Review Article

Conduction System Pacing: Redefining Resynchronization Therapy in Heart Failure

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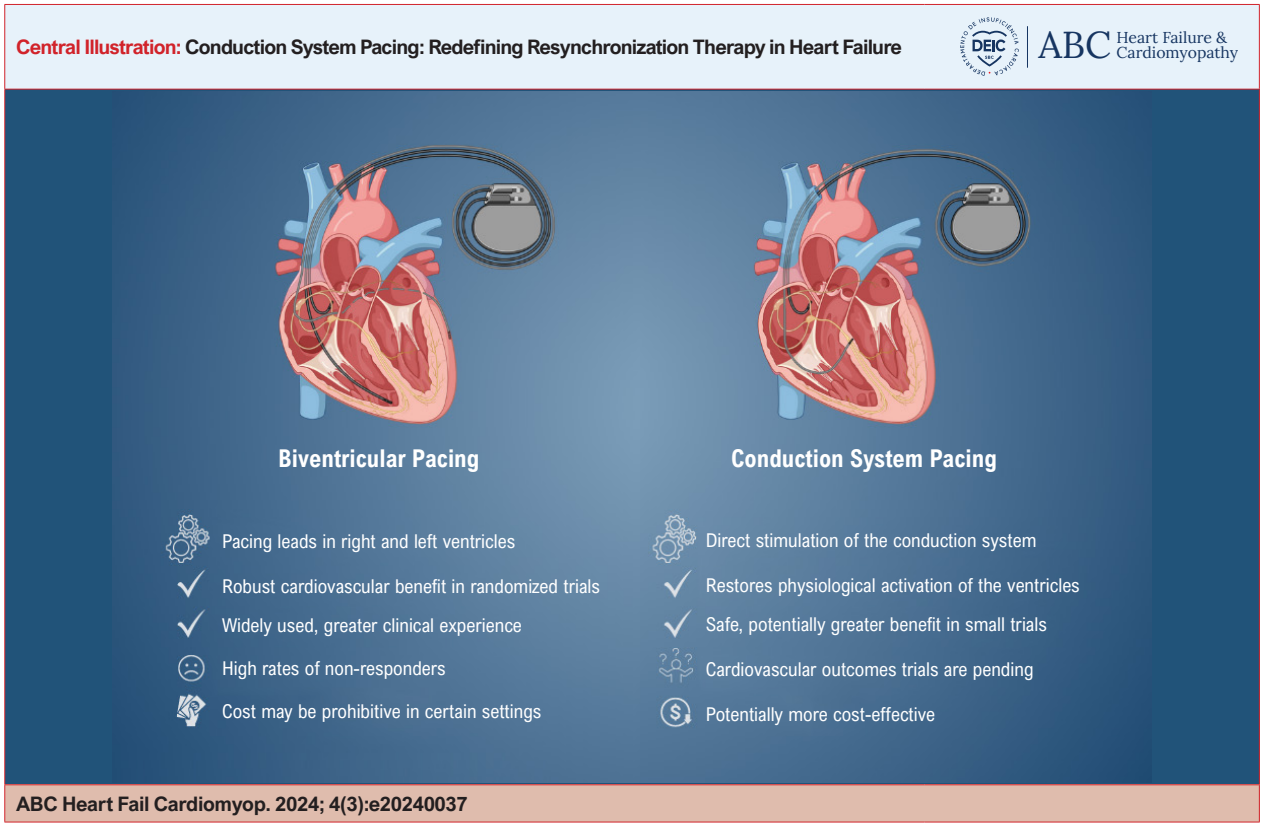

Abstract

Cardiac resynchronization therapy is a foundational treatment in patients with heart failure with reduced ejection fraction (HFrEF) and left bundle branch block (LBBB). Although resynchronization has traditionally been performed via biventricular pacing, this approach may be limited by a high rate of non-responders and elevated cost. Conduction system pacing, sometimes referred to as "physiologic" pacing, involves direct stimulation of the heart's intrinsic conduction pathways and has emerged as a promising alternative. Large intercontinental registries have supported the safety of conduction system pacing in different settings, with high procedural success and low complication rates that are comparable to biventricular pacing. Moreover, in small, randomized trials, conduction system pacing has led to similar or greater improvements in left ventricular ejection fraction and QRS duration versus biventricular pacing, potentially at a lower cost. Ongoing cardiovascular outcomes trials are expected to conclusively determine the role of conduction system pacing in the management of patients with HFrEF and LBBB.

