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Pacing of the specialized His Purkinje conduction system: 'HOW and FOR WHOM'

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The human heart's conduction system consists of specialized cardiomyocytes that generate and transmit electrical impulses, leading to the rhythmic and synchronized contraction of the atria and ventricles, which is crucial for the normal cardiac cycle. In conduction system pacing (CSP), pacing leads are placed in the His bundle region and the left bundle branch area to achieve physiological cardiac activation. This method offers a more natural alternative to the myocardial stimulation provided by conventional right ventricular pacing and biventricular pacing. In this review, we describe the implantation techniques for CSP and discuss the current recommendations for their use.

Introduction

Cardiac pacing is the cornerstone treatment of symptomatic and life-threatening bradyarrhythmias, and right ventricular pacing (RVP) has been the primary strategy for decades to improve survival and quality of life in this setting.[1] However, several trials and meta-analysis demonstrated that chronic RVP can have detrimental effects, leading to adverse remodelling, impaired left ventricular systolic function or atrial fibrillation (AF) developing, particularly in patients with pre-existing cardiomyopathies.[2,3] These findings sparked increased interest in exploring alternative pacing sites and methods to enhance left ventricular (LV) contraction: biventricular pacing (BVP) and conduction system pacing (CSP) are the current alternatives to prevent adverse remodelling and ensure synchronization of the LV.

His Bundle Pacing (HBP) and, more recently, left bundle branch area pacing (LBBAP) emerged as the reliable alternative to preserve the physiological ventricular activation, showing promising effects on LV function and clinical outcomes in patient's candidate to resynchronization therapy.[4-6] Nevertheless, increasing evidence in literature confirms the safety and efficacy of CSP, although it is not yet recommended as a first-line indication in the guidelines.

In this review, we aim to describe the assumptions behind CSP, the technicalities of the implanting procedure and follow-up and discuss the latest evidence about CSP.

Anatomy and pathophysiological properties of the His Purkinje system

In 1893, Sir Wilhelm His Jr identified a protected strand of specialized heart tissue linking the atria and ventricles. But, it was not until 1906 that Tawara revealed the electrical properties of these histologically distinct cells

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(predominantly Purkinje type), showing how impulses travel from the atrioventricular (AV) node to the His bundle, bundle branches and their ventricular terminations, providing furnishing the anatomical basis for the theory of longitudinal dissociation in the His bundle postulated by Kaufmann and Rothberger in 1919.[4,7]

The His bundle (HB) can be divided anatomically into three portions: penetrating portion, which penetrates the fibrous membranous septum close to the mitral ring; non-branching portion, which has a variable length in muscular ventricular septum; branching portion closely related to the aortic annulus, which branches off to give the left and right bundle branches. Cabrera *et al.*[4,7] described three possible sites of penetration of HB: in 53.7% of the cases the penetration was found in an atrial location distant from the septal leaflet insertion of the hinge point of the tricuspid valve septal leaflet, in 31.7% at the level of the hinge point, and in 14.6% it's positioned below the level of hinge point within the ventricular component of the membranous septum.

The left bundle branch (LBB) originates just below the membranous septum between the right and non-coronary aortic cusps. This thick, band-like structure takes a sub-endocardial course on the left side of the septum, typically splitting into three fascicles: septal, anterior, and posterior. The septal branch supplies the mid-septal area, but it has a very variable anatomy because can also originate from the anterior or posterior fascicle, or from a network of connections between them. The left anterior fascicle, being thin and long, extends towards the anterolateral papillary muscle, while the left posterior fascicle, which is thick and short, moves towards the posteromedial papillary muscle. These fascicles branch out into a vast network of Purkinje fibres to supply the LV.[4,7]

In the 1970s, Durrer first described the electrical activation sequence of the human heart by mapping left ventricular activation using intramural electrodes. This demonstrated the specialized features of the His-Purkinje system (HPS) and the tri-fascicular nature of the LBB.[8] The HPS starts the ventricular activation from the LBB in endocardial areas on the left interventricular septum surface, then proceeds from left to right septum towards the apicobasal direction of the ventricles through the Purkinje system ramifications.[4] Damages within the HPS, therefore, can lead to conduction disturbances, bundle branch block and potentially life-threatening bradycardias. Restoring the specialized HPS's integrity is the appealing paradigm for CSP, aimed at maintaining physiological ventricular action or restoring cardiac synchronization.

