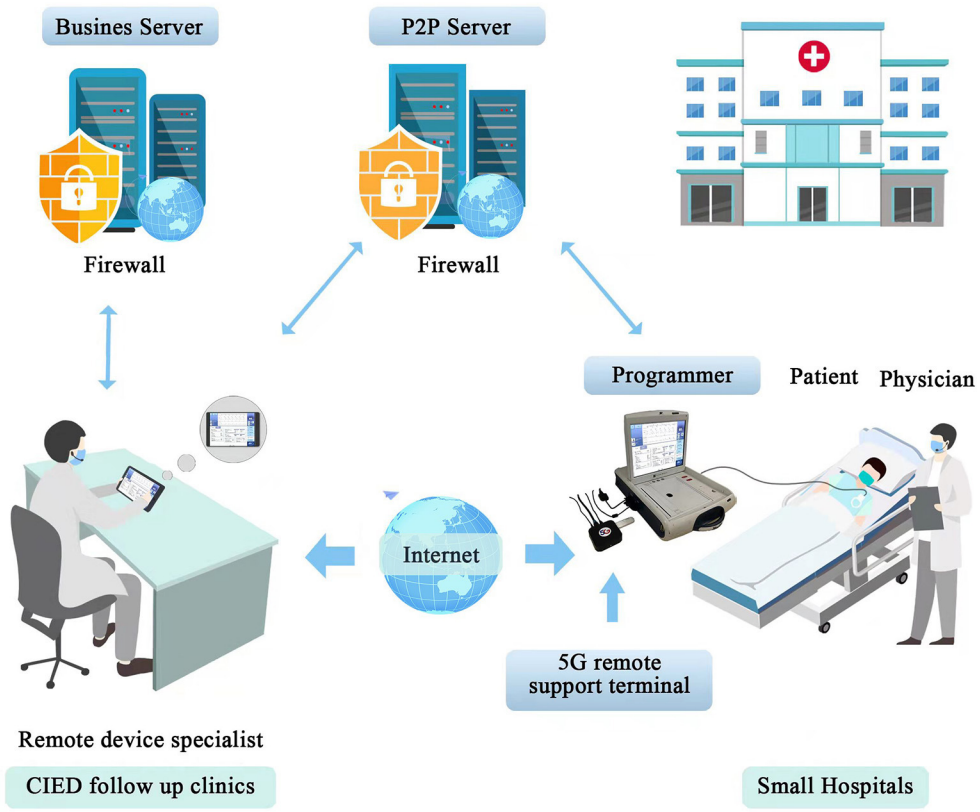

FIGURE 1 | The organization of a realtime remote programming system. The 5G-cloud follow up platform comprises a 5G remote support terminal that is externally connected to the programmer, a PAD installed with a 5G-cloud follow up application, and a remote service system deployed on cloud servers. The P2P Server is used to establish the communication between the 5G remote support terminal and the 5G-cloud follow-up application when the designated account is logged in. Then the 5G remote support terminal is directly connected with the 5G-cloud follow-up application via internet. No network or software is required for the on-site programmer. Remote control of the on-site programmer can be realized by simply connecting to the 5G remote support terminal and using simulated mouse and keyboard information. No direct data interact between the computer and the on-site programmer. The Business Server is used for the second verification to establish remote connection and storing audit logs. This system enables follow up clinics could provide realtime remote programming of CIEDs for small hospitals (primary medical and health care institutions) that lack follow up clinics or device specialists. The application of this system in a hospital includes expeditious remote device programming in different scenarios, such as urgent MR scanning, lead testing during the CIED implantation procedure, and patients in the emergency department. PAD indicates tablet personal computer; CIEDs, cardiac implantable electronic devices; P2P Server, Pointer-to-Pointer Server.

Abbreviations: CIEDs, cardiac implantable electronic devices; RM, remote monitoring; VT, ventricular tachycardia; VF, ventricular fibrillation; COVID-19, coronavirus disease 2019.

the designated device. The remote device specialist then had complete control of the programmer functions to evaluate and reprogram the device as appropriate. Third, data transmission was securely encrypted using the RSA/AES 2048-bit asymmetric cryptographic algorithm and sophisticated end-to-end secure communication protocols. Fourth, the servers were deployed in server rooms with protections including multilayer firewalls, customized antivirus scanning, vulnerability scanning and intrusion detection to ensure data security. Fifth, the whole remote operation process was saved via screen recording which allowed users to audit the logs later. Sixth, in case of communication between the on-site programmer and the remote device specialist's PAD is interrupted, the CIED device will revert to the original settings.

RESULTS

Case 1 An 83-year-old man with dilated cardiomyopathy and a complete left bundle branch block underwent implantation of a cardiac resynchronization therapy defibrillator (CRTD, Quadra Assura MP^{TM} 3371-40, St. Jude Medical, USA) in May 2019. In September 2021, he was diagnosed with Dukes D stage rectal cancer and accepted expectant treatment. Beginning in October 2021, he suffered from recurrent paroxysms of palpitation, accompanied by occasional shocks. In November 2021, he was admitted to a small hospital due to syncope. At arrival to the hospital, the patient was hemodynamically stable (arterial blood pressure of 100/47 mmHg). A physical examination and an electrocardiogram (baseline rhythm: sinus rhythm/DDD pacing mode, 74 beats/min) did not provide evidence of acute decompensation of heart failure or acute coronary syndrome. Laboratory examinations found the level of hemoglobin was decreased (110 g/L) and the brain natriuretic peptide level was slightly increased (1,786.58 pg/ml). Electrolyte abnormalities and hyperthyroidism were excluded. Because of the lack of qualification to reprogram a CRTD, the local medical staff contacted the device specialist from the author's hospital for emergent technical assistance.

Remote device interrogation demonstrated a total of 64 episodes of ventricular fibrillation (VF), 31 episodes of non-persistent events, and 1 episode of supraventricular tachycardia. The maximum frequency of VF episodes was 45 times within 26 h. Antitachycardia pacing (ATP) terminated 54 of the 64 episodes of VF. Ten episodes of VF were unaffected by ATP and required a shock for termination. The shocks were ineffective in 2 episodes of VF, with successful termination by a subsequent shock.

The device was remotely reprogrammed as follows without the loss of connectivity or programmability: VF shock energy output 2, 30 J to 36 J; value of the VF R-R interval, 12 to 18; VT-2, therapy 2 shock energy output, 15 J to 30 J; VT-2, therapy 3 shock energy output, 30 J to 36 J; left ventricular pulse width 2, 2.5 V to 1.75 V.

Case 2 A 77-year-old woman with sick sinus syndrome and paroxysmal atrial fibrillation underwent implantation of a single chamber pacemaker (Accent^{TM} SR RF 1,210, St. Jude Medical, USA) in VVIR pacing in July 2019. In December 2021, she presented to the emergency department due to palpitations and general debility. At hospital arrival, the patient was hemodynamically stable (arterial blood pressure 146/84 of mmHg). An electrocardiogram examination detected atrial fibrillation with rapid ventricular rates (130 beats/min). The emergency room physician applied for emergent device evaluation. To minimize personnel exposure to COVID-19 infection, we remotely interrogated and tested the device from the cloud follow up center. The result of remote interrogation found the device was in VVIR pacing mode and the maximum sensor-based rate was 130 beats/min. The ventricular lead parameters were in normal ranges. Before receiving further medication treatment, the atrial fibrillation was autoterminated.

Case 3 A 69-year-old woman with sick sinus syndrome underwent implantation of a dual-chamber pacemaker (Accent^{TM} DR 2112, St. Jude Medical, USA) in DDD pacing in 2019. In November 2021, she presented to the author's follow-up clinic due to pacemaker syndrome. Device evaluation results showed that her device was in backup VVI mode: the base rate was 67 beats/min, and the ventricular pulse amplitude was 5.0 V. To address this emergent situation, we contacted the manufacturer's representative in Abbott China (Shanghai) for technical support. After obtaining written informed consent from the patient, we began the realtime remote programming session by contacting the remote manufacturer's representative via video call. Once getting the specific password from St. Jude Medical (Sweden), the remote manufacturer's representative successfully reset the device and reprogrammed it to DDD pacing of 60 bpm. We checked with patient's activities, there was no evidence of exposure to strong electro-magnetic field. Since the device have restored successfully, we monitored the patient. At follow-up after realtime reprogramming, the palpitation was completely remitted, and there were no signs of recurrence.

DISCUSSION

CIED patients who have symptoms suggesting arrhythmia or a possible device malfunction warrant urgent office evaluation. The presented 3 clinical cases varying in scenarios adopted realtime remote programming at the time the device required emergent in-person evaluation and reprogramming. All remote testing and programming sessions were safe and efficient, without any adverse interaction with other aspects of a standard in-office visit. The clinical use of the realtime remote programming of CIEDs provides novel strategies to manage cardiac devices with malfunctions considered urgent or time sensitive.

The Organization of a Realtime Remote Programming System

The construction of a realtime remote programming system among CIED follow up clinics and small hospitals lacking device specialists may provide substantial benefits for patients needing urgent device reprogramming. In addition, the potential application of this system in a hospital includes expeditious remote device programming in different scenarios, such as urgent

MR scanning, lead testing in CIED implantation procedures, and patients in emergency departments. This system enables clinical device specialists to provide rapid and device-specific expertise, without being in the physical presence of a patient.

The Potential Beneficial Effects of Realtime Remote Programming on CIED Patient Management

Geographic isolation from follow up clinics is a common barrier for in-office CIED evaluations (3). Patients and their caregivers often travel long distances to attend these appointments. During the COVID-19 pandemic, where possible, non-urgent in-office visits should be reasonably avoided (4). Compared with in-office visits alone, RM of CIEDs plus in-office visits resulted in significantly reduced number of unscheduled visits and improved outcomes, without increasing the risk of major adverse events (5, 6). However, as of today, remote programming of CIEDs is not allowed, in view of safety concerns. Realtime remote programming, crossing geographic, social, and cultural barriers, largely reduces the negative effects of geographic barriers and limited resources of follow-up clinics on the postimplantation management of CIEDs. Patients could travel to their local medical institutions and then establish a realtime remote programming session with assigned electrophysiologists who are thousands of miles away. Thus, realtime remote programming may be regarded as an update of routine in-office CIED evaluations and has the potential to improve the management of CIED follow-up.

The Implementation of Realtime Remote Programming to Minimize Potential Exposure to COVID-19 Infection

In addition to decreasing the response time to urgent events, we implemented realtime remote programming to minimize the potential exposure of medical staff and patients to COVID-19 infection. During the COVID-19 pandemic, the adoption of telemedicine has been rapidly increasing (7). Aiming at the pandemic, RM should be used in most circumstances to reduce the need for non-urgent clinic visits (4). If remote programming is available in the vicinity of a patient's residence or place of work, transregional or long-distance transportation could be avoided. Remote programming of CIEDs enables electrophysiologists to remotely manage CIED patients without the need for a physical presence. This measure contributes to protecting patients and health care teams from COVID-19 exposure. We believe that the integrated application of RM and realtime programming is an ideal organizational model for cardiac device management according to patient profiles, thus minimizing troubleshooting during follow up.

Communication Protocols to Authenticate and Protect the Connection

The challenges of implementing remote programming of CIEDs are no longer technical (8). The concerns surrounding remote programming are focused on patient safety and cybersecurity issues. The enrolled realtime remote programming system has several layers of protection, including a two-step verification, an asymmetric cryptographic algorithm, sophisticated end-to-end secure communication protocols, and private cloud deployment to protect the cybersecurity of the information and communications. Meanwhile, as an additional safety feature to protect the patient, during each realtime programming session, a physician was always beside the patient to provide assistance, observe the patient, and communicate with the remote electrophysiologist via video/voice call. The onsite medical staff was in charge of turning on the programmer and applying the programmer wand to the patient's device. It is important to remark that the engaged medical staff should know how to troubleshoot and circumvent occasionally arising technical problems.

Limitations

The present study has some potential limitations. First, as this was a single-center, observational research consisting of only 3 cases, it is insufficient to get the conclusion of safety of the remote programming. Thus, there is a great need for larger studies with rigorous study protocols to confirm this issue. Since the remote programming has not been officially approved for clinical use, clinical researchers of remote programming should strictly abide by the laws and medical ethics. Second, the cloud follow-up system only works with Abbott (St. Jude) devices for the time being, further study extending this service model to other brands of CIED would have greater clinical significance.

CONCLUSIONS

Realtime remote programming is safe and efficient, without any adverse interaction with other aspects of standard in-office visits. The implementation of realtime remote programming not only largely reduces the response time to urgent events, but also has great benefits to minimize potential exposure to COVID-19 infection. The integrated application of RM and realtime programming is an ideal organizational model to ensure optimal CIED management. With the judicious application of this tool, broader applications, along with the further development of new paradigms and protocols are urgently needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Third People's Hospital of Chengdu. The patients/participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SX was the major contributor in the collection, analysis and interpretation of data, and drafting of the manuscript. JL, LT, JH, SY, LQ, XC, YL, and ZZ participated in performance of the real time remote programming, and the collection and analysis of data. JL and HL revised the manuscript for important intellectual content. LC designed the study, had full access to all of the data in the study, and finally approved the manuscript submitted. All authors read and approved the final manuscript.

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CASE REPORT
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Initial Experience in Transvenous Implantation of a Left Ventricular Lead With a Novel Venogram Balloon Catheter

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Aim: The most challenging and time-consuming stage of cardiac resynchronization therapy (CRT) device implantation is coronary sinus (CS) cannulation and left ventricular epicardial electrode implantation. This paper reports the initial clinical experience of CS cannulation and left ventricular lead implantation guided by a novel venogram balloon catheter (Lee's venogram balloon catheter).

Methods and Results: Consecutive patients eligible for CRT were deemed suitable for this novel venogram balloon catheter. Parameters such as left ventricular lead implantation time, procedure time, and fluoroscopy time were recorded. CS cannulation with LV lead implantation guided by Lee's venogram balloon catheter was successful in all 5 patients, including 4 challenging cases. The total fluoroscopy and procedural durations were 5.0 ± 3.0 and 57.4 ± 12.5 min, respectively. No adverse catheter-related events occurred during the procedures.

Conclusion: This initial study of an innovative venogram balloon catheter demonstrated that it greatly facilitated CS cannulation and successful LV lead placement in all patients undergoing CRT system implantation. This significantly shortened the learning curve and showed a decrease in left ventricular lead implantation time, procedure time, and fluoroscopy time.

Keywords: cardiac resynchronization therapy, congestive heart failure, left ventricular lead implantation, coronary sinus, venogram balloon catheter

WHAT'S NEW?

A novel venogram balloon catheter with coronary sinus shaping for implantation of left ventricular pacing lead, it is being reported for the first time.

This catheter can facilitate the coronary sinus cannulation, simplify procedures, and improve the success rate of LV lead implantation.

Several large randomized clinical trials have shown that cardiac resynchronization therapy (CRT) achieved by intraventricular and interventricular electrical mechanical desynchronization through left or biventricular pacing can effectively improve the symptoms and hemodynamic of patients with chronic congestive heart failure (CHF) and significantly reduce mortality and

morbidity (1). Coronary sinus (CS) cannulation is an important stage of CRT device implantation. It is of great importance in both CS imaging and the placement of the left ventricular electrode in the appropriate region. In addition, CS cannulation is the greatest cause of procedure failure; it is also the most time-consuming and challenging aspect (2–4). Approximately 10% of attempts to place (left ventricle) LV leads are ultimately unsuccessful (5). Failure to access the CS remains the most important reason for difficult LV lead placement (4–6). Although the frequency and success of these techniques vary according to the operator, standard cannulation with a CS catheter is usually performed. Another challenge that an operator might face is that of the difficult anatomy of the coronary venous system, including sharply angulated or tortuous venous branches; due to the anatomical characteristics of the CS (4), the LV electrode is routinely implanted through the left axillary vein, and the implantation procedure becomes particularly difficult in cases that need to be implanted on the right side. As with all invasive procedures, one of the most important factors to consider in CRT implantation is radiation exposure. Shortening the fluoroscopy time is as important as the success of the procedure. Better tools and improved techniques should result in improved success rates, decreased procedure time, and decreased fluoroscopic exposure for the implanting physician. In this paper, five cases of CRT LV electrode implantation guided by a novel venogram balloon catheter (Lee's venogram balloon catheter) *via* the right axillary vein were also reported, and the experience was summarized.

METHODS

Population

Between October 2021 and November 2021, 5 patients with a prior pacemaker or ICD undergoing CRT upgrade were prospectively enrolled. This study complied with the Declaration of Helsinki, and the protocol was approved by the local ethics committee. Informed written consent was obtained from each patient. A comprehensive CRT pre-assessment included the New York Heart Association functional class, Minnesota Living with Heart Failure Questionnaire score, 6-min walk distance, and echocardiographic assessment of LV systolic function with 2-dimensional and 3-dimensional (3D) datasets. Patients fulfilling standard CRT criteria [New York Heart Association functional class II–IV drug refractory heart failure, left ventricle ejection fraction (LVEF) $< 35\%$, and QRS > 150 ms] were included in the study (1).

Prior to implantation, all patients underwent clinical examination, a 12-lead electrocardiogram (ECG) recording, and routine transthoracic echocardiography (TTE). Transthoracic echocardiography was performed to assess baseline LV function and the location of infarct scars, whenever present.

CATHETER DESCRIPTION

Lee's venogram balloon catheter (**Figure 1**), made of thermoplastic polyurethane (TPU), is a 6-Fr catheter with coronary sinus shaping. It has a central lumen, this permits one 0.035″ Radifocus **guidewire** or two 0.014″ guidewires access, transduction of pressures through a manifold, and contrast injections. There is another port for balloon occlusive venogram. The working balloon is made of a polyamide material.

Implant Procedure

The first step involves the insertion of a 23-cm-long 9-Fr splitable introducer sheath through standard left axillary venous access (if necessary, right axillary vein can also be selected), with the tip positioned at the junction of the superior vena cava and high right atrium. Next, a 9 French (Direct^{TM} PL 115, St. Jude) CS sheath is inserted through the sheath and placed in the right atrium, with Lee's venogram balloon catheter (APT Medical, PRC) advanced through the lumen to the mid to lower right atrium. CS cannulation was performed by advancing a 0.035 inch Radifocus guidewire (Terumo Co., Japan) to the region of the CS ostium *via* a preformed Lee's venogram balloon catheter and probing to locate the CS ostium. Left anterior oblique (LAO) fluoroscopic views guided Lee's venogram balloon catheter cannulated into the CS. After successful cannulation, a Radifocus guidewire (Terumo Co., Japan) was advanced into the distal CS. Following confirmation of unrestricted guidewire movement within the distal CS, great cardiac vein (GCV) and anterior interventricular vein (AIV), Lee's venogram balloon catheter was advanced over the wire into the CS body. The Radifocus guidewire (Terumo Co., Japan) was withdrawn, and a CS venogram (anteroposterior; left-anterior-oblique 45°) was then performed to identify branches suitable for placement of the LV lead. A suitable coronary venous branch was selectively cannulated using a runthrough-NS floppy guidewire (Terumo) passed through Lee's venogram balloon catheter lumen, with the catheter essentially functioning as a guide for support. Once the guidewire entered the targeted vein, the guidewire was advanced deep into the distal segment of the vein to provide a track for the lead to enter into the vein and reach the desired final position. Advancing the lead while retracting the wire (the "push-pull" technique) wedges the lead tip into narrow venous segments and stabilizes the lead after withdrawing the Lee's venogram balloon catheter. The pacing parameters were measured, and if satisfactory, the introducer sheath was carefully pulled and split outside the body.

Statistical Analysis

Continuous variables are given as the mean ± *SD*, and categorical variables are given as percentages or frequencies.

RESULTS

The LV lead was successfully implanted in a target vein in all 5 patients without acute complications. Values for procedure time, fluoroscopy time, fluoroscopy dose, and contrast volume are summarized in **Table 1**. The mean skin-to-skin (from first incision to last stitch and dressing) procedure time was 57.4 ± 12.5 min. The LV lead implantation time was 12.6 ± 4.9 min. The fluoroscopy time was 5.0 ± 3.0 min. In

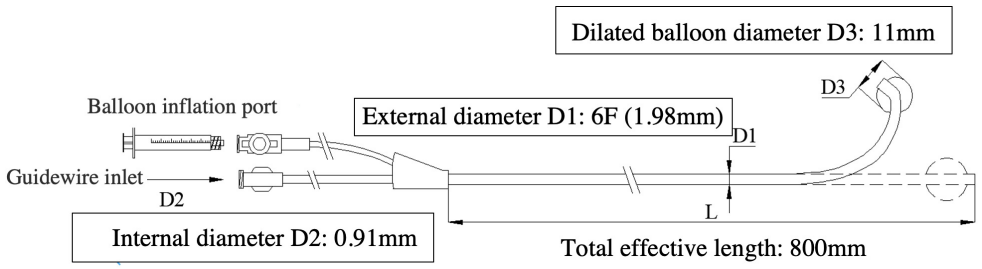

FIGURE 1 | The Lee's venogram balloon catheter (6F-11 mm-CS) with coronary sinus shaping, has an open lumen, over-the-wire design, which tracks over the guidewire and allows access to any site of the coronary vein system. Schematic diagram of the Lee's venogram balloon with: balloon inflation port and guidewire port for access to central lumen.

TABLE 1 | Baseline clinical data of the five patients.

Case no.	Gender	Age	Ischemic cardiomyopathy	upgrade to CRT	CRT/CRT-D	QRS duration (ms)	LVEDD (mm)	LVEF (%)	NYHA class
1	Male	85	Yes	No	CRT	164	72	31	3
2	Male	84	Yes	No	CRT-D	177	76	28.2	4
3	Male	74	Yes	No	CRT	171	77	33.8	3
4	Female	73	No	Yes	CRT	160	67	45	3
5	Male	64	Yes	Yes	CRT	224	55	40.6	3

CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

TABLE 2 | Procedural details.

Case no.	LV lead implantation (min)	Procedure time (min)	Fluoroscopy time (min)	Right-sided CRT/CRT-D	Guiding catheter/sheath	Guidewire
1	8	59	0.8	No	CPS direct™ PL Peelable Outer Guide Catheter, St. Jude	Radifocus guide wire
2	10	55	3	No	CPS direct™ PL Peelable Outer Guide Catheter, St. Jude	Runthrough NS × 2
3	20	75	5	No	CPS direct™ PL Peelable Outer Guide Catheter, St. Jude	Runthrough NS × 2
4	10	40	8	Yes	CPS direct™ PL Peelable Outer Guide Catheter, St. Jude	Runthrough NS × 2
5	15	58	8	No	CPS direct™ PL Peelable Outer Guide Catheter, St. Jude	Runthrough NS × 2

LV, left ventricle.

one patient (20%), fluoroscopy times of < 60 s were achieved (**Table 2**). No adverse events occurred during the procedures or within 24 h of follow-up.

CASE DESCRIPTION

Case #1: Patient With Advanced HF Functional New York Heart Association Class III

An 85-year-old male with symptomatic HF (NYHA class III) despite optimal drug therapy, ischemic cardiomyopathy, depressed LVEF (31%), and QRS duration of 164 ms with left bundle branch abnormality morphology was referred to the Cardiology Division for further evaluation. Given the severe HF symptoms and the patient profile, CRT was desired. The LV electrode was successfully deployed *via* Lee's venogram balloon catheter according to the above implant procedure steps (**Figure 2** and Video 1). The selected epicardial pacing site was posterolateral, and the pacing threshold after anchoring the LV lead (Quartet 1458Q, St Jude Medical) was 1.3 V at 0.5 ms. The procedure time was 59 min. The LV lead implantation time was 8 min. The fluoroscopy time was 48 s. During implantation and in post-procedure follow-up, biventricular pacing was observed *via* ECG. Echo analysis indicated acute improvement in mechanical synchrony of contraction and increased LVEF.

Case # 2: Patient With Acute Angulated Venous Branches

An 84-year-old male with ischemic cardiomyopathy, low LVEF (28%), and advanced HF functional NYHA class IV was referred to the Cardiology Division for further evaluation. The patient had

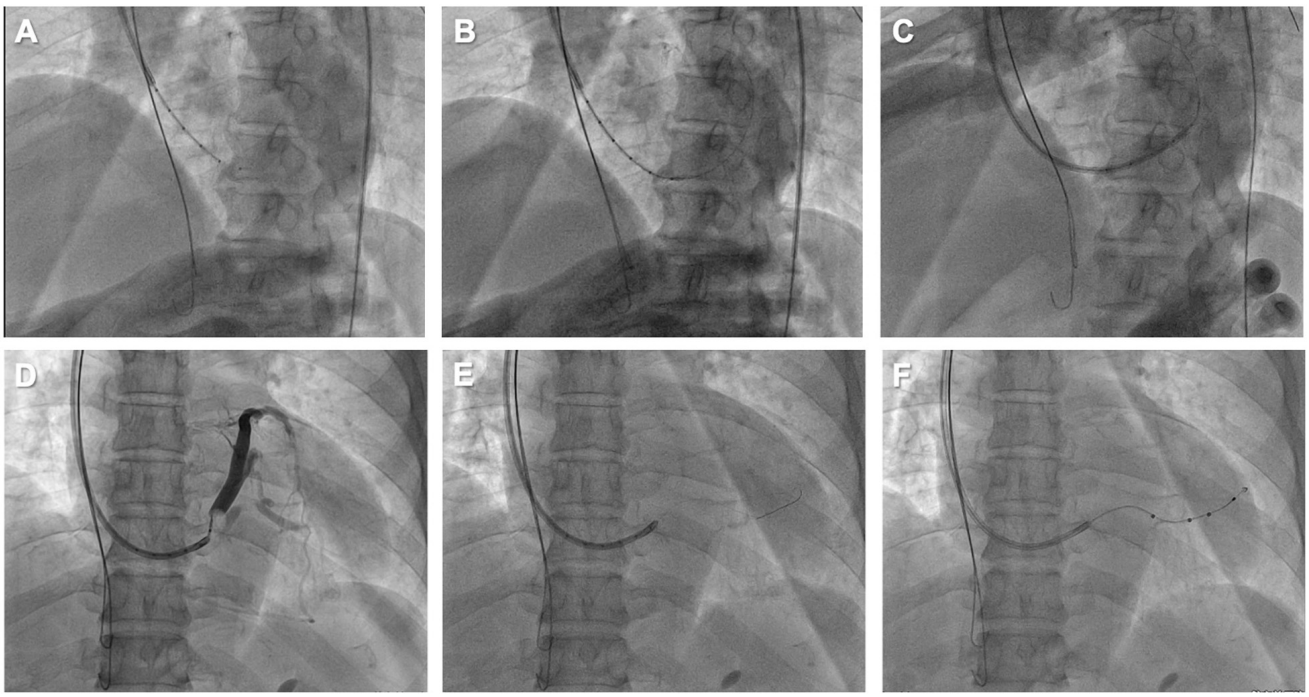

FIGURE 2 | (A) Lee's venogram balloon catheter advanced through the 9 French CS sheath lumen to the CS ostium. **(B)** Radifocus guidewire was successfully cannulated into the coronary sinus through Lee's venogram balloon central lumen. **(C)** The Radifocus guidewire is advanced to the distal CS and used to advance the inner guide and 9 French CS sheath into the CS. **(D)** Lee's venogram balloon occlusion angiogram of the CS in anteroposterior projection. **(E)** The advance runthrough-NS floppy guidewire into target vein along Lee's venogram balloon lumen. **(F)** Once the guidewire is into the target branch, the Lee's venogram balloon is removed and the LV lead is advanced over the guidewire.

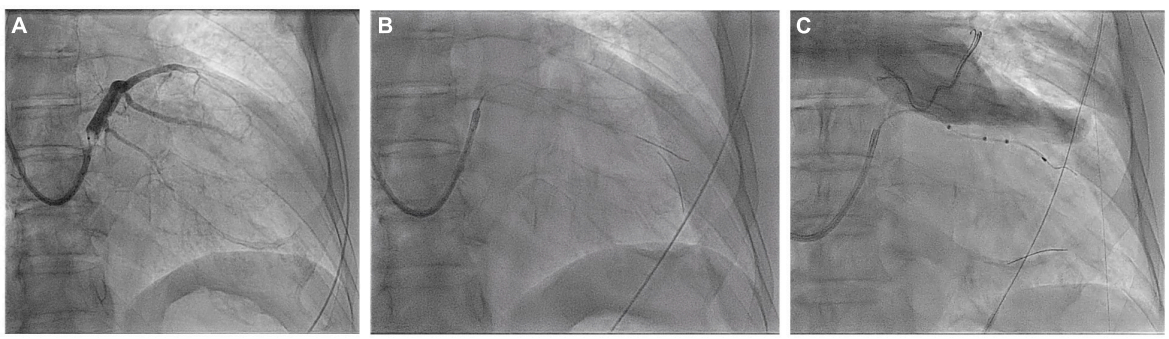

FIGURE 3 | Coronary sinus venogram **(A)** and fluoroscopic images identifying the sharply angulated posterolateral branch of the coronary sinus **(B)** and the placement of the LV pacing lead using the double wire technique **(C)** (see text for details).

three-vessel disease treated with multiple percutaneous coronary interventions; conventional angiography performed at admission showed stent patency and no further stenosis was amenable to treatment. Due to a left bundle branch block and QRS duration of 177 ms, he was treated with a cardiac resynchronization therapy with a defibrillator CRT-D device. In this patient, the desired vein had an acute angle of take-off, which made it difficult to access (**Figure 3A** and Video 2). Even when the vein could be subselected with a guidewire, there may have been inadequate support to track the lead over the wire without prolapse of the guidewire back into the CS. A way to approach this problem is to double-wire the acute take-off vein. As described by Chierchia (7), two 0.014″ runthrough-NS floppy guidewires (Terumo) are placed in the sharply angulated vein that "opens the vein," reducing tortuosity and providing much more support. The positioning of this second guidewire against the vein's wall effectively reduced the acuteness of the angle of the side branch, which permitted the over the-wire LV to be further advanced over the guidewire to reach a stable pacing position (**Figure 3B** and Video 2). Both wires were then retracted, leaving the LV lead (Quartet 1458Q, St Jude Medical) in position (**Figure 3C**). Pacing threshold was 0.5 V at a pulse width of 0.5 ms.

Case 3: Patient With Acute Angulated Venous Branches Coupled With an Enlarged Right Atrium

A 77-year-old man with ischemic cardiomyopathy and persistent atrial fibrillation was referred to our center because of drug refractory heart failure. At admittance, the ECG showed atrial fibrillation with a wide QRS complex of 171 ms. Transthoracic echocardiography and left ventricular angiography were performed, which showed severe left ventricular dysfunction (EF = 34%), moderate mitral valve regurgitation, and left ventricular apical aneurysm. The indication for cardiac resynchronization therapy (CRT) was made. A 9 French (CPS Direct^{TM} PL 115, St. Jude) CS sheath was inserted in the enlarged right atrium using left axillary venous access. However, right atrial enlargement makes it difficult for conventional electrophysiological catheters to enter the CS; even if the electrophysiological catheter can enter the CS, it is difficult to provide sufficient support to introduce the CS sheath into the CS. Using Lee's venogram balloon catheter, these difficulties can be easily overcome with the support of a Radifocus guidewire (Terumo Co., Japan) (**Figure 4A** and Video 3). The venogram showed a very angulated anterolateral side branch (**Figure 4B** and Video 3). The Radifocus guidewire was advanced in this side branch into the anterolateral branch. Lee's venogram balloon catheter subselectively entered the anterolateral side branch along the Radifocus guidewire (**Figure 4C** and Video 3). Then, the Radifocus guidewire was pulled out, and a runthrough-NS floppy guidewire (Terumo) was sent into the anterolateral side branch from the lumen of Lee's venogram balloon catheter. Negotiating the acute angle with the LV lead consistently pushed the CS guiding sheath back into the right atrium. Another runthrough-NS floppy guidewire was inserted into the anterolateral branch as a second wire to attempt to straighten the angle of the vessel (**Figure 4D** and Video 3). The positioning of this second guidewire against the vein's wall effectively reduced the acuteness of the angle of the side branch and provided enough support, which permitted the over the wire LV lead (Quartet 1458Q, St Jude Medical) to be further advanced over the runthrough-NS floppy guidewire to reach a stable pacing position (**Figures 4E,F**). Both wires were then retracted, leaving the LV lead in position. Pacing threshold was 1.2 V at a pulse width of 0.5 ms.

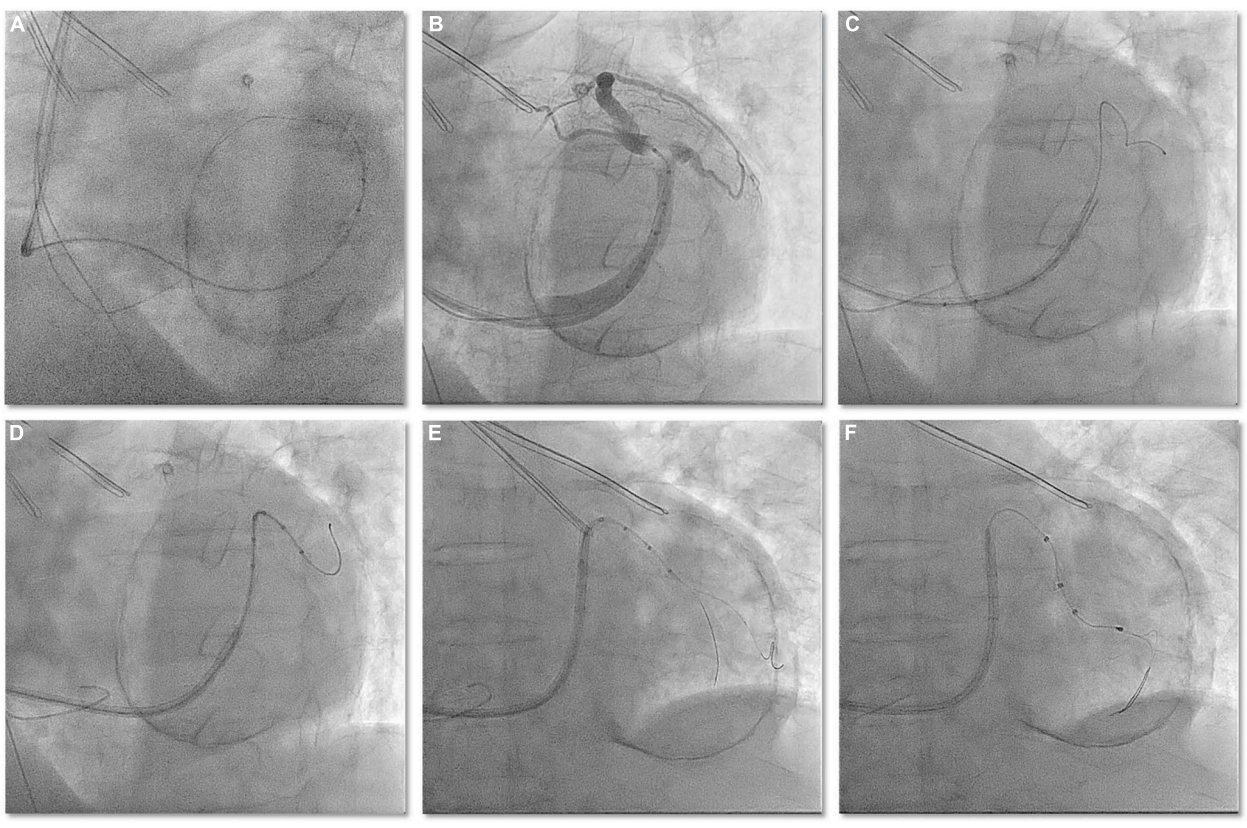

FIGURE 4 | (A) In the case of obvious enlargement of the right atrium, the Radifocus guidewire can be easily cannulated into the CS guided by Lee's venogram balloon. **(B)** Lee's venogram balloon CS venography showed acute angled anteriolateral veins. **(C)** Radifocus guidewire subselectively entered the anterolateral side branch. **(D)** Lee's venogram balloon catheter subselectively entered the anterolateral side branch along the Radifocus guidewire. **(E)** After withdraw the Radifocus guidewire, double guidewires subselectively entered the anterolateral side branch along the Lee's venogram balloon. **(F)** LV lead is advanced into anteriolateral veins over the guidewire.

Case #4: Upgrade of Single Chamber Ventricular Pacemakers to Cardiac Resynchronization Therapy *via* the Right Axillary Vein

A 73-year-old female patient was referred to our center to upgrade a single-chamber pacemaker (implanted 4 years ago for sick sinus dysfunction) to a CRT system, following the symptoms of worsening dyspnea for 2 years, which progressed to dyspnea at rest. An ECG showed a prolonged PR interval, a left bundle branch block, and an anterior left fascicular block. The QRS interval was 160 ms in duration. A two-dimensional echocardiogram revealed a dilated LV with an end-diastolic diameter of 67 mm, an LVEF of 45%, and severe mitral regurgitation. The previously implanted right side right ventricular lead functioned well and was thus kept in place. A straight curve 9 French (CPS Direct^{TM} PL 115, St. Jude) CS sheath was inserted in the CS using right axillary venous access. The right-sided LV lead implantation poses a unique challenge given the multiple angles the sheath must take before engaging the CS. Moreover, RA enlargement expands the subeustachian space and distorts the eustachian ridge, creating a barrier to CS entry. In this greatly enlarged RA, a Lee's venogram balloon catheter inside a conventional guide catheter extends the reach of the system and directs a guidewire or contrast injection superiorly toward an upwardly angulated CS (**Figure 5A** and Video 4). Radifocus guidewire subselected lateral side branch *via* Lee's venogram balloon catheter after CS venogram (**Figure 5B** and Video 4). The catheter was also subselected along the guidewire into the lateral side branch, and then the guidewire was withdrawn (**Figure 5C** and Video 4). To increase the supporting force, two runthrough-NS floppy guidewires (Terumo) were inserted into the lateral side branch *via* the Lee catheter. The St Jude Quartet Model 1458Q quadripolar LV lead was subsequently advanced over the wire into the lateral side branch (**Figure 5D** and Video 4). Both wires were then retracted, leaving the LV lead (Quartet 1458Q, St Jude Medical) in position (**Figures 5E,F**). The pacing threshold was 1.2 V at a pulse width of 0.5 ms.

