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His-purkinje system pacing upgrade improve the heart performances in patients suffering from pacing-induced cardiomyopathy with or without permanent atrial fibrillation

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ABSTRACT

Introduction: The efficacy and safety of his-purkinje system pacing (HPSP) upgrades in patients with pacing-induced cardiomyopathy (PICM) and atrial fibrillation (AF) are still unknown.

Methods and results: Patients with PICM were continuously enrolled from January 2018 to March 2020. All patients were further divided into AF subgroup and sinus rhythm subgroup. Clinical data including echocardiographic examination parameters, electrocardiogram (ECG) measurements, and New York Heart Association (NYHA) classification, were assessed before and after the procedure. The HPSP upgrades, including his bundle pacing (HBP) and left bundle branch pacing (LBBP) were completed in 34 of 36 (94%) patients, Complications including electrode dislodged, perforation, infection or thrombosis were not observed in the perioperative period. During a mean of 11.52 ± 5.40 months of follow-up. The left ventricular ejection fraction (LVEF) increased significantly (33.76 ± 7.54 vs 40.41 ± 9.06, $P < 0.001$), and the QRS duration decreased (184.22 ± 23.76 ms vs 120.52 ± 16.67 ms, $P < 0.001$) after the upgrades. LVEDD reversed from 59.29 ± 7.74 mm to 53.91 ± 5.92 mm ($P < 0.001$), and the NYHA functional class also improved to 2.00 ± 0.76 from 2.55 ± 0.91 at the first follow-up ($P < 0.001$). The left atrium (LA) size also slightly decreased compared to the initial state (47.44 ± 7.14 mm VS 45.56 ± 7.78, $P = 0.010$). BNP significantly decreased from a median value of 458.06 (256.35–755.10) to 172.31(92.69–552.14) ($P = 0.004$). The threshold did not increase significantly (1.18 ± 0.76 mv@0.4 ms vs 1.26 ± 0.91mv @ 0.4 ms, $P = 0.581$). These improvements in patients with AF were similar with those in patients without AF ($P > 0.05$).

Conclusions: HPSP upgrades improved the heart performance and reversed the left ventricular remodeling in patients suffering from PICM with or without AF, and it should be a promising choice in these patients.

1. Introduction

It is well known that long-term right ventricular pacing (RVP) might lead to a long QRS duration (QRSd) and left ventricular (LV) dyssynchrony and consequently result in LV systolic dysfunction. Many studies have demonstrated that conventional pacing sites (i.e., the apex or septum) could increase mortality and hospitalization of heart failure in pacemaker-dependent patients [1–3]. However, the incidence of PICM remains relatively high, with no response to cardiac resynchronization therapy (CRT) for these patients. The biventricular pacing upgrade is still not the optimal recommendation (IIb) for these patients in recent guidelines [4].

What would help those patients with PICM? His-Purkinje system pacing, including HBP and LBBP, was chosen as an alternative procedure in patients with indications of bradycardia or heart failure [4]. The safety and efficiency have been confirmed by recent publications [5–7]. However, studies focusing on the outcome of HBP and LBBP upgrades in PICM patients are extremely rare [8,9]. It is unknown whether this is an effective procedure in patients with PICM and AF. We consequently performed this study to investigate the clinical outcome of HBP and LBBP upgrades in these patients.

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2. Methods

2.1. Patient enrollment

Patients with PICM were continuously enrolled from January 2018 to March 2020 in the first affiliated hospital of Dalian Medical University. The inclusion criteria were as follows:

1) Patients with prior RVP implantation (including DDD and VVI pacemaker.) and the percentage of RVP > 40%
2) A LVEF of ≤40% caused by a new onset LVEF decrease of >10% from baseline, without other identifiable causes.
3) Patients underwent the HPSP upgrade procedure at our hospital. We excluded patients with other identifiable causes of heart failure, such as myocardial infarction, severe valvular heart disease, arrhythmia-related cardiomyopathy, and long-term uncontrolled hypertension.

The clinical data were assessed before and after HBP upgrade, including echocardiographic examination parameters, ECG measurements, and NYHA classification.

Permanent AF refers to AF in which cardioversion has failed and AF that has been sustained for more than 1 year.

