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Should His-bundle pacing be preferred over CRT following AVJ ablation?

Zak Loring, MD^{a,b} [cardiology fellow] and Albert Y. Sun, MD^{a,c} [Assistant Professor of Medicine]

^aDivision of Cardiology, Section of Electrophysiology, Duke University Medical Center, Durham, NC

^bDuke Clinical Research Institute, Durham, NC

^cDivision of Cardiology, Section of Electrophysiology, Durham VA Medical Center, Durham, NC

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Introduction:

Atrial fibrillation (AF) is a common arrhythmia with increasing prevalence¹ and is associated with frequent hospitalizations and high treatment costs.² When AF occurs in the setting of heart failure (HF), the deleterious effects are magnified. While the loss of atrial “kick” and atrio-ventricular (AV) synchrony both contribute to this acquired morbidity, perhaps the most dramatic detrimental hemodynamic effects occur in the setting of AF with rapid ventricular rates (RVR). Rate control strategies in this scenario can be challenging due to the negative inotropic effects of some pharmacologic agents as well as subsequent symptomatic bradycardia (e.g. tachycardia-bradycardia syndrome).³ Pharmacologic rhythm control agents are limited to dofetilide and amiodarone in patients with structural heart disease and reduced left ventricular ejection fraction.³ Catheter ablation procedures have been shown to improve outcomes in patients with HF and reduced ejection fraction (HFrEF);^{4,5} however the single procedure success rates of catheter ablation are lower in patients with HFrEF and persistent AF and can require multiple procedures.^{6,7}

Creation of iatrogenic heart block via catheter ablation of the AV junction (AVJ) with pacemaker implantation can achieve complete, though irreversible, rate control in patients

CORRESPONDING AUTHOR Zak Loring MD: 2301 Erwin Road, DUMC 3845, Durham, NC, 27710, zak.loring@duke.edu.

AUTHOR CONTACT INFORMATION ZL: 2301 Erwin Road, DUMC 3845, Durham, NC, 27710, zak.loring@duke.edu, AYS: 2301 Erwin Road, Durham, NC 27710, albert.sun@duke.edu.

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with incessant AF with RVR⁸; and incidentally was the first condition in which catheter ablation in man was performed.⁹ Patients undergoing AVJ ablation with normal ejection fractions are given single-site right ventricular (RV) pacemakers as standard of care; in patients with reduced ejection fractions however, randomized trials demonstrated that cardiac resynchronization therapy (CRT) via biventricular (BiV) pacemaker systems results in improved clinical outcomes.¹⁰ Given the high pacing burden after AVJ ablation, pacing in a more physiological way is preferred to reduce the risk of pacemaker induced cardiomyopathy due to frequent RV pacing.¹¹ BiV pacemakers utilizing coronary sinus (CS) lead placement have been the mainstay of physiological pacing in the past; however, His-bundle pacing (HBP) has emerged as an alternative and promising pacing method that mimics physiologic activation patterns by directly stimulating the patient's native conduction system.¹² Ongoing clinical trials such as the His-SYNC trial ([Clinicaltrials.gov NCT02700425](https://clinicaltrials.gov/ct2/show/study/NCT02700425)) are comparing clinical outcomes between these two strategies in HF patients, as the superior choice is not currently known. This review will describe the benefits and drawbacks of BiV pacing and HBP in the setting of HF and AVJ ablation.

Biventricular Pacemakers

Compared to single site RV only pacing, BiV pacemakers provide more physiologic pacing by coordinating activation of the septum (via an RV lead) and lateral wall (via a CS lead) of the left ventricle (LV), allowing for a more synchronous LV contraction. Utilization of BiV pacing in patients with HF and left bundle branch block (LBBB) have been shown to improve clinical outcomes in multiple large clinical trials, and since being approved by the FDA in 2001, the use of BiV pacing has steadily increased over time.^{13,14,15}

BiV Pacemakers in AV block:

