European Journal of Heart Failure (2016)
doi:10.1002/ejhf.605

# Cardiac resynchronization therapy guided by multimodality cardiac imaging

**Matteo Bertini[1]*, Donato Mele[1], Michele Malagù[1], Andrea Fiorencis[1], Tiziano Toselli[1], Francesca Casadei[1], Teresa Cannizzaro[2], Cristina Fragale[1], Alessandro Fucili[1], Elena Campagnolo[1], Giorgio Benea[2], and Roberto Ferrari[3]**

[1]Department of Cardiology, University of Ferrara, S. Anna Hospital, Cona-Ferrara, Italy; [2]Department of Radiology, University of Ferrara, S. Anna Hospital, Cona-Ferrara, Italy; and [3]Department of Cardiology and LTTA Centre, University Hospital of Ferrara and Maria Cecilia Hospital, GVM Care & Research, E.S. Health Science Foundation, Cotignola, Italy

*Received 23 February 2016; revised 8 April 2016; accepted 6 June 2016*

**Aims** Up to 30–45% of implanted patients are non-responders to CRT. We evaluated the role of a 'CRT team' using cardiac magnetic resonance (CMR) and longitudinal myocardial strain to identify the target area defined as the most delayed and viable region for LV pacing.

**Methods and results** A total of 100 heart failure patients candidates for CRT divided into two groups were enrolled. Group 1 consisted of 50 consecutive patients scheduled for CRT and prospectively included. Group 2 (control) consisted of 50 patients with a CRT device implanted according to standard clinical practice and matched for age, sex, and LVEF with group 1. Patients were evaluated at baseline and at 6-month follow-up. In group 1, patients underwent two-dimensional speckle-tracking assessment of longitudinal myocardial strain and CMR imaging to identify the target area for LV lead pacing. A positive response to CRT was defined as a reduction of ≥15% of the LV end-systolic volume at 6-month follow-up. A total of 39 (78%) patients of group 1 were classified as responders to CRT whilst in group 2, only 28 (56%) were responders ($P = 0.019$). The 'CRT team' identified as target for LV pacing the lateral area in 30 (60%) patients, and the anterolateral or posterolateral areas in 12 (24%) patients. In 8 (16%) patients, the target was far from the lateral area, in the anterior or posterior areas. The patients with concordant position exhibited the highest positive response (93.1%) to CRT.

**Conclusions** Multimodality cardiac imaging as a guide for CRT implantation is useful to increase response rate.

**Keywords** Heart failure • Cardiac resynchronization therapy • Left ventricular lead position

## Introduction

Cardiac resynchronization therapy (CRT) for heart failure (HF) patients improves symptoms, LV systolic function and survival.[1,2] However, 30–45% of the patients do not benefit and are considered non-responder to CRT.[3] The lack of response is explained in terms of poor substrate to resynchronize (i.e. total scar burden, etc.) or of difficulties in the implant (i.e. LV pacing not at the most delayed region or presence of scar at the LV pacing site).[4,5] Factors related to age, gender, aetiology, or associated co-morbidities (severe ischaemic heart disease, renal failure, etc.) may also negatively influence the response to CRT. Some of these factors may be modified, whereas others are unchangeable. Among modifiable factors, there is the issue of LV lead placement. To overcome this problem, radial strain derived from two-dimensional speckle-tracking echocardiography (2D-STE) was used to place the LV lead in the most delayed myocardial segment.[6,7] However, even radial strain has limitations and was restricted to basal and/or mid-ventricle myocardial segments.[6,7] Other authors proposed a multimodality imaging approach, but data are still scarce and not conclusive.[8] Surprisingly, longitudinal myocardial strain, which allows an accurate and reproducible

*Corresponding author. Department of Cardiology, University of Ferrara, S. Anna Hospital, Via Aldo Moro 8, 44124 Cona-Ferrara, Italy. Tel: +39 532 236269, Fax: +39 532 236593, Email: doc.matber@gmail.com

measure of contraction of all myocardial segments, has never been considered.

We evaluated the role of a 'CRT team' using cardiac magnetic resonance (CMR) and longitudinal myocardial strain to identify the target area defined as the most delayed and still viable region for LV stimulation.

# Methods

## Study population and protocol

This is a single-centre proof of concept study.

The population consisted of two groups of a total of 100 HF patients candidates for CRT, according to the European Society of Cardiology (ESC) guidelines.[9] Inclusion criteria were: NYHA functional class II–IV, LVEF ≤35%, or QRS duration >120 ms. Exclusion criteria were: age <18 years, pregnancy, upgrading of pacemaker or cardioverter-defibrillator, recent (<3 months) acute coronary syndrome, percutaneous angioplasty or cardiac by-pass surgery, or heart transplantation. The aetiology of HF was considered ischaemic in the presence of significant CAD (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or history of myocardial infarction or coronary revascularization.