The physiological properties of the HB should be considered when performing CSP. Longitudinal dissociation of HB implies that bundle branch blocks can be caused by conduction block/delay of fibres in the HB already predesignated to either left or right bundle branch.[9] Pacing the conduction system distally to the site of block, as Upadhyay *et al.*[9] demonstrated with invasive mapping of the HB and LV septum, could reverse the conduction abnormalities. However, CSP resulted in incomplete correction in LV dyssynchrony secondary to distal conduction system blocks or myocardial tissue disease with intact His-Purkinje conduction. In such cases, a more completed resynchronization seems achievable from combining pacing the HPS with epicardial pacing of LV through BVP as observed in studies on His-optimized cardiac resynchronization therapy (HOT-CRT) and LBBAP-optimized CRT (LOT-CRT).[10,11]

Other potential, but unproven, mechanisms for corrective impact on bundle branch blocks of CSP include the virtual electrode effect, transverse connections between the bundles, and the retrograde activation of the HB and the right bundle branch (RBB) with LBBAP.[4]

How to perform His Bundle Pacing

The first case report of permanent HBP was published by Deshmukh *et al.* in 2000. Even if HBP faces technical challenges due to the narrow target zone which is surrounded by electrically inert fibrous tissue, this study demonstrated the feasibility of HBP in patients with permanent AF who were candidates for AV junction ablation.[12,13]

At the beginning of the HBP era, the procedures were performed by reshaping conventional stylets, using mapping catheters from the groin to identify the target HB region, and with the additional implantation of a backup lead in the RV. Initial studies reported a success rate of only 66%, with high pacing thresholds (2.4 ± 1.0 V at 0.5 ms) and prolonged procedure times.[12,13]

In 2014, Sharma *et al.* refined the implanting technique, achieving an 80% success rate for permanent HB lead implantation by using a lumen-less lead (LLL) with an exposed helix, delivered through pre-shaped sheaths without the need for mapping or bailout catheters. The Medtronic SelectSecure model 3830 pacing lead (4.1F, isodiametric, lumen-less, exposed helix) was the most commonly used lead for HBP, delivered via a 9F deflectable sheath (SelectSite C304, Medtronic) or a 7F fixed curve sheath (C315HIS, Medtronic).[12,13]

More recently, several vendors have introduced specialized sheaths for HBP. Biotronik has launched the Selectra 3D, a pre-shaped sheath available in three lengths with different primary curve widths (40, 55, or 65 mm). Boston Scientific has released the Site Selective Pacing Catheters, which come in four pre-shaped curves (SSPC1-4, models 9181–9184). Abbott has introduced the Agilis HisPro steerable catheter, featuring two distal tip electrodes that can sense intracardiac electrograms (EGM) and pace. These sheaths can be used with conventional stylet-driven extendable-helix leads (SDL). However, adapting SDL for HBP typically requires preventive measures to avoid partial unwinding of the extendable helix, as manual rotations on the outer body of the lead might cause the inner coil to not follow the external lead body rotations. Initial studies describe the comparable acute success of LLL and SDL for HBP.[14] But, there is limited evidence supporting the use of SDL in HBP, and only a small number of physicians employ SDLs for this purpose.[15] However, future studies should assess the potential differences in the long-term performance of the two pacing leads.

All of these technological advancements in HBP led to an improvement in implant success rates, reaching a range of 80–93%, as demonstrated by the HOPE HF trial.[16]

Step-by-step approach to implantation

After securing venous access, the sheath is advanced across the tricuspid annulus. The His bundle region is then mapped using the HB lead, moving from the ventricular to the atrial side with rotation and withdrawal of the sheath body.[12,13] Mapping for the His potential is performed in unipolar configuration with EGM visualized by an electrophysiological recording system (sweep speed 100 mm/s) or by a pacing system analyzer. Mapping can be facilitated by standard fluoroscopic views, especially the left anterior oblique (LAO) view, to ensure the lead is perpendicular to the septal surface. Rotating the sheath counter clockwise typically causes infero-posterior movement (usually towards the septum), while clockwise rotation results in anterosuperior movement. The best target site is that with a clear His potential, an R-wave to P-wave ratio of at least 2:1 and HB capture threshold <1.5 V at 0.5 ms. When HB potentials are not recorded, pace mapping at high output (5 V @ 1 ms) is generally performed. When HB capture is confirmed the lead is screwed to achieve final fixation. Presence of HB current of injury (COI) and deep negative deflection in unipolar HB electrogram are predictive signs of good outcomes in HBP.[17,18] In challenging situations where it is not easy to record HB potential or in cases of complex anatomy, using a deflectable sheath (SelectSite C304-HIS, Medtronic) or a sheath-in-sheath approach (fixed C315His inside a right-sided multipurpose outer coronary sinus sheath) have been described as potential alternatives.[19]

How to perform left bundle branch area pacing

In 2016, Mafi-Rad *et al.*[20] described the feasibility of deep septal pacing by using a custom-designed lead in the mid-distal septum and providing acute haemodynamic benefits over RVP.

