Review

Multipoint Left Ventricular Pacing as Alternative Approach in Cases of Biventricular Pacing Failure

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Abstract: Cardiac resynchronization therapy (CRT) is a cornerstone in the treatment of dyssynchronous heart failure with reduced ejection fraction. However, the phenomenon of non-response has plagued CRT since its initial application. Notwithstanding issues such as failure to capture the left ventricle, lower-than-required pacing delivery percent and failure to optimize atrioventricular and interventricular delays, there are patients who fail to exhibit adequate response to CRT in its classical biventricular pacing (BiVP) form. Several modalities have been proposed as a means to remedy this issue, including pacing the conduction system itself – His or left bundle branch pacing, allowing for intrinsic conduction in some myocardial segments, pacing the left ventricle from multiple points in the coronary sinus (multi-point pacing), or even combining the above (e.g. His/left bundle pacing and BiVP leading to His/left bundle-optimized CRT). In the present review we present recent evidence for the advantages and disadvantages of each modality and attempt to formulate a pathophysiology and simulation-based strategy to determine the best way forward for delivering CRT in non-responders to BiVP.

Keywords: cardiac resynchronization therapy; multipoint left ventricular pacing; left ventricular resequencing; conduction system pacing

Introduction

Cardiac resynchronization therapy (CRT) remains a cornerstone of dyssynchronous heart failure with reduced ejection fraction (HFrEF) management. Randomized clinical trials [1–4] have consistently shown CRT efficacy in alleviating symptoms and prolonging life, even in the absence of defibrillation capacity [5]. Reversal of dyssynchrony has effects beyond improved chamber mechanics [6], including better excitation – contraction coupling at the cardiomyocyte level, reduced diastolic calcium levels, correction in connexin expression and localization, as well as restoration of the costamere quasi-organelle, which leads to improved cell-cell and cell-matrix communication and thus adaptability. Resumption of the adult gene expression pattern has also been reported, associated with improved work at slightly reduced efficiency. The notion of reduced arrhythmogenesis in the context of CRT delivery merits more consideration [7–9]. Aside from reducing mechanical stretch and thus mechanosensitive channel activation and ischemia-associated arrhythmogenesis, CRT leads to cellular conformational changes which restore proximity of T-tubules to the sarcomere (potentially altering junctophilin expression), thus reducing the magnitude of calcium spikes necessary to trigger calcium-induced calcium release [10,11]. Indeed, it appears that CRT reduces the incidence of ventricular arrhythmias by 14% (p=0.044) in the primary prophylaxis population while having no effect on secondary prophylaxis patients [12].

However, all cohorts and registries have consistently reported a percentage of non-response to CRT, delivered through biventricular pacing (BiVP), in the 30% range[13,14]. Of the causes associated

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with this finding, unsuitable coronary vein system anatomy, disease progression, arrhythmia occurrence (e.g., atrial fibrillation), right ventricular dysfunction (due to intrinsic causes or to the BiVP itself) have been reported, among others[15,16]. Moreover, ischemic cardiomyopathy and non-left bundle branch block (LBBB) QRS complex morphology are well-known predictors of non-response to BiVP-based CRT [17].

The Concept of Resequencing

In the case of textbook left bundle branch block, cardiac resynchronization therapy can be achieved either by pacing the most belatedly activated portion of the left ventricle (posterior-inferior basal wall segment) through a lead inserted in the coronary sinus (CS), in other words conventional BiVP, or by pacing the left bundle itself – left bundle area pacing - LBAP, the second approach being, not unexpectedly, associated with improved outcomes. In this context, any improvements in QRS complex duration are translatable to improved synchrony and mechanical function. However, when more pronounced and diffuse intraventricular conduction abnormalities are present, often intertwined but not always coinciding with segmental contractility deficits (e.g. an area with affected conduction may alter the timing of an adjacent segment with normal contractility), it is perhaps more prudent to consider the issue of left ventricular dysfunction in the conceptual framework of resequencing, rather than resynchronizing[18,19].

