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Physiologic Pacing in 2025: Guidance Made Simple

Corrado De Marco, MD

Introduction

Conventional right ventricular pacing (RVP), particularly at the right ventricular apex, has long been the standard approach for ventricular pacing in patients requiring permanent pacemakers. However, RVP has been shown to introduce electrical and mechanical dyssynchrony, resulting in adverse remodelling, atrial fibrillation, and heart failure.[1] The deleterious effects of a high RVP burden have been demonstrated in the MOST[1] and DAVID[2] trials, wherein patients with ventricular pacing >40% were identified as being at risk of increased adverse clinical outcomes, such as hospitalization for heart failure and death (hazard ratio [HR] 1.61; 95% confidence interval [CI] 1.06–2.44).[2]

In patients with baseline ventricular systolic dysfunction and left bundle branch block or a high ventricular pacing burden, cardiac resynchronization therapy (CRT) using conventional biventricular pacing (BiVP) has been shown to be superior to RVP in preventing ventricular dilation, hospitalization for heart failure, and death.[3,4] Both the BLOCK-HF trial,[3] which compared BiVP to RV pacing in patients with a left ventricular ejection fraction (LVEF) ≤50% and a high pacing burden, and the MADIT-CRT trial,[4] which compared implantable cardioverter-defibrillator therapy alone to CRT with defibrillator in patients with LVEF ≤30% and QRS duration ≥130ms, showed a reduction in all-cause mortality and heart failure events in the BiVP group (HR 0.74; 95% CI 0.60–0.90 and HR 0.66; 95% CI 0.52–0.84, respectively). However, approximately one-third of patients do not respond to conventional BiVP. Moreover, the benefits of conventional BiVP have not been consistently shown across all cohorts.[5]

To overcome the detrimental effects of RVP and the limitations of conventional BiVP, conduction system pacing (CSP) was introduced.[6] This approach harnesses the His-Purkinje system, thereby delivering stimulation mimicking native ventricular activation. The two primary CSP techniques, His bundle pacing (HBP) and left bundle branch area pacing (LBBAP), have demonstrated promise in improving both electrical synchrony and clinical outcomes.[6,7]

Historical Background and Development

HBP was first described in 2000 as a technique for maintaining physiologic ventricular activation in patients with rapid atrial fibrillation and an intact conduction system undergoing atrioventricular node ablation.[8] Despite its physiological advantages early adoption of HBP was limited by technical challenges such as high pacing thresholds and lead instability.

Introduced in 2017, LBBAP[9] involves delivering pacing impulses to the left bundle branch (LBB) or to adjacent areas within the left ventricular septum, resulting in capture of the left-sided conduction system. This technique offers near-physiological ventricular activation, while overcoming the principal limitations of HBP.

Each CSP technique manifests as narrow QRS complexes on a standard 12-lead electrocardiogram (ECG). In the case of HBP, the resultant paced QRS morphology should be virtually indistinguishable from the patient's native QRS. LBBAP, on the other hand, will be characterized by a large pacing spike (due to unipolar pacing) and a QRS morphology demonstrating a qR pattern in V1 and a short spike-to-R-wave peak time in V6 **(Figure 2B)**. The specific criterion for LBBAP will be discussed in greater detail later.

Anatomical Considerations

An anatomical understanding of the atrioventricular conduction system is essential for proper CSP implantation and subsequent interpretation of the type of physiological capture obtained. The compact atrioventricular node (AVN) lies in the triangle of Koch, which is bordered anteriorly by the septal tricuspid leaflet, posteriorly by the tendon of Todaro, and has its base at the ostium of the coronary sinus.[10] The transition from the compact AVN to the bundle of His exhibits high variability. It may occur within the triangle of Koch, at the commissure of the anterior and septal tricuspid leaflets, or in the ventricular membranous septum.[10] As the bundle of His emerges from the interventricular septal crest, it branches into the left and right bundles.[10] The LBB thereafter typically fans out into three main fascicles: anterior, septal, and inferior/posterior.[11] The LBB therefore offers a wide target zone for achieving effective physiological pacing. In fact, it has been shown that only 9% of patients undergoing LBBAP are paced at the LBB proper[12]; the remainder are paced via one of the LBB's fascicles. Slight differences in the frontal axis of the paced ECG can be observed depending on which segment of the LBB is activated by the pacing impulse **(Figure 3)**.

