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ORIGINAL RESEARCH

Epicardial and Endocardial Ablation Based on Channel Mapping in Patients With Ventricular Tachycardia and Chronic Chagasic Cardiomyopathy: Importance of Late Potential Mapping During Sinus Rhythm to Recognize the Critical Substrate

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BACKGROUND: Ventricular tachycardia (VT) in patients with chronic chagasic cardiomyopathy (CCC) is associated with considerable morbidity and mortality. Catheter ablation of VT in patients with CCC is very complex and challenging. The main goal of this work was to assess the efficacy of VT catheter ablation guided by late potentials (LPs) in patients with CCC.

METHODS AND RESULTS: Seventeen consecutive patients with refractory VT and CCC were prospectively included in the study. Combined endo-epicardial voltage and late activation mapping were obtained during baseline rhythm to define scarred and LP areas, respectively. The end point of the ablation procedure was the elimination of all identified LPs. Epicardial and endocardial dense scars (<0.5 mV) were detected in 17/17 and 15/17 patients, respectively. LPs were detected in the epicardial scars of 16/17 patients and in the endocardial scars of 14/15 patients. A total of 63 VTs were induced in 17 patients; 22/63 (33%) were stable and entrained, presenting LPs recorded in the isthmus sites. The end point of ablation was achieved in 15 of 17 patients. Ablation was not completed in 2 patients because of cardiac tamponade or vicinity of the phrenic nerve and circumflex artery. Three patients (2 with unsuccessful ablation) had VT recurrence during follow-up (39 months).

CONCLUSIONS: Endo-epicardial LP mapping allows us to identify the putative isthmuses of different VTs and effectively perform catheter ablation in patients with CCC and drug-refractory VTs.

Key Words: catheter ablation ■ Chagas cardiomyopathy ■ ventricular tachycardia

Chronic chagasic cardiomyopathy (CCC) is an important endemic disorder in Latin American countries. In past decades, due to notable migration, Chagas disease has been introduced to many developed countries in Europe, North America, and the Western Pacific region.[1] The principal manifestation of chronic infection with *Trypanosoma cruzi* is cardiac disease in ≈30% of patients, where ventricular tachycardia (VT) and sudden cardiac death are still very important clinical challenges.[2,3]

The arrhythmogenic substrate is very complex in patients with CCC and includes the frequent involvement of the subepicardial layer. Several hypotheses have been proposed regarding the pathophysiology of

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CLINICAL PERSPECTIVE

What Is New?

- Chagas heart disease is still an important cause of heart failure and sudden death in Latin American countries.
- Subepicardial myocardial scarring is an important substrate of ventricular tachycardia.
- Late potentials are a marker of abnormal conduction channels through epicardial and endocardial myocardial scars and can be used as a target of the substrate-based approach to treat refractory ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy.
- The impact of late potentials on the channel definition of VT substrates in patients with chronic chagasic cardiomyopathy has not yet been completely defined.

What Are the Clinical Implications?

- Identification of conduction abnormalities by late potential mapping in sinus (or baseline) rhythm may improve ventricular tachycardia ablation efficiency.
- Late potentials recorded during sinus rhythm have a strong correlation with slow conduction in critical VT substrate in patients with Chagas cardiomyopathy.
- Catheter ablation guided by late potential elimination may be a better approach to reduce VT in patients with Chagas heart disease.

Nonstandard Abbreviations and Acronyms

CCC	chronic chagasic cardiomyopathy
CZ	core zone
EZ	entrance zone
IDP	isolated diastolic potential
LAZ	late activation zone
LP	late potential

cardiac involvement in CCC, especially chronic myocarditis and microvascular disturbances leading to myocardial ischemia.[4,5] Accordingly, these pathogenic factors that produce fibrosis and scarred myocardium leave a unique pattern on the arrhythmic substrate of chagasic patients, with predominant scar distribution in the apex and perivalvular aspect of the left ventricle (LV).[4–7]

