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Advancing Heart Failure Treatment: The Role of Multipoint Pacing in Cardiac Resynchronization Therapy

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ABSTRACT

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Cardiac resynchronization therapy (CRT) with biventricular pacing is a standard therapy for patients with heart failure, reduced ejection fraction, and electrical dyssynchrony. However, approximately 30% of patients do not respond to CRT. Multipoint pacing (MPP) has emerged as an innovative strategy that paces multiple left ventricular sites to achieve more comprehensive resynchronization. This review explores the evolution of MPP, including the underlying scientific rationale, clinical evidence from key trials, technological considerations of quadripolar leads and programmability, patient selection criteria, optimization strategies, and future directions. Early feasibility studies demonstrated acute hemodynamic improvements with MPP. Larger trials have shown superior outcomes with MPP compared to conventional biventricular pacing, including increased CRT response rates, reduced hospitalizations, and improved ejection fraction and reverse remodeling. However, recent multicenter trials found no significant differences between the population's MPP and biventricular pacing. Ongoing research aims to refine patient selection for MPP and optimize lead positioning and programming configurations to maximize benefits. As technological capabilities expand, MPP promises to provide tailored, physiological pacing therapies that may enhance outcomes for heart failure patients requiring CRT. This comprehensive review examines the various aspects of MPP, including its scientific foundation, clinical evidence, technological considerations, impact on patient quality of life, and future implications. By critically assessing the current literature and identifying gaps in knowledge, we aim to provide a thorough understanding of MPP's role in the evolving landscape of heart failure management.

KEYWORDS:

Cardiac resynchronization therapy, Multipoint pacing, heart failure, dyssynchrony

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1. Introduction

Heart failure (HF) presents a significant global health burden, affecting millions and incurring substantial economic costs. Its complex pathophysiology involves structural and functional abnormalities of the heart, leading to reduced cardiac output and impaired tissue perfusion. Despite advancements in pharmacological and device-based therapies, a significant proportion of HF patients experience debilitating symptoms and poor quality of life, highlighting the need for continuous innovation in treatment strategies. Cardiac Resynchronization Therapy (CRT) has emerged as a

cornerstone in managing advanced HF, particularly for patients with reduced left ventricular ejection fraction and electrical dyssynchrony. CRT aims to restore coordinated contraction of the ventricles through biventricular pacing (BiVP), which involves simultaneous pacing of the right ventricle and left ventricle via strategically placed leads. In numerous clinical trials, this approach has demonstrably improved symptoms, exercise capacity, and survival [1,2]

Approximately 33% of patients do not respond to Cardiac Resynchronization Therapy (CRT), and identifying reliable markers for response remains a challenge [3]. Factors that may reduce CRT response include increased scar burden, certain scar locations, extreme mechanical dyssynchrony, and comorbidities [4]. Gender and heart failure etiology also influence CRT outcomes [5]. Current CRT implantation techniques aim for posterolateral LV lead placement, but patient responses remain variable [6,7]. Recent approaches focus on implanting LV leads in late-activated segments to improve CRT response [8,9]. The STARTER trial found this method reduced death or HF hospitalization but achieved only 30% accuracy in targeting late-activated segments [10]. Pacing in scarred myocardium correlates with poorer CRT response, and the degree of scarring intensifies the negative impact [11]. Multipoint pacing (MPP) has improved clinical outcomes and reversed LV remodeling [12]. A randomized study found a higher proportion of MPP patients had reduced end-systolic volume and improved NYHA functional class compared to biventricular pacing [13]. A meta-analysis revealed MPP correlated with improved functional class and hemodynamic parameters but had lower projected battery longevity [12]. Multipolar LV leads can avoid diaphragmatic stimulation and select from multiple pacing vectors, potentially enabling specific targeting of viable and late-activated myocardium. More evidence is required to confirm whether multipolar leads enhance CRT outcomes, but their use is increasing [14].

