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Endo-Epicardial Homogenization of the Scar Versus Limited Substrate Ablation for the Treatment of Electrical Storms in Patients With Ischemic Cardiomyopathy

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Objectives This study investigated the impact on recurrences of 2 different substrate approaches for the treatment of these arrhythmias.

Background Catheter ablation of electrical storms (ES) for ventricular arrhythmias (VAs) has shown moderate long-term efficacy in patients with ischemic cardiomyopathy.

Methods Ninety-two consecutive patients (81% male, age 62 ± 13 years) with ischemic cardiomyopathy and ES underwent catheter ablation. Patients were treated either by confining the radiofrequency lesions to the endocardial surface with limited substrate ablation (Group 1, n = 49) or underwent endocardial and epicardial ablation of abnormal potentials within the scar (homogenization of the scar, Group 2, n = 43). Epicardial access was obtained in all Group 2 patients, whereas epicardial ablation was performed in 33% (14) of these patients.

Results Mean ejection fraction was 27 ± 5. During a mean follow-up of 25 ± 10 months, the VAs recurrence rate of any ventricular tachycardia (VTs) was 47% (23 of 49 patients) in Group 1 and 19% (8 of 43 patients) in Group 2 (log-rank p = 0.006). One patient in Group 1 and 1 patient in Group 2 died at follow-up for noncardiac reasons.

Conclusions Our study demonstrates that ablation using endo-epicardial homogenization of the scar significantly increases freedom from VAs in ischemic cardiomyopathy patients. (J Am Coll Cardiol 2012;60:132–41) © 2012 by the American College of Cardiology Foundation

Patients with ischemic heart disease and reduced left ventricular systolic function are at high risk for developing sustained ventricular arrhythmias (VAs) and sudden cardiac death (1). Ventricular monomorphic tachycardia is the most common arrhythmia in these patients, and reentry is the most common underlying mechanism (1). Implantable cardioverter-

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defibrillators (ICDs) are mandatory in these patients and have shown efficacy in reducing mortality (1). However, several studies suggest that ICD shocks may reduce quality of life and increase mortality (1, 2). In order to reduce ICD shocks and improve quality of life, antiarrhythmic drugs (AADs) can be administered in these patients, although with several side effects and unsatisfactory results (1). The presence of the ICD allowed us to define a condition of ventricular instability characterized by the presence of multiple VAs in a brief period of time (3). Electrical storm (ES) is defined as the occurrence of ≥3 episodes of sustained VA requiring ICD intervention in the 24 h (3). In patients with secondary prophylaxis ICD implantation, the reported incidence of ES ranges from 10% to 40%, whereas in the primary prevention group, the range is between 3% and 5% (3–9). The clinical management of these patients involves multiple treatment modalities, including medical treatment with AADs and antiadrenergic drugs, catheter ablation, and sophisticated systems for hemodynamic support (4). The reported mortality at follow-up is high, and the ES has been reported as a predictor for cardiovascular death (6,10–12).

In order to improve quality of life and reduce the VA episodes, catheter ablation has been considered as a valid treatment option in addition to medical treatment in this setting, although only a moderate long-term efficacy at follow-up has been reported (13,14). These procedures are very challenging due to technical aspects, hemodynamic intolerance, and the complex arrhythmia substrates (4,14).

The complex anatomy of the endocardial scar and multiple potential reentrant pathways as well as initiators represents the main limitations of VAs ablation (15–19). This is why a limited substrate ablation might abolish circuits relevant to the arrhythmia burden at the time of the procedure (4,14). However, whether more extensive ablation targeting every area showing diseased recordings could be more successful at long term is unknown.

We sought to investigate the impact on recurrences of 2 different substrate approaches for the treatment of these arrhythmias.

Methods

Patient population. Ninety-two consecutive patients with ischemic cardiomyopathy and ES (defined as ≥3 ICD interventions in 24 h) undergoing ablation at 5 different institutions were enrolled in this prospective study. All patients had an ICD before the ablation and suffered from ES despite AADs such as beta-blockers, dofetilide, amiodarone, mexiletine, sotalol, and ICD therapies. Exclusion criteria included severe renal insufficiency, mobile left ventricle thrombus, unstable angina, severe aortic stenosis and end-stage heart failure (New York Heart Association functional class IV with a limited survival expectation at 12 months), previous coronary artery bypass graft, age <18 years, and prior failed VA ablations.

From March 2007 to August 2008, consecutive patients were treated only by confining the radiofrequency lesions to the endocardial surface with limited substrate ablation (Group 1, n = 49, conventional ischemic ventricular tachycardia [VT] ablation), whereas from September 2008 to December 2009, consecutive patients were treated by endocardial and epicardial ablation of all potentials within and around the scar (homogenization procedure, Group 2, n = 43).

The study was approved by the Institutional Review Board at each participating center, and all patients signed an informed written consent.

Abbreviations and Acronyms

AAD = antiarrhythmic drug
CI = confidence interval
ECG = electrocardiogram
ES = electrical storm
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia

Electrophysiology study and catheter ablation. All patients underwent the procedure in the fasting state under conscious sedation. Arterial blood pressure and O_2 saturation monitoring was obtained in all patients. Antiarrhythmic medications were stopped several days before the procedure when applicable. Standard transvenous multipolar catheters were placed into the cardiac chambers appropriate for the arrhythmia being studied.