In 2017, Huang pioneered the LBBAP technique by implanting a lead deep in the right ventricular septum, distal to the HB, to capture the LBB in a patient with heart failure (HF) and LBB block. This approach resulted in a more stable pacing position and improved pacing parameters. Additionally, over a 1-year follow-up, there was a significant narrowing of the QRS complex duration, as well as improvements in left ventricular ejection fraction (LVEF) and functional class.[21] Most experience in LBBAP has been obtained using a SelectSecure3830 pacing lead (Medtronic), a LLL, delivered via a 7F fixed curve sheath (C315HIS, Medtronic) or 9F deflectable sheath (SelectSite C304-HIS, Medtronic).[22] Recently several studies have shown the feasibility of LBBAP using standard stylet-driven leads and SDL are widely used, exclusively or also with LLL, by over half of implanting physicians. Using SDL, helix may be kept retracted during mapping of the His or the LBBAP lead insertion site (to avoid snagging) or, alternatively, extended.[15]

Step-by-step approach to implantation

The distal HB potential is annotated in right anterior oblique 20–30° fluoroscopic view using the delivery sheath and the lead.[15] If the HB potential is difficult to identify, the tricuspid annulus can be used as an anatomical marker or an RV angiogram can be quite helpful. After that, the sheath is turned clockwise and gently advanced 1.5–2 cm into the ventricle towards the RV basal septum. Zhang *et al.*[23] described a simplified approach to localize the LBB dividing into nine sections (3×3) the fluoroscopic image of the ventricle, resulting in lower fluoroscopy time and similar outcomes. At this stage, unipolar tip pacing is performed to identify the site where the paced QRS shows a 'W' morphology in V1 with an intermediate QRS axis (discordant axis in II and III). Once confirmed that the delivery catheter is perpendicular to the interventricular septum in LAO 30–40°, the pacing lead is screwed deep inside the septum with rapid rotations until the paced QRS morphology resembles right bundle branch conduction delay or right bundle branch block (RBBB) pattern in lead V1 (qR or rsR'). A study by Jastrzebski *et al.* suggested performing LBBAP using an uninterrupted pacing-while-screwing technique until RBBB paced QRS morphology or RBBB ventricular extrasystoles (fixation beats) appear. Fixation beats are triggered by the lead when approaching and irritating the LBB area.[24] As the lead penetrates inside the septum, the impedance gradually rises until a drop is observed approaching the LV endocardium. Ponnusamy *et al.*[25] reported a decline in unipolar pacing impedance until values <450 Ω in the case of septal perforation (sensitivity 100%, specificity 96.4%). Myocardial COI (*Figure 1*) also has a biphasic behaviour, rising in the first part of screwing (20–35 mV) and decreasing as the lead reaches the left side of the septum (10–12 mV).[26] Fascicular potential can often be appreciated (generally in the case of preserved LBB conduction) and indicate the LBB has been reached (*Figure 2*). A contrast injection through the side port of the sheath can be performed in the LAO to visualize the right ventricular septal wall and confirm the lead depth in the septum. Additionally, knowing the distance between the screw tip and the ring electrode (i.e. 10.8 mm for LLL), the evidence of anodal ring capture can provide a rough estimate of lead depth into the septum.

New implantation techniques in LBBAP have been described in the literature with the aim of minimizing the use of fluoroscopy. Case reports demonstrated the feasibility of a zero-fluoroscopy or near-zero-fluoroscopy approach using 3D electroanatomical mapping (EAM).[27,28] Richter and colleagues enrolled 32 consecutive patients with structural heart disease and conduction abnormalities who underwent an attempt at EAM-guided LBBAP and demonstrated a success rate of 91% with a total fluoroscopy time <1 min.[29]

How to confirm conduction system capture

The key of a successful CSP procedure is to demonstrate the output-dependent changes in QRS morphology as an expression of the capture exclusive of the specialized conduction system (selective capture) or both the conduction system and surrounding myocardial tissue (non-selective capture).[4,19]

His Bundle Pacing is considered selective (S-HBP) when there is has an isoelectric interval between the pacing spike and the onset of a QRS complex in the surface electrocardiogram (ECG) (similar to native HV interval) and a discrete local electrogram on unipolar recordings.