This review delves into MPP's multifaceted aspects, exploring its scientific basis, clinical evidence, technological considerations, impact on patient quality of life, and prospects. By critically evaluating the current state of knowledge and identifying existing gaps, we aim to provide a comprehensive understanding of MPP's role in the evolving landscape of heart failure management.

2. Dyssynchrony

The intricate pathophysiology of HF often originates from an initial cardiac insult leading to acute ventricular dysfunction. To compensate, the body initiates a cascade of neurohormonal and adrenergic adaptations, initially aiming to preserve cardiac output and maintain systemic perfusion. However, chronic activation of these compensatory mechanisms, including the renin-angiotensin-aldosterone system and the sympathetic nervous system, results in maladaptive remodeling, encompassing changes in cardiac structure, function, and metabolism [15, 16]. This remodeling process ultimately exacerbates cardiac dysfunction and perpetuates the cycle of HF. Adding to the complexity of HF, a significant subset of patients develop electrical conduction abnormalities, manifesting as intraventricular dyssynchrony [17].

Dyssynchrony refers to the discoordinated contraction of the ventricles, disrupting the normally synchronized sequence of electrical activation and mechanical contraction. Various factors can lead to this, with the most frequent ones being left bundle branch block (LBBB) and right ventricular (RV) pacing. In LBBB, the electrical impulse is delayed in reaching the left ventricle, causing the septum to contract before the lateral wall. This creates an inefficient "tug-of-war" effect, where the septum's contraction energy is partially wasted by stretching the still-relaxing lateral wall. Similarly, RV pacing bypasses the heart's natural conduction system and can lead to dyssynchronous activation and contraction patterns. Furthermore, myocardial infarction or other cardiac injuries can lead to the formation of scar tissue within the ventricle, disrupting the normal electrical conduction pathways and contributing to dyssynchrony [17-20].

3. Consequences of Dyssynchrony and Remodeling

The consequences of dyssynchrony are multifaceted, impacting both the mechanical function and the underlying structure of the heart. The discoordinated contraction pattern leads to reduced systolic function, with decreased ejection fraction and stroke volume [17-20]. This translates to a reduced cardiac output and an inability to meet the body's metabolic demands. Dyssynchrony also increases the workload on the myocardium, leading to increased wall stress and oxygen demand [18]. This can further exacerbate myocardial damage and contribute to a cycle of progressive remodeling and worsening HF.

Dyssynchrony triggers a cascade of maladaptive remodeling processes. The heart undergoes structural and geometric changes, including chamber dilation, alterations in shape, and regional wall thickness variations [17-20]. These changes can be understood as the heart's attempt to compensate for the inefficient contraction pattern. For example, the late-activated lateral wall, which has to work harder, may thicken over time. Additionally, alterations in the heart's intricate fiber architecture occur, further impacting the efficiency of contraction [17, 18]. Dyssynchrony can also impact the function of the mitral valve, leading to mitral regurgitation [21] This backflow of blood into the left atrium further reduces the forward cardiac output and increases the workload on the heart, contributing to a vicious cycle of worsening HF. The impaired relaxation and filling of the ventricle during diastole contribute to elevated filling pressures and pulmonary congestion, leading to symptoms such as shortness of breath and fatigue [15, 20].

At the cellular and molecular level, dyssynchrony interacts with the underlying HF substrate to induce regional variations in protein expression and activity [18, 19]. This includes changes in key calcium-handling proteins, such as SR Ca2+-ATPase and phospholamban, which are essential for regulating myocardial contractility and relaxation. Furthermore, activation of stress-response pathways and downregulation of connexin 43, a protein crucial for electrical coupling between heart cells, contribute to electrical heterogeneity and increase the risk of arrhythmias [18, 19]. These molecular and cellular changes can be seen as the heart's response to the increased stress and workload imposed by dyssynchrony.