The LV activation and contraction pattern resulting from RV only pacing is similar to the patterns seen in LBBB prompting investigators to hypothesize that BiV pacing may be superior to RV only pacing in patients anticipated to have a high pacing burden.¹⁶ The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial demonstrated that in patients with atrioventricular (AV) block, New York Heart Association (NYHA) symptom class I-III HF and an LV ejection fraction (LVEF) $\geq 50\%$, patients randomized to BiV pacing had fewer adverse clinical outcomes, more LV remodeling and more symptomatic improvement compared to patients randomized to RV only pacing.¹⁷⁻¹⁹ Subsequent to the release of the BLOCK-HF trial, preliminary results from the Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace) trial were reported evaluating the difference in death or HF hospitalization between patients with AV block and HF randomized to BiV pacing vs RV only pacing.²⁰ The BioPace trial had a similar patient composition to BLOCK-HF but enrolled patients with less severe AV block (1st and 2nd degree AV block as well as patients with AF and a ventricular rate ≤ 60 beats/min) and higher average EFs (55% vs 40%). The results showed a trend towards superiority of BiV pacing that did not reach statistical significance, including in the subgroup of patients with EF $< 50\%$.²¹ A systematic review of studies comparing BiV pacing or HBP (physiologic pacing) to RV only pacing in patients without severe LV systolic dysfunction (EF $> 35\%$) found that patients with EF $> 35\%$ but

52% were more likely to benefit from physiologic pacing compared to RV only pacing.²² The most recent guidelines provide a IIa recommendation for use of pacing methods that maintain physiologic ventricular activation (i.e. BiV pacing or HBP) in patients with an LVEF between 36% and 50% who are expected to require ventricular pacing more than 40% of the time.²³ These studies and guidelines support the superiority of physiologic pacing over RV only pacing in patients with AV block and reduced EF.

BiV Pacemakers after AVJ Ablation:

Multiple studies have evaluated the effectiveness of BiV pacing in the setting of AVJ ablation. The post-AV nodal evaluation (PAVE) study randomized 184 patients undergoing AVJ ablation for AF with RVR to BiV pacing or RV only pacing and evaluated 6-minute walk distances, quality of life and LVEF at 6 months follow up.¹⁰ Patients randomized to BiV pacing had better 6-minutewalk distances and LVEF improvement compared to patients randomized to RV only pacing. Additionally, patients with LVEF < 45% had the greatest improvement in 6-minute walk distances. The Ablate and Pace in Atrial Fibrillation (APAF) trial also compared BiV pacing to RV only pacing in 186 patients undergoing AVJ ablation and showed that BiV pacing was associated with fewer HF deaths, HF hospitalization or worsening HF symptoms compared to RV only pacing.²⁴

BiV pacing was designed to normalize LV activation in patients with underlying dyssynchrony; however, in patients without significant electrical dyssynchrony at baseline, it can cause iatrogenic dyssynchrony.²⁵ Patients with narrow QRS complexes (<120ms) have been shown not to respond to BiV pacing and BiV pacing may be harmful in these patients leading to increased mortality.²⁶ Consistent with the possibility of harm, the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial evaluating BiV pacing in patients with HF and a QRS duration <120ms was stopped by the Data Safety and Monitoring Board over safety concerns.²⁷ A meta-analysis also suggested a signal towards harm with use of BiV pacing in patients with QRS durations < 130ms.²⁸ While these studies were not done in patients with AV block or those undergoing AVJ ablation, they raise concerns about the efficacy of BiV pacing in patients without underlying conduction disease. The APAF investigators conducted another trial to investigate the effectiveness of AVJ ablation and BiV pacing in patients with narrow QRS complexes (< 110ms) to better understand this issue. The Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy (APAF-CRT) trial randomized 102 patients with AF, narrow QRS complexes (< 110ms) and at least one HF hospitalization in the previous year to either AVJ ablation and BiV pacing or pharmacologic rate control.²⁹ AVJ ablation and BiV pacing resulted in lower rates of HF death, HF hospitalization or worsening HF symptoms compared to pharmacologic rate control. The results of this trial suggest that BiV pacing after AVJ ablation is an effective strategy even in the absence of underlying conduction disease.