Keywords

Cardiac Resynchronization Therapy; Left Bundle Branch Block; Bundle of His; Heart Failure

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Introduction

Cardiac resynchronization therapy (CRT) is a cornerstone in the treatment of heart failure with reduced ejection

fraction (HFrEF) and left bundle branch block (LBBB).[1-3] Traditionally, CRT has been achieved through biventricular pacing, which involves a left ventricular lead placed in the coronary sinus in addition to right ventricular and right atrial leads as used in conventional pacemakers.[4,5] However, the use of this technique is limited by elevated rates of non-responder patients, of up to 40%, in addition to its elevated cost, which can be prohibitive in low- or middle-income countries.[6-9]

Conduction system pacing, which involves direct stimulation of the heart's intrinsic conduction system, is a promising alternative to overcome the limitations of biventricular pacing. While this technique had limited applicability in the early 2000s, technological advancements in mapping and pacing leads have allowed conduction system pacing to become globally available as a safe and effective option to achieve cardiac resynchronization.[10-12] Pivotal studies explored direct His bundle pacing, establishing a foundation for this approach.[13,14] In 2017, the first reported case of left bundle branch area pacing[15] represented the dawn of a new chapter in resynchronization therapy and heart failure management.

Physiology of conduction system pacing

LBBB and ventricular dyssynchrony often occur as a consequence of cardiac remodeling in patients with advanced heart failure. Individuals with LBBB, QRS duration > 120-150 ms, and left ventricular ejection fraction (LVEF) ≤ 35% have a guideline-based indication to undergo CRT with the goal of decreasing disease morbidity and mortality.[16-18] In biventricular pacing, the traditional approach used in CRT, the delayed activation of the posterolateral wall is targeted with early pacing of the left ventricular lead, in addition to pacing of the right ventricular lead. This approach acknowledges the patient's faulty conduction system and overcomes the intrinsic dyssynchrony by stimulating the cardiac muscle directly in both ventricles.[19] Conduction system pacing, on the other hand, directly targets the His-Purkinje system from the right ventricle to restore the patient's ventricular activation pathways (Central Illustration).[20] This approach encompasses a range of techniques designed to engage the His-Purkinje system, including His bundle pacing and left bundle branch area pacing, allowing the operator to select the best approach for each patient. Conduction system pacing is sometimes referred to as "physiological pacing" because it leverages the intrinsic conduction system rather than focusing on direct muscle stimulation.[21]

Modalities of conduction system pacing

His Bundle Pacing

His bundle pacing was the first modality of conduction system pacing.[22] Capturing the His bundle became feasible with the development of specialized technology: a specific pacing lead is used to map the His bundle region, and a sheath is positioned at the tricuspid annulus, guiding lead placement in the membranous septum.[23] Tests performed during the procedure determine whether the lead captures His bundle tissue alone or in combination with surrounding ventricular tissue, referred to as selective and non-selective pacing, respectively. Direct His bundle pacing aims to restore the patient's conduction system and activate both ventricles concomitantly to improve dyssynchrony. However, because the His bundle lies proximally in the conduction pathway, this type of pacing is not well suited to overcome peripheral conduction disease and distal blocks in the left bundle.[24]

Left bundle branch area pacing

In 2017, after a failed attempt at His bundle pacing, an operator positioned the pacing lead 15 mm deeper into the interventricular septum towards the right ventricle apex and captured the left bundle branch for the first time.[15] Over the last decade, direct left bundle branch area pacing has become a viable alternative for patients with LBBB requiring CRT. In fact, given the high thresholds often required for His bundle pacing, left bundle branch area pacing has become the preferred method of conduction system pacing in many cases.[25,26] Typical LBBB, as defined by ECG features, is thought to indicate a proximal block that can more readily be corrected with left-bundle capture.[27] Consistent with this physiological observation, patients with typical LBBB exhibit better clinical response to conduction system pacing.[28]

