Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead

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Aims
Pacing from multiple sites in the left ventricle (LV) may bring about further resynchronization of the diseased heart compared with biventricular (BiV) pacing. We compared acute haemodynamic response (LV $dP/dt_{\text{max}}$) of multisite and BiV pacing using a quadripolar LV lead.

Methods and results
In 21 patients receiving cardiac resynchronization therapy, a quadripolar LV lead and conventional right atrial and ventricular leads were connected to an external pacing system. A guidewire pressure sensor was placed in the LV for continuous $dP/dt$ measurement. Four multisite pacing configurations were tested three times each and compared with BiV pacing using the distal LV electrode. Nineteen patients had useable haemodynamic data. Median increase in LV $dP/dt_{\text{max}}$ with BiV vs. atrial-only pacing was 8.2% (interquartile range 2.3%, 15.7%). With multisite pacing using distal and proximal LV electrodes, median increase in LV $dP/dt_{\text{max}}$ was 10.2% compared with atrial-only pacing (interquartile range 6.1%, 25.6%). In 16 of 19 patients (84%), two or more of the four multisite pacing configurations increased LV $dP/dt_{\text{max}}$ compared with BiV pacing. Overall, 72% of all tested configurations of multisite pacing produced greater LV $dP/dt_{\text{max}}$ than obtained with BiV pacing. Pacing from most distal and proximal electrodes was the most common optimal configuration, superior to BiV pacing in 74% of patients.

Conclusion
In the majority of patients, multisite pacing improved acute systolic function further compared with BiV pacing. Pacing with the most distal and proximal electrodes of the quadripolar LV lead most commonly yielded greatest LV $dP/dt_{\text{max}}$.

Keywords
Cardiac resynchronization therapy • Biventricular pacing • Left ventricular dysfunction • Devices for heart failure • Haemodynamics • Multisite pacing

Introduction
Cardiac resynchronization therapy (CRT) reverses remodelling of the dilated left ventricle (LV) and reduces morbidity and mortality in patients with symptomatic heart failure, prolonged electrical delay, and impaired systolic function receiving optimal pharmacological therapy.1–8 The immediate effect of biventricular (BiV) pacing may be observed by invasive haemodynamic measurement of peak increase in LV pressure (LV $dP/dt_{\text{max}}$), reflecting cardiac contractility.9–11 Prior studies have demonstrated beneficial effects of CRT on LV $dP/dt_{\text{max}}$,12–14 and have used this index to determine optimal atrioventricular (AV) delay and interventricular paced timing intervals, explore alternative pacing sites, and guide lead placement.15–19 Although there is an evolving understanding of the relationship between acute haemodynamic changes from CRT and clinical response to therapy, it is well recognized that the outcome of CRT varies among patients. In a sizeable fraction, there is little functional or clinical improvement.20,21 Potential reasons may include suboptimal LV pacing site, non-uniform
What’s new?

- Comparison of haemodynamics of biventricular (BiV) and multisite pacing with a multipolar left ventricular (LV) lead.
- Rigorous method with invasive haemodynamic measurement, performing each test configuration three times, compared with baseline BiV measurements before and after.
- Median increase in LV dP/dtmax over atrial pacing: 8.2% using BiV, 10.2% using multisite with most distal and proximal electrodes, 10.3% using best multisite pacing configuration.
- Of all tested configurations of multisite pacing, 72% produced greater LV dP/dtmax than obtained with BiV pacing.
- Distal/proximal multisite pacing is the most common optimal configuration, superior to BiV in 74% of patients.

