Impact of VV optimization in relation to left ventricular lead position: an acute haemodynamic study

Fakhar Z. Khan1, Munmohan S. Virdee2, Philip A. Read1, Peter J. Pugh1, David Begley2, Simon P. Fynn2, and David P. Dutka1*

1Addenbrooke’s Hospital, Hills Road, Cambridge CB2 2QQ, UK; and 2Papworth Hospital, Papworth Everard, Cambridge CB23 8RE, UK

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Aims
Left ventricular (LV) lead placement to the most delayed segment offers the greatest potential benefit to cardiac resynchronization therapy (CRT). We assessed the impact of interventricular (VV) optimization on acute changes in cardiac output (CO) in patients with and without LV pacing of the most delayed segment.

Methods
In 124 patients, the most delayed segment was defined by speckle tracking radial strain and the LV lead position by biplane fluoroscopy. Patients were classified as either a concordant (LV lead at latest site), adjacent (within one segment), or remote (two or more segments away) LV lead. Atrioventricular (AV) and VV delays were optimized by echocardiography. Cardiac output was measured non-invasively and a 20% increase in CO from baseline (intrinsic) defined acute response. Changes in CO in patients with concordant, adjacent, or remote LV leads were recorded following atrioventricular optimization alone (AV OPT) and after combined AV and VV optimization (AV/VV OPT).

Compared with AV OPT pacing, AV/VV OPT produced a greater rise in CO (5.45 ± 1.1 vs. 5.76 ± 1.2 L/min, \(P = 0.001\)) and higher acute response rates (48.4 vs. 61.3%, \(P = 0.041\)). In adjacent patients, compared with AV OPT pacing, AV/VV OPT settings increased the response rate from 36.4 to 63.6% (\(P = 0.037\)). VV optimization had no effect on acute response rates in patients with remote (26.7 vs. 33.3%, \(P = 0.581\)) or concordant LV leads (65.6 vs. 72.1%, \(P = 0.438\)).

Conclusion
VV optimization overcomes some but not all of the deleterious effects of a suboptimal LV lead position.

Keywords
CRT • VV delay • LV lead • Cardiac output

Introduction
Cardiac resynchronization therapy (CRT) can offer improvements in morbidity and mortality in patients with advanced heart failure and ventricular conduction delay.1–4 Despite careful patient selection, up to a third of recipients fail to demonstrate any clinical benefit or left ventricular (LV) reverse remodelling. Improved clinical and echocardiographic outcomes including reductions in heart failure hospitalizations and mortality are seen where there is concordance between the position of the LV lead tip and the latest area of activation.5–8 These improvements in outcome appear to be directly related to the degree of concordance between the LV lead tip and maximally delayed site.5 Conversely, suboptimal LV lead placement at sites remote from the latest area of activation may even be detrimental by promoting further dyssynchrony. Left ventricular lead placement is, however, limited by the availability of suitable coronary veins and therefore placement of leads to optimal sites may not be feasible in a significant number of CRT implants.8,9 Individual optimization of pacemaker settings has been shown to improve the acute haemodynamic effects of CRT and alteration of in the sequence of interventricular activation (VV delay) has been proposed as a method for overcoming the potential deleterious effect of a suboptimal lead position.10–12

We aimed to investigate the impact of VV delay optimization on acute changes in cardiac output (CO) measured non-invasively based on bio-reactance using a commercially available device.
At implantation, the device was programmed with an atrioventricular (lower rate limit 40) to achieve atrial synchronous biventricular pacing. All devices were set to DDD-mode (Guidant, St Paul, MN, USA). All devices were classified into one of three groups: concordant-lead position at the left ventricle lead position was determined as basal or mid. Any patients with an apical lead position were excluded for the purpose of this study. All patients were classified into one of three groups: concordant-lead position at the level of maximal delay.

### Methods

#### Cardiac resynchronization therapy patient population

One hundred and thirty-five patients with advanced heart failure (NYHA class III or IV), sinus rhythm, left bundle branch block (QRS > 120 ms), and impaired LV systolic function (LV ejection fraction < 35%) despite optimal medical treatment were recruited into the study. The study was approved by the local ethics committee and the study protocol complied with the guidelines set out in the Declaration of Helsinki. All participants gave written informed consent.

