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Review Article

Effectiveness of bundle of His pacing for cardiac resynchronization therapy in patients with heart failure combined with wide QRS complex: a meta-analysis

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Abstract: Objective: To evaluate systematically the feasibility and effectiveness of His Bundle Pacing (HBP) for cardiac resynchronization therapy. Methods: A comprehensive search was conducted in PubMed, EMbase, WOS, Cochrane Library, Medline, and SinoMed for studies published between December 2003 and December 2023. Primary clinical outcomes included implantation success, QRS wave duration, pacing threshold, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), New York Heart Association (NYHA) cardiac function class, and complications. Data were extracted and summarized, and meta-analysis was performed by Revman 5.3 software. Results: Fourteen studies involving a total of 555 patients were included. The overall success rate for HBP implantation was 83.2% (462/555). Compared to baseline values, QRS duration was significantly reduced (MD=48.29, 95% CI: 45.20 to 51.38, P<0.01, I^2=85%), LVEF was significantly increased (MD=-13.62, 95% CI: -15.46 to -11.79, P<0.01, I^2=74%), LVEDD was smaller (MD=5.83, 95% CI: 4.44-7.22, P<0.01, I^2=78.2%), and NYHA showed significant improvement (MD=1.24, 95% CI: 1.14-1.35, P<0.01, I^2=97.2%). At follow-up, pacing threshold increased (MD=-0.28, 95% CI: -0.43 to -0.12, P<0.01, I^2=0%), and pacing impedance decreased (MD=51.62, 95% CI: 23.67 to 79.56, P<0.01, I^2=56%).Conclusion: HBP is effective for cardiac resynchronization therapy. HBP significantly reduces QRS duration and improves LVEF in heart failure patients.

Keywords: His bundle pacing, cardiac resynchronization therapy, wide QRS wave, ventricular pacing, meta-analysis

Introduction

Restoration of cardiac electrical synchronization through physiological conduction by His bundle pacing (HBP) has emerged as a viable alternative to traditional cardiac resynchronization therapy (CRT). By activating the His-Purkinje conduction system, HBP generates a physiologic ventricular activation sequence, which may be more advantageous for enhancing cardiac function and reversing ventricular remodeling. Several prospective randomized studies have shown that Biventricular Pacing (BVP) improves the quality of life in patients with heart failure, enhances NYHA functional class, improves left ventricular ejection fraction (LVEF) and reverses ventricular remodeling. In addition, BVP is a well-established treatment for patients undergoing atrioventricular node ablation who require more than 40% right ventricular pacing. However, it is estimated that 30%-40% of patients receiving biventricular pacing have CRT non-response and no clinical benefit [1].

CRT is currently used to treat severe ventricular systolic dysfunction (LVEF≤35%) with a wide QRS complex (>120 ms), aiming to improve quality of life and reduce heart failure readmissions, and decrease all-cause mortality. Conventional CRT (i.e., biventricular pacing) involves placing pacing electrodes in the right ventricle and outside the left ventricle through the coronary venous branches, or surgically attaching electrodes to the left ventricular epicardium, with both electrodes pacing simultaneously to achieve electro-mechanical synchronization of the ventricles. However, traditional

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CRT faces several challenges: about 30% of patients do not respond to CRT, surgical failure rates are high (due to factors like the absence of an ideal target vein, electrode dislocation or malposition, phrenic nerve stimulation, and elevated electrode threshold), and the procedure is costly. In addition, the complexity of traditional CRT surgery and long learning curve limit its widespread application.

HBP has emerged as an alternative, involving the placement of a pacing electrode at the His bundle site to directly capture the heart's intrinsic conduction system. This method maximizes the electro-mechanical synchronization of the ventricles, reduces QRS duration, and offers a more physiologic pacing mode. Early studies have shown that HBP can achieve resynchronization therapy in patients with heart failure, improve cardiac function, and reduce the hospitalization and mortality rate of heart failure. The latest guidelines recommend HBP as a class IIa treatment option for patients with heart failure with low LVEF and those requiring long-term biventricular pacing.

Presently, HBP is being evaluated as a frontline treatment strategy for CRT, although the existing data have yet to be consolidated to quantify its benefits, risks, and key metrics [2]. Therefore, we conducted a systematic review and meta-analysis to assess the available literature on HBP for cardiac resynchronization therapy.

Methods

Inclusion and exclusion criteria

The included literature comprised clinical trials examining the use of HBP in adult patients (>18 years) with heart failure and a wide QRS complex. The following outcomes were observed: (1) QRS duration; (2) LVEF; (3) pacing threshold; (4) pacing impedance; (5) New York Heart Association (NYHA) functional class; (6) left ventricular end-diastolic diameter (LVEDD); (7) left ventricular end-systolic diameter (LVESD); (8) mitral valve regurgitation; (9) tricuspid valve regurgitation; (10) and B type natriuretic peptide (BNP) levels. At a minimum, the primary endpoints (1) QRS duration and (2) LVEF of the included studies were required to provide detailed data. The meta-analysis was registered with INPLASY (International Platform of Registered Systematic Review and Meta-Analysis Protocols, registration number 576388).

Literature search and retrieval strategies

(1) Literature search: a systematic search was conducted in PubMed, EMbase, WOS, Cochrane Library, Medline, and SinoMed from December 2003 to December 2023. The search included all English-language studies on HBP for heart failure; (2) The search formula: the search strategy used was: (HBP OR Root Para hisian pacing) AND (Cardiac Resynchronization Therapy OR CRT). This formula was designed to capture publications containing the following keywords: atrioventricular bundle pacing, HBP, His bundle pacing, and terms related to His pacing, such as "Bundle of His [Mesh]" and "Cardiac Pacing, Artificial [Mesh]".

Literature screening, data extraction, and quality assessment

Literature was screened according to strict inclusion and exclusion criteria. Two cardiovascular physicians specializing in cardiovascular medicine independently reviewed the retrieved literature, excluded studies that clearly not meeting the inclusion criteria, and assessed the full texts of studies that might meet the criteria to determine whether they qualified for inclusion. In case of disagreement, a third senior cardiovascular physician was consulted to assist in the adjudication process. The two evaluators extracted the relevant data using a predefined data extraction form, including: (1) Study details: title, first author, and year of publication; (2) Baseline characteristics: sample size, gender distribution, mean age, implantation success rate, follow-up duration; (3) Outcome measures and pertinent specific data. The methodologic quality of the included studies was independently assessed using the Newcastle Ottawa Scale (NOS) criteria established by P. Juni et al. [3]. Studies were classified based on their total NOS scores: score ≥7 indicated high quality, 4-6 indicated moderate quality, and ≤3 indicated low quality studies (**Table 1** and **Figure 1**).