In all patients in Group 2 before ablation and systemic heparinization, and only when required in patients in Group 1 (after systemic heparinization reversal, see later text), subxiphoid epicardial access was obtained by fluoroscopic guidance as previously described (20).

Before epicardial ablation, coronary angiography was performed at operator's discretion to avoid coronary artery damage. Epicardial phrenic nerve capture was identified by eliciting diaphragmatic stimulation with bipolar pacing at 20 mA with a pulse width of 10 ms from the distal pole of the ablation catheter.

Endocardial mapping was performed in all patients, whereas epicardial mapping was performed once the epicardial space was accessed in all Group 2 patients. Mapping in the coronary sinus was performed via the femoral vein approach. Left ventricular mapping was performed via the retrograde aortic or transseptal approach.

Tridimensional electroanatomical maps (CARTO, Biosense Webster, Diamond Bar, California), including activation and voltage map, were obtained in sinus rhythm and/or during hemodynamically stable VT with the 3.5-mm open irrigated tip catheter (Biosense Webster) in all patients with the fill threshold setting at 15 mm. Intracardiac signals were filtered at 30 to 400 Hz.

All patients underwent bipolar substrate mapping with standard scar settings defined as normal tissue greater than 1.5 mV and severe scar <0.5 mV. Dense scar was defined as areas with amplitudes less than the baseline noise level of the recording system, and these areas were color coded as

gray. Maps included more points around areas of scar, particularly focusing on the scar border and electrograms within the scar. Normal tissue was less densely mapped. Areas of fractionated or late potentials were tagged with dots colored to denote the electrograms type. These notations were done irrespective of the voltage obtained. Maps were considered complete when the entire chamber of interest was completely mapped and all scar borders were clearly defined. Intracardiac echocardiography was used to assist in defining mechanical structures, monitoring for potential complications, and assisting in trans-septal puncture.

In both groups, ablation was performed using an open irrigated 3.5-mm catheter. In Group 1, ablation was performed at putative VT(s) exit site(s) for at least 1 min until local electrogram abatement and/or loss of capture (high-output pacing up to 20 mA with a pulse duration of 10 ms) were achieved, with up to 50 W and a temperature limit of 40°. In Group 2, ablation was performed at each single site showing abnormal electrograms for at least 30 s with up to 50 W and a temperature limit of 40° if the abnormal potential disappeared quickly, but it was prolonged in case of persistent recordings.

The radiofrequency parameters in the epicardium were the same as in the endocardium. Systemic anticoagulation was achieved by intravenous heparin with a minimum activation clotting time of 300 s.

No specific anticoagulant therapy was instituted after ablation, although all patients were under treatment with either aspirin or clopidogrel (or both).

Ablation in Group 1. STANDARD VT ABLATION. Conventional mapping techniques including pace mapping, activation mapping, and entrainment mapping were used to define the mechanism of the arrhythmias and identify potential sites for ablation. After substrate mapping was completed, an electrophysiology study was performed with the intention of inducing the clinical VT. The clinical tachycardia was defined as matching the clinical cycle lengths and morphology seen on the 12-lead electrocardiograms (ECGs) and on the ICD interrogation when available.

Programmed ventricular stimulation was performed including 3 extra stimuli from 2 different right ventricle sites, burst pacing, and using medications such as intravenous isoproterenol (up to 5 μg/min). If the clinical tachycardia was not inducible, pacing was performed within the area of scar. Once a VT was induced, standard activation/entrainment mapping were performed (if tolerated), and ablation was performed until the VT was no longer inducible. After that, the stimulation protocol was repeated and continued until refractoriness of the 3 extrastimuli or induction of ventricular fibrillation (VF) from 2 different sites. Earliest activation was defined in reference to a surface ECG lead. If possible, complete activation maps of the chamber of interest were performed. Furthermore, entrainment mapping and pace mapping techniques were used to confirm appropriate ablation sites. Ablation was performed at the optimal ablation sites based on the preceding criteria, preferentially in tachycardia to observe cycle length slowing and termination. The target for ablation of tolerated VTs was identified by mid-diastolic electrograms and confirmed by entrainment with concealed fusion. Potential channels within the scar were identified by substrate mapping and targeted only when confirmed to be part of the VT circuits by entrainment mapping. Short linear ablation lesions were placed across the VT isthmus to terminate any inducible VTs (14).

In patients who did not tolerate the ventricular tachycardia, we adopted a stepwise approach consisting of the following: 1) programmed ventricular stimulation to induce the clinical VT; 2) localization of the myocardial infarct through 3-dimensional electroanatomical voltage mapping; and 3) selective targeting of the potentially "arrhythmogenic areas" of the infarct with catheter ablation based on the morphology of the clinical VT and the induced VTs. The 12-lead ECGs were obtained for all inducible arrhythmias. Therefore, a high-density 3-dimensional substrate map of the left ventricle was obtained. Once the substrate map was constructed, we used a standardized approach to identify the limited regions of the infarct that represented the arrhythmogenic tissue to selectively target for catheter ablation. The most widely adopted approach was pace mapping during sinus rhythm or ventricular pacing (in case of pacemaker-dependent rhythm) predominantly along the infarct border zone, as defined according to voltage criteria on 3-dimensional map (i.e., bipolar voltages between 0.5 and 1.5 mV). Multiple pace-mapping points (at least 20 collected approximately 5 mm apart, ranging from 20 to 40) were acquired in each patient, moving the catheter along the scar. The pace-mapping points showing with the best match with the clinical/induced VT morphology were tagged in a different color. The site with a paced 12-lead QRS morphology matching >10/12 ECG leads of an inducible monomorphic VT was presumed to be the exit site of that VT and was targeted for ablation with short linear lesions. The latter were performed starting from the scar border zone toward the center of the substrate (dense scar) and composed of multiple and contiguous sequential lesions. The lesions were empirically extended to cover all the presumed VT(s) exit site(s), according to previously collected pace mapping data.

