PERSPECTIVES IN CONTRAST

His-bundle pacing is the best approach to physiological pacing

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The complete electrical activation sequence of the human heart was first described by Durrer et al[1] in the late 1960s and was based on mapping of the first 5 ms of left ventricular (LV) activation using 870 intramural electrodes. They noted 3 distinct endocardial areas excited synchronously in the LV, proving the trifascicular nature of the left conduction system (LCS): (1) high anterior paraseptal wall; (2) central left upper interventricular septum; and (3) distal posterior paraseptal wall. In a field in which electrical disturbances of 5–10 ms are associated with diverging clinical outcomes, the preservation and/or restoration of this intricate and perfectly specialized activation is the basis for physiological pacing. We propose that His-bundle pacing (HBP) is the only form of cardiac stimulation that can precisely reproduce this evolutionarily conserved form of intrinsic activation.

With increased implementation, recent concerns have emerged whereby (1) HBP implantation is technically more challenging with a long learning curve[2]; and (2) thresholds for His capture may unpredictably rise after device placement.[3] In response to these issues (given current technology), left bundle branch area pacing (LBBAP) as pioneered by Huang et al[4] has been introduced as a novel form of physiological pacing, potentially overcoming many of the limitations of HBP while maintaining all of the advantages.[4,5] Although LBBAP may yield pacing thresholds more similar to myocardial pacing, whether this form of permanent pacing can be successfully targeted in all patients is unclear. Furthermore, there is a current knowledge gap about how to distinguish capture of the LCS from capture of the left ventricular septum (LVS) only.

KEYWORDS Biventricular pacing; Cardiac resynchronization therapy; His-bundle pacing; Left bundle branch block; Pacemaker; Right bundle branch block (Heart Rhythm O^2 2020;1:68–75)

Dr Upadhyay reports consulting and speaking fees from Abbott, Biotronik, Medtronic, and Zoll Medical. Dr Tung reports speaking fees from Abbott and Boston Scientific. Please note that the opinions expressed in this article are not fully reflective of the authors' clinical practice, with intentional polarization of their discussion points for the present commentary. **Address reprint requests and correspondence:** Dr Roderick Tung, The University of Chicago Medicine, Center for Arrhythmia Care, 5841 S Maryland Ave, MC 6080, Chicago, IL 60637. E-mail address: rodericktung@uchicago.edu.

We respectfully submit that HBP is the best approach to fully achieve physiological pacing based on the following arguments:

1. Only HBP results in complete recruitment of intrinsic LCS activation
2. Available clinical evidence for HBP far outnumbers that for LBBAP
3. Lack of definitive evidence and criteria for capture of the LCS
4. Generalizability of LBBAP is unknown and largely untested outside of China, particularly in the presence of septal scar and ischemic substrates

Complete recruitment of HPS

Is fascicular pacing adequate? Although multiple reports of LBBAP suggest recruitment of the common left bundle, many published illustrations of this technique do not demonstrate this in practice. The presence of a superior axis (seen in multiple published figures) is not consistent with capture of the LBB but rather left posterior fascicular pacing.[6,7] Only HBP results in complete anterograde activation of the trifascicular LCS. A recent high-resolution mapping study in an animal model highlights distal capture within the fascicles in the majority of cases.[8] Although retrograde activation of the proximal system likely is better than myocardial pacing, whether this region of myocardium contributes substantially to synchronous cardiac contraction remains unclear.

Clinical evidence with HBP outnumbers that with LBBAP

In 2018, Zanon et al[9] reported a systematic review of HBP in 17 single-arm and 9 comparative studies totaling 1438 patients. Mean implant success rate was approximately 85% across these studies. Among 8 studies reporting change in left ventricular ejection fraction (LVEF) after HBP, they found an average 5.9% increase after pacing (P = .001). The largest prospective cohort study comparing HBP with right ventricular pacing (RVP) evaluated the outcomes of 304 patients with successful HBP vs 433 RVP controls.[10] In that study, Abdelrahman et al[10] found that HBP was associated with a reduction in a composite of all-cause mortality, heart failure (HF) hospitalization, and need for upgrade to

 https://doi.org/10.1016/j.hroo.2020.03.001

biventricular pacing (BiV) at mean follow-up of 4.3±3.9 years. The primary outcome was reduced by 29% in all-comers and 35% in patients with at least 20% ventricular pacing burden. Reduction in all-cause mortality nearly reached significance (hazard ratio [HR] 0.73; $P = .058$), and HF hospitalization was significantly reduced (HR 0.63; $P = .021$).

Particularly when viewed in conjunction with other reports having ≥12-month outcomes (Table 1), there is now considerable evidence supporting HBP in clinical practice. Longer-term lead performance has now been reported with follow-up to 5 years. Although longitudinal follow-up consistently demonstrates rising thresholds prompting more frequent lead revisions than RVP, long-term clinical benefit with reduction in HF hospitalization is consistent,[11,12] even in the setting of premature battery depletion. The summary of clinical evidence for LBBAP with ≥12-month median follow-up is given in Table 2, which includes a singular study with a subgroup of 8 patients who underwent LBBAP along with 44 HBP patients who had undergone atrioventricular (AV) nodal ablation. Median follow-up has been either none (acute immediate implantation) to 3 months.[6,13,14] Given this complete lack of evidence-based outcomes in intermediate and long-term follow-up, it is only prudent to withhold broader application of LBBAP at the present time until more data are available.

