A Simultaneous X-MRI and Non Contact Mapping Study of the Acute Hemodynamic Effect of Left Ventricular Endocardial and Epicardial Cardiac Resynchronization Therapy in Humans

Running Title: Ginks et al: Mechanistic Insights Using Endocardial Pacing In Humans

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Abstract

Background—Cardiac resynchronization therapy (CRT) utilising endocardial left ventricular (LV) pacing may be superior to conventional CRT. We studied the acute hemodynamic response to conventional CRT and LV pacing from different endocardial sites using a combined cardiac MRI and LV non-contact mapping protocol to gain insights into the underlying mechanisms.

Methods and Results—Fifteen patients (63±10yrs, 12 male) awaiting CRT were studied in a combined X-Ray and MRI (XMR) laboratory. Delayed enhancement Cardiac MR (DE-CMR) was performed to define areas of myocardial fibrosis. Patients underwent an electrophysiological study incorporating endocardial and epicardial LV pacing. Acute haemodynamic response was measured using a pressure wire within the LV cavity to derive LV dP/dt max. Non-contact mapping (NCM) was employed to define areas of slow conduction. There was a significant improvement in all LV pacing modes versus baseline (p<0.001). LV endocardial CRT from the best endocardial site was superior to conventional CRT with a 79.8±49.0% vs. 59.6±49.5% increase in LV dP/dt max of from baseline (p < 0.05). The hemodynamic benefits of pacing were greater when LV stimulation was performed outside of areas of slow conduction defined by NCM (p <0.001). DE-CMR was able to delineate zones of slow conduction seen with NCM in ischemic patients but was unreliable in non-ischemic patients.

Conclusions—Endocardial LV pacing appears superior to conventional CRT although the optimal site varies between subjects and is influenced by pacing within areas of slow conduction. DE-CMR was a poor predictor of zones of slow conduction in non-ischemic patients.

Key Words: cardiac resynchronization therapy; endocardium; electrophysiology; magnetic resonance imaging
Cardiac Resynchronization Therapy (CRT) is an established treatment for selected patients with heart failure. However, the mechanisms of benefit remain relatively poorly understood, giving rise to uncertainty about key issues in developing optimal therapeutic strategies tailored to specific patients. A better understanding of these mechanisms may enable us to increase the proportion of patients deriving benefit from CRT, since “non-responder” rates are as high as 30-40%. In addition, it may be possible to maximise the clinical response in those patients who do benefit.

CRT has been considered fundamentally as an electrical treatment designed to resynchronize the ventricular activation pattern in the failing heart. Indeed, LV lead positioning at an electrically delayed site conferred benefits on acute hemodynamic response to CRT\(^1\), and response to biventricular pacing has been associated with a shorter paced QRS duration\(^2\). Several studies, most recently by Ypenburg et al., have demonstrated that LV lead positioning concordant with the site of latest mechanical activation is associated with improvements in reverse LV remodelling and prognosis\(^3\). In keeping with this concept, other investigators have demonstrated using acute hemodynamic studies that the optimal LV lead position varies considerably between patients, and may need to be optimised on an individual basis\(^4,5\). However, a major limitation of the coronary sinus approach is the limited number of optimal sites available to capture.

Endocardial pacing may be superior to epicardial pacing as it gives rise to a more physiological propagation of both electrical and mechanical activation\(^6\). A second advantage of endocardial pacing is the ability to access a greater variety of sites in the LV than when compared to a transvenous approach via the coronary sinus. This is especially important to avoid areas of ischemic scar, as it has been demonstrated that an adverse response to CRT results from pacing in areas of scar\(^7\). However, areas of slow conduction have been demonstrated using non-contact mapping even in the absence of ischemic scar\(^8\) and this
principle may therefore apply to patients with non-ischemic cardiomyopathy. These areas are identified qualitatively by the electrical activation pattern of the LV endocardium and local conduction velocity or quantitatively either by the low amplitude of local electrograms or using dynamic substrate mapping. Pacing the LV within such areas of slow conduction has been shown to give rise to a lesser hemodynamic response, and this is one mechanism which may account for inter-individual variability in CRT response overall. Areas of slow conduction can be identified using delayed enhancement cardiac MR (DE-CMR) imaging in the context of ischemic heart disease. While myocardial fibrosis may also be detected using DE-CMR in patients with non-ischemic cardiomyopathy, it is not known whether zones of slow conduction can reliably be identified using this technique.

