Cardiac magnetic resonance-derived anatomy, scar, and dyssynchrony fused with fluoroscopy to guide LV lead placement in cardiac resynchronization therapy: a comparison with acute haemodynamic measures and echocardiographic reverse remodelling

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Aims
Left ventricular (LV) lead positioning for cardiac resynchronization therapy (CRT) is largely empirical and operator-dependent. Our aim was to determine whether cardiac magnetic resonance (CMR)-guided CRT may improve the acute and the chronic response.

Methods and results
CMR-derived anatomical models and dyssynchrony maps were created for 20 patients. The CMR targets (three latest activated segments with <50% scar) were overlaid on to live fluoroscopy. Acute haemodynamic response (AHR) to LV pacing was assessed using an intra-ventricular pressure wire. Chronic CRT response (end-systolic volume reduction ≥15%) was assessed 6 months post-implantation. All patients underwent successful CMR-guided LV lead placement. A CMR target segment was paced in 75% of patients. The mean change in LVdP/dtmax for the CMR target was +14.2 ± 12.5 vs. +18.7 ± 11.9% for the best AHR in any segment and +12.0 ± 13.8% for the segment based on coronary sinus (CS) venography. Using CMR guidance, the acute responder rate was 60 ± 50% on the basis of venography. At 6 months 60% of patients were echocardiographic responders. Of the echocardiographic responders, 92% were successfully paced in a CMR target segment compared with only 50% of non-responders (P = 0.04).

Conclusion
CMR guidance compared well when validated against the AHR. Lead placement was possible in the CMR target region in most patients with an AHR comparable with the best achieved in any CS branch. The chronic response was significantly better in patients paced in a CMR target segment. These results suggest that CMR guidance may represent a clinically useful tool for CRT.

Keywords
Cardiac resynchronization therapy • Heart failure • Haemodynamics • Imaging • Magnetic resonance imaging
Introduction
Cardiac resynchronization therapy (CRT) is an established treatment for heart failure but ~30% of patients do not respond, which may be related in part to suboptimal lead positioning. Pacing the posterolateral left ventricle (LV) generally produces the best haemodynamic response, however, patients may not respond if they have scar in the paced region. Large-scale studies have shown no difference in the CRT response when the lead is placed in an anterior, posterior, or lateral position, but a mid or basal location appears superior to an apical position.

There is significant variation in the acute haemodynamic response (AHR) when pacing different regions of the LV with the optimal location varying among patients. Pacing the latest mechanically activated region of the LV is associated with better CRT outcomes and the recent TARGET study showed that an echocardiographic-guided approach resulted in an improved CRT response. We have previously used cardiac magnetic resonance (CMR)-derived anatomy and scar data fused with fluoroscopy to achieve successful CRT implantation. We have previously used cardiac magnetic resonance (CMR)-derived anatomy and scar data fused with fluoroscopy to achieve successful CRT implantation. We have previously used cardiac magnetic resonance (CMR)-derived anatomy and scar data fused with fluoroscopy to achieve successful CRT implantation. We set out to acutely compare CMR guidance with an optimal acute haemodynamic LV lead position anywhere within the CS, measured with a pressure wire and the site chosen on the basis of CS angiography alone. We set out to assess the chronic response to CMR-guided LV lead placement on the basis of echocardiographic reverse remodelling 6 months post-CRT implantation.

Methods
Study population
Patients fulfilling standard CRT criteria (NYHA class II–IV drug refractory heart failure, LVEF ≤ 35%, and QRS ≥ 120 ms) were included (Table 1). Patients in atrial fibrillation were not excluded. The study was approved by the local Ethics Committee and written informed consent was obtained from each patient. Baseline assessment of NYHA class, Minnesota Living with Heart Failure Questionnaire score, 6 min walk distance, VO₂ max, LVEF, left ventricular ejection fraction, LVESV, LVEF on statin, LVESV on ACE-I or ARB, LVESV on aldosterone antagonist, LVEF on betablocker, NYHA Class (II/III), 6MWD, MLWHFQ score, VO₂ max, sinus rhythm, Heart rate (bpm), PR interval (ms), MLWHFQ score, 6MWD, VO₂ max (mL/kg/min), and Heart rate (bpm) were measured. Patients with a contraindication to CMR or significant renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m²) were excluded. Three patients who had been recruited for the study were excluded because it was not possible to access the CS (one patient), because of intraoperative CS dissection (one patient), and because only one CS vein was accessible (one patient).

