Conduction System Pacing for CRT: A Physiological Alternative

Bengt Herweg [1,2] Mishal Mumtaz [1] and Pugazhendhi Vijayaraman [3]

1. Division of Cardiovascular Sciences, University of South Florida Morsani College of Medicine, Tampa, FL, US; 2. Tampa General Hospital. Tampa, FL, US; 3. Geisinger Heart Institute, Wilkes-Barre, PA, US

Abstract

There are many factors contributing to the failure of conventional CRT with biventricular pacing, including coronary anatomy and an inability to stimulate diseased tissue. In this paper, we review evolving conduction system pacing (CSP), a physiological alternative to conventional CRT. CSP allows correction of bundle branch block and provides new opportunities to address multiple limitations of conventional CRT. Further studies are required to determine how the techniques are best applied in specific clinical situations.

Keywords

Conduction system pacing, CRT, left bundle branch area pacing, biventricular pacing

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Correspondence: Bengt Herweg, Division of Cardiovascular Sciences, USF Health South Tampa Center, 2 Tampa General Circle, Tampa, FL 33606, US. E: Bengt@usf.edu

The significance of longitudinal dissociation in the His bundle and the ability to correct left bundle branch block (LBBB) by pacing of the distal His bundle were described in the 1970s by Narula, Scherlag et al. and El-Sherif et al.[1–3] These early observations in human hearts and animal models formed the basis of CRT with conduction system pacing (CSP) to correct LBBB. However, it took 22 years until Deshmukh et al. demonstrated that permanent His bundle pacing (HBP) can be performed and another 5–10 years for Morina-Vazquez et al. and Lustgarten et al. to demonstrate correction of LBBB by permanent HBP.[4–6] A timeline of developments in CRT and CSP is shown in *Figure 1*.

Ventricular conduction disturbance, most commonly LBBB, is present in approximately one-third of heart failure (HF) patients, leading to loss of synchronous ventricular contraction. CRT using simultaneous biventricular pacing (BVP) was first conceptualised and patented by Mower in 1990 for the non-pharmacological management of HF.[7] In 1994, Cazeau et al. reported the acute haemodynamic response and clinical follow-up for a patient with cardiomyopathy and LBBB who underwent four-chamber pacing (including implantation of a left ventricular [LV] epicardial lead).[8] Currently, CRT with BVP is the only HF therapy that improves cardiac function, functional capacity and survival while decreasing cardiac workload and hospitalisation for HF.[9–11] Although observational data on CRT with CSP are promising, randomised controlled clinical trials are needed to determine whether the clinical results following CSP are similar to those seen following conventional CRT with BVP.[12,13] In addition, it may be useful in selected cases to combine BVP and CSP resynchronisation strategies in the form of His-optimised (HOT)- or left bundle-optimised (LOT)-CRT (*Figure 2*).

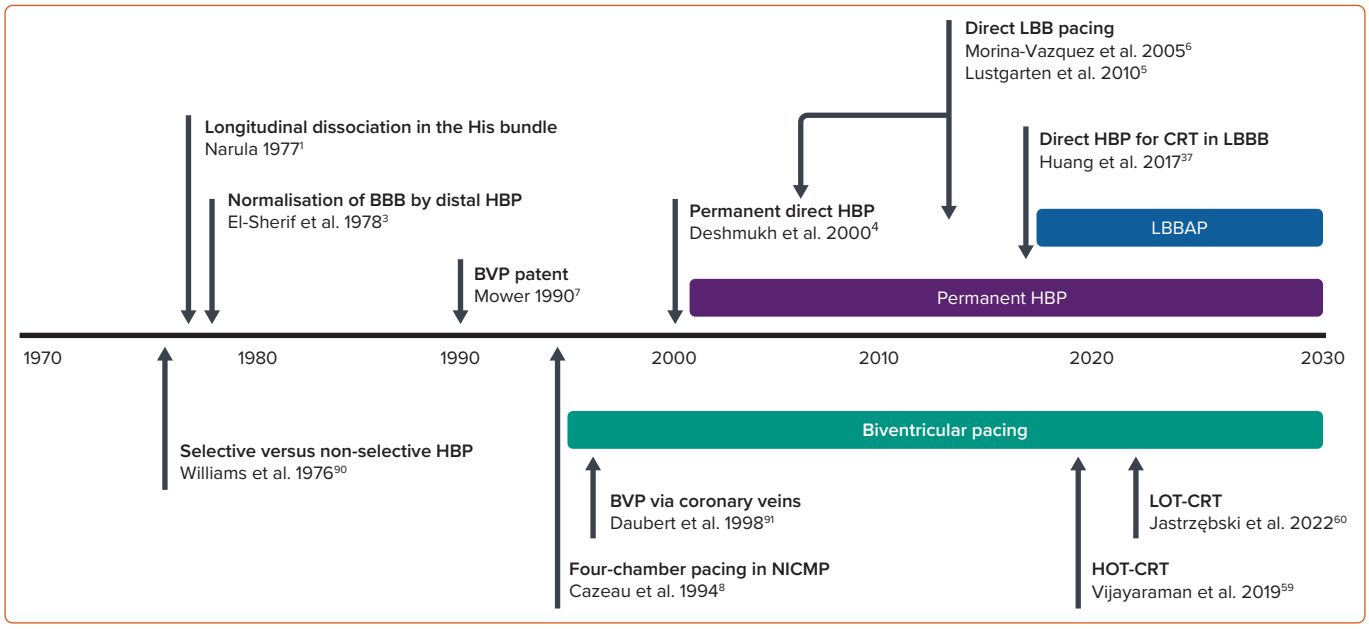
Challenges encountered during CSP include frequently elevated capture thresholds and/or loss of left bundle (LB) capture with HBP, an inability to penetrate the septum due to septal scar with LB branch area pacing (LBBAP) and tricuspid regurgitation associated with the implantation of LBBAP leads in close proximity (≤16 mm) to the tricuspid annulus.[14–16]