Step-by-step approach to HBP

The leads most commonly used in current applications of HBP are the Medtronic SelectSecure model 3830 lead (Medtronic, Minneapolis, MN) and the model C315His fixed-curve delivery sheath (Medtronic). Medtronic also introduced the deflectable SelectSite C304-HIS sheath as another means for mapping the His signal and may have practical utility in dilated right atrium. More recently, Boston Scientific launched the Site Selective Pacing Catheters (SSPC1-4, models 9181-9184; Boston Scientific, Marlborough, MA) to be utilized with 6F or 7F leads. Common to all current vendors is the concept of sheath-driven delivery of leads to the His-bundle region.

The approach to implant has been described previously.[15] In brief, mapping for the His potential is performed in unipolar configuration with electrograms visualized by an electrophysiological recording system at 100 mm/s sweep speed (Prucka CardioLab, GE Healthcare, Waukesha, WI) and through the device programmer. The sheath is delivered across the tricuspid annulus, and the His-bundle region is mapped from the ventricular to the atrial aspect with rotation and withdrawal of the sheath body. Counterclockwise rotation of the sheath results in inferoposterior movement (usually toward the septum), whereas clockwise rotation results in anterosuperior movement. The aim is a region with a clear His potential and an appropriate R-wave to p-wave amplitude (generally >3:1). Mapping is performed using standard fluoroscopic views, particularly in the left anterior oblique view to ensure that the lead is opposed to the septal surface of the heart rather than the more mobile tricuspid annulus or leaflet. In patients in whom the sheath does not easily record a His potential, the approach at our center is to manually reshape the fixed-curve sheath first before utilizing a deflectable sheath. In some patients with significantly dilated atrial size, a sheath-in-sheath approach (by delivering the fixed C315 through a right-sided multipurpose outer coronary sinus sheath) may be utilized to improve reach. Perhaps most critical at implant is evaluating output-dependent morphologic (ODM) changes to determine that His-bundle capture is indeed present. (Please refer to online supplemental videos for additional suggestions and tips regarding implant.)

Selective vs nonselective capture in HBP

The *sine qua non* of conduction system pacing is the demonstration of ODM changes in QRS reflecting isolated or selective His-Purkinje capture compared to septal myocardial capture (nonselective).[16] Both selective and nonselective HBP have been shown to be associated with comparable impact on mechanical synchrony as assessed by myocardial perfusion imaging, and both were better than RV septal pacing.[17] Similarly, both selective and non-selective HBP are associated with similar ventricular depolarization characteristics (eg, QRS area) and ultra–high-frequency electrocardiogram–derived measures of electrical dyssynchrony, both of which were superior to RV myocardial capture.[18] When evaluating clinical outcomes, in a study combining 350 patients at 2 centers, there was no significant statistical difference in time to all-cause death or HF hospitalization between patients with nonselective HBP vs patients with selective HBP. Importantly, no differences in HF hospitalization were observed (HR 0.925; $P = .96$), with nearly superimposable curves in the study.[19]

In contrast to HBP, the output-dependent morphologic changes associated with LBBAP are often much more subtle, showing changes in the qR pattern in lead V_1 with output change that likely reflect loss of LVS capture but sometimes are difficult to discern even on 12-lead ECG. In part, this may result because of the depth or course of the lead in the interventricular septum. In contrast to HBP, unipolar vs bipolar pacing (associated with anodal stimulation of the RV septum) and AV timing also can dramatically change the degree of fusion, even in a narrow QRS patient.[5] The optimal pacing configuration and impact remain to be elucidated for this strategy.

Corrective HBP

A particularly exciting early observation for HBP was that it could be used to significantly narrow the QRS of patients with bundle branch block. In 2005, corrective HBP was reported in a patient with left bundle branch block (LBBB) in whom a coronary sinus lead could not be placed for traditional BiV for cardiac resynchronization therapy (CRT). HBP was associated with marked QRS narrowing and a morphology that seemed consistent with intact Purkinje activation.[20] The finding has now been reproduced in a number of case series[15,21–32] and was examined in an investigator-initiated

Table 1 Studies of HBP with median or mean follow-up ≥12 months (n = 19 studies)

