

Localization of Left Ventricular Lead Electrodes in Relation to Myocardial Scar in Patients Undergoing Cardiac Resynchronization Therapy

Arnaud Bisson, MD; Julien Pucheux, MD; Clémentine Andre, MD; Anne Bernard, MD, PhD; Bertrand Pierre, MD; Dominique Babuty, MD, PhD; Laurent Fauchier, MD, PhD; Nicolas Clementy, MD

Background—The efficacy of cardiac resynchronization therapy may be reduced in the event of pacing within myocardial fibrosis. We aimed to develop a method to determine the anatomical relationships between the left ventricular (LV) lead and myocardial fibrosis.

Methods and Results—In consecutive patients indicated for cardiac resynchronization therapy, cardiovascular magnetic resonance imaging with late gadolinium enhancement assessment was performed before implantation. After implantation, an injected computed tomography scanner (CT scan) was performed. The 2 imaging techniques were fused to assess the LV lead position relative to myocardial scar. A total of 68 patients were included. Myocardial scar was found in 29 (43%) and was localized in lateral segments in 14 (21%). Scar was significantly associated with male sex, ischemic cardiomyopathy, a Selvester score adapted to left bundle branch block (LBBB Selvester), and Selvester criteria for localizing lateral fibrosis (V2 S/S' ratio). Image fusion was feasible in all patients. Position within myocardial scar was confirmed for 6 electrodes in 3 patients. Prolonged QRS duration during LV pacing $\geq 139\%$ predicted electrode positioning within scar tissue (sensitivity, 83%; specificity, 91%; $P=0.002$).

Conclusions—In cardiac resynchronization therapy patients, fusion between preimplantation cardiovascular magnetic resonance and a postimplantation injected computed tomography scan is a feasible technique. Prolongation of the QRS duration during LV pacing predicts pacing within myocardial scar. Accurate location of LV lead pacing electrodes on the epicardial surface relative to myocardial scar, either by imaging or ECG analyses, may help improve cardiac resynchronization therapy response in selected patients. (*J Am Heart Assoc.* 2018;7:e009502. DOI: 10.1161/JAHA.118.009502.)

Key Words: cardiac resynchronization therapy • fibrosis • image fusion • left ventricular lead

Myocardial fibrosis, quantified by measuring the extent of late gadolinium enhancement (LGE) in a cardiovascular magnetic resonance (CMR) imaging study, is associated with a worse response to cardiac resynchronization therapy (CRT), particularly if it is sizable, transmural, or located in posterolateral left ventricular (LV) segments where the LV lead is usually positioned.^{1,2} CMR remains the gold standard, but cannot be performed routinely, especially because of noise or incompatibility after implantation of an intracardiac device.

From the Cardiology Department (A. Bisson, C.A., A. Bernard, B.P., D.B., L.F., N.C.) and Radiology Department (J.P.), Centre Hospitalier Universitaire Trousseau et Faculté de Médecine, Université de Tours, France.

Correspondence to: Arnaud Bisson, MD, Service de Cardiologie, CHRU de Tours, avenue de la République, 37170, Chambray les Tours, France. E-mail: arnaud.bisson37@gmail.com

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The primary objective was to develop a reliable method for precisely locating the position of the LV lead electrodes on the epicardial surface in relation to the myocardial scar areas in patients implanted with a CRT device. The secondary objective was to establish simpler electrocardiographic tools to predict pacing within scar zones.

Methods

The data, analytical methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Consecutive patients, indicated according to guidelines³ for CRT defibrillator implantation, were prospectively included. Patients had to be in sinus rhythm with a typical left bundle branch block (LBBB)⁴ of duration ≥ 130 ms.

Clinical Perspective

What Is New?

- This study emphasizes, for the first time, the feasibility and the benefits of imaging fusion between preimplantation cardiovascular magnetic resonance imaging and postimplantation injected computed tomography scanner to localize left ventricular lead pacing electrodes in relation to myocardial scar in patients undergoing cardiac resynchronization therapy.

What Are the Clinical Implications?

- This technique might help to identify and optimize potential nonresponders to cardiac resynchronization therapy and thus improve outcomes.

The local ethics committee for human research approved the study protocol. All patients signed informed consent before inclusion.