More specifically, it is likely that, in such advanced dyssynchrony cases, solely focusing on shortening the QRS segment may necessitate early pacing of areas with few working cardiomyocytes which affect QRS duration but do not contribute to contractility, thus missing the ultimate goal of improved ventricular function [18,20]. On the other hand, an alternative *sequence* of ventricular activation, tailored on an individual patient basis, may offer improved function, not always associated with the shortest QRS duration. As an example, myocardial segments differ on myosin phosphorylation patterns, allowing fine-tuning contraction *duration* [21] (e.g., in the papillary muscles). This, and several other concepts, such as cavity three-dimensional shape in order to avoid formation of vortices [22] are lost when QRS duration is the focus– taken to the extreme this argument suggests that even in cases where QRS duration is not prolonged, yet there are multiple segmental motion abnormalities, the classical activation sequence may not be the optimal sequence any longer – however there are no robust clinical data to support this – although efforts to use BiVP in HFrEF with normal QRS duration have been reported – with promising results [23].

The Notion of Multipoint Pacing

It follows that, in the case of a ventricle with the pathology described above (multiple segmental conduction and contractility abnormalities, all intertwined) the addition of a second left ventricular activation wavefront may offer more options for properly resequencing the ventricular activation pattern in order to simulate as much as possible the optimal sequence and maximize ventricular function [19]. Consequently, the notion of left ventricular multipoint pacing (MPP) was introduced, in which two different left ventricular pulses may be delivered through a (quadripolar) CS lead. Pacing dipoles and pulses can be differentiated into “local” i.e., between two CS lead poles and “extended” i.e., comprising a CS pole and the right ventricular coil. For physiological reasons, no pulses may share the same cathode because the local myocardium will already have been excited by the first pacing pulse, rendering it refractory to the second. In addition to the generation of 2 activation wavefronts, it has been postulated that pacing at an increased pulse energy may lead to anodal stimulation which, in the case of local dipoles, may actually be beneficial inasmuch as it leads to the generation of an additional wavefront [24] – in any case this phenomenon is thought to occur frequently even in BiVP with CS lead-only dipoles.

Augmentations to both MPP and BiVP have been described; the one most likely to constitute meaningful addition to their effect being the concept of anticipatory LV pacing (in the form of MPP or BiVP) – leading to conduction system-based right ventricular activation thus both elimination iatrogenic dyssynchrony and adding another propagation wavefront [25,26]. Precise programming

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will require ECG-imaging in order to deduce proper programmable delays [27,28]. Taken to the extreme, a "multi-fusion" pacing approach has been described, with a right ventricular pacing pulse being added – regarding outcomes, this approach led on average to QRS duration reductions of almost 40msec [29]. The ability to take advantage of intrinsic conduction regarding right ventricular activation is in stark contrast to what has been described with LBAP, where the bipolar pacing configuration (potentially capturing both bundles – i.e. a distal quasi-His pacing) actually led to worse outcomes than the unipolar one (only capturing the left bundle), attributed to preferential septal activation through the intact right bundle [30].

Due to complex interplays, advanced "digital twin – level" models of cardiac activation latency and contractility will be necessary in order to assess the global effects of each resequencing option. It is likely that ECG imaging (for conduction) and cardiac magnetic resonance imaging [cMRI – assessing substrate, viability (stress protocols) and contractility] will be sine qua non for acquiring data to be processed and processed, even by means of quantum computing (which excels in optimization problems), in order to derive both the optimal activation sequence and the optimal placement of the CS lead [31–34].

Clinical Evidence

Before presenting current clinical evidence regarding the role of MPP as a CRT modality in BiVP non-responders, it should be highlighted that most studies attempted to optimize MPP using QRS duration as touchstone, which broadly contradicts the whole framework discussed previously. Furthermore, a clear distinction should be made between studies including patients with LBBB QRS morphology and those enrolling patients with nonspecific intraventricular conduction delays, given that in the latter case MPP effects may be more pronounced than those of conventional BiVP.