Group 1 consisted of 50 consecutive HF patients scheduled for CRT and prospectively included from April 2014 to June 2015. Group 2 (control) consisted of 50 HF patients with CRT implanted according to standard clinical practice from January 2013 to March 2014 and matched for age, sex, and LVEF with group 1.

Patients were evaluated at baseline (before implantation) and at 6-month follow-up. Baseline evaluations included: assessment of clinical status (NYHA functional class) and laboratory evaluation of renal function; as well as a comprehensive conventional echocardiography. In group 1, patients also underwent 2D-STE assessment of longitudinal myocardial strain and CMR imaging. All clinical and echocardiographic evaluations were repeated after 6 months, except for CMR imaging.

The study was approved by the local Ethics Committee, and patients signed informed consent.

## Conventional and speckle-tracking echocardiography

The 2D-STE protocol for image acquisition and analysis of longitudinal myocardial strain has been described in detail in a previous study.[10] A complete transthoracic echocardiography examination was performed using a commercially available ultrasound system (Vivid E9; GE Medical Systems, Milwaukee, WI, USA) equipped with a 3.5 MHz phased-array transducer. Image and Doppler acquisitions were obtained at held end-expiration. For the 2D-STE image acquisition, sector size and depth were adjusted to achieve optimal visualization of the whole LV myocardium in the three standard apical views (four-chamber, two-chamber, and long-axis view) with a frame rate between 60 and 100 fps. The LV longitudinal myocardial strain was assessed using a commercially available software (EchoPAC PC 112; GE Medical Systems). End-systole was defined as aortic valve closure in the apical long-axis view. The regions of interest (ROIs) were manually outlined at end-systole by marking the endocardial borders in the apical views. A manual adjustment was performed when the automated tracking was suboptimal. Time-to-peak longitudinal myocardial strain was automatically calculated throughout the myocardium for each LV apical view and reported spatially—from base to apex and circumferentially—in a polar plot map using a colour-coded parametric representation. A 16-segment model of the left ventricle was used for evaluation of time-to-peak longitudinal myocardial strain at a segmental level.

## Cardiac magnetic resonance

The CMR protocol for image acquisition and analysis has been described in detail previously.[10,11] All images were acquired using a 1.5-T magentic resonance imaging system optimized for cardiovascular applications (Signa HDX; GE Medical Systems). An 8-channel phased-array surface coil was used. Localization was performed using breath-hold single-phase steady-state free precession (SSFP) images of true anatomical axes of the heart. Subsequently, cine SSFP and delayed enhancement (DE) sequences were obtained. The DE images (fast-gradient-echo inversion-recovery) were acquired 7–10 min after an i.v. bolus of 0.15 mmol/kg body weight of gadolinium-diethylenetriamine penta-acetic acid (gadobutrol; Schering, Germany), followed by saline flush. The inversion time was adapted individually to null normal myocardium. LV end-diastolic and end-systolic volumes (EDV and ESV), stroke volume (SV), and EF were calculated according to standard methods. For myocardial DE analysis, CMR images were analysed using the software Segment CMR (Medviso, Lund, Sweden).

## Identification of the target area for left ventricular lead placement

The identification of the target area was achieved in steps.

The first step consisted of the exclusion of the scar area, defined as the area with delayed enhancement >75% of the myocardial wall, identified by CMR. In patients with non-ischaemic cardiomyopathy, the area with subepicardial fibrosis, even though non-transmural, was also identified and discharged. The second step was aimed at establishing (according to bull's eye of global longitudinal strain timings) the most delayed area between non-fibrotic segments (*Figure 1*). The target area for LV lead position was then defined as the most delayed non-fibrotic area. Consequently, the LV lead was placed there and its position was confirmed using biplane fluoroscopy.

## Cardiac resynchronization therapy device implantation

All patients received a biventricular pacemaker with cardioverter-defibrillator function (Boston Scientific, St. Paul, MN, USA; Medtronic Inc., Minneapolis, MN, USA; Biotronik, Berlin, Germany; or St. Jude Medical, St. Paul, MN, USA). The right atrial and ventricular leads were positioned conventionally. An extensive coronary sinus venogram documenting all collateral veins was obtained. The use of a balloon catheter for coronary sinus venography was at the physician's discretion. After the venography, the insertion of the LV pacing lead was performed. An 8-F guiding delivery catheter was used to place the LV lead (Boston Scientific, Medtronic, Biotronik, or St. Jude Medical) in the coronary sinus. All LV leads were implanted transvenously, and positioned according to multimodality imaging information, avoiding scar and subepicardial fibrotic segments and targeting the most delayed non-fibrotic area whenever anatomy was suitable.

