Multipoint left ventricular pacing provides additional echocardiographic benefit to responders and non-responders to conventional cardiac resynchronization therapy

Carlo Pappone1*, Žarko Ćalović1, Amarild Cuko1, Luke C. McSpadden2, Kyungmoo Ryu2, Caroline D. Jordan2, Massimo Saviano1, Mario Baldì1, Alessia Pappone1, Luca Dozza3, Luigi Giannelli1, Nikolaos Fragakis1, Gabriele Vicedomini1, and Vincenzo Santinelli1

1Department of Arrhythmology, GVM Care & Research, Maria Cecilia Hospital, Via Corriera, 1, Cotignola, RA 48010, Italy
2St. Jude Medical, Sylmar, CA, USA
3Clinical Research Unit, E.S. Health Science Foundation, Maria Cecilia Hospital, Cotignola, Italy

Cardiac resynchronization therapy (CRT) with multipoint left ventricular (LV) pacing [MultiPointTM Pacing (MPP), St. Jude Medical, Sylmar, CA, USA] improves LV function and clinical response relative to conventional CRT in patients receiving a de novo device implant. We hypothesized that patients with a previously implanted conventional CRT device would receive additional benefit by switching to MPP. Patients receiving a CRT implant (Unify Quadra MPTM or Quadra Assura MPTM CRT-D and QuartetTM LV lead, St. Jude Medical) were programmed to conventional CRT (i.e. biventricular pacing with right ventricular and single LV sites) optimized by intraoperative haemodynamic measurements. After 12 months of conventional therapy, patients were reprogrammed to MPP and re-evaluated at 16 months post-implant. Response to CRT was prospectively defined as reduction in end-systolic volume (ESV) of ≥15% relative to baseline as determined by a blinded observer. Eight patients with an implanted CRT device [New York Heart Association III, ejection fraction (EF) 30±5%, QRS 149±18 ms] received 12 months of conventional CRT and were switched to MPP. After 12 months of conventional CRT, ESV reduction and EF increase relative to baseline were −18±12 and +5±4%, respectively, and six of eight (75%) patients were considered CRT responders. After 4 months of MPP, two of two (100%) patients classified as non-responders to conventional CRT became responders with additional reduction in ESV of −33 and −20% and improvement in EF of +15 and +4%. The remaining six patients classified as responders experienced additional reduction in ESV of −13±21% and improvement in EF of +7±7% after switching to MPP. Multipoint LV pacing may provide additional improvement to LV function in patients receiving conventional CRT.

KEYWORDS
Heart failure; Cardiac resynchronization therapy; CRT response; Multipoint pacing

Introduction
Symptomatic heart failure patients with prolonged QRS duration benefit from cardiac resynchronization therapy.
Switch from conventional CRT to multipoint LV pacing

(CRT), but the therapy is partly limited by the 30–40% of patients that do not respond adequately. Multipoing left ventricular (LV) pacing [MultiPoint™ Pacing (MPP), St. Jude Medical, Sylmar, CA, USA] is a new CRT modality that enables sequential pacing from two LV sites (LV1 and LV2) through a quadripolar LV lead and from one right ventricular (RV) site. MultiPoint™ Pacing provides benefit to acute LV haemodynamics, and peak radial strain and to mid-term LV function beyond conventional CRT. Previous studies have focussed on the acute and chronic benefits of MPP in patients receiving de novo CRT systems. In this study, we hypothesized that patients receiving conventional CRT would receive additional benefit by switching the CRT programming to MPP.

Methods

Patient selection

Patients implanted with a CRT device with the ability to deliver MPP (Unify Quadra MP™ or Quadra Assura MP™, St. Jude Medical) initially programmed to conventional simultaneous biventricular pacing and who were switched to MPP were included in this analysis. Informed consent was obtained from all patients. Pre-implant inclusion criteria were an approved indication for CRT implant according to current ESC/EHRA guidelines. Primary exclusion criteria were New York Heart Association (NYHA) Class IV and myocardial infarction within 40 days prior to enrolment.

Implant procedure

Patients were implanted with an MPP-enabled CRT device according to standard practice. A quadripolar LV lead (Quartet™, L V lead, St. Jude Medical) with electrodes D1, M2, M3, and P4 (distal to proximal) was targeted to a lateral, posterolateral, or anterolateral branch of the CS.

Device programming

The CRT device was programmed post-implant to simultaneous biventricular pacing with LV vector selection based on intraoperative haemodynamic measurements. Pressure–volume (PV) loops were recorded during a pacing protocol including conventional CRT interventions with either a distal or a proximal LV electrode paced simultaneously with the RV. The intervention resulting in the largest relative increase in $dP/dt_{\text{Max}}$ was selected for programming. Device pacing settings were left unchanged for the following 12 months.