Methods

Study population

The protocol for this prospective acute haemodynamic comparison of BiV and multisite pacing at Montreal Heart Institute was approved by the local institutional review board. The study (clinicaltrials.gov identifier NCT00964938) enrolled patients with standard CRT indication providing written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Implant procedure

Procedures were performed under conscious sedation, with a steady rate of intravenous propofol and remifentanil. The environment was kept as quiet as possible to minimize changes in underlying physiological state of the patient. The quadrupolar LV and conventional right atrial (RA) and RV leads were implanted using standard techniques. Left ventricular lead implantation was targeted to a CS tributary along the left lateral wall. The leads were connected to an external multichannel stimulation system that delivered pacing to electrodes of the LV, RV, and RA leads. The naming convention for the four LV electrodes, from distal tip electrode to proximal ring electrode, was D1, M2, M3, and P4. Each of the four LV electrodes was connected for pacing in extended bipolar configuration with the cathode in the LV and the RV coil used as anode. Capture thresholds from all electrodes were recorded, and the proximal P4 electrode was replaced by M3 in the pacing protocol if P4 did not capture the ventricle.

Haemodynamic assessment protocol

Acute haemodynamic measurements were recorded using a 0.014-inch guidewire pressure sensor and recording system (PressureWire Certus, RadiAnalyzer and PhysioMon software, St Jude Medical, Inc.). The guidewire was introduced at the femoral artery and inserted retrograde into the LV for continuous measurement of pressure and dP/dt. A bolus of intravenous unfractionated heparin was administered to reduce risk of thrombo-embolic complication. To avoid rate-dependent variability, all pacing was delivered at a fixed rate ~10% above the patient’s intrinsic heart rate, using a single AV delay that produced the highest LV dP/dtmax for BiV pacing.

Test configurations included BiV pacing, using the LV lead’s distal D1 electrode in extended bipolar configuration, and simultaneous multisite pacing using two or more LV electrodes as cathodes in extended bipolar configuration. Configurations were delivered simultaneously with RV bipolar simulation. Test configurations were performed in a pre-determined randomized sequence for 30 s each during haemodynamic recording. A measurement protocol was specifically developed to minimize effects of noise, physiological drift over time, and beat-to-beat variations. At the same time, the measurements needed to be completed within a short time to avoid clinical deterioration and minimize the possibility of adverse haemodynamic consequences. Four multisite pacing configurations were tested three times each in randomized order, with return to baseline recording using standard BiV pacing after each test configuration. The multisite pacing configurations used extended bipolar pacing from all LV electrodes: from distal and most proximal electrodes, from distal and middle electrodes, and from middle and most proximal electrodes. After the pacing and haemodynamic measurement protocol was completed, the quadrupolar LV lead was removed and replaced by a standard bipolar LV lead as part of a permanent CRT system.

Haemodynamic data

Cardiac cycles included in LV dP/dtmax calculations were selected in post-processing analysis performed while blinded to the pacing configuration. Ectopic ventricular beats and the two subsequent beats were excluded, as were the first few beats after activating a new pacing configuration. Each 30 s LV dP/dtmax recording spanned multiple complete respiratory cycles. To minimize impact of respiration and physiological variation, LV dP/dtmax was measured during three separate recordings for each test configuration.

Left ventricular pressure data for individual beats were analysed using Excel (Microsoft Corp.) and Matlab (The MathWorks, Inc.). Relative change for each multisite pacing configuration was computed with reference to baseline BiV measurements immediately before and after the test configuration. Atrial-only pacing was also performed at the same rate, and compared with adjacent BiV recordings. The acute haemodynamic response of a test configuration was reported as the mean of relative change among all recordings for that configuration. Figure 1 contains an example of LV dP/dtmax data for a patient. Each bar represents the mean value for a single recording. In the calculation for pacing configuration T2 (multisite pacing using LV electrodes D1
and M3), the relative change is calculated with reference to the average of standard BiV recordings before and after pacing configuration T2. The overall effect of the pacing configuration is reported as the mean among the three readings.

**Statistical analysis**

Change in LV $dP/dt_{\text{max}}$ was also calculated for each configuration with respect to atrial pacing. Since the Shapiro–Wilk statistic showed non-normal distribution across patients, median and interquartile range of changes in LV $dP/dt_{\text{max}}$ were reported with respect to atrial pacing (along with mean and standard deviation for historical comparison). Wilcoxon signed-rank tests were used to compare differences in LV $dP/dt_{\text{max}}$ compared with atrial pacing, obtained from the various pacing configurations. For each multisite pacing configuration, patients were ranked in order of improvement in LV $dP/dt_{\text{max}}$ over standard BiV pacing. Spearman correlation of the rankings was used to determine whether the same patients tended to achieve greater improvement, regardless of pacing configuration. Customized patient groupings were developed based on empirical categorization of acute haemodynamic response. A $P$ value below 0.05 was considered to be statistically significant. Analyses were performed using SAS version 9.2 (SAS Institute Inc.).