Statistical analysis

The meta-analysis was performed using the Cochrane Review Manager software (RevMan 5.3). Continuous outcomes were quantified as

Table 1. General information of the included studies

Study	Study design	Intervention	Major Indications	Comparison	Implantation success rate (%)
Barba-Pichardo (2013) [5]	Prospective cohort study	Implantation of permanent HBP	CRT and ICD failed	Single-arm study	56.3
Ajijola (2017) [1]	Retrospective cohort study	Implantation of permanent HBP	CRT	Single-arm study	76.2
Huang (2018) [16]	Prospective cohort study	Implantation of permanent HBP	CRT	Single-arm study	75.7
Shan (2017) [26]	Prospective cohort study	Implantation of permanent HBP	CRT and non-responsive PICM	Single-arm study	88.9
Sharma (2018) [25]	Retrospective cohort study	Implantation of permanent HBP	CRT	Single-arm study	94.9
Sharma (2017) [27]	Retrospective cohort study	Implantation of permanent HBP	CRT	Single-arm study	89.6
Boczar (2019) [12]	Prospective cohort study	Implantation of permanent HBP	ICD/CRT	Single-arm study	None
Vijayaraman (2018) [28]	Retrospective cohort study	Implantation of permanent HBP	CRT	Single-arm study	90.9
Ye (2018) [24]	Prospective cohort study	Implantation of permanent HBP	CRT (Upgrade to CRT)	Single-arm study	85.7
Lustgarten (2010) [13]	Retrospective cohort study	Implantation of permanent HBP	CRT	Single-arm study	96.6
Upadhyay (2019) [6]	Prospective cohort study	Implantation of permanent HBP	CRT	Single-arm study	None
Deshmukh (2004) [17]	Prospective cohort study	Implantation of permanent HBP	HF AF AVB	Single-arm study	72.2
Huang (2017) [29]	Retrospective cohort study	Implantation of permanent HBP	HF AF is performed with AVNA	Single-arm study	80.8
Vijayaraman (2017) [30]	Prospective cohort study	Implantation of permanent HBP	AF is performed with AVNA	Single-arm study	95.2

LVEF, Left Ventricular Ejection Fraction; LVEDD, Left Ventricular End-Diastolic Diameter; LVESD, Left Ventricular End-Systolic Diameter; NYHA, New York Heart Association; HBP, His Bundle Pacing; CRT, Cardiac Resynchronization Therapy; AF, Atrial Fibrillation; AVNA, Atrioventricular Node Ablation; AVB, Atrioventricular Block; BNP, B-Type Natriuretic Peptide; ICD, Implantable Cardioverter Defibrillator; PICM, Pacemaker Induced Cardiomyopathy; HF, Heart Failure.

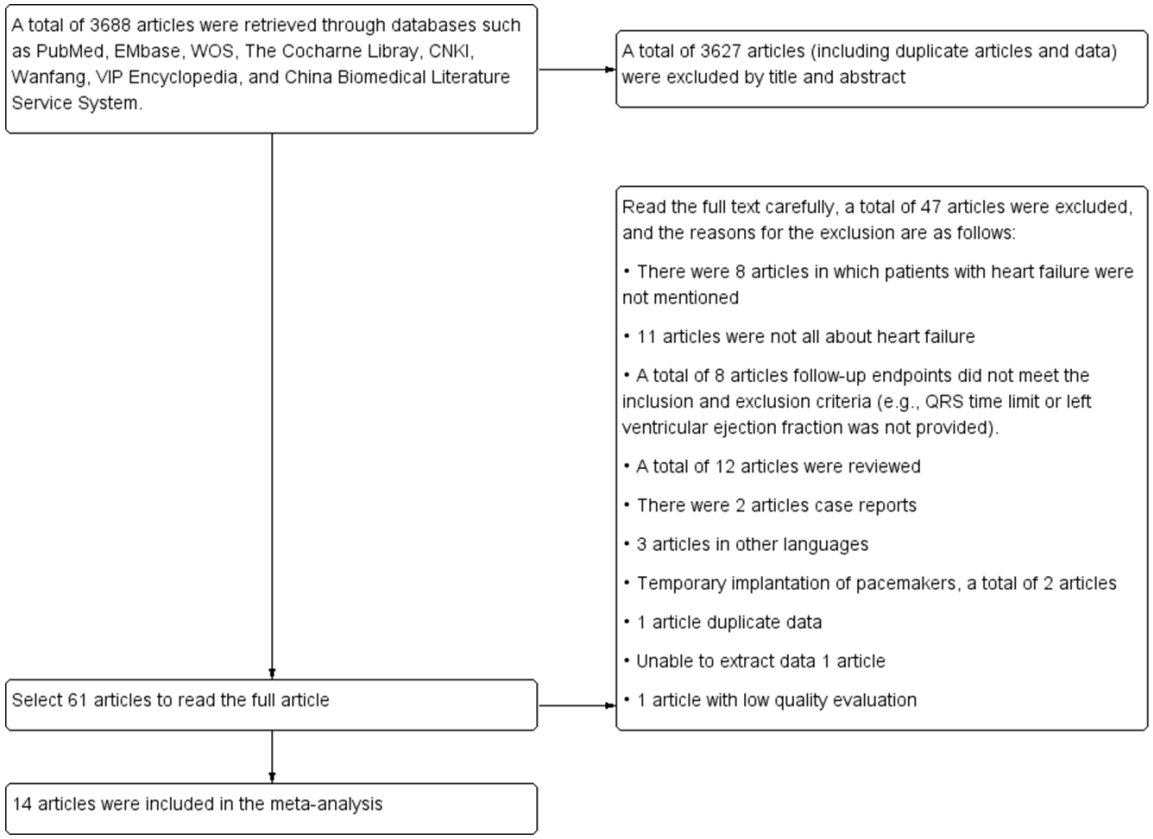

Figure 1. Literature screening flowchart.

standardized mean differences (SMDs) with 95% Confidence Intervals (CIs). Heterogeneity was assessed by calculating I^2, with values exceeding 50% indicating substantial heterogeneity. A fixed-effects model was employed to pool study results when heterogeneity was minimal; otherwise, a random-effects model was used. Potential publication bias was qualitatively examined using funnel plots within RevMan software. Funnel plot asymmetry, indicated by significant divergence in CI distribution, prompted further analysis using Stata software. Begg's and Egger's tests were also performed to determine the presence of publication bias.