Reentry is the major mechanism of VT associated with scarred myocardium in CCC.[7] The reentry circuits can be large and complex, extending transmurally over several centimeters through the ventricular epicardium and endocardium.[6–8] The presence of multiple reentry circuits giving rise to multiple and unstable VTs does not allow extensive activation and entrainment mapping.[8] Low-amplitude areas mapped by tridimensional systems can be used to identify scarred tissue and critical circuit components of scar-related VTs.[8,9] Additionally, confluent areas of myocardial fibrosis frequently exhibit late potentials (LPs), which are recorded during sinus rhythm.[10,11] Catheter ablation of areas exhibiting delayed electrograms has been associated with a decrease in VT recurrence in patients with previous myocardial infarction and nonischemic cardiomyopathy.[11–13]

Few studies focusing on VT or voltage mapping as a target of ablation have demonstrated the feasibility of catheter ablation in chagasic patients with short-term follow-up.[8,14] The importance of LP and channel mapping in patients with CCC as a target of substrate-based ablation has not yet been demonstrated. The purpose of this study was to assess the value of LPs encountered during baseline rhythm to identify potential target sites for VT ablation in chagasic patients. Secondary, this study aims to characterize the electrophysiological chagasic substrate for reentrant VT.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

From December 2007 to April 2009, 17 consecutive chagasic patients referred for VT ablation were prospectively enrolled after providing written informed consent. All patients had a previous diagnosis of CCC. Ischemic heart disease was excluded by prior coronary angiography. Inclusion criteria consisted of documented episodes of sustained VT, despite antiarrhythmic drug therapy, requiring cardioversion or implantable cardioverter-defibrillator (ICD) discharge. The institutional Ethics Committee approved the study protocol.

Electrophysiologic Study, Vascular Access, and Pericardial Puncture

Vascular access was obtained through the femoral vein, with patients under deep sedation and in a postabsorptive state. One quadripolar catheter was positioned in the right ventricle, and programmed ventricular stimulation (PVS) from at least 2 sites (apex and outflow tract) was performed using up to 3 extra stimuli to induce VT.

In all patients, a catheter was placed into the pericardial space using a transthoracic subxiphoid puncture approach (without pericardial dye injection). Briefly, the pericardial space was entered with a 17-gauge Tuohy needle, and a guidewire was passed through the needle over which an 8-F long sheath was advanced.[15] Next, femoral artery access was obtained for the retrograde aortic approach and LV endocardial mapping in all patients. Transeptal puncture was additionally used in 3 patients to assist LV mapping. Five thousand units of heparin (50 units/kg) were administered followed by an additional 1000 units per hour. An activated clotting time of >250 seconds was targeted.

Substrate Mapping

All 17 patients underwent endo-epicardial mapping during sinus rhythm (n=15) or ventricular pacing (n=2). A nonirrigated catheter with an 8 mm tip electrode (Navistar, Biosense Webster, Diamond Bar, CA, USA) or a 3.5 mm irrigated tip catheter (Thermocool-Navistar) with a 1 mm tip-to-ring interelectrode distance was used in conjunction with a 3-dimensional CARTO system for bipolar ventricular mapping. Intracardiac bipolar signals were recorded in the CARTO system (30–400 Hz filtering) and in the digital EPTracer system (CardioTek, Maastricht, Netherland) with filtering at 30 to 500 Hz. Unipolar electrograms were filtered at 2 to 240 Hz. The window of interest on the CARTO system was selected to encompass all electrograms that were representative of ventricular systole and, after the QRS complex, the first half of diastole.

Voltage mapping was acquired point by point, and the peak-to-peak signal amplitude of the bipolar electrogram was measured automatically (Figure 1). Normal ventricular myocardium was defined as sites with a bipolar amplitude >1.5 mV. Dense scars were considered areas with signal amplitudes <0.5 mV. The border zone was defined as a transition zone between dense scarring and normal tissue. The local electrogram amplitude was estimated by the color display of the voltage maps in the CARTO system. Namely, the purple color represented a signal amplitude >1.5 mV, and the red color depicted a signal amplitude <0.5 mV with the remaining color ranges (blue, green, and yellow) defining the intermediate electrogram amplitude (0.5–1.5 mV). To ensure adequate sampling density and complete representation of abnormal myocardial area, the fill threshold of the CARTO system was initially set at 15 to 20 mm and after definition of low-voltage areas, reduced to <5 mm for high-density mapping (at least 4 points to each cm^2).

