Left bundle branch pacing set to outshine biventricular pacing for cardiac resynchronization therapy?

Batta A, et al. Left-bundle branch pacing vs BiVP

Abstract
The deleterious effects of long-term right ventricular pacing necessitated the search for alternative pacing sites which could prevent or alleviate pacing-induced cardiomyopathy. Until recently, biventricular pacing (BiVP) was the only modality which could mitigate or prevent pacing induced dysfunction. Further, BiVP could resynchronize the baseline electromechanical desynchrony in heart failure and improve outcomes. However, the high non-response rate of around 20%-30% remains a major limitation. This non-response has been largely attributable to the direct non-physiological stimulation of the left ventricular myocardium bypassing the conduction system. To overcome this limitation, the concept of conduction system pacing (CSP) came up. Despite initial success of the first CSP via His bundle pacing (HBP), certain drawbacks including lead instability and dislodgements, steep learning curve and rapid battery depletion on many occasions prevented its widespread use for cardiac resynchronization therapy (CRT). Subsequently, CSP via left bundle branch area pacing (LBBP) was developed in 2018, which over the last few years has shown efficacy comparable to BiVP-CRT in small observational studies. Further, its safety has also been well established and is largely free of the pitfalls of the HBP-CRT. In the recent metanalysis by Yasmin et al, comprising of 6 studies with 389 participants, LBBP-CRT was superior to BiVP-CRT in
terms of QRS duration, left ventricular ejection fraction, cardiac chamber dimensions, lead thresholds, and functional status amongst heart failure patients with left bundle branch block. However, there are important limitations of the study including the small overall numbers, inclusion of only a single small randomized controlled trial (RCT) and a small follow-up duration. Further, the entire study population analyzed was from China which makes generalizability a concern. Despite the concerns, the meta-analysis adds to the growing body of evidence demonstrating the efficacy of LBBP-CRT. At this stage, one must acknowledge that the fact that still our opinions on this technique are largely based on observational data and there is a dire need for larger RCTs to ascertain the position of LBBP-CRT in management of heart failure patients with left bundle branch block.

Key Words: Biventricular pacing; Cardiac resynchronization therapy; Conduction system pacing; Left bundle branch-area pacing; Left bundle branch block; Electromechanical dssynchrony

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Core Tip: The deleterious effects of long-term right ventricular pacing necessitated the search for alternative pacing sites which could prevent or alleviate pacing-induced cardiomyopathy. Until recently, biventricular pacing (BiVP) was the only modality which could mitigate or prevent pacing-induced dysfunction. Left bundle branch-area pacing (LBBP) was developed in 2018, which over the last few years has shown efficacy comparable to BiVP-cardiac resynchronization therapy (CRT) in small observational studies. However, as of now our opinion is largely based on observational data which are inherently prone to selection biases. Hence, there is an urgent need for larger randomized controlled trials which will ascertain the role of LBBP-CRT in the future.
INTRODUCTION