Non-response/Incomplete Response to Biventricular Pacing

Responses to BVP are variable and range from complete normalisation of cardiac function to a lack of benefit. There are many potential reasons for the failure of conventional CRT (*Table 1*).[17] For example, the delivery of LV pacing depends on the coronary venous anatomy and can be complicated by suboptimal LV lead position (apical or anterior cardiac vein), a high LV threshold, lead dislocation and diaphragmatic pacing.[18] Other factors limiting the use of conventional CRT include myocardial scar, fibrosis and an inability to effectively stimulate diseased tissue, and can result in slow myocardial impulse propagation and LV latency, with these effects amplified by the presence of right ventricular anodal capture.[19–22] The inability to stimulate severely diseased myocardium or myocardial scar (associated with a stimulus-to-QRS latency ≥80 ms) presents a major obstacle to the effective delivery of CRT. Lesser degrees of latency (≥40 ms) are observed in almost 20% of patients undergoing CRT, and are more frequent in patients with ischaemic cardiomyopathy.[23]

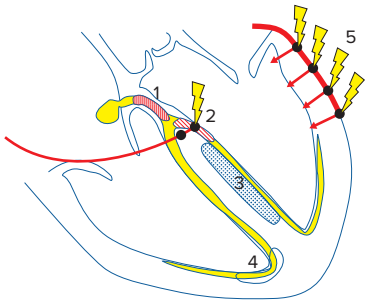
Many of the challenges to conventional CRT have been improved by ventriculo-ventricular interval programmability, which allows for the pre-excitation of slowly conducting scar tissue; quadripolar LV leads, which allow for electronic repositioning; multipoint stimulation; and targeted LV pacing from the LV lateral base.[24–26] Furthermore, the measurement of sensed and paced interventricular delays may help predict the response to BVP and in the selection of patients who may benefit from CSP.[27] In conventional CRT, fusion of LV pacing with the spontaneously conducted QRS has major advantages, and the release of device-based fusion optimisation algorithms, such as adaptive CRT (Medtronic) and SyncAV (Abbott), has resulted in improved clinical responses and a decreased

Figure 1: Timeline of the Development of CRT and Conduction System Pacing



BBB = bundle branch block; BVP = biventricular pacing; HBP = His bundle pacing; HOT-CRT = His-optimised CRT; LBBB = left bundle branch block; LBBAP = left bundle branch area pacing; LOT-CRT = left bundle-optimised CRT; NICMP = non-ischaemic cardiomyopathy.

Figure 2: Possible CRT Strategies



Possible CRT strategies:
- HBP-CRT = Site 1
- LBBP-CRT = Site 2
- BVP-CRT = Sites 4 and 5
- HOT-CRT = Sites 1 and 5
- LOT-CRT = Sites 2 and 5

BVP = biventricular pacing; HBP = His bundle pacing; HOT-CRT = His optimised-CRT; LBBP = left bundle branch pacing; LOT-CRT = left bundle-optimised CRT. Source: Herweg et al. 2022.[92] Reproduced with permission from Elsevier.

incidence of AF.[28–31] However, many patients have underlying atrioventricular (AV) block, not allowing the delivery of fused CRT. Furthermore, CRT requires LV pre-excitation, which may conflict with the delivery of ventricular pacing at the optimal AV interval. These obstacles limit the application of conventional CRT. However, CSP, alone or in conjunction with LV pacing, may prove to be a viable solution in some of these cases. The His–Purkinje system is an endocardial structure. In terms of CRT response, studies have shown that endocardial stimulation in closer proximity to the specialised conduction system is more effective than epicardial stimulation, and may represent a form of distal CSP.[32,33] Finally, both conventional CRT and CSP can be derailed by AF and frequent premature ventricular contractions, requiring ablation of either the AV junction or the premature ventricular contraction focus.[34]

Physiological/Haemodynamic Advantages of Conduction System Pacing

A compelling rationale for the use of CSP is its ability to restore physiological ventricular activation and repolarisation. The extent to which normal physiological activation of the ventricular myocardium is achieved depends on the pacing strategy and pacing site (*Figure 3*). Although correction of LBBB by selective HBP (with the recruitment of fibres predestined to become the LB) represents the purest form of physiological resynchronisation, it is not feasible in all patients and its use is limited by high pacing thresholds, a low signal amplitude with compromised sensing and oversensing of His and atrial potentials.[35,36] In contrast, deep septal LBBAP, initially described by Huang et al., is associated with better pacing thresholds, a larger signal amplitude and decreased potential of unwanted oversensing of atrial electrograms.[37,38] The larger target area for LBBAP may be associated with a shorter time to master the technique.[39] However, deep septal LBBAP is compromised by the non-selective premature capture of the septal myocardium and later activation of the right ventricle, with the potential to diminish the resynchronisation effect. The critical common denominator for all forms of CSP appears to be the early capture of the specialised conduction system, which may not always be easily achieved.