Cardiac resynchronization therapy (CRT) has emerged as a cornerstone in the management of HF patients with dyssynchrony. By restoring coordinated ventricular contraction through biventricular pacing (BiVP), CRT addresses the root cause of dyssynchrony and its detrimental effects. CRT improves pump function, enhances relaxation, and reduces regional workload disparities [1, 2, 3, 22]. These improvements translate into increased cardiac output, reduced symptoms, and improved quality of life for patients [1, 2, 3, 22]. However, a subset of CRT recipients, known as "non-responders," do not experience the expected benefits of therapy [4, 23]. This has led to the exploration of alternative pacing strategies, such as MPP [1, 12, 24, 25]. The rationale behind MPP is to achieve more comprehensive ventricular resynchronization by pacing multiple sites within the left ventricle, addressing the potential limitations of conventional biventricular pacing [1, 12, 24, 25].

MPP aims to:

1. Improve Electrical Synchrony: MPP can correct the conduction delays caused by LBBB or scar tissue, ensuring more coordinated activation of the left ventricle and improving the contraction efficiency
2. Reduce Regional Wall Motion Abnormalities: By pacing multiple sites, MPP can improve the contraction of specific regions with impaired function, leading to a more homogenous contraction pattern and improved overall ventricular performance.
3. Optimize LV Mechanics: MPP can improve the overall mechanical efficiency of the left ventricle, leading to increased stroke volume, cardiac output, and improved hemodynamic parameters.

This approach aims to overcome issues like residual dyssynchrony and anatomical variations in conduction pathways that may limit the effectiveness of standard CRT.

4. Chronological Evolution of MultiPoint Pacing Clinical Trials

The evolution of MPP for cardiac resynchronization therapy (CRT) has been a journey marked by a series of clinical trials spanning over a decade. Each study has contributed to our understanding of this innovative pacing strategy, from early observational studies focusing on feasibility and acute effects to larger, randomized trials assessing long-term clinical outcomes and the importance of optimal programming. The early experimental evidence of multisite pacing showed improved activation propagation and minimized functional block in canine models [26]. This laid the groundwork for the first human studies, such as the TRIP-HF study conducted in 2008which compared triple-site versus dual-site biventricular stimulation in heart failure patients. Although ventricular resynchronization did not show a significant difference, triple-site pacing demonstrated improvements in left ventricular ejection fraction and reverse remodeling, suggesting advantages over conventional biventricular pacing [27].

A study conducted in 2012, aimed to explore the potential of multi-site left ventricular pacing as a treatment for patients with a postero-lateral scar. They found that multi-site pacing resulted in a greater acute hemodynamic response than single-site pacing, along with improvements in dyssynchrony parameters and scar burden [28]. The the substudy of TRUST trial evaluated the feasibility, safety, and lead performance of triple-site CRT systems over a 1-year follow-up, demonstrating high success rates but increased complexity compared to conventional CRT implantation [29]. A randomized double-blind crossover trial supported the functional benefits of MPP, showing improvements in walking distance and quality of life scores with triventricular pacing [30]. The higher complication rate, longer procedure times, and lack of dedicated pulse generators have led to the abandonment of 3-V CRT [31].

The focus shifted to multipoint pacing within a single left ventricular vein using quadripolar leads. Numerous studies primarily investigated MPP's acute hemodynamic and echocardiographic effects. These studies consistently demonstrated that MPP could acutely increase left ventricular dP/dtmax, radial strain, and LVOT velocity time integral while reducing dyssynchrony compared to BiVP [32-36]. A study conducted in 2014 investigated the impact of multipoint pacing on left ventricular electrical and mechanical dyssynchrony, finding that multipoint pacing led to significant reductions in electrical delay and improvements in mechanical dyssynchrony parameters, suggesting the potential of multipoint pacing in enhancing cardiac synchronization [37].

Subsequent studies provided insights into the mechanisms underlying MPP's benefits, such as quicker wavefront propagation, larger capture of left ventricular mass, and improvements in LV dyssynchrony and contractility [38-42]. A study demonstrated that acute benefits translated into improved CRT response rates and left

ventricular reverse remodeling over a 1-year follow-up [36]. Similarly, another study compared MPP vs BIP in terms of clinical outcomes and LV reverse remodeling in a prospective observational study of 193 patients, showing that the MPP group had lower heart failure hospitalizations and greater improvements in LVEF and LV end-systolic volume [43]. Larger prospective, multicenter trials further supported the clinical benefits of MPP, showing improved composite scores, higher left ventricular ejection fraction, and non-inferiority to BiVP in terms of CRT response. The IRON-MPP trial which was carried out in 2017, addressed the impact of MPP on device longevity, highlighting the importance of balancing clinical benefits with device management considerations [42,44,45].

