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STATE-OF-THE-ART REVIEW

Cardiac Conduction System Pacing

A Comprehensive Update

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ABSTRACT

The field of cardiac pacing has changed rapidly in the last several years. Since the initial description of His bundle pacing targeting the conduction system, recent advances in pacing the left bundle branch and its fascicles have evolved. The field and investigators' knowledge of conduction system pacing including relevant anatomy and physiology has advanced significantly. The aim of this review is to provide a comprehensive update on recent advances in conduction system pacing. (J Am Coll Cardiol EP 2023;9:2358–2387) © 2023 by the American College of Cardiology Foundation.

The field of cardiac pacing has changed rapidly over the last several years. Since the initial description of His bundle pacing (HBP) targeting the conduction system, recent advances in left bundle branch pacing (LBBP) and its fascicles has increased implant options for physiological pacing. New insights into conduction system pacing (CSP), including relevant anatomy and physiology, have made physiologic pacing a relevant choice for all pacing indications. The aim of this state-of-the art review is to provide a comprehensive update on recent developments in CSP. This review highlights topics and concepts discussed at the Sixth Annual Physiology of Pacing Symposium

NEW INSIGHTS INTO CARDIAC ANATOMY OF THE CONDUCTION SYSTEM

Revisiting the clinical anatomy of the conduction system[1] from the viewpoint of clinicians is a necessary step to appreciate the crucial and elegant discovery made by Prof Sunao Tawara over 100 years

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HIGHLIGHTS

- HBP and the recent advances in LBBAP have increased the physiologic pacing options.
- New insights into the anatomy and physiology of conduction system pacing are clinically relevant.
- Confirmation of conduction system capture and restoration of electrical synchrony is essential for successful CRT.
- Large-scale randomized clinical trials are necessary to establish the role of CSP in the management of bradycardia and heart failure.

ago. Tawara discovered the atrioventricular (AV) node and established the concept of the AV conduction system as we understand it now.[2] His work proved the anatomic link from the AV node to the bundle of His (penetrating portion of the AV bundle), its division into the left and right bundle branches, and Purkinje fibers. His assumption that the conduction velocity of excitation in the AV conduction system, except within the AV node, would be fast has subsequently proven to be correct.[2] His meticulous micro- and macroscopic observations eventually enabled him to "draw" one of his classic illustrations (**Figure 1**).

Following the discovery made by the pioneering work of Purkinje, His, and Tawara,[2] numerous insights on the cardiac conduction system have accumulated over the last century,[3-7] revealing complexity and variations of anatomy and function of the AV conduction system in mammalian hearts.

The work of Dr Wallace A. McAlpine[8] using pressure-perfused and fixed human hearts provides an excellent appreciation of anatomy for electrophysiologists. Another approach using micro-computed tomography also provides promising direction to demonstrate the clinically relevant anatomy of the conduction system.[9] McAlpine's approach allows us to dissect the central components of the AV conduction system in the context of the nondistorted heart (Supplemental Figures 1 and 2).[10] When removing epicardial adipose tissue from the inferior pyramidal space,[11] the inferoseptal process of the left ventricle (LV)[8,10,12] and AV nodal artery are unveiled. Here, the AV node can be localized to the right side of the central fibrous body (right fibrous trigone) before penetrating it (**Figure 2**), revealing the AV node as an epicardial structure. The tendon of Todaro connecting to the central fibrous body can also be macroscopically dissected[8] to show the real 3-dimensionality (3D) of the triangle of Koch.[13-16] Histological data can be placed in the context of a nondistorted heart viewed from clinically familiar angles (Supplemental Figures 1 and 2). Furthermore, these accumulated insights allow us to digitally reconstruct a virtual AV conduction system in a 3D nondistorted heart,[13] which is very useful to conceptualize CSP (**Figure 2**, Supplemental Figures 3 and 4). Dissection and visualization of bundle branches and Purkinje fibers remain challenging especially in the human hearts but can be approximated as shown in **Figures 1 and 2**.

HEMODYNAMICS OF CSP

Acute hemodynamic measurements reflect acute changes in cardiac function that can be quantified and are therefore a useful tool in guiding the development of new pacing approaches.[17] These measurements allow the immediate impact of pacing therapy to be evaluated, which allows different pacing approaches to be compared within the same patient. Early studies of right ventricular pacing (RVP), in patients with severe bradycardia caused by complete heart block, observed large acute hemodynamic improvements. When cardiac resynchronization therapy (CRT) with biventricular pacing (BVP) was developed, the observation of improvement in acute hemodynamic measurements provided the justification for chronic implantation and investigation in long-term outcome studies.[18,19]

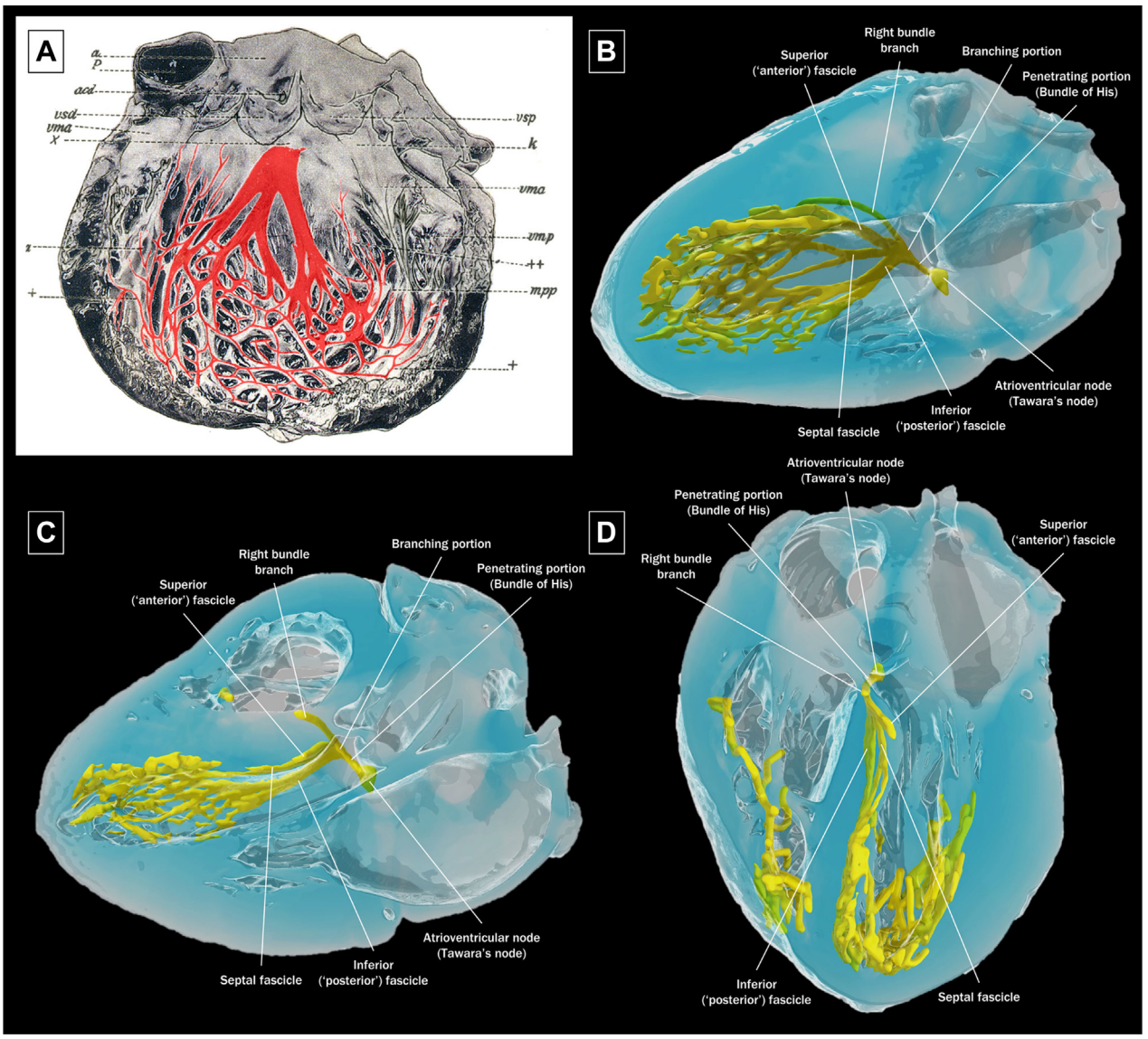
CSP using HBP or left bundle branch area pacing (LBBAP) has the potential to restore or preserve normal physiological activation (**Central Illustration**). LBBAP includes both LBBP where there is clear evidence of direct LBB capture and left ventricular septal pacing (LVSP) without direct capture of the LBB. Acute hemodynamic studies have been used to compare CSP with RVP and BVP and to compare different methods for delivering CSP. The findings from these studies are summarized in this review.

Hemodynamic measures are not static; there are considerable natural variations caused by the numerous biological phenomena, including respiration and other autonomic phenomena. It is important to take steps to minimize the impact of the

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional
AV = atrioventricular
BVP = Biventricular pacing
CRT = cardiac resynchronization therapy
CSP = conduction system pacing
ECGi = electrocardiographic imaging
e-DYS = electrical dyssynchrony
HBP = His bundle pacing
HOT = His optimized
IVCD = intraventricular conduction delay
LBBB = left bundle branch block
LBBAP = left bundle branch area pacing
LBBP = left bundle branch pacing
LOT = left bundle branch optimized
LV = left ventricle
LVEF = left ventricular ejection fraction
LVAT = left ventricular activation time
LVSP = left ventricular septal pacing
ns = nonselective
RBBB = right bundle branch block
RV = right ventricle
RVP = right ventricular pacing
s = selective
SDAT = standard deviation of the ventricular activation time
V6RWPT = V_6 R-wave peak time
VAT = ventricular activation time
UHF = ultra-high frequency

FIGURE 1 **Tawara's Illustration and its 3D Reconstruction**



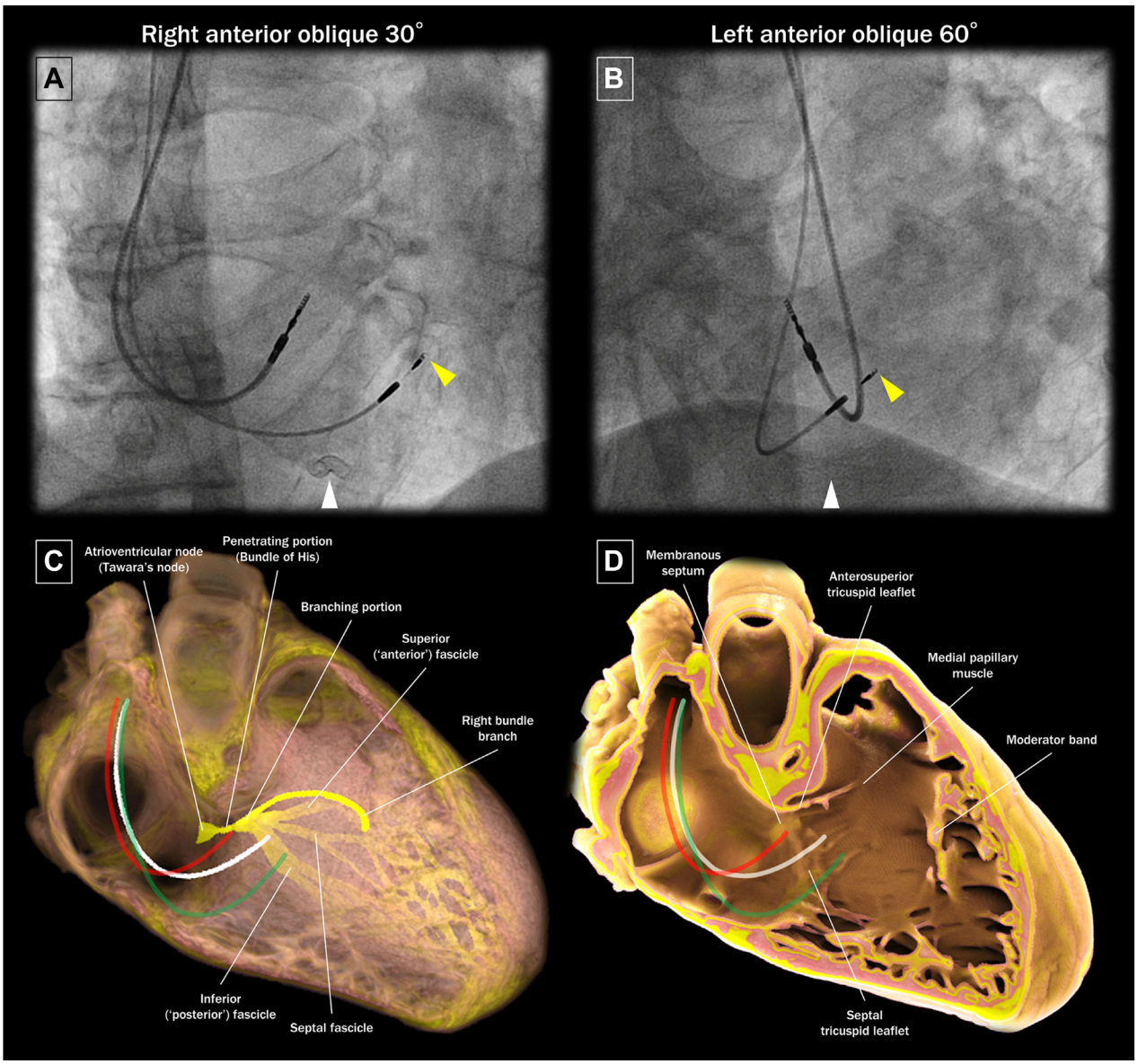
Tawara's classic illustration of the atrioventricular conduction system[2] (A) was reconstructed on the three-dimensional (3D) field (B to D) created from the computed tomographic data set obtained from a pressure-perfused and fixed heart.[1] (B to D) Apical 2- (B), 3- (C), and 4-chamber (D) sections. These digital data sets can be used to produce 3D printing models. Note that for the apical 4-chamber section (D), the paired piece of the one usually seen during transthoracic echocardiography is selected to show the substantial portions of the conduction system.

spontaneous biological variability on the overall findings, otherwise the results of the study may be misleading.[18] This can be done by keeping heart rate constant, averaging multiple beats, making a comparison to a reference setting, and taking multiple repeated measurements.[19,20]

CSP VS RVP: BRADYCARDIA INDICATIONS. RVP produces nonphysiological ventricular activation that can adversely affect cardiac function in susceptible individuals.[21] CSP aims to deliver more physiological ventricular activation and thereby avoid the detrimental effects on cardiac function. The findings from acute hemodynamic studies[22-26] suggest that CSP achieves these objectives.