MPP in Non-Responders to BiVP

Compared to optimized BiVP, MPP has been shown to exhibit greater increases regarding $\frac{dP}{dt_{max}}$, external myocardial work and velocity-time integral at the left ventricular outflow tract (VTI_{lvot}) in the acute phase [35–38]. However, although initial reports were encouraging concerning long-term outcomes and response rates at 12 months (Pappone et al [39]reported changes in end-systolic LV volume and LV ejection fraction of -25% and +15% with MPP and -18% and +5% with BiVP, respectively), the landmark MultiPoint Pacing Trial [40] only showed noninferiority of MPP response rates compared to BiVP at 3 and 9 months. It should be noted that MPP effects were heavily dependent on programming, and it was through this trial that the notion of wide (>30mm) anatomical separation between the two LV dipoles and short (5msec) interventricular delay conferring the most benefit was established – interestingly there was no direct $MPP_{opt.anatomy}$ vs BiVP comparison.

The single arm HUMVEE clinical trial [41](employing a cross-over design) uniquely used VTI_{lvot} maximization as the endpoint for optimizing MPP programming. All patients received similarly optimized BiVP for 6 months before switching to optimized MPP for another 6 months. Furthermore, if possible, a local CS dipole with the widest possible anatomical separation between its poles was used as the first LV pulse, followed by a second extended second LV pulse configuration with the assumption that this configuration would lead to lateral wall stiffening before apex contraction, facilitating expulsion. There was no attempt to promote intrinsic conduction for right ventricular activation and the interventricular delay was set to 5msec, per MPPT findings. Significant improvements were noted regarding 6-min walking distance, NYHA class and LV functional parameters (VTI_{lvot}, stroke volume, ejection fraction, but *not* QRS duration) – although these only persisted when the programmed MPP pacing configuration actually functioned at 12 months – there was a significant 20% of patients with no suitable dipoles at the end of the study. Limitations included potential carry-over effect and inability to assess additional parameter improvement with continuous BiVP *after* the first 6 months. Interestingly, ischemic patients appeared to benefit more from MPP than

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their nonischemic counterparts, possibly owing to the more diffuse conduction and contraction abnormalities.

As frequently mentioned, the MORE-CRT MPP study [42] failed to demonstrate increased conversion to responders (defined as >15% decrease in LV endsystolic volume) with MPP activation as compared to continued BiVP pacing. Once more, there was evidence for the effects of anatomical dipole separation, however programming was left to the physicians' discretion. This was recapitulated in a 2021 meta-analysis [43] confirming absence of meaningful additional effects of MPP on top of BiVP in randomized trials, with the potential exception of wide dipole anatomical separation, as mentioned multiple times. In stark contrast, a recent (2024) secondary analysis of data from the MORE-CRT MPP cohort [44], focusing on patients with sufficient delivery of CRT (>97% of time, i.e. patients *actually being treated*) showed a statistically significant, including in the multivariate analysis, *increase* in the occurrence of the composite primary endpoint of freedom from cardiac death and heart failure-related hospitalizations and LV endsystolic volume reduction ≥15% (HR 1.55, p=0.04). Notably, of its constituent metrics, both response rates and heart failure-related hospitalizations were significantly reduced in MPP receivers. An additional insight offered by this analysis, useful in constructing a general framework for MPP value, even when pitted against LBAP, is that, contrary to BiVP, its effectiveness remains even in cases with pronounced dispersion of intrinsic LV electrical delay – i.e. when its segments differed significantly in their activation timing, not unexpected based on the generation of an additional wavefront and the capture of more myocardial mass through wide anatomic separation of the LV pulses. In fact, a dispersion of activation timing between LV segments >20msec [45] or 30msec [44] has been associated with an advantage of MPP over BiVP regarding response rates (35.5% vs 17.7%, p=0.0335).

