Optimizing lead placement for pacing in dyssynchronous heart failure: The patient in the lead

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Cardiac resynchronization therapy (CRT) greatly reduces morbidity and mortality in patients with dyssynchronous heart failure. However, despite tremendous efforts, response has been variable and can be further improved. Although optimizing left ventricular lead placement (LVLP) is arguably the cornerstone of CRT, the procedure of LVLP using the transvenous approach has remained largely unchanged for more than 2 decades. Improvements have been developed using scar location and electrical and/or mechanical mapping, and interest in conduction system pacing as an alternative to biventricular pacing has emerged recently. Conduction system pacing is promising but may not be suitable for all patients with dyssynchronous heart failure. This review underscores the importance of a patient-tailored approach and discusses the potential applications of both conduction system pacing and targeted biventricular CRT.

KEYWORDS Cardiac resynchronization therapy; Dyssynchrony; Heart failure; Lead placement; Left bundle branch block

Introduction

Biventricular pacing (BVP) has been an established device therapy for the treatment of patients with dyssynchronous heart failure (HF) for more than 20 years, but various challenges remain.1 The cornerstones of obtaining maximal response in cardiac resynchronization therapy (CRT) is optimizing left ventricular lead placement (LVLP).2 It is striking that the actual procedure of lead implantation has remained largely unaltered, with the majority of leads being placed empirically, without evaluation of the underlying electromechanical substrate. As an alternative to conventional BVP, two distinct approaches to improve contemporary LVLP are being investigated.

One method of optimizing LVLP is stimulating the native conduction system (ie, conduction system pacing [CSP]), which drastically alters the way we place the left ventricular (LV) lead. The second method of improving LVLP is using a guided and target-based approach for transvenous lead deployment.1 Although CSP and targeted BVP both seem promising, determining the optimal LVLP can be difficult. Not only is it unclear which patients would benefit from CSP compared to BVP, but, equally important, uncertainty exists concerning how to determine the optimal pacing target in BVP. In this review, we discuss the potential applications and shortcomings of both approaches and underscore the importance of a target-based approach that is tailored to the patient. The etiology of LV conduction delay and the mechanisms that complicate CSP and targeted BVP also are discussed.

Heterogeneity of abnormal left intraventricular conduction

Various conditions that result in scar or fibrosis may cause functional and/or structural damage to the His-Purkinje system or LV myocardium (Figure 1).3 In turn, significantly impaired inter- and intraventricular conduction may occur. An important conduction delay is characterized by QRS prolongation (QRS ≥130 ms) on the surface electrocardiogram (ECG), but considerable heterogeneity among left bundle...
branch block (LBBB) patterns exists. These differences are dependent on the location (proximal vs distal and myocardial) and extent (focal vs diffuse) of the lesion causing the conduction disorder. Consequentially, not all cardiac segments will necessarily exhibit the same extent of activation delay. Pacing a segment that exhibits significantly more electrical dyssynchrony will result in more pronounced reduction in LV activation times than can be achieved by
pacing a relatively early activated segment. Therefore, it can be argued that, for BVP, differences in ventricular activation warrant different positions of the LV lead in order to obtain optimal resynchronization. To this end, accurate distinction between true LBBB and non-LBBB seems important. Although specific ECG criteria for LBBB have been defined, various definitions exist, and lack of interobserver agreement complicates clinical decision-making. Moreover, impaired myocardial conduction can mimic LBBB QRS morphology, even in the absence of concomitant His-Purkinje lesions. Interpretation of the LBBB ECG can be difficult and misleading because a variety of distinct septal and LV activation patterns are concealed. Regardless of ECG classification, both subgroups (LBBB and non-LBBB) are treated using the same empirical approach of transvenous LVLP. This in part explains the lower response rates associated with non-LBBB despite the potential presence of an electrical substrate that is amendable by CRT.

