Haemodynamic effects of cardiac resynchronization therapy using single-vein, three-pole, multipoint left ventricular pacing in patients with ischaemic cardiomyopathy and a left ventricular free wall scar: the MAESTRO study

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Aims

The clinical response to cardiac resynchronization therapy (CRT) is variable. Multipoint left ventricular (LV) pacing could achieve more effective haemodynamic response than single-point LV pacing. Deployment of an LV lead over myocardial scar is associated with a poor haemodynamic response to and clinical outcome of CRT. We sought to determine whether the acute haemodynamic response to CRT using three-pole LV multipoint pacing (CRT3P-MPP) is superior to that to conventional CRT using single-site LV pacing (CRTSP) in patients with ischaemic cardiomyopathy and an LV free wall scar.

Methods and results

Sixteen patients with ischaemic cardiomyopathy [aged 72.6 ± 7.7 years (mean ± SD), 81.3% male, QRS: 146.0 ± 14.2 ms, LBBB in 14 (87.5%)] in whom the LV lead was intentionally deployed straddling an LV free wall scar (assessed using cardiac magnetic resonance), underwent assessment of LV +dP/dtmax during CRT3P-MPP and CRTSP. Interindividually, the ΔLV +dP/dtmax in relation to AAI pacing with CRT3P-MPP (6.2 ± 13.3%) was higher than with basal and mid CRTSP (both P < 0.001), but similar to apical CRTSP. Intraindividually, significant differences in the ΔLV +dP/dtmax to optimal and worst pacing configurations were observed in 10 (62.5%) patients. Of the 8 patients who responded to at least one configuration, CRT3P-MPP was optimal in 5 (62.5%) and apical CRTSP was optimal in 3 (37.5%) (P = 0.0047).

Conclusions

In terms of acute haemodynamic response, CRT3P-MPP was comparable to apical CRTSP and superior to basal and distal CRTSP. In the absence of within-device haemodynamic optimization, CRT3P-MPP may offer a haemodynamic advantage over a fixed CRTSP configuration.

Keywords

Cardiac resynchronization therapy • Multipoint pacing • Multipolar leads • Haemodynamics

Introduction

Cardiac resynchronization therapy (CRT) is well established as a therapy for patients with heart failure, impaired left ventricular (LV) function, and a wide QRS complex. Even after a successful implantation, however, the response to CRT is variable.1 This may be due to the underlying aetiology of heart failure2 and to suboptimal LV lead deployment over scarred myocardium.3–5

Intuitively, simultaneous multipoint LV pacing could achieve more effective resynchronization than pacing from a single site by...
bypassing scarred myocardium. Improvement in the acute haemodynamic response to CRT has been observed with simultaneous, two-vein LV pacing.6 This procedure, however, is associated with lower implant success rates and a longer implantation time.7,8 Multipolar (MP) LV leads overcome such implantation issues and permit electronic repositioning of LV pacing sites as well as single-vein, simultaneous multipoint pacing (MPP). 9 Acute10,11 and short-term12 have suggested that simultaneous MPP from a single LV lead is associated with an improved haemodynamic response and LV reverse remodelling.

It is unclear whether MPP CRT is superior to CRT using single-site LV pacing (CRTSP) when the LV lead is deployed over scarred myocardium. We hypothesized that simultaneous MPP may generate multiple wavefronts that may, independently or by summation, lead to a more rapid and uniform LV synchronization and hence, a better haemodynamic response than CRTSP. In this context, we explored whether CRT using a three-point LV MPP (CRT3P-MPP) is superior to CRTSP in patients who are least likely to respond to CRT, namely those with ischaemic cardiomyopathy in whom the LV lead is deployed over an LV free wall scar.

**Methods**

The Multipoint pAcing and Electronic repoSitioning in the opTimization of left ventriculaR pacing site in cardiac resynchrOnization therapy (MAESTRO) study is an acute study of the haemodynamic effects of CRT3P-MPP in patients undergoing CRT.