Case #5: Target Vessel Ostium Low and Steep Angles for Upgrading a Pre-existing DDD Pacemaker to Cardiac Resynchronization Therapy

64-year-old male with ischemic cardiomyopathy, low LVEF (40%), and advanced HF functional NYHA class III was referred to the Cardiology Division for further evaluation. Coronary artery bypass grafting was performed 14 years ago for three-vessel coronary artery disease, and double-chamber pacemaker implantation was performed 10 years ago

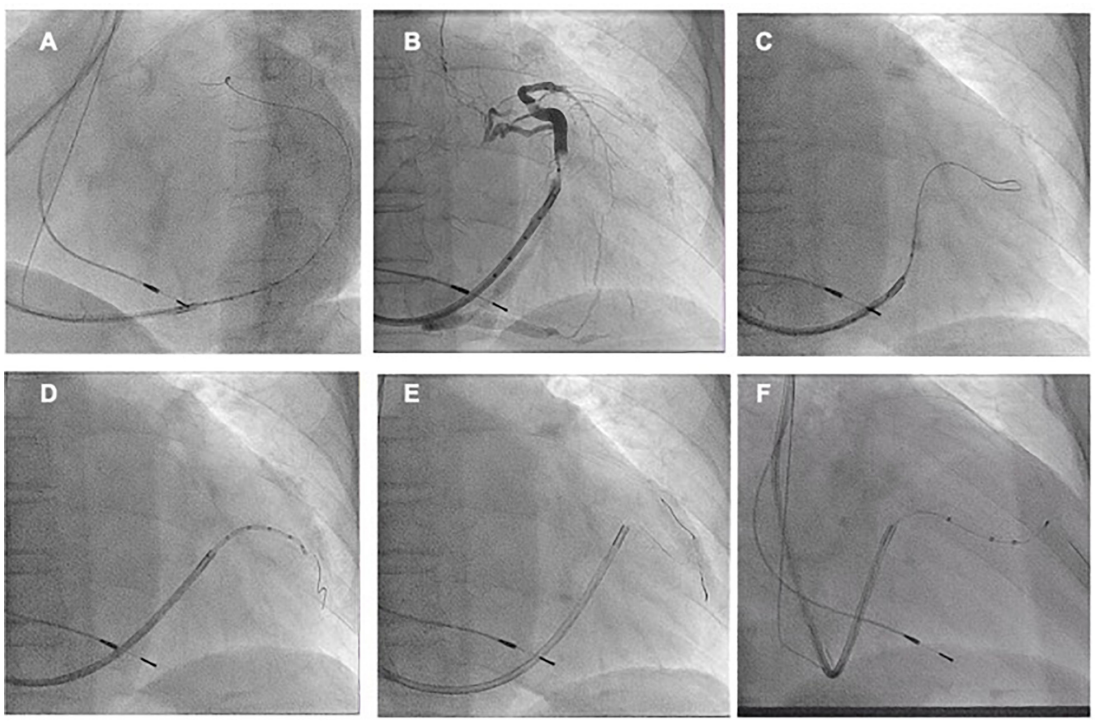

FIGURE 5 | (A) After the right axillary venous puncture, the CS cannulation catheter (CPS Direct^{TM} PL Peelable Outer Guide Catheter ST-JUDE) was guided through the Lee's venogram balloon catheter to the CS ostium, and then the CS was cannulated in the left anterior oblique position by passing the Radifocus guidewire through the Lee's venogram balloon. **(B)** Upon cannulation of the CS, the CS sheath is advanced over the Lee's venogram balloon into the CS. Then, a coronary venous angiogram is obtained with contrast injection to delineate the venous anatomy and select the target vein (arrow). **(C,D)** After the Radifocus guidewire was subselected to enter the target vein, Lee's venogram balloon catheter enters the target vein along the Radifocus guidewire. Lee's venogram balloon catheter was then withdrawn. **(E,F)** After proceeding the double wires to the target branch, the LV lead was finally delivered to the lateral branch over the wire.

for sick sinus syndrome. Coronary computed tomographic angiography performed at admission showed bridge vessel patency and no further stenosis amenable to treatment. ECG at admission showed DDD pacing mode, pacing QRS duration 224 ms. Transthoracic echocardiography and left ventricular angiography were performed, which showed severe left ventricular dysfunction (LVEF = 41%) and segmental inferior wall motion abnormalities. The indication for a CRT was made. The CS venogram *via* Lee's venogram balloon catheter showed a very angulated and tortuous target vein (inferolateral side branch) (**Figure 6A** and Video 5). Moreover, the target vein ostium was low, and without a guidewire anchor, the CS guiding sheath easily prolapsed back into the right atrium. One runthrough-NS floppy guidewire (Terumo) was sent through Lee's venogram balloon catheter to the great cardiac vein for anchoring and then through Lee's venogram balloon catheter into the second runthrough-NS floppy guidewire (Terumo) to the target vein (**Figure 6B** and Video 5). Since the target vein is still sharply angled with a guidewire, the guidewire in the great cardiac vein is also delivered into the target vein. Using this "double wire technique," tortuosities in the target branch are straightened, allowing uninhibited lead advancement (**Figure 6C** and Video 5). The "double wire technique" reduces the abruptness of the angle of sharply angulated CS side branches by placing two wires in the target vessel. By keeping both wires in the side branch, a wire that is positioned against the wall of the vein can decrease the sharp angle, permitting the over the wire LV lead (Quartet 1458Q, St Jude Medical) to be finally delivered to the inferolateral branch over the other guidewire (**Figure 6D** and Video 5).

Complications

No adverse catheter-related events occurred during the procedures. No reoperation due to LV leads capture loss, phrenic nerve pacing, or infection occurred during follow-up.

DISCUSSION

In this article, we demonstrate the feasibility and safety of using Lee's venogram balloon catheter to guide CS cannulation and St Jude Quartet Model 1458Q quadripolar LV lead implantation. We demonstrated this in five patients who had standard indications for CRT, in whom this catheter was used as a first-line tool.

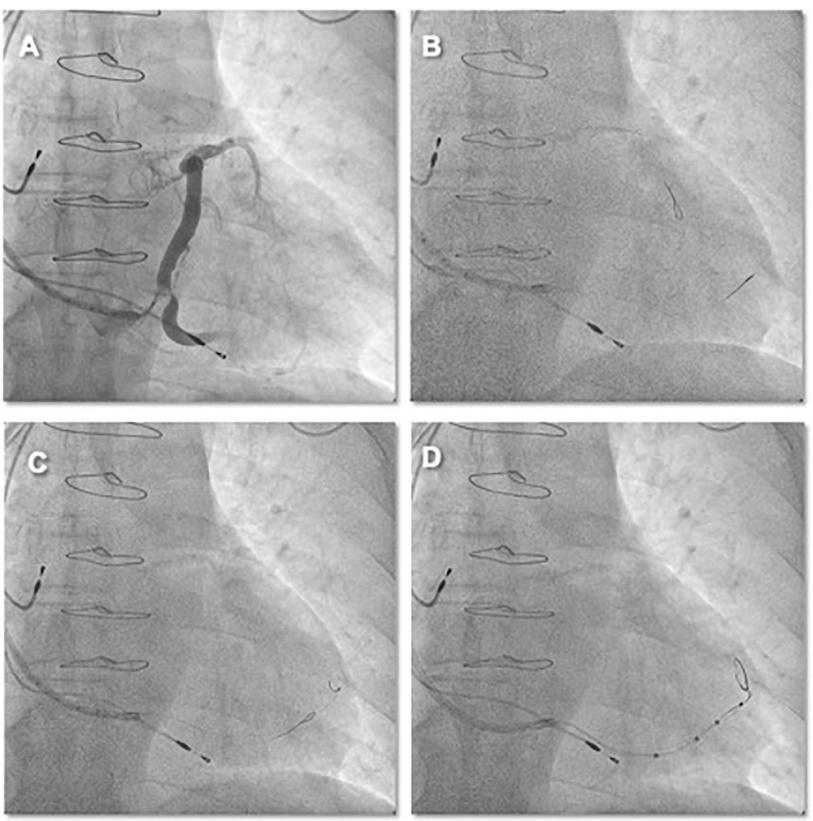

FIGURE 6 | (A) CS venography by Lee's venogram balloon showed that the target vessel ostium was low, sharply angled, and close to the CS ostium. Without runthrough-NS floppy guidewire anchorage, the CS sheath was easy to prolapse out of the CS. **(B)** One runthrough-NS floppy guidewire was sent to the great cardiac vein *via* Lee's venogram balloon for anchoring. **(C,D)** The positioning of the second guidewire through Lee's venogram balloon against the vein's wall effectively reduced the acuteness of the angle of the side branch and this permitted the over the wire LV lead to be further advanced over the runthrough-NS floppy guidewire to reach a stable pacing position.

Our preliminary experience shows that Lee's venogram balloon catheter has the following advantages. First, Lee's venogram balloon catheter shape was compatible with patient's coronary sinus location, so this catheter facilitates CS cannulation. Second, under the guidance of Radifocus guidewire, Lee's venogram balloon catheter can be safely advanced to the distal end of great cardiac vein to avoid dissection. Once the Lee's catheter and the Radifocus guidewire reach the distal end of the coronary sinus, they can provide sufficient support to facilitate the delivery of the CS sheath, especially in cases where CS cannulation is difficult, such as patients with right atrial enlargement or patients with right-sided CRT implantation. Third, compared with the conventional catheters, Lee's venogram balloon catheter can integrate three operation steps: coronary sinus cannulation, coronary sinus venography, and guidewire into the target vessel, which simplifies the procedure and process and shortens the procedure time. Further combination of the double-wire technique can effectively overcome the difficulty of sharply angulated CS branches during left ventricular electrode implantation. Finally, it is no longer more expensive than traditional EP catheters and is comparably priced.

The use of Lee's venogram balloon catheter-guided CS cannulation along with guidewire and balloon hence provides a multiplicity of features within a single tool. It is possible that the novel venogram balloon catheter may shorten the learning curve for each individual operator. Larger studies are required for a comparison with standard techniques.

CONCLUSION

In this article, we describe a novel Lee's venogram balloon catheter guiding CS cannulation and LV lead implantation. This catheter involves utilizing a CS venogram balloon with a central lumen that can provide contrast injection and allow access to the CS over the guidewire. Once familiar, this catheter may provide a less complicated strategy that improves success rates, decreases procedure time, and decreases fluoroscopic exposure for the implanting physician.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University. The patients/participants provided their written informed consent to participate in this case study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JD and DY: conceptualization, methodology, software, investigation, formal analysis, writing—original draft, visualization, and writing—review and editing. JH: data curation and writing—original draft. LW: visualization and investigation. CW, DL, FZ, and CY: resources, supervision, software, and validation. XL: conceptualization, funding acquisition, resources, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Criteria for differentiating left bundle branch pacing and left ventricular septal pacing: A systematic review

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Background: As a novel physiological pacing technique, left bundle branch pacing (LBBP) can preserve the left ventricular (LV) electrical and mechanical synchronization by directly capturing left bundle branch (LBB). Approximately 60–90% of LBBP were confirmed to have captured LBB during implantation, implying that up to one-third of LBBP is actually left ventricular septal pacing (LVSP). LBB capture is critical for distinguishing LBBP from LVSP.

Methods and results: A total of 15 articles were included in the analysis by searching PubMed, EMBASE, Web of Science, and the Cochrane Library database till August 2022. Comparisons of paced QRS duration between LVSP and LBBP have not been uniformly concluded, but the stimulus artifact to LV activation time in lead V5 or V6 (Stim-LVAT) was shorter in LBBP than LVSP in all studies. Stim-LVAT was used to determine LBB capture with a sensitivity of 76–95.2% and specificity of 78.8–100%, which varied across patient populations.

Conclusion: The output-dependent QRS transition from non-selective LBBP to selective LBBP or LVSP is direct evidence of LBB capture. LBB potential combined with short Stim-LVAT can predict LBB capture better. Personalized criteria rather than a fixed value of Stim-LVAT are necessary to confirm LBB capture in different populations, especially in patients with LBB block or heart failure.

KEYWORDS

left bundle branch pacing, left ventricular septal pacing, QRS complex, electrocardiogram, electrophysiology

Introduction

Left bundle branch pacing (LBBP) is a novel physiological pacing technique, in which the active fixation pacing lead delivered by the pre-shaped sheath advanced *via* a trans-ventricular septal approach to directly capture the proximal left bundle branch (LBB) or its branches underneath the left ventricular (LV) septal endocardium to preserve the normal sequence of LV electrical activation and mechanical contraction (1). LBBP can be divided into selective LBBP (SLBBP) and non-selective LBBP (NSLBBP) depending on whether or not the septal myocardium around the LBB is captured (2).

The implantation process of LBBP and LVSP is similar in that both of them are advanced from right ventricular (RV) septum *via* a trans-ventricular septal approach to LV septum, and both of them can produce relatively narrow paced QRS duration and continuously dynamic changes of paced QRS morphology from left bundle branch block (LBBB) to right bundle branch block (RBBB) pattern. LVSP, on the other hand, is fairly straightforward because there is no need to confirm the LBB capture by recording of LBB or His bundle potential, accurate initial pacing localization on fluoroscopy, or extra pacing maneuvers (3, 4). Approximately 60–90% of LBBP were confirmed to have captured LBB during implantation, implying that up to one-third of captures from the left septum are actually LVSP (5, 6). Currently, some researches have provided reliable strategy for distinguishing LBBP from LVSP, with sensitivity ranging from 70 to 100% and specificity reaching 100% (3, 6, 7). In this review, we will focus on the electrical differences between LBBP and LVSP, as well as describe the electrophysiological and electrocardiographic criteria for differentiating LBBP and LVSP.

Search strategy and outcomes

Electronic databases, including PubMed, EMBASE, Web of Science, and the Cochrane Library database were comprehensively searched (until August 2022) to identify primary references using the terms of (1) "left bundle branch pacing" OR "left bundle branch area pacing" and (2) "left ventricular septal pacing." We excluded animal studies, abstracts, reviews, editorial and individual case reports. References from the relevant articles were reviewed and related articles were identified. A total of 15 articles were selected for detailed review (3–17) (Table 1).

Physiology and practicality of LVSP

Back in 1970, Durrer et al. measured the total excitatory process of seven isolated normal human hearts by as many as 870 intramural terminals (18). Within 5 ms of the occurrence of the LV action potential, the three LV endocardial areas were first activated synchronously that were high on the anterior para-septal wall just below the attachment of the mitral valve, central on the LV septal endocardium, and posterior para-septal about one-third of the distance from apex to base. The excitatory propagated rapidly across these three areas during the following 5–10 ms, and fusing by 15–20 ms (18). Pacing in these first activated areas of the LV septal endocardium can thus be expected to obtain the intrinsic physiological excitation sequence. Subsequently, Little et al. demonstrated in 1982, using echocardiography on nine open-chest dogs, that pacing from the left side of the interventricular septum exhibited the identical sequence of interventricular septal excitation and motion as the intrinsic sinus rhythm (19). Peschar et al. investigated LV systolic and diastolic function using pressure-volume relations with normal sinus rhythm, LVSP, conventional RV pacing, various epicardial sites pacing, and combinations of pacing schemes, and found that LVSP could best maintain normal LV pump function, which possibly due to LVSP producing physiological electrical propagation (19).

In 2016, Mafi-Rad et al. studied LVSP in sick sinus syndrome (SSS) patients with normal cardiac structure and found that LVSP had an immediate effect on LV hemodynamics comparable to atrial pacing and superior to RV apex pacing (RVAP) and RV septal pacing (RVSP) (20). Furthermore, LVSP has a shorter pacing QRS duration than RVAP and RVSP (144 ± 20 vs. 172 ± 33 vs. 165 ± 17 ms, $P = 0.02$ and 0.004, respectively) (20). At 6 months of follow-up, pacing parameters of LVSP remained stable with no lead-related complications. Recently, it was demonstrated that LVSP provides outstanding electrophysiological and hemodynamic performance in patients undergoing cardiac resynchronization therapy (CRT) indications, at least as well as conventional biventricular pacing (BVP) and potentially His bundle pacing (HBP) (21).

Physiology and practicality of LBBP

LBB, originating in branching portion of the His bundle located underneath the junction of the non-coronary cusp and the right coronary cusp of the aortic valve, distributed in a broad ribbon-like structure in the LV septal sub-endocardium (22, 23). LBB has two main fascicles, the slender left anterior fascicle that heads the anterior papillary muscle and the thick left posterior fascicle (LPF) that heads the posterior papillary muscle of the mitral valve. Furthermore, virtually all of the LV septal fibers, which originate from LPF, were interlaced into a network that radiates to the inferior third of endocardium on left side of the interventricular septum (23). Because of the abundant interfascicular network connections of LV septal fibers, it is possible that when one of the fascicles is blocked, the QRS duration is not significantly prolonged. The ribbon-like structure and interfascicular network connections of LBB make LBBP implantation easier than HBP.

LBBP has electrophysiological advantages over HBP in addition to anatomical advantages. According to the longitudinal dissociation theory, LBB and RBB have been predominantly separated by the insulated fiber sheath inside His bundle (22, 24, 25). The majority of bundle branch blocks may be in the main bundle branch within His bundle. Narula et al. normalized the bundle branch block with distal HBP, shortening the intrinsic prolonged HV interval by 20–35 ms (24). Upadhyay et al. used LV septal mapping in LBBB patients, and concluded that the site of block of complete LBBB was at the level of left-sided His bundle in 72% and in the LBB trunk in the others (26). This provides an electrophysiological basis

TABLE 1 Study characteristics of included studies.

Study	Patient number	Indication	LBB captured n (%)	Paced QRS duration (ms)			Stim-LVAT (ms)		
				LBBP	LVSP	*P*	LBBP	LVSP	*P*
Qian et al. (7)	68	Bradycardia	47 (69%)	113.4 ± 9.8	120.7 ± 10.7	0.005	None	None	None
Zhang et al. (8)	106	Bradycardia	78 (74%)	115.0 ± 9.4	126.6 ± 12.5	<0.01	70.8 ± 5.7	83.3 ± 7.8	<0.01
Jastrzebski et al. (6)	468	Bradycardia and/or HF	124 (26%)	154.5 ± 21.2 (NSLBBP)	159.3 ± 20.2	None	74.7 ± 12.0 (NSLBBP)	None	None
				175.8 ± 26.5 (SLBBP)			74.4 ± 13.0 (SLBBP)		
Heckman et al. (5)	50	Bradycardia, AVN ablate	31 (62%)	123 ± 22	None	None	73 ± 15	81 ± 13	0.138
Wu et al. (3)	None	Bradycardia and/or HF with LBBB	30 (21 of non-LBBB; 9 of LBBB)	134.3 ± 14.9 (non-LBBB)	141.7 ± 16.6	0.003	70.7 ± 7.7	90.8 ± 15.2	<0.001
				138.4 ± 15.4 (LBBB)	144.7 ± 14.0	0.027	81.7 ± 8.4	97.4 ± 13.1	<0.001
Curila et al. (12)	68	Bradycardia	None	104 (100, 108)	103 (100, 107)	>0.05	70 (66, 73)	86 (84,89)	<0.01
Curila et al. (13)	96	Bradycardia	57 (59%)	LBBP < LVSP (non-quantitative)		<0.001	68 (65, 71) (NSLBBP)	86 (83, 89)	<0.001
							70 (67, 73) (SLBBP)		
Vijayaraman et al. (14)	32	LBBB	25 (78%)	141 ± 15	None	None	75.2 ± 8.8 (NSLBBP)	90.4 ± 9.1	<0.001
							76.9 ± 8.3 (SLBBP)		
Jastrzebski et al. (9)	468	Bradycardia and/or HF	124 (26%)	154.5 ± 21.2 (NSLBBP)	159.3 ± 20.2	None	78.4 ± 10.8 (NSLBBP)	98.4 ± 13.9	None
				144.5 ± 24.4 (SLBBP)					
Shimeno et al. (10)	51	Bradycardia without LBBB	21 (41%)	137 ± 9 (NSLBBP)	135 ± 7	>0.05	60 ± 4 (NSLBBP)	76 ± 7	<0.01
				154 ± 11 (SLBBP)			60 ± 4 (SLBBP)		
Chen et al. (4)	43	Bradycardia without LBBB	27 (63%)	135.6 ± 10.9	141.6 ± 13.6	0.118	65.8 ± 8.1	81.6 ± 7.3	<0.001
Peng et al. (15)	59	Bradycardia	46 (78%)	105.3 ± 15.6	109.2 ± 9.6	0.287	72.0 ± 10.0	86.4 ± 12.3	0.001
Zhou et al. (16)	46	Bradycardia and/or HF	23 (50%)	104.26 ± 19.00	118.09 ± 23.20	0.032	48.70 ± 13.67	58.70 ± 13.67	0.032
Shimeno et al. (11)	126	Bradycardia	52 (41%)	135 ± 16 (NSLBBP)	141 ± 16	None	62 ± 9	72 ± 10	<0.001
				150 ± 22 (SLBBP)					
Qian et al. (17)	118	Bradycardia and/or HF ± LBBB	90 (76%)	115.9 ± 20.3 (Bradycardia)	135.3 ± 21.0	0.004	67.8 ± 7.8	80.9 ± 10.4	<0.001
				136.0 ± 14.4 (HF ± LBBB)	152.2 ± 15.9	0.005	77.1 ± 8.8	94.6 ± 10.4	<0.001

LBB, left bundle branch; Stim-LVAT, stimulus artifact to left ventricular activation time in lead V5 or V6; LBBP, left bundle branch pacing; NSLBBP, non-selective LBBP; SLBBP, selective LBBP; LVSP, left ventricular septal pacing; AVN, atrioventricular node; HF, heart failure; LBBB, left bundle branch pacing.

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for LBBP, allowing it to capture the LBB immediately beyond the conduction block with a low output (27), overcoming the limitations of HBP with high pacing output and even loss of capture (28, 29).

In 2017, Huang et al. performed LBBP on a patient with dilated cardiomyopathy and heart failure whose LBBB was not corrected by HBP. The typical LBBB with QRS duration of 180 ms was corrected by LBBP beyond the conduction block with a low pacing output, and then the accompanying RBBB morphology was eliminated by adjusting the atrioventricular delay (27). A number of studies have demonstrated the long-term safety, stability and superiority of LBBP as a physiologic pacing strategy for high-degree atrioventricular block, SSS, and atrioventricular node ablation, etc. (30–37). LBBP has also proved to be a promising method for delivering CRT for typical LBBB patients with low LV ejection fraction, improving heart failure symptoms and LV function greater than conventional BVP (38–40).

LBBP vs. LVSP

In theory, LBBP rapidly conducts electrical excitation through the intrinsic His-Purkinje system, accelerating the process of LV lateral wall depolarization while comparatively delaying the RV excitation, resulting in electrical dyssynchrony between the left and right ventricles (12, 13). LVSP, unlike LBBP, only captures the LV septal myocardium, and the electrical excitation in the interventricular septum is transversely conducted at the same time, so that the LV delayed excitation partially overlaps with the RV delayed excitation, resulting in a more balanced but non-physiological synchronization of the interventricular electrical excitation (2, 41).

According to the current study, the short-term effects of LBBP and LVSP on cardiac function seem to be less substantial in practice (4–6, 9, 10, 12, 13, 16). There was no consistent outcome in terms of paced QRS duration, although practically all investigations demonstrated that the stimulus artifact to LV activation time (LVAT) in lead V5 or V6 (Stim-LVAT) of LBBP was shorter than that of LVSP (Table 1). Shimeno et al. showed that the paced QRS duration of NSLBBP and LVSP was similar (135 ± 7 vs. 137 ± 9 ms, $P > 0.05$), while capturing LBB reduced the Stim-LVAT by about 10 ms or more (76 ± 7 vs. 60 ± 4 ms, $P < 0.01$) (10). Curila et al. showed no significant difference in the paced QRS duration between LBBP and LVSP [104 (100, 108) vs. 103 (100, 107) ms, $P > 0.05$], similar to the results reported by Peng et al. (105.3 ± 15.6 vs. 109.2 ± 9.6, $P = 0.287$) (15). However, in another study by Curila et al., the paced QRS duration of LBBP was shorter than that of LVSP in close proximity to LBB (13). A retrospective study by Zhou et al. found that LBBP and LVSP had stable pacing parameters and no significant difference in LV function improvement. However, LVSP has the advantage of shorter implantation time than LBBP (38.13 ± 11.52 vs. 53.52 ± 14.39 min, $P < 0.001$), although paced QRS duration is slightly longer (118.09 ± 23.20 vs. 104.26 ± 19.00 ms, $P = 0.032$). It should be noted that the Stim-LVAT of LBBP and LVSP in this study were 48.70 ± 13.67 and 58.70 ± 13.67 ms, respectively, which are significantly shorter than those in any other studies (16). While only one study found no significant difference in Stim-LVAT between LBBP and LVSP (73 ± 15 vs. 81 ± 13 ms, $P = 0.138$), this study proved that LBBP seems to result in a small, but significant, improvement in ventricular synchrony when compared to LVSP by calculating QRS area using electrocardiography and vectorcardiogram (5).

In terms of comparing electrical synchrony between the left and right ventricles, utilizing ultra-high frequency electrocardiography, Curila et al. concluded that LBBP had more interventricular electrical desynchrony than LVSP, although LBBP preserves physiological LV depolarization (12, 13). Jastrzebski et al., in addition to showing that LVSP has longer Stim-LVAT and paced QRS duration than LBBP, established that LVSP has superior interventricular electrical synchrony by comparing the difference of R-wave peak time in V1 and V6 (V6-V1) of LBBP and LVSP (9). Interventricular synchrony is during LVSP improved compared to LBBP, however, at the cost of worsened LV activation. Chen et al. recently employed coronary sinus (CS) electrogram mapping to investigate the difference in LV electrical excitation sequence between LBBP and LVSP (4). In the absence of LBBB, the physiological electrical excitation on the CS electrogram propagates from LV lateral to posterior wall, implying that the ventricular electrogram signal recorded in the distal CS was ahead of the proximal CS. By using CS electrogram mapping, Chen et al. studied 27 LBBP patients and 16 LVSP patients and found that the LV electrical activation sequence of all LBBP were identical to intrinsic rhythm, whereas, that of all LVSP were non-physiological with the earliest activation region changed from lateral to posterior wall (4). Qian et al. first used SPECT imaging to assess ventricular mechanical synchrony in 68 bradycardia patients undergoing LBBP, demonstrating that a constant Stim-LVAT of <76 ms and recorded LBB potential had favorable LV mechanical synchrony and could be used as a criterion to determine LBB capture (7).

How to differentiating LBBP and LVSP

Stim-LVAT

Confirming LBB capture is essential for distinguishing LBBP from LVSP. Stim-LVAT, measured at high output pacing and threshold pacing, remained shortest and constant with 100% specificity for determining LBB capture (1, 3). During the decreasing of the pacing output, the transition from NSLBBP to SLBBP or LVSP is frequently observed. The Stim-LVAT remains the shortest and consistent during the transition from NSLBBP

to SLBBP if the lead tip is placed in the LBB trunk or its branches, and an isoelectric interval exists between the pacing artifact and the ventricular electrogram signal. If the lead tip is close to the LBB, NSLBBP will be converted to LVSP and Stim-LVAT will be rapidly extended by 10 ms during the output decrease (3). This is because the lead tip may capture both LV septal myocardium and LBB at a high-output pacing voltage, while only LV septal myocardium can be captured at a low-output pacing voltage, resulting in delayed LV electrical activation. However, Shimeno et al. reported that only 41.2% of LBB area pacing showed the output-dependent QRS transition from NSLBBP to SLBBP or LVSP (11).

LBB potential and retrograde His potential

LBB potential should be recorded in all patients with normal left conduction system (1, 3), but the presence of LBB potential is not direct evidence of LBB capture. In reality, ~68–98% of non-LBBB patients who completed LBBP (6, 39, 42) and a small fraction of those who completed LVSP can record the LBB potential. Chen et al., for example, recorded LBB potential in 88.9% of LBBP and also in 12.5% of LVSP. They assumed that the LBB potential recorded by LVSP was the far-field potentials downstream of LBB, and at this time, a higher pacing output was needed to conduct retrogradely to present a His potential (4). As a result, whether or not LBB potential was recorded could not be utilized as a criterion for LBB capture. The appearance of LBB potential could only indicate that the lead tip was close to the LBB area (3).

Theoretically, for non-LBBB patients, the interval between His potential and LBB potential recorded in sinus rhythm should be same as the interval between LBBP pacing artifact and retrograde His potential (3). At the output was <1.0 V/0.5 ms, retrograde HB and/or anterograde LBB potential recorded from HBP or multielectrode linear catheter which was placed across the aortic valve were evidence of direct LBB capture (3). However, not all patients who complete LBBP can record LBB potential.

The value of criteria for differentiating LBBP and LVSP

The predictive value of criteria for distinguishing LBBP from LVSP is summarized in Supplementary Table 1. In the non-LBBB group, Wu et al. calculated that Stim-LVAT had a specificity of 95% and sensitivity of 82% for LBB capture at 75 ms, and a specificity and sensitivity of 93 and 76% for LBB capture at 85 ms for LBBB group (3). Jastrzebski et al. reported that the optimal Stim-LVAT value for differentiating between LBBP and LVSP in patients with normal left conduction system was 83 ms, while in patients with LBBB the optimal Stim-LVAT value was 101 ms (6). In addition, they proposed a method to effectively predict LBB capture by combining LBB potential and LVAT in lead V6. For non-LBBB patients, the criterion of "paced LVAT in lead V6 (measured from QRS onset) ≤native LVAT in lead V6 (+10 ms)" for LBB capture has 98 and 85.7% sensitivity and specificity, respectively. For non-LBBB patients whose LBB potential can be recorded, the sensitivity and specificity of the criterion of "paced Stim-LVAT (measured from stimulus) ≤LBB potential to LVAT in lead V6 (+10 ms)" for LBB capture were 88.2 and 95.4%, respectively. They also proposed the use of the V6-V1 interval as a discriminating criterion (9). The transition from NSLBBP to SLBBP prolonged the interval of stimulus artifact to late R-wave in lead V1 (RWPTV1; 120.7 ± 16.7 vs. 138.5 ± 21.5 ms, $P < 0.001$) and Stim-LVAT (119.3 ± 14.5 vs. 125.6 ± 13.8 ms, $P < 0.001$). The transition from NSLBBP to LVSP resulted in an increase in Stim-LVAT by ≥15 ms (78.4 ± 10.8 vs. 98.4 ± 13.9 ms) but only minimally influenced RWPTV1 (77.2 ± 13.6 vs. 76.6 ± 14.1 ms, $P = 0.36$). Consequently, during SLBBP, the V6-V1 interval was longest, intermediate during NSLBBP, and shortest during LVSP (62.3 ± 21.4 vs. 41.3 ± 14.0 vs. 26.5 ± 8.6 ms, respectively). The optimal value of V6-V1 interval for distinguishing NSLBBP from LVSP was 33 ms, with a specificity of 90% and a sensitivity of 71.8%, while the V6-V1 interval for confirming the LBB capture was 44 ms, with a specificity of 100% (9). Recently, Chen et al. reported that when LBB potential was recorded in conjunction with Stim-LVAT ≤ 85 ms, the specificity and sensitivity of LBB capture were 93.7 and 95.2%, respectively, whereas if no LBB potential was recorded, Stim-LVAT ≤ 70 ms could also be considered as LBB capture, and vice versa, LVSP (4).

Stim-LVAT varies across patient populations and is prolonged in large ventricular size or LBBB in patients with heart failure (HF) (17), suggesting that determining LBB capture with a fixed value of Stim-LVAT is challenging. As a result, a personalized criterion to confirm LBB capture is beneficial. Jastrzebski et al. used the difference between the native V6 intrinsicoid deflection time (IDT) and the transseptal deflection time (TCT) to predict the LBB capture. The sensitivity and specificity of "paced LVAT in lead V6 (measured from QRS onset) +10 ms < (IDT-TCT)" for confirming LBB capture in LBBB patients were 77.8 and 100%, respectively (6). Vijayaraman et al. determined the Stim-LVAT of LBBB patients during HBP, NSLBBP, SLBBP, and LVSP and found it to be 91.7 ± 8.4, 75.2 ± 8.8, 76.9 ± 8.6, and 90.4 ± 9.1 ms, respectively ($P < 0.001$; LBBP vs. HBP and LVSP) (14). The delta Stim-LVAT between HBP and LBBP or LVSP (ΔStim-LVAT) was then used to confirmed the LBB capture. When ΔStim-LVAT was 8 ms, the specificity and sensitivity of LBB capture in LBBB patients were 93.3 and 100%, respectively. When >10 ms, 100 and 81% (14). Recently, Qian et al. established that ΔStim-LVAT may be utilized as

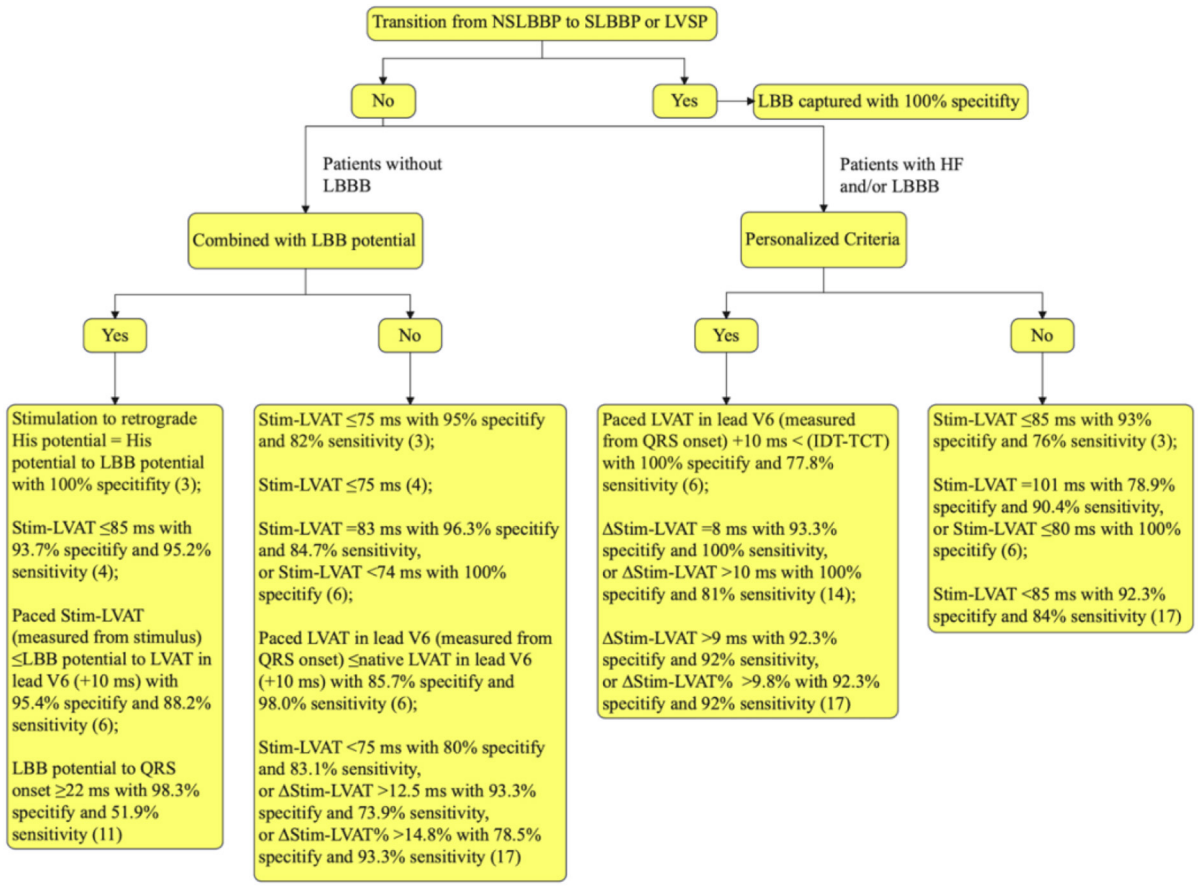

FIGURE 1
Flowchart for confirming LBB capture. LBB, left bundle branch; LBBB, LBB block; NSLBBP, non-selective LBB pacing; SLBBP, selective LBB pacing; LVSP, left ventricular septal pacing; HF, heart failure; Stim-LVAT, stimulus artifact to left ventricular activation time in lead V5 or V6; LVAT, left ventricular activation time; IDT, the native V6 intrinsicoid deflection time, measured from the earliest QRS onset in any surface lead (global method), not to the point of the highest amplitude, but to the end of the slur/plateau in QRS, that is to the beginning of the final rapid downsloping phase of R wave in lead V6; TCT, the transseptal conduction time, measured from earliest QRS onset in any surface lead to the endocardial indication of the arrival of the depolarization wavefront to the LBB area; ΔStim-LVAT, the Stim-LVAT discrepancy between His bundle pacing and LBBP or LVSP; ΔStim-LVAT%, ΔStim-LVAT divided by Stim-LVAT of His bundle pacing.

a reliable criterion to distinguish LBBP from LVSP in HF patients with or without LBBB. A cut-off value of ΔStim-LVAT > 9 ms confirmed LBB capture with 92% sensitivity. Furthermore, the percent reduction in ΔStim-LVAT, ΔStim-LVAT divided by Stim-LVAT of HBP (ΔStim-LVAT%), also shows excellent accuracy for LBB capture (17). The flowchart for confirming LBB capture in patients is summarized in Figure 1.

Conclusion

The transition from NSLBBP to SLBBP or LVSP is the gold standard for confirming LBB capture, but it may not be achieved due to similar capture thresholds for LBB and nearby myocardium. In this scenario, the recorded LBB potential combined with short Stim-LVAT can predict LBB capture and ventricular mechanical synchrony better. Personalized criteria, such as ΔStim-LVAT, ΔStim-LVAT%, or comparison of paced LVAT and difference between IDT and TCT, can be utilized to confirm LBB capture in patients with HF or LBBB.

Author contributions

KZ: conceptualization and writing—original draft preparation. LL and JL: contribute to our revised draft and provide useful comments. DC and QL: supervision and writing—reviewing and editing. All

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Three-dimensional electroanatomical mapping guidelines for the selection of pacing site to achieve cardiac resynchronization therapy

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Objectives: We aimed to evaluate the feasibility of left ventricular electroanatomical mapping to choose between left bundle branch area pacing (LBBAP) or coronary venous pacing (CVP).

Background: There are several ways to achieve left ventricular activation in cardiac resynchronization therapy (CRT): LBBAP and CVP are two possible methods of delivering CRT. However, the criteria for choosing the best approach remains unknown.

Methods: A total of 71 patients with heart failure, reduced ejection fraction, and left bundle branch block (LBBB) were recruited, of which 38 patients underwent the three-dimensional electroanatomical mapping of the left ventricle to accurately assess whether the left bundle branch was blocked and the block level, while the remaining 33 patients were not mapped. Patients with true LBBB achieved CRT by LBBAP, while patients with pseudo-LBBB achieved CRT by CVP. After a mean follow-up of 6 months and 1 year, the QRS duration and transthoracic echocardiography, including mechanical synchrony indices, were evaluated.

Results: Twenty-five patients with true LBBB received LBBAP, while 13 without true LBBB received CVP. Seventeen patients received LBBAP, and 16 patients received CVP without mapping. Paced QRS duration after the implantation of LBBAP and CVP was significantly narrower in the mapping subgroup compared to the non-mapping subgroup. A significant increase in post-implantation left ventricular ejection fraction was observed in patients with LBBAP or CVP, and the mapping subgroup were better than the non-mapping subgroup. After a 12-month follow-up, atrioventricular, intraventricular, and biventricular synchronization were significantly improved in the mapping subgroup compared to non-mapping groups in both LBBAP and CVP.

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Conclusion: In our study, three-dimensional electroanatomical mapping was used to choose LBBAP or CVP for heart failure patients, which proved feasible, with better cardiac resynchronization in the long-term follow-up. Therefore, three-dimensional electroanatomical mapping before CRT appears to be a reliable method for heart failure patients with LBBB who are indicated for CRT.