Results

Literature inclusion and basic information

A total of 3,688 studies were screened through keyword searches, and 14 studies that met the inclusion criteria were finally included in this study (**Figure 1**). The overall implantation success rate was 83.2% (462/555). Six of the studies focused on patients with CRT indications, CRT implantation failure, CRT nonresponse, and pacing-induced cardiomyopathy. One study focused on patients with atrial fibrillation requiring atrioventricular node ablation and a high percentage of ventricular pacing. Another study did not specify particular indications but included patients who met the criteria for class Ia pacemakers and had a cardiac function class of grade II-IV, as per the cardiac electrophysiology and pacing guidelines of the Chinese Medical Association. The quality of the included literature was evaluated using the NOS score, and general information of the included studies is shown in **Figures 2** and **3**.

ECG QRS time frame: Fourteen studies involving a total of 328 patients measured the QRS duration on electrocardiogram (ECG) at both baseline and follow-up. Compared to baseline, QRS duration was significantly shorter at follow-up (MD=48.29, 95% CI: 45.20 to 51.38, $P<0.01$, $I^2=85\%$). Subgroup analyses, stratified by study type (prospective vs retrospective), showed that the QRS durations at follow-up

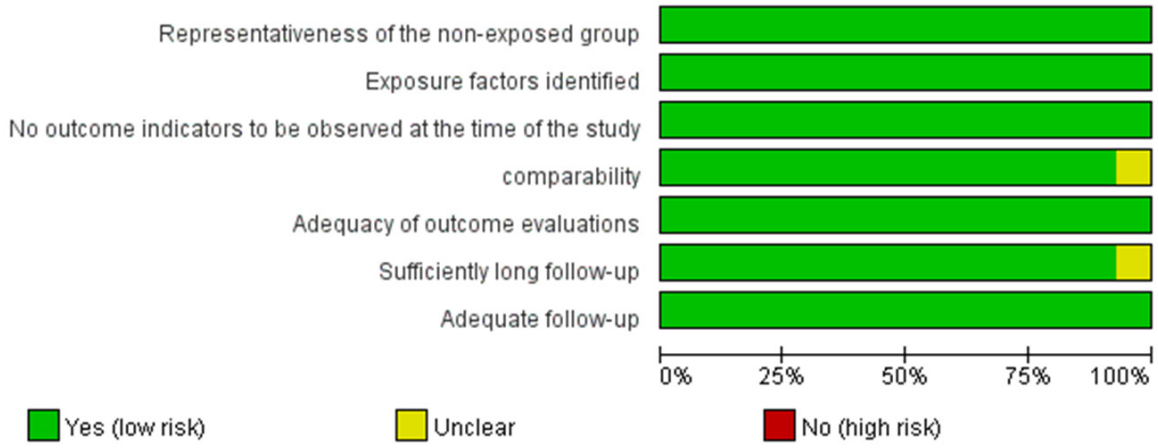

Figure 2. Risk of bias graph.

was significantly shorter compared to baseline values (prospective: MD=58.42, 95% CI: 53.52-63.32, P<0.01, I^2=84%; retrospective: MD=41.60, 95% CI: 37.61-45.58, P<0.01, I^2=74%) (**Figure 4**).

Echocardiographic correlation data: (1) LVEF (**Figure 5**): A total of 220 patients underwent LVEF measurement, and follow-up results showed a significant increase in LVEF compared to baseline (MD=-13.62, 95% CI: -15.46 - -11.79, P<0.01, I^2=74%). Subgroup analyses indicated that LVEF was significantly elevated at follow-up compared to baseline in both prospective and retrospective studies (prospective: MD=-15.06, 95% CI: -17.83 - -12.29, P<0.01, I^2=87%; retrospective: MD=-12.50, 95% CI: -14.95 - -10.05, P<0.01, and I^2=0%). (2) LVEDD (**Figure 6**) and LVESD (**Figure 7**): LVEDD measurement was performed in 165 patients, and LVEDD was significantly reduced at follow-up compared to baseline (MD=5.83, 95% CI: 4.44-7.22, P<0.01, I^2=78.2%). Subgroup analysis showed that both prospective and retrospective studies showed a significant reduction in LVEDD at follow-up compared to baseline levels (prospective: MD=8.17, 95% CI: 5.61-10.72, P<0.01, I^2=46%; retrospective: MD=4.84, 95% CI: 3.18-6.50, P=0.02, I^2=90%). LVESD measurements were performed in 23 patients, and the difference in LVESD at follow-up (MD=5.83, 95% CI: 2.43-9.24, P=0.05, I^2=70%) was not significant compared to baseline. (3) Degree of mitral regurgitation (**Figure 8**) and tricuspid regurgitation (**Figure 9**): The degree of mitral regurgitation and the degree of tricuspid regurgitation were measured in 66 and 52 patients, respectively. Compared to baseline, the degree of mitral regurgitation (MD=0.56, 95% CI: 0.28-0.84, P<0.01, I^2=0) and the degree of tricuspid regurgitation (MD=0.34, 95% CI: 0.02-0.65, P=0.04, I^2=0) were significantly reduced.

Pacing threshold versus pacing impedance: (1) Pacing threshold (**Figure 10**): A total of 240 patients underwent pacing threshold measurements, and the pacing threshold increased at follow-up compared to baseline (MD=-0.28, 95% CI: -0.43 - -0.12, P<0.01, I^2=0%). Subgroup analyses showed that pacing thresholds increased significantly at follow-up compared to baseline levels in both prospective and retrospective studies (prospective: MD=-0.33, 95% CI: -0.55 - -0.10, P<0.01, I^2=0%; retrospective: MD=-0.24, 95% CI: -0.45 - -0.026, P=0.03, I^2=49%). (2) Bundle-branch block correction threshold (**Figure 11**): The measurements were conducted in 163 patients, showing an increase in the bundle-branch block correction threshold at follow-up compared to baseline (MD=-0.32, 95% CI: -0.58 - -0.06, P=0.01, I^2=0%). Subgroup analyses showed a significant increase in the threshold at follow-up compared to baseline levels in the prospective study (MD=-0.42, 95% CI: -0.77 - -0.07, P=0.02, I^2=36%); however, in the retrospective study, the increase was not significant (MD=-0.20, 95% CI: -0.58-0.18, P=0.30, I^2=0%). (3) Pacing impedance (**Figure 12**): Measurements were conducted in 120 patients, with a significant decrease observed at follow-up (MD=51.62, 95% CI: 23.67-79.56, P<0.01, I^2=56%).