Implantation Technique

Due to issues associated with HBP, notably high pacing thresholds and lead instability, it has fallen out of favour at the expense of LBBAP. As such, the increased adoption of LBBAP has led to significant advances in the development of dedicated pacing leads, both lumenless and stylet-driven, as well as improvements in delivery sheath technology.

The key to successful LBBAP lead implantation is penetration of the interventricular septum at a target site likely to result in capture of the left sub-endocardial conduction system. Fluoroscopic guidance **(Figure 1)** is essential, with alternating views between the right anterior oblique (RAO) and left anterior oblique (LAO) projections to ensure an appropriate lead course. Initial penetration is usually targeted at an angle of 10-40° with respect to the horizontal plane in the LAO 30-40° view, with subsequent adjustments made using the RAO view (at approximately 10-20°) for orientation along the anterior-posterior axis.

As the lead progresses through the septum, depth of penetration and presence of conduction system capture can be assessed using several different techniques.[13]

1. The unipolar paced QRS morphology will become gradually narrower, a Qr/qR/rsR'/R morphology will appear in lead V1, and the V6 R-wave peak time (V6RWPT) will progressively shorten.
2. The presence of fixation beats, which correspond to PVCs induced by the mechanical trauma of lead advancement, correlate well with the depth of lead penetration. Fixation beats that display a terminal R-wave in V1 suggest that penetration to the left-sided conduction system is either near or achieved.
3. Unipolar pacing impedance usually rises upon initial penetration, then falls as the left ventricular (LV) endocardium is approached. A sudden impedance drop of >200 ohms is usually a sign that perforation into the LV has occurred, and that the lead should be pulled back.

4. Myocardial current of injury will demonstrate a rise (to 20-35 mV) on initial penetration, followed by a gradual decrease (to 10-12 mV) as the lead penetrates toward the LV subendocardium.

While the indicators described above strongly suggest that the LV conduction system has been attained, they do not constitute definitive proof of conduction system capture.[13] More precise criteria for conduction system capture are required, with the most commonly used being:

1. V6RWPT <75 ms (or <80 ms in patients with native conduction system disease), as illustrated in **Figure 2A**;
2. V6-V1 R-wave interpeak interval >44ms, also illustrated in **Figure 2A**;
3. QRS transition from non-selective to selective-left bundle branch pacing (LBBP) or LV septal pacing, characterized by an increase in V1 R-wave peak time (V1RWPT) >10 ms or an increase in V6RWPT >15 ms, respectively, during the performance of a pacing threshold test; and
4. LBB potential-V6RWPT equal to pacing stimulus-V6RWPT (±10 ms).

As the adoption of CSP becomes more widespread, rigorous adherence to the established criteria is essential for true physiologic pacing to ensure maximal benefit for patients.