#### Cardiac resynchronization therapy implantation

In all patients, coronary sinus lead placement (Easytrak 2, Guidant Corporation, St Paul, MN, USA; or Attain-SD 4189, Medtronic Inc., Minneapolis, MN, USA) was preferentially to the basal or mid-segment of a lateral or posterior vein. Patients with apically positioned LV leads were not included in this study. The right atrial lead was positioned in the right atrial appendage and the right ventricular lead was placed in the mid-septum in 49.2% (n = 61) patients and at the right ventricular (RV) apex in 50.8% (n = 63) patients. Fifty patients (40.3%) received a CRT-defibrillator (Cognis, Guidant, St Paul, MN, USA) with the remainder 74 patients (59.7%) receiving CRT-pacing alone (Contak Renewal, Guidant, St Paul, MN, USA). All devices were set to DDD-mode (lower rate limit 40) to achieve atrial synchronous biventricular pacing. At implantation, the device was programmed with an atrioventricular (AV) delay of 120 ms and VV delay was set nominally at 0 ms.

#### Study protocol

Within 2 weeks of CRT implantation, all patients underwent optimization of the AV delay according to the maximal velocity time integral of the transmitral flow (MV VTI). At the optimized AV delay, VV delays were altered in 20 ms steps from –60 ms (LV preactivation) to +60 ms and optimized by echocardiography to the setting producing the greatest LV outflow tract (LVOT) VTI. Non-invasive cardiac output measurements (NICOM) were recorded for each patient following atrioventricular delay optimization alone (AV OPT) and after additional optimization of the VV delay (AV/VV OPT). Non-invasive cardiac output measurement recordings were made for at least 3 min at 30 s intervals after at least 1 min of pacing and therefore measurements were the average of at least six readings. At each setting, pacing occurred for at least 1 min before simultaneous acquisition of the pulsed wave Doppler and haemodynamic data. Non-invasive cardiac output measurement recordings were made for 3 min at 30 s intervals and the measurements at each stage were therefore the average of six readings. In all devices, AV delay interval refers to the interval of stimulation between the right atrium and the RV. Therefore, during LV pre-activation, the programmed AV delay was the optimal AV delay during simultaneous biventricular stimulation plus the VV delay being investigated.

### Echocardiography

Transthoracic Doppler echocardiography was performed in all subjects before and within 2 weeks (for device optimization) of CRT implantation, using a commercial machine (Vivid 7, General Electric Medical Systems, Horten, Norway) equipped with a 3.5 MHz phased array transducer. Acquisitions were digitally stored and post-processed offline (General Electric EchoPAC, version 5.1.0, Horten, Norway). Left ventricular volume and LV ejection fraction were calculated using the Simpson biplane method according to the guidelines of the American Society of Echocardiography. Pulsed-wave Doppler analysis of the transmitral inflow and LV outflow were used for the respective optimization of AV and VV delay intervals. All recordings were made in the left lateral position at end expiration with particular care taken to ensure consistent sample volume placement at the tip of the mitral valve to record transmitral flow and in the LVOT to record ejection velocities. The MV VTI and LVOT VTI were manually traced online and averaged over three beats to determine optimal pacemaker settings. Intraventricular dyssynchrony was assessed at baseline in all patients by colour-coded tissue velocity imaging (TVI). Sample volumes were placed in the basal portions of the septum and LV lateral wall, and the time from the QRS onset to the peak systolic myocardial velocity at each point was measured.

### Speckle tracking echocardiography to determine region of maximal delay

The region of latest activation was determined by radial strain speckle tracking analysis of the baseline grey-scale LV short-axis images as previously described. In essence, all images were recorded with a frame rate of >30 frames/s and the endocardial cavity was traced using a point-and-click technique in end-systole with special care taken to adjust tracking of all segments. A second larger concentric circle was then automatically generated and manually adjusted near the epicardium. Speckle tracking automatically analysed frame-by-frame movement of the stable patterns of natural acoustic markers, or speckles, to generated time–strain curves over the cardiac cycle for six segments (septal, anteroseptal, anterior, posterior, lateral, and inferior) at each of the basal and mid-LV short-axis levels. The time from the onset of the QRS to peak radial strain was obtained for all six segments (Figure 1) at each level. The site of the latest segments of activation were determined from the 12 analysed segments along with the anteroseptal—posterior (AS–P) wall delay and the maximal time difference between the earliest and latest activated segments as markers of LV dyssynchrony.