Additionally, a color-codec map of the local activation delay was created using the same anatomical template as that used for the voltage map. Manual adjustments of all LPs recorded after the latest surface QRS complex were used for the late activation (LAT) map (Figure 2). The local activation was annotated at the latest deflection of the bipolar electrogram. The latest split component of isolated diastolic potential (IDP) was taken to represent local activation, and this was annotated. For late fractionated potentials (LFPs), reference was also made to the latest positive deflection of the bipolar fragmented electrogram. The minimum cutoff on the color scale was set as the interval between the QRS peak used for the CARTO reference and the latest surface QRS complex recorded (QRS_{peak}–QRS_{end} interval). Thus, areas exhibiting LPs, termed the late activation zone (LAZ), are displayed in purple in the LAT maps. The LAZ was subdivided into 2 regions: the entrance (EZ) and core (CZ). The EZ of the LAZ was always present and was localized at the edge of the scar border zone (within the purple region of the LAT map), showing arbitrary extension of 1/3 of the total area of the LAZ (Figure 2).

Late potentials were defined as any low-voltage electrogram (<1.5 mV) with a single or multiple continuous component(s) recorded after the end of the QRS complex (Figure 3). Isolated diastolic potentials were characterized as a single high-frequency component occurring after the end of the latest surface QRS complex, separated from the first component of the local electrogram by at least 20 ms of isoelectric interval.[10,16] Late fragmented potentials were classified as wide-duration electrograms (≥50 ms) with multicomponent delayed signals (≥3 positive deflections).[8,17]

After substrate mapping, baseline PVS was performed to induce VT. If VT was sustained and well tolerated, entrainment mapping was utilized to define the central isthmus, which was tagged in the substrate mapping.[18] If VT was unstable as a result of hemodynamic intolerance, tachycardia was terminated by overdrive pacing or cardioversion. Pacemapping to match VT morphologies (≥10/12) was then utilized to define exit sites along the border of any low-voltage regions. Slow conduction sites were assumed on the basis of pacing sites with a long stimulus to QRS delay (S-QRS >50 ms).[19] Therefore, putative VT channels were defined by at least 2 different sites with identically paced QRS morphology and different (at least one >50 ms) S-QRS intervals (Figure 2).

Areas of scarring (<0.50 mV) and LAZ were measured by manually drawing a continuous line around the area of interest using the software for area quantification from the CARTO system.

Catheter Ablation

Under guidance by endo-epicardial substrate mapping, ablation of all LAZs was performed during baseline rhythm aiming to completely eliminate LPs (Figure 4). In patients in whom VT was inducible and well tolerated, ablation was initially guided by entrainment to identify