Using a combined cardiac MRI and LV non-contact mapping protocol we sought to determine whether endocardial pacing gives rise to a superior acute hemodynamic response compared to epicardial pacing and to gain insights into the underlying mechanisms of benefit. We aimed to determine whether pacing outside zones of slow conduction confers greater benefit and whether these zones could be visualised using DE-CMR.

Methods

Patients

The St Thomas’ Hospital local ethics committee approved the study. All patients provided written informed consent. Patients were at least 18 years old and fulfilled conventional criteria for CRT. Patients with hemodynamically significant aortic valve disease, mechanical right heart valve or aortic valve, peripheral vascular disease, atrial arrhythmia, or contraindication to anticoagulation were excluded, being unable to undergo the invasive mapping study. Patients with renal failure (estimated Glomerular Filtration Rate <30ml/kg/min/1.73m²) were excluded due to risk of renal injury from iodinated contrast
during the invasive study or from gadolinium based contrast agents used in cardiac MR imaging.

Baseline assessment included NYHA functional class, 12 lead ECG and 2D echocardiography. Patients with ischemic and non-ischemic cardiomyopathy were studied at least one week prior to undergoing standard CRT. The etiology of heart failure was confirmed on the basis of clinical history, 12 lead ECG, coronary angiogram and cardiac MRI.

**Cardiac MRI Protocol**

Cardiac MRI was used to quantify LV function and volumes, and delayed enhancement imaging was performed following the administration of gadolinium-based contrast agent to assess the burden and distribution of myocardial scar or fibrosis. CMR was performed on a 1.5T scanner (Philips Medical Systems) and delayed enhancement imaging was performed 15-20mins following the administration of 0.1-0.2mmol/kg gadopentetate dimeglumine (Magnevist®, Bayer Healthcare) using conventional inversion recovery techniques.

**Invasive EP & Non-contact mapping (NCM) Protocol**

The invasive EP study was performed in a hybrid X-ray / MRI (XMR) interventional cardiac catheter laboratory. Patients underwent cardiac MRI immediately prior to transfer to the X-ray environment, allowing registration of MRI, X-ray and NCM data within the same co-ordinate space for accurate tissue characterisation. Registration of these data sets was performed using methods described previously.

Patients were sedated using diazemuls (5-10mg). Bilateral femoral venous access was used to place quadripolar catheters (St Jude Medical, USA) to the high right atrium, His bundle and right ventricular apex to perform atrial and ventricular sensing and pacing. The coronary sinus (CS) was intubated and a multipolar catheter (Cardima, USA) was passed to a
postero-lateral or lateral branch (depending on coronary venous anatomy) to perform epicardial LV pacing as in conventional CRT. A NCM array (St Jude Medical, USA) was passed via the femoral artery retrogradely across the aortic valve to the LV cavity. Via the other femoral artery, a decapolar catheter (St Jude Medical, USA) was passed to the LV cavity to perform endocardial pacing from different sites within the LV (rove catheter). A pressure wire (Radi Medical Systems, Uppsala, Sweden) - a high fidelity wire acquiring data at 500Hz - was placed retrogradely to the LV cavity to perform acute hemodynamic measurements.

**Figure 1.** PA X-Ray view showing position of catheters within the heart during the invasive EP study.

Intravenous heparin (70u/kg) was administered to achieve systemic anticoagulation (target activated clotting time 300-350s). The EnSite 3000 system (St Jude, Minnesota, USA) consists of a 9F multi-electrode array mapping catheter which uses the inverse solution method to reconstruct endocardial potentials within the LV cavity. The accuracy of this technique has been validated previously. The chamber geometry is reconstructed using a locator signal from a steerable EP catheter.

