Evaluation of electrocardiogram and echocardiographic characteristics of pre-and post-operation of His bundle pacing: A comprehensive review and meta-analysis

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Abstract

Objective: Although His bundle pacing (HBP) has shown an improved therapeutic effect than conventional pacing in terms of reducing cardiovascular mortality, the basic characteristics of HBP has not been defined systematically. Therefore, a systematical review and meta-analysis on the HBP characteristics can be timely and favorable. In this study, we aimed to clarify the electrocardiogram and echocardiographic characteristics of the pre- and post-operation of HBP.

Methods: Patients with HBP were exclusively included in this study. By evaluating their electrocardiogram characteristics, echocardiographic parameters, and cardiac function, the therapeutic effect of HBP was assessed.

Results: A total of 23 studies were included in the analysis. The overall implant success rate for HBP was 83.64%. After HBP treatment, the paced QRS duration dropped from 147.73±19.46 ms to 116.84±17.32 ms (p<0.001). Left ventricular ejection fraction (LVEF) increased from 34.87%±9.62% to 46.40%±9.64% (p<0.001), and NYHA functional class improved from 2.90±0.57 to 1.78±0.58 within the HBP group (SMD-2.09; 95% CI-2.53,-1.64, p<0.001).

Conclusion: HBP can significantly reduce the QRS duration, resulting in improvement of cardiac function in most patients. In addition, this approach is applicable to most patients without limitations.

Keywords: His bundle pacing, electrocardiogram, echocardiogram, cardiac function, meta-analysis

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Introduction

Myocardial remodeling (MR) often occurs in patients with cardiovascular diseases, resulting from an abnormal neurohumoral regulation owing to the heart failure (HF) (1, 2). Normally, after the infarction, heart tissue goes through macro and micro-remodeling. Non-elastic fibrotic tissue replaces the healthy myocardium, and the architecture of the left ventricle deforms from an efficient elliptical shape into a spherical chamber, resulting in alteration of ventricular dilatation (3). Often these changes lead to heart dysfunction in vulnerable patients, developing into HF (4).

Cardiac resynchronization therapy (CRT) has been clinically used to treat HF in patients with impaired left ventricular function or a wide QRS complex (5). Previous studies indicate that CRT could improve cardiac structure and function and slow the pro-

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HIGHLIGHTS

- Indices included QRS duration, left ventricular ejection fraction, New York Heart Association, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, 6 minute walk distance, and brain natriuretic peptide before and after His bundle pacing (HBP) were clarified comprehensively, which could be substantial evidence of cardiac reverse remodeling.
- High success rates (83.64%) demonstrated the applicability of HBP.
- The correlation of difference values between QRSd and LVEF were assessed for the first time after HBP, which indicated that the conduction pathway, especially physiologic pacing could improve cardiac function.

gression of HF, resulting in an improvement in the quality of life (6). The mechanism associated with the process of remodeling mainly is "asynchrony." Atrioventricular delay leads to delay of ventricular contraction and decrease of diastolic filling, the left ventricle maintains its function through a compensatory response (Frank-Starling mechanism) at an early stage. Systolic mitral regurgitation also occurs as a result of mitral valve ring dilation. CRT modifies functional blocks, which are associated with mechanical dyssynchrony. Compared with optimal pharmacological therapy (OPT), CRT leads to a 20% reduction in death or hospitalization (7).

However, some studies (8) have demonstrated that CRT could potentially increase the risk of pro-arrhythmic effects. It may be caused by reversal of the normal activation sequence by epicardial pacing, which leads to the prolongation of the QT interval and transmural dispersion of repolarization (TDR), creating a substrate and trigger for recurrent arrhythmias (9-11). Therefore, the understanding of the electrophysiological mechanism has gained importance in the field of cardiac electrophysiology. The understanding of His Purkinje system (HPS) based on physiological pacing has particularly attracted significant research interest owing to its wide clinical usage (12). The activation of HBP by HPS can mimic rapid parallel ventricular activation and has been a new clinical strategy, demonstrating an improved therapeutic effect. To date, the electrocardiogram and echocardiographic characteristics of the preHBP and postHBP has yet to be systemically defined. Therefore, in this study, we aimed to provide a clear description of the electrocardiogram and echocardiographic characteristics, helping clinicians have a better understanding of HBP.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (13).

Search strategy and selection criteria

Databases including PubMed, EMBase, Cochrane library, Web of science, CNKI, and Wanfang data were used, and keywords including His bundle pacing, cardiac failure, cardiac dysfunction, cardiac remodeling were selected to screen the literature. Furthermore, the literature was further filtrated using the following criteria: (1) the study object was human; (2) exclusive definition of successful HBP, including direct HBP and para-HBP; (3) effective parameters include QRS duration (QRSd), left ventricular ejection fraction (LVEF), New York Heart Association (NYHA), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left arterial dimension (LA), 6-minute walk distance (6MWD), and brain natriuretic peptide (BNP). The exclusion criteria included incomplete results; case reports, conference abstracts, reviews, editorials, or notes; missing specific parameters listed in the inclusion criteria; and animal experiments. The search strategy and exclusion criteria are presented in Figure 1.

Data extraction and quality assessment

Data extraction was performed independently by 2 researchers. The following data were extracted, including first author's name, study publication year, design [randomized control trial (RCT), cohort study, and observational study], patient characteristics (sex, age), sample size, setting (QRSd, LVEF), interventions, and follow-up period. In addition, indices including echocardiographic indices (LVESD, LVEDD, LA, MR) and cardiac functional capacity (NYHA functional class, 6MWD) were further selected with baseline and post-intervention data, and the difference of the selected indices between preHBP and postHBP were identified.

The methodological qualities of the RCTs were assessed by the Cochrane Collaboration bias risk tools for random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Observational trials or cohort studies were assessed using key study design components presented in the Newcastle-Ottawa scale.

