A comparison of left ventricular endocardial, multisite, and multipolar epicardial cardiac resynchronization: an acute haemodynamic and electroanatomical study

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Aims

Alternative forms of cardiac resynchronization therapy (CRT), including biventricular endocardial (BV-Endo) and multisite epicardial pacing (MSP), have been developed to improve response. It is unclear which form of stimulation is optimal. We aimed to compare the acute haemodynamic response (AHR) and electrophysiological effects of BV-Endo with MSP via two separate coronary sinus (CS) leads or a single-quadripolar CS lead.

Methods and results

Fifteen patients with a previously implanted CRT system received a second temporary CS lead and left ventricular (LV) endocardial catheter. A pressure wire and non-contact mapping array were placed into the LV cavity to measure LVdP/dt max and perform electroanatomical mapping. Conventional CRT, BV-Endo, and MSP were then performed (MSP-1 via two epicardial leads and MSP-2 via a single-quadripolar lead). The best overall AHR was found using BV-Endo pacing with a 19.6 ± 13.6% increase in AHR at the optimal endocardial site over baseline (P = 0.001). There was an increase in LVdP/dt max with MSP-1 and MSP-2 compared with conventional CRT, but this was not statistically significant. Biventricular endocardial pacing from the optimal site was significantly superior to conventional CRT (P = 0.039). The AHR achieved when BV-Endo pacing was highly site specific. Within individuals, the best pacing modality varied and was affected by the underlying substrate. Left ventricular activation times did not predict the optimal haemodynamic configuration.

Conclusion

Biventricular endocardial pacing and not MSP was superior to conventional CRT, but was highly site specific. Within individuals, however, different methods of stimulation are optimal and may need to be tailored to the underlying substrate.

Keywords

Cardiac resynchronization therapy • Multisite pacing • Haemodynamics • Electrophysiology mapping

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure, but 30–40% of patients do not respond.1–3 The optimal site of acute haemodynamic response (AHR) to CRT varies between patients and may need to be individualized.2–4 In an effort to improve CRT response, alternative methods of CRT delivery, including biventricular endocardial (BV-Endo) and multisite epicardial pacing (MSP), have been developed. Pacing the left ventricle (LV) endocardially or from more than one coronary sinus (CS) site can improve CRT response.5,6,7 The implantation of two separate CS leads is technically challenging, and recently introduced quadripolar LV leads can deliver MSP through a single lead.8,9 Biventricular endocardial pacing is not limited by CS anatomy allowing lead positioning to a target area, which may give rise to a more physiological electrical and mechanical propagation with a better AHR,10 particularly in patients with an ischaemic cardiomyopathy.11 A recent chronic canine study on ischaemic heart failure demonstrated that...
What’s new?

- This is the first study to compare the acute hemodynamic response and electrophysiological effects of Multi-Site Pacing (MSP) using two separate coronary sinus leads with MSP using a single quadripolar pacing lead and with biventricular endocardial pacing.
- Consistent with animal work, we have found that biventricular endocardial pacing was significantly better than conventional CRT and better overall than either method of MSP tested.
- Within patients, however, the best endocardial pacing site and the best pacing modality vary and thus the method of CRT delivery needs to be tailored to the individual.

BV-Endo pacing was superior to MSP delivered from separate epicardial leads, but the site of best BV-Endo response varied. To date, no studies in patients with heart failure have compared BV-Endo pacing with MSP delivered from two epicardial CS sites and from a single-quadripolar lead to determine which is optimal.

We hypothesized that different forms of LV stimulation would produce different haemodynamic responses in chronic heart failure patients, which would be determined by the LV electrical activation pattern. We performed a head-to-head comparison of the AHR to BV-Endo pacing and MSP via two CSLV leads and via a single-quadripolar lead. Non-contact electro-anatomical mapping (NCM) was performed to define the underlying substrate and the effect of different forms of stimulation on the LV endocardial activation time (LVATs).