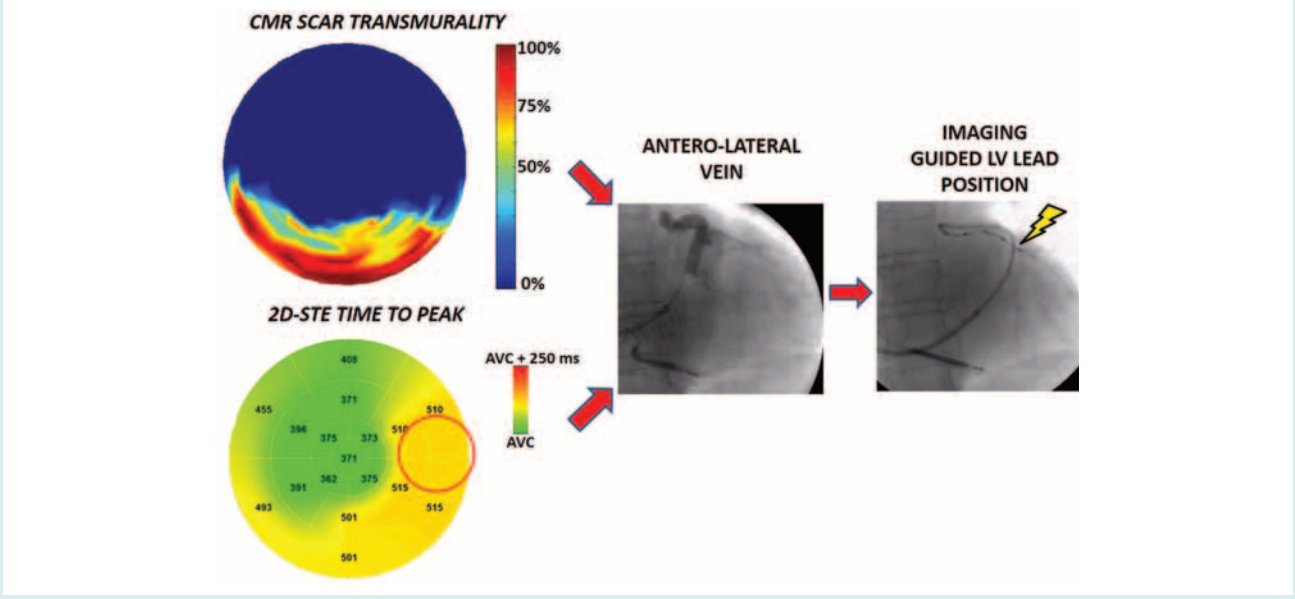


**Figure 1** Example of identification of the target area for LV lead position. Cardiac magnetic resonance (CMR) shows scar transmurality in inferior, posterior, and postero-lateral areas, whereas the antero-lateral area is viable. Two-dimensional speckle tracking longitudinal strain analysis of timings (2D-STE TIME TO PEAK) shows the most delayed segments in the antero-lateral mid-, and basal portion (red circle). The LV lead was placed in the antero-lateral vein in the mid- and basal portion. AVC, aortic valve closure.

## Left ventricular lead position

The LV lead position was determined using biplane fluoroscopy classification.[12] In the right anterior oblique view, the distance between the coronary sinus/mitral plane and the cardiac apex was divided into three parts and the LV lead position was classified into three groups: basal, mid-ventricular, and apical. In the left anterior oblique view, the anterior, antero-lateral, lateral, postero-lateral, and posterior positions were defined according to the literature.[13] When a perfect match between target area identified by multimodality imaging and LV lead placement was achieved, the position was defined as being concordant; when the LV lead was placed close to the target area identified by multimodality imaging (i.e. the segment at the border), the position was defined as adjacent; finally, when the LV lead was placed far from the target area identified by multimodality imaging (at least one segment far away), the position was defined as discordant.

## Response definition

A positive response to CRT was defined as a reduction of ≥15% of the LV end-systolic volume (LVESV) at 6-month follow-up.[14–16] The response was then further categorized into four different grades: (1) super-responders (reduction of LVESV ≥30%); (2) responders (reduction of LVESV between 30% and 15%); (3) non responders (reduction of LVESV between 15% and 0%); and (4) negative responders (reduction of LVESV ≤0%).[17,18] The interobserver variability for LVESV was 5.7% (4.5 mL) as previously reported.[19]

## Statistical analysis

All continuous variables had a normal distribution (as evaluated with Kolmogorov–Smirnov tests). Summary statistics for these data are therefore presented as means ± SD. Categorical data are presented as numbers and percentages. Paired and unpaired *t*-test and Fischer's exact tests were used for appropriate comparisons. $\chi^2$ test was used to compare the percentage of responders to CRT between the two groups, and to assess the differences in the prevalence of response to CRT between the groups of patients with different LV lead positions. All statistical tests were two-sided, and a *P*-value <0.05 was considered significant. A statistical software program SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

# Results

## Baseline characteristics

Reliable speckle-tracking was obtained in 46 (92%) HF patients of group 1, while CMR was reliable in 86% as 7 (14%) patients could not perform CMR because of claustrophobia, severe renal dysfunction, or contrast allergy. As shown in *Tables 1* and *2* at baseline, there were no differences in clinical, ECG, and echocardiographic characteristics between the two groups. *Table 3* relates to the electrical parameters. In group 1, the impedance of the right ventricular lead was significantly lower than in group 2, with no differences in right ventricular thresholds. The LV quadripolar lead was used more often in group 1 than in group 2 (64% vs. 10%, $P < 0.001$; *Table 3*).