Keene et al[22] performed a within patient comparison of HBP and RVP in 18 patients with intermittent heart block and mean left ventricular ejection fraction

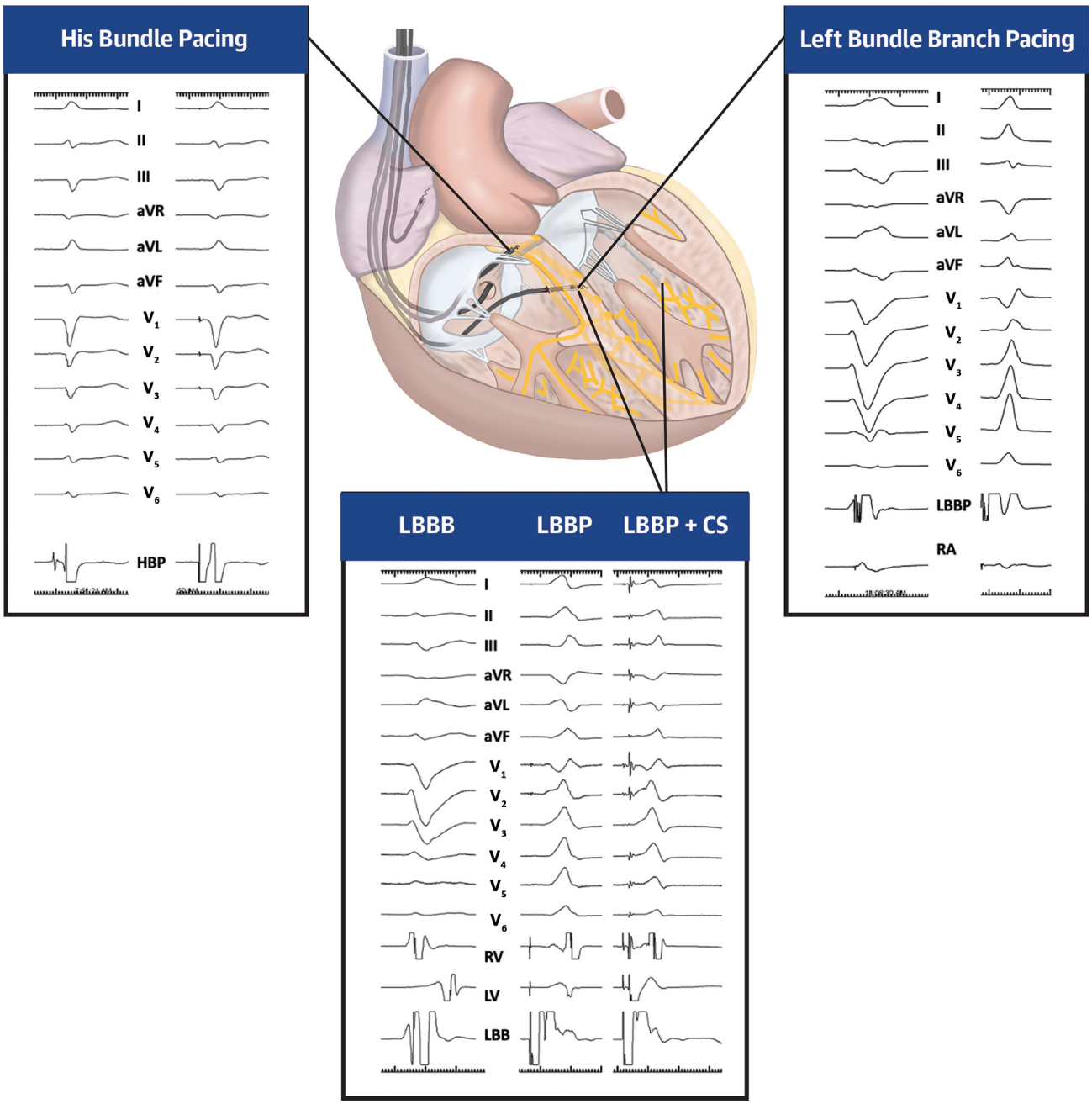
FIGURE 2 **Conduction System Pacing**



Fluoroscopic images (A,B) show the His-bundle pacing (yellow arrowheads). White arrowheads indicate the stent placed in the distal right coronary artery. Virtual simulation images viewed from the right anterior oblique direction (C,D) show the His-bundle pacing (red), and left bundle branch pacing (white, green). (C) The estimated location of components of the atrioventricular conduction system (refer to Supplemental Figure 3A). (D) The relevant structures, including the membranous septum and septal tricuspid leaflet, of the conduction system. From images C and D, it is reasonable to estimate that the potential risk of tricuspid regurgitation induced by the mechanical interaction between active fixation leads and septal tricuspid leaflet, including impingement, perforation, and entrapment, will be minimized if the lead (red) is fixed near the commissure between the septal and anterosuperior tricuspid leaflets, or if the lead (green) is fixed sufficiently distant from the tricuspid annulus. Also, image D suggests the potential risk of perforation of the membranous septum during His-bundle pacing. (A,B) Images courtesy of Dr Chung Wei-Hsin. (C,D) Virtual images were created using commercially available workstation (Ziostation2, version 2.9.8.4; AMIN Co, Ltd; Ziosoft Inc with post hoc modification using dedicated volume-rendering software (SARA-Engine, pita4 mobile LLC).

(LVEF) of 44%. HBP delivered a shorter QRS duration (−56 milliseconds; 95% CI: −67 to −46 milliseconds; $P < 0.0001$) and improved acute systolic blood pressure by mean of 5.0 mm Hg (95% CI: 2.8-7.1 mm Hg; $P < 0.0001$) compared to RVP.[22] Zanon et al[23] performed a within-patient comparison of myocardial perfusion, using scintigraphy with technetium 99m Tc-methoxy isobutyl isonitrile after 3 months of His

CENTRAL ILLUSTRATION **Conduction System Pacing: Anatomic Location and ECG Responses of Conduction System Pacing Are Shown**



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CS = conduction system; ECG = electrocardiogram; HBP = His bundle pacing; LBBB = left bundle branch block: LBBP = left bundle branch pacing; LV = left ventricular; RA = right atrial; RV = right ventricular.

bundle and RVP. They observed that myocardial perfusion during HBP was significantly better than during RVP (0.44 ± 0.5 vs 0.71 ± 0.53, respectively; $P = 0.011$).[23] Michalik et al[24] compared HBP and RVP in patients with AV conduction disorders and preserved LVEF. They found that there was a decline in global longitudinal strain and increase in peak systolic dispersion and left atrial volume index after 6 months in patients receiving RVP. Whereas global longitudinal strain was unchanged and peak systolic dispersion and left atrial volume index decreased in patients who received HBP.[24] In contrast, however, Wen et al[25] did not observe a difference in strain measurements after 6 months in patients receiving LBBAP and RV septal pacing.[25]

CSP VS BVP FOR CRT. Left bundle branch block (LBBB) results in delayed and dyssynchronous activation of the LV, which is deleterious in patients with heart failure. BVP improves the activation pattern, shortening left ventricular activation time (LVAT) and improving cardiac function. Long-term studies have demonstrated substantial reduction in morbidity and mortality in patients with heart failure. However, it is not always possible to implant a lead in the coronary sinus, and BVP delivers only relatively modest improvements in QRS duration and VAT. AV delay shortening in addition to ventricular resynchronization appears to be an important mechanism through which BVP delivers improvement in acute hemodynamic function. Supporting this hypothesis, it was shown that HBP delivered to retain native LBBB activation (ie, without correction of LBBB) and delivered two-thirds of the hemodynamic improvement delivered by BVP: 5.1 mm Hg (95% CI: 2.0-8.2; $P = 0.0026$) and 7.1 mm Hg (95% CI: 3.6-10.7; $P < 0.001$).[26] CSP has therefore been investigated as an alternative to BVP in cases of failure to implant an LV lead via the coronary sinus, and also to determine whether it can provide more effective ventricular resynchronization.

HBP BUNDLE CRT VS BVP-CRT. A within-patient comparison of the effects of His bundle CRT and BVP-CRT, on ventricular activation (measured using electrocardiographic imaging [ECGi]) and acute hemodynamic function, was performed in patients with heart failure and LBBB. In 18 of 23 patients, LVAT was significantly shortened by HBP-CRT. In these patients, HBP-CRT delivered more effective ventricular resynchronization than BVP-CRT (LVAT: −26 milliseconds; 95% CI: −41 to −21 milliseconds; $P = 0.002$) did.[27] This translated into a significantly greater improvement in acute hemodynamic response, with an ∼60% increase in acute systolic blood pressure compared to BVP-CRT (+4.6 mm Hg; 95% CI: 0.2-9.1 mm Hg; $P = 0.04$). These findings suggest that HBP-CRT has the potential to deliver more effective ventricular resynchronization and improve cardiac function in patients when LBBB can be successfully corrected with HBP-CRT.

HOT-CRT VS BVP-CRT. Whereas HBP-CRT shows considerable promise, it is not possible to achieve ventricular resynchronization in all patients with an LBBB pattern on the 12-lead ECG. Conduction block may occur in the proximal LBB, in which case the conduction system needs to be targeted more distally using LBBAP to restore normal LV activation. In patients with nonspecific intraventricular conduction delay, VAT may be prolonged because of intramyocardial disease with intact Purkinje activation, and VAT is unlikely to be corrected with CSP.

Zweerink et al[28] evaluated the effectiveness of His bundle optimized (HOT)-CRT in 19 patients where HBP failed to shorten QRS duration. The HOT-CRT approach combines HBP with LV pacing using a coronary venous lead with pacing that is "optimized" between the 2 leads to produce the narrowest fused QRS width between the intrinsic conduction system and LV epicardial stimulation. They recruited patients with LV impairment and a range of different ventricular conduction abnormalities. They found that the HOT-CRT pacing configuration produced a 24% greater reduction in LVAT compared to BVP-CRT (LVAT: −22 milliseconds; 95% CI: −33 to −10 milliseconds; $P = 0.002$). These findings suggesting that HOT-CRT is a promising approach for patients in which CSP alone fails to deliver ventricular resynchronization.

LBBAP VS BVP. LBBAP offers several potential technical advantages, compared to HBP using currently available tools, including low and stable thresholds, the potential to treat more distal conduction system disease, and potentially a faster learning curve.[29]

Liang et al[30] undertook an acute within-patient comparison of LBBAP with BVP in patients with LBBB and LV impairment mainly caused by nonischemic cardiomyopathy. They observed that LBBAP produced a significantly greater reduction in QRS duration compared to BVP (−11 milliseconds; 95% CI: −17 to −4 milliseconds; $P = 0.003$) and greater reduction in QRS area (−85 μVs; 95% CI: −113 to −56 μVs; $P < 0.001$). This improved ventricular resynchronization was associated with a significantly greater acute hemodynamic improvement (LBBAP produced a 6% greater increase in LV dP/dt (a measure of initial velocity of myocardial contractile force) than BVP did; $P = 0.002$). In a study powered for noninferiority, Pujol-Lopez et al[31] randomized 70 patients to CSP (either HBP [4 of 35] or LBBAP) or BVP, the primary

endpoint was change in LVAT measured using ECGi 45 days postimplantation. Twenty-three percent of patients crossed over from CSP to BVP and 6% crossed over from BVP to CSP. In the intention-to-treat analysis, CSP was found to be noninferior to BVP (Δ LVAT CSP: −28 ± 26 milliseconds vs BVP: −21 ± 20 milliseconds; mean difference: −6.8 milliseconds; 95% CI: -18.3 milliseconds to 4.6 milliseconds; $P < 0.001$ for noninferiority). CSP was found to deliver a significantly greater reduction in LVAT (Δ LVAT: −36 ± 19 milliseconds vs −16 ± 23 milliseconds).[31]

HBP-CRT VS LBBAP-CRT. Whereas LBBAP offers several technical advantages compared to HBP, a potential disadvantage is that it results in less physiological biventricular activation, because RV activation typically does not occur via the conduction system. Ali et al[32] performed a within-patient acute hemodynamic study, comparing the 2 pacing modalities, to establish whether the delayed RV activation adversely affects cardiac function. The study included 19 patients with LBBB and LV impairment.[32] Noninvasive electrical mapping confirmed the assumption that HBP produces more rapid biventricular activation compared to LBBAP (Δ total VAT HBP: −46 ± 15 milliseconds, Δ total VAT LBBAP: −36 ± 17 milliseconds; $P = 0.03$). But LBBAP was not inferior to HBP with respect to reduction in LVAT (Δ LVAT HBP: −43 ± 16 milliseconds, Δ LVAT LBBAP: −45 ± 17 milliseconds; $P = 0.65$). Interestingly the delayed RV activation with LBBAP did not adversely affect hemodynamic response ($P = 0.8$).

HBP IN PATIENTS WITH ISOLATED LONG PR INTERVAL AND LV IMPAIRMENT. PR interval prolongation adversely affects ventricular filling and may lead to diastolic mitral regurgitation further reducing cardiac output. Therefore, PR prolongation may represent an electrical treatment target that can be corrected with pacing therapy. Sohaib et al[33] observed that AV-optimized HBP improved acute hemodynamic function when delivered to patients with a long PR interval, LV impairment, and normal QRS duration or right bundle branch block (RBBB). A mean 4.1 mm Hg improvement in systolic blood pressure was observed that represents ∼60% of the hemodynamic benefit achieved with BVP in patients with LBBB.[33] These encouraging findings led to the HOPE-HF (His Optimized Pacing Evaluated for Heart Failure) trial, which was a double-blind crossover trial assessing the impact of AV-optimized HBP. Whereas the primary outcome of peak oxygen uptake or the secondary endpoint of LVEF did not change significantly, symptomatic improvement (secondary endpoints of quality of life and symptomatic preference) was observed with this pacing approach in patients with long PR interval and LV impairment.[34,35]

DOES PROGRAMMING ANODAL CAPTURE DURING LBBAP OFFER A HEMODYNAMIC BENEFIT? A proposed solution to the delayed RV activation during LBBAP is to advance RV activation through anodal capture. But there was uncertainty regarding the mechanism by which early RV activation is achieved (capture of right bundle or RV myocardial capture), whether this produces hemodynamic benefit. These questions were addressed in a study of 21 patients using ECGi. The ventricular epicardial propagation maps demonstrated that RV septal myocardial capture, rather than right bundle capture, was the mechanism for earlier RV activation. Whereas anodal capture produced a shorter QRS duration, it did not produce additional hemodynamic benefit.[36]

BVP VS LV ENDOCARDIAL PACING. Several investigators have previously demonstrated that LV endocardial pacing provides superior electrical resynchronization compared to epicardial coronary sinus pacing by rapidly engaging the Purkinje conduction system. CSP using HBP or LBBAP may be the purest form of LV endocardial pacing. Salden at al[37] compared LV endocardial pacing with BVP in patients with a CRT indication. They observed that endocardial LVSP produced equivalent improvements in LV dP/dt to that obtained with BVP (+17% ± 10% vs +17% ± 9%). Endocardial LVSP may be analogous to deep septal pacing without confirmed LBB capture and may provide insights into LBBAP. These findings are provocative suggesting that conduction system capture was neither required nor targeted during the delivery of endocardial LVSP.

TECHNIQUES TO MEASURE VENTRICULAR SYNCHRONIZATION

The urge to achieve synchronous ventricular activation via the intrinsic conduction system led to the development of more physiological methods of pacing, such as BVP, HBP, and LBBAP (LBBP or LVSP). The most frequently encountered type of ventricular capture during LBBAP and HBP is the simultaneous capture of the conduction system and surrounding ventricular myocardium (ie, nonselective [ns]HBP and nsLBBP), which is responsible for creating 2 different electrical wave fronts that activate the ventricles. The first wave front uses the conduction system, whereas His bundle capture results in rapid activation of both ventricles, LBB capture results in rapid LV but delayed RV activation. Besides activation of the conduction system, a second wave front

arises from the local activation of myocardium surrounding the pacing electrode. This local myocardial excitation is responsible for QRS widening by creating a pseudo-delta wave. However, the effect of such ventricular activation on ventricular synchrony was not known until recently.

The ventricular activation pattern during the nsHBP, selective (s) HBP, and myocardial pacing of the para-Hisian area was studied using an ultra-high-frequency (UHF)-ECG by Curila et al.[38] They showed that although nsHBP led to a wider QRS duration than sHBP, ventricular synchrony measured using UHF-ECG and expressed as electrical dyssynchrony (e-DYS) (time difference between the first and last activation under leads V_1-V_8) was the same (**Figures 3A and 3B**). It was also shown that both sHBP and nsHBP resulted in ventricular synchrony similar to normal intrinsic rhythm of patients with narrow QRS interval. On the other hand, myocardial pacing in the para-Hisian area significantly worsened ventricular dyssynchrony (**Figure 3E**). The comparable effects of nsHBP and sHBP on ventricular activation and contraction were confirmed by other studies using echocardiography, single-photon emission computed tomography, ECGi, and direct endocardial and epicardial activation measurement in animals.[39-41] Therefore, nsHBP may be more suitable for clinical practice than sHBP because it does not worsen ventricular activation patterns and may be a safer pacing strategy. Few studies have included patients with bundle branch block or intraventricular conduction delays (IVCDs), so the effect of nsHBP on ventricular synchrony is still unclear in these patients.