Methods

The study complies with the Declaration of Helsinki, the protocol was approved by the local ethics committee and informed consent was obtained from each patient. We studied 15 patients with the standard criteria for CRT [New York Heart Association (NYHA) Class II–IV drug refractory heart failure, LVEF < 35%, and QRS ≥ 120 ms] who had been previously implanted with a CRT-defibrillator (CRT-D) system incorporating a quadripolar LV pacing lead (Quartet Model 145SQ, St Jude Medical). Patients with a mechanical aortic valve or significant peripheral vascular disease were excluded. Baseline assessment included NYHA functional class, electrocardiogram, and 2D echocardiography pre-CRT implant. Heart failure aetiology was confirmed on the basis of clinical history, coronary angiography, and cardiac magnetic resonance imaging.

Invasive haemodynamic and electroanatomical study

Patients underwent an invasive study at least 3 months following CRT-D implant. Light sedation was used. Bilateral femoral venous access was attained to place a quadripolar electrophysiological catheter in the high right atrium and a bipolar LV pacing lead (EPI2) (QuickFlex Micro 125BT/92 LV, St Jude Medical) via a long sheath (SL3, St Jude Medical), in a CS vein tributary as far separated as possible from the chronically implanted LV lead. A steerable 6F Livewire decapolar catheter (St Jude Medical) was passed from a femoral artery retrogradely to perform endocardial pacing from multiple sites within the LV cavity (Figure 1). A non-contact mapping (NCM) array was passed via 10F femoral arterial access (in the contralateral femoral artery) retrogradely across the aortic valve into the LV cavity. The NCM array was used to reconstruct endocardial potentials within the LV cavity and the chamber geometry was reconstructed using a locator signal from the LV decapolar catheter. Intravenous heparin (70 µg/kg) was administered to achieve systemic anticoagulation (target-activated clotting time 300–350 s).

A 0.014 inch diameter high-fidelity Certus PressureWire and PhysioMon software (RADI Medical Systems) was placed retrogradely into the LV cavity via the NCM to assess real-time mean peak LVdP/dt_{max} Atrial pacing (AAI) or right ventricular (RV) pacing (AF patient) at 5–10 beats above the intrinsic rate was considered baseline and was kept constant when testing different pacing modes. A waiting period of at least 20 s was respected after any change in pacing settings or lead position to achieve haemodynamic stabilization. Results at each pacing site were expressed as a percentage change from baseline to minimize the effect of drift in LVdP/dt_{max}. Baseline was reassessed prior to and after every change in pacing modality and comparisons were made to a mean of these two readings.

Endocardial and multisite pacing protocol

Multisite epicardial pacing was performed in turn from the two separate CS LV leads (MSP-1) and via the chronically implanted quadripolar LV lead alone (MSP-2). The implanted CRT-D system was uploaded with investigational software for the duration of the acute study to allow delivery of two simultaneous LV pacing vectors from the chronically implanted quadripolar lead (see the Supplementary material online for details).

A pacing protocol was performed as follows (rate 5–10 b.p.m. above the intrinsic rate, paced and sensed AV delay 100 ms, AAI pacing as baseline and repeated after each pacing mode):

1. RV only
2. Conventional CRT using the chronic LV lead (one quadripolar lead vector (V1) and RV with 0 ms V–V delay)
3. Conventional CRT using the temporary epicardial lead (EPI2) and RV with 0 ms V–V delay
4. MSP-1: RV + EPI2 + V1 (one quadripolar lead vector, temporary epicardial lead and RV with 5 ms V–V delay)
An acute haemodynamic and electroanatomical study

Biventricular endocardial stimulation was repeated with the LV decapolar catheter placed randomly in up to four different endocardial positions, including anterior, lateral, inferior, and septal sites. In all patients, one of these four sites was chosen to approximate LV endocardial stimulation at the same site as the chronically implanted epicardial LV lead. Capture was verified for each pacing modality by looking for a change in QRS morphology at a paper speed of 200 mm/s. This was also validated with reference to LV pacing by analysis of the activation wave front on NCM.