Two months post-implant, coinciding with the commencement of the investigation reported here, MPP was activated. Left ventricular pacing vectors for MPP were empirically chosen to pace first with the distal electrode (D1) as cathode and second from the most proximal electrode not having a high capture threshold (>5 V) or causing phrenic nerve stimulation. The sequence of pacing was defined in advance to be LV1 → LV2 → RV in all patients. Minimum programmable LV1–LV2 delays (5 ms) and LV2–RV delays (20 ms for Unify Quadra MP™ and 5 ms for Quadra Assura MP™) were empirically selected based on our previous experience. No optimization of atrioventricular delay was performed for either conventional CRT or MPP.

Echocardiographic and clinical exam

Patients underwent echocardiographic and clinical evaluation prior to implant (baseline), at 12 ± 1 months post-implant, and at 4 ± 1 months after the switch to MPP (16 ± 1 months post-implant). A transthoracic echocardiography system (iE33, Philips, Amsterdam, The Netherlands) was used to measure LV end-systolic (ESV) and end-diastolic volume (EDV) and to derive the ejection fraction (EF). Changes in LV ESV were expressed as a percent change relative to baseline or 12 months and changes in LV EF were expressed as an absolute difference relative to baseline or 12 months. We prospectively defined CRT response by the commonly used criterion of reduction in ESV of ≥15% relative to baseline.

Statistical analysis

Comparisons between measurements after 12 months of conventional CRT and after 4 months of MPP were made with a 2-sample paired t-test. A $P$-value of <0.05 was considered significant. All continuous variables are expressed as mean ± standard deviation.

Results

Study population

Twelve patients were switched to MPP after 12 months of conventional CRT and underwent echocardiographic and clinical evaluation within the 4 ± 1 month window. Eight patients had echocardiographic data deemed evaluable and were included in subsequent analyses. Baseline patient characteristics pre-implant from these eight patients are shown in Table 1.

Implant procedure and post-implant device programming

The quadripolar LV lead (Quartet™, St. Jude Medical) position was classified along the LV short axis as lateral in six patients (75%), anterolateral in one patient (13%), and posterolateral in one patient (13%). Left ventricular lead position along the LV long axis was classified as apical in two

### Table 1 Baseline patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline value (n = 8 patients)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 6</td>
</tr>
<tr>
<td>Gender: male (%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>Ischaemic aetiology, n (%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>NYHA functional class III, n (%)</td>
<td>8 (100%)</td>
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<tr>
<td>LVEF, %</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>LV ESV (mL)</td>
<td>156 ± 47</td>
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<tr>
<td>LV EDV (mL)</td>
<td>224 ± 74</td>
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<tr>
<td>QRS duration (ms)</td>
<td>149 ± 18</td>
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<tr>
<td>LBBB morphology, n (%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 13</td>
</tr>
</tbody>
</table>
patients (25%), mid-ventricular in four patients (50%), and basal in two patients (25%). The RV lead was placed in the RV apex in five patients (63%) and in a septal position in three patients (38%). Left ventricular pacing vectors programmed post-implant for conventional CRT are shown in Table 2.

**Echocardiographic and clinical findings at 12-month follow-up**

After 12-months of conventional CRT, the ESV reduction and EF increase relative to BASELINE in this group of patients was $-18 \pm 12$ and $+5 \pm 4\%$, respectively, and six of eight (75%) patients were considered CRT responders. All patients improved from NYHA functional class III to class II.

**MultiPoint™ Pacing programming**

Left ventricular vector combinations and pacing delays for MPP programmed at the end of the 12-month visit are shown in Table 2. The LV1 cathode was D1 in eight of eight (100%) patients, whereas the LV2 cathode was P4 in three of eight (37.5%) patients, M3 in two of eight (25%) patients, and M2 in three of eight (37.5%) patients.

**Changes in echocardiographic and clinical findings after 4 months of MultiPoint™ Pacing**

After 4 months of MPP, the ESV reduction and EF increase relative to baseline was significantly improved compared with after 12 months of conventional CRT (ESV: $-31 \pm 18\%$, $P = 0.048$; EF: $+13 \pm 8\%$, $P = 0.017$, see Figure 1). New York Heart Association functional class improved to class I in three of eight (37.5%) patients and remained at class II in the remaining five of eight (62.5%) patients. Patient characteristics and follow-up measurements from all patients are shown in Table 3.

The two patients classified as non-responders to conventional CRT at the 12-month exam both became responders with MPP while experiencing an additional reduction in ESV of $-33$ and $-20\%$ and an improvement in EF of $+15$ and $+4\%$ relative to the 12-month exam (Figure 2).