Acute Haemodynamic Effects of Conduction System Pacing

Acute haemodynamic studies have shown that CSP may result in superior electrical and mechanical resynchronisation compared with BVP.[40,41] Arnold et al. demonstrated reduced QRS duration and LV activation times, a reduced dyssynchrony index and an improved arterial blood pressure response with HBP than with BVP.[40] Furthermore, Ali et al. demonstrated that HBP delivered better ventricular resynchronisation than LBBAP because right ventricular activation was slower during LBBAP.[42] However, LBBAP was not inferior to HBP with respect to LV electrical resynchronisation and the acute haemodynamic blood pressure response.[42]

Elliott et al. demonstrated superior electrical resynchronisation and a higher proportion of acute haemodynamic responders during biventricular (BiV) endocardial pacing and LBBAP compared with BiV epicardial pacing.[43] Electrical resynchronisation was similar between BiV endocardial pacing and LBBAP; however, septal scar seemed to attenuate the response to LBBAP.[43]

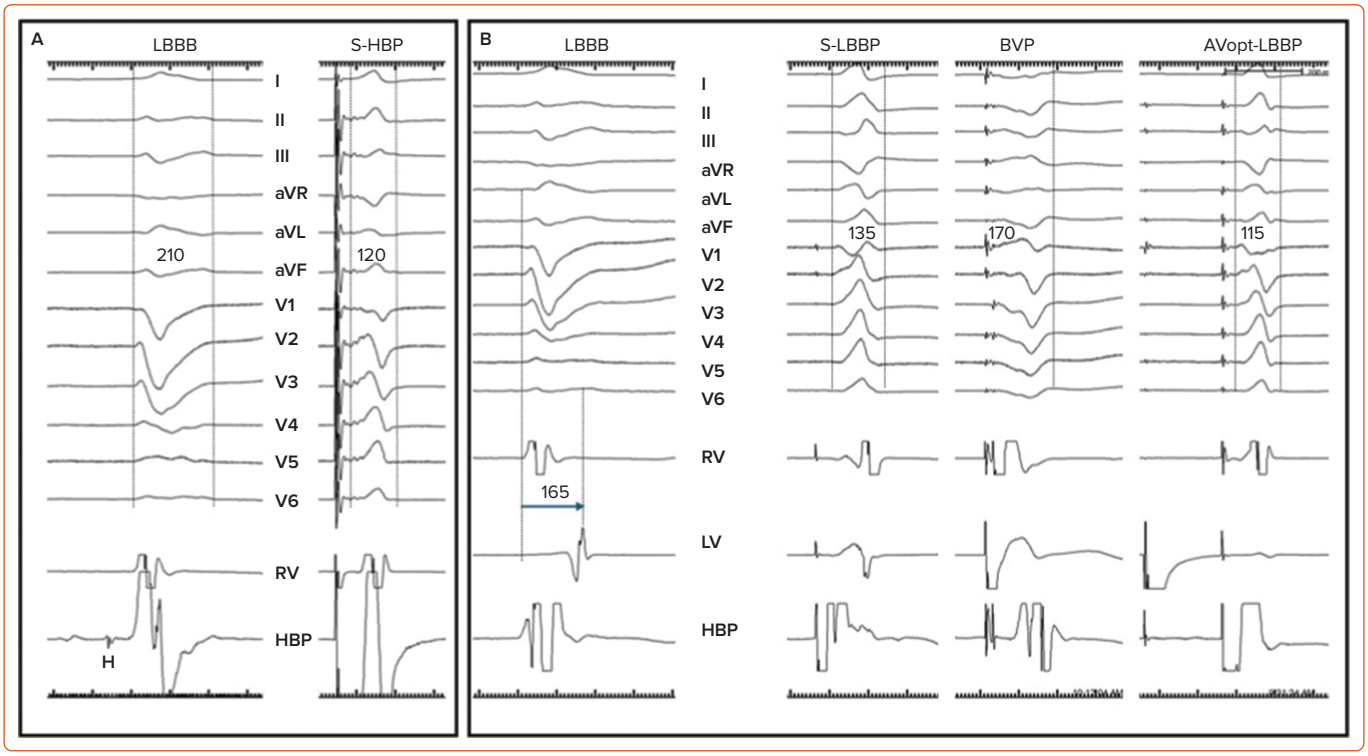
Although conventional CRT achieves a reduction in LV dyssynchrony, CSP may result in complete restoration of cardiac electrical depolarisation and