Author	Year	N*	Average follow-up (mo)	Study type	Inclusion	Clinical outcome
Deshmukh et al[21]	2000	18	23	Single-center cohort	Systolic HF, AVN ablation, narrow QRS	Improved LV volumes, fractional shortening, CT ratio
Deshmukh and Romanyshyn[44]	2004	54	42	Single-center cohort	Systolic HF , persistent AF, narrow QRS	Improved LVEF, functional class; subset with CPT showed longer exercise time, higher O_2 uptake, later anaerobic threshold
Occhetta et al[45]	2006	18	12	Crossover, blinded, randomized study	AVN ablation, narrow QRS	Improved functional class, QOL, 6MWT; reduced mitral and tricuspid regurgitation
Kronborg et al[46]	2014	34	24	Crossover, double-blinded, randomized study	High-grade AVB, narrow QRS	Improved LVEF, mechanical synchrony; no difference in functional class or QOL
Vijayaraman et al[47]	2015	100	19	Single-center cohort	High-degree AVB or AVN ablation, narrow and wide QRS	HBP feasible in nodal and infranodal block with only slight rise in thresholds in follow-up
Huang et al[25]	2017	52	21	Single-center cohort	Systolic HF, AVN ablation, narrow QRS	Improved LVEF, LV volumes, functional class; reduced diuretic use
Vijayaraman et al[24]	2017	42	19	Single-center cohort	AVN ablation, narrow QRS	Improved LVEF, functional class
Vijayaraman et al[48]	2017	20	70	Single-center cohort	High-degree AVB, narrow QRS	LVEF remained despite high-degree, chronic pacing
Vijayaraman et al[12]	2018	94	60	Single-center cohort	AVB, SND, slow AF, narrow QRS	LVEF remained stable, lower incidence of pacing cardiomyopathy; reduced HF hospitalization; higher rate of lead revision and generator change
Sharma et al[29]	2018	39	15	Multicenter cohort	RBBB, systolic dysfunction	Improved LVEF, functional class
Abdelrahman et al[10]	2018	332	24	Multicenter cohort	AVB, SND, slow AF, narrow QRS	HBP with reduction of combined endpoint of death, HF hospitalization, or upgrade compared to RVP
Ajijola et al[15]	2018	21	12	Multicenter cohort	CRT-eligible	Improvement in LVEF, LVEDD, NYHA class
Sharma et al[26]	2018	106	14	Multicenter cohort	CRT-eligible	Improvement in LVEF, NYHA class
Sarkar et al[49]	2019	22	15	Single center cohort	AVB, narrow QRS, CRT-eligible	Improved LVEF in patients with systolic dysfunction at baseline; stable thresholds
Huang et al[30]	2019	74	37	Single-center cohort	CRT-eligible, LBBB only	Improved LVEF, LV volumes, functional class; stable correction thresholds at 3 y
Zanon et al[11]	2019	844	36	Multicenter cohort	AVB, SND, slow AF, narrow QRS	Rise in capture thresholds at 3 y; fixed-curve sheath with lower thresholds than early deflectable sheath
Vijayaraman et al[31]	2019	27	14	Multicenter cohort	CRT-eligible for combined His and LV pacing	QRS narrowing; improved LVEF, functional class
Boczar et al[50]	2019	14	14	Multicenter cohort	Permanent AF, CRT-eligible	Improved LVEF, functional class
Upadhyay et al[33,34]	2019	20	12	Multicenter, prospective, single-blinded, randomized, controlled trial	CRT-eligible	His-CRT with superior QRS narrowing than BiV-CRT in on-treatment analysis; trend toward greater LVEF improvement that did not reach significance

6MWT = 6-minute walk test; AF = atrial fibrillation; AVB = atrioventricular block; AVN = atrioventricular node; BiV = biventricular pacing; CPT = cardiopulmonary testing; CRT = cardiac resynchronization therapy; CT = cardiothoracic; HBP = His-bundle pacing; HF = heart failure; LBBB = left bundle branch block; LV = left ventricle; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QOL = quality of life; RBBB = right bundle branch block; RVP = right ventricular pacing; SND = sinus node disease.

*Number of patients in whom HBP was attempted.

Table 2 Studies of LBBAP with median or mean follow-up ≥12 months (n = 1 study)

Author	Year	N*	Average follow-up (mo)	Study type	Inclusion	Clinical outcome
Wang et al[51]	2019	8 LBBAP 44 HBP	30.5	Single-center cohort	Persistent AF, HF with ICD, AVN ablation	Improved LVEF and volumes; fewer inappropriate shocks in patients receiving HBP/LBBAP vs OMT

ICD = implantable cardioverter–defibrillator; LBBAP = left bundle branch area pacing; OMT = optimal medical therapy; other abbreviations as in Table 1.
*Number of patients in whom His-bundle pacing was attempted.

randomized controlled trial of HBP vs BiV for CRT (His-SYNC Pilot Trial) (Figure 1).[33,34] Outcomes have been largely consistent across these studies, namely, QRS correction with HBP is associated with lower success rates than in narrow QRS, and pacing output requirements usually are higher. For patients receiving HBP for HF indications, however, HBP-CRT seems feasible, and improvement in LVEF seems commensurate with BiV-CRT, particularly when used as a bailout for failed coronary sinus lead implant. Larger pivotal studies are required to formally assess the impact of primary HBP-CRT on clinical outcomes. To date, only a single article on LBBAP for CRT-indicated patients with mean follow-up of 6 months[35] and one other report on the acute effects on mechanical synchrony in LBBB patients with a pacemaker indication[36] have been published.

LVS vs LCS

At the 2019 3rd Annual International Physiology of Pacing Symposium (Chicago, IL), there was general consensus that although intraseptal pacing offers promise and versatility, there was an urgent need to establish consistent criteria to differentiate LCS from LVS during attempted LBBAP. We believe that the need for such a distinction is magnified in patients with wide QRS relative to those with narrow QRS, in whom LVS may be sufficient to prevent pacing-induced cardiomyopathy.