Activation maps were also attempted in patients who could only tolerate short periods of VT and was limited to the area of abnormal electrograms. Every effort was exercised to also adopt entrainment mapping if the monomorphic VT was at least transiently hemodynamically stable.

In patients with persistent inducibility after endocardial ablation, epicardial access, mapping, and ablation were performed. In this subset of patients, systemic heparinization was reversed with protamine before obtaining the epicardial access.

Regarding the mapping procedure, once scar was defined, the isthmus of slow conduction was identified by activation and entrainment mapping when applicable. In the case of nontolerated VTs, ablation was performed guided by electroanatomical mapping and pace mapping, limiting the

applications to the site of origin of the VTs (Fig. 1). Cardiopulmonary support was used in 4 patients with the left ventricle assist device (Impella Recover LP 2.5, ABIOMED, Inc., Danvers, Massachusetts) due to prolonged hypotension after repeated VT inductions and external cardioversions. As previously mentioned, in this group, the mean duration of each ablation lesion was longer compared with the homogenization group and lasted for at least 1 min. After ablation, programmed electrical stimulation with and without isoproterenol was repeated as previously described. Any reliably inducible VTs were targeted for further ablation, and the entire stimulation protocol was repeated subsequently until the endpoint was achieved.

Ablation in Group 2. HOMOGENIZATION OF THE SCAR. Both voltage and activation mapping procedures were the same as previously described except for careful identification of fractionated or delayed electrograms. The purpose of activation mapping was to confirm that the VT was associated with the identified scars. In this group, based on the substrate map, ablation was empirically extended throughout the entire scar (homogenization of the scar) endocardially. In addition to voltage criteria, "abnormal" electrograms both in the endocardium and the epicardium including delayed and fragmented recordings were targeted. Epicardially, we targeted the area presenting abnormal recordings when it contained at least 3 abnormal electrograms. After endocardial ablation, the epicardial scar was remapped, and if areas of abnormal recordings were still present, then ablation was performed. In this regard, "normal" electrograms were defined as electrograms with 3 or fewer sharp and discrete deflections from baseline, amplitude >1.5 mV, duration <70 ms (and/or ratio amplitude/duration >0.046) (21). Any electrograms not fitting the latter definition were categorized as "abnormal" and targeted for ablation. In the presence of dense scar at the noise level, no ablation was delivered, and epicardial homogenization was performed only in patients showing large areas of epicardial delayed or fractionated potentials.