Table 1: Challenges Associated With Biventricular Pacing and Possible Solutions

Challenges	Conventional solutions	Solutions offered by CSP
Delivery of LV pacing is limited by cardiac venous anatomy • Loss of capture • Lead dislocation • Suboptimal lead position (e.g. apical, ACV or MCV) • Diaphragmatic pacing	• Quadripolar LV lead • Epicardial LV lead • QLV-guided lead placement • Endocardial LV pacing	CSP can address many of these problems: CSP does not rely on coronary venous anatomy and is not associated with the complications encountered during coronary venous pacing, such as poor lead position, and does not cause diaphragmatic pacing
Suboptimal RV/LV depolarisation balance scar • Slowed myocardial impulse propagation in diseased tissue • LV latency (long stimulus-to-QRS interval) • RV anodal capture	• Quadripolar LV lead • Multisite/multipoint LV pacing • Endocardial LV pacing	• May deliver more effective CRT in these scenarios if there is no septal scar
AV synchrony • Inter-/intra-atrial block • Late atrial sensing • Lack of LV pre-excitation due to fusion	• AV junctional ablation (precludes fused/adaptive CRT)	• Can be used in conjunction with AV junctional ablation and maintain a narrow QRS
AV block • Inability to deliver fused BVP		• HOT-CRT/LOT-CRT allow combination of CSP and LV pacing (equivalent to fused CRT)
Non-LBBB • RBBB • IVCD	Questionable clinical outcomes of BVP in patients with QRS ≤150 ms	• CSP may be associated with better outcomes in this population
Competing PVC or AF derailing CRT	• Ablation	• May decrease the burden of ventricular and atrial arrhythmias
Ventricular pro-arrhythmia	• Inhibit LV pacing = no CRT	• May improve with CSP

ACV = anterior cardiac vein; AV = atrioventricular; BVP = biventricular pacing; CSP = conduction system pacing; HOT-CRT = His optimised CRT; IVCD = intraventricular conduction defect; LBBB = left bundle branch block; LOT-CRT = left bundle optimised CRT; LV = left ventricular; MCV = mid-cardiac vein; PVC = premature ventricular contraction; QLV = intrinsic left ventricular electric delay; RBBB = right bundle branch block; RV = right ventricular.

Figure 3: Comparison of His Bundle Pacing, Left Bundle Pacing and Biventricular Pacing in a Patient With Left Bundle Branch Block



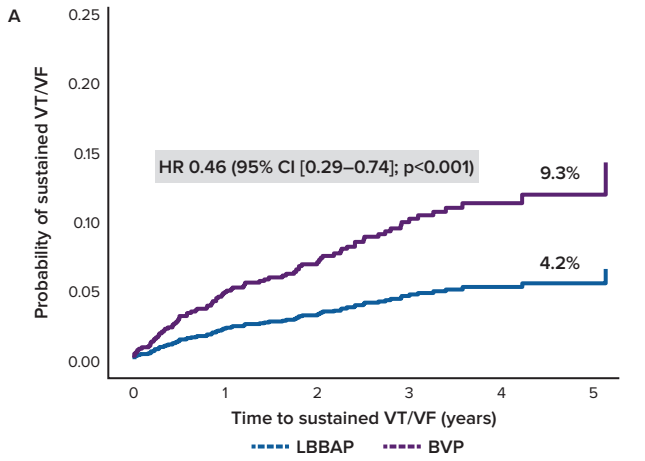
Twelve-lead ECGs and intracardiac electrograms in a patient with LBBB undergoing different CRT strategies. A: S-HBP. B: S-LBBP, BVP and AVopt-LBBB. Both S-HBP and AVopt-LBBB achieve comparable, more complete electrical resynchronisation than conventional BVP. AVopt = atrioventricular-optimised fused left bundle branch pacing; BVP = biventricular pacing; LBBB = left bundle branch block; LV = left ventricle; RV = right ventricle; S-HBP = selective His bundle pacing; S-LBBP = selective left bundle branch pacing.

repolarisation. There is limited evidence that normalisation of ventricular activation by His–Purkinje CSP is associated with improved diastolic function.[44,45]

Reduction in Ventricular and Atrial Arrhythmias

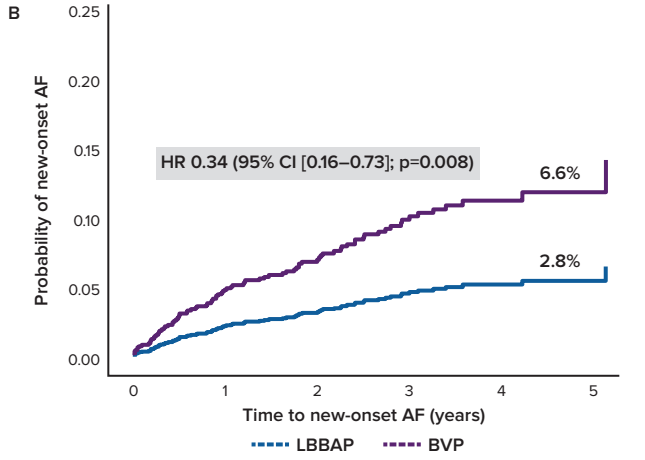
Physiological resynchronisation by CSP may lower the risk of arrhythmias. In a large multicentre observational study, LBBAP was

