Cardiac resynchronization therapy (CRT), with or without implantable cardioverter-defibrillator backup, has been shown to reduce mortality and heart failure (HF) hospitalization in patients with severe HF.1,2 CRT alone has also been shown to reduce sudden death, probably because of beneficial left ventricular (LV) remodeling and reduced ventricular arrhythmias.3 Despite this, CRT-induced proarrhythmia has been reported as a clinically serious, rare, and unpredictable phenomenon.4–7 Patients usually present with recurrent sustained ventricular tachycardia (VT)/electrical storm (ES), refractory to antiarrhythmic drugs, often accompanied with heart failure/cardiogenic shock.7 Although suppression of recurrent VT with catheter ablation has been reported,25 treatment most often required inactivation of LV pacing, depriving these patients of the beneficial effects of resynchronization.5,6 Prognosis is poor, even after control of recurrent VT, with a 50% mortality rate and frequent progression to refractory HF.7

Background—The mechanism of cardiac resynchronization therapy (CRT)–induced proarrhythmia remains unknown. We postulated that pacing from a left ventricular (LV) lead positioned on epicardial scar can facilitate re-entrant ventricular tachycardia. The aim of this study was to investigate the relationship between CRT-induced proarrhythmia and LV lead location within scar.

Methods and Results—Twenty-eight epicardial and 63 endocardial maps, obtained from 64 CRT patients undergoing ventricular tachycardia ablation, were analyzed. A positive LV lead/scar relationship, defined as a lead tip positioned on scar/border zone, was determined by overlaying fluoroscopic projections with LV electroanatomical maps. CRT-induced proarrhythmia occurred in 8 patients (12.5%). They all presented early with electrical storm (100% versus 39% of patients with no proarrhythmia; P<0.01), requiring temporary biventricular pacing discontinuation in half of cases. They more frequently presented with heart failure/cardiogenic shock (50% versus 7%; P<0.01), requiring intensive care management. Ventricular tachycardia was re-entrant in all. The LV lead location within epicardial scar was significantly more frequent in the proarrhythmia group (60% versus 9% P=0.03 on epicardial bipolar scar, 80% versus 17% P=0.02 on epicardial unipolar scar, and 80% versus 17% P=0.02 on any-epicardial scar). Ablation was performed within epicardial scar, close to the LV lead, and allowed CRT reactivation in all patients.

Conclusions—CRT-induced proarrhythmia presented early with electrical storm and was associated with an LV lead positioning within epicardial scar. Catheter ablation allowed for resumption of biventricular stimulation in all patients. (Circ Arrhythm Electrophysiol. 2014;7:1064-1069.)

Key Words: cardiac resynchronization therapy ■ catheter ablation ■ tachycardia, ventricular

Electrical Storm Induced by Cardiac Resynchronization Therapy Is Determined by Pacing on Epicardial Scar and Can be Successfully Managed by Catheter Ablation

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Background—The mechanism of CRT-induced proarrhythmia remains unknown. Some authors have suggested that prolongation of the transmural dispersion of repolarization, by reversal of the activation sequence caused by LV epicardial pacing, can promote polymorphic VT9,10 while others have indicated re-entry as the likely mechanism.4,8

We report our experience in managing CRT-induced proarrhythmia with catheter ablation and postulate that pacing from the epicardium using an LV lead positioned on scar could influence critical components of a re-entrant circuit and induce re-entrant VT. For that purpose, the relationship between

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CRT-induced proarrhythmia and LV lead tip location within scar was investigated.

Methods
Consecutive patients between January 2010 and May 2013 with a CRT device and drug-refractory VT, undergoing VT ablation at San Raffaele VT Unit, were included. The study was approved by the institutional review committee, and all patients gave written informed consent.

CRT-Induced Proarrhythmia
The presence of CRT-induced proarrhythmia was determined using presentation characteristics, archived clinical records, and device interrogation. Patients were classified as CRT-induced proarrhythmia or no CRT-induced proarrhythmia. The definition used was based on previously published series. In primary prevention, CRT-induced proarrhythmia was defined as VT or ES within 1 month of implantation. ES was defined as ≥3 VT episodes requiring implantable cardioverter-defibrillator shock within 1 day. In secondary prevention, proarrhythmia was considered positive if there had been no VT in the previous 3 months and ES occurred within 1 month of implantation. Patients in whom the temporal relationship between implant and VT occurrence could not be ascertained were excluded. Patients in whom the occurrence of VT was considered unrelated to the implant were classified as no CRT-induced proarrhythmia.