2.2. Upgrade procedure

The 4.1F 3830 (SelectSecure, Medtronic, Minneapolis, MN) pacing lead was delivered using the C315HIS (Medtronic, Minneapolis, MN) sheath. His bundle electrograms were mapped in a unipolar configuration and recorded on the recording system (Prucka Cardiolab, GE Healthcare, Waukesha, WI). To locate the optimal site for the His bundle lead, the sheathes and leads were delivered to the ventricular end for the distal HBP/LBBP, and the pacing rate was decreased to 30 bpm for an escape rhythm. If no his electrogram was observed, pace mapping was conducted to identify a site with evidence for His bundle capture. His bundle pacing was acceptable when capture threshold was lower than 2.0 V/1.0 ms. LBBP would be further performed when HBP failed. For these patients with ventricular pacing dependent, right ventricular backup pacing was routinely retained if threshold of his bundle pacing was higher than 2.0v/0.5 ms. In patients with permanent AF who required a dual chamber pacemaker, the 3830 lead was connected to the right atrial (RA) port and right ventricular (RV) was remained in RV port. In patients who received a new CRT defibrillator (D) or CRT pacemaker (P) device, the RA lead remained in atrial port, RV lead remained in the RV port as a back-up. The 3830 lead was connected to the left ventricular (LV) port.

Table 1
Baseline characteristics of patients upgrade to HBP.

	PICM patients ($n = 34$)
Age (years)	69.69 ± 13.75
male (n, %)	22 (64.7%)
Diabetes mellitus (n, %)	6 (17.6%)
Coronary heart disease (n, %)	5 (14.7%)
Hypertension (n, %)	23 (67.6%)
Renal dysfunction (n, %)	3 (8.8%)
CLBBB (n, %)	3 (8.8%)
Lipid-regulating drugs (n, %)	9 (26.5%)
Anticoagulants (n, %)	17 (50.0%
ACEI/ARB/ARNI (n, %)	12 (35.3%)
β -blockers (n, %)	29 (85.3%)
ARNI (n, %)	6 (17.6%)
Diuretics (n, %)	29 (85.3%)
Digoxin (n, %)	7 (20.6%)
LVEF before RVP (%)	51.77 ± 8.19
LVEF before HBP (%)	33.76 ± 7.54
LVEDD before RVP (mm)	54.83 ± 7.35
LVEDD before HBP (mm)	59.29 ± 7.74
NYHA classification	2.55 ± 0.91
BNP(median, ng/L)	458.06(256.35–755.10)
QRS duration (ms)	184.2 ± 23.67
VP percentage (%)	90.54 ± 24.01%

CLBBB: complete left bundle branch block; *ACEI:* angiotensin converting enzyme inhibitors; *ARB* angiotensin receptor blocker; *ARNI*: angiotensin receptor neprilysin inhibitors; *LVEDD* left ventricular end-diastolic diameter; *LVEF* left ventricular ejection fraction; *VP:* ventricular pacing.

2.3. Follow-up

Patients had follow-up visits in the cardiology and device clinic at the 1st, 3rd, 6th, 12th, 18th and 24th months. Clinical data, including the NYHA class, QRS duration, device programming information and echocardiography parameters, were recorded.

2.4. Statistical analysis

Continuous variables are expressed as the mean ± SD (standard deviation) and were compared with paired *t*-tests for normally distributed data. Categorical variables are expressed as percentages (%) and were compared using χ^2 tests. Nonparametric tests were used if the data were not normally distributed. All statistical tests were two-tailed; $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

Permanent HBP or LBBP was successful in 34 of 36 patients. The average LVEF value was dramatically low (33.76 ± 7.54% vs. 51.77 ± 8.19%) after right ventricular septal pacing for 79.18 (19–321) months, and 12 patients showed elective replacement indicators (ERIs) at the latest programming before the upgrade procedure. Permanent HBP upgrades were successful in 29 of 34 patients, and LBBP upgrades were successful in 5 patients. Upgrades were unsuccessful in 2 patients, 4 patients were re-hospitalized due to an acute exacerbation of heart failure-one of the 4 patients died of heart failure within 12 months of follow-up. Nine patients (26.5%) had infranodal block. CRT devices with RV backup were implanted in 13 (38.2%) patients. Dual-chamber pacemakers were implanted in 20 patients (58.8%), and implantable cardioverter defibrillator (ICD) were implanted in 1 patient (3%). The baseline characteristics were shown in Table 1.

