Physiology of Left Ventricular Septal Pacing and Left Bundle Branch Pacing

Jesse Rijks, MD[a], Justin Luermans, MD, PhD[a,b], Luuk Heckman, MD[c], Antonius M.W. van Stipdonk, MD, PhD[a], Frits Prinzen, PhD[c], Joost Lumens, PhD[d], Kevin Vernooy, MD, PhD[a,b,*]

KEYWORDS

• Left ventricular septal pacing • Left bundle branch pacing • Bradycardia pacing
• Cardiac resynchronization therapy • Physiologic pacing

KEY POINTS

- Electrical activation of the left ventricle starts in the left bundle branch followed by three endocardial areas at the left side of the interventricular septum.
- Right ventricular pacing is associated with adverse effects such as heart failure and atrial fibrillation.
- Left ventricular septal pacing results in (near) physiologic activation of the left ventricle and shows promising results in cardiac resynchronization therapy.
- Left bundle branch pacing proves to maintain or restore (in LBBB) left ventricular electrical and mechanical synchrony with promising results in cardiac resynchronization therapy.
- Implantation techniques for LVSP and LBBP are similar, although more advanced electrophysiological knowledge and equipment is needed to verify left bundle branch capture.
- Theoretically left bundle branch pacing leads to a more synchronous activation of the left ventricle due to capture of the specialized conduction system.

INTRODUCTION

For decades in cardiac pacing, the right ventricular (RV) apex has been the preferred site for ventricular stimulation.[1] The RV apex has proved to be an easily accessible and stable site for lead fixation. However, RV pacing (RVP) causes electrical and mechanical dyssynchrony of the heart, frequently leading to a reduced systolic left ventricular function.[2,3] This, so-called, pacing-induced cardiomyopathy has been associated with an increased risk for heart failure (HF) hospitalization, atrial fibrillation (AF), and cardiovascular death.[4,5] Following the recognition of these adverse effects of RVP, new pacing strategies to maintain or restore interventricular and intraventricular synchrony have been developed. These techniques include biventricular pacing (BVP) and His bundle pacing (HBP). BVP is applied by implantation of 2 ventricular pacing leads. One lead is positioned in the RV, and the other lead is placed on the left ventricular free wall via the coronary sinus. Simultaneous stimulation of the leads aims to restore the ventricular electrical synchrony. Despite the more

[a] Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre (MUMC+), the Netherlands; [b] Department of Cardiology, Radboud University Medical Centre (RadboudUMC), Nijmegen, the Netherlands; [c] Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, the Netherlands; [d] Department of Biomedical Engineering, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, the Netherlands
* Corresponding author. Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, PO BOX 5800, Maastricht 6202 AZ, the Netherlands.
E-mail address: Kevin.vernooy@mumc.nl

Card Electrophysiol Clin 14 (2022) 181–189
https://doi.org/10.1016/j.ccep.2021.12.010

synchronous electrical activation, biventricular pacing still results in a nonphysiologic activation.

The most physiologic form of pacing is provided by HBP, as there is complete recruitment of the conduction system to both ventricles. HBP remains challenging due to several factors. First, implantation is challenging with a narrow anatomic target zone, resulting in moderate success rates varying from 81% to 87% after ~40 procedures.[6,7] Furthermore, HBP has been associated with high pacing thresholds and low R wave amplitudes, possibly resulting in atrial oversensing and ventricular undersensing.[8] Another downside of HBP is the possible failure of recruitment of conduction in distal conduction disorders.[7,9] More recently, left ventricular septal pacing (LVSP) and left bundle branch pacing (LBBP) were introduced.

In this review the authors elaborate on the physiology and potential beneficial effects of LVSP and LBBP.

PHYSIOLOGIC ACTIVATION OF THE LEFT VENTRICLE

Electrical Activation

In 1970, Durrer and colleagues[10] described the physiologic electrical activation of the left ventricle in 7 isolated human hearts. During sinus rhythm (SR) with normal ventricular activation through the His-Purkinje system, the activation of the left ventricle starts in the left bundle branch(LBB). The investigators found that, subsequently, 3 endocardial areas are activated first. These areas are located high on the anterior paraseptal wall just below the attachment of the mitral valve, central on the left-sided surface of the interventricular septum (IVS), and on the posterior paraseptal wall about one-third of the distance from apex to base.[10]

In the IVS electrical activation starts on the left septal surface in the middle third part anteriorly and at the lower third part at the junction of septum and posterior wall.[10] The activation then proceeds from the left to the right septum and in apico-basal direction.[10]

