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CLINICAL RESEARCH

Non-invasive three-dimensional electrical activation mapping to predict cardiac resynchronization therapy response: site of latest left ventricular activation relative to pacing site

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Aims Pacing remote from the latest electrically activated site (LEAS) in the left ventricle (LV) may diminish response to cardiac resynchronization therapy (CRT). We tested whether proximity of LV pacing site (LVPS) to LEAS, determined by non-invasive three-dimensional electrical activation mapping [electrocardiographic Imaging (ECGI)], increased likelihood of CRT response.

Methods and results Consecutive CRT patients underwent ECGI and chest/heart computed tomography 6–24 months of post-implant. Latest electrically activated site and the distance to LVPS (d_p) were assessed. Left ventricular end-systolic volume (LVESV) reduction of ≥15% at clinical follow-up defined response. Logistic regression probabilistically modelled non-response; variables included demographics, heart failure classification, left bundle branch block (LBBB), ischaemic heart disease (IHD), atrial fibrillation, QRS duration, baseline ejection fraction (EF) and LVESV, comorbidities, use of CRT optimization algorithm, angiotensin-converting enzyme inhibitor(ACE)/angiotensin-receptor blocker (ARB), beta-blocker, diuretics, and d_p. Of 111 studied patients [64 ± 11 years, EF 28 ± 6%, implant duration 12 ± 5 months (mean ± SD), 98% had LBBB, 38% IHD], 67% responded at 10 ± 3 months post CRT-implant. Latest electrically activated sites were outside the mid-to-basal lateral segments in 35% of the patients. d_p was 42 ± 23 mm [31 ± 14 mm for responders vs. 63 ± 24 mm non-responders ($P <$

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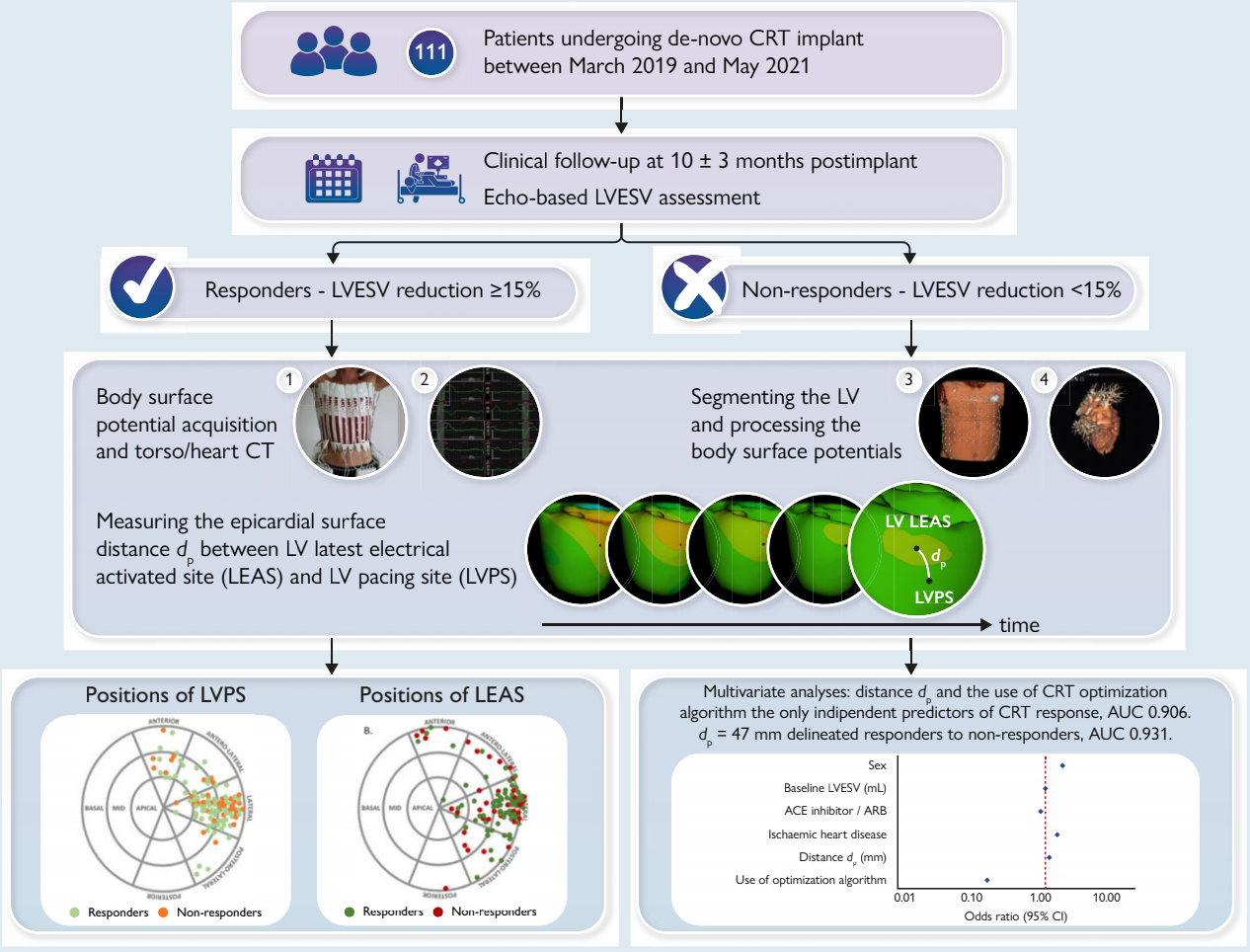
0.001)]. Longer d_p and the lack of use of CRT optimization algorithm were the only independent predictors of non-response [area under the curve (AUC) 0.906]. d_p of 47 mm delineated responders and non-responders (AUC 0.931).