Other indicators of evaluation of cardiac function: (1) NYHA functional class (**Figure 13**): A

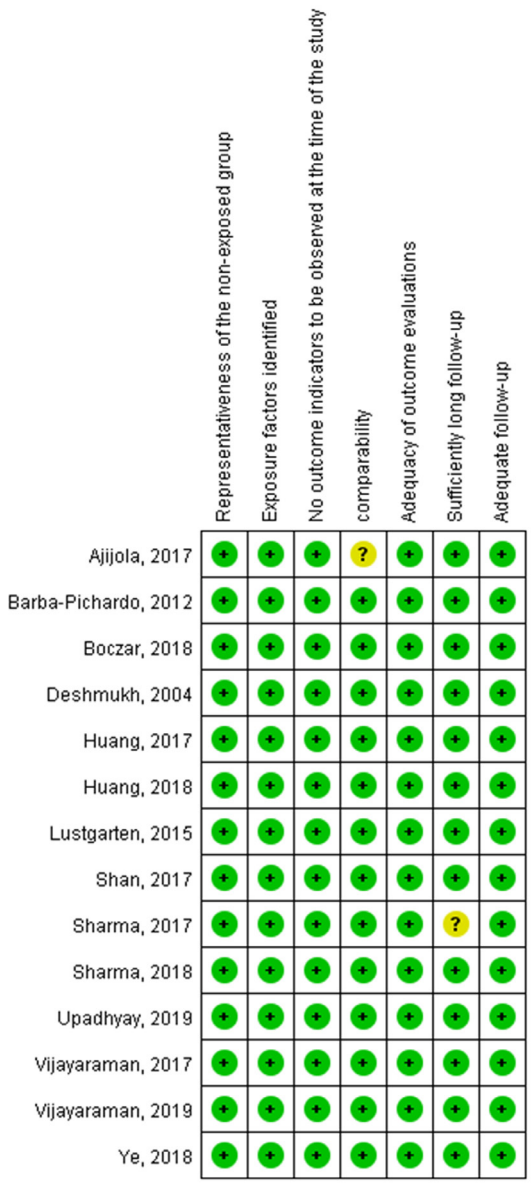

Figure 3. Risk of bias summary.

total of 217 patients were assessed for NYHA functional class, and the results showed significant improvement at follow-up compared to baseline (MD=1.24, 95% CI: 1.14-1.35, P< 0.01, I^2=97.2%). Subgroup analyses showed that both prospective and retrospective studies showed significant decreases in NYHA class (prospective: MD=1.67, 95% CI: 1.50-1.84, P<0.01, I^2=0%; retrospective: MD=1.01, 95% CI: 0.89-1.14, P<0.01, I^2=63%). (2) BNP (**Figure 14**): 52 patients, all in prospective studies, underwent BNP measurement, and BNP levels significantly decreased at follow-up compared to baseline (MD=501.29, 95% CI: 308.73-693.86, P<0.01, I^2=0%).

Publication bias

The literature included in this review comprised only published studies. Funnel plot analysis was performed for changes in QRS duration and LVEF in the included literature. The distribution of effect sizes was not completely symmetrical, suggesting potential publication bias for QRS duration. This was confirmed by Begg's and Egger's tests, with the funnel plot of QRS duration indicating possible publication bias (P=0.04). However, the funnel plot for LVEF did not show significant publication bias (P=0.229) (**Figure 15**).

Sensitivity analysis

A sensitivity analysis was carried out to assess the robustness of the results in relation to assumptions and methodologies. The analysis revealed that the meta-analysis results exhibited low sensitivity and high stability, indicating reliable findings.

Discussion

The eight studies included in this meta-analysis were of high quality, ensuring the reliability of the results. A total of 555 patients with heart failure and wide QRS wave complexes were treated with His Bundle Pacing (HBP), and short-term follow-up revealed significant improvement in intraventricular mechanical conduction synchronization, as well as heart function and structure. Notably, these improvements were accompanied by an increase in pacing thresholds, the threshold for bundle-branch block correction, and a decrease in pacing impedance. Heart failure with wide QRS wave complexes represents an advanced stage of cardiovascular disease. Compared to drug therapy alone, CRT has been shown to reduce mortality in patients with advanced heart failure; however, some patients still experience worsening symptoms and an increased incidence of atrial fibrillation (AF) [4-7]. According to the 2020 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure [8], patients with chronic AF and heart failure requiring a high percentage of ventricular pacing (>40%) are appropriate candidates for CRT.

