A novel approach for left ventricular lead placement in cardiac resynchronization therapy

Citation for published version (APA):

Uyen Chau Nguyen, N. V., Mafi-Rad, M., Aben, J-P., Smulders, M. W., Engels, E. B., van Stipdonk, A. M. W., Luermans, J. G. L. M., Bekkers, S. C. A. M., Prinzen, F. W., & Vernooy, K. (2017). A novel approach for left ventricular lead placement in cardiac resynchronization therapy: Intraprocedural integration of coronary venous electroanatomic mapping with delayed enhancement cardiac magnetic resonance imaging. *Heart Rhythm*, 14(1), 110-119. <https://doi.org/10.1016/j.hrthm.2016.09.015>

Document status and date:

Published: 01/01/2017

DOI:

[10.1016/j.hrthm.2016.09.015](https://doi.org/10.1016/j.hrthm.2016.09.015)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

A novel approach for left ventricular lead placement in cardiac resynchronization therapy: Intraprocedural integration of coronary venous electroanatomic mapping with delayed enhancement cardiac magnetic resonance imaging

Uyên Châu Nguyễn, MD, MSc,* Masih Mafi-Rad, MD, PhD,[†] Jean-Paul Aben, BSc,[‡] Martijn W. Smulders, MD,[†] Elien B. Engels, PhD,* Antonius M.W. van Stipdonk, MD,[†] Justin G.L.M. Luermans, MD, PhD,[†] Sebastiaan C.A.M. Bekkers, MD, PhD,[†] Frits W. Prinzen, PhD,* Kevin Vernoooy, MD, PhD[†]

From the *Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands, [†]Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands, and [‡]Pie Medical Imaging, Maastricht, the Netherlands.

BACKGROUND Placing the left ventricular (LV) lead at a site of late electrical activation remote from scar is desired to improve cardiac resynchronization therapy (CRT) response.

OBJECTIVE The purpose of this study was to integrate coronary venous electroanatomic mapping (EAM) with delayed enhancement cardiac magnetic resonance (DE-CMR) enabling LV lead guidance to the latest activated vein remote from scar.

METHODS Eighteen CRT candidates with focal scar on DE-CMR were prospectively included. DE-CMR images were semi-automatically analyzed. Coronary venous EAM was performed intraprocedurally and integrated with DE-CMR to guide LV lead placement in real time. Image integration accuracy and electrogram parameters were evaluated offline.

RESULTS Integration of EAM and DE-CMR was achieved using 8.9 ± 2.8 anatomic landmarks and with accuracy of 4.7 ± 1.1 mm (mean $\pm$ SD). Maximal electrical delay ranged between 72 and 197 ms (57%–113% of QRS duration) and was heterogeneously

located among individuals. In 12 patients, the latest activated vein was located outside scar, and placing the LV lead in the latest activated vein remote from scar was accomplished in 10 patients and prohibited in 2 patients. In the other 6 patients, the latest activated vein was located in scar, and targeting alternative veins was considered. Unipolar voltages were on average lower in scar compared to nonscar (6.71 ± 3.45 mV vs 8.18 ± 4.02 mV [median $\pm$ interquartile range], $P < .001$) but correlated weakly with DE-CMR scar extent ($R = -0.161$, $P < .001$) and varied widely among individual patients.

CONCLUSION Integration of coronary venous EAM with DE-CMR can be used during CRT implantation to guide LV lead placement to the latest activated vein remote from scar, possibly improving CRT.

KEYWORDS Cardiac resynchronization therapy; Left ventricular lead placement; Electroanatomic mapping; Delayed enhancement cardiac magnetic resonance

(Heart Rhythm 2017;14:110–119) © 2016 Heart Rhythm Society. All rights reserved.

Introduction

Despite the proven effectiveness of cardiac resynchronization therapy (CRT), the issue remains that a substantial proportion of patients fails to benefit.¹ Part of this reduced

benefit has been attributed to a suboptimal left ventricular (LV) lead position.² Recent studies have suggested that positioning the LV lead in the region of latest electrical activation provides superior outcome compared with the conventional anatomic approach.³ However, pacing in or near myocardial scar diminishes the effectiveness of CRT.⁴ Additionally, computer simulations have demonstrated that the maximal hemodynamic effect is achieved when the LV lead is located as remote as possible from scar.⁵ Thus, placing the LV lead in the electrically latest activated region remote from scar is desired to improve CRT response.