Data synthesis and statistical analyses

Dichotomous variables were reported as proportions, and continuous variables were primarily presented as mean±standard deviation. The standard mean differences (SMD) with 95% confidence intervals for the indices were plotted as forest plots. Publication bias risk was estimated using funnel plot and Egger's test. Pooled analyses were implemented through fixed-effect models, whereas random-effect models were applied when significant heterogeneity was established across studies. Heterogeneity between studies was assessed using the Q statistic, and its extent was calculated by the I^2 test to determine if variability between studies resulted from heterogeneity or chance. The effect of each study on the overall therapeutic effect was assessed by sensitivity analysis using the leave-one-out approach. Meta-analyses were performed using Stata soft-

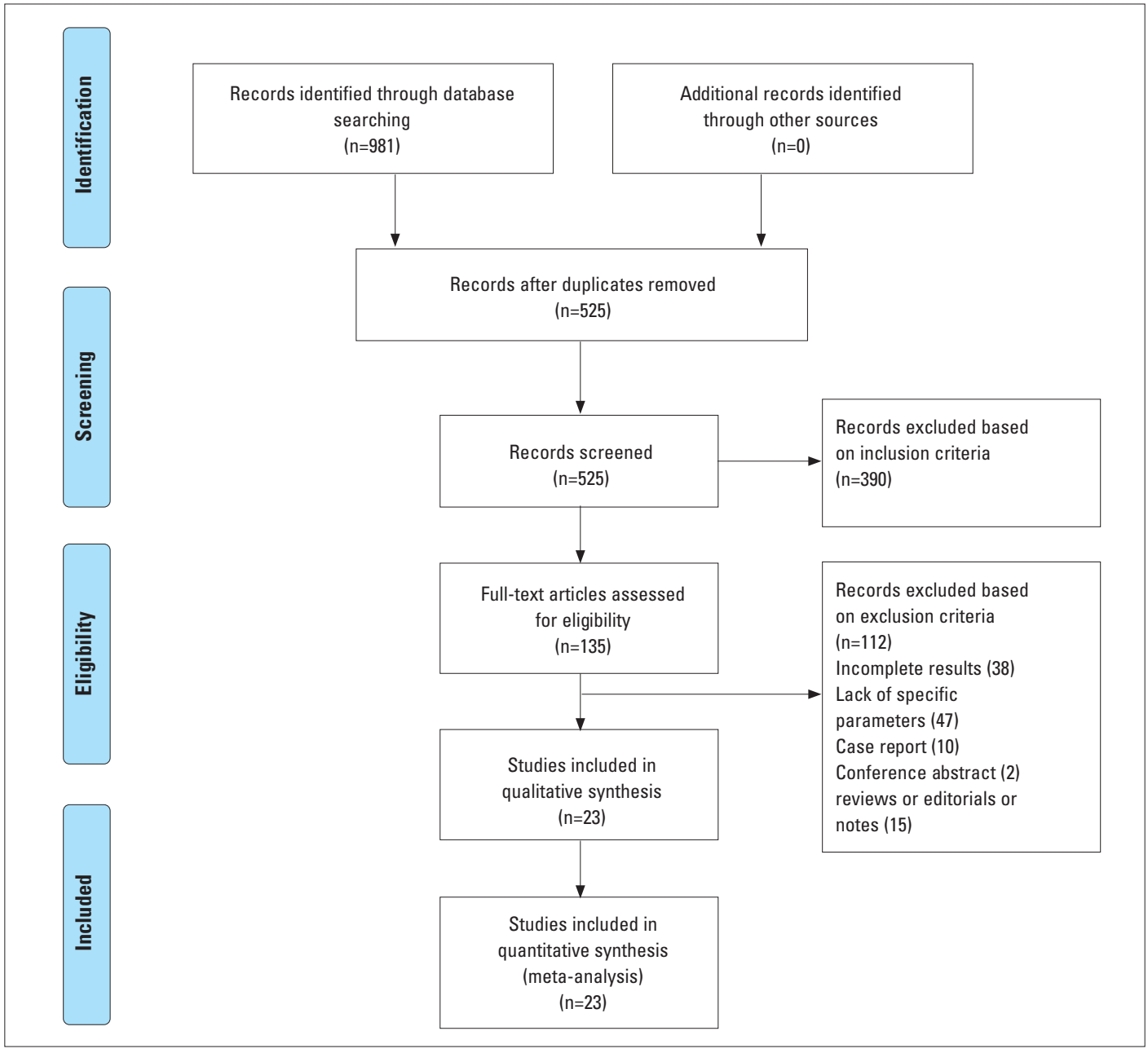

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram showing detailed study selection process

ware 11.0 and GraphPad Prism 6.01. Pearson and Spearman correlations were used as appropriate according to the Shapiro-Wilk test to decide if the data were normally distributed.

Results

Baseline characteristics of eligible studies

After using keywords to search across different databases, a total of 981 articles ranging from 2000 to 2020 was retrieved. After carefully analyzing each individual literature, 23 satisfied studies were included for meta-analysis (Fig. 1). The successful rate of HBP was 83.64% (772/923) based on the 23 valid studies. In those studies, there were 400 patients from a total of 574 patients with wide QRS duration (69.69%) (QRSd >120 ms), and 452 patients from 565 patients showing reduced LVEF (88.86%) (LVEF <50%). The baseline characteristics and discrepancy of preHBP and postHBP are displayed in Table 1 and Figure 2.

