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Integration of cardiac magnetic resonance imaging, electrocardiographic imaging, and coronary venous computed tomography angiography for guidance of left ventricular lead positioning

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Aims

An appropriate left ventricular (LV) lead position is a pre-requisite for response to cardiac resynchronization therapy (CRT) and is highly patient-specific. The purpose of this study was to develop a non-invasive pre-procedural CRT-roadmap to guide LV lead placement to a coronary vein in late-activated myocardium remote from scar.

Methods and results

Sixteen CRT candidates were prospectively included. Electrocardiographic imaging (ECGI), computed tomography angiography (CTA), and delayed enhancement cardiac magnetic resonance imaging (DE-CMR) were integrated into a 3D cardiac model (CRT-roadmap) using anatomic landmarks from CTA and DE-CMR. Electrocardiographic imaging was performed using 184 electrodes and a CT-based heart-torso geometry. Coronary venous anatomy was visualized using a designated CTA protocol. Focal scar was assessed from DE-CMR. Cardiac resynchronization therapy-roadmaps were constructed for all 16 patients [left bundle branch block: $n = 6$; intraventricular conduction disturbance: $n = 8$; narrow-QRS (ablate and pace strategy); $n = 1$; right bundle branch block: $n = 1$]. The number of coronary veins ranged between 3 and 4 per patient. The CRT-roadmaps showed no ($n = 5$), 1 ($n = 6$), or 2 ($n = 5$) veins per patient located outside scar in late-activated myocardium [$\geq 50\%$ QRS duration (QRSd)]. Final LV lead position was outside scar in late-activated myocardium in 11 out of 14 implanted patients, while a LV lead in scar was unavoidable in the remaining three patients.

Conclusion

A non-invasive pre-implantation CRT-roadmap was feasible to develop in a case series by integration of coronary venous anatomy, myocardial-scar localization, and epicardial electrical activation patterns, anticipating on clinically relevant features.

Keywords

Cardiac resynchronization therapy • Left ventricular lead • Image integration • Coronary venous anatomy • Computed tomography angiography • Electrocardiographic imaging • Cardiac magnetic resonance imaging • Myocardial scar • Heart failure

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What's new?

- A non-invasive cardiac resynchronization therapy (CRT) roadmap was developed by integration of cardiac magnetic resonance imaging, electrocardiographic imaging, and computed tomography angiography to guide left ventricular lead placement.
- The advantage of the present CRT-roadmap is that it comprises detailed imaging of the coronary veins with respect to the scar substrate localization as well as high-resolution epicardial electrical activation patterns.
- This CRT-roadmap was implemented in a case series to demonstrate its feasibility in anticipating during implantation by the use of a single non-invasive 3D cardiac model.

Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with heart failure (HF), impaired left ventricular (LV) systolic function, and prolonged QRS duration (QRSd). Nevertheless, one-third of eligible patients fail to benefit from CRT.¹ An appropriate LV lead position is a pre-requisite for response to CRT and is highly patient-specific. There is increasing evidence that scar tissue should be avoided in LV lead placement. Pacing in scar regions can impact CRT by causing regional slowing of conduction. Furthermore, a LV-lead position in scar is associated with a diminished clinical response to CRT^{2,3} and proarrhythmic events.⁴ To date, delayed-enhancement cardiac magnetic resonance imaging (DE-CMR) remains the clinical gold standard for the assessment of focal scar.

Besides avoiding scar, the region of latest activation on the LV inferolateral wall is preferred given that the rationale of biventricular pacing is to resynchronize the LV. A LV lead position with an electrical delay of $\geq 50\%$ of QRSd is associated with an improved haemodynamic and long-term clinical response to CRT.^{5,6} As the site of late activation is heterogeneously distributed among individuals,^{7,8} mapping local activation is desirable.⁹ Electrocardiographic imaging (ECGI) can reconstruct the electrical activation of the epicardium non-invasively by using body surface potential measurements (BSPM) and a patient-specific heart-torso geometry.¹⁰ Electrical dyssynchrony and local electrical delay identified by ECGI is representative of epicardial contact mapping,¹¹ and may be combined with other imaging modalities non-invasively to guide LV lead placement.

Although it seems that careful positioning of the LV lead is important, coronary venous anatomy puts major constraints on the available LV pacing sites, due to the high inter-patient variability regarding the trajectory, shape, and number of veins.¹² The coronary venous tree generally does not cover all segments of the LV, and some veins may be difficult to cannulate with the LV lead because of anatomical limitations. Coronary venous anatomy is conventionally visualized by fluoroscopic angiography, although computed tomography angiography (CTA) may enable three-dimensional (3D) non-invasive visualization, which helps in the pre-procedural anticipation on patient-specific coronary venous anatomy.

The objective of this study was to assess the feasibility of a patient-tailored implantation by creating a pre-procedural multimodality

CRT-roadmap by integration of 3D images from focal scar localization on DE-CMR, epicardial activation sequence from ECGI, and coronary venous anatomy from CTA. This CRT-roadmap was used in a case series to guide LV lead placement to a coronary vein in an electrically late-activated region remote from scar.

Methods

Study population

Consecutive patients referred for CRT device implantation were prospectively enrolled from April till December 2017 at Maastricht University Medical Centre. Patients were orally approached at the outpatient clinic and received a patient information form. Only patients with contraindications for CTA or CMR (e.g. severe kidney dysfunction, contrast media intolerance, and claustrophobia) and who clearly stated that they were not willing to participate in any clinical study, were not actively approached for participation in the study.

Patients underwent ECGI, CTA, and CMR up to 2 months prior to implantation. An overview of all processes involving the CRT-roadmap construction is provided in *Figure 1*. The institutional Review Board approved the study protocol, and patients gave written consent for participation in the study.