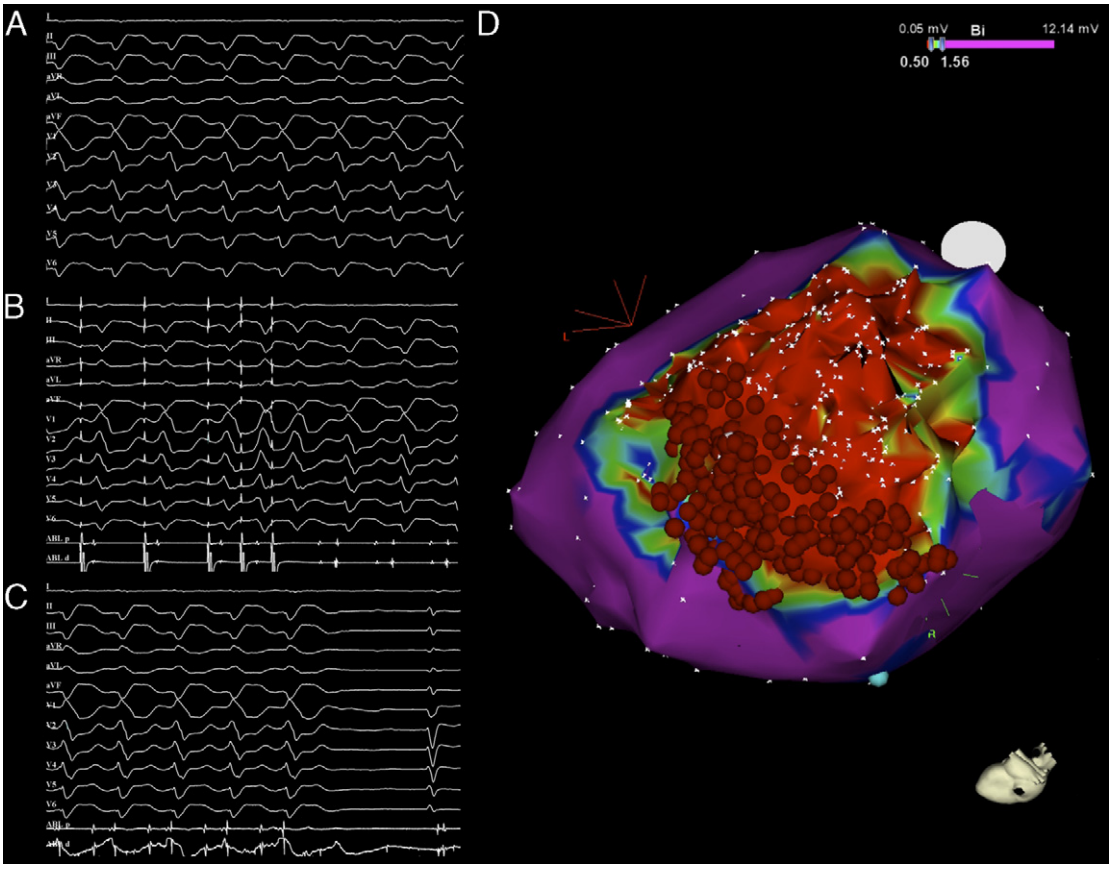

Figure 1 VT Ablation in a Patient From Group 1

(A) The 12-lead electrocardiogram (ECG) of the ventricular tachycardia (VT). **(B)** Induction of the VT with programmed ventricular stimulation from within the critical isthmus. **(C)** Interruption of the VT during ablation in the isthmus. **(B,C)** From top to bottom, 12-lead ECG and ablation catheter recording (distal to proximal). **(D)** Bipolar voltage map of the left ventricle (LV) endocardium. Regions in **red** represent scar (bipolar voltage <0.5 mV), and **purple** regions represent normal myocardium (bipolar voltage >1.5 mV). Other colored regions represent abnormal myocardial regions (bipolar voltage between 0.5 and 1.5 mV). The scar is located in the inferobasal LV. **Red dots** display ablation point across the VT isthmus. Note: the number of ablation dots might overestimate the actual number of ablation applications, because some dots were acquired during the same radiofrequency application.

The goal of this ablation strategy was covering the entire scar with ablation lesions targeting abnormal electrograms. In the first 10 patients, pacing was performed at high output (up to 20 mA with a pulse duration of 10 ms) from within the ablated area, but capture was not seen and not tested in later patients. Ablation at the border zone or within the dense scar had the same procedural endpoint (i.e., abolition of all abnormal potentials) (Figs. 2 and 3). At the end of the ablation, programmed stimulation with and without isoproterenol was performed in all cases to test the inducibility of any VAs following extensive substrate ablation.

Procedural endpoint. Although with a different ablation technique, in both groups after ablation the acute procedural endpoint was the noninducibility of any monomorphic VTs before and after the administration of isoproterenol (up to 5 μg/min). Induction of nonclinical very fast VT (cycle length <200 ms), or VF, ventricular flutter, or fast polymorphic VT were not considered as a procedural endpoint and were not taken into account.

Follow-up. In all patients, screening for pericardial effusion was routinely done at the end of the procedure by intracardiac echocardiography and fluoroscopy. In case of patients' symptoms or low blood pressure after the procedures, transthoracic echocardiography was performed before discharge.

All patients were followed up with remote monitoring as well as implantable device interrogations and office visits every 3 months thereafter to assess recurrences.

Arrhythmia recurrence was defined as arrhythmias receiving device-based treatments (anti-tachycardia pacing [ATP] or shock). After ablation, the previously ineffective AADs were given and discontinued 3 months later. After the procedures, all ICDs were programmed to detect VTs slower than the clinical VTs. No differences in the programming modality in between groups were present.

Statistical analysis. Continuous data are described as mean ± SD and as numbers and percentages if categorical. Student *t* test, chi-square test, and Fisher exact test were used to compare differences across groups. Multivariable Cox regression analysis was used for identifying significant predictors of VA recurrence while controlling for clinically relevant covariates. All potential confounders were entered into the model based on significant univariable association or prior knowledge or expected clinical relevance, regardless of their statistical significance. The proportional hazard