Evaluation of ECG and echocardiographic characteristics

A typical transition of ECG morphology was measured after the implantation of HBP. Paced QRS duration was reported in 21 studies, including 574 patients. The overall paced QRSd was significantly shorter than the baseline (116.84±17.32 ms vs. 147.73±19.46 ms, p<0.001) (Table 2). Among those patients, QRSd

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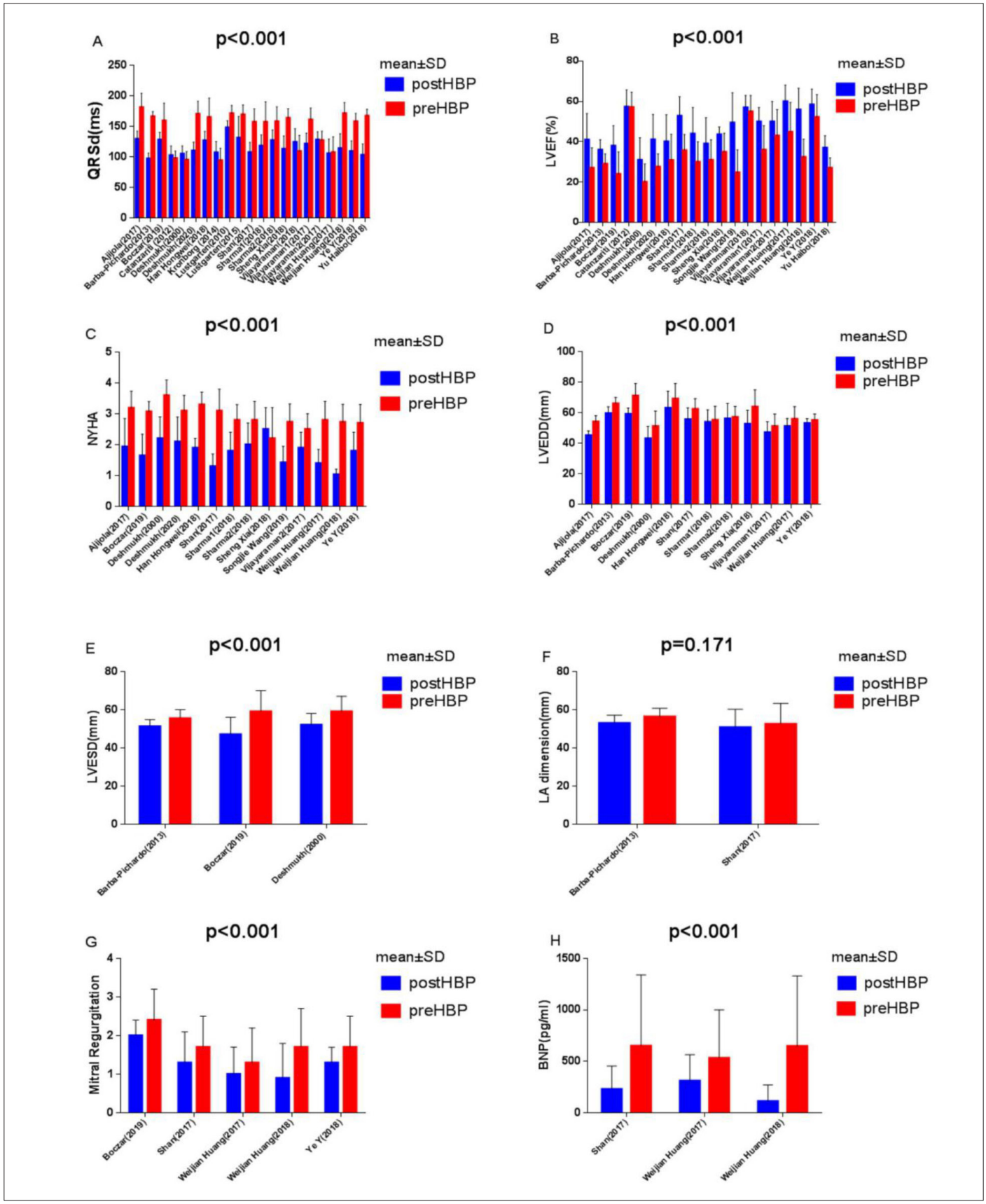

Figure 2. Comparison between postHBP and preHBP: (a) QRS duration; (b) left ventricular ejection fraction; (c) New York Heart Association; (d) left ventricular end-diastolic diameter; (e) left ventricular end-systolic diameter; (f) left arterial dimension; (g) mitral regurgitation; (h) brain natriuretic peptide