Intraseptal pacing was first described by Mafi-Rad et al.[37] Is LBBAP or LVS pacing "good enough" to maintain physiological electromechanical activation? Besides producing a paced QRS with a right bundaloid configuration in lead V_1 (itself suggestive of at least partial RV delay), few data on clinical outcomes with LBBAP or LVS have been reported, with even fewer reports comparing these outcomes to RVP or HBP.[6,7,13,35,36,38] The clearest distinction between LBBAP and LVS pacing can be identified at implant if a left bundle potential is observed during lead delivery. In recent studies of narrow QRS patients, a left bundle potential is observed at implant in as low as 27% and up to 80% of occasions.[6,7] This raises the possibility that many patients undergo LVS rather than LCS.

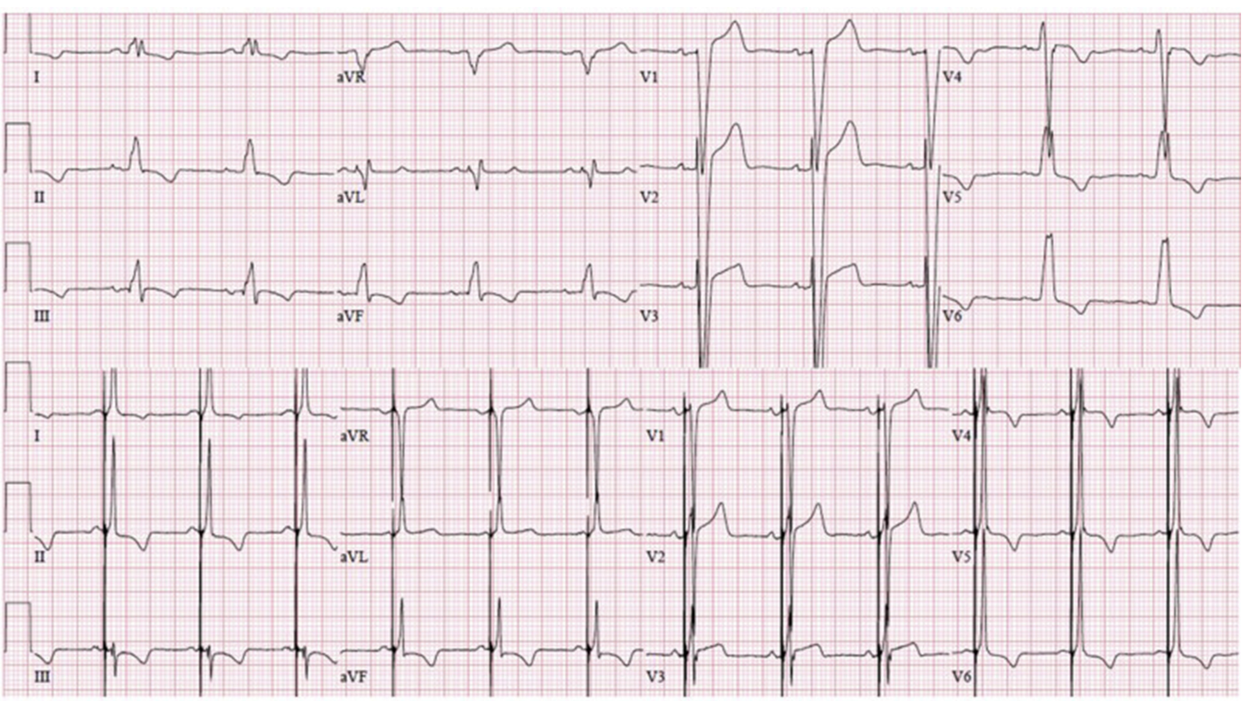

Figure 1 Complete correction of wide QRS (**top:** left bundle branch block) with His-bundle pacing (HBP), restoring physiological conduction through intrinsic activation of the His–Purkinje system (**bottom:** corrected HBP).