Hemodynamic Effects of BiV Pacing:

Ventricular activation in BiV pacing results in as many as three independent wave fronts (RV pacing lead, LV pacing lead and any intrinsic conduction). Canine studies have compared total activation times (TAT) and LV contraction (as measured by LV dP/dT [first derivative

of LV pressure]) during atrial pacing (simulating native conduction) and multiple combinations of A-RV and A-LV pacing intervals. BiV pacing resulted in higher LV dP/dT and lower TAT than RV-pacing at all tested AV intervals.³⁰ The hemodynamic effects of different pacing patterns have also been studied in patients with HF. A study of eleven HF patients with pre-existing LBBB compared LV dP/dT in atrial pacing (similar activation to RV only pacing given pre-existing LBBB), BiV pacing, and LV only pacing. BiV and LV only pacing resulted in higher stroke volumes and dP/dT than the asymmetric activation seen in atrial pacing with underlying LBBB.³¹ These studies demonstrate that the synchronous activation resulting from BiV pacing results in superior LV mechanical function compared to asymmetric activation seen in RV only pacing.

Challenges with BiV Pacemakers:

While the outcomes for BiV after AVJ ablation appear to be superior to RV only pacing, the need for a coronary sinus lead placement increases the complexity of implantation, fails in some patients, and can make device extraction more challenging. A systematic review comparing complications between dual chamber ICD and BiV devices revealed that implantation success in BiV devices was significantly lower (98.9% vs 92.5%) with higher rates of lead dislodgement during follow up (5.9% vs 1.8%).³² (Van Rees). BiV devices also introduced additional risk with CS lead implantation resulting in coronary venous complications in 2.0% of cases.³² If lead extraction is necessary (e.g. for systemic infection), CS lead extraction presents unique challenges due to the complexity of the anatomy and post-extraction venous occlusion can limit re-implantation options.³³ While major complications with lead extraction are rare (approximately 1.8%), low LVEF and higher NYHA class are associated with higher risk of major complication and mortality respectively.³⁴

His Bundle Pacemakers

Pacing the heart via the His bundle takes advantage of the patient's intrinsic conduction system to allow for activation most similar to patients' naturally occurring myocardial activation pattern. It was first described in a canine model 1967 by Sherlag et al. where Teflon coated stainless steel wires were inserted into the His bundle through the lateral atrial wall and showed that pacing from this site produced a QRS complex that was indistinguishable from the morphology during sinus rhythm or atrial pacing.³⁵ Sherlag et al. were subsequently able to demonstrate His bundle recordings in man using a catheter based approach.³⁶ The first permanent HBP in man was described in 2000 in a study of 18 patients being treated for refractory AF with RVR with AVJ ablation in which His bundle stimulation was successful in 14 of the patients and permanent HBP using a fixed screw-in lead successfully achieved in 12 patients.¹² With the ability to chronically pace the His bundle via permanent pacemakers, further investigations of HBP as a means of achieving CRT were pursued.

HBP in AV Block:

Given the physiologic activation patterns achievable with HBP, it is an attractive therapeutic solution for patients presenting with AV block. A randomized, double blinded, cross-over

study comparing HBP to RV only pacing in patients with AV block, narrow QRS complexes (<120ms), and preserved LVEF (>40%). The study showed that HBP was successful in 85% of patients and achieved higher post-intervention LVEF compared to RV only pacing.³⁷

One might expect AV block, particularly block due to infranodal disease, may not be as responsive to HBP. However, microscopic examination of the His bundle supported the previously postulated theory of functional longitudinal dissociation of the His bundle.^{38,39} This theory purported that the fibers within the His bundle were predestined for the bundle branches and that proximal lesions could result bundle branch blocks which could be overcome by pacing the His bundle distal or adjacent to the site of block. Indeed, early pacing studies demonstrated that HBP could overcome LBBB, previously thought to be due to conduction disease distal to the His bundle.⁴⁰ A study of patients referred for pacemaker evaluated HBP outcomes regardless of type of AV block (84 patients had narrow QRS, 98 patients had wide QRS complexes).⁴² Successful HBP was achieved in 73% of patients (44 of the 84 patients with narrow QRS, 15 of the 98 with wide QRS complex) suggesting that while some patients with wide QRS are correctable with HBP, it is not universal. Other hypothesized mechanisms by which HBP can overcome LBBB include differential source-sink relationship during pacing compared to intrinsic conduction (due to different anisotropy ratios in the intracellular and interstitial space) and/or the virtual electrode polarization effect (in which electrical stimulus can alter refractoriness of adjacent tissue allowing conduction in previously non-conducting tissue).^{41,43}