**Patients**

Inclusion criteria were left ventricular ejection fraction (LVEF) ≤ 35%, a QRS ≥ 120 ms, New York Heart Association (NYHA) Classes II–IV, and ischaemic cardiomyopathy. Exclusion criteria were frequent

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**Figure 1** The MP LV lead. (A) Schematic diagram of the 16-pole Pathfinder mapping catheter (Cardima, Inc., Duluth, GA). A: connector; B: 2.5 F diameter (0.84 mm); C: electrode length of 0.8 mm; D: inter-electrode length of 2 mm; E: electrode spacing of 6 mm; F: tip coil length of 15 mm; G: maximum proximal-to-distal electrode spacing of 70.8 mm. (B) Right anterior oblique fluoroscopic view of the heart following instrumentation, prior to application of pacing protocols, showing the MP LV lead deployed in a posterolateral vein. In the procedure, a right atrial lead was deployed in the right atrial appendage, and RV lead was deployed in the RV apex. A pressure wire was introduced into the LV cavity via a catheter.
ventricular ectopics, atrial fibrillation, mechanical aortic valve or significant valvular disease, and significant peripheral vascular disease. The aetiology of heart failure was confirmed on the basis of clinical history, the finding of impaired LV function on echocardiography. The diagnosis of ischaemic cardiomyopathy with transmural or subendocardial myocardial scar was defined by late-gadolinium enhancement cardiac magnetic resonance (CMR). The study was approved by the local Ethics Committee and complied with the Declaration of Helsinki. All patients provided written informed consent.

Procedure set-up
Patients were sedated with intravenous midazolam (5–10 mg) and fentanyl (50–100 μg), titrated to achieve deep, conscious sedation without respiratory depression, and assessed using continuous pulse oximetry. Left cephalic and/or single-puncture axillary/subclavian access was used as access for all leads. Right atrial leads were deployed in the right atrial appendage and right ventricular (RV) leads in the RV apex. A temporary MP LV lead (Pathfinder, Cardima, Inc., Duluth, Georgia) (Figure 1A) was deployed in the coronary vein with the intention of overlaying scar tissue, localized using a pre-implant CMR scan. Simultaneously, a second operator introduced a 0.014″ high-fidelity pressure wire (PressureWire Certus, St Jude Medical, Minnesota) retrogradely through the aortic valve and into the LV cavity using a multipurpose catheter, introduced via the right femoral artery for the measurement of beat-to-beat intraventricular pressure (Figure 1B). Systemic anticoagulation was achieved with peripheral intravenous heparin, titrated to achieve activated clotting time of 350 s during the procedure.

Pacing protocol
As shown in Figure 2, atrial pacing (AAI) at 10 beats above the intrinsic heart rate was used as reference. A sampling period of 10 beats prior and 10 beats immediately after activating biventricular pacing (BVP) was used for analysis. This was repeated four times (15 s) for each BVP intervention to minimize sampling error, the effects of respiration, and variation in loading conditions. The BVP order was randomized for each patient. BVP was delivered by apical RV pacing in combination with the following LV pacing configurations (LVPCs): distal: poles 1–2; middle: poles 9–10; proximal: poles 15–16; simultaneous 3P-MPP: poles 1–2, 9–10, and 15–16. The paced atrioventricular (AV) delay was 120 ms, and the interventricular (VV) delay was 0 ms (simultaneous) for all LVPCs. Intraoperatively, LV capture was verified by visualizing changes in QRS morphology in chest lead V2. Capture was also checked for all LVPCs on the offline analysis. The MP LV lead has 16 poles, with electrode lengths of 0.8 mm, an inter-electrode spacing of 2 mm, electrode-pair spacing 6 mm, and a distal-to-proximal pole spacing of 70.8 mm.

Lead positions
The tip of MP LV lead was deployed as distally as possible in a coronary vein overlaying myocardial scar, as shown in Figure 1. The position of the pacing poles on the MP LV lead was then used to define pacing vectors according to the convention of Albertsen et al. Briefly, the position of pacing poles along the long axis of the LV (basal, mid, or apical) was determined by measuring the distance from the coronary sinus (assumed to run along the AV groove) to the apex, using 30° right anterior oblique fluoroscopic view. The circumferential position over the LV free wall was determined using the o’clock method, in which the great cardiac vein (anterior interventricular vein) is assumed to be at a 12 o’clock position and the inferior vein at a 6 o’clock position. The precise segment subtended by the LV poles was identified using these coordinates, with reference to the AHA 17-segment model. In this study, LV pacing pole position (basal, mid, and apical) refers to the myocardial segment subtended by the LV pacing poles, rather than the position of the pacing poles along the lead. This is an important distinction, as pacing poles on the MP LV lead did not always coincide with anatomical myocardial segments (Supplementary material online, Table S1).
Data analysis