**Proximal and distal LBBB**

To determine the best pacing strategy for LBBB, it is crucial to know the location of the conduction disorder. The term LBBB is often used interchangeably as both a clinical condition and an anatomic entity. Anatomically speaking, however, an LBBB pattern is not necessarily located within the left bundle branch itself. This became particularly clear as early as 1977 after a study by Narula, who reported full normalization of the QRS complex after pacing the His bundle in patients with LBBB. However, it was not until recently that Upadhyay et al clearly showed that nearly half of patients with LBBB have a proximal conduction block. In the case of “proximal” LBBB, lesions actually are localized within the bundle of His (ie, left intrahisian block). As a result, electrical impulses are blocked at this point, and left intraventricular activation ensues solely after (undisrupted) activation of the right ventricle (RV) has reached the LV endocardium through transseptal conduction. Electrical impulses thereby bypass the native conduction system and rather are transmitted through the myocardium. The result is significantly delayed LV activation, which often occurs in a distinct homogeneous fashion. A “distal” LBBB is present in about 18% of patients with LBBB QRS morphology. Here, the block is located below the His bundle (ie, infrahisian block), within the left bundle branch itself. LV conduction is blocked along the trajectory of the left bundle fascicles, and intraventricular activation continues following a similar pattern of transseptal activation originating from the RV. Importantly, the variability in the location of a conduction block in patients with LBBB was elegantly demonstrated by Upadhyay et al. Despite complying with strict definitions of LBBB, mapping studies revealed that one-third of LBBB patients have intact His-Purkinje activation and normal transseptal activation times (Figure 1). This suggests that the cause of electrical delay likely lies elsewhere in the LV myocardium despite exhibiting an LBBB morphology.

**Nonspecific intraventricular conduction delay**

Alternatively, nonspecific intraventricular conduction delay can be present. Here, more complex and heterogeneous patterns of ventricular activation are present. These patterns can be reflected on the ECG as a broad QRS complex in the absence of typical features of right bundle branch block and LBBB. In the context of an underlying electrical substrate that can be corrected by CRT, these patients are commonly referred to as having non-LBBB. Derval et al performed invasive 3-dimensional electroanatomic mapping to illustrate the fundamental differences in LV activation patterns in non-LBBB (average QRS 150 ms) compared to LBBB (American Heart Association/Heart Rhythm Society/American College of Cardiology [AHA/HRS/ACC] criteria). Purkinje potentials at the site of LV endocardial breakthrough were identified in all non-LBBB patients but never for patients with LBBB. In addition, non-LBBB was characterized by activation that originated from multiple (instead of a single) endocardial LV breakthroughs at the septum, with distinct areas of localized pockets of slow conduction along the LV free wall. Consequentially, failing to meet both Strauss and AHA/HRS/ACC criteria (ie, non-LBBB) reliably excludes damage to the His-Purkinje system with specificity of 91%. Although CRT in patients with non-LBBB is debatable, 30% to 50% of these patients exhibit dominant LV electrical delay that is amendable by CRT, and as such they should not be denied treatment.

**Challenge of electromechanical dissociation**

Mechanical discoordination, when caused by electrical dysynchrony, is believed to contribute to impaired LV function and therefore is an important substrate for CRT as well. Importantly, the extent of electromechanical uncoupling is variable and dependent on electrical and nonelectrical substrates, including regional hypococontractility and myocardial scar (Figure 2). Here, lack of coupling implies electrical depolarization of a cardiac segment without synchronous myocardial fiber shortening. Due to uncoupling, however, sites of latest mechanical activation occur more frequently in a nonlaterally located segment than electrical activation, which complicates selection of optimal transvenous LVLP. Based on our understanding of conduction disorders that cause dyssynchrony, two distinct approaches to enhance LVLP in dyssynchronous HF can be proposed (Figure 1).

