

Recent approaches to His-Purkinje system pacing

Li-Ting Cheng¹, Jun-Meng Zhang¹, Ze-Feng Wang¹, Hui-Kuan Gao², Yong-Quan Wu¹

¹Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China;

²Department of Cardiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China.

Abstract

Objective: Physiologic cardiac pacing is a novel technique which has been largely popularized in recent decades. His bundle pacing (HBP) has been long considered the most physiologic pacing method; however, with the widespread implementation of this method, its disadvantages have become apparent. In this context, left bundle branch pacing (LBBP)—directly engaged in the His-Purkinje system—has been foreseen as the best pacing method to mimic physiologic activation patterns. This review aimed to summarize recent approaches to physiologic cardiac pacing.

Data sources: This review included fully peer reviewed publications up to July 2018, found in the PubMed database using the keywords “His bundle branch pacing,” “right ventricular pacing,” and “physiologic pacing.”

Study selection: All selected articles were in English, with no restriction on study design.

Results: The HBP has been studied worldwide, and is currently considered the most physiologic pacing method. However, it has disadvantages, such as high pacing threshold, unsatisfactory sensing and long procedure times, among others. Although LBBP is theoretically superior to HBP, the clinical relevance of this difference remains under debate, as few large randomized clinical trials with LBBP have been published.

Conclusions: Although HBP indeed appears to be the most physiologic pacing method, it has certain shortcomings, such as high pacing threshold, difficult implantation due to specific anatomic features, and others. Further studies are required to clarify the clinical significance of LBBP.

Keywords: His-Purkinje pacing; His bundle pacing; Cardiac resynchronization therapy; Left bundle branch pacing

Introduction

Pacemaker techniques are part of regular therapeutic armamentarium for patients with syncope, sick sinus disease, atrioventricular block (AVB), neuromuscular disease, and even heart failure.^[1,2] Pacemaker implantation has a long history. Hyman was the very first to come up with the idea of “artificial pacemakers” in 1932, when he implanted a needle into the right atrium (RA) and created a heartbeat.^[3] In 1957, Weirich *et al*^[4] were the first to affix electrodes to the ventricular wall. Two years later, Furman and Schwedel^[5] introduced endocardial pacing, which was the foundation for percutaneous direct cardiac pacing techniques.

Views on pacemakers have evolved from being seen as electrical pumps to a technique capable of resynchronizing the heartbeat. To attain improved cardiac function and restore cardiac electrical conduction, pacemaker techniques have strived to elucidate the best method for

physiologic pacing. However, the optimal implantation sites for the electrodes have been objects of discussion for decades.^[6] His-Purkinje system pacing is currently considered the most physiologic pacing method, as the pacing lead is directly engaged in the conduction system and creates a narrow QRS wave similar to that of a normal heart beat. This study summarizes recent advancements in this field.

Anatomy of the cardiac conduction system

As seen in electro-mechanical activation, normal cardiac conduction begins in the sinoatrial node and then spreads to activate both the left and right atria through Bachman bundle and other internodal tracts. Then, the electrical excitation proceeds through the atrioventricular node (AVN), which delays the conduction to the ventricles and provides a time interval for this chamber to fill with blood. Then, a specialized fibered bundle in the RA, the His bundle (HB), drives the electrical force forward to activate ventricular muscle. Then, through the left and right bundle

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Correspondence to: Dr. Yong-Quan Wu, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China
E-Mail: wuyongquan67@163.com

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branches beneath the HB, the Purkinje network is activated, which assures synchronous myocyte contraction.^[7-9] Indeed, this physiologic activation pattern goes sequentially through the HB, the bundle branches, the Purkinje network, and the Purkinje ventricular myocardium to finally initiate the contraction of the ventricular myocardium.^[9]

Conventional right ventricular apex pacing

Pacing sites in the right ventricle

Since the inception of artificial pacemakers, multiple pacing sites have been studied. Electrodes have been placed in the right ventricular apex (RVA), the right ventricular septum (RVS), the right ventricular outflow tract, and others.^[6]

Because it is easily reached and stably fix, right ventricular apex pacing (RVAP) is the most frequently used approach for permanent cardiac pacing. Current evidence suggests RVAP significantly improves cardiac function.^[10]

RVAP decreases heart function in the long term

Although pacemakers are life saving, they do have adverse effects. With the lengthening of the follow-up periods in studies, a growing number of problems have been found. Bellmann *et al*^[11] found patients with RVAP and a high pacing percentage were prone to developing new-onset heart failure. Pacing-induced cardiomyopathy has been related to structural and functional changes induced by the implantation of pacemakers.