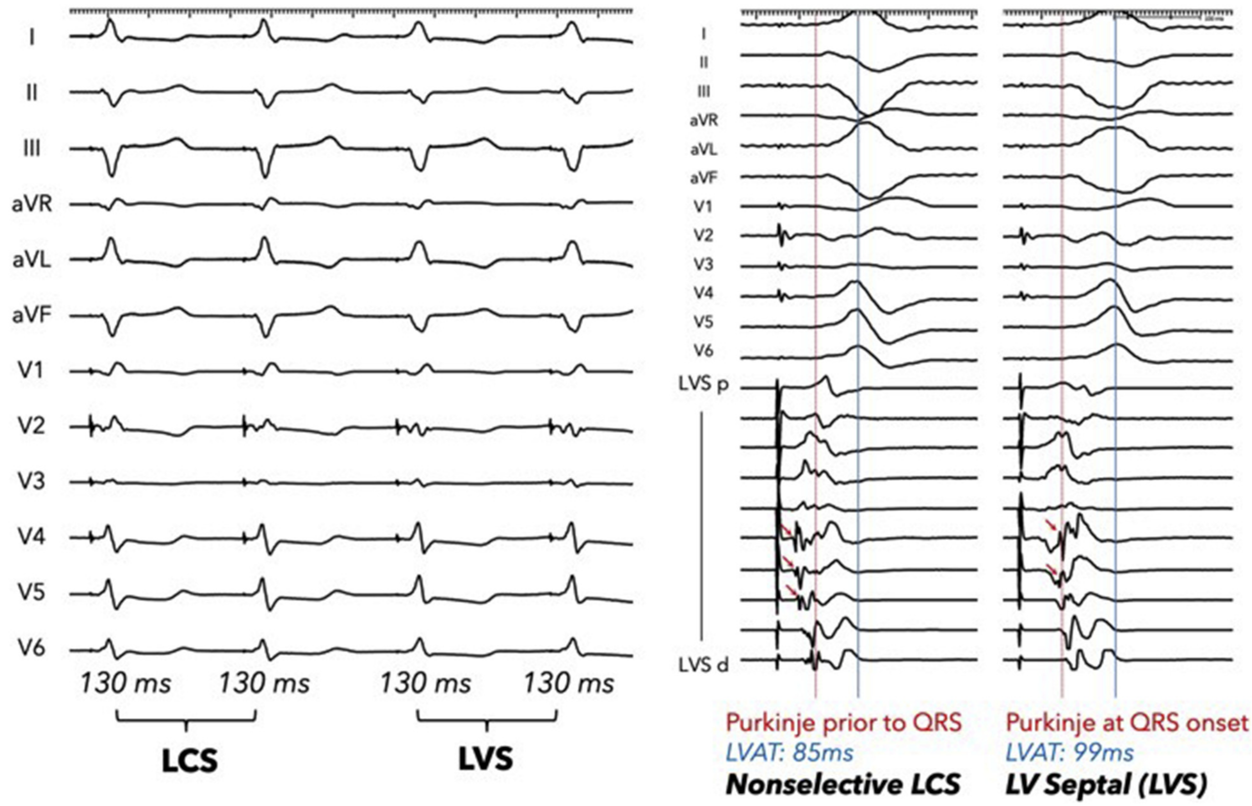

Figure 2 Subtle differences in surface QRS morphology with LCS and LVS. Both exhibit an isoelectric segment after the stimulus; however, intracardiac recordings show evidence of septal capture. High-density mapping of the septum shows presystolic recruitment of Purkinje, which proves LCS, whereas passive Purkinje is still activated at QRS onset during LVS. No data suggest whether these responses are equivalent. LCS = left conduction system; LVAT = left ventricular activation time; LVS = left ventricular (LV) septum.

In patients with complete LBBB, the situation is more complicated because the left bundle potential also can be visualized after the QRS is corrected (usually requiring placement of a simultaneous HBP lead) and focal block is circumvented. Surrogates such as LV activation time (LVAT) have been proposed to assess lateral wall delay based on the surface 12-lead ECG,[39,40] although correlation with intracardiac LVS mapping is absent.

In a recent short-term study of 27 patients undergoing traditional BiV-CRT, temporary LVS was performed intraprocedurally to compare the acute hemodynamic effects of BiV versus LVS. LVS was associated with comparable improvements in electrical resynchronization (as measured by the multielectrode ECG belt) and LV dP/dT assessment as BiV.[41] In a subset of 14 patients, comparable results were found between HBP and LVS. In the accompanying editorial, however, an example was shown of markedly reduced cardiac work (as measured by pressure–volume loop) in a patient with underlying LBBB undergoing LVS vs corrective HBP, which was more physiological.[42] It probably is premature to ascertain whether LVS pacing is sufficient to achieve comparable hemodynamic benefit as conduction system capture. What has been clearly shown is that RV septal pacing is not as beneficial as His-bundle capture, and concerns for myocardial delay or scar limiting septal activation remains an active area of research.

Figure 2 illustrates the subtle differences during LBBAP with and without capture of LCS demonstrated by left-sided multielectrode recordings. Relatively narrow QRS duration of 130 ms is seen in both QRS morphologies that are preceded by isoelectric segment after the pacing stimulus. Left septal mapping demonstrates LVS activation during the isoelectric segment and is indicative of a "concealed" pseudo–delta wave not detectable by surface interpretation. Presystolic recruitment is seen during LCS, and only myocardial capture is seen with decrease in stimulus output (<2 V). Purkinje activation is seen during QRS onset during LVS, however, and this *may* be sufficient to preserve physiological activation, although clearly more work is needed. LVAT may be useful to distinguish the 2 forms of capture during LBBAP, but differences in clinical outcome remain completely unknown.