Cardiac MR image acquisition and processing
Respiratory and cardiac-gated CMR images were acquired on a Philips Achieva 1.5T MR system (Philips Healthcare, Best, The Netherlands). Two-, three-, and four-chamber and multiple slice short-axis cine steady-state free-precession images were acquired. Contrast-enhanced CMR images of the coronary veins and myocardial scar were acquired using previously described methods in a single examination. The epi-cardial LV surface and endocardial surface of the right ventricle, left atrium, and right atrium were extracted automatically using a model-based segmentation algorithm. The CS was manually segmented from the whole heart images and used to yield a detailed anatomical model including the main branches (Figure 1A). A modified American Heart Association (AHA) 16-segment LV model was created using the TomTec 4D analysis software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The same analysis tool created a regional volume map showing the mechanical delay motion curves of the 16 segments and calculated the systolic dysynchrony index (SDI). The position and extent of scar was determined from LGE CMR images (segments with >50% transmural LGE were considered non-viable). Scar data were manually segmented from the short-axis stack images using the ITK-SNAP software and registered to the whole heart CMR data, facilitating scar visualization on the anatomical model and on a 16-segment bullseye plot (Figure 2A and B).

MR dyssynchrony and target segments
Segments with >50% area scar were excluded as targets as were antero-septal segments as pacing these would result in an activation pattern similar to RV pacing. Segments were excluded if their regional volume curve was flat (overall regional volume change < 2.5 mL) suggesting akinesia (Figure 3A). Before CRT implantation, two imaging specialists

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
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</tr>
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<tbody>
<tr>
<td>Patients</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>66 (12)</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>30/15</td>
</tr>
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<td>NYHA Class (II/III)</td>
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<td>On ACE-I or ARB (%)</td>
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<td>LVEF (%)</td>
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<td>Heart rate (bpm)</td>
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<td>PR interval (ms)</td>
<td>169 (19)</td>
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<tr>
<td>QRS duration (ms)</td>
<td>152 (19)</td>
</tr>
<tr>
<td>QRS morphology (LBBB/non-specific IVCD)</td>
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</table>

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota Living with Heart Failure Questionnaire Score; NYHA, New York Heart Association; 6MWD, 6 minute walk distance.

Two-, three-, and four-chamber and multiple slice short-axis cine steady-state free-precession images were acquired. Contrast-enhanced CMR images of the coronary veins and myocardial scar were acquired using previously described methods in a single examination. The epi-cardial LV surface and endocardial surface of the right ventricle, left atrium, and right atrium were extracted automatically using a model-based segmentation algorithm. The CS was manually segmented from the whole heart images to yield a detailed anatomical model including the main branches (Figure 1A). A modified American Heart Association (AHA) 16-segment LV model was created using the TomTec 4D analysis software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The same analysis tool created a regional volume map showing the mechanical delay motion curves of the 16 segments and calculated the systolic dysynchrony index (SDI). The position and extent of scar was determined from LGE CMR images (segments with >50% transmural LGE were considered non-viable). Scar data were manually segmented from the short-axis stack images using the ITK-SNAP software and registered to the whole heart CMR data, facilitating scar visualization on the anatomical model and on a 16-segment bullseye plot (Figure 2A and B).

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Figure 1 (A) A posteroanterior view of a whole heart segmentation showing cardiac chambers and the coronary venous system (LV dark blue, RV green, LA orange, RA light blue, and CS red). (B) The modified AHA 16-segment model of the LV as a bullseye plot (Sept, septum; Ant, anterior; Lat, lateral; Inf, inferior). (C) The LV model created from CMR cine imaging and labelled according to the 16-segment model shown in the bullseye plot overlaid on to the CMR four-chamber view.

Figure 2 (A) A full thickness scar in red overlaid on to the LV epicardial surface. (B) The same patient’s full thickness scar overlaid in grey on to a 16-segment bullseye plot of the LV. The cyan outline around the bullseye plot represents the CS. The white arrows indicate the same region of scar in both (B and C) for this patient.

Figure 3 (A) Regional volume map. Time is a percentage of the total cardiac cycle on the x-axis and volume change (mL) on the y-axis. In this example segment 11 is the latest mechanically activated segment but is excluded as a potential target because the regional volume change from peak is <2.5 mL. The target segments in this patient are therefore 10, 9, and 4 (no scar seen on LGE imaging in these segments). (B) The CMR model overlaid on to the fluoroscopic image in real-time showing the LV lead placed in segment 15.
agreed on the three latest mechanically activated target segments with less <50% scar. The implanter was blinded to this process.