In 2017, the MultiPoint Pacing Trial reaffirmed the safety and effectiveness of MPP, showing it to be non-inferior to biventricular pacing in terms of non-responder rates at both 3 and 9 months [45]. Specific MPP programming, such as wider electrode spacing and near-simultaneous pacing delays, showed potential benefits in improving CRT response and converting non-responders to responders, as identified in a sub-analysis of the trial. A double-blinded randomized trial found that MPP led to greater improvements in LV synchrony and function compared to biventricular pacing (BiVP), emphasizing MPP's potential to enhance cardiac resynchronization therapy outcomes [46]. Additional studies evaluated real-world outcomes of quadripolar vs bipolar LV leads in large observational studies, demonstrating that quadripolar leads (used for MPP) were associated with lower mortality, heart failure hospitalization, and non-response rates, as well as being cost-effective despite higher upfront costs [47-49]. Further studies confirmed the long-term clinical benefits of MPP over BIP in large real-world cohorts [50-52]. Optimal programming of MPP was highlighted by reported studies reflecting it enhanced hemodynamics, systolic blood pressure, and CRT response compared to suboptimal programming and biventricular pacing [53-54].

The MORE-CRT MPP trial was a landmark study that enrolled 5,850 patients across two phases to assess the impact of MPP on treating echocardiographic non-responders to 6 months of standard BiVP. In phase I, after 6 months of standard BiVP, 39.3% of patients were classified as echocardiographic non-responders (<15% reduction in LVESV). These non-responders were randomized to continue BiVP or switch to MPP for the next 6 months [54]. The primary endpoint, conversion rate from non-responder at 6 months to responder (≥15% LVESV reduction) at 12 months, showed no significant difference between MPP (29.4%) and BiVP (30.4%) in the overall cohort. However, the MPP subgroup with >98% ventricular pacing had a significantly higher conversion rate (43% vs 32%) [54]. In phase II, the protocol was modified to require MultiPoint Pacing with a large Anatomical Separation (MPP-AS) of at least 30 mm between the two left ventricular (LV) pacing sites. This change was based on a trend observed in phase I suggesting a potential benefit of increased anatomical separation. Phase II enrolled an additional 3,929 patients (for a total of 5,850 across both phases). Despite the protocol change requiring ≥30 mm separation, the AS-treated analysis of phase II patients showed no significant difference in the non-responder to responder conversion rate between MPP-AS and BiVP. This suggests that increasing the anatomical separation between LV pacing sites does not necessarily improve outcomes in CRT non-responders [55].

More contemporary studies have shown long-term benefits of MPP in terms of reverse remodeling and clinical improvement compared to BiV in a Middle-Eastern population. This prospective observational study compared the long-term effects of MPP versus BiVP in 184 patients (92 in each group) with heart failure and conventional CRT indications. Patients were followed for a mean of 18 months, and the study found that MPP was associated with significantly higher rates of echocardiographic response (68% vs. 50%), clinical composite score improvement (78% vs. 61%), and NYHA class improvement (72% vs. 54%) compared to BiVP. These results suggest that MPP may provide long-term benefits over BiVP in reverse remodeling and clinical improvement in this population [13].

A systematic review and meta-analysis conducted in 2018 included 11 studies with a sample of 29,606 patients and assessed the outcomes of multipoint pacing (MPP) versus conventional biventricular pacing (BiVP). This analysis demonstrated that MPP was associated with a significant reduction in heart failure-related hospitalizations, improvements in left ventricular ejection fraction (LVEF), an increased rate of positive response to cardiac resynchronization therapy (CRT), and a decrease in both all-cause and cardiovascular mortality. These findings suggest MPP is a potentially superior alternative to BiVP in enhancing clinical outcomes for CRT patients [56].