Generalizability of LBBAP and other concerns

The bulk of the clinical experience with LBBAP has emerged from China, based on the initial innovation by Huang et al.[4] For both narrow and wide QRS patients, the Huang technique has been tested and used predominantly in a nonischemic population having smaller body mass and septal thickness. The presence of fibrotic scar within the septum may serve as a barrier to successful intraseptal fixation with acceptable

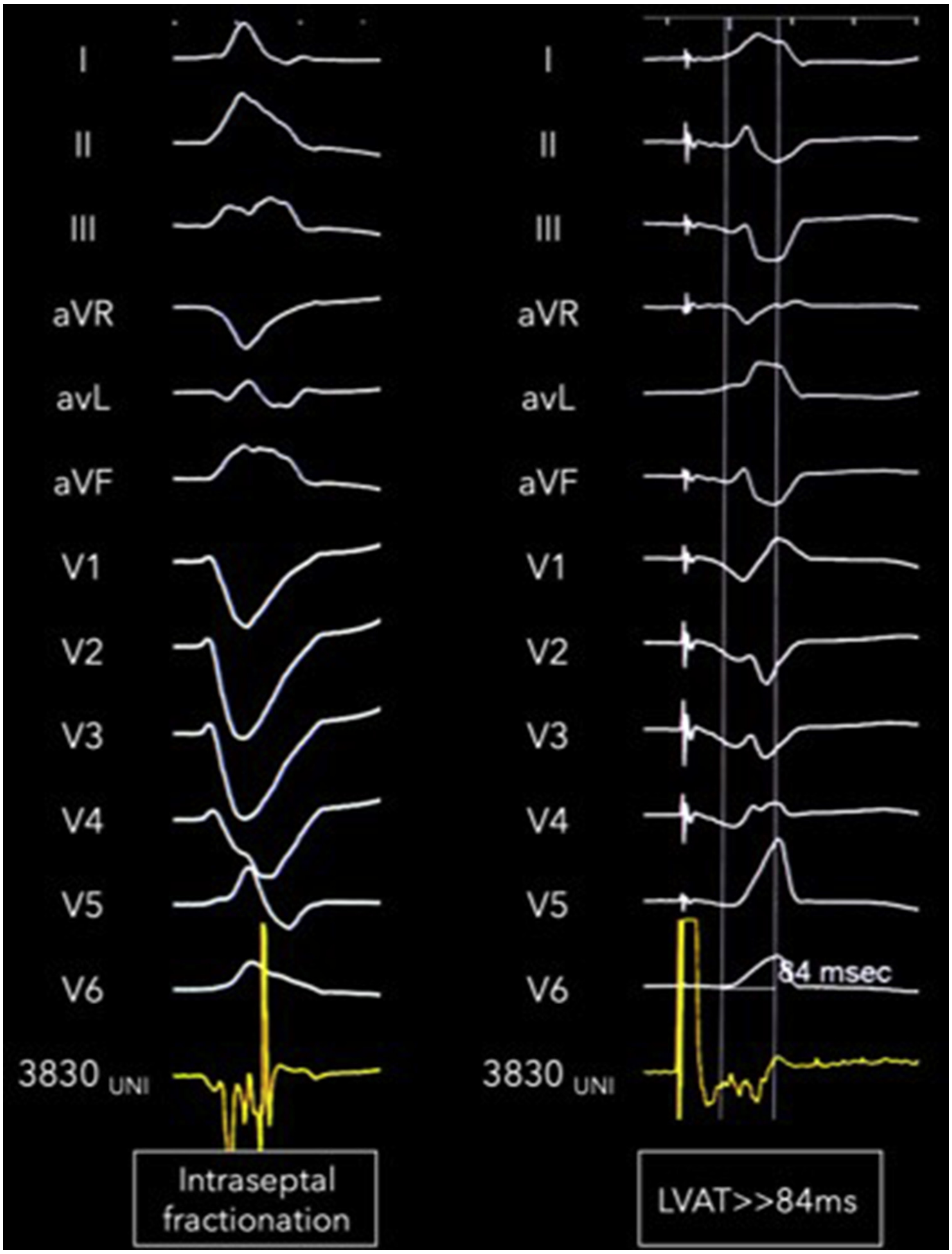

Figure 3 Evidence of intraseptal substrate that impedes the ability to fix the lead deeper and correct wide QRS. Unipolar electrogram shows significant fractionated local recording within the septum. Without including the S-QRS, the left ventricular activation time (LVAT) is already 84 ms from intrinsicoid deflection, signifying inability to achieve cardiac resynchronization therapy by left bundle branch area pacing.

thresholds. Patients with ischemic cardiomyopathy need to be systematically studied. In a limited experience, we have found a higher rate of failure in wide QRS correction in patients with septal substrate, evidenced by both magnetic resonance imaging[43] and local electrogram characteristics (Figure 3). Moreover, LBBAP may not be suited for patients with right bundle branch block patterns and indication for CRT as RV activation may be persistently delayed.

Lastly, the impact of intraseptal fixation to achieve "deep" septal pacing, with or without LCS, on lead extraction is completely unknown at the present time. As the depth of penetration is relatively superficial with HBP, it would be expected that intramyocardial endothelialization may present a greater degree of difficulty during extraction. Additionally, penetration of the lead into and beyond the LV subendocardium may theoretically expose the lead tip to the blood pool and increase thrombogenicity (as seen with endocardial pacing in the LV).

Pacing at the His bundle, which is anatomically ensheathed in the central fibrous body of the heart, is distinct from simple myocardial capture and often demands greater pacing output. Acknowledgment of the current limitations with HBP is appropriate but reflect limitations that are commonplace in the early evolution of a new technology and are inherent to the anatomy of this specific target. Indeed, early replacement of pulse generators may offset the benefits of this pacing modality in the current state. However, we remain optimistic that investments in improved engineering of delivery sheaths and leads with increased battery capacity may mitigate these limitations in the quest for perfect physiological resynchronization.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2020.03.001.