Coronary venous electroanatomic mapping (EAM) can assess the electrical activation pattern of the coronary venous

Prof. Dr. Prinzen has received research grants from Medtronic, St. Jude Medical, Sorin, MSD, and Biotronik. Dr. Vernoooy received research grants from Medtronic and St. Jude Medical. Mr. Aben is an employee of Pie Medical Imaging. Dr. Smulders received a research grant from the Netherlands Heart Foundation. Dr. Nguyễn received a Kootstra Talent Fellowship grant from Maastricht University. **Address reprint requests and correspondence:** Dr. Uyên Châu Nguyễn, Department of Physiology, Cardiovascular Research Institute Maastricht, PO-Box 616, 6200MD, the Netherlands. E-mail address: chau27@gmail.com.

system during CRT implantation and guides LV lead placement to the latest activation region.⁶ Delayed enhancement cardiac magnetic resonance (DE-CMR) is the gold standard for evaluating the location and extent of myocardial scar. Integration of DE-CMR imaging with coronary venous EAM takes advantage of the benefit of both modalities by enabling 3-dimensional (3D) visualization of the location of the latest activated region within the coronary veins with respect to the distribution of scar. The aims of the present study were (1) to integrate preprocedural 3D scar segmentation from DE-CMR images with intraprocedural coronary venous EAM, (2) to use the integrated 3D image as a real-time navigational tool to guide LV lead placement to the latest activated vein remote from scar during CRT implantation, (3) to assess the accuracy of this integration, and (4) to compare electrogram (EGM) unipolar voltages from scar with normal myocardium.

Methods

Study population

Consecutive patients referred for CRT device implantation with a class I/IIa indication according to European Society of Cardiology guidelines⁷ and focal scar on preprocedural DE-CMR were prospectively enrolled. The institutional review board from Maastricht University Medical Center approved the study protocol.

Cardiac magnetic resonance imaging and analysis

CMR images were acquired during multiple breath-holds on a 1.5-/3.0-Tesla system (Philips Intera/Ingenia/Achieva, Best, The Netherlands) with a cardiac software package. After survey images and coil calibration, ECG-gated cine images were obtained using a steady-state free precession sequence (slice thickness 6–8 mm, slice gap 6–10 mm, TR/TE 2.9–4.3/1.5–1.7 ms, flip angle 50°–80°, field of view 320–384 mm, matrix 256–560 × 256–560) in the following orientations: single slice 2-chamber, 3-chamber, 4-chamber, and short-axis covering the entire LV. Subsequently, a 2D inversion recovery gradient echo sequence was used for delayed enhancement (TR/TE 4.0–6.1/1.2–3.0 ms, slice thickness 7–10 mm, flip angle 10°–25°, field of view 300–384 mm, matrix 240–576 × 240–576), 10 minutes after an intravenous bolus of 0.15 mmol/kg gadobutrol (Gadovist Bayer Schering Pharma, Zurich, Switzerland).

CMR images were analyzed offline using customized software (CAAS MRV3.4, Pie Medical Imaging, Maastricht, The Netherlands). A single observer performed the CMR analysis under supervision of an experienced CMR reader. Endocardial and epicardial contours were manually traced in end-diastolic and end-systolic short-axis cine images to determine LV functional parameters, and in short-axis DE-CMR images (Figure 1A), together with the coronary sinus (CS) to construct a 3D cardiac model. Scar was semi-automatically quantified using the full-width half maximum method by providing a seed point in the hyperenhanced region and applying a multipass region-growing algorithm.⁸

Each DE-CMR short-axis slice was subdivided into 96 segments, and scar fraction was computed for each segment. Traced DE-CMR contours were converted into 3D surface meshes (Figure 1B), using custom software programmed in MATLAB r2013a (MathWorks, Natick, MA) with a file format that could be imported into EnSite NavX (St. Jude Medical, St. Paul, MN).