CMR Imaging

Before CRT implantation, CMR was performed in all patients on a 1.5 Tesla system (MAGNETOM Avanto; Siemens Healthineers, Erlangen, Germany) according to the following standardized protocol: The cine images were acquired with an ECG-gated balanced steady-state free precession sequence during breath-holds, in short-axis covering the whole LV, and in 2- and 4-chamber LV long-axis. LGE inversion/recovery and phase-sensitive inversion recovery sequences were performed 10 minutes after intravenous injection of 0.2 mmol/kg of gadoteric acid (Dotarem; Guerbet, Villepinte, France) in short-axis, and in 2- and 4-chamber LV long-axis. Scar was considered transmural whenever LGE was $\geq 50\%$ of ventricular wall thickness in ≥ 1 segment. LV segmental analysis was first based on a 17-segment model, and then converted into a 5-segment model to fit the electrocardiographic analysis. Anterior-septal, inferior-septal, and septal-apical segments corresponded to the septal segment; anterior-lateral, inferior-lateral, and apical-lateral segments corresponded to the lateral segment; apex and apical, anterior, and inferior segments retained the same denomination.^{5,6}

Implantation

These were initial implants of biventricular implantable cardioverter defibrillators placed through a transvenous approach. LV leads were either bi- or quadripolar leads. LV lead positioning by the coronary sinus was performed according to the physician's preference and blinded from magnetic resonance imaging (MRI) analysis.

Computed Tomography Scan

After implantation in patients with presence of LGE, an ECG-gated computed tomography (CT) scan was performed on a SOMATOM Definition AS128 (Siemens Healthineers) after intravenous injection of 80 mL of Iohexol (Omnipaque 350; GE Healthcare, Marlborough, MA). Contrast CT scanning was not performed in case of severe renal impairment.

Image Registration

Rigid registration of MRI-LGE 4-cavity images and injected CT scan slices was performed. The IntelliSpace Portal's "Automatic Registration" software module (version 5.0.2; Philips Healthcare, Best, The Netherlands) was used to carry out semiautomatic registration of images of cavity volumes, bolstered injecting contrast media injection during CT scan data acquisitions. Manual adjustment on fiducial points was then performed, if necessary. In order to better discriminate the pacing electrodes, metal noise artifacts were reduced using optimal windowing. Three-dimensional synchronization between the 2 sets of images (CT scan and MRI) made it possible to collate anatomically the scar areas shown on MRI images and the LV lead pacing electrodes observed as hyperdense bulges on CT scan images.

ECG Analyses

The Selvester score, described for the first time in 1972, was developed to locate and gauge the size of myocardial scar through resting ECG analysis of subtle changes in cardiac electrical activity. This QRS scoring, the most frequently cited and studied in the scientific literature on this topic, was rigorously validated in comparison first to autopsy-measured myocardial infarct in the 1980s and, second, to CMR imaging. A recent revision of this score was developed to thwart ECG confounders (ie, bundle branch/fascicular blocks and ventricular hypertrophy), which was not possible with the older version. We have therefore calculated this Selvester QRS scoring adapted for LBBB morphology⁷ at baseline as well as a derived criterion to locate scar in lateral segments (wave ratio $S/S' \geq 1.5$ in V2).⁵ Baseline QRS complex duration was measured using in-machine automated measurement (QRSd) software.

After implantation, the following data were collected from a 12-lead ECG in mono-LV pacing for each pacing electrode (cathode):

1. QRSd,
2. R-wave peak time,
3. QRSd prolongation (paced QRSd/baseline intrinsic QRSd),
4. spike-to-QRS onset delay, and

5. capture threshold, performed with a pace duration between 0.35 to 0.5 ms, according to the manufacturer's nominal programming.

ECG analyses were performed by 2 trained cardiologists, blinded from MRI results.