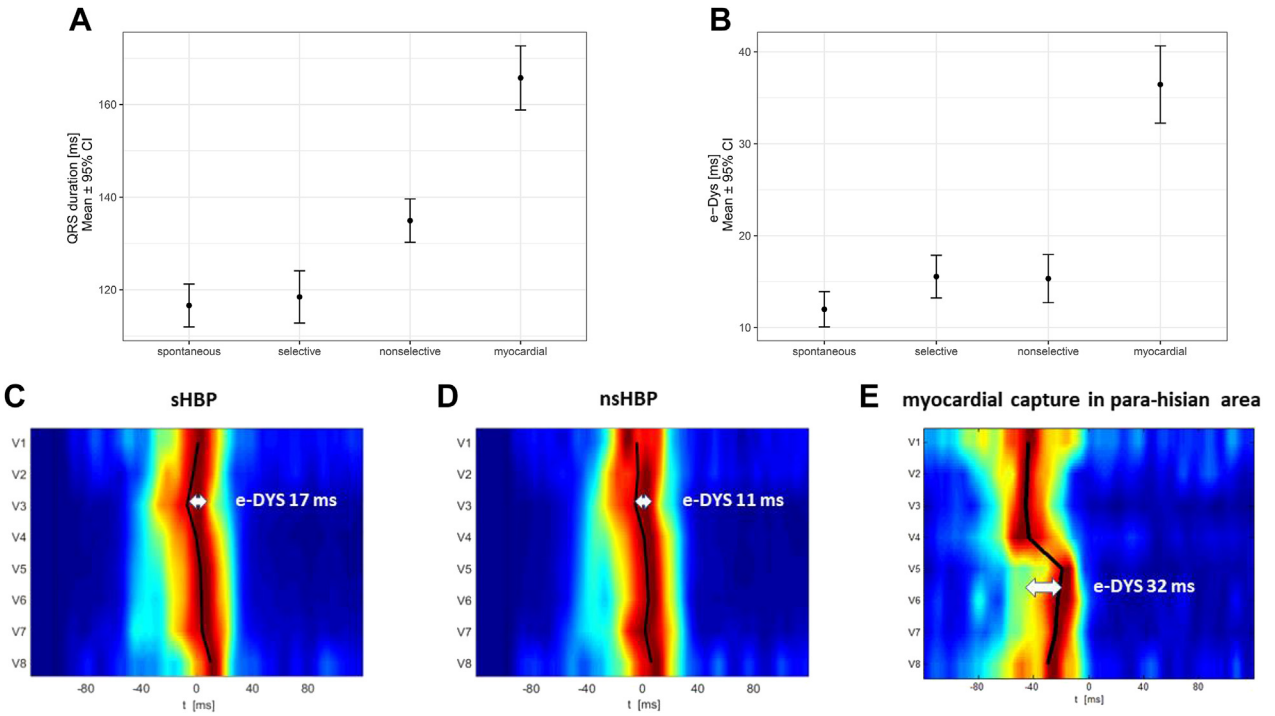
Due to the limitations of HBP, direct pacing of the LBB or LV septum has received increased interest in recent years as an alternative physiologic pacing method. Both LBBP and LVSP provide more physiological ventricular activation than RVP despite delayed RV activation and a wider QRS interval, which in V_1 has a pseudo RBBB morphology.[42,43] A detailed study of ventricular activation patterns using a UHF-ECG[44] showed that both nsLBBP and LVSP have, on average, the same QRS duration and are less physiological than nsHBP (Supplemental Figures 5A and 5B). LVSP preserved the same absolute level of ventricular synchrony as nsHBP, but it led to a left-to-right activation pattern and less physiological LV lateral wall activation (ie, a broader depolarization map under V_6-V_8) compared to LBBP and nsHBP. On the other hand, nsLBBP preserved the same pattern of LV lateral wall activation as nsHBP, but it delayed RV activation and worsened left-to-right interventricular dyssynchrony compared to both HBP and LVSP (Supplemental Figure 5E). Notably, pacing locations referred to as LVSP in this study were often shown to be some distance from the LBB and, on average, were 3-mm shallower than pacing depths with nsLBBP.

In other studies, different ventricular dyssynchrony measures were studied in patients with CSP. The standard deviation of the ventricular activation time (SDAT) determined by using an ECG belt system was used to compare LVSP with LBBP. The SDAT was determined from 40 electrodes on the chest and was used as a measure of ventricular e-DYS. The study found no significant difference in SDAT between LVSP and LBBP. However, the study was small and may have been underpowered to detect minor SDAT differences.[45] Salden et al[37] investigated the electrophysiological and hemodynamic effects of LVSP and nsHBP in heart failure patients undergoing CRT implantation; they showed that the SDAT during LVSP was comparable to nsHBP. More recently, SDAT was also used to guide CRT implantation and optimization in a randomized trial in patients with non-LBBB. However, SDAT could not predict the clinical response to CRT, suggesting that SDAT may not be the best measure to study ventricular dyssynchrony in different pacing strategies.[46]

Another well-studied measure of ventricular synchrony is the QRS area. The QRS area is the sum of the area under the QRS complex of the calculated vectorcardiographic X, Y, and Z leads derived from a digital 12-lead ECG. It has been shown in several large CRT cohorts to be a potential tool for predicting clinical and echocardiographic CRT response.[47] Moreover, it can also be used to guide LV lead implantation. Recently, the QRS area was studied in bradycardia patients undergoing LBBAP. During LVSP without evidence of LBB capture, the QRS area was slightly higher than in LBBP; however, the absolute difference was small.[48] In addition, in patients with normal ventricular activation, the QRS area during LBBAP was close to the values of the intrinsic QRS, which indicates that LBBAP maintains ventricular synchrony at near-physiologic levels. Moreover, this study showed improvement of ventricular synchrony was achieved with each step of lead progression into the interventricular septum (Supplemental Figure 6).

Comparisons of the difference between LVSP and LBBP were all affected by a lack of definition for LVSP. In contrast to LBBP, where there is capture of the LBB, LVSP was defined more vaguely as deep septal pacing without the presence of LBB capture and with a QRS pattern of late r/R in V_1. However, this late r/R can, be present at various depths of the pacing lead inside the interventricular septum,[49] which may affect the resultant ventricular activation pattern (Supplemental Figure 6). Also, UHF-ECG studies on

FIGURE 3 Ultra High Frequency ECG in HBP



QRS duration (A), electrical dyssynchrony (e-DYS) (B), and ventricular depolarization maps during selective (s) and nonselective (ns) His-bundle pacing (HBP), and myocardial capture in the para-Hisian area (C to E) as visualized by ultra-high frequency electrocardiography. Ventricular activations are similar for e-DYS (time difference between the first and last activation) during sHBP and nsHBP, respectively. In comparison, myocardial capture in the para-Hisian area, the e-DYS was 32 milliseconds.

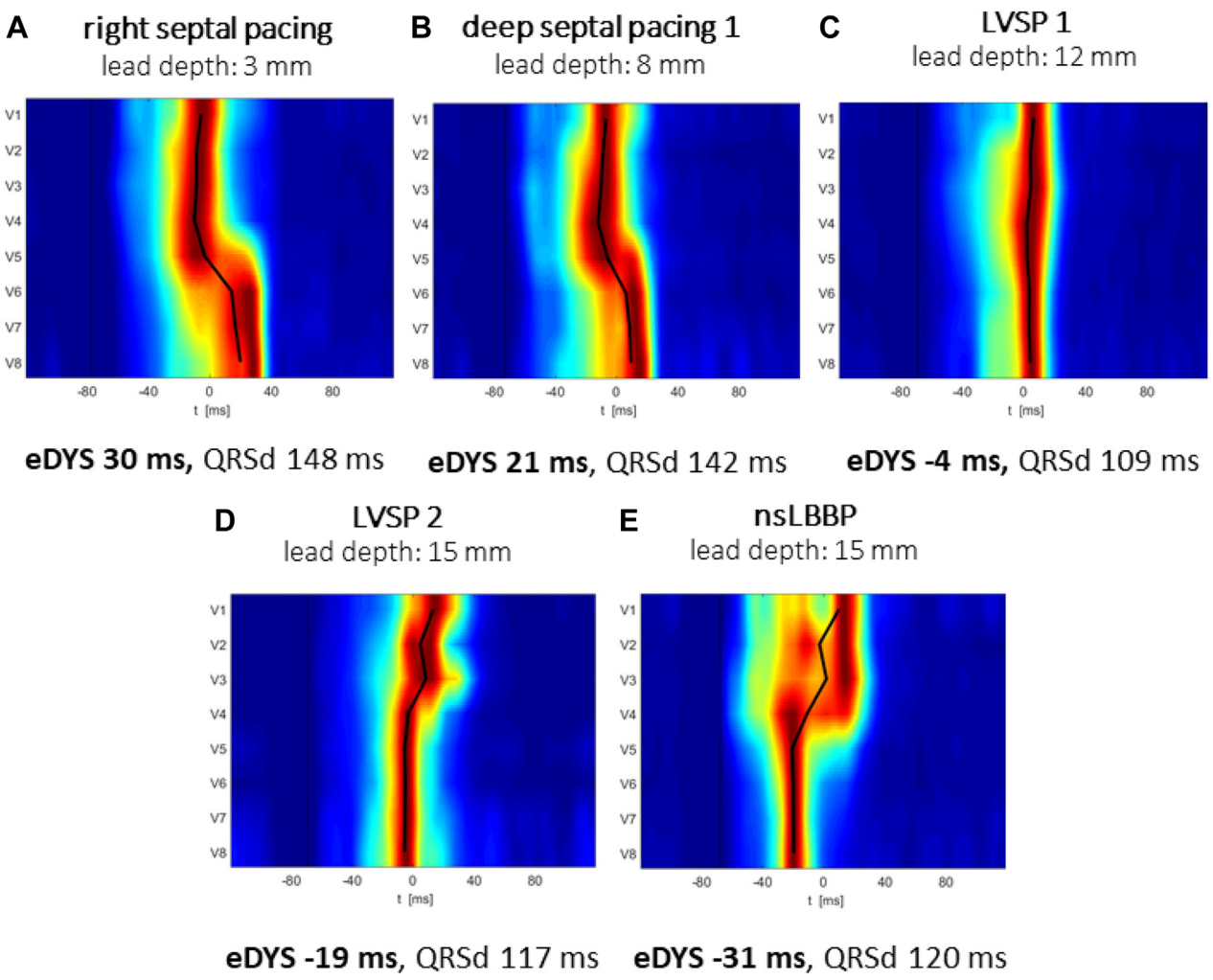
ventricular activation patterns showed that LVSP with a late r/R or rs in V_1, which occurred with pacing at 66%-80% of the septal thickness, resulted in worse LV activation than nsLBBP. In contrast, LVSP close to the LBB (ie, LVSP that is transitioned from nsLBBP during decremental output pacing) had LV activation patterns that were similar to those of nsLBBP. An example of the change in the UHF-ECG pattern of ventricular activation while pacing the interventricular septum at various depths and 2 types of LVSP is shown in Figure 4.

Moving the lead deeper into the interventricular septum results in different levels of inter- and intraventricular synchrony. When pacing the RV septum, the primary determinant of ventricular dyssynchrony is delayed LV lateral wall activation, which is reduced as the lead is progressed deeper into the septum. The best interventricular synchrony is achieved in pacing locations when the first late r occurs in V_1; however, LV activation can be improved by pacing from deeper positions. The most physiological LV activation pattern is observed during nsLBBP but at the cost of increasing left-to-right interventricular dyssynchrony.

CRITERIA FOR CAPTURE OF THE LEFT CONDUCTION SYSTEM

Confirmation of His bundle capture is generally quite straightforward because output-dependent transitions in QRS morphology are observed in >90% of cases. Capture of the left conduction system, either proximal LBB or its fascicles (left fascicular pacing) is considered as the optimal endpoint for LBBAP procedure. At the usual pacing output (ie, >1.5-2.0 V at 0.4 milliseconds), LBBAP nearly always results in capture of the septal myocardium, regardless of whether simultaneous LBB capture is present. Therefore, determination of LBB capture requires differentiation between LVSP only and nsLBBP, which is the simultaneous capture of septal myocardium and LBB.

FIGURE 4 Transseptal Decrease in Ventricular Dyssynchrony When Pacing at Various Depths of the Interventricular Septum

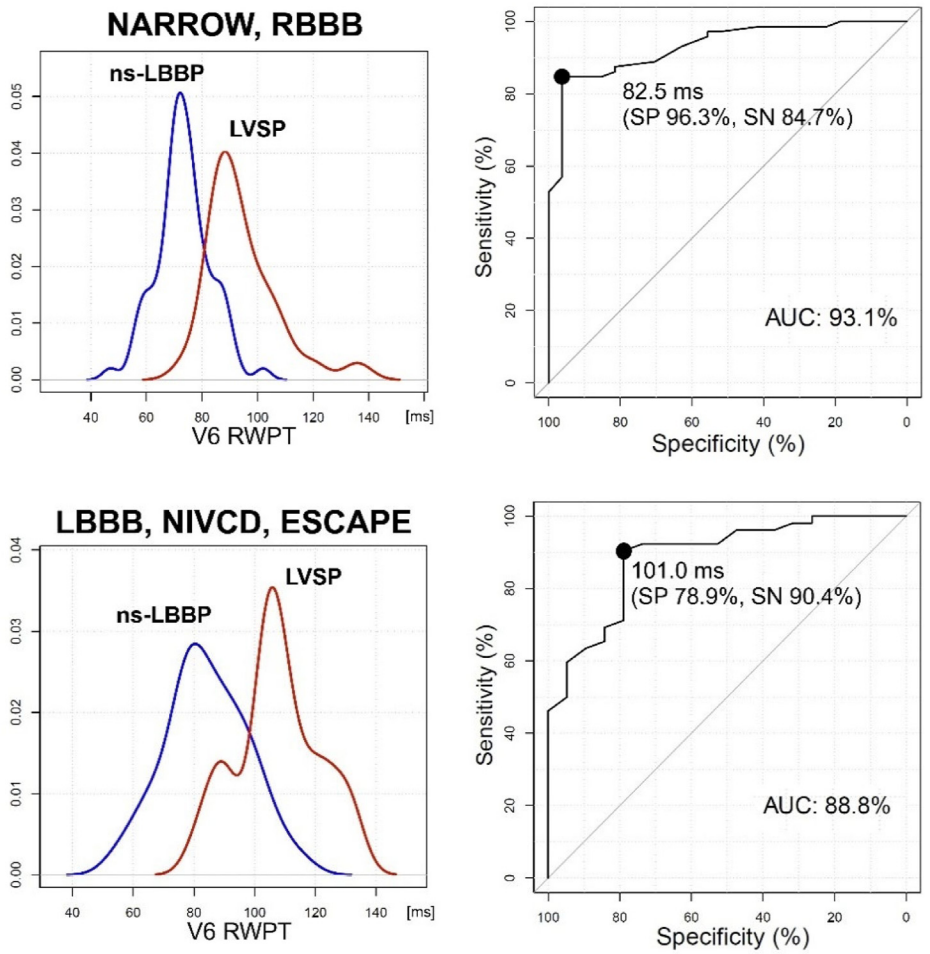


(A) Right septal pacing resulted in an electrical dyssynchrony (e-DYS) of 30 milliseconds caused by delayed left ventricular lateral wall activation. Left ventricular lateral wall delay and QRS duration (QRSd) were reduced when pacing at a depth of 8 mm (B), and the best interventricular synchrony with the shortest QRSd was observed at a depth of 12 mm during left ventricular septal pacing 1 (LVSP1) with a small late r in V_1 (C). Pacing at deeper positions during LVSP2 (which transited from nonselective left bundle branch pacing during the decremental output pacing) and nonselective left bundle branch pacing resulted in QRSd prolongation caused by the increase in left-to-right interventricular dyssynchrony with delayed right ventricular lateral wall activation (D,E).