It has been demonstrated that endocardial conduction is much faster than endocardium-to-epicardium conduction.[11] One of the reasons for this difference in conduction speed is the more uniform geometric alignment of myocardial fibers in the subendocardium when compared with the epicardium[11]; this facilitates a preferential flow current and more rapid conduction parallel to the aligned myocardial fibers in the endocardium.[12] Another study showed that myocardial fiber arrangement rotates between endocardial and epicardial surfaces,[13] possibly contributing to a nonaligned area slowing endocardium-to-epicardium conduction. Furthermore, most of the endocardium contains a layer of Purkinje tissue, electrically parallel with the myocardium, contributing to the faster spreading of the endocardial activation front.[14]

Mechanical Activation

The electrical activation or action potential triggers calcium influx, which initiates calcium-induced calcium release. This released calcium binds to the myofibrils, resulting in contraction of the cardiac muscle cells.[15] Various studies in canine hearts showed the close relation between electrical activation and subsequent mechanical activation.[16–18] This tight coupling in a normal synchronous activated left ventricle leads to a synchronous LV contraction.[19]

ADVERSE EFFECTS OF RIGHT VENTRICULAR PACING

Pathophysiology of Right Ventricular Pacing

Different ventricular activation sequences, induced by artificial electrical stimulation (pacing), have been described to influence cardiac pump function.[20] In RVP, electrical activation mainly depends on slow conduction through the myocardial cells (from the right side of the IVS to left side of the IVS and subsequently the left ventricle) instead of using the fast-conducting Purkinje fibers, leading to a dyssynchronous electrical activation. This dyssynchronous activation can lead to a depressed systolic and diastolic LV function.[3] However, the overall dyssynchronous activation does not fully explain the occurrence of pacing-induced LV dysfunction, as total ventricular activation time on the surface electrocardiogram (ECG) (QRS duration) correlates poorly to the occurrence of LV dysfunction.[3] When focusing on electromechanical coupling in RVP, it has been shown that not only the shift of activation in time contributes to a depression of LV function. Strain imaging, used to display electromechanical coupling in RVP, shows a completely different morphology of shortening patterns, indicating discoordination of contraction. This discoordination is characterized by early systolic shortening in early activated regions and systolic prestretch in late-activated regions. Later in systole the opposite phenomenon is observed. Late-activated regions show pronounced shortening, whereas early activated regions may be stretched.[21–23] In considerable dyssynchrony, for instance in RVP, this results in the external work (calculated as the area of the fiber stress-fiber length loop) in early activated regions to be close to zero or even negative and

double the normal values in late activated regions, leading to an inefficient contraction.[23]

Clinical Outcomes of Right Ventricular Pacing

The possible adverse effects of RVP first became clinically apparent in patients in the Mode Selection (MOST) trial, a randomized trial comparing DDD pacing versus VVI pacing in patients with a pacing indication due to bradycardia. In 1339 patients with narrow QRS and preserved LV ejection fraction at baseline, it was shown that the percentage of ventricular pacing is a strong predictor for development of AF and HF hospitalization.[4] Later, the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial showed similar results. Patients with an indication for ICD implantation and reduced LV ejection fraction, but without bradycardia, were randomized to dual chamber pacing (DDDR-70) and ventricular back-up pacing (VVI-40). The ventricular pacing percentage was markedly higher in the dual-chamber pacing group compared with the ventricular back-up pacing group, 60% versus 1%, respectively. Dual-chamber pacing showed no clinical benefit over ventricular back-up pacing and even showed a worse outcome regarding the composite end point of death and HF hospitalization.[5] The fact that not every individual treated with RVP will develop pacing-induced cardiomyopathy indicates that more factors contribute to this. It is shown that the presence of structural heart disease, that is, hypertrophy and diastolic dysfunction, contribute to prolonged paced QRS duration and therefore electrical dyssynchrony, independent of the pacing site (RV apex vs RV outflow tract).[24] Furthermore, a lower preimplantation LV ejection fraction, higher ventricular pacing rates, and second- or third-degree atrioventricular block as indication for pacing are associated with higher percentages of pacing-induced cardiomyopathy.[25]

LEFT VENTRICULAR SEPTAL PACING

Acute Effects of Left Ventricular Septal Pacing

After the recognition of the potential adverse effects of RVP, the search for more physiologic forms of pacing gained interest. As described in the first paragraph, during normal SR with normal ventricular activation through the His-Purkinje system, the electrical impulse first exits the Purkinje system at sites on the LV endocardial surface of the IVS. It was therefore hypothesized that pacing near these exit sites will result in a more physiologic activation of the LV. In a canine experiment in 1982, Little and colleagues[26] showed that pacing on the left side of the IVS resulted in the following similar findings as during SR: the IVS was activated from left to right, preejection LV pressure exceeded RV pressure, and IVS motion was the same in LVSP and normal SR.[26] Moreover, invasively measured LV stroke volume and contractility (expressed by LV dP/dTmax) were found to be better during LVSP when compared with RVP in a study in 7 anesthetized open-chest dogs with healthy hearts, despite longer QRS duration in LVSP as compared with RVP[27]; this supports the earlier hypothesis that LV function is dependent not only on QRS duration but more importantly on the sequence of activation.