Non-contact mapping analysis

An acute haemodynamic and electroanatomical study

Patient demographics

Fifteen male subjects were studied. The mean age was 64 ± 7 years and the mean LVEF was 27 ± 9%. Subjects were predominantly ischaemic [10 of 15 (67%)]. The mean QRS duration was 160 ± 39 ms with left bundle branch block (LBBB) morphology in 13 and intraventricular conduction delay (IVCD) in 2. In 13 of 15 subjects, the chronically implanted quadripolar LV lead was in a lateral/posterolateral vein, and in 2 an anterior/anterolateral position was used due to inability to achieve satisfactory stimulation in the posterolateral vein. The mean time from CRT implantation to multisite pacing study was 225 ± 123 days (Table 1).

Procedural success

An invasive haemodynamic protocol was successfully completed in all 15 subjects. In one subject, it was not possible to perform LV endocardial pacing or to collect full NCM data due to tortuous arterial access. In two further subjects, it was not possible to collect full NCM data; one due to recurrent ventricular tachycardia when placing the NCM array in the LV cavity; the other due to a technical failure after array deployment in the LV. A pacing protocol was still performed without NCM data in all the three subjects. There were no procedural complications.

Haemodynamic response to different forms of pacing

LVDp/dtmax was successfully measured in all 15 subjects. Conventional CRT via the chronic LV lead gave an 11.5 ± 13.6% increase in AHR compared with baseline (P = 0.005). Conventional CRT using the temporary epicardial lead (EP2, anterior position) gave a 9.6 ± 13.7% increase in AHR (P = 0.017). Multisite epicardial pacing-1 gave a 15.8 ± 11.4% (P < 0.001) and MSP-2 gave a 15.5 ± 11.9% increase in AHR (P < 0.001) (Figure 2 and Table 2). The greatest AHR was seen with BV-Endo pacing at the optimal LV endocardial site which gave a 19.6 ± 13.6% increase in AHR (P < 0.001). Figure 3 demonstrates the mean difference in percentage change from

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD) or numbers</th>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 7</td>
</tr>
<tr>
<td>Male (%)</td>
<td>100</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>27 ± 9</td>
</tr>
<tr>
<td>NYHA Class (II/III)</td>
<td>2/13</td>
</tr>
<tr>
<td>Ischaemic/non-ischaemic (%)</td>
<td>10/5 (67/33)</td>
</tr>
<tr>
<td>Sinus rhythm/atrial fibrillation</td>
<td>13/2</td>
</tr>
<tr>
<td>QRS duration</td>
<td>160 ± 39 ms</td>
</tr>
<tr>
<td>QRS morphology</td>
<td>13/2</td>
</tr>
<tr>
<td>(LBBB/non-specific IVCD)</td>
<td></td>
</tr>
</tbody>
</table>

IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Figure 2. Acute haemodynamic response achieved using different pacing modalities—AHR as percentage change in LVDp/dtmax over baseline (AAI/VVI pacing) on y-axis. Conventional CRT, chronic LV lead (RV + V1). BV Endo opp quartet, biventricular endocardial pacing at an endocardial site approximating the chronically implanted epicardial lead.
Acute haemodynamic response to biventricular endocardial pacing by location

The superiority of BV-Endo pacing was highly site specific and optimal BV-Endo pacing was significantly better than the worst BV-Endo site (19.6 ± 13.6 vs. 8.5 ± 14.1%, P = 0.007). Biventricular endocardial stimulation approximating the chronically implanted LV lead gave an AHR of 12.2 ± 17.6%, which was not significantly different from conventional CRT at the same site (P = 0.876) and was inferior to optimal BV-Endo (P = 0.007) (Figure 4). There was significant variability for individual subjects between the best (optimal) and worst BV-Endo sites (Figure 5).

