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Conduction System Pacing for Cardiac Resynchronization Therapy: The 31-Million-Dollar Question

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Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for medically refractory heart failure (HF), with a reduction in hospitalization and mortality in addition to improved cardiac function and functional capacity shown in landmark clinical trials.[1,2] Cardiac resynchronization therapy is also indicated for patients with systolic dysfunction requiring frequent ventricular pacing (>40%) to prevent deleterious remodeling and cardiomyopathy associated with ventricular pacing.[3]

Current Limitations

Cardiac resynchronization therapy has traditionally been accomplished with biventricular pacing (BiVP), in which leads are implanted into the right ventricular apex and coronary sinus to simultaneously pace the left and right ventricles. Despite the benefits of CRT, approximately one-third of patients with HF do not improve with BiVP.[4] Furthermore, up to 7% of BiVP implants are unsuccessful because of technical difficulties in positioning the left ventricular lead.[2,3] Given these limitations of BiVP, alternative methods of achieving CRT via conduction system pacing (CSP) in the form of His bundle pacing (HisBP) and left bundle branch pacing (LBBP) have been developed.

Recent Developments

Conduction system pacing is a more physiologic form of pacing in which the native cardiac conduction system is directly recruited to reestablish electrical and mechanical synchrony. In patients with HF and advanced conduction system disease in the form of bundle branch block, CSP often produces a marked reduction in QRS duration due to recruitment of fibers distal to the site of the delay. Deshmukh et al[5] first reported the feasibility of permanent HisBP in 2000. Since then, numerous studies have demonstrated the efficacy of HisBP to improve echocardiographic parameters and functional capacity in addition to narrowing QRS duration in CRT-eligible patients.[6,7] His bundle pacing is also an effective rescue strategy for BiVP nonresponders or patients in whom a BiVP device cannot be implanted.[6] However, HisBP is associated with high pacing thresholds due to the fibrous structure around the His bundle and can be technically challenging to accomplish. More recently, LBBP, pioneered by Huang et al in 2017,[8]

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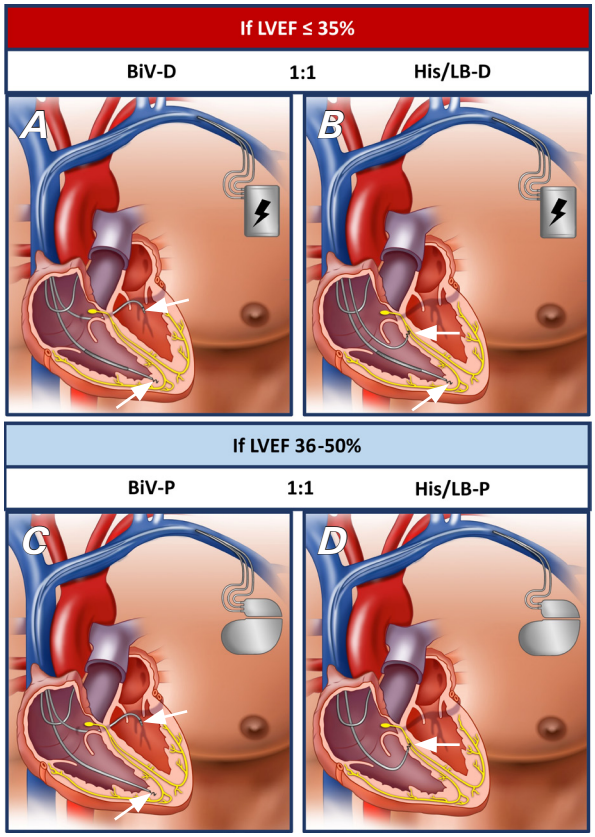

Fig. 1 Patients in the Left vs Left randomized clinical trial are randomized in a 1:1 ratio between treatment arms, separately within strata based on LVEF (≤35% vs 36%-50%) at the time of randomization. **A**) BiV-D with ICD lead implanted into the RV apex and LV epicardial lead into the coronary sinus (arrows). **B**) His/LB-D with an ICD lead implanted into the RV apex and a pacemaker lead, replacing the conventional LV epicardial lead, implanted into either the His or LBB position (arrows). Only LB-D is illustrated (not His). **C**) BiV-P with pacemaker lead implanted into the RV apex and LV epicardial lead into the coronary sinus (arrows). **D**) His/LB-P with a pacemaker lead implanted into the His or LBB position (arrows). Only LB-P is illustrated (not His).

BiV-D, biventricular defibrillator; BiV-P, biventricular pacemaker; ICD, implantable cardioverter defibrillator; LBB, left bundle branch; LB-D, left bundle branch defibrillator; LB-P, left bundle branch pacemaker; LV, left ventricle; LVEF, left ventricular ejection fraction; RV, right ventricle.

Adapted with permission from Khan K, Kim JA, Gurgu A, Khawaja M, Cozma D, Chelu MG. Innovations in cardiac implantable electronic devices. *Cardiovasc Drugs Ther.* 2022;36(4):763-775. doi:10.1007/s10557-021-07163-5.[11]

Abbreviations and Acronyms

BiVP	biventricular pacing
CRT	cardiac resynchronization therapy
CSP	conduction system pacing
HF	heart failure
HisBP	His bundle pacing
LBBP	left bundle branch pacing
LVEF	left ventricular ejection fraction
RCT	randomized controlled trial

was developed as a novel approach for CSP. Compared with HisBP, LBBP is associated with low and stable capture thresholds and potentially higher procedural success rates because of the larger target area. An additional benefit of LBBP is the ability to provide backup septal capture in case of loss of left bundle branch capture. Similar to HisBP, LBBP often leads to marked improvement in left ventricular ejection fraction (LVEF) and QRS duration.[9]

Techniques for CSP have been refined in the past decade, with a pacing lead (SelectSecure 3830; Medtronic) now Food and Drug Administration approved for both HisBP and LBBP. Although large observational studies have demonstrated a greater degree of improvement in LVEF and QRS duration in addition to improved clinical outcomes with CSP than with BiVP,[7,9] randomized controlled trials (RCTs) comparing the 2 technologies remain scarce to date and are limited by their small sample sizes and short follow-up. Within these confines, RCTs comparing CSP with BiVP for CRT have shown promising results so far with regard to surrogate end points such as LVEF or other echocardiographic parameters.[7] Nevertheless, it remains uncertain how these surrogate endpoints translate into hard clinical end points such as mortality or hospitalization for HF.

The ongoing Left vs Left RCT (ClinicalTrials.gov identifier NCT05650658)[10] is the largest clinical trial comparing CSP and BiVP in CRT-eligible patients and is anticipated to provide further insight into the optimal approach to CRT (Fig. 1).[11] The trial will include 2,136 patients followed up for at least 3 years. Unlike previous trials, the Left vs Left RCT will be adequately powered for superiority of the primary composite end point of death and HF hospitalization. The trial is currently in the feasibility phase, which will be followed by the full-scale study that is expected to run until 2029.

Future Directions

Dedicated and improved leads and delivery sheaths, particularly with LBBP, are needed to further improve CSP implant success and safety. Updated devices and algorithms for CSP to achieve optimal CRT are also being developed and may further improve the efficacy of this approach. Last, the long-term outcomes of CSP remain a further area of study.

In conclusion, CSP is a more physiologic method for attaining CRT than is conventional BiVP, with several clinical trials currently underway to establish the efficacy and safety of this technique.

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