Practical methods for determination of LBB capture are based on assessment of paced QRS morphology and maneuvers that induce QRS transition, which is the sudden change of QRS morphology related to the change in capture type from nsLBBP to either myocardial capture (LVSP) or sLBB capture.[50] Endocardial mapping of His bundle and fascicular potentials to prove LBB capture has application mainly for mechanistic investigation but can be of practical use if dual-lead implantation technique is employed.

V_6 R-WAVE PEAK TIME. The most widely used QRS characteristic to determine left conduction system capture is paced V_6 R-wave peak time (V_6RWPT) or peak LVAT in V_6, a QRS measure that is related to the local activation time of the lateral wall of the LV. Activation of the lateral wall of the LV is faster during nsLBBP than during LVSP, resulting in an average difference in V_6RWPT of 20 milliseconds. Change in V_6RWPT was empirically used to confirm LBB capture during the early days of LBBAP. Jastrzebski et al[51] studied 124 patients with confirmed

FIGURE 5 Density Diagrams and ROC Curves for V_6RWPT During nsLBBP Capture and LVSP

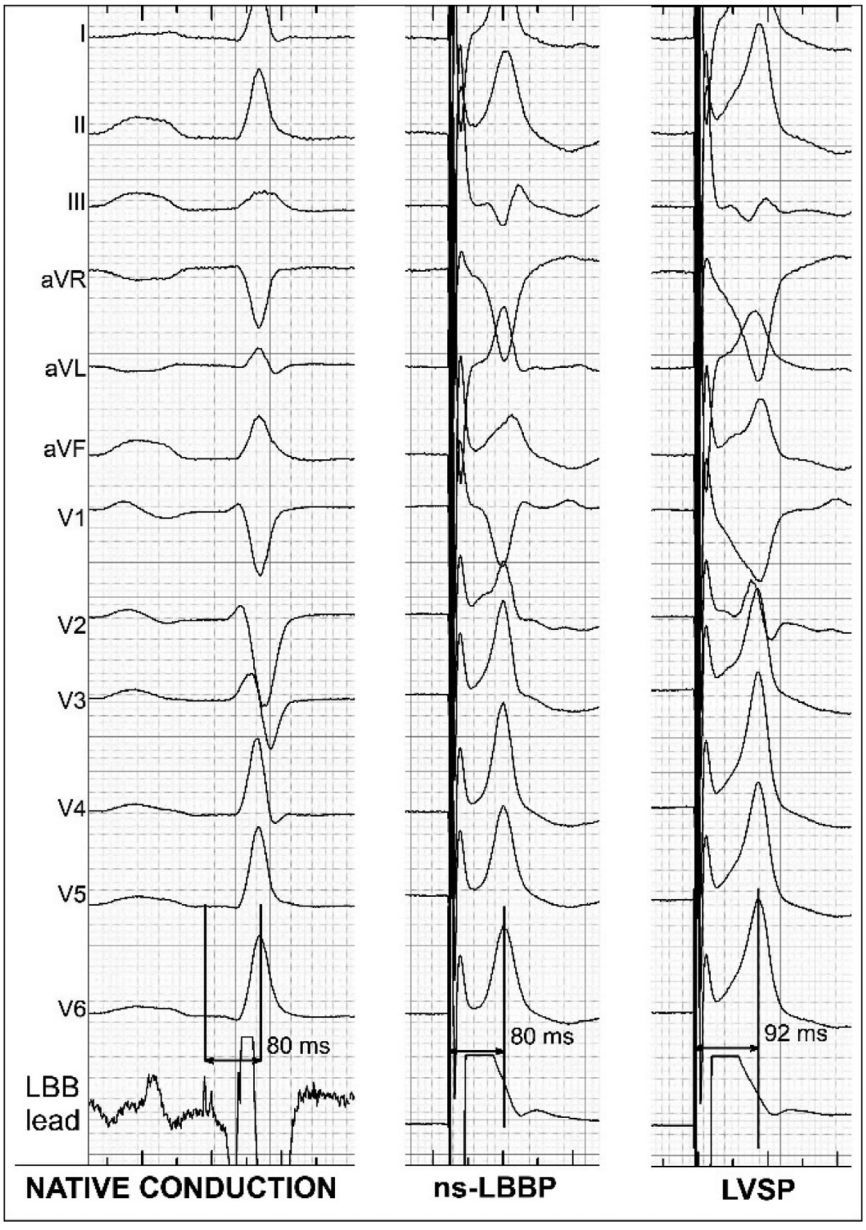


(Top) Results for patients with narrow QRS interval or isolated right bundle branch block (RBBB). (Bottom) Results for patients with damaged left conduction system: left bundle branch block (LBBB), nonspecific intraventricular conduction delay (NIVCD), wide escape rhythm, or asystole. There is considerable overlap between V_6 R-wave peak time (V_6RWPT) values between nonselective left bundle branch (nsLBBP) and left ventricular septal pacing (LVSP) especially in patients with damaged left conduction system. Modified with permission from Jastrzebski et al.[51] AUC = area under the curve; ROC = receiver-operating characteristic; SN = sensitivity; SP = specificity.

diagnosis of LBB capture (evidence for transition from nsLBBP to sLBBP or LVSP during threshold testing or programmed stimulation) to develop more objective criteria based on peak LVAT or RWPT. V_6RWPT values <75 milliseconds are nearly 100% specific for nsLBBP whereas values of 80-85 milliseconds have the best balance of sensitivity/specificity. A major limitation of this criterion is low sensitivity, especially for patients with heart failure, wide escape rhythms, LBBB, and IVCD. In such situations LV activation/V_6RWPT might be much longer despite LBB capture because there is widespread LV conduction slowing and/or multisite left conduction system disease that is not corrected by LBBAP. To increase sensitivity of V_6RWPT criterion in patients with LBBB/IVCD, RBBB with fascicular block or wide escape rhythm/asystole different cutoffs for diagnosis of LBB capture should be used: 80 milliseconds for high specificity, and 90-100 milliseconds for optimal overall diagnostic accuracy (**Figure 5**).[51]

The V_6RWPT criterion is more accurate when an individualized paced V_6RWPT cutoff value is used for diagnosis. This individualized value can be easily obtained during implantation by measuring the LBB

FIGURE 6 **LBB Capture**

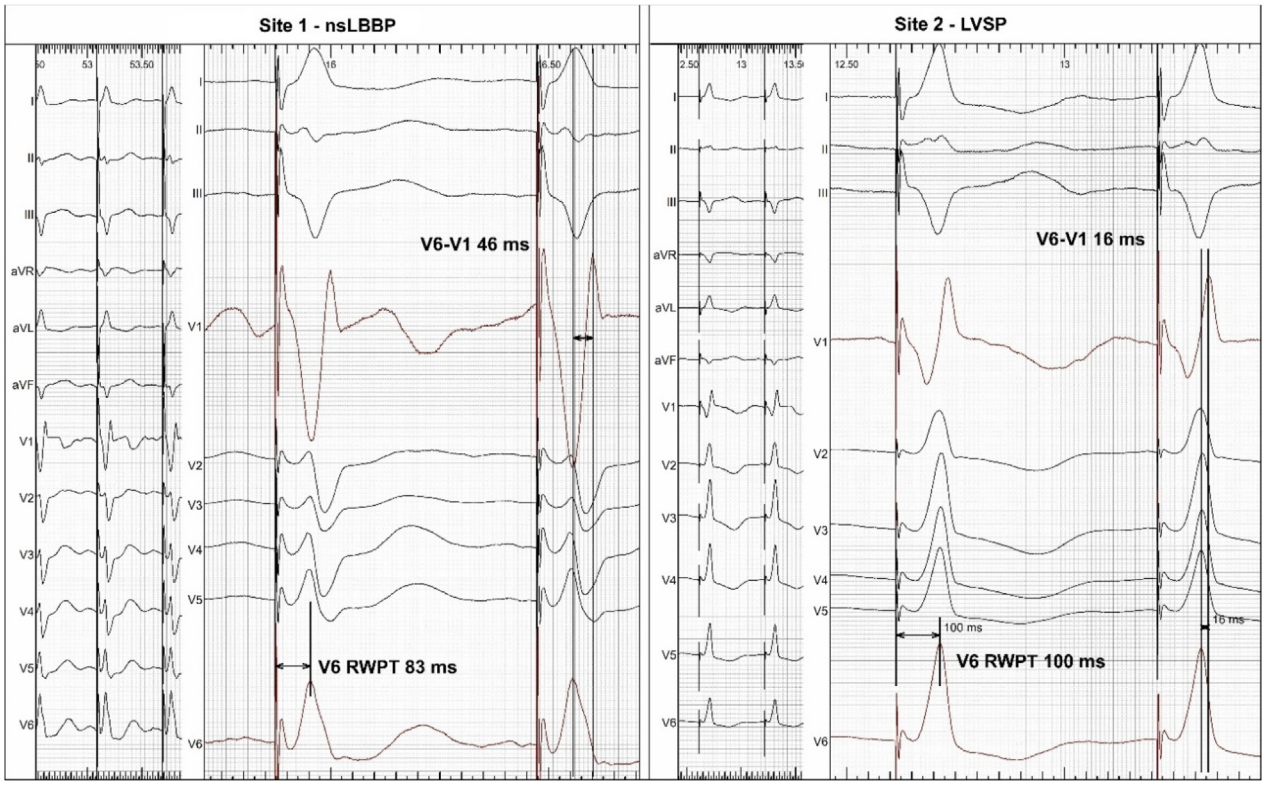


During nsLBBP capture, the interval from the LBB potential to the V_6 R-wave peak during native conduction equaled the interval from the stimulus to the V_6 R-wave peak. During loss of LBB capture, resulting in only myocardial LVSP, the interval from the stimulus to the R-wave peak was longer. Abbreviations as in Figures 4 and 5.

potential to V_6 R-peak interval observed during conducted supraventricular beat with non-LBBB morphology (Figure 6). When LBB is captured, these 2 intervals are necessarily the same because the activation pathways during pacing and intrinsic activation are the same. Endocardial mapping of His bundle and fascicular potentials to prove LBB capture has application mainly as a research tool but can be of practical use if the dual-lead technique is used.

V_6-V_1 INTERPEAK INTERVAL. During LVSP, activation spreads from the septum to right and left

FIGURE 7 Two LBBAP Sites in the Same Patient



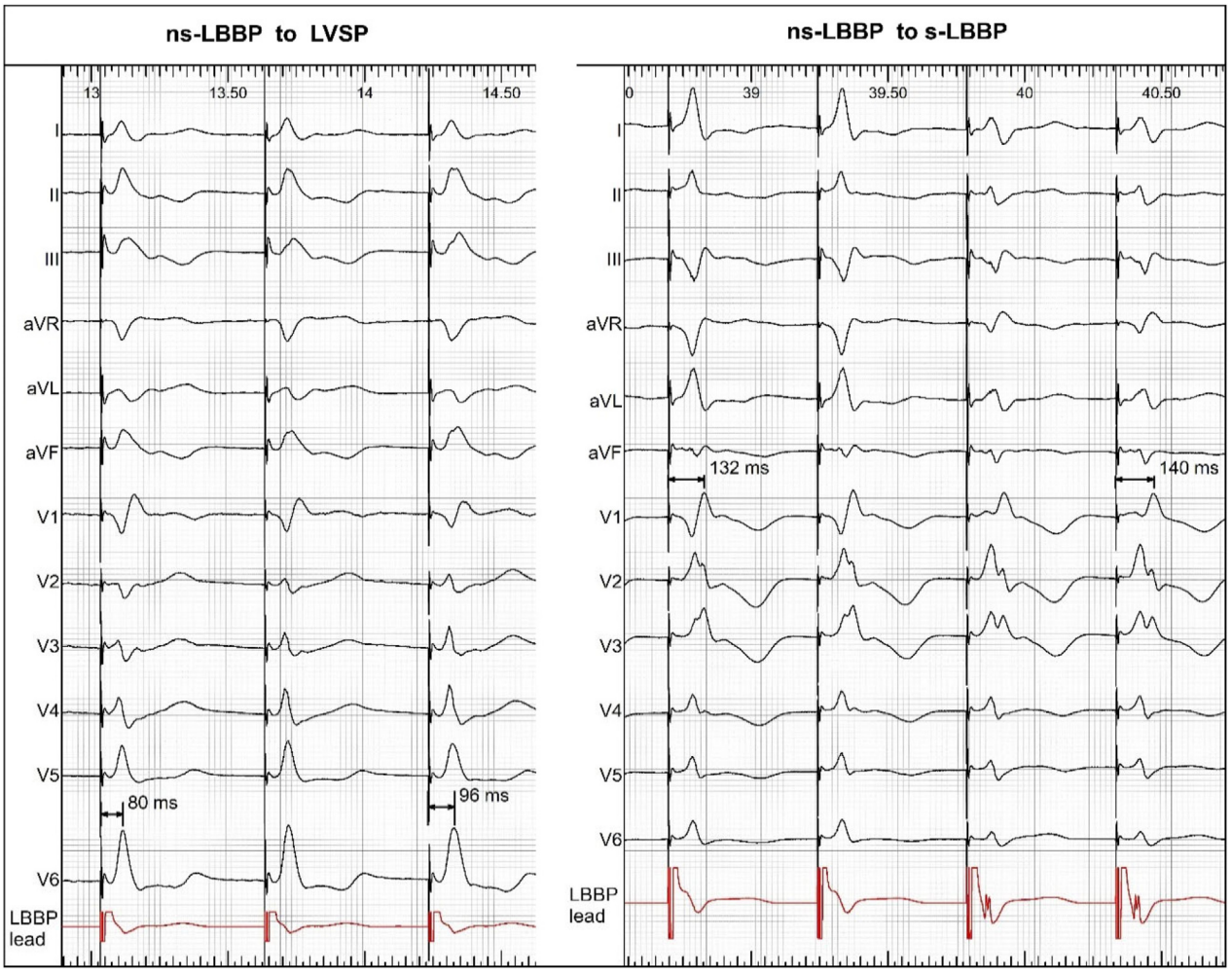
In the first pacing site, lack of LBB potential and V_6RWPT of 83 milliseconds (ie, over the 75 milliseconds cutoff) makes the diagnosis of LBB capture uncertain. Only application of the V_6-V_1 criterion allows to make a firm diagnosis as values >44 milliseconds are nearly 100% specific for LBB capture. In the second position, illustrating LVSP, R-wave peaks at V_6 and V_1 occur nearly simultaneously, resulting in V_6-V_1 interpeak interval during threshold testing of only 16 milliseconds, which is typical for lack of LBB capture. Modified with permission from Jastrzebski et al.[50] LBBAP = left bundle branch area pacing; other abbreviations as in Figures 4 and 5.

ventricles resulting in similar delay of LV free wall and RV free wall. Consequently, paced R-wave peaks in V_1 and V_6 occur nearly simultaneously, and the V_6-V_1 interpeak interval is short. In contrast, during nsLBBP, activation of RV is delayed in comparison to LV activation, hence the V_6-V_1 interval is longer (Figure 7).