## Left ventricular lead position

*Figure 2* reports the positioning of the LV lead. There was no difference between groups ($P = 0.11$). In particular, in group 1, the LV lead was placed in anterior, antero-lateral, lateral, postero-lateral, or posterior veins in 1 (2%), 7 (14%), 36 (72%), 6 (12%), and 0 (0%)

**Table 1 Clinical characteristics at baseline**

| | Group 1 (imaging guided) ($n = 50$) | Group 2 (standard practice) ($n = 50$) | *P*-value |
|---|---|---|---|
| Age (years) | 67.3 ± 9.7 | 65.6 ± 8.4 | 0.37 |
| Gender (male/female) | 37/13 | 38/12 | 1 |
| NYHA class | | | 0.19 |
| II | 29 (58%) | 25 (50%) | |
| III | 17 (34%) | 24 (48%) | |
| IV | 4 (8%) | 1 (2%) | |
| 6-min walking test (m) | 275 ± 155 | 255 ± 126 | 0.49 |
| QRS duration (ms) | 156 ± 24 | 154 ± 30 | 0.70 |
| LBBB | 27 (54%) | 26 (52%) | 1 |
| Aetiology | | | 1 |
| Non-ischaemic | 27 (54%) | 26 (52%) | |
| Ischaemic | 23 (46%) | 24 (48%) | |
| CABG | 5 (10%) | 8 (16%) | 0.55 |
| PCI | 21 (42%) | 15 (30%) | 0.30 |
| CrCl <60 mL/min | 23 (46%) | 18 (36%) | 0.42 |
| Hypertension | 41 (82%) | 35 (70%) | 0.24 |
| Dyslipidaemia | 28 (56%) | 26 (52%) | 0.84 |
| CAD family history | 11 (22%) | 14 (28%) | 0.65 |
| Smoking history | 18 (36%) | 22 (44%) | 0.54 |
| Diabetes | 12 (24%) | 17 (34%) | 0.38 |
| Medication | | | |
| Antiplatelet | 34 (68%) | 29 (58%) | 0.41 |
| ACE inhibitors/ARBs | 46 (92%) | 47 (94%) | 1 |
| Beta-blockers | 44 (88%) | 44 (88%) | 1 |
| Statins | 32 (64%) | 30 (60%) | 0.84 |
| Diuretics | 45 (90%) | 43 (86%) | 0.76 |
| Oral anticoagulants | 10 (20%) | 16 (32%) | 0.25 |

CABG, coronary artery by-pass graft; CrCl, creatinine clearance.

**Table 2 Echocardiographic characteristics at baseline**

| | Group 1 (imaging guided) ($n = 50$) | Group 2 (standard practice) ($n = 50$) | *P*-value |
|---|---|---|---|
| LVEDV (ml) | 197 ± 51 | 204 ± 60 | 0.49 |
| LVESV (ml) | 142 ± 47 | 148 ± 51 | 0.54 |
| LVEF (%) | 29 ± 6 | 29 ± 6 | 0.44 |
| Mitral regurgitation | | | 0.30 |
| Non-severe (1–2+) | 33 (66%) | 27 (54%) | |
| Severe (3–4+) | 17 (34%) | 23 (46%) | |
| Left atrium area ($cm^2$) | 25 ± 6 | 25 ± 6 | 1 |

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

patients, respectively; in group 2, it was placed in 1 (2%), 8 (16%), 24 (48%), 17 (34%), and 0 (0%) patients, respectively.

## Follow-up

At 6-month follow-up, in group 1 there was a significant decrease in (i) QRS duration (from 156 ± 24 to 142 ± 23 ms, $P < 0.001$); (ii) LVEDV (from 197 ± 51 to 167 ± 52 mL, $P < 0.001$); and (iii) LVESV (from 142 ± 47 to 102 ± 45 mL, $P < 0.001$) with a significant increase in LVEF (from 29 ± 6% to 42 ± 11%, $P < 0.001$) and a significant increase of 6 min walking test distance (from 275 ± 155 to 348 ± 140 m, $P < 0.001$). In group 2, QRS duration also decreased, but not significantly, from 154 ± 30 to 145 ± 23 ms ($P = 0.062$), while LVEDV and LVESV were significantly reduced (from 204 ± 60 to 187 ± 60 mL, $P = 0.026$, and from 148 ± 51 to 121 ± 55 mL, $P < 0.001$, respectively), resulting in an increase of LVEF (from 29 ± 6% to 37 ± 9%, $P < 0.001$; *Figure 3*). Finally, in group 2, the 6 min walking test distance also significantly increased (from 255 ± 126 to 289 ± 112 m, $P = 0.002$).