RVAP and desynchronized pacing patterns

What causes pacing-induced cardiomyopathy? By comparing the pacing at the outflow site with that at the inflow site of the right ventricle, Kawakami *et al*^[12] discovered QRS duration may be closely related to the pacing site. This has fueled current research to find an ideal leading position for minimizing the impairment of left ventricle function during pacing.

A 15-year retrospective study indicated pacing-induced cardiomyopathy was correlated with paced QRS duration.^[13] Several studies have also concluded paced QRS duration is a predictor of pacing-induced cardiomyopathy. Khurshid *et al*^[14] demonstrated male patients with wider QRS duration were at high risk of pacing-induced cardiomyopathy.^[14] In a latter study, they found pacing-induced cardiomyopathy could be reversed by cardiac resynchronization therapy (CRT), and confirmed prolonged QRS duration to be a predictor for pacing-induced cardiomyopathy and myocardial fibrosis.^[15]

A brief summary of RVAP

Although RVAP can achieve electro-mechanical activation, it is by far inferior to physiologic activation patterns. Changes in hemodynamics and QRS duration due to the desynchronized contraction caused by these pacemakers have been identified as important factors for pacing-induced cardiomyopathy.^[16]

The ideal ventricular pacing site remains elusive. As previous studies have highlighted, the quintessence of pacemakers is

to mimic normal heartbeats, which indispensably need narrow QRS waves. HB pacing (HBP) has been notoriously promoted in recent years. This pacing method is directly engaged in the His-Purkinje system, with an obvious improvement in both hemodynamics and clinical outcomes.^[17,18] In 2000, Deshmukh *et al*^[19] pioneered the use of HBP in humans. Since then, HBP has been accepted as the most physiologic pacing method worldwide.

His bundle pacing

Definition of HBP

While HBP has been widely implemented, its definition remains unclear to some extent. In its inception in 2000, Deshmukh *et al*^[19] defined HBP to have the following characteristics: (1) HBP directly activates the His-Purkinje system directly as corroborated in electrocardiography (ECG) monitoring with narrow QRS complexes; (2) The pace-ventricular interval is almost equal to the His-ventricular interval; (3) It has a lower pacing output. QRS widening is absent during HBP. As per the recommendations published by Vijayaraman *et al*,^[20] HBP has been defined as an HV > 35 mV.

Nevertheless, an overwhelming majority were confused by the concept, with numerous studies focusing on the wrong terms. According to the pacing sites, HBP can be divided into selective HBP (S-HBP) and non-selective HBP (NS-HBP), also known as direct HBP and para-HBP, respectively [Figure 1]. S-HBP has been defined to have the following features: (1) The stimulated QRS (S-QRS) onset interval is equal to the native His-QRS onset interval; (2) Ventricular pacing is stimulated by the His-purkinje system instead of ventricular muscle; (3) Paced QRS morphology is the same as native QRS morphology; (4) To a certain degree, S-HBP can develop into NS-HBP at a higher threshold.^[20] In contrast to S-HBP, NS-HBP can cause pseudo-excitation patterns in 12-lead surface ECG and possibly originate prolonged QRS intervals.^[21]

A study by Occhetta *et al*^[22] found that compared with RVAP, NS-HBP could improve New York Heart Association (NYHA) classification, exercise tolerance, and quality of life. Furthermore, Upadhyay *et al*^[23] proposed NS-HBP to be useful enough, as it can activate sufficient biventricular myocardium.

However, several studies have criticized the validity of NS-HBP, especially in patients with widened QRS and indications for CRT. Thus, researchers such as Ellenbogen^[24] hold S-HBP to be true physiologic pacing. Further studies are required to separately verify the clinical value of S-HBP and NS-HBP.