**Current and future approaches to resynchronization**

In contrast to resynchronizing the heart by pacing both ventricles nearly simultaneously in BVP, direct stimulation of the His-Purkinje system through CSP is possible as well. To this end, there has been a resurgence in interest in His bundle pacing (HBP) in CRT. Other alternative strategies for CSP include left bundle branch pacing (LBBP) and left ventricular septal pacing (LVSP). Because of their practical overlap, both are collectively referred to as left bundle branch...
area pacing (LBBAP). Unlike HBP and LBBP, however, LVSP activates fast conducting superficial subendocardial fibers and therefore does not require capture of the native conduction system. CSP allows for physiological ventricular activation with fast (endocardial-initiated) impulse conduction, evidenced by near-complete normalization of the QRS (Figure 3).

Comparing CSP to BVP

The primary benefit of CSP is its potential to establish physiological ventricular activation. Additional advantages of CSP include the independence from limited venous access or phrenic nerve stimulation. Although Abdelrahman et al demonstrated the feasibility and effectiveness of HBP in patients with a standard RV pacing indication, few studies are...
performed in which HBP was applied in a cohort of patients with dyssynchronous HF. Huang et al\textsuperscript{17} demonstrated in 56 patients that, after 3-year follow-up, those who received permanent HBP had drastically improved LV ejection fraction by $>$50% of baseline value. Nonetheless, in $\sim$25% to 50% of patients, permanent HBP is not feasible due to fixation failure or inadequate thresholds necessary for the correction of LBBB, despite compliance with criteria for LBBB morphology.\textsuperscript{17,19} These findings are in line with the mapping study of Upadhyay et al,\textsuperscript{3} who demonstrated that less than half of patients with a strict LBBB pattern had true intrahisian conduction block.

Because of the relatively low percentage of patients with intrahisian block, LBBAP may be a more interesting approach to CSP in the majority of patients. LBBAP requires less precision than HBP, and lower and more stable pacing capture thresholds can be achieved.\textsuperscript{15} Therefore, LBBP circumvents many of the technical limitations of HBP, resulting in significantly better feasibility of 90%–98% in LBBB patients.\textsuperscript{20} Moreover, improvement in LV ejection fraction after HBP and LBBP is nearly identical but significantly better than during BVP (24% vs 17%).\textsuperscript{19} A recent study showed the first results for LVSP in 27 patients.\textsuperscript{16} LVSP resulted in more pronounced QRS reduction than BVP, although acute hemodynamic benefit (AHB) seemed to be similar compared to conventional CRT.\textsuperscript{10}

Taken together, both HBP and LBBAP are exciting alternatives to conventional BVP, with promising early evidence of safety and efficacy. However, lead positioning in LBBAP is less critical than during HBP, rendering it less technically challenging and more widely applicable for the majority of patients and implanters. Unfortunately, long-term results on safety (eg, dislodgment, potential septal perforation, challenging lead extraction) and hard clinical endpoints in large randomized trials are still lacking. Moreover, because a key aspect of LVSP is bypassing slow conduction across the septum (30–70 ms in LBBB), whether LBBAP can resynchronize LV activation in patients with normal septal activation remains to be investigated. It is important to realize that some LBBB and most non-LBBB patients have intact Purkinje activation and exhibit LV activation onset within the septum that is comparable to that of patients with narrow QRS (Figure 2B vs Figure 2D).\textsuperscript{4,7} Therefore, CSP may be best suited for LBBB patients with a functional His-Purkinje lesion (ie, potential superresponders), although these patients may invariably improve with BVP as well (Figure 1). In non-LBBB, however, optimally targeting the LV free wall (ie, BVP) seems more appropriate.\textsuperscript{9}