Cardiac magnetic resonance imaging

Standard clinical CMR images were acquired prior implantation during multiple breath-holds on a 1.5-T system (Philips Ingenia, Best, the Netherlands). A 2D inversion recovery gradient echo sequence was used for delayed enhancement 10 min after an intravenous bolus of 0.15 mmol/kg gadobutrol (Ultravist, Bayer Healthcare, Berlin, Germany). CMR images were analysed offline using customized software CAAS MRV3.4 (Pie Medical Imaging, Maastricht, The Netherlands). A single observer performed the CMR analysis under supervision of an CMR reader with over 10 years of experience (EACVI level 3). 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 to define the myocardium and construct a 3D cardiac model.

In case of a single hyperenhanced region, scarred infarct detection was automatically performed by using the full width at half maximum criteria by indicating a region as scarred tissue. In case of multiple and more heterogeneous hyperenhanced regions infarct detection was performed by manually moving the threshold slider incorporated in CAAS. Myocardium with an intensity above the threshold of the slider was subsequently automatically segmented as infarct. Infarct segmentations using the latter technique were than manually edited when necessary. Traced DE-CMR contours (*Figure 1*) were converted into 3D surface meshes in STL-formats.

Computed tomography of the heart, thorax, and coronary veins

Computed tomography angiography images were acquired with a third generation dual-source Somatom Definition Force CT scanner (Siemens Healthineers, Forchheim, Germany). A non-enhanced low-dose thorax CT scan was performed to determine the electrode positions for BSPM, followed by a cardiac contrast enhanced CTA scan for ECGI reconstruction purposes and for coronary venous anatomy. A test bolus was injected at the level of the coronary sinus (CS) or ascending aorta to assess optimal delay for contrast administration. Delay was calculated by time-to-peak +10 or +20 s for the CS or ascending aorta, respectively.¹³

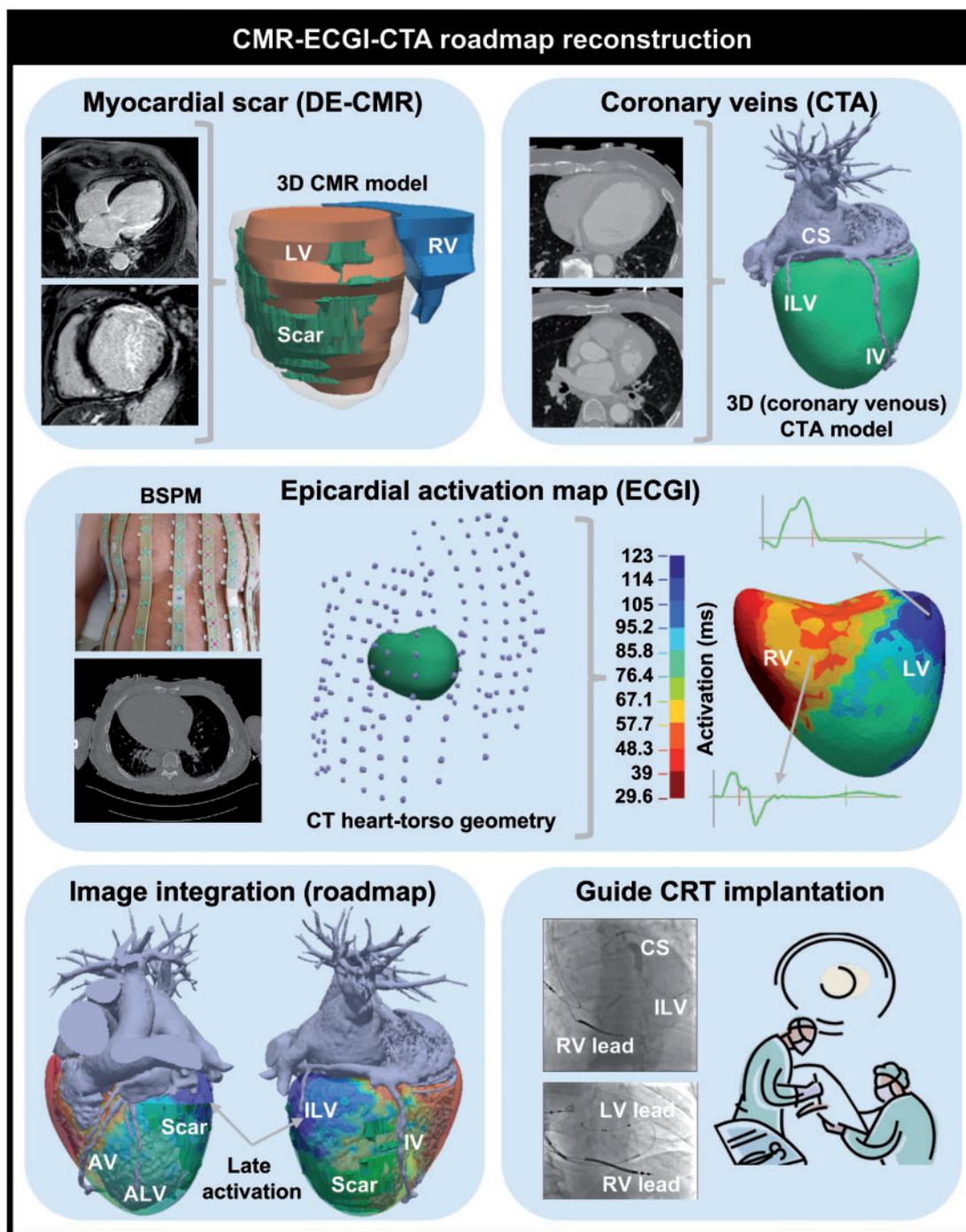


Figure 1 Workflow for CMR-ECGI-CTA roadmap reconstruction for CRT implantation guidance. Images are taken from Patient 3. AV, anterior vein; BSPM, body surface potential measurement; CMR, cardiac magnetic resonance imaging; CS, coronary sinus; CTA, computed tomography angiography; DE-CMR, delayed enhancement cardiac magnetic resonance imaging; ECGI, electrocardiographic imaging; ILV, inferolateral vein; IV, inferior vein; LV, left ventricle; RV, right ventricle.