Advantages of HBP

Management of intra-His bundle block and sick sinus syndrome with HBP

Paced QRS duration is the audit standard for physiologic pacing, while electro-mechanical activation can be evaluated with the NYHA functional classification and quantification of the ejection fraction (EF). Most studies utilize these indexes. In a study by Ye *et al*,^[25] 12 patients'

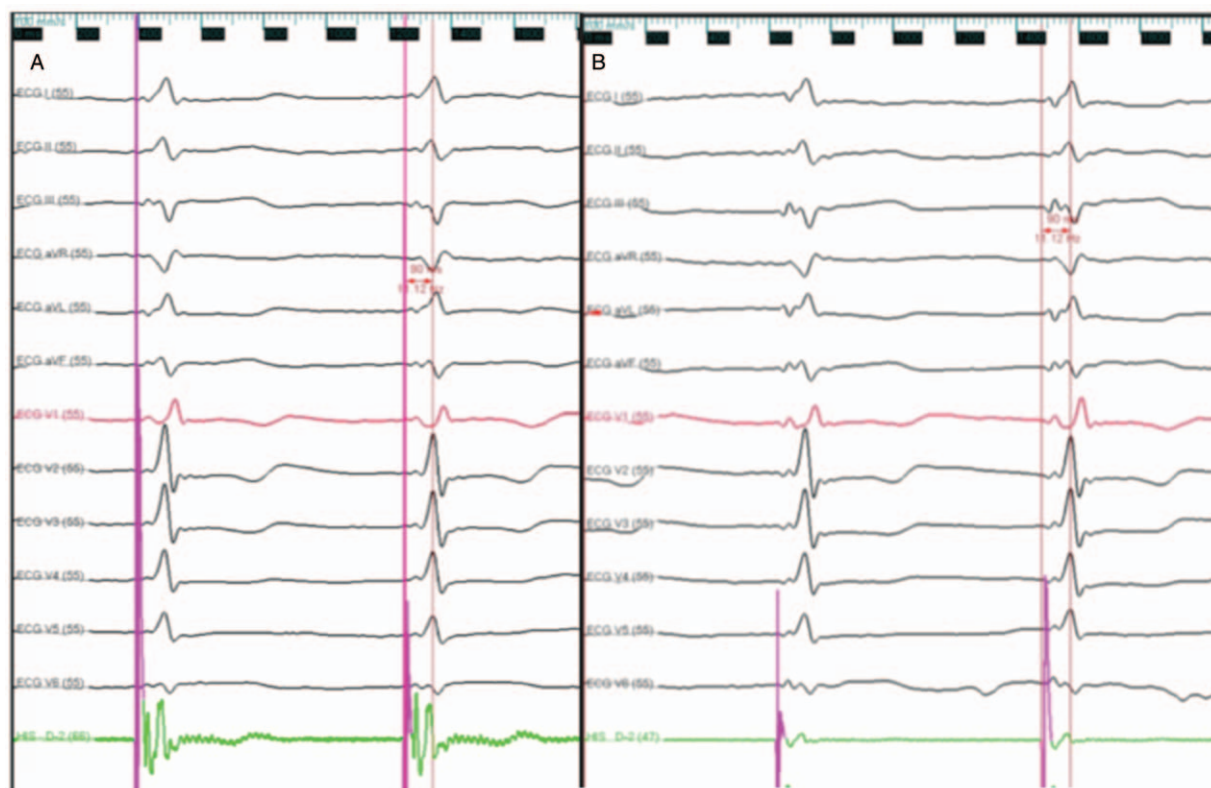


Figure 1: Selective and non-selective his-bundle pacing (S-HBP and NS-HBP). A 12-lead electrocardiogram and intracardiac electrograms in a patient with complete heart block. (A) S-HBP: Pacing at 1V@0.5 ms. (B) NS-HBP: Pacing at 5V@1.0 ms. The sweep speed is 100 mm/s.

pacemakers were changed from RVAP to HBP. After surgery, EF improved and paced QRS duration decreased from 157.8 ± 13.3 to 109.3 ± 16.9 ms; and after 6 months of follow-up, their NYHA functional status also improved. In a multi-center research with 755 participants, patients were divided into an HBP group and a RVAP group. HBP was successfully performed in 304 out of 332 patients, and during a mean follow-up time of 725 ± 423 days, there were significant reductions in all-cause mortality, heart failure hospitalization and upgrades to biventricular pacing in the HBP group.^[26] Furthermore, a long-term follow-up also showed patients with non-apical-located leading tips had a better prognosis than patients with RVAP.^[27] After comparing HBP with RVAP, Sharma *et al*^[28] found the latter could reduce the rate of hospitalization, while Teng *et al*^[29] also observed HBP could extremely reduce the duration of paced QRS.