Beat-to-beat LV intraventricular pressure, 12-lead surface electrocardiogram (ECG) and electrograms (EGM) data were acquired simultaneously using the Prucka system (General Electric, Connecticut). Analysis was undertaken offline. The RASCHlab v0.3.0 software package (Raphael Schneider, Medtronic, Inc.) was used to annotate segments according to pacing protocol. The dataset was then converted into a MATLAB (The Mathworks, Inc., Massachusetts) compatible format for further analysis. Non-captured beats and ventricular ectopic beats plus the subsequent two beats were identified visually and excluded from further analysis. Results are expressed as mean of the medians calculated for each of the four iterations for each intervention and expressed as percentage change in LV $+dP/dt_{\text{max}}$ in relation to reference AAI pacing (Figure 2). An acute haemodynamic response was defined as a $\geq 10\%$ increase in LV $+dP/dt_{\text{max}}$. The optimal and worst pacing sites were defined as those with the highest and lowest mean LV $+dP/dt_{\text{max}}$, respectively, in relation to AAI pacing.

Cardiac magnetic resonance

This was undertaken using a 1.5 Tesla scanner (Avanto, Siemens, Erlangen, Germany) and a phased array cardiac coil. A short-axis LV stack was acquired using a steady state in free precession sequence (repetition time 3.0–3.8 ms; excitation time 1.0 ms; image matrix 224 $\times$ 224; field of view 36–42 cm; flip angle 45°) in sequential 7 mm slices (3 mm inter-slice gap) from the AV ring to apex. Acquisition was performed during gated 8 s breath-holds (20 phases). Left end-diastolic (LVEDV) and end-systolic (LVESV) ventricular volumes were quantified using semi-automatic manual planimetry of all short-axis SSFP cine images with CMR 42 analysis software (CVI, Inc., Calgary). The observer was blinded to echocardiographic and clinical data.

Cardiac magnetic resonance

This was undertaken using a 1.5 Tesla scanner (Avanto, Siemens, Erlangen, Germany) and a phased array cardiac coil. A short-axis LV stack was acquired using a steady state in free precession sequence (repetition time 3.0–3.8 ms; excitation time 1.0 ms; image matrix 224 $\times$ 224; field of view 36–42 cm; flip angle 45°) in sequential 7 mm slices (3 mm inter-slice gap) from the AV ring to apex. Acquisition was performed during gated 8 s breath-holds (20 phases). Left end-diastolic (LVEDV) and end-systolic (LVESV) ventricular volumes were quantified using semi-automatic manual planimetry of all short-axis SSFP cine images with CMR 42 analysis software (CVI, Inc., Calgary). The observer was blinded to echocardiographic and clinical data.

For scar imaging, short-axis slices identical to the LV stack were acquired using a segmented inversion-recovery technique 10 min after the intravenous administration of gadolinium–diethylenetriaminepentaacetic acid (0.1 mmol/kg). Myocardium was nulled by adjusting inversion times (260–400 ms). Myocardial scars were confirmed as ischaemic in aetiology if they were subendocardial or transmural in coronary artery territories, according to McCrohon et al. 13 An LV free wall scar was defined as a transmural or subendocardial scar in the LV free wall portion (lateral to AV line) of segments 1, 4, 5, 6, 7, 10, 11, 12, 13, 15, 16, and 17, according to the AHA 17-segment model.

Statistical analysis

All results are expressed as mean $\pm$ standard deviation (SD). Each pacing protocol was compared with each other using ANOVA, with a post hoc Tukey correction. The t-test was used to compare optimal
vs. worst BVP protocols. A P-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS v22.0. (SPSS, Inc., Chicago, IL) and MedCalc v12. (MedCalc, Broekstraat, Belgium).