Conclusion The distance between LV pacing site and latest electrical activation is a strong independent predictor for CRT response. Non-invasive electrical evaluation to characterize intrinsic activation and guide LV lead deployment may improve CRT efficacy.

Graphical Abstract



Keywords Cardiac resynchronization therapy • Heart failure • Non-invasive 3D electrical activation mapping • Electrocardiographic imaging • ECGI • Ischaemic cardiomyopathy • Dilated cardiomyopathy

What's new?

- The distance between the left ventricular (LV) pacing site and the site of latest electrically activated LV (d_p) during native rhythm influences the success of cardiac resynchronization therapy (CRT).
- Non-invasive three-dimensional electrical activation mapping (ECGI) has the ability to assess d_p.
- We found d_p and the use of CRT optimization algorithms to be the only independent predictors of CRT response in multivariate analysis.
- This non-invasive method has the potential to direct CRT LV lead positions based on a pre-acquired ECGI map.
- This practice may improve CRT response and needs to be evaluated prospectively in an intention-to-treat trial.

Introduction

Cardiac resynchronization therapy (CRT) for symptomatic patients with heart failure (HF), left ventricular (LV) dysfunction, and broad QRS duration suppresses HF events and improves survival.[1] However, 'non-response' persists at 30%.[2] Possible mitigating solutions include optimizing LV lead positioning. Usually, in practice, this is placed empirically, on basis of capture thresholds, and avoidance of zones of

scar/fibrosis and phrenic nerve stimulation, and loosely directed to the posterolateral LV [considered the site of terminal LV activation in left bundle branch block (LBBB)].[3] However, LV pacing from the region of late electrical activation may be more effective.[4,5] Ideally, pre-implant non-invasive determination of this location is preferable.[6]

A novel method of non-invasive three-dimensional (3D) electrical activation mapping, also called electrocardiographic imaging (ECGI), utilizes a dense array of body surface electrodes around the patient's torso combined with the patient-specific heart and torso geometry obtained from computed tomography (CT) or magnetic resonance imaging (MRI) to non-invasively reconstruct epicardial or both epi- and endocardial electrical activation in a single heartbeat.[7] Electrocardiographic imaging has demonstrated the ability to assess the entire ventricular activation sequence with good correlation to invasive contact mapping technique in native rhythms with wide QRS, bundle branch block, and paced rhythms.[8,9] In CRT, ECGI has shown to be able to predict acute and chronic response by assessing LV baseline electrophysiological activation and degree of ventricular dyssynchrony.[10,11] Effects of LV pacing are less certain. A simplified method acquiring a limited array of body surface potential mapping (BSPM) but without any reference to heart anatomy failed to show improvement in CRT response when using BSPM to guide LV lead placement and programming.[12]

We sought to utilize ECGI to characterize LV electrical activation and identify the latest electrically activated LV site (LEAS) in patients treated with CRT, hypothesizing that the distance d_p between the LEAS and the LV pacing site (LVPS) predicts CRT response. If confirmed, optimal LV lead placement may be guided in the future by precise, pre-acquired ECGI.

Methods

Patient population

We studied patients who had received CRT for Class I or Class IIa indications without a history of prior implanted cardiac devices and regardless of CRT response at five clinical centres in Europe. Left ventricular lead placement, device programming (including use of CRT optimization algorithm), and follow-up (FU) followed physician preference and site protocol. At the time of enrolment, patients were either in sinus rhythm or atrial fibrillation (AF) with bi-ventricular pacing rate >90%, without prior AV-nodal ablation, not pacemaker-dependent, and with a creatinine clearance level >45 mL/min. The study was conducted in accordance with the Declaration of Helsinki, and other applicable local and national regulations. Data processing was performed in compliance with the EU General Data Protection Regulation and all applicable national laws. The study protocol was approved by local ethics committees of the medical institutions that participated in the study. All patients gave written informed consent to participate in the study.

Clinical follow-up

All patients had clinical FU visits between 6 and 12 months of post-implant, including echocardiographic assessment. Cardiac resynchronization therapy non-response was defined as left ventricular end-systolic volume (LVESV) reduction of <15%. Left ventricular end-systolic volume was assessed from bi-plane transthoracic echocardiography. A sub-group of patients ($n = 22$) of anonymized pre- and post-CRT studies, chosen on availability, were reviewed by an independent echocardiography core lab blinded to all other patient data. Inter-observer variability was determined by comparing site classification and core lab classification of CRT response, quantified using Cohen's Kappa coefficient, results being available in Supplementary material online, *Appendix SA*.