**Results**

The protocol was successfully completed in 21 of the 26 patients enrolled. Three subjects were excluded due to difficulty in placing the guidewire pressure sensor. The procedure was aborted in two additional subjects, one without a suitable distal vein for LV lead placement and the second due to communication failure in the haemodynamic measurement system. Characteristics of the remaining 21 patients are listed in Table 1. The quadripolar LV lead was placed in a lateral branch in 10 patients; in a posterolateral branch in 6; and in an anterolateral branch in the remaining 5 patients. The proximal P4 electrode reached a location that could stimulate the ventricle in 16 of 21 patients (76%).

![Figure 1](https://academic.oup.com/europace/article-abstract/15/7/984/554362) Example of LV $dP/dt_{\text{max}}$ calculation for a single pacing configuration. Bars, shown from left to right in order of recording, represent mean $dP/dt_{\text{max}}$ during each pacing configuration. Standard BiV pacing is repeated after each multisite pacing configuration. In the example calculation shown for multisite pacing using LV electrodes D1 and M3 as cathodes (marked D + M), each $\Delta dP/dt_{\text{max}}$ is calculated as the relative increase during the test recording with reference to average of preceding and following recordings of BiV pacing. Relative change for each recording of the test configuration is used in calculation of mean $\Delta dP/dt_{\text{max}}$. In the example shown, relative change for the three measurements of multisite pacing with D1 and M3 is 10.1%, 5.8% and 6.2%; mean $\Delta dP/dt_{\text{max}}$ is 7.4%.

**Haemodynamic data**

Duration of the pacing procedure and haemodynamic recordings was $34 \pm 8$ min. In two subjects, pressure and $dP/dt$ data contained extracardiac noise that generated erroneous $dP/dt_{\text{max}}$ readings; these two were excluded from haemodynamic data analysis. Pacing was performed at a rate of $89 \pm 16$ beats per minute in the 19 analysed patients. In 17 of the 19 (89%) patients, at least one multisite pacing configuration produced an increase in LV $dP/dt_{\text{max}}$ compared with standard BiV pacing. In 16 of 19 (84%) patients, two or more of the four configurations were improved compared with BiV pacing. In 9 of 19 (47%) patients, all four multisite pacing configurations increased LV $dP/dt_{\text{max}}$ compared with BiV pacing. In total, 72% of all tested multisite pacing configurations yielded improvement in LV $dP/dt_{\text{max}}$. Although the best pacing configuration varied among patients, the configuration using most distal and proximal electrodes improved LV $dP/dt_{\text{max}}$ in
Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>N = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60 ± 14 years</td>
</tr>
<tr>
<td>Gender</td>
<td>9 Female (43%), 12 male (57%)</td>
</tr>
<tr>
<td>Aetiology of heart disease</td>
<td>10 Ischaemic cardiomyopathy (48%), 11 dilated cardiomyopathy (52%)</td>
</tr>
<tr>
<td>NYHA functional class at time of implant</td>
<td>19 Class III (90%), 2 Class II (10%)</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>22 ± 5%</td>
</tr>
<tr>
<td>Conduction delay</td>
<td>21 Left bundle branch block (100%)</td>
</tr>
<tr>
<td>Sensed QRS duration</td>
<td>144 ± 16 ms (18 patients without permanent ventricular pacing)</td>
</tr>
<tr>
<td>Arrhythmia history</td>
<td>9 Atrial (43%), 10 Ventricular (48%)</td>
</tr>
<tr>
<td>Pharmacological therapy</td>
<td>14 Angiotensin-converting enzyme inhibitor (67%), 7 angiotensin receptor blocker (33%), 21 β-adrenergic receptor antagonist (100%), 19 diuretic of any type (90%), 16 anti-platelet (76%), 10 cardiac glycoside (48%), 6 antiarrhythmic drug (29%), 2 calcium channel antagonist (10%), 7 nitrates (33%), 16 statins (76%)</td>
</tr>
</tbody>
</table>