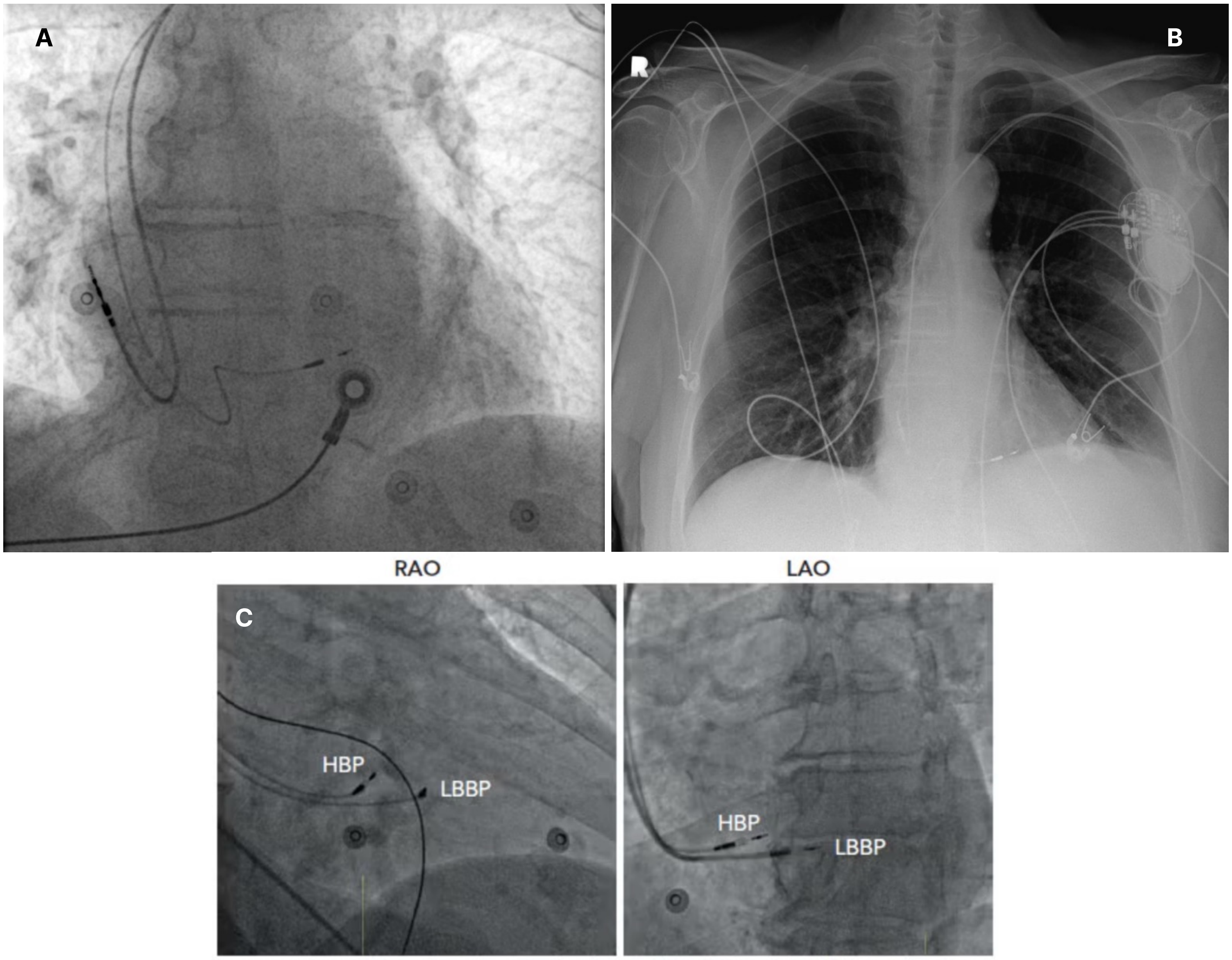

Figure 1. Panels A and B illustrate the mid-ventricular, septal position of the right ventricular lead used for left bundle branch pacing (LBBP), as seen on fluoroscopy (A) and post-procedural chest X-ray (B). Panel C shows an example of both a His bundle pacing lead (HBP) and an LBBP in the same patient, in both right anterior oblique (RAO) and left anterior oblique (LAO) projections; *courtesy of Corrado De Marco, MD*

Possible Complications

As with any new technique, a knowledge of relevant complications, both during and after implantation, is essential to ensuring optimal patient care.

Septal perforation is the most frequently encountered peri-procedural complication, occurring in up to 15% of cases.[13] It is most readily identified by a sudden drop in pacing impedance, a low current of injury (typically <2.3 mV), and/or by the penetration of contrast into the LV during septal angiogram.[13] If septal perforation is missed during implant or presenting later, after the implantation, it may manifest clinically as systemic embolism resulting from thrombus formation on a lead that has inadvertently entered the LV cavity. Therefore, any patient presenting with stroke or systemic embolism following LBBAP implantation should undergo testing aimed at eliminating this specific complication.

Septal hematomas occur more rarely, and usually asymptomatic or mildly symptomatic, and occasionally present with mild chest pain, which usually resolves spontaneously. Even more rarely, mechanical trauma to coronary vessels may occur during lead deployment, though acute coronary events are highly uncommon. In some cases, coronary venous fistula may develop due to perforation of the lead helix into a coronary vein. However, reported cases have shown that the lead position can often be maintained without adverse clinical effects, provided that a successful LBBAP is achieved.[12] Coronary artery fistulas have been reported in rare instances as well. These are generally asymptomatic and are usually incidentally noted on post-procedural transthoracic echocardiography, which may show a diastolic jet from the LV septum into the RV.