A pacing protocol was then performed in the following order: (Rate 100bpm, AV delay 100ms, VV simultaneous, DDD mode where applicable): AAI, RV, conventional CRT (BIV-CS), LV endocardial (LV-EN) and BIV endocardial (BIV-EN: RV and LV endocardial). In all modes involving LV endocardial pacing we positioned the LV rove catheter in a random order in four different endocardial positions: these always included anterior, lateral and posterior sites. Capture was verified in VVI mode at each pacing site. In order to exclude fusion between intrinsic activation and LV pacing, QRS morphology was analysed to establish that there was no significant variability when compared to DDD mode.
This was also validated with reference to LV pacing by analysis of the activation wavefront on non-contact mapping.

Hemodynamic and electrophysiological parameters were assessed at baseline and in each pacing mode once steady state pacing was achieved for a minimum of one minute. In between pacing modes, measurement of intrinsic haemodynamics was repeated after at least 30 seconds of sinus rhythm, so as to account for baseline drift. We used the pressure wire to derive real-time mean peak dP/dt max as a marker of LV contractility, with three measurements in each pacing mode taken over a minimum of 10 seconds. The change from intrinsic rhythm in acute haemodynamics as a result of pacing was calculated and expressed as a percentage compared to baseline SR. Endocardial maps were obtained in sinus rhythm and in each pacing configuration.

**Derivation of LV activation time**

Virtual unipolar electrograms recorded from the endocardial surface were used to measure the duration of LV activation. The electrograms were acquired at 1200Hz, giving a temporal resolution of 0.83ms. The high pass filter was set at 8Hz. The onset of activation was defined as the first peak negative dV/dt at any point in the LV. The end of LV activation was defined as the time of the latest peak negative unipolar electrogram on the virtual endocardial surface.

**Definition of regions of slow conduction**

Dynamic substrate mapping (DSM) was performed after completion of the procedure to define areas of consistently low peak negative voltage, using a method validated previously. Zones of slow conduction were delineated as regions which the activation wavefront failed to enter, with the endocardial voltage amplitude threshold set at 30% of the maximum endocardial voltage recorded.

**Categorisation of LV lead position**
For endocardial and epicardial LV lead positions, the location of the LV lead tip was attributed in a binary fashion to being in or outside the predefined areas of slow conduction using DSM.

The greater number of accessible locations endocardially provided a more robust assessment of the effect of pacing in different regions. We assessed the effect on acute hemodynamics of the endocardial LV lead position in the long axis (divided into basal, mid ventricular or apical sites) and in the short axis (divided into anterior, posterior or lateral sites). The effect of position of the CS lead was not included in this assessment as the CS lead was placed empirically in the postero-lateral or lateral vein.

**Statistical analysis**

Continuous variables are expressed as mean (SD). Comparisons were made using the Student’s t-test or one-way ANOVA for independent samples and paired t-tests or Repeated Measures ANOVA (RMANOVA) for paired samples of more than one group. A two-tailed p-value <0.05 was considered significant. Statistical analysis was performed using the Statistics Package for the Social Sciences (SPSS) v 15 (SPSS Inc., Chicago, Illinois) or MedCalc v 11.2 (MedCalc software, Mariakerke, Belgium)

**Results**

**Patient Demographics**

Patient demographics of the 15 patients studied are shown in Table 1 and represent a typical cohort suitable for CRT. The majority were non-ischemic patients since the invasive EP study excluded patients with significant peripheral vascular disease. Patients were all NYHA class III with left bundle branch block.

**Procedural success**
The invasive EP protocol was completed in 14/15 (93%) patients. In one patient, the procedure was abandoned as it was impossible to pass the array into the LV due to tortuosity of the femoral artery. There were no procedural complications.

**Acute hemodynamic response to endocardial versus epicardial pacing**

The acute hemodynamic response to pacing is shown in Figure 2. This is displayed as the mean change in mean peak dP/dt in each pacing configuration, compared with baseline (sinus) rhythm. Percentage changes in hemodynamics from sinus rhythm were 8.6±19.1%, 4.6±23.8%, 82.5±51.1%, 79.8±49.0% and 59.6±49.5% for AAI, RV, LV-EN, BIV-EN and BIV-CS modes respectively. For endocardial LV pacing modes the results in Figure 2 correspond to the optimal LV endocardial site defined as that which produced the greatest hemodynamic benefit[5].