KEYWORDS

three-dimensional electroanatomical mapping, left bundle branch area pacing, coronary venous pacing, cardiac resynchronization therapy (CRT), heart failure

Introduction

Cardiac resynchronization therapy (CRT) remains an important therapy for heart failure patients with biventricular desynchronization (1–3). There are currently several ways to achieve left ventricular activation in CRT, of which coronary venous pacing (CVP) and left bundle branch area pacing (LBBAP) are two possible methods of delivering CRT (4, 5). Although there is a non-response rate of up to 30%, significant sound evidence demonstrates that traditional cardiac resynchronization therapy (coronary venous pacing to the left ventricle) can significantly improve major adverse cardiovascular events in patients with heart failure (6). In recent years, the His-Purkinje system pacing has emerged, especially for the treatment of the left bundle branch area pacing (LBBAP) for cardiac resynchronization. Although LBBAP is generally considered to be a second-line strategy to BiV pacing, as its benefits over conventional CRT have not been demonstrated in randomized trials, some studies have shown that LBBAP is effective and safe in clinical trials (7–9). However, for patients with heart failure and a left bundle branch block (LBBB), there is currently no research that demonstrates which criteria should be used to choose left ventricular pacing to achieve CRT. Earlier studies suggested that patients with heart failure and LBBB can be divided into two categories: one is a true left bundle branch block (including slow conduction), and the other is that the conduction of the left bundle branch is generally normal while the left ventricular local Purkins or myocardial conduction is delayed and lead to the ECG features of LBBB (10). Through the three-dimensional electroanatomical mapping of the left ventricle, it is possible to accurately assess whether the left bundle branch is blocked and the block level (11). This study hypothesizes that, first, for patients with a true left bundle branch block, CRT can be achieved through the left bundle branch regional pacing. For patients with heart failure whose left bundle branch conduction is normal but the ECG shows LBBB, classical CRT to implant the left ventricular electrode in the lateral cardiac vein can be achieved. Second, the X image of the tip of the mapping catheter in the left bundle branch area or the latest activation area of the left ventricle can be used as a reference for the implantation of the left ventricular electrode, thereby facilitating CRT surgery.

Abbreviations: CRT, Cardiac resynchronization therapy; CVP, Coronary venous pacing; LBBAP, Left bundle branch area pacing; LBBB, Left bundle branch block; LVEF, Left ventricular ejection fraction; IVMD, Interventricular mechanical delay; Ts-SD12, Standard deviation of Ts of 12 LV segments; TTE, Transthoracic echocardiography.

Methods

Study population

This observational study recruited 71 consecutive patients with heart failure (HF) having reduced left ventricular ejection fraction (LVEF) and LBBB who had indications for CRT (Figure 1). Inclusion criteria for the study were LBBB with QRSd $>$ 130 ms, LVEF $<$ 35%, and corresponding to the New York Heart Association functional class II to IV. All patients received standard medical treatment for at least 3 months before the implantation of the device. Twelve-lead electrocardiography (ECG) confirmed LBBB in all patients as defined by the American Heart Association, the American College of Cardiology Foundation, and the Heart Rhythm Society in 2009. Patients who could not give consent or were clinically unstable were excluded. All participants provided written informed consent. The study was approved by the Ethics Review Board of the First Affiliated Hospital of Kunming Medical University.

Three-dimensional electroanatomical maps of the LV

A right femoral artery puncture and intubation was performed using the Seldinger method with an 8-Fr arterial sheath, and 35 units of unfractionated heparin per kilogram was administered. A mapping catheter (THERMOCOOL, 4 mm tip, Biosense Webster Inc., California, USA or mini-basket array catheter, Boston Scientific, Washington, DC, USA)

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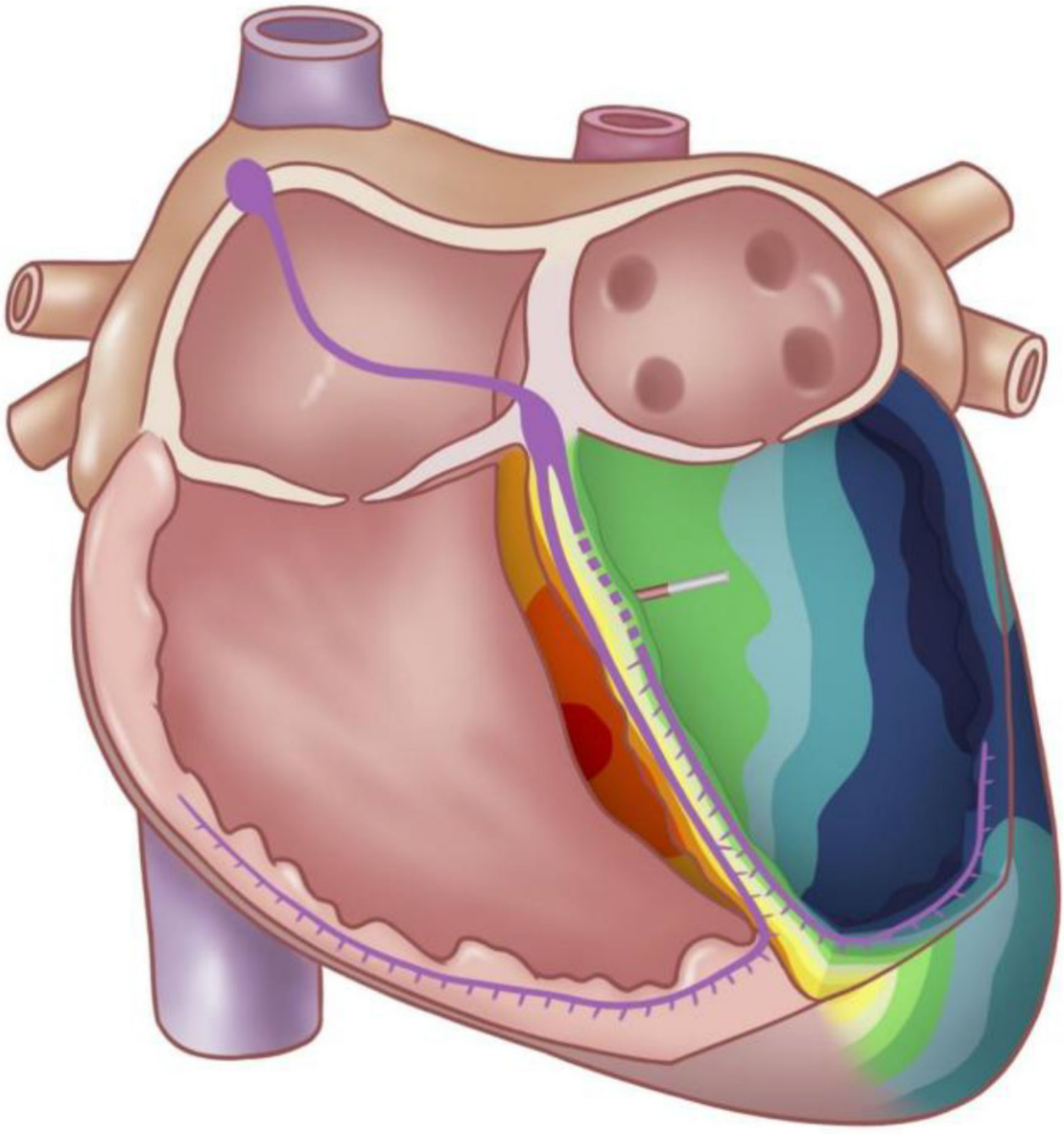

GRAPHICAL ABSTRACT
This study shows that three-dimensional electroanatomical mapping, with better cardiac resynchronization, provides informed guidance to choose between LBBAP or CVP for patients with heart failure.

was inserted from the sheath and advanced through the aortic valve with the J curve into the left ventricular (LV). Three-dimensional electroanatomical maps of the LV were reconstructed using a non-fluoroscopic navigation system (Fast Anatomical Mapping, CARTO 3®, version 6, Biosense Webster Inc. California USA) or electromagnetic navigation system (Rhythmia, Boston Scientific, Washington, DC, USA). First, activation mapping under sinus rhythm was performed to clarify the electroanatomical activation sequence of the left ventricle, especially the earliest and latest activation parts. Second, the potential of the His left bundle branch was mapped from the bottom to the apex of the left ventricular septum.

If the obvious potential was not mapped in the left bundle branch area, the mechanical stimulation in this area could occasionally improve the left bundle branch potential and induce subsequent premature ventricular contraction. Then, electrical stimulation was applied in the upper-middle area of the left bundle branch, and a QR or rSR morphology in surface lead V1 was observed, indicating there was a left bundle branch block or slow conduction. In the next

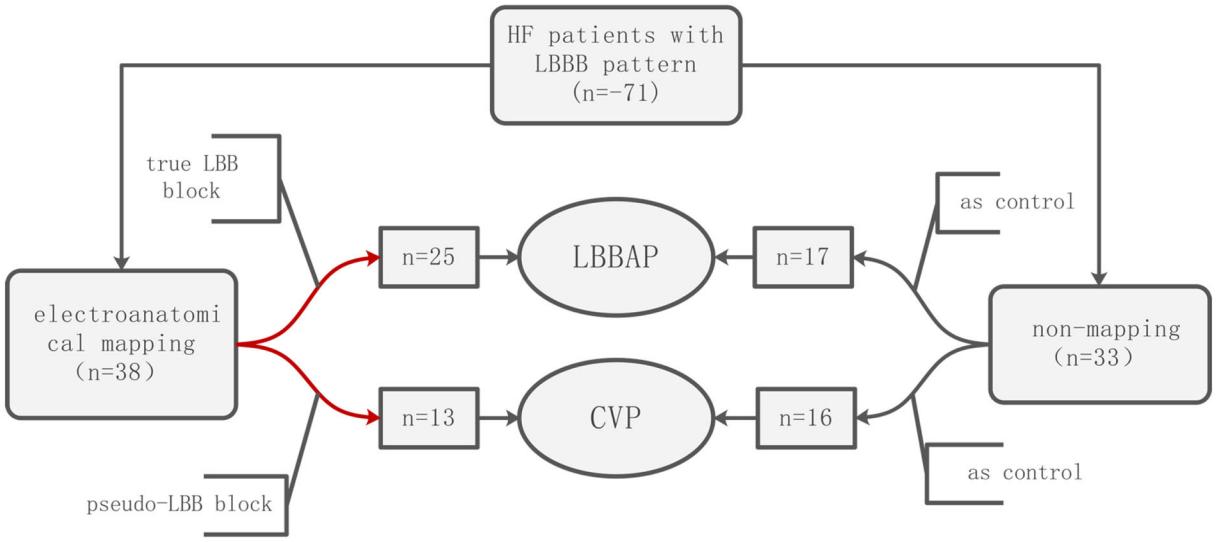

FIGURE 1
Patient flow.

step, LBBAP was planned, and the X-ray image of the location of the mapping catheter tip was recorded to guide the placement of the left bundle branch area electrode (Figure 2).

If the potential was mapped in the entire left bundle branch area, it indicated the patient's left bundle branch conduction was normal. Classical CRT with coronary venous pacing was planned, and the mapping catheter tip was placed on the latest activation part of the left ventricular activation; the X-ray image recorded the placement of the coronary venous electrode (Figure 3).

Implantation procedure of CRT

Venous access was obtained *via* the left axillary vein for all patients. The atrial active fixed electrode was placed in the right atrial appendage. The right ventricular defibrillator electrode was first placed in the apex of the right ventricle.

For the patient with LBBAP-CRT, the pacing lead (model 3830, 69 cm, Medtronic Inc., Minneapolis, MN, USA) was inserted through a fixed-curve sheath (C315 His, Medtronic Inc.). An intracardiac electrogram was recorded from the lead tip by using the electrophysiological recording system (Bard Electrophysiology Lab System, MA, USA). The tip of the mapping catheter placed in the area of the left bundle branch in the left ventricle was recorded at the right anterior oblique (RAO) 30° position and left anterior oblique (LAO) 45° as references. The sheath and lead tip were advanced to the right ventricular septum that was directly opposite the mapping catheter tip and subsequently rotated in a counterclockwise fashion so the lead tip was in a perpendicular orientation to the interventricular septum (IVS). A "W"-shaped pacing morphology in surface lead V1 was observed at this location. As the lead tip was gradually screwed into the IVS, a rightward shift of the second notch in the "W"-shaped pacing morphology could be observed. The lead tip was in the final position after a QR or rSR morphology in surface lead V1 was achieved.

For patients with CVP-CRT, the tip of the mapping catheter at the area of the last activation in the left ventricle was recorded at the RAO 30° and LAO 45° positions as references. After retrograde angiography of the coronary sinus, the lateral veins or posterolateral veins that were the closest to the tip of the mapping catheter were used to target the blood vessel implanted with left ventricular lead (Figure 4).

Programming of devices

A pacemaker was programmed to close the pacing function of the right ventricular pacing electrode but maintain the defibrillation function. The left ventricular lead pacing was gradually prolonged until the intracardiac electrogram showed atrial sensing–ventricular sensing. The atrial-ventricular delay (AVD) was shortened by 10-ms steps, and the ECG QRS duration was the narrowest. The corresponding AVD was optimized when the ECG QRS duration was the narrowest.

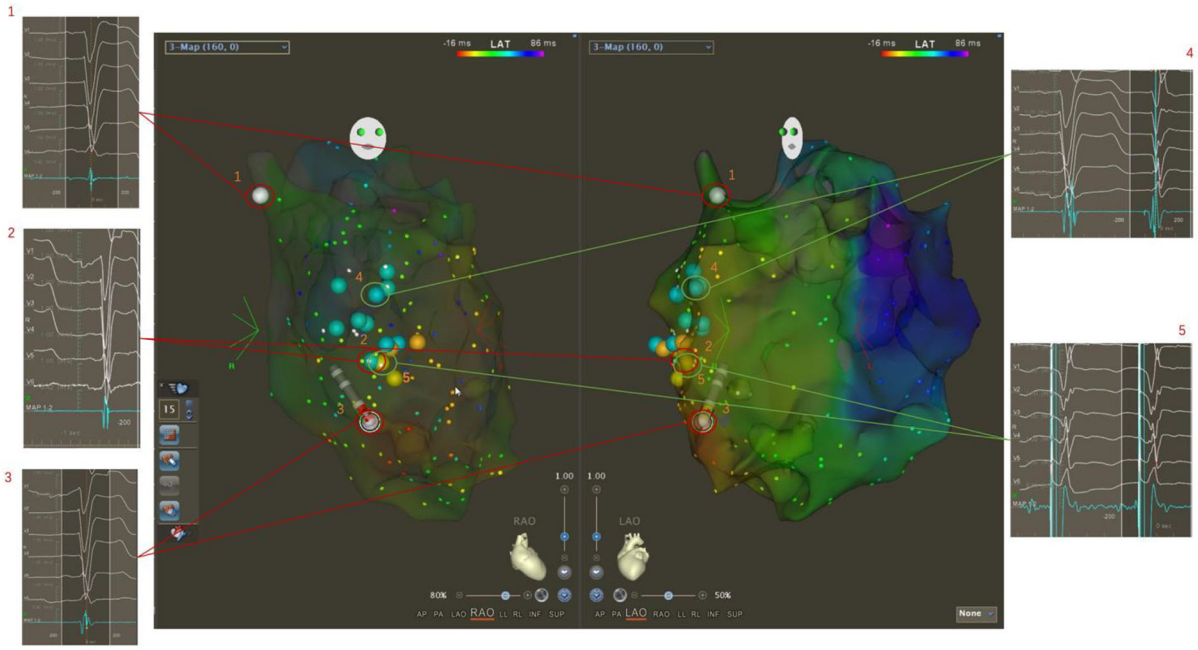

FIGURE 2
Three-dimensional electroanatomical mapping showing delayed conduction of the left bundle branch. The potentials of His and the left bundle branch were not mapped from the bottom to the apex of the left ventricular septum (1, 2, 3). The occasional mechanical stimulation in the left bundle branch area increased the potential and induced the subsequent narrow premature ventricular contraction (4). Then, electrical stimulation was performed in the upper middle area of the left bundle branch, and a QR or rSR morphology in the surface lead V1 was seen, which indicated there was a left bundle branch block or slow conduction. In the next step, LBBAP was planned (5).

Cardiac electrical synchrony evaluation

Cardiac electrical synchrony was assessed using the QRS duration of a 12-lead surface ECG. The surface ECG was obtained before and after the implantation. The QRS duration was measured from the onset of the intrinsic or paced QRS to the end of the QRS complex in all 12 leads. The left ventricular electrical synchrony was assessed using the LV activation time (LVAT), which was estimated by measuring the time from the intracardiac pacing spike to the R-wave peak of the QRS complex in lead V5 and V6. The widest-paced QRS duration and the wider LVAT were adopted for analyses. Two independent, experienced ECG specialists, blinded to the study, measured these two parameters.

Cardiac mechanical synchrony evaluation

A Vivid E9 Doppler echocardiography (GE, USA) with M5S and 4V probes was used, with an emission frequency of 2.5 MHZ. The echocardiography examination was performed by the same echocardiologist, who was blinded to the study groups. The following indicators before and after the CRT operations were measured in the patients: the left ventricular ejection fraction (LVEF); the atrioventricular synchronous index: EA peak distance (E/A pd); the interventricular synchronous index: interventricular mechanical delay (IVMD); and the left ventricle synchronous index: standard deviation of Ts of 12 LV segments (Ts-SD12).

Follow-up

The NYHA classifications were measured. Adverse events during the follow-up were recorded, including rehospitalization due to heart failure or death of the subjects, and the medical expenses essential for the mechanical treatment of chronic heart failure for the patients in the study group were also accurately recorded.

All patients underwent transthoracic echocardiography performed by an experienced specialist who was blinded to the study at the baseline as well as the 6th-month and 12-month follow-ups. The echocardiac measurement indicators, mentioned above, were recorded. Lead parameters, including R-wave amplitudes, capture thresholds, and pacing impedances were measured 1 week after the implantation.

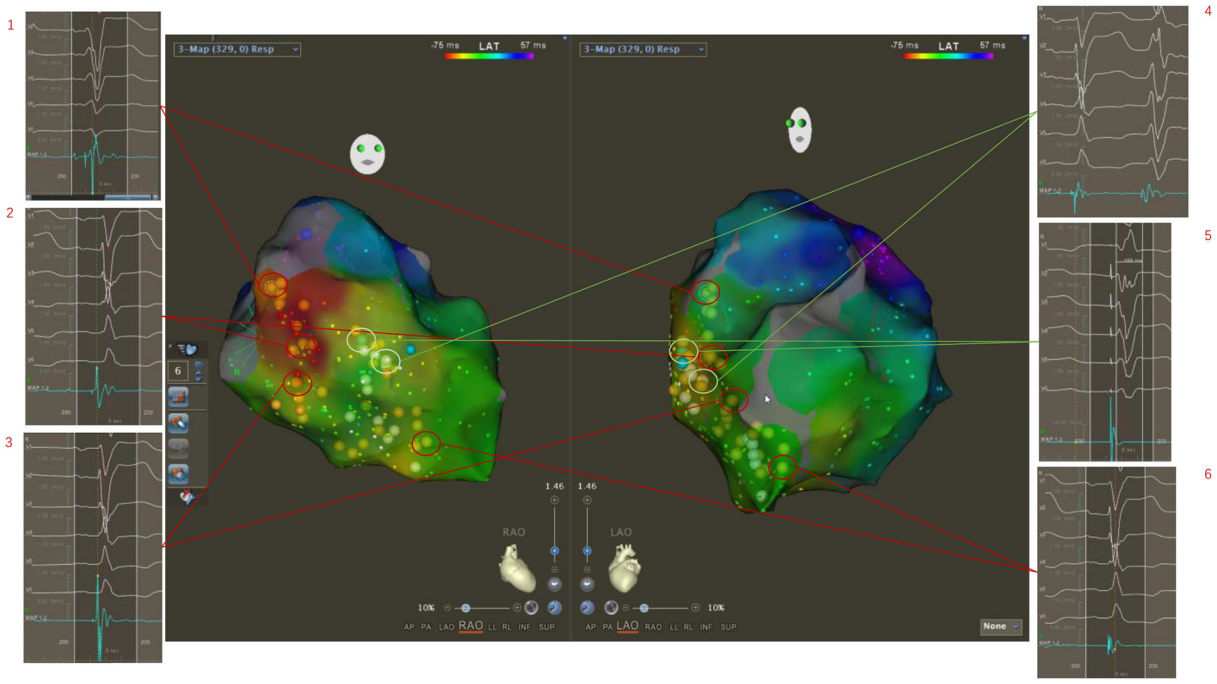

FIGURE 3
Three-dimensional electroanatomical mapping showed normal conduction of the left bundle branch although ECG showed LBBB pattern. The potentials of His and the left bundle branch were mapped from the bottom to the apex of the left ventricular septum (1, 2, 3, 6). The occasional mechanical stimulation in the left bundle branch area induced the subsequent wide premature ventricular contraction (4). Then, the electrical stimulation was performed in the upper middle area of the left bundle branch, and a wide rSR morphology in surface lead V1 was seen, which indicated the left bundle branch was normal (5). Classical CRT with coronary venous pacing was planned.

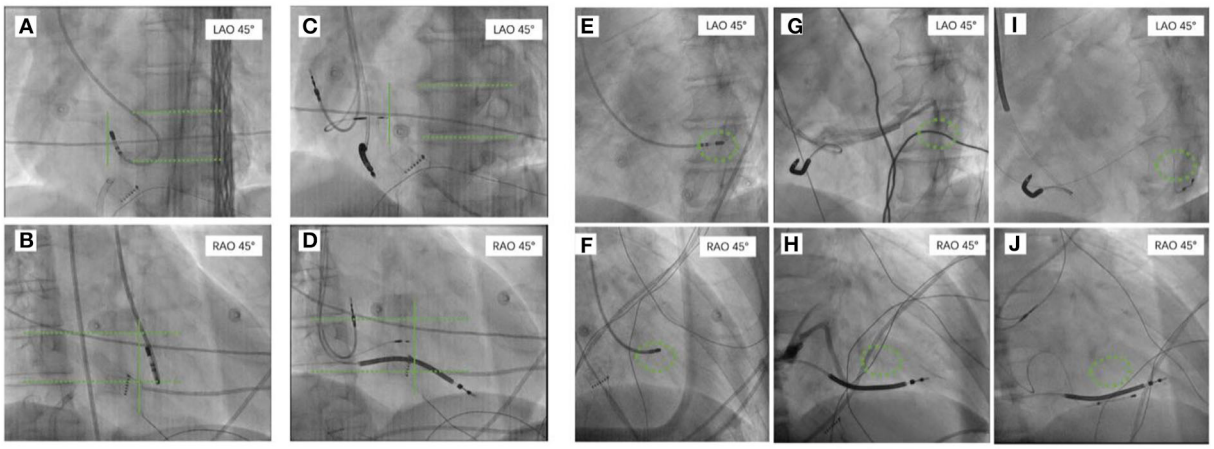

FIGURE 4
The tip of the mapping catheter under X-ray recorded at the right anterior oblique (RAO) 30° position and left anterior oblique (LAO) 45°. For patients who were planning to undergo LBBAP, the tip of the mapping catheter at the area of the left bundle branch in the left ventricle was recorded at RAO 30° and LAO 45° as references **(A,B)**. The 3,830 electrode was implanted on the right ventricular septum surface corresponding to the tip of the ablation catheter at RAO 30° and LAO 45° **(C,D)**. For patients who were planning to undergo CVP, the tip of the mapping catheter that was placed on the intima surface of the last activation of the left ventricle was recorded at RAO 30° and LAO 45° as references **(E,F)**. Coronary venography was performed to identify the cardiac vein **(G,H)** closest to the tip of the ablation catheter as the target for implantation of the left ventricular electrode **(I,J)**. RAO, the right anterior oblique; LAO, the left anterior oblique; CVP, coronary venous pacing; LBBAP, left bundle branch area pacing.

Statistical analysis

The continuous variables were presented as means ± standard deviations (SDs), and categorical variables were expressed as frequencies and proportions. Chi-square tests were used to compare categorical variables between the two subgroups. If variables were normally distributed, the parametric test (*t*-test) was adopted; if not, the non-parametric test (Mann–Whitney *U*-test) was used to compare numeric variables. Data at the baseline and follow-ups were compared by paired Wilcoxon signed rank tests. All statistical analyses were performed using SPSS 21.0 (IBM Corp, Armonk, NY, USA). The *P*-value statistical significance threshold was 0.05, two-tailed.

Results

Patients

A total of 71 patients were analyzed in this study, and 38 patients underwent three-dimensional mapping, of which 25 patients received left bundle branch area pacing LBBAP, and 13 patients received coronary venous pacing CVP; 33 patients did not receive mapping, of which 17 patients received left bundle branch area pacing LBBAP, and 16 patients received coronary venous pacing CVP. The baseline characteristics of the patients are summarized in Table 1. In the LBBAP group, 71.4% were diagnosed with dilated cardiomyopathy, and 14.2% were diagnosed with ischemic cardiomyopathy. Of the patients with no mapping, 12 were diagnosed with dilated cardiomyopathy, and two were diagnosed with ischemic cardiomyopathy. In the CVP group, 93.1% were diagnosed with dilated cardiomyopathy, and 3.4% were diagnosed with ischemic cardiomyopathy. Baseline age, gender, etiology, echocardiographic measurements, electrocardiogram parameters, and other items were not significantly different between the LBBAP and CVP subgroups.

Electroanatomic mapping

Thirty-eight patients successfully performed LV electroanatomical mapping. Twenty-five patients had delayed conduction of the left bundle branch, of which nine cases were in the middle and upper part of the left bundle branch, and 16 cases were in the left-sided His fibers. No true complete block of the left bundle branch was found, which had slow conduction rather than an inability to conduct. In other words, the bundle branch potential that is usually obscured in the local V wave was advanced by electrical or mechanical stimulation, and we saw an induced premature ventricular contraction that had a QR or rSR morphology in surface lead V1. It showed that left bundle branch conduction was delayed, which was the next step for the inclusion of CRT with LBBAP. In 16 cases, the left bundle branch potential was completely mapped from the bottom of the heart to the apex, and it was always ahead of the local myocardial activation, suggesting the left bundle branch conduction was normal. The next step was to achieve CRT through CVP.

Lead parameters

The lead parameters, including capture thresholds, pacing impedances, and R-wave amplitudes are provided in the Supplementary materials.

Complications

One LBBAP mapped patient was diagnosed with hemopneumothorax about 4 h after successful surgery, and the patient underwent closed thoracic drainage and blood transfusion therapy. No patient with a loss of capture, lead removal, or late lead dislodgement was observed. Echocardiography showed the pacing lead was positioned at the sub-endocardium of IVS in all LBBAP patients.

Electrical synchrony evaluation

In the LBBAP group, paced QRS duration 1 week after the implantation was significantly narrower than the baseline in both the mapping (165.72 ± 17.34 ms vs. 119.00 ± 20.88 ms, $p < 0.001$) and no mapping subgroups (164.00 ± 18.20 ms vs. 134.71± 20.30 ms, $p = 0.002$). Furthermore, the paced QRS duration exhibited a significant difference between the mapping and no mapping subgroups (119.00 ± 20.88 ms vs. 134.71 ± 20.30 ms, $p = 0.02$). In the CVP group, paced QRS duration 1 week after the implantation was significantly narrower than the baseline in the mapping (170.54 ± 29.82 ms vs. 131.62 ± 11.67 ms, $p = 0.001$) and no mapping subgroups (163.88 ± 24.35 ms vs. 142.7 ± 14.74 ms, $p < 0.001$); paced QRS duration showed a considerable difference between the mapping and no mapping subgroups (131.62 ±11.67 ms vs. 142.7 ± 14.74 ms, $p = 0.035$). The reductive value of QRS duration from baseline to post-operation was significant only in the CVP mapping and non-mapping groups (−21.13 ± 14.58 vs. −40.54 ± 21.66, $p = 0.008$; see Figure 5).

Mechanical synchrony evaluation

In the LBBAP group, 6 months after undergoing CRT, the LVEF, intraventricular synchronization index Ts-SD12, and atrioventricular synchronization index EA/RR were significantly

TABLE 1 Baseline characteristics of patients analyzed ($n = 71$).

	LBBAP			CVP		
	Mapping ($n = 25$)	No mapping ($n = 17$)	p-values	Mapping ($n = 13$)	No mapping ($n = 16$)	p-values
Age, year	65.84 (10.45)	63.18 (8.85)	0.4	62.08 (11.49)	63.13 (14.41)	0.833
Male	11	13	0.06	10	10	0.45
Diagnosis						
DCM	18	12	0.78	11	16	0.10
Ischemic cardiomyopathy	4	2		1	0	
Other*	3	3		1	0	
Atrial fibrillation	3	3	0.67	0	3	0.09
Previous MI	6	2	0.07	1	1	1.00
NYHA functional class						
III and above	20	9	0.14	9	8	0.71
LVEF, %	31.16 (8.23)	28.24 (7.40)	0.25	30.62 (4.25)	27.31 (5.07)	0.072
IVS thickness, mm	9.36 (1.78)	9.06 (2.28)	0.63	9.62 (1.89)	9.38 (1.93)	0.739
LVEDD, mm	71.32 (9.13)	66.53 (7.08)	0.08	69.62 (9.78)	69.69 (8.17)	0.983
AVVTI	19.47(6.84)	17.25 (4.74)	0.32	20.09 (4.85)	17.6 (4.10)	0.169
Ts-SD 12	145.57 (18.93)	144.38 (41.72)	0.91	144.09 (27.84)	141.53 (44.40)	0.868
IVMD	58.19 (28.69)	71.62 (28.94)	0.2	67 (29.23)	62.8 (30.48)	0.727
EA distance/RR interval	0.28 (0.08)	0.26 (0.07)	0.43	0.27 (0.05)	0.22 (0.07)	0.069
Drug therapy						
β-blocker	24	17	1	12	11	0.18
ACEI/ARB	14	10	1	6	6	1
Spironolactone	23	15	1	12	10	0.1
ARNI	8	9	0.21	7	10	0.7
PR interval, ms	180.96 (49.61)	183.82 (47.06)	0.85	182.92 (35.06)	165.44 (27.96)	0.146
QRS duration, ms	165.72 (17.34)	164.00 (18.20)	0.76	170.54 (29.82)	163.88 (24.35)	0.513
QRS notch width, ms	56.00 (8.57)	42.18 (8.96)	< 0.001	41.69 (17.19)	42.19 (15.02)	0.935
Type of CRT						
CRT-D	18	15	0.19	8	15	0.1
CRT-P	5	1		4	1	
Double chamber	2	1		1	0	

*Other includes the following: alcoholic cardiomyopathy, hypertensive cardiomyopathy, and non-compaction of myocardium.
DCM, dilated cardiomyopathy; MI, myocardial infarction; NYHA, The New York Heart Association; LVEF, left ventricular ejection fraction; IVS, interventricular septum; LVEDD, left ventricular end-diastolic dimension; AVVTI, aortic valve velocity time integral; Ts-SD 12, standard deviation of 12-segment time to peak systolic velocity; IVMD, interventricular mechanical delay time; ARNI, angiotensin receptor neprilysin inhibitor; CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacemaking.

improved when compared to the baseline in the LBBAP mapping subgroup (LEVF 31.16 ± 8.23% vs. 37.64 ± 6.18%, $p < 0.001$; Ts-SD12 145.57 ms ± 18.93 vs. 111.38 ± 18.74 ms, $p < 0.001$; EA/RR 0.28 ± 0.08 vs. 0.30 ± 0.08, $p = 0.026$). In the LBBAP no mapping grouping, the LVEF and the intraventricular synchronization index Ts-SD12 significantly improved when compared to the baseline (LEVF 28.24 ± 7.40% vs. 32.71 ± 6.99%, $p = 0.001$; Ts-SD12 144.38 ± 4 1.72 ms vs. 131.62 ± 38.02 ms, $p = 0.001$). Between the two subgroups, there were significant differences in LEVF, IVMD, and Ts-SD12 (LVEF 37.64 ± 6.18% vs. 32.71 ± 6.99%, $p = 0.009$; IVMD 46.38 ± 22.67 ms vs. 69.77 ± 31.64 ms, $p = 0.043$; and Ts-SD12 111.38 ± 18.74 ms vs.131.62 ±38.02 ms, $p = 0.007$). In the 12 month follow-up, echocardiography parameters including LVEF, atrioventricular synchronization index EA/RR, biventricular synchronization index IVMD, and intraventricular synchronization index Ts-SD 12 were significantly improved when compared to the baseline data in the mapping subgroup (LEVF 31.16 ± 8.23% vs. 52.36 ± 6.05%, $p < 0.001$; IVMD 58.19 ± 28.69 ms vs. 39.90 ± 17.99 ms, $p = 0.002$; Ts-SD12 145.57 ± 18.93 ms vs. 121.24 ± 27.43 ms, $p = 0.001$; and EA/RR 0.28 ± 0.08 vs. 0.34 ± 0.10, $p = 0.001$). LVEF, IMVD, and Ts-SD12 significantly improved when compared to the baseline in the LBBAP no mapping subgroup (LEVF 28.24 ± 7.40% vs. 40.60 ± 7.84%, $p = 0.001$; IVMD 71.62 ± 28.94 ms vs. 50.23 ± 21.43 ms, $p = 0.008$; and Ts-SD12 144.38 ± 41.72 ms vs. 123.62 ± 38.23 ms,

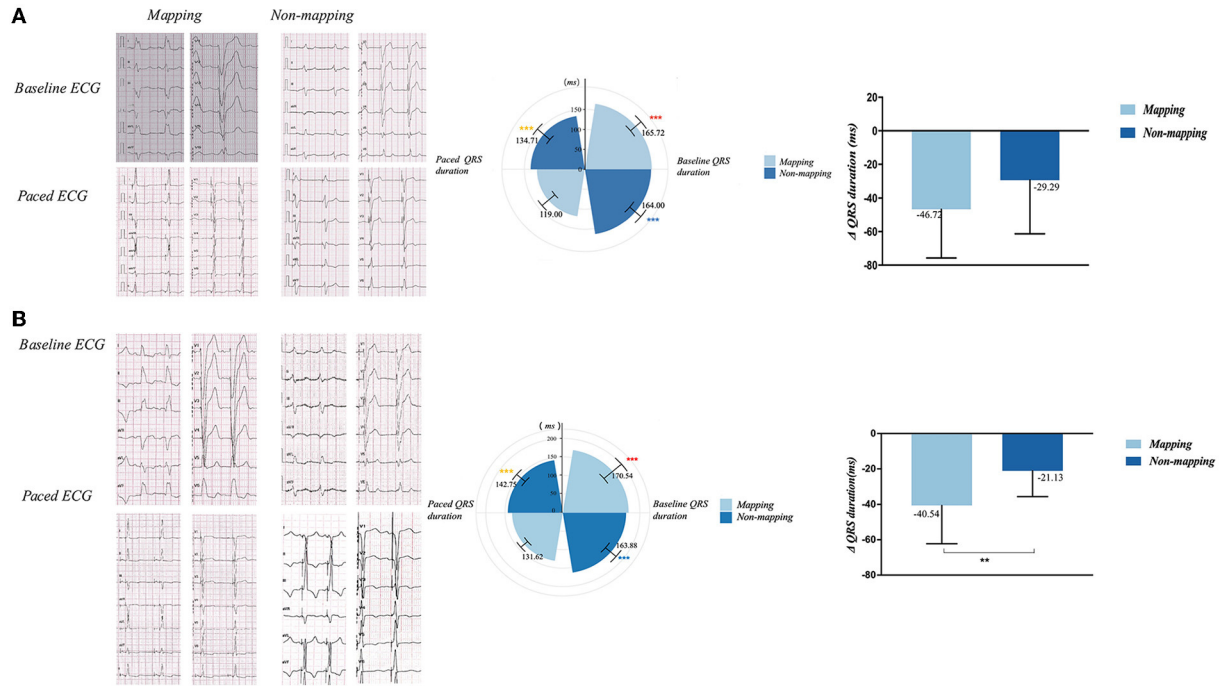

FIGURE 5
QRS duration and QRS duration variation of mapping and non-mapping group in LBBAP **(A)** and CVP **(B)** before and 1-week after the operation. ***$p < 0.001$ vs. paced QRS duration in mapping group; ***$p < 0.001$ vs. paced QRS duration in non-mapping group; ***$p < 0.001$ vs. paced QRS duration in mapping group; *$p < 0.05$; **$p < 0.01$; CVP, coronary venous pacing; LBBAP, Left bundle branch region pacing.

$p = 0.003$). Furthermore, the LVEF, EA/RR, IVMD, and Ts-SD 12 exhibited a significant difference between the mapping and no mapping subgroups (LEVF 52.36 ± 6.05% vs. 40.60 ± 7.84%, $p < 0.001$; IVMD 39.90±17.99 ms vs. 50.23 ± 21.43 mm, $p = 0.024$; TSSD121.24 ± 27.43 ms vs.123.62 ± 38.23 ms, $p = 0.029$; and EA/RR 0.34 ± 0.10 vs. 0.29 ± 0.06, $p = 0.014$; Figures 6A,C and Supplementary Table 2).

Although in the CVP group, the mapping subgroup's LVEF, intraventricular synchronization index Ts-SD12, and IVMD were noticeably enhanced 6 months after CRT (LVEF 30.62 ± 4.25% vs. 35.77 ± 5.76%, $p = 0.013$; Ts-SD12 144.09 ± 27.84 ms vs. 130.82 ± 32.80 ms, $p = 0.003$; and IVMD 67.0 ± 29.23 ms vs. 55.72 ± 23.43 ms, $p = 0.022$). The LVEF and IVMD were significantly improved when compared to the baseline in the no mapping subgroup (LVEF 27.31 ± 5.07% vs. 29.06 ± 4.67%, $p = 0.001$; IVMD 62.80 ± 30.48 ms vs. 59.60 ± 28.76 ms, $p = 0.001$); and there was a great disparity in LVEF, EA/RR, IVMD, and Ts-SD 12 between the mapping and no mapping subgroups (LVEF 35.77 ± 5.76% vs. 29.06 ± 4.67%, $p = 0.001$; Ts-SD12 130.82 ± 32.80 ms vs. 137.27 ± 34.16 ms, $p = 0.01$; IVMD55.72 ± 23.43 ms vs. 59.60 ± 28.76 ms, $p = 0.043$; EA/RR 0.29 ± 0.04 vs. 0.22 ± 0.05, $p = 0.002$). At 12-month follow-up, the LVEF, EA/RR, IVMD, and Ts-SD 12 were observed to have significantly improved when compared to the baseline data in the mapping subgroup (LVEF 30.62 ± 4.25% vs. 39.92 ± 5.87%, $p = 0.01$; Ts-SD12 144.09 ± 27.84 ms vs. 127.0 ± 35.62 ms, $p = 0.006$; IVMD 67.0 ± 29.23 ms vs. 52.45 ± 24.17 ms, $p = 0.016$; EA/RR 0.27 ± 0.05 vs. 0.40 ± 0.05, $p = 0.003$); LVEF and IMVD were substantially improved when compared to the baseline in the LBBAP no mapping subgroup (LVEF 27.31 ± 5.07% vs. 33.88 ± 6.24%, $p < 0.001$; IVMD 62.8 ± 30.48 ms vs. 57.53 ± 20.81 ms, $p = 0.004$). In addition, the LVEF, EA/RR, IVMD, and Ts-SD 12 exhibited a significant difference between the mapping and no mapping subgroups (LVEF 39.92 ± 5.87% vs. 33.88 ± 6.24%, $p < 0.001$; Ts-SD12 127.0 ± 35.62 ms vs. 119.73 ± 21.43 ms, $p < 0.001$; IVMD 52.45 ± 24.17 ms vs. 57.53 ±20.81 ms, $p = 0.006$; EA/RR 0.40 ± 0.05 vs. 0.23 ± 0.70, $p < 0.001$; Figures 6B,D and Supplementary Table 3).