Mapping and Ablation Procedure
Patients underwent VT ablation using the Carto 3 ( Biosense Webster, Diamond Bar, CA) or EnSite Velocity (St. Jude Medical Inc., Milwaukee, WI) 3-dimensional electroanatomical mapping systems. In a subset of 11 patients, the CartoUniv module was available. Ablation was performed using double LV endocardial (retrograde aortic and transseptal) and epicardial access. High-density (interpolation fill threshold of 5 mm in scar areas and 10 mm elsewhere) LV substrate mapping was undertaken. Normal bipolar and unipolar voltages were defined as ≥1.5 and ≥28 mV, scar as an area with a signal amplitude ≤0.5 and ≤5 mV, and border zone (BZ) as areas with a bipolar and unipolar voltage of 0.5 to 1.5 and 5 to 8 mV, respectively, both in endocardium and epicardium. Our standard ablation strategy was used which involved targeting late potentials and induced VT, aiming for VT noninducibility and complete late potential abolition as end points.

Determination of the Relationship Between the LV Lead Position and Scar
The LV lead position was visualized using stored anteroposterior, 30° left and 30° right anterior oblique fluoroscopic projections. The images were overlaid with the same projection of the LV electroanatomical map obtained from the ablation procedure to ascertain the lead location with respect to scar. A positive lead/scar relationship was defined as the LV lead tip being positioned within scar or BZ. The presence of a lead/scar relationship was assessed in epicardial bipolar (epi-bi), epicardial unipolar (epi-uni), endocardial bipolar (endo-bi), and endocardial unipolar (endo-uni) maps. A lead/scar relationship with any-epicardial (epi-bi or epi-uni) and any-endocardial scar (endo-bi or endo-uni) was also assessed. In patients undergoing ablation with the CartoUniv module, which allows online superimposition of the electroanatomical map and fluoroscopic images, the location of the lead with respect to scar was directly visualized. A pre-study analysis in this subgroup was undertaken using the CartoUniv system to validate the accuracy of the fluoroscopy method: all LV lead/scar relationships (for epi-bi, epi-uni, endo-bi, and endo-uni maps) were performed separately by both methods, and a comparison of results was undertaken. The 8 true positive, 21 true negative, 2 false positive, and 1 false-negative matches obtained, yielded an 89% sensitivity and 91% specificity for the fluoroscopy method, indicating successful validation. All relationships were determined by 2 observers blinded to the proarrhythmia history. Borderline cases were determined by a third observer. The presence of lead/scar relationships were compared between patients with and without proarrhythmia.

Statistical Analyses
Continuous variables are presented as means±SD or medians (25th and 75th percentiles) and categorical variables as frequencies and percentages. Comparisons between groups were undertaken using the t test or non-parametric tests for continuous variables and Fisher exact test for proportions. Power analysis in this sample size was undertaken using G*Power (Version 3.1), yielding a power of 0.80 for the primary outcome. The data were analyzed using the SAS System (version 9.4, SAS Institute, Cary, NC) and Stata software (Version 13.1, StataCorp LP, College Station, TX). All analyses were performed on an intention-to-treat basis. A 2-sided P<0.05 was considered statistically significant.

Results
Seventy-four consecutive patients with a transvenously implanted CRT and drug-refractory VT/ES requiring ablation were included. Three patients were excluded because of an initial unexplained temporal relationship between implant and first VT. Seven patients were excluded because of insufficient electroanatomical mapping point density at the LV lead location. A total of 28 epicardial and 63 endocardial maps in 64 patients were included.

Patient Characteristics
CRT-induced proarrhythmia occurred in 8 patients (12.5%), all presenting with monomorphic VT, that was incessant in 5 patients (63%). Their clinical features are reported in Table 1.