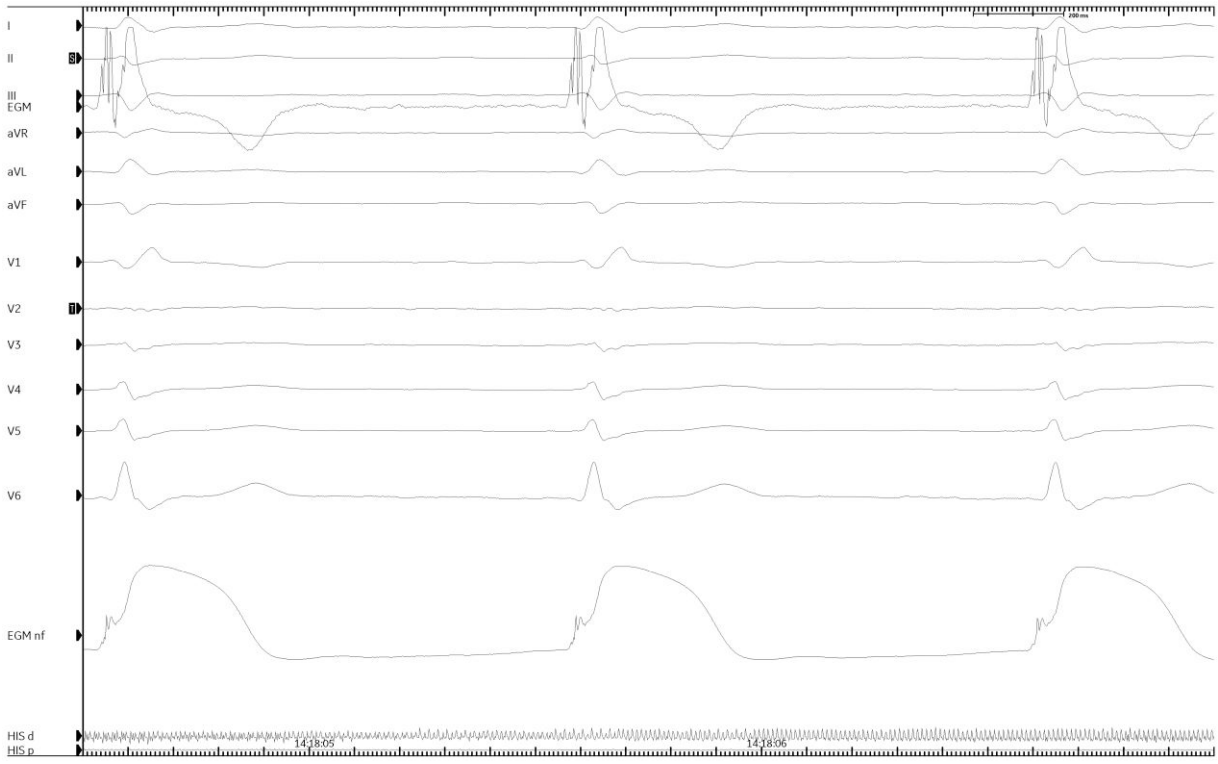

Figure 1 An example of current of injury. This image records the 12-lead and the unfiltered unipolar electrogram of the tip of the left bundle branch area pacing lead (sweep speed 200 mm/s). Current of injury is evident as an ST-segment elevation due to electrode fixation trauma and focally damaged endocardial cell membranes.