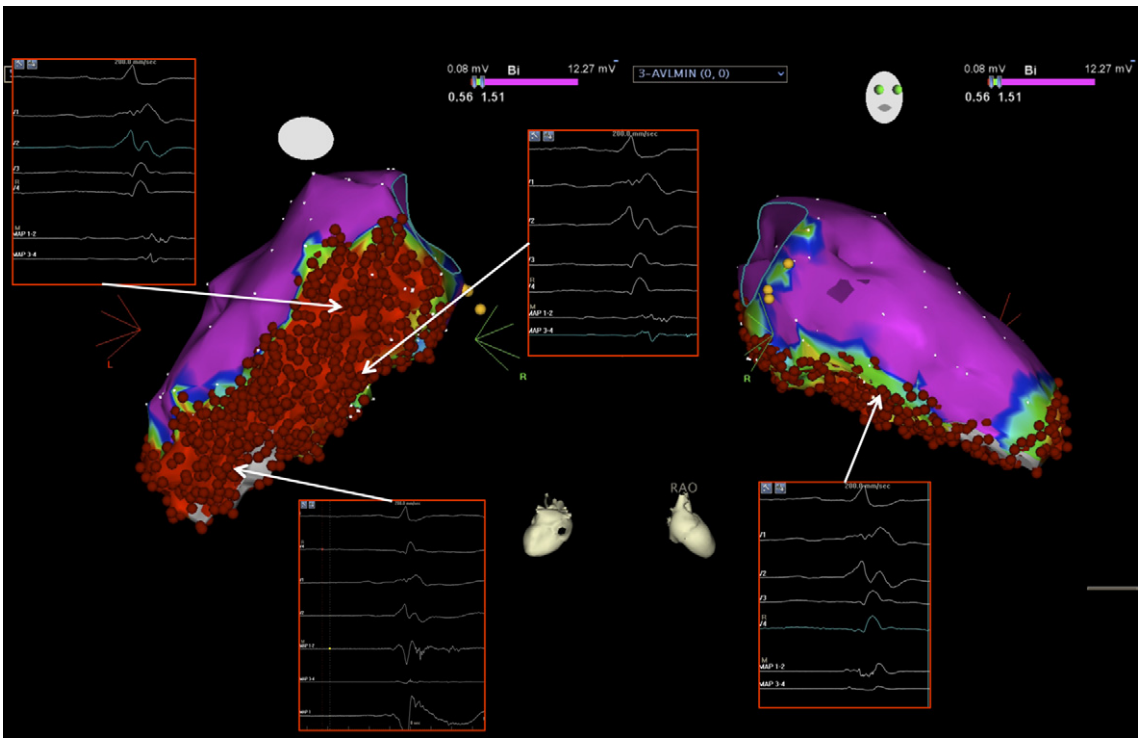

Figure 2 Bipolar Voltage Map of the LV Endocardium in a Patient From Group 2

Regions in **red** represent scar (bipolar voltage <0.5 mV), and **purple** regions represent normal myocardium (bipolar voltage >1.5 mV). Other colored regions represent abnormal myocardial regions (bipolar voltage between 0.5 and 1.5 mV). The scar is located in the inferior left ventricle (LV). This patient had ventricular tachycardia storm despite amiodarone 400 twice per day + mexiletine 150 three times per day. The entire scar has been targeted with extensive ablation **(red dots)**. Electrograms (EGMs) of representative endocardial mapping sites are shown with **white arrows**. In each EGM recording, electrocardiogram leads I, V_1 through V_4, and EGMs on proximal (MAP 3-MAP 4) and distal (MAP 1-MAP 2) ablation catheter are shown. Note: the number of ablation dots might overestimate the actual number of ablation applications, because some dots were acquired during the same radiofrequency application.

Figure 3 **Bipolar Voltage Map of the LV in a Patient From Group 2**

(A) Endocardial and **(B)** epicardial maps (inferior views) are shown. Definitions of scar or normal myocardium remained the same as in Figures 1 and 2. Electrograms (EGMs) of representative endocardial and epicardial mapping site are shown with **white arrows**. In each EGM recording, electrocardiogram leads I, II, and V_3 and electrograms on proximal (MAP 3-MAP 4) and distal (MAP 1-MAP 2) ablation catheter are shown. Radiofrequency applications **(red dots)** were applied at sites demonstrating abnormal recordings. Note: the number of ablation dots might overestimate the actual number of ablation applications, because some dots were acquired during the same radiofrequency application.

assumption for the covariates was tested by Schoenfeld residual analysis.

Continuous predictors, left ventricular ejection fraction (LVEF), VT episodes, and VT cycle length, were dichotomized at <30%, >2, and >300, respectively, before entering into the model. The hazard ratio (HR) and 95% confidence interval (CI) of VA recurrence were computed. Recurrence-free survival over time was calculated by the Kaplan-Meier method, and log-rank statistics was used to compare the groups. Cohen's kappa was used to estimate intercenter agreement in group assignment. All tests were 2-sided, and a p value of 0.05 was considered statistically significant. Analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Ninety-two consecutive patients (80% male, 62 ± 13 years, LVEF 26% ± 9%) with ischemic cardiomyopathy and ES undergoing radiofrequency ablation constituted our study population. All patients had previously experienced treatment failure with 2 ± 0.9 AADs. As described in the Methods section, patients were divided into 2 groups according to enrollment time. Difference in intercenter distribution of patients in Groups 1 and 2 was assessed using the kappa statistic. No statistically significant bias was noted (kappa = 0.57, $p < 0.01$). Among the groups, no significant difference in baseline clinical and electrophysiologic characteristics was observed (Table 1). Importantly, no statistical differences were observed in terms of VT cycle lengths, percentage of hemodynamically stable VTs, and scar size (130 ± 54 cm^2 vs. 137 ± 66 cm^2, p = 0.58) (Table 2).

Ablation data. During the ablation, sustained VT was inducible in 46 patients (94%) in Group 1 and 42 patients (98%) in Group 2 (p = 0.373). Of these, 36 of 46 Group 1 patients (78%) and 34 of 42 Group 2 patients (81%) had inducible clinical VT. The remaining 10 of 46 Group 1 patients (22%) and 8 of 42 Group 2 patients (19%) had only nonclinical induced VT (Table 2). In Group 1, epicardial access and ablation was performed in 4 patients(8%) due to inducible VTs after endocardial ablation. As previously

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Table 1 Baseline Characteristics and Medical Therapy of the Study Population

	Group 1 (n = 49) Endocardial Substrate Ablation	Group 2 (n = 43) Homogenization of the Scar	p Value
Age, yrs	61 ± 10	62 ± 8	0.113
Male	42 (85)	32 (75)	0.173
Hypertension	30 (61)	25 (59)	0.763
Diabetes	8 (16)	6 (13)	0.752
BMI	28 ± 6	28 ± 4	0.279
COPD	4 (8)	3 (6)	1.000
LVEF	27 ± 5	24 ± 8	0.463
History of AF	19 (38)	22 (51)	0.233
Medications			
Beta-blocker	45 (92)	36 (84)	0.231
ACEI or ARB	35 (72)	29 (67)	0.678
Sotalol	3 (6)	2 (5)	0.656
Statins	29 (60)	28 (64)	0.558
Clopidogrel	5 (10)	5 (12)	1.000

Values are mean ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction.

mentioned, in these patients, the anticoagulation was reversed with protamine, and the epicardial access was obtained in the same ablation session.