Patients received 72 mL pre-warmed Iopromide 300 (Ultravist, Bayer Healthcare, Berlin, Germany) at a flow rate of 6 mL/s directly followed by an 84 mL mixed bolus (20% contrast, 80% saline) at the same flow rate and a 40 mL saline flush at a flow rate of 3 mL/s. Total iodine load was 26.6 (21.6 + 5) g iodine. Coronary venous anatomy was classified

according to the American Heart Association 17-segment heart model and evaluated under supervision of a radiologist with 7 years' experience in cardiac CTA. Segmentations of the torso, epicardium, blood pool, and coronary veins (Figure 1) were semi-automatically performed in Seg3D v2.4 (SCI, University of Salt Lake City, UT, USA).

Electrocardiographic imaging: reconstruction and analyses

Body surface potential measurement recordings of 2 kHz during intrinsic rhythm were carried out with ~184 torso electrodes using the ActiveTwo system (BioSemi, Amsterdam, the Netherlands).¹⁰ The epicardial CTA segmentations were re-sampled and smoothed in PreView (SCI, University of Utah, USA) to create a mesh with circa 2000 nodes. All BSPM electrodes were segmented from the low-dose CT thorax in Seg3D and used to build a torso mesh in MATLAB R2016B (MathWorks, Natick, MA, USA). The BSPM recordings and refined epicardium-torso mesh was used for inverse reconstruction (Figure 1) of epicardial potentials using the Tikhonov regularization algorithm.¹⁰ Epicardial unipolar electrograms (EGM) were reconstructed for every node by concatenating potentials over time. Epicardial activation times were automatically computed from BSPM QRS-onset to the steepest spatiotemporal down-slope in the local EGM QRS-complex.¹⁰

Image integration

Segmentations of the coronary veins and blood pool from CTA, epicardium from CTA with ECGI reconstructed activation times, and DE-CMR derived endocardium, epicardium, and scar were imported as STL- or VTK-files in the multi-platform data analyses and visualization application software Paraview 5.1.0 (Kitware Inc., Clifton Park, NY, USA). Delayed enhancement cardiac magnetic resonance imaging segmentations were manually translated to match the co-ordinate system of the CTA meshes

by creating a (rough) first fit and by fine-tuning from multiple planes. The most important anatomic landmarks used for integration were the LV and RV epicardium, LV endocardium on CMR with the LV blood pool on CTA, interventricular septum, and LV and RV endocardial apex. The appropriateness of the integrated image was based on visual evaluation. After proper translation of the DE-CMR geometry towards the CTA geometry, co-ordinates of the translation matrix (X, Y, and Z-direction) were used to visualize the DE-CMR scar substrate on top of the CTA derived ECGI-epicardium, blood pool, and coronary veins. More detailed information on the image integration process is provided in Figure 2. The finalized CRT-roadmap with CMR-ECGI-CTA integration (Figure 1) was presented to the implanting electrophysiologist in 3D prior and during CRT implantation.

Cardiac resynchronization therapy implantation

The right atrial lead was targeted towards the right atrial appendage, while the RV lead was targeted towards the apical septum. Left ventricular-lead placement was targeted towards the coronary vein remote from scar in a region of maximum electrical delay on the CRT-roadmap and preferably at the LV free wall. If the major course of the vein from a region with maximal delay on ECGI was located in scar, an alternative vein was targeted remote from scar, provided that the delay was still sufficiently late, preferable $\geq 50\%$ QRSd.^{5,6}

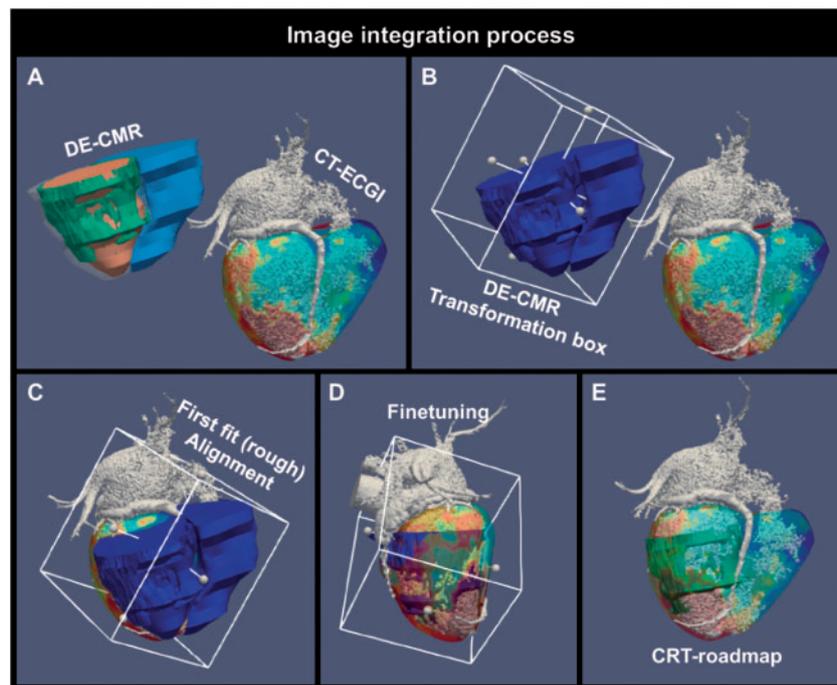


Figure 2 Detailed overview of the image integration process. (A) Segmentations from DE-CMR (LV and RV endocardium and epicardium, scar) and CTA-ECGI (epicardium, blood pool, coronary veins) data are imported as separate objects in the visualization platform Paraview. (B) All separate DE-CMR segmentations are grouped into a single dataset (blue object) to prepare transformation. (C) A first fit (rough) translation is carried out by dragging the transformation box of the DE-CMR data in a single plane to the CTA geometry. (D) The translation is more refined by performing small translations of the DE-CMR data in multiple planes. (E) After proper integration, only DE-CMR scar is visualized on top of the CTA geometry in the CRT-roadmap to ensure a structured overview. CMR, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; DE-CMR, delayed enhancement cardiac magnetic resonance imaging; ECGI, electrocardiographic imaging.