Other possible complications, similar to those encountered during standard RVP implantation,

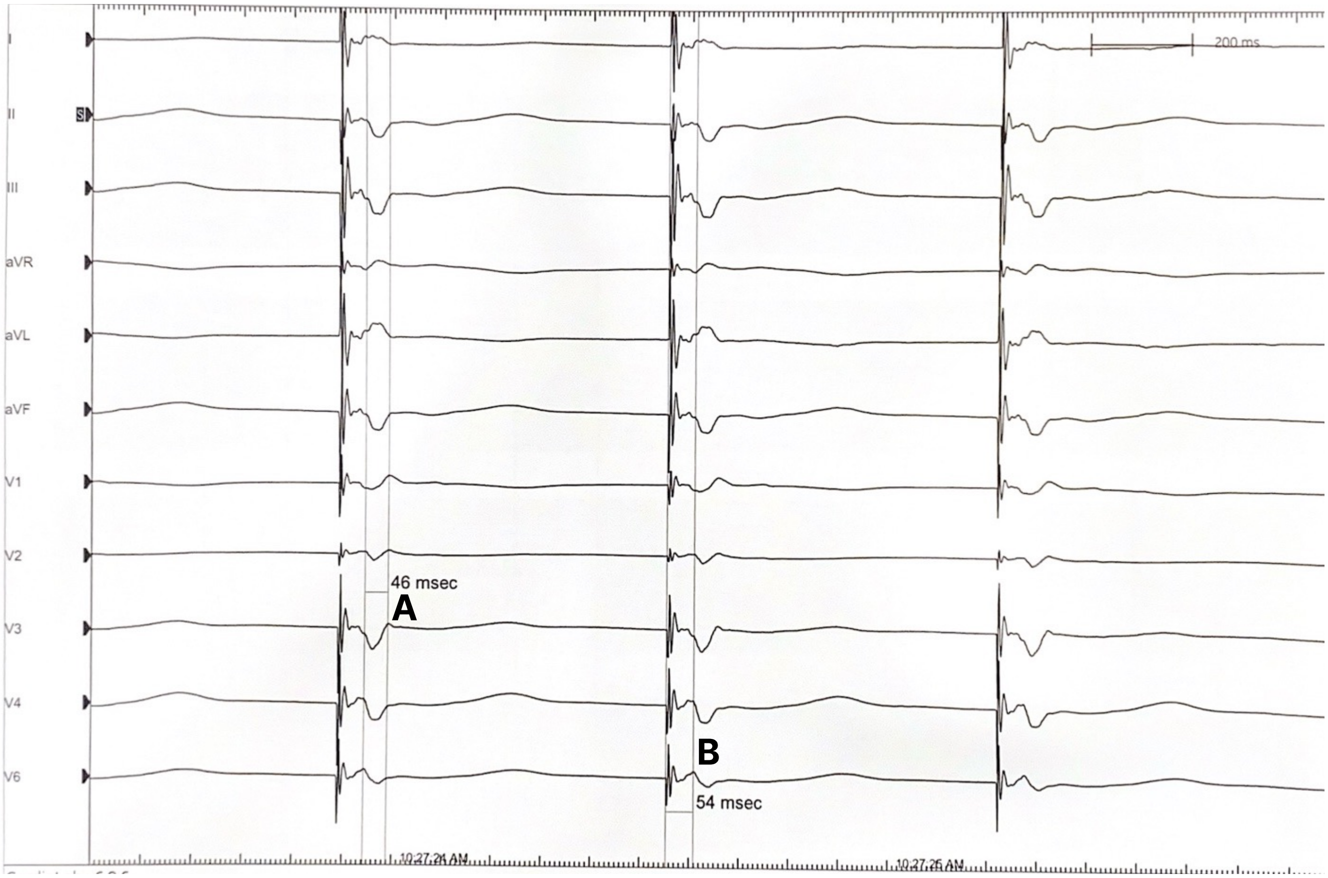

Figure 2A. Two of the most commonly used left bundle branch pacing (LBBP) criteria: a) V6-V1 interpeak (measured from the peak of the R-wave in V6 to the peak of the R or R'-wave in V1) interval >44 ms, and b) V6 R-wave peak time <75 ms in V6; *courtesy of Corrado De Marco, MD* include tricuspid regurgitation, lead dislodgment, rise in lead threshold, or loss of capture.