Left ventricular septal pacing

Left ventricular septal pacing involves placing a lead deeply into the interventricular septum.[29] This approach is typically used when lead placement in the membranous portion of the septum fails and left bundle branch capture criteria are not met, leaving left ventricular septal pacing as a fallback alternative within the conduction system spectrum.[30] Left ventricular septal pacing stimulates both myocardial tissue and the intrinsic conduction system. Combining muscular and non-optimal conduction system pacing could offer more physiological ventricular activation than purely muscular stimulation, potentially reducing dyssynchrony.[31]

Optimized cardiac resynchronization therapy

Conduction system pacing may result in suboptimal resynchronization in patients with intraventricular conduction delay, non-LBBB, and atrial fibrillation.[32] In these cases, further adding a lead to a distal branch of the coronary sinus, as performed in biventricular pacing, may improve response to CRT.[32] This hybrid approach is termed "optimized" therapy: when conduction system pacing alone fails to correct ventricular dyssynchrony, a left ventricular lead may be added to His-bundle pacing or left bundle pacing (referred to as HOT-CRT and LOT-CRT, respectively).[33,34]

Safety and efficacy

Registries

The role of conduction system pacing in heart failure resynchronization has grown rapidly. Initially, the applicability

of His bundle pacing was limited due to concerns regarding higher pacing thresholds, which could theoretically lead to long-term consequences.[35] In contrast, left bundle branch area pacing has shown stable pacing thresholds and shortened QRS duration, which, in addition to robust clinical benefit data, consolidated its position as the preferred first-line conduction system pacing technique.[36] While large randomized trials of conduction system pacing in HFrEF are ongoing, multicenter registries have provided preliminary data on safety and effectiveness. The Multicentre European Left Bundle Branch Area Pacing Outcomes Study (MELOS) registry included 696 patients with HFrEF and 1,837 with bradycardia referred for conduction system pacing. Among patients with HFrEF, 82.2% of resynchronization procedures with conduction system pacing were successful. Overall, the complication rate was 11.7%, most commonly left ventricle perforation (3.7%) and septal lead dislodgement (1.5%). There were no periprocedural deaths or thromboembolic events. Independent predictors of septal lead implant failure included a larger left ventricular end-diastolic diameter (odds ratio [OR] 1.53 for every 10 mm enlargement) and a longer QRS duration (OR 1.08 per 10 ms increase).[37]

In 2022, Dal Forno et al. reported the first Brazilian case series on left bundle branch area pacing, showing a 96.2% success rate, a periprocedural reduction in QRS duration from a median of 146 ms to 120 ms ($p = 0.001$), and a 4% complication rate.[38]

The International Left Bundle Branch Area Pacing Collaborative Study Group (I-CLAS) is an intercontinental registry studying clinical outcomes in patients requiring CRT. Across 325 patients who underwent conduction system pacing in 8 centers, the success rate was 85% overall and reached 92% in patients with typical LBBB criteria. Complications comprised 4.2% of cases, most commonly lead dislodgement (2.5%), none of which were life-threatening.[39] In a subsequent analysis of 1,778 patients who underwent successful CRT, including 797 who received conduction system pacing, procedural complications were significantly lower with conduction system pacing than with biventricular pacing (3.8% vs. 7.5%, $p < 0.001$). Patients who underwent conduction system pacing, compared with biventricular pacing, had a shorter paced QRS duration (128 ms vs. 144 ms, $p < 0.001$), greater improvement in LVEF (13% vs. 10%, $p < 0.001$), and higher rates of hyper-responders (34% vs. 25%, $p < 0.001$), defined as either an improvement in LVEF of ≥20% or an achieved LVEF ≥50%. Conduction system pacing was also associated with a lower incidence of heart failure hospitalizations (12% vs. 19%, $p = 0.002$),[40] new-onset atrial fibrillation (2.8% vs 6.6%, $p = 0.008$), and malignant ventricular arrhythmias (4.2% vs. 9.3%, $p < 0.001$).[41]