Table 1. Characteristics of included studies

First Author (year) refs	Study design	Sex (M/F)	Age (years, mean ± SD)	Patients (n, FU/total)	Settings	Interventions	FU (M or Y, mean ± SD)	Indices
Ajijola et al., 2017 (14)	Retrospective	12/4	62±18	16/21	QRSd>120 ms LVEF<40%	HBP	12 M	QRSd, LVEF, NYHA, LVEDD
Barba-Pichardo et al., 2013 (15)	Prospective	10/6	67.56±5.81	9/16	QRSd>120 ms LVEF<40%	HBP	31.33±21.45 M	QRSd, LVEF, LVEDD, LVESD, LA
Boczar et al., 2019 (16)	Cohort study	11/3	67.35±10	13/14	QRSd>120 ms LVEF<40%	CRT-D+HBP, ICD+HBP, ICD/CRT-D to ICD+HBP	14.4 M	QRSd, LVEF, NYHA, LVEDD, LVESD, MR
Catanzariti et al., 2012 (17)	Cohort study	16/10	71.6±8.8	26	QRSd<120 ms LVEF>50%	RVAP, HBP	34.6±11 M	QRSd, LVEF
Deshmukh et al., 2000 (18)	Retrospective	NR	69±10	12/18	QRSd<120 ms LVEF<40%	DHBP	23.4±8.3 M	QRSd, LVEF, NYHA, LVEDD, LVESD
Deshmukh et al., 2020 (19)	Retrospective	14/7	70.7±9.9	21	QRSd>120 ms LVEF<40%	HBP	29 M	QRSd, LVEF, NYHA
Han et al., 2018 (20)	Retrospective	17/5	62.1±11.2	14/22	QRSd>120 ms LVEF<40%	HBP	18.6±10.7 M	QRSd, LVEF, NYHA, LVEDD, 6MWD
Kronborg et al., 2014 (21)	RCT	30/8	66.5±10, 67.8±10	38	QRSd>120 ms LVEF≥50%	RVSP, HBP	HBP 12 M, RVSP 12 M	QRSd, LVEF
Lustgarten et al., 2010 (22)	Cohort study	6/4	68.67 (52.62,80.46)*	10	QRSd>120 ms	BiVP, DHBP	NR	QRSd
Lustgarten et al., 2015 (23)	RCT	NR	NR	12/21	QRSd>120ms LVEF<40%	BiVP,HBP	HBP 6 M+BiVP 6 M	QRSd, 6MWT
Moriña-Vázquez et al., 2020 (24)	Prospective	NR	66	36/48	QRSd>120ms LVEF<40%	p-HBP	1 M	QRSd, LVEF
Shan et al., 2018 (25)	Prospective	9/11	70.6±12.9	16/18	QRSd>120 ms LVEF<40%	HBP	36.2±14.2 M	QRSd, LVEF, NYHA, LVEDD, LA, MR
Sharma et al. 1, 2018 (26)	Retrospective	74/32	71±12	95/106	QRSd>120 ms LVEF<40%	Primary HBP, Rescue HBP	14 M	QRSd, LVEF, NYHA
Sharma et al. 2, 2018 (27)	Retrospective	33/6	72±10	37/39	QRSd>120 ms LVEF<40%	Primary HBP, Rescue HBP	15±23 M	QRSd, LVEF, NYHA, LVEDD
Sheng et al., 2018 (28)	Retrospective	62/26	67.6±11.4	88/105	QRSd>120 ms LVEF<40%	HBP	15 M	QRSd, LVEF, NYHA, LVEDD
Wang et al., 2019 (29)	Retrospective	64/22	67.75±9.98	52/86	QRSd<120 ms LVEF<40%	HBP	3.05 M	LVEF, NYHA
Vijayaraman et al., 2018 (30)	Case control study	NR	72±14, 76±11	98, 75/94	QRSd<120 ms LVEF<50%	RVP, HBP	5 Y	QRSd, LVEF
Vijayaraman et al. 1, 2017 (31)	Retrospective	13/7	74±14	20	QRSd>120 ms LVEF<40%	HBP, GC	70±24 M	QRSd, LVEF, LVEDD
Vijayaraman et al. 2, 2017 (32)	Retrospective	19/23	74±11	40/42	QRSd>120 ms LVEF<45%	HBP	19±14 M	QRSd, LVEF, NYHA
Huang et al., 2017 (33)	Prospective	26/16	72.8±8.3	42/52	QRSd<120 ms LVEF<45%	HBP	21.1±9.3 (median 20) M	QRSd, LVEF, NYHA, LVEDD, MR
Huang et al., 2019 (34)	Prospective	43/31	69.6±9.2	72/74	QRSd<120 ms LVEF<40%	HBP	3 Y	QRSd, LVEF, NYHA, MR
Ye et al., 2018 (35)	Prospective	9/3	70.8±8.9	12/14	QRSd>120 ms LVEF>50%	HBP	14.8±12.4 M	QRSd, LVEF, NYHA, LVEDD, MR
Yu et al., 2018 (36)	Observational	10/8	67.5±9.3	16/18	QRSd>120 ms LVEF<40%	HBP	1 M	QRSd, LVEF

*: M [P25, P75]
QRSd - QRS duration; LVEF - left ventricular ejection fraction; HBP - His bundle pacing; NYHA - New York Heart Association; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-systolic diameter; LA - left arterial dimension; 6MWD - 6-minute walk distance; MR - mitral regurgitation

Anatol J Cardiol 2021; 25: 845-57
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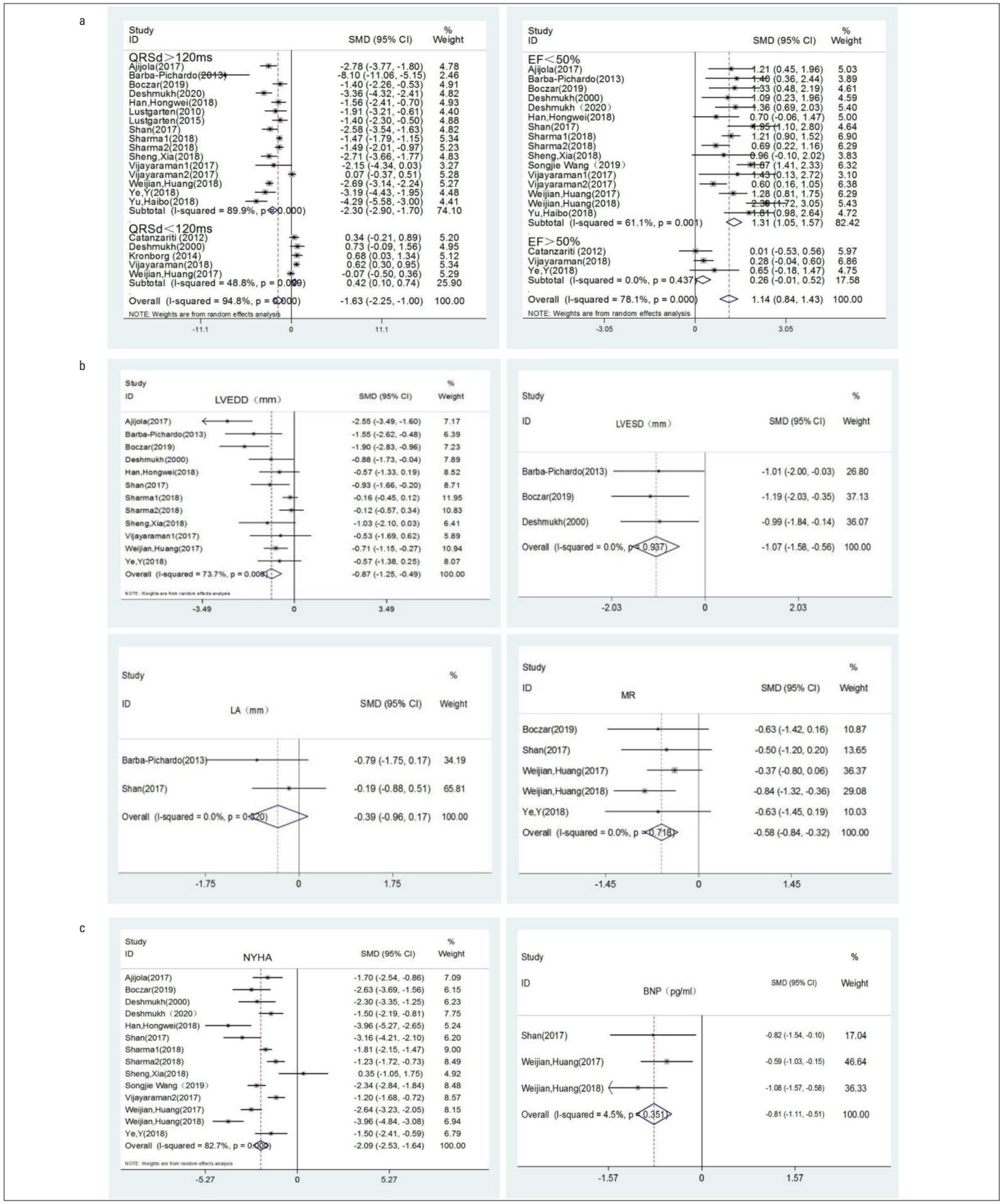