To summarize, in theory, MPP offers the potential for more precisely sculpting the choreography of LV activation, adjusted to its current condition (which suggests that it is subject to change with time), ensuring optimal performance [46]. However, MPP is heavily reliant on programming and this, in combination with the absence of an accepted initial programming that can be subsequently improved upon is a serious practical limitation of MPP, pending development of advanced simulation models, offering patient-tailored solutions. The concept of interventricular dispersion of activation magnitude is the only currently available predictor for MPP superiority over BiVP.

CS-CRT vs BiVP

His bundle pacing has always been an attractive alternative pacing modality, ensuring avoidance of pacing-induced cardiomyopathy[47]. Moreover, in cases of LV dyssynchrony attributed to LBBB, conduction system-based CRT (CS-CRT), including both His bundle-based and left bundle-based CRT (HB-CRT and LB-CRT, respectively) has consistently been shown to be superior to conventional BiVP, including when intrinsic activation of the RV is pursued [28,48,49]. In the HOT-CRT trial, HB-CRT showed improvements in the primary efficacy endpoint, namely LV ejection fraction improvement at 6 months (+12.4% vs +8%, p=0.02). Similar findings have been reported with LB-CRT [50], an approach mitigating several disadvantages of HB-CRT, including high long-term thresholds and difficulties in implantation whilst being noninferior concerning echocardiographic and functional outcomes[51]. LB-CRT can be safely performed in cases of either HB-CRT failure or need to revise the His bundle lead[47] Not only is LB-CRT more often feasible than either HB-CRT and BiVP, but it moreover leads, compared to the latter, to significantly reduced QRS duration and significantly increased LV ejection fraction, both in absolute and in relative terms. Unsurprisingly, the above effect is driven by an increase in the super-response rate (61.22% vs 39.22%), given that, should the LB be successfully paced in a patient with LBBB, the chances of super-response are higher. Similar findings were reported in a 2024 nonrandomized study, with non-responders to BiVP exhibiting significant decrease in QRS duration and increase in LV ejection fraction and converting to CRT responders in an impressive 48% [52]. Notably, the presence of LBBB conferred a ninefold higher probability for response to upgrading to LB-CRT. The above have been confirmed in a meta-analysis[53], reporting on 11 studies (1 RCT and 10 observational) having enrolled in total 3141

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patients, where LB area pacing was associated with 29% lower mortality and 41% lower risk for HF-related hospitalization. NYHA functional class was also significantly improved with LB area pacing compared to BiVP. Notably, the percentage of patients enrolled by studied with LBBB presence as a criterion was 16%, demonstrating the applicability of LB area pacing even in cases without typical LBBB.

Fusion Power

Left bundle pacing-optimized adaptive CRT (LOT-CRT) aims to combine the best of both worlds and enable combined utilization of conduction system endocardial (LB) and epicardial (CS – working myocardium) LV pacing, with the potential to prove advantageous in cases with coexistence of proximal and distal conduction abnormalities in the LV- the latter not being amenable to correction by LB pacing alone. Indeed, LOT-CRT leads to significantly shorter QRS duration compared to LB-CRT (in the 20msec range [54,55], with predictors being associated with more advanced disease (such as LV diameter ≥66mm, LV ejection fraction ≤35% and QRS morphology of LBBB with a duration ≥130msec). A multicenter trial aiming to assess differences in LV $\frac{dP}{dt_{max}}$ in the acute setting between LB-CRT, BiVP and LOT-CRT [30] reported that, following optimization in atrioventricular delay, the latter 2 fared better than the former, both in its unipolar and, especially, its bipolar form. Interestingly, although BiVP exhibited (marginally) the greatest increase in LV $\frac{dP}{dt_{max}}$ (26.4% vs 25.8% vs LOT-CRT), LOT-CRT was associated with the greatest shortening of QRS duration, a fact pointing to the validity of the assumption that resequencing is a more adequate pursuit than resynchronization and QRS duration is not its optimal indicator. Finally, LOT-CRT *was* superior to LB-CRT in those with baseline QRS >171msec (14.5% higher LV $\frac{dP}{dt_{max}}$, 20.8msec additional QRS shortening) – thus again in more advanced electrical and structural disease. Notably, due to lead connectology (LB lead connected to RV pacing port, CS lead connected to LV port), LB pacing during LOT-CRT was in the bipolar configuration, associated with anodal stimulation in 54% of cases, leading to reduced effectiveness, as discussed previously. Therefore, the theoretically optimal configuration of (adaptive) unipolar LOT-CRT remains elusive (especially in cases of a defibrillator where unipolar pacing programming is not allowed).