A meta-analysis in 2021, which examined 15 studies and 1,895 patients, analyzed MPP's effectiveness versus conventional BiVP in heart failure patients. The study defined the primary endpoint as a clinical response, measured by changes in the New York Heart Association (NYHA) functional class. Another meta-analysis, which included seven studies with 1,390 patients, provided additional insights into MPP's effectiveness, offering a broader perspective on its benefits in cardiac resynchronization therapy. Secondary endpoints included delta LV dP/dtmax, LVESV, hospitalization for heart failure, all-cause death, and projected battery longevity. The meta-analysis showed that MPP was superior to BiVP in terms of clinical response and acute hemodynamic improvement (delta LV dP/dtmax) but not in terms of LVESV, hospitalization for heart failure, or

all-cause death. Additionally, MPP was associated with a shorter projected battery life compared to BiVP [12,25].

A systematic review and meta-analysis analyzed the effectiveness of MPP versus conventional CRT, incorporating randomized and non-randomized studies. Key studies included the MPP trial (2017), the MORE-CRT MPP study (2019), and several prospective observational studies. The findings indicated that MPP showed greater efficacy in non-randomized studies compared to randomized ones in terms of parameters like echocardiographic improvement, more than 15% reduction in LV end-systolic volume (LVESV), and improvement of at least one NYHA class. However, the analysis highlighted substantial heterogeneity in study designs, complicating overall interpretation of results.

In conclusion, while some studies have shown promising results in terms of improved left ventricular function, reverse remodeling, and clinical outcomes, others have yielded mixed findings. As research progresses, larger, well-designed trials with standardized protocols will be essential to further elucidate the role of MPP in enhancing CRT response and improving the lives of heart failure patients.

5. Patient Selection

Clinical trials have demonstrated the benefits of multipoint pacing (MPP) over conventional biventricular pacing (BVP) for cardiac resynchronization therapy (CRT), including improved cardiac remodeling, clinical outcomes, safety, and long-term prognosis [56]. However. International guidelines have been slow to incorporate MPP recommendations, partially due to mixed results from large real-world registries and implementation studies. The 2023 HRS/APHRS/LAHRS guideline suggests considering MPP in CRT patients who fail to improve despite optimal medical therapy, particularly those with suboptimal lead position or phrenic nerve capture at higher outputs [57].

6. Clinical Evidence

Several studies have explored the relative performance of MPP and BVP, providing insights into patient characteristics that may influence responses (Table 1) [58]. In patients with non-ischemic cardiomyopathy and left bundle branch block (LBBB), BVP appears effective, likely due to the clear conduction block that can be resynchronized [59-60]. Conversely, in ischemic patients with diffuse conduction abnormalities, the additional wavefronts generated by MPP may be particularly beneficial [53].

Acute hemodynamic studies consistently show MPP can enhance cardiac contractility and output compared to BVP, with improvements, most pronounced when the MPP vectors are widely spaced to engage a larger myocardial volume [33, 35, 36, 46]. However, long-term clinical impact has been more variable, with some larger multicenter trials finding no significant differences between MPP and BVP in composite clinical scores or echocardiographic response [36, 54].

7. Optimization

While the primary goal of CRT has been to narrow the QRS complex based on the assumption that restoring electrical synchrony improves mechanical synchrony, emerging evidence suggests the sequence of myocardial activation may be equally important. Advanced imaging and computational modeling studies show the optimal activation sequence can vary widely between individuals based on factors like scar location, conduction velocities, and myofiber orientation [61-63]. In some cases, a slightly wider QRS with a more physiological activation pattern may yield better outcomes than a narrower QRS with a less favorable Sequence.