**Fallacy of empirical lead placement in CRT**

**RV lead position and LV-only pacing**

Studies that investigated whether a nonapical RV lead position, closer to the His-Purkinje system, could improve outcome in CRT found no differences in echocardiographic or clinical endpoints as opposed to a conventional RV lead position.\textsuperscript{21} However, paced effects (eg, interlead delays) were not used to determine optimal RV lead position. Alternatively, preserving intrinsic conduction via the right bundle branch altogether in LV-only pacing seems to be a safe but nonsuperior alternative to BVP.\textsuperscript{32} However, most studies were limited by suboptimal comparison between BVP and LV-only pacing, because the important aspect of fusion with intrinsic right bundle conduction during LV-only pacing was not always considered.\textsuperscript{23} The ongoing AdaptResponse Trial investigates RV-synchronized LV-only fusion pacing compared to BVP and will be the first trial that is sufficiently powered to assess hospitalization and mortality outcomes.\textsuperscript{24} Whether the potential utility of RV-paced wavefronts in reducing transseptal conduction times is a prerequisite for optimal resynchronization in selected patients remains to be investigated.\textsuperscript{25} This may hold true especially in LV-only patients in whom fusion with the right bundle conduction is inadequate. It is important to note that fusion is highly sensitive to the intrinsic atrioventricular conduction time.\textsuperscript{26}

**Optimal LV pacing site is patient-specific**

Accumulated evidence in over 4200 patients from various landmark trials taught us that, on group level, no single site is consistently superior (or inferior) to another with respect to long-term outcome.\textsuperscript{21,27,28} Conversely, the inter- and intrapatient heterogeneity of the optimal LV pacing site becomes apparent in many interventional studies in which AHB was systematically explored during BVP at various sites. PACing a suboptimal site improves the maximum rate of LV pressure rise ($dP/dt_{max}$) on average by $\pm$13%. Combining the results of all studies suggests that this can be further improved by an additional 9 percentage points (range 3%–16%) when the optimal site is targeted (Figure 4 and Supplemental Table 1).\textsuperscript{2,29} Although the question remains to what extent AHB contributes to clinical improvement, each patient will benefit from the largest improvement of LV function.\textsuperscript{30} We should acknowledge that hemodynamic variation may in part originate from bias caused by multiple measurements, physiological variability, and analytical error of $dP/dt_{max}$ assessment. Nonetheless, most studies limited the amount of samples and prevented bias by rigorous methodology.

The robustness of these findings as a whole is also underscored by a more recent study. Van Everdingen et al\textsuperscript{31} demonstrated that considerable intrapatient hemodynamic variation occurs even among different electrode configurations of a quadripolar lead, spaced at minimum just 20 mm apart. This may be explained by the substantial but unpredictable differences in LV propagation seen on ECG imaging, despite pacing adjacent LV electrodes.\textsuperscript{32} Therefore, we may conclude that the influence of a variety of factors on optimal LVLP is reflected by the large individual variation in paced effects and hemodynamics, and LVLP is highly patient-specific. Because measures of both LV $dP/dt_{max}$ and stroke work were consistent across all studies, these findings emphasize the need for
individualized targeting of the optimal pacing site. In line with this, one study proved that successfully pacing a predefined and patient-specific segment resulted in more pronounced AHB compared to empirical placement. Therefore, it is not surprising that simply adding LV-pacing vectors through multipoint pacing is not necessarily beneficial compared to optimized BVP, supporting the notion that optimizing lead placement is at least equally important. Conversely, because BVP (ie, epicardial LV stimulation) is hampered by relatively slow wavefront propagation, adequate depolarization may be particularly difficult to achieve in patients with highly pronounced LV dilation. Whether programming multipoint pacing with the widest electrode spacing and minimal delay can result in better outcomes, which may be especially useful in non-LBBB patients and/or clear LV enlargement, remains to be demonstrated. One important question remains, however: besides avoiding in-scar pacing, on what basis should we determine the optimal location for LVLP?

**Targeted lead placement in biventricular CRT**

**Electrically guided**

Gold et al found that BVP with the lead positioned at the longest LV electrical delay (ie, higher QLVs) correlates to increased AHB and predicts reverse remodeling. Importantly, although QLVs may be used to select the optimal vein, QLVs cannot be used for selection of the optimal electrode of a quadripolar lead when placed in an already optimal area. A possible explanation is that a correlation with LV end-systolic volume reduction seems driven by shorter QLV values (cutoff value ~95 ms) and seems to be most applicable when large disparities between the measured QLV are present. Moreover, when compared to an anatomic approach, QLV-guided implantation may only be beneficial in patients with typical LBBB morphology.