Electrical parameters: QRS durations left ventricular activation patterns and times

The mean QRS in the 12 subjects with NCM data was 166 ± 42 ms and was significantly longer with RV pacing (194 ± 34, P = 0.017). None of the CRT modalities resulted in a statistically significant change in QRS duration compared with intrinsic QRS. Conventional CRT via the chronic LV lead gave a QRS of 158 ± 15 ms (P = 0.466), conventional CRT via EPI2 resulted in a QRS duration of 180 ± 35 ms (P = 0.116). Multisite epicardial pacing-1, MSP-2, and BV-Endo pacing at the optimal haemodynamic site did not significantly change QRS duration [161 ± 25 ms (P = 0.662), 157 ± 14 ms (P = 0.414), and 163 ± 36 ms (P = 0.774), respectively] (Tables 2 and 3, Figure 6).

The intrinsic LV activation pattern seen in the 12 subjects with full NCM data was Type I in 6 and Type II in 6. The LVAT in intrinsic rhythm was 71 ± 21 ms. Conventional CRT via the chronically implanted LV lead significantly shortened the LVAT to 52 ± 19 ms (P = 0.034); however, conventional CRT via EPI2 did not (63 ± 25; P = 0.440). With MSP-1 LVAT shortened significantly to 54 ± 17 ms (P = 0.040). With MSP-2, the LVAT was 56 ± 20 ms (P = 0.063) and at the optimal haemodynamic BV-Endo site, the LVAT was not significantly reduced from baseline at 55 ± 25 ms (P = 0.057).

Discussion

The principal findings were as follows: (i) BV-Endo stimulation at the optimal site gave the best AHR overall and was significantly better than conventional CRT (whereas the two forms of MSP were non-superior to conventional CRT). (ii) There was considerable variability in the optimal haemodynamic pacing site both endocardially and epicardially. (iii) Changes in AHR were not associated with significant changes in the endocardial LVAT. (iv) There was considerable variability in the optimal pacing modality between individuals.

Our acute responder rate with conventional CRT was 46% in a predominantly ischaemic cohort (67%), emphasizing the need for alternate therapies if \( \text{LVd} \text{d}_{max} \) truly does predict response to CRT. This is consistent with previously published work from our institution \(^{11, 19} \) and others. \(^{20} \) Biventricular endocardial pacing

### Individual variation

Within individuals, the best pacing modality varied (Table 3). Conventional CRT with the chronic LV lead gave an AHR of ≥10% (acute haemodynamic responder) \(^7 \) in 7 of 15 (46%) subjects, and CRT using EPI2 gave an AHR of ≥10% in only 5 of 15 (33%) subjects. Multisite epicardial pacing-1 gave an AHR of ≥10% in 9 of 15 (60%) and MSP-2 in 10 of 15 (67%) patients. Biventricular endocardial gave an AHR of ≥10% in 11 of 14 (79%) patients. Twelve of 14 (86%) subjects acutely responded either to a form of MSP or to BV-Endo pacing.