In the LBBAP group, patients who received mapping before the operation showed significantly greater improvement in LVEF and Ts-SD 12 at 1-year follow-up, compared to those who underwent CRT without mapping (LVEF: 1.41 ± 15.81 vs. 14.72 ± 10.22, $p = 0.002$; Ts-SD12: −37.54 ± 24.77 vs. −70.90 ± 29.94, $p = 0.002$; Figure 6E left column). With regard to CVP, both the LVEF at 6-month follow-up and synchronization indicators at 12-month follow-up exhibited significantly greater absolute variation in those whose left ventricular was mapped before CRT, as clarified in Figure 6E (right column).

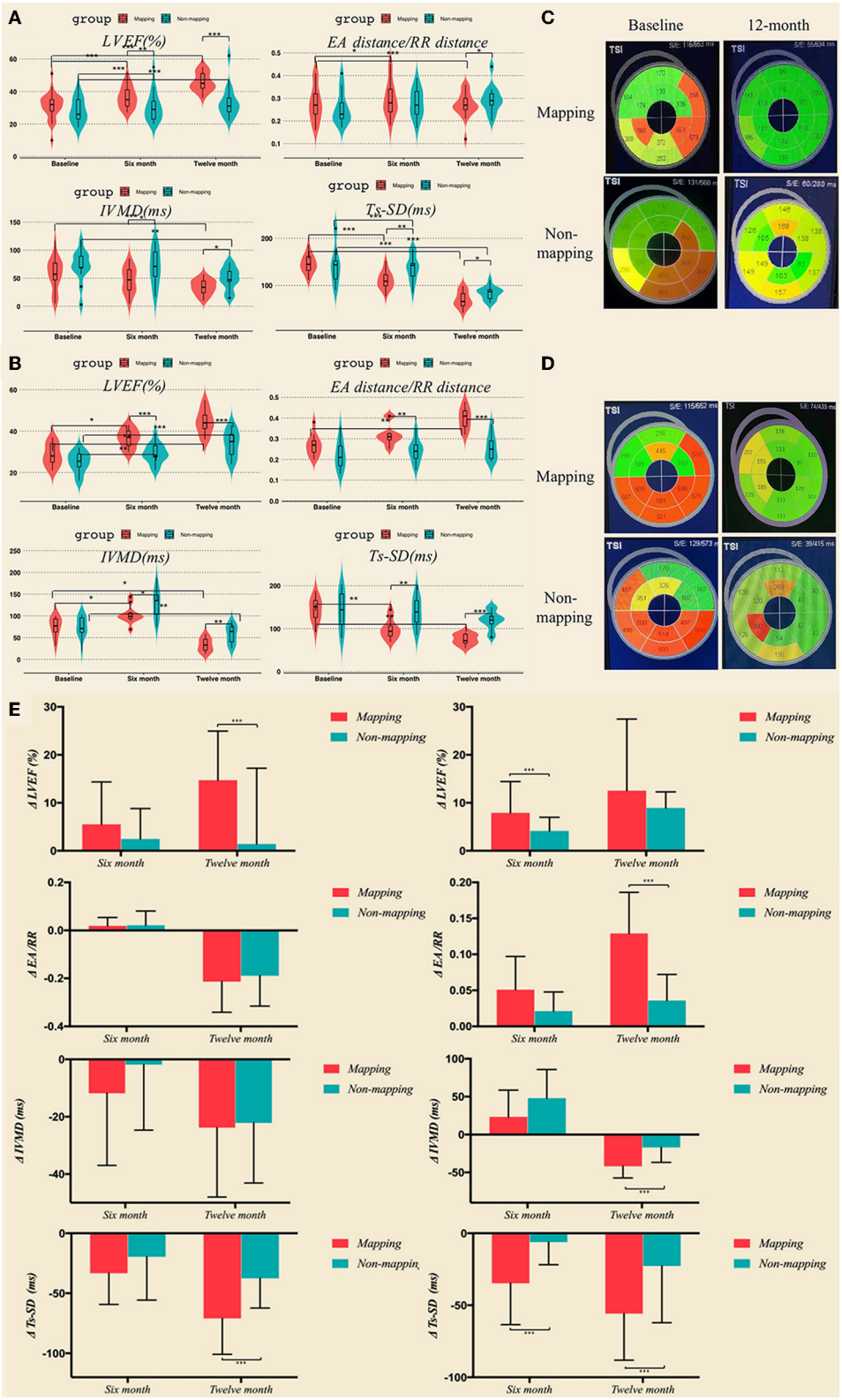

FIGURE 6
LVEF and synchronization parameters including EA distance/RR duration, IVMD, and Ts-SD 12 in LBBAP **(A)** and CVP **(B)** at baseline, 6 months, and 12 months after the operation measured by transthoracic echocardiography. **(C,D)** Bulls-eye view of real-time three-dimensional echocardiography at baseline and 12 months after the operation. **(E)** LVEF and synchronization parameters variation in LBBAP and CVP group at 6 months and 12 months. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. CVP, coronary venous pacing; LBBAP, Left bundle branch region pacing.

Clinical outcome

All LBBP patients survived with greater improvement in cardiac function during a mean follow-up of 11.5 ± 3.3 months in the LBBAP group. During the clinical follow-up, NYHA classification was found to be improved compared to the baseline in both the mapping and no mapping subgroups of the LBBAP group and CVP group. No statistically significant difference was observed in clinical indicators between the two groups after the operation.

Discussion

At present, there are several ways to correct the CLBBB to achieve the CRT. The classical implantation of the left ventricular electrode through the lateral cardiac vein and the implantation of the left ventricular electrode in the left bundle branch are two possible methods of delivering CRT. Left bundle branch area pacing is emerging recently, while considered to be a second-line strategy to BiV pacing, as its benefits over conventional CRT have not been demonstrated in randomized trials. There is no research on the criteria for choosing between these two methods for patients with heart failure and CLBBB who conform to the CRT indications. A new study demonstrated that LBBP-CRT had better electromechanical resynchronization and higher clinical and echocardiographic response than BVP-CRT in HFrEF patients with LBBB (12).

This study first demonstrated that three-dimensional electroanatomical mapping of the left ventricle can be used to determine the conduction in the left bundle branch and the level of blockage. If the left bundle branch is blocked or slowed, CRT is achieved by pacing in the left bundle branch area; if the left bundle branch conduction is normal, CRT is achieved by the traditional lateral cardiac vein pacing. Second, the X-imaging of the tip of the mapping catheter in the left bundle branch area or the latest activated area of the left ventricle can be used as an important reference for the implantation of the left ventricular electrode into the target point or vessel during CRT implantation, which simplifies the surgical procedure.

Different subtypes of left bundle branch block

Left bundle branch block has received increased attention in past last decade. It has largely been associated with the implementation of the CRT and accumulative data demonstrate a considerably higher rate of response in patients with LBBB QRS morphology (13). Historically, wide (≥120 ms) QRS patterns with dominant S-waves in lead V1 have been aggregated into the broad categorization of an LBBB pattern. However, it is worth noting that these criteria were introduced in 1941 on a dog model and extrapolated to humans. The prevailing definition of the LBBB pattern was developed by the American Heart Association, the Electrocardiography and Arrhythmias Committee, the Council on Clinical Cardiology, the American College of Cardiology Foundation, and the Heart Rhythm Society (AHA/ACCF/HRS) in 2009. The LBBB pattern required a QRS ≥ 120 ms with a broad notched or slurred R-wave in leads I, aVL, V5, and V6 (14). In 2011, Strauss and colleagues proposed a cut-off of ≥140 ms in men and ≥130 ms in women as well as the requirements of a QS or RS in leads V1–V2 and mid-QRS notching or slurring in two or more of leads V1, V2, V5, V6, I, and aVL (15).

Tung et al. (10) commenced electrophysiology testing to delineate the activation patterns of the proximal left conduction system with multielectrode catheters in patients presenting for cardiac resynchronization. They reported that in patients with LBBB, the block was most often localized to the left-sided His fibers (46%). Less commonly, the LBBB was found distal to the His recording site (18%), at locations in which an atrial electrogram was not recorded. These locations were anatomically consistent with the block in the distal branching bundle or proximal left bundle-branch. The remainder (36%) of the patients with an LBBB pattern did not demonstrate a complete conduction block. Assessment of local ventricular electrograms showed an intact Purkinje activation and the QRS was wide, most likely because of conduction slowing more distally. Multiple ECG criteria have been assessed, but without using a "gold standard" of determination of whether the block was present (10).

Direct placement of the pacing electrode is difficult (16), there are three difficulties for doctors performing this operation: finding the His bundle potential, controlling the depth of rotation in the septum, and choosing other sites if the position is inappropriate. In this study, the left bundle branch area of the left ventricular septum could be paced directly through the mapping electrode, and offer an X-ray image as a location reference. Similarly, the activation of the left ventricle is well-represented by maps in CVP.

Left univentricular pacing achieving CRT

To ensure a 100% biventricular capture, a conventional CRT used the short and fixed AV delay and an abandoned intrinsic activation from the right bundle branch (17). Activation from non-physiological biventricular pacing caused slow propagation and inverse conduction in the His-Purkinje system, resulting in an intraventricular pseudo-resynchronization (17, 18). In this study, a pacemaker was programmed to close the pacing function of the right ventricular pacing electrode while maintaining the defibrillation function. The left bundle branch area pacing without right ventricular pacing not only corrected LBBB but also generated a relatively normal pattern of

ventricular activation, such that one activation wave was in front of the left bundle branch by pacing, while the other activation wave was from the intrinsic conduction of the right bundle branch (19). Coronary venous pacing advanced the last excited area of the left ventricle, which synchronized with the intrinsic activation from the left and right bundle branch. Synchronizing the LBBAP or CVP with intrinsic activation to achieve physical resynchronization can improve CRT efficacy (20).

Efficacy of CRT guided by mapping

After the three-dimensional electroanatomical mapping, patients with complete left bundle branch block were chosen for LBBAP. We observed a significant reduction in QRS duration and an improvement in LVEF in the mapping subgroup of CVP and LBBAP, which suggested that implantation of CRT after three-dimensional electroanatomical mapping results in better cardiac resynchronization. For patients with a true left bundle branch block, CRT can be achieved through the left bundle branch regional pacing by correcting LBBB and restoring normal physiological LV activation.

Limitations

Being a retrospective study, the main weakness is that patients were not randomized to mapping or non-mapping groups. Therefore, the homogeneity of the data is relatively poor and the level of evidence is not strong.

In this study, electroanatomical mapping of the left ventricular cavity was performed by puncturing the femoral artery and administering heparin (30 IU/Kg). After the mapping, protamine was given to neutralize the heparin (1 mg:100 IU), and the implantation of CRT was continued. Although it was not found in this study, the complications of vascular puncture and the risk of blood oozing from the pocket are theoretically increased during this step.

This study was a single-center prospective study, and the sample size was relatively small. Even though our study demonstrated novel criteria for choosing between CVP or LBBAP, which is safe and feasible, larger and randomized controlled trials should be conducted to verify its long-term safety and clinical benefits.

Conclusion

For heart failure patients with LBBB who are indicated for CRT, left ventricular electroanatomical mapping before CRT, which determines whether the left bundle branch is blocked or not, is a safe, feasible way to choose between LBBAP or CVP. The benefit of the pre-procedural mapping is that patients with intact left bundle branch conduction (and slow distal conduction) are filtered out and do not receive LBBAP, as they are unlikely to benefit. In addition, the X-ray image of the mapping catheter tip at the left bundle branch area, or the latest activation area of LV can provide a positioning reference for the implantation of the left ventricular electrode into the target area.

Perspectives

What is known?

There are currently two ways to achieve left ventricular activation in CRT. One is to place a left ventricular electrode in the coronary venous pacing (CVP), and the other is to place a left ventricular electrode in the left bundle branch area.

What is new?

For patients with heart failure and left bundle branch block (LBBB), there is currently no research that recommends which criteria should be used to choose left ventricular pacing to achieve CRT.

What is next?

Further studies with larger and randomized controlled trials should be conducted to verify the findings of this study and identify the long-term safety and clinical benefits of three-dimensional electroanatomical mapping-guided CRT.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Board of the First Affiliated Hospital of Kunming Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JW and LZ designed and supervised the study. B-TH, JW, and L-JP performed CRT implantation and drafted this manuscript. XT performed statistical analyses. HL, W-JS, XT, CW, X-XS, RL, S-ML, Z-XL, and J-HZ followed the patients and optimized the parameters. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.843969/full#supplementary-material

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The real-time remote testing and programming of cardiac implantable electronic devices: A case series report

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Minimizing the number of personnel in the cardiac catheterization laboratory (CCL) and the times of CCL door openings contribute to reduce the infection risk of medical staff and patients, particularly during the COVID-19 pandemic. The usage of 5G-CTP system enables device specialists to conduct remote parameter testing and programming without entering the CCL, potentially reducing the exposure risk of medical staff and patients to COVID-19 infection.

KEYWORDS

cardiac implantable electronic devices, remote parameter testing, 5G cloud technology support platform, COVID-19, door openings

Introduction

The ongoing COVID-19 pandemic has caused extensive devastation throughout the globe and remains the most serious threat to public health since the end of World War II (1), necessitating collective efforts from the entire global population to mitigate the spread of this disease. Owing to their ongoing workplace exposure to the causative virus responsible for this pandemic (SARS-CoV-2), healthcare workers are more likely to suffer from severe disease relative to individuals in other classes of occupations (8.1 vs. 4.1%) (2). This is particularly true for individuals working in operating rooms (ORs), who are particularly likely to suffer from nosocomial infections owing to the large numbers of personnel and mobility in these settings. To minimize the spread of COVID-19 and other diseases, restricting the number of personnel in the OR to the greatest extent possible is of great importance.

Patients preparing to undergo an operation similarly face an increased risk of COVID-19 exposure, and the risk is further amplified for older adults with various comorbidities who are more likely to suffer from severe disease. Frequent OR door openings have also been identified as a risk factor for patients and personnel in an

operative setting, and no more than 10 door openings per hour has been used as a surrogate marker for hygiene discipline in the OR (3). When the OR door is frequently opened, this can lead to the disruption of the laminar airflow (4), potentially resulting in surgical site microbial contamination (5, 6), thus exposing patients to a higher risk of surgery-associated infection (7). These OR door openings also have potential impact on surgical teams, further exacerbating the potential for infection or operative errors. As such, counts of OR door openings are often used to gauge the organization and discipline of a given surgical team (8).

In this study, a specific technological approach was used to minimize the number of personnel in a CCL and the associated number of door openings.

Methods

For this study, a 5G cloud technology support (5G-CTP) system (China Telecom Corporation Limited Shanghai Branch, Shanghai, China) was utilized that enables real-time remote testing and programming during cardiac implantable electronic device (CIED) implantation procedures over internet connections or wireless networks without requiring entry into the CCL by clinical device specialists (**Figure 1**). This 5G-CTP system is comprised of a 5G remote support terminal, a tablet equipped with the 5G-cloud control software (China Telecom Corporation Limited Shanghai Branch, Shanghai, China), and a remote service system implemented on a cloud-based server (9–12).

Prior to device implantation, a feldsher or an instrument nurse connected the 5G remote support terminal to the bedside programmer (Merlin Patient Care System Programmer Model 3650, St. Jude Medical Inc., MN, USA) in the CCL, then the device specialist logged into the 5G cloud control software with a two-step verification procedure, as detailed in prior preliminary reports (9–12), thus enabling the establishment of a remote connection with the programmer, providing complete control thereof. During the implantation procedure, the device specialist was able to maintain real-time communication with the implanting physician using an interphone system, and conducted lead parameter testing through the use of the 5G cloud control software to aid implanting physicians in the selection of optimal lead placement while remaining outside the CCL. When implantation was completed, final programming parameters were remotely completed, and the entirety of the remote operative process was recorded through screen recording allowing for subsequent auditing.

For this study, patients were enrolled in an observational trial (ChiCTR2100046883) exploring the feasibility and clinical reliability of this 5G-CTP system in CIED patients. In total, three representative cases that were performed at the Third People's Hospital of Chengdu, which is a tertiary care center where ~430 CIED implantation procedures are performed each year, are herein discussed. All patients provided written informed consent to participate, and the ethical review committee of the Third People's Hospital of Chengdu approved this study ([2021]S-184).

Results

Case 1: A 76-year-old male suffering from hypertension underwent the implantation of a dual-chamber pacemaker (St. Jude Accent MRI^{TM} PM2124) for sick sinus syndrome. During the implantation procedure, the 5G-CTP system was used to monitor lead parameters. Device personnel were able to support this implantation process while remaining outside the CCL without the need for frequent door openings. No loss or delay of communication or programmability was observed, and the pacing thresholds, impedance, and sensing thresholds of the atrial and ventricular leads were tested to 1 and 0.6 V, 2 and 21 mV, 503 and 763Ω, respectively. The device was successfully programmed to a DDD of 60 bpm with corresponding lead parameter values within the target range.

Case 2: A 77-year-old male that had been diagnosed with dilated cardiomyopathy with complete left bundle branch block and comorbid diabetes mellitus, hypertension, and chronic cardiac dysfunction, underwent the implantation of a cardiac resynchronization therapy device (CRTP, St. Jude Allure Quadra^{TM} RFPM3242). During the lead placement procedure, the interphone system was used to enable device personnel to communicate with operators in real-time, while the 5G-CTP system was used to aid in the selection of an optimal position for lead placement. When the pacing thresholds, impedance, and sensing thresholds of the atrial and ventricular leads were tested to 0.6 and 0.75 V, 2.6 and 11.7 mV, and 410 and 360Ω, respectively, the implanting physician fixed the leads. After the procedure was complete, the pacing capture threshold remained stable, and the sensing threshold and lead impedance were within the target range. No adverse interactions with standard CCL care protocols were associated with the use of this 5G-CTP system.

Case 3: An 87-year-old female suffering from atrial fibrillation with rapid ventricular rates was implanted with a dual-chamber pacemaker (Medtronic ADAPTA® L ADDRL1) and underwent atrioventricular junction ablation. The stability of the connection between the 5G-CTP system and the 3650 Merlin analyzer was confirmed by the device specialist. The CCL staff activated the analyzer, while lead parameter testing was performed by the off-site device specialist. When the pacing thresholds, impedance, and sensing thresholds of the atrial and ventricular leads were tested to 0.6 and 0.6 V, 2.1 and 17.1 mV, and 358 and 784Ω, respectively, by an off-sire device specialist, the implanting physician fixed the leads. No pacing inhibition or connectivity interruptions were observed between the 5G-CTP

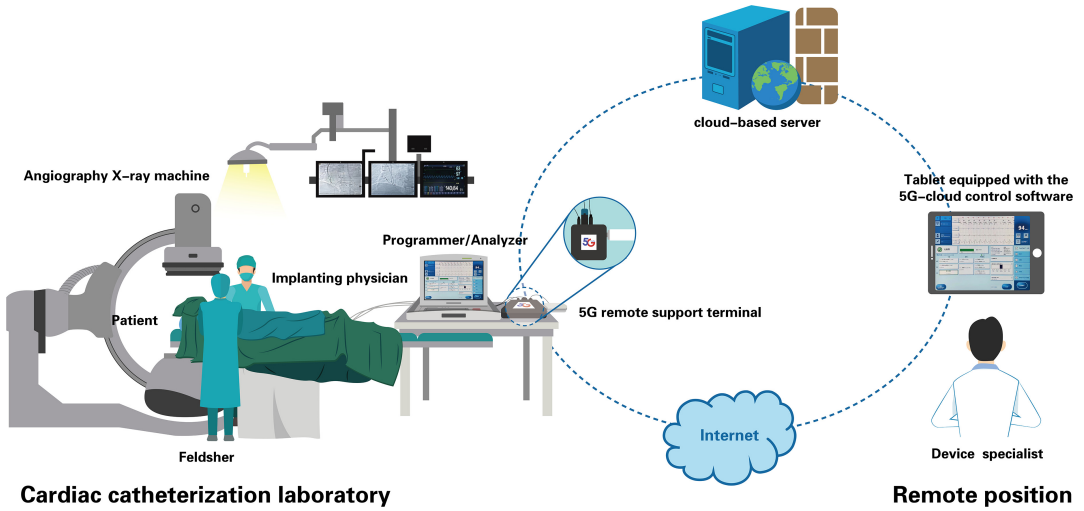

FIGURE 1
Schematic representation of real-time remote testing and programming of cardiac implantable electronic devices through the 5G-CTP system. This 5G-CTP system is comprised of a 5G remote support terminal, a tablet equipped with the 5G-cloud control software, and a remote service system implemented on a cloud-based server. Prior to device implantation, a feldsher connected externally the 5G remote support terminal to the bedside programmer in the CCL. When confirming the communication is stable, the feldsher got contact with the device specialist. The device specialist logged into the 5G cloud control software subsequently to establish remote connection with the 5G remote support terminal and the programmer. Then he had the complete control of the programmer, and was able to conduct lead parameter testing and programing of implanted device remotely during the implantation procedure to aid implanting physicians in the selection of optimal lead placement. When implantation was complete, final programming parameters were also remotely completed.

TABLE 1 Clinical characteristics of the enrolled patients.

	Case 1	Case 2	Case 3
Age, years	76	77	87
Gender	Men	Men	Women
Body mass index (kg/m^2)	29.7	19	28.1
LVEF, %	56	46	61
Comorbidity	Hypertension	Diabetes mellitus Hypertension Chronic cardiac dysfunction	Atrial fibrillation
Implant indications	Sick sinus syndrome	DCM with complete LBBB	2nd/3rd degree AV block
Implanted device	Dual-chamber pacemaker	CRT-P	Dual-chamber pacemaker
Device implant	First implantation	First implantation	First implantation
Duration for operation/min	80	312	92
Duration for leads parameter testing/min	25	200	36
Frequency for leads parameter testing/beats	7	17	9
Intraoperative leads parameter testing results			
Atrial leads			
Pacing thresholds/V	1	0.6	0.6
thresholds/mV	2	2.6	2.1
Impedance/Ω	503	410	358
Ventricular leads			
Pacing thresholds/V	0.6	0.75	0.6
Sensing thresholds/mV	21	11.7	17.1
Impedance/Ω	763	360	784

LVEF, left-ventricular ejection fraction; DCM, dilated cardiomyopathy; LBBB, left bundle branch block; CRT-P, cardiac resynchronization therapy without defibrillator.

system and the 3650 Merlin analyzer during radiofrequency ablation. Lead measurements were within normal ranges, and final programming was remotely completed successfully.

The baseline characteristics and lead parameter testing outcomes of the enrolled patients are presented in Table 1.

Discussion

Clinical device specialists traditionally provide bedside expertise in the CCL that is specific to the utilized devices in the context of CIED implantation. Traditional CCL care procedures generally require an implanting physician, a feldsher, an instrument nurse, and a clinical device specialist providing bedside expertise in the CCL. However, increasing the number of personnel in the CCL and the number of CCL door openings leave medical personnel and patients at a higher risk of infection, particularly during the COVID-19 pandemic. This risk is particularly pronounced for older adults over 60 years of age, who are more likely to suffer from severe disease (13). Notably, most patients who undergo CIED implantation are in this age group. By utilizing a 5G-CTP system, it is possible for device specialists to conduct real-time zero-contact parameter testing and programming while remaining remotely located, thereby decreasing the number of CCL door openings and the number of personnel in the CCL without compromising patient safety (14). The use of this technology can help minimize the exposure of medical staff and patients to COVID-19. In addition, when providing bedside care, device specialists must wear leaded aprons and thyroid shields. Even with these precautions, they will still suffer from slight radiation exposure. By enabling remote operative procedures, this 5G-CTP system enables real-time device-specific expertise while mitigating both infection- and ionizing radiation-related risks for device specialists.

The utilized 5G-CTP system incorporates robust cybersecurity protocols designed to ensure patient data safety, as detailed in prior preliminary reports (9–12). The medical safety of patients is also the major concern during CIED implantation sessions, and a temporary pacemaker will be implanted before surgery in those patients with complete AV-block or complete sick sinus syndrome with a heart rate < 30 bpm to ensure the patient's safety. No adverse interactions with temporary pacemakers were associated with the use of this 5G-CTP system. Therefore, the 5G-CTP system can be applied to this subset of patients without adverse events. This technology can be applied for a range of applications such as the remote programming of various devices, including in CIED patients necessitating emergency reprogramming (9), as well as for patients in areas where medical resources are limited and post-implantation follow-up analyses are necessary (11). The potential use of 5G-CTP system in different clinical scenarios indicates the value of this system as a promissing modality for CIED patient management.

The three cases presented herein highlight the efficacy and feasibility of this real-time remote parameter adjustment approach. Since these three initial cases, we have routinely utilized this technology during CIED implantation procedures without any communication problems or adverse events to date. We have also been conducting a prospective randomized controlled study to examine the safety and efficacy of the 5G-CTP system in CIED implantation procedures and to assess its effect on parameter testing time. While in-person interactions with device specialists in the CCL are preferable, this technology is an effective alternative that can be used for the duration of the global COVID-19 pandemic.

Limitations

This was a single-center observational study that enrolled just three cases. As such, further large-scale prospective randomized controlled studies are necessary to confirm the safety and efficacy of this 5G-CTP system as a tool to aid in CIED implantation procedures. As such, caution is warranted in the application of this technology in the context of CIED implantation pending the results of further clinical research. Although there is currently only one vendor with equipment that can readily function with this 5G-CTP system (St. Jude Medical Inc., Saint Paul, MN, USA), the general concept and service model are applicable to all vendors.

Conclusion

In summary, this 5G-CTP system can effectively enable the real-time testing and programming of lead parameters in the context of CIED implantation without requiring device specialists to enter into the CCL, thereby reducing the number of CCL door openings, reducing the potential for COVID-19 exposure for both healthcare workers and patients. However, additional large-scale multi-center prospective research will be critical to confirm the utility and safety of this technology.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by The Third People's Hospital of Chengdu. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YuL was the major contributor in drafting the manuscript. SX, LT, JL, YaL, WH, and ZZ put forward

constructive comments and suggestions. SX and HL revised the manuscript for important intellectual content. LC designed the study and finally approved the manuscript submitted. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Clinical outcomes of subcutaneous vs. transvenous implantable defibrillator therapy in a polymorbid patient cohort

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Background: The subcutaneous implantable cardioverter-defibrillator (S-ICD) has been designed to overcome lead-related complications and device endocarditis. Lacking the ability for pacing or resynchronization therapy its usage is limited to selected patients at risk for sudden cardiac death (SCD).

Objective: The aim of this single-center study was to assess clinical outcomes of S-ICD and single-chamber transvenous (TV)-ICD in an all-comers population.

Methods: The study cohort comprised a total of 119 ICD patients who underwent either S-ICD (n = 35) or TV-ICD (n = 84) implantation at the University Hospital Frankfurt from 2009 to 2017. By applying an inverse probability-weighting (IPW) analysis based on the propensity score including the Charlson Comorbidity Index (CCI) to adjust for potential extracardiac comorbidities, we aimed for head-to-head comparison on the study composite endpoint: overall survival, hospitalization, and device-associated events (including appropriate and inappropriate shocks or system-related complications).

Results: The median age of the study population was 66.0 years, 22.7% of the patients were female. The underlying heart disease was ischemic cardiomyopathy (61.4%) with a median LVEF of 30%. Only 52.9% had received an ICD for primary prevention, most of the patients (67.3%) had advanced heart failure (NYHA class II–III) and 16.8% were in atrial fibrillation. CCI was 5 points in TV-ICD patients vs. 4 points for patients with S-ICD (p = 0.209) indicating increased morbidity. The composite endpoint occurred in 38 patients (31.9 %), revealing no significant difference between patients implanted with an S-ICD or TV-ICD (unweighted HR 1.50, 95 % confidence interval (CI) 0.78–2.90; p = 0.229, weighted HR 0.94, 95% CI, 0.61–1.50, p = 0.777). Furthermore, we observed no difference in any single clinical endpoint or device-associated outcome, neither in the unweighted cohort nor following inverse probability-weighting.

Conclusion: Clinical outcomes of the S-ICD and TV-ICD revealed no differences in the composite endpoint including survival, freedom of hospitalization and device-associated events, even after careful adjustment for potential confounders. Moreover, the CCI was evaluated in a S-ICD cohort demonstrating higher survival rates than predicted by the CCI in young, polymorbid (S-)ICD patients.

KEYWORDS

S-ICD, TV-ICD, implantable cardioverter-defibrillator (ICD), sudden cardiac death, subcutaneous ICD, transvenous ICD

Introduction

Sudden cardiac death (SCD) is reported to account for 30% of all cardiovascular death causes in Germany taking 65.000 lives per year (1). Implantable cardioverter-defibrillators (ICD) have been proven to efficiently prevent sudden cardiac arrhythmic death in pivotal trials (2–4).

Advances in ICD programming have reduced the burden of shocks, but lead-related complications remain an unalterable drawback of transvenous implantable cardioverter-defibrillator (TV-ICD) therapy, resulting in significant morbidity (5). Transvenous sensing and defibrillation leads are associated with both infective and mechanical complications, such as endocarditis, pneumothorax, venous occlusion, lead fracture, and cardiac perforation (6).

The subcutaneous implantable cardioverter-defibrillator (S-ICD) has been designed to overcome lead-related complications and device endocarditis lacking the ability for pacing or resynchronization therapy and can therefore be used only in selected patients (7). Current American and European guidelines recommend S-ICD therapy as a class IIa indication in patients without indication for pacing, cardiac resynchronization or anti-tachycardic pacing (8, 9).

Observational studies demonstrated clinical efficacy of the S-ICD with an initial high inappropriate shock rate up to 13 % due to limited discrimination abilities (10, 11). Although the rate of inappropriate shocks seems to be lower in patients implanted with S-ICD and channelopathy in a substudy of the EFFORTLESS trial (12). The Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy (PRAETORIAN) trial evaluated 849 patients with primary preventive ICD indication lacking the indication for pacing who were randomly assigned to receive either a TV-ICD or S-ICD demonstrating non-inferiority of the S-ICD regarding inappropriate shocks and device-related complications (13). Although this is the first randomized controlled trial to evaluate S-ICD and TV-ICD patients, a significant proportion of S-ICD and TV-ICD candidates have been excluded a priori (e.g., patients with history of device-associated complications or secondary prevention indication for SCD). The UNTOUCHED trial (Understanding Outcomes With the S-ICD in Primary Prevention Patients With Low Ejection Fraction) was designed to evaluate the inappropriate shock rate in a more typical, contemporary S-ICD cohort (14). In this study, 1,111 patients were implanted with an S-ICD. Due to optimized programming algorithms and application of filters (e.g., the smart pass filter to overcome T-wave oversensing), the inappropriate shock rate was 3.1% year (14). Of note, only patients with primary prevention indication for SCD have been included (14). Thus, there is a need for real-world data to investigate whether results of these studies can be extrapolated to daily clinical practice (15, 16). In the present study, we aimed to investigate clinical outcomes in an all-comers cohort of patients with primary and secondary preventive indication for ICD therapy, and also patients who were implanted with a previous defibrillator, receiving either a single chamber TV-ICD or a S-ICD.

Methods

Patient population

This retrospective observational cohort study is based on data of 192 consecutive patients either implanted with a single chamber TV-ICD ($n = 140$) or a S-ICD ($n = 52$) at the Frankfurt University Hospital, Division of Cardiology from 2009 to 2017. Seventy-three patients were excluded from analysis due to missing data to apply propensity score adjustment resulting in 119 patients included in the final study cohort. The devices used were S-ICDs (Boston Scientific, Marlborough, Massachusetts) and TV-ICDs (Biotronik, Berlin, Germany; Boston Scientific; Medtronic, Dublin, Ireland; and St. Jude Medical, Saint Paul, Minnesota). The majority of TV-ICD patients were implanted under local anesthesia, while most of the S-ICD patients received analgosedation in preparation for DFT testing. Patient demographic data were abstracted from the patient files. All patients consented to data use for quality and research purposes. The study was approved by the IRB of the

J.W. Goethe University and conforms to the ethical guidelines of the Declaration of Helsinki.

Data collection and follow-up

Data were retrospectively collected from the index hospitalization at the time of the initial S-ICD / TV-ICD implantation and at each follow-up visit which took place every 6 months or at the time of unscheduled visits in the out- or in-patient clinic. Data collection included patient characteristics such as age, indication for defibrillator therapy, echocardiographic data [e.g., left ventricular ejection fraction (LVEF)], and relevant cardiovascular and non-cardiac comorbid conditions. ECG parameters such as atrioventricular (AV) conduction and QTc were additionally assessed. NYHA-classification was assessed at implantation and every follow-up visit. Pertinent medication use (heart failure medication, statins, and antiarrhythmic drugs) was documented. To correct for potential extracardiac comorbidities, the Charlson Comorbidity Index (17) was calculated for every patient. This index incorporates 19 primary diseases and the patient's age by a point system. The higher the calculated score, the lower the one-year survival rate (17). All relevant information was entered into a customized database. For missing data, particularly in case of missed follow-up visits, family members, treating physicians, or other hospitals were contacted to retrieve the missing information.

Study endpoints

Our study data were primarily evaluated on a composite endpoint (overall survival, freedom of hospitalization, freedom of device-related events) following inverse probability of treatment weighting. For explorative purposes overall survival, freedom of hospitalization and freedom of device-related events were also assessed individually without adjustment for multiple comparisons to characterize the study population in the unadjusted and adjusted study cohort and to report its comparability with previous studies. Freedom of device-related events was calculated from time to inappropriate therapy, time to appropriate therapy and time to first system infection. Appropriate therapy was defined as shocks for ventricular tachycardia (VT) or ventricular fibrillation (VF). Inappropriate therapy consisted of shocks for heart rhythms other than VT or VF. Kaplan-Meier method followed by Cox proportional-hazards regression were performed to report the outcomes in the unweighted or with inverse probability weighting (IPW) in the weighted study cohort. Further, rate of appropriate and inappropriate device discharge and device-associated complications was provided.

Statistical analysis

Based on the non-randomized nature of this retrospective observational cohort study, an established statistical technique (propensity score method) was applied to yield a balanced distribution of baseline characteristics in the study cohort and to allow direct head-to-head comparison of the study outcome parameters between TV-ICD and S-ICD, which has been widely used in perioperative and cardiovascular clinical trials (18–22). We preferred a propensity score-based method, which retains the patient data and creates a pseudo population with an optimal covariate balance, over other statistical methods (e.g., conventional multivariable regression methods) to improve adjustment for measured confounders in a small dataset and to address potential confounding by indication (TV-ICD vs. S-ICD) when using observational data. Indeed, inverse probability weighting based on the propensity score is an established approach to deal with potential confounding factors in observational studies and for confounding by indication (23, 24). By applying the inverse probability weighting method, individual patients of the original study population ($n = 119$) were differentially weighted, thus resulting in a statistical pseudo population with simulated additional observations ($n = 231$) in which baseline patient characteristics in the weighted S-ICD ($n = 111$) and TV-ICD ($n = 120$) group are balanced (24–27). Briefly, the propensity score was calculated using a logistic regression model, in which the type of ICD (TV-ICD or S-ICD) has been regressed as dependent variable on relevant baseline characteristics (28). Corresponding weights for patients in the S-ICD group were calculated by $\frac{1}{PS}$ and for those in the TV-ICD by $\frac{1}{1-PS}$ as previously described (29). Weights were incorporated in subsequent analyses comparing the cardiovascular study outcome parameter between both ICD groups, in which the distribution of measured confounding factors is independent of ICD type. Both, balance of measured and unmeasured covariates, is achieved only in randomized, placebo-controlled trials, which has to be taken into account when interpreting our results. Absolute standardized difference ≤ 0.1 for measured covariates suggested appropriate balance between the groups, except for usage of class III AAD and digitalis glycosides (Figure 1).

Statistical analysis was performed with SPSS statistical software version 27.0 (IBM). Analysis of data distribution was performed with the Kolmogorov–Smirnov and Shapiro–Wilk Test. Continuous variables are presented as median with interquartile range (IQR) or means with standard deviations (SD) based on data distribution unless otherwise noted. Categorical variables are provided with absolute numbers (n) and percentages (%). We used the students *T*-test or Mann Whitney U test (when appropriate) to compare continuous variables and the Pearson chi-square test or Fisher exact test to compare categorical variables in the unweighted cohort. Two-sided tests were used and $p < 0.05$ were considered statistically

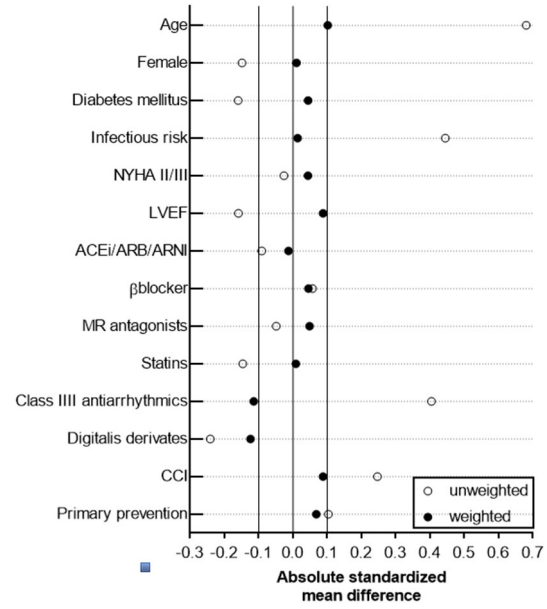

FIGURE 1
Forrest plot for standardized mean differences of covariates included in the IPW model.

significant. To estimate confounder-adjusted KM survival curves with weighted log-rank testing, the R package *RISCA* (v0.8.2) was used (30, 31). Survival analysis and visualization was further facilitated using the R package *survminer* (v0.4.9) and *survival* (v3.1-8).

For exploratory purposes median follow-up time for survival was calculated according to the inverse Kaplan–Meier method.