The deleterious effects of long-term right ventricular pacing necessitated the search for alternative pacing sites which could prevent or alleviate pacing-induced cardiomyopathy[1]. The major breakthrough in this regard was the development of biventricular pacing (BiVP) around 3 decades ago. BiVP was initially introduced as a treatment for dyssynchronous heart failure. With time, it was realized that it could prevent or offset the pacing-induced left ventricular dysfunction which account for 25% of all dyssynchronous heart failure[2,3]. BiVP could resynchronize the baseline electromechanical dyssynchrony in heart failure with reduced ejection fraction (HFrEF) with resultant positive effects on cardiac function, functional status and overall mortality[4]. The most common method of achieving this resynchronization via BiVP involves the placement of an electrode in the epicardial posterior-basal wall of the left ventricle via the coronary sinus. Over the years this method of cardiac resynchronization therapy (CRT) has been proven to be safe and efficacious in managing selected patients with electromechanical dyssynchrony and HFrEF. However, the high non-response rate of around 20%-30% has remained a major limitation[5,6]. This non-response has been largely attributable to the direct non-physiological stimulation of the left ventricular myocardium bypassing the conduction system (His-Purkinje in myocardium) and the variation in myocardium characteristics at the left ventricular pacing site. Further there is wide variation reported in the coronary sinus anatomy and limited pacing sites constrained by the coronary sinus branches which also accounts for non-response in a large fraction of cases[7]. Another major concern which applies to all methods of achieving CRT is the fact that there is practically no objective measure that could indicate the effectiveness of the therapy acutely due to the remodelling involved and hence, there is a great need for a way to accurately determine the response and enable optimization at the time of device implantation. Certain parameters including biventricular activation times and biventricular dyssynchrony indexes have been deployed to predict post-implantation response but do not necessarily correlate with clinical outcomes on follow-up.
These limitations of the BiVP-CRT paved the way for research into the more physiological pacing sites for CRT which would allow for direct stimulation of the native conduction system. The first major development in conduction system pacing (CSP) was the use of His bundle pacing (HBP) in the year 2000 by Deshmukh et al\textsuperscript{[8]}, which showed a net incremental benefit amongst HFpEF patients who had persistent atrial fibrillation. However, major drawbacks including the lead instability and dislodgements, steep learning curve, long fluoroscopy times and early battery depletion on many occasions has prevented its widespread use for CRT\textsuperscript{[9-11]}. In 2018 Huang and colleagues demonstrated that direct pacing through the interventricular septum, close to the main trunk of left bundle branch could overcome much of the limitations of the HBP and provided stable lead parameters over the long run\textsuperscript{[12]}. Since then a few observational reports have demonstrated the benefit of this left bundle branch-area pacing (LBBP) as a means of CRT in candidates who were not eligible for BiVP-CRT\textsuperscript{[13]}. One must be aware that LBBP refers to a broader term which includes selective LBBP, non-selective LBBP and left ventricular septal pacing. Since there are only minor differences in the pacing thresholds and resynchronization achieved, these are often used interchangeably in literature\textsuperscript{[14]}. The early experience does suggest that LBBP-CRT seems to be at least as effective as BiVP-CRT with respect to cardiac hemodynamics and functions. However, the evidence at this stage is largely observational with only a single small randomized controlled trial (RCT) comparing LBBP-CRT with BiVP-CRT\textsuperscript{[15]}. Hence, there is a dire need for larger RCTs with long-term follow-up and meta-analysis of these RCTs.

**LBBP-CRT vs BiVP-CRT**

In the recent meta-analysis published by Yasmin et al\textsuperscript{[16]} published in the January issue of world journal of cardiology, comprising of 6 studies (1 RCT and 5 comparative observational studies) with 389 participants (159 in LBBP-CRT vs 230 in BiVP-CRT); LBBP-CRT was superior to BiVP-CRT in regards to improvement in left ventricular ejection fraction, cardiac chamber dimensions, lead thresholds, and functional status. Further, they demonstrated a significant reductions in brain natriuretic peptide
concentration at follow up in the LBBP-CRT group compared to BiVP-CRT. Perhaps most of the positive impacts of LBBP-CRT stem from a significantly lower QRS duration compared to BiVP-CRT which indicates a more efficient resynchronization and subsequent cardiac contraction. The result of this meta-analysis is indeed the reflection of growing evidence in support of LBBP as the preferable method of achieving CRT. Further, recent evidence even supports the cost effectiveness of CSP based CRT which can achieve satisfactory resynchronization with conventional pacemakers in patients who otherwise do not warrant defibrillation[17].