Figure 4: Cox Survival Curves



No. patients with outcome

LBBAP	707	629	404	198	41	6
BVP	707	628	482	333	170	59



No. patients with outcome

LBBAP	436	397	255	123	24	3
BVP	454	404	317	229	115	38

A: Probability of sustained VT/VT over time among all patients (n=1414). LBBAP was associated with a lower incidence of sustained VT/VF in patients undergoing CRT compared with BVP.
B: Probability of new-onset AF over time in patients without a prior history of AF (n=890). LBBAP was associated with a lower incidence of new-onset AF compared with BVP. BVP = biventricular pacing; LBBAP = left bundle branch area pacing; VT = ventricular tachycardia. Source: Herweg et al. 2024.[46] Reproduced with permission from Wolters Kluwer Health.

associated with a lower incidence of sustained and non-sustained ventricular tachyarrhythmias and new-onset AF compared with BVP (*Figure 4*).[46] Physiological resynchronisation with CSP may not be associated with the ventricular pro-arrhythmia that is occasionally encountered with BVP and is likely a consequence of the reversal of activation in the LV lateral wall (epi- to endocardial) and the location of LV leads within scar tissue.[47–50]

In a prospective study of patients with non-ischaemic cardiomyopathy undergoing CRT with HBP for LBBB correction, Moriña-Vázquez et al. observed gradual improvement in multiple repolarisation parameters associated with arrhythmic death (QT interval, QT dispersion, T wave duration, the interval from the peak of the T wave to the end of the T wave [Tp–Te] and the Tp–Te:QT ratio).[51] The use of permanent HBP to manage ventricular arrhythmias that developed after the initiation of BVP and were unresponsive to anti-arrhythmic and ablative therapies has been reported.[52] More complete resynchronisation with CSP may diminish the incidence of ventricular and atrial arrhythmias.[46]

Conduction System Pacing in Right Bundle Branch Block and Intraventricular Conduction Defect

Conventional CRT in patients with non-LBBB (i.e. right bundle branch block [RBBB] and intraventricular conduction defect [IVCD]) is currently recommended for patients with a QRS duration >150 ms, but is less established in patients with RBBB and a QRS duration ≤150 ms.[53] A meta-analysis of five randomised clinical trials showed that QRS duration >140 ms is a powerful predictor of the effects of CRT on morbidity and mortality independent of QRS morphology in patients with HF and moderate to severe LV dysfunction.[54]

In a study of patients with New York Heart Association (NYHA) class II–IV HF, reduced LV ejection fraction (EF) and RBBB with a QRS duration >120 ms, HBP was successful in 37 of 39 (95%) patients, with narrowing of the RBBB in 29 of 37 patients (78%).[55] The His capture and bundle branch block correction thresholds were 1.1 ± 0.6 and 1.4 ± 0.7 V at 1.0 ms, respectively.[55] After a mean (± SD) follow-up of 15 ± 23 months, QRS narrowed from 158 ± 24 to 127 ± 17 ms (p=0.0001), LVEF increased from 31 ± 10% to 39 ± 13% (p=0.004) and NYHA functional class increased from 2.8 ± 0.6 to 2.0 ± 0.7 (p=0.0001) with HBP.[55]

In another study of 121 patients (mean age 74 ± 12 years, mean LVEF 35 ± 9%; 25% female, 49% ischaemic cardiomyopathy), LBBAP was successful in 107 (88%).[56] The QRS axis at baseline was normal in 24% of patients, with the left axis in 63% of patients and right axis in 13% of patients. The LBBAP threshold and R wave amplitudes were 0.8 ± 0.3 V at 0.5 ms and 10 ± 9 mV at implantation, respectively, and remained stable during a mean follow-up period of 13 ± 8 months.[56] LBBAP resulted in narrowing of the QRS duration from 156 ± 20 to 150 ± 24 ms (p=0.01) with a mean R wave peak time in V6 of 85 ± 16 ms.[56] LVEF improved from 35 ± 9% to 43 ± 12% (p<0.01).[56] Clinical and echocardiographic responses were observed in 60% and 61% of patients, respectively. Female sex and a reduction in QRS duration with LBBAP were predictive of an echocardiographic response and super-response.[56]

Combination of Conduction System Pacing With Conventional CRT

In advanced cardiomyopathy, LBBB and IVCD may coexist. This may amplify LV asynchrony because LV activation in the setting of LBBB relies on long myocardial conduction pathways, and coexisting IVCD will further delay myocardial activation. Therefore, CSP may paradoxically improve the impact of coexisting IVCD. Under these circumstances, resynchronisation may be more complete if the intervention is at the level of the specialised conduction system in conjunction with sequential LV pacing (in myocardial areas activated late).