The paced V_6-V_1 interval criterion addresses some limitations of the V_6RWPT criterion.[52-54] Long V_6RWPT might be caused not only by lack of LBB capture but also by initial latency, slower propagation via diseased HPS, substantial LV dilatation, or, often, a combination of these factors. The V_6-V_1 interpeak interval is likely less influenced by these limitations. If there is substantial initial latency or slow conduction through the myocardium, it will affect to a similar degree the timing of the activation of the RV and LV. Consequently, the R-wave peak will be delayed in both V_1 and V_6, and the V_6-V_1 interpeak interval will not be much effected. A value of V_6-V_1 interpeak interval >44 milliseconds is highly specific for diagnosis of LBB capture, whereas values of 33-40 milliseconds show optimal sensitivity/specificity balance. Combined use of V_6RWPT and V_6-V_1 interpeak criteria increases the diagnostic yield of ECG analysis.[54,55]

DIAGNOSIS OF LBB CAPTURE BY DEMONSTRATION OF QRS MORPHOLOGY TRANSITION. Threshold test. Perhaps the most straightforward and highly specific diagnostic method is based on differences in capture threshold between left conduction system and septal myocardium. Unfortunately, this difference is very often small or absent, resulting in lack of QRS transition and hence low sensitivity of this test (30%-70% during procedure, 15%-30% during follow-up). Sensitivity can be increased by performing threshold test immediately after lead deployment

FIGURE 8 **Diagnostic QRS Transition During Threshold Test**



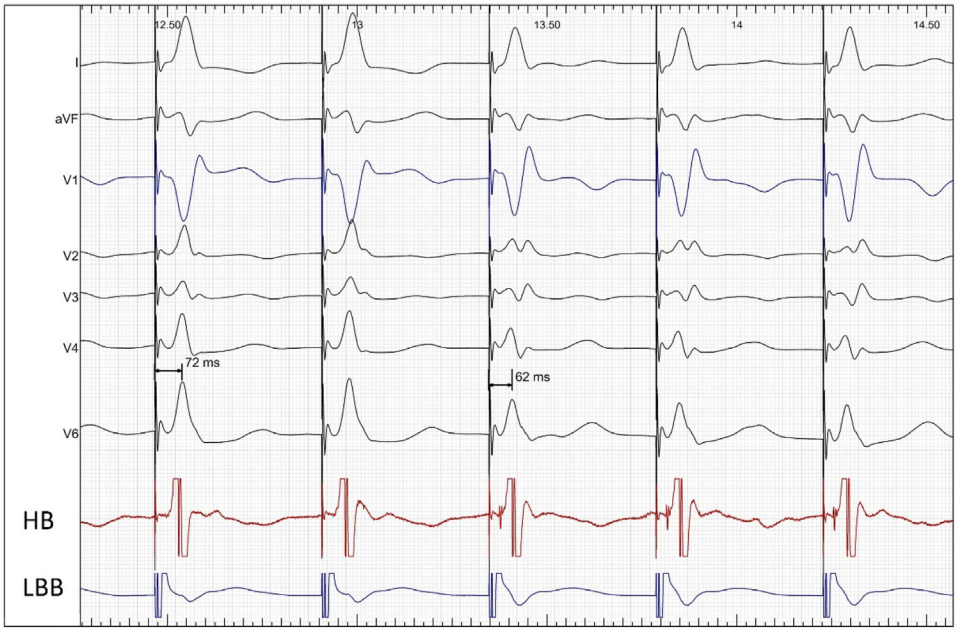
(Left) Very subtle transition from nsLBBP to LVSP. There is diagnostic prolongation in V_6 R-wave peak time, increase in R-wave amplitude in V_2-V_4 and change of ST-segment from isoelectric to downsloping in V_6. (Right) Obvious QRS transition from nsLBBP to sLBBP indicated by sudden prolongation of V_1 R-wave peak time; deepening of S waves in leads I, V_5, and V_6; prolongation of isoelectric interval after pacing stimulus; and appearance of discrete local potential on endocardial channel (LBBP lead). Abbreviations as in Figures 4 and 5.

when the local trauma transiently increases myocardial threshold and by performing threshold test multiple times during the procedure at different pulse widths.

Threshold test should be conducted in unipolar pacing mode at a constant rate with output slowly decreased until loss of capture. Simultaneously, 12-lead QRS morphology and endocardial recordings are monitored for sudden QRS transition and change in local endocardial activation pattern (Figure 8). QRS change to be considered diagnostic of LBB capture needs to conform to some criteria for transition. For nsLBBP → LVSP transition, the V_6RWPT should prolong ≥10 milliseconds, and for nsLBBP → to s-LBBP there should be broadening of the V_1 R/r wave with increase in V_1RWPT and/or deepening of the S wave in leads I, V_5, and V_6; alternatively, there should be a sudden appearance/prolongation of latency in surface ECG and discrete local potential on the endocardial channel.

Programmed stimulation. The refractory periods of the conduction system tissue and myocardium are different. Using programmed stimulation it is possible to obtain capture of only one of these tissues, either conduction system (selective response) or septal myocardium (myocardial response)

FIGURE 9 Continuous Recording of ECG and Endocardial Channels From the HB and LBB

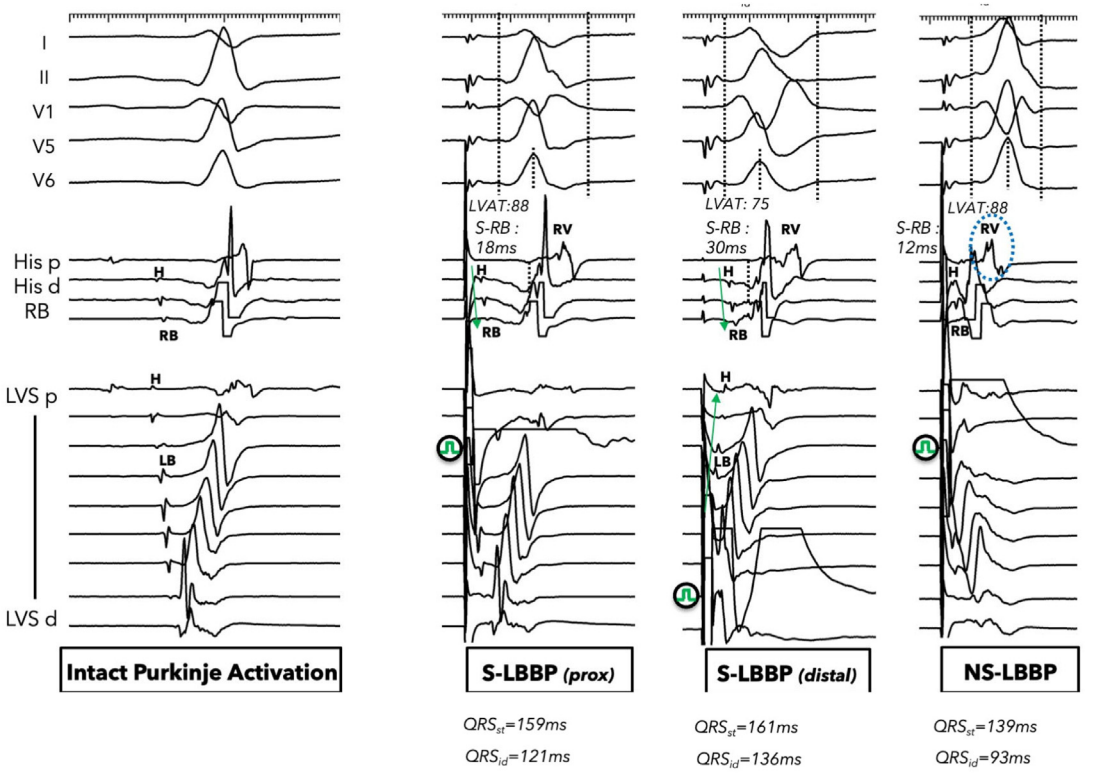


Continuous recording of electrocardiography (ECG) and endocardial channels from the His bundle (HB) and left bundle branch (LBB) leads during lead rotation enables us to make a diagnosis of LBB capture already at the stage of lead deployment in the septum. After second QRS interval, there is beat-to-beat QRS transition that indicates the moment of LBB capture. This moment can be recognized by sudden shortening of V_6 R-wave peak time by 10 milliseconds or more and by increase in V_1 R-wave amplitude. HB recording, illustrating sudden appearance of retrograde HB potential after the pacing stimulus, is not necessary to recognize diagnostic beat-to-beat QRS transition; it serves here as additional evidence that the beat-to-beat QRS change was indeed related to the capture of the left conduction system.

(Supplemental Figures 7 and 8). Both these responses are equivalent to QRS transition during threshold test and are diagnostic of LBB capture because they prove that the QRS transition in question was a nonselective QRS transition (ns-LBBP), composed by simultaneous depolarization of the 2 tissues. However, whereas selective response is 100% specific for LBB capture, myocardial response must be differentiated from a similar, albeit nonspecific response that maybe seen during LVSP. Dedicated pacing protocols, based on physiology of the His Purkinje system compared to the RV make it possible to evoke both myocardial and selective response in the same individual. Moreover, these dedicated protocols can augment the difference in refractory periods between LBB and septal myocardium and hence increase the diagnostic yield of programmed stimulation. Programmed stimulation is especially useful in patients with potentially long V_6RWPT (eg, heart failure, LBBB) and lack of QRS transition during thresholds test.

Lead-position-dependent QRS transition. When continuous pacing technique is used during lead rotations to achieve LBBAP, beat-to-beat-paced QRS changes can be observed as the lead gets deeper into the septum. This enables us to observe the moment of LBB capture, which is indicated by sudden V_6RWPT shortening and other morphologic changes in QRS complex (normalization of repolarization in V_5 and V_6; appearance of S waves in leads I, V_5, and V_6; and sudden increase in r′ amplitude in lead V_1 (**Figure 9**).[56,57] This QRS transition is identical to the QRS transition that can be observed during threshold testing. The continuous pacing technique requires a rotational adapter that connects the distal pin of the pacing lead with the external pacemaker and at the same time does not hamper lead rotations. Simple, self-made, or commercial solutions are available for Medtronic SelectSecure MRI Surescan 3830 lead, whereas for stylet leads this can be easily achieved by connecting to the stylet. This technique requires use of an electrophysiology recording system because it is often difficult to ascertain the moment of capture in real time. Confirming LBB capture during lead rotation often requires review of the moment of lead deployment with careful assessment/measurement of several consecutive QRS complexes.

FIGURE 10 Selective and Nonselective Pacing From Proximal LB and Distal Purkinje in a Patient With Narrow QRS Interval



Both QRS duration measurements are narrower during nonselective (NS) capture, where local ventricular electrogram is recruited immediately after the pacing stimulus. In contrast, selective (S) capture of proximal (prox) left bundle branch shows preservation of local and surface isoelectric segments with presystolic Purkinje activation before ventricular activation. During NS pacing, the basal right ventricle (His p, blue dashed circle) is advanced earlier by direct septal capture, compared to late activation during S capture, which corresponds to the terminal R′ in V_1. S pacing more distally shows delayed retrograde activation of the His (H) and right bundle (RB), which occur after QRS onset, resulting in less synchronization and wider QRS durations. Reproduced with permission from Sun et al.[58] His d = His distal; His p = His proximal; LB = left bundle; LVAT = left ventricular activation time; LVS = left ventricular septal; LVS d = left ventricular septal distal; LVS p = left ventricular septal proximal; other abbreviations as in Figure 5.

Influence of pacing site and capture selectivity on QRS characteristics and LVAT. It is important to note that the type of capture has not been proven to translate into different clinical outcomes caused by secondary rapid engagement of the His Purkinje system with LVSP. On the other hand, 10-20 milliseconds may have a dramatic impact on remodeling in patients undergoing CRT. To assess for differences in LVSP vs LBBP in addition to differentiating between the type of pacing, it is important for us to acknowledge that we do not understand the determinants of clinical response to pacing.

Direct pacing from the left conduction system offers the ability to gain further understanding of QRS characteristics during CSP. In a cohort of patients in which paired analysis of selective and nonselective capture were available from multielectrode diagnostic catheters, it was demonstrated that sLBBP exhibited wider QRS durations than nsLBBP did.[58] Therefore, QRS narrowing during LBB capture is predicated on recruitment of the basal septum and more rapid activation of the right bundle antegradely (Figure 10). This is in contradistinction to HBP, in which nonselective capture exhibits a wider QRS narrowing than sHBP does. It is important to understand that LBB stimulation, which can achieve rapid His Purkinje recruitment results in interventricular dyssychrony with incomplete or complete RBBB

pattern and narrow QRS interval is often achieved with AV fusion optimization with intrinsic RBB activation.

An important limitation of determining QRS duration is whether to measure from the QRS onset or the onset of stimulus artifact. There is more subjectivity when measuring from the earliest intrinsicoid deflection, and intracardiac correlation reveals that many pseudo delta waves during sLBB capture show little to no amplitude. However, when measuring from stimulus, LBB capture is typically associated with QRS durations of >120 milliseconds, which is counterintuitive for the achievement of electrical resynchronization.

Aside from QRS duration, peak LVAT or RWPT in V_6 has been proposed to represent the time required to depolarize the bulk of the LV myocardium. Rapid conduction through the His-Purkinje system results in shorter V_6RWPT and, hence, is an indicator of conduction system vs septal pacing. Whereas it has been proposed that LBBAP with conduction system capture is defined by V_6RWPT <75 milliseconds in patients with narrow QRS interval and <85 milliseconds in patients with wide QRS interval, V_6RWPT >85 milliseconds can be observed during CSP. Importantly, the site of stimulation is another unfactored variable in the determination of peak LVAT or V_6RWPT. Stimulation of a fascicle more distally from a potential with shorter Purkinje-to-ventricle interval than a proximal site results in a shorter RWPT. This is akin to S-QRS intervals in scar-related ventricular tachycardia, in which sites closer to the exit have shorter latency between the stimulus and myocardial depolarization (in this case, the conduction system). **Figure 11** shows the tradeoff between shorter RWPT (LVAT) and wider QRS interval caused by distal stimulation because synchronization with the right bundle/RV is dependent on a longer path to retrogradely activate the His bundle or transseptal conduction. Whether a shorter RWPT/LVAT or narrower QRS interval is more optimal physiologically needs prospective assessment. In this context, shorter RWPT/LVAT may represent less intraventricular dyssynchrony with more interventricular dyssynchrony (wider QRS interval). Further studies are needed to assess for differences with LBBAP and sites of stimulation (distal vs proximal).

CSP IMPLANT TECHNIQUES

Conduction system pacing has been increasingly adopted in the real world over the past decade.[59] The 2 main sites along the conduction system for lead implantation include the His bundle and LBB. Due to challenges related to implant technique, lower implant success rates, and reported increases in capture threshold with HBP, LBBAP has gained more popularity given better R-wave sensing and lower and stable capture thresholds.[60,61]

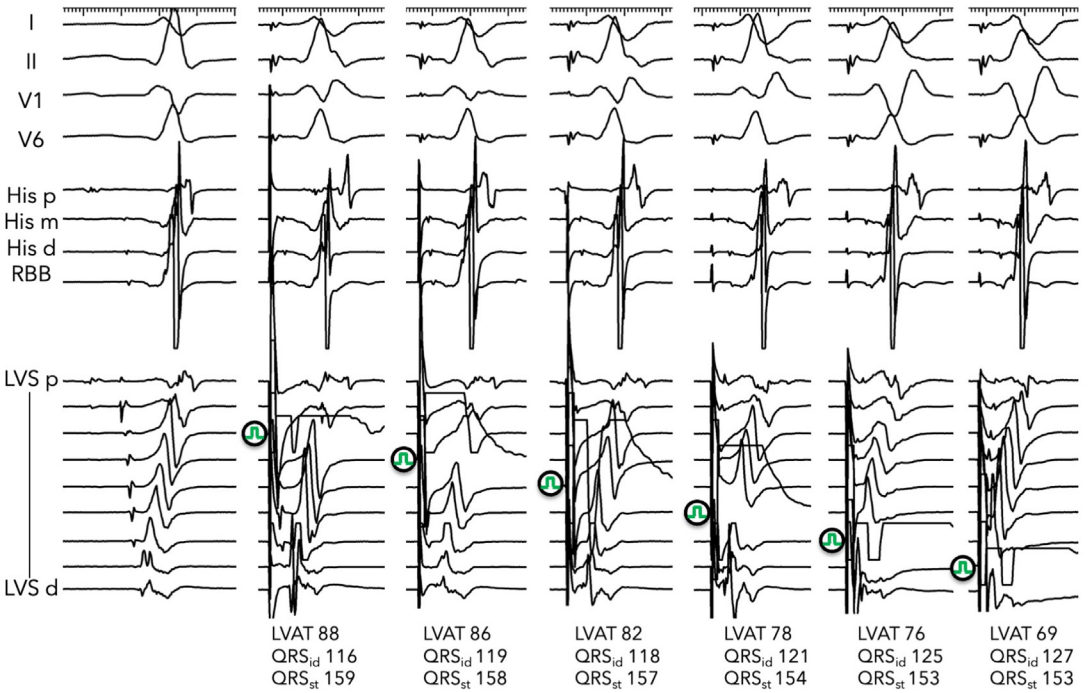
UPDATES IN IMPLANT TOOLS. With increasing adoption of CSP, there have been various advances in delivery sheaths for targeted lead implantation at the conduction system, for patients with normal cardiac anatomy as well as for specific situations such as right-sided implants and patients with enlarged and dilated hearts. **Table 1** highlights some of the newer delivery catheters for implantation. Zanon et al[62] evaluated the comparative effectiveness of the C315 preshaped delivery sheath (Medtronic Inc) with the Selectra 3D sheath (Biotronik Inc) among 151 patients demonstrating a similar success rate for implantation.