CS-MPP?

No trial has assessed the potential benefits of combining conduction system (His and LB) and multipoint pacing (CS-MPP), let alone in the presence of additional augmentations, such as allowing for intrinsic RV activation and pursuing a multi-fusion approach. This is surprising, considering that hardware does not differ from that of H/LOT-CRT. Given that up to 4 ventricular stimuli will be administered (His/left bundle, LV1, LV2, RV) and additional wavefronts will be generated either by intrinsic activation or by anodal stimulation, such an approach will absolutely necessitate a digital twin approach, with data from CMR and ECG imaging being integrated in order to determine the optimal configuration for patient-tailored CRT delivery. In a still experimental setting [56,57], optical pacing may allow for almost limitless pacing sequence selections, inasmuch as illuminating an endocardial area of 1cm^2, following transfection with genes encoding light-sensitive ion channels, suffices for eliciting ventricular activation. Given that different channels are sensitive to different wavelengths, it follows that an array of colored flashes in the heart may in the future determine the choreography of left ventricle. Moreover, insertion of transmural implantable multi light-emitting diode optical probes has been shown [57], in animal models, to allow for transmural pacing.

Conclusions

Dyssynchrony has profound effects on cardiac function on the mechanical, electrical, cellular, and molecular levels. Thus, CRT is of paramount importance in alleviating these deleterious changes, although plagued by the phenomenon of non-response. The course of CRT has gone from BiVP being

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the sole available method to the existence of LB-CRT, MPP-CRT, LOT-CRT and (theoretically) CS-MPP. Although rigid evidence is not yet available, physiology and subgroup analyses allow for certain deductions. In cases without response to BiVP, following activation of all available add-ons and optimization of atrioventricular and interventricular delay, one may surmise that for patients with more defined conduction abnormalities and lower intraventricular activation dispersion (<20msec), H/LB-CRT should be considered, whereas in those with extensive distal disturbances in conduction and contractility, with increased dispersion (especially >30msec), the MPP approach should be prioritized. The former approach has the disadvantage of requiring the implantation of an additional lead; however, it also allows for the eventual application of CS-CRT or even CS-MPP, if the device is capable of providing them. Future developments in ECG imaging, CMR, optical pacing and cardiac simulation will further advance or completely overhaul our approach to treating dyssynchronous heart failure.

Table 1.

Feature	BiVP	MPP	CS-CRT
Clearly defined target population	Yes – based on landmark trials	No – a single criterion (electrical dispersion) is currently available for suggesting MPP additional benefit	Indications similar to CRT – there is a trend towards preferential implantation in those with textbook conduction deficits, however benefits extend to non-specific abnormalities as well
Complexity of implantation	Identical		Simpler, especially for LB-CRT
Maintenance of suitable dipoles presence	Most often	Attrition rate of up to 20%	Almost always in LB-CRT Most often in HB-CRT
Simplicity of programming	Average	Complex	Simple
Acute and long-term effects	Both MPP and CP-CRT appear to perform better than BiVP, especially when applied in most suitable cases – i.e., pronounced LV electrical dispersion and LBBB, respectively. H/LOT-CRT have been shown to be superior to conventional BiVP in terms of responder rates and QRS shortening.		
Pairing with additional modalities (Multi-fusion, hybrid approaches)	Feasible in all - however LB-CRT has to be delivered in the bipolar configuration in the presence of a defibrillator, potentially decreasing its efficacy.		

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