**Results**

**Baseline characteristics**

Sixteen patients [aged 72.6 ± 7.7 years (mean ± SD), 81.3% male] with ischaemic cardiomyopathy, a QRS of 146.0 ± 14.2 ms, LBBB in 14 (87.5%), and on maximum tolerated pharmacological therapy were studied (Table 1). All patients had evidence of a subendocardial or a transmural myocardial infarction over the LV free wall on CMR, and all leads were proved to have been deployed over an LV scar. The haemodynamic protocol was successfully completed in all patients. One post-procedural femoral haematoma required manual compression. No acute or other peri-procedural complications were observed. No arrhythmias were observed during any of the pacing protocols.

![Figure 4](https://example.com/figure4.png)

**Figure 4** Comparison of optimal and worst LVPCs in individual patients. (A) Individual patient mean %ΔLV + dP/dt<sub>max</sub> in the optimal (turquoise) and worst (red) pacing configurations, in relation to AAI pacing. The dotted line denotes the ≥10% ΔLV + dP/dt<sub>max</sub> used as definition of response. For statistical analysis, see Table 2; (B) ΔLV + dP/dt<sub>max</sub> in pooled optimal and worse pacing configurations.
**Interindividual analysis**

This revealed that the \( \Delta LV + dP/dt_{max} \) with CRT\(_{3P-MPP}\) (6.2 \( \pm \) 13.3\%) was higher than that with basal and mid CRT\(_{SP}\) (both \( P < 0.001 \)), but similar to that with apical CRT\(_{SP}\) (Figure 3A). Accordingly, the haemodynamic response rates for CRT\(_{3P-MPP}\) were similar to those for apical CRT\(_{SP}\) and higher than those for basal and mid CRT\(_{SP}\) (Figure 3B).

**Intraindividual analysis**

As shown in Figure 4A, each patient had an optimal and a worst LVPC. As given in Table 2, significant differences in the intraindividual \( \Delta LV + dP/dt_{max} \) to optimal and worst pacing configurations were observed in 10 (62.5\%) patients and amounted to as much as a 21.7\% change in 1 patient. When pooled together into optimal and worst sites was as much as 22\% in one patient. These findings support the notion that ‘electronic repositioning’ within an MP lead ofﬁfers an opportunity for optimizing a haemodynamic response over a broad area of LV lateral wall, particularly in more anterior than posterior and more apical than basal. We should consider, however, that in MADIT–CRT, the superiority of an apical position was associated with a worse clinical outcome. This finding is at odds with animal studies, which have shown that an optimum response to CRT can be achieved over a broad area of LV lateral wall, particularly in more anterior than posterior and more apical than basal. This is consistent with our finding of a comparable haemodynamic response with CRT\(_{3P-MPP}\) and apical CRT\(_{SP}\) in patients with ischaemic cardiomyopathy.

### Table 2 Comparison of the optimal and worst LV pacing configurations

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Mean % difference in ( \Delta LV + dP/dt_{max} )</th>
<th>95% CI</th>
<th>( p^* )</th>
<th>Optimal configuration</th>
<th>Worst configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.79</td>
<td>-2.72 to 6.31</td>
<td>0.3792</td>
<td>APICAL</td>
<td>MID</td>
</tr>
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<td>2</td>
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<td>BASAL</td>
</tr>
<tr>
<td>3</td>
<td>1.51</td>
<td>-4.98 to 8.00</td>
<td>0.5995</td>
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<td>3P-MPP</td>
</tr>
<tr>
<td>4</td>
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<td>MID</td>
</tr>
<tr>
<td>5</td>
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</tr>
<tr>
<td>6</td>
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<td>7</td>
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<td>BASAL</td>
</tr>
<tr>
<td>8</td>
<td>17.3</td>
<td>13.0–21.7</td>
<td>&lt;0.0001</td>
<td>APICAL</td>
<td>MID</td>
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<tr>
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<td>20.3</td>
<td>15.7–24.9</td>
<td>&lt;0.0001</td>
<td>APICAL</td>
<td>BASAL</td>
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<tr>
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<td>3.36–6.96</td>
<td>0.0003</td>
<td>3P-MPP</td>
<td>BASAL</td>
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<tr>
<td>13</td>
<td>7.89</td>
<td>5.36–10.4</td>
<td>0.0002</td>
<td>3P-MPP</td>
<td>BASAL</td>
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<tr>
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<td>APICAL</td>
</tr>
<tr>
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</tr>
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<td>0.0013</td>
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\( p^* \)-value refers to difference between optimal and worst \( \Delta LV + dP/dt_{max} \) for each patient.