A subsequent study, comparing different sites of LV pacing, RVP, and normal SR in anesthetized, open-chest dogs, showed that LV function measured in terms of LV dP/dT max and LV stroke work (calculated as the loop area in the pressure-volume loop) was indeed maintained during LVSP to a level comparable with normal SR (**Fig. 1**).[28]

Long-Term Effects of Left Ventricular Septal pacing

The aforementioned studies showed the beneficial acute hemodynamic effects of LVSP but did not

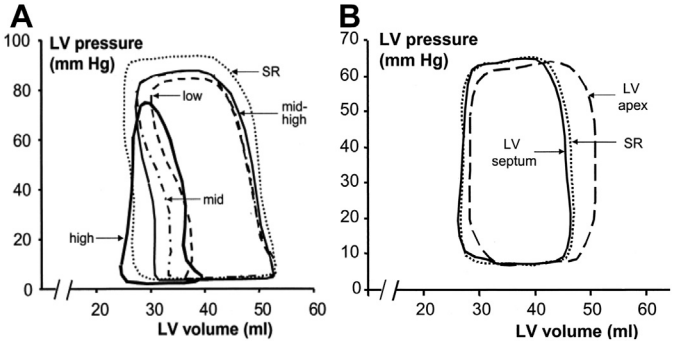

Fig. 1. (*A*) Pressure volume loops during sinus rhythm (SR) with normal intrinsic ventricular activation and during pacing at the low, mid, mid-high, and high right ventricular (RV) septum. Note that the loop area in the RV-paced loops is smaller than during SR, indicating lower LV stroke work. (*B*) Pressure volume loops during SR and during pacing the left ventricular septum (LVSP) and left ventricular apex. Note that the pressure volume loop during LVSP is comparable with SR. (*Modified from* Peschar M, de Swart H, Michels KJ, Reneman RS, Prinzen FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. J Am Coll Cardiol. 2003;41(7):1218-1226. https://doi.org/10.1016/s0735-1097(0300091-3; with permission.)

investigate the long-term effects of LVSP. The longer term effects of LVSP were studied in canine hearts after 16 weeks of pacing and were compared with RVP and normal SR.[29] First, it was demonstrated that LVSP led to a rapid activation of the LV endocardium, resulting in a pattern that, of all tested pacing sites, most closely resembled the pattern during normal SR, albeit that the RV free wall was slightly delayed. MRI tagging was used to determine strain patterns. During 16 weeks of RVP, circumferential strain was significantly lower in the IVS and higher in the LV free wall. Furthermore, dP/dTmax was significantly lower during RVP compared with baseline, both at implantation and after 16 weeks of pacing. Such differences were not observed during LVSP. The contraction pattern in LVSP was very similar to normal SR. The pattern for regional time to peak shortening (time to peak shortening [ms] of the septal, anterior, lateral, and posterior segments relative to the earliest activated region) were identical for LVSP and normal SR. Besides this, external efficiency (ratio of stroke work, calculated as the loop area in the pressure-volume loop, and oxygen consumption) was decreased by 30% to 40% during RVP, when compared with normal SR, whereas there was no decrease in efficiency during LVSP.[29]

Left Ventricular Septal Pacing in the Human Heart

After preclinical studies successfully demonstrated the advantages of LVSP over RVP and even showed that electrical and mechanical activation and their subsequent hemodynamic effects were comparable with normal SR, clinical studies were needed. The first study of LVSP in patients was conducted in 10 patients with structurally normal hearts with mainly a pacing indication because of sick sinus syndrome.[30] Acute hemodynamic measurements showed that in LVSP values of LV dP/dtmax were maintained to levels comparable with baseline atrial pacing with normal ventricular conduction.[30] Furthermore, the acute hemodynamic benefits of LVSP over RVP were consistently observed in all patients. Not only were favorable hemodynamic effects observed, but QRS duration was shorter during LVSP (144 ms $\pm$ 20 ms) than during RV septal pacing (165 ms $\pm$ 17 ms).[30] This large difference in QRS duration and the differences in hemodynamic effect between LVSP and RV septal pacing, although pacing sites are only $\sim$1 cm apart, might be due to a significant delay in transseptal conduction during RV septal pacing. This causes delayed LV electrical and mechanical activation with even more pronounced delayed contraction of the LV lateral wall, causing both interventricular and intraventricular dyssynchrony.[31] On the other hand, it is imaginable that LVSP causes significant delay in RV electrical and mechanical activation, inducing interventricular dyssynchrony. Although LVSP maintains physiologic septal and LV activation, a delayed electrical activation of the right RV free wall is observed in LVSP. Data on the hemodynamic effects of delayed RV activation during LVSP are not available yet.