To date, there have been no dedicated leads designed for CSP. The most frequently used lead for CSP has been the Medtronic 3830 lead, which is a 4.1-F lumenless lead with a 1.8-mm exposed helix. This lead has gained U.S. Food and Drug Administration approval for both HBP and LBBAP. More recently, other active fixation stylet-driven leads have been deployed successfully for CSP. However, only limited data are available on these leads.

De Pooter et al[63] compared feasibility and success rates of LBBAP among 50 patients and demonstrated that the use of stylet-driven pacing leads was feasible (87% success) and yielded comparable implant success to LBBAP with the lumenless 3830 lead (89% success). LBBAP thresholds were low and comparable with both types of leads. However, the longer-term performance of stylet-driven leads need further evaluation. Similar findings were observed in the observational study for LBBP by Zanon et al.[62]

UPDATES IN IMPLANT TECHNIQUES. With LBBP, identifying the initial location for lead penetration through the muscular interventricular septum is usually performed by first identifying the His bundle and the using that as a landmark. However, in some cases this can be challenging. More recently, Liu et al[64] described a contrast-based visualization technique by defining the tricuspid valve in 60 patients undergoing LBBP. This technique decreased the procedural and fluoroscopic durations for LBBP implantation with fewer lead repositioning attempts. Jiang et al[65] described a novel 9-partition method to help localize the region for successful HBP and LBBP among 70 patients. The region between the apex and the ventricular contraction ring was divided into

FIGURE 11 Impact of Pacing More Distally in the Left Conduction System on LVAT and QRS Duration



At more distal sites, the local Purkinje electrogram to ventricular interval is shorter, which results in shorter LVAT. However, because of a longer course of retrograde LB activation into the RB, less synchronization yields a wider intrinsicoid QRS (QRS_{id}) interval. The impact on QRS measured from stimulus interval is variable because the LVAT shortens but QRS interval widens at more distal sites. Sequential pacing from more distal bipole pairs in a patient with normal QRS interval shortens LVAT but results in widening of QRS_{id} interval because of progressively delayed retrograde conduction into the RB. Reproduced with permission from Sun et al.[58] Abbreviations as in **Figures 5 and 10**.

9 partitions using right anterior oblique fluoroscopic views. HBP leads were distributed in the second partition, and 94.3% (33 of 35) of LBBAP leads were in the junctional area of second and fifth partitions. The distance from the lead tip to the junction of the noncoronary cusp and right coronary cusp (using computed tomography imaging) was 3.8 ± 0.6 cm and 1.9 ± 0.2 cm for LBBP and HBP, respectively.

The value of fixation beats by Jastrzębski et al,[66] template and "M" beats by Ponnusamy et al[67] during rapid lead rotation through the interventricular septum has added value in improving the negative predictive value and the specificity of LBB capture, respectively.

ADVANCES IN CSP FOR CRT. Among patients with LBBB/IVCD, Ravi et al[68] demonstrated the use of a vision wire-guided lateral LVATs helped with intraprocedural decision making regarding the type of CRT: HBP, LBBAP, or BVP-CRT. If LVAT shortened significantly with CSP, it suggested the patient had true LBBB and CSP was used; if CSP failed, then BVP-CRT was performed (Supplemental Figure 9).[68]

Left bundle branch pacing optimized (LOT)-CRT combines LBBP with coronary vein pacing in patients with wide QRS interval with incomplete correction with LBBP alone. Jastrzębski et al[69] recently published an international collaborative series demonstrating an 81% success rate with LOT-CRT resulting in a dramatic QRS reduction from 182 ± 25 milliseconds at baseline to 144 ± 22 milliseconds ($P < 0.0001$) and a modest improvement in LVEF.

FLUOROLESS AND 3D-MAPPING TECHNIQUE. One of the critical points in CSP compared to standard apical pacing has been advocated as a longer exposure to

TABLE 1 Specialized Delivery Catheters for CSP

Sheath	C315 His	C304 His	C304	SSPC1	SSPC2	SSPC3	SSPC4	Selectra 3D
Company	Medtronic	Medtronic	Medtronic	Boston Scientific	Boston Scientific	Boston Scientific	Boston Scientific	Biotronik
Shape	Preshaped, septal curve	Deflectable and preshaped	Deflectable	Preshaped, "C"	Preshaped, multipurpose	Preshaped, extended hook	Preshaped, right-sided	Preshaped (3 different shapes available)
Introducer	7-F	9-F	9-F	8-F	8-F	8-F	8-F	9-F
Usable length, cm	43	43	40	40	40	40	40	32-39
Inner diameter	5.4-F	5.7-F	5.7-F	6.5-F	6.5-F	6.5-F	6.5-F	7.3-F
Outer diameter	7-F	8.4-F	8.4-F	8-F	8-F	8-F	8-F	8.7-F
Integrated valve	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Hydrophilic coating	Yes	No	No	NA	NA	NA	NA	Yes
Braiding	Yes, 16 × 16	Yes, 8 × 8	Yes, 8 × 8	NA	NA	NA	NA	Yes
Horizontal reach, mm	79	79	37	NA	NA	NA	NA	NA
Vertical reach, mm	43	44	46	NA	NA	NA	NA	NA
Designed for	RA and RV septal location	RA and RV septal location	RA and RV septal location	RA septal location	RA and RV septal location	Dilated RA and RV septal location	Right-sided device implant	RA and RV septal location/Right side/ DCM
Right-sided device implant	Yes, can be reshaped for better torque transmission	Designed for left-sided implant	Designed for left-sided implant	Designed for left-sided implant	Designed for left-sided implant	Designed for left-sided implant	Yes	Yes
DCM	Sheath in sheath delivery	Deflection can be used to increase reach	Deflection can be used to increase reach	See SSPC3	See SSPC3	Yes	See SSPC3	Yes

Adopted from Ravi V, El Baba M, Sharma PS. His bundle pacing: tips and tricks. *Pacing Clin Electrophysiol*. 2021;44(1):26-34.
CSP = conduction system pacing; DCM = Dilated cardiomyopathy; NA = not available; RA = right atrial; RV = right ventricular.

x-rays. Indeed, Zanon et al[70] demonstrated that HBP is feasible using minimum or no fluoroscopy in 39 of 41 patients with a success rate of 95% and selective capture in 59% of cases. The idea of this study was localizing the His bundle with mapping using a standard electrophysiology recording system. With this technique the operator is concentrating only on the electrograms and the final HBP lead position was reached in 31 patients (79.4%) without fluoroscopy, only guided by electrograms. In 8 patients a minimal fluoroscopic approach (mean: 8 seconds) was used. This experience has the limitation of being conducted in a highly experienced center with HBP implants; however, it highlights the concept of an electrophysiologic procedure in contrast to an interventional/radiologic procedure. Similarly, Sharma et al[71] demonstrated the safety and feasibility of HBP implant guided by 3D electroanatomic mapping systems with extremely low fluoroscopic exposure. Similar outcomes have been reported by Richter et al[72] in 58 patients, indicating the feasibility and safety of routine electroanatomically guided HBP lead implantation in a real-world cohort of patients with a great reduction in radiation exposure. The potential advantage of this technique can be reflected in a precise localization of the His bundle with limited fluoroscopy (Supplemental Figure 10). In case of LBBAP, the lead is moved toward the septum to a previously tagged site. Three-dimensional electroanatomic mapping allowed the real-time visualization of the lead penetrating the septum. Switching the connection from unipolar to bipolar, the whole bipole of the lead is visible to better evaluate the lead orientation and ensure it is perpendicular to the septum. Three-dimensional electroanatomic mapping also allows to measure the distance of the starting point from the His bundle cloud and the length of the penetrating part of the lead into the septum. Moreover, some challenging anatomies such as congenital cardiac diseases or extremely enlarged right atria that are usually associated with a high percentage of implant failure may benefit from this combination of technologies.[73]

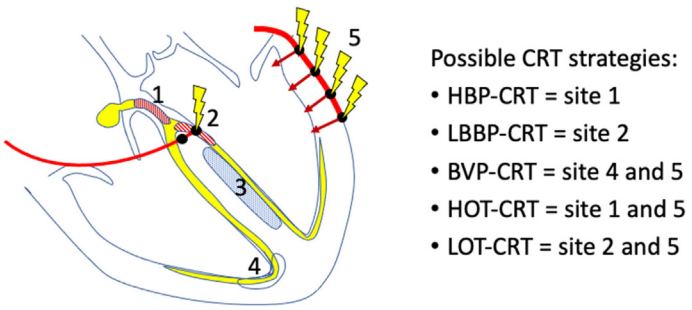
HYBRID APPROACHES TO CSP

Whereas conventional BVP has shown benefit in patients with heart failure and conduction system disease, there are limitations to its success, resulting in widely variable clinical response. Several observational and acute hemodynamic studies have demonstrated improved electrical resynchronization and echocardiographic response with CSP or combined sequential stimulation of the conduction system and

the epicardial LV via the coronary venous system (Figure 12).[74] HOT- or LOT-CRT are currently under investigation.

Currently, CRT by BVP is the only heart failure therapy that improves cardiac function, functional capacity, and survival while decreasing cardiac workload and hospitalizations. Response to BVP is variable, ranging from complete normalization of cardiac function to lack of benefit to worsening heart failure. One obstacle for effective CRT delivery is slow impulse propagation and stimulus-to-QRS latency in severely diseased myocardium and myocardial scar. Suboptimal coronary venous lead placement secondary to coronary venous anatomy also presents challenges. Furthermore, many patients have AV block, omitting delivery of fused CRT, or an IVCD coexisting with bundle branch block, complicating CRT delivery. In advanced cardiomyopathy, coexisting LBBB and IVCD may amplify LV dyssynchrony, because LV activation in the setting of LBBB relies on prolonged myocardial cell-to-cell conduction. Thus, coexistent IVCD further delays activation of some myocardial segments. Therefore, CSP may paradoxically improve the impact of a coexistent IVCD. In these circumstances, resynchronization may be more complete when intervened on at the level of the specialized conduction system followed by sequential epicardial LV pacing in areas of late myocardial activation (Figure 13). Many challenges of conventional CRT have been overcome with VV-interval programmability, device-based fusion optimization algorithms, quadripolar LV leads allowing electronic repositioning, multipoint stimulation, and targeted LV pacing from the LV lateral base. CSP, alone or in conjunction with LV epicardial pacing, may yield a viable solution to some of the obstacles outlined (Figure 14).

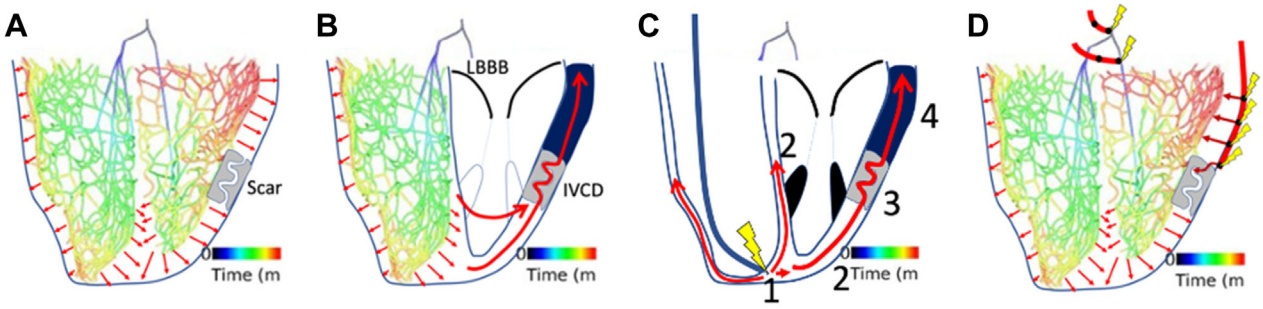
FIGURE 12 Locations for Permanent Lead Placement and Possible CRT Strategies Using CSP



Locations for permanent lead placement and possible cardiac resynchronization therapy (CRT) strategies using conduction system pacing (CSP). BVP = biventricular pacing; HBP = His bundle pacing; HOT = His optimized; LBBP = left bundle branch pacing; LOT = left bundle branch optimized.

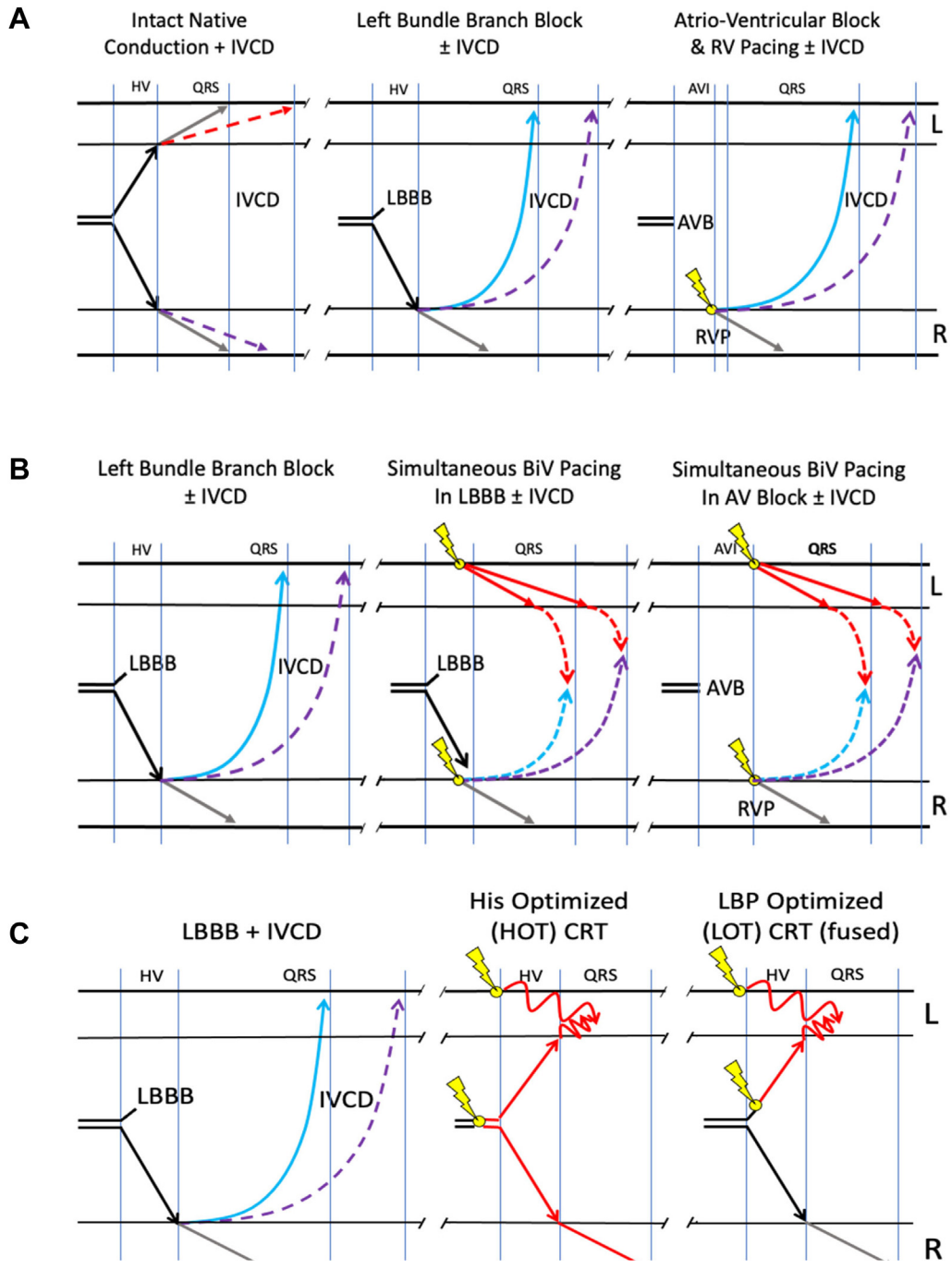
OBSERVATIONAL STUDIES ON HOT- OR LOT-CRT. In a small retrospective, observational multicenter study, HOT-CRT was performed in a series of 27 patients with LBBB/IVCD where partial or insignificant QRS narrowing was achieved by HBP alone compared with baseline (Supplemental Figure 11). All patients had therapy-refractory NYHA functional class III-IV

FIGURE 13 Pathophysiology of Coexistent LBBB and IVCD



(A) Intact His-Purkinje conduction in a patient with a small left ventricular scar. (B) With left bundle branch block (LBBB), left ventricular activation now relies on cell-to-cell myocardial conduction through diseased myocardial tissue and scar amplifying the effective intraventricular conduction delay (IVCD). (C) A similar situation applies to the scenario of atrioventricular block and right ventricular pacing amplifying the IVCD. (D) Management of coexistent LBBB and IVCD by His- or left bundle–optimized cardiac resynchronization therapy.