In Group 2, epicardial access and mapping were obtained in all patients, whereas epicardial ablation was performed in 14 cases (33%) due to the presence of delayed, fragmented, or low voltage potentials on the epicardial surface of the scar after endocardial ablation. When compared with Group 1, in Group 2, a higher procedure time (3.6 ± 1.3 h vs. 4.8 ± 1.5 h, $p < 0.001$), fluoroscopy time (32 ± 14 min vs. 38 ± 11 min, $p = 0.017$), and radiofrequency time (39 ± 17 vs. 74 ± 21, $p < 0.001$) were reported (Table 2). No statistical difference was present between the endocardial maps and epicardial 3-dimensional mapping points (360 ± 15 vs. 370 ± 20 endocardial, and 420 ± 10 vs. 410 ± 6 epicardial) respectively in Group 1 and in Group 2.

Coronary angiography was performed in 17 patients in Group 1 (35%) and in 12 patients in Group 2 (28%; $p = 0.485$).

Acute success of radiofrequency cardiac ablation. At the end of the procedures, all patients in both groups were free from inducible or spontaneous VT. The acute procedural endpoint was achieved in 100% cases. Induction of very fast VT (cycle length ≤200 ms) or VF, ventricular flutter, or fast polymorphic VT after ablation occurred in 9 patients (18%) in Group 1 and in 5 patients (12%) in Group 2 ($p = 0.37$).

Complications. No periprocedural complication occurred. One patient in Group 1 and 1 patient in Group 2 died at follow-up for noncardiac reasons. One hematoma in Group 1 and 1 hematoma in Group 2 not requiring surgery were reported. No post-procedural pericarditis, phrenic nerve palsy, right ventricle puncture, coronary vessel damages, and strokes/transient ischemic attacks (peri-procedural and at follow-up) were reported.

Long-term follow-up. The overall duration of follow-up for the study population was 25 ± 10 months. However, compared with patients in Group 2 (median 21 months, interquartile range 19 to 25 months), who were enrolled at a later period, patients in Group 1 had a longer follow-up (median 36 months, interquartile range 27 to 42 months, $p < 0.001$). In order to exclude the possible confounding effect of shorter follow-up, assessment of the VT-free survival was limited to 22 months for both groups. The probability of recurrence-free survival was significantly lower in Group 1 (26 [53%] vs. 35 [81%], log-rank $p = 0.006$). Furthermore, no significant difference in long-term freedom from arrhythmia recurrence was found among Group 1 patients who had VT termination during ablation as compared with those in whom the same endpoint could not be achieved due to hemodynamic instability during VT ($p = 0.67$ for comparison).

Kaplan-Meier survival curves are displayed in Figure 4. The post-procedure AAD use to control recurrent VT (amiodarone and mexiletine in the majority of patients) was considerably decreased in Group 2. Of the 35 patients who were VA free in Group 2, 31 (88%) were off amiodarone and/or mexiletine compared with 8 (31%) of 26 VA-free patients off amiodarone and/or mexiletine in Group 1 ($p < 0.001$). Distribution of VA-free survival was identical across participating centers; no statistically significant trend in long-term success was observed ($p = 0.157$).

Of the 8 patients with VT recurrences in Group 2 (6 with ICD shock, 2 with ATP) at follow-up, 6 (75%, all those

Table 2 Procedural Parameters and Scar Locations

	Group 1 (n = 49) Endocardial Substrate Ablation	Group 2 (n = 43) Homogenization of the Scar	p Value
Inducible clinical sustained VT	36 (74)	34 (80)	0.245
Nonsustained VT cycle length	340 ± 52	320 ± 40	0.317
Sustained VT cycle length	410 ± 57	430 ± 48	0.476
VT induced	46 (94)	42 (98)	0.793
Number of VTs induced	2 (1–4)	2 (1–5)	0.601
Mappable VT	8 (16)	6 (14)	0.752
Unmappable VT	37 (76)	33 (77)	0.889
Location of scar			
Anterior	21 (43)	18 (42)	0.923
Inferior	27 (55)	22 (51)	0.706
Inferoposterior	3 (6)	4 (9)	0.566
Posterior	5 (10)	6 (14)	0.580
Apex	5 (10)	4 (9)	0.885
Septum	4 (8)	3(7)	0.830
Scar size, cm^2	130 ± 54	137 ± 66	0.580
Procedure time, h	3.6 ± 1.3	4.8 ± 1.5	<0.001
Fluoroscopy time, min	32 ± 14	38 ± 11	0.017
RF time, min	39 ± 17	74 ± 21	<0.001
Epicardial access (n)	4 (8)	43 (100)	<0.001
Epicardial access and ablation (n)	4 (8)	14 (33)	<0.001

Values are mean ± SD, median (range), or n (%).