Figure 3. a) Subgroup analysis of forest plot showing changes between post- and preHBP for QRS duration and left ventricular ejection fraction. b) Forest plot showing changes between post and pre-HBP for left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left arterial dimension, mitral regurgitation. c) Forest plot showing changes between post and pre His bundle pacing BP for New York Heart Association and brain natriuretic peptide

Table 2. Overall calculated parameters of all the patients included in this analysis

Parameters	Q value	I^2 value (%)	*P*-value	SMD	95% CI	Z value	*P*-value
QRSd (ms)	386.92	94.8	0.000	-1.626	-2.254, -0.998	5.08	0.000
EF (%)	82.35	78.1	0.000	1.136	0.838, 1.434	7.47	0.000
NYHA	74.99	82.7	0.000	-2.088	-2.535, -1.641	9.15	0.000
LVEDD (mm)	41.84	73.7	0.000	-0.871	-1.253, -0.489	4.47	0.000
LVESD (mm)	0.13	0.0	0.937	-1.072	-1.584, -0.560	4.11	0.000
MR	2.10	0.0	0.718	-0.580	-0.841, -0.320	4.37	0.000
BNP (pg/mL)	2.09	4.5	0.351	-0.804	-1.106, -0.509	5.30	0.000
LA (mm)	0.99	0.0	0.32	-0.394	-0.957,0.170	1.37	0.171

BNP - brain natriuretic peptic; EF - ejection fraction; QRSd - QRS duration; LVEF - left ventricular ejection fraction; NYHA - New York Heart Association; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-systolic diameter; LA - left arterial dimension; MR - mitral regurgitation

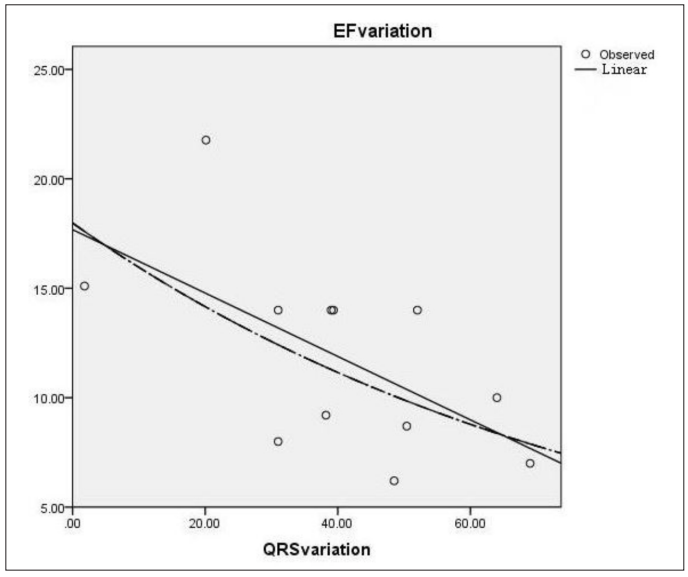

Figure 4. Fitting curve using 11 regression models to explore the relationship between left ventricular ejection fraction and QRS duration changes

>120 ms at baseline was reported in 17 studies containing 400 patients. Subgroup analysis showed that there was significant difference in paced QRSd within baseline QRSd >120 ms (SMD 2.30; 95% CI 2.90–1.70), whereas limited difference was observed within the QRSd <120 ms (SMD 0.42; 95% CI 0.10–0.74) as shown in Figure 3a.

Echocardiographic characteristics

LVEF was reported in 19 studies, including 565 patients. Impressively, notable improvements of LVEF were identified within postHBP than in preHBP (46.40±9.64% vs. 34.87±9.62%, p<0.001). The subgroup analysis of the same group showed similar results as for LVpEF and LVrEF (SMD 0.26; 95% CI 0.01–0.52 vs. SMD 1.31; 95% CI 1.05–1.57) (Fig. 3a, Table 2). Structural cardiac changes observed through the echocardiogram were characterized as LVEDD, LVESD, MR, and LA. Interestingly, apart from LA showing limited improvement (SMD 0.39; 95% CI 0.96–0.17), the rest of echocardiographic structural parameters indicated excellent recovery within the postHBP group, and the specific values of LVEDD (SMD 0.87; 95% CI 1.25–0.49), LVESD (SMD 1.07; 95% CI 1.58–0.56), and MR (SMD 0.58; 95% CI 84–0.32) are shown in Figure 3b.

Evaluation of cardiac function

A total of 402 patients from 14 studies successfully received HBP treatment, correlating to NYHA functional class. Of these, 399 patients were followed up after the treatment. The results showed that after HBP treatment, NYHA improved significantly from 2.90±0.57 at baseline to 1.78±0.58 (SMD 2.09; 95% CI 2.53–1.64, p<0.001). BNP reported in 3 studies (25, 33, 34), reduced from 609.33±613.77 pg/ml to 216.6±212.8 pg/ml. MWD demonstrated increasing trends within postHBP (398.5±45 m) than in preHBP (248.5±57 m). However, the result was inconclusive because of the limited data reported (Fig. 3c) (20, 23).