Results

Patient characteristics

We analyzed a total of 119 patients either implanted with a single-chamber TV-ICD or S-ICD. The S-ICD group comprised 35 (29.4 %) patients, while 84 patients (70.6 %) were included in the TV-ICD control group. During a median follow-up of 512 days (95 % CI, 228.5–795.5 days), the estimated 1.5-year overall survival rate in the study cohort was 95.0%. The baseline characteristics of both groups are summarized in Table 1. The median age of the entire population was 66.0 years, 22.7 % of the patients were female. Approximately two-thirds of the study cohort suffered from ischemic cardiomyopathy with a median left ventricular ejection fraction of 30%. Sixty-three (52.9 %) of the ICD systems were implanted for primary prevention. Most of the patients had New York Heart Association (NYHA) class II / III heart failure (67.3%), and 16.8% of the patients had atrial fibrillation. Patient characteristics were similar between both groups except for a higher age ($p = 0.001$) and differences in heart failure medication ($p = 0.026$) in the TV-ICD group, while infectious risk factors ($p = 0.004$) such as diabetes or oral immunosuppressive therapy were more prevalent in the S-ICD group. However, the standardized mean differences indicated further residual unequally distributed confounding factors (Table 1).

In the adjusted study population following inverse probability weighting based on the propensity score, an improved overall balance of baseline characteristics and standardized mean differences was achieved, indicating that the weighted study cohorts were comparable in important baseline characteristics (Figure 1 and Table 1).

Clinical outcomes

Composite endpoint

In the unweighted study group, no significant differences in the composite endpoint (survival, freedom of hospitalization, and freedom of device-related events) were observed between patients implanted with an S-ICD or TV-ICD (event number 14 vs. 24) over a follow-up time of 1.5 years using the Kaplan-Meier estimate (p = 0.226) or Cox-regression (HR 1.50, 95 % confidence interval (CI) 0.78–2.90; $p = 0.229$) (Supplementary Figure 1A). Importantly, the hazard ratio for the adjusted composite end point was 0.94 (95 % CI, 0.61–1.50; $p = 0.777$) without differences in the TV-ICD group and S-ICD group (p for log rank = 0.890) in the weighted study group (Figure 2A).

Survival

During the study follow-up time, a total of 6 patients (5.0%) died (3 TV-ICD / 3 S-ICD) in the unadjusted cohort. The main causes of death were cardiac non-arrhythmic. One S-ICD patient died due to electrical storm while living alone. Again, S-ICD therapy was not different to TV-ICD therapy in our study cohort concerning overall survival (HR 2.50, 95 % CI 0.5–12.0, $p = 0.278$) (Supplementary Figure 1B). These results were robust on the weighted analysis (HR 2.52, 95 % CI 0.76–8.30, $p = 0.129$) (Figure 2B).

Freedom of hospitalization

Concerning freedom of hospitalization, S-ICD therapy showed no differences compared to TV-ICD therapy (HR 1.7; 95 % CI, 0.85–3.40, $p = 0.134$) with consistent results on weighted analysis (HR 1.20; 95 % CI, 0.75–1.90, $p = 0.446$) (Figure 2C and Supplementary Figure 1C). Here, a total of 33 hospitalizations occurred during the follow-up period of 1.5 years (20 TV-ICD and 13 S-ICD) in the unweighted group. The main reasons for hospitalization were cardiovascular in 22 cases (15 TV-ICD and 7 S-ICD) followed by device-related problems in 6 cases (1 TV-ICD and 5 S-ICD). Non-cardiac and other reasons for hospitalization were rare (4 for TV-ICD and 1 S-ICD).

TABLE 1 Baseline characteristics of the unweighted and weighted study cohort.

	Unweighted				Weighted			
	TV-ICD ($n = 84$)	S-ICD ($n = 35$)	SDM	p-Value	TV-ICD ($n = 120$)	S-ICD ($n = 111$)	SDM	p-Value
Age, years	68 (55–77)	54 (43–71)	0.68	0.001	66 (48–76)	66 (50–74)	0.10	0.554
CCI, pts	5 (3–7)	4 (2–6)	0.25	0.209	5 (2–7)	4 (3–6)	0.09	0.528
Female, *n* (%)	20 (23.8)	7 (20.0)	−0.15	0.811	28 (23.6)	26 (23.9)	0.01	1.000
LVEF, %	30 (25–45)	30 (23–40)	−0.16	0.513	30 (25–45)	30 (25–35)	0.09	0.808
Diabetes mellitus, *n* (%)	26 (31)	9 (25.7)	−0.16	0.662	35 (29.1)	34 (30.7)	0.04	0.886
Infectious risks, *n* (%)	28 (33.3)	22 (62.9)	0.44	0.004	50 (41,6)	47 (42.2)	0.01	1.000
Prevention, *n* (%)			0.10	0.553			0.07	0.507
Primary	46 (54.8)	17 (48.6)			64 (53.8)	65 (58.5)		
Secondary	38 (45.2)	18 (51.4)			55 (46.2)	46 (41.5)		
NYHA class, *n* (%)			−0.03	0.800			0.04	0.262
I	24 (28.6)	10 (28.6)			32 (26.5)	27 (24)		
II	38 (45.2)	13 (37.1)			55 (45.8)	58 (52.9)		
III	19 (22.6)	10 (28.6)			28 (23.7)	17 (15.4)		
IV	3 (3.6)	2 (5.7)			5 (3.9)	9 (7.9)		
B-blockers, *n* (%)	76 (90.5)	34 (97.1)	0.06	0.279	111 (92.8)	109 (98.1)	0.05	0.061
Digitalis glycosides, *n* (%)	19 (22.6)	6 (17.1)	−0.24	0.625	25 (20.8)	20 (18)	−0.12	0.621
Class III AAD, *n* (%)	7 (8.3)	5 (14.3)	0.40	0.332	14 (11.4)	11 (10)	−0.11	0.833
ARB/ACEi/ ARNI, *n* (%)	83 (98.8)	31 (88.6)	−0.09	0.026	116 (97)	106 (95.5)	−0.01	0.741
MR antagonists, *n* (%)	56 (66.7)	22 (62.9)	−0.05	0.679	82 (68.5)	81 (72.7)	0.05	0.472
Statins, *n* (%)	60 (71.4)	21 (60.0)	−0.15	0.281	80 (67.2)	75 (67.9)	0.01	1.000
AV time, ms	169 (150–186)	160 (146–184)		0.312	168 (150–186)	160 (148–172)		0.049
QTc interval, ms	435 (416–461)	445.3 (410–460)		0.543	440 (417–464)	429 (410–460)		0.747
CCI, predicted 1-year survival, %	21 (0–77)	53 (2–90)		0.058	21 (0–90)	53 (2–77)		0.316
Heart disease, *n* (%)				0.494				0.482
Ischemic	55 (65.5)	18 (51.4)			76 (63.3)	67 (60.6)		
Dilated	17 (20.2)	10 (28.6)			26 (22.1)	30 (27.2)		
Congenital	3 (3.6)	1 (2.9)			6 (4.8)	2 (2)		
Other	9 (10.7)	6 (17.1)			12 (9.8)	11 (10.3)		
ECG rhythm, *n* (%)				0.404				0.086
Sinus rhythm	66 (83.5)	24 (72.7)			97 (85.5)	84 (77)		
AF	12 (15.2)	8 (24.2)			15 (13.4)	19 (17.6)		
Paced	1 (1.3)	1 (3.0)			1 (1)	6 (5.4)		
Obesity, *n* (%)	16 (20.8)	8 (22.9)		0.808	21 (19.8)	25 (22.2)		0.622
CKD, *n* (%)	19 (22.6)	8 (22.9)		1.000	28 (23)	24 (22)		0.540

TV-ICD, transvenous implantable cardioverter-defibrillator; S-ICD, subcutaneous implantable cardioverter-defibrillator; SDM, standardized mean difference; CCI, Charlson Comorbidity Index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; AAD, antiarrhythmic drugs; ARB, angiotensin receptor blockers; ACEi, angiotensin-converting-enzyme inhibitors; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; MR antagonists, mineralocorticoid receptor antagonists; AV time, atrioventricular time; ECG, electrocardiogram; AF, atrial fibrillation; CKD, chronic kidney disease; PAD, peripheral artery disease.

Comorbidity predicted survival with Charlson Comorbidity Index

Patients with TV-ICD had relevant lower projected 1-year survival rates based on CCI system (TV-ICD 21 vs. S-ICD 53%, $p = 0.058$) (Table 1). In contrast, the KM estimated survival rate at one-year in the study cohort was 97.5 % and between patients with S-ICD and TV-ICD (94.3 vs. 98.8%, p for log rank = 0.152), which differed from the CCI projected survival rate indicating that the CCI may not be of profound predictive value in a defibrillator cohort.

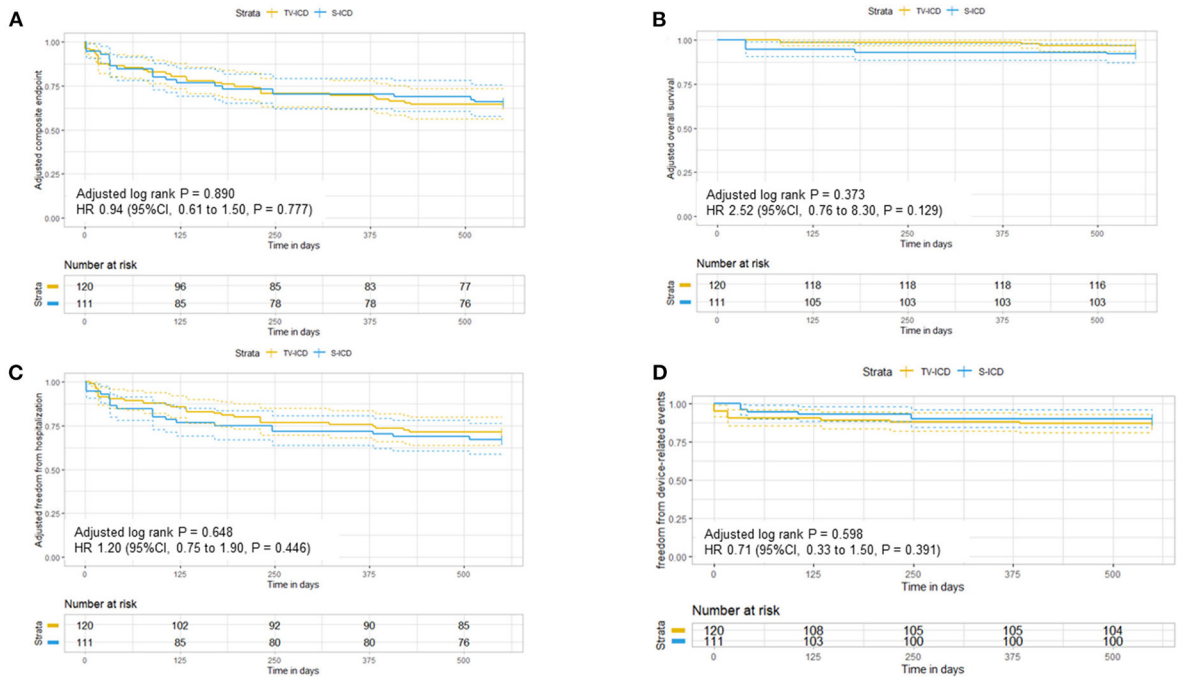

FIGURE 2
Adjusted Kaplan-Meier curves in patients with subcutaneous and transvenous ICD following inverse probability weighting for **(A)** the composite endpoint, **(B)** overall survival, **(C)** freedom of hospitalization, and **(D)** freedom of the device-related events at 1.5 year.

Freedom of device-related events

During the follow-up period, a total of 17 appropriate ICD-shocks occurred in the unweighted study cohort. Fourteen TV-ICD patients and 3 S-ICD patients received appropriate shocks due to VT or VF without significant differences on Cox-Regression analysis between the two ICD types (unweighted HR 0.99, 95 % CI 0.26–3.8, $p = 0.988$ and weighted HR 1.2, 95 % CI 0.75–1.9, $p = 0.446$). Inappropriate shocks were rare ($n = 3$) and occurred in patients implanted with TV-ICD. Of these, two patients were inadequately shocked for rapidly conducted atrial fibrillation and one patient was inadequately treated for 1:1 conducted atrial flutter. Furthermore, device-related events combining appropriate and inappropriate therapy or system infection did statistically not differ between patients implanted with TV-ICD or S-ICD in the unweighted (HR 1.6, 95% CI, 0.46–5.7, $p = 0.464$) and weighted analysis (HR 0.71, 95 % CI 0.33–1.50, $p = 0.391$) (Figure 2D and Supplementary Figure 1D), respectively.

Device-associated complications

Device-associated complications were systemically assessed, while no statistical comparison was provided for these endpoints given the rare event rate. No device dysfunction was observed during the follow-up period. In S-ICD patients, device dysfunction due to programming (e.g., vector programming) was also not observed. A total of 2 lead complications occurred in TV-ICD patients (1 fracture, 1 insulation dysfunction) necessitating revision. No lead complications occurred in S-ICD patients. A total of 7 infections were observed: 2 lead infections (1 TV-ICD / 1 S-ICD) and 4 pocket infections (1 TV-ICD / 3 S-ICD). One patient with TV-ICD had both lead and pocket infection. These infectious complications led to 3 surgical revisions, one S-ICD patient with pocket infection was managed with antibiotic therapy.

Discussion

Main findings

This single-center analysis revealed no differences in the composite endpoint as well as survival, freedom of hospitalization or of device-associated outcomes alone in a real-world cohort comparing the subcutaneous ICD and the transvenous ICD. These results persisted even after careful adjustment using inverse probability weighting based on the propensity score. In addition, this is the first study to assess the Charlson Comorbidity Index in a real-life cohort comparing S-ICD and TV-ICD, revealing higher projected survival rates in S-ICD patients compared to TV-ICD patients, although interpretation of these differences may be regarded as hypothesis generating since the CCI has been developed primarily as a

tool for adjusting the prognostic value of comorbidities in a statistical model.

Survival

To date, there is no clinical study evaluating survival in S-ICD patients as a primary outcome (13, 32–35). In the randomized controlled PRAETORIAN trial, Knops and colleagues described death from any cause as secondary outcome demonstrating no statistically significant difference between patients with S-ICD and TV-ICD (HR = 1.23; 95 % CI. 0.89–1.70) (13). Comparable to our study results, the main cause of death was cardiac-non arrhythmic followed by non-cardiac causes. Of note, 22% of the TV-ICD patients died of SCD while in S-ICD patients SCD as a primary cause of death occurred in 26% (13). In our study, only one S-ICD patient died of SCD. Several clinical trials used propensity-score matching as primary statistical method to pseudo-randomize TV-ICD and S-ICD therapy in a real-life cohort (32–35). Their results, as well as the results from the PRAETORIAN trial, were incorporated in a recently published meta-analysis by Fong and colleagues revealing no significant difference in mortality between the two ICD types (36). Interestingly, the authors provided a pooled Kaplan-Meier analysis to investigate the survival probability. Visual inspection indicates divergence of the two curves after a 4-year follow-up favoring a better survival in patients with S-ICD, although differences were not statistically significant (36). The EFFORTLESS S-ICD registry was designed to obtain clinical outcome data in S-ICD patients implanted with early generation devices (10). Recently, long-term results have been published and demonstrate an encouraging 5-year survival rate of 90.7% (37). The UNTOUCHED trial was designed to evaluate the inappropriate shock rate in a more typical, contemporary S-ICD cohort (14% having chronic kidney disease) (14). Here, the one-year-survival rate was 94.9% (14), which is comparable to the one-year survival observed among S-ICD patients in our cohort. In contrast to the study population in the UNTOUCHED trial, our study cohort incorporated almost 50% patients with secondary preventive ICD indication. Most recently, the ATLAS trial (avoid transvenous leads in appropriate subjects) included 503 patients being randomized to receive either a TV-ICD or S-ICD to evaluate perioperative complications (38). The survival rate was 98.8% within the S-ICD cohort at 6 months in a relatively young study population with a mean age of 49 years (38).

Charlson Comorbidity Index and polymorbidity

This is the first study to evaluate the Charlson Comorbidity Index (CCI) in a S-ICD study population. In accordance with several other defibrillator studies (39–43), we used the CCI to visualize and to correct for potential extracardiac comorbidities. We observed particularly high CCI scores (for S-ICD patients a median CCI of 4; for TV-ICD patients a median CCI of 5) in our study cohort compared to the existing literature (39, 40, 42). Bhavnani and colleagues, for instance, investigated early mortality (< 1 year after ICD implantation) in an elderly ICD population (age about 78 years) with a mean CCI of 2.8. Here, a CCI above 5 was associated with an incidence of 78% for early mortality (39). In a large cohort of CRT-recipients a CCI > 5 was also an independent predictor of mortality regardless of indication for ICD-therapy (40). However, Poupin et al. compared 121 elderly ICD-patients (mean age 78 years) in a 1:2 fashion with younger ICD-patients (mean age 66 years) as controls (42). In the elderly patients with a CCI of 4 or higher, the 5-year follow-up survival rate was 28 % and therefore significantly lower compared to elderly patients with lower CCI indices. In line with the younger ICD population included in our study, the mean survival rate of the control ICD population was remarkably higher with 72% (42) suggesting that increased age partially drives mortality in the context of interpreting high CCI indices. Although the reported studies questioned the appropriateness of ICD implantations in patients with CCI > 5 (39, 40) or even > 4 (42), the high survival rates observed in our study cohort (in contrast to the predicted survival rates by the CCI score) suggest that it would have been arguable to withhold ICD implantation from these young but polymorbid patients. Another reason for the encouraging clinical performance could have been S-ICD implantation per se, as this technique reduces electrode movement, lead-related complications and procedural complications like pneumothorax therefore reducing morbidity in total (38, 44). Consequently, our results might add value to the discussion about the guideline's class III indication for ICD-implantation in patients with a life expectancy of <1 year (8, 9), which is very often difficult to assess and define in clinical practice.

Hospitalization

In the PRAETORIAN trial, only hospitalization for heart failure was assessed as secondary endpoint (13). Concerning cardiac-non arrhythmic hospitalization no significant difference was observed between S-ICD and TV-ICD patients (13). In this study, we observed numerically higher freedom of hospitalization rates in TV-ICD patients compared to S-ICD patients, though this difference did not persist after adjustment on the propensity-score. A higher CCI score as well as an older age in the TV-ICD patient population might account for the observed differences in our study cohort. To date, there are no other clinical studies evaluating causes of hospitalization in patients with S-ICD and TV-ICD.

Device-associated complications

Device-associated complications were distributed equally between the two ICD types in our study except for lead-related complications, although the relatively small number of patients in this cohort needs to be taken into account when interpreting the results. We did not observe technical or mechanical problems with S-ICDs leads, while one lead infection occurred in a S-ICD patient. This is in line with the results from Fong's meta-analysis observing significantly lower lead-related complications in S-ICD patients (RR = 0.14; 95% CI 0.07–0.29; $p < 0.0001$) (36) as well as according to data from the PRAETORIAN trail and Brouwers dual-center propensity score-matched cohort (32). Fong observed no significant difference in device-related complications (RR = 0.59; 95 % CI 0.33–1.04; $p = 0.07$) (36). In a single-center experience investigating 70 S-ICD patients vs. 197 TV-ICD patients on the endpoints of the PRAETORIAN study, no differences in device complications were observed (16). Of note, 30 % of the patients had a secondary preventive ICD-indication (16). This is also in line with our study results as 51% of our S-ICD patients received an ICD for secondary prevention (rate in TV-ICD patients: 45%). Su and colleagues evaluated safety of S-ICD vs. TV-ICD therapy concerning inappropriate shocks, device-related infections and survival in a recently published meta-analysis comprising 7 studies. Su described no differences in device-related infections between the two ICD groups (OR = 1.57; 95% CI: 0.67–3.68) (45). In contrast, data from the recently published Monaldi Registry comparing 607 patients either implanted with S-ICD or TV-ICD demonstrate significantly lower adjusted risk for ICD related infections (OR = 0.07; 95% C. I. 0.009-0.55; $p = 0.01$) (15). Preliminary analysis from the randomized-controlled ATLAS trial demonstrated superiority of the S-ICD regarding lead-related complications with a relative risk reduction of 92% (OR = 0.08; 95% C. I. 0.00–0.55; $p = 0.003$) (38, 46). In fact, we observed numerically more pocket infections in S-ICD patients in our study cohort. Accordingly, Rordorf et al. reported a significantly higher risk of pocket complications defined as hematoma, erosion or infection in S-ICD patients compared to patients with TV-ICDs (OR = 2.18; 95 %CI 1.30–3.66; $p = 0.003$) in a recently published meta-analysis by evaluation of 13 studies comparing S-ICD and TV-ICD therapy (47).

Clinical implications

This real-world study investigated patients with primary and secondary preventive indication for ICD therapy receiving either a single chamber TV-ICD or a S-ICD and revealed that results for both ICD types with respect to the composite endpoint, survival, freedom of hospitalization, and freedom of device-associated complications did not differ. Additionally, we believe that non-lead related device complications can and will be further diminished in S-ICD patients as reported by the preliminary analysis of the ATLAS trial (38). Therefore, we provide additional evidence to recently published data from the PRAETORIAN trial in our all-comers study cohort of patients with primary and secondary preventive indication for ICD therapy and add clinical outcome data concerning survival and freedom of hospitalization to the existing literature. Further, this is the first study to evaluate S-ICD patients based on the CCI to correct for extracardiac comorbidities revealing a higher survival rate than predicted by the high CCI indices, at least in part, for relatively young ICD patients with increased burden of morbidity included in this study.

Limitations

Our study is retrospective in nature, hence all potential limitations of such a design apply to this analysis. We aimed to minimize confounding by carefully adjusting data by performing a propensity-score based analysis. Despite this, residual confounding in observational studies cannot be entirely excluded, especially for unmeasured confounders. Balance of measured and unmeasured covariates is achieved only in randomized, placebo-controlled trials. Additionally, the low inclusion rate and low event number in our study as well as potential selection bias have to be taken into account when interpreting the results of this study. Although the results are in line with recent reports, there was a limited number of patients included in this study. Strengths of this study are detailed evaluation of clinical outcome data, incorporation of a real-world study cohort and evaluation of the Charlson Comorbidity Index, although the CCI has been evaluated but not validated in TV-ICD patients (39–43) or S-ICD patients.

Conclusion

Our single-center observational study revealed no differences of the transvenous ICD compared to subcutaneous ICD regarding survival, freedom of hospitalization and device-associated complications in a real-world cohort. These results persisted even after careful adjustment for measured confounders using the Charlson Comorbidity Index and inverse probability weighting based on the propensity score. Of note, this is the first study to evaluate CCI in a S-ICD population demonstrating higher survival rates than predicted by the high CCI indices for young ICD patients with increased burden of morbidity included in this study.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by IRB J. W. Goethe University/University Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

BK, SH, MV, and JE contributed to conception and design of the study. FO, FH, FM, MV, and JE organized the database. BK, FB, and JE performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

Author JE reports receiving consultant fees, travel support and lecture fees from ZOLL Medical, travel grants from Bayer Vital, St. Jude Medical/Abbott, Novartis and lecture fees from Servier, Pfizer and Bayer Vital and was a fellow of the Boston Scientific heart rhythm fellowship program. Author MV reports consulting fees and/or non-financial support from Biotronik, Medtronic, and Pfizer, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Case report: Left bundle branch pacing guided by real-time monitoring of current of injury and electrocardiography

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Background: Left bundle branch (LBB) pacing (LBBP) has recently emerged as a physiological pacing mode. Current of injury (COI) can be used as the basis for electrode fixation position and detection of perforation. However, because the intermittent pacing method cannot monitor the changes in COI in real time, it cannot obtain information about the entire COI change process during implantation.

Case summary: Left bundle branch pacing was achieved for treatment of atrioventricular block in a 76-year-old female. Uninterrupted electrocardiogram and electrogram were recorded on an electrophysiology system. In contrast to the interrupted pacing method, this continuous pacing and recording technique enables real-time monitoring of the change in ventricular COI and the paced QRS complex as the lead advances into the interventricular septum. During the entire screw-in process, the COI amplitude increased and then decreased gradually after reaching the peak, followed by a small but significant, rather than dramatic, decrease.

Conclusion: This case report aims to demonstrate the clinical significance of changes in COI and QRS morphology for LBBP using real-time electrocardiographic monitoring and filtered and unfiltered electrograms when the lead is deployed using a continuous pacing technique. The technique could be used to confirm LBB capture and avoid perforation.

KEYWORDS

left bundle branch pacing, current of injury (COI), electrocardiogram (ECG), intracardiac electrogram, continuous recording technique

Introduction

Left bundle branch (LBB) pacing (LBBP) provides stable pacing parameters by directly capturing the conduction system in the left ventricular sub-endocardium (1). The pacing lead should be deployed deep enough into the ventricular septum to capture LBB; however, this carries the risk of perforation during lead implantation. A decrease

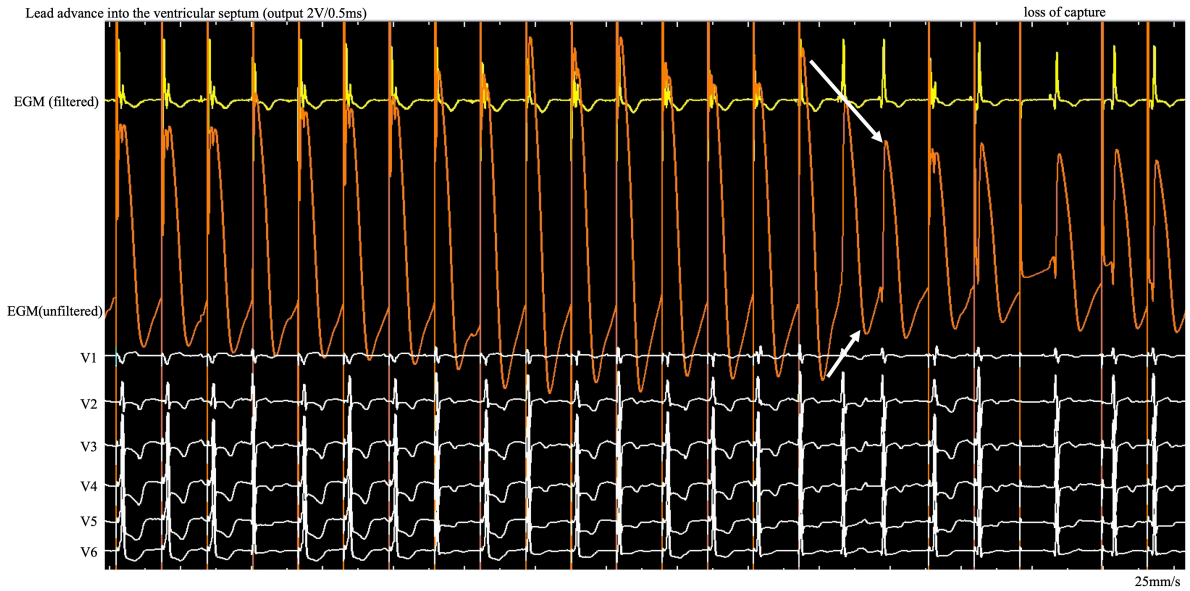

FIGURE 1
During the entire screw-in process, the COI amplitude increased and then decreased gradually after reaching the peak, followed by a small but significant abrupt decrease. COI, current of injury; ECG, electrocardiogram; EGM, intracardiac electrogram.

in unipolar impedance, loss of capture, and absence of current of injury (COI) are signs of septal perforation (2). Previous studies used the intermittent pacing method to interruptedly monitor COI and paced QRS morphology, which may miss a lot of information during the transseptal implantation and enable observation of real-time changes in COI only when the lead is retracted (3, 4). One such study demonstrated that the real-time COI value during screwing in should be widely adopted in daily practice (4). Our study aimed to obtain continuous parameters from real-time monitoring of the surface electrocardiogram (ECG) and filtered and unfiltered intracardiac electrogram (EGM) to guide lead deployment.

Case report

A 76-year-old woman with atrial fibrillation and third-degree atrioventricular block underwent LBBP. Echocardiography examination revealed left ventricular end-diastolic diameter of 44 mm and left ventricular ejection fraction of 75%. Uninterrupted ECG and EGM were recorded on an electrophysiology system using John Jiang's connecting cable (Xinwell Medical Technology Co., Ltd., Ningbo, Zhejiang, China) (5, 6). In contrast to the interrupted pacing method, this continuous pacing and recording technique enables real-time monitoring of changes in ventricular COI and the paced QRS complex as the lead advances into the interventricular septum. We previously described the LBBP implantation procedure in detail (7, 8). During the entire screw-in process, the COI amplitude increased, peaked, and gradually decreased, followed by a small but significant abrupt decrease (**Figure 1**). Simultaneously, the impedance dropped from 691 to 532 Ω, and the myocardium capture was lost. This indicates septal perforation. No transition from left ventricular septal pacing to non-selective LBBP (NSLBBP) or NSLBBP to selective LBBP was observed during implantation. With no evidence of LBB capture, the electrode was retracted for the second implant. Repositioning to another site was uneventful. Smooth transition of paced QRS morphology from the LBB block pattern to the right bundle branch block pattern was observed as the lead advanced from the right to left side of the septum. After the COI amplitude peaked, the electrode was rotated very slowly to avoid a sudden drop in COI until the LBB area was reached. An abrupt shortening of the V6 R-wave peak time (V6RWPT) and a discrete EGM were subsequently observed (**Figure 2**), indicating LBB capture (9). The pacing threshold at the end of procedure was 0.7 V/0.5 ms. The lead was placed at a depth of 14 mm (**Supplementary Figure**).

Discussion

Current of injury is a marker of active fixation electrode stability and the adequate capture threshold (10–12). COI, detectable on unfiltered EGM, is characterized by ST-segment elevation from baseline due to focal tissue trauma caused by the advancement of the lead tip into the septum. Su et al. described the COI abruptly disappeared when perforation happened

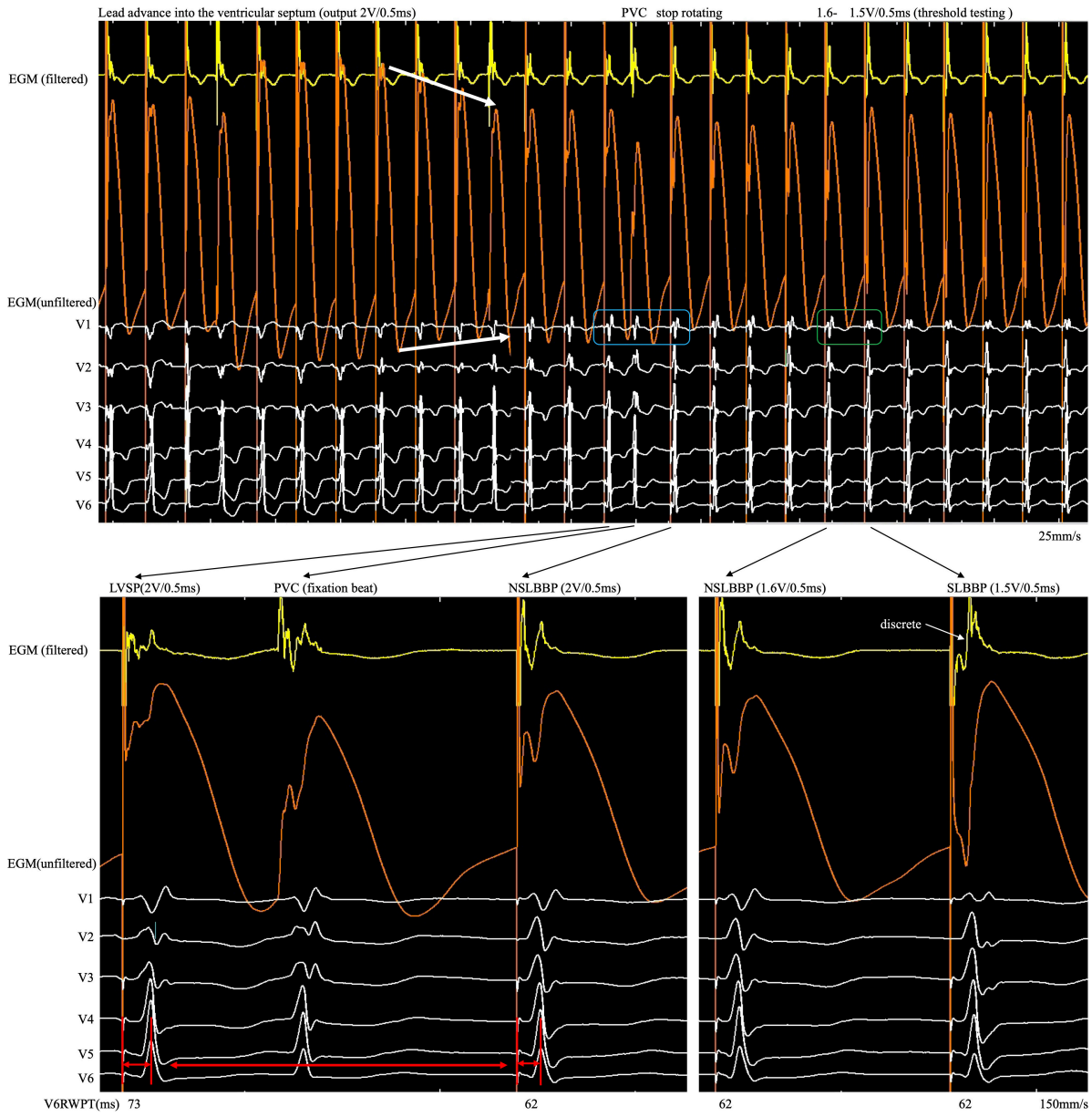

FIGURE 2
After the COI amplitude increased to its highest value, the electrode was rotated very slowly to avoid a sudden drop in COI until the LBB area was reached. An abrupt shortening of V6RWPT, discrete EGM and fixation beat were observed. COI, current of injury; LBB, left bundle branch; LBBP, left bundle branch pacing; SLBBP, selective left bundle branch pacing; NSLBBP, non-selective left bundle branch pacing; ECG, electrocardiogram; EGM, intracardiac electrogram; RWPT, R-wave peak time; PVC, premature ventricular complex.

(13). Ponnusamy et al. demonstrated that decreased COI amplitude differed significantly before versus after perforation (COI amplitude decreased from 15.4 ± 11.6 to 0.9 ± 0.6 mV) (3). However, the current intermittent pacing technique cannot monitor unfiltered EGM in real time. Therefore, it is unknown exactly when perforation occurs and how EGM changes therein. Some important practical considerations for implantation with deep septal lead deployment are when not to screw in further and when to reposition the lead.

Here we found a gradual increase in COI, followed by a gradual decrease, as the lead was gradually screwed into the septum. The possibility of microperforation should be considered after a small but significant, rather than dramatic, decrease in COI amplitude and the existence of impedance decrease with myocardial capture loss on unfiltered unipolar EGM (**Figure 1**, white arrow). Lead rotation should be stopped immediately to avoid complete entry into the ventricular cavity. The screw site must be repositioned, and the pacing output

testing must be repeated in the same manner. The continuous pacing and recording technique in clinical practice allows real-time monitoring of the entire perforation process and early termination of the helix screwing to prevent immediate complete septal perforation in the event of a small and abrupt COI decrease.

Although changes in impedance and COI were observed during lead fixation, they were insufficient to confirm LBB capture. Because the myocardium and conduction system involve different tissues, they have different electrophysiological characteristics. Different ECG and EGM morphology was observed when different tissues were captured. Therefore, it is necessary to confirm LBB capture, demonstrated as dynamic changes in paced QRS morphology (14). However, subtle but significant changes in paced QRS morphology and EGM are difficult to observe in real time using the intermittent pacing technique but can be recorded by the continuous recording technique. When the rSR pattern suddenly changes to the r'SR pattern in lead V1 (**Figure 2**, blue rectangle) and V6RWPT abruptly shortens between the morphology of two adjacent paced QRS complexes (**Figure 2**, red arrow), the implantation process should be ceased, and threshold testing should be performed. When reducing the output, the discrete component in the filtered EGM and transition from the r'SR pattern to the M pattern on the ECG (**Figure 2**, green rectangle) are observed. In high- and low-output testing, V6RWPT is constant and remains the shortest value requiring measurement. If the V6RWPT of the high output is shorter than that of the low output, the lead must be screwed in slightly to keep the V6RWPT of the high and low outputs constant.

Conclusion

First, when the COI amplitude peaks, the electrode must be rotated very slowly. Second, when the QRS morphology changes dynamically (such as V6RWPT abruptly shortening with the rSR pattern transition to the r'SR pattern) and there is evidence of LBB capture, the rotation should be stopped. Third, when a small but significant decrease in COI amplitude occurs with a decrease in impedance and loss of capture, the implantation should be stopped and the screw-in site be repositioned. This technique could be used to confirm LBB capture and avoid perforation.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Hwa Mei Hospital, University of Chinese Academy of Sciences Ethics Committee Review. The patients/participants provided their written informed consent to participate in this study and for the publication of this case report. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

LJ owns the patent for John Jiang's connecting cable.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1025620/full#supplementary-material

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Physician antibiotic hydration preferences for biologic antibacterial envelopes during cardiac implantable device procedures

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Background: Cardiac implantable electronic device (CIED) infection is a potentially serious complication of CIED procedures. Infection risk mitigation includes using guideline-recommended pre-operative intravenous antibacterial prophylaxis (IV ABX). The use of antibiotic-eluting CIED envelopes has also been shown to reduce infection risk. The relationship between and potential benefits associated with guideline-recommended IV ABX in combination with antibacterial envelopes have not been characterized.

Methods: Biologic envelopes made from non-crosslinked extracellular matrix (ECM) were implanted into 1,102 patients receiving CIEDs. The implanting physician decided patient selection for using a biologic envelope and envelope hydration solution. Observational data was analyzed on IV ABX utilization rates, antibacterial envelope usage, and infection outcomes.

Results: Overall compliance with IV ABX was 96.6%, and most patients received a biologic envelope hydrated in antibiotics (77.1%). After a mean follow-up of 223 days, infection rates were higher for sites using IV ABX <80% of the time vs. sites using ≥80% (5.6% vs. 0.8%, $p = 0.008$). Physicians demonstrated preference for hydration solutions containing gentamicin in higher-risk patients, which was found by multivariate analysis to be associated with a threefold reduction in infection risk (OR 3.0, 95% CI, 1.0–10.0).

Conclusion: These findings suggest that use of antibiotics, particularly gentamicin, in biologic envelope hydration solution may reduce infection risk, and use of antibacterial envelopes without adjunct IV ABX may not be sufficient to reduce CIED infections.

Clinical trial registration: [https://clinicaltrials.gov/], identifier [NCT02530970].

KEYWORDS

cardiovascular implantable electronic device (CIED), defibrillator, envelope, antibacterial envelope, extracellular matrix, ICD (implantable cardioverter-defibrillator), infection, pacemaker

Introduction

Cardiac implantable electronic devices (CIEDs) are important tools in the management of patients with a variety of arrhythmia and heart failure disorders. Expanding device indications, newer CIED technology, and population demographics have resulted in continuous growth in the use of CIEDs (1). This growth in volume has been associated with higher complication rates including infection. Reported rates of CIED infections range from approximately 1–3% for *de novo* implantations with reported rates up to 7% following device replacements and higher rates observed among patients with risk factors that have been associated with CIED infection (2–5). Several factors have been postulated as influencing CIED infection rates, which exceed overall CIED implantation growth rates, including an aging demographic profile, the presence of more comorbidities, and a greater prevalence of infection risk factors among recipients (3, 5–13).