### Left ventricular lead localization

Left ventricular lead position was determined from biplane fluoroscopy and the post-implant frontal and lateral chest radiographs as described by Albertsen et al. as anterior, lateral, posterior, or inferior. In the frontal and right anterior oblique projections the LV lead position was determined as basal or mid. Any patients with an apical lead were excluded for the purpose of this study. All patients were classified into one of three groups: concordant-lead position at the site of latest activation, adjacent-LV lead only one segment away from the optimal site, or remote LV lead positioned more than one segment from the optimal site.

### Non-invasive cardiac output recordings

Non-invasive cardiac output measurements were performed using a commercially available system based on bio-reactance technology (Cheetah Medical, Portland, Oregon, USA). Beat-to-beat CO is measured by the application of a high-frequency electrical current of...
known amplitude and frequency across the thorax and detecting changes in intra-thoracic volume and thoracic electrical capacitive and inductive properties. Bio-reactance-based signals are inherently more robust and less susceptible to external interference compared with bio-impedance signals because of the ability to use high-tuned notch filters. The NICOM system is comprised of a high-frequency (75 kHz) sine wave generator and four dual-electrode ‘stickers’ placed on either side of the body. The system is precise and sufficiently responsive to enable monitoring CO in patients with a wide range of circulatory dysfunction.

During data acquisition, telemetry between the pacemaker and programmer was turned off to minimize interference. Non-invasive cardiac output measurement was recorded for each patient during intrinsic conduction with CRT switched off, during AV delay optimization alone (VV delay = 0 ms) and combined AV and VV delay optimization.

Definition of acute response to cardiac resynchronization therapy

Previous work by our group using NICOM in 47 patients has shown that acute improvements in CO from baseline early after CRT are highly predictive of LV reverse remodelling. Compared with intrinsic conduction with CRT switched off, an improvement in CO of >20% predicts a >15% reduction in LV end-systolic volume reduction at 3 months with a sensitivity of 86% and specificity of 92%. In the apical present study, an acute improvement of >20% in CO has therefore been adopted to define acute response to CRT.

Statistical analysis

Statistical analysis was performed using commercially available software (GraphPad Prism 5 for Windows, San Diego, CA, USA). For continuous data, Student’s t-test or an ANOVA was used to compare differences in continuous variables and a $\chi^2$ test was used for categorical variables. A P-value of <0.05 was considered as statistically significant. All data are expressed as mean ± SD. Same day reproducibility of CO measurements by NICOM is expressed as the SD of the difference between two paired measurements and as a percentage of variability (SD divided by the average value of the variable).

Results

Patient population and baseline characteristics

Of the 135 patients assessed, a total of 11 patients were excluded due to inadequate echocardiographic imaging quality for speckle analysis (n = 8) and failure to implant an LV lead primarily due to coronary sinus dissection (n = 3). Five patients had an early LV lead dislodgement requiring a second procedure, all of whom were retained in the study and therefore a total of 124 patients were included. The distribution of the latest site of activation and the lead position are reported in Figures 2 and 3, respectively. The proportions of patients with concordant, adjacent, and remote LV lead positions were 49.2% (n = 61), 26.6% (n = 33), and 24.2% (n = 30), respectively. The baseline characteristics, baseline TDI dyssynchrony, and speckle tracking dyssynchrony parameters were similar between all major groups (Table 1).

Optimal atrioventricular and VV delay settings

For all patients, the optimal AV delay (determined by the MV VTI) varied from 80 to 200 ms. An AV delay of 80 ms was the optimal setting in 13 (10.5%) patients, 100 ms in 26 (21.0%) patients, 120 ms in 28 (22.6%) patients, 140 ms in 25 (20.2%) patients, 160 ms in 14 (11.3%) patients, 180 ms in 13 (10.4%) patients, and 200 ms in four (4.0%) patients. The optimal VV delay varied from −60 to 20 ms. By echocardiography, a VV delay of −60 ms was the optimal setting in 15 (12.1%) patients, −40 ms in 40 (32.3%) patients, and −20 ms in 69 (55.6%) patients.
patients, −20 ms in 36 (29.0%) patients, 0 ms in 30 (24.2%) patients, and +20 ms in 3 (2.4%) patients. There were no differences in the optimal mean AV or VV delays according to lead position or underlying etiology (Table 1). The MV VTI and LVOT VTI readings during intrinsic conduction, AV OPT settings, and AV/VV OPT settings are reported in Table 2.