FIGURE 14 Ladder Diagrammatic Presentation of LBBB and IVCD and Their Management by Different Resynchronization Strategies



(A) Different presentations of IVCD. (B) Treatment of LBBB and coexistent IVCD by conventional CRT. (C) Treatment of LBBB and IVCD by HOT- and LOT-CRT. AVB = atrioventricular block; AVI = AV interval; BiV = biventricular; HV = His - ventricular interval; L = left; LBP = left bundle pacing; R = right; RV = right ventricular; RVP = right ventricular pacing; other abbreviations as in Figures 5, 12, and 13.

heart failure symptoms and a baseline LVEF ≤35%. HOT-CRT resulted in improved electrical resynchronization when compared to conventional BVP or HBP. The QRS duration was reduced from 183 ± 27 milliseconds to 120 ± 16 milliseconds (34%) by HOT-CRT compared with 162 ± 18 milliseconds (11%) by BVP and 151 ± 25 milliseconds (17%) by HBP alone ($P <$ 0.05). Investigators observed significant echocardiographic and clinical improvement in patients with advanced heart failure who were treated with HOT-CRT.[28,75,76]

A single center, prospective, nonrandomized observational study investigated LOT-CRT compared to BVP. Twenty-one patients with CRT indication and NYHA functional class II-IV were enrolled, 10 in the LOT-CRT group and 11 in the BVP group. In the LOT-CRT group, the QRS duration decreased from 158.0 ± 13.0 milliseconds at baseline to 132.0 ± 4.5 milliseconds (16%) with BVP ($P = 0.019$) and 123.0 ± 5.7 milliseconds (22%) with LBBP ($P < 0.01$) to 121.0 ± 3.8 milliseconds with LOT-CRT, which was not significant when compared to LBBP alone. LOT-CRT demonstrated narrower QRS duration (121.0 ± 3.8 milliseconds) compared to BVP (133.3 ± 8.2 milliseconds; $P = 0.001$). At 9-month follow-up, both groups demonstrated improved LVEF, QRS duration, and NYHA functional class. The investigators concluded LOT-CRT was feasible in this patient cohort. There were no adverse events reported.[78]

A multicenter observational study reported 112 patients with CRT indication undergoing LOT-CRT. The implant success rate was 81%. LOT-CRT resulted in improved electrical resynchronization when compared to conventional BVP or LBBP alone. The QRS duration was reduced from 182 ± 267 milliseconds to 144 ± 22 milliseconds (21%) by LOT-CRT compared with 170 ± 30 milliseconds (7%) by conventional BVP and 162 ± 23 milliseconds (11%) by LBBP alone ($P < 0.001$). LVEF and NYHA functional class improved from 28.5 ± 9.9 to 37.2 ± 12.0 ($P <$ 0.001) and 2.9 ± 0.6 to 1.9 ± 0.6 ($P < 0.0001$), respectively.[69]

The CSPOT (Conduction System Pacing Optimized Therapy; NCT04905290) trial is an ongoing prospective, observational, acute hemodynamic crossover trial comparing traditional BVP, LBBP, and LOT-CRT (**Table 2**, LOT-CRT section). At implantation, all subjects undergo an acute pacing protocol comparing BVP, LBBP, and LOT-CRT, serving as their own control. The primary outcomes include electrical resynchronization response at time of implant and hemodynamic response measured by LV dP/dt_{max}. Secondary outcomes at 6-month follow-up include change in LVEF, LV end-systolic volume, and a clinic composite score based on mortality, heart failure events, termination of device function, NYHA functional score, and a patient global assessment.

The HOT-CRT (His-Purkinje Conduction System Pacing Optimized Trial of Cardiac Resynchronization Therapy; NCT04561778) trial is an ongoing randomized, prospective, single-blinded trial of 100 patients investigating the overall success rate of HOT-CRT vs BVP (**Table 2**, HOT-CRT section). In this trial, CSP first arm will also evaluate the need for combining conduction system lead placement in patients with incomplete electrical resynchronization. Acute outcomes include change in QRS duration and incidence of major periprocedural complications. Primary outcomes include improvement in LVEF at 6 months and freedom from major complications or need for CRT lead revision at 6 months. Secondary outcomes include heart failure hospitalizations, change in NYHA functional class, LV end-systolic volume index at 6 months, ventricular tachycardia or ventricular fibrillation requiring implantable cardioverter-defibrillator therapy, and change in quality-of-life scores. Currently, in absence of randomized controlled clinical trial data, HOT-/LOT-CRT should be viewed as investigational. Whereas there are some data on the role of BVP in patients with non-LBBB, there are limited data on CSP in patients with non-LBBB.

CLINICAL TRIALS

There are 7 small (29-167 patients) published randomized clinical trials examining the role of CSP (HBP or LBBP) in patients with heart failure with reduced ejection fraction (LVEF <35%-40%) and different underlying conduction abnormalities: left bundle branch block, atrial fibrillation with AV node ablation, and prolonged PR (**Table 3**).[79-83]

In a crossover study by Lustgarten et al,[79] the QRS duration was narrowed in the majority of patients with ischemic disease and only about one-half of the nonischemic patients (21 of 29) with HBP. Quality of life, NYHA functional class, 6-minute walk test, and LVEF were improved with the same degree by both BVP and HBP compared to baseline. In the HIS SYNC (His Bundle Pacing Versus Coronary Sinus Pacing for Cardiac Resynchronization Therapy) pilot trial of 40 patients with indication for CRT, there was no statistically significant difference in the QRS duration and LVEF change by both BVP and HBP compared to baseline at 6 months, although numerical estimates were higher in the HBP arm.[80] There was no observed significant difference in CV hospitalization or death at 12 months between the 2 groups. Crossover from HBP

TABLE 2 Cardiac Resynchronization Therapy

First Author, Year	Design	Indication	N	Success (%)	Follow-Up (mo)	Echocardiographic Hemodynamic	QRS	Outcomes
HOT-CRT								
Vijayaraman,[75] 2019	Retrospective, multicenter, observational	HOT-CRT in LBBB and IVCD with QRS duration ≥140ms or AV block with LBBB type escape	27	93	12	LVEF: 24%→38% LVEDD: 65→59 mm, LVEDV: 225→200 mL, LVESV: 171→138 mL Super-response: 28%	Duration Baseline: 183 ms BiV: 162 ms HBP: 151 ms HOT-CRT: 120 ms	NYHA: 3.3→2.0 Reduced HF hospitalizations Reduced loop diuretic and aldosterone antagonist doses
Zweerink,[28] 2021	Prospective, single-center, observational	CRT	19		NA	Baseline LVEF: 31%	Duration Baseline: 142 ms HBP: 142 ms BiV: 154 ms HOT-CRT: 126 ms	HOT-CRT acutely improves ventricular electrical synchrony compared to BiV and HBP HOT-CRT reduced LVAT by 21% compared to HBP
Deshmukh,[76] 2021	Retrospective, single- center	CRT indication in which His pacing did not result in resynchronization	21	100	32	LVEF 27%→41%	Duration Baseline: 170 ms HBP: 157 ms BiV: 141 ms HOT-CRT: 110 ms	NYHA: 3→2 HOT-CRT resulted in superior acute electrical synchrony in this population
Vijayaraman, 2023[77a]	Randomized, prospective, double-blinded, crossover	CRT indication	100[b]		6	LVEF LV chamber dimensions LV volumes LV end-systolic volume index	Duration change	Improvement in LVEF Freedom from major complications HF hospitalizations NYHA functional class Quality of life
LOT-CRT								
Jastrzebski,[78] 2021	Prospective, multicenter, observational	CRT indication or nonresponders to BiV CRT	112	81	[3]3	LVEF: 29%→37% ($P < 0.0001$) LVEDD: 62→59 mm Super-response: 24%	Duration Baseline: 181 ms LOT-CRT: 144 ms LBBP: 162 ms BVP: 170 ms	LOT-CRT provides significantly greater resynchronization than LBBP or BiV CRT NYHA: 2.9→1.9
Feng,[79] 2022	Prospective, single-center, observational	CRT indication Atrial fibrillation excluded	21	90	9	LVEF BVP: 34%→46% LOT-CRT: 32%→45%	Duration BVP: 176→133 ms LOT-CRT: 158→121 ms	LOT-CRT Feasible Superior to BVP, associated with shorter QRS duration Improved NYHA functional class and LVEF during the follow-up period of 9 mo
C-SPOT,[a] NCT04905290	Prospective, observational, acute hemodynamic study	CRT indication	60[b]		6	Change in LVEF Change in LVESV	Acute change in QRS duration	Resynchronization response at implantation Hemodynamic response Change in NYHA functional class
Vijayaraman,[a] NCT04561778	Randomized, Prospective, double-blinded, Cross Over	CRT indication	100	[b]	6	LVEF LVEDD, LVESD LVEDV, LVESV LVESV index	QRS duration change	Improvement in LVEF Freedom from major complications HF Hospitalizations NYHA functional class Quality of life

[a]Not yet published. [b]Estimated.

AV = atrioventricular; BiV = biventricular; CRT = cardiac resynchronization therapy; C-SPOT = Conduction System Pacing Optimized CRT; HBP = His bundle pacing; HOT = His optimized; HF = heart failure; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; LBBP = left bundle branch pacing; LOT = left bundle branch optimized; LVAT = left ventricular activation time; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; NA = not available.

TABLE 3 Randomized Clinical Trials for CSP

First Author, Year	Treatments	Size	Population	Primary Endpoint	Other Endpoints	Follow-Up (mo)	Country
Lustgarten et al,[80] 2015	HBP vs BVP	29	CRT indication QRSd >130 ms (28 LBBB, 1 RBBB)	Feasibility QRSd	QoL NYHA 6MWT LVEF	12	USA
His-SYNC,[81] 2019	HBP vs BVP	41	CRT indication LVEF ≤35% QRSd >120 ms NYHA II-IV	QRSd LVEF at 6 mo, CV hospitalization or death at 12 mo		12	USA
His-Alternative,[82] 2021	HBP vs BVP	50	LVEF ≤35% LBBB NYHA II-IV	His bundle lead implant success	QRSd LVEF LVSV NYHA 6MWT NT-proBNP procedure time fluoroscopy time radiation dose lead measures	6	Denmark
LBBP RESYNC,[31] 2022	LBBP vs BVP	40	LVEF ≤40%, NICMP, LBBB, NYHA II-IV	LVEF	Echo measurements, NT-proBNP, NYHA, 6MWT, QRSd, CRT response	6	China
LEVEL-AT,[54] 2022	CSP vs BVP	70	LVEF ≤35%, LBBB ≥130 ms or non-LBBB QRS ≥150 ms or AV block	LVAT	LVESV, death, or HFH	6	Spain
ALTERNATIVE AF,[83] 2022	HBP vs BVP	40	Persistent AF + AVNA, LVEF ≤40%, RSs <120 ms or RBBB NYHA II-IV	LVEF		18 (crossover at 9 mo)	China
HOPE-HF,[35] 2022	HBP vs no pacing	167	PR ≥200 ms, LVEF ≤40%, QRS ≤140 ms, or RBBB	Peak Vo_2	QoL, LVEF, patients' symptomatic preference	12 (crossover at 6 mo)	UK

6MWT = 6-minute walk test; AF = atrial fibrillation; AVNA = atrioventricular node artery; BVP = biventricular pacing; CV = cardiovascular; HFH = heart failure hospitalization; His-Alternative = His Pacing Versus Biventricular Pacing in Symptomatic HF Patients With Left Bundle Branch Block; His-SYNC = His Bundle Pacing versus Coronary Sinus Pacing for Cardiac Resynchronization therapy; HOPE-HF = His Optimized Pacing Evaluated for Heart Failure; LBBP RESYNC = Left Bundle Branch Pacing Versus Biventricular Pacing for Cardiac Resynchronization Therapy; LEVEL-AT = LEft VEntricuLar Activation Time Shortening With Physiological Pacing vs Biventricular Resynchronization Therapy; LVSV = left ventricular stroke volume; NICMP = nonischemic cardiomyopathy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = NYHA functional class; PR = PR interval; QoL = quality of life; QRS = QRS interval; QRSd = QRS duration; QRSs = QRS shortening; RBBB = right bundle branch block; other abbreviations as in Tables 1 and 2.

to BVP was high at 48% because of the requirement to achieve QRS narrowing by >20%, to QRS width of <130 milliseconds, correction thresholds <5 V at 1 millisecond, and enrollment of IVCD patients.

In a randomized study of 50 patients with LBBB and LVEF <35%, HBP corrected the QRS duration in 96% of patients with LBBB (defined by Strauss criteria), suggesting that the conduction defect is at the level of His in fibers committed to become the LBB. Permanent HBP was feasible in 72% of patients randomized.[81] QRS duration, LVEF, and clinical and physical parameters at 6 months were not significantly different in an intention-to-treat analysis with HBP or BVP. However, LVEF was significantly improved and LV end-systolic volume was significantly lower at 6 months in patients with HBP compared to BVP in a per-protocol analysis. Furthermore, pacing thresholds were higher at implant and 6 months with HBP compared to BVP.