References

1. Durrer D, van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. Circulation 1970;41:899–912.
2. Keene D, Arnold AD, Jastrzebski M, et al. His bundle pacing, learning curve, procedure characteristics, safety, and feasibility: insights from a large international observational study. J Cardiovasc Electrophysiol 2019;30:1984–1993.
3. Kim J, Goldbarg S, Leung S, Yang H, Slotwiner D. Increased threshold in nonselective His-bundle pacing suspected to be caused by amiodarone. HeartRhythm Case Rep 2019;5:112–114.
4. Huang W, Su L, Wu S, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. Can J Cardiol 2017;33:1736 e1731–1736 e1733.
5. Zhang S, Zhou X, Gold MR. Left bundle branch pacing: JACC review topic of the week. J Am Coll Cardiol 2019;74:3039–3049.
6. Li X, Li H, Ma W, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. Heart Rhythm 2019; 16:1766–1773.
7. Li Y, Chen K, Dai Y, et al. Left bundle branch pacing for symptomatic bradycardia: implant success rate, safety, and pacing characteristics. Heart Rhythm 2019;16:1758–1765.
8. Qian Z, Hou X, Wang Y, et al. Physiological left bundle branch pacing validated by ultra-high density ventricular mapping in a swine model. Circ Arrhythm Electrophysiol 2020;13:e007898.
9. Zanon F, Ellenbogen KA, Dandamudi G, et al. Permanent His-bundle pacing: a systematic literature review and meta-analysis. Europace 2018;20:1819–1826.
10. Abdelrahman M, Subzposh FA, Beer D, et al. Clinical outcomes of His bundle pacing compared to right ventricular pacing. J Am Coll Cardiol 2018; 71:2319–2330.
11. Zanon F, Abdelrahman M, Marcantoni L, et al. Long term performance and safety of His bundle pacing: a multicenter experience. J Cardiovasc Electrophysiol 2019; 30:1594–1601.
12. Vijayaraman P, Naperkowski A, Subzposh FA, et al. Permanent His-bundle pacing: long-term lead performance and clinical outcomes. Heart Rhythm 2018; 15:696–702.
13. Hou X, Qian Z, Wang Y, et al. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. Europace 2019; 21:1694–1702.
14. Vijayaraman P, Subzposh FA, Naperkowski A, et al. Prospective evaluation of feasibility and electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. Heart Rhythm 2019;16:1774–1782.
15. Ajijola OA, Upadhyay GA, Macias C, Shivkumar K, Tung R. Permanent His-bundle pacing for cardiac resynchronization therapy: initial feasibility study in lieu of left ventricular lead. Heart Rhythm 2017;14:1353–1361.
16. Vijayaraman P, Dandamudi G, Zanon F, et al. Permanent His bundle pacing: recommendations from a Multicenter His Bundle Pacing Collaborative Working Group for standardization of definitions, implant measurements, and follow-up. Heart Rhythm 2018;15:460–468.
17. Zhang J, Guo J, Hou X, et al. Comparison of the effects of selective and non-selective His bundle pacing on cardiac electrical and mechanical synchrony. Europace 2018;20:1010–1017.
18. Curila K, Prochazkova R, Jurak P, et al. Both selective and nonselective His bundle, but not myocardial, pacing preserve ventricular electrical synchrony assessed by ultra-high-frequency ECG. Heart Rhythm 2019. pii S1547-5271(19) 31028-8.
19. Beer D, Sharma PS, Subzposh FA, et al. Clinical outcomes of selective versus nonselective His bundle pacing. JACC Clin Electrophysiol 2019;5:766–774.
20. Morina-Vazquez P, Barba-Pichardo R, Venegas-Gamero J, Herrera-Carranza M. Cardiac resynchronization through selective His bundle pacing in a patient with the so-called infraHis atrioventricular block. Pacing Clin Electrophysiol 2005; 28:726–729.
21. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. Circulation 2000;101:869–877.
22. Barba-Pichardo R, Manovel Sanchez A, Fernandez-Gomez JM, Morina-Vazquez P, Venegas-Gamero J, Herrera-Carranza M. Ventricular resynchronization therapy by direct His-bundle pacing using an internal cardioverter defibrillator. Europace 2013;15:83–88.
23. Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, et al. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. Heart Rhythm 2015;12:1548–1557.
24. Vijayaraman P, Subzposh FA, Naperkowski A. Atrioventricular node ablation and His bundle pacing. Europace 2017;19(Suppl_4):iv10–iv16.
25. Huang W, Su L, Wu S, et al. Benefits of permanent His bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. J Am Heart Assoc 2017;6:e005309.
26. Sharma PS, Dandamudi G, Herweg B, et al. Permanent His-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. Heart Rhythm 2018;15:413–420.
27. Shan P, Su L, Zhou X, et al. Beneficial effects of upgrading to His bundle pacing in chronically paced patients with left ventricular ejection fraction <50. Heart Rhythm 2018;15:405–412.
28. Ye Y, Zhang Z, Sheng X, et al. Upgrade to his bundle pacing in pacing-dependent patients referred for pulse generator change: feasibility and intermediate term follow up. Int J Cardiol 2018;260:88–92.
29. Sharma PS, Naperkowski A, Bauch TD, et al. Permanent His bundle pacing for cardiac resynchronization therapy in patients with heart failure and right bundle branch block. Circ Arrhythm Electrophysiol 2018;11:e006613.
30. Huang W, Su L, Wu S, et al. Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block. Heart 2019;105:137–143.
31. Vijayaraman P, Herweg B, Ellenbogen KA, Gajek J. His-optimized cardiac resynchronization therapy to maximize electrical resynchronization. Circ Arrhythm Electrophysiol 2019;12:e006934.
32. Morina-Vazquez P, Moraleda-Salas MT, Manovel-Sanchez AJ, et al. Early improvement of left ventricular ejection fraction by cardiac resynchronization through His bundle pacing in patients with heart failure. Europace 2020;22:125–132.
33. Upadhyay GA, Vijayaraman P, Nayak HM, et al. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. J Am Coll Cardiol 2019;74:157–159.
34. Upadhyay GA, Vijayaraman P, Nayak HM, et al. On-treatment comparison between corrective His bundle pacing and biventricular pacing for cardiac resynchronization: a secondary analysis of the His-SYNC Pilot Trial. Heart Rhythm 2019; 16:1797–1807.
35. Zhang W, Huang J, Qi Y, et al. Cardiac resynchronization therapy by left bundle branch area pacing in patients with heart failure and left bundle branch block. Heart Rhythm 2019;16:1783–1790.
36. Zhang J, Wang Z, Cheng L, et al. Immediate clinical outcomes of left bundle branch area pacing vs conventional right ventricular pacing. Clin Cardiol 2019; 42:768–773.
37. Mafi-Rad M, Luermans JG, Blaauw Y, et al. Feasibility and acute hemodynamic effect of left ventricular septal pacing by transvenous approach through the interventricular septum. Circ Arrhythm Electrophysiol 2016; 9:e003344.
38. Chen K, Li Y, Dai Y, et al. Comparison of electrocardiogram characteristics and pacing parameters between left bundle branch pacing and right ventricular pacing in patients receiving pacemaker therapy. Europace 2019;21:673–680.
39. Chen X, Wu S, Su L, Su Y, Huang W. The characteristics of the electrocardiogram and the intracardiac electrogram in left bundle branch pacing. J Cardiovasc Electrophysiol 2019;30:1096–1101.
40. Gao MY, Tian Y, Shi L, et al. Electrocardiographic morphology during left bundle branch area pacing: characteristics, underlying mechanisms, and clinical implications. Pacing Clin Electrophysiol 2020; https://doi.org/10.1111/pace.13884.
41. Salden F, Luermans J, Westra SW, et al. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. J Am Coll Cardiol 2020;75:347–359.