RF = radiofrequency; VT = ventricular tachycardia.

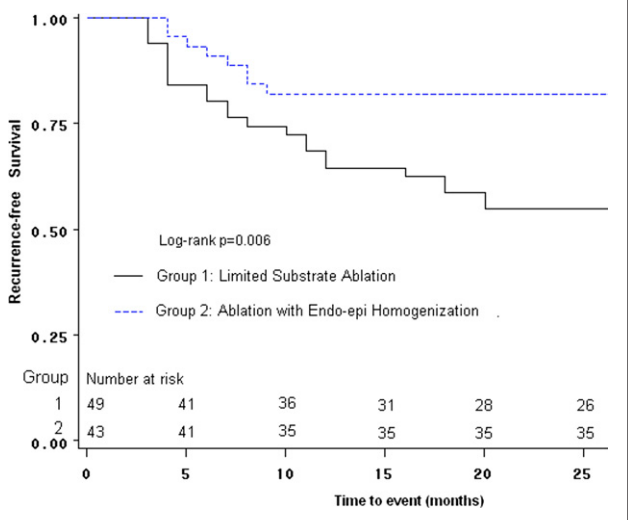

Figure 4 **Ventricular Arrhythmia/ICD Therapy-Free Survival by the Ablation Approach**

The Kaplan-Meier curve shows a statistically significant difference between Group 1 (standard ablation approach) and Group 2 (endo-epicardial homogenization approach) at 25 ± 10 months follow-up. ICD = implantable cardioverter-defibrillator.

with ICD shock) underwent a repeat procedure. Of these patients, 1 patient had a VT recurrence from outside the scar area, 1 patient with a large inferior myocardial infarction required ablation in the right ventricle, 3 patients underwent epicardial homogenization not performed during the initial procedure, and only 1 patient required additional ablation along the endocardial scar that was previously ablated. Of the 23 patients with VT recurrences of Group 1, 19 (83%) underwent repeat ablation. All these patients were treated with a scar homogenization approach (5 [26%] with an endo-epicardial ablation).

Predictors of recurrence. As observed from the univariable analysis, ablation with homogenization of scar was a determinant of VA-free survival (HR: 0.44; 95% CI: 0.14 to 0.86, p = 0.014). No significant association was observed for other covariates tested in the univariable model; age (HR: 1.03; 95% CI: 0.92 to 1.07; p = 0.473), sex (HR: 1.44; 95% CI: 0.89 to 2.50, p = 0.204), LVEF (HR: 0.85; 95% CI: 0.39 to 1.85; p = 0.670), VT cycle length (>300) (HR: 1.53; 95% CI: 0.60 to 3.89; p = 0.308), scar size (HR: 1.15; 95% CI: 0.74 to 1.79; p = 0.527), and amiodarone use (HR: 1.01; 95% CI: 0.99 to 1.03; p = 0.487).

Multivariable analysis of recurrence-free survival was performed with the Cox proportional hazards model. Covariates with clinical importance were entered into the model irrespective of univariable association. After controlling for important covariates (age, sex, LVEF, VT cycle length, scar size), ablation with endo-epicardial homogenization of the scar was found to be associated with significantly lower risk for VT recurrence (HR: 0.46; 95% CI: 0.21 to 0.87; p = 0.025). Ablation with endo-epicardial homogenization had 62% decreased risk for VT recurrence compared with endocardial ablation alone (Fig. 4). Other baseline risk factors such as sex, age, LVEF, and VT cycle length did not show any significant influence on long-term outcome.

A second model was run by adding more covariates (amiodarone use, VT episodes [>2], and VT cycle length) to the first model. The results from this model were not different from those of the first one (i.e., homogenization of scar exhibited significant association with VA-free survival). On the other hand, including additional predictors did not add significant prediction power to the basic model, whereas it incurred the risk of overfitting and reduced generalizability.

Discussion

Main findings. This is the first study showing that extensive ablation within the scar area in patients with ischemic heart disease and ES increases the freedom from VAs at long-term follow-up. Moreover, in the multivariate analysis, the technique used for the ablation (homogenization of the scar) was the only predictor of a better outcome. These results are novel and suggest a new ablation approach for the treatment of ischemic patients with ES.

None of our patients undergoing ablation had an untreated reversible trigger favoring the VAs such as acute coronary ischemia, electrolyte abnormalities, or acute heart failure worsening. Therefore, it appears that in patients with stable ischemic heart disease and recurrent VAs, a larger area of tissue needs to be ablated to modify the substrate responsible for VAs.

General. Ischemic heart disease is the prevalent cardiac disease in Western countries and, if associated with myocardial infarction and low ejection fraction, exposes patients to a higher risk of VT and sudden cardiac death. Following the MADIT 2 (Multicenter Automatic Defibrillator Implantation Trial 2) study, international guidelines have suggested the implantation of ICDs in these patients (1,22). Despite the presence of the device, the presence of recurrent VTs and ES represents a marker for increased mortality (23).

AADs are often used but are frequently ineffective and laden with side effects (24). Catheter ablation of VAs in patients with ischemic cardiomyopathy and ES have shown moderate results at long-term follow-up, even after the introduction of open irrigated ablation (4,5,9,11,15,25).