These insights call for a paradigm shift in CRT optimization, from focusing solely on electrical synchrony to identifying and replicating the patient-specific ideal activation sequence using more sophisticated electromechanical characterization tools. Multipoint pacing has been made easily achievable through the development of a left ventricular (LV) quadripolar lead and the concurrent development of cardiac resynchronization therapy (CRT) devices capable of multiple electrical outputs (Table 2) [64]. The use of a quadripolar lead has improved patient outcomes and even survival compared to a conventional bipolar LV pacing lead, due to fewer requirements for lead replacement and elimination of phrenic nerve. Stimulation (Figure 1) [65].

8. Optimization Strategies

Recent studies have highlighted the importance of individualized strategies to optimize MPP programming parameters for each patient. A study conducted in 2020 demonstrated that optimizing MPP with wide anatomical separation between the LV1 (basal) and LV2 (mid-ventricular) pacing sites significantly improved LV reverse remodeling and echocardiographic response rates compared to conventional BVP in both BVP responders and non-responders (Figure 2) [67].

The overall response rate increased from 63% with BVP to 90% with optimized MPP programming. Multimodal Techniques developed a novel "multi-fuse pacing" (MFP) a technique combining MPP with controlled septal fusion from the RV lead, and an AV-delay shortening algorithm **(Figure 3)** [67]. In this proof-of-concept study, MFP programming significantly reduced QRS duration acutely compared to baseline, with greater QRS narrowing in patients with strictly defined LBBB versus non-specific intraventricular Conduction delay **(Figure 4)** [66].

9. Patient-Specific Optimization

A study optimized the LV lead position based on electrical delay mapping and acute hemodynamic response using pressure-volume loop measurements [38]. Combining

this patient-specific LV lead optimization with MPP markedly improved 1-year outcomes like LV reverse remodeling, NYHA class improvement, and composite clinical score, compared to standard CRT without individualized programming.

10. Empiric vs. Hemodynamic Guidance

A study conducted in 2019 compared two MPP programming approaches - hemodynamic optimization guided by pressure-volume loop measurements versus an empiric strategy of maximizing the spatial separation between LV cathodes [69]. Interestingly, both methods resulted in similar long-term CRT response rates of around 77%, suggesting an empiricwide-spaced LV lead configuration may provide a simple, non-invasive alternative to hemodynamic guidance.

Delay Optimization studies specifically investigated the impact of optimizing the interventricular (VV) and intraventricular (LV) delays in MPP [69]. They found that a delay setting of VV 25ms and LV 25ms led to significantly improved cardiac index and QRS narrowing compared to nominal settings, suggesting this delay configuration may be an optimal starting point for many MPP patients. Multiple strategies have been explored to optimize MPP programming, from empiric wide-spaced LV lead positions to multimodal techniques combining various pacing sites/vectors and computational modeling to predict the ideal patient-specific activation sequence. Larger randomized trials are still needed to definitively establish the most effective optimization approach.

FUTURE DIRECTIONS AND CONCLUSION

As the field of Cardiac Resynchronization Therapy (CRT) evolves, the integration of Multipoint Pacing (MPP) offers promising avenues for enhancing treatment outcomes in heart failure patients. Future research should focus on technological innovations such as the development of advanced pacing devices and the integration of artificial intelligence to optimize pacing strategies. Enhanced imaging techniques and advanced cardiac mapping will play crucial roles in improving lead placement and therapy effectiveness.

Additionally, refining patient selection criteria through clinical, genetic, and imaging data is critical to identifying patients who would most benefit from MPP. Longitudinal studies and comparative research are essential to assess the long-term benefits and effectiveness of MPP compared to other therapies. Efforts should also be made to increase global access to this technology and provide education for healthcare providers on the nuances of MPP.

In conclusion, Multipoint Pacing represents a significant advancement in managing heart failure via CRT. It shows promise in improving clinical outcomes through enhanced electrical synchrony and myocardial performance. The ongoing innovation and research in MPP aim to optimize treatment protocols and expand their applicability, ultimately improving response rates and quality of life for heart failure patients. The future of MPP in CRT looks to provide tailored therapies that are more effective and widely accessible.