An I-CLAS substudy on sex-specific outcomes found that women had a trend towards greater improvement in LVEF with left-bundle pacing compared with men (17.7% vs 10.3%, respectively).[42] Improvements in LVEF, end-diastolic volume, and end-systolic volume were particularly robust in women with LBBB, nonischemic cardiomyopathy, and QRS duration > 150 ms. In this observational study, women who received conduction system pacing had a 60% lower rate of heart failure hospitalizations compared with those receiving biventricular pacing (hazard ratio [HR], 0.40; 95% CI, 0.24 to 0.69; $p < 0.001$); the difference in men was attenuated and not statistically significant (HR, 0.80; 95% CI, 0.60 to 1.10; $p = 0.13$).[42]

The I-CLAS registry also assessed conduction system pacing outcomes in patients with failed biventricular pacing due to inability to access the coronary sinus (n = 156) or nonresponse to standard biventricular CRT (n = 44). The success rate of conduction system pacing implants was 94%, with a 5% non-fatal complication rate. LVEF improved from an average of 29% at baseline to 40% at approximately 12 months of follow-up ($p < 0.001$).[43] Managing patients who do not respond to biventricular pacing remains a challenge. In this situation, an alternative device upgrade can be achieved by adding a septal lead targeting the intrinsic conduction system.

Randomized controlled trials

Five randomized controlled trials have directly compared conduction system pacing with biventricular pacing in patients with HFrEF and bundle branch block (Table 1).[44-49] Follow-up ranged from 6 to 12.2 months, and the sample size varied from 40 to 100 participants. Initially, the conduction system pacing approach only included His bundle pacing, which led to high crossover rates and elevated pacing thresholds. In the His-SYNC trial, the first pivotal study, there was a 48% crossover rate from His bundle pacing to biventricular pacing.[44,45] Similarly, the His-Alternative Trial had a 28% crossover rate, mostly due to the high thresholds used to correct the LBBB.[46] The high number of procedure failures was linked to distal bundle blocks and non-specific intraventricular conduction delays, in which operators were either unable to correct the bundle branch block or required elevated thresholds. As techniques advanced to incorporate distal and deeper lead placement with left bundle branch area pacing, procedure success increased. In the two most recent clinical trials, crossover rates were numerically lower in patients randomized to conduction system pacing than in those randomized to biventricular pacing. Additionally, across each of the five clinical trials, patients randomized to conduction system pacing had a numerically lower rate of procedural complications. These results from randomized trials validate initial findings from observational studies and further demonstrate the safety and feasibility of conduction system pacing in the management of HFrEF.

All five studies were primarily designed to assess surrogate endpoints, including rates of successful lead implantation, change in QRS duration, improvement in left ventricular ejection fraction, and change in left ventricular activation time. Meta-analyses including the five trials reported greater improvement in LVEF (mean difference [MD], 3.6%; 95% CI, 1.53 to 5.74; $p < 0.01$) and reduction in QRS duration (MD, -4.03 ms; 95% CI, -7.95 to -0.11; $p = 0.04$) in the conduction system pacing group.[50] These trials were underpowered to assess the

Table 1 – Clinical trials comparing conduction system pacing versus biventricular pacing in patients with heart failure and reduced ejection fraction

Randomized trial	Key inclusion criteria	Sample size	Female, n (%)	Ischemic, n (%)	Complete LBBB, n (%)	Crossover, n (%)		Periprocedural complications, n (%)		Change in QRS duration (ms)†		Change in LVEF (%)†	
						CSP to BVP	BVP to CSP	CSP	BVP	CSP	BVP	CSP	BVP
His-SYNC[44,45]	NYHA I–IV, LVEF ≤ 35%, LBBB and non-LBBB, QRS > 120 ms	40	15 (38)	26 (65)*	25 (62)	10 (48)	5 (26)	1 (2,5)	3 (7,5)	-28¶‡	-13‡	+5,6¶‡	+3,5¶‡
His-Alternative[46]	NYHA II–IV, LVEF ≤ 35%, LBBB, QRS > 130 ms for women or > 140 ms for men	50	18 (36)	11 (22)	50 (100)	7 (28)	1 (4)	0 (0)	1 (4)	-34¶	-33¶	+16	+13
LBBP-RESYNC[47]	NYHA II–IV, LVEF ≤ 40%, LBBB, QRS > 130 ms for women or > 140 ms for men	40	20 (50)	0 (0)	40 (100)	2 (10)	4 (20)	1 (5)	0 (0)	-43¶	-38¶	+21¶	+16¶
LEVEL-AT[48]	NYHA I–IV, LVEF ≤ 35%, LBBB and QRS ≥ 130 ms or non-LBBB and QRS ≥ 150 ms	70	22 (31)	22 (31)	43 (61)	8 (23)	2 (6)	4 (11)	4 (11)	-53¶	-48¶	+12	+13
HOT-CRT[49]	NYHA II–IV and either (i) LVEF ≤ 35%, LBBB, and QRS > 120 ms, or (ii) LVEF ≤ 50%, non-LBBB, and QRS > 150 ms	100	31 (31)	39 (39)	62 (62)	2 (4)	9 (18)	3 (6)	10 (20)	-27¶	-25¶	+12¶	+8¶