At 6-month follow-up, 39 (78%) patients of group 1 were classified as responders to CRT. In group 2, there were only 28 (56%) CRT responders ($P = 0.019$; *Figure 4*). Categorizing the response to CRT showed more super-responders and fewer negative responders in group 1 than in group 2. In particular, there were 27 (54%) super-responders in group 1 and 16 (32%) in group 2 ($P = 0.026$), 12 (24%) responders in group 1 and 12 (24%) in group 2 ($P = 1.00$), 6 (12%) non-responders in group 1 and 9 (18%) in group 2 ($P = 0.40$), and 5 (10%) negative responders in group 1 and 13 (26%) in group 2 ($P = 0.035$; *Figure 5*).

**Table 3 Electrical parameters at cardiac resynchronization therapy device implantation**

| | Group 1 (imaging guided) ($n = 50$) | Group 2 (standard practice) ($n = 50$) | *P*-value |
|---|---|---|---|
| Atrium | | | |
| Sensing (mV) | 3.3 ± 1.4 | 3.2 ± 1.7 | 0.67 |
| Threshold (V) | 0.6 ± 0.4 | 0.8 ± 0.4 | 0.11 |
| Impedance (Ω) | 523 ± 165 | 525 ± 142 | 0.95 |
| Right ventricle | | | |
| Sensing (mV) | 16.1 ± 6.5 | 15.1 ± 6.5 | 0.48 |
| Threshold (V) | 0.7 ± 0.5 | 0.7 ± 0.3 | 0.89 |
| Impedance (Ω) | 635 ± 187 | 780 ± 270 | 0.002 |
| Left ventricle | | | |
| Sensing (mV) | 14.4 ± 8.5 | 13.2 ± 7.1 | 0.52 |
| Threshold (V) | 1.1 ± 0.8 | 1.2 ± 0.7 | 0.36 |
| Impedance (Ω) | 843 ± 298 | 812 ± 305 | 0.60 |
| Left ventricular lead | | | <0.001 |
| Monopolar | 2 (4%) | 11 (22%) | |
| Bipolar | 16 (32%) | 34 (68%) | |
| Quadripolar | 32 (64%) | 5 (10%) | |

## Target area

The 'CRT team' identified as target for LV pacing the lateral area in 30 (60%) patients, and, more precisely, the basal lateral in 10 (20%) patients and the mid-lateral in 20 (40%) patients. In the remaining 12 (24%) patients, the antero-lateral or postero-lateral areas were considered the target, while in 8 (16%) patients the target was far from the lateral area in the anterior or posterior areas (*Figure 6*).

In 29 (58%) patients, the LV lead could be placed exactly at the target area (concordant position), in 18 (36%) patients just close to the target area (adjacent position), whereas in 3 (6%) patients it was not possible to reach the target area (discordant position).

The patients with a concordant position exhibited the highest response rate compared with those with an adjacent and discordant position (93.1% vs. 61.1% vs. 33.3%, respectively, $P = 0.006$). In particular, LV lead positioning in the target area resulted in 17 (59%) super-responders, 10 (34%) responders, 2 (7%) non-responders, and no negative responders. Interestingly, failure to reach the target area resulted in less response: adjacent positions resulted in 10 (56%) super-responders, 1 (5%) responder, 3 (17%) non-responders, and 4 (22%) negative responders; whereas for the discordant positions, there were no super-responders, only 1 (33%) responder, 1 (33%) non-responder, and 1 (33%) negative responder ($\chi^2 = 15.1$, $P = 0.020$; *Figure 7*).

# Discussion

This study shows that when a CRT device is implanted following the suggestions provided by a 'CRT team' using multimodality cardiac imaging, it results in a higher percentage of favourable responses with an increased number of super-responders. Furthermore, the multimodality imaging used revealed that the LV target area for stimulation may differ from patient to patient, with the need to be *a priori* identified. Finally, the anatomy of the coronary sinus vein did not allow the target area to be reached only in 6% of the patients. Taken together, these data suggest that CRT device implantation guided by a team using a multimodality approach is feasible and, if the validity is confirmed in a randomized trial, may be performed in routine practice. This approach can provide better results than the standard CRT approach.