<p>| Table 1. Characteristics of the Patients With Proarrhythmia |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Pathogenesis</th>
<th>LVEF</th>
<th>First Device</th>
<th>Prevention</th>
<th>Time to First VT</th>
<th>HF</th>
<th>LV Lead Inactivation</th>
<th>Access Type</th>
<th>Ablation Strategy</th>
<th>Lead/Scar Relation</th>
<th>LV Lead Reactivated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76 M</td>
<td>Ischemic</td>
<td>22</td>
<td>ICD</td>
<td>Secondary</td>
<td>Post-op</td>
<td>No</td>
<td>No</td>
<td>Endo</td>
<td>LP</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>67 M</td>
<td>IDCm</td>
<td>28</td>
<td>CRT-D</td>
<td>Secondary</td>
<td>Post-op</td>
<td>No</td>
<td>No</td>
<td>Endo-uni</td>
<td>PM</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>50 M</td>
<td>IDCm</td>
<td>20</td>
<td>ICD</td>
<td>Secondary</td>
<td>3 d</td>
<td>No</td>
<td>Yes</td>
<td>Endo-uni</td>
<td>VTM</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>59 F</td>
<td>IDCm</td>
<td>25</td>
<td>CRT-D</td>
<td>Primary</td>
<td>26 d</td>
<td>Yes</td>
<td>Yes</td>
<td>Endo-uni</td>
<td>VTM+LP</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>59 M</td>
<td>Ischemic</td>
<td>30</td>
<td>CRT-D</td>
<td>Primary</td>
<td>Same day</td>
<td>Yes</td>
<td>Yes</td>
<td>Endo-uni</td>
<td>VTM+LP</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>70 M</td>
<td>Ischemic</td>
<td>15</td>
<td>CRT-D</td>
<td>Primary</td>
<td>Same day</td>
<td>Yes</td>
<td>Yes</td>
<td>Endo-uni</td>
<td>LP</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>66 M</td>
<td>Valvular</td>
<td>15</td>
<td>ICD</td>
<td>Primary</td>
<td>Same day</td>
<td>Yes</td>
<td>No</td>
<td>Endo-uni</td>
<td>VTM+LP</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CRT-D indicates cardiac resynchronization therapy with a defibrillator; endo, endocardial; endo-uni, endocardial unipolar; F, female; HF, heart failure; ICD, implantable cardioverter-defibrillator; IDCm, idiopathic dilated cardiomyopathy; LP, late potentials; LV, left ventricle; LVEF, LV ejection fraction; M, male; PM, pacemapping; VT, ventricular tachycardia; and VTM, VT mapping.
In the overall population, the time from implant to first VT was 225 (3–730) days; however, it was shorter in the proarrhythmia group at only 0.5 (0–2.5) days. Fifty percent (4 patients) had been upgraded from an implantable cardioverter-defibrillator. Comparisons between patients with and without proarrhythmia are presented in Table 2. The proarrhythmia group had a higher proportion of unipolar and quadripolar leads implanted ($P=0.02$). All LV lead types were present at similar proportions in the proarrhythmia group. Patients with proarrhythmia had lower LV ejection fraction (22±6 versus 28±7%; $P=0.03$). All patients with proarrhythmia presented in ES versus 39% of patients with no proarrhythmia ($P<0.01$). Half of patients with proarrhythmia presented with acute HF or cardiogenic shock versus 7 percent in the no proarrhythmia group ($P<0.01$). All patients with proarrhythmia required intravenous amiodarone and lidocaine. Intensive care unit management was necessary in 5 patients (63%) because sedation was required and general anesthesia was ultimately needed in 3 (38%) to control ES. Fifty percent (4 patients) required intra-aortic balloon pump support. Vasopressors and additional calcium sensitizing agents (levosimendan) were required in 4 (50%) and 2 patients (25%), respectively. The LV lead was deactivated in half of cases. In the remaining, a proarrhythmic mechanism was not initially recognized, and they soon proceeded to VT ablation. No attempt to reposition the LV lead was undertaken, as a management strategy based on hemodynamic stabilization followed by endo-epicardial ablation was adopted.

### Catheter Ablation for CRT-Induced VT

In all patients with proarrhythmia, monomorphic VT was inducible (mean cycle length 447±110 ms; median number of VTs induced 3 [2–4], median number of VTs ablated 2 [1–2]) and entrainment proved re-entry as the causative mechanism. An epicardial approach was performed in all but 3 patients, in whom it was avoided because of prior cardiac surgery. After detailed substrate mapping, the ablation strategy included VT mapping in 5 patients and abolition of late potentials during sinus rhythm in 4 and 2 patients, respectively. Ablation was performed within the epicardial scar, in close proximity to the LV lead, in 4 (80%) patients undergoing an epicardial procedure (Figures 1 and 2). Proximity of coronary arteries precluded complete late potential abolition in 3 patients, in which ablation was therefore also applied endocardially (Figure 2). In the 3 patients with only endocardial access, ablation was performed within endocardial scar/BZ. Except for 1 patient with a quadripolar lead (Figure 2) in which loss of LV capture from the proximal bipoles occurred, no impact of ablation on lead parameters was observed. In all patients, ablation allowed for the maintenance of biventricular stimulation, previously deactivated in 4 for ES suppression. During a median follow-up period of 10 (6–25) months, 1 patient with severe LV pump failure who refused a ventricular assist device died 2 weeks...
after discharge without further recurrences. The remaining patients with proarrhythmia are alive.