Some researchers have even directly compared cardiac function in the same patients with either RVAP or HBP. By using scintigraphy, Zanon *et al*^[30] evaluated 12 patients treated during 3 months with RVAP and another 3 months of HBP. After 6 months, HBP was found to be superior in improving myocardial blood flow, and reducing left ventricular desynchronization and mitral regurgitation.

Catanzariti *et al*^[31] also assessed 26 patients under both HBP and RVAP; however, unlike Zanon method, they started with HBP. After a mean follow-up period of 34.6 ± 11 months, the switch to RVAP after HBP was determined

to decrease left ventricular ejection fraction (LVEF) and increase mitral regurgitation incidents.

Atrial fibrillation, AVN ablation, and HBP

Atrial fibrillation is a common arrhythmia closely related to heart failure.^[32] In these patients, long-term rate and rhythm control are key, with medication, radiofrequency catheter ablation, AVN ablation, and pacemaker implantation being the standard approaches.^[33] For patients with irreversible causes of atrial fibrillation and intolerant to medication, HBP is a reasonable choice.

In 2007, Lu *et al*^[34] used isolated working swine heart models to verify that pacemaker leads could be successfully implanted between the AVN and the HB after creating a complete AVB. Their work raised a new treatment approach for patients with atrial fibrillation and rapid heart rate. Vijayaraman *et al*^[35] replaced AVN ablation plus RVA treatment with AVN ablation plus HBP. After a mean follow-up of 19 ± 14 months, LVEF increased by up to 50%, and NYHA functional classification improved.

CRT and HBP

Heart failure is the end stage of cardiac disease, associated with elevated rates of hospitalization, mortality, and morbidity. Traditional dual-chamber pacemakers are preferred for patients with bradycardia. What are the options for patients with left bundle branch block (LBBB) and heart failure?

The LBBB promotes left ventricular delays in contraction and desynchronization of the left and right ventricle, and

leads to heart failure. CRT is an advanced choice for correcting these conduction abnormalities.^[36] Besides pacing the RA and right ventricle, an additional lead is placed through the coronary sinus to pace the epicardium of the left ventricle.^[36] Current guidelines recommend CRT for patients with QRS duration > 150 ms, LBBB and EF < 35%.^[37,38]

However, CRT has its disadvantages. In contrast to physical cardiac conduction, CRT paces the right ventricle from the apex and the left ventricle from the epicardium of its free wall, which somehow changes the pattern of each heartbeat.^[39]

Dabrowski *et al*^[40] have suggested HBP can be seen as a physiologic resynchronization therapy, describing striking improvement in patients under this treatment after a follow-up of up to 2 years. Gopinathannair *et al*^[41] evaluated 488 patients with an EF lower than 20% with either implanted cardioverter defibrillator or CRT after treatment with a left ventricular assist device. They found no significant difference in survival and hospitalization rates during follow-up.

In addition, placing the left ventricular electrode is difficult in patients with severe vascular diseases, which may significantly limit the clinical feasibility of this approach.

To conclude, CRT may not be the best pacing method for patients with heart failure. Multisite pacing, endocardial left ventricular pacing and leadless pacing have been used to improve resynchronization.^[1] However, these alternatives aggravate the economic burden of patients and are different from the physiologic activation patterns.

As one of the most physiologic pacing methods, HBP has been studied as an approach to optimize traditional CRT. In a study by Lustgarten *et al*^[42] on patients with QRS duration > 130 milliseconds, there were significant reductions in QRS duration in patients with HBP compared to baseline and patients with biventricular pacing. EF also improved in patients with HBP. Ajijola *et al*^[43] also explored this in a study with 29 patients, of which 21 succeeded in implantation. During the 1-year follow-up, patients on HBP responded similarly to those on CRT. In a multicenter study, Sharma *et al*^[44] demonstrated that compared to CRT, HBP could significantly shorten paced QRS duration and improve LVEF, and NYHA functional classification.