The remaining six patients classified as responders to conventional CRT experienced additional reduction in ESV of $-13 \pm 21\%$ and improvement in EF of $+7 \pm 7\%$ relative to the 12-month exam after switching to MPP. Five of the six responders to conventional CRT remained responders with MPP, with four patients experiencing additional ESV change of at least $-10\%$. One of the six responders to 12 months of conventional therapy experienced ESV increase from 137 to 159 mL and EF decrease from 35 to 31% and was considered a non-responder with MPP (see Patient 3 in Table 3).

![Figure 1](https://academic.oup.com/eurheartjsupp/article-abstract/17/suppl_A/A12/413962 by guest on 11 March 2019)
MultiPoint™ Pacing delivered through a quadripolar LV lead has thus far been shown to provide acute benefit as measured by LV $dP/dt_{\text{Max}}$, LV dyssynchrony, LV peak radial strain, LV PV loop parameters, and LV electrical activation. Additionally, our recent work has suggested mid-term improvement in LV reverse remodelling and LV function with MPP over conventional CRT. However, previous evaluations of MPP have focussed on patients receiving de novo CRT implants. In this study, we evaluated the role of programming settings to deliver MPP in patients already receiving conventional CRT and observed further improvements in LV ESV and LV EF beyond that seen with conventional CRT. Previous work has demonstrated an acute and chronic benefit of biventricular pacing with MPP in a single CS branch when compared with conventional CRT in de novo CRT implants. An early feasibility study utilizing pressure wire measurements by Thibault et al. in 21 patients showed an increase in LV $dP/dt_{\text{Max}}$ with MPP compared with simultaneous biventricular pacing. A multicentre study using tissue Doppler imaging and speckle tracking echocardiography, Rinaldi et al. demonstrated an improvement in acute mechanical LV dyssynchrony and in acute global peak LV radial strain during delivery of MPP. A recent study of 15 patients compared MPP in a single CS branch with multisite LV pacing with two leads in two different CS branches and found no difference in acute LV $dP/dt_{\text{Max}}$ improvement between the two dual LV pacing modalities, which both offered significant improvement over baseline pacing. In a study evaluating intraoperative LV haemodynamics, our group reported significant improvement in systolic and diastolic parameters during the best tested MPP intervention relative to the best tested conventional BiV pacing intervention using PV loop analysis. After randomization to receive biventricular pacing with MPP or conventional CRT optimized by PV loop measurements, mid-term follow-up results showed greater reduction in LV ESV and improvement in LV EF in the MPP group.

While prior studies of MPP delivered from a single CS branch have focussed on de novo CRT implants, the effect of adding a second LV pacing site to patients with a previously implanted CRT system has been evaluated in the V3 trial. Non-responders to conventional CRT for at least 6 months were randomized to receive triple-site ventricular pacing with the addition of a second LV lead or continue with conventional biventricular pacing. After 12 months, the group receiving a second LV lead showed no improvement relative to the conventional CRT group in the primary endpoint of clinical composite score or in secondary endpoints including echocardiographic indices of remodelling.

In the current study, we evaluated the addition of a second LV pacing site by activating MPP in both responders and non-responders to 12 months of conventional biventricular pacing. We observed significant improvement in LV reverse remodelling and LV function after 4 months of MPP compared with the improvement after 12 months of conventional CRT in our patient population. In particular, the two patients identified as non-responders to

<table>
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<tr>
<th>Patient</th>
<th>QRS duration (ms)</th>
<th>QRS morphology</th>
<th>ESV (mL)</th>
<th>EF (%)</th>
<th>NYHA class</th>
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<tr>
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<td>Non-LBBB</td>
<td>236</td>
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<td>6</td>
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<td>7</td>
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<td>124</td>
<td>LBBB</td>
<td>174</td>
<td>28</td>
<td>III</td>
</tr>
</tbody>
</table>

*Non-responder after 12 months of conventional CRT according to ESV decrease $<15\%$. 
Conclusions

Multipoint LV pacing, when activated in patients with a pre-existing CRT device, may provide additional benefits beyond those gained from conventional biventricular pacing. In a small, non-randomized study population, we observed significant improvements in LV end-systolic volume and LV EF after activation of MPP in a combined group of both responders and non-responders to 12 months of conventional CRT. Our results suggest that activating MPP may be a potential strategy to convert non-responding patients to responders or to further improve response in patients already responding to the conventional therapy. Further randomized studies are needed to confirm these observations in a larger population.

Conflict of interest: L. M., K. R., and C. J. are employees of St. Jude Medical. C. P. has received consultancy fees from St. Jude Medical and Biotronik.

References


Figure 2 Changes in end-systolic volume and ejection fraction with conventional cardiac resynchronization therapy and MultiPointTM Pacing. Change in (A) left ventricular end-systolic volume and (B) left ventricular ejection fraction as a percentage relative to baseline after 12 months of conventional cardiac resynchronization therapy followed by 4 months of MultiPointTM Pacing.