Table 2  Patients grouped by number of multisite pacing configurations producing higher LV dP/dt<sub>max</sub> than standard BiV pacing (top), and by configuration giving highest LV dP/dt<sub>max</sub> (bottom)

<table>
<thead>
<tr>
<th>Number of patients (%) of patients</th>
<th>Number of multisite pacing configurations superior to BiV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All four</td>
</tr>
<tr>
<td></td>
<td>Three of four</td>
</tr>
<tr>
<td></td>
<td>Two of four</td>
</tr>
<tr>
<td></td>
<td>One of four</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Best pacing configuration</td>
<td>Multisite (distal/proximal)</td>
</tr>
<tr>
<td></td>
<td>Multisite (all electrodes)</td>
</tr>
<tr>
<td></td>
<td>Multisite (distal/mid)</td>
</tr>
<tr>
<td></td>
<td>Standard BiV pacing</td>
</tr>
<tr>
<td></td>
<td>Multisite (mid/proximal)</td>
</tr>
<tr>
<td></td>
<td>Atrial-only pacing</td>
</tr>
</tbody>
</table>

Table 2 contains a summary of pacing configurations that produced improvement in LV dP/dt<sub>max</sub>. All pacing configurations shown in the table are extended bipolar. For example, distal/proximal refers to D1 and P4 cathodes with RV coil anode. If P4 did not capture the ventricle, distal/proximal used D1 and M3 as cathodes and distal/mid used D1 and M2 as cathodes.

All pairwise correlations of the ranking of patients by change in LV dP/dt<sub>max</sub> compared with BiV pacing for any two multisite pacing configurations reached statistical significance, with correlations ranging from 0.70 (P = 0.0009) to 0.84 (P < 0.0001).

Table 3 summarizes the percent change in LV dP/dt<sub>max</sub> achieved by BiV pacing and multisite pacing compared with atrial pacing, in all patients. Biventricular pacing improved LV dP/dt<sub>max</sub> by a median of 8.2% (interquartile range 2.3%, 15.7%) compared with atrial-only pacing. The best of the four multisite pacing configurations yielded a median of 10.3% (7.0, 28.6%) improvement. Left ventricular dP/dt<sub>max</sub> increased by 10.2% (6.1%, 25.6%) over atrial-only pacing with the distal and proximal electrode configuration. The best multisite pacing configuration selected for each patient had a significantly higher LV dP/dt<sub>max</sub> compared with BiV pacing (W = 68, P = 0.005). Similarly, the multisite pacing configuration using distal and proximal electrodes for all patients generated a significantly higher LV dP/dt<sub>max</sub> compared with BiV pacing (W = 60, P = 0.014).

Prior evaluations of CRT using LV dP/dt<sub>max</sub> have reported the response among patients with parametric statistics. Mean improvement with BiV pacing was 13.3% over atrial-only pacing. The best of four multisite pacing configurations increased LV dP/dt<sub>max</sub> by 17.5%, and the benefit achieved by using distal and proximal electrodes in all patients was 16.5%. Incremental improvement using best multisite pacing configuration was 4.3% in absolute terms, amounting to a relative increase of 32.2% above BiV pacing.

Group analysis

Change in LV dP/dt<sub>max</sub> using standard BiV and multisite pacing for each patient is shown in Figure 2. Patients are sorted in descending order of response to BiV pacing. Patients were empirically classified on the basis of haemodynamic response into the following categories: acute response to standard BiV pacing (≥10% increase in LV dP/dt<sub>max</sub>) further improved (≥5%) by multisite pacing (N = 4; 21%), acute response to BiV pacing (≥10%) not further improved (<5%) by multisite pacing (N = 4; 21%), modest-to-poor response to BiV pacing (<10%) improved (≥5% absolute or ≥20% relative) by multisite pacing (N = 8; 42%), and little acute haemodynamic change with either BiV pacing or multisite pacing (N = 3; 16%).