There was a significant improvement in all LV pacing modes compared with sinus rhythm, AAI and RV pacing (p<0.001, RMANOVA). There was additional acute hemodynamic benefit in LV endocardial and BIV endocardial pacing configurations from the optimal site versus conventional CRT delivered from the coronary sinus. (BIV-CS mode, p < 0.05).

Corresponding changes in LV total endocardial activation time and QRS duration (derived from NCM and the surface ECG respectively) are shown in Figure 3. LVTAT was not reduced in any mode versus sinus rhythm. QRS duration was significantly increased by RV pacing versus all other modes (p<0.05).

**Site specificity of response to LV stimulation**

**Importance of Zones of Slow Conduction**

For each endocardial and epicardial LV lead position, we ascertained whether the lead tip was inside or outside a zone of slow conduction, as defined by NCM. The mean
hemodynamic response was expressed as a percentage change from baseline, and is shown in Figure 4, plotted against the LV lead position in relation to the zone of slow conduction.

LV stimulation within an area of slow conduction was associated with a reduction in the degree of hemodynamic response in all LV endocardial pacing configurations (p <0.001).

LV total activation time (LVTAT) and QRS duration were calculated according to the position of the LV lead in or outside of areas of slow conduction. The mean LVTAT when the LV lead was in an area of slow conduction was 78.6 ± 22.4ms versus 84.9 ± 21.8ms when the lead was not within these areas (p=0.59). The corresponding values for QRS duration were 148.6 ± 25.5 and 154.9 ± 32.9ms respectively (p=0.95). LV total activation time and QRS duration were not shortened when the LV lead was outside the area of slow conduction, suggesting that mechanism of hemodynamic benefit may be an improvement in mechanical efficiency which is not underpinned by more rapid electrical activation of the myocardium.

**Importance of LV lead position by region**

For LV endocardial pacing configurations there was considerable variability in the degree of hemodynamic response in different regions of the LV endocardium. The smallest acute hemodynamic response across all patients in LV-EN mode was 12.6±10.4% (range 0 to 28.2%) from baseline and the largest increase was 40.6±23.0% (range 16.8 to 92.5%). In BIVEN mode the smallest increase was 12.8±10.1% (range -0.12 to 29.3%) and the largest was 40.8±21.9% (range 16.8 to 90.6%).

The hemodynamic response to pacing in these modes is shown in Figure 5, according to the relationship of the lead position to areas of slow conduction.

When the LV endocardial lead was outside an area of slow conduction, a lateral position of the LV lead was optimal, with posterior position being the next best. An anterior position of the LV lead gave the least hemodynamic response in this situation. When the LV
lead was in an area of slow conduction, the hemodynamic response was superior when the LV lead was placed anteriorly.

Hemodynamic response according to the position of the endocardial LV lead in the long axis of the heart is shown in Figure 6. There were no significant differences in acute hemodynamic response between basal, mid and apical LV lead positions.

**Comparison of Non-Contact Mapping with Delayed Enhancement Cardiac MR (DE-CMR)**

Table 2 summarises MRI and non-contact mapping patient characteristics

Ten patients had non-ischemic etiology of heart failure on the basis of the history, a normal coronary angiogram and absence of sub-endocardial late enhancement on MR imaging. Of these, none had late gadolinium enhancement of any distribution on cardiac MR. 6/10 patients with non-ischemic cardiomyopathy had lines of conduction block, despite the absence of late enhancement on DE-CMR (Figure 7).

This suggests that DE-CMR is not capable of identifying areas of slow conduction in this patient group. However, late enhancement was demonstrated in all 5 patients with ischemic cardiomyopathy. In this group, there was a reasonable correlation between areas of slow conduction and distribution of scar, as shown in Figure 8.

**Discussion**

**Hemodynamic effects of endocardial and epicardial pacing**

This small mechanistic study demonstrates that endocardial LV pacing has the potential to confer a superior hemodynamic benefit compared to conventional CRT delivered from the coronary sinus. The degree of acute hemodynamic response at the optimal site was surprisingly high in both endocardial and epicardial LV pacing configurations (79.8±49.0% and 59.6±49.5% respectively). This reflects the fact that this was a highly selected population
with marked LV dyssynchrony (with mean QRS duration 164ms) in which a non-ischemic heart failure etiology predominated. Furthermore, comparison was made with baseline sinus rhythm rather than fixed rate atrial pacing, so a proportion of this percentage increase may be secondary to rate-dependent changes in LV dP/dt.