### Table 2 Changes in LVd/dt\text{max}, QRS duration, and LVAT with different pacing modalities vs. baseline

<table>
<thead>
<tr>
<th></th>
<th>Percentage change in LVd/dt\text{max} (%)</th>
<th>QRS (ms)</th>
<th>LVAT (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>166 ± 42</td>
<td>71 ± 21</td>
<td></td>
</tr>
<tr>
<td>RV + V1</td>
<td>11.5 ± 13.6</td>
<td>158 ± 15</td>
<td>52 ± 19</td>
</tr>
<tr>
<td></td>
<td>P = 0.005</td>
<td>P = 0.466</td>
<td>P = 0.034</td>
</tr>
<tr>
<td>RV + EPI2</td>
<td>9.6 ± 13.7</td>
<td>180 ± 35</td>
<td>63 ± 25</td>
</tr>
<tr>
<td></td>
<td>P = 0.017</td>
<td>P = 0.116</td>
<td>P = 0.440</td>
</tr>
<tr>
<td>MSP-1</td>
<td>15.8 ± 11.4</td>
<td>161 ± 25</td>
<td>54 ± 17</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td></td>
<td>P = 0.662</td>
<td>P = 0.040</td>
</tr>
<tr>
<td>MSP-2</td>
<td>15.5 ± 11.9</td>
<td>157 ± 14</td>
<td>56 ± 20</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td></td>
<td>P = 0.414</td>
<td>P = 0.063</td>
</tr>
<tr>
<td>BV-Endo optimal</td>
<td>19.6 ± 13.6</td>
<td>163 ± 36</td>
<td>55 ± 20</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td></td>
<td>P = 0.774</td>
<td>P = 0.057</td>
</tr>
</tbody>
</table>

Changes in LVd/dt\text{max}, for 15 patients. QRS and LVAT for the 12 patients with full NCM data.
produced an AHR of ≥10% in ~80% of patients. It has been postu-
lated that the mechanism of acute haemodynamic benefit with LV
endocardial stimulation may be more effective mechanical recruit-
ment of the myocardium rather than shortening of the LVAT,11 but
as we found no significant difference between stimulating epi-
and endocardially from the same site, we cannot prove that this is
the method of AHR improvement seen with BV-Endo pacing in this study.

Table 3  Lead positions, vectors, aetiology, and activation patterns

<table>
<thead>
<tr>
<th>Patient Quartet position</th>
<th>V1</th>
<th>V2</th>
<th>EPI2</th>
<th>Responder to CRT/MSP/ENDO</th>
<th>Aetiology (activation pattern)</th>
<th>Line of block/septal break through site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Posterolateral</td>
<td>D1-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>N/N/(N/A)</td>
<td>N/A/basal</td>
</tr>
<tr>
<td>2</td>
<td>Lateral</td>
<td>D1-RV coil</td>
<td>P4-RV coil</td>
<td>Anterior</td>
<td>YYY</td>
<td>N/Type I/basal</td>
</tr>
<tr>
<td>3</td>
<td>Posterolateral</td>
<td>D1-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>YYY</td>
<td>I (Type II)/Anterior/apical</td>
</tr>
<tr>
<td>4</td>
<td>Lateral</td>
<td>D1-RV coil</td>
<td>P4-RV coil</td>
<td>Anterior</td>
<td>YYY</td>
<td>I (Type II)/Anterior/mid</td>
</tr>
<tr>
<td>5</td>
<td>Posterolateral</td>
<td>D1-RV coil</td>
<td>P4-RV coil</td>
<td>Anterior</td>
<td>YYY</td>
<td>N/Type I/N/A/basal</td>
</tr>
<tr>
<td>6</td>
<td>Posterolateral</td>
<td>D1-RV coil</td>
<td>P4-RV coil</td>
<td>Anterior</td>
<td>YYY</td>
<td>N/A/basal</td>
</tr>
<tr>
<td>7</td>
<td>D1-RV coil</td>
<td>P4-RV coil</td>
<td>Anterior (prox)</td>
<td>YYY</td>
<td>I (Type I)</td>
<td>N/A/basal</td>
</tr>
<tr>
<td>8</td>
<td>Lateral</td>
<td>D1-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>YYY</td>
<td>I (Type II)/Anterior/apical</td>
</tr>
<tr>
<td>9</td>
<td>Posterolateral</td>
<td>D1-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>N/N/N</td>
<td>I/Type I/N/A/basal</td>
</tr>
<tr>
<td>10</td>
<td>Lateral</td>
<td>D1-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>N/N/Y</td>
<td>I (Type I)/Anterior/mid</td>
</tr>
<tr>
<td>11</td>
<td>Lateral</td>
<td>D1-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>N/N/Y</td>
<td>I (Type I)/Anterior/mid</td>
</tr>
<tr>
<td>12</td>
<td>Posterolateral</td>
<td>M2-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>N/Y/Y</td>
<td>N (Type II)/Posterior/apical</td>
</tr>
<tr>
<td>13</td>
<td>Posterolateral</td>
<td>M2-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>N/Y/N</td>
<td>N (Type II)/Anterior/mid</td>
</tr>
<tr>
<td>14</td>
<td>Lateral</td>
<td>D1-RV coil</td>
<td>P4-RV coil</td>
<td>Anterior</td>
<td>N/Y/Y</td>
<td>N (Type II)/Anterior/basal</td>
</tr>
<tr>
<td>15</td>
<td>Posterolateral</td>
<td>D1-RV coil</td>
<td>M3-RV coil</td>
<td>Anterior</td>
<td>N/N/N</td>
<td>I/Type I/N/A/basal</td>
</tr>
</tbody>
</table>