Because of small differences in intrinsic activation delay when LVLP already is optimal, electrical indices such as LV-paced to RV-sensed wavefront propagation (ie, LVp-RVs) correlate poorly to QLV as well. Therefore, LV-paced activation effects are highly unpredictable when based on stimulation site alone, despite widely variable acute electrical responses. Where QLV is a measure of intrinsic electrical dyssynchrony, the difference between left and right paced-to-sensed interlead delays (LVp-RVs > RVp-LVs) can be used as a measure of paced LV-dyssynchrony. Paced LV dyssynchrony is associated with scar and local electrical disturbances and is independently associated with nonresponse, even in addition to QLV. Regardless, paced-to-sensed interlead delays are not associated with LVLP or acute stroke work increase, underscoring the heterogeneity of optimal LVLP. Additionally, LV latency as indicated by stimulus-to-QRS onset ≥40 ms also can be measured, which may be used to predict mortality and hospitalization for HF. Although LV latency is associated with ischemic etiology, its presence can be related to any cause of impaired impulse propagation, prolonged refractoriness, or conduction disorders. Alternatively, preimplantation ECG imaging (eg, body surface mapping or ECG imaging) or paced reduction of QRSAREA may allow for more accurate distinction between optimal and suboptimal cardiac segments.

**Image-guided**

Three of six studies comparing image-guided LVLP with an empirical approach reported significantly more reverse remodeling and/or percentage of responders in the treatment group (Table 1). However, in the TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) and STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) studies, assessment of strain at the apex...
could not be performed, even though an apical position may be optimal in a substantial amount of patients (Supplemental Table 2). Although the utility of strain for detecting scarred segments is poor (sensitivity 33%), these positive effects cannot solely be attributed to targeting the latest mechanically activated segment. In contrast to TARGET and STARTER, 2 studies allowed targeting electrically delayed segments using QLV guidance in the control group and were unable to demonstrate significant differences in reverse remodeling between both groups. Stephansen et al performed QLV mapping in any accessible coronary sinus branch and concluded that this approach is equally effective compared to an echocardiographically guided approach based on a mechanical delay. Importantly, however, procedural time was significantly longer, radiation doses were higher, more in-scar pacing occurred, and optimization of interventricular pacing delay was only performed in the electrically guided group. Lastly, it should be considered that LVLP in patients with non-LBBB and patients with QRS duration $\leq$150 ms is less critical, because these patients already have a clear electrical substrate, regardless of the segment targeted. In line with this, superior outcomes associated with image-guided LVLP in STARTER were almost completely driven by patients with non-LBBB and patients with QRS duration $<150$ ms.

### Which modality should we use for guidance?

Various methods to determine optimal lead location can be considered before and during implantation of a biventricular pacemaker (Figure 5). It is particularly important that in-scar pacing is avoided because of its 6-fold increased risk for cardiovascular death or hospitalization for HF. In LBBB patients, an electrically guided approach may be noninferior to an image-guided approach. In patients with non-LBBB