Study examination

Non-invasive 3D electrical activation mapping was undertaken at a single study visit occurring 6–24 months of post-implantation (Amycard 01C system, EP Solutions SA, Switzerland; for method validation see Supplementary material online, *Appendix SB*).[7] In brief, pacing in patients' CRT devices was deactivated for several minutes to allow acquisition of unipolar body surface potentials in native rhythm for 10 s using 224 surface electrodes evenly distributed around the torso. The electrodes were arranged in strips that adapted to the patient's torso anatomy. Following the collection of body surface potentials, ECG-gated CT scans of the torso and heart with intravenous contrast were undertaken (with the body surface electrodes still attached to the torso; Figure 1A). The body and arm positions were the same during collection of body surface potentials and CT imaging in individual patients and were both done during breath-holding.

For analysis, first, a geometrical model in the form of a triangular mesh of the patient's torso was created automatically based on the torso CT scan (*Figure 1B*). The software of the Amycard 01C system identified the location of all electrodes, placed them on the mesh model, and assigned the corresponding body surface potential signal to each of them. Then, the cardiac CT scan was segmented to create a mesh model of the ventricles (excluding the atria). The LVPS was identified manually on the cardiac CT images using the software's fluoroscopy visualization mode and information about LV lead geometry and active pole number. The LV lead position was marked on the mesh model of the ventricles. The inverse calculation yielded a time series of isopotential maps of the ventricular activation. The LEAS was defined as the area of convergence of the isopotentials at the end of the ventricular depolarization period and its location was marked on the ventricular mesh model. The geodesic distance d_p between LEAS and LVPS measured along the epicardial surface of the mesh model was assessed by two observers, blinded to patient characteristics and outcomes. The LVPS and LEAS were assigned a position on an 18-segment LV model.

Statistical analysis

Continuous variables are summarized with mean and standard deviation, normal distribution was verified using the Kolmogorov–Smirnov test, and between-group comparisons were made using Student's *t*-test. Categorical variables are presented as absolute number of occurrences and associated frequency (%), and between-group comparisons were made using χ^2 test. A *P*-value of <0.05 was considered statistically significant.

As the intention was to predict outcome of CRT, a logistic regression model that probabilistically model non-response to CRT was fitted to the patient data, and in the process of model building, the subset of variables which best identified subjects who were non-responders were selected. First, univariate analyses were conducted. Any variable with *P*-value < 0.25 was selected as candidate for the multivariate model. Second, the multivariate analysis was conducted using a backward stepwise procedure and stopping rule was satisfied when the Akaike information criteria (AIC) was the lowest. The univariate, the full, and the final statistical models are presented in the Results section. Seventy per cent of the data ($n = 76$) were used for training and the remaining 30% ($n = 35$) for testing performance of the model. Variables tested included patients demographics (age, gender), baseline characteristics (New York Heart Association (NYHA) class, LBBB, ischaemic heart disease, baseline ejection fraction (EF), history of AF, QRS duration native rhythm, baseline LVESV), comorbidities (diabetes, hypertension, renal disease, cerebrovascular disease, hyperlipidaemia), relevant current medication [angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB), beta-blocker, diuretics], the use of CRT optimization algorithm (yes/no), and the distance d_p.

Furthermore, optimal cut-off point analyses based on the receiver operating characteristics (ROC) curve and the Youden index analysis for relevant variables were conducted. Cardiac resynchronization therapy response, location of LVPS and LEAS, and pacing threshold analysis were extended separately to the ischaemic and non-ischaemic subgroup, respectively.

Statistical analysis was performed using R software [version 4.1.2 (2021-11-01): A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org)].

Results

Study population

One hundred and eleven patients undergoing implant between March 2019 and May 2021 were included in the study. Subject characteristics