42. Vijayaraman P, Nayak HM, Ellenbogen KA. Left ventricular septal versus left bundle branch pacing: a new beginning in cardiac resynchronization therapy? J Am Coll Cardiol 2020;75:360–362.
43. Kannan A, Jameria Z, Chen A, et al. MRI predictors of nonresponse to corrective his bundle pacing in patients with left bundle branch block. Paper presented at Physiology of Pacing Symposium, Chicago, Illinois, November 1, 2019.
44. Deshmukh PM, Romanyshyn M. Direct His-bundle pacing: present and future. Pacing Clin Electrophysiol 2004;27(6 Pt 2):862–870.
45. Occhetta E, Bortnik M, Magnani A, et al. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. J Am Coll Cardiol 2006;47:1938–1945.
46. Kronborg MB, Mortensen PT, Poulsen SH, Gerdes JC, Jensen HK, Nielsen JC. His or para-His pacing preserves left ventricular function in atrioventricular block: a double-blind, randomized, crossover study. Europace 2014;16:1189–1196.
47. Vijayaraman P, Naperkowski A, Ellenbogen KA, Dandamudi G. Electrophysiologic insights into site of atrioventricular block: lessons from permanent His bundle pacing. JACC Clin Electrophysiol 2015;1:571–581.
48. Vijayaraman P, Dandamudi G, Lustgarten D, Ellenbogen KA. Permanent His bundle pacing: electrophysiological and echocardiographic observations from long-term follow-up. Pacing Clin Electrophysiol 2017;40:883–891.
49. Sarkar R, Kaur D, Subramanian M, et al. Permanent His bundle pacing feasibility in routine clinical practice: experience from an Indian center. Indian Heart J 2019;71:360–363.
50. Boczar K, Slawuta A, Zabek A, et al. Cardiac resynchronization therapy with His bundle pacing. Pacing Clin Electrophysiol 2019;42:374–380.
51. Wang S, Wu S, Xu L, et al. Feasibility and efficacy of His bundle pacing or left bundle pacing combined with atrioventricular node ablation in patients with persistent atrial fibrillation and implantable cardioverter-defibrillator therapy. J Am Heart Assoc 2019;8:e014253.