Electroanatomic mapping

Intraprocedural coronary venous EAM was performed as described previously.⁶ A guidewire that permits unipolar sensing and pacing was inserted into the CS and connected to EnSite NavX. The guidewire was manipulated to all CS tributaries, creating an anatomic 3D map while simultaneously determining electrical delay during intrinsic ventricular activation. A representative coronary venous EAM is shown in Figure 1C. Electrical delay was measured from QRS onset to the peak negative slope on the unipolar intracardiac EGM and expressed as percentage of total QRS duration (QRSd). The right ventricular (RV) lead was targeted toward the apex, determining its position using fluoroscopy, and was identified on the EAM. The CS ostium was identified by positioning an electrophysiologic catheter (St. Jude Medical) in the right atrium and advancing it toward the CS. The position at the ostium was confirmed by contrast injection. Coronary venous anatomy was evaluated on coronary venograms and classified according to the American Heart Association 17-segment heart model to ensure consistency with the anatomic classification used in CMR.⁹

Image integration

After the mapping procedure, the preprocedural DE-CMR 3D meshes were imported into EnSite NavX and integrated with the coronary venous EAM. For this purpose, anatomic landmarks were set at the RV apex, CS ostium, and anterior and inferior interventricular veins and sulci on both the EAM and DE-CMR geometries. Subsequently, the coordinate system of the coronary venous EAM was automatically superimposed and adjusted to the DE-CMR-derived geometry using a dynamic registration algorithm, allowing local refinement while leaving other areas unaffected.¹⁰ A representative integrated 3D EAM-CMR image of a study patient is shown in Figure 1D and the corresponding bullseye plot in Figure 1E.

LV lead placement

Using the integrated EAM-CMR image, LV lead placement was targeted at the coronary vein with maximal electrical delay. If the vein with maximal electrical delay was located in scar (segmental scar fraction >0%), an alternative vein was targeted remote from scar, provided that the electrical delay in this vein was considered sufficiently late, preferably >95 ms or >50% of QRSd, based on current evidence and recommendations.¹¹ The LV lead was connected to EnSite NavX to allow real-time navigation of the LV lead to the target region in the integrated image. Bipolar or quadripolar

Image integration workflow patient no. 5

Figure 1 Image integration workflow of patient 5. Delayed enhancement cardiac magnetic resonance (DE-CMR) segmentations (**A**) were carried out preprocedurally to construct 3-dimensional meshes (**B**). Coronary venous electroanatomic mapping (EAM) (**C**) was integrated with the DE-CMR mesh intraprocedurally (**D**). **E**: Corresponding bullseye plot in which the ILV was latest activated and located in scar. Therefore, the LV lead was targeted toward the second latest activated vein (ALV) remote from scar. ALV = anterolateral vein; AV = anterior vein; CS = coronary sinus; ILV = inferolateral vein; IV = inferior vein; LAO = left anterior oblique; LV = left ventricle; QRSd = QRS duration; RAO = right anterior oblique; RV = right ventricle.

leads were used. The pole with a low voltage threshold without phrenic nerve stimulation was selected for pacing.

Integration accuracy evaluation

Coordinates of the EAM-CMR image were exported offline after implantation and rotated using the principal component analyses to align all vertices per DE-CMR slice in 1 XY-plane at the same Z-value as demonstrated in Figure 2A. For every DE-CMR short-axis slice, a centroid was computed by averaging the epicardial vertices of the same Z-value. Inner vein edges were detected by selecting vertices nearest to the

centroid. Integration errors were computed as the Euclidean distance between the DE-CMR epicardium and the coronary venous EAM vertex nearest to the centroid per DE-CMR slice (Figure 2B). Euclidean distances were computed at multiple sites for every DE-CMR short-axis slice (Figure 2C) and averaged to compute the image integration error per patient using custom software in MATLAB.

Electrogram analyses

EGM peak-to-peak unipolar voltages were automatically computed using custom software in MATLAB. To compare

Image integration accuracy computation

Figure 2 Image integration accuracy computation in MATLAB. **A:** Three-dimensional coordinates were rotated, aligning all vertices belonging to a CMR slice to the same Z-height. **B:** The Euclidean distance was measured between the epicardium and the vertices of the veins nearest to the centroid. **C:** In this patient, measurements were performed at 30 sites. CMR = cardiac magnetic resonance; EAM = electroanatomic mapping.

voltages with scar, each DE-CMR short-axis slice was subdivided into 16 segments (instead of the 96 segments for LV lead guidance). EGM locations were matched with the scar fraction of the nearest DE-CMR segment. A segment was considered as nonscar when the scar fraction was 0% and as scar when the scar fraction was >0%.