Image overlay and registration
An in-house developed platform based on Philips EP Navigator (Philips Healthcare) was used to overlay and register the CMR data during CRT implantation. Accurate registration of the CMR to fluoroscopic images was achieved using posteroanterior (PA), left anterior oblique (LAO) 30°, and right anterior oblique (RAO) 30° views with a catheter looped in the right atrium. The EP navigator software automatically maintained alignment between the model and the live fluoroscopy throughout the procedure with respiratory motion compensation. We have previously shown that the above methods facilitate accurate overlay and registration of three-dimensional (3D) anatomical models to live fluoroscopic images (Figure 3B).13,24

Implantation and comparison of MR guidance with acute haemodynamics
AHR was evaluated using a 0.014-inch diameter high fidelity Certus PressureWire and PhysioMon software (Radi Medical Systems, Uppsala, Sweden) introduced into the LV via a femoral or radial artery as described previously.35 The LV lead was placed in as many different CS veins and positions as possible. PAC was performed in the DDDLV mode with a fixed AV delay 100 ms (VVI LV in AF patients) 5–10 beats above the intrinsic rate, LVdP/dt max was recorded for at least 20 s to ensure steady-state conditions. LVdP/dt max during atrial pacing (AAI) or RV pacing (AF patients) at 5–10 beats above the intrinsic rate was considered baseline and 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. These methods have previously been shown to reliably measure LVdP/dt max.25–28 Results at each pacing site were expressed as a percentage change from the baseline. To minimize drift, the baseline was reassessed prior to and after every LV lead reposition and comparisons were made to a mean of these two readings. Data from premature ventricular complexes was excluded. To minimize drift, the baseline was reassessed prior to and after every LV lead reposition and comparisons were made to a mean of these two readings. Data from premature ventricular complexes was excluded. The LV lead was finally placed in or as close as possible to the CMR target segment. AV and VV delays were optimized with pressure wire guidance at the end of the procedure.

CMR guidance vs. anatomical target segments
Each CS vein position paced was marked on still images of the CS venogram. At least two views (PA, RAO 30° or LAO 30°) were assessed by an independent expert implanter (J.P.S.). All positions in which it was possible to obtain haemodynamic data were ranked in order of preference based solely on the CS venograms. The AHR achieved pacing in the highest ranked angiographic position without phrenic nerve stimulation (PNS) was compared with the CMR-guided targets.

Additional time requirement
The extra data processing and analysis required to produce the detailed anatomical model of the heart and to identify the latest mechanically activated segments of the LV without scar or akinesis added ~2 h to the standard CMR analysis time for each patient. Importing the CMR data to the EP Navigator system prior to implantation and overlay and registration of this data to the fluoroscopic images added ~30 min to the procedure time. The mean implantation procedure time was 180 ± 35 min including the pressure wire-guided optimization at the end of the procedure. For the purposes of this study we placed the LV lead in as many different CS positions as possible (not just the target position); thus we would expect the procedure time for a CMR-guided approach to LV lead placement as a part of routine practice to be shorter than in this study.

Follow-up and response
Patients were followed up at 6 months with repeat assessment of NYHA class, MLWHFQ, 6MWD, VO2 max, and echocardiographic parameters. Echocardiographic reduction in the end systolic volume (ESV) ≥15% at 6 months was used to define reverse remodelling (echo responder).29,30 A clinical composite score (CCS)31 was used to assess clinical response.

Statistical analysis
Statistical analysis was performed on JMP (version 9.0.1, Marlow, Buckinghamshire, UK). Group comparisons were performed using a t-test or an appropriate non-parametric test (Wilcoxon rank sum, Kruskal–Wallis). Pearson’s correlation coefficient was used to measure the linear relationship between two variables and χ² to compare categorical variables. All results are expressed as mean ± SD. P-values < 0.05 were considered statistically significant.

Results
A total of 20 segments in seven patients were excluded as potential LV lead targets because of the full thickness scar seen on CMR LGE imaging (Table 2): in two patients the full thickness scar was seen in the anterior or anterolateral segments and in five patients in the posterior and/or postero-lateral/lateral segments. A further 11 segments in seven patients (five non-ischaemic and two ischaemic in aetiology) were excluded as potential LV lead targets because of a flat volume curve suggestive of akinesis (despite viability according to CMR LGE imaging): in four patients the segments excluded were anterior or anterolateral and in three patients the segments excluded were posterior or posteroseptal.