Statistical Analyses

JMP (version 9.0.1; SAS Institute Inc, Cary, NC) and STATA (MP 13; StataCorp LP, College Station, TX) softwares were used. Patient characteristics were collected as percentages and averages \pm SD. Comparisons were made using nonparametric tests as appropriate: The Wilcoxon W and Kruskal–Wallis tests were used for comparing values between 2 independent groups and the chi-squared test for comparing categorical data. Harrell's c-statistic was calculated as a measure of model performance, and results are expressed as area under the receiver operating characteristic area under the curve with 95% confidence intervals. $P<0.05$ was considered statistically significant. Inter-rater reliability was quantified using 2-way random-effects intraclass correlation assessing absolute and relative agreement. Agreement was considered poor whenever intraclass correlation coefficient was <0.50 , moderate between 0.51 and 0.75, good between 0.76 and 0.90, and excellent when >0.90 .⁸

Results

Population

A total of 68 consecutive patients were included. Baseline characteristics are detailed in Table 1 and Figure 1.

Twenty-nine of these patients (43%) had LGE on MRI sequences, of which 14 (21%) were localized in lateral segments. LGE was more likely to be found in male patients with an ischemic cardiomyopathy. Higher LBBB-adapted Selvester scores and Selvester criteria localizing lateral fibrosis ($V2\ S/S' \text{ ratio} \geq 1.5$) were also found in patients with LGE (Table 2).

A Selvester score ≥ 5 predicted myocardial scar with a sensitivity of 76%, a specificity of 67%, a positive predictive value of 63% and a negative predictive value of 79% (area under the curve=0.72 [0.61–0.83]). Inter-rater reliability in the measurement of the Selvester score was good with an absolute agreement of 0.89 (95% confidence interval, 0.85–0.93; $P<0.0001$) and a relative agreement of 0.94 (95% confidence interval, 0.91–0.97; $P<0.0001$). The $V2\ S/S' \text{ ratio} \geq 1.5$ had a 35% sensitivity, a 100% specificity, a 100% positive predictive value, and an 86% negative predictive value.

Among the 68 implanted patients, 44 had a quadripolar LV lead and 24 a bipolar 1, which represents 224 electrodes all together. The position of each electrode was determined using biplane fluoroscopy in the right anterior oblique and the left

Table 1. Baseline Patient Characteristics (n=68)

Variables	n (%) or Mean \pm SD
Age, y	66.9 \pm 10.5
Sex, women	19 (27.9)
Ischemic cardiomyopathy	28 (41.2)
ECG analysis	
QRSd, ms	165 \pm 19
Selvester score	5.1 \pm 2.4
Selvester lateral +	5 (7.4)
MRI analysis	
LVEF, %	27 \pm 7
EDLVV, mL/m ²	140 \pm 44
LGE +	29 (42.6)
No. of segments	1.9 \pm 2.9
Septal	13 (19.1)
Anterior	12 (17.6)
Lateral	14 (20.6)
Inferior	20 (29.4)
Apical	7 (10.3)
Transmurality $\geq 50\%$	20 (29.4)

EDLVV indicates end-diastolic left ventricular volume; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; QRSd, QRS duration.

anterior oblique views. One hundred twenty-nine (58%) electrodes were localized in the lateral wall, as recommended (Figure 2).

Image Fusion

MRI-CT was performed in most of the patients presenting lateral LGE. Mean dose length product was 349.55 mGy-cm and mean

Table 2. Patient Characteristics According to LGE After MRI Analysis

Variables	LGE (n=29)	No LGE (n=39)	P Value
Age, y	67.9 \pm 9.8	66.1 \pm 11	NS
Sex, women	3 (10.3)	16 (41)	0.004
Ischemic cardiomyopathy	18 (62.1)	10 (25.6)	0.002
ECG analyses			
QRSd, ms	164 \pm 20	165 \pm 18	NS
Selvester score	6.1 \pm 2.5	4.3 \pm 2	0.002
Selvester lateral +	5 (17.2)	0	0.003
MRI analysis			
LVEF, %	28 \pm 6	26 \pm 7	NS
EDLVV, mL/m ²	143 \pm 40	138 \pm 47	NS

EDLVV indicates end diastolic left ventricular volume; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NS, not significant; QRSd, QRS duration.