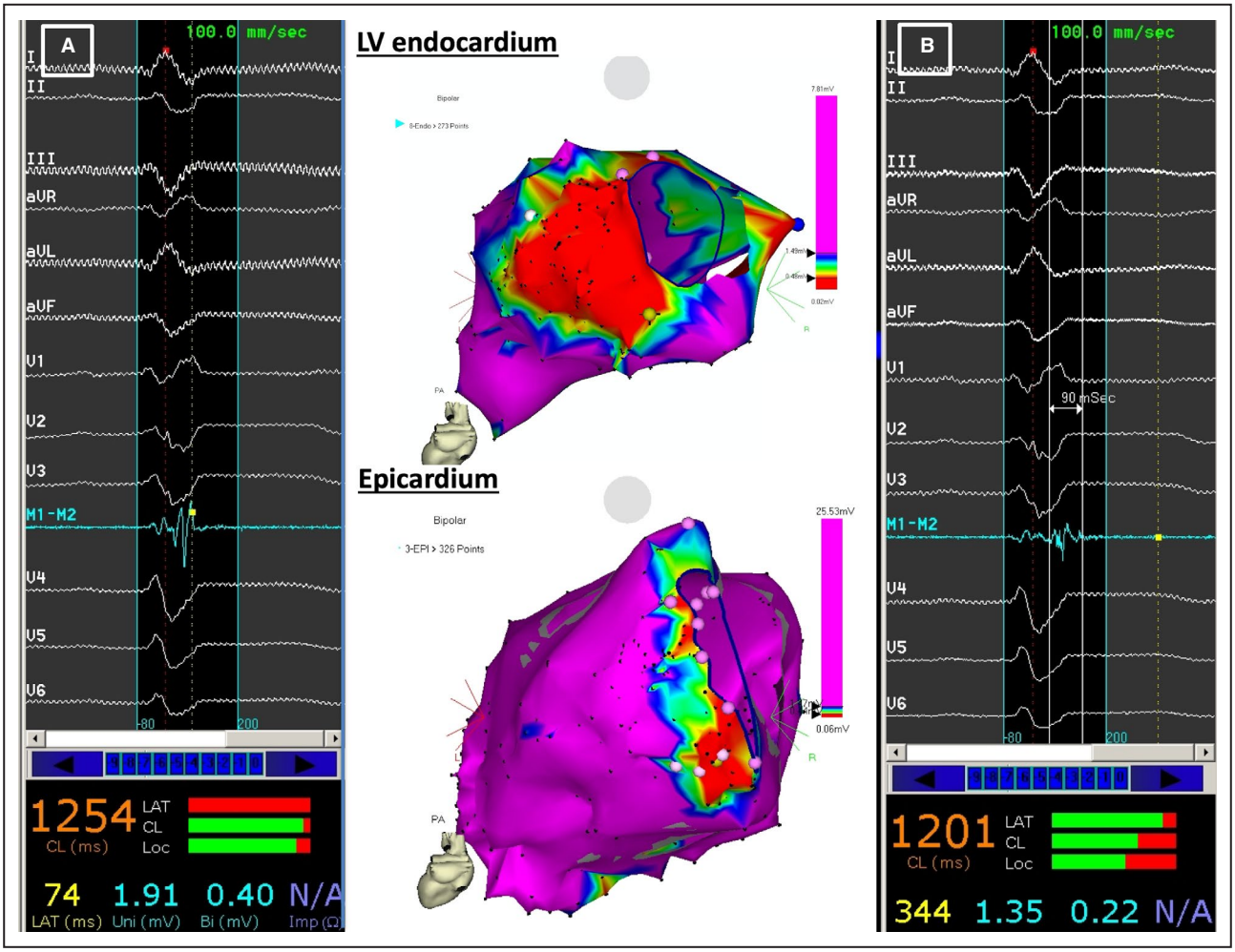

Figure 1. Endo-epicardial ventricular bipolar voltage mapping during sinus rhythm (patient 3).
A low-voltage area exhibiting late potentials was identified in posterolateral basal segments of the left ventricle. A sample of 2 electrograms recorded during point-by-point mapping is indicated by the abnormal signals in the border zone (**A**) and dense scar (**B**). In this color-coded voltage map, red indicates a dense scar (<0.5 mV); purple, normal tissue (>1.5 mV); and the remaining colors represent the border zone (0.5–1.5 mV).

the critical isthmus.[18] After the baseline rhythm was restored, ablation was continued to completely eliminate LPs. If poorly tolerated VTs were induced, tachycardia was interrupted, and ablation was then conducted under baseline rhythm with the same end point, targeting LAZs.