3.2. Clinical outcomes of upgrades

The clinical outcomes before and after upgrades were shown in Table 2. After upgrades, the LVEF significantly increased from baseline 33.76 ± 7.54% to 40.41 ± 9.06% ($P < 0.001$) (Fig. 1A). The paced QRSd markedly decreased from 184.2 ± 23.76 ms at baseline to 120.5 ± 16.67 ms after HPSP ($P < 0.001$) (Fig. 1B). The LVEDD reversed from 59.29 ± 7.74 mm to 53.91 ± 5.92 mm ($P < 0.001$) (Fig. 1C). The NYHA functional class improved to 2.00 ± 0.76 from 2.55 ± 0.91 at

Table 2
Clinical outcomes of upgrades.

	Baseline ($n = 34$)	Final follow-up ($n = 34$)	*P* value
QRSd (ms)	184.2 ± 23.67	120.5 ± 16.67	<0.001
NYHA classification	2.55 ± 0.91	2.00 ± 0.76	<0.001
Final LA size	47.44 ± 7.14	45.56 ± 7.78	0.010
LVEDD (mm)	59.29 ± 7.74	53.91 ± 5.92	<0.001
MR	10	6	0.219
TR	10	8	0.727
LVEF (%)	33.76 ± 7.54	40.41 ± 9.06	<0.001
BNP(median, ng/L)	458.06(256.35–755.10)	172.31(92.69–552.14)	0.004

LA left atrium, *LVEDD* left ventricular end-diastolic diameter, *LVEF* left ventricular ejection fraction, *MR* mitral regurgitation, *TR* tricuspid regurgitation.

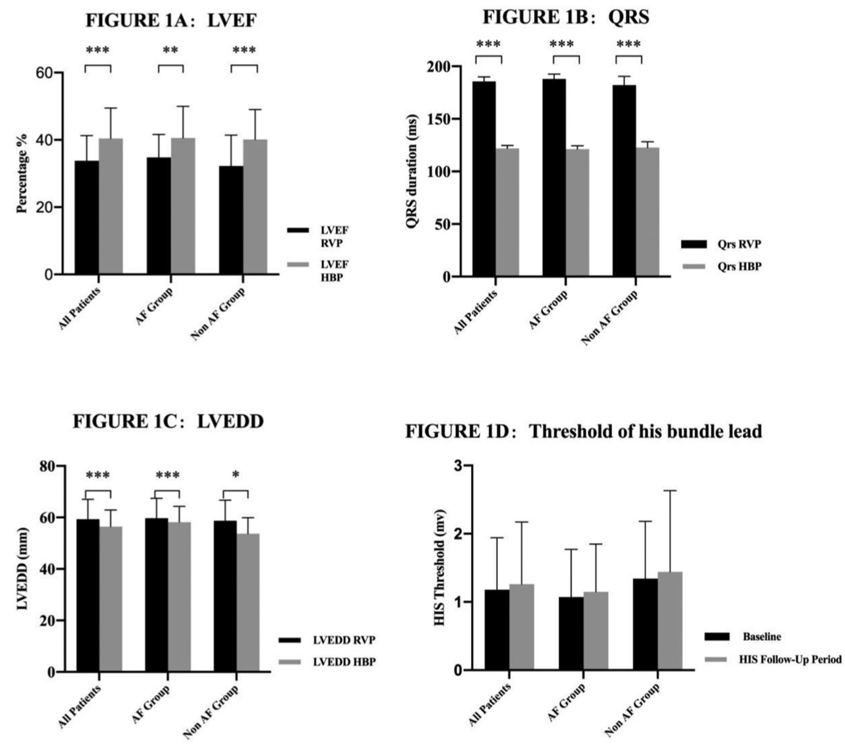


Fig. 1. A. Comparison of changes in LVEF before and after HBP upgrad, B. Comparison of changes in QRSd between RV and HBP, C. Comparison of changes in LVEDD between RV and HBP, D. Comparison of changes in threshold of HBP between post-operative time and follow-up period.

baseline during follow-up ($P < 0.001$). BNP significantly decreased from a median value of458.06(256.35–755.10) to 172.31(92.69–552.14) ($P = 0.004$). Similar results were observed in HBP and LBBP groups (Table 3).

3.3. Clinical outcomes of upgrades in patients with permanent AF

Twenty-one patients had permanent AF. These improvements of cardiac function and remodeling were also observed in patients with permanent AF after upgrades (Table 4). To note, left atrium (LA) size also slightly decreased from 59.29 ± 7.74 mm at baseline to 56.44 ± 6.46 after HPSP ($P = 0.010$). No significant difference was found in mitral (10/6, $P = 0.219$) or tricuspid regurgitation (10/8, $P = 0.727$) before and after HPSP.

There was no significant difference in the improvement of the LVEF between the patients with or without AF ($P = 0.424$). LVEDD and QRSd also had no significant difference between the two subgroups.