The observed success of LBBAP is reported higher than HBP. LBBAP was superior to BVP in LVEF improvement, reductions in LV end-systolic volume, and N-terminal pro-B-type natriuretic peptide at 6 months compared to BVP in a small, randomized study of 40 patients.[82] There were comparable changes in NYHA functional class, 6-minute walk distance, QRS duration, and rates of CRT response. Similarly, in another randomized study of 70 patients, there was no significant difference in LVAT at 45-day or QRS duration, LVEF, LV end-systolic volume, NYHA functional class, and combined endpoint of mortality or heart failure hospitalizations at 6-month follow-up compared to baseline between CSP or BVP.[31]

In a population with symptomatic heart failure (LVEF <40%), persistent atrial fibrillation, and requiring AV node ablation, HBP was found to improve LVEF by a statistically significant but modest degree compared to BVP in a randomized, crossover trial.[83]

In a randomized, double-blind, crossover trial of 167 patients with heart failure with reduced EF (LVEF <40%), prolonged PR interval >200 and relatively narrow QRS interval, or RBBB, HBP did not

TABLE 4 Ongoing or Planned Clinical Trials for Conduction System for Bradyarrhythmias

Trial Name NCT # Status	Treatments	Size	Population	Primary Endpoint	Other Endpoints	Follow-Up (mo)	Country
LEFT Bundle Pacing vs Standard Right Ventricular Pacing for Heart Failure NCT05015660 Recruiting	LBBP vs RVP	100	LVEF ≥50%, high-degree AVB with anticipated RVP >90%	LVESVi, implant success, feasibility	CV death, HFH, death, LVEF, NT-proBNP, AF progression, TR, MR, lead parameters, QoL, safety	24	Canada
PHYSPAVB NCT05214365 Recruiting	His/LBBP vs RVP	200	LVEF >50%, AV block	PICM	LVESV, septal flash, AF, HFH, NYHA 6MWT, NT-proBNP, QoL, safety	12	Spain
LEAP NCT04595487 Recruiting	LVSP vs RVP	470	LVEF >35%, second or third AVB, or atrial arrhythmia with slow VR, expected VP >20%	Combined death, HFH, and LVEF	Death, HFH, combined death and HFH, AF, LVEF, QoL, safety, QALY, CEA, BIA	12	the Netherlands
PROTECT-SYNC NCT05585411 Not recruiting	LBBP vs RVP	450	Bradyarrhythmia with anticipated RVP >40%	Composite, HFH, and upgrade to CRT	Death, CV death, HFH, implant success, safety, LVEF, AF, cardiopulmonary exercise parameters	24	South Korea
LEAP-Block NCT04730921 Recruiting	LBBP vs RVP	458	LVEF ≥50%, AVB patients with anticipated RVP >40%	Composite death, HFH, and upgrade to CRT	Death and HFH, and upgrade to CRT, echo parameters, implant success, safety, device parameters, atrial arrhythmias	24	China
OptimPacing NCT04624763 Recruiting	LBBP vs RVP	683	LVEF >35%, NYHA I-III, second or third AV block or persistent or permanent AF with VR <50 beats/min	Combined death, HFH, and PICM	Echo parameters, NT-proBNP, NYHA 6MWT, QoL, safety	36	China
PROTECT HF	CSP vs RVP	2,600	LVEF >35%, high burden of VP	Cardiovascular death, HFH, QOL, upgrade		48	UK, world

AVB = atrioventricular block; LEAP = LVSP vs RVP in Patients With AV Conduction Disorders; LEAP-Block = Impact of Left Bundle Branch Area Pacing vs Right Ventricular Pacing in Atrioventricular Block; LVESVi = left ventricular end systolic volume index; LVSP = left ventricular septal pacing; MR = mitral regurgitation; OptimPacing = Protection of Cardiac Function With Left Bundle Branch Pacing in Patients With Atrioventricular Block; PHYSPAVB = Physiological Pacing for AV Block to Prevent Pacemaker-Induced Cardiomyopathy; PICM = pacemaker induced cardiomyopathy; PROTECT-HF = Physiological versus Right ventricular pacing Outcome Trial Evaluated for Bradycardia Treatment - Heart Failure; PROTECT-SYNC = Preventive Effect of Left Bundle Branch Area Pacing Versus Right Ventricular Pacing on All Cause Death, Heart Failure Progression, and Ventricular Dyssynchrony in Patients With Substantial Ventricular Pacing; QALY = quality-adjusted life-year; RVP = right ventricular pacing; TR = tricuspid regurgitation; VP = ventricular pacing; VR = ventricular rate; other abbreviations as in Tables 2 and 3.

increase peak oxygen uptake but significantly improved quality of life and was symptomatically preferred by a clear majority of patients. Importantly, HBP did not adversely affect ventricular function at 6 months.[35]

The planned and ongoing clinical trials cover most of the clinical scenarios that require significant amounts of ventricular pacing either caused by high-degree AV block (Table 4) or for CRT (Table 5). Furthermore, a number of trials examine CSP in specific clinical scenarios such as atrial fibrillation in the context of slow ventricular rate or AV node ablation for rate control (Table 6) and after transaortic aortic valve replacement (Table 7). Many of those clinical trials are powered to assess hard outcomes. In aggregate, these trials will enroll diverse patient populations.

Table 8 summarizes the advantages and disadvantages of CSP vs BVP for CRT.

CLINICAL TRIALS FOR BRADYARRHYTHMIAS. There are fewer trials that employ HBP alone compared to LBBAP or both. This is likely caused by the limitations of HBP compared to LBBAP. The smaller studies have surrogate primary endpoints and shorter follow-up whereas larger clinical trials are powered to examine clinically relevant outcomes such as mortality, heart failure hospitalizations, and development of pacing-induced cardiomyopathy and have longer follow-up. The inclusion criteria include not only patients with normal LVEF (>50%) but in some studies extend to LVEF as low 35%. Comparison with RVP reflects different pacing practices in most countries for LVEF 35%-50%. In the United States, the favored modality is BVP for LVEF 35%-50% and high-degree AV block based on current guidelines. Left vs Left (Table 3) compares HBP/LBBAP to BVP in patients with LVEF 35%-50% and those with <35%. Whereas most trials are examining the efficacy and safety of CSP, the LEAP (LVSP vs RVP in Patients With AV Conduction Disorders) trial is unique in determining whether LVSP is sufficient without a requirement to capture the LBB. These studies will help establish the role of CSP for the appropriate patient population.

TABLE 5 Ongoing or Planned Clinical Trials for CSP for CRT

Trial Name NCT # Status	Treatments	Size	Population	Primary Endpoint	Other Endpoints	Follow-Up (mo)	Country
LIT-HF NCT05572957 Recruiting	His/LBBP vs GDMT	50	NICMP, LVEF≤35%, NYHA II-III, <3 mo GDMT SR, LBBB	% with LVEF ≤35% and/or VAs	Health economics, LVEF, LVESV, LVEDV, NT-proBNP, NYHA, QoL, safety	18	China
HIS-CRT NCT05265520 Recruiting	HBP vs BVP	120	IIa, IIb indication for CRT-D, RBBB	LVEF	QRSd, LVESV, LVEDV, NT-proBNP	6	USA
HOT-CRT NCT04561778 Enrollment complete	HOT/LOT vs BVP	100	LVEF ≤35%, LBBB QRSd >120 ms or LVEF ≤50%, RVP >40%, NYHA II-IV	LVEF, safety, success	HFH, death, VT/VF, crossover, NYHA, QRSd, LVESVi, QoL	6	USA
REINVENT-CRT NCT05652218 Not recruiting	LBBP vs BVP	20	LVEF >35%, LBBB, NYHA I- IV	MPI		6 (crossover 3 mo)	USA
HIS-alt_2 NCT04409119 Recruiting	His/LBBP vs BVP	125	LVEF ≤35%, NYHA II-IV, LBBB, or RVP >90%	LVEF, QRS narrowing	LVEF, 6MWT, NYHA, QoL, QRSd, NT-proBNP, safety	6	Denmark
LBBAP-AFHF NCT05549544 Recruiting	LBBP vs BVP	60	Heart failure, LVEF <50%, NYHA II-IV, permanent AF, QRSd <130 ms, AVNA or slow VR with anticipated RVP ≥40%	LVEF	Implant success, safety, echo parameters, NT-proBNP, death, and HFH	6	China
CSP-SYNC NCT05155865 Recruiting	His/LBBP vs BVP	60	LVEF ≤35%, LBBB, NYHA II-III	LV volume, LVEF, NYHA, NT-ProBNP, 6MWT, QoL	Myocardial work redistribution, QRSd, arrhythmia, safety	12	Slovenia
CONSYST-CRT NCT05187611 Recruiting	His/LBBP vs BVP	130	LVEF ≤35%, LBBB, QRSd ≥130 ms or LVEF ≤35%, non-LBBB, QRSd ≥150 ms or LVEF <40%, AVB or LVEF≤35%, NYHA III-IV, AF, QRSd ≥130 ms	Composite death, cardiac transplant, HFH, LVEF	LVEF, LVESV, composite of death, cardiac transplant, HFH, QRSd, septal flash, NYHA	12	Spain
Safety and Effectiveness of Left Bundle Branch Pacing in Patients With Cardiac Dysfunction and AV Block NCT05553626 Not recruiting	LBBP vs BVP	160	LVEF <50%, NYHA I-III, second or third AVB, or RVP >40%	LVEF	LVESV, implant success, death and HFH, safety, QRSd, TR	12	China
LeCaRT NCT05365568 Recruiting	LBBP vs BVP	170	CRT indication, NYHA II-IV, LBBB QRSd >130 ms or non-LBBB QRSd, >150 ms, or wide paced QRSd	Composite death, HFH, implant failure, CIED re-intervention	Procedure time, fluoroscopy time, QRSd, 6MWT, LVESV, ICD therapies	12	Belgium
LEFT-BUNDLE-CRT NCT05434962 Recruiting	LBBP vs BVP	176	I or IIa indication for CRT, LBBB	CRT response	LVEF, clinical outcome, 6MWT, QoL, HFH, death, cardiac transplantation, VAs, safety	12	Spain
PhysioSync-HF NCT05572736 Not recruiting	His/LBBP vs BVP	304	LVEF ≤35%, LBBB, QRSd ≥130 ms	Composite death, HFH, LVEF	Cost-effectiveness, QoL, NYHA, 6MWT NT-proBNP, LVEF QRSd, CV death and HFH, LVAT	12	Brazil
Left vs Left NCT05650658 Not recruiting	His/LBBP vs BVP	2,136	LVEF ≤50%, QRSd ≥130 ms or anticipated RVP >40% or upgrade to CRT because of RVP >40%	Composite death and HFH	QoL, death, HFH, and LVESVi >15%, CV death, NYHA, 6MWT, NT-proBNP, AF, ICD therapies, echo parameters	66	USA, Canada

CIED = cardiac implantable electronic device; CONSYST-CRT = Conduction System Pacing vs Biventricular Resynchronization Therapy in Systolic Dysfunction and Wide QRS; CRT-D = cardiac resynchronization therapy defibrillator; CSP-SYNC = Conduction System Pacing Versus Biventricular Pacing for Cardiac Resynchronization; GDMT = guideline directed medical therapy; HIS-alt_2 = Direct His/LBB Pacing as an Alternative to Biventricular Pacing in Patients With HFrEF and a Typical LBBB; HIS-CRT = His-Bundle Corrective Pacing in Heart Failure; HOT-CRT = His-Purkinje Conduction System Pacing Optimized Trial of Cardiac Resynchronization Therapy; ICD = implantable cardioverter-defibrillator; LBBAP-AFHF = Clinical Efficacy of Left Bundle Branch Area Pacing for Patients With Permanent Atrial Fibrillation and Heart Failure; LeCaRT = Left Bundle Branch Area Pacing for Cardiac Resynchronization Therapy: A Randomized Study; LEFT-BUNDLE-CRT = The Left Bundle Cardiac Resynchronization Therapy Trial; Left vs Left = Left vs Left Randomized Clinical Trial; LIT-HF = LBBP as Initial Therapy in Patients With Nonischemic Heart Failure and LBBB; LVEDV = left ventricular end diastolic volume; MPI = myocardial perfusion imaging; PhysioSync-HF = Conduction System Pacing Versus Biventricular Resynchronization in Patients With Chronic Heart Failure; REINVENT-CRT = Resynchronization Comparison in LBBB and Normal or Mildly Reduced Ventricular Function With CRT; SR = sinus rhythm; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Tables 1-4.

TABLE 6 Ongoing or Planned Trials for CSP for AF

Trial Name NCT # Status	Treatments	Size	Population	Primary Endpoint	Other Endpoints	Follow-Up (mo)	Country
LBBAP-AFHF NCT05549544 Recruiting	LBBP vs BVP	60	LVEF<50%, NYHA II-IV, permanent AF QRSd <130 ms, AVNA or slow VR with anticipated RVP ≥40%	LVEF	Implant success, safety, echo parameters, NT-proBNP, death, and HFH	6	China
CONDUCT-AF NCT05467163 Not recruiting	His/LBBP vs BVP	82	LVEF <50%, QRSd ≤ 120 ms, perAF (>6 mo) refractory to AAD or failed CA and AVNA	LVEF at 6 mo	HFH, CV death, LVESV, LVEDV, NYHA, 6MWT, QoL, NT-proBNP	24	Slovenia, Austria, Bulgaria, Croatia, Romania
RAFT-P&A NCT05428787 Not recruiting	LBBP vs BVP	284	AF and AVNA, NYHA I-Iva, NT-proBNP > 600 or >400 if HFH within 12 mo	NT-proBNP	Composite HFH and death, QoL, 6MWT, echo parameters	12	Canada

AAD = antiarrhythmic drugs; CA = catheter ablation; CONDUCT-AF = Conduction System Pacing Versus Biventricular Pacing After Atrioventricular Node Ablation; perAF = persistent atrial fibrillation; RAFT-P&A = Resynchronization in Patients With HF in AF Trial Undergoing Pace and AVNA Strategy With LBBAP Compared With BiV Pacing; other abbreviations as in Tables 1-5.

FUTURE PERSPECTIVES

While we await the completion of larger randomized clinical trials on CSP, several important unanswered questions remain at the forefront of investigation:

- Is LBBAP as good as HBP?
- What is the most optimal criteria for left conduction system capture?
- Are there differences in clinical outcomes between proximal and distal LBBAP?
- Is LBB capture necessary to achieve maximal benefits in patients with bradycardia and patients requiring CRT (LBBP vs LVSP)?
- What is the clinical impact of delayed RV activation with LBBAP, particularly in patients with heart failure?
- What is the clinical impact of CSP in patients with diastolic heart failure and AV block or bundle branch block?

The long-term integrity of both lumenless vs stylet-driven leads and the feasibility of lead extraction from His bundle region and deep septal location needs to be carefully evaluated. Early observations in case reports and small series support the use of CSP in special populations such as painful LBBB and LBBB-induced cardiomyopathy. Similarly, others have explored the utility of leadless LV endocardial pacing for CRT. Advances in leadless pacing technology may lead to future possibilities of leadless CSP. Diligent scientific evaluation will likely usher in a promising future for CSP.

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TABLE 7 Ongoing or Planned Clinical Trials for CSP After TAVR

Trial Name NCT # Status	Treatments	Size	Population	Primary Endpoint	Other Endpoints	Follow-Up (mo)	Country
PHYS-TAVI NCT04482816 Not recruiting	His/LBBP vs RVP	24	TAVR, AVB, LVEF >50%	Combined survival, NYHA, 6MWT	LVEF, Septal flash, 6MWT, NYHA, MR, NT-proBNP, HFH, QRSd, QoL, GLS	12	Spain
PLANET NCT05024279 Recruiting	LBBP vs RVP	30	TAVR, LVEF ≥50%, second AVB, third AVB bradycardic AF with anticipated RVP >20%	QRSd	Death, CV death, HFH, LVEF, echo, NYHA, NT-proBNP, 6MWT, QoL, arrhythmias	24	Germany
Left Bundle BRAVE NCT05541679 Not recruiting	LBBP vs RVP	46	TAVR, bradycardia or first AVB, second AVB type I or II, high-grade AVB, or third AVB	GLS, LVEF, safety endpoints	QoL, NYHA, 6MWT, HFH, death, NT-proBNP, echo parameters, device parameters	18 (crossover at 9 mo)	USA

GLS = global longitudinal strain; Left Bundle BRAVE = Comparison of Left Bundle Branch Area Versus Right Ventricular Septal Pacing in Patients With High-degree Conduction Disease After Transcatheter Aortic Valve Replacement; PHYS-TAVI = Physiological vs Right Ventricular Pacing in Patients With Normal Ventricular Function Post-TAVI; PLANET = Left Bundle Branch Area Pacing in Patients After TAVR; TAVR = transcatheter aortic valve replacement; other abbreviations as in Tables 1 to 4.

TABLE 8 Advantages and Disadvantages of CSP vs BVP for CRT

Advantages	Disadvantages
Comparable success rates (with LBBAP)	Lower success rates (with HBP)
Narrower paced QRSd	Not ideal in patients with IVCD
More physiological biventricular activation	Lack of large-scale randomized data
Better acute hemodynamics	
Higher echocardiographic response rates[a]	
Higher clinical response rates in some patient groups, observational studies[a]	
Possible lower HFH and mortality in some patient groups[a]	

[a]Based on both small, single-center studies and larger-scale, multicenter observational data.

LBBAP = left bundle branch area pacing; other abbreviations as in Tables 1 to 3.

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APPENDIX For supplemental figures and a reference, please see the online version of this paper.