HBP after AVJ Ablation:

The initial demonstration of permanent HBP by Deshmukh, *et al.* was performed in patients with refractory AF with RVR undergoing AVJ ablation.¹² In a subsequent series of patients with AF and RVR, narrow QRS complex, and HF undergoing AVJ ablation, HBP was successful in 39 of 54 (72%) of patients resulting in an average increase in LVEF from 23% to 33% after 42 months.⁴⁴ More recent case series of HBP after AVJ ablation in patients have shown higher implant success rate (81–95%) and also demonstrated improvements in LVEF and LV volumes with a more significant improvement in patients with reduced LVEF prior to implantation.^{45,46} A cross-over study compared HBP to RV only pacing in 16 patients with AF and narrow QRS after AVJ ablation and found that HBP was associated with improved interventricular electromechanical delay, NYHA improvement, quality of life scores, 6-minute walk distances and AV valve regurgitation compared to RV only pacing.⁴⁷ The superiority of HBP over RV only pacing was reinforced by a recent meta-analysis found that HBP results in higher LVEF, NYHA class improvement, less dyssynchrony and shorter QRS duration compared to RV only pacing as well as by a study demonstrating better clinical outcomes with HBP compared to RV only pacing.^{48,49}

Hemodynamic Effects of HBP:

Hemodynamic studies of HBP have shown that compared to RV-only pacing, HBP produced superior hemodynamics compared to RV only pacing. Aortic flow and dP/dT have been shown to be higher with HBP compared to RV only pacing and closely mirrored that seen in atrial pacing or native conduction.^{50,51} In patients with high degree AV block and narrow QRS (<120ms), HBP resulted in higher echocardiographic acute measures of cardiac output

(left ventricular outflow tract velocity time integral [LVOT VTI]), and less interventricular dyssynchrony compared to RV only pacing.⁵² Additionally, a study of myocardial perfusion during pacing showed that HBP results in a more physiologic blood flow compared to RV only pacing.⁵³

Pressure volume loops comparing LV hemodynamics during BiV pacing, LV only pacing and HBP+LV pacing showed improved function compared to baseline conduction in patients with LBBB; however, BIV pacing and LV only pacing required optimization of AV delays to achieve optimal hemodynamics, whereas HBP+LV pacing improved function at all tested AV intervals.³¹ The authors suggest that this robustness of response to AV delay is due to the ability for HBP to more effectively recruit the RV conduction system compared to BiV pacing. This effect would seemingly also favor HBP in the setting of AF given the loss of AV synchrony associated with the dysrhythmia.

Challenges in HBP:

Part of the explanation as to the 33-year gap between the first description of HBP and its use in a permanent pacing device in humans stems from the difficulty in securing a permanent lead that consistently allows capture of the His bundle. The development of specialized pacing leads (Select Secure 3830, Medtronic, Minneapolis, Minnesota) and delivery sheaths (C315His, C304 SelectSite, Medtronic) have been instrumental in making this technology more practically achievable in clinical practice.⁵⁴ Even with these tools, it can be difficult to achieve selective HBP (pure His capture pacing as opposed to non-selective HBP where both the His and adjacent RV tissue is captured, Figure 1); however, some studies have shown that non-selective HBP may improve ventricular dyssynchrony just as effectively as selective HBP.^{55–57} HBP typically requires higher output to achieve consistent capture; however, these thresholds are typically stable during follow up and rarely result in premature battery depletion and early generator change.^{49,58,59} Concurrent AVJ ablation presents even further challenges given the close proximity of the AVJ and optimal HBP pacing site. In fact, some operators advocate using successful HBP sites as a target to determine the optimal AVJ locations for ablation.⁶⁰ Careful monitoring of pacing threshold should be performed during ablation to avoid unwanted increases in HBP pacing thresholds during and after ablation.⁴⁶