Ablation was performed with an 8 mm nonirrigated-tip catheter (n=16) or 3.5 mm irrigated-tip catheter (n=1). If a nonirrigated-tip catheter was used, radiofrequency energy was delivered with a power of 50 to 70 W (endocardial) or 50 W (epicardial) and a temperature limit of 55 to 60 °C. When an irrigated-tip catheter was preferred, the energy was set with a power of 25 to 40 W and a temperature limit of 45 °C (irrigation 17–30 mL/min). Coronary angiography was performed before epicardial ablation to avoid injury to the coronary arteries. Similarly, the phrenic nerve course was assessed by high-energy stimulation (20 mA at 2 ms) during epicardial mapping, and ablation was averted near the places of phrenic capture. Substrate-based ablation was performed in the epicardium with radiofrequency applications no closer than 1 cm to a coronary vessel or site demonstrating phrenic nerve capture with local pacing.

The end point of the procedure was the complete elimination of the LPs. After the radiofrequency delivery covering all LAZs, remapping was performed in these areas where LPs were previously recorded. Additional substrate ablation was then performed in the presence of residual LPs until the complete abolition of all late activities was achieved. When the end point was reached, unipolar pacing (10 mA at pulse width 2 ms) was performed in the region previously exhibiting the delayed electrograms. If pacing capture occurred, radiofrequency ablation was restarted until the local tissue was rendered electrically unexcitable.