Statistical analysis

Statistical analyses were performed using SPSS19.0 (SPSS Inc, Chicago, IL). Continuous variables are expressed as mean $\pm$ SD or median $\pm$ interquartile range and dichotomous variables as frequencies/percentages. Voltages were compared using Mann–Whitney *U* tests, Kruskal–Wallis tests, and partial correlation analyses. *P* < .05 was considered significant, with and 2-tailed approaches used.

Results

Patient characteristics

Eighteen consecutive patients referred for CRT device implantation with an ESC class I/IIa indication and focal scar on preprocedural DE-CMR were included in the study. Patient characteristics are given in Table 1. Detailed DE-CMR analyses per patient are given in Table 2.

Table 1 Patient characteristics

Demographics	
No. of patients	18
Age (years)	69.2 $\pm$ 8.0
Male	16 (89)
Body mass index (kg/m ²)	28 $\pm$ 4
Ischemic cardiomyopathy	17 (94)
Dilated cardiomyopathy	1 (6)
New York Heart Association functional class	
II	12 (67)
III	6 (33)
CMR left ventricular function	
Left ventricular ejection fraction (%)	24.4 $\pm$ 6.4
End-diastolic volume (mL)	297.8 $\pm$ 82.5
End-systolic volume (mL)	228 $\pm$ 74.9
Stroke volume (mL)	69.0 $\pm$ 18.6
ECG characteristics	
Sinus rhythm	17 (94)
Atrial fibrillation	1 (6)
QRS duration (ms)	157.4 $\pm$ 23.8
Left bundle branch block	12 (67)
Interventricular conduction disturbance	6 (33)
Medication	
Antiplatelet	11 (61)
Coumarins	7 (39)
Beta-blockers	17 (94)
Calcium antagonists	4 (22)
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	15 (83)
Nitrates	7 (39)
Diuretics	15 (83)
Statin	14 (78)

Values are given as mean $\pm$ SD or n (%) unless otherwise indicated.
CMR = cardiac magnetic resonance.

Table 2 DE-CMR investigations

Patient no.	LV mass (g)	Scar (% LV mass)	AHA localization of scar			
			Basal	Mid	Apical	Apex
1	121	7	IS/I/IL	IS/I/IL	I	—
2	102	15	IS/I/IL/AL	I/IL	—	—
3	141	4	—	AS/A	S/A	—
4	230	14	AS/IS/I	AS/IS/I	A/S/I	—
5	128	13	IS/I/IL	IS/I/IL	S/I/L	—
6	246	9	I/IL/AL	I/IL	I/S	—
7	166	20	A/AS	AL/A/AS/IS	All	Apex
8	164	18	—	IL/AL/A/AS	All	Apex
9	101	16	IS/I/IL	A/AS/IS/I/IL	All	—
10	138	17	All	I/IL/AL	L	—
11	137	25	AS/IS/I/IL/AL	A/AS/IS/I/IL	All	Apex
12	118	9	IS/I/IL/AL	IS/I/IL/AL	S	—
13	227	12	AS/IS/I/IL	I/IL	All	—
14	145	3	IS/I/IL	IS/I	S	—
15	198	10	I/IL/AL/A	I/IL/AL	I/S	—
16	157	16	IS/I/IL	IS/I/IL	I	—
17	213	24	I/IL/AL	AS/IS/I/IL	All	Apex
18	180	20	AS/I/IL	AS/IS	All	—

A = anterior; AHA = American Heart Association; AL = anterolateral; AS = anteroseptal; DE-CMR = delayed enhancement cardiac magnetic resonance; I = inferior; IL = inferolateral; IS = inferoseptal; L = lateral; LV = left ventricular; S = septal.

CRT implantation

A *de novo* CRT defibrillator was implanted in 17 patients. One patient was upgraded from an implantable cardioverter-defibrillator to a CRT defibrillator. Seven patients received a bipolar lead and 11 patients a quadripolar lead. No procedural complications occurred.