Left Ventricular Septal Pacing in Cardiac Resynchronization Therapy

Subsequently to showing that LVSP leads to an electrical and mechanical activation of the left ventricle comparable with normal SR, LVSP was explored as alternative pacing strategy for cardiac resynchronization therapy (CRT) for dyssynchronous HF.

In patients with HF induced by LBBB it makes sense to create the most physiologic sequence of activation by pacing at the earliest activated site in the left ventricle with fast endocardial spread of activation. Also, in LBBB the use of the LVSP site seems favorable because a considerable part of the total dyssynchrony in LBBB originates from the delay in conduction across the IVS.[32] Rademakers and colleagues[33] explored LVSP in CRT in both ischemic and nonischemic canine LBBB hearts. LVSP, in combination with RVP, resulted in electrical (measured as QRS duration and total activation time) and acute hemodynamic (measured as LVdP/dT max and stroke work) benefits similar to conventional BVP (generally applied as CRT pacing strategy), when compared with baseline LBBB.[33] An acute hemodynamic pacing study, comparing LVSP with BVP in 12 patients with HF with an indication for CRT, confirmed these results.[33] More recently, an extensive acute electrical and hemodynamic study was performed, comparing LBBB with LVSP, LVSP in combination with RVP (LVSP + RVP), BVP, and HBP, in patients undergoing CRT implantation. QRS duration, QRS area determined by vectorcardiography, and standard deviation of activation time (SDAT) obtained with the ECG belt were measured as indicators of electrical dyssynchrony. LV function was determined by measuring the LV dP/dT max. LVSP resulted in a larger reduction in electrical dyssynchrony than BVP and LVSP + RVP compared with baseline AAI pacing with LBBB, while being similar to HBP. Regarding LV function, improvement in LV dP/dtmax was similar in LVSP, BVP, and HBP with an increase of $\sim$17% compared with baseline

LBBB (Fig. 2).[34] These results indicate that LVSP provides short-term hemodynamic improvement and electrical resynchronization comparable with BVP and even HBP in patients undergoing CRT.

LEFT BUNDLE BRANCH PACING

In normal ventricular conduction via the His-Purkinje system, electrical activation of the endocardium on the left-sided IVS is preceded by activation of the His bundle and subsequently the LBB.

Pacing the LBB has recently been introduced as an alternative method of physiologic pacing to maintain left ventricular synchrony.[35] The LBB arises from the branching portion of the His bundle. The proximal left bundle spreads out beneath the LV subendocardium, forming a wider target for pacing when compared with the narrow His bundle.[7] Zhang and colleagues[36] analyzed ECG parameters in 23 consecutive patients undergoing LBBP. At baseline QRS duration in the LBBP group was 130 ms ± 43.3 ms, whereas after LBBP implantation QRS duration shortened to 112 ms ± 12 ms. Echocardiographic strain imaging in LBBP showed similar global longitudinal strain rates when compared with baseline normal SR.[37] When comparing mechanical synchrony between LBBP and conventional RVP using 2-dimensional echocardiographic strain imaging, there was a significantly shorter maximal time difference to peak strain in LBBP (66 ms in LBBP vs 149 ms in RVP),[38] indicating a more synchronous left ventricular activation in LBBP. Another study evaluated BNP and diastolic echocardiographic parameters measured before and 7 days after permanent LBBP or RVP.[39] BNP levels were significantly lower in the LBBP group compared with RVP. Peak E-wave velocity and E/e' decreased and e' increased significantly after 7 days compared with preimplantation in the LBBP group, whereas there were no significant changes in the RVP group.[39]

When comparing LBBP with HBP, looking at mechanical synchrony using phase analysis of single-photon emission computed tomography myocardial perfusion imaging, no differences regarding left ventricular mechanical synchrony between LBBP and HBP were found in 56 pacemaker-indicated patients with normal cardiac function.[40]