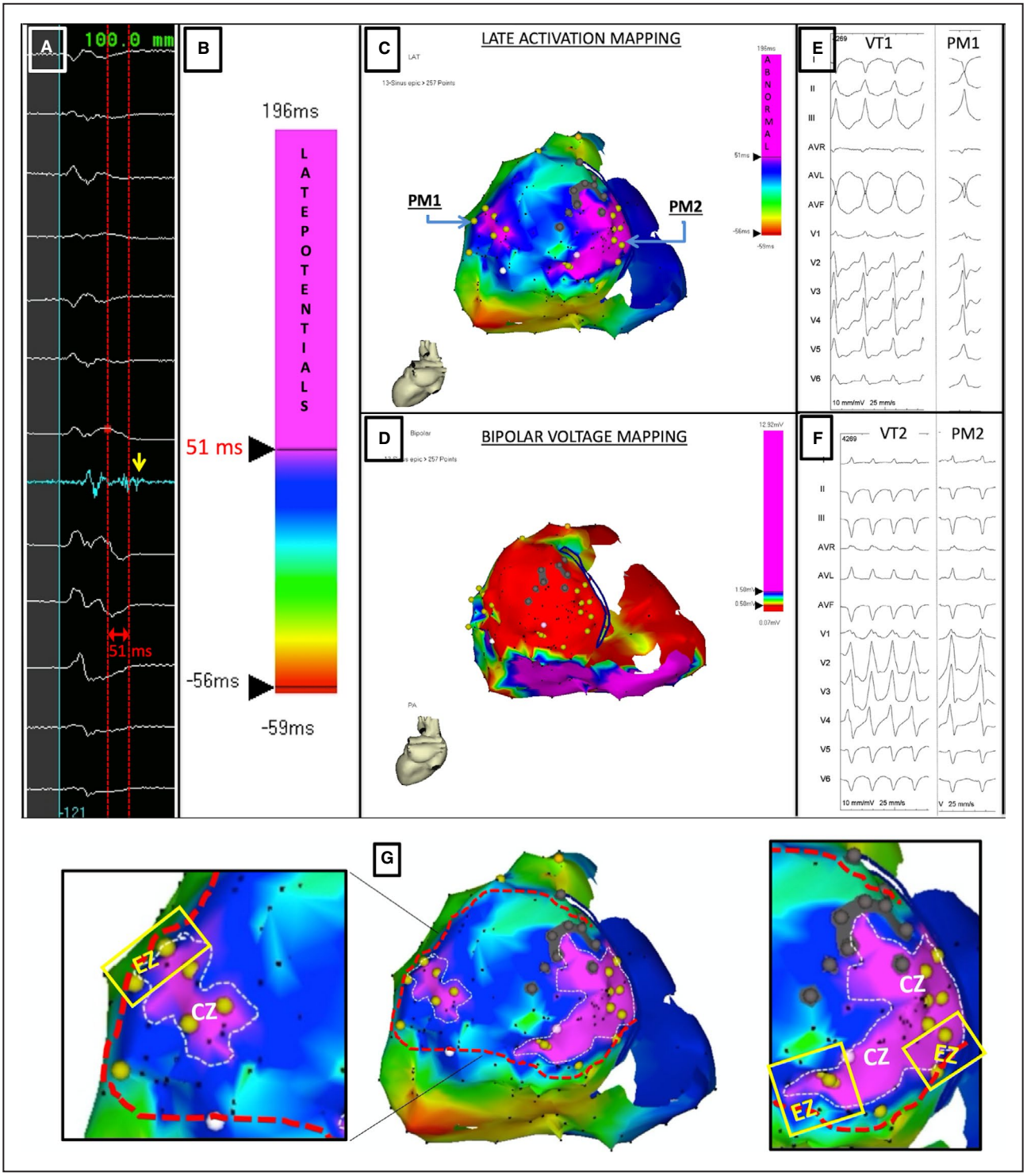

Figure 2. Epicardial arrhythmogenic substrate defined by voltage and activation mapping during sinus rhythm (patient 8). Activation mapping was initially set up (**A**) using the measure of the QRS_{peak}–QRS_{end} interval (51 ms) that was inserted as the cutoff for the color scale (**B**). Two nonconfluent areas containing late potentials, displayed in purple (**C**), were identified within the epicardial dense scar (**D**). Pace mapping performed in these 2 regions, termed late activation zones (LAZ), was related to inducible ventricular tachycardias (VT); pacemap 1 (PM1) matched to VT1 (**E**), and pacemap 2 (PM2) matched to VT2 (**F**). The sectors of the LAZ (white dashed line) are represented as the core zone (CZ), within the dense scar (red dashed line), and the entrance zone (EZ—yellow box), near of the border of the scar (**G**).