Importantly the site of optimal benefit differs widely between patients. Pacing within areas of slow conduction was associated with a lesser degree of acute hemodynamic benefit. Areas of fibrosis/scarring correlating with NCM could be seen with DE-CMR in all patients with ischemic cardiomyopathy. However 60% of patients with non-ischemic cardiomyopathy had areas of slow conduction associated with poor response which could not be predicted using delayed enhancement cardiac MR.

These findings are in keeping with those of a recent acute hemodynamic study which demonstrated that endocardial and epicardial pacing in the same region of the left ventricle gave rise to similar improvements in LV dP/dt max. Garrigue et al. evaluated the chronic effects of biventricular endocardial pacing and demonstrated improved systolic performance with this approach compared with conventional CRT. One key mechanism of potential benefit of endocardial over epicardial pacing may be that this approach facilitates pacing outside areas of slow conduction, as a greater area of the myocardium is accessible when lead delivery is not constrained by the coronary venous anatomy. In addition, an endo- to epicardial mechanical activation is more physiological. Endocardial pacing reproduces the gradient of LV contraction in systole in an endo- to epicardial direction engaging the subendocardial Purkinje network. This may result in more rapid myocardial recruitment, maximising the contractile response of the viable recruited myocytes. The difference between the angles of fibre orientation between the endo- and epicardial layers could also facilitate this more rapid myocardial recruitment.


**Electrical versus mechanical mechanisms of benefit**

We have also demonstrated that the acute hemodynamic benefit from left ventricular pacing is independent of left ventricular endocardial activation time, which is not reduced in comparison with sinus rhythm. These findings suggest that the mechanism of acute hemodynamic benefit may be more effective mechanical recruitment of the LV myocardium rather than shortening of the LV electrical activation time. Detailed MR and mapping studies in the canine ventricle have also shown that mechanical benefit occurs independently of electrical resynchronization²⁰. Clinically, the concept that mechanical resynchronization is a more important mechanism of benefit of CRT is supported by the fact that positioning of the LV lead at the site of latest mechanical activation confers the maximal clinical benefit³, ²¹. The magnitude of the hemodynamic response will depend upon the rate of myocardial recruitment, the viability of the contracting tissue and the proportion of the ventricle that can contribute to the stroke volume.

**Variations in hemodynamic response to LV pacing**

We have shown that LV lead positioning within zones of slow conduction is associated with a lesser degree of acute hemodynamic response. This is consistent with the results of a previous study we conducted which evaluated the hemodynamic response from pacing inside and outside zones of slow conduction¹⁰. This is likely to reflect less effective capture of the myocardium and slower mechanical propagation across the left ventricle. This mechanism may in part explain the significant intra-individual and inter-individual variability that has been found in other studies in the optimal LV lead position in patients undergoing CRT⁴, ⁵. In our study, a lateral position of the LV endocardial lead was shown to be superior to posterior or anterior lead positions when pacing outside areas of slow conduction. This is
consistent with the premise that resynchronization therapy is best delivered using a laterally positioned electrode so as to reverse the effect of LV dyssynchrony, which gives rise to late activation of the lateral LV wall. When the endocardial LV lead was positioned within an area of slow conduction, it appeared that an anterior position may achieve greater hemodynamic benefit than a lateral position. This is in keeping with the finding in other studies of patients with ischemic cardiomyopathy that positioning the LV lead in an area of postero-lateral scar confers an adverse outcome\textsuperscript{7, 22, 23}.

**Electro-anatomical and MRI correlates**

The relationship between myocardial scar and areas of late enhancement on cardiac MR (DE-CMR) in patients with ischemic cardiomyopathy is well known\textsuperscript{24}. In our study, there was a correlation between areas of scar and zones of slow conduction, as previously noted\textsuperscript{11}.