Correlation and regression analyses

Potential correlation between difference values of functional capacity and MR indices were similar to normal distributions, which were calculated using Pearson correlation. Intriguingly, no significant correlation between difference values of improvements was identified, and the specific values were QRS and NYHA, r=0.104, p=0.775; QRS and LVEDD, r=0.010, p=0.977; LVEF and NYHA, r=0.463, p=0.178; LVEF and LVEDD, r=–0.246, p=0.466; NYHA and LVEDD, r=–0.125, p=0.730. Meanwhile, if studies deviated from the data (25, 34) presented on scatter plots were excluded, possible correlation between LVEF and QRSd (r=–0.602, p=0.039) was demonstrated. Curve fitting for 11 models was selected, and the linear regression model was chosen as the applicable mode according to the statistical results (R2=36.2%, p=0.039) (Table 3). The regression equation was (Fig. 4).

Analysis of sensitivity and quality assessment

Sensitivity analysis suggested that studies (30, 34) showed that QRSd (30, 35), LVEF (36), and LVEDD were heterogeneous.

Anatol J Cardiol 2021; 25: 845-57
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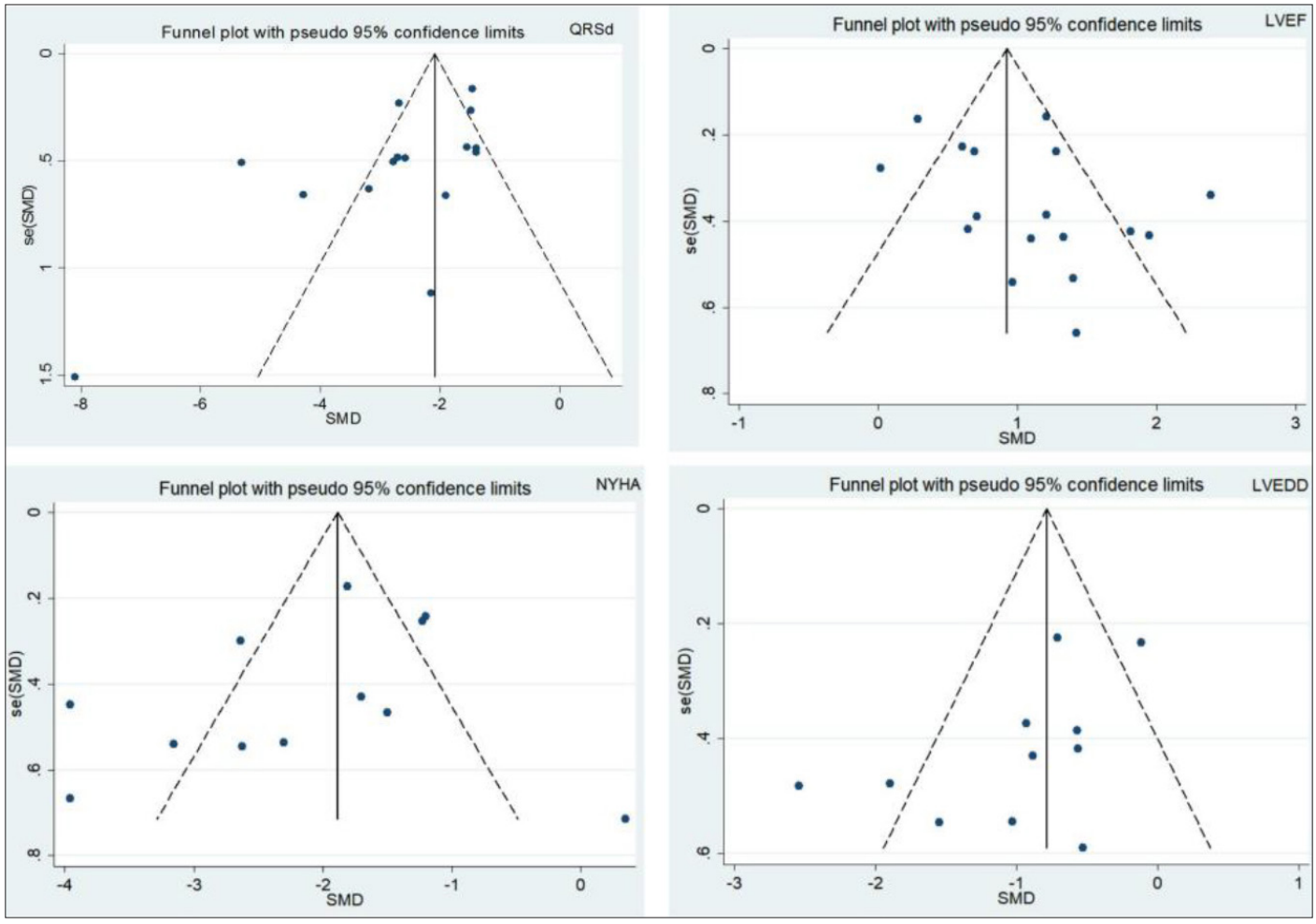

Figure 5. Funnel plot estimating publication bias for changes of main parameters following QRS duration, left ventricular ejection fraction, New York Heart Association, left ventricular end-diastolic diameter

Table 3. Model summary and parameter estimates in analyzing relation of LVEF and QRSd

Model summary and parameter estimates
Dependent variable: Ejection fraction variation

	Model summary					Parameter estimates	
Equation	**R square**	**F**	**df1**	**df2**	**Sig.**	**Constant**	**b1**
Linear	.362	5.671	1	10	.039	17.678	-.145
Compound	.351	5.405	1	10	.042	17.979	.988
Growth	.351	5.405	1	10	.042	2.889	-.012
Exponential	.351	5.405	1	10	.042	17.979	-.012

The independent variable is QRS variation.