LV lead placement in at least two separate CS branches was completed in 20 patients (see Table 1). At least one anterior and one lateral or posterolateral LV segment were paced in all patients. Validation of the registration between the 3D roadmap and the 2D X-ray images was performed using balloon occlusion coronary venograms with a 2D registration error of 1.2 ± 0.7 mm. AHR measurements were recorded in a mean of 4.7 ± 1.6 different LV segments per patient. Successful LV pacing in a CMR target was achieved in 15 of 20 patients (75%). In five patients it was impossible to measure the AHR in a CMR target because of PNS, failure to capture, or absence of an accessible target vein (four of five patients were ischaemic with the scar adjacent to the target). The CMR-targeted AHR in these patients was based on the nearest position to a target segment successfully paced.

CMR-guided vs. conventional LV lead placement
Acute response
The mean increase in LVdP/dt max with CMR guidance (AHR from paced target segment in 15 patients and closest successfully paced segment in 5 patients in whom the target was not reached) was +14.2 ± 12.5 vs. +18.7 ± 11.9% (P = 0.69) for the best AHR and +3.4 ± 9.0% (P < 0.001) for the worst AHR.
in any segment. This compared with an increase in $dP/dt_{\text{max}}$ of $+12.0 \pm 13.8\%$ ($P = 0.23$) for the highest ranked segment based on CS venography. The mean change in the AHR seen in just the 15 patients in whom a target segment was paced was $15.8 \pm 12.7\%$ and the mean change in the AHR seen in all non-scarred segments was $9.1 \pm 9.9\%$ ($P = 0.003$). A positive significant correlation between the best overall AHR achieved in each patient and the CMR-derived SDI was seen ($r = 0.63$, $P = 0.003$).

A HR of $\geq 10\%$ has been shown to be a sensitive and specific predictor of chronic CRT response and was seen in 70% of our patients in at least one segment. Out of 20, 12 (60%) patients were AHR responders when paced in a CMR target segment vs. 10 of 20 (50%) when paced on the basis of CS venography ($P = 0.5$). Of the eight patients in whom the CMR target segment did not result in an AHR $\geq 10\%$, only two had an AHR $\geq 10\%$ in a non-target segment, suggesting that if a patient is an acute non-responder despite pacing in a target segment, pacing in a non-target segment has only a small chance of improving the outcome. The likelihood of acute non-response was greatly increased by the presence of scar as five of six acute non-responders had a scar on CMR (Table 2). Conversely, of the 11 patients without a CMR scar, only 1 was not an acute responder.

Pressure-wire-guided AV and VV optimization at the end of the procedure confirmed the non-inferiority of DDDLV pacing to conventional biventricular (BiV) pacing: the mean best DDDLV $dP/dt_{\text{max}}$ was $1112 \pm 220$ vs. $1058 \pm 202$ mmHg for the best optimized BiV pacing mode ($P = 0.06$).

### Chronic response
At 6 months 12 of 20 (60%) patients were echocardiographic responders (reduction in the ESV of $\geq 15\%$). The eight echocardiographic non-responders all had an ischaemic aetiology. Consistent with previous clinical trials, the greater proportion of patients were clinical rather than echocardiographic responders with 75% having an improvement in CCS at 6 months. Out of 12, 11 (92%) echocardiographic responders were successfully paced in a CMR target
segment compared with only four of eight (50%) echocardiographic non-responders ($P = 0.04$). Thus only one of the five patients who were not paced in a target segment reverse remodelled. Out of 14, 10 (71%) patients with an acute AHR of ≥10% at implantation were echocardiographic responders.

**Discussion**

We have used CMR to guide LV lead placement and compared the results acutely to an optimal haemodynamic standard and angiographic approach and chronically with reverse remodelling. We were able to accurately acquire and process CMR-derived CS anatomy, scar, and dyssynchrony data (derived from a single CMR scan) and fuse these with live fluoroscopy during CRT implantation. We were able to pace in at least one CMR target segment in the majority of patients, which gave rise to an AHR comparable with the best possible in any segment. In keeping with previous studies, we showed a marked difference in the AHR dependent on the LV pacing site, which may explain the suboptimal CRT response if a purely anatomical approach is used. Our results show that simply pacing in a non-scarred region will not give a good AHR, but a combination of no scar and late mechanical activation gives an AHR approaching the best that can be achieved anywhere. Indeed, if a target segment is successfully paced, it is unlikely that any other segment will give rise to a significantly better acute response.

Our chronic results show that 92% of patients who reverse remodelled successfully had the lead positioned in a CMR target segment. A CMR-guided approach to LV lead placement appears to have been particularly helpful in patients 5, 9, and 17 (Table 2). In these three patients the CS angiography target was posterior or posterolateral but all were successfully paced in the anterior or anterolateral CMR target segments and were found to have reverse remodelled at 6 months. Thus, our technique of using CMR guidance may facilitate an implanter to individualize their approach to the patient and may guide them to an optimal target segment that is not in a conventional posterior or posterolateral site. Whether this will lead to an improved chronic outcome against a standard approach is as yet unproved and would require a randomized study of CMR-guided CRT.