Myocardial fibrosis can also be visualised using this technique in patients with non-ischemic cardiomyopathy in some cases\textsuperscript{12}. However, in our study, areas of slow conduction were demonstrated using non-contact mapping in 60% of patients with non-ischemic cardiomyopathy in whom no late enhancement was seen using DE-CMR. It is feasible that cardiac MR is not capable of detecting the low degrees of diffuse fibrosis which are thought to be associated with slow conduction in this condition\textsuperscript{25}. Late gadolinium enhancement using cardiac MR remains a qualitative rather than quantitative evaluation. It provides a relative comparison of degrees of scarring or fibrosis in different regions. As a result, homogeneous diffuse fibrosis at the microscopic level may not manifest as late enhancement to the observer. An alternative explanation for the failure of cardiac MR to detect zones of slow conduction is that fibrosis is not present in these areas, but that other properties of the
myocardium are affected by the disease process. This may include gap junction or ion channel remodelling which interfere with activation wavefront propagation.

**Clinical implications**

Current understanding of response to CRT in patients with ischemic cardiomyopathy is that overall scar burden as well as scar density in proximity to the LV lead tip are associated with an adverse or diminished clinical or echocardiographic response to CRT\(^7\), \(^{26}\), \(^{27}\). Our findings suggest that the presence of areas of slow conduction may account for the variability in response to LV pacing in non-ischemic as well as ischemic cardiomyopathy. Furthermore, while these areas can be visualised in ischemic cardiomyopathy using DE-CMR, this is not the case for patients with non-ischemic cardiomyopathy. This is one potential explanation for lack of response to CRT in a significant proportion of this patient population and reinforces the need for positioning the LV lead on an individual basis. An alternative approach to addressing this problem is the use of multi-polar leads or multi-site pacing, thereby avoiding areas of slow conduction which are associated with a diminished response.

Our data suggest that the principal mechanism of acute hemodynamic benefit from CRT is an improvement in LV mechanical rather than electrical activation. Endocardial LV or biventricular pacing gives rise to a superior hemodynamic response compared to conventional CRT. The clinical utility of this approach remains limited at present due to the risk of thrombo-embolic complications and left-sided valvular endocarditis.

However, in the situation when transvenous delivery of the coronary sinus lead has failed, endocardial pacing represents a viable alternative to surgical LV lead placement, in particular if the risks of general anaesthetic are high. Another group of patients who may
benefit from this approach are non-responders to conventional CRT without suitable coronary venous anatomy for epicardial lead placement.

**Study limitations**

Our study involved a small population of carefully characterised of patients and further work is required to confirm these findings in a larger population. Our protocol incorporated pacing endocardially in the left ventricle at multiple sites, in order to assess the effect of different endocardial positions. The order of pacing sites was not randomly selected and therefore this could be a source of bias. We have acquired information on LV endocardial activation times and QRS duration (reflecting biventricular activation). We do not have full information on transmural LV activation, which would be too invasive to acquire in vivo. It is recognised that the accuracy of non-contact mapping reduces with increasing cavity size of the LV, which represents an important limitation in this study of patients with left ventricular dilatation. The mean equatorial distance from the center of the array to the endocardial surface in this study was 37±11mm. In the study by Schilling et al. validating non-contact mapping against contact electrograms (EGMs), perfect timing matches were obtained as far as 52mm from the center of the array, although differences in timing of EGMs increased gradually at distances over 34mm. Chamber dilatation may therefore be anticipated to affect accuracy of activation time measurement rather than identification of regions of slow conduction.

**Conclusions**

Endocardial CRT may offer a potential for a superior response in patients undergoing CRT. Our data suggest that the response to endocardial pacing is site-specific and is negatively affected by stimulation within area of slow conduction or fibrosis. In patients with ischemic cardiomyopathy, DE-CMR can identify these areas and may be utilised in order to
guide LV lead placement. DE-CMR was not able to detect areas of slow conduction in patients with non-ischemic cardiomyopathy. It is feasible that LV lead positioning within such areas would confer an adverse response to therapy, analogous to positioning of the LV lead in an area of scar in patients with ischemic cardiomyopathy. Therefore, this may represent a mechanism of non-response to CRT in this patient group.
Sources of Funding