Change in LV dP/dt<sub>max</sub> for each of these patient groupings is shown in Figure 3. Overall, the acute response rate to CRT further improved in 12 of 19 (63%) patients with multisite pacing compared with BiV pacing.

Discussion

Main findings

The rigorous protocol for recording LV dP/dt<sub>max</sub> provided a sensitive method of identifying true acute haemodynamic effects associated with additional LV pacing sites with a quadripolar LV lead for CRT. In the vast majority of patients, multisite pacing using
two or more LV electrodes increased cardiac contractility beyond values achieved by BiV pacing. An increase in contractility was observed in all but 2 of the 19 patients from at least 1 of the 4 tested multisite pacing configurations, and from nearly 75% of all configurations tested. Although the magnitude of response was highly variable, the proof of concept that pacing from multiple electrodes may acutely augment contractile coordination in diseased hearts was demonstrated, compared with standard BiV pacing using the tip electrode. Synchronization of additional myocardium carries the potential of further augmenting systolic function.

The optimal multisite pacing configuration differed among patients, even if choice of pacing configuration did not markedly change which patients received greatest benefit. Pacing from the most distal and proximal electrodes most frequently yielded the highest LV $dP/dt_{\max}$ values and provided results that closely approximated individualized optimal configurations. Such a setting, therefore, appears reasonable as an empirical or nominal configuration. The noted improvement from a pacing configuration including the most proximal electrode suggests an advantage of pacing from multiple zones in the long-axis of the LV. The potential benefit of an added pacing site several centimetres from the lead tip is also not inconsistent with recent observations linking apical positioning of a conventional LV lead with worse outcome from CRT.20,30 However, selecting two LV pacing electrodes with shorter distance, either in the distal or proximal direction, appeared to reduce the benefit of multisite pacing.

<table>
<thead>
<tr>
<th></th>
<th>Standard BiV pacing using distal LV electrode</th>
<th>Best of four multisite pacing configurations</th>
<th>Pacing using distal and proximal LV electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± standard deviation</td>
<td>13.3 ± 16.6%</td>
<td>17.5 ± 17.4%</td>
<td>16.5 ± 16.9%</td>
</tr>
<tr>
<td>Third quartile (75th percentile)</td>
<td>15.7%</td>
<td>28.6%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Median</td>
<td>8.2%</td>
<td>10.3%</td>
<td>10.2%</td>
</tr>
<tr>
<td>First quartile (25th percentile)</td>
<td>2.3%</td>
<td>7.0%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

**Table 3** Acute percent change in LV $dP/dt_{\max}$ for all patients compared with atrial pacing, using BiV pacing, best of four multisite pacing configurations, and multisite pacing with distal and proximal electrode.

**Figure 2** Percent change in LV $dP/dt_{\max}$ in each of the 19 patients compared with atrial pacing, using BiV and the best of four multisite pacing configurations. Results are sorted in descending order of acute haemodynamic response to BiV pacing. Horizontal bars show percentage improvement in LV $dP/dt_{\max}$ for BiV pacing (light blue) and incremental improvement from best of four multisite pacing configurations (red). Striped bars indicate change in direction from multisite pacing. Patients are identified according to category of response to BiV and multisite pacing.
Although our study was limited to the acute setting, there is a growing body of literature suggesting that acute increases in LV $dP/dt_{\text{max}}$ are associated with longer-term benefits. A recent study found that acute haemodynamic improvement, defined as a 10% increase in LV $dP/dt_{\text{max}}$ with pacing, predicted reverse remodelling of the dilated LV at 6-month follow-up, with 94% sensitivity and 64% specificity.\(^{19}\) Another study evaluated the relationship between echocardiography-based LV $dP/dt_{\text{max}}$ and clinical events in 53 patients.\(^{31}\) Patients were classified as high responders (over 25% increase in $dP/dt$ with CRT), low responders (0–25% increase in $dP/dt$ with CRT), and non-responders (decrease in $dP/dt$ with CRT). Overall, 89% of high responders, 59% of low responders, and 38% of non-responders were free of events at 12-month follow-up.\(^{31}\)