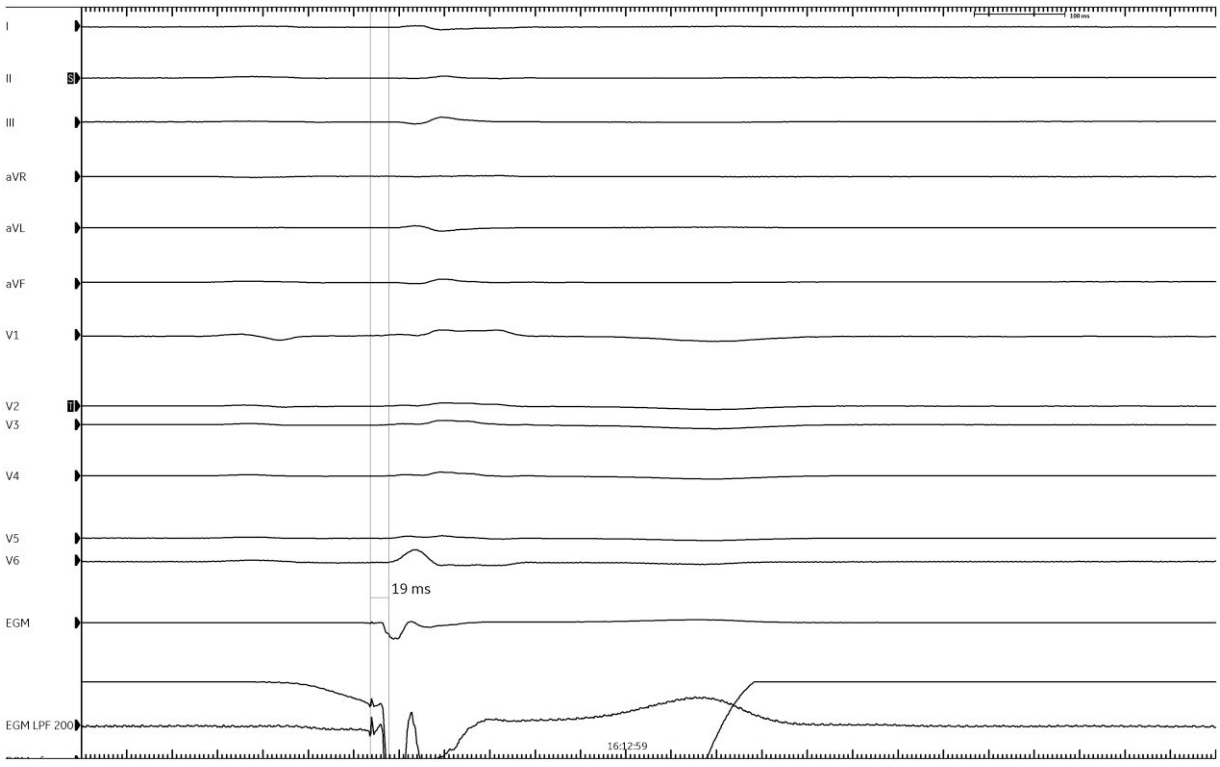

Figure 2 An example of fascicular potential. An interval <25 ms between the recorded potential and QRS suggests that recorded potential is a left bundle fascicular potential and not a left bundle trunk potential (generally 25–35 ms).

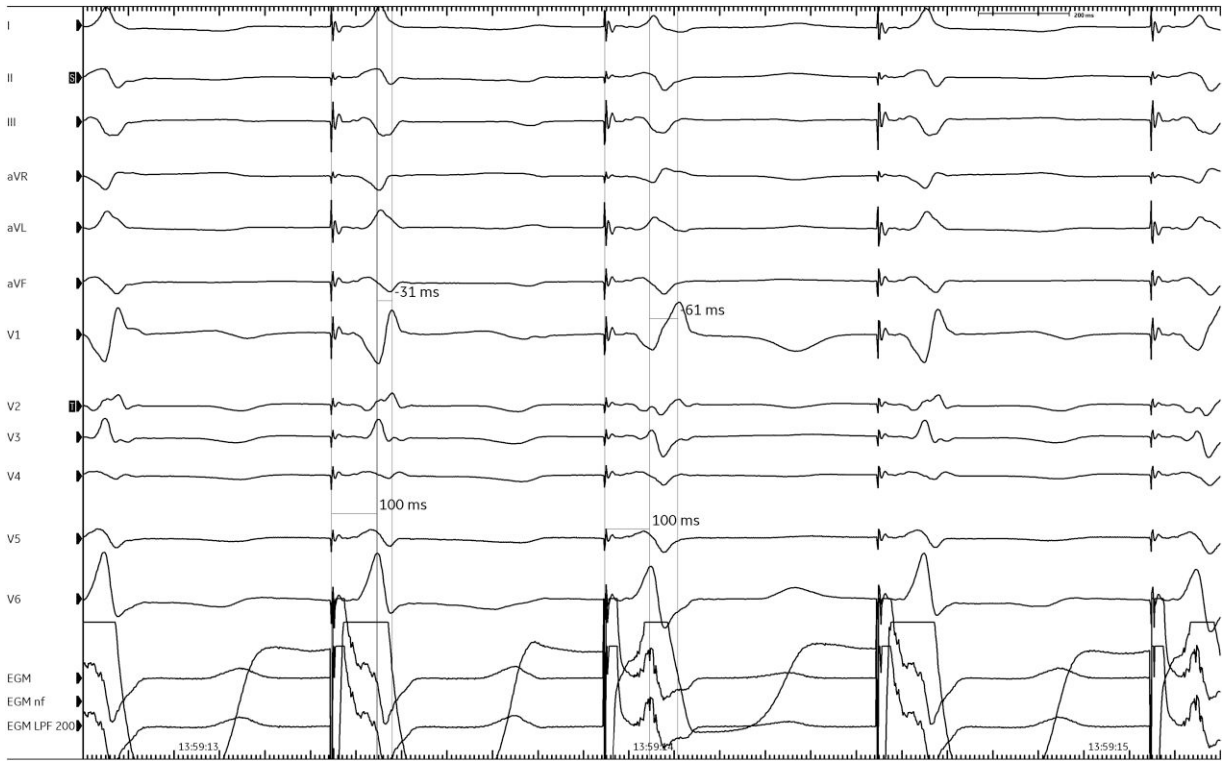

Figure 3 An example transition of QRS morphology from non-selective-left bundle branch abnormality to selective-left bundle branch abnormality during threshold test. This image captures the 12-lead and the unipolar electrogram (filtered and unfiltered electrograms) of the tip of the lead (sweep speed 100 mm/s). Transition from non-selective-left bundle branch abnormality to selective-left bundle branch abnormality is evident as a change in QRS morphology with a prolonged V6–V1 interpeak interval but without a significant increase of left ventricular activation time (<10 ms).