## Multimodality cardiac imaging and cardiac resynchronization therapy response

Our study confirms the importance of targeting the most delayed viable LV segment to improve CRT response.[6,7] The TARGET and STARTER trials showed that this can be achieved by using 2D-STE.[6,7] However, the approach used in these trials is limited as the analysis of radial strain is possible only at the mid-ventricle level, and requires great expertise as the strain curves can be

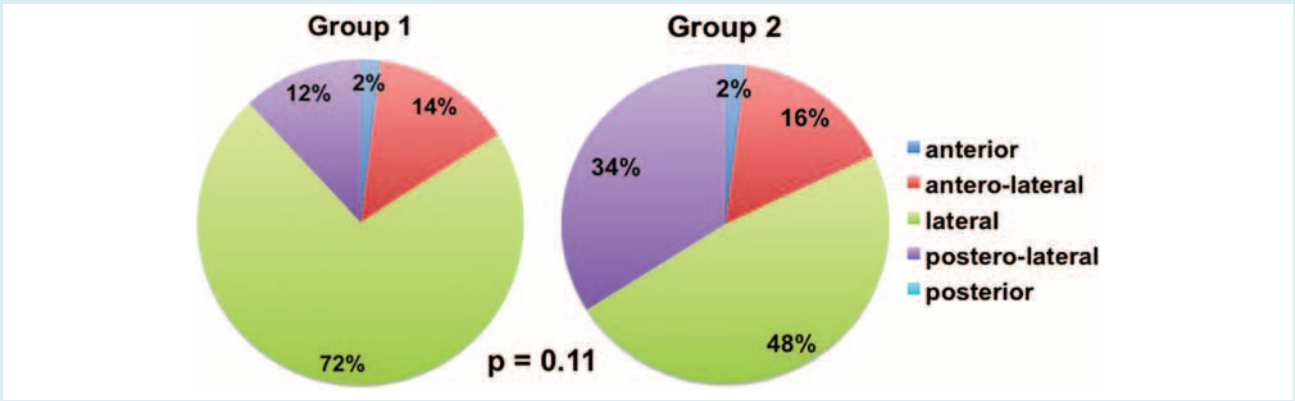


**Figure 2** Distribution of the left ventricular lead positions between the two groups.

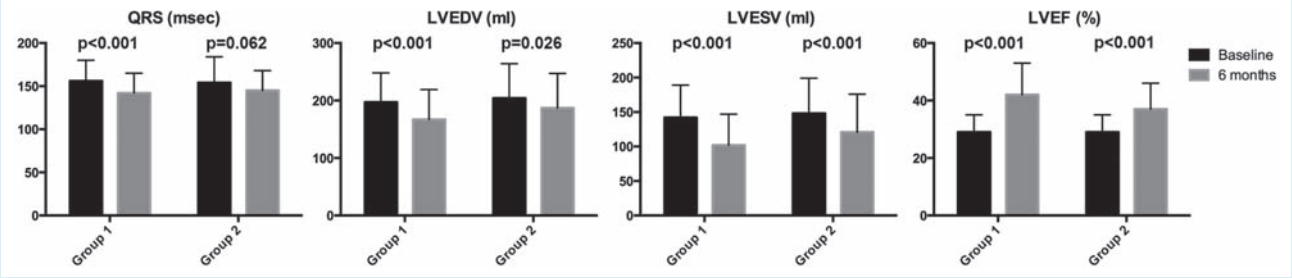


**Figure 3** Changes in QRS duration, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF from baseline to 6-month follow-up.

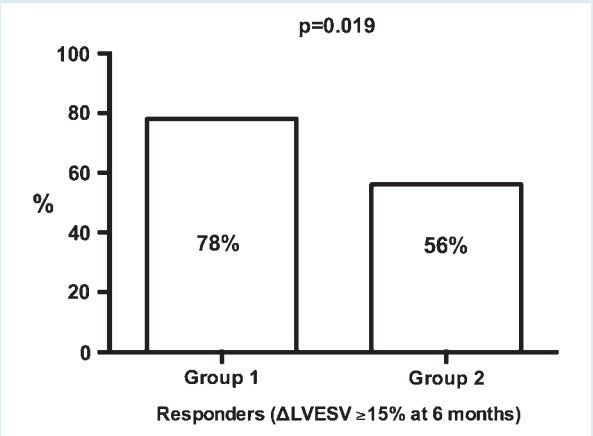


**Figure 4** Percentage of responders to CRT in groups 1 and 2. LVESV, left ventricular end-systolic volume.

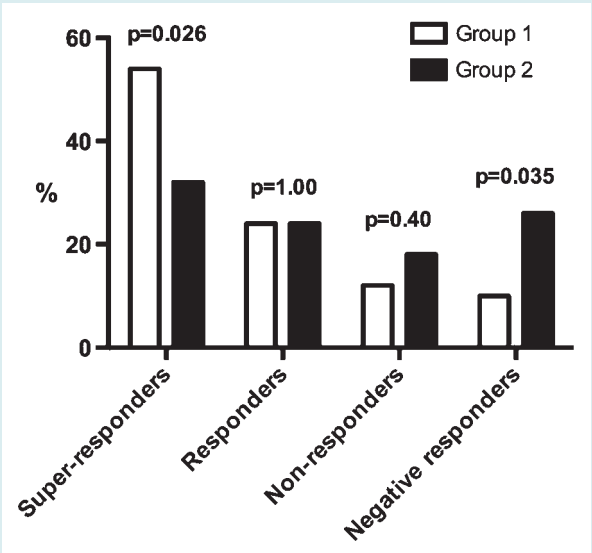


**Figure 5** Percentage of super-responders, responders, non-responders, and negative responders to CRT in groups 1 and group 2.

noisy, difficult to interpret, and represent the average value of single segments. As a consequence, it has been recently shown that identification of scar tissue by 2D-STE radial strain has a low accuracy (sensitivity 33%, specificity 72%).[8] To overcome these limitations, we used a new multimodality cardiac imaging approach based on the peculiarities of CMR and 2D-STE longitudinal strain assessments.