Table 3
Clinical outcomes in patients with HBP and LBBP.

	HBP group ($n = 29$)	LBBP group ($n = 5$)	*P*
Age	68.93 ± 14.06	69.80 ± 12.42	0.898
Gender (male, %)	19(65.5%)	4(80.0%)	0.523
VP percent (%)	92.61 ± 19.10	78.96 ± 44.19	0.532
initial QRSd (ms)	184.00 ± 25.27	184.00 ± 23.54	1.000
final QRSd (ms)	119.04 ± 16.29*	131.75 ± 21.11*	0.174
initial NYHA classification	2.76 ± 0.83	2.60 ± 0.89	0.699
final NYHA classification	1.95 ± 0.76*	2.00 ± 0.82*	0.906
initial LA size (mm)	47.07 ± 7.64	49.60 ± 2.19	0.155
final LA size (mm)	45.41 ± 8.06*	46.40 ± 6.62	0.798
initial LVEDD (mm)	59.03 ± 7.82	60.80 ± 7.92	0.645
final LVEDD (mm)	56.31 ± 6.59*	57.20 ± 6.34	0.781
initial LVEF (%)	34.10 ± 7.95	31.80 ± 4.49	0.536
final LVEF (%)	45.41 ± 8.06*	46.40 ± 6.62	0.563

* $P < 0.05$ comparison between before HBP or LBBP procedure and last follow-up.

3.4. Lead outcome of upgrades

The pacemaker parameters including threshold, sensed R wave and impedance were recorded after a median follow-up period of 8.9 months (Table 5). The threshold of HPSP did not increased

Table 4
Clinical outcomes in patients with or without AF.

	AF group ($n = 21$)	Sinus rhythm group ($n = 13$)	*P*
Age	66.62 ± 14.59	73 ± 10.21	
Gender (male, %)	15(65.2%)	8(53.3%)	
VP percent (%)	85.48 ± 29.95	98.32 ± 3.02	0.135
initial QRSd (ms)	185.35 ± 21.79	182.08 ± 28.98	0.731
final QRSd (ms)	119.35 ± 16.26*	122.83 ± 18.95*	0.600
initial NYHA classification	2.69 ± 0.91	2.33 ± 0.67	0.377
final NYHA classification	2.06 ± 0.75*	1.77 ± 0.63*	0.261
initial LA size (mm)	51.05 ± 6.45	41.62 ± 3.36	<0.001
final LA size (mm)	49.71 ± 6.83	38.85 ± 3.13*	<0.001
initial LVEDD (mm)	59.67 ± 7.74	58.69 ± 8.03	0.727
final LVEDD (mm)	54.05 ± 5.88*	53.69 ± 6.22*	0.868
initial LVEF (%)	34.71 ± 6.38	32.23 ± 9.18	0.358
final LVEF (%)	40.57 ± 9.38*	40.15 ± 8.90*	0.898

LA left atrium, *LVEDD* left ventricular end-diastolic diameter, *LVEF* left ventricular ejection fraction, *MR* mitral regurgitation, *TR* tricuspid regurgitation.
* $P < 0.05$ comparison between before HBP procedure and last follow-up.

Table 5
Lead outcomes during the operation and final follow-up.

	Baseline	Final follow-up	*P* value
VP percentage (%)	81.67 ± 32.16%	92.79 ± 19.15%	0.124
Threshold (V@0.4 ms)	1.18 ± 0.76	1.26 ± 0.91	0.581
Threshold in AF subgroup	1.07 ± 0.70	1.15 ± 0.70	0.582
Threshold in Non-AF subgroup	1.34 ± 0.84	1.44 ± 1.19	0.788
Impedance (Ω)	616.76 ± 148.89	493.09 ± 118.85	0.108
Sensed R wave (mV)	4.85 ± 2.08	4.56 ± 1.94	0.148

VP ventricular pacing.

significantly (1.18 ± 0.76 mv@0.4 ms vs 1.26 ± 0.70mv @ 0.4 ms, P = 0.581) (Fig. 1D). Sensed R (4.85 ± 2.08 vs. 4.56 ± 1.94, P = 0.148) and lead impedance (616.76 ± 148.89 vs. 493.09 ± 118.85, P = 0.108) remained relatively stable during the follow-up duration.

4. Discussion

We proved that HBP and LBBP upgrades can improve the heart function, thus reverse the left ventricular remodeling in patients with PICM. Furthermore, we first demonstrated the improvement could also be found in patients with PICM and permanent AF.