LV Lead/Scar Relationship and Proarrhythmia

Epicardial Scar (28 Patients)
The LV lead was located on epicardial scar in the majority of patients with proarrhythmia (Table 3). A relationship between the LV lead position and epi-bi scar was found in 3 of 5 (60%) patients with proarrhythmia versus 2 of 23 (9%) patients without proarrhythmia ($P=0.03$). The LV lead was located on epi-unipolar scar in 4 of 5 (80%) patients with proarrhythmia versus 4 of 23 (17%) patients without proarrhythmia ($P=0.02$). A relationship between the LV lead position and any-epicardial scar was found in 4 of 5 (80%) patients with proarrhythmia versus 4 of 23 (17%) patients without proarrhythmia ($P=0.02$).

Endocardial Scar (63 Patients)
A location of the LV lead within endocardial scar was not statistically different between groups (Table 3). The LV lead was positioned opposite the endo-bi scar in 3 of 8 (38%) patients with proarrhythmia versus 7 of 55 (13%) patients without proarrhythmia ($P=0.11$). A relationship between the LV lead position and endo-unipolar scar was found in 5 of 8 (62%) patients with proarrhythmia versus 19 of 55 (35%) patients without proarrhythmia ($P=0.10$). A relationship between the LV lead position and anyendocardial scar was found in 6 of 8 (75%) patients with proarrhythmia versus 20 of 55 (36%) patients without proarrhythmia ($P=0.06$). Kappa coefficient was 0.92 for epi-bi maps, 1 for epi-unii, 0.81 for endo-bi, and 0.93 for endo-uni maps.

Discussion
CRT-induced proarrhythmia is an uncommon but life-threatening complication of CRT implantation frequently causing ES and hemodynamic deterioration. This study provides new insights into the mechanisms of this condition, raising the hypothesis that an LV lead positioned on epicardial scar could be a determinant of proarrhythmia. The data from this study confirm that CRT-induced proarrhythmia presents with ES and is a clinically malignant event, occurring in patients with an advanced state of LV depression and causing further compromise into states of severe HF and cardiogenic shock. However, it is still an under recognized phenomenon in clinical practice, which reinforces the need to comprehend its mechanism to identify its occurrence and develop strategies to avoid proarrhythmia.

Identifying High-Risk Patients
ES was shown to occur as an early event. According to the data of our study, it is rare for CRT-induced proarrhythmia to develop later than 3 days after the implant. This early presentation is indicative that recurrent VT relates directly to pacing, as opposed to progression of an underlying cardiomyopathy or a reflection of end-stage HF. This suggests that a more prolonged period of in-hospital monitoring after institution of CRT might be considered, should a postimplant ES occurs.
Mechanism: LV Lead Position as a Determinant of Proarrhythmia

The electrophysiological findings (monomorphic and inducible VTs, ablation guided by entrainment and completed by ablation of local late potentials) strongly support intramycardial re-entry as the mechanism. In this setting, a close spatial relationship of the LV lead to the scar appeared to be critical for the development of proarrhythmia. The relationship between the pacing lead and the potentially proarrhythmic tissue can evolve with remodeling or later scaring, and thus, one cannot exclude that this mechanism may be still responsible for ventricular arrhythmia developing later after implantation, even if in the last case it would be hardly suspected clinically. The influence of LV lead position on the risk of ventricular arrhythmias was evaluated in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) trial.13 In this cohort of 797 patients, an anterior location was associated with a higher risk of arrhythmic events compared with posterior or lateral locations. Patients with anterior lead positions had more prior myocardial infarctions than patients with lateral and posterior locations. In our study, in which the relation between the LV lead position and the scar was specifically investigated, the LV lead location within epicardial scar was significantly more frequent in the proarrhythmia group. Invariably, in our series, the effective ablation site was coincident with the scar, and in 5 of 8 cases, epicardial ablation was required to modify effectively the arrhythmogenic substrate and prevent recurrence.

Strategies to Avoid Proarrhythmia

Practical implications of these observations include accurate preprocedural imaging to avoid placing the LV lead in close proximity to the scar/BZ. Avoiding an LV lead position that causes a long stimulus to QRS interval (>40ms) during implant threshold testing also seems advisable, as it likely corresponds to re-entry circuit slow conduction zones.15 The use of multipolar LV leads may offer a substantial advantage in this setting, allowing a broader choice of stimulus sites, should the initial choice prove arrhythmogenic. Direct surgical epicardial lead placement undertaken via a limited thoracotomy may provide an alternative approach to place the LV lead outside the scar/BZ area.