### Table 1

|                  | Bai et al$^\text{11}$ | Khan et al$^\text{44}$ | Saba et al$^\text{45}$ | Sommer et al$^\text{48}$ | Bertini et al$^\text{46}$ | Stephansen et al$^\text{49}$ |
|------------------|-----------------------|------------------------|------------------------|--------------------------|---------------------------|-----------------------------|
| No. of patients  | 104                   | 220                    | 187                    | 182                      | 100                       | 122                         |
| Design           | Cohort                | RCT                    | RCT                    | RCT                      | Cohort$^*$                 | RCT                         |
| Blinded          | Yes                   | Yes                    | Yes                    | Yes                      | NR                        | Yes                         |
| Method           | Echo$^1$              | Echo                   | Echo                   | CT and Echo              | Echo and MRI$^3$           | Echo, Rb-PET, CT            |
| Male (%)         | 67                    | 79                     | 73                     | 79                       | 79                        | 75                          |
| LBBB (%)         | 100                   | 99                     | 53                     | 100                      | 53                        | 100                         |
| QRS (ms)         | 154                   | 158                    | 159                    | 166                      | 155                       | 169                         |
| ICM (%)          | 59                    | 56                     | 62                     | 49                       | 47                        | 50                          |
| $\triangle$LVESV (%) | Guided   | 33 $\pm$ 33           | 30 $\pm$ 29           | 34 $\pm$ 23              | 39 $^3$                   | 25 $\pm$ 36                  |
|                  | Control               | 13                     | 26 $\pm$ 23           | 20 $\pm$ 25              | 33 $\pm$ 23              | 22                          |
| $P$ value        | .428                  | .001                   | <.05                   | NS                       | NR                       | .71                         |

CT = computed tomography; Echo = echocardiography; LBBB = left bundle branch block; LVESV = left ventricular end-systolic volume; (values in % ± standard deviation when available); MRI = magnetic resonance imaging; NR = not reported; NS = not significant; Rb-PET = rubidium-82 positron emission tomography; RCT = randomized controlled trial.

$^*$With retrospective control group.
$^1$Intracardiac echocardiography coupled with vector velocity imaging.
$^3$$>75\%$ late gadolinium enhancement in ischemic cardiomyopathy (ICM) or subendocardial fibrosis for nonischemic cardiomyopathy.
$^x$No relative reduction reported, calculated from group results.

### Figure 5

Examples of pre- and intraprocedural methods for selecting the optimal left ventricular (LV) lead location. The optimal target for LV lead placement is determined by assessing scar tissue (left) and electromechanical activation patterns (middle). Right: Various paced effects can be considered to further assist implanting physicians during the procedure. The list is not all-encompassing. MRI = magnetic resonance imaging; STE = speckle tracking echocardiography. 3D = 3-dimensional; 4D = 4-dimensional.
morphology, however, image-guided LVLP resulted in superior outcome compared to contemporary placement, whereas a QLV-guided approach failed to do so. 39,50 Although previously mentioned limitations of an electrically guided approach should be considered, image-guided approaches may have insufficiently utilized potential as well.

Because better outcomes are associated with targeting late LV electrode activation and optimizing paced-to-sensed interlead delays, (further) improving LVLP during the procedure also can be considered. 540–42 Intraindividually, however, LV-paced electrical effects are highly variable, unpredictable, and correlate poorly to intrinsic electrical delay. 32,36 Finally, knowing where to optimally place the lead is meaningless when a target cannot be reached, and suboptimal positions can only be partly improved by optimizing device programming. 2 The difficulty and variability of targeted LVLP are illustrated by the frequency of within-target LVLP, ranging from 30% to 63% between all studies (Supplemental Table 2). Whether intraoperative visualization of optimal targets (eg, using fusion with fluoroscopy) can increase these numbers warrants further investigation.

Conclusion
Among patients eligible for CRT, there is great diversity of both the extent and the location of conduction disorders causing an electromechanical delay. Unfortunately, this distinction cannot easily be made based on the surface ECG and does not influence LVLP in our current practice. Therefore, contemporary lead placement in BVP is hampered by an empirical approach, despite clear evidence for considerable intraindividual variation in the segment that results in optimal AHB. As an alternative to BVP, future strategies presumably will include HBP for patients with conduction disorders within the bundle of His and LBBAP for patients exhibiting infrahisian block. However, patients with non-LBBB have normal septal activation and are less likely to benefit from CSP. BVP with the LV lead targeted away from scar and toward late activated segments may provide the best results for these patients.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.02.011.

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