Navigation of the LV lead during the implantation procedure was based on fluoroscopic angiography. Quadripolar LV leads were used as first choice. Several quadripolar leads have been developed with varying shapes and inter-electrode spacing, of which some extend an entire coronary vein.¹⁴ A pacing vector within the target region, low voltage thresholds, without phrenic nerve stimulation, and preferably longest Q-LV was selected for pacing.

To assess the electrical delay at the RV (Q-RV) and LV (Q-LV) lead, simultaneous recording of the surface electrocardiogram (ECG) and sensed RV and LV unipolar EGM during intrinsic rhythm were obtained from the pacemaker/ICD programmer. Q-RV and Q-LV were measured in milliseconds from QRS-onset on the surface ECG to the steepest downslope of the sensed RV or LV EGM.

Data analyses

Statistical analyses were performed using MATLAB. Continuous variables are expressed as mean \pm standard deviation and dichotomous variables as frequencies and percentages. Final LV lead position in relation to the CRT-roadmap was visually evaluated for every patient. Q-RV and Q-LV measurements were compared with corresponding ECGI delays using Spearman correlation analyses and Wilcoxon signed-rank tests.

Results

Patient characteristics

A total of 16 patients planned for CRT device implantation were prospectively included. Patients had a variety of conduction disturbances [left bundle branch block (LBBB): $n = 6$, intraventricular conduction disturbance (IVCD): $n = 8$; narrow-QRS (ablate and pace strategy): $n = 1$; right bundle branch block (RBBB): $n = 1$]. Fifteen patients were referred for a *de novo* implantation, and one patient for an upgrade

from a dual-chamber pacemaker. Patient characteristics are provided in *Table 1*.

CMR-electrocardiographic imaging-computed tomography angiography investigations and cardiac resynchronization therapy-roadmap reconstruction

CMR was performed in 15 out of 16 patients. In one patient who already had a dual-chamber pacemaker, CMR was not performed. The delayed enhancement sequence was of insufficient quality in one patient due to suboptimal cardiac triggering during acquisition. In three patients, DE-CMR was negative, suggesting the absence of scar, while the remaining 11 patients had an average of $20 \pm 11\%$ focal scar in the LV (*Table 1*).

Coronary venous CTA and low-dose thorax CT was successfully performed in all patients. The number of available coronary veins varied from 3 to 4 per patient. Body surface potential measurements and ECGI reconstructions were also successfully carried out in all patients.

Cardiac resynchronization therapy-roadmaps could be constructed for all 16 patients. In 14 patients, CMR-ECGI-CTA integration was performed; while in two patients only ECGI-CT integrations were created due to absence of adequate DE-CMR data. A representative CRT-roadmap is provided in *Figure 3*, while a detailed overview of the CMR-ECGI-CTA CRT-roadmaps is provided in *Figure 4*. There were a total of 57 available coronary veins present on the 16 CRT-roadmaps, of which 25 veins were located on the LV lateral wall. Nine out of these 25 LV free wall coronary veins were less suitable for LV-lead placement as these were located in scar or in a region of

Table 1 Patient characteristics

Pt	Sex	Age	iCMP	NYHA	DE-CMR ^a	LVEF (%)	LVEDV (mL)	LVESV (mL)	ECG rhythm	QRS morphology	QRSd (ms)
1	M	70	Yes	2	13%	28	307	220	AF	IVCD	134
2	M	67	Yes	2	21%	28	278	200	Sinus	LBBB	152
3	M	72	Yes	2	15%	11	505	449	Sinus	LBBB	138
4	F	77	No	2	0%	25	232	174	Sinus	LBBB	148
5	F	59	Yes	3	32%	20	246	197	Sinus	IVCD	158
6	M	70	Yes	2	28%	36	235	150	Sinus	LBBB	162
7	M	79	Yes	3	No CMR	30	–	–	RV paced	LBBB	162
8	M	76	Yes	2	Inadequate	20	359	286	Sinus	IVCD	150
9	M	61	No	3	9%	43	245	145	Sinus	IVCD	120
10	M	66	No	2	0%	24	244	186	Sinus	LBBB	158
11	M	80	No	3	31%	22	275	215	Sinus	IVCD	122
12	M	76	Yes	3	10%	25	266	203	AF	IVCD	135
13	F	53	No	3	0%	23	233	161	Sinus	Narrow	82
14	M	70	Yes	2	28%	10	452	413	Sinus	IVCD	150
15	M	80	Yes	2	15%	20	232	181	AF	IVCD	142
16	M	72	Yes	2	38%	23	358	275	Sinus	RBBB	160

AF, atrial fibrillation; DE-CMR, delayed enhancement cardiac magnetic resonance imaging; iCMP, ischemic cardiomyopathy; IVCD, intraventricular conduction disturbance; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association functional class; RBBB, right bundle branch block.

^aScar on DE-CMR depicted in % of LV mass. Left ventricular parameters (LVEF, LVEDV, and LVESV) are all derived from CMR with exception of Patient 7. In Patient 8, the delayed enhancement sequence was inadequate to quantify scar, although cine images were sufficient for evaluation of LV functional parameters.