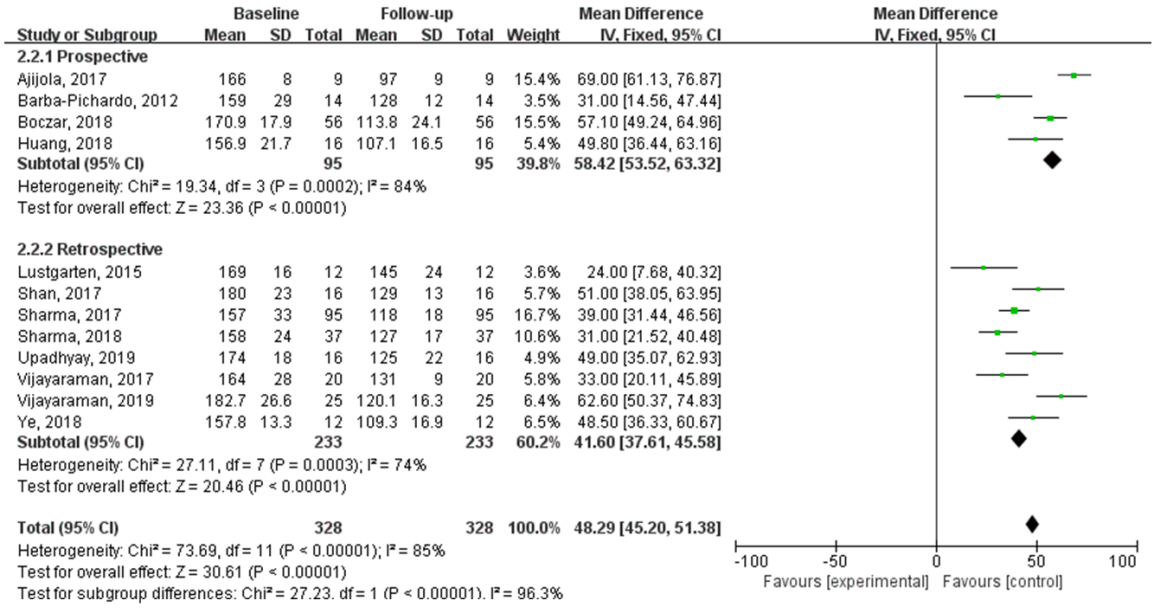

Figure 4. Meta-analysis of the effect of HBP on electrocardiogram QRS duration. HBP, His Bundle Pacing.

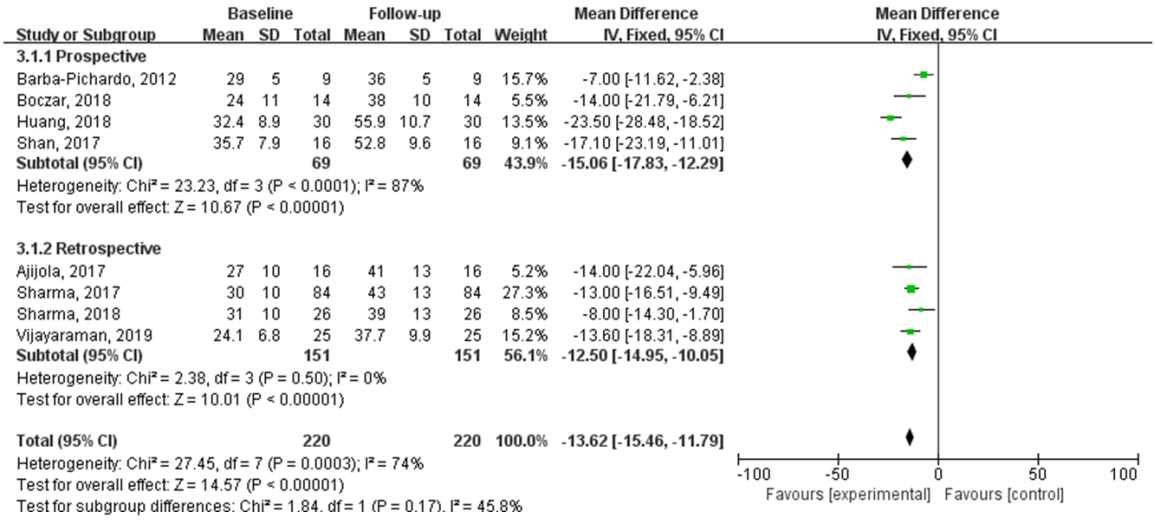

Figure 5. Meta-analysis of the effect of HBP on LVEF. HBP, His Bundle Pacing; LVEF, Left Ventricular Ejection Fraction.

Despite this, HBP offers a more physiologic alternative, addressing some of the limitations of CRT. Zanon et al. [9] further confirmed the efficacy and feasibility of HBP through a meta-analysis, demonstrating that HBP can significantly increase LVEF and improve cardiac function compared to both right ventricular pacing and biventricular pacing.

There are limited studies on HBP for the treatment of heart failure with wide QRS waves, so a meta-analysis was performed to assess its therapeutic efficacy more comprehensively. In this meta-analysis, QRS duration was measured in 328 patients, and the results indicated a significant reduction in QRS duration at follow-up compared to baseline, suggesting that HBP therapy effectively corrected cardiac electro-mechanical synchrony [10-12]. Lustgarten et al. [13] initially performed temporary HBP in 10 patients undergoing CRT implantation, and found that QRS duration was significantly shorter than those with self or biventricular pacing, with a shorter time required for HBP implanta-

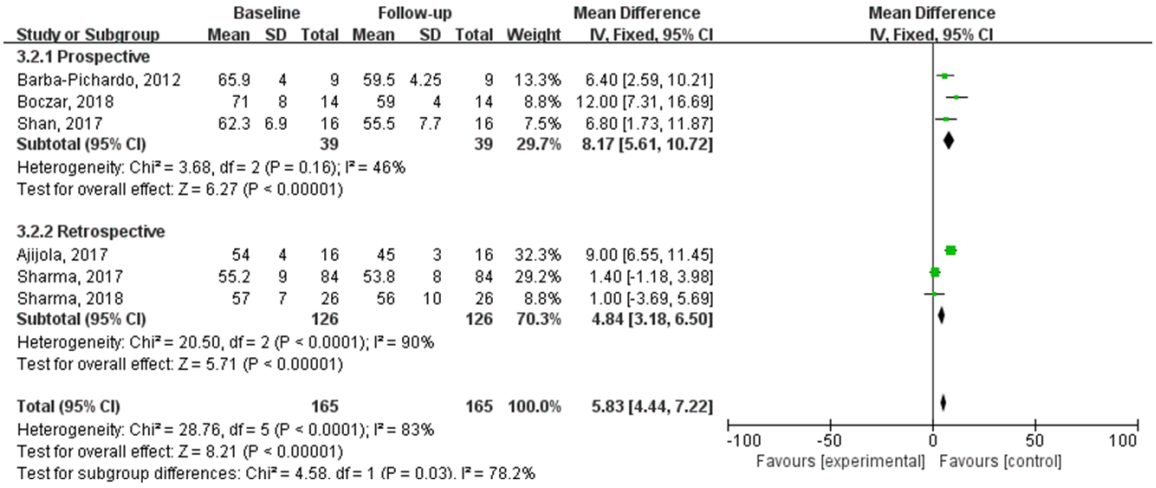

Figure 6. Meta-analysis of the effect of HBP on LVEDD. HBP, His Bundle Pacing; LVEDD, Left Ventricular End-Diastolic Diameter.