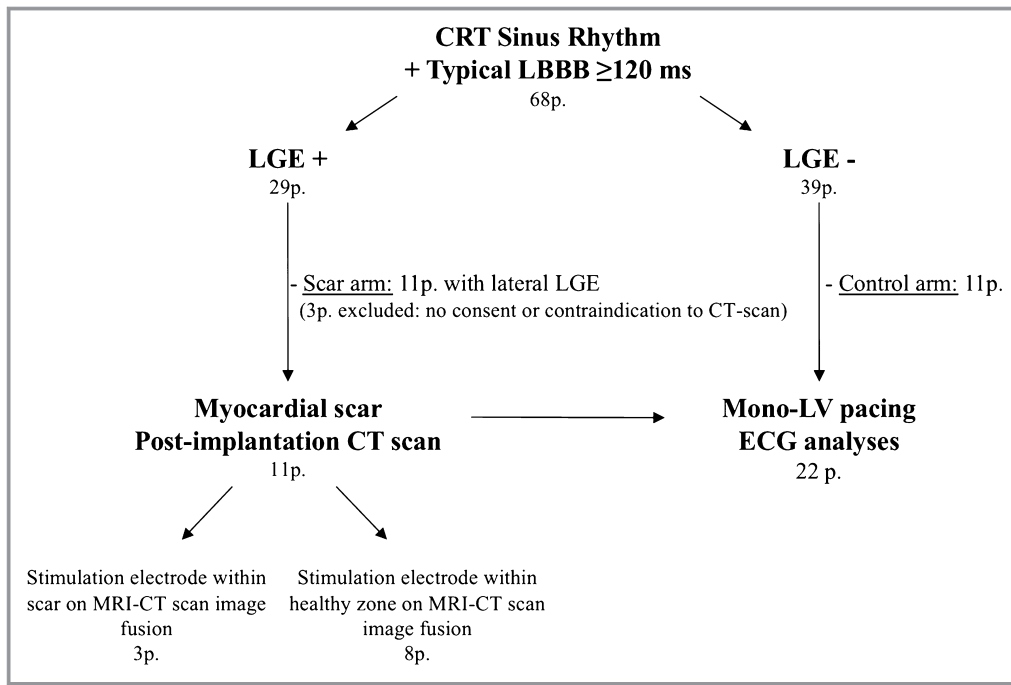


Figure 1. Study flow chart. CRT indicates cardiac resynchronization therapy; CT scan, computed tomography scanner; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; MRI, magnetic resonance imaging; p., patients.

effective dose 5.94 mSv. Those subjects not undergoing CT were excluded for the following reasons: severe renal impairment (2); lack of consent (1). Additional ECG analyses of all LV pacing configurations were performed in the 11 patients with

image fusion and 11 control patients showing no LGE on MRI (Figure 3). Image fusion was feasible in 100% of cases.

Position within myocardial scar was confirmed for 6 electrodes in 3 patients (Figure 4), without statistically relevant difference in baseline characteristics. V2 S/S' ratio ≥ 1.5 was more frequent in patients with confirmed LV lead location within scar tissue ($P=0.04$; Table 3). Of the 6 electrodes within scar tissue, 3 were in relation to transmural scarring and the other 3 to a mid-wall scar area. Ventricular capture threshold was similar for electrodes within and outside the scar region. Myocardial scar segments were anterior-lateral-medial for 4 electrodes, anterior-apical for 1, and lateral-apical for 1 other. Two patients were implanted with a quadripolar lead, and 1 had up to 3 electrodes within the scar area. The patient implanted with a bipolar lead had both electrodes within scar tissue.

Only QRSD prolongation during mono-LV pacing was significantly associated with a position in a myocardial fibrosis area ($P<0.01$; Table 4). A QRSD prolongation $\geq 139\%$ predicted localization within scar with a sensitivity of 83%, a specificity of 91%, a positive predictive value of 46%, and a negative predictive value of 97% (area under the curve=0.88 [0.80–0.96]).