*Complete left bundle branch block using criteria determined by Strauss et al.27 ¶ $p < 0.05$ between conduction system pacing and biventricular pacing. * Patients with coronary artery disease at baseline. † Results were reported using the intention-to-treat analysis with six months of follow-up. Differences were extracted directly or derived from mean or median values, as reported in each trial. ‡ Due to high crossover rates, a secondary analysis reported six-month follow-up results by treatment received. Change in QRS duration was -49 ms ($p < 0.001$) with conduction system pacing (n = 16) and -1 ms ($p = 0.82$) with biventricular pacing (n = 24). Median changes in LVEF were +7.2% and +5.9%, respectively ($p = 0.17$). BVP: biventricular pacing; CSP: conduction system pacing; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association functional class.*

efficacy of conduction system pacing on cardiovascular outcomes.

Guidelines

The 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing lists conduction system pacing as a class IIa recommendation for CRT when biventricular pacing fails and as a class IIb recommendation as an alternative first-line treatment in patients with heart failure with LVEF ≤ 35%, QRS duration ≥150 ms, LBBB, sinus rhythm, New York Heart Association (NYHA) class II-IV, and on optimized medical therapy. Additionally, His or left bundle pacing are recommended as class IIb for heart failure patients with mildly reduced ejection fraction (36-50%), LBBB, and QRS ≥150 ms to maintain LVEF.[51] The 2021 ESC Guidelines on cardiac pacing and CRT updated His bundle pacing to a class IIa recommendation for patients undergoing CRT who are unable to have a coronary sinus lead implanted. These guidelines refer to conduction system pacing as a "promising novel technique for delivering CRT" and indicate that recommendations will likely be updated once data from future randomized studies become available.[16] The 2023 Brazilian Guidelines for Cardiac Implantable Electronic Devices recommend conduction system pacing as class IIa for CRT in patients with symptomatic heart failure, LVEF ≤35%, and QRS ≥130 ms, and as class IIb for biventricular pacing nonresponders.

Perspectives

Randomized trials are expected to provide the definitive answer as to whether conduction system pacing will become the standard CRT procedure in patients with HFrEF and LBBB. To address the current gap, the authors are conducting the PhysioSync-HF Trial (NCT05572736), a multicenter, randomized, patient-blinded trial designed to assess non-inferiority in a hierarchical endpoint of all-cause mortality, heart failure hospitalizations, urgent visits for heart failure, and change in LVEF from baseline to 12 months. The study has enrolled 179 participants across 14 sites in Brazil and is expected to complete follow-up by the end of 2024. The Left vs. Left Trial (NCT05650658) is the first randomized trial of conduction system pacing in HFrEF patients that is well-powered to investigate effects on all-cause mortality and heart failure hospitalizations. The trial is anticipated to enroll 2136 participants and be finalized in 2029.

Conclusion

Conduction system pacing has rapidly emerged as a feasible alternative for cardiac resynchronization therapy in patients with HFrEF and LBBB. Observational studies and small randomized trials have reported improvements in surrogate outcomes, such as left ventricular ejection fraction and QRS duration, in patients receiving conduction system pacing compared with standard biventricular pacing. Ongoing randomized studies designed to assess cardiovascular outcomes are expected to determine

whether conduction system pacing will become the standard of care in heart failure management.

Author Contributions

Conception and design of the research and Writing of the manuscript: Ternes CMP, Zimerman A; Critical revision of the manuscript for content: Zimerman A.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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