Evidence in Support of Conduction System Pacing

The body of evidence in support of CSP has significantly grown in recent years. Studies have emerged comparing CSP to both RVP and BiVP. However, the existing literature at present is based almost entirely on observational data and is limited by small patient numbers.

CSP Versus RVP

Early studies comparing HBP with RVP demonstrated that HBP could prevent LV dyssynchrony, mitigate the development of mitral and tricuspid regurgitation, and preserve LVEF.[14] However, initial evidence demonstrating clinical benefits of HBP compared to RVP was scarce.

As the focus with regards to CSP has shifted to LBBAP in recent years, more data has emerged. The earliest studies demonstrated that LBBAP resulted in LV synchrony comparable to native conduction, despite a slightly wider paced QRS than the native QRS due to the delayed right ventricular activation. Notably, the degree of LV synchrony was markedly better with LBBAP than with RVP.[12]

In one of the largest observational studies comparing CSP to RVP, Tan et al. demonstrated that CSP, comprising 95 patients with HBP and 136 patients with LBBP was associated with a 47% reduction in the primary composite outcome of heart failure hospitalization, need for upgrade to BiVP, or all-cause mortality compared to 628 patients receiving RVP. This benefit was observed in patients with >20% ventricular pacing.[15]

Overall, in comparison with RVP, CSP has shown better ventricular synchrony, less marked valvular regurgitation, and improved LVEF preservation. Moreover, observational data suggests the clinical benefits of CSP over RVP are significant.