Although better than medical therapy, the success rate of the ablation cannot be considered optimal. For these reasons, new technologies and new tools are under investigation to increase the success rate of catheter ablation (26,27).

Several studies have shown that catheter ablation has a better success rate at follow-up when compared with AADs for the treatment of VAs. The success rate ranges from 51% to 67% and increases in patients with acute efficacy after ablation (no further mappable VT) (14,28–30).

Specifically for patients with ES, recent studies have also shown the superiority of catheter ablation to conventional medical therapy (4), and catheter ablation in this setting

may be life-saving. There is also evidence that VT ablation may offer significant benefit compared with standard medical therapy as a first-line therapy in patients with a single episode of VT who are undergoing secondary prevention ICD implantation (31,32).

Most studies have shown that the absence of any VTs at the inducibility test after ablation was associated with an increased success rate at follow-up when compared with series where the acute success was restricted to the noninducibility of the clinical VT (14,28–30).

Our study confirms these findings. However, noninducibility of VT(s) was achieved as an endpoint in both groups, and the different success rate at follow-up may only be explained by the different ablation strategy. We can speculate that the tissue edema created during ablation could render a reentrant circuit located in deeper layers or in the surrounding myocardium transiently inactive.

A limited endocardial ablation that does not eliminate all potential channels and re-entrant circuits might be a potential cause of ablation failure (33). Of note, a higher number of patients discontinued AADs in the "homogenization" group, highlighting the importance of this ablation approach. Interestingly, the endo-epicardial homogenization approach never required hemodynamic support during the procedure in any of our patients (vs. 4 [8%] of Group 1 patients), as this approach eliminates the need for mapping and ablation during tachycardia. These findings, although preliminary, further extend the benefit of endo-epicardial homogenization, possibly reducing the risks and the costs of the procedures.

From a pathophysiological perspective, the incremental effectiveness of endo-epicardial scar homogenization in the current population of patients with ischemic VT could be explained by the evolution over the years of post-infarction arrhythmogenic substrates, which reflects the evolution of reperfusion therapies for acute myocardial infarction. In the pre-thrombolytic era, persistent occlusion of the infarct-related artery generated an area of transmural necrosis, ultimately leading to a central fibrotic core with a thin border zone with viable bundles of myocytes interspersed among healed fibrotic tissue (16). The introduction of pharmacological and mechanical reperfusion therapies has led to a higher percentage of nontransmural necrosis, with heterogeneous infarct cores containing bundles of surviving myocytes and fibrotic tissue surrounded by similarly complex border zones merging into normal myocardium (16).

Notably, Kumar et al. (34) recently reported a significant association in humans between the timing of coronary reperfusion with primary percutaneous coronary intervention and the 2-year rate of spontaneous VAs, with an incidence ranging from 0% to 14% according to different timings of coronary reperfusion.

Moreover, the occurrence of the "no-reflow" phenomenon (17), of distal embolization of thrombotic material during mechanical reperfusion (18), and varying degrees of reperfusion-related myocardial injury have further increased the complexity of the substrate for post-infarction VT, generating multiple slow conduction channels within the dense scar, with VT exit points located in different areas, including the subendocardial scar, the border zone, or even in the mid-wall or subepicardial myocardial layers. As a result, the presence of multiple slow conduction channels within the scar and the possibility of mid-wall or epicardial VT exit sites (19,29) provide the rationale for an extensive endo-epicardial scar homogenization to treat the current population of patients with post-infarction VT. Furthermore, a more extensive ablation approach is also justifiable by recent mechanistic data on the distribution and characteristics of late potentials within the scar (35).

Accordingly, in contrast to what was previously reported in ischemic VT ablation, a higher number of patients in our study required epicardial ablation (14).

The results of our study are in line with these concepts because they show that a more aggressive approach that covers the entire scar area is associated with a better outcome. In contrast to what was previously reported in ischemic VT ablation, a higher number of patients required epicardial ablation (14). In interpreting our results, one could argue that the clinical relevance of delayed and fragmented potentials in the endocardium and in the epicardium is different from what we have previously believed. As previously mentioned, post-infarction VTs may also be concealed around the entire scar area and not limited to a single isthmus. Moreover, the improved success in Group 2 is likely a result of homogenization, as there was not a significant difference between the outcome of patients undergoing epicardial compared with those who only had endocardial homogenization.

Study limitations. The major limitation of our study is the absence of a formal randomization. Although we acknowledge this limitation, the comparison of the ablation strategies has been done in consecutive patients and in a prospective design. Furthermore, all the procedures have been performed by highly experienced operators. A minority of patients in each group had mappable VT, although the number of mappable VTs was similar to that in previous studies on ES (4). Furthermore, an endo-epicardial homogenization approach is not suitable for patients with previous coronary artery bypass grafting who, however, represent the minority of patients with myocardial infarction undergoing coronary revascularization in the current era (36).

Finally, we cannot exclude that a more dense pace mapping would have resulted in a better outcome in Group 1 patients. However, because we empirically targeted a large area around the presumed VT exit site (Fig. 1), it is unlikely that this might explain the lower success rate in Group 1.

Conclusions

Our study demonstrates that ablation using endo-epicardial homogenization of the scar significantly increases freedom from VAs in patients with ischemic cardiomyopathy and electrical storm. Further randomized trials are warranted to confirm the clinical relevance of our study.

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