**Optimizing left ventricular pacing sites**

Several large clinical studies have shown no difference in clinical outcome from different pacing sites over the LV free wall. On the other hand, a sub-analysis of the MADIT–CRT (Multicenter Automatic Deﬁbrillator Implantation Trial–Cardiac Resynchronization Therapy) study showed that an apical LV pacing position was associated with a worse clinical outcome. This finding is at odds with animal studies, which have shown that an optimum response to CRT can be achieved over a broad area of LV lateral wall, particularly in more anterior than posterior and more apical than basal. This is consistent with our finding of a comparable haemodynamic response with CRT\(_{3P-MPP}\) and apical CRT\(_{SP}\) in patients with ischaemic cardiomyopathy.

The intraindividual analysis showed that patients had different optimal LVPCs. The difference in \( \Delta LV dP/dt_{max} \) between the best and worst sites was as much as 22\% in one patient. These findings support the notion that ‘electronic repositioning’ within an MP lead offers an opportunity for optimizing a haemodynamic response over a conventional bipolar LVPC. It follows, therefore, that the choice of a fixed pole on the basis of threshold alone, as is usual practice, may not achieve the best haemodynamic response. Further studies could explore whether haemodynamic optimization of LVPCs in an MP platform, perhaps undertaken using an appropriate sensor, leads to simulating LV activation. We found that (1) there were varying haemodynamic responses to CRT, depending on which pacing configuration was used; (2) intraindividually, CRT\(_{3P-MPP}\) was optimal in 44\% of patients and apical CRT\(_{SP}\) was optimal in 56\%; and (3) in patients who responded haemodynamically to at least one configuration, CRT\(_{3P-MPP}\) was optimal in 63\%.

**Discussion**

We have assessed the haemodynamic response to different LVPCs of an MP LV pacing lead, including CRT\(_{3P-MPP}\), in patients who are least likely to respond to CRT, namely those with ischaemic cardiomyopathy in whom the LV lead is deployed over an LV free wall scar. A long proximal-to-distal interpole distance (70.8 mm) was used in order to maximize the amount of myocardium available for simultaneous LV activation. We found that (1) there were varying haemodynamic responses to CRT, depending on which pacing configuration was used; (2) intraindividually, CRT\(_{3P-MPP}\) was optimal in 44\% of patients and apical CRT\(_{SP}\) was optimal in 56\%; and (3) in patients who responded haemodynamically to at least one configuration, CRT\(_{3P-MPP}\) was optimal in 63\%.
however, the ‘baseline’ adopted in this study was RV pacing, rather than intrinsic rhythm or AAI pacing. Consequently, we can infer that in relation to RV pacing, the $\Delta LV + dP/dt_{\text{max}}$ is higher for MPP than for CRT$_{SP}$, but no conclusions can be drawn regarding the effects of MPP in comparison with intrinsic biventricular conduction. On the other hand, Thibault et al. have shown that MPP was associated with a higher LV + dP/dt$_{\text{max}}$ than conventional (AAI) bipolar pacing and that MPP was the best pacing configuration in 72% of patients. Ri- naldi et al. have shown that MPP improves mechanical dyssynchrony, assessed using tissue Doppler imaging. In the present study, CRT$_{3P-MPP}$ was the optimum configuration in 44% of all patients and in 63% of patients who responded to at least one configuration. Studies on MPP have so far assessed the effects of two-point LV pacing using a quadrupolar lead (St Jude Medical, Sylmar, CA) spanning 47 mm from proximal to distal pole. In the present study, MPP was delivered simultaneously from three pole pairs, spanning a greater distance of 70.8 mm along the LV free wall, which covered the entire anatomical distance from base to apex in 10 (62.5%) pa- tients. While both the distance covered by the lead and the energy delivered simultaneously vary between our study and others, the findings are broadly consistent.