Left Bundle Branch Pacing in Cardiac Resynchronization Therapy

LBBP has also been performed in CRT candidates as an alternative for BVP. LBBP showed a significant shortening of QRS duration from 168 ms ± 38 ms to 119 ms ± 12 ms, when compared with baseline LBBB.[36]

The positive effects of LBBP in LBBB are probably due to pacing beyond the site of conduction block in the left bundle.[37] The correction of LBBB during LBBP indicates its usefulness in CRT. Huang and colleagues[41] performed LBBP in 63 patients with nonischemic cardiomyopathy,

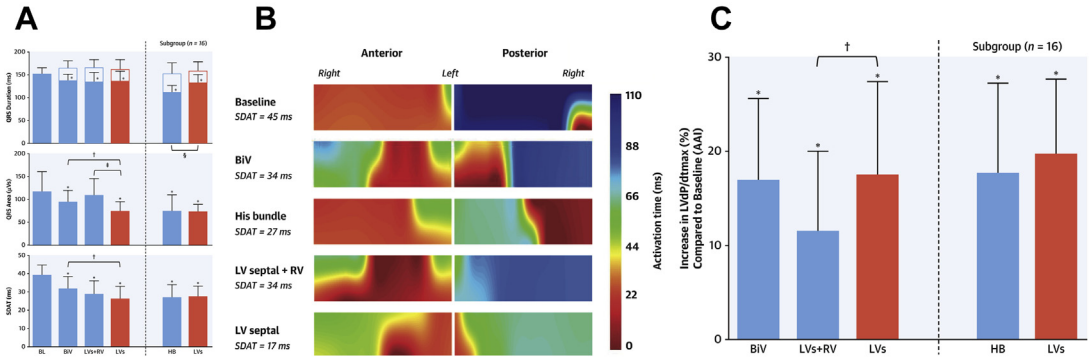

Fig. 2. (*A*) QRS duration as time between onset QRS to end QRS (*closed bars*) and as time between pacing stimulus to end QRS (*open bars*) (*upper panel*), QRS area determined by vectorcardiography (*middle panel*) and SDAT obtained with ECG belt (lower panel), during baseline LBBB(BL), biventricular pacing (BiV), LVSP + RVP, LVSP alone, and during HBP and LVSP. Results are presented as mean ± SD. **P* < .05 versus BL; †*P* < .05 BVP versus LVSP; ‡*P* < .05 LVSP + RV versus LVSP; §*P* < .05 HB versus LVSP. (*B*) Isochronal maps together with corresponding SDAT during baseline LBBB, BVP, HBP, LVSP + RVP, and LVSP alone. (*C*) Acute hemodynamic effects measured as percentual increase in LV dP/dtmax compared with baseline LBBB during BVP, LVSP + RVP, and LVSP alone and in a subgroup during HBP and LVSP. Results are presented as mean ± SD. **P* < .05 versus BL; †*P* < .05 LVSP + RV versus LVSP. (*Modified from* Salden FCWM, Luermans JGLM, Westra SW, et al. Short-Term Hemodynamic and Electrophysiological Effects of Cardiac Resynchronization by Left Ventricular Septal Pacing. J Am Coll Cardiol. 2020;75(4):347-359. https://doi.org/10.1016/j.jacc.2019.11.040; with permission)

LBBB, and an indication for CRT. There was significant shortening of QRS duration and within 75% of included patients improvement of LVEF greater than 50% at 1-year follow-up.[41] A large retrospective multicenter study regarding LBBP in CRT showed clinical response (improvement in NYHA class $\geq$1 without HF hospitalization) and echocardiographic response ($\geq$5% improvement in LVEF) in 72% and 73% of patients, respectively.[42]

LEFT VENTRICULAR SEPTAL PACING OR LEFT BUNDLE BRANCH PACING?

Although implantation techniques do not differ that much, in LBBP (as opposed to LVSP) more advanced electrophysiological knowledge and equipment is needed to verify LBB capture. Recording of a 12-lead ECG for assessment of QRS morphology and measurement of left ventricular activation time (LVAT), measured from the pacing spike to the peak of the R wave in lead V5 or V6, is usually performed. Furthermore, intracardiac electrograms from the tip of the lead are used for searching the His potential as a reference point and recording of the LBB potential to identify the LBB region. Moreover, electrophysiological knowledge on the response of ventricular pacing maneuvers is helpful to confirm LBB capture.[7] The LVSP implantation method is more straightforward, as it is not necessary to identify LBB capture. The paced QRS morphology, visible on 12-lead ECG, is used to validate the right position on the right side of the IVS. Advancement of the lead through the IVS is monitored by QRS morphology, either via continuous pacing[43] or via evaluating fixation beats (ectopic ventricular beats caused by lead fixation).[44] A qR morphology in V1 indicates deep left-sided septal deployment. Deep septal deployment can also be evaluated by septal contrast angiography. **Fig. 3** shows the location of the left ventricular septal lead in LVSP and LBBP.