BiV vs HBP

As tempting as it may be to declare HBP the modality of choice after AVJ in patients with HF given the rather dramatic ability to preserve native physiologic conduction, the optimal pacing modality will likely be determined by many factors other than simply a desire for a narrow vs wide paced QRS morphology. Unfortunately, there are no head to head randomized outcomes trials comparing BiV pacemakers to HBP. The available evidence is limited with preliminary findings primarily available in the form of observational studies and long term efficacy and safety data are still lacking. Despite this, the preponderance of data appears to favor HBP. One such study demonstrated that when used as an alternative CRT strategy in patients in whom BiV pacing is not feasible, HBP improved NYHA class and echocardiographic parameters.⁶¹ A small, cross-over trial (n=12 completed cross-over patients) comparing HBP to BiV pacing in a CRT eligible population found that HBP and BiV pacing had similar effects on clinical and echocardiographic outcomes at 1 year.⁶² A

multicenter analysis of patients undergoing HBP after either non-response to BiV pacing or as a primary alternative to BiV pacing showed a high implant success rate (90%) and demonstrated significant narrowing of QRS duration, increase in LVEF and improvement in NYHA class (example in Figure 2).⁶³ With the improved physiologic parameters and growing body of literature, in our center HBP is often attempted first in patients with depressed EFs needing AVJ ablation. If difficulty is encountered with either lead placement or suboptimal thresholds are obtained, BiV pacing is pursued as the second option.

Conclusions:

AF and HF are growing epidemics that share many risk factors and negatively impact one another. While, AVJ ablation with pacemaker implantation can be an effective strategy to achieve better rate control and improve clinical outcomes in patients with refractory AF and RVR, the choice between BiV pacing versus HBP is still not clear. HBP provides favorable physiologic electrical activation and hemodynamic profiles with shorter procedure time and no requirement for CS lead placement (Figure 3). However, with His bundle lead implant failure rates still reported as high as 40%,⁶⁴ combined AVJ and HBP continues to be limited despite the positive physiologic impact of HBP. Improvements in implant technique as well future head-to-head clinical trials will have profound impact on management decisions in this rapidly growing population for years to come.

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KEY POINTS

- Atrial fibrillation (AF) and heart failure (HF) are associated with high morbidity and mortality.
- Atrioventricular junction (AVJ) ablation with pacemaker implantation can be used in patients with incessant AF with rapid ventricular rate.
- The optimal choice of pacing strategy for patients with HF after AVJ ablation is unknown.
- His bundle pacing (HBP) and biventricular (BiV) pacing both offer more physiologic activation compared to right ventricle only pacemakers.
- This review describes the benefits and drawbacks of HBP and BiV pacing in HF patients after AVJ ablation.

SYNOPSIS

Atrial fibrillation (AF) and heart failure (HF) are associated with high morbidity and mortality which is particularly detrimental when patients develop rapid ventricular rates (RVR). Atrioventricular junction (AVJ) ablation with pacemaker implantation has been used as a method of achieving rate control in patients with incessant AF with RVR. Right ventricular (RV) only pacing is known to be harmful in the setting of HF. His bundle pacing (HBP) and biventricular (BiV) pacing both offer durable pacing solutions that offer more physiologic activation. This review describes the benefits and drawbacks of HBP and BiV pacing in HF patients after AVJ ablation.

Figure 1. Non-selective and selective His bundle Pacing example:

An 80 year old woman with atrial fibrillation underwent His bundle implantation. A: Native condition demonstrating a narrow QRS complex; B: Pacing at high output results in non-selective His bundle capture with a widening of the QRS complex; C: Selective His bundle capture with narrow QRS complex, similar to native conduction.

Figure 2. Case example of HBP after poor response to BiV Pacing:

An 82 year old man with worsening HF after BiV Pacing implemented for permanent AF and heart block. A: Baseline ECG demonstrated a normal QRS width of 106ms, with a nonischemic cardiomyopathy and EF 35%; B: After placement of a BiV Pacemaker the QRS width increased to 146ms with a resultant decrease in EF to 25%; C: HBP pacing was implemented with selective His capture resulting in a return to a narrow QRS width of 108ms and subsequent improvement of EF to 45%.

Figure 3. Advantages and disadvantages of HBP and BiV pacing:

Summary of the advantages and disadvantages of His bundle and biventricular pacing.