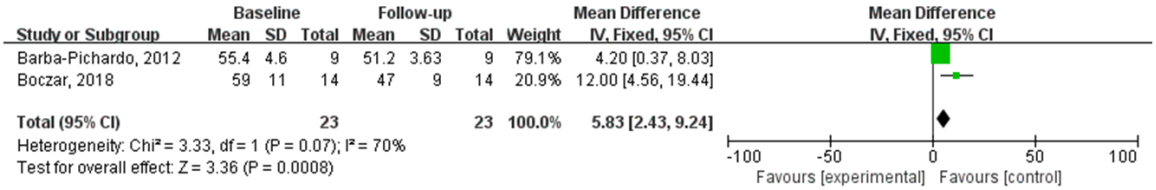

Figure 7. Meta-analysis of the effect of HBP on LVESD. HBP, His Bundle Pacing; LVESD, Left Ventricular End-Systolic Diameter.

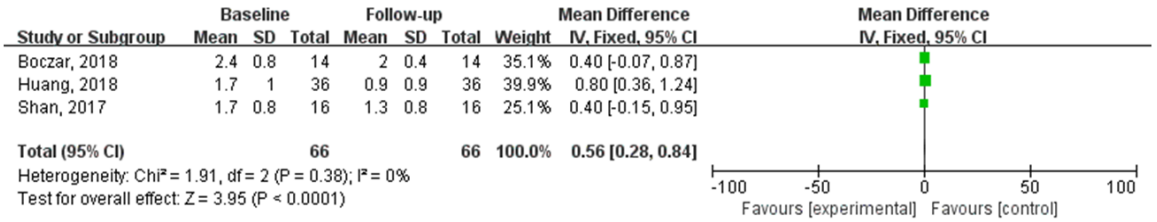

Figure 8. Meta-analysis of the effect of HBP on mitral regurgitation. HBP, His Bundle Pacing.

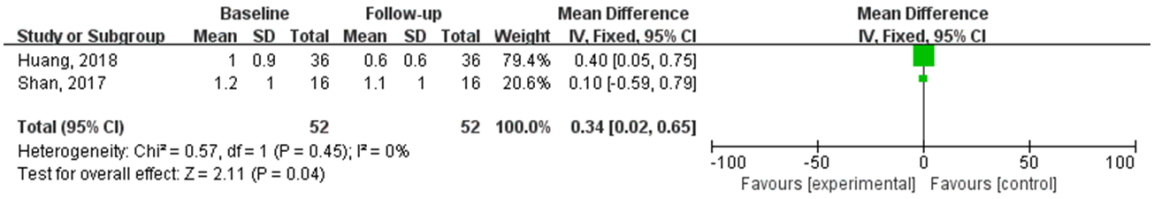

Figure 9. Meta-analysis of the effect of HBP on tricuspid regurgitation. HBP, His Bundle Pacing.

tion compared to left ventricle electrode lead implantation. Zhang et al. [14] evaluated left ventricle mechanical synchronization by applying phase analysis of resting nuclide myocardial imaging. Their findings demonstrated that HBP maintains normal electrical excitation sequence and mechanical synchronization in the left ventricle post-surgery. The HIS-SYNC study

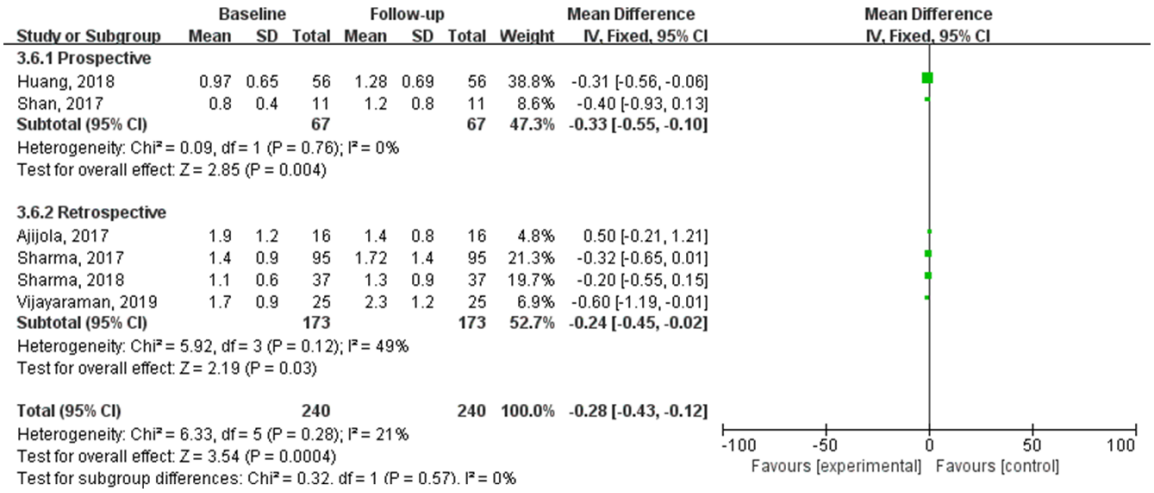

Figure 10. Meta-analysis of the effect of HBP on pacing threshold. HBP, His Bundle Pacing.

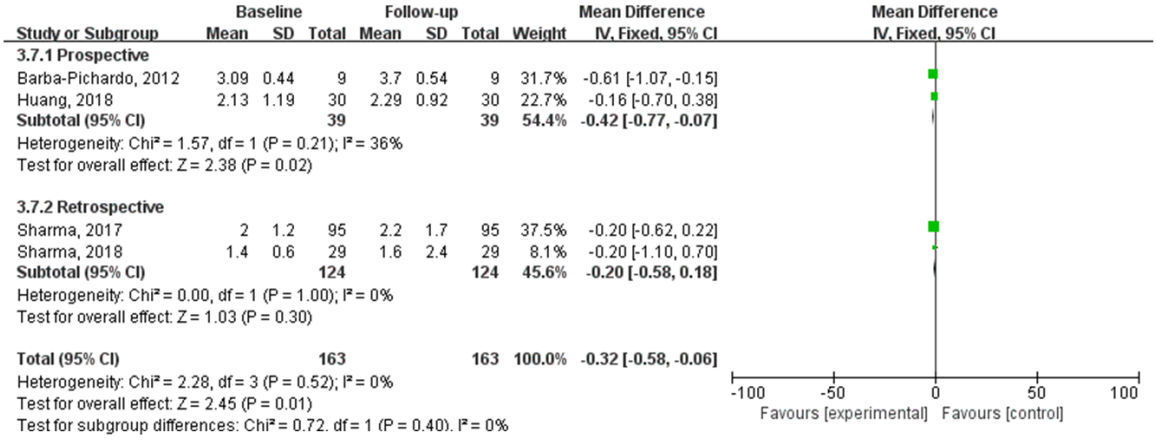

Figure 11. Meta-analysis of the effect of HBP on bundle-branch block correction threshold. HBP, His Bundle Pacing.