Non-selective-HBP is considered when there is a pseudo-delta wave between the pacing spike and the QRS complex and no discrete local electrogram on unipolar recordings. Selective HBP can also be confirmed using device EGM: a near-field electrogram with a time to peak of more than 40 ms, a near-field initial positive deflection after the pacing spike, or a far-field QRS duration of <120 ms was consistent with S-HBP. The absence of HB capture at implant or a loss of HB capture during follow-up (septal capture only) can be confirmed by QRS notching or slurring in ECG leads I, V1, V4–V6, and a prolonged R-wave peak time (RWPT) of >100 ms in V6.[30]

In LBBAP, to differentiate non-selective (NS)-left bundle branch abnormality (LBBP) and selective (S)-LBBP from left ventricular septal pacing is mandatory to prove LBB capture. The transition of QRS morphology during threshold test (in unipolar mode) demonstrates capture in two different types of tissues, the conduction system and the myocardium, with different excitability[13,31] (*Figures 3* and *4*). Jastrzebski *et al.* described the usefulness of programmed electrical stimulation to differentiate LBB capture vs. LV septal myocardial capture based on their differential effective refractory periods. Response to premature beats is classified as myocardial when the paced QRS morphology changes to myocardial-only capture (broader QRS, with a slur/notch/plateau and with change in amplitude/polarity in several leads), or S-LBB when the paced QRS morphology transforms to a typical RBB morphology preceded by a latency.[32] Same group also described other surrogated electrocardiographic ('physiology based') criteria to confirm LBB capture: in patients with non-left bundle branch abnormality (LBBB) rhythm could be confirmed when the delay of the LBBB potential to R-wave peak in V6 in native-non-paced rhythm equals (±10 ms) the stimulus to R-wave peak in V6 during pacing (V6RPWT); in patients with LBBB at baseline, the capture of the LBB can be confirmed when the paced V6RWPT is shorter than the native V6 intrinsicoid deflection by more than the trans-septal conduction time. In patients with narrow QRS or isolated RBBB, V6RWPT < 74 ms (in patient with LBBB ≤ 80 ms) was 100% specific for LBB capture.[33] More recently, the V6–V1 interpeak interval has been proposed as a novel criterion for diagnosing LBB area capture. Distinct patterns of right and left ventricular activation translating into different combinations of RWPT in V1 and V6 can result from various combinations of direct capture/non-capture of the septal myocardium and the LBB. Consequently, the V6–V1 interpeak interval could differentiate the three types of LBBAP capture. In that study, the optimal value of the V6–V1 interval value for the differentiation between ns-LBB and left ventricular septal capture was 33 ms with a specificity of 100% for the diagnosis of LBB capture obtained with a cut-off value of >44 ms.[34]

However, all these surrogated criteria and cut-offs for LBB capture vary on the anatomy of the heart and depend on the height where catheter is implanted and need to be validated in future larger studies. Instead, direct markers of LBB capture are recorded His potential