However, the difference between the parameters diminished if one of included studies was excluded. Two randomized controlled trials (21, 23) were assessed separately because of their limited quantities but excellent data quality. Twenty-one observational studies were assessed by the Newcastle-Ottawa quality assessment (Table 4). No significant publication bias was revealed either by Egger's test with all the p values >0.05 or the vertical funnel plot in Figure 5.

Discussion

A novel method for pacing through the His bundle site was discovered in canines by Scherlag for the first time in 1967 and applied to human patients in 1970 (37). Since then, the theory of physiologic pacing method had been intensively studied, and the procedural strategy for HBP has been optimized constantly. In 2000, Deshmukh et al. (18), for the first time, performed perma-

Table 4. Study population and quality assessment of included non-RCT

First Author	Study population	Selection	Comparability	Outcome
Ajijola et al., 2017 (14)	Patients who had indications for CRT (bundle-branch block with QRS >120 ms, NYHA functional class II–IV, EF <35%) over a 2-year period (2014–2016) at 2 academic centers were included.	★★★★	★	★★★
Barba-Pichardo et al., 2013 (15)	A population with refractory heart failure derived for CRT and internal cardioverter defibrillator insertion. Of these, patients in whom LV stimulation via the coronary sinus was not achievable and DHBP obtained left bundle branch block disappearance were included.	★★★	★	★★
Boczar et al., 2019 (16)	Patients with permanent AF, HF, BBB with QRS complex width >130 ms, and impaired LVEF underwent implantation of ICD/CRT systems with HBP.	★★★★	★★	★★★
Catanzariti et al., 2012 (17)	Patients who received both an HBP lead and an RVAP lead, as backup, all devices were programmed to obtain HBP. Patients without an implanted apical right ventricular lead, those with major comorbidities, and those who did not attend follow-up visits at our center were excluded from the analysis.	★★★★	★★	★★★
Deshmukh et al., 2000 (18)	Patients who had a history of chronic AF, dilated cardiomyopathy, and normal activation (i.e., QRS ≤120 ms) were screened for permanent DHBP using an electrophysiology catheter.	★★★	★	★★★
Deshmukh et al., 2020 (19)	Patients who had sequential HBP and left ventricular pacing were identified by reviewing all the patients with follow-up within 5 years with a Select Secure pacing lead	★★★	★	★★★
Han et al., 2018 (20)	We retrospectively collected data from 22 patients with CHF who underwent pacemaker implantation with permanent HBP in Wuhan Asia Heart Hospital from April 2013 to January 2018	★★★★	★	★★★
Lustgarten et al., 2010 (22)	Patients who presented at the Fletcher Allen Healthcare for de novo BiV–ICD therapy from March 2008 to March 2009	★★★★	★★	★★★
Moriña-Vázquez et al., 2020 (24)	Patients with HF and baseline LVEF <35%, LBBB (QRS >130 ms and QS or rS pattern in lead V1), and CRT indication from January 2018 to February 2019	★★★★	★	★★★
Shan et al., 2017 (25)	Patients with symptomatic heart failure who had undergone RV pacing or BiV pacing and considered for upgrade to pHBP.	★★★	★	★★★
Sharma et al. 1, 2018 (26)	Patients who failed or were eligible for BVP based on current recommendations. All patients had NYHA class II to IV heart failure symptoms and a baseline LVEF ≤50%.	★★★★	★★	★★★
Sharma et al. 2, 2018 (27)	Patients with reduced LVEF, RBBB, QRS duration ≥120 ms, and NYHA class II to IV heart failure.	★★★	★★	★★★
Sheng et al., 2018 (28)	We consecutively recruited 105 patients scheduled to have permanent HBP implantation from January 2013 to December 2017 at Sir Run Run Shaw Hospital, Zhejiang University College of Medicine.	★★★★	★	★★★
Wang et al., 2019 (29)	Patients with persistent AF and HF who had indications for ICD implantation were enrolled.	★★★★	★	★★★
Vijayaraman et al., 2018 (30)	Patients underwent new permanent pacemaker implantation for the treatment of bradycardia during the period of January 2011 to October 2011, according to current AHA/ACC/HRS guidelines at Geisinger Health System were included in the study.	★★★★	★★	★★★
Vijayaraman et al. 1, 2017 (31)	Patients who had undergone successful permanent HBP between the years 2006 and 2014 and presented subsequently for GC due to routine battery depletion.	★★★★	★★	★★★
Vijayaraman et al. 2, 2017 (32)	Patients who had undergone attempts at permanent HBP and AVNA either simultaneously or at different times.	★★★★	★	★★★
Huang et al., 2017 (33)	Patients who underwent AVNA and had longstanding persistent AF with rate control and received a pacemaker or implanted cardioverter-defibrillator or CRT device.	★★★★	★	★★★

Anatol J Cardiol 2021; 25: 845-57
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Table 4. Study population and quality assessment of included non-RCT (Continue)

First Author	Study population	Selection	Comparability	Outcome
Huang et al., 2019 (34)	The inclusion criteria: (1) an ECG showing a wide QRS complex (>130 ms) and the morphology of typical complete LBBB; (2) patients had heart failure with NYHA Class II–IV symptoms; (3) patients were indicated for CRT or pacing therapy; (4) patients were at least 18 years old and not pregnant. Excluded: (1) non-specific intraventricular conduction delay or RBBB; (2) patients with a life expectancy <12 months; (3) patients declining guideline-indicated pacing therapy.	★★★★	★	★★★
Ye et al., 2018 (35)	Patients with permanent AF and RVP, who were referred for pulse generator change. Patients with RVP burden >40% were included.	★★★★	★	★★★
Yu et al., 2018 (36)	Patients with CRT indications and HPCD from March 2016 to December 2017 in General Hospital of Shenyang Military Region were enrolled in this study.	★★★★	★	★★★

A maximum of 4 stars (★★★★) for selection, 2 (★★) for comparability, and 3 (★★★) for outcome
CRT - cardiac resynchronization therapy; HPCD - His Purkinje conduction disease; AF - atrial fibrillation; RVP - right ventricular pacing; RBBB - right bundle branch block; QRSd - QRS duration; LVEF - left ventricular ejection fraction; HBP - His bundle pacing; NYHA - New York Heart Association; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-systolic diameter; LA - left arterial dimension; LBBB - left bundle branch block; AVNA - atrioventricular nodal ablation; HF - heart failure; ICD - implantable cardioverter-defibrillator; DHBP - direct HBP; PHBP - permanent HBP

nent HBP on 14 patients. Impressively, 12 patients showed improved cardiac function after the treatment, despite 2 recorded deaths in the 8th and 36th months, indicating the clinical applicability and therapeutic effect of HBP.