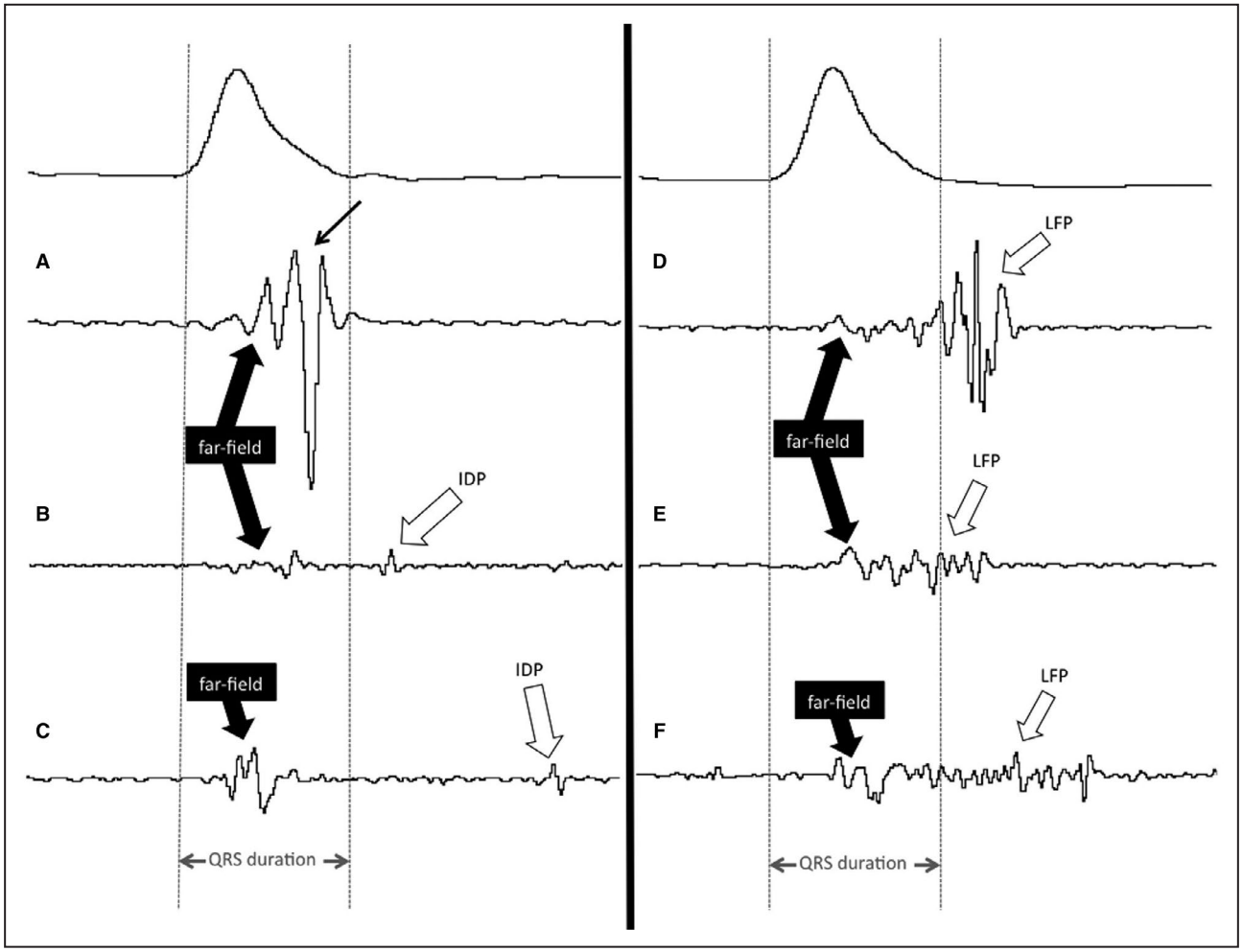

Figure 3. Abnormal bipolar electrograms typically recorded in the chagasic substrate (patient 13).
A, Low-amplitude electrogram (0.56 mV) with duration of 50 ms and 2 positive deflections recorded in the border zone of left ventricular endocardial scar; (**B**) low-voltage signal (0.20 mV) displaying an isolated diastolic potential (IDP) recorded 42 ms after the end of QRS; (**C**) another sample of IDP with an amplitude of 0.14 mV and an interval between end QRS and split signal of 132 ms. Both delayed electrograms (**B** and **C**) were recorded inside of the late activation zone (LAZ) and dense scar area of the endocardium and epicardium, respectively; (**D**) late fragmented potential (LFP) showing multicomponent deflections (5 positive deflections) after the end of QRS (latency of 50 ms) was recorded near the border zone of the endocardial scar (0.40 mV) and within of the entrance of the LAZ; (**E** and **F**) both LFPs exhibiting a delayed (48 ms) and very delayed (120 ms) signal after the QRS was recorded inside of the core of the LAZ and dense scar of the endocardial (0.25 mV) and epicardial (0.18 mV) mapping, respectively.

The noninducibility of VTs was evaluated at the end of the procedure as a secondary end point.

Postprocedure Care

Vascular sheaths were withdrawn immediately after the procedure. Pericardial long sheaths were retracted after dry pericardial aspiration was confirmed. Before hospital discharge, all patients were evaluated by transthoracic echocardiography (TTE). ICD therapies were reprogrammed with VT and ventricular fibrillation zones. Patients were monitored for at least 48 hours in the hospital. Amiodarone was administered to all patients unless contraindicated or not tolerated.

Clinical Follow-Up

Patients were followed at 1, 4, and 6 months and then every 6 months thereafter. Ventricular tachycardia recurrence was assessed by patient interview, ECG recording or interrogation of the ICD. The ICD was routinely programmed to include a monitoring zone (≥120 beats/min) to facilitate the identification of any asymptomatic recurrence of VT. TTE was conducted at 12 and 24 months to reassess ventricular function. If no VT episode was documented, amiodarone was withdrawn or reduced between 4 and 12 months of follow-up (Figure S1). The clinical end point was recurrence of VT. Follow-up was ended when the last patient completed 24 months (Abril 2011).