Electroanatomic mapping

Intraprocedural coronary venous EAM was accomplished in all patients without complications. Mapping time was 20 $\pm$ 4 minutes, and total fluoroscopy time was 19 $\pm$ 6 minutes. Coronary venous angiography in all 18 patients revealed a total of 63 CS branches, of which 92% were mapped. The mapped veins per patient are described in Table 3.

EAMs were generated from 77.6 $\pm$ 23.2 unique anatomic points per patient. Maximal electrical delay ranged between 72 and 197ms (57%–113% of QRSd; Table 3) and was diversely anatomically distributed (Figure 3A).

Image integration

Constructing the 3D surface meshes out of DE-CMR data preprocedurally took 25 $\pm$ 5 minutes. Image integration during the procedure took 10 $\pm$ 5 minutes using 8.9 $\pm$ 2.8 anatomic landmarks. Image integration accuracy was performed with a Euclidean distance mean of 4.7 $\pm$ 1.1 mm and

Table 3 Electroanatomic mapping investigations

No.	Mapped veins	LAV	Electrical delay LAV ms (% QRSd)	DE-CMR veins outside scar	LAV located outside scar	Final LV lead position	LV lead outside scar in LAV
1	AV, ILV, IV	Basal-ILV	143 (92)	AIV, ILV	Yes	Basal-ILV	Yes
2	AV, ALV	Basal-ALV	197 (113)	AIV, ALV	Yes	Mid-ALV	Yes
3	AV, ALV, IV	Mid-IV	121 (72)	ALV, IV	Yes	Mid-IV	Yes
4	AV, ALV, IV	Basal-ALV	174 (83)	AV, ALV	Yes	Basal-ALV	Yes
5	AV, ALV, ILV	Mid-ILV	167 (89)	AV, ALV	No	Mid-ALV	No: in 2nd LAV outside scar
6	AV, ALV, ILV	Basal-ALV	152 (91)	AV, ALV	Yes	Basal-ALV	Yes
7	AV, 2xALV, IV	Basal-AV	119 (81)	2x ALV, IV	No	Mid-ALV2	No: in 2nd LAV outside scar
8	AV, ALV, 2xILV	Mid-ALV	130 (81)	ALV, ILV2	Yes	Mid-ILV2	No: in 2nd LAV outside scar (small vein)
9	AV, ALV, IV	Mid-ALV	107 (75)	ALV	Yes	Mid-ALV	Yes
10	AV, ALV, ILV	Mid-ALV	95 (72)	—	No	Mid-ALV	No: in LAV in scar (all veins in scar)
11	AV, ALV, ILV, IV	Mid-ILV	87 (66)	—	No	Mid-ILV	No: in LAV in scar (all veins in scar)
12	AV, ILV, IV	Basal-ILV	90 (64)	AV	No	Apical-ILV	No: in LAV in scar (other veins low electrical delay)
13	AV, ALV, IV	Mid-ALV	72 (57)	AV, ALV	Yes	Mid-ALV	Yes
14	AV, ILV, IV	Basal-ILV	178 (113)	AV, ILV	Yes	Mid-ILV	Yes
15	AV, ALV, ILV, IV	Mid-ILV	105 (77)	AV, ALV	No	Mid-ILV	No: in LAV in scar (other veins low electrical delay)
16	AV, ALV, ILV, IV	Mid-ILV	171 (92)	AV, ALV, ILV	Yes	Mid-ILV	Yes
17	AV, ALV, IV	Mid-ALV	188 (99)	ALV	Yes	Mid-ALV	Yes
18	AV, ALV, IV	Mid-ALV	168 (99)	Basal/mid-ALV	Yes	Apical-ALV	No: in LAV in scar (lead instability)

AV = anterior vein; AIV = anterior interventricular vein; ALV = anterolateral vein; DE-CMR = delayed enhancement cardiac magnetic resonance; IV = inferior vein; ILV = inferolateral vein; LAV = latest activated vein; LV = left ventricular; QRSd = QRS duration.

SD of 3.3 ± 0.9 mm, and was measured at 25.3 ± 6.3 sites per patient.