There have been a few observational studies on HOT-CRT.[57,58] In a small retrospective observational multicentre study, HOT-CRT was performed in a series of 27 patients with LBBB/IVCD in whom partial or insignificant QRS narrowing was achieved by HBP alone compared with baseline.[59] At baseline, all patients had therapy-refractory NYHA class III–IV HF symptoms and LVEF ≤35%. After device implantation, HOT-CRT resulted in improved electrical resynchronisation compared with conventional BVP or HBP alone. The QRS duration decreased from 183 ± 27 to 120 ± 16 ms

(34%) with HOT-CRT, compared with a decrease from 183 ± 27 to 162 ± 18 ms (11%) with conventional BVP (p<0.05).[59] The investigators observed significant echocardiographic and clinical improvement in patients with advanced HF treated with HOT-CRT.[59]

A multicentre observational study of 112 patients with CRT indication undergoing LOT-CRT reported an implant success rate of 81%.[60] LOT-CRT resulted in improved electrical resynchronisation compared with conventional BVP or LB branch pacing (LBBP) alone. The QRS duration decreased from 182 ± 267 to 144 ± 22 ms (21%) with LOT-CRT, to 170 ± 30 ms (7%) with conventional BVP and to 162 ± 23 ms (11%) with LBBP alone (p<0.001).[60] Improvements were also seen in LVEF (from 28 ± 10% to 37 ± 12%; p<0.001) and NYHA functional class (from 2.9 ± 0.6 to 1.9 ± 0.6; p<0.0001).[60]

In the HOT-CRT prospective randomised controlled trial, 100 patients (31% female, mean [± SD] age 70 ± 12 years, LVEF 31.5 ± 9.0%) were randomised to either the HOT-CRT arm (n=50) or BVP arm (n=50).[61] If CSP resulted in incomplete electrical resynchronisation, a coronary sinus lead was added. HOT-CRT was successful in 48 (96%) patients and BVP-CRT was successful in 41 (82%; p=0.03).[61] The QRS duration decreased significantly from 164 ± 26 to 137 ± 20 ms in the HOT-CRT arm and from 166 ± 28 to 141 ± 19 ms in the BVP arm. Fluoroscopy duration was similar in the HOT-CRT and BVP arms (18.8 ± 12.4 versus 23.8 ± 12.4 minutes, respectively; p=0.05), as was procedure duration (119 ± 42 versus 114 ± 36 minutes, respectively; p=0.5).[61] The change in LVEF at 6 months (primary outcome) was greater in the HOT-CRT than BVP arm (12.4 ± 3.0% versus 8.0 ± 10.1%; p=0.02), whereas the primary safety endpoint was similar (98% versus 94%, respectively; p=0.62). An echocardiographic response (i.e. improvement in LVEF >5%) occurred in 80% and 61% of patients in the HOT-CRT and BVP arms, respectively (p=0.06). Complications occurred in 3 (6%) and 10 (20%) patients in the HOT-CRT and BVP arms, respectively (p=0.03).[61] It is important to understand that HOT-CRT was only delivered and necessary in five patients (in whom CSP resulted in incomplete resynchronisation). Therefore, the results of this trial are more supportive of CSP by LBBAP (which was, in fact, delivered per protocol in 46/57 patients including patients cross over).

CSPOT (NCT04905290) is a prospective observational acute haemodynamic cross-over trial comparing conventional BVP, LBBP and LOT-CRT (*Supplementary Table 1*). At device implantation, all subjects underwent an acute pacing protocol comparing BVP, LBBP and LOT-CRT, serving as their own control. The primary outcomes of the electrical resynchronisation response at the time of implantation and the haemodynamic response measured by LV dP/dt_{max} have been published.[62]

LOT-CRT decreased QRS duration more than LBBAP and BVP. LOT-CRT increased LV dP/dtmax similarly to BVP and more than LBBAP alone. Compared with patients with LBBB, those with IVCD experienced less QRS reduction during resynchronisation pacing but similar improvements in LV dP/dtmax. The incremental value of LOT-CRT over LBBAP on LV dP/dtmax was most pronounced in subjects with a baseline QRS ≥171 ms and in subjects with deep septal pacing only. Further, anodal capture during bipolar LBBAP resulted in a diminished LV contractile force and earlier RV activation but no change in QRS duration when compared with unipolar LBBAP.[62]

Secondary outcomes at the 6-month follow-up include change in LVEF, LV end-systolic volume and a composite score based on mortality, HF events, termination of device function, NYHA functional class and patient global assessment.

Mapping Guidance in Choice of CRT

Upadhyay et al. performed LV endocardial septal mapping with a multielectrode catheter in patients with and without LBBB.[63] Of the patients with an LBBB pattern, complete conduction block within the proximal left conduction system was observed in 64% (n=46) and intact Purkinje activation was seen in the remaining 36% (n=26).[63] Intact Purkinje activation was observed in all controls (no LBBB). The site of block in patients with complete conduction block was at the level of the left His bundle in 72% and in the proximal LB branch in 28%.[63] HBP corrected wide QRS in 54% of patients with an LBBB pattern and in 85% of those with complete conduction block (94% left intrahisian, 62% proximal LB branch).[63] Correction of QRS with HBP was not seen in any patient with intact Purkinje activation.[63] Whether high-density mapping of the His–Purkinje system can predict implant success rates for permanent CSP remains to be investigated. An explanation for the findings reported by Upadhyay et al. may be that patients with slowed conduction or block in the more distal segments of the LB may not respond well to proximal HBP or LBBAP.