The difference between LVSP and LBBP is capture of the LBB in LBBP and only myocardial capture in LVSP. In LBBP, theoretically a more synchronous electrical activation of the left ventricle is obtained by capturing the specialized conduction system.[45] While attempting LBBP, actual LBB capture rates differ in literature, with capture rates varying from 60% to 90%[46–48]; this means that a considerable amount of patients intendedly being treated with LBBP are in fact treated with LVSP. A recent study compares LV electrical synchrony between LBBP and LVSP by determining QRS area and LVAT (both markers of electrical synchrony).[46] LBB capture was defined by the presence of (1) paced (pseudo) RBBB morphology, (2) recording of an LBB potential during intrinsic rhythm, (3) constant left ventricular activation time during high- and low-output pacing, and (4) demonstration of transition from nonselective LBBP to selective LBBP or nonselective LBBP to LVSP. The study showed that, compared with conventional RV pacing, the largest reduction in QRS area and LVAT are achieved at the first steps penetrating the IVS and that a reasonably acceptable level of ventricular synchrony is achieved when an R′ becomes apparent in lead V1 (evidence of pacing at the

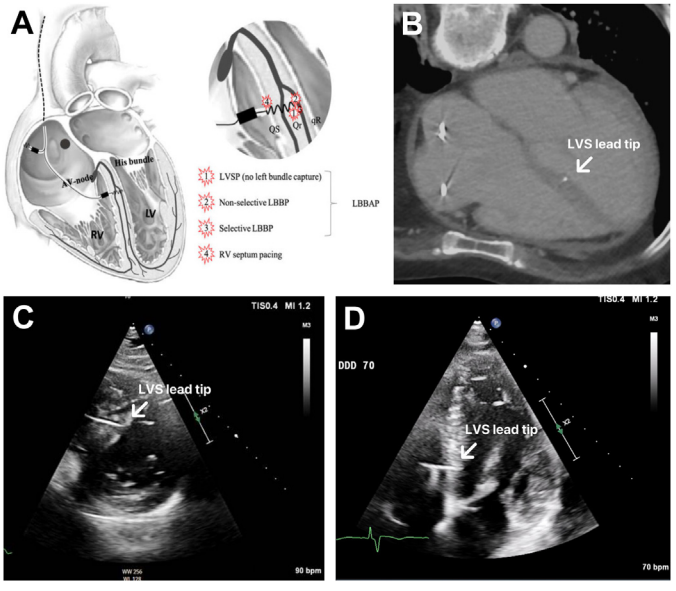

Fig. 3. Location of the LVSP/LBBP lead. (A)The heart and conduction system. It is illustrated where the lead is positioned in the interventricular septum. The different definitions of capture are shown and which QRS morphologies are typically seen. (*B*) Cardiac CT image showing the LVSP/LBBP lead tip deployed deep in the interventricular septum (IVS). (*C*) Parasternal short axis transthoracic echo (TTE) view showing the LVSP/LBBP lead tip in the IVS. (*D*) Apical 4 chamber TTE view showing the LVSP/LBBP lead tip in the IVS. (*Panel A modified from* Heckman LIB, Luermans JGLM, Curila K, Van Stipdonk AMW, Westra S, Smisek R, Prinzen FW, Vernooy K. Comparing Ventricular Synchrony in Left Bundle Branch and Left Ventricular Septal Pacing in Pacemaker Patients. Journal of Clinical Medicine. 2021; 10(4):822. https://doi.org/10.3390/jcm10040822.)

left side of the IVS).[46] Comparing LVSP and LBBP using ultrahigh-frequency ECG indicates that although LV lateral wall depolarization is accelerated in LBBP compared with LVSP, LBBP results in greater interventricular dyssynchrony, because the RV is activated relatively later.[45] This difference in interventricular synchrony is most likely due to immediate left-to-right transseptal depolarization in LVSP and delayed left-to-right transseptal depolarization in (selective) LBBP, resulting in a more balanced ventricular depolarization in LVSP, compared with (selective) LBBP.[45,49] Most of the aforementioned studies focus on the acute or short-term effect of LVSP and LBBP. Data on long-term effects are lacking and needed. Furthermore, the differences and similarities between LVSP and LBBP need to be explored beyond the current knowledge.