Cardiac implantable electronic device infections are associated with substantial morbidity and mortality that augment healthcare costs (1, 2). Based upon information obtained from the National Inpatient Sample database, which is the largest all-payor US-based inpatient database, the mortality rate due to lead extraction was 4.5%, with higher mortality rates in patients >85 years old (5.3%) when compared to those aged 18–44 years (2.5%, $p < 0.001$) (14). Furthermore, the mortality rate among patients undergoing lead extraction associated with an infection was four times higher than rates observed among patients undergoing extraction for another reason. This analysis also demonstrated that there was a 53% increase in the number of hospitalizations due to CIED infections, a doubling in the percentage of lead extractions secondary to infection (14–29%), and a 41% overall increase in total number of extractions between 2003 and 2011. The economic impact associated with CIED infection was also substantial with a 53% increase in mean hospitalization charges ($91,348–$173,211, $p < 0.001$). Retrospective studies of commercial and Medicare databases have reported mean payments for the management of CIED infections ranging from $22,856 to $77,397 per patient with average adjusted annual medical costs 2.4 times greater for patients with a CIED infection (15, 16).

Based on these clinical and economic concerns, infection prevention is a key consideration associated with the implantation of cardiac devices. Evidence-based prophylactic approaches include the utilization of guideline-directed preoperative intravenous antibacterial prophylaxis (IV ABX), the use of strict skin antisepsis, and potentially the employment of antibacterial CIED envelopes (1, 17–19). In the large Prevention of Arrhythmia Device Infection Trial (PADIT), there was no difference in the CIED infection rate between patients receiving a conventional perioperative antibiotic regimen vs. those undergoing an incremental antibiotic approach (19). The 0.9% hospitalization-for-infection rate in the overall population and 1.11% rate in the high-risk group establish standards for best-in-class infection rates, especially given the large and geographically diverse enrollment (19,603 patients from 28 centers) (19).

Two types of CIED envelopes that are designed to stabilize the CIED within the pocket are available for use in the US. The biologic envelope is made from a decellularized, non-crosslinked extracellular matrix derived from porcine intestinal submucosa (SIS ECM) (**Figures 1A–C**) (20). The non-biologic envelope consists of an absorbable multifilament block copolymer coated with an absorbable polyarylate polymer containing the drug substances rifampin and minocycline (20).

The use of non-biologic envelopes has been associated with a reduced incidence of CIED infections in high-risk patients in a controlled trial (21). Published studies suggest that non-biologic surgical materials potentially can trigger a robust foreign body response, including chronic inflammation and fibrous encapsulation of the material, rather than fostering integration into host tissues (22–25). However, it remains uncertain whether non-biologic products employed in a standard surgical arena generate the same tissue response as those products employed as a CIED envelope. In contrast, materials made from biologic non-crosslinked ECM have been shown to foster greater tissue integration and vascular ingrowth, a modulated inflammatory response, and rapid clearance of bacteria (22, 23, 25–31).

Biologic envelopes are hydrated prior to use by the implanting physician, who may elect to add antibiotics to the hydration solution to augment local antibiotic levels and enhance the inherent antimicrobial properties of the ECM. Once implanted, growth factors released from the ECM stimulate angiogenesis and allow host immune cells to penetrate the remodeling envelope (32–34). The immunomodulatory process that ECM triggers during remodeling leads to decreased scar tissue formation and a vascularized capsule, fostering the development of a healthy long-term pocket (23, 25, 33, 34). ECM-based materials have also been shown to natively promote the removal of bacteria after implantation, and compounds with inherent antimicrobial properties are released during remodeling, potentially mitigating infection risk (29–31, 34).

The CanGaroo® Envelope (Aziyo Biologics, Inc., Silver Spring, MD, USA) is a biologic ECM envelope constructed of 4-ply decellularized, non-crosslinked, lyophilized SIS ECM. Recently published data suggest that the CanGaroo Envelope can reduce the risk of device migration and erosion and may facilitate device removal, when future exchange or revision is required, due to reduced scar formation, encapsulation, and foreign body response (35, 36).

In this manuscript, we combined data from two post-market observational studies (SECURE and CARE) with the aim of evaluating differences in real-world clinical decision making with regard to the use of antibiotic solutions for rehydration of the biologic envelope and the use of IV ABX when the envelope

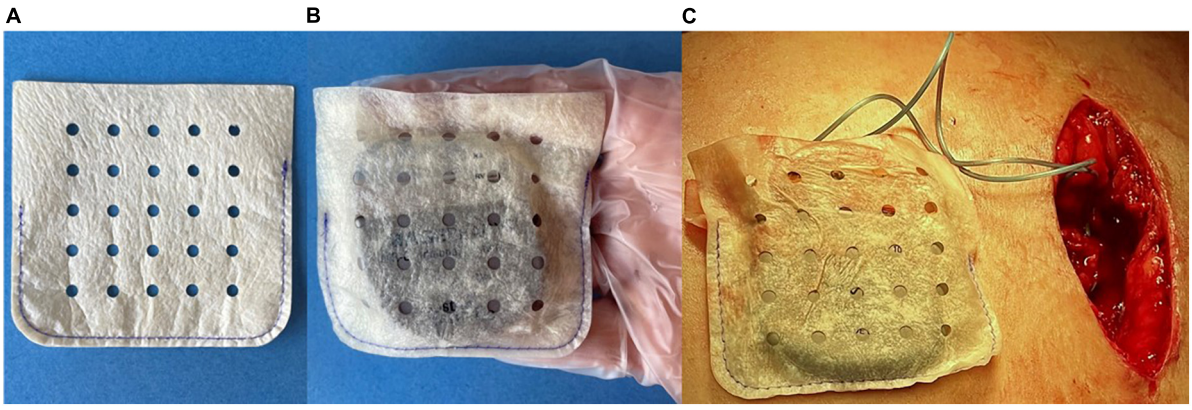

FIGURE 1
(A) A medium-size biologic CanGaroo® Envelope made from 4-ply lyophilized, decellularized, non-crosslinked extracellular matrix derived from porcine intestinal submucosa (SIS ECM). **(B)** Once hydrated by the implanting physician per manufacturer instructions, the biologic envelope handles well and conforms to the device. **(C)** Intraoperative photo of the hydrated biologic envelope just prior to being placed within the tissue pocket.

was implanted in a broad population of patients undergoing implantation of a CIED.

Materials and methods

Study design

This report includes findings from 2 studies. SECURE (NCT02530970) was a prospective, multicenter, post-market, observational study conducted at 39 sites in the United States between September 2015 and November 2017. CARE was a retrospective, post-market observational study conducted at Piedmont Athens Regional Hospital in Athens, GA, USA of patients who received treatment between August 2014 and July 2015. Both studies were designed to evaluate clinical outcomes following the use of the CanGaroo Envelope in patients who underwent implantation of a CIED. Patients were eligible for enrollment if they received a CanGaroo Envelope at the time of their CIED implantation. Patient selection for receiving an envelope was left to the discretion of the participating physicians.

All patients underwent a comprehensive medical history and clinical examination prior to implantation. Study protocols were approved by the Institutional Review Board of each participating center, and all patients provided informed consent. The studies were conducted in accordance with the Declaration of Helsinki and regulatory and institutional requirements.

Surgical technique

Cardiac implantable electronic device implantation was performed according to standard techniques. The envelope size was selected by the investigator, based on the size of the CIED being implanted. In both studies, the envelope hydration solution and choice of antibiotics, if used, were left to individual physician discretion.

The CIEDs were connected to the leads and the leads were secured to the underlying tissue before the CIED was placed into the envelope and subsequently implanted. The pre- and post-procedure medication regimens as well as clinical treatment were performed according to the routine practice of each center.

Data collected

Patient, procedural, and follow-up data were collected on standardized case report forms by site clinical personnel and reviewed by the investigator or qualified study monitors.

Data collected at baseline included limited demographic information, patient medical history, and device and procedural details. In the SECURE study, findings related to complications were collected at the following time points: the first post-operative visit, 4–6 weeks, 3 months following the index procedure, and at an extended follow-up visit just prior to study closure. In the CARE study, data on complications were collected at the following time points: the first post-operative visit, 4–6 weeks, and any other follow-up visits prior to study closure.

Outcome measures

Clinical outcome measures included the incidence rates of pocket infection, superficial cellulitis, superficial surgical site infection, hematoma, lead dislodgement, and other complications (all collected outcome measures can be found in

Supplementary Table 1). A major CIED infection was defined as infection requiring surgical intervention (i.e., system removal, pocket revision, etc.) or treatment with long-term antibiotic therapy (if system removal was not possible) to manage one of the following: (1) superficial cellulitis in the region of the CIED pocket with wound dehiscence, erosion, or purulent drainage; (2) deep incisional or organ/space (pocket) surgical site infection; (3) persistent bacteremia; or (4) endocarditis. Minor CIED infections included those that did not meet one or more of the criteria for major infection.

Safety outcomes were determined by analysis of all device-related adverse events. Device-related events were defined as clinical signs, symptoms, or conditions that were deemed by the investigator to be causally related to the implantation or the performance of the envelope. Causality was adjudicated by the investigators as not related, possibly related, or probably related to the implantation procedure or envelope.

Infection risk factor characterization

Data collected for each patient's baseline medical history included infection risk factors based on information in previous studies, which identified factors significantly associated with an increased risk for CIED-related infections: oral systemic anticoagulants, chronic steroid use, renal insufficiency, diabetes, peripheral vascular disease, coronary artery disease, chronic obstructive pulmonary disease, obesity, malnutrition, smoking status, congestive heart failure, malignancy, hypertension, the presence of two or more leads, prior device infection, pocket re-entry within 2 weeks of initial implant, and device replacement/revision (3, 8, 11). Numeric scores were calculated for each patient based on the total number of their respective positive infection risk factors. For cohort analysis comparisons, patients with 0 or 1 infection risk factors were grouped together, and patients who had 2 or more ($\geq$2) infection risk factors were grouped together.

Cohort group definitions

For cohort analysis, patients were grouped by the type of solution used to hydrate their envelope (i.e., saline or saline with one or more antibiotics added). Results are categorized by rehydration solution group and abbreviated throughout the rest of the manuscript as: *Saline* (saline only without any antibiotics), *Gent Only* (saline with gentamicin only), *Any ABX + Gent* (saline with gentamicin, potentially with one or more other antibiotics), and *Any ABX − Gent* (saline with one or more antibiotics, not including gentamicin) (**Box 1**). Statistical comparisons were evaluated between the *Saline* and *Gent Only* groups, and *Any ABX + Gent* and *Any ABX − Gent* groups.

BOX 1 Patient cohorts referenced in this manuscript, and the respective envelope hydration solutions chosen by physicians in real-world practice.

Cohort name	Envelope hydration solution(s) used
Total	All known hydration solutions combined.
Saline	Hydration in saline only without any antibiotics.
Gent Only	Hydration in saline with gentamicin only.
Any ABX + Gent	Hydration in saline with gentamicin, potentially with one or more other antibiotics.
Any ABX − Gent	Hydration in saline with one or more antibiotics, not including gentamicin.

Use of preoperative intravenous antibiotic prophylaxis (IV ABX)

Data was collected on the real-world use (and non-use) of IV ABX within the standardized case report forms used for both studies. The rate of IV ABX compliance was determined for each study site by totaling all patients who received IV ABX during their procedure and dividing that number by the total number of patients enrolled by that site. Sites were then grouped into categories of IV ABX compliance: 100% compliance, $\geq$80% compliance, and <80% compliance.

Statistical analysis

Continuous variables were assessed for normality. The cohort was then described using means with standard deviations for continuous variables and counts with percentages for categorical variables. Independent samples *t*-tests were used to compare mean differences between groups. Categorical variables were compared using Pearson chi-square tests for comparisons with expected cell counts $\geq$5. Fisher's exact tests were reported if $\geq$1 expected cell count was <5. *P*-values were considered statistically significant if <0.05. To account for familywise error, the significance threshold can be compared at <0.001. SPSS version 26 (IBM, Armonk, NY, USA) was used for statistical analyses.

Results

A total of 1,102 patients (n = 94 CARE, n = 1,008 SECURE) at 40 centers (n = 1: CARE, n = 39: SECURE), who received a CIED device implantation using a biologic ECM envelope hydrated in a known solution, were included in the analysis. Nine patients were excluded because the hydration solution used in these cases was unknown. The mean duration of follow-up for the overall sample was 223.7 $\pm$ 173.0 days. A total of 252 patients (22.9%) received biologic envelopes hydrated in *Saline*, 73 (6.6%) *Gent Only*, 227 (20.6%) *Any ABX + Gent*, and 623

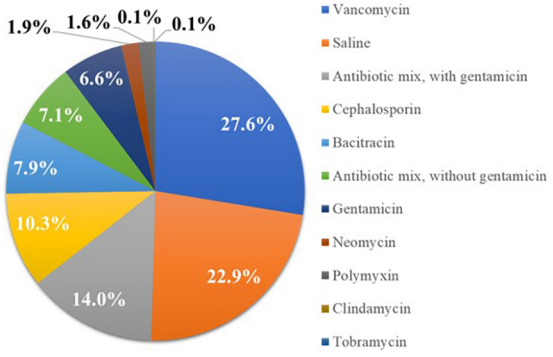

FIGURE 2
Percentage of patients receiving biologic extracellular matrix (ECM) envelopes hydrated in different solutions prior to implantation. Most implanting physicians chose envelope hydration solutions containing antibiotics.

(56.5%) *Any ABX − Gent*. The specific antibiotics selected by implanting physicians in the study are illustrated in Figure 2.

Background characteristics

The demographics and medical histories of enrolled patients are shown in Tables 1, 2. There were no significant differences between subgroups in age (mean 72 years), gender (60.9% male), or mean BMI (28.8 kg/m^2).

Attributed to the non-randomized design and large sample size, a few significant differences emerged between treatment groups with regard to race, ethnicity, and medical history (Tables 1, 2). There was a significant difference detected for the races treated in the Any ABX + Gent vs. Any ABX − Gent groups ($p < 0.001$) (Table 1). For ethnicity, there were less Hispanic or Latino patients in the Saline group (0.0%).

With regard to medical history, significant differences between treatment groups were found (Table 2). Current smokers were treated more often with Gent Only vs. Saline ($p < 0.001$), yet there was no difference in patients receiving Any ABX + Gent vs. other antibiotics (Gent Only or Any ABX − Gent). Patients with diabetes were preferentially treated with solutions that did not contain gentamicin: either Saline or Any ABX − Gent. Hydration solutions containing antibiotics other than gentamicin were used in patients with hypertension, however, the opposite was true for patients on oral anticoagulants who were treated preferentially with Any ABX + Gent. Any ABX − Gent was chosen significantly more often for patients who were obese (BMI ≥30 kg/m^2) and those with peripheral vascular disease. Finally, patients with heart failure received Gent Only more frequently than Saline, but when comparing antibiotic solutions physicians preferentially did not choose those containing gentamicin. No significant differences were found between groups for chronic steroid use, COPD, malnutrition, malignancy, or renal insufficiency.

Patients who underwent pre-procedure temporary pacing (PPTP) were more often treated with Any ABX − Gent. However, patients who had a pocket re-entry within 2 weeks of their original implant were preferentially treated with an envelope hydration solution of Gent Only. There were no significant differences in hydration solutions between patients who suffered prior device infections at least 12 months prior to their current procedure.

Procedure- and device-related factors

Procedure and device-related factors are shown in Table 3. In general, implanting physicians demonstrated a preference for Saline as a hydration solution for low-powered devices (e.g., pacemakers and CRT-P: $p < 0.001$) and an antibiotic solution for high-powered devices (e.g., ICD and CRT-D: $p < 0.001$ vs. Gent Only). Regarding the type of antibiotic hydration used, implanting physicians had a preference for using gentamicin-containing solutions for high-power devices ($p = 0.004$) while there was no antibiotic preference for low-power devices ($p = 0.137$). For re-operations ($p < 0.001$) and capsulectomy procedures ($p = 0.009$), antibiotic hydration was preferred to Saline. Similarly, gentamicin was the preferred antibiotic for re-operation procedures ($p < 0.001$ vs. Saline, $p = 0.018$ vs. Any ABX − Gent) and capsulectomy procedures ($p = 0.009$ vs. Saline, $p < 0.001$ vs. Any ABX − Gent).

Infection and other adverse events

There were 28 reported hematomas (2.5%), 14 of which required intervention (1.3%). In no case did hematoma and infection co-occur. There were no significant differences between treatment groups for any individual adverse event, including among subgroups (e.g., use of high- vs. low-power devices). There were also 14 (1.3%) other events reported such as lead dislodgement/revision, pocket revision, erosion, and erythema/fever without differences between groups (Table 4).

Overall, there were 19 major CIED infections (1.7%) and 15 minor CIED infections (1.4%) (Table 4). Major infections included 12 pocket infections (1.1%) and 7 instances of superficial cellulitis with dehiscence, erosion, or purulent drainage (0.6%). One patient had bacteremia, endocarditis, and pocket infection. Overall, there were no significant differences detected between the groups. Analysis of time to onset of infection also did not identify any significant differences among treatment groups for major, minor, or pocket infections at any timepoint through 90 days (0–30 days or 31–90 days, Table 4). However, across all timepoints, there was a trend toward statistical significance in the incidence of pocket infections between Any ABX + Gent (0 pocket infections [0%]) and Any ABX − Gent (10 pocket infections [1.6%]) ($p = 0.070$), suggesting a potential

TABLE 1 Patient demographics.

Characteristic	Total (N = 1,102)	Saline (n = 252)	Gent Only (n = 73)	Any ABX + Gent (n = 227)	Any ABX − Gent (n = 623)	*p-value*	
						Saline vs. Gent Only	ABX + Gent vs. ABX − Gent
Age, years, mean ± *SD*	72.0 ± 12.0	72.3 ± 11.4	73.6 ± 11.8	72.0 ± 11.7	71.8 ± 12.3	0.406	0.849
Gender, male, *n* (%)	671 (60.9)	145 (57.5)	45 (61.6)	135 (59.5)	391 (62.8)	0.531	0.382
BMI, mean ± *SD*	28.8 ± 6.7	28.6 ± 6.5	28.8 ± 8.5	28.4 ± 7.3	29.1 ± 6.6	0.835	0.719
Race, *n* (%)						0.266	**<0.001**
White	874 (79.3)	207 (82.1)	65 (89.0)	205 (90.3)	462 (74.2)	–	–
Black or African American	174 (15.8)	26 (10.3)	7 (9.6)	12 (5.3)	136 (21.8)	–	–
Asian	17 (1.5)	10 (4.0)	0 (0.0)	3 (1.3)	4 (0.6)	–	–
Native Hawaiian or Other Pacific Islander	9 (0.8)	6 (2.4)	0 (0.0)	1 (0.4)	2 (0.3)	–	–
American Indian or Alaska Native	7 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)	6 (1.0)	–	–
Other	11 (1.0)	2 (0.8)	0 (0.0)	4 (1.8)	5 (0.8)	–	–
Unknown	10 (0.9)	1 (0.4)	1 (1.4)	1 (0.4)	8 (1.3)	–	–
Ethnicity, *n* (%)						1.00	0.499
Non-hispanic or Latino	1065 (96.6)	249 (98.8)	73 (100.0)	220 (96.9)	596 (95.7)	–	–
Hispanic or Latino	31 (2.8)	0 (0.0)	0 (0.0)	7 (3.1)	24 (3.9)	–	–
Unknown	6 (0.5)	3 (1.2)	0 (0.0)	0 (0.0)	3 (0.5)	–	–

Bolded values are those that have a significant *P*-value.

benefit to the use of gentamicin for the prevention of pocket infections.

A multivariate logistic regression model was used to predict the likelihood of infection (either major or minor) from the use of gentamicin while adjusting for the risk factors of obesity and diabetes as demonstrated in Table 5. Covariates in this model were statistically significant, including a history of obesity (odds ratio [OR] 2.3, 95% CI, 1.0 – 5.1) and diabetes (OR 0.2, 95% CI, 0.1 – 0.8). A group difference emerged at the trend level ($p = 0.083$) such that the omission of gentamicin was associated with a threefold increase in risk for infection (OR 3.0, 95% CI, 1.0 – 10.0). The model area under the curve (AUC) was 0.70 (95% CI, 0.60 – 0.78).

When subjects were grouped by number of standard infection risk factors (0–9), 88.7% had at least 1 risk factor, and the majority of patients (58.6%) had 2 or more (Table 6). Significantly more patients with 2 or more (≥2) risk factors were in the Gent Only vs. Saline group (p = 0.026) or Any ABX − Gent group vs. Any ABX + Gent group (p = 0.035).

Use of preoperative intravenous antibiotic prophylaxis (IV ABX)

Overall compliance with IV ABX across all study sites was 96.6% (range 11–100%), similar to WRAP-IT (94.2%), (21) but varied by site: 23 sites (58%) administered IV ABX 100% of the time, 32 sites (80%) administered ≥90% of the time, and 36 sites (90%) administered ≥80% of the time. Only 4 sites (10%) used IV ABX less than 80% of the time.

Sites with higher IV ABX compliance (≥80% use) demonstrated a trend toward a lower overall rate of CIED pocket infection than sites with <80% IV ABX compliance (0.9% vs. 2.9%) (Figure 3A). These differences were significantly more pronounced when stratifying for antibacterial biologic envelope usage in conjunction with IV ABX ≥80% site compliance vs. <80% compliance (0.8% vs. 5.6%) (Figure 3B). For sites with IV ABX compliance ≥80%, the use of an antibacterial vs. saline-only hydration envelope was associated with a trend toward a lower infection rate (0.8% vs. 1.1%) (Figure 3C).

Patients who received antibacterial biologic envelopes had a significantly higher average number of infection RFs compared to patients who received saline-hydrated biologic envelopes (2.1 vs. 1.7, $p < 0.001$). Similarly, sites with higher IV ABX compliance (≥80%) tended to treat patients with slightly higher average infection RFs vs. sites that used IV ABX on <80% of their patients (2.0 vs. 1.8, p = 0.077).

Discussion

This study represents the largest dataset of the biologic envelope usage to date. Real-world clinical decision-making regarding the choice of hydration solution for biologic CIED envelopes varies among implanting physicians. Determining how physicians make these decisions and how their choices impact clinical outcomes is important to identify best practices.

TABLE 2 Patient medical history.

Condition	Total (N = 1,102)	Saline (n = 252)	Gent Only (n = 73)	Any ABX + Gent (n = 227)	Any ABX − Gent (n = 623)	*p-value*	
						Saline vs. Gent Only	ABX + Gent vs. ABX − Gent
Current smoker	128 (11.6)	13 (5.2)	13 (17.8)	23 (10.1)	92 (14.8)	<**0.001**	0.080
CAD	20 (1.8)	0 (0.0)	0 (0.0)	6 (2.6)	14 (2.3)	–	0.736
Diabetes	331 (30.0)	74 (29.4)	10 (13.7)	52 (22.9)	205 (32.9)	**0.007**	**0.005**
Hypertension	45 (4.1)	2 (0.8)	0 (0.0)	3 (1.3)	40 (6.4)	1.00¥	**0.003**
Systemic anticoagulant use	273 (24.8)	81 (32.1)	20 (27.4)	68 (30.0)	124 (19.9)	0.440	**0.002**
BMI > 30 kg/m^2	417 (37.8)	93 (36.9)	24 (32.9)	72 (31.7)	252 (40.4)	0.528	**0.020**
PVD	86 (7.8)	16 (6.3)	5 (6.8)	6 (2.6)	64 (10.3)	0.793¥	<**0.001**
CHF/HF	468 (42.5)	84 (33.3)	39 (53.4)	82 (36.1)	302 (48.5)	**0.002**	**0.001**
Chronic steroid use	14 (1.3)	3 (1.2)	0 (0.0)	1 (0.4)	10 (1.6)	1.00¥	0.184
COPD	8 (0.7)	0 (0.0)	0 (0.0)	1 (0.4)	7 (1.1)	–	0.362
Malnutrition	12 (1.1)	0 (0.0)	0 (0.0)	3 (1.3)	9 (1.4)	–	0.893
Malignancy	47 (4.3)	12 (4.8)	4 (5.5)	11 (4.8)	24 (3.9)	0.763¥	0.519
Renal insufficiency	138 (12.5)	35 (13.9)	7 (9.6)	20 (8.8)	83 (13.3)	0.335	0.075
Prior device history						0.992	<**0.001**
PPTP – yes	67 (6.1)	7 (2.8)	2 (2.7)	4 (1.8)	56 (9.0)	–	–
PPTP – unknown	133 (12.1)	3 (1.2)	1 (1.4)	3 (1.3)	127 (20.4)	–	–
Pocket re-entry*	5 (0.5)	0 (0.0)	2 (2.7)	3 (1.3)	2 (0.3)	**0.050**	0.091
Prior device infection**	20 (1.8)	3 (1.2)	0 (0.0)	4 (1.8)	13 (2.1)	1.00	0.765

Values are given as n, (%) unless otherwise indicated.
CAD, coronary artery disease; CHF/HF, congestive heart failure/heart failure; COPD, chronic obstructive pulmonary disease; Gent, gentamicin; PVD, peripheral vascular disease; PPTP, pre-procedure temporary pacing.
*Within 2 weeks of initial implant.
**> 12 months before current procedure.
¥ Fisher's exact test used because ≥1 expected cell count was <5.
Bolded values are those that have a significant P-value.

In the current analysis, the use of biologic envelopes hydrated in antibiotic solutions containing gentamicin generally was associated with reduced risk for infection compared to antibiotic solutions not containing gentamicin. Many implanting physicians seemed to perceive the use of gentamicin as beneficial in limiting infection risk as they tended to select solutions containing gentamicin for patients with the highest infection risk.

The overall rate of infection through 90 days in this analysis was 3.1%, divided closely among major (1.7%) and minor (1.4%) CIED infections. This incidence of infection is consistent with the low rate of infection previously reported in the WRAP-IT trial, (21) and other literature for *de novo* placements (∼1–3%), (2–4) particularly when considering the high-risk status of most patients in this study and the randomized trial. Most subjects (58.6%) in this study had 2 or more infection risk factors. Patients were, on average, overweight (mean BMI 28.8 kg/m^2, 37.8% obese), nearly half had heart failure (42.5%), about one-third had diabetes (30%), one quarter used systemic anticoagulants (24.8%), and many had renal insufficiency (12.5%) or were current smokers (11.6%). For comparison, the WRAP-IT trial enrolled Envelope subjects with similar infection risk factors: mean BMI was 29.1 kg/m^2, 68% had cardiomyopathy, 31% had diabetes, 39.5% were on anticoagulants, and 16.8% had renal dysfunction (21). Smoking status was not reported by the authors.

Multiple studies have demonstrated variation in infection rates based on procedure- and patient-related factors, including *de novo* placements vs. reoperations, the type of device implanted (e.g., pacemaker vs. CRT-D), patient comorbidities, and the use of antibiotic therapy or antibiotic eluting envelopes (37). The prospective WRAP-IT and PADIT studies, which intentionally enrolled patients with high infection risk, demonstrated that low infection rates (∼1% major infections) can be achieved in complex procedures and patients through the use of evidence-based approaches, such as the use of incremental perioperative antibiotics or antibiotic eluting envelopes (19, 21).

In our study, over 40% of the subjects were undergoing reoperation for device replacement, a procedure that is associated with infection rates ranging up to 7% in previous studies (2–5). Indeed, implanting surgeons showed a preference for hydration solutions that included antibiotics, particularly

TABLE 3 Device and procedural details.

Characteristic	Total (N = 1,102)	Saline (n = 252)	Gent Only (n = 73)	Any ABX + Gent (n = 227)	Any ABX − Gent (n = 623)	*p-value*	
						Saline vs. Gent Only	ABX + Gent vs. ABX − Gent
High vs. low-powered CIED							
Low powered	549 (49.8)	148 (58.7)	32 (43.8)	101 (44.5)	300 (48.2)	<**0.001**	0.137
Pacemaker	494 (44.8)	140 (55.6)	21 (28.8)	85 (37.4)	269 (43.2)	–	–
CRT-P	55 (5.0)	8 (3.2)	11 (15.1)	16 (7.0)	31 (5.0)	–	–
High powered	505 (45.8)	100 (39.7)	33 (45.2)	111 (48.9)	294 (47.2)	<**0.001**	**0.004**
ICD	260 (23.6)	63 (25.0)	10 (13.7)	41 (18.1)	156 (25.0)	–	–
CRT-D	245 (22.2)	37 (14.7)	23 (31.5)	70 (30.8)	138 (22.2)	–	–
Pocket/lead revision and/or lead replacement	48 (4.4)	4 (1.6)	8 (11.0)	15 (6.6)	29 (4.7)	–	–
CIED procedure type							
Re-operative procedure	449 (40.7)	75 (29.8)	48 (65.8)	115 (50.7)	259 (41.6)	<**0.001**	**0.018**
Procedural information						<**0.001**	0.274
CIED only	1054 (95.6)	248 (98.4)	65 (89.0)	212 (93.4)	594 (95.4)	–	–
Pocket revision only	14 (1.3)	4 (1.6)	3 (4.1)	3 (1.3)	7 (1.1)	–	–
Lead addition	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	–	–
Lead revision only	27 (2.5)	0 (0.0)	5 (6.9)	10 (4.4)	17 (2.7)	–	–
Other*	5 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	4 (0.6)	–	–
Capsulectomy performed	(n = 449)	(n = 75)	(n = 48)	(n = 115)	(n = 259)	**0.009**	<**0.001**
Yes	213 (47.4)	24 (32.0)	25 (52.1)	81 (70.4)	108 (41.7)	–	–
Unknown	33 (7.3)	5 (6.7)	7 (14.6)	7 (6.1)	21 (8.1)	–	–

Values are given as n, (%) unless otherwise indicated.
*Lead replacement only and lead revision/replace, pocket and lead revision, pocket/lead revision + lead replacement.
Bolded values are those that have a significant P-value.

gentamicin, for patients undergoing reoperation, regardless of device type (Table 3). With regard to type of device, there was a preference for gentamicin-containing solutions when surgeons implanted high- vs. low-power devices, a finding consistent with studies that have identified complex devices as risk factors for CIED infection (2–4, 11).

Interestingly, there were no significant differences between groups with regard to patients with prior device infections (Table 2). The majority of this group received biologic envelopes hydrated in Any ABX − Gent (n = 13). There was a preference for gentamicin over saline among the few patients undergoing pocket re-entry (p = 0.050). However, the total number of patients in these subgroups was small (n = 20 total prior device infections, 1.8%; n = 5 pocket re-entry, 0.5%), limiting further interpretation of these outcomes.

In our study population, the presence of multiple infection risk factors was significantly associated with the use of antibiotics in the hydration solution: Gent Only was chosen over Saline, and Any ABX − Gent was chosen over Any ABX + Gent. Based on this analysis, the threshold at which surgeons demonstrated a preference for envelope hydration in antibiotics is 2 or more risk factors. The results of the logistic regression modeling further support the use of gentamicin in high-risk patients. This adjusted model found that the omission of gentamicin from the CIED hydration solution was associated with a threefold increase in risk for infection (OR 3.0, 95% CI, 1.0 – 10.0), although it did not reach statistical significance (p = 0.083). The AUC was 0.70 (95% CI, 0.60 – 0.78), which suggests good discriminative ability.

Although both our study and the WRAP-IT trial (21) enrolled subjects with similar clinical profiles and resulted in similar outcomes, there are obvious design differences between both studies which allow us the opportunity to continue improving clinical outcomes by expanding our knowledge on device envelopes and their appropriate use. The purpose of this study was to observe physician practice patterns during real-world usage of the biologic envelope, so patients were not randomized. In our study, physicians could enroll subjects receiving any brand of CIED with the biologic envelope, which supports the safety and efficacy of antibiotic-eluting envelopes when used with various manufacturer CIEDs, as also found in previous smaller studies (9, 13, 17, 36, 38). Finally, we looked closely at preoperative antibiotic prophylaxis compliance (which similar to the WRAP-IT trial was not controlled in our study) in conjunction with envelope usage, which revealed diverse and some concerning practice patterns. This finding is also corroborated by a recent independent survey of implanting physicians in the USA, which is further described below (39).

TABLE 4 Adverse events.

Adverse event	Total (N = 1,102)	Saline (n = 252)	Gent Only (n = 73)	Any ABX + Gent (n = 227)	Any ABX − Gent (n = 623)	*p-value*	
						Saline vs. Gent Only	ABX + Gent vs. ABX − Gent
Infection							
Major CIED infection	19 (1.7)	5 (2.0)	1 (1.4)	1 (0.4)	13 (2.1)	1.00¥	0.129¥
Pocket infection†	12 (1.1)	2 (0.8)	0 (0.0)	0 (0.0)	10 (1.6)	1.00¥	0.070¥
Superficial cellulitis*	7 (0.6)	3 (1.2)	1 (1.4)	1 (0.4)	3 (0.5)	1.00¥	1.00
Bacteremia or endocarditis†	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	–	1.00¥
Minor CIED infection**	15 (1.4)	4 (1.6)	2 (2.7)	2 (0.9)	9 (1.4)	0.620¥	0.737¥
Infections 0–30 days	(n = 1,102)	(n = 252)	(n = 73)	(n = 227)	(n = 623)	–	–
Major	11 (1.0)	1 (0.4)	1 (1.4)	1 (0.4)	9 (1.4)	0.399¥	0.304¥
Pocket	7 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)	6 (1.0)	1.00¥	0.351¥
Infections 31–90 days	(n = 1,020)	(n = 238)	(n = 70)	(n = 210)	(n = 572)	–	–
Major	8 (0.8)	4 (1.7)	0 (0.0)	0 (0.0)	4 (0.7)	0.578¥	0.579¥
Pocket	5 (0.5)	1 (0.4)	0 (0.0)	0 (0.0)	4 (0.7)	1.00¥	0.579¥
Hematoma							
Total sample	28 (2.5)	9 (3.6)	1 (1.4)	5 (2.2)	14 (2.2)	0.467¥	0.969
Hematoma requiring intervention	14 (1.3)	3 (1.2)	1 (1.4)	4 (1.8)	7 (1.1)	1.00¥	0.496¥
Other adverse events							
Lead dislodgement/revision	3 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.3)	–	1.00¥
Pocket revision	6 (0.5)	1 (0.4)	1 (1.4)	2 (0.9)	3 (0.5)	0.399¥	0.614¥
Erosion	2 (0.2)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1.00¥	–
Erythema/fever	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	–	0.569¥

Values are given as n, (%) unless otherwise indicated.
*Superficial cellulitis with dehiscence, erosion, or purulent drainage.
**Infections that did not meet one or more of the criteria for major infection.
¥ Fisher's exact test used because ≥1 expected cell count was <5.
†One subject had pocket infection, bacteremia, and endocarditis.

CIED envelopes and choice of antibiotics

Previous studies have established the efficacy of antibiotic eluting CIED envelopes for reducing infection risk, particularly in high-risk patients (21, 40–42). Meta-analyses of published studies report >60% reductions in major CIED infections with these devices (40–42). Options for antibiotic envelopes include the previously described non-biologic envelope impregnated with rifampin and minocycline or hydration of the biologic CanGaroo Envelope in saline containing one or more antibiotics. Surgeons in the current study used a wide variety of antibiotics, often in combination (**Figure 2**). No subjects in our database received a hydration solution containing rifampin and/or minocycline. However, this finding may have been due to limited availability of these antibiotics in the OR. Because potential pathogens can vary by patient and hospital, there may be advantages to allowing implanting physicians to select antibiotics based on their knowledge of local and patient factors.

Our study outcomes suggest potential advantages to the use of gentamicin in high-risk patients. Gentamicin is an aminoglycoside with broad-spectrum bactericidal activity, including against *Staphylococcus* species, which are the most commonly identified pathogens in CIED infections, (43) and aerobic Gram-negative organisms. The main clinical limitation of gentamicin is its association with risks for nephrotoxicity and ototoxicity when administered systemically (44). Conversely, local administration of gentamicin has demonstrated efficacy in multiple surgical indications, including preventing CIED-related infections, without the risks of systemic exposure (42, 45–48).

Preclinical studies indicate that biologic CIED envelopes soaked in gentamicin can deliver high concentrations of gentamicin to the surrounding tissues, with minimal systemic exposure, providing excellent efficacy against *Staphylococcus* spp. and other CIED pathogens (42, 45, 49). One preclinical study, which compared biologic envelopes soaked in gentamicin, vancomycin, or both, found greater *in vitro* antimicrobial activity with gentamicin compared to vancomycin (49). A retrospective clinical study of 1266 consecutive patients undergoing CIED replacements reported no CIED-related infections requiring device extraction with the use of a gentamicin-soaked collagen sponge over a mean of 3.5 years of follow-up (4,285 patient-years), even in this

TABLE 5 Summary of logistic regression model predicting the presence of any major or minor infection.

	Odds ratio (95% CI)	*p-value*
Obesity (BMI > 30 kg/m^2)	2.3 (1.0–5.1)	**0.049**
Diabetes	0.2 (0.1–0.8)	**0.018**
No gentamicin	3.0 (1.0–10.0)	0.083
Model AUC	0.70 (0.60–0.78)	

Bolded values are those that have a significant *P*-value.

high-risk population (45). Data from other cardiac surgical procedures also support the efficacy of local gentamicin delivery using ECM or collagen sponges to prevent wound infections (47, 48, 50).

ECM biomaterials and infection risk

Compared with non-biologic biomaterials, such as those used in other types of CIED envelopes, biomaterials made from biologic non-crosslinked ECM, such as CanGaroo, have been shown to foster greater tissue integration and vascular ingrowth, a reduced inflammatory response, and more rapid clearance of bacteria (22, 23, 25–31). Because of these characteristics, biologic ECM envelopes may be preferred for higher-risk patients, such as those in the current analysis. Indeed, two recent studies of patient characteristics associated with the use of a biologic envelope identified a preference for these devices in patients who were elderly and had poor tissue quality, had a history of prior device infection, or had major infection risk factors (36, 38).

Hydration of biologic envelopes in antibiotic solutions has the additional advantage of providing antibiotics where they are most needed. In preclinical studies, biologic envelopes hydrated in antibiotic solutions showed a biphasic pattern of antibiotic release, with an initial bolus followed by sustained release over several days (49). Because CIED infections presumably occur at the time of implantation, high and sustained local antibiotic concentrations should be ideal for infection prevention. As shown clinically in a randomized controlled trial, antibiotic-eluting envelopes can have a sustained effect on lowering infection risk in CIED patients (21).