Non-physiological dyssynchronous ventricular activation induced by the conventional pacing method, especially right ventricular apical pacing, accelerates the progression of ventricular remodeling, developing pacing-induced cardiomyopathy (38, 39). Although biventrivular pacing has been demonstrated as an effective way to lower the incidence of cardiac events, it is only applicable to patients with LVEF <50% and atrioventricular block (40). Compared with conventional pacing methods including right ventricular pacing (RVP) and biventricular pacing (BiVP), HBP impulses Purkinje fiber directly instead of activating ventricular myocytes. In addition, by capturing the His bundle stimulus when depolarizing, HBP can accelerate the conduction speed through the ventricular electromechanical synchronization, unlike the pathway via myocardium (41). Moreover, direct HBP has been demonstrated as an alternative and effective method for CRT when the conventional method of left ventricular resynchronization via the coronary sinus fails (15).

In this study, we summarized the comprehensive characteristics of patients undergoing HBP and systematically evaluated the effect of postHBP compared with preHBP. The follow-up time involved in the analysis ranged from 1 month to 5 years. Most data were concluded from single-center observational studies, and only 2 RCTs (21, 23) were included, which may limit the data quality of this meta-analysis owing to the strict inclusion criteria for RCTs. However, our aim was to describe the electrocardiogram and echocardiographic characteristics of the preHBP and postHBP. In addition, the comparison between conventional pacing parameters (RVP, BiVP, etc.) and HBP parameters was out of the scope of this study.

A total of 923 patients were enrolled in the 23 studies selected. HBP was successfully performed on 772 patients with a success rate of 83.64%, which is close to the success rate of 84.8% reported by Zanon et al. (42). In Zanon et al.'s (42) meta-analysis, 1,438 patients from 26 studies were included, and the clinical outcomes including pacing thresholds, complications, and mortality were excluded from this study. Among 923 patients included in this study, 400 (69.69%) in 574 patients presented with wide QRS duration (QRSd >120 ms), and 452 (88.86%) in 565 patients had a reduced LVEF (<50%). Average QRSd at baseline was 147.73±19.46 ms and was 116.84±17.32 ms at follow-up, which was an average 31 ms drop in QRSd ($p<0.001$). Subgroup analysis further revealed that HBP could significantly rectify the conduction system, particularly within wide QRS complex (QRSd >120 ms). Sipahi et al. (43) reported that only patients with LBBB and systolic heart failure benefited from CRT, whereas patients with wide QRS did not benefit from CRT because of the conduction abnormalities. Tang et al. (44) reported that patients with LBBB had a better outcome than non-LBBB patients, and a potential correlation between benefit and QRS morphology was identified. We hypothesize this correlation between QRS and therapeutic effect can be a great clinical indicator to select suitable patients for HBP.

Average LVEF at baseline was 34.87±9.62%, which increased to 46.4±9.64% at follow-up, an average 11.5% increase in LVEF ($p<0.001$). Subgroup analysis demonstrated that LV contraction of postHBP improved significantly regardless of the baseline LVEF level, indicating patients with or without cardiac dysfunction can benefit from HBP. However, only 3 studies (17, 30, 35) reported baseline LVEF >50%, and the lack of sufficient data may lead to inconclusive findings within this group. Therefore, further investigations and research are essential to provide additional information for conclusive result. The observed improvement based on echocardiogram in LVEDD, LVESD, and MR had been

confirmed. After the mean follow-up time of 19.4 months for 399 patients, the NYHA functional class improved significantly from 2.90±0.57 at baseline to 1.78±0.58 (p<0.001) after the treatment. Interestingly, although there is a lack of sufficient data to accurately reflect the result, 6MWD data presented in limited studies showed significant increase. Together, this is evidence that restoration of ventricular electromechanical synchronization and reverse remodeling could contribute to improvement in cardiac function after HBP treatment.

Curve fitting indicated that different value of LVEF improved similar to that of QRS, with increasing of the QRSd difference value. LVEF showed a declining trend (r=–0.602, p=0.039), whereas the different value correlation of the rest of the indices were not determined. Wang et al. (45) demonstrated a linear correlation between LVEF and LVEDD, but with a low r value. Although there was no direct correlation between LVEF and LVEDD and other indices in this study, we believe that further studies with increased number of patients can reveal the potential connection between these indices.

Existing problems with the use of HBP including higher threshold, increased risk of failure to capture, prolonged procedural and fluoroscopy times, as well as reduced battery longevity (12, 46) have limited the wider use of HBP in current clinical setting. However, significant technological development has been made for implanting His bundle pacemakers. The high success rate (83.64%) demonstrates that technological advancement can overcome the limitation of HBP, which may revolutionize the field of cardiac pacing.

Study limitations

This study had certain limitations. Limited quantitative experiment of life condition evaluations, such as 6MWD, were conducted with the selected studies; and inadequate results were included to demonstrate the associated complex adverse events. Furthermore, the endpoint events and complications of HBP were overlooked by this study. Therefore, because of the limited analysis of NYHA and 6MWD, the potential drawbacks of HBP drawn from the study could be a false positive.

Conclusion

HBP could reduce the QRS duration and improve cardiac function significantly in most patients. Although drawbacks were identified during long-term follow-up, HBP is still a promising approach owing to its applicability to a wider patient group with improved therapeutic effect, resulting in the improvement of life quality.

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