SUMMARY

LVSP and LBBP are emerging forms of ventricular pacing, due to their more physiologic pattern of electrical activation of the left ventricle and probably better feasibility than HBP. Both animal and patient studies have demonstrated their (near) physiologic electrical and mechanical activation of the left ventricle. Although data in large randomized trials regarding long-term effects are lacking, these new pacing strategies form a promising alternative to conventional RVP in bradycardia pacing. Studies regarding CRT show promising results for both LVSP and LBBP.

CLINICS CARE POINTS

- LVSP and LBBP result in (near) physiologic electrical and mechanical activation of the left ventricle.
- Studies regarding CRT show promising results for both LVSP and LBBP.
- More studies regarding long-term effects of LVSP and LBBP are needed.
- More studies comparing LVSP and LBBP are needed to further evaluate and compare both pacing strategies.

CONFLICT OF INTEREST

F. Prinzen: research grants from Medtronic, Abbott, MicroPort CRM, and Biotronik. K. Vernooy: consultancy agreement with Medtronic, Abbott, and Philips. J. Luermans: Consultancy agreement with Medtronic.

REFERENCES

1. Burri H, Starck C, Auricchio A, et al. EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and implantable cardioverter-defibrillators: endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin-American Heart Rhythm Society (LAHRS). Europace 2021;23(7):983–1008.
2. Nielsen JC, Kristensen L, Andersen HR, et al. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 2003;42(4):614–23.
3. Prinzen FW, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. Pacing Clin Electrophysiol 2002;25(4 Pt 1):484–98.
4. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107(23):2932–7.
5. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288(24):3115–23.
6. 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(10):1984–93.
7. Ponnusamy SS, Arora V, Namboodiri N, et al. Left bundle branch pacing: a comprehensive review. J Cardiovasc Electrophysiol 2020;31(9):2462–73.
8. Vijayaraman P, Dandamudi G. How to perform permanent his bundle pacing: tips and tricks. Pacing Clin Electrophysiol 2016;39(12):1298–304.
9. Vijayaraman P, Naperkowski A, Ellenbogen KA, et al. Electrophysiologic Insights into site of atrioventricular block: Lessons from permanent His bundle pacing. JACC Clin Electrophysiol 2015;1(6):571–81.
10. Durrer D, van Dam RT, Freud GE, et al. Total excitation of the isolated human heart. Circulation 1970;41(6):899–912.
11. Myerburg RJ, Gelband H, Nilsson K, et al. The role of canine superficial ventricular muscle fibers in endocardial impulse distribution. Circ Res 1978;42(1):27–35.
12. Roberts DE, Hersh LT, Scher AM. Influence of cardiac fiber orientation on wavefront voltage, conduction velocity, and tissue resistivity in the dog. Circ Res 1979;44(5):701–12.