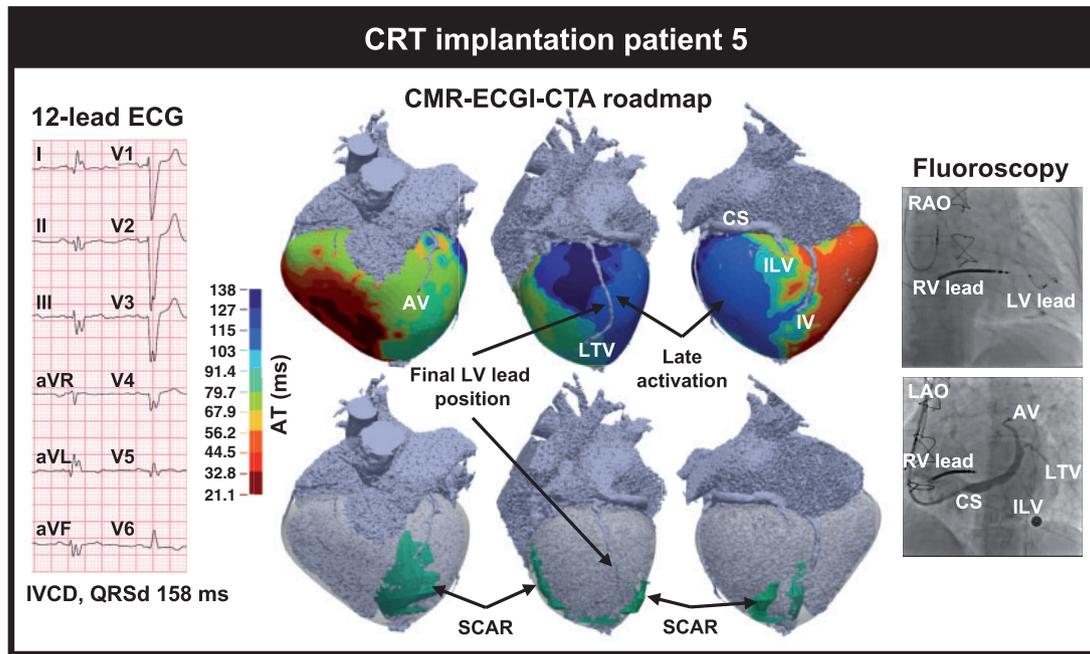


Figure 3 Representative CMR-ECGI-CTA roadmap of Patient 5 for CRT implantation. AT, activation time; AV, anterior vein; CMR, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; CS, coronary sinus; CTA, computed tomography angiography; ECGI, electrocardiographic imaging; ILV, inferolateral vein; IV, inferior vein; IVCD, interventricular conduction disturbance; LAO, left anterior oblique; LTV, lateral vein; LV, left ventricle; RAO, right anterior oblique.

early activation (<50% QRSD) on the CRT-roadmap. Sixteen out of 25 LV free wall coronary veins were located remote from scar in late-activated myocardium ($\geq 50\%$ QRSD) on the CRT-roadmap and subsequently considered suitable for LV-lead placement. The CRT-roadmap showed that there were no ($n=5$), one ($n=6$), or two ($n=5$) veins per patient located outside scar in late-activated myocardium ($\geq 50\%$ QRSD) on the CRT-roadmap, thus potential candidates for lead positioning.

Cardiac resynchronization therapy device implantation and left ventricular-lead placement

Fourteen out of 16 patients underwent CRT implantation. In one patient (no. 9) implantation was cancelled after construction of the CRT-roadmap due to improved left ventricular ejection fraction (LVEF) on CMR. One patient (no. 14) died suddenly before the scheduled CRT implantation unrelated to the study protocol or CRT procedure due to an out of hospital cardiac arrest.

A standard left-sided CRT implantation was used in 13 out of 14 patients, while a right-sided implantation approach was carried out in one patient (no. 4) because of a persistent left-sided superior cava with no left innominate vein visualized on the pre-procedural CTA. Mean fluoroscopy time was 32 ± 9 min, mean radiation dose was 389 ± 276 mGy, and mean total procedural time was 159 ± 40 min.

Detailed information on the final LV-lead placement in relation to the CRT-roadmap per individual patient is provided in Figure 4 and summarized in Figure 5. The LV lead was positioned outside the scar

in 11 out of 14 patients. In the remaining three patients (nos 2, 6, and 16), scar extended to all LV free wall segments and could not be avoided. In two patients (nos 3 and 4) cannulation of the initial target vein was not possible due to limited coronary venous anatomy. Electrocardiographic imaging delay at the LV lead was $\geq 50\%$ in 13 out of 14 patients and $< 50\%$ in 1 patient. In 11 patients, the LV lead was placed both outside scar and in an area with $\geq 50\%$ QRSD, and considered as optimal positions.

Electrocardiographic imaging epicardial activation times vs. invasive measurements

Intra-procedural intrinsic Q-LV and Q-RV measurements were performed in all 14 implanted patients. Three Q-RV measurements were excluded from the analyses, as these patients had a mid-septal RV lead position as the septum is not reconstructed by ECGI, and therefore the RV lead location was too far located from the ECGI epicardial activation maps. Representative Q-RV and Q-LV measurements are provided in Figure 6. Overall there was a good correlation ($R: 0.85, P < 0.001$) between Q-LV/Q-RV and ECGI delays (Figure 7). Electrocardiographic imaging delays showed lower values compared to invasive measurements (difference -15 ± 26 ms, $P = 0.0295$).