Cardiac magnetic resonance imaging allows accurate identification of non-viable or fibrotic LV areas. In particular, CMR recognizes transmural scar myocardium and also identifies subepicardial fibrosis, which cannot be detected by 2D-STE radial strain. This is important as stimulation of subepicardial scar tissue could be mechanically ineffective and also potentially pro-arrhythmogenic, and should therefore be avoided. It follows that CMR could be essential in the case of non-ischaemic cardiomyopathies.

Longitudinal strain assessment by 2D-STE offers advantages over the radial strain. It is more reproducible,[20] allows a comprehensive assessment of the left ventricle (and not only of the mid-ventricle portion), and can be displayed using polar plot maps which are easy to interpret, avoiding measurements and facilitating communication between members of the 'CRT team' (electrophysiologists and imaging physicians).

## Relationship between cardiac resynchronization therapy response and target area

Our data highlight that the target area is not the same for all patients. Thus, there is no an optimal LV pacing site for CRT but an optimal pacing site for each patient. Stimulation from the optimal area is ideal as the concordant or adjacent position determined the highest percentage of super-responders (59% and 56%, respectively) without a single negative responder. We could not reach the target area only in 6% of patients, suggesting that non-favourable vein anatomy is a limitation for CRT implantation in a small number of patients.

Finally, these findings underline the importance of a multidisciplinary approach to HF patients candidates for CRT.[21] The current method based on analysis of polar plots allows easy communication between the imaging physician and electrophysiologist in order to plan the optimal strategy for CRT device implant.

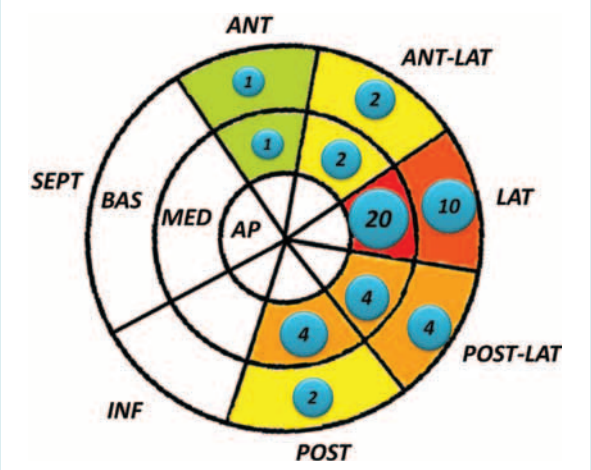


**Figure 6** Distribution of the target areas identified by multimodality imaging.

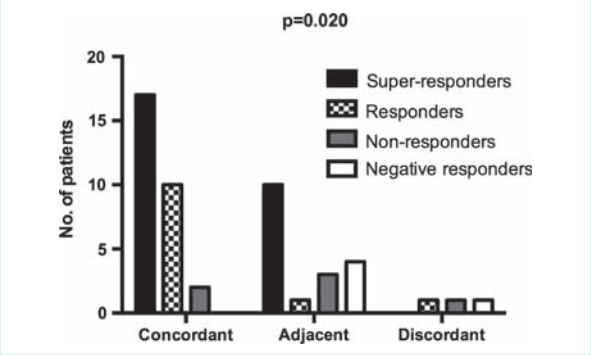


**Figure 7** Number of super-responders, responders, non-responders, and negative-responders to CRT in the concordant, adjacent, and discordant LV lead position.

## Study limitations

One of the major limitation of our study is that the control group was retrospectively acquired. However, group 1 was prospective and these results represent the first step to be confirmed by a proper randomized controlled trial.

A second limitation is the small number of patients enrolled. The sample size chosen, however, was sufficient to highlight the differences between the two different approaches to CRT.

A third limitation may be related to CMR feasibility that is limited by claustrophobia or renal dysfunction.

A fourth limitation is that the use of multimodality imaging increases the costs of CRT procedures. However, improving the implantation strategy results in better benefit of CRT, which may compensate the extra cost for multimodality imaging.

Finally, as specified in the Results, in group 1 more quadripolar LV leads and fewer unipolar LV leads were used as compared with group 2, and this could have influenced the results.[22] It was not possible to avoid this since group 1 patients were implanted more recently, when technological advancement meant that quadripolar LV leads were available.

## Conclusion

Multimodality cardiac imaging as a guide for CRT implantation is useful to increase the response rate. In particular, the combination of information derived from CMR imaging and 2D-STE discussed *a priori* by a 'CRT team' allowed the identification of the optimal LV pacing site.