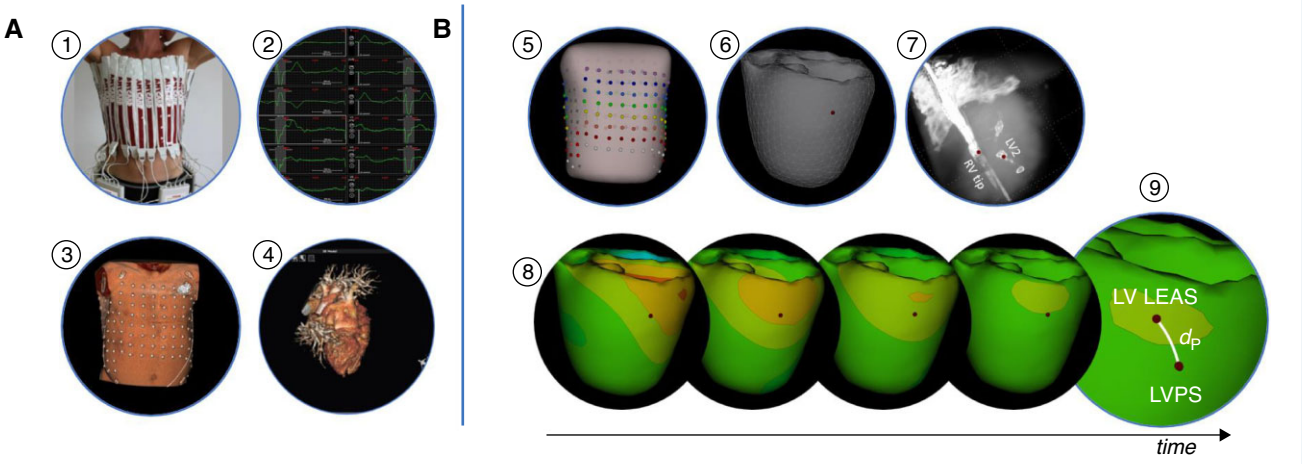


Figure 1 (*A*) Body surface potential acquisition; 224 electrodes were applied to the patient's torso (1), and unipolar body surface potentials were acquired during native rhythm (2). On CT, a torso scan (3) and a contrast-enhanced heart scan during breath hold (4) were performed while the electrodes were still attached to the torso. (*B*) Processing the body surface recordings; A mesh model of the torso was generated, and electrode positions were identified (5). The ventricles were segmented on the cardiac scan and a mesh model was generated (6). The LVPS was identified on the cardiac scan and its location marked on the ventricular mesh model (7). The inverse calculation yielded a time series of isopotential maps (8) on which the LEAS was identified and the geodesic distance d_p to the LVPS measured (9). CT, computed tomography; LV, left ventricle; LVPS, left ventricular pacing site; LEAS, latest electrically activated LV site.

are provided in *Table 1*. Clinical FU and echocardiographic exams were undertaken 10 ± 3 months post-CRT implant. Overall, LVESV decreased from 183 ± 87 mL at baseline to 130 ± 80 mL (paired reduction of 31 ± 25%, $P < 0.001$) with 67% of patients being volumetric responders. In the responder group, LVESV was 172 ± 91 and 97 ± 59 mL at baseline and FU, respectively (paired reduction of 45 ± 18%, $P < 0.001$). In contrast, LVESV did not change in the non-responder group, 202 ± 78 vs. 195 ± 78 mL, respectively (paired reduction of 4% ± 11%, $P = 0.06$).

Non-invasive three-dimensional electrical activation mapping

The study examination occurred 12 ± 5 months post CRT-implant. In one subject, the contrast-enhanced cardiac CT suffered from motion artefacts and could not be segmented; the non-contrast torso scan provided, however, sufficient detail to create the epicardial model. Creation of isopotential maps and determination of the location of LVPS and LEAS were possible in all subjects, and the assessment of the distance d_p was in agreement between the two observers in all subjects.

The positions of LVPS were found outside the mid- and basal-lateral segments in 33% of the patients [34% and 32% ($P = 0.89$) for the responder and non-responder groups, respectively; *Figure 2*]. The locations of the LEAS were more basal and subject to a larger angular spread than LVPS. In 35% of the patients, the LEAS was outside the mid-to-basal area [30% and 46% ($P = 0.09$) for the responder and non-responder groups, respectively]. The analysis of the locations of LVPS and the corresponding LEAS in individual patients in the non-responder group revealed that in some patients, the LVPS was positioned on the lateral wall whereas the LEAS was found to be in a more anterior or more posterior position, and vice-versa (*Figure 2*).

The distance d_p between the LEAS and the LVPS varied from 2 to 137 mm (42 ± 23 mm) in individual patients. In the responder group, the d_p was 31 ± 14 mm, whereas in the non-responder group, it was 63 ± 24 mm ($P < 0.001$).

Logistic regression model building

In the univariate analysis, the variables gender, baseline LVESV, ACE inhibitor or ARB, ischaemic heart disease, distance d_p, and the use of CRT optimization algorithm were selected; in the subsequent multivariate analysis, the variables distance d_p and the use of CRT optimization algorithm were selected for the final logistic regression model as they in combination yielded the lowest AIC value for the model. The corresponding *P*-value in the final model was <0.001 and 0.06 for the distance d_p and the use of CRT optimization algorithm, respectively (*Figure 3* and Supplementary material online, *Figure SC1*). The final logistic regression model yielded an area under the curve (AUC) of 0.906. Notably, among 22 patients (20%, spread amongst four of the five clinical sites) in whom a CRT optimization algorithm was used (in all cases the Medtronic AdaptivCRT™ algorithm), 19 (86%) were responders. The distances d_p for the responders and non-responders where CRT optimization algorithm was used ranged from 10 to 55 mm (35 ± 10 mm), and 54 and 80 mm (67 ± 11 mm), respectively ($P < 0.001$).

Optimal cut-off point analysis

The optimal cut-off point analysis showed that a value of $d_p = 47$ mm divided the responder and non-responder groups to provide the best balance between sensitivity and specificity (sensitivity 87%, specificity 92%, positive predictive value 84%, and negative predictive value 93%) and AUC of 0.931 (*Figure 4*).

Ischaemic and non-ischaemic subgroups

Cardiac resynchronization therapy response was 55% and 74% in the ischaemic and non-ischaemic subgroups, respectively. Left ventricular pacing site was outside the basal-lateral area in 31% and 35% ($P = 0.68$) of the patients in the ischaemic and non-ischaemic sub-group, respectively, whereas the LEAS was outside the basal-lateral area in 36% and 35% ($P = 0.92$), respectively.