Discussion

In the present study, the feasibility of creating a non-invasive pre-implantation CRT-roadmap was evaluated in a case series by integration

Pt	CMR-ECGI-CTA integration					CRT-roadmap decision making		Final LV lead placement		LV lead remote from scar in late activation?
	A	AL	L	IL	I	Number LV veins	Target positions	Position	ECGI AT, ms (% QRSd)	
1	+	-	+	+	+	4	1: L	Mid-L	75 (56)	Yes, remote from scar in intermediate activated vein.
2	+	+	-	-	+	3	None	Mid-AL	78 (51)	No, in scar and intermediate activated vein.
3	+	+	-	+	+	4	1: IL	Basal-IL	105 (76)	Yes, through IV anastomosis to the ILV (angulation).
4	+	+	-	-	+	3	1: AL	Mid-I	95 (64)	Yes, but not on free wall. ALV vein too angulated.
5	+	-	+	+	+	4	2: L, IL	Mid-L	135 (85)	Yes. RV thrombus; implantation postponed 6 months.
6	+	-	+	+	+	4	None	Basal-L	75 (46)	No, in scar and early activated vein.
7	+	+	-	+	+	4	2: AL, IL	Mid-AL	135 (83)	Yes, in late activated vein. No CMR data (upgrade).
8	+	-	+	+	+	4	2: L, IL	Mid-L	135 (90)	Yes, but all veins were late activated. No CMR data.
9	+	-	+	-	+	3	None	-	-	CRT cancelled.
10	+	-	+	+	+	4	2: L, IL	Apex-IL	155 (98)	Yes, in late activated vein. No scar on CMR.
11	+	-	+	-	+	3	1: L	Mid-L	62 (51)	Yes, remote from scar in intermediate activated vein.
12	+	-	+	-	+	3	1: L	Mid-L	95 (70)	Yes, remote from scar in intermediate activated vein.
13	+	+	-	+	+	4	2: AL, IL	Mid-AL	45 (55)	Yes, in late activated vein. No scar on CMR.
14	+	-	+	-	+	3	None	-	-	CRT cancelled.
15	+	+	-	+	+	4	1: AL	Mid-AL	115 (81)	Yes, remote from scar in late activated vein.
16	+	-	+	-	+	3	None	Mid-L	90 (56)	No, all veins in scar.

Legend

- No vein
- ⊕ Late activated vein (≥50% QRSd)
- ⊖ Early activated vein (<50% QRSd)
- ⊕ Very late activated vein (≥75% QRSd)
- Final LV lead segment
- DE-CMR scar

Figure 4 Patient-specific information on the CRT-roadmap and final LV lead placement. CMR-ECGI-CTA integration, CRT-roadmap, and final LV lead position. A, anterior; AL, anterolateral; AT, activation time; CMR, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; CTA, computed tomography angiography; DE-CMR, delayed enhancement cardiac magnetic resonance imaging; ECGI, electrocardiographic imaging; I, inferior; IL, inferolateral; L, lateral; LV, left ventricle; RV, right ventricle.

CMR, ECGI, and CT to guide LV-lead placement. The advantage of the present CRT-roadmap, with respect to all previous imaging-guided approaches, is that it comprises detailed imaging of the coronary veins and scar substrate as well as high-resolution epicardial electrical activation patterns, facilitating decision-making during implantation by the use of a single non-invasive 3D cardiac model.

Towards a tailored left ventricular-lead placement

Several imaging-guided approaches for LV-lead placement have emerged, of which the largest in this regard are STARTER¹⁵ and the TARGET² studies. Both studies used echocardiography and demonstrated an association between reduced mortality and a LV lead position in late-activated myocardium. The TARGET study additionally underlined the importance of avoiding scar, by showing an almost five-fold mortality reduction when the LV lead was placed outside scar.² The importance of guiding LV lead placement away from scar using DE-CMR is further emphasized in a large cohort of consecutive CRT candidates by Leyva *et al.*³ A LV lead position in scar compared to non-scar was associated with an over 6-fold increase in cardiac death and an increased risk for hospitalization and major adverse cardiovascular events.³

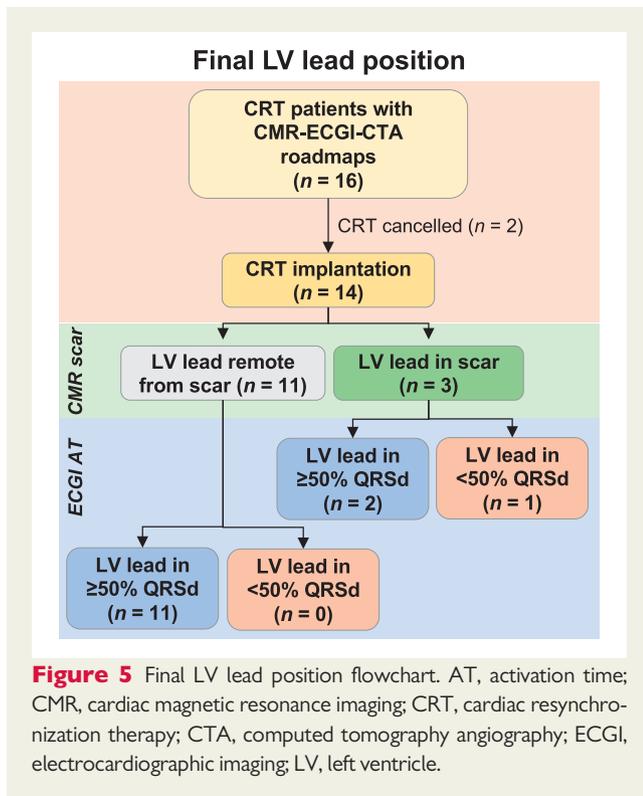
A recent smaller study by Kockova *et al.*¹⁶ compared an CMR-guided (away from scar, in late mechanical activation) LV lead

placement approach with a Q-LV guided approach. Interestingly, the use of CMR did not lead to a significant reduction in cardiovascular death or hospitalization, suggestion that the use of Q-LV solely may diminish the relative benefit from CMR.¹⁶