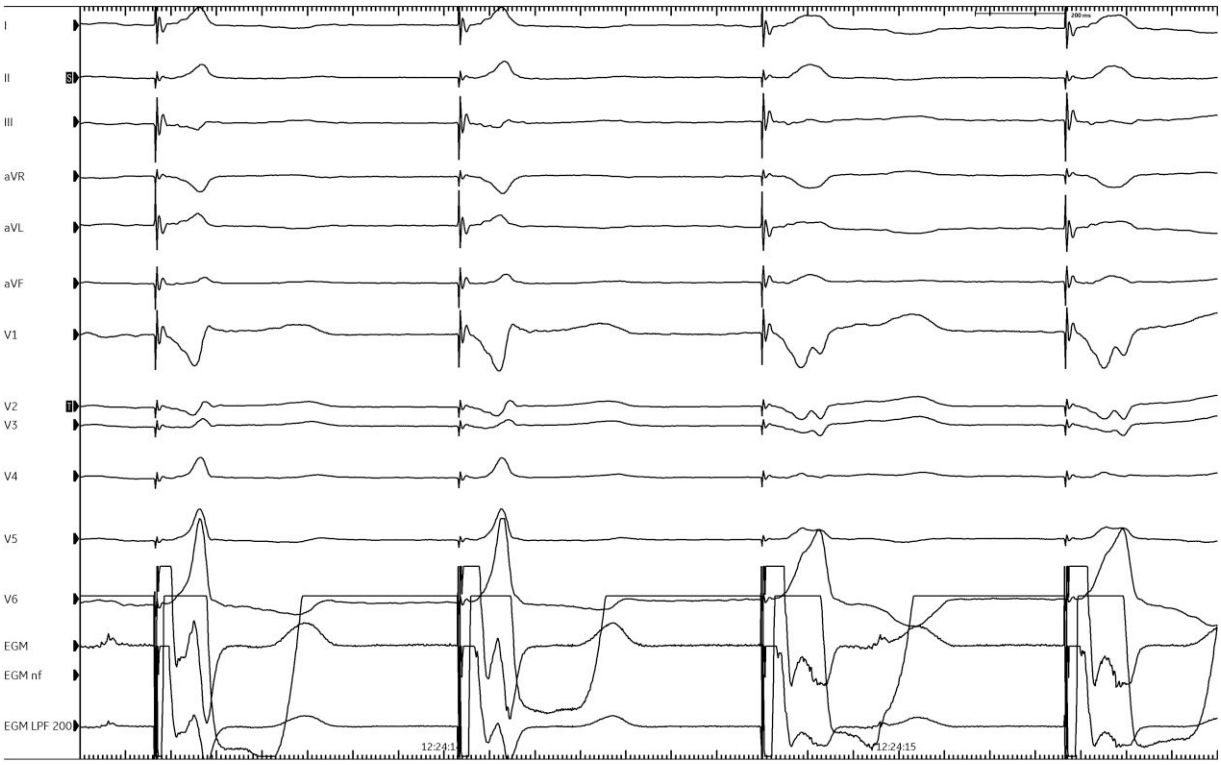

Figure 4 An example transition of QRS morphology from non-selective-left bundle branch abnormality to deep left septal myocardial capture during threshold test. Transition from non-selective-left bundle branch abnormality to myocardial capture is evident as a wider QRS with a prolonged left ventricular activation time.

and/or anterograde left conduction system potential during LBB pacing.[35]

How to manage device programming and follow-up in conduction system pacing

The success of CSP also depends on proper device programming and troubleshooting at follow-up. Since most currently available devices are not explicitly designed for CSP, the knowledge of device programming settings is essential to reach the optimization of CSP.[36]

Firstly, it is crucial to indicate in the device notes and in patient card the presence of CSP and to which port has been connected the pacing lead in HB position or LBB area (especially in case of conduction system optimized CRT: HOT-CRT and LOT-CRT). The pin of the generator to which the CSP lead is connected depends upon the baseline rhythm, the presence of an RV backup lead and the indication for pacing (bradycardia or CRT). Pacing vector in HBP and LBBAP is generally programmed in unipolar [not available in most implantable cardioverter defibrillators (ICDs)] or extended bipolar on the CSP lead.

During device follow-up it is essential to acquire a contemporary 12-lead ECG to determine the different types of captures during threshold tests. The capture threshold test should always be performed in VVI mode to have a paced QRS and avoid pseudo-fusions. Right ventricular capture management algorithms should be inactivated in HBP because they are based on detection of the evoked potential, which is absent in case of selective His bundle capture.

A major issue in HBP is sensing (when His lead is connected to RV port): ventricular undersensing may occur due to lower EGM amplitude than traditional RV pacing and oversensing of atrial or HB potentials may also lead to pacing inhibition and asystole in third degree AV block. Therefore, setting a fixed sensitivity is preferred over automatic sensitivity, which can result in oversensing phenomena. Instead, sensing is generally not an issue with LBBAP as the R-wave amplitude is similar as traditional RV pacing, without the interference of atrial or HB potentials.

In patients in sinus rhythm with residual AV conduction, it is essential to optimize the AV delay to obtain capture of LV. For HBP, the HV interval should be subtracted from the desired AV delay. For LBBAP, the pacing stimulus may be synchronized with the intrinsic RBB activation.

When a CSP lead is connected to an LV port in CRT generator, the RV lead serves for ventricular sensing (preventing oversensing and undersensing in HBP), backup pacing or delivering therapy (in the case of implantable cardioverter defibrillator). Sequential pacing can be programmed with CSP anticipating RVP with a long V–V interval or, alternatively, pacing from only the CSP lead may avoid unnecessary battery drain once stable thresholds with the CSP have been verified. Automatic AV and VV optimization algorithms should be inactivated because they are designed for BVP and may result in altered device functioning in CSP.