Left ventricular pacing thresholds were 1.72 ± 0.93 and 1.89 ± 0.98 mV (pulse duration 0.4 ms; $P = 0.67$) for the ischaemic and non-ischaemic subgroup, respectively.

Table 1 Patient characteristics

	All ($n = 111$)	Responders ($n = 74$)	Non-responders ($n = 37$)
Age (years)	64 ± 11	65 ± 11	62 ± 11
Gender (M/F)	74/26%	68/32%	86/14%
NYHA Class II/III	31/69%	28/72%	39/61%
LBBB	98%	97%	100%
Ischaemic heart disease	38%	31%	51%
Active smoker	17%	18%	15%
Hypertension	65%	69%	58%
Renal failure	9%	10%	6%
Diabetes mellitus	26%	28%	21%
Hyperlipidaemia	56%	55%	58%
Cerebrovascular disease	8%	6%	12%
Peripheral vascular disease	8%	3%	18%
History of AF	18%	18%	19%
ACE inhibitor or ARB	79%	76%	89%
Beta-blocker	97%	96%	98%
Diuretics	85%	83%	93%
Baseline EF (%)	28 ± 6	28 ± 6	27 ± 7
QRS duration native rhythm (ms)	172 ± 21	171 ± 21	172 ± 21
Baseline LVESV (mL)	183 ± 87	172 ± 91	202 ± 78
LV pacing threshold (mV)	1.82 ± 0.96	1.85 ± 1.01	1.78 ± 0.87
Use of CRT optimization algorithm	21%	27%	9%
BiV pacing (%)	96 ± 3	97 ± 3	93 ± 4
FU post-implant (months)	10 ± 3	10 ± 3	9 ± 3
LVESV at FU (mL)	130 ± 80	97 ± 59	195 ± 78
Reduction (paired) LVESV at FU (mL)	53 ± 56	76 ± 54	7 ± 22
Reduction (paired) LVESV at FU (%)	31 ± 25	45 ± 18	4 ± 11
Interval from implant to study examination (months)	12 ± 5	12 ± 5	12 ± 6

If nothing else stated, values are given as mean ± SD.
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; AF, atrial fibrillation; BiV, bi-ventricular pacing; EF, ejection fraction; FU, follow-up; LBBB, left bundle branch block; LV, left ventricle; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.

Discussion

This is the first study to assess the impact on CRT efficacy of the relationship between distance (d_p) of pacing site and the position of the latest electrically activated LV site during intrinsic conduction, determined by non-invasive 3D electrical activation mapping. Distance d_p and the use of CRT optimization algorithms were the only independent predictors of CRT response in multivariate analysis. A distance d_p of more than 47 mm represented a clear cut-off for predicting volumetric responders to CRT.

Cardiac resynchronization therapy seeks to correct LV activation delay resulting from LBBB. Logically, pacing the zone of latest activation during intrinsic conduction may be most effective. Some prior studies assessed this by directing LVPS close or adjacent to the mechanically latest activated segments of the LV, based on echocardiography.[13,14] Results were somewhat scattered in terms of improvement in CRT response, and the latest mechanical activation site could not always be identified. It has recently been shown that echo-based optimization of CRT device settings (AV delay and VV delay) does not always correlate with optimal reduction in ventricular activation time.[15]

Since CRT is an electrical therapy directed towards an electrical disorder, it appears more intuitive to pace closer to the site of *electrical* activation. Our results support this notion, showing improved response to CRT when this condition is met independently of the use of CRT optimization algorithm.

Among notable secondary findings, the presence of ischaemic heart disease did not correlate with CRT response in this study. Also, the proportion of LEAS being outside the mid-to-basal area in the ischaemic sub-group was very similar to the entire study population (36% vs. 35%), indicating that LEAS location is patient-specific and equally important in both ischaemic and non-ischaemic cardiomyopathy. The presence and distribution of LV scar or fibrosis were unavailable in our study. However, the lack of difference between LV pacing thresholds in ischaemic and the non-ischaemic subgroups indicates that LV pacing was directed to viable myocardium, i.e. avoiding fibrosis or scar. This is important because prior studies have shown that patients with extensive fibrosis or scar in the region of the LV pacing site show lower response rates to CRT.[16]

Clinical implications

Attempts at improving CRT efficacy have emphasized patient selection, e.g. QRS morphology and duration. Although intra-procedural