D1, quadripolar LV lead tip electrode; M2, quadripolar LV lead distal ring electrode; M3, quadripolar LV lead middle ring electrode; P4, quadripolar LV lead proximal ring electrode; I, ischaemic aetiology; N, non-ischaemic aetiology; I, Type I activation pattern; II, Type II activation pattern; N/A, activation data not available.

**Figure 4** Comparison of AHR when BV-Endo pacing—stimulation from best and worst endocardial positions, BV-Endo pacing opposite the quadripolar LV lead and conventional CRT via the chronic LV lead (RV + V1). P values are corrected for multiple comparisons using the Bonferroni method; *statistically significant.

**Figure 5** Acute haemodynamic response to BV-Endo pacing at best and worst endocardial sites in individual patients—blue bars represent AHR at the best site and the red bars represent the AHR at the worst site.

**Multisite and endocardial pacing haemodynamics**

Epicardial MSP did not confer a statistically significant increase in AHR compared with conventional CRT. For MSP-1, there was a 4.3% absolute increase in LVdP/dtmax (37% relative increase) and for MSP-2 a 4% absolute increase (35% relative increase). This would suggest that MSP may be able to give some degree of haemodynamic benefit, and that delivery via a single lead may be as efficacious as multiple leads. Only with optimal BV-Endo pacing was there a significant
increase in LVdP/dt\textsubscript{max} (8.1% absolute increase, 70% relative increase) compared with conventional CRT (P = 0.04), suggesting that site selection is critically important. Notably, BV-Endo pacing at a site approximating the chronically implanted (predominantly posterolateral) epicardial lead was not better than conventional CRT at the same location, and stimulation of the latest mechanically activated segment of the LV was not better than pacing other regions. This suggests that conventional LV epicardial pacing strategies do not predict the optimal site for endocardial LV pacing.

Comparison with previous studies

In a chronic canine heart failure model, Strik et al.\textsuperscript{20} demonstrated improvement in AHR with LV endocardial pacing compared with conventional epicardial CRT, which could be explained by the shorter path length and more rapid conduction resulting from endocardial LV pacing. Our findings are in keeping with those of Derval et al.\textsuperscript{2} who showed not one pacing site was best for all patients with non- ischemic cardiomyopathy and the choice needed to be tailored to the individual. As in our study, Derval et al. found no significant increase in LVdP/dt\textsubscript{max} at the endocardial site approximating the epicardial site. Our results are also in keeping with those of Spragg et al.\textsuperscript{4} who found that the location of optimal LV endocardial pacing varied among patients with ischaemic cardiomyopathy, and that individual tailoring may improve CRT response in such patients. In a canine model, Bordachar et al.\textsuperscript{12} compared endocardial and epicardial MSP pacing, and showed that LV endocardial pacing was superior to MSP delivered from separate sites, and that the optimal site of LV endocardial stimulation was critical. In Bordachar’s study, MSP was delivered from separate leads, whereas we have performed MSP with both separate leads and also from a single-quadripolar lead. Our results suggest that although LV endocardial pacing appears to be the superior form of CRT in certain patients, MSP delivered via multiple or single-quadripolar leads may improve CRT response.