As noted, the current study included high proportions of patients with multiple infection risk factors (58.6%), receiving high-powered devices (45.8%), and undergoing re-operation (40.7%). Despite these high-risk features, the overall infection rate was modest at 3.1%, with about half being major infections (1.7%). Although this incidence is based on a relatively modest follow-up period (mean 224 ± 173.0 days, with no infections reported after 102 days), and the total number would be expected to increase marginally with longer follow-up (51, 52), these initial findings suggest that surgeons' use of antibacterial biologic envelopes (particularly containing gentamicin) may have reduced the risk of infection. Further reductions might be achieved with wider use of gentamicin, possibly in addition to other antibiotics, when hydrating the biologic envelopes prior to implantation, and proper employment of IV ABX. Based on the data discussed above, the CanGaroo Envelope was recently cleared in the E.U. for hydration in 20 mL of gentamicin (40 mg/mL) prior to implantation, although this hydration solution is not currently cleared for use in the U.S. (53).

Infection risk mitigation should be a multi-pronged approach

Observation of physician decision-making with real-world usage of antibacterial envelopes during CIED implantations demonstrated variable usage of pre-operative IV antibacterial prophylaxis (IV ABX). Across all sites, the overall rate of IV ABX compliance in our real-world study was 96.6%. However, a concerning number of patients undergoing CIED implantation did not receive guideline-recommended IV ABX and this group had a higher infection rate. Our findings are similar to recently published results from an independent survey of antibiotic use during CIED implantation in the United States. Although the survey respondents reported a 97% rate of routine use of pre-operative systemic antibiotics (similar to our 96.6% overall compliance rate), the authors also found that there were wide variations in implanter practices (39).

Even in a randomized, controlled trial evaluating the infection risk reduction of a non-biologic antibacterial envelope, only 94.2% of study sites followed guideline-recommended IV ABX (21). In our study tracking real-world physician practice, the rate of IV ABX compliance was only slightly higher. Most sites (90%) administered IV ABX to ≥80% of their patients, yet only 80% of sites administered IV ABX to their patients ≥90% of the time. Only about half (58%) of sites in this study employed IV ABX 100% of the time. Surprisingly, 10% of sites used IV ABX <80% of the time.

Sites employing IV ABX ≥80% of the time had a lower overall rate of CIED pocket infection than sites with <80% IV ABX compliance (0.9% vs. 2.9%), which was significantly more pronounced when antibacterial envelopes were used alongside IV ABX (0.8% vs. 5.6%) (**Figures 3A,B**). The patients who received antibacterial envelopes had a significantly higher average number of infection RFs compared to patients who received saline-hydrated biologic envelopes, yet for sites with IV ABX compliance ≥80% who hydrated the biologic envelope in an antibacterial vs. saline-only hydration solution, the use of an antibacterial envelope was associated with a trend toward a lower infection rate (0.8% vs. 1.1%) (**Figure 3C**). Thus, patients with higher infection risk were more frequently receiving infection prevention therapies compared to lower-risk patients.

TABLE 6 Analysis by number of infection risk factors by treatment group.

No. infection risk factors	Total (N = 1,102)	Saline (n = 252)	Gent Only (n = 73)	Any ABX + Gent (n = 227)	Any ABX − Gent (n = 623)	*p-value*	
						Saline vs. Gent Only	ABX + Gent vs. ABX − Gent
0–1	456 (41.4)	120 (47.6)	24 (32.9)	103 (45.4)	233 (37.4)	**0.026**	**0.035**
≥2	646 (58.6)	132 (52.4)	49 (67.1)	124 (54.6)	390 (62.6)		

Values are given as n, (%) unless otherwise indicated.
Bolded values are those that have a significant P-value.

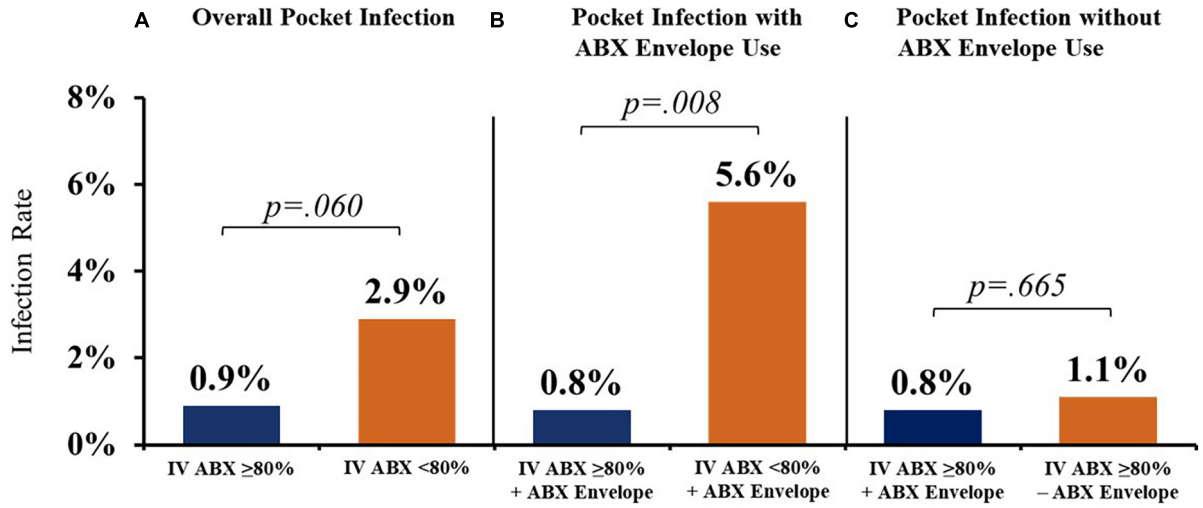

FIGURE 3
Cardiac implantable electronic device (CIED) pocket infection rates with various prevention strategies. **(A)** Higher IV ABX compliance (≥80% use) was associated with a lower overall rate of CIED pocket infection vs. sites with <80% IV ABX compliance. **(B)** When stratifying for antibacterial biologic envelope usage in conjunction with IV ABX ≥80% site compliance vs. <80% compliance, there was a significant difference in pocket infection rates. **(C)** Use of an antibacterial (vs. saline-only) envelope was associated with a trend toward a lower infection rate for sites with IV ABX compliance ≥80%. IV ABX, pre-operative IV antibacterial prophylaxis; ABX envelope, biologic envelope hydrated with antibiotic solution.

Considering the use of IV ABX falls under the guideline recommendations, it is unclear the rational for not using IV ABX on every patient. Three potential reasons to explain the discrepancy could be that: (1) some physicians are following outdated practice or institutional standards, (2) there is a false sense of security when using antibacterial envelopes that IV ABX is not needed in conjunction, or (3) when treating patients with lower infection risk, IV ABX is not considered as often. Our observations align with the current guideline recommendations which recommend IV ABX use during 100% of CIED implantations (18). These findings suggest that the use of antibacterial envelopes without adjunct IV ABX is not sufficient to reduce CIED infections.

Limitations

The major limitations of this study are its non-randomized design, limited duration of follow-up, and single-arm design. The lack of randomization allowed for bias in the selection of enrolled patients for implantation with biologic envelopes, institutional policies, or physician standard of care for use of guideline-recommended IV ABX, and in the decision to use or not to use specific antibiotics or antibiotic combinations for envelope hydration. Because of the lack of randomization and the single-arm design, which prevented comparisons with other treatment approaches, the intention of this analysis was to describe real-world surgeon practice patterns. Although the overall sample was relatively large (N = 1,102), only about 20% of cases included the use of gentamicin (n = 227). Finally, the duration of follow-up may not have captured late adverse events, limiting data on long-term efficacy of the biologic envelope.

Significant differences were identified between treatment groups with regard to race and ethnicity. These differences may reflect surgeon choices based on underlying infection risk factors in these subgroups. Alternatively, they may suggest

treatment bias based on race and ethnicity. These possibilities should be addressed in future studies that are specifically designed to analyze infection risk and treatment decisions based on race and ethnicity.

Conclusion

The results of this analysis provide further evidence that biologic CIED envelopes are associated with low infection risk, especially when combined with guideline-recommended intravenous antibacterial prophylaxis. In this high-risk population, the use of a biologic envelope led to a low rate of major infections (<2%). The results further suggest that hydration of the biologic envelope in antibiotic-containing solutions, particularly gentamicin, may help to reduce infection risk. Allowing implanting physicians to select appropriate antibiotics during rehydration may have advantages in targeting antimicrobial therapy to local and patient-specific factors. Larger studies are needed to better understand these potential benefits and define the clinical role of antibiotic selection for CIED envelope hydration.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by WIRB-Copernicus Group (WCG® IRB). The patients/participants provided their written informed consent to participate in this study.

Author contributions

TD substantially contributed to the drafting of the manuscript. TD and DW substantially contributed to the conception, design, data collection, and analysis of the work. JC and DW contributed their expertise to the analysis and interpretation of data and to reviewing and editing the manuscript. All authors accept accountability for the accuracy of this work, and drafted, revised, and approved the final version of the manuscript to be published within this journal.

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Conflict of interest

TD works for an institution that performs research for HUYA Bioscience, Boston Scientific, Medtronic, Abbott, Milestone, CVRx Inc., and Biotronik and was an advisor for PaceMate, Preventice, and CVRx Inc., receives honoraria/speaking/consulting fees from Sanofi, and was a member of the review committee for several Abbott research projects. JC was a consultant for Aziyo Biologics, Inc. and Abbott.

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Supplementary material

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High-pass filter settings and the role and mechanism of discrete ventricular electrograms in left bundle branch pacing

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Objective: The characteristics of discrete intracardiac electrogram (EGM) in selective left bundle branch (SLBB) pacing (SLBBP) have not been described in detail previously. This study aimed to examine the effect of different high-pass filter (HPF) settings on discrete local ventricular components in an intracardiac EGM and to analyze its possible mechanisms.

Methods: This study included 144 patients with indications of permanent cardiac pacing. EGMs were collected at four different HPF settings (30, 60, 100, and 200 Hz) with a low-pass filter at 500 Hz, and their possible mechanisms were analyzed.

Results: LBBP was successfully achieved in 91.0% (131/144) of patients. SLBBP was achieved in 123 patients. The occurrence rates of discrete local ventricular EGM were 16.7, 33.3, 72.9, and 85.4% for HPF settings of 30, 60, 100, and 200 Hz, respectively. The analysis of discrete EGM detection showed significant differences between the different HPF settings. By using the discrete local ventricular component and isoelectric interval as the SLBB capture golden standard, the results of EGMs revealed that the 30 Hz HPF has a sensitivity of 19% and specificity of 100%. The 60 Hz HPF had a sensitivity of 39% and a specificity of 100%. The 100 Hz HPF had a sensitivity of 85% and a specificity of 100%. The 200 Hz HPF had a sensitivity of 100% and specificity of 100%.

Conclusion: An optimal HPF setting of 200 Hz is recommended for discrete local ventricular EGM detection. A discrete local ventricular EGM should exhibit an isoelectric interval. A steep deflection and high-frequency ventricular EGM morphology nearly identify an intrinsic EGM morphology.

KEYWORDS

left bundle branch pacing (LBBP), conduction system pacing, discrete electrogram, isoelectric interval, high-pass filter settings

Highlights

- Left bundle branch (LBB) pacing (LBBP) is a novel native conduction system pacing strategy.
- Identifying discrete local ventricular electrogram (EGM) is crucial for accurately diagnosing selective LBB capture.
- Identifying discrete local ventricular EGM is a challenging task.
- This study aimed to evaluate the diagnostic accuracy of discrete local ventricular EGMs by adjusting high-pass filters with different settings in LBBP.
- The morphology of the discrete local ventricular EGMs was retrospectively observed and analyzed to explore the possible mechanisms of their formation.
- Different high-pass settings do not affect the identification of Purkinje potential.

Introduction

Left bundle branch (LBB) pacing (LBBP) is a novel native conduction system pacing strategy (1). Changes in the intracardiac ventricular electrograms (EGMs) are usually assessed during LBBP implantation via an electrophysiological recording system (EPS) (2). A discrete local ventricular EGM and an isoelectric interval have been previously used as criteria to confirm the selective LBB (SLBB) capture, which suggests that only the conduction system was captured, and the myocardium was lost. Therefore, identifying discrete local ventricular EGM is crucial for accurately diagnosing SLBB capture (3). Filtered unipolar electrograms were obtained in previous studies, usually with settings of 30 and 100/300/500 Hz (4–6), for LBBP. However, filtering could remarkably change the morphology of the ventricular EGM, introducing the possibility of errors in the evaluation of electrograms. When the high-pass filter (HPF) of the LBB lead channel is set to 30 Hz and clipping is set at 3 cm, the entire ventricular endocardial signal may not be observed owing to the large amplitude in the EGM. Therefore, identifying discrete local ventricular EGMs is a challenging task. We hypothesized that an HPF other than 30 Hz improved the detection of discrete local ventricular EGM. Therefore, in the present study, we aimed to evaluate the accuracy of discrete local ventricular EGM in diagnosing selective LBBP (SLBBP) in different HPF settings and analyze its possible mechanisms.

Materials and methods

Patient population and definition of LBB capture

This retrospective observational study enrolled consecutive patients who underwent successful permanent pacemaker implantation. LBBP uses John Jiang's connecting cable (Xinwell Medical Technology Co., Ltd., Ningbo, Zhejiang, China) for the continuous pacing and recording technique, and the procedure has been described by us elsewhere (7–10). The study protocol was approved by the Ethics Committee of the Hwa Mei Hospital, Ningbo, China. Written informed consent was obtained from all patients.

Successful LBBP is defined as follows. LBB capture is characterized by paced QRS morphology of the right bundle branch block (RBBB) pattern and all of the following criteria: (1) differential pacing at 8 and 2 V, producing the shortest and constant V6 R-wave peak time and (2) demonstration of left ventricular septal (LVS) to non-selective LBB capture transition during constant output while advancing the lead and non-selective to SLBB capture during unipolar pacing threshold assessment (4, 11). The discrete local ventricular component and isoelectric interval with decrementing output during the EGM recording were used as the golden standard of the SLBB capture (3, 4, 12, 13).

Data recording and analysis

The baseline patient characteristics and indications for pacing were documented. Twelve-lead electrocardiogram (ECG) and EGM from the pacing lead were continuously recorded with an EPS (EP-Workmate, Abbott Laboratories, Chicago, IL, USA). For each patient, high- and low-pass filter (LPF) settings of 200 and 500 Hz were performed during the live case (9). The differences in discrete local ventricular EGM morphologies were collected and analyzed offline using four different HPF settings (30, 60, 100, and 200 Hz), and the LPF was set at 500 Hz. To ensure high precision, the analysis of discrete local ventricular EGM morphology was performed using endocardial channel recording, digital calipers, fast sweep speed (200 mm/s), and appropriate signal augmentation. The clipping was set at 3 cm, and the amplitude was set at 0.5 mV/cm.

The characteristics of the various transitions in discrete local ventricular EGM morphology were analyzed retrospectively after the procedure. All EGM morphologies were independently analyzed by two medical practitioners who were highly experienced in EGM interpretation. When (1) the isoelectric interval, (2) the paced initial steep deflection, and (3) high-frequency local ventricular EGM nearly identical to the intrinsic ventricular EGM could be observed independently by both doctors at different HPF settings, the observation was marked as a discrete local ventricular EGM (patients with left bundle branch block (LBBB) meeting criteria 1 and 2 because intrinsic LBB conduction cannot be observed). The EGM readers were blinded to the study's purpose. In the absence of concordance between the two readers, a third cardiologist practitioner adjudicated the results.

Statistical analysis

All continuous data are presented as mean ± standard deviation (SD). Categorical data were presented as numbers and percentages. We used Student's *t*-test to compare continuous variables. To evaluate the diagnostic accuracy of detecting discrete local ventricular EGM, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of different HPF settings were calculated. A *p*-value < 0.05 was considered statistically significant. The statistical software IBM SPSS Statistics for Windows (version 26.0, IBM Corp, Armonk, NY, USA) was used for analysis.

TABLE 1 Baseline characteristics, pacing indications, and baseline echocardiography and ECG data of patients who underwent attempts at LBBP.

	LBBP (*n* = 131)	LVSP (*n* = 13)	*p*
Age (years)	73.5 ± 9.1	77.3 ± 9.9	0.51
Male	77 (60.2)	7(53.4)	
Pacing indication (*n*)			
Atrioventricular block	84 (64.1)	9 (69.2)	
Sick sinus syndrome	44 (33.6)	2 (15.4)	
Atrial fibrillation with bradycardia	7 (5.3)	2 (15.4)	
Heart failure	5 (3.8)	0(0)	
Comorbidities (*n*)			
Hypertension	77 (58.8)	10 (76.9)	
Diabetes mellitus	35 (26.7)	3 (32.1)	
Cardiomyopathy	10 (7.6)	0(0)	
Coronary heart disease	23 (17.6)	3 (23.1)	
Atrial fibrillation	37 (28.2)	5 (38.5)	
LVEF (%)	63.6 ± 10.2	65.0 ± 6.4	0.46
LVDD (mm)	49.9 ± 7.2	50.2 ± 3.6	0.07
QRS morphology (*n*)			
Narrow QRS	95 (72.5)	8(61.5)	
RBBB	21 (23.9)	0(0)	
LBBB	14 (15.9)	0(0)	
NIVCD	2 (2.3)	1(14.3)	
Procedure-related parameters			
LBB potential observed (*n*)	94 (71.9%)	0(0)	
Threshold (V/0.5 ms)	0.61 ± 0.41	0.61 ± 0.33	0.99
R-wave amplitude (mV)	14.7 ± 6.7	9.9 ± 4.0	0.05
Impedance (Ω)	733.7 ± 137.6	730.7 ± 120.1	0.69
Lead depth (mm)	14.8 ± 2.6	14.6 ± 1.5	0.07

Patients who underwent LVSP were those in whom LBBP failed. LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; RBBB, right bundle branch block; LBBB, left bundle branch block; NIVCD, non-specific intraventricular conduction disturbance; LBB, left bundle branch; LBBP, left bundle branch pacing; LVSP, left ventricular septal pacing. Continuous data were presented as mean ± standard deviation.
$p < 0.05$ was considered statistically significant.

Results

From April 2021 to September 2022, data for 144 patients who underwent pacemaker implantation were consecutively and retrospectively collected from a single institution (Hwa Mei Hospital, University of Chinese Academy of Sciences). Their mean age was 73.9 ± 9.2 years, and 63/144 (43.8%) were females. Clinical and procedure-related characteristics of the study population are shown in Table 1. Successful LBBP with evidence of LBB system capture was achieved in 131 patients (91.0%). SLBBP was achieved in 123 patients (85.4%) during the threshold testing. Eight patients were confirmed as having non-selective LBBP (NSLBBP). In thirteen patients, LBBP failed because of the inability to capture the LBB. These patients eventually underwent LVS pacing. The pacing indications in the 131 patients who achieved LBBP were sick sinus syndrome in 44 (33.6%), atrioventricular block in 84 (64.1%), atrial fibrillation with bradycardia in 7 (5.3%), and heart failure in 5 (3.8%). LBB potential (Po_{LBB}) was recorded in 94 (71.9%) of 131 patients.

The performance of the discrete local ventricular EGM detection with different HPF is shown in Figures 3–5. The discrete local ventricular EGM occurrence rates for different EGM setup channels were compared. The results of the discrete local ventricular EGM detection are summarized in Tables 2, 3. The occurrence rates of discrete local ventricular EGM were 16.7% (24/144), 33.3% (48/144), 72.9% (105/144), and 85.4% 123/144) for HPF settings of 30, 60, 100, and 200 Hz, respectively (Table 2). The analysis of discrete ECG detection showed significant differences between the different HPF settings (Table 3). Using the discrete local ventricular component and isoelectric interval as the SLBB capture gold standard, the results of EGMs indicated that the 30 Hz HPF

TABLE 2 Detection of discrete local ventricular EGM at different high-pass filter settings.

	30 Hz	60 Hz	100 Hz	200 Hz
Presence of discrete local ventricular EGM	24 (16.7)	48 (33.3)	105 (72.9)	123 (85.4)
Absence of discrete local ventricular EGM	120 (83.3)	96 (67.7)	39 (27.1)	21(14.6)

Data are presented as numbers (%). EGM, intracardiac electrogram.

TABLE 3 Results and diagnostic accuracy of different high-pass filter for detecting discrete local ventricular EGM.

	30 Hz	60 Hz	100 Hz	200 Hz
Sensitivity % (95% CI)	0.19 (0.13–0.27)	0.39 (0.30–0.48)	0.85 (0.77–0.91)	1.00 (0.96–1.00)
Specificity % (95% CI)	1.00 (0.80–1.00)	1.00 (0.80–1.00)	1.00 (0.80–1.00)	1.00 (0.80–1.00)
PPV % (95% CI)	1.00 (0.82–1.00)	1.00 (0.90–1.00)	1.00 (0.95–1.00)	1.00 (0.96–1.00)
NPV % (95% CI)	0.17 (0.11–0.25)	0.21 (0.14–0.31)	0.53 (0.37–0.69)	1.00 (0.80–1.00)

95% CI, 95% Confidence interval; EGM, intracardiac electrogram; NPV, negative predictive value; PPV, positive predictive value.

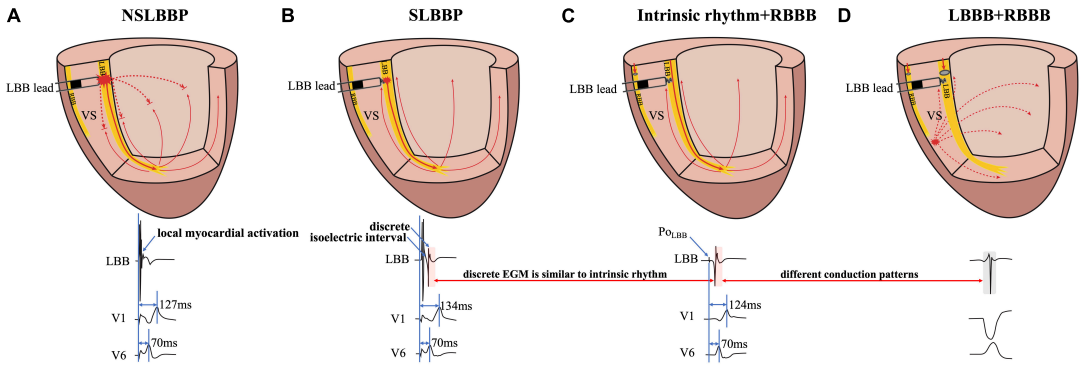

FIGURE 1
Schematic diagram of different conduction patterns in a patient with RBBB and intermittent LBBB. **(A)** NSLBBP captures both the local myocardium and LBB without the presence of isoelectric interval and discrete local ventricular EGM. **(B)** In SLBBP, pacing electrical stimulation is conducted through the conduction system to the apex and propagates to the base of the interventricular septum. Isoelectric interval and discrete local ventricular EGM were observed. **(C)** Intrinsic conduction antegrade to the apex and propagates to the base. Morphology of intrinsic and paced ventricular EGMs was nearly identical (red rectangle). **(D)** The EGM morphology of LBBP is similar to the native rhythm but different from the EGM morphology of LBBB (red and gray rectangle). NSLBBP, non-selective left bundle branch pacing; SLBBP, selective left bundle branch pacing; EGM, intracardiac electrogram; LBB, left bundle branch; LBBB, left bundle branch block; RBBB, right bundle branch block; VS, ventricular septum.

had a sensitivity of 19% and specificity of 100%. Furthermore, the PPV was 100 and 17%, respectively. The 60 Hz HPF had a sensitivity of 39% and specificity of 100% for SLBB capture, with a PPV of 100% and NPV of 21%. The 100 Hz HPF had a sensitivity of 85% and specificity of 100%, with a PPV of 100% and NPV of 53%. The 200 Hz HPF had a sensitivity of 100% and specificity of 100% for SLBB capture, with a PPV of 100% and NPV of 100%.

Discussion

Left bundle branch pacing includes NSLBBP and SLBBP. In NSLBBP, both the LBB and the local ventricular myocardium are directly captured by the pacing stimulus, in parallel and not in sequence and therefore the paced ventricular EGM morphology is not identical to the local native ventricular EGM morphology (**Figure 1A**). SLBBP was defined as only capturing the LBB with a typical RBBB morphology as well as a discrete isoelectric component between the pacing stimulus and the onset of discrete and identical local ventricular activation due to local myocardium not being directly captured (**Figure 1B**). A discrete local ventricular EGM is a characteristic of an SLBBP (2). It appears as a current deflection wave with a short isoelectric interval and large amplitude with an HPF setting of 30 Hz.

The isoelectric interval is often observed between the pacing artifact and the paced discrete ventricular component. This phenomenon includes the true isoelectric interval (time required for immediate peri-electrode tissue excitation or a local response) and local conduction time (time required for propagated excitation to recruit sufficient local myocardial tissue to produce the ventricular EGM) (14). Typically, the isoelectric interval is short (<30 ms) (4). An increased isoelectric interval may result from nonhomogeneous excitation propagation from the stimulation site and conduction delay in the His–Purkinje system (14). A previous study positioned a linear multielectrode catheter along the left ventricular septum to record intracardiac signals from the base to the apex to assess left ventricular activation sequences (15). According to the "V"-shaped conduction pattern observed in this study, the mechanism underlying the formation of the isoelectric interval may be associated with the propagation of impulse or pacing stimulus through the conduction system, reaching the distal part of the His–Purkinje system to excite the apical myocardium, and subsequent propagation to the basal myocardium in the interventricular septum by the electrode sensing (**Figure 2**).

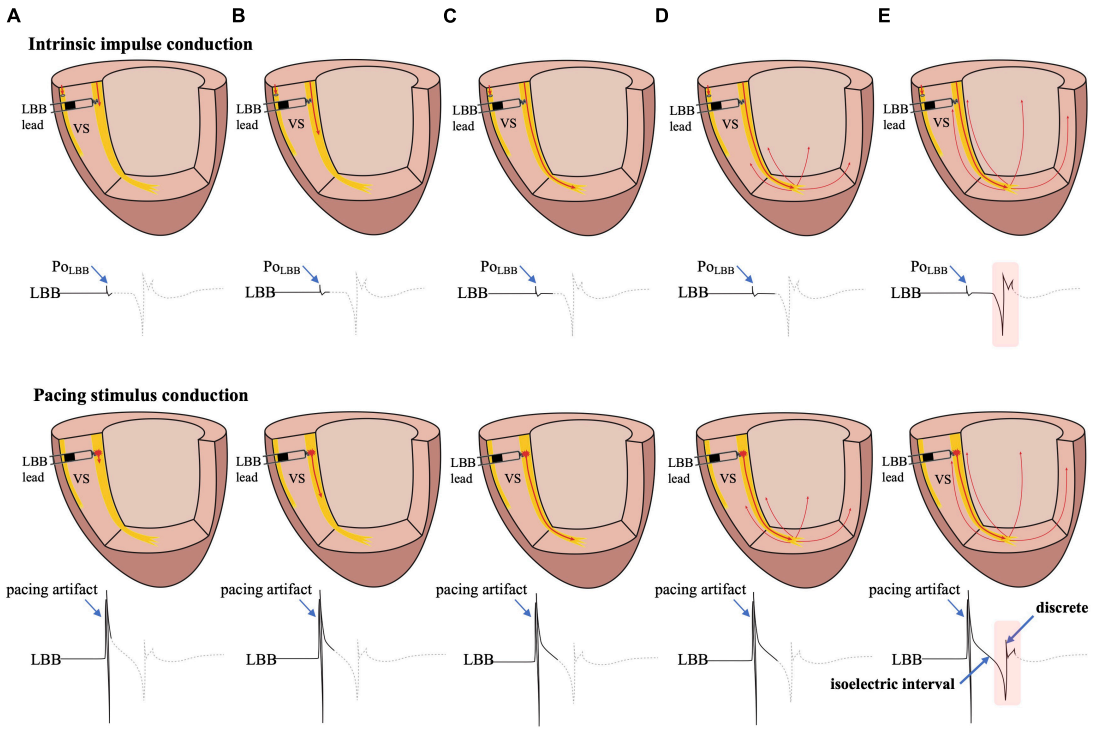

FIGURE 2
The possible mechanism of the formation of the isoelectric interval and discrete electrogram. **(A)** Intrinsic impulse or pacing stimulus in the LBB is sensed by the tip lead. **(B–D)** The formation process of the isoelectric interval. **(E)** Intrinsic impulse or pacing stimulus reaches the distal end of the His-Purkinje system, excites the apical myocardium, propagates into the basal myocardium, and is then sensed by the tip lead, manifesting as an isoelectric interval and discrete electrogram. Abbreviations as in **Figure 1**.

In non-LBBB patients, the discrete local ventricular EGM was nearly identical to the native ventricular EGM morphology (**Figures 1–5**, red rectangle). Intrinsic and paced ventricular EGMs were nearly identical in patients with intermittent LBBB with native anterograde conduction (**Figure 3**, red rectangle). Therefore, we speculate that in patients with complete LBBB, although the native rhythm (intrinsic conduction) cannot be observed, the EGM morphology of the intrinsic LBB conduction should be consistent with the EGM morphology of LBB pacing. Additionally, we observed inconsistent ventricular EGM morphology on the tip lead due to different LBBB and intrinsic conduction pathways (**Figure 3**, gray rectangle).

In previous studies, high- and LPF settings of 30 and 500 Hz were set to record the EGM. Clinicians usually employ a 30 Hz HPF to record Po_{LBB} (5). However, with this HPF, discrete local ventricular EGMs may be missed easily because the clipping level limits the display range and does not allow the user to view large-amplitude endocardial signals (**Figures 4**, **5**, blue rectangle). Additionally, in some patients, demonstration of the isoelectric interval and discrete local electrogram may be challenging due to short stimulus to ventricular intervals, effects of stimulus artifact, and far-field recording by the pacing lead (**Figures 3–5**, green rectangle) (16). In contrast, pacing artifacts and separation of ventricular components can be observed in some cases, which are easily confused with true discrete local ventricular EGM (**Figures 4**, **5**, red dashed frame). However, these observations do not represent the SLBB capture. Based on the observations in our study, the paced initial steeply deflected ventricular EGM morphology should be nearly identical to the intrinsic ventricular EGM morphology with an isoelectric interval to be considered SLBBP (**Figures 1–5**, red rectangle).

The HPF is designed to eliminate unwanted lower frequencies by allowing frequencies higher than the filter settings to pass. The higher the frequency, the lower the baseline wander. The LPF passes frequencies lower than the cutoff frequency and attenuates higher frequencies. The lower the frequency, the lower is the baseline noise. The change in the signal produced by filtering depends on the frequency of the unfiltered signal. Variations in the HPF produced marked changes in electrogram morphology, introducing the possibility of inaccurately assessing discrete local ventricular EGM (**Figures 4**, **5**, blue rectangle). Accurate interpretation of discrete local ventricular EGMs highly depends on the magnitude of the ventricular component. An excessive amplitude affects the identification of a discrete local ventricular EGM. Therefore, with clipping set to 3 cm and amplitude set to 0.5 mV/cm, we attempted to show the intact and entire ventricular EGM more clearly by adjusting the HPF setting to confirm SLBB capture

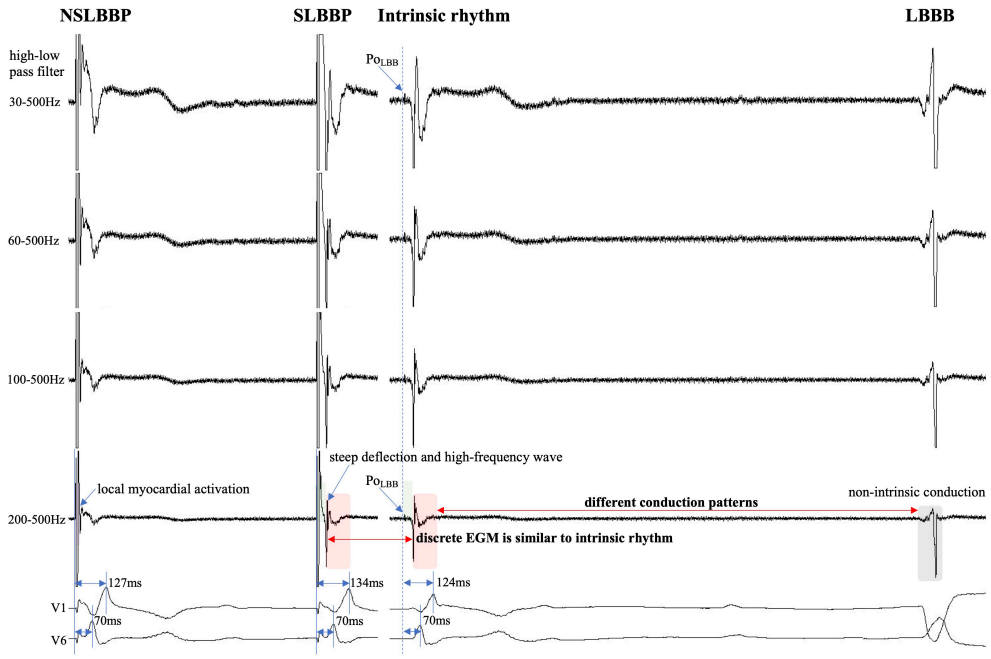

FIGURE 3
Discrete local ventricular EGM morphology resembles ventricular EGM morphology of intrinsic rhythm (red rectangle). The EGM morphology of LBBP is similar to the native rhythm but is completely different from the EGM morphology of LBBB (red and gray rectangle). Po_{LBB} can be observed at different high-pass filter settings (blue dashed line). Isoelectric interval does not appear during local myocardial activation (purple rectangle). Isoelectric interval is affected by pacing artifacts (green rectangle). Abbreviations as in **Figure 1**.

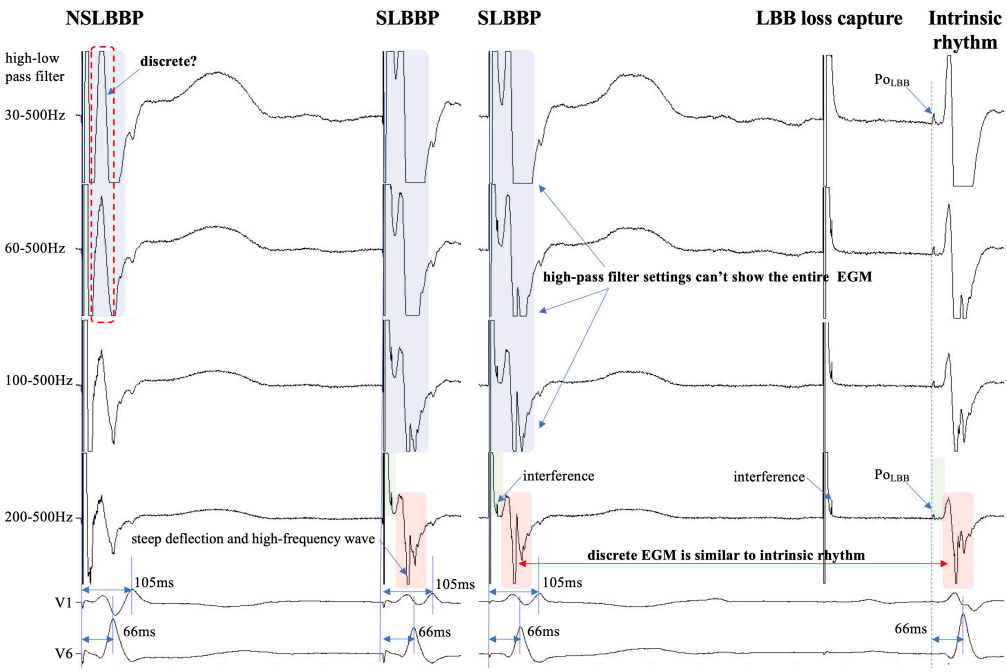

FIGURE 4
Discrete ventricular components cannot be accurately identified because the entire EGM morphology cannot be displayed (blue rectangle). Steep deflection and high-frequency discrete local ventricular EGM morphology are similar to ventricular EGM morphology of intrinsic rhythm (red rectangle). Isoelectric interval is affected by pacing artifacts (green rectangle). Po_{LBB} can be observed at different high-pass filter settings (blue dashed line). Abbreviations as in **Figure 1**.

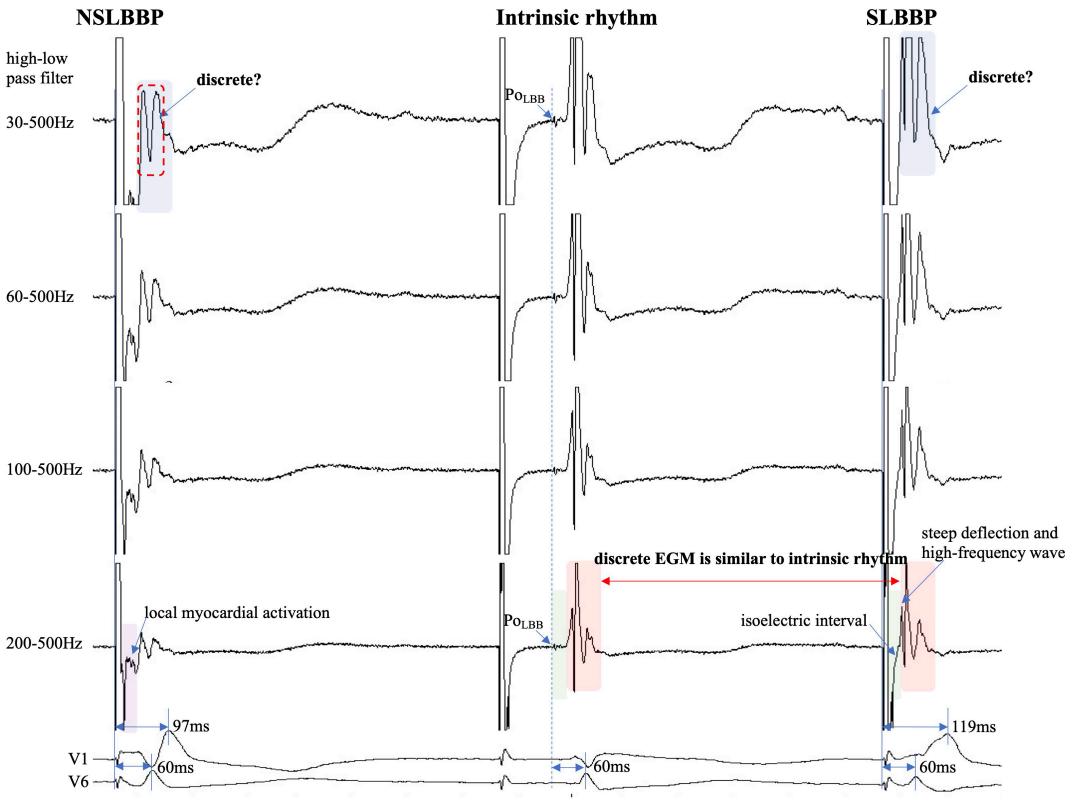

FIGURE 5
Discrete ventricular components cannot be accurately identified because the entire EGM morphology cannot be visualized (blue rectangle). Discrete local ventricular EGM morphology resembles ventricular EGM morphology of intrinsic rhythm (red rectangle). The isoelectric interval of paced rhythm and native rhythm (green rectangle). Changes in high-pass filter settings do not affect the identification of Po_{LBB} (blue dashed line). Isoelectric interval does not appear during local myocardial activation (purple rectangle). Abbreviations as in **Figure 1**.

by identifying discrete local ventricular EGM and isoelectric interval.