Prior investigations, such as the study by Duckett et al.\(^{19}\) that used a 10% threshold increase in LV $dP/dt_{\text{max}}$ to predict remodelling, have largely relied on a single measurement of each pacing configuration. Each test was performed once and compared with
an individual baseline measurement. Reanalysing our data using such traditional methodology, 9 of 19 (47%) patients experienced at least 10% increase in LV dP/dtmax in the first recording of BiV pacing. With the best multisite pacing configuration, 15 of 19 (79%) patients had at least 10% increase in LV dP/dtmax. Similarly, the group of patients that would qualify as high responders (over 25% increase in dP/dt) would increase from 3 of 19 (16%) with BiV pacing to 9 of 19 (47%) with multisite pacing. Taken together, these data suggest a potential for multisite pacing to increase the response rate to CRT when compared with BiV pacing. Table 4 summarizes the number and percentage of patients from the present study fitting into the various categories of response using the historical dP/dt analysis comparing each individual recording with an initial baseline measurement, and with the method developed for the present study comparing each recording with baseline BiV pacing immediately before and after, and taking an average from three recordings.

Limitations
While multisite pacing appeared to confer incremental haemodynamic benefit, the strength of this study’s results is limited by the small number of patients. The study was not designed to address the question of lead positioning or potential adverse effects of apical pacing. All single-site BiV pacing used the tip LV electrode, rather than identifying the site of greatest haemodynamic response or selecting the most basal electrode. A small number of pre-selected multisite pacing configurations were tested to quantify precisely the acute haemodynamic effect, instead of identifying optimal electrode configuration and timing for each patient. The unique protocol of this study makes it difficult to compare results with prior reports on LV dP/dtmax. Finally, as the quadripolar LV lead was used for an acute pacing protocol and replaced with a permanent LV lead, no information is available on clinical outcomes or follow-up with multisite pacing.

Conclusions
A rigorous protocol with multiple recordings of each pacing configuration and repeated baseline measurements demonstrated that multisite pacing using two or more pacing sites in a quadripolar LV lead was superior to BiV pacing from the tip electrode in improving acute systolic function in 89% of patients. Although the optimal configuration varied among patients, pacing from the most distal and proximal electrodes most commonly yielded the maximum improvement in LV dP/dt. Multisite pacing, therefore, carries the potential to improve outcomes with CRT. Prospective follow-up studies are required to demonstrate clinical benefit.

Conflicts of interest
B.T. received research support and consulting fees from St Jude Medical, Medtronic, and Sorin Group. P.K. received research support and lecturing fees from St Jude Medical and Medtronic, and served as consultant for Boston Scientific. E.K., E.R., and T.G.F. are employees of St Jude Medical. P.P. was an employee of St Jude Medical at the time this work was conducted.

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References
Magnetic resonance imaging of a percutaneously ligated left atrial appendage

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A 56-year-old man with a history of persistent and refractory atrial fibrillation (AF) presented with a cerebrovascular accident. Cardioversion was attempted previously, however his AF recurred. A cardiac magnetic resonance imaging (MRI) was done (panels A, B) and he underwent extensive AF ablation which improved exercise tolerance. Owing to inconsistent anticoagulation with warfarin and intolerance to dabigatran he was offered percutaneous exclusion of the left atrial appendage (LAA) via an epicardial approach with the Lariat®. A left atrial angiogram and an intraoperative transesophageal echocardiogram were performed to confirm occlusion of the appendage (panels C, D). Three months after Lariat® closure of the LAA, a repeat AF ablation was planned and the patient underwent a second MRI which allowed assessment of LAA closure (panels E, F). The LAA is widely recognized as the likely source of thrombi in patients with non-valvular AF. Exclusion of the LAA with the Lariat® demonstrates complete occlusion of the appendage by magnetic resonance as well as angiographic imaging and may be useful in patients who are poor candidates for chronic anticoagulation.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/magnetic-resonance-imaging.pdf