LV lead placement

Table 3 gives an overview of the position of the latest activated veins, the mapped veins located outside scar, and the final LV lead position per patient. As also can be seen in the decision-making flowchart of LV lead placement in Figure 3B, the latest activated vein was located outside scar in 12 patients. Of these patients, the LV lead was placed outside scar in the latest activated vein in 10 patients; one representative patient is shown in Figure 4A. This was hampered in 2 patients: in patient 8 because of a small vein as shown in Figure 4B (here the LV lead was finally placed in the second latest activated vein outside scar) and in patient 18 because of lead instability (here the LV lead was finally placed in the apical segment of the latest activated vein in scar). In 6 patients, the latest activated vein was located in scar. In these patients, the LV lead was placed in the second latest activated vein outside scar ($n = 2$; patients 5 and 7) as shown in the representative patient of Figure 1, or still in the latest activated vein in scar as all alternative veins were also located in scar ($n = 2$; patients 10 and 11) as shown in

Figure 4C, or not sufficiently electrically delayed ($n = 2$; patients 12 and 15), as shown in Figure 4D.

Electrogram voltages

A total of 1015 EGMs were analyzed from nonscar ($n = 504$) and scar ($n = 511$). Voltages were 8.18 ± 4.02 mV (median $\pm$ interquartile) in nonscar and 6.71 ± 3.45 mV in scar (Mann–Whitney U , $P \leq .001$). There was a significant but weak correlation between voltages and DE-CMR scar fraction (partial correlation $R -0.161$, $P < .001$). Voltages were highly different between patients, whereas differences within each patient between voltages from nonscar vs scar were absent or small, as shown in the voltage distribution box plots per individual patient in Figure 5. Even nonscar voltages varied widely (Kruskal–Wallis, $P \leq .001$) among individuals, discouraging the use of voltage criteria for delineation of scar.

Discussion

In this study, we demonstrated a novel approach of DE-CMR integration with coronary venous EAM to guide LV lead placement in real time to the latest electrically activated coronary vein remote from scar. In two-thirds of our patients,

A Distribution latest activated vein **B Final left ventricular lead position**

Figure 3 **A:** Anatomic distribution of latest activated vein. Each circled number represents a patient. *White circles* represent locations outside scar. *Black circles* represent in scar. A = anterior; AL = anterolateral; AS = anteroseptal; I = inferior; IL = inferolateral; IS = inferoseptal; L = lateral; S = septal. **B:** Decision-making flowchart of left ventricular (LV) lead position. In one-third of patients, the latest activated vein was located in scar, prohibiting optimal LV lead positions. CRT = cardiac resynchronization therapy; LAV = latest activated vein.

an optimal LV lead position was electroanatomically present and could be achieved in the majority of cases using this “guided” approach. In the other third of our patients, the latest activated vein was located in scar and an alternative vein was targeted. Accuracy of image integration was 4.7 ± 1.1 mm in concordance with previous studies.¹² Significant differences between individual EGM voltages from nonscar vs scar were absent in a substantial group of patients and voltage distributions between patients varied greatly, making DE-CMR still the preferred method for scar delineation.

LV lead placement

Placing the LV lead in an area with long electrical delay was associated with reduced hospitalizations for heart failure and all-cause mortality in an observational study of 144 patients.³ Coronary venous EAM to target the latest activated vein was additionally performed in cohorts of 25 and 32 patients and demonstrated, similar to our study, that the site of latest

activation is heterogeneously distributed. Placing the LV lead at a site of late electrical activation is therefore desired to improve CRT response.

From an electrophysiologic perspective, pacing in scar is also less effective, as slow conduction disturbs resynchronization. Concordantly, pacing in scar in a cohort of 559 patients led to a higher risk of cardiovascular death, sudden cardiac death, and lower echocardiographic CRT response compared to pacing outside scar.² Therefore, placing the LV lead in scar should be avoided when possible.