Cardiac output measurements during atrioventricular optimization and atrioventricular/VV optimization pacing

There were no differences in heart rate in patients during CO recordings at each pacemaker setting (intrinsic conduction vs. AV OPT vs. AV/VV OPT: 75.4 ± 11.1 vs. 76.1 ± 10.5 vs. 75.9 ± 12.1 bpm, respectively, P > 0.05). In all patients, the mean CO during intrinsic conduction was 4.56 ± 1.1 L/min and compared with AV OPT settings, AV/VV OPT biventricular pacing was associated with higher CO (AV OPT vs. AV/VV OPT: 5.45 ± 1.1 vs. 5.76 ± 1.2 L/min, P < 0.001, mean increase from baseline: 19.5 ± 29 vs. 26.3 ± 31%, P < 0.001). During intrinsic conduction there were no significant differences in baseline CO between patients with either a concordant, adjacent, or remote lead. Similar CO readings were seen in patients with concordant and adjacent LV leads during AV OPT pacing and AV/VV OPT pacing. However, at both AV OPT and AV/VV OPT settings, CO measurements were significantly lower in patients with a remote LV lead compared with those with either a concordant or adjacent lead (Figure 4 and Table 3).

Acute response to cardiac resynchronization therapy during atrioventricular optimization and atrioventricular/VV optimization pacing according to left ventricular lead position

Taking acute response to CRT as >20% improvement in CO from baseline, in all patients, higher response rates were seen in patients

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**Table 1** Baseline characteristics of all patients in both major groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Concordant (n = 61)</th>
<th>Adjacent (n = 33)</th>
<th>Remote (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (year)</td>
<td>67 ± 11</td>
<td>70 ± 10</td>
<td>68 ± 11</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>48 (78.6)</td>
<td>25 (75.8)</td>
<td>23 (76.7)</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>58/3</td>
<td>31/2</td>
<td>28/2</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy, n (%)</td>
<td>27 (44.3)</td>
<td>16 (48.5)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy, n (%)</td>
<td>34 (55.7)</td>
<td>17 (51.5)</td>
<td>14 (46.7)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>20 (32.8)</td>
<td>10 (30.3)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean ± SD (mmHg)</td>
<td>119 ± 20</td>
<td>124 ± 19</td>
<td>121 ± 20</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mean ± SD (mmHg)</td>
<td>63 ± 10</td>
<td>69 ± 6</td>
<td>66 ± 11</td>
</tr>
<tr>
<td>QRS duration, mean ± SD (ms)</td>
<td>158 ± 25</td>
<td>160 ± 26</td>
<td>156 ± 25</td>
</tr>
<tr>
<td>Left ventricular end diastolic volume, mean ± SD (mL)</td>
<td>185 ± 92</td>
<td>196 ± 62</td>
<td>193 ± 92</td>
</tr>
<tr>
<td>Left ventricular end systolic volume, mean ± SD (mL)</td>
<td>145 ± 76</td>
<td>154 ± 70</td>
<td>152 ± 76</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, mean ± SD (%)</td>
<td>24 ± 8</td>
<td>22 ± 7</td>
<td>23 ± 8</td>
</tr>
<tr>
<td>Use of ACEI or ARB (%)</td>
<td>93.5</td>
<td>90.5</td>
<td>93.3</td>
</tr>
<tr>
<td>Use of β-blocker (%)</td>
<td>80.6</td>
<td>71.4</td>
<td>80.0</td>
</tr>
<tr>
<td>Use of spironolactone (%)</td>
<td>58.0</td>
<td>61.9</td>
<td>60.0</td>
</tr>
<tr>
<td>Use of loop diuretics (%)</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Interventricular delay, mean ± SD (ms)</td>
<td>41 ± 23</td>
<td>42 ± 21</td>
<td>40 ± 26</td>
</tr>
<tr>
<td>Septal to lateral wall delay, mean ± SD (ms)</td>
<td>89 ± 24</td>
<td>91 ± 19</td>
<td>95 ± 21</td>
</tr>
<tr>
<td>Anteroseptal-posterior wall delay, mean ± SD (ms)</td>
<td>210 ± 56</td>
<td>195 ± 63</td>
<td>221 ± 53</td>
</tr>
<tr>
<td>Optimal AV delay, mean ± SD (ms)</td>
<td>133 ± 26</td>
<td>131 ± 28</td>
<td>126 ± 28</td>
</tr>
<tr>
<td>Optimal VV Delay, mean ± SD (ms)</td>
<td>−26.4 ± 20.5</td>
<td>−21.2 ± 26.2</td>
<td>−24.6 ± 23.1</td>
</tr>
</tbody>
</table>
during AV/VV OPT pacing compared with AV OPT settings (48.4 vs. 61.3%, \(P = 0.041\)). Significantly lower response rates were seen in patients with a remote LV lead position compared with either an adjacent (33.3 vs. 63.6%, \(P = 0.047\)) or a concordant lead position (33.3 vs. 72.1%, \(P = 0.018\)). VV optimization had no effect on overall acute response rates in patients with either a concordant (AV OPT vs. AV/VV OPT: 65.6 vs. 72.1%, \(P = 0.438\)) or remote LV lead position (AV OPT vs. AV/VV OPT: 26.7 vs. 33.3%, \(P = 0.581\)). However, in patients with an adjacent LV lead, VV optimization significantly improved acute response rates (AV OPT vs. AV/VV OPT: 36.4 vs. 63.6%, \(P = 0.027\)) (Figure 5).

