Title:Permanent His Bundle Pacing in atrioventricular block patients：A systematic review and meta-analysis

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【Abstract】

- Background:Cardiac pacemakers are still an effective method for the treatment of atrioventricular block diseases(AVB). Ventricular pacing results in adverse clinical outcome. For patients with atrioventricular conduction system disease, minimization ventricular pacing not be used to reduce the proportion of ventricular pacing and improve cardiac function. Recent studies have shown that His bundle pacing(HBP) can be an effective treatment for patients with atrioventricular block . The purpose of this study was to evaluate the effectiveness of His bundle in patients with AVB.
- Methods:We searched the studies from Pubmed,Embase and Cochrane Library database to evaluate the application of HBP in patients with AVB. From these studies, we extrated and summarized the related data such as implantation success rate, QRS width, pacing threshold at baseline and follow-up, assessment left ventricular function, complications.
- Results:This Meta- analysis included eight studies, including 430 patients. The success rate of implantation varied from 65% to 93%. The main indications of HBP were patients with AVB, including patients with atrioventricular node block and intranodal block. Left ventricular function(left ventricular ejection fraction) was not significantly improved during follow-up. The duration of QRS after HBP implantation was more narrow (113±18ms). Compared with the baseline level, the threshold of HBP was not significantly increased during follow-up. During an average of 12 months of follow-up, pacemaker-related complications occurred in 16 patients.
- Conclusion:Permanent HBP has shown promising results for patients with AVB in small observational studies. Randomized controlled trials are needed to assess the efficacy of HBP in these patients.
- Key words:Permanent His bundle pacing,Atrioventricular block,Pacing threshold

1. Introduction

The disadvantage of Right ventricular pacing（RVP）gradually come to be recognized.RVP leads to dyssynchrony of myocardial electro-mechanical activity and increases the risk of heart failure[1].In order to be more in line with physiological pacing,Minimization ventricular pacing (MPV) can reduce the proportion of ventricular pacing and protect cardiac function, but in patients with complete atrioventricular block, ventricular pacing is inevitable[2].As a relatively physiologic pacing mode, permanent His bundle pacing(HBP) is expected to correct patients with AVB, preventing the deleterious effects of RV pacing on left ventricular (LV)function.Correlational studies has been successfully in patients with AVB and preserved His-Purkinje conduction,but the success rates shown different range[3].Surprisingly,studies have demonstrated that HBP is not only valid in patients with AV nodal block,but can correct patients with infranodal block[4].Due to the relatively complex operation of HBP, high threshold, battery depletion and other reasons, HBP is not recommended as a routine pacemaker in patients with AVB.There have been many published studies and single-centre reports of HBP, but there have been no large randomized clinical trials.Thus,we systematically reviewed currently literature and carried out this meta-analysis to estimate the feasibility of HBP in patients with AVB.The reporting of this systematic review follows current standards.

2. Methods

2.1 Data Sources and Searches

A systematic search of electronic database including Cochrane Library,Embase,and PubMed.The search was performed to locate full-text publications through 3 January 2019.For the search,we uesd the Boolean search terms were:'His bundle'OR 'Para hisian'AND'pacing'.

2.2 Study selection and data extraction

Titles and abstracts retrieved from the search were reviewed.Articles were included if they reported permanent His-bundle or Para-Hisian pacing in patients with AVB.Nonoriginal articles,studies that not corrected AVB patients,case reports,review articles editorials/letters,not in English and had duplicated data were excluded.Two authors assessed final determination on article inclusion.We extracted data included:number of enrolled patients,success rate of implantation,type of pacing,follow-up duration,baseline characteristics of patients,indication for implantion,QRS duration and LVEF atbaseline and follow-up in different pacing mode, pacing threshold at baseline and followup, occurrence of increased pacing threshold at follow-up,complications and mortality.We evaluate the overall average values through extracted data as continuous variables, means, standard deviations, and sample sizes.

2.3 Statistical analysis

We used Review Manager 5.3 (Cochrane, London, UK) to perform data analysis using random effects models and I^2 statistic used to assess statistical heterogeneity. Sensitivity analyses were conducted to identify potential heterogeneity by leaving out any study. Publication bias was evaluated by generating afunnel plot of the logarithm of effectsize against the standard error for each trial. A P value less than 0.05was considered statistically significant in all analyses.