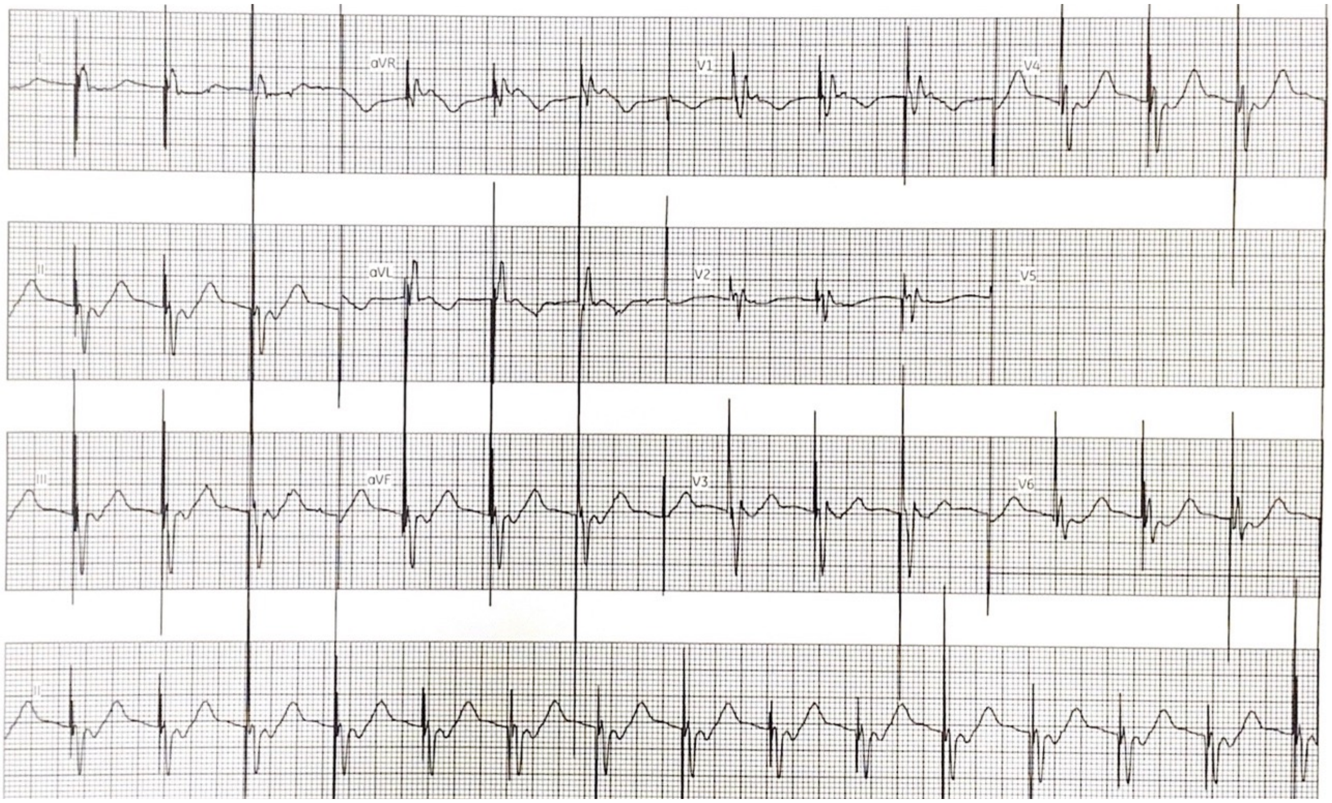

Figure 2B. The post-implant electrocardiogram (ECG) (taken with the patient still lying on the procedure table) for the same case as in *Figure 2A*. Note the hallmark features of the left bundle branch area pacing (LBBAP), most notably the large pacing spike, the qR pattern in V1, and the short spike-to-R-wave interval in V6. Lead V5 not pictured due to electrode connectivity problem during ECG recording; *courtesy of Corrado De Marco, MD*

CSP Versus Biventricular Pacing

BiVP represents a well-established cornerstone of ventricular resynchronization in patients requiring CRT. However, CSP is increasingly being employed as an alternative to traditional BiVP delivered via a coronary sinus lead.

To date, only two randomized trials have compared HBP to conventional CRT with BiVP. The HIS SYNC[16] trial compared HBP to BiVP in 41 patients, though significant cross-over between groups (48% from HBP to BiVP and 25% from BiVP to HBP) represents a significant limitation of the trial. Moreover, it found no statistically significant differences between groups in the reduction of QRS duration or improvement of LVEF. Similarly, the His-Alternative trial[17] randomized a cohort of 50 patients meeting CRT criteria to either HBP or BiVP. The trial showed no statistically significant differences in clinical and echocardiographic improvements, however, pacing thresholds were higher in the HBP group.

Similar trials have been published comparing LBBAP to conventional CRT with BiVP. As with HBP, most of these studies are retrospective and observational. A common theme that emerges is that LBBAP provides results comparable to HBP, while providing the advantage of lower pacing thresholds, reduced risk of far-field oversensing of atrial signals, and easier mastery of the implantation technique.[18] In a large, retrospective, observational study of 1,004 patients with LVEF of 36-50% and either LBB block or a need for ventricular pacing, CRT delivered via CSP, primarily via LBBP, was independently associated with a significant reduction in the primary composite endpoints of time to death or heart failure hospitalization (22% in the CSP group versus 34% in the BiVP group, hazard ratio 0.64, p=0.025).[19]