Ponnusamy et al. demonstrated that the presence of septal scar with transmural late gadolinium enhancement on cardiac magnetic resonance predicted LBBAP implant failure with high sensitivity and specificity.[16] A preprocedural MRI with gadolinium may therefore be a useful adjunct test to plan CRT procedures with either CSP or BVP depending on the distribution of the myocardial scar.

Available Evidence and Ongoing Trials

His Bundle Pacing

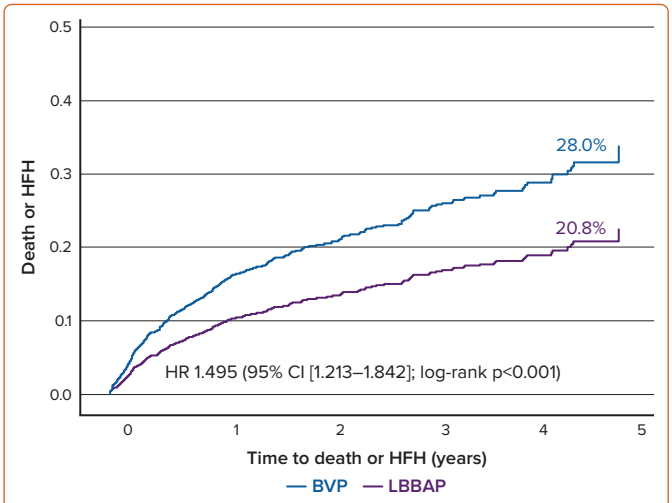
Numerous studies have investigated HBP with LB recruitment as a potential CRT strategy (*Supplementary Table 1*).[5,36,40,44,55,64–71] These studies demonstrated a marked reduction in QRS duration, improved LVEF and improved NYHA functional class. However, it is important to acknowledge that most of these studies are observational and non-randomised. Only two studies have randomised HBP against BVP with a limited number of participants.[44,72]

The HIS SYNC trial was a randomised pilot study comparing CRT with HBP to CRT with BVP in 41 patients.[73] Due to an inability to achieve appropriate resynchronisation and QRS narrowing, 10 of 21 (48%) patients crossed over from the HBP arm to the BVP arm. Similarly, 5 of 20 (25%) patients in the BVP arm crossed over to the HBP arm due to an inability to achieve appropriate coronary venous lead placement. This emphasises the complementary nature of both pacing techniques. However, the HIS SYNC trial showed a trend towards a more significant reduction in QRS duration with HBP. At a median follow-up of 6.2 months, the HBP and BVP arms showed similar improvements in LVEF.[73]

Vinther et al. published a small randomised study of 50 patients comparing CRT with HBP to CRT with BVP in patients with HF and LBBB.[72] CRT with HBP resulted in similar clinical and physical improvements to those seen with BVP at the expense of higher pacing thresholds. In all, 28% of patients crossed over from HBP to BVP because of an inability to achieve LB capture.[72]

The HOPE-HF trial assessed whether AV-optimised HBP is superior to no pacing in patients with HF, an LVEF ≤40%, a PR interval ≥200 ms and either a QRS duration ≤140 ms or RBBB.[74] The study found that HBP did not

Figure 5: Cox Survival Curve Analysis for the Composite Endpoint of Death or Heart Failure Hospitalisation Over Time (n=1,778)



Cox survival curve analysis demonstrated a statistically significant reduction in the primary composite outcome of all-cause mortality or HFH with LBBAP compared with BVP.[89] BVP = biventricular pacing; HFH = hospitalisation for heart failure; LBBAP = left bundle branch area pacing. Source: Vijayaraman et al. 2023.[89] Adapted with permission from Elsevier.

increase peak oxygen uptake, but did significantly improve quality of life.[74] The HOPE-HF trial highlights the potential of HBP as a promising alternative to traditional pacing methods for patients with HF with first-degree AV block.[74]

In summary, although HBP can achieve excellent electrical resynchronisation in most patients, its use appears to be limited by elevated pacing thresholds, low R wave amplitude and oversensing of atrial electrograms, as well as more distal conduction block below the level of the His bundle.[36,40,64,65] Suboptimal long-term lead performance due to elevated capture thresholds and/or loss of LB capture requires lead revision in 7–11% of patients undergoing HBP.[14,36]

Left Bundle Branch Area Pacing

There are many observational and two small randomised studies investigating LBBAP as a CRT strategy (*Supplementary Table 1*).[75–85] According to these studies, LBBAP has emerged as a viable alternative to HBP and is associated with lower pacing thresholds, larger R wave amplitude and a lack of far-field oversensing of atrial electrograms. The LBBAP technique can be mastered in a shorter period of time.[86–88] The discussion below is limited to the larger observational studies and the few randomised trials.