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Table 1. Comparison of the advantages and disadvantages of MPP and BVP [58]

Feature	BVP	MPP
Clearly defined target population	Several landmark trials have established the DyssHF population that *may* benefit from CRT in its classical BVP mode-however there is no certainty that these patients *will* benefit.	Although still unresolved, it appears that DyssHF patients with extensive, non-specific intraventricular conduction abnormalities benefit more from multiple LV pulses which shorten LV activation time. Of note, CRT devices from all major manufacturers are MPP-capable (not with the same options), allowing for easy transition if deemed necessary.
Complexity of implantation	Identical.	
Presence of suitable dipoles	Almost always achievable (quadripolar leads).	Due to constraints regarding dipole combination, although multiple BVP-suitable dipoles may be present, their serial use may be unfeasible. Also, rates of MPP loss of up to 20% have been reported.
Ease of programming	A basic setting has emerged that is often followed in practice-LV/RV pulses either simultaneous (nominal setting) of with up to 30 msec LV precedence. However, regarding reaping maximal benefit, programming becomes exponentially more laborious/complex (see text for details).	There is no consensus regarding a basic setting that could be subsequently be improved upon. This notwithstanding, most relevant trials have suggested opting for dipoles allowing for maximizing left ventricular myocardial mass capture, thus exploiting the innate advantage over BVP, and using minimal delay between LV pulses. Moreover, achieving *optima*l settings is quite cumbersome and resource-intensive (see text).
Acute effects	In most studies with direct BVP-MPP comparison, the latter outperformed the former regarding acute hemodynamic effects, at least when basic settings (see above) were used.	
Long-term effects	Firmly established survival benefits, at least compared to pharmacotherapy.	Encouraging findings regarding reduced cardiovascular mortality and performance status compared to BVP, even in their respective *optimized* modes (non-randomized studies and meta-analyses).
Pairing with additional modalities (LV-only pacing, QRS fusion, magnetic resonance guidance)	Identical. However, MPP offers more versatility and can better adapt to the suggestions of advanced LV output optimization approaches.	

In general, MPP could be considered an enhanced version of conventional BVP, offering more options, especially when non-response remains an issue. Admittedly, the core issue of whether MPP should be pursued in patients with satisfactory response to BVP cannot be resolved, inasmuch as there are randomized long-term trials of the two modalities.

Table 2. Commercially Available Pacing Algorithms for Single-Lead Left Ventricular Multipoint Pacing and Possible Pacing Configuration [64]

Feature Name	Boston Scientific Multisite Pacing	St. Jude Multipoint Pacing	Medtronic Multiple Point Pacing	Biotonik MutiPole Pacing
CE Mark Status	Established 1Q 2017	Approved	Approved	Approved
Pacing Vectors Available	17	10	5	12
LVa – LVb Timing Offset	Independent cathodes 0-100 ms	Independent cathodes 5-80 ms offsets	Tied cathodes, no offsets	Independent cathodes 0-50 ms
Automatic Programming Recommendation	Yes SmartVector algorithm automatically recommends settings	Yes Options for choosing based on RV-LV or widest spacing	None for MPP	Unknown
Pacing Configuration	Bi-V LV only	Bi-V	Bi-V LV only	Bi-V

CE = European Commission; Bi-V= biventricular; LV= left ventricular; MPP = Multipoint Pacing; RV = right ventricular