**Conflict of interest:** R.F. reports that he received an honorarium from Servier for steering committee membership, consulting, and speaking, and support for travel to study meetings from Servier. In addition, he received personal fees from Boehringer-Ingelheim, Novartis, Merck Serono, and Irbtech. All other authors have no conflict of interest to declare.

## References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
3. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, Hlatky MA, Rowe BH. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. *JAMA* 2007;**297**:2502–2514.
4. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, Tang WH. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. *J Am Coll Cardiol* 2009;**53**:765–773.
5. Bax JJ, Gorcsan J 3rd.. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. *J Am Coll Cardiol* 2009;**53**:1933–1943.
6. Adelstein E, Alam MB, Schwartzman D, Jain S, Marek J, Gorcsan J, Saba S. Effect of echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy on mortality and risk of defibrillator therapy for ventricular arrhythmias in heart failure patients (from the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region [STARTER] trial). *Am J Cardiol* 2014;**113**:1518–1522.
7. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol* 2012;**59**:1509–1518.
8. Bakos Z, Ostenfeld E, Markstad H, Werther-Evaldsson A, Roijer A, Arheden H, Carlsson M, Borgquist R. A comparison between radial strain evaluation by speckle-tracking echocardiography and cardiac magnetic resonance imaging, for assessment of suitable segments for left ventricular lead placement in cardiac resynchronization therapy. *Europace* 2014;**16**:1779–1786.
9. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281–2329.

10. Mele D, Fiorencis A, Chiodi E, Gardini C, Benea G, Ferrari R. Polar plot maps by parametric strain echocardiography allow accurate evaluation of non-viable transmural scar tissue in ischaemic heart disease. *Eur Heart J Cardiovasc Imaging* 2016;**17**:668–677.
11. Mele D, Chiodi E, Lombardi M, Bighi S, Feggi L, Milanesi M, Ferrari R. [Magnetic resonance imaging for the evaluation of patients undergoing cardiac resynchronization therapy. Advantages, limitations and perspectives]. *G Ital Cardiol (Rome)* 2010;**11**:800–814.
12. Albertsen AE, Nielsen JC, Pedersen AK, Hansen PS, Jensen HK, Mortensen PT. Left ventricular lead performance in cardiac resynchronization therapy: impact of lead localization and complications. *Pacing Clin Electrophysiol* 2005;**28**:483–438.
13. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, Barsheshet A, Cannom D, Goldenberg I, McNitt S, Daubert JP, Zareba W, Moss AJ. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. *Circulation* 2011;**123**:1159–1166.
14. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J III, St John SM, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;**117**:2608–2616.
15. Bertini M, Hoke U, van Bommel RJ, Ng AC, Shanks M, Nucifora G, Auger D, Jan Willem Borleffs C, van Rijnsoever EP, van Erven L, Schalij MJ, Marsan NA, Bax JJ, Delgado V. Impact of clinical and echocardiographic response to cardiac resynchronization therapy on long-term survival. *Eur Heart J Cardiovasc Imaging* 2013;**14**:774–781.
16. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;**112**:1580–1586.
17. Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009;**53**:483–490.
18. van der Heijden AC, Hoke U, Thijssen J, Borleffs CJ, van Rees JB, van der Velde ET, Schalij MJ, van Erven L. Super-responders to cardiac resynchronization therapy remain at risk for ventricular arrhythmias and benefit from defibrillator treatment. *Eur J Heart Fail* 2014;**16**:1104–1111.
19. Mele D, Teoli R, Cittanti C, Pasanisi G, Guardigli G, Levine RA, Ferrari R. Assessment of left ventricular volume and function by integration of simplified 3D echocardiography, tissue harmonic imaging and automated extraction of endocardial borders. *Int J Cardiovasc Imaging* 2004;**20**:191–2012.
20. Bertini M, Ng AC, Antoni ML, Nucifora G, Ewe SH, Auger D, Marsan NA, Schalij MJ, Bax JJ, Delgado V. Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy. *Circ Cardiovasc Imaging* 2012;**5**:383–391.
21. Swedberg K, Cleland J, Cowie MR, Nieminen M, Priori SG, Tavazzi L, van Veldhuisen DJ, Alonso-Pulpon L, Camm J, Dickstein K, Drexler H, Filippatos G, Linde C, Lopez-Sendon J, Santini M, Zannad F. Successful treatment of heart failure with devices requires collaboration. *Eur J Heart Fail* 2008;**10**:1229–1235.
22. Forleo GB, Di BL, Bharmi R, Dalal N, Panattoni G, Pollastrelli A, Tesauro M, Santini L, Natale A, Romeo F. Hospitalization rates and associated cost analysis of cardiac resynchronization therapy with an implantable defibrillator and quadripolar vs. bipolar left ventricular leads: a comparative effectiveness study. *Europace* 2015;**17**:101–107.