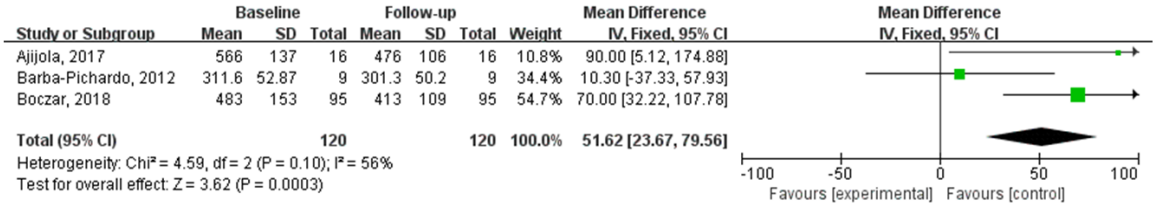

Figure 12. Meta-analysis of the effect of HBP on pacing impedance. HBP, His Bundle Pacing.

was the first randomized controlled trial comparing HBP with biventricular pacing, and the results showed that HBP offered better electrical synchronization and significantly improved cardiac function [15]. However, since the study did not provide detailed echocardiographic data, it was not included in this analysis. HBP is a pacing modality that mimics normal cardiac excitation and conduction [16]. Electrical impulses are conducted through the Hirshhorn-Purkinje fiber system, with a faster conduction rate than the myocardium, which maintains synchronized ventricular contractions to a greater extent, shortens the QRS duration, improves left ventricular function, and reduces the risk of postoperative death. Thus, HBP is

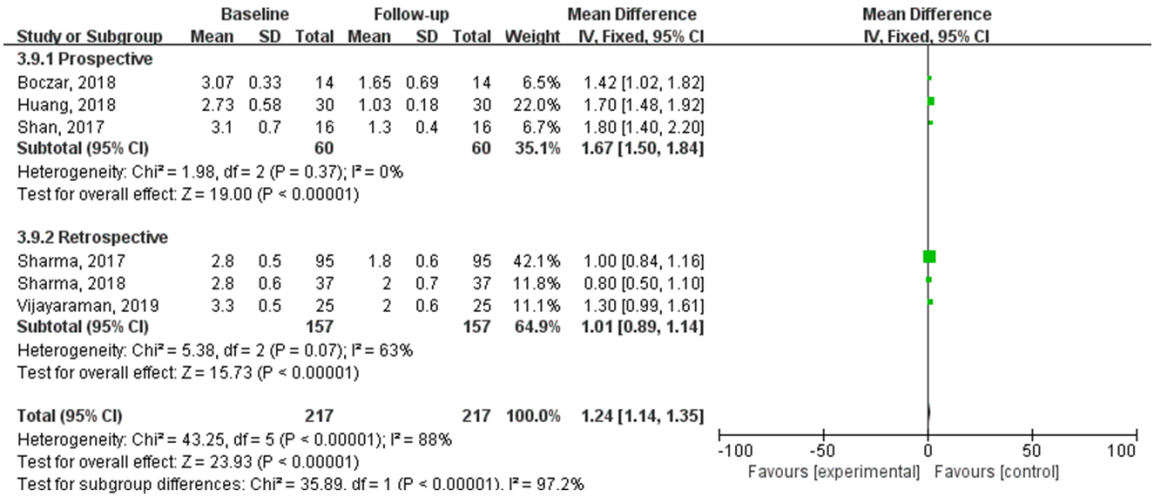

Figure 13. Meta-analysis of the effect of HBP on NYHA function classification. HBP, His Bundle Pacing; NYHA, New York Heart Association.

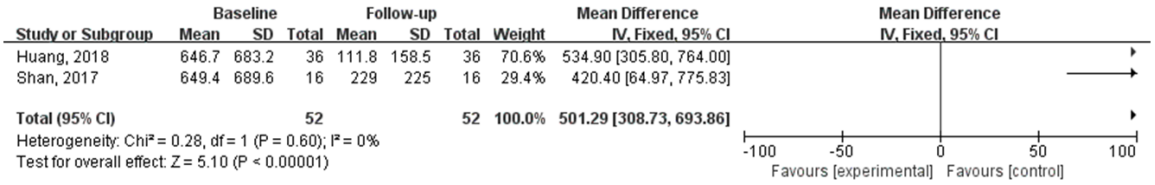

Figure 14. Meta-analysis of the effect of HBP on BNP level. HBP, His Bundle Pacing; BNP, B-Type Natriuretic Peptide.

considered more consistent with optimal physiologic pacing, offering advantages over traditional pacing techniques [17-21].

In the current meta-analysis, significant improvements were observed in LVEF, LVEDD, severity of both mitral and tricuspid regurgitation, NYHA functional classification, and BNP levels at follow-up compared to baseline. These changes indicate a notable enhancement in cardiac function among heart failure patients, likely resulting from the restoration of mechanical synchronization and reverse ventricular remodeling achieved through resynchronization therapy. Deshmukh et al. [17, 22] first reported on the combination of auriculoventricular node ablation and HBP in patients with atrial fibrillation, noting a significant reduction in LVEDD and a significant increase in LVEF in patients after pacing. Subsequent small-sample studies (54 patients included) supported these findings. Occhetta et al. [23] conducted a study with 16 patients who underwent AV node ablation and were randomized to either HBP or right ventricular apical pacing. The HBP group showed a more pronounced improvement in interventricular electro-mechanical delay compared to the right ventricular apical pacing group. Additionally, post-procedure improvements were seen in NYHA functional classification, quality of life scores, 6-minute walk test results, and the degree of mitral and tricuspid regurgitation showed significant enhancements when contrasted with pre-procedural values. Ye et al. [24] showed that compared to patients with LVEF>40%, patients with LVEF<40% who underwent HBP showed significant improvement in cardiac function.