3. Results

3.1 Study characteristics

The literature screening flow chart(Figure 1) shows process and outcome.Finally,8 studies including 430 patients with AVB were included in these meta-analysis(Table 1).There were 3 single-arm studies and 5 comparativestudies included in theanalysis. Types of HBP reported included: direct HBP, Para-Hisianpacing, selective HBP, and non-selective HBP.Theaverage age was 71.9 years and 67.5%of patients were male. Through different reports,implant success rate shows varied range from 65%-93%.Four studies reported patients with AVB,normal cardiac function and QRS < 120ms[5-8].The other reports include patients with longstanding AVBand >95% RV pacing[9] ,patinets after prosthetic valve (PV) surgery[10],patients can be corrected by HBP and acute threshold < 2.5V/ms[3].The remaining reports mainly studied patients with infranodal and nodal block [11].

3.2 Compare RVP with HBP at left ventricular ejection fraction(LVEF)

For comparative studies,there was no significant difference in baseline LVEF. During a mean follow-up of 12months,comparison of follow-up LVEF with HBP and RVP groups shows HBP group lightly higher than RVP group,but there is no statistically significant(53.8±9.4 vs 45.5±10,p=0.10,I^2=88%,Figure 2A).After adjustment of Heterogeneit Analysis,removing a study,the outcome has not changed(I^2=0,p=0.07,Figure 2B).

3.3 Compare RVP with HBP at QRS width

For comparative studies,there was no significant difference in baseline QRS width. During the same follow-up period,the QRS width in HBP and RVP groups presents significant stastiscal difference.QRS width in HBP groups more narrow than RVP groups(113±18ms vs 163±14ms,p < 0.00001,I^2=11%,Figure 3).

3.4 Pacing threshold in HBP patients at baseline and follow-up

Despite different follow-up times,there was a trend of increased threshold at follow-up compared to baseline,but the difference has not statistically significant(1.6±1.0V/ms vs 1.5V±1.0V/ms,p=0.06,I^2=56%,Figure 4).

3.5 Sensitivity analysis and Risk bias

Leaving out any study to assess Sensitivity analysis did not influence the direction or magnitude of the above results, except for threshold in baseline and follow-up, indicating that no single study overly affected most of the findings. Due to the limited number of included studies for correction threshold, sensitivity analysis might not be suitable in the situation.Considering the small number of literatures involved,funnel plot is insufficient to illustrate the situation.We conducted the risk bias images to guarantee methodological quality(Figure 5A,B).Through the risk bias assessment, it can be found that the inherent random bias risk of all studies is higher.

4. Discussion

We systematically assessed publications on permanent pacing at or near the His-bundle which was comprised of 8 researches about HBP in AVB patients. Our study demonstrates the safety and feasibility of HBP when applied to patients with AVB and get a relatively success rate.Due to a lack of large-scale randomized clinical tiral,the existing meta-analysis can reflect the effectiveness of HBP to a certain extent.Our meta-analysis demonstrates that: (1) comparing with RVP,HBP has not improved LV function in patients with AVB;(2)through the contrast analysis between two groups,HBP could produce favorable QRS duration in patients with AVB; (3) during the follow-up period,pacing threshold in HBP was not found to increase.

With the hemodynamic disorder caused by single chamber pacing, the adverse clinical consequences are gradually made public. At present, HBP is closer to physiological pacing in the treatment of irreversible bradycardia, especially in patients with atrioventricular block, which the proportion of ventricular pacing can not be reduced in MVP. In this study, we found that HBP did not significantly improve the baseline LVEF of patients compared with RVP. However, the current studies have been proved that HBP can improve LVEF, and improve cardiac function[12]. Analysis of the results of this Meta analysis and other studies found that it may be related to the source of the study data, the study selected patients with normal cardiac function accounted for 41.4%.

Due to HBP conforms to the activation order of his bundle-Purkinje fiber conduction system, we found that the QRS width in HBP group was significantly narrower than that in RVP group. QRS duration can reflect the synchronization of ventricular contraction and relaxation.We find that if QRS duration too long, ventricular long-term mechanical activity is not synchronized.It can cause cardiac function deterioration and cardiac insufficiency. Currently study discovered that the probability of heart failure was higher in patients with QRS > 150ms and lower in QRS< 130ms[13]. This study may suggest that HBP can achieve better electro-mechanical synchronization and have little effect on long-term cardiac function compared with RVP group, but the improvement of cardiac function is less in this study because of the small proportion of patients with heart failure. It can not fully show the improvement of cardiac function. In theory, narrow QRS wave is beneficial to cardiac function, but the effect of HBP on cardiac function needs to be confirmed by long-term follow-up.