Image-guided CRT

Several image-guided techniques to place the LV lead at a site of late activation remote from scar have been described. Prospectively targeting the LV lead toward the latest segment of contraction outside scar using preprocedural echocardiographic speckle tracking 2D radial strain imaging was performed in the TARGET trial.¹³ In that study, 220 patients were randomized 1:1 in a TARGET or an unguided CRT group. The TARGET group had a greater proportion of responders compared to the unguided group (70% vs 55%, $P = .031$). The LV lead was placed significantly more within the latest mechanical segment. Nevertheless, the presence of scar at the LV lead was not significantly different in the TARGET vs the control group. One can imagine that when the venous anatomy is limited to scar, positioning the LV lead in scar is inevitable, as this was also the case in part of our population. All-cause mortality in the long term was furthermore reduced when the LV lead was placed in the latest activated segment (5%) vs an adjacent (9%) or remote (24%) segment. All-cause mortality in patients with scar at the LV pacing site was much higher than in patients without scar at the LV pacing site (29% vs 6%, respectively), thus illustrating the importance of pacing outside scar.¹³

Bakos et al¹⁴ integrated computed tomography, magnetic resonance imaging, and echocardiography to create preprocedural bullseye maps with information on mechanical delay, coronary veins, and scar in 39 patients. LV lead target segments were identified before implantation. In approximately half of the patients, no coronary vein in the segment with the latest mechanical delay was present, indicating the importance of only detecting delays in areas of coronary venous anatomy.

LV lead guidance was also performed by overlaying preprocedural CMR-derived anatomic-mechanical maps with intraprocedural fluoroscopy to guide the LV lead to the mechanically latest segment with <50% scar.¹⁵ Using this approach, Shetty et al¹⁵ were able to guide the LV lead to a segment with <50% scar and three latest mechanically activated in 15 of 20 patients. From the echocardiographic CRT responders, 92% was paced in the CMR target segment vs 50% in the nonresponders, confirming that hemodynamic response was more frequently accompanied with a concordant LV lead position.

As previous studies on LV lead guidance mainly focused on integrating DE-CMR with mechanical activation maps

Representative patients

Figure 4 Examples of integrated images and corresponding bullseye plots. Traced delayed enhancement cardiac magnetic resonance contours indicate endocardium and scar. **A:** In patient 6, the left ventricular (LV) lead was in the latest activated vein (ALV) outside scar. **B:** In patient 8, optimal LV placement was hampered because the ALV was too small and here the LV lead was placed in the second latest activated vein (ILV2). **C:** In patient 10, all target veins were surrounded by scar, prohibiting an optimal LV lead position. **D:** In patient 12, the LV lead was placed in the ILV in scar because all alternative veins were early activated. Abbreviations as in [Figure 1](#).

Figure 5 Box plots of electrogram unipolar voltages in nonscar vs scar per individual patient. P values are based on Mann–Whitney U tests. UV = unipolar voltage.

derived from echocardiography or CMR, our study is the first to incorporate electroanatomic information from the coronary veins acquired by EAM, which is relevant because LV lead placement is limited to coronary venous anatomy. Using intraprocedural integration instead of preprocedural bull's eye maps also has the advantage of allowing real-time LV lead navigation.

Clinical implications

DE-CMR to evaluate scar before CRT implantation is being increasingly adopted as standard care in many centers. In addition, most EAM vendors have already adopted a tool to integrate CT or CMR-based geometries, as image integration is already common practice in other electrophysiologic fields. Expanding its application in CRT may have potential impact on the prognosis of this patient population.

In our experience, scar typically is not a well-defined transmural entity but is more heterogeneously spread, making it more challenging to determine whether the venous anatomy is embedded in scar. Therefore, using real-time integration is particularly of added value in patients with lateral scar because target veins are often located in this area.

Coronary venous EAM has proven itself as a safe technique requiring reasonable procedural times.^{6,16} All procedures in our study occurred without complications, and image integration did not prolong the implantation time, mainly because constructing the DE-CMR mesh, the most time-consuming aspect, was performed before the procedure.

In about one-third of our population, the latest activated vein was located in scar tissue, prohibiting optimal LV lead placement. Still, we believe that even in these patients coronary venous EAM with DE-CMR integration may be of added value. Information on the final LV lead position

with regard to scar and electrical activation may be useful in patient follow-up and provides additional insight in (non-) response after CRT.

Study limitations

This was a single-center study using only a small population. Many factors affect the prognosis of heart failure, and because these patients are heterogeneous, larger populations are needed to evaluate the superiority of our “guided” approach compared to the conventional approach regarding response to CRT.