More refined approaches incorporating multimodality imaging to tailor LV-lead placement have also emerged. Pre-procedural 2D bullseye plots with information on CT, DE-CMR, and echocardiography were constructed by Bakos *et al.* to define a late-activated segment outside scar. Interestingly, in about half of the patients, the target segment couldn't be reached due to lack of coronary veins, confirming in the importance of visualizing the coronary venous anatomy.¹⁷

Recently, Behar *et al.* overlaid CMR-derived scar and mechanical activation on the fluoroscopic angiogram to guide LV-lead placement.¹⁸ The benefit of the latter approach was that the CMR scanner was installed in the same facility as the catheter laboratory enabling real-time imaging and CRT implantation in a single procedure, enhancing clinical workflow.

The majority of all imaging-guided CRT studies incorporate mechanical activation. As CRT is primarily an electrical therapy, a more detailed assessment of local electrical activation may provide incremental value.^{5,6} In the present study local epicardial electrical activation was assessed non-invasively, using an in-house developed ECGI system validated in animal models.¹⁰ A good correlation was additionally found between invasive electrical delay measurements and ECGI activation times.



Only a few other studies incorporated electrical activation for LV lead guidance. Invasive coronary venous electro-anatomic mapping⁷ has been used by our group and has been integrated with DE-CMR⁹ to navigate LV-lead placement intra-procedurally. Although a LV lead position remote from scar in late electrical activation was achieved in the majority of patients, its application requires refined skills of the implanting physician to map all coronary veins.

One study by Dawoud *et al.*¹⁹ similarly incorporated coronary venous anatomy, scar extent, and electrical activation non-invasively for CRT by integration of CT with ECGI. The authors subsequently demonstrated the feasibility of ECGI-CT integration in a pre-clinical setting of 6 canine models.

The present CRT-roadmap requires both CT and CMR imaging and thus may be more complex than the use of solely CMR¹⁸ or echocardiography.^{2,15}

Clinical implications

In the present study, the LV lead was properly positioned remote from scar tissue and in late-activated myocardium in 79% of patients. The CRT-roadmap in the current study was primarily used for LV-lead placement, but its application in patient selection by computing inter-ventricular dyssynchrony^{11,20} from ECGI together with information on scar and coronary venous anatomy is well within range and an important goal in the near future. Electrocardiographic imaging parameters reflecting inter-ventricular dyssynchrony superior in CRT response prediction compared to the conventional 12-lead ECG include ventricular electrical uncoupling²⁰ and activation delay vector.²¹

Visualization of the coronary venous anatomy by CTA pre-procedurally may support planning of the implantation strategy. Additionally, using the current CTA protocol yielded a high

concordance (85%) between coronary venous CTA and fluoroscopic angiography.¹³ In the current study, cannulation of the initial target vein was not possible due to suboptimal coronary venous anatomy (angulation at the ostium in Patients 3 and 4 described in *Figure 4*) and in one patient, a right-sided implantation approach was used due to a persistent left-sided superior vena cava (Patient 5). In case of suboptimal coronary venous anatomy or extensive scarring around the veins, one could anticipate by the use of specific lead types or even consider alternative approaches for biventricular pacing including a surgical placed epicardial lead, endocardial pacing,²² or transseptal pacing.²³

The issue of radiation exposure from CTA however merits discussion. The radiation dose of a standard CTA acquired using an advanced multidetector computed tomography scanner is associated with an effective dose of 0.21 mSv.²⁴ Despite the radiation burden, CTA had several benefits including a high spatial resolution which is particularly relevant for visualization of small and delicate blood vessels,²⁵ and a short acquisition time making it a patient friendly technique. Furthermore, the quantity of radiation exposure may be kept at a minimum by advancing the acquisition protocol.²⁶ The amount of radiation can also be put into perspective as it is only a small fraction compared to the amount of radiation exposed to the patient during CRT implantation. The entrance skin dose during CRT implantation may depend on the implanting physician and complexity of the procedure (e.g. fluoroscopy and implantation time), though doses of 1000 ± 600 mGy have been reported.²⁷

Electrocardiographic imaging alone could be of added value post implantation as well, by assessing the levels of dyssynchrony during different pace settings, potentially improving CRT delivery. With our current ECGI system, extensive ECGI measurements post implantation, can reliably be performed using the original heart-torso geometry exempting the need for a repeat CT.²⁸

The utility of CMR-ECGI-CTA integration may even stretch beyond that of CRT alone. A 3D cardiac CMR-ECGI-CTA model could, for instance, be used to localize the origin of premature ventricular contractions or ventricular tachycardia (VT) and guide ablation whilst still avoiding injury of vulnerable coronary arteries or nerves. In a recent study by Cuculich *et al.*,²⁹ ECGI was integrated with coronary arteries on CT and scar or ischemia on CMR or single photon emission computed tomography to guide VT ablation, pioneering a complete non-invasive approach of diagnostics and therapy in electrophysiology.

Limitations

This was a case series study with a limited number of patients. Additionally, baseline functional parameters including LVEF and volumes were based on CMR measurements, prohibiting follow-up measurements by the same imaging technique as CMR may be contraindicated in patients with some CRT device types. Nowadays, United States Food and Drug administration approved CMR compatible CRT devices have emerged,³⁰ enabling the use of CMR for outcome assessment for instance by assessing LV volumes and mechanical changes (e.g. feature tracking from cine CMR of tagging) after CRT implantation. Although these some CRT devices may be CMR compatible, the device can still cause substantial artefacts, potentially affecting the reliability of LV volume assessments.