**Comparison of ischaemic and non-ischaemic patients**

Similar CO readings were seen between patients with ischaemic and non-ischaemic cardiomyopathy during intrinsic conduction, AV OPT pacing and AV/VV OPT (Figure 6). VV optimization significantly improved acute response rates in patients with ischaemic cardiomyopathy (AV OPT vs. AV/VV OPT 40.7 vs. 59.3%, \(P = 0.043\)) but had no difference in non-ischaemic patients (AV OPT vs. AV/VV OPT 55.4 vs. 63.1%, \(P = 0.437\)).

In patients with non-ischaemic cardiomyopathy, there were no significant differences in response rates with VV optimization according to LV lead position. However, in patients with an underlying ischaemic aetiology, significant differences in acute response were seen in patients with an adjacent LV lead position but not in those patients with either a concordant or a remote LV lead (Figure 7).

**Reproducibility**

Reproducibility assessments were made for CO measurements by repeating the pacing protocol in 10 randomly selected patients on the same day. For each patient CO measurements were repeated in the same conditions at least 2 h apart and the same day variability was 0.66 L/min (14%).

**Discussion**

The major findings of our study are two-fold. First, we demonstrate that, compared with AV optimization alone, combined AV and VV optimization is associated with greater acute improvements in CO. This benefit is seen in all patients irrespective of LV lead position although the extent to which CO rises is significantly attenuated in patients with a remote LV lead position. Secondly, when defining acute response to CRT as a >20% improvement in CO, higher response rates are seen in patients with concordant and adjacent leads compared with those with an LV lead position remote to the area of maximal dyssynchrony. Sequential pacing appears to have little impact on acute response rates in patients with either a concordant lead position or a lead position remote to the maximal site of delay. In patients with marginally suboptimal lead positions (adjacent group) VV optimization is associated with improvements in acute response rates, suggesting that sequential biventricular pacing is able to overcome some, but not all, of the deleterious effects of a discordant LV lead position. This benefit seems to be restricted to patients with underlying ischaemic aetiology.

LV pacing at sites of maximal delay have been reported in a number of studies to be associated with greater improvements in NYHA class, LV reverse remodelling and greater reductions in morbidity and mortality.5,8,9 This is consistent with our observation of greater acute response rates with closer proximity of the LV lead.
lead to the segment of latest activation. The role of VV optimization, however, continues to remain controversial. Although sequential biventricular pacing has been reported to confer acute haemodynamic benefits\textsuperscript{12,26} and improvements in myocardial efficiency following CRT,\textsuperscript{27} longer term benefits of improved clinical outcomes and LV reverse remodelling are yet to be demonstrated. Both the DECREASE HF multicentre randomized trial evaluating 306 patients (6 months following VV optimization on the basis of the intracardiac electrogram)\textsuperscript{28} and the Rhythm II ICD\textsuperscript{29} randomized study of 126 patients (using the aortic VTI to determine optimal VV settings) reported no differences in NYHA class and 6 min walk test performances between simultaneous and sequential biventricular pacing. The IN SYNC III study has shown that individually tailored echocardiographic-guided VV delay settings can increase LV stroke volume\textsuperscript{30} and so from the point of view of changes in acute haemodynamics, the data from these and other smaller studies suggest that VV optimization may be beneficial in selected patients. Our study identifies such a potential subgroup of CRT recipients and suggests that VV optimization does indeed improve acute response rates in some patients with suboptimal lead positions and, although a marginally discordant lead position can be overcome, lead placement to very remote sites is detrimental and appears not to be recoverable. Our findings are consistent with a recent smaller study using \( \frac{dP}{dt} \) measurements showing that although the best response to CRT is seen in patients with optimal LV lead placement, device optimization can to some extent partially compensate for a non-optimal lead position.\textsuperscript{31} The mechanisms underlying this are unclear. However, in the present study, as the benefit is seen only in patients with underlying ischaemic heart disease this suggests that conduction through areas of scar may be important. The presence of scar may result in slower conduction through the LV in the ischaemic patients and therefore the contribution of LV pacing to LV activation may be limited. Interventricular optimization may compensate for this by facilitating an earlier start of activation from the LV lead and this appears to be particularly important where there is a suboptimal lead position.