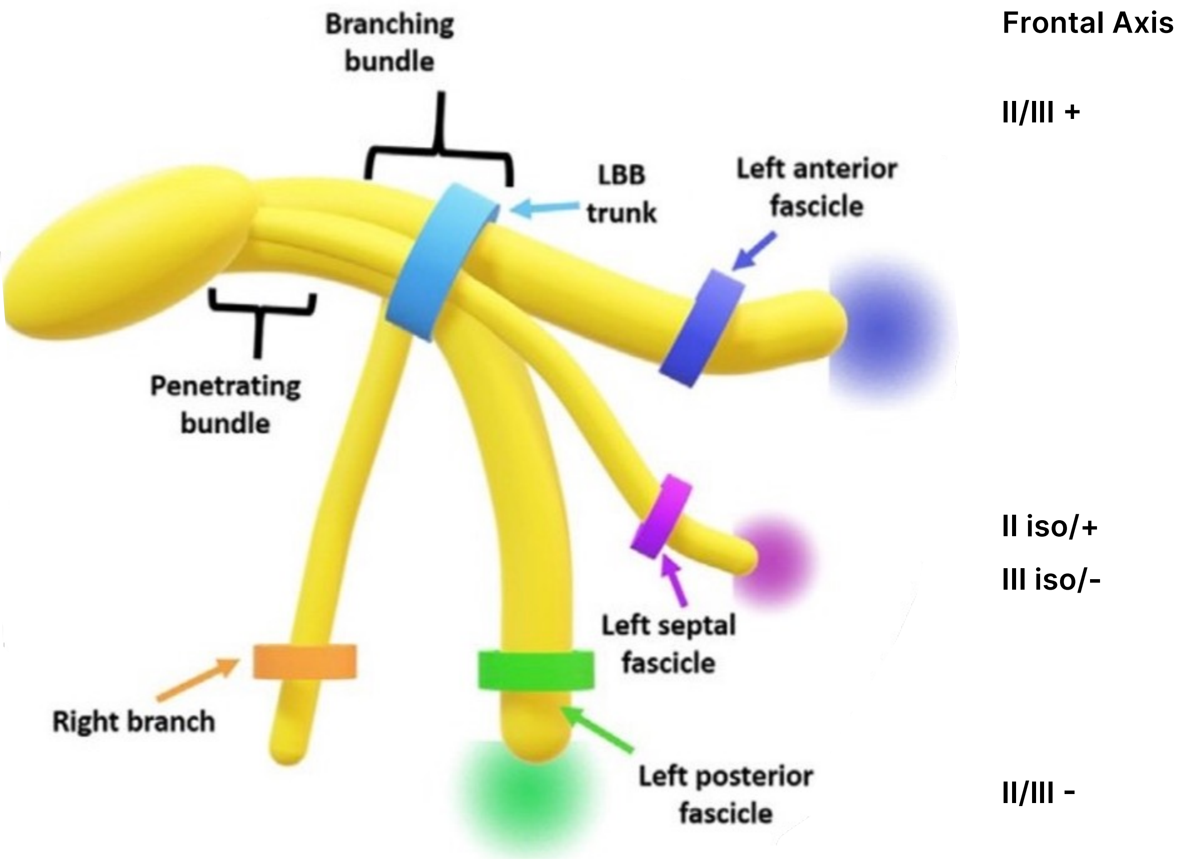

Figure 3. A schematic representation of the left bundle branch (LBB) and its fascicles: anterior (in navy blue), septal (in violet), and posterior (in green). The frontal axis (listed at right) may vary depending on the location of the pacing lead helix; *courtesy of Corrado De Marco, MD*

Nonetheless, there is a distinct lack of sufficiently powered, randomized, controlled trials comparing conventional BiVP to CSP. The ongoing Left versus Left trial is currently the largest clinical trial comparing CSP to BiVP, with a planned enrolment of 2,136 patients and follow-up extended up to three years. Until data from adequately powered randomized, controlled trials is published, CSP should be seen only as a viable bailout to conventional BiVP, and not as an alternative to clinically validated conventional BiVP. In instances when CRT is indicated, CSP should be performed in cases where BiVP implantation proves challenging provided that true HBP or LBBAP can be achieved.

Combined CSP and Biventricular Pacing

Small, observational studies have examined the benefit of combined CSP and conventional BiVP, referred to as HOT-CRT when HBP is combined with conventional BiVP, and LOT-CRT when LBBAP is combined with conventional BiVP. Both HOT-CRT and LOT-CRT resulted in LVEF improvement, QRS duration reductions, and improvements in New York Heart Association (NYHA) functional class, outcomes comparable to CSP alone and superior to traditional BiVP.[20] However, no randomized controlled trials on the subject have been published to date.

Future Directions and Conclusion

As the implantation techniques for conducting CSP continue to evolve and more clinicians are trained, the use of CSP is becoming more widespread. While it is most commonly used in cases where the burden of ventricular pacing is expected to be high, such as in complete AV block or post-AV nodal ablation, it is also emerging as a practical alternative in cases of failed traditional BiVP implantation.

The promise of CSP is undeniable, and the coming years are certain to bring a surge of evidence that will better quantify its merits. While early data are certainly encouraging, large-scale, multicenter, randomized controlled trials comparing CSP to other pacing modalities are yet to be published. Several such studies are currently underway.

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Financial Disclosures

C.M.: None declared

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