The scope of this study was to explore the technical feasibility of the CRT-roadmap. The superiority of such image-guided approach compared to conventional implantation strategies requires a clinical

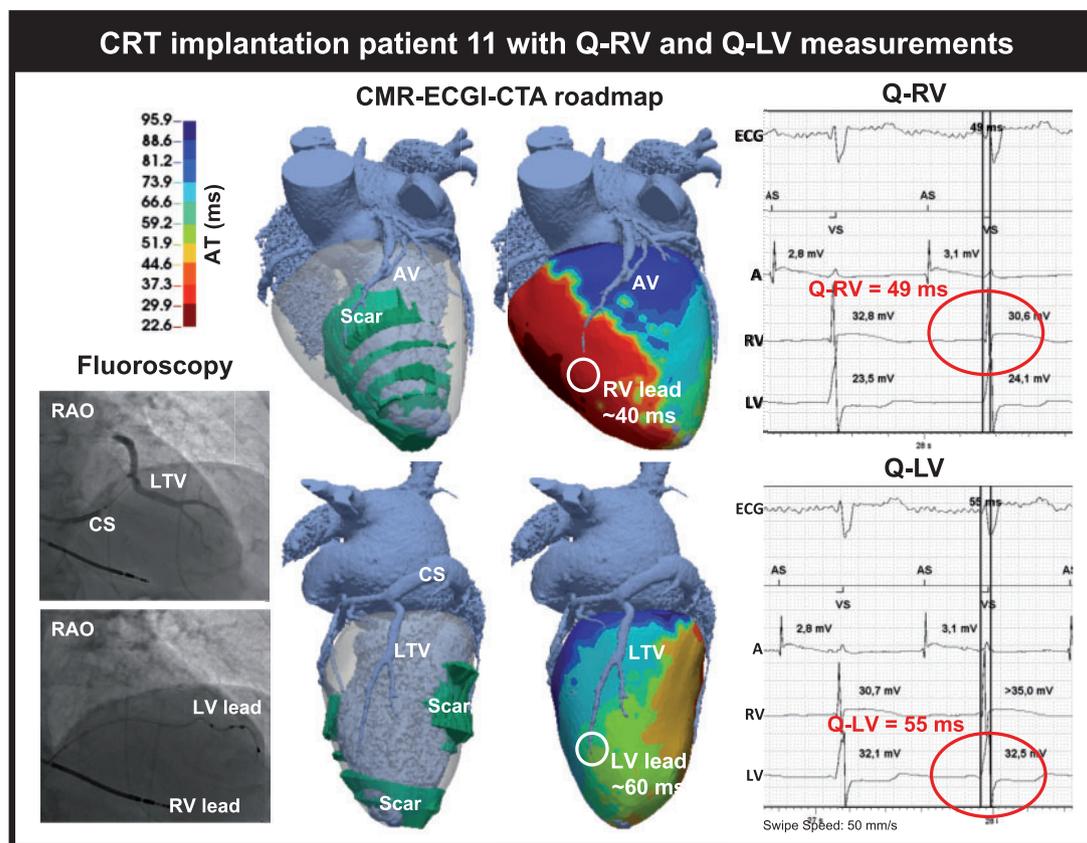


Figure 6 Electrocardiographic imaging activation map of Patient 11 with invasive Q-RV and Q-LV measurements. AT, activation time; AV, anterior vein; CMR, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; CS, coronary sinus; CTA, computed tomography angiography; ECGI, electrocardiographic imaging; LAO, left anterior oblique; LTV, lateral vein; LV, left ventricle; RAO, right anterior oblique; RV, right ventricle.

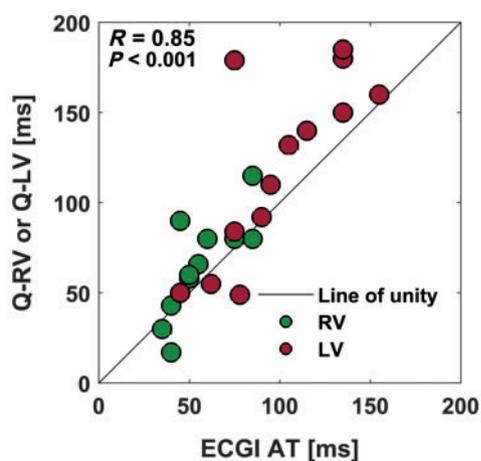


Figure 7 Spearman correlation analysis between activation time (AT) measured intra-procedurally at the RV and LV lead (Q-RV and Q-LV, respectively) vs. associated ECGI AT. ECGI, electrocardiographic imaging; LV, left ventricle; RV, right ventricle.

trial with LV reverse remodelling as primary endpoints, randomizing an image-guided approach, using the CMR-ECGI-CTA roadmap, vs. a conventional LV lead placement. Secondary endpoints may include New York Heart Association functional class improvement, mortality, hospitalization, while tertiary endpoints may include ECG characteristics, procedural times, and radiation burden.

Potential differences between coronary venous anatomy imaged by CTA and fluoroscopic angiography may exist due to different stages of congestion and the time difference between the two investigations. All of our patients were clinical stable with respect to their HF status and did not suffer from acute decompensation in the time interval between the CTA exam and CRT implantation.

CMR can be contra-indicated in patients with existing pacing systems. In this subgroup of CRT candidates, alternative CT metrics for scar such as wall thinning, wall motion,¹² or delayed enhancement CT could be considered.

Conclusion

In the present study, the development and implementation of a novel CRT-roadmap, that comprehends detailed imaging of the coronary

veins and scar substrate as well as high-resolution epicardial electrical activation patterns, was evaluated in a case series. The feasibility of this CRT-roadmap in facilitating decision-making during implantation by the use of a single non-invasive 3D cardiac model is demonstrated, potentially improving outcome.

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