The recently published I-CLAS observational study compared the clinical outcomes of 1,778 patients with HF with an LVEF of ≤35% undergoing CRT with either BVP or LBBAP.[89] Paced QRS duration during LBBAP was significantly shorter than baseline (128 ± 19 versus 161 ± 28 ms, respectively; p<0.001) and significantly shorter than during BVP (144 ± 23 ms; p<0.001). Following CRT, LVEF improved from 27 ± 6% to 41 ± 13% (p<0.001) with LBBAP and from 27 ± 7% to 37 ± 12% (p<0.001) with BVP, with the change from baseline being significantly greater with LBBAP (13 ± 12% versus 10 ± 12%; p<0.001).[89] Propensity-matched analysis demonstrated that LBBAP was associated with an improved composite endpoint of HF hospitalisations and all-cause mortality than BVP (20.8% versus 28%; HR 1.495; 95% CI [1.213–1.842]; p<0.001; *Figure 5*).[89]

Wang et al. conducted a small prospective randomised clinical trial (NCT04110431) comparing LBBAP to BVP in 40 patients with non-ischaemic cardiomyopathy, HF and reduced LVEF (≤40%).[84] In all, 10% of patients in the LBBAP arm and 20% of patients in the BVP arm crossed over. An intention-to-treat analysis showed a significantly higher LVEF improvement at 6 months after LBBAP than BVP (mean difference 5.6%; 95% CI [0.3–10.9]; p=0.039). The LBBAP arm also did have greater reductions in LV end-systolic volume (−24.97 ml; 95% CI [−49.58, −0.36 ml]) and N-terminal pro B-type natriuretic peptide (−1,071.80 pg/ml; 95% CI [−2,099.40, −44.20 pg/ml]), and comparable changes in NYHA functional class, 6-minute walk distance, QRS duration and rates of CRT response compared with the BVP-CRT arm.[84]

The ongoing Left vs Left Randomized Clinical Trial (NCT05650658) is the largest clinical trial comparing CSP and BVP in CRT-eligible patients. The trial will include 2,136 patients followed up for at least 3 years. Unlike previous trials, the Left vs Left Randomized Clinical Trial will be adequately powered for the superiority of the primary composite endpoint of death and hospitalisation for HF. The trial is expected to run until 2029.

The His-Bundle Corrective Pacing in Heart Failure trial (NCT05265520) is an ongoing trial to evaluate the efficacy and mechanism of benefit of HBP-enhanced CRT versus CRT with BVP in patients with HF and RBBB.

Until data from randomised clinical trials become available, CSP for CRT (in particular LBBAP) should be viewed as a viable bailout strategy in scenarios in which conventional CRT is challenging (see *Table 1*), and should only be considered if capture of the LB can be achieved, resulting in appropriate QRS reduction.

Conclusion

The discovery of longitudinal dissociation and proximal conduction block of fibres predestined to become the LB or right bundle, and the ability to correct bundle branch block by pacing from the distal His bundle are the basic physiological principles underlying the use of CSP for CRT. Because permanent CSP was not possible, early CRT attempts revolved around BVP. Many factors contribute to the failure of conventional CRT with BVP and include challenging coronary venous anatomy, diaphragmatic stimulation, the inability to effectively stimulate diseased tissue and the inability to deliver fused CRT in patients with complete AV block. Epicardial LV stimulation with reversed epicardial-to-endocardial activation and pacing from scar tissue in the LV lateral wall likely explain the potential pro-arrhythmogenicity of conventional CRT. Many of the challenges associated with conventional CRT with BVP have been improved by ventriculo-ventricular interval programmability, quadripolar leads, targeted LV lead placement and endocardial LV stimulation. The introduction of HBP and LBBAP, allowing bundle branch block correction, has opened up new opportunities to address the limitations of conventional CRT with BVP, including unfavourable coronary anatomy, the inability to place a coronary venous LV lead, LV latency and exit block, ventricular pro-arrhythmia and the inability to deliver fused CRT in patients with AV block. It is likely that, in future, both BVP and CSP will be used in a complementary manner, even combining both strategies if needed. Further studies are needed to determine the hierarchical sequence of how to apply the individual techniques in specific clinical situations. ❑

Clinical Perspective

- The introduction of permanent CSP in the form of HBP and LBBAP allows for bundle branch block correction and addresses several limitations associated with conventional CRT with BVP.
- Some of the limitations associated with conventional CRT by BVP can be addressed using CSP alone and others by combining CSP with coronary venous LV pacing in the form of HOT-CRT or LOT-CRT.
- Although CSP was found to be comparable to BVP or even superior resynchronisation with CSP has been demonstrated, data from randomised controlled clinical trials are lacking. CSP for CRT should currently be viewed as an alternative option for clinical scenarios in which BVP is challenging.
- It is likely that BVP and CSP will be used in a complementary manner in the future. The hierarchical sequence of how to apply individual techniques in specific clinical situations remains to be determined.

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