The impact of VV optimization in relation to a marginally suboptimal LV lead position also has important implications in the prospective targeting of LV leads to optimal sites as coronary venous anatomy can be very restrictive. For example, when coronary lead position is reviewed in the context of the area of latest activation by tissue synchronization imaging and speckle tracking echocardiography as in the studies by Murphy et al.\textsuperscript{7} and Becker et al.,\textsuperscript{8} LV

### Table 3 Cardiac output readings according to left ventricular lead position for all patients

<table>
<thead>
<tr>
<th>Device setting</th>
<th>Concordant</th>
<th>Adjacent</th>
<th>Remote</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Mid</td>
<td>Basal</td>
</tr>
<tr>
<td>Intrinsic</td>
<td>4.53 ± 1.2</td>
<td>4.58 ± 1.1</td>
<td>4.81 ± 1.1</td>
</tr>
<tr>
<td>AV OPT</td>
<td>5.74 ± 1.2</td>
<td>5.70 ± 1.1</td>
<td>5.62 ± 1.1</td>
</tr>
<tr>
<td>AV/VV OPT</td>
<td>6.12 ± 1.2</td>
<td>6.08 ± 1.1</td>
<td>5.96 ± 1.1</td>
</tr>
</tbody>
</table>

**Figure 5** Acute response rates defined as an improvement of cardiac output from baseline by $>20\%$ in patients according to left ventricular lead position. The data show no effect of VV optimization in response rates in patients with either a concordant or remote lead but significant differences between atrioventricular optimization and AV/VV OPT in the adjacent group.

**Figure 6** Changes in cardiac output at each device setting in patients according to underlying aetiology showing no significant differences ($P = 0.53$) between patients with ischaemic and non-ischaemic cardiomyopathy.
lead tip concordance to the area (or in the vicinity) of maximal delay is seen in only 65% (35 out of 54) and 55% (32 out of 58) patients, respectively. This suggests that achieving optimal site LV pacing may require a non-transvenous approach in a significant number of patients. Surgical epicardial LV lead placement is not restricted by the limitations of coronary venous anatomy but is historically associated with higher morbidity and achieving lead placement to the lateral or posterior wall (the most common sites of maximal delay) has often been a challenge. Alternative methods of transseptal and transapical LV lead placements, which are not limited by coronary venous anatomy, have been reported with success but only in very few selected patients. Our findings suggest that lead positioning to sites adjacent to the region of maximal delay coupled with VV delay optimization may be an acceptable alternative to lead placement via a surgical route. The findings, however, need to be corroborated in a larger randomized study.

**Limitations of our study**

Our study is limited to only demonstrating the acute haemodynamic benefit of sequential pacing. The impact of VV optimization according to LV lead position on clinical improvements and LV reverse remodelling is yet to be defined. Furthermore, we have not investigated the potential underlying mechanism that requires further systematic study. There may be other reasons that will influence the amount of LV improvement by VV delay optimization that were not considered in this study such as the RV lead position and interventricular conduction delay.

**Conclusions**

VV optimization is associated with acute improvements in CO and increases in acute response rates in patients undergoing CRT. The greatest impact of VV optimization is seen in patients where there is a marginal discrepancy between the region of maximal delay and the position of the LV lead, suggesting that VV optimization can overcome some but not all of the deleterious effects of a suboptimal lead position. The long-term impact of VV optimization on LV reverse remodelling and clinical outcomes is yet to be defined.

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