Coronary venous EAM requires practice by electrophysiologists, although it can be performed within reasonable times when performed by those with adequate skill.^{6,16}

The integration process in our study was complicated because 2 anatomies were fused and DE-CMR images were acquired during end-diastole but EAM generation was not ECG triggered. Nevertheless, rotation errors were minimized by mapping the RV apex and CS ostium, creating additional matching points on both geometries.

Conclusion

We demonstrate a novel image-guided CRT approach with integration of intraprocedural coronary venous EAM with DE-CMR enabling real-time LV lead navigation. This image-guided approach can be implemented using standard DE-CMR scans and image integration tools that already are incorporated in most EAM systems. DE-CMR is still the preferred method for scar delineation, as EGM voltages correlated poorly with DE-CMR scar.

Acknowledgements

The authors gratefully acknowledge Peter Bakker and Arjan Bennink from St. Jude Medical for technical support during the EAM procedures.

References

1. Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: the magnitude of the problem and the issues. *Circ J* 2011;75:521–527.
2. Leyva F, Foley PW, Chalil S, Ratib K, Smith RE, Prinzen F, Auricchio A. Cardiac resynchronization therapy guided by late gadolinium-enhancement cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2011;13:29.
3. Kandala J, Upadhyay GA, Altman RK, Parks KA, Orencole M, Mela T, Kevin Heist E, Singh JP. QRS morphology, left ventricular lead location, and clinical outcome in patients receiving cardiac resynchronization therapy. *Eur Heart J* 2013;34:2252–2262.
4. Wong JA, Yee R, Stirrat J, et al. Influence of pacing site characteristics on response to cardiac resynchronization therapy. *Circ Cardiovasc Imaging* 2013;6: 542–550.
5. Huntjens PR, Walmsley J, Ploux S, Bordachar P, Prinzen FW, Delhaas T, Lumens J. Influence of left ventricular lead position relative to scar location on response to cardiac resynchronization therapy: a model study. *Europace* 2014;16 (Suppl 4):iv62–iv68.
6. Rad MM, Blaauw Y, Dinh T, Pison L, Crijns HJ, Prinzen FW, Vernooy K. Left ventricular lead placement in the latest activated region guided by coronary venous electroanatomic mapping. *Europace* 2015;17:84–93.
7. Brignole M, et al. 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). *Europace* 2013;15: 1070–1118.
8. Amado LC, Gerber BL, Gupta SN, Rettmann DW, Szarf G, Schock R, Nasir K, Kraitichman DL, Lima JA. Accurate and objective infarct sizing by contrast-enhanced magnetic resonance imaging in a canine myocardial infarction model. *J Am Coll Cardiol* 2004;44:2383–2389.
9. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539–542.
10. SJM. EnSite fusion dynamic registration tool. Supplement to the EnSite system instructions for use. International edition. In: St. Paul, MN: St. Jude Medical; 2007.
11. Gold MR, Birgersdotter-Green U, Singh JP, Ellenbogen KA, Yu Y, Meyer TE, Seth M, Tchou PJ. The relationship between ventricular electrical delay and left ventricular remodelling with cardiac resynchronization therapy. *Eur Heart J* 2011;32:2516–2524.
12. Wijnmaalen AP, van der Geest RJ, van Huls van Taxis CF, Siebelink HM, Kroft LJ, Bax JJ, Reiber JH, Schalij MJ, Zeppenfeld K. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. *Eur Heart J* 2011;32:104–114.
13. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elvik 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.
14. Bakos Z, Markstad H, Ostenfeld E, Carlsson M, Roijer A, Borgquist R. Combined preoperative information using a bullseye plot from speckle tracking echocardiography, cardiac CT scan, and MRI scan: targeted left ventricular lead implantation in patients receiving cardiac resynchronization therapy. *Eur Heart J Cardiovasc Imaging* 2014;15:523–531.
15. Shetty AK, Duckett SG, Ginks MR, et al. 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. *Eur Heart J Cardiovasc Imaging* 2013;14:692–699.
16. Niazi I, Ryu K, Hood R, Choudhuri I, Akhtar M. Three-dimensional electroanatomic mapping of the coronary veins during cardiac resynchronization therapy implant: feasibility and possible applications. *J Interv Card Electrophysiol* 2014;41:147–153.