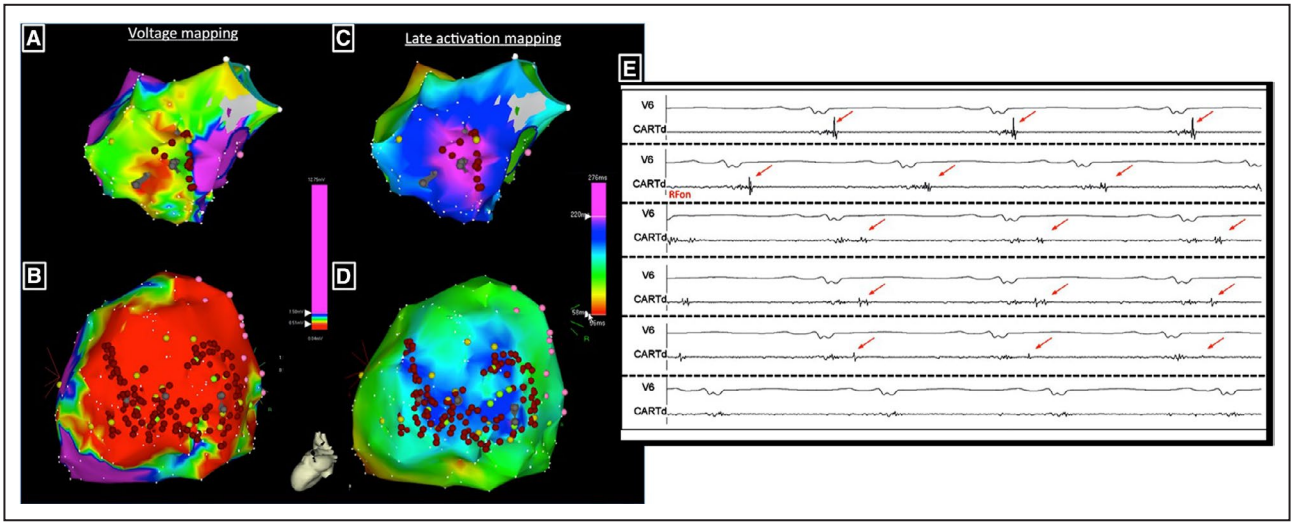

Figure 4. Complete elimination of the late potentials by endo-epicardial catheter ablation (patient 16).
Left ventricle endocardial (**A** and **C**) and epicardial (**B** and **D**) mapping are displayed in posterosuperior and posterolateral projections, respectively. Bipolar voltage mapping identified a large confluent transmural epicardial (**B**) and endocardial (**A**) scar that includes areas exhibiting late potentials, as shown in the late activation maps (**C** and **D**). Red dots represent the sites where radiofrequency (RF) energy was delivered to eliminate all late potentials. In the right image (**E**), progressive slowing of an isolated diastolic potential (arrow) until disappearance is shown during delivery of RF ablation.

Statistical Analysis

Categorical variables are expressed as absolute numbers and percentages. Quantitative variables are expressed as the mean±SD or median and interquartile ranges (IQR; 25th–75th percentile). For comparing continuous variables, Student paired or unpaired *t* test or a nonparametric test (used as an alternative to Student *t* test) were used as appropriate. Linear mixed-effect model was used to study the association between the area (scar and LAZ) encountered in the endocardial and epicardial surface adjusting for the relatedness (scar and LAZ) that occur on the same subject; area (scar and LAZ) or percentage of LAZ in the scar was used as dependent variable and surface mapped (endo or epi) and substrate (scar or LAZ) was used as fixed factors. A $P \leq 0.05$ was considered statistically significant. Arrhythmic event-free survival was graphically displayed according to the Kaplan-Meier method and compared by long-rank. The sensitivity, specificity, and positive and negative predictive values were assessed to define the accuracy of LP elimination as an ablation end point. Data were analyzed by SPSS 28.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Clinical Characteristics

A total of 17 patients were included in the study (Table 1). The mean age was 55±7 years, and 12 patients (65%) were men. The mean left ventricular ejection fraction (LVEF) assessed by TTE was 37±7%. According to the New York Heart Association (NYHA) Functional Classification, 10 patients were class II, 5 were class III, and 2 were