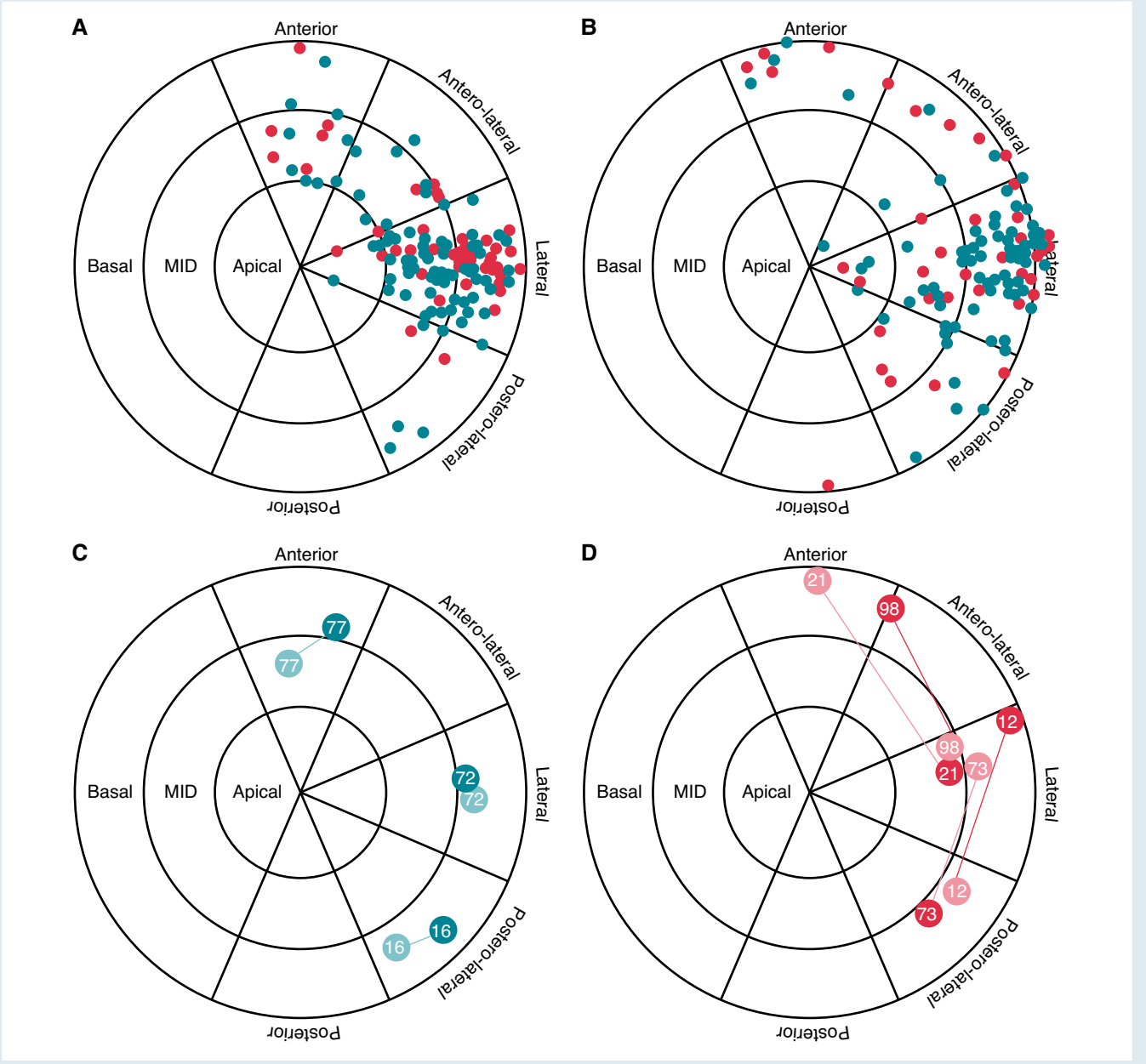


Figure 2 Eighteen-segment polar plot model showing the positions and distribution of the LVPS (*A*) and LEAS (*B*). Responders are shown in blue and non-responders in red. (*C*) Examples of LVPS (lighter colour) and the corresponding LEAS (darker colour) positions for three responders: For patient *n* ° 77, an anterior LEAS was matched well with an anterior LVPS, similar for the other patients with both LEAS and LVPS in the lateral and posterolateral segment, respectively. (*D*) Examples of LVPS (lighter colour) and the corresponding LEAS (darker colour) positions for four non-responders: For patient *n*° 21, the LVPS was placed in a lateral position, whereas the LEAS lay anteriorly. For patient *n*° 98, it was the other way round with LEAS in the lateral segment whereas the LVPS was placed in an anterolateral position. Similarly, for patients *n*° 12 and 73, where LVPS and LEAS positions did not match. LV, left ventricle; LVPS, left ventricular pacing site; LEAS, latest electrically activated LV site.

techniques to optimize LV lead placement have received less attention, their value should not be overlooked.[6] We show that current standard of care, i.e. empiric LV lead positioning, will miss sites of latest activation in a large minority of patients since the LEAS was found outside posterolateral LV in >30% of patients (and almost one out of two in the non-responder group). Although some operators use electrical activation delay recorded at the LV lead during native rhythm (Q-LV interval) as a guide,[4] a randomised controlled clinical trial failed to show the benefit of selecting pacing site on the basis of this interval in patients with non-LBBB.[17] Q-LV describes substrate, i.e. extent of LV delay occurring during LBBB, which correlates well with QRS duration, itself correlating with probability of response.[18]

Body surface potential mapping in CRT has received recent attention. However, a recent prospective controlled randomized trial failed to demonstrate improvement in CRT response using BSPM to guide LV lead placement based on the metrics of a reduction in ventricular standard deviation of activation time or LV total activation time.[12] This may be because of limited array of electrodes, lack of anatomical