Finally, in ICDs with a CSP lead in the atrial port, all dual-chamber discrimination algorithms should be inactivated, as only single-chamber discriminators can be safely used.[36]

Conduction system pacing: for whom

Catanzariti *et al.*[37] demonstrated long-term positive effects of HBP: in this study, they compared the electromechanical effects of RV apical pacing vs. HBP in patients undergoing permanent implantation of a HB pacing lead: marked improvements in echocardiographic indices of ventricular synchrony were demonstrated when the patients were assigned to HBP mode, with a reduction in mitral regurgitation and improvement in LVEF. Moreover, small randomized controlled trials (RCTs) confirmed that HBP preserves LVEF and mechanical synchrony as compared with RV septal pacing.[38] Based on these data, ESC 2021 pacing guideline recommends HBP: (i) as an alternative to RVP in patient with AV block, LVEF $>40\%$ who are anticipated to have $>20\%$ ventricular pacing (Class IIb, Level of evidence C); (ii) in CRT candidates in whom coronary sinus lead implantation is unsuccessful (Class IIa, Level of evidence B); (iii) in patient in whom a 'pace-and-ablate' strategy for rapidly conducted supraventricular arrhythmia is indicated, particularly when the intrinsic QRS is narrow (Class IIb, Level of evidence C). His Bundle Pacing is the ideal form of physiological pacing, but its widespread use is hindered by technical challenges at implantation and during follow-up. Moreover, in patients treated with HBP, guidelines suggest the implantation of an RV lead as a 'backup' for pacing in specific situations (e.g. pacemaker dependency, high-grade AVB, intranodal block, high pacing threshold, and planned AV junction ablation).[1]

Even if LBBAP is not included in the ESC 2021 pacing guideline (much of the relevant data were not available when guidelines were formulated), lower pacing thresholds, better sensing and a less technically demanding procedure have positioned LBBAP as the favourite technique among CSP. To support this claim, since 2019 several small observational studies demonstrated safety ad feasibility of LBBAP in bradyarrhythmias and as an alternative method to CRT for patients with heart failure with reduced ejection fraction (HFrEF) combined with either a wide or narrow QRS.[39,40] Also a multicentric registry-based observational study involving 2533 patients (MELOS) demonstrated feasibility of LBBAP as a primary pacing technique with lead implantation success rate for bradyarrhythmia and HF indications was 92.4 and 82.2%, respectively.[41]

Conduction system pacing vs. biventricular pacing

Biventricular pacing is a proven treatment for patients with HFrEF and ventricular dyssynchrony, more specifically in patient with LBBB, reducing significantly mortality, HF hospitalizations, and symptoms.[42] However, several observational studies and small RCTs demonstrated non-inferiority of CSP in improving echocardiographic parameters and clinical outcomes. Left Ventricular Activation Time Shortening with CSP vs Biventricular Resynchronization Therapy (LEVEL-AT), a randomized non-inferiority trial involving 70 patients, showed similar degrees of cardiac resynchronization, ventricular reverse remodelling, and clinical outcomes attained by CSP as compared to BVP.[43] Vijayaraman *et al.*[44] conducted an observational study enrolling 477 consecutive patients with indications for CRT to compare the clinical outcomes between CSP and BVP: their findings revealed significantly lower rates of death and HF hospitalizations with a greater LVEF improvement in the CSP group over a 27-month follow-up period. Recently, the I-CLAS study, a retrospective analysis of 1778 patients, found that LBBAP significantly outperformed BVP in terms of echocardiographic response and hyper-response rates, particularly in patients with LBBB.[45] Also a randomized trial, LBBP-RESYNC, demonstrated greater LVEF improvement than BVP in HF patients with non-ischaemic cardiomyopathy and LBBB.[6]

In a recently published paper, Diaz *et al.* studied the electromechanical implications of LBBP vs. deep septal pacing (LVSP): they demonstrated that in patients undergoing CRT, LBBP was associated with a significant increase in freedom from HF-related hospitalizations compared with LVSP and BVP, while results between BVP and LVSP are similar. This study highlights how capturing the LBB is the central element to ensure LV resynchronization.[46]

Conclusions

Despite technical challenges during implantation and follow-up, CSP remains the most physiologic of the available pacing method. Although large RCTs with long-term follow-ups are still lacking, current data suggests that CSP, particularly LBBAP, is both safe and feasible. Further improvements in tools for implanting procedures and new dedicated device functions are expected to address CSP's current limitations. Moreover, the results of the ongoing RCTs aiming to provide the superiority of CSP over the standard of care (RVP and BVP) will define the true potential of CSP.

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Data availability

This manuscript is a review article therefore there are no original data to share. All cited studies are properly referenced.

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