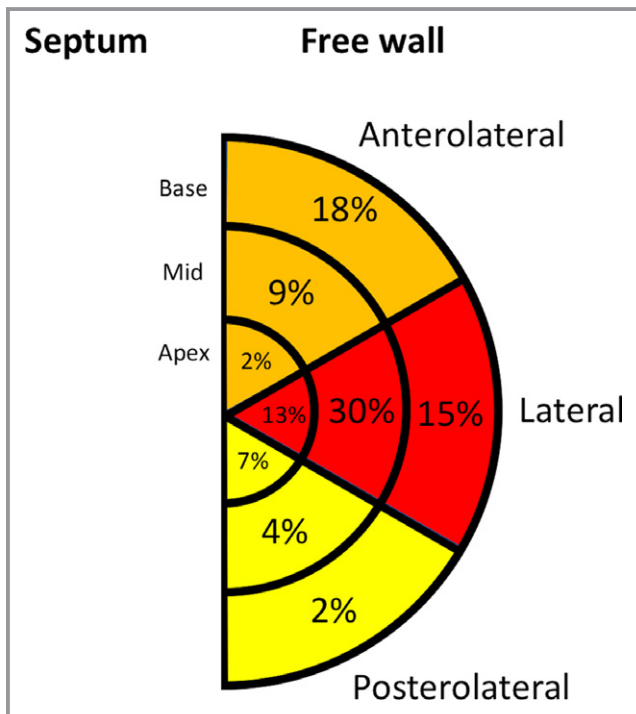


Figure 2. Final position of LV lead electrodes (N=224). LV indicates left ventricle; N, number of electrodes.

Discussion

Main Results

In this study, we, for the first time, developed a method using CMR/CT image fusion to accurately localize LV lead electrode

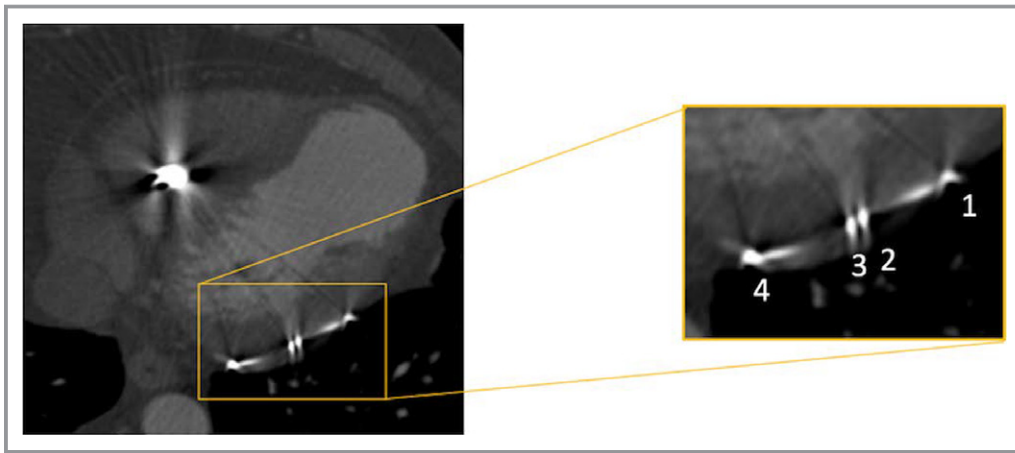


Figure 3. Injected CT scan visualization of the 4 stimulation electrodes of a quadripolar LV lead (model 4398; Medtronic, Minneapolis, MN). Electrodes are numbered from the most distal (no. 1) to the most proximal (no. 4) in the zoomed window (right side). CT scan indicates computed tomography scanner; LV, left ventricle.

position in relation to myocardial scar in patients implanted with a CRT device. The main results are: (1) CMR/CT image fusion is a feasible and highly reliable method; (2) LV pacing within scar tissue is not infrequent in a typical CRT population;

(3) QRSd prolongation during mono-LV pacing, rather than elevated capture threshold, predicts LV pacing within the scarred area; and (4) quadripolar leads allow thorough vector optimization of LV pacing outside scar zones.