Management of CRT-Induced Proarrhythmia

Conventional manoeuvres usually include deactivation of LV stimulation and antiarrhythmic drugs, both potentially leading to worsening HF.5,7 Beyond these manoeuvres, a satisfactory hemodynamic stabilization was achieved by the early institution of sedation or general anesthesia and hemodynamic support, as dictated by our management strategy within a dedicated ventricular arrhythmia unit.13

The strategy of detailed substrate analysis and modification by catheter ablation appeared highly effective in preventing arrhythmia recurrence, and most importantly, allowed the reestablishment of CRT therapy. Because of the distinct mechanism of the arrhythmia, a first line endo-epicardial approach seems highly indicated. Successful ablation was usually achieved with radiofrequency applications within the epicardial scar where the LV lead was located, targeting both VT and late potentials. The proximity of the coronary arteries or phrenic nerve may sometimes limit a complete epicardial substrate ablation, necessitating either specific manoeuvres or concomitant endocardial ablation, as circuit configurations involving subepicardial, intramural, and subendocardial re-entry pathways may be involved.

Limitations

This study was undertaken in a single dedicated VT referral unit. Because CRT-induced proarrhythmia is rare, and referral to a VT unit is expected because of the frequent association with ES, VT centers could in fact represent a unique opportunity to gather and study these patients. There is an inherent referral bias because of the noninclusion of CRT recipients without VT or those managed medically. However, the methodology used in this study (extensive endocardial and epicardial LV mapping)
would be inapplicable in these less symptomatic patients, and other less invasive methods for LV lead/scar relationship analysis would be needed in this population. We acknowledge that the small number of patients with proarrhythmia in our study can be a limitation. The use of different methodologies to assess the lead/scar relationship constitutes a limitation. However, we highlight the fact that the fluoroscopy method used in our study was successfully validated by the CardioUniv in a prestudy analysis, and thus, its use seems acceptable in patients undergoing ablation before the availability of the former system.

Conclusions

CRT-induced proarrhythmia presents with ES that related to re-entry in all cases. A proarrhythmia history was associated with an LV lead position within epicardial scar. In our series, ES was successfully managed with acute stabilization in an intensive care unit setting followed by epicardial catheter ablation, allowing for the maintenance of biventricular pacing and acute survival in all patients.

Acknowledgments

We would like to thank all the staff at the San Raffaele VT Unit and intensive care unit for their tireless work and professionalism.

Disclosures

Dr Bella is a consultant for St. Jude Medical and has received honoraria for lectures from Biosense Webster, St Jude Medical, and Biotronik. Drs Silberbauer and Oloriz are Advanced European Intensive Care Unit for their tireless work and professionalism. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

Despite the proven benefits of cardiac resynchronization therapy (CRT) on heart failure morbidity and mortality, cases of CRT-induced proarrhythmia have been reported. Although rare, it is described as a clinically malignant condition, presenting with recurrent sustained ventricular tachycardia/electrical storm, refractory to antiarrhythmic drugs and often associated with cardiogenic shock. The mechanism of this arrhythmia is still unknown, a treatment strategy is lacking, and this poor prognosis entity remains under recognized in clinical practice. In this study, we report our experience in managing CRT-induced proarrhythmia in a dedicated ventricular tachycardia unit, and we raise the hypothesis that pacing from the epicardium using a left ventricle lead positioned on epicardial scar can be a responsible mechanism. In our cohort, all patients with proarrhythmia presented with electrical storm, associated with heart failure cardiogenic shock in half of cases. The treatment strategy included acute stabilization in an intensive care unit setting with multiple antiarrhythmic drugs and early institution of sedation/general anesthesia and hemodynamic support, followed by endo-epicardial substrate catheter ablation. In most cases, ablation was successfully achieved with radiofrequency applications within the epicardial scar where the left ventricle lead was located. This strategy allowed reestablishment of CRT and acute survival in all patients. The left ventricle lead was more frequently located within epicardial scar in the proarrhythmia group (80% versus 17%; P = 0.02). This finding, along with the early presentation of re-entrant ventricular tachycardia and its successful ablation within epicardial scar, warrants further investigation on the hypothesis of pacing epicardial scar as a possible mechanism for CRT-induced proarrhythmia.
Electrical Storm Induced by Cardiac Resynchronization Therapy Is Determined by Pacing on Epicardial Scar and Can be Successfully Managed by Catheter Ablation

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