While the results seem promising, one must examine the encouraging results with due caution. Firstly, the meta-analysis largely comprised of observational data which is inherently prone to selection biases which may have concealed some of the outliers belonging to the LBBP-CRT group. Further, the single RCT included had only 40 patients and a 6 months follow-up[15]. All the studies originated in China and hence the generalizability of the results remains to be established. Further, data on long-term lead durability in the LBBP-CRT has not been established which at least theoretically remains a concern given the mechanical stress at the hinge point on interventricular septum.

The analysis could have included data from a large recent observational study by Vijayaraman et al[18] including data of 1778 patients from 15 centres around the globe. Arguably this remains the highest quality of evidence to date and does provide more evidence in support of LBBP-CRT over BiVP-CRT in HFrEF patients with electromechanical dyssynchrony. Further, they concluded that LBBP-CRT was effective either as a bailout intervention to BiVP-CRT or as a primary treatment modality. Again, despite the accumulating evidence in support of LBBP-CRT, one must acknowledge the urgent need for larger RCTs which will indeed deepen our understanding of this modality and form the basis of our practice in the future. As of now, the increasing utilization of CSP is largely based on the expert option on the observational data and our understanding of physiology behind CSP[19]. To this end, 4 large RCTs comparing the clinical outcomes following LBBP-CRT or BiVP-CRT are on the way which will go a long way in defining the role of these modalities in treatment of HFrEF (Table 1).
A document on definitions, current evidence and techniques to achieve CSP (HBP and LBBP) was recently published in a clinical consensus statement\[20\]. The current Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society guidelines on pacing gives LBBP-CRT a class 2a recommendation for preventing heart failure in patients in whom BiVP-CRT cannot be achieved. Further, a 2b recommendation was given for LBBP-CRT as an alternative to BiVP-CRT for interventionists with adequate experience with CSP\[21\].

The most recent development in the search for ideal CRT modality involves combined stimulation of the conduction system and epicardial left ventricular myocardium via the coronary sinus\[22\]. This was developed in order to correct the multiple electrical dyssynchronies that are often present in advanced heart failure patients. For this reason CSP alone may not be sufficient to resynchronize the myocardium in the presence of distal His-Purkinje disease which is better resynchronized with a coronary sinus lead which allows for recruitment of myocardial areas with late electrical activation. Unsurprisingly, small observational studies with either His-left ventricular stimulation approach: His-optimized CRT (HOT-CRT) or LBBAP-left ventricular stimulation approach: left bundle branch optimized CRT (LOT-CRT) have shown to perform better in terms of cardiac chamber function and volumes than either CSP or BiVP-CRT alone\[23,24\]. However, the lack of wide scale experience and better quality data remains a major reason for low clinical application as of now. On many occasions especially in non-LBBB patients, choosing the ideal site for CRT via CSP is challenging because progression of conduction block distal to the pacing site remains a possibility which will limit clinical success in the long run. Hence, for these patients HOT-CRT and LOT-CRT may be the best option. Figure 1 illustrates the various pacing strategies mentioned above.

At this stage, one must also keep in mind that despite the promise of CSP, certain challenges are likely to be encountered in clinical practice and the industry would need to come with technologies and delivery systems to overcome these challenges. These include the long-term lead durability and efficacy, its extractability and worsening tricuspid valve regurgitation with time\[22\].
CONCLUSION

LBBP has emerged as a formidable alternative to BiVP as a strategy for CRT. The theoretical benefits of physiological pacing (LBBP-CRT) via the conduction system so far have translated into improved clinical outcomes compared to BiVP-CRT which stimulates the left ventricular myocardium directly. This recent meta-analysis also supports the growing body of evidence demonstrating the superiority of LBB-P-CRT over BiVP-CRT in regards to improvement in QRS duration, left ventricular ejection fraction, cardiac chamber dimensions, lead thresholds, and functional status. However, despite the accumulating evidence in support of LBBP-CRT, one must acknowledge the fact that as of now our opinion is largely based on observational data which are inherently prone to selection biases. Hence, there is an urgent need for larger RCTs which will ascertain the role of LBBP-CRT in the future.
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