4.1. His-purkinje system pacing improves cardiac performances

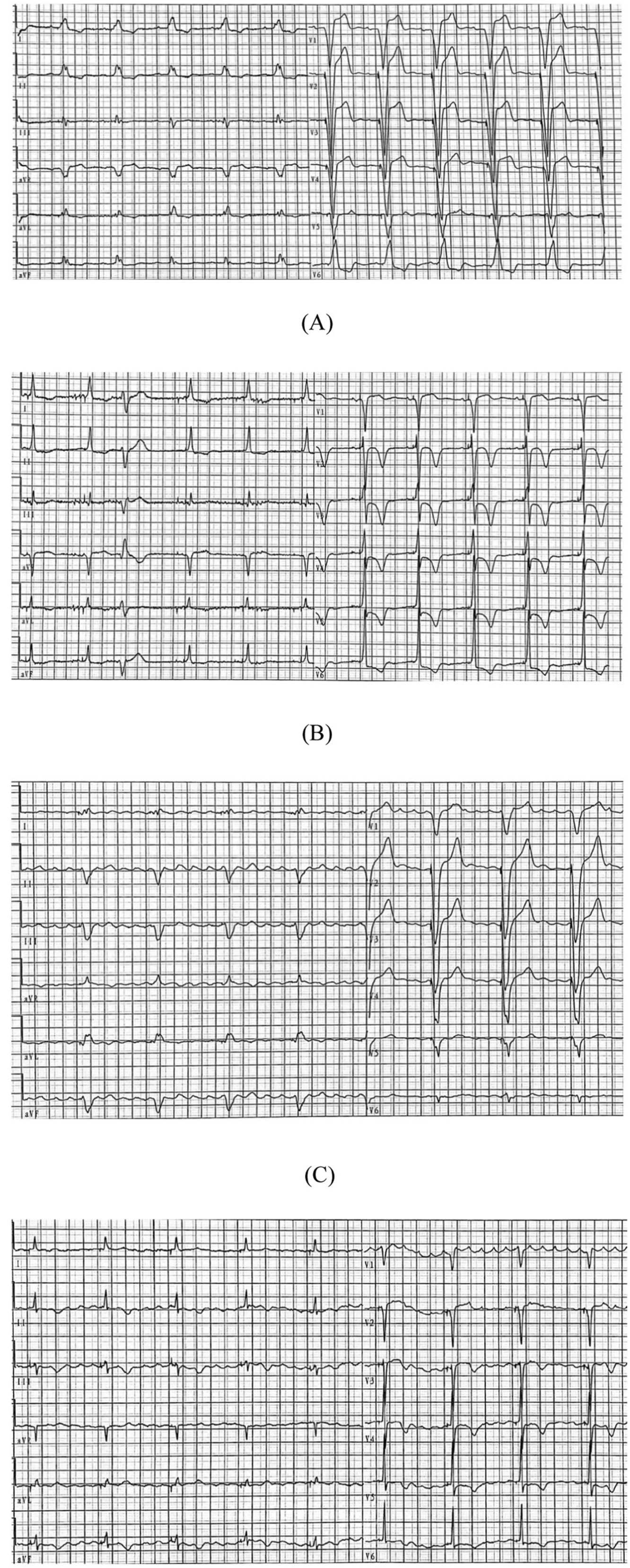
The chronic RVP might induce inter- and intraventricular dyssynchrony, which is detrimental to left ventricular function and associated with heart failure and increased mortality [10]. The incidence of PICM was relatively high [11]. However, about 30% of patients had no response to CRT [12]. A series of publications have suggested that HBP could provide favorable clinical results in patients with CRT indications [9,13]. Notably, Sharma et al. indicated that HBP showed a positive clinical response in CRT non-responsive patients [5]. The His-SYNC trial [14] was the first prospective, randomized trial to compare the performance of HBP and conventional CRT. The narrower QRS was observed in HBP group but the improvement of cardiac function and survival were indifferent between the CRT group and HBP group. Consistently with the studies of Vijayaraman and Sung, our findings also demonstrated the clinical benefits of HBP upgrades in PICM patients [8,11]. Furthermore, we also found that the ratio of response to HBP/LBBP upgrade were relatively high (31/34,89.66%) in patients with PICM. Furthermore, 12 patients met replacement indicators before the upgrade procedure, which indicated that HBP is still efficient and should be a promising choice even in the patients with long-term RVP.