When left ventricular lead implantation fails, HBP is a life-saving treatment. Morina-Vazquez *et al*^[45] enrolled 16 patients with heart failure who could not achieve left ventricular pacing through the coronary sinus. Ultimately, 13 (81%) of these patients successfully underwent HBP implantation, and during the mean follow-up of 31.33 ± 21.45 months, all patients survived with an improved NYHA functional classification.

Disadvantages of HBP

HBP is not suitable for patients with infra-His bundle block

His region pacing has been suggested for patients with supra-His bundle block. In patients with infra-His block,

HBP with higher implantation sites could not achieve physiologic electro-mechanical activation.

HBP implantation is difficult

Due to the limited anatomic size of the HB and the presence of fibrotic tissue around it, HBP is difficult successfully achieve.^[46,47] The implantation of HBP requires long procedure times, and ultimately, many HBP attempts end as truly para-HBP, which can only be considered an alternative. Indeed, up to 45% of attempts at HBP appear to fail.^[48]

Implantation of HB leads can easily injure the bundle branch

Patients who undergo HBP can suffer acute trauma to the HB, which could lead to bundle branch block. In a study by Vijayaraman *et al*^[49] on 358 patients without His-Purkinje diseases who underwent HBP, 28 patients (7.8%) suffered acute injuries to the HB, of which 9 developed conduction block during follow-up.

HBP has a high threshold

The thresholds for HBP are higher than for other procedures.^[50] In 2010, Barba-Pichardo *et al*^[51] enrolled 182 patients for pacemaker implantation, with 73% of them responding to the treatment. Due to the high thresholds, only 44% patients got HBP treatment. Zhang *et al*^[52] also compared pacing thresholds between patients with HBP and RVAP, with these thresholds being significantly higher for the former. These thresholds indicate HBP require powerful and long-lasting pacing systems.

HBP may be complicated by abnormal sensing

Because the HB is surrounded by fibrotic tissue instead of muscle, the amplitude of HBP electrograms is low and the sensing ability of HBP may be decreased.^[20]

Left bundle branch pacing: a new method arises

Although HBP has been accepted worldwide in recent years, it still has plenty of shortcomings. His-Purkinje pacing from the left bundle branch may be a noteworthy attempt at improving this method.

In 2017, Huang *et al*^[53] succeeded in implanting a pacing lead to the left bundle branch. Compared to conventional right ventricular pacing, left bundle branch pacing (LBBP) can yield narrower paced QRS waves, and thus more physiologic pacing. Moreover, LBBP may obtain other advantages over HBP, including lower thresholds and higher R wave amplitude, while also being easier to fix.

Our center has already treated 15 patients with LBBP, with 13 of them succeeding with low-threshold pacing [Figure 2], suggesting LBBP is a feasible choice for patients with indications for RVAP. Unfortunately, implantation failed in 2 of these patients. Because of inexperience, one of them got mild dislocation while we disconnected the sheath (C315HIS). On the contrary, we could not screw into the ventricular septum of the other patient due to the presence of fibrosis related to a previous myocardial infarction.

From our point of view, LBBP may be a choice for individualized treatment of patients with related indications. LBBP requires lower threshold than HBP. LBBP is also a potential treatment for patients with infra-His block.



Figure 2: Baseline, selective left bundle branch pacing (S-LBBP) and non-selective bundle branch pacing (NS-LBBP). A 12-lead electrocardiogram and intracardiac electrograms in a patient with complete heart block. (A) Baseline. (B) S-LBBP: Pacing at 5V@0.5 ms. (C) NS-LBBP: Pacing 0.5V@0.5 ms. The sweep speed is 100 mm/s.

However, for patients with severe fibrosis of the RVS, implantations may become more difficult. Likewise, in patients with dilated cardiomyopathy and mechanical desynchronization, LBBP may not be a better choice than CRT, even if they preserve electrical synchronization.

For patients with infra-His bundle block, Herweg *et al*^[54] have tried treatments with para-HBP and implantations in sites distal to the block zone. We considered the possibility LBBP could solve infra-His block.

Conclusion

The future of cardiac pacing is promising.^[55] Although HBP indeed is the most physiologic pacing method, limitations remain, including high pacing thresholds, difficult implantation due to the specific anatomical variations, and others. Theoretically, LBBP is superior to HBP theoretically, yet the clinical correlate of this proposition remains under debate. Large randomized clinical trials are still lacking. Further studies are required to verify the clinical significance of LBBP.

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Conflicts of interest

None.

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