The His bundle region is inthe central fibrous body minimally surrounded bymyocardial tissue.Due to the particularity of his bundle anatomy,unless the lead tip penetrates the fibrous insulation of the His bundle or is in closeproximity, the His capture thresholds can be significantly higher.Nevertheless,as the development of technology,the specialized pacing lead (SelectSecure 3830, Medtronic, Minneapolis, Minnesota) and sheaths (C315His, C304 SelectSite, Medtronic) has made permanent HBP feasible in routine clinical practice[14].Some studies believe that pacing threshold in HBP would increased during the follow-up period.In our study,pacing threshold did not increase significantly.Compared with high His bundle capture thresholdsreported with traditional pacing leads in earlystudies, recent investigations show acceptable Hiscapture thresholds both at implant and during longterm follow-up. The threshold did not show a significant increasing in this study may be related to many factors, such as the development of technology, the gradual proficiency of clinical technology, the short time required to fix the electrode, the small amplitude of electrode displacement and so on. To some extent, this study shows that His bundle pacing should not be abandoned because of the high pacing threshold.

The definitions and scopeof safety assessments differed by study.The common complications include loss of capture, sensing issues，pocketinfection, device dehiscence, elevated thresholds, exit block, deviceerosion,dislodgement and so on. We analysis the all studies about the safety of lead found that during the follow-up period, there were 16 complicationsobserved in 430 patients.developed postoperative complications, including 8 patients with lead revision, 1 patient with pocket infection, 7 patients with loss of capture.Because of lack of information about timing and follow-up,we can not estimate the overall complication rates using Kapla-Meier.

In 2000, Deshmukn was used for the first time in patients with cardiac insufficiency with chronic atrial fibrillation. Permanent HBP was successfully implanted and cardiac function was improved during follow-up, and the pacing threshold was stable[15]. Subsequently, HBP was gradually used in clinical practice.Because the adverse clinical outcome of ventricular pacing can not be improved, HBP has become the focus of pacemakers. MPV can also be used to reduce the proportion of ventricular pacing in patients with sinus node disfunction（SND）, but it is not suitable for patients with AVB, and onlypatients who have AVB can be expected to benefit from amore physiological pacing site.Direct His pacing is the only pacingmode allowing a normal ventricular activation and would,from a theoretical point of view, be superior to biventricularpacing. Para-His pacing, resulting in a near-normal ventricularactivation with respect to QRS width and axis, may be as goodas or even better than biventricular pacing in patients with anarrow QRS and AVB.

At present, the clinical adaptation sign of HBP is not clearly defined. In 2018, AHA has listed HBP in the guidelines to recommend (IIa).It recommends patients with atrioventricular block who have an indication for permanent pacing with a left ventricular ejection fraction between 36% and 50%,can choose HBP or CRT[16].It can be seen that the clinical status of HBP has been gradually improved.

4.1 Study limitations

This meta-analysis has so important limitations that we should caution interpretation of the results.At first,the number of included patients was limited and some studies were cohort studies with inherent limitations that reduced the internal validity compared to randomized controlled trials.Through the Risk bias image,we find the overall studies a have a higher risk of bias because they are not randomly controlled.Secondly,these data relied on the physician reporting of the various applications of HBP, thus we were not able to confirm nor assess each application independently. For example, the definitions for selective/ non-selective HBP appear to vary from one study to another.In fact,we don't have a uniform standard definition.Thirdly, some dataincluding pacing pulse width and follow-up time, were variable andinconsistent, which may influence the study uniformity.Recent,an International HBP Collaborative working group has published a report to set standards[17].

5. Conclusion

HBP has achieved gratifying clinical results in some studies. In this study, it was found that HBP could significantly improve the synchronization of electro-mechanical activity in patients with AVB and obtain narrow QRS waves. Whether the improvement of cardiac function and the increase of pacing threshold lead to battery depletion need to be replaced in advance and other clinical needs still need to be confirmed by long-term follow-up. Randomizedcontrolled trialsis still needed to fully evaluate the safety and efficacy of HBP in the treatment of AVB.

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definitions, implant measurements and follow-up. Heart Rhythm 2017;15:460–8.

Figure legends

Figure 1 Flowchart of selection process for articlesincluded in the meta-analysis

Figure 2A LVEF：compared RVP with HBP

Figure 2B adjustment of Heterogeneit analysis

Figure 3 QRS in RVP and HBP

Figure 4 Pacing threshold at baseline and follow-up

Figure 5A Risk of bias graph

Figure 5B Risk of bias summary