**Comparison with previous studies**

Two-dimensional echo speckle-tracking radial strain analysis has been used to identify the latest mechanically activated LV segments and targeting these regions is associated with an improved echocardiographic response and prognosis post-CRT. Non-contrast CMR has also been used to identify the site of latest mechanical activation by radial strain analysis. These previous studies, however, either used dyssynchrony imaging data to retrospectively analyse whether the LV lead was placed in a concordant or discordant region of the LV or used multiple fluoroscopic views at the time of implantation to approximate the actual target region suggested by radial strain analysis. We have previously shown that CMR-derived data of CS anatomy and scar can be registered onto fluoroscopy during CRT implantation with a good validation between CMR-derived and fluoroscopic parameters and the potential to facilitate CRT in patients with previously failed implantations and unusual anatomy. These previous studies did not use CMR-derived dyssynchrony data to target LV lead placement and this is the first study to use CMR-derived dyssynchrony and scar analysis fused with fluoroscopy to guide LV lead placement and compare it with a haemodynamic standard.

**Comparison with the angiographic approach**

The acute CMR response rate was greater (60%) vs. (50%) with an angiographic approach. One might argue that using an angiographic approach gives a similar outcome to a complex CMR-guided approach and may be unnecessary. It should, however, be stated that the choice of lead position using angiography was made by an international expert implanter and an alternative argument would be that using such a CMR guidance system may facilitate even a relatively inexperienced implanter to achieve the same result as that of an experienced operator. The large difference in the AHR between the best and worst positions in each patient...
highlights the fact that if the wrong target vein is chosen, this may result in a suboptimal outcome. The benefit of a CMR-guided approach over a standard approach may be that CMR-derived dyssynchrony and scar may predict the likelihood of a favourable response. In our patients, the greater the degree of dyssynchrony, the greater is the acute response. Similarly, the presence of scar was associated with a poor response. Thus a preoperative CMR may guide lead placement and also be useful in predicting which patients are likely to respond on the basis of the baseline dyssynchrony and scar. This may facilitate physicians to target potential non-responders and consider non-standard CRT approaches such as endocardial or multi-site pacing.

In this study 92% of the patients who reverse remodelled were paced in a CMR target, whereas in the chronic non-responders a high proportion of patients were unable to be paced in a CMR target (only 50% were paced in a target CMR segment). All of the non-responders were ischaemic and this may reflect the generally poor response to CRT in patients with scar. In several patients the venous anatomy precluded reaching the CMR target segment and this raises the possibility of an endocardial approach guided by CMR in such patients.

**Study limitations**
This study is limited by its small size and lack of control group but is a proof of concept for CMR CRT guidance. A range of AV delays could not be assessed because of time limitations and, for the same reason, the study was limited to measuring the AHR to LV rather than BiV pacing. It is possible that DDD-Biv pacing would be superior and more comparable with a normal CRT strategy. DDDLV pacing was the only option, however, to ensure a steady state for accurate haemodynamic measurements, and previous studies have demonstrated the non-inferiority of DDDLV compared with DDD-Biv pacing.28,35 Data from our group have suggested a good correlation between the AHR and chronic response in terms of favourable LV reverse remodelling (<15% reduction in the ESV at 6 months) predominantly in non-ischaemic patients.36 Other studies, however, have shown that baseline LVdP/dtmax rather than acute change at implantation are predictive of the outcome in terms of symptoms and mortality.36 Improvement in dyssynchrony rather than the AHR may be a more reliable predictor of CRT response and, accordingly, our data show a good correlation of the AHR and the degree of CMR-derived LV dyssynchrony, suggesting that the AHR is related to dyssynchrony and its correction.

**Conclusion**
It is feasible to acquire, overlay, and accurately register CMR-derived anatomical, scar, and dyssynchrony data to guide CRT implantation. LV lead placement was possible in at least one target region in most patients and gave an AHR comparable with the best that could be achieved in any branch of the CS. Patients successfully paced in a CMR target had a better chronic response to CRT than those that were not. A CMR-guided approach to LV lead placement may therefore increase the proportion of patients who respond to CRT and increase the level of response in ‘responders’. Whether CMR image guidance produces a reduction in procedure time, fluoroscopy time, and radiation dose and improves long-term outcomes needs to be evaluated in a randomized controlled study.

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