4.2. His-purkinje system pacing improves cardiac performances in patients with AF

To date, the majority of randomized controlled trials and recommendation of current guidelines for CRT upgrades focus on the patients with PICM and sinus rhythm. Nevertheless, the biventricular pacing upgrade is still a class II recommendation in 2016 guidelines from ESC. The efficacy of CRT upgrade was unfavorable in patients with AF due to the potential reduction of biventricular pacing percentage [17,18]. Quite different with those studies, in our study, 62% of patients had AF and similar clinical responses with the patients with sinus rhythm. Thus, the HPSP could reverse the ventricular remodeling caused by interventricular and atrioventricular dyssynchrony and long-term RVP. However, no significant changes in MR and TR were observed in these patients. It is possible that the LA expanded mainly as a result of long-standing atrial fibrillation rather than PICM. Regarding MR/TR, a previous study [15] found that the LA size and MR reduced significantly after restoration of sinus rhythm in AF patients. A reason for the enlarged LA and worsening MR could be the lack of rhythm control treatment in patients with AF. In addition, our study identified few cases of mitral and tricuspid regurgitation, but these cases were insufficient to show a statistical difference. For the patients dependent on ventricular pacing, would HBP be the optimal choice? We still need more evidence in future studies (Fig. 2).

4.3. Current knowledge of upgrade procedure

HBP has been thought to be associated with several limitations, such as higher capture thresholds, especially in BBB or infranodal block; lower R-wave amplitudes; and increased risk for lead revisions from late threshold increase. As mentioned above, survival prognosis of HBP application was still unclear due to a lack of randomized evidence.



(A)

(B)

(C)

(D)

Fig. 2. 12-lead ECG was recorded at a paper speed of 25 mm/s and voltage of 10 mm/mV before and after the procedure in patients with and without AF. A. ECG of PICM patient with III°AVB and sinus rhythm before upgrade procedure. B. ECG of PICM patient with III°AVB after upgrade procedure, non-selective his bundle pacing was fulfilled. C. ECG of PICM patient with atrial fibrillation before upgrade procedure. D. ECG of PICM patient with atrial fibrillation after upgrade procedure, non-selective his bundle pacing was fulfilled.

Thus, HBP has not been widely generalized in clinical practice and is a class IIa indication in the latest guidelines for the management of bradyarrhythmia [16]. In our study, we found that the distal HBP and LBBP were helpful for the better capture thresholds and R-wave. The distal HBP and LBBP pacing, fixed in the septal myocardium, could provide ideal capture thresholds and high R-wave amplitudes. The key point for successful pacing is to bypass conduction blocks of the distal his bundle or proximal left bundle. We were able to achieve distal HBP /LBBP in 34 of 36 patients with infranodal AV block in this study, which proved the possibility to achieve high success rates of physiologic pacing in ventricular pacing dependent patients. The long-term effects of his-purkinje pacing on the septal contractile stress need to be further evaluated.

4.4. Safety of upgrades for patients with PICM

Vijayaraman et al. demonstrated that the HBP threshold could remain relatively stable after 2 years of follow-up [8]. A recent publication confirmed this finding in a larger sample and showed over 90% of patients have a capture threshold less than 2.5 V @ 1 ms after a median follow-up of 3 years [17]. In the 2 patients in which HBP failed, we were not able to capture the distal His-Purkinje system even at high output. In the prior study by Vijayaraman et al. [9], the success rate of HBP upgrade was 95% (57/60) in western population with AV block. These finding suggest that the progression of conduction dysfunction was extremely rare even in PICM patients. These results extend the long-term data about the threshold for HBP. According to our results, the threshold for HBP was not significantly higher after the follow-up period of more than 12-months. Device malfunction, lead perforation and embolization were not found during follow-up. The technical challenges in HBP are highly dependent on the operators' experience [18–20].

Although the results presented are favorable, there are some limitations in the present study. First, HBP was conducted by an experienced team, and there were high success rates in our study along with potential patient selection bias. Second, the present study focused on PICM patients with reduced LVEFs. PICM patients with preserved LVEFs may have unique pathological progress and deserve more clinical assessment. Third, long-term pacing performance of his pacing lead and the potential risks of lead extractions need further careful evaluation. Finally, our sample size is relatively small, thus our findings need to be further investigated in a larger population of patients with PICM.

5. Conclusions

HBP and LBBP upgrades significantly improved the heart performance and reversed the left ventricular remodeling in patients suffering from PICM with or without AF, and it should be actively considered in patients with PICM.

Disclosures

None declared.

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