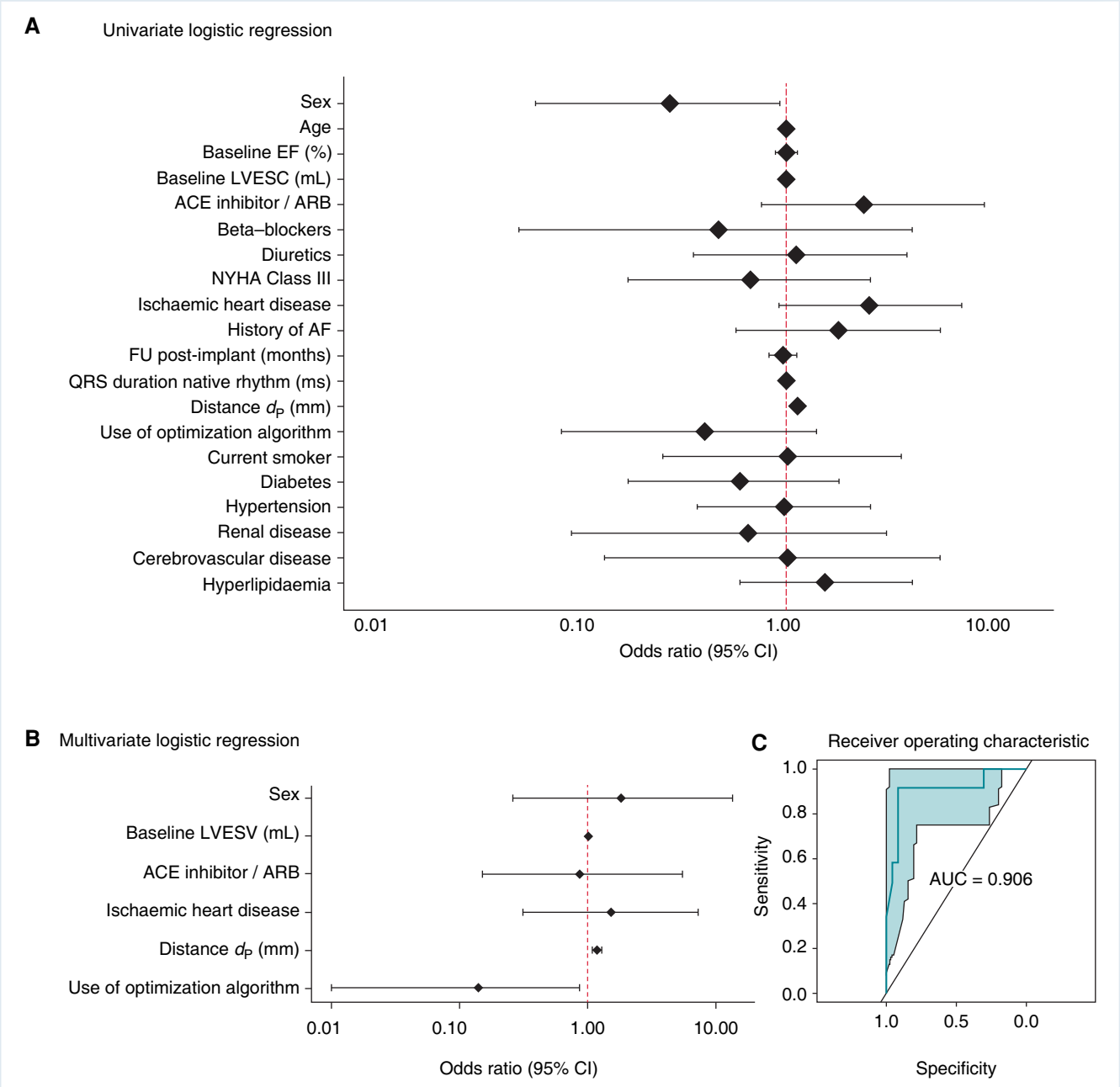


Figure 3 Logistic regression model building. Forest plot with odds ratio (OR) and 95% confidence interval (CI) for the result of the univariate analysis (*A*), the subsequent multivariate analysis (*B*), and the ROC curve of the final logistic regression model including only the two variables distance d_p and the use of CRT optimization algorithm with an AUC of 0.906 (*C*).

registration, and/or ineffective metrics of electrical resynchronization. In this study, detailed ECGI mapping in conjunction with anatomical registration enabled identification of the site of latest electrical LV activation. Our results suggest that LV pacing close to the site of latest electrical activation provides improved volumetric response to CRT. These findings expand the current pre-implantation planning strategy for CRT by enabling a non-invasive identification of the target pacing area coupled to identification of a suitable coronary vein. Conversely, if access is unfavourable, alternative resynchronization approach such as conduction system pacing or endocardial pacing may be considered. Moreover, CRT non-responders who received an LV multi-polar lead without ECGI pre-implantation planning may in some cases benefit from a post-implant ECGI study to select an alternative LV pacing pole closer to the LEAS, with assessment of the paced activation sequence to guide programming.