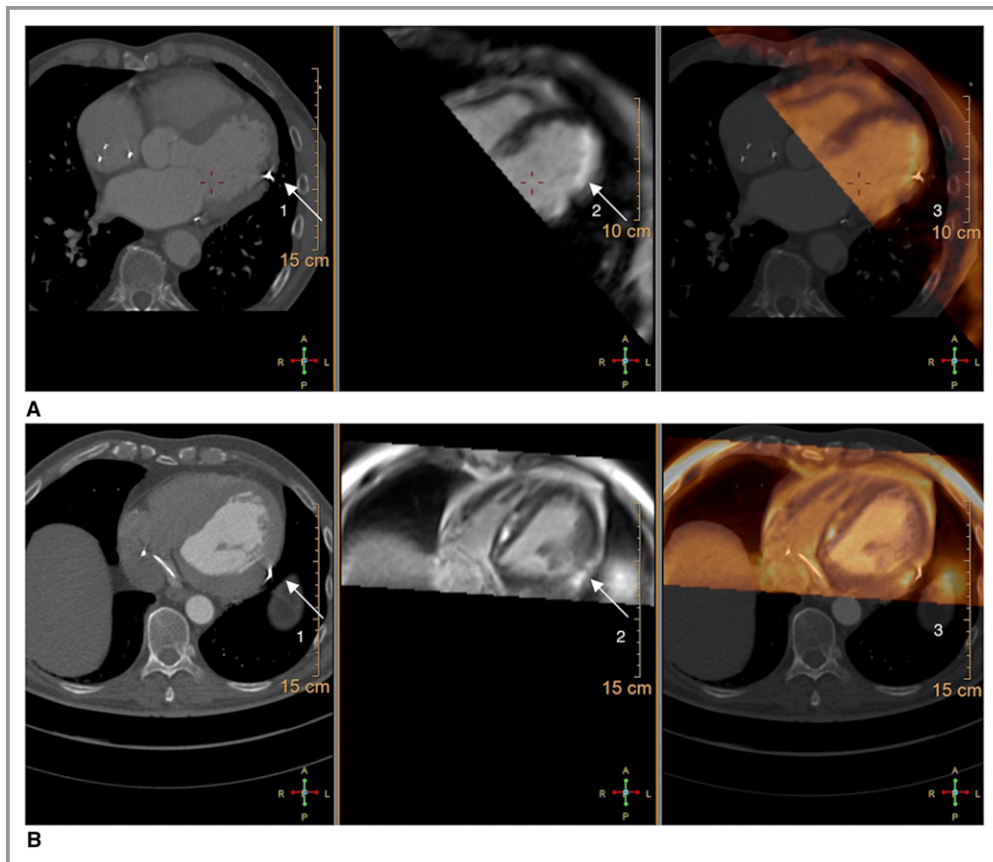


Figure 4. Localization of an LV pacing electrode within myocardial scar area in 2 patients (A and B) after MRI-CT scan image fusion. Arrow 1 shows LV electrode view in injected CT scan, arrow 2 indicates MRI LGE, and arrow 3 gives the location of the pacing electrode on the fusion image. CT scan indicates computed tomography scanner; LGE, late gadolinium enhancement; LV, left ventricle; MRI, magnetic resonance imaging.

CRT and Myocardial Scar

The quest for an optimal target area for implantation of LV leads in order to improve CRT response still remains a challenge. Even if better outcomes are observed when the LV lead is implanted in the lateral LV wall, multimodality imaging studies reveal that the optimal LV site for stimulation may differ from patient to patient and thus needs to be individually identified a priori.⁹ Indeed, LV pacing within myocardial scar areas is rare, but often harmful. Patients at higher risk are those with fibrosis located in the lateral segments,¹⁰ where the LV lead is usually positioned. We found the LV lead to be actually located in a scar area in 14% of cases, according to previous studies.^{10,11} LV pacing within scar zones has been shown to be associated with acute cardiac dysfunction¹² and absence of response to CRT.¹⁰ The choice of the LV lead implantation site is known to be a key parameter in CRT patients, with a delicate balance, in specific cases, between pacing in the more electromechanically delayed area¹³ and distance from myocardial scar.¹⁴ Multimodal approaches using a combination of different imaging techniques to localize the most delayed viable LV segment seem promising.⁹ However, coronary sinus and cardiac vein anatomy is highly variable, limiting options for LV lead positioning,¹⁵ and it is difficult to affirm that the LV lead is really positioned outside of a scarred area, because rough peroperative evaluation of final LV lead position, routinely performed by biplane fluoroscopy, remains highly questionable.^{2,16}

Image fusion between an MRI image with LGE and a postimplantation injected CT scan is a reliable technique that

Table 3. Patient Characteristics According to Presence of Scar Tissue at the LV Pacing Site

Variables	Electrodes Outside Scar* (n=47)	Electrodes Within Scar (n=3)
Age, y	66.7±10.9	62±7.9
Sex, women	17 (36.2)	0
Ischemic cardiomyopathy	16 (34)	2 (66.7)
ECG analyses		
QRSd, ms	166±18	151±17
Selvester score	4.8±2.6	5.7±2.5
Selvester lateral +	2 (4.3)	1 (33.3)
MRI analysis		
LVEF, %	26.9±6.7	33±2
EDLVV, mL/m ²	140.4±46.1	116±31

EDLVV indicates end diastolic left ventricular volume; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; QRSd, QRS duration.