The success rate of HBP implantation remains relatively low, primarily due to the unique anatomy of the Hitchcock's bundle, which makes precise localization challenging. Anatomical variations further complicate the procedure, requiring advanced technical skills from the operator, particularly in patients with enlarged atria, where the difficulty in locating the His bundle is even greater [12, 25]. The pacing threshold for HBP is typically high, and over time, fibrosis of surrounding tissues can lead to

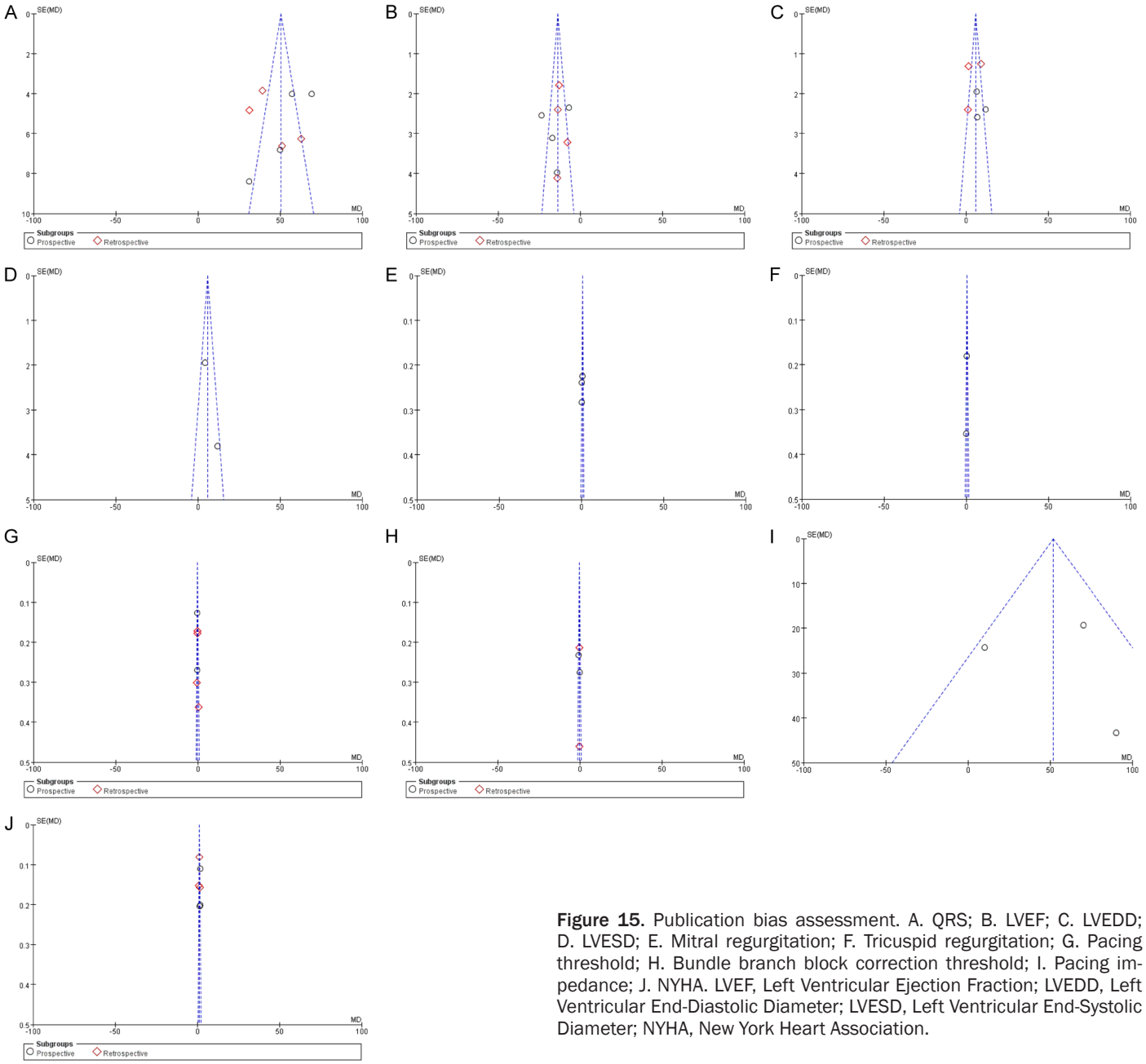

Figure 15. Publication bias assessment. A. QRS; B. LVEF; C. LVEDD; D. LVESD; E. Mitral regurgitation; F. Tricuspid regurgitation; G. Pacing threshold; H. Bundle branch block correction threshold; I. Pacing impedance; J. NYHA. LVEF, Left Ventricular Ejection Fraction; LVEDD, Left Ventricular End-Diastolic Diameter; LVESD, Left Ventricular End-Systolic Diameter; NYHA, New York Heart Association.

an increase in this threshold, thereby reducing the operational lifespan of the pacemaker. Consequently, the replacement rate within the first 5 years following HBP implementation is notably higher compared to that of right ventricular pacemakers. Specifically, the 5-year replacement rate for HBP is significantly elevated relative to right ventricular pacing systems. Owing to the anatomic characteristics of the His bundle, the sensing amplitude for HBP is often low, and the pacing threshold is higher. Additionally, the threshold for correcting bundle branch block via HBP is also elevated, contributing to greater power consumption and, ultimately, a shortened service life of the pulse generator [8]. The electrode placement near the tricuspid annulus further increases the risk of dislocation. Furthermore, HBP has been in clinical use for a limited duration, with a paucity of supporting evidence and a lack of data on long-term efficacy.

This meta-analysis evaluated the efficacy of HBP in the treatment of heart failure, providing valuable insight for future therapeutic strategies. However, the study has several limitations. The number of patients included was relatively small, and most studies were cohort-based with small sample sizes, which inherently limits their internal validity compared to randomized controlled trials. Additionally, data on the effect of HBP on outcomes were limited and yielded substantial heterogeneity. Furthermore, most studies only provided follow-up data on echocardiographic outcomes, and did not provide details related to rehospitalization rates due to heart failure, surgical complications, and so on.

In summary, HBP shows promise in shortening QRS duration, maintaining normal electrical activity, and significantly improving cardiac function in patients with heart failure, offering valuable guidance for clinical decision-making. However, since HBP remains in the early stages of investigation, large-scale randomized controlled trials are required to continuously monitor pacing thresholds, and impedance, and assess its long-term efficacy and safety.

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Disclosure of conflict of interest

None.

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