Strengths and limitations of the study

This is the largest study to characterize the site of latest electrical LV activation in LBBB patients, finding that this deviated from the anticipated position in more than 30% of cases (confirming observations from an earlier pilot ECGI study[8]). Left ventricular pacing lead position

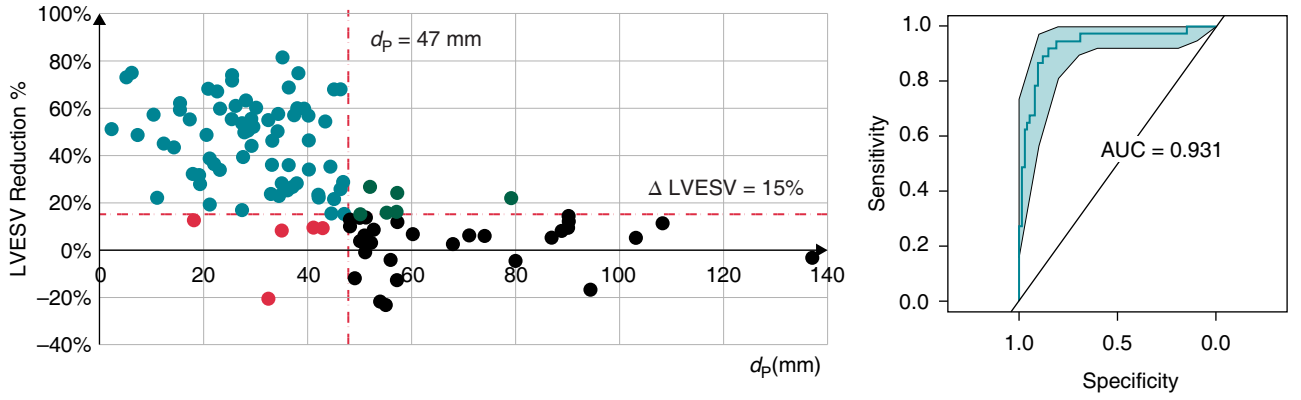


Figure 4 A plot for all patients ($n = 111$) where the distance d_p is shown on the *x*-axis and LVESV reduction on the *y*-axis (left panel). The dashed horizontal line divides responders (LVESV reduction ≥ 15%) and non-responders (LVESV reduction < 15%). The dashed vertical line corresponds to $d_p = 47$ mm, the cut-off value that provides the best balance between sensitivity and specificity for responders and non-responders (blue dots - true responders, black dots - true non-responders, red dots - false responders and green dots - false non-responders). The corresponding ROC curve for the optimal cut-off point analysis with $d_p = 47$ mm (right panel). AUC, area under the curve; LVESV, left ventricular end-systolic volume; ROC, receiver operating characteristics.

was determined accurately with a CT scan, overcoming limitations of fluoroscopy. The large baseline LVESV of 183 mL positions our study group among those patients with least favourable outcome to CRT.[19] Hence, our findings for potentially improving CRT efficacy in this potentially disadvantaged category are especially important.

While the accuracy of ECGI in detecting the early activation zone has been previously documented,[7] the accuracy of LEAS localization is fraught with inherent challenges due to the uncertainties of the true localization. A comparison with invasive 3D mapping on a limited number of patients formed the basis for this study (see Supplementary material online, *Appendix SB*). The favourable results of this study, obtained on a large number of patients and using a clinical outcome measure, support the validity of LEAS identification by ECGI.

The distance d_p was assessed at the time of the single study visit, i.e. 12 ± 5 months of post-implantation, whereas the CRT response was measured at the clinical FU, 10 ± 3 months of post-implantation. This assumes that the location of the LEAS does not shift significantly in the period following implantation and that the measured distance between LEAS and LVPS remained unchanged after CRT implantation. The study did not include an echo core lab, but standard was verified in a sample population (see Supplementary material online, *Appendix SA*). Due to pandemic restrictions, the on-site support to the investigational sites was limited to initial training on body surface potential acquisitions, but despite this, all sites managed to acquire data of sufficient quality and conduct the required CT scans per protocol.

The study includes only patients with LBBB. Q-LV data were not acquired during implantation by the sites, and as such, its relation to the distance d_p could not be assessed. Lead position was not directed on the basis of pre-implant imaging. The hypothesis that this practice improves CRT response needs to be evaluated prospectively in an intention-to-treat trial, where guidance of lead position but also pole selection may be included.

Conclusion

The distance between the LV pacing site and the site of the latest electrical activation during native rhythm, identified non-invasively by 3D electrical activation mapping, is a strong independent predictor for CRT response. Non-invasive electrical evaluation to characterize intrinsic activation and guide LV lead deployment may improve CRT efficacy.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: N.V.—consulting fees/honoraria from Abbott, Boston Scientific, Biotronik, Medtronic, and Impulse Dynamics; A.A.—consultant to Boston Scientific, Cairdac, Corvia, Microport CRM, EP Solutions, EPD Philips, and Radcliffe Publishers; he received speaker fees from Boston Scientific, Medtronic, and Microport; he participates in clinical trials sponsored by Boston Scientific, Medtronic, EPD Philips, and XSpline; and has intellectual properties with Boston Scientific, Biosense Webster, and Microport CRM; A.T.—shareholder, consultant, and recipient of the financial research support from EP Solutions and consulting fees/honoraria from Abbott, Biosense Webster, and Medtronic; F.L.—consultant and recipient of the financial research support from Medtronic, Abbott, Boston Scientific, Biotronik, and Microport. All remaining authors have declared no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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