*Patients without LGE in MRI or with a healthy myocardial implantation site of LV electrodes on MRI-CT scan image fusion.

Table 4. Per-Electrode (Cathode) ECG Analyses During Mono-LV Pacing (84 Electrodes in 22 Patients)

Variables	Electrodes Outside Scar (n=78)	Electrodes Within Scar (n=6)
Threshold, V	1.77±1.7	0.74±0.6
QRSd, ms	199±32	206±12
QRSd prolongation, %	115±19	142±14
IDD max, ms	146±30	145±14
IDD in V1, ms	127±35	143±15
Spike-to-QRS peak, ms	39±29	52±12
No capture (max output)	15	0

IDD indicates intrinsicoid deflection delay; QRSd, QRS duration.

precisely determines where each electrode, and not just roughly the whole lead, is located relative to scar tissue. This technique was easily performed in 100% of cases, with excellent visualization of each pacing electrode as a high-density “flashing bulge” on the CT scan.¹⁷ It may be proposed when myocardial scar, assessed by CMR imaging, is thought to lie in the neighborhood of the LV lead (lateral segments), in order to optimize device settings by selecting a pacing cathode within healthy tissue.

Electrocardiographic analyses may also be helpful. The Selvester score adapted to LBBB and the V2 S/S' ratio during intrinsic rhythm may help to select patients requiring further image fusion analyses.^{5,18}

We also showed that pacing within myocardial scar is not associated with higher pacing thresholds, contrary to a widespread idea. LV pacing threshold may then be more closely related to the amount of epicardial contact of the pacing cathode with the underlying myocardium, and/or the orientation of the pacing vector, than to the degree of fibrotic invasion of the underlying tissue. However, underlying scar tissue translates into a conduction delay, leading to a significant prolongation of the paced as compared with the intrinsic QRS. As a simple screening tool, a rather short QRSd prolongation during mono-LV pacing may then be associated with a favorable pacing site.

Perspectives

Based on these results, we propose a stepwise approach to help identify from simple ECG analyses those patients who may require additional imaging investigations (Figure 5). For that purpose, the Selvester score adapted to LBBB threshold was lowered to 3 to obtain a 90% negative predictive value (sensitivity, 97%; specificity, 23%). Before CRT implantation, patients with a Selvester score adapted to LBBB ≥ 3 are at risk of myocardial scar and therefore would require an MRI

to localize fibrosis. Conversely, if the score is <3 or if MRI shows no fibrosis in the lateral wall, no further exploration is needed and the lateral basal wall should be targeted as usual. After implantation, in case of nonresponse, or if lateral fibrosis is suspected, QRSD prolongation during mono-LV pacing can be assessed for each cathode. A QRSD prolongation <139% rules out LV pacing within scar tissue, whereas a QRSD prolongation ≥139% should entail precise CT-MRI image fusion in order to safely select an LV pacing cathode within healthy myocardium. QRSD prolongation may also be used during implantation for peroperative lead repositioning.

Quadripolar leads should be preferred to bipolar ones in most cases; twice as many pacing electrodes (and even more pacing configurations) and a roughly doubled distance between the more-proximal and the more-distal electrodes

facilitate pacing outside scar tissue with decent threshold and without phrenic nerve capture and provide better balance between stability and basal LV pacing position.

Limitations

The limited sample size was mainly attributed to a low prevalence of myocardial scar in lateral segments in this population of patients with typical LBBB, with a subsequent low number of electrodes actually within the scar. ECG analyses may incur inter- and intraobserver variabilities, beat-to-beat variations of QRS morphology attributed to pseudo-fusions, and complexity of score measurements. Further large, prospective studies may be needed to assess the potentially harmful consequences of LV pacing within scarred areas.