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Disclosures

Matthew Ginks received an educational grant from St Jude Medical. Pier Lambiase receives an educational grant and is a member of the speaker bureau for St Jude Medical, and receives funding from the National Institute for Health Research. Reza Razavi and Kawal Rhode receive funding from the European Commission Framework Programme 7 and the Engineering and Physical Sciences Research Council – Medical Research Council. Marcus Simon is an employee of St Jude Medical. Aldo Rinaldi is an advisor to St Jude Medical and Medtronic.
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<td>LVESD (mm)</td>
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NYHA: New York Heart Association; EF: ejection fraction; LVEDD: LV end-diastolic dimension; LVESD: LV end-systolic dimension.
Table 2

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* ICM: ischemic cardiomyopathy; † DCM: Dilated cardiomyopathy
‡ Type I activation pattern represents smooth, homogeneous activation of the LV from septum to lateral wall. Type II describes a U-shaped activation pattern around a region of conduction block.
§ Very lateral line of conduction block resulted in type I activation pattern.
Figure Legends

**Figure 1.** X-ray image of non-contact mapping array, electrophysiologic catheters and pressure wire in situ during a typical case. The right atrial wire is out of the field of view.

**Figure 2.** Percentage change in hemodynamics from baseline by pacing mode in response to pacing at optimal site.

AAI: Atrial pacing only; RV: DDD RV; LV-EN: DDD LV Endocardial; BIV-EN: DDD Biventricular Endocardial; BIV-CS: Conventional CRT

**Figure 3.** LV total activation time and QRS duration by pacing mode.

**Figure 4.** Effect of LV lead position in relation to areas of slow conduction on acute hemodynamic response, shown as percentage change from baseline sinus rhythm.

**Figure 5.** Change in hemodynamics from sinus rhythm by LV pacing region (short axis) and position of the endocardial LV lead in relation to zone of slow conduction.

**Figure 6.** Change in hemodynamics from sinus rhythm by LV pacing region (long axis) and position of the endocardial LV lead in relation to zone of slow conduction.

**Figure 7.** Upper panel: Short axis stack of DE-CMR images of a patient with non-ischemic cardiomyopathy. There is no evidence of myocardial scar or fibrosis. Middle panel: Dynamic substrate map of the same patient in antero-posterior projection. The zone of slow conduction is delineated by a solid white line, which covers the lateral aspect of the anterior LV wall. Virtual unipolar electrograms from two points equidistant (34mm) from the array are shown in yellow from within (left) and outside the zone of slow conduction (right). The sample electrogram from within the region of slow conduction is fractionated and of lower amplitude, demonstrating that the reduced...
amplitude of electrograms in these regions is not artefact arising as a result of distance from the array. Lower panel: Images 1 to 10 show the activation map of the same patient in 25ms steps (LAO view on the left of each image, RAO view on the right). The wavefront is seen to propagate from the anterior septum towards the lateral LV wall. When it reaches the line of conduction block on the border of the slow conduction zone, the activation wavefront passes inferior to this region, around the LV apex and on to the posterior wall.

**Figure 8.** Upper panel: Late enhancement images of patient 11 with a previous myocardial infarction affecting the territory of the left anterior descending coronary artery. Middle panel: Dynamic substrate map of patient 11 in the right lateral projections. The zone of slow conduction is delineated by a solid white line, which covers the anterior aspect of the LV wall. Virtual unipolar electrograms (yellow) from within (left) and outside the zone of slow conduction (right) which are equidistant (30mm) from the array. A sample electrogram from within the area of slow conduction is seen to be fractionated and of low amplitude, whereas the electrogram from a region of normal myocardium at the same distance from the array is of greater amplitude. Lower panel: Activation map of patient 11. The progression of the depolarisation wavefront can be seen crossing from a breakout point in the septum towards the lateral wall (images 1 to 4). The wavefront then reaches a line of block and regresses before passing inferiorly and posteriorly (images 5 to 8) to activate the rest of the LV.
LV lead position in relation to slow conduction zone

p < 0.001
Pacing Mode and Relationship of LV Lead to Zone of Slow Conduction
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A Simultaneous X-MRI and Non Contact Mapping Study of the Acute Hemodynamic Effect of Left Ventricular Endocardial and Epicardial Cardiac Resynchronization Therapy in Humans

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