To the best of our knowledge, no previous study has identified a discrete local ventricular EGM by adjusting the band-pass filter with different setup conditions in LBBP. One purpose of this study was to define the impact of different HPF settings on the accuracy of discrete electrogram identification. These parameters were compared for different HPF values of 30, 60, 100, and 200 Hz. The unipolar electrogram signal morphology was subsequently analyzed. Our research suggested that the occurrence rates of discrete local ventricular EGM were 16.7, 33.3, 72.9, and 85.4% for HPF settings of 30, 60, 100, and 200 Hz, respectively. Although some discrete local ventricular EGM can be observed at 30 Hz HPF, the sensitivity is low (sensitivity, 19%; specificity, 100%) and it is difficult to accurately identify all discrete local ventricular EGM. However, the 200 Hz HPF had a sensitivity of 100% and specificity of 100% for SLBB capture. When 30 Hz HPF identification of discrete local ventricular EGM was difficult, the 200Hz setting can accurately identify discrete local ventricular EGM (**Figures 4**, **5**). This means that this HPF setup can identify all discrete local ventricular EGM. For other HPF such as 300 Hz, we also tried and found that the sensitivity was still 100% but would affect the identification of the Po_{LBB}. The result suggests that an optimal HPF setting of 200 Hz is recommended for detecting discrete local ventricular EGM. We also tried adjusting the LPF to observe the discrete local ventricular EGM, but found that these settings did not increase the identification accuracy of the discrete local ventricular EGM. Moreover, a discrete Purkinje potential precedes the onset of local ventricular EGM. Filtered unipolar electrograms were obtained at 30 Hz and 500 Hz to record the Po_{LBB} (6). An LPF was used to eliminate the noise. In our study, the LPF was 500 Hz, although the HPF settings differed. This indicates that such an HPF setting does not affect the identification of the Po_{LBB} (**Figures 3**–**5**, blue dashed line).

Study limitations

This study has several limitations. This retrospective study was performed at a single center and included a relatively small number of patients. Although the intrinsic and paced EGMs were also nearly identical in patients with intermittent

LBBB, there is still a lack of evidence suggesting that paced discrete local ventricular EGM is nearly identified as native EGM in patients with complete LBBB. We used only one particular manufacturer EPS. It is possible that the ability to detect discrete local ventricular EGM might differ depending on the EPS used because of differences in signal processing algorithms. Therefore, it is unknown whether the results of this study can be extended to other patient groups or different EPSs. To address these issues, a larger study including different patient groups and EPSs is needed. Randomized controlled and prospective trials are needed to confirm the findings of this study and to provide guidance to clinicians. Outcome data in terms of persistence of the sensed findings, ventricular function, or quality of life-based are lacking.

Conclusion

We demonstrated that an HPF setting of 30 Hz, routinely used in clinical practice, cannot reliably meet the clinical requirements of discrete local ventricular EGM detection. Our results suggest that clinicians can adjust HPF appropriately to improve discrete local ventricular EGM diagnosis, and a 200 Hz filter may be a desirable choice. A discrete local ventricular EGM should show an isoelectric interval, and a steep deflection and high-frequency ventricular EGM morphology nearly identify an intrinsic EGM morphology.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study protocol was approved by the Ethics Committee of the Hwa Mei Hospital, Ningbo, China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JS and LJ conceived and designed the experiment. HW and LZ analyzed the data. JZ and SZ performed the statistical analysis. JS and LP wrote the manuscript. HL and LJ revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

LJ owns the patent for John Jiang's connecting cable.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cardiac magnetic resonance outperforms echocardiography to predict subsequent implantable cardioverter defibrillator therapies in ST-segment elevation myocardial infarction patients

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Background: Implantable cardioverter defibrillators (ICD) are effective as a primary prevention measure of ventricular tachyarrhythmias in patients with ST-segment elevation myocardial infarction (STEMI) and depressed left ventricular ejection fraction (LVEF). The implications of using cardiac magnetic resonance (CMR) instead of echocardiography (Echo) to assess LVEF prior to the indication of ICD in this setting are unknown.

Materials and methods: We evaluated 52 STEMI patients (56.6 ± 11 years, 88.5% male) treated with ICD in primary prevention who underwent echocardiography and CMR prior to ICD implantation. ICD implantation was indicated based on the presence of heart failure and depressed LVEF (≤ 35%) by echocardiography, CMR, or both. Prediction of ICD therapies (ICD-T) during follow-up by echocardiography and CMR before ICD implantation was assessed.

Results: Compared to echocardiography, LVEF was lower by cardiac CMR (30.2 ± 9% vs. 37.4 ± 7.6%, $p < 0.001$). LVEF ≤ 35% was detected in 24 patients (46.2%) by Echo and in 42 (80.7%) by CMR. During a mean follow-up of 6.1 ± 4.2 years, 10 patients received appropriate ICD-T (3.16 ICD-T per 100 person-years): 5 direct shocks to treat very fast ventricular tachycardia or ventricular fibrillation, 3 effective antitachycardia pacing (ATP) for treatment of ventricular tachycardia, and 2

ineffective ATP followed by shock to treat ventricular tachycardia. Echo-LVEF $\leq$ 35% correctly predicted ICD-T in 4/10 (40%) patients and CMR-LVEF $\leq$ 35% in 10/10 (100%) patients. CMR-LVEF improved on Echo-LVEF for predicting ICD-T (area under the curve: 0.76 vs. 0.48, p = 0.04).

Conclusion: In STEMI patients treated with ICD, assessment of LVEF by CMR outperforms Echo-LVEF to predict the subsequent use of appropriate ICD therapies.

KEYWORDS

myocardial infarction, implantable cardioverter-defibrillator, cardiac magnetic resonance, ventricular tachyarrhythmias, left ventricular ejection fraction

1. Introduction

Revolutionary advances in treatment of patients presenting with ST-segment elevation acute myocardial infarction (STEMI) during recent decades has led to a spectacular improvement in prognosis (1). However, despite optimized medical therapy, and in most cases revascularization, the risk of sudden cardiac death is substantial (2, 3).

Left ventricular ejection fraction (LVEF) is the cornerstone for non-invasive risk stratification after STEMI and the main parameter to select patients to undergo prophylactic implantable cardioverter-defibrillator (ICD) implantation, which decreases the risk of sudden cardiac death by treating life-threatening arrhythmias as they arise (4). Current guidelines recommend ICD implantation to reduce sudden cardiac death in patients with New York Heart Association (NYHA) class II–III and LVEF $\leq$ 35% despite optimal medical therapy for $>$ 3 months and at least $\geq$ 6 weeks ($\approx$40 days) after STEMI (4, 5).

Nevertheless, most patients treated with an ICD will never require appropriate ICD therapies (ICD-T). In a cohort including five landmark ICD trials, barely one in five patients (18%) were treated with ICD-T during follow-up (6), and the rate was even lower (2.6% at 30 months) among primary prevention patients in a contemporary registry (7). Although ICD-T could be considered potentially lifesaving in those cases, there is an unmet need for strategies aimed at better selection of patients who really benefit from ICD implantation.

Quantification of the scar zone after STEMI and more precise measurement of LVEF could potentially improve patient selection. LVEF by echocardiography (Echo) is routinely performed both at predischarge and during follow-up in most patients. However, cardiac magnetic resonance (CMR) imaging provides the gold standard measurement of LVEF (8, 9) and major crossover between LVEF categories have been shown when Echo and CMR values are compared (10). Additionally, CMR can characterize infarct size (IS), an important predictor of arrhythmic risk (11). However, the utility of CMR before ICD implantation has neither been established in clinical practice nor studied in specific trials, so its usefulness in this scenario is unknown.

Against this background, we aimed to compare LVEF by Echo and CMR measured before ICD implantation for ability to predict ICD-T in a STEMI population treated with ICD in primary prevention.

2. Materials and methods

2.1. Study group

This study was derived from an ongoing, single-center prospective registry including all patients discharged for a first reperfused STEMI between 2004 and 2021 who were treated with primary percutaneous coronary intervention (pPCI) and followed in a specific outpatient clinic in our hospital. Clinical management was as recommended in specific STEMI guidelines (5). Patient informed consent was obtained. The study was approved by the local Human Research Ethics Committee and complied with the 1975 Declaration of Helsinki guidelines.

Patient characteristics including Global Registry of Acute Coronary Events (GRACE) and TIMI (Thrombolysis in Myocardial Infarction) scores, Killip class at admission, peak creatine kinase MB mass and TIMI flow grade in the culprit artery (before and after reperfusion) were recorded.

2.2. ICD implantation

Selection criteria for this analysis were patients treated with ICD in primary prevention in which pre-implantation Echo and CMR had been performed. After at least 6 weeks of optimized medical therapy, symptomatic (NYHA class II–III) patients with LVEF $\leq$ 35% by Echo, CMR or both underwent ICD implantation. Median time from STEMI to ICD implantation was 40.93 (15.43–188.86) weeks. The flowchart of patients and reasons for exclusion can be consulted in **Supplementary Figure 1**.

A single lead was positioned in the right ventricular apex using transvenous access. Five (9.6%) patients with expected need for pacing due to atrioventricular block were fitted with an additional auricular lead, and an additional left ventricular lead through the coronary sinus was implanted as cardiac resynchronization therapy in three (5.8%) patients. The ICD generator was placed in a prepectoral pocket in the left upper chest.

Standard three-zone programming was initially provided, with approximate ranges of 175–210 bpm for slow ventricular tachycardia, 210–250 bpm for fast ventricular tachycardia, and $>$ 250 bpm for ventricular fibrillation. Subsequent changes in programming were not systematically recorded in the registry. Remote patient monitoring was

provided for most patients (n = 35, 67.3%) and in-person medical visits were scheduled on a yearly basis. If remote monitoring was not available, in-person follow-up visits were scheduled every 6 months.

2.3. Echocardiography

All patients underwent echocardiographic examination before ICD implantation. Median time from Echo to ICD implantation was 13 (3.75–24.86) weeks. Local cardiologists carried out studies, quantified parameters and prospectively included the data in the local database.

LVEF (%), left ventricular (LV) end-diastolic volume (ml) and LV end-systolic volume (ml) were assessed using the biplane method of disks (modified Simpson's rule). Right ventricle function was estimated by tricuspid annular plane systolic excursion (TAPSE, in mm), which was measured in the apical 4-chamber view using the M-mode. Diastolic mitral flow A and E wave velocities (m/s) were recorded. Left atrium diameter (mm) was also registered.

2.4. CMR

All patients were examined with a 1.5 T System (Sonata Magnetom, Siemens, Erlangen, Germany) using a standardized protocol (10, 12) before ICD implantation. Median time from CMR to ICD implantation was 10.43 (3.71–27.86) weeks (difference vs. time from Echo to ICD implantation: $p = 0.51$).

Images were acquired by a phased-array body surface coil during breath-holds and were ECG-triggered. Local cardiologists specialized in CMR imaging with > 15 years of experience and accredited by the European Society of Cardiology interpreted the studies. Images were examined using customized software (Syngo, Siemens, Erlangen, Germany).

Cine images were acquired in two-, three-, and four-chamber views, and in short-axis views using a steady-state free precession sequence (repetition time/echo time: 2.8/1.2 ms; flip angle: 58°; matrix: 256 × 300; field of view: 320 × 270 mm; slice thickness: 7 mm). LVEF (%), LV end-diastolic volume index (ml/m^2), LV end-systolic volume index (ml/m^2), and LV mass index (g/m^2) were calculated by manual planimetry of endocardial and epicardial borders in short-axis view cine images.

Late gadolinium enhancement (LGE) imaging was performed 10 min after administering gadolinium-based contrast in the same locations as in the cine images, using a segmented inversion recovery steady-state free precession sequence (repetition time/echo time: 750/1.26 ms; flip angle: 45°; matrix: 256 × 184; field of view: 340 × 235 mm; slice thickness: 7 mm). Inversion time was adjusted to nullify normal myocardium.

Areas showing LGE were visually quantified by manual planimetry. Infarct size (IS) was assessed as the percentage of LV mass showing LGE. Microvascular obstruction (MVO) was defined as the number of segments displaying a lack of contrast uptake in the tissue core showing late gadolinium enhancement; the 17-segment model was applied.

2.5. LVEF and IS categorization

Patients were categorized as LVEF ≤ 35% or LVEF > 35% by Echo and CMR following current recommendations for ICD implantation in primary prevention in ischemic cardiomyopathy (4, 5). Occurrence of the clinical endpoint was analyzed in these LVEF categories.

2.6. Endpoint and follow-up

The clinical endpoint of this study was occurrence of life-threatening ventricular tachyarrhythmias requiring appropriate ICD-T [antitachycardia pacing (ATP), cardioversion, or both]. ICD therapies were considered appropriate when ATP, cardioversion or both were used to treat ventricular tachycardia or ventricular fibrillation, and inappropriate when ATP, cardioversion or both were used for treatment of heart rhythms other than ventricular tachycardia or ventricular fibrillation, such as fast atrial fibrillation. Events were prospectively adjudicated by clinical cardiologists *via* periodic review of regional electronic health records and remote home-monitoring systems if applicable.

2.7. Statistical analysis

The one-sample Kolmogorov–Smirnov Test was used to test normal data distribution. For continuous parametric variables, data are expressed as mean ± standard deviation and analyzed by Student's t-test. Continuous non-parametric variables are shown as median plus interquartile range and compared with Mann–Whitney U test. Qualitative variables are presented as percentage and compared by Chi-square test or Fisher's exact test.

The association between variables and time to first ICD-T was assessed by multivariable Cox proportional hazard regression models. Variables with p-value < 0.1 in univariate analysis were included as cofactors in multivariate analysis. Results are presented as hazard ratio (HR) and 95% confidence interval (CI).

Receiver operating characteristic curves were computed to analyze the sensitivity, specificity, and positive and negative predictive value of Echo- and CMR-derived LVEF (≤ 35% or > 35%) categories to predict subsequent ICD-T. Areas under the curve for continuous Echo- and CMR-derived LVEF were compared by means of Z test.

Statistical significance was considered for two-tailed p-values < 0.05. The SPSS statistical package version 21.0 was used.

3. Results

3.1. Cohort description

In our cohort of 52 STEMI patients treated with ICD in primary prevention, mean age was 56.56 ± 11 years, most were male (n = 46, 88.5%) and smoking was the most prevalent cardiovascular risk factor (n = 36, 69.2%). Most patients in our cohort were Caucasian/White (n = 49, 94.3%), while a minority were Asian (n = 1, 1.9%), North African Black (n = 1, 1.9%), or Latin American (n = 1, 1.9%).

TIMI flow grade 3 after pPCI was achieved in 39 (75%) patients. Mean GRACE risk score was 137.5 ± 36.51 points, largely indicating moderate to high risk. Baseline characteristics of the cohort are depicted in **Table 1**.

3.2. Echo and CMR indices

On pre-ICD Echo and CMR, patients displayed extensive infarction, LV dysfunction, and dilated LV volumes (**Table 1**). Mean Echo-LVEF was 37.42 ± 7.61% compared to mean 30.19 ± 9% CMR-LVEF. Mean IS measured by CMR was 37.61 ± 12.7% of LV mass. The mean absolute difference of LVEF measured by Echo vs. CMR was -7.23 ± 11.51% ($p < 0.001$). In most patients ($n = 41$) LVEF was lower by CMR than Echo; in these cases, the mean absolute difference was -11.81 ± 7.34% ($p < 0.001$). In a minority of patients ($n = 11$) LVEF was higher by CMR than Echo; mean absolute difference in these cases was 9.8 ± 7.4% ($p = 0.001$). No interaction was found between patients undergoing Echo and CMR ≥ 12 or < 12 weeks apart ($p = 0.3$, **Supplementary Figure 2**).

3.3. Predictors of ICD-T

During a mean follow-up of 6.08 ± 4.16 years (316.04 ± 216.12 weeks), 10 patients underwent appropriate ICD-T: 5 direct shocks to treat very fast ventricular tachycardia ($n = 3$) or ventricular fibrillation ($n = 2$), 3 effective ATP for treatment of ventricular tachycardia, and 2 ineffective ATP followed by shock to treat ventricular tachycardia. A total of 6 patients received 17 additional recurrent ICD-T treatments: 8 direct shocks, 1 effective ATP, and 8 ineffective ATP followed by shock. The rate of appropriate ICD-T during follow-up was 3.16 per 100 person-years.

On univariate analysis, patients with ICD-T during follow-up presented with higher heart rate on admission (102.8 ± 14.34 bpm vs. 85.83 ± 20.82 bpm, $p = 0.019$). No significant differences were noted regarding Echo indices before ICD implantation. However, on preimplantation CMR, patients with ICD-T during follow-up had lower CMR-LVEF (23.7 ± 7.8 vs. 31.74 ± 8.64, $p = 0.01$) and more extensive IS (46.88 ± 13.24 vs. 35.41 ± 11.67, $p = 0.009$) than patients without this adverse outcome.

On multivariable analysis (**Supplementary Table 1**), first ICD-T could be predicted by CMR-LVEF [HR 0.9 (0.83–0.99) per %, $p = 0.02$] and heart rate on admission [HR 1.05 (1–1.1) per beat per min, $p = 0.03$]. The predictive power of IS was marginally significant [HR 1.05 (0.99–1.12) per % of LV mass, $p = 0.11$]. Pre-ICD Echo-LVEF did not appear to accurately predict use of ICD-T in either univariate or multivariable analyses.

3.4. ICD-T stratification by LVEF categories

Using the recommended cutoff of LVEF ≤ 35% to select patients eligible for ICD implantation in primary prevention, we stratified our cohort into two groups by both pre-ICD Echo and CMR (**Figure 1**). Using Echo-LVEF, LVEF ≤ 35% identified only 4 out of 10 (40%) patients who received appropriate ICD-T during follow-up. In contrast, CMR-LVEF ≤ 35% before ICD implantation identified 10 out of 10 (100%) patients who underwent appropriate ICD-T during follow-up. In our population of ICD carriers in primary prevention, therefore, Echo-LVEF ≤ 35% had 40% sensitivity, 52.4% specificity, 16.7% positive predictive value and 78.6% negative predictive value for appropriate ICD-T, compared to the 100% sensitivity, 23.8% specificity, 23.8% positive predictive value, and 100% negative predictive value of CMR-LVEF ≤ 35% (**Table 2**). MACE per 100 person-years across the Echo and CMR LVEF categories is depicted in **Figure 2**. CMR-LVEF outperformed Echo-LVEF for predicting ICD-T (area under the curve 0.76 vs. 0.48, $p = 0.04$).

4. Discussion

In our population of STEMI patients treated with ICD for primary prevention, the main findings of our study are as follows: (1) LVEF measured by CMR outperformed Echo-LVEF and CMR-IS to predict ICD-T; (2) CMR-LVEF ≤ 35% accurately identified 100% of patients who would require ICD-T (100% sensitivity and negative predictive value), and (3) no ICD-T were registered during follow-up in patients with CMR-LVEF > 35%.

4.1. LVEF and ICD in primary prevention

In conjunction with other clinical parameters, LVEF is the cornerstone for early out-of-hospital cardiac arrest prediction in STEMI patients (3). Patients with reduced (< 50%) LVEF have an increased risk of adverse events (10) and sudden cardiac death (3). However, LVEF can fluctuate widely either upward or downward, and together with the magnitude or absence of recovery, LVEF level several weeks after myocardial infarction is a relevant marker of adverse events including sudden cardiac arrest (13, 14). Since a trend toward recovery is usually seen in patients with reduced LVEF, remeasurement of this parameter is fundamental after the acute phase (12, 15). Nonetheless, in clinical practice reassessment rates are relatively low, even in patients with LVEF < 40% in acute phase (16), and this less closely monitored LVEF results in a lower likelihood of being treated with an ICD (17).

4.2. Echocardiography vs. CMR for risk stratification

Echocardiography has traditionally been the imaging technique of choice for patient follow-up and specifically for LVEF measurement. Indeed, clinical trials for ICD in primary prevention in ischemic heart disease have mostly relied on echocardiography for measuring LVEF and selecting the most appropriate cut-off for patient selection (18, 19).

Nevertheless, CMR imaging is the current gold standard for accurate and reproducible LVEF measurement (8, 9). Unfortunately, agreement between LVEF values by echocardiography and CMR is poor, especially if patients with LVEF of 35% or less are included (20). This has also been observed specifically in STEMI patients, an effect probably exacerbated by the presence of segmental wall motion abnormalities (10, 21).

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TABLE 1 Baseline, Echo, and CMR characteristics of the entire cohort and of patients with and without ICD-T.

	All patients (*n* = 52)	ICD-T (*n* = 10)	No ICD-T (*n* = 42)	*P*-value
Clinical variables				
Age (years)	56.56 ± 11	53.6 ± 12.55	57.38 ± 10.64	0.33
Male sex (%)	46 (88.5)	9 (90)	37 (88.1)	1
Diabetes mellitus (%)	14 (26.9)	3 (30)	11 (26.2)	1
Hypertension (%)	25 (48.1)	3 (30)	22 (52.4)	0.3
Hypercholesterolemia (%)	25 (48.1)	7 (70)	18 (42.9)	0.17
Smoker (%)	36 (69.2)	7 (70)	29 (69)	1
Heart rate on admission (bpm)	89.1 ± 20.74	102.8 ± 14.34	85.83 ± 20.82	0.019
Systolic pressure (mmHg)	127.33 ± 25.19	128.1 ± 20.7	127.14 ± 26.36	0.92
Killip class (%)				0.69
1	36 (69.2)	6 (60)	30 (71.4)	
2	10 (19.2)	3 (30)	7 (16.7)	
3	2 (3.8)	0 (0)	2 (4.8)	
4	4 (7.7)	1 (10)	3 (7.1)	
Time to reperfusion (hours)	190 (135–432.5)	482 (194–559)	180 (120–420)	0.23
Peak creatine kinase MB mass (ng/ml)	300 (180–489)	482 (194–559)	300 (141.25–427.5)	0.17
Infarct location (%)				0.82
Anterior	44 (84.6)	9 (90)	35 (83.3)	
Inferior	7 (13.5)	1 (10)	6 (14.3)	
Lateral	1 (1.9)	0 (0)	1 (2.4)	
TIMI flow grade before pPCI (%)				0.16
0	32 (61.5)	4 (40)	28 (66.7)	
1	3 (5.8)	1 (10)	2 (4.8)	
2	9 (17.3)	4 (40)	5 (11.9)	
3	8 (15.4)	1 (10)	7 (16.7)	
TIMI flow grade after pPCI (%)				0.61
0	2 (3.8)	0 (0)	2 (4.8)	
1	0 (0)	0 (0)	0 (0)	
2	11 (21.2)	3 (30)	8 (19)	
3	39 (75)	7 (70)	32 (76.2)	
GRACE risk score	137.5 ± 36.51	143.5 ± 42.73	136.07 ± 35.3	0.57
TIMI risk score	3.38 ± 2.48	3.7 ± 1.95	3.31 ± 2.6	0.66
Residual ST-segment elevation (*n* of derivations)	2.76 ± 1.79	2.33 ± 1.41	2.89 ± 1.89	0.42
QRS duration (ms)	97.73 ± 19.07	99.78 ± 12.95	97.28 ± 20.3	0.73
Left bundle branch block (%)	2 (3.8)	1 (10)	1 (2.4)	0.35
Echo indices before ICD implantation				
Echo-LVEF (%)	37.42 ± 7.61	37.6 ± 5.72	37.38 ± 8.05	0.94
Echo-LV end-diastolic volume (ml)	146.78 ± 43.55	135.4 ± 50.61	148.61 ± 42.97	0.54
Echo-LV end-systolic volume (ml)	90.36 ± 30.48	77.4 ± 29.81	92.45 ± 30.54	0.31
TAPSE (mm)	20.83 ± 4.14	22 ± 3.61	20.67 ± 4.25	0.61
E wave velocity (m/s)	0.78 ± 0.31	1.21 ± 0.52	0.72 ± 0.22	0.15
A wave velocity (m/s)	0.65 ± 0.21	0.57 ± 0.35	0.66 ± 0.2	0.56
Left atrium diameter (mm)	38.31 ± 4.78	37.13 ± 4.16	38.57 ± 4.91	0.45

(Continued)

TABLE 1 (Continued)

	All patients (n = 52)	ICD-T (n = 10)	No ICD-T (n = 42)	P-value
CMR indices before ICD implantation				
CMR-LVEF (%)	30.19 ± 9	23.7 ± 7.8	31.74 ± 8.64	0.01
CMR-LV end-diastolic volume index (ml/m^2)	116.12 ± 32.9	123.6 ± 49.77	114.29 ± 27.9	0.58
CMR-LV end-systolic volume index (ml/m^2)	82.52 ± 30.83	96.2 ± 46.31	79.1 ± 25.28	0.29
LV mass (g/m^2)	94.17 ± 19.44	96.29 ± 23.32	93.66 ± 18.82	0.75
Infarct size (% of LV mass)	37.61 ± 12.7	46.88 ± 13.24	35.41 ± 11.67	0.009

bpm, beats per min; CMR, cardiovascular magnetic resonance; Echo, echocardiography; GRACE, Global Registry of Acute Coronary Events; ICD-T, implantable cardioverter-defibrillator therapies; IS, infarct size; LV, left ventricular; LVEF, left ventricular ejection fraction; pPCI, primary percutaneous coronary intervention; TAPSE, tricuspid annular plane systolic excursion; TIMI, Thrombolysis in Myocardial Infarction. In patients with atrial fibrillation at the time of echocardiography, E and A wave velocities were not considered for analyses.

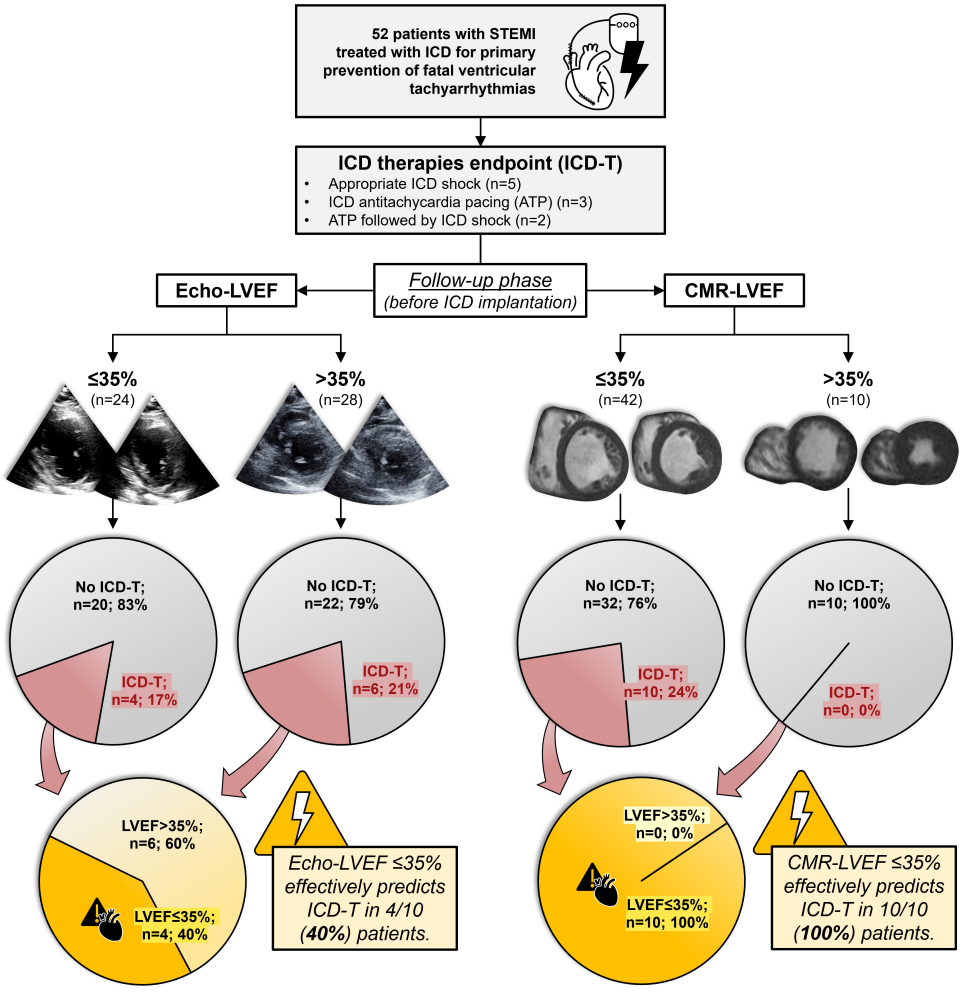

FIGURE 1
Stratification of ICD-T according to Echo and CMR LVEF categories before ICD implantation. Occurrence of life-threatening ventricular tachyarrhythmias (manifesting as appropriate ICD therapies) was analyzed in a population of STEMI patients treated with ICD for primary prevention. Patients were categorized by pre-ICD LVEF (≤ 35% vs. >35%) *via* Echo or CMR. Compared to Echo-LVEF, CMR-LVEF categories allowed for detection of 100% of ICD-T (when CMR-LVEF was ≤ 35%) and exclusion of ICD-T (when CMR-LVEF was > 35%). ATP, antitachycardia pacing; CMR, cardiac magnetic resonance; Echo, echocardiography; ICD, implantable cardioverter-defibrillator; ICD-T, appropriate implantable cardioverter-defibrillator therapies; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation acute myocardial infarction.

4.3. LVEF to predict ICD therapies

Basing the decision to implant an ICD in primary prevention solely on LVEF has several limitations as an approach, as well as a relatively low pooled sensitivity (59.1%) and specificity (77.8%) for predicting major arrhythmic events after myocardial infarction (22). In fact, most patients with LVEF ≤ 35% will never require ICD-T if implanted with an ICD. Across five landmark ICD trials, only 18% of patients were treated with ICD-T during follow-up (6). The rate is even lower (2.6% at 30 months) among primary prevention patients

TABLE 2 ROC curve characteristics of LVEF categories by Echo and CMR before ICD implantation to predict appropriate ICD-T.

Variable	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Echo-LVEF ≤ 35%	40%	52.4%	16.7%	78.6%
CMR-LVEF ≤ 35%	100%	23.8%	23.8%	100%

CMR, cardiovascular magnetic resonance; Echo, echocardiography; ICD-T, implantable cardioverter-defibrillator therapies; IS, infarct size; LVEF, left ventricular ejection fraction; ROC, receiver operating characteristic.

in a contemporary registry (7), probably due to improved preventive therapies. The rate of appropriate ICD-T during follow-up was 3.16 per 100 person-years in our cohort, similar to previously published cohorts. As an example, in the Danish ICD register patients with ischemic heart disease and ICD implanted for primary prevention showed an appropriate ICD-T rate of 4.12 per 100 person-years (23).

Furthermore, as most contemporary STEMI patients maintain a relatively preserved LVEF after the acute event, the majority of sudden cardiac deaths and arrhythmic events occur in this subset regardless of their reduced risk of arrhythmic events (24, 25). There is a considerable risk of sudden cardiac arrest in STEMI patients with LVEF 35–50%, a population in which ICD is generally not indicated in primary prevention (26). Indeed, in our study most (60%) appropriate ICD-T occurred in patients with Echo-LVEF > 35%. As previously noted, therefore, Echo-derived LVEF is not a sensitive predictor of ICD-T.

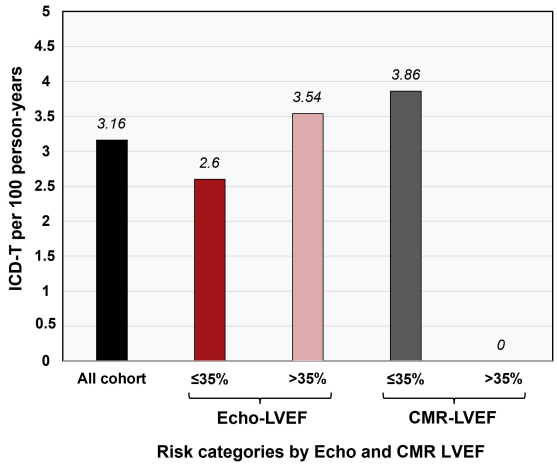

FIGURE 2
ICD-T per 100 person-years across Echo and CMR LVEF categories before ICD implantation. CMR, cardiac magnetic resonance; Echo, echocardiography; ICD, implantable cardioverter-defibrillator; ICD-T, appropriate implantable cardioverter-defibrillator therapies; LVEF, left ventricular ejection fraction.

4.4. CMR to predict ICD therapies

The efficacy of CMR imaging to predict the use of appropriate therapies in ICD carriers is an understudied area, despite being a non-invasive and safe technique with proven predictive value in STEMI patients (10, 12). Studies have shown that CMR-derived LVEF (27) and IS (27, 28) can predict adverse arrhythmic cardiac events and ICD-T. In fact, CMR-LVEF outperforms Echo-LVEF to predict a composite endpoint of all-cause death or ICD-T in ICD carriers in primary prevention with ischemic and non-ischemic cardiomyopathy (29). Likewise, quantification of myocardial fibrosis and gray zone fibrosis in CMR can predict sudden cardiac death and an arrhythmic endpoint in a mixed (ischemic and non-ischemic) population of cardiac implantable electronic device receivers (30). Interestingly, in patients with no evidence of fibrosis in CMR, sudden cardiac death can be virtually excluded. However, in our STEMI cohort the presence of at least some degree of myocardial necrosis was universal, and CMR-LVEF appears more useful to predict (or exclude) ICD-T during follow-up.

Occurrence of pre-ICD CMR-LVEF ≤ 35% identified all patients (100%) in this cohort who would undergo ICD-T during follow-up, clearly outperforming pre-ICD Echo-LVEF ≤ 35%, which had only 40% sensitivity to detect ICD-T. The presence of CMR-LVEF > 35% thus indicates a low risk of adverse arrhythmic events and can pinpoint a population in which ICD implantation should be withheld. In contrast, the possibility of adverse arrhythmic events could not be ruled out in the subgroup with Echo-LVEF > 35%.

We hypothesize that these findings can be explained by the increased accuracy of LVEF measurement by CMR (i.e., LVEF ≤ 35% by CMR represents a truly reduced LVEF) and the lower LVEF obtained by CMR compared to echocardiography (i.e., LVEF > 35% by CMR represents a truly not-severely reduced LVEF).

In the selection of STEMI patients who could benefit from an ICD in primary prevention, clinicians should weigh up the risk of undertreatment, which would deprive certain patients of potentially life-saving therapy in case of fatal ventricular arrhythmias, against the risk of overtreatment, which would increase provider costs and morbidity associated with complications and inappropriate therapies in patients fitted with a device. Based on our data, a LVEF ≤ 35% cut-off by CMR imaging could accurately identify all patients who would require ICD-T during follow-up, and most importantly, safely exclude ventricular tachyarrhythmias in patients with CMR-LVEF > 35%, in whom theoretically an ICD would render no preventive benefit.

4.5. Study limitations

Our cohort is limited in the number of recruited patients and compiled variables. Additionally, patients were included over a long period (between 2004 and 2021) during which time there were variations in acute and chronic STEMI treatment. Only STEMI patients who underwent both echocardiography and CMR before ICD implantation were selected, so the cohort may not be entirely representative of the whole STEMI population. Another drawback is the time difference between Echo and CMR and ICD implantation in our cohort; performing these techniques sequentially over a short period could have allowed better comparison. Patients not undergoing ICD implantation were not studied, which allowed us to accurately analyze the occurrence of ICD-T but limited our

results to ICD carriers. Changes in ICD programming were not systematically recorded during follow-up. Furthermore, although most patients showed extensive infarction, underwent CMR study and ischemic etiology could be inferred as the most probable cause, other underlying cardiomyopathies could not be ruled out with absolute certainty. Lastly, the implications of ICD implantation based on CMR-LVEF vs. Echo-LVEF should be explored in specifically designed, prospective, and randomized studies. Due to the observational nature of our study no formal recommendations regarding ICD indication can be inferred.

5. Conclusion

In STEMI patients treated with ICD in primary prevention, assessment of LVEF by CMR outperforms Echo-LVEF to predict subsequent appropriate ICD therapies. Occurrence of CMR-LVEF $\leq$ 35% identified all patients who would undergo ICD therapies (100% sensitivity and negative predictive value). Strategies aimed at selective ICD implantation based on CMR data should be further explored in properly designed studies.

Data availability statement

The datasets presented in this article are not readily available because of privacy and ethical restrictions. Requests to access the datasets should be directed to VB, vicente.bodi@uv.es.

Ethics statement

The study was reviewed and approved by the Comité Ético de Investigación con Medicamentos of the Hospital Clínico Universitario de Valencia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

VM-G, NP, and VB: conceptualization and writing—original draft. VM-G, NP, JG, ML-L, JM, CR-N, ED, HM-G, AG-P, ÁF-D-L-O, ÁM-B, LB, JS-G, and CA: data curation. VM-G, NP, JG, ML-L, JM, CR-N, ED, HM-G, AG-P, ÁF-D-L-O, ÁM-B, LB, JS-G, CA, and VB: formal analysis. JN, AB-G, FC, and VB: funding acquisition. VM-G, NP, JG, ML-L, JM, and VB: investigation and methodology. VM-G, NP, CR-N, and VB: project administration. VM-G, NP, JG, ML-L, JM, CR-N, ED, HM-G, AG-P, ÁF-D-L-O, ÁM-B, LB, JS-G, CA, JN, AB-G, FC, RR-G, and VB: resources. JN, AB-G, FC, RR-G, and VB: supervision and writing—review and editing. VM-G, NP, JG, and VB: validation and visualization. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.991307/full#supplementary-material

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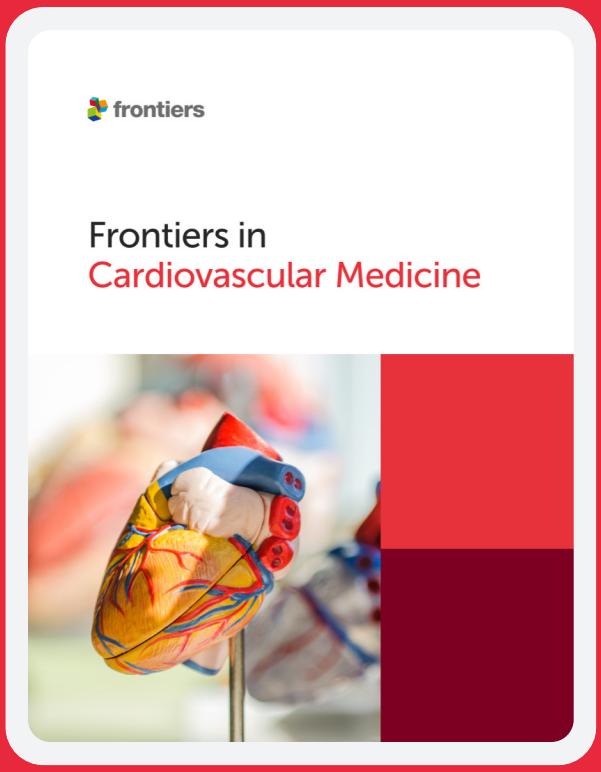

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