13. Streeter DD Jr, Spotnitz HM, Patel DP, et al. Fiber orientation in the canine left ventricle during diastole and systole. Circ Res 1969;24(3):339–47.
14. Spach MS, Huang SN, Ayers CR. Electrical and anatomic study of the Purkinje system of the canine heart. Am Heart J 1963;65:664–73.
15. Eisner DA, Caldwell JL, Kistamas K, et al. Calcium and excitation-contraction coupling in the heart. Circ Res 2017;121(2):181–95.
16. Prinzen FW, Augustijn CH, Allessie MA, et al. The time sequence of electrical and mechanical activation during spontaneous beating and ectopic stimulation. Eur Heart J 1992;13(4):535–43.
17. Badke FR, Boinay P, Covell JW. Effects of ventricular pacing on regional left ventricular performance in the dog. Am J Phys 1980;238(6):H858–67.
18. Wyman BT, Hunter WC, Prinzen FW, et al. Mapping propagation of mechanical activation in the paced heart with MRI tagging. Am J Phys 1999;276(3): H881–91.
19. Sengupta PP, Tondato F, Khandheria BK, et al. Electromechanical activation sequence in normal heart. Heart Failure Clin 2008;4(3):303–14.
20. CJ W. The muscular reactions of the mammalian ventricles to artificial surface stimuli. Am J Phys 1925;73:346–78.
21. Prinzen FW, Augustijn CH, Arts T, et al. Redistribution of myocardial fiber strain and blood flow by asynchronous activation. Am J Phys 1990;259(2 Pt 2):H300–8.
22. Delhaas T, Arts T, Prinzen FW, et al. Regional fibre stress-fibre strain area as an estimate of regional blood flow and oxygen demand in the canine heart. J Physiol 1994;477(Pt 3):481–96.
23. Prinzen FW, Hunter WC, Wyman BT, et al. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 1999;33(6):1735–42.
24. Ogano M, Tsuboi I, Iwasaki YK, et al. Structural heart disease, not the right ventricular pacing site, determines the QRS duration during right ventricular pacing. Heart Vessels 2021;36(12):1870–8.
25. Safak E, Ince H, Gkouvatsou L, et al. Pacing-induced cardiomyopathy in chronic right ventricular apical pacing: a midterm follow-up study. Eur J Med Res 2019;24(1):23.
26. Little WC, Reeves RC, Arciniegas J, et al. Mechanism of abnormal interventricular septal motion during delayed left ventricular activation. Circulation 1982;65(7):1486–91.
27. Prinzen FW, Van Oosterhout MF, Vanagt WY, et al. Optimization of ventricular function by improving the activation sequence during ventricular pacing. Pacing Clin Electrophysiol 1998;21(11 Pt 2):2256–60.
28. Peschar M, de Swart H, Michels KJ, et al. Left ventricular septal and apex pacing for optimal pump function in canine hearts. J Am Coll Cardiol 2003; 41(7):1218–26.
29. Mills RW, Cornelussen RN, Mulligan LJ, et al. Left ventricular septal and left ventricular apical pacing chronically maintain cardiac contractile coordination, pump function and efficiency. Circ Arrhythm Electrophysiol 2009;2(5):571–9.
30. 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(3):e003344.
31. Strik M, van Deursen CJ, van Middendorp LB, et al. Transseptal conduction as an important determinant for cardiac resynchronization therapy, as revealed by extensive electrical mapping in the dyssynchronous canine heart. Circ Arrhythm Electrophysiol 2013;6(4):682–9.
32. Prinzen FW, Auricchio A. Is echocardiographic assessment of dyssynchrony useful to select candidates for cardiac resynchronization therapy? Echocardiography is not useful before cardiac resynchronization therapy if QRS duration is available. Circ Cardiovasc Imaging 2008;1(1):70–7.
33. Rademakers LM, van Hunnik A, Kuiper M, et al. A possible role for pacing the left ventricular septum in cardiac resynchronization therapy. JACC Clin Electrophysiol 2016;2(4):413–22.
34. 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(4):347–59.
35. 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(12):1736 e1731–3.
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(8):768–73.
37. 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(12):1766–73.
38. Sun Z, Di B, Gao H, et al. Assessment of ventricular mechanical synchronization after left bundle branch pacing using 2-D speckle tracking echocardiography. Clin Cardiol 2020;43(12):1562–72.
39. Liu Q, Yang J, Bolun Z, et al. Comparison of cardiac function between left bundle branch pacing and right ventricular outflow tract septal pacing in the short-term: a registered controlled clinical trial. Int J Cardiol 2021;322:70–6.
40. 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(11):1694–702.

41. Huang W, Wu S, Vijayaraman P, et al. Cardiac resynchronization therapy in patients with Nonischemic cardiomyopathy using left bundle branch pacing. JACC Clin Electrophysiol 2020;6(7):849–58.
42. Vijayaraman P, Ponnusamy S, Cano O, et al. Left bundle branch area pacing for cardiac resynchronization therapy: results from the international LBBAP Collaborative study group. JACC Clin Electrophysiol 2021;7(2):135–47.
43. Jastrzebski M, Moskal P. Reaching the left bundle branch pacing area within 36 heartbeats. Kardiol Pol 2021;79(5):587–8.
44. Jastrzebski M, Kielbasa G, Moskal P, et al. Fixation beats - a novel marker for reaching the left bundle branch area during deep septal lead implantation. Heart Rhythm 2020;18(4):562–9.
45. Curila K, Jurak P, Jastrzebski M, et al. The left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates left ventricular lateral wall depolarization. Heart Rhythm 2021;18(8):1281–9.
46. Heckman LIB, Luermans J, Curila K, et al. Comparing ventricular synchrony in left bundle branch and left ventricular septal pacing in pacemaker patients. J Clin Med 2021;10(4).
47. Jastrzebski M, Kielbasa G, Curila K, et al. Physiology-based electrocardiographic Criteria for left bundle branch capture. Heart Rhythm 2021;18(6):935–43.
48. Heckman L, Vijayaraman P, Luermans J, et al. Novel bradycardia pacing strategies. Heart 2020;106(24):1883–9.
49. Jastrzebski M, Burri H, Kielbasa G, et al. The V6-V1 interpeak interval: a novel criterion for the diagnosis of left bundle branch capture. Europace 2021;24(1):40–7.