**The influence of scar**

It is well recognized that an ischaemic aetiology of heart failure is as- sociated with a worse outcome than non-ischaemic cardiomyop- athy. We have previously shown that LV pacing over myocardial scar during CRT is associated with a worse clinical outcome. Using pressure–volume loops and CMR, De Roest et al. have recently shown that pacing over myocardial scar is associated with a reduction in cardiac stroke work, whereas pacing from viable myocardium led to a significant increase. We hypothesized that multiple wavefronts arising from simultaneous LV pacing may circumvent myocardial scar and lead to a better haemodynamic re- sponse. Accordingly, we deliberately deployed the LV lead straddling scarred myocardium. In the present study, we have found that even in patients who are least likely to respond to CRT (ischaemic cardiomyopathy with the LV lead deployed over myocardial scar), CRT$_{3P-MPP}$ leads to a haemodynamic response in 44% of pa- tients. Of the patients who responded to at least one LVPC, CRT$_{3P-MPP}$ was best in 63% of cases. This is consistent with a bio- physical modelling study of Niederer et al., who found that in the presence of scar, MPP resulted in an incremental improvement in LV + $dP/dt_{\text{max}}$ over conventional CRT$_{SP}$ and that maximizing the activation wave area, as would also be expected from CRT$_{3P-MPP}$, increased the acute haemodynamic response to CRT.

**Clinical implications**

This study shows that there is an intraindividual variability in the haemodynamic response to CRT. Our findings indicate that tailoring of pacing configurations is required to achieve the optimum re- sponse in individual patients. However, our extensive, invasive protocol is not applicable to routine clinical practice. On the other hand, our study suggests that MPP is as good as the best bipolar op- tion in some patients and better than others. Although further clin- ical outcome studies are clearly required, our findings make a case for the use of MPP in non-responders to CRT, perhaps in patients with ischaemic cardiomyopathy and an LV free wall scar.

**Three-pole left ventricular multipoint pacing**

An advantage of MP leads is the potential to pace simultaneously from different poles. Speculatively, multiple wavefronts arising from simultaneous LV pacing achieve more effective intraventricular synchronization and hence, a better haemodynamic response. In an acute study, Pappone et al. undertook LV pressure–volume loop assessments in 44 patients receiving a quadripolar LV lead. In relation to baseline, the best MPP intervention was associated with an increase in LV + $dP/dt_{\text{max}}$ stroke work, stroke volume, and LVEF, compared with the best CRT$_{SP}$ configuration. Importantly, to a clinical benefit. Speculatively, an appropriate algorithm could run through a number of LVPCs and identify the best $\Delta LV + dP/dt_{\text{max}}$ for each patient, on an iterative basis following device implantation.

**Figure 5** Haemodynamic response to all pacing configurations in individual patients. Typical examples of patients who derived a significant $\Delta LV + dP/dt_{\text{max}}$ in response to the all (a), some (b), and no (c) LVPCs. Results are shown in the form of radar maps, in which $\Delta LV + dP/dt_{\text{max}}$ in response to the different pacing configurations is plotted.
Limitations

An important limitation of this study, as similar studies, is the small number of patients studied. Notwithstanding, data acquisition in each patient was extensive, and pacing protocols were randomized in order to minimize sampling error and the effects of respiration and loading conditions. We should consider that $\Delta L V + dP/dt_{\text{max}}$ does not necessarily relate to a benefit from CRT.21

Conclusions

We have shown that, in patients who are least likely to respond to CRT, namely those with ischaemic cardiomyopathy in whom the LV lead is deployed over an LV free wall scar, CRT leads to varying haemodynamic responses, depending on the pacing configuration used. Intraindividually, CRT$_{3P-MPP}$ confers a comparable response to a bipolar, apical CRT$_{SP}$, and a superior response to basal and mid CRT$_{SP}$. In haemodynamic responders, CRT$_{3P-MPP}$ appears to be optimal in just over half of patients. Further clinical studies are needed to determine whether CRT$_{3P-MPP}$ is superior to CRT$_{SP}$ in patients with ischaemic cardiomyopathy and an LV free wall scar.

Supplementary material

Supplementary material is available at Europace online.

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