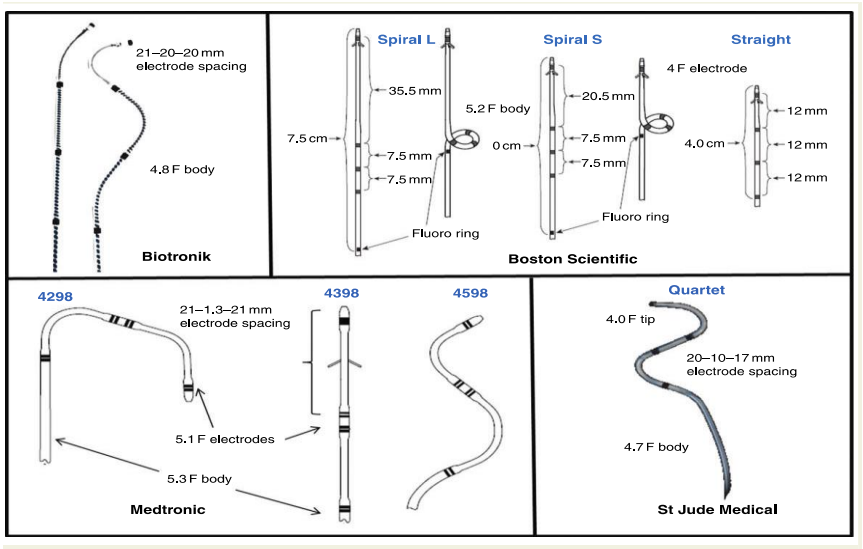

Figure 1. Currently available quadripolar LV leads, showing differences in lead design (reproduced/adapted and with permission from Boston Scientific, St Jude Medical, and Medtronic) [65].

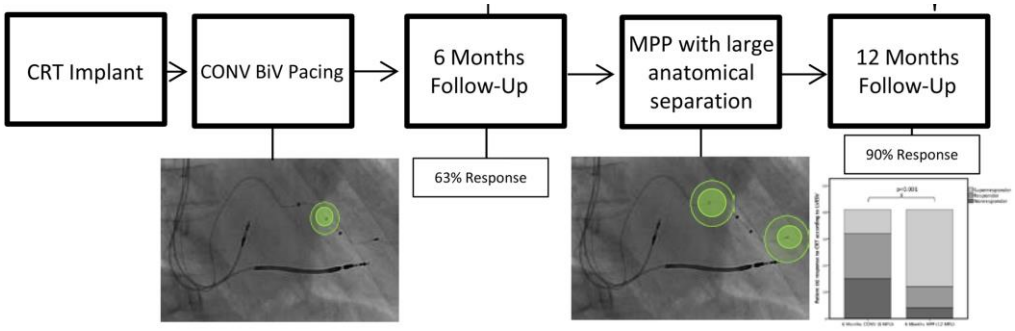

Figure 2. Graphic illustration for MultiPoint Pacing [65].

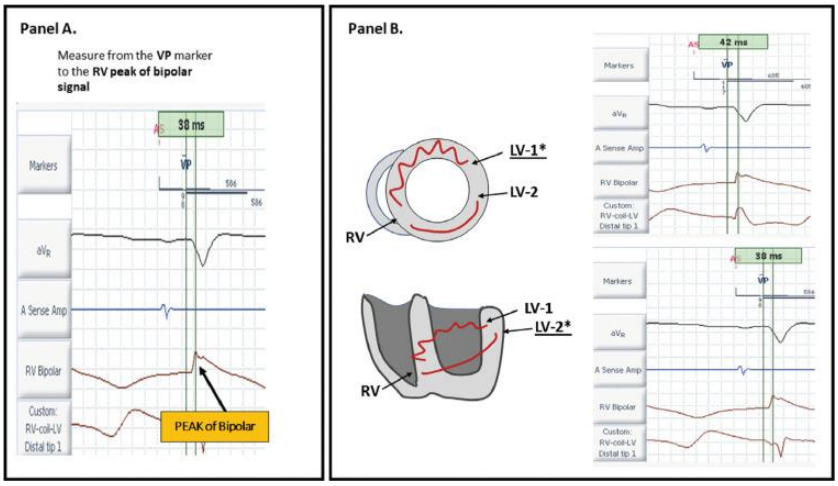

Figure 3. Intracardiac EGM measurements were utilized to determine settings and measure the SRAT (left). The distance between the RV coil and LV distal tip was employed to visualize the onset of septal activation, measured to the positive peak of the RV bipolar EGM. In this example, the SRAT was confirmed to be 80 ms. EGM stands for electrogram; LV denotes left ventricular; RV represents right ventricular; SRAT refers to septal onset to right ventricular time [67].