Our NCM data are in keeping with the findings of Strik et al.,\textsuperscript{20} in that the optimal BV-Endo site did not produce a significant reduction in LVAT. Indeed, although epicardial stimulation did not produce the optimal AHR, it tended to shorten the LVAT compared with the optimal endocardial site. This may appear to be counterintuitive as one might expect the optimal haemodynamic site to be associated with a greater degree of electrical resynchronization, but consistent with recently published canine work by Lumens et al.\textsuperscript{21} pacing-induced haemodynamic improvement can occur without electrical resynchronization. These findings may be explained by the fact that the endocardial LVAT represents only \(\sim\)40% of the total activation time of the ventricles.\textsuperscript{20} With endocardial pacing, wave front propagation begins at a single point in the LV endocardium and therefore endocardial LVAT may be longer than if epicardial stimulation is performed as by the time the epicardial stimulus has reached the endocardium it has spread out over a wider area thus making endocardial LVAT paradoxically shorter.

Study limitations

This study is limited by its small sample size. Given the highly invasive and time-consuming nature of the study, however, this is unavoidable. The order of the pacing vector sequence was not altered randomly and thus we cannot rule out sustained effects from earlier pacing sequences. Ideally, a range of AV delays and VV delays would have been assessed, but this was not possible because of time constraints. Our measures of LV activation were endocardial, and we did not study epicardial activation; however, our QRS duration data provide a measure of total electrical activation of the heart. Conventional CRT was delivered predominantly via a chronically implanted lead in a lateral or posterolateral position, and it is possible that stimulation from an alternative site may have provided a better AHR. Specifically, we did not pace via the CS opposite the best BV-Endo site in every patient, and thus, we cannot exclude the possibility that epicardial pacing opposite the best BV-Endo site in each patient would be just as good.

This study did not specifically address the issue of localization of the optimal endocardial stimulation site, and we did not specifically look at areas of myocardial scar in relation to lead positioning. Our assessment of AHR may not necessarily translate into chronic response; however, previous work from our institution has suggested a good correlation with chronic response, albeit predominantly in non-ischaemic patients.\textsuperscript{17}

Given that the mean time from CRT implant to multisite pacing study was 225 \(\pm\) 123 days, it could be argued that some patients had reverse remodelled, and that this would affect the results of CRT. A recent study by Knappe et al.,\textsuperscript{22} however, suggests that interruption of CRT, even after 12 months, resulted in an acute worsening of LV size and function LA volumes and RV function, with concomitant worsening of ventricular synchrony, and thus, the beneficial reverse remodelling associated with CRT may be mostly dependent on active pacing.

Clinical implications

Permanent LV endocardial pacing is not as straightforward as implanting a conventional CRT device, as it requires a trans-septal
puncture, life-long anticoagulation and may interfere with the mitral valve apparatus. Implantation of two CS leads is more straightforward than LV endocardial lead implantation, but is still technically challenging. A form of epicardial MSP did increase the acute response rate with an acute responder rate of 60% for MSP-1 and 67% for MSP-2 vs. 46% for conventional CRT, suggesting that epicardial MSP may have a clinically relevant role. If an improved AHR can be achieved simply by utilizing MSP from a single-quadrupolar LV lead with no further invasive procedures required, this may be a useful option.

Conclusion

Biventricular endocardial LV pacing from the optimal endocardial site appears to be superior overall to conventional CRT. The two forms of MSP tested (via multiple leads or a single-quadrupolar lead) were not significantly superior to conventional CRT overall, but there was considerable variability in the optimal pacing method within individuals. Further work is required to assess the chronic effects of LV endocardial and MSP in humans and also to assess techniques, which may allow identification of the optimal pacing site in individuals receiving CRT.

Supplementary material

Supplementary material is available at Europace online.

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