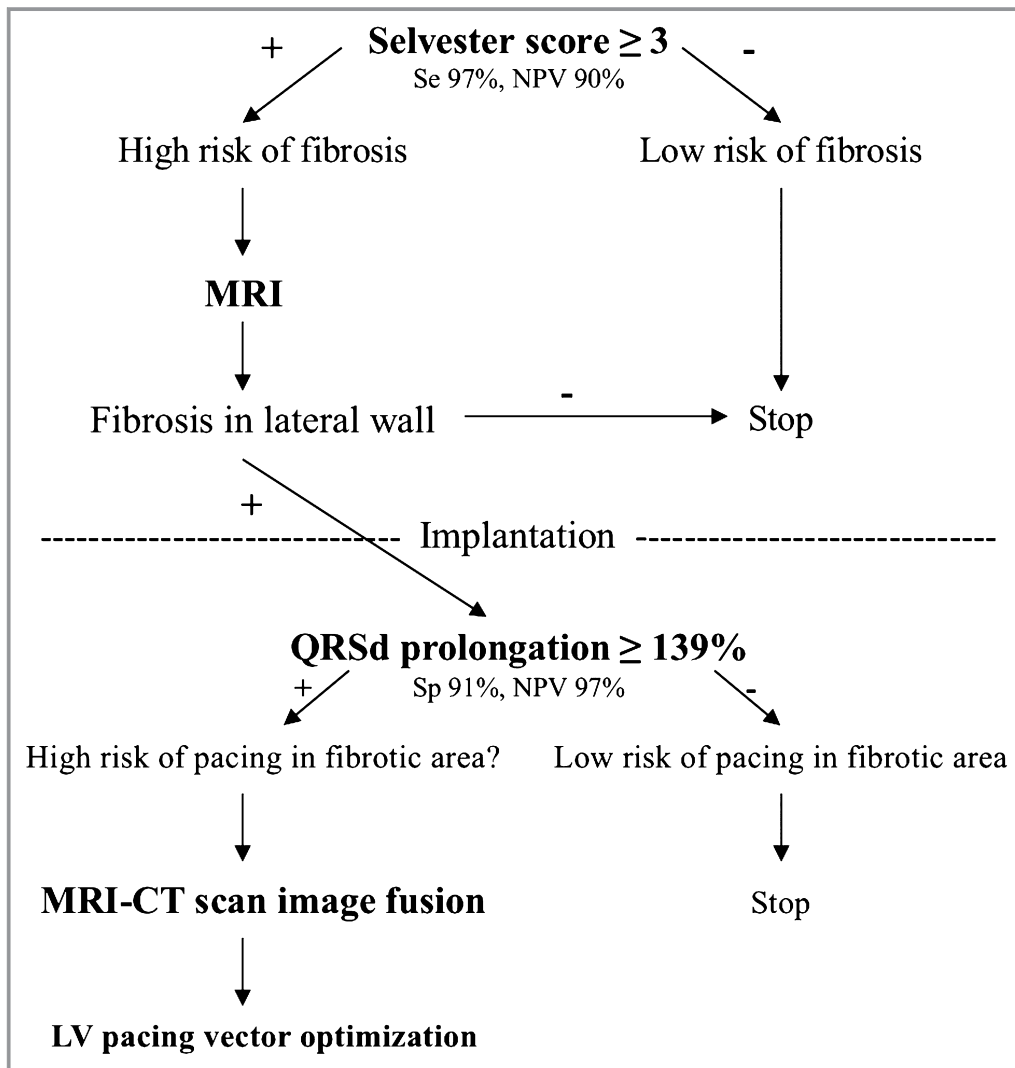


Figure 5. Stepwise approach for investigations to assess LV lead location relative to myocardial fibrosis area. CT scan indicates computed tomography scanner; LV, left ventricle; MRI, magnetic resonance imaging; NPV, negative predictive value; QRSD, QRS duration; Se, sensitivity; Sp, specificity.

Conclusions

In CRT patients, fusion between preimplantation CMR images and postimplantation injected CT scans is a feasible imaging technique. QRSD prolongation during LV pacing predicts pacing within myocardial scar tissue. Accurate location of each LV lead pacing electrode on the epicardial surface relative to myocardial scar, either by imaging or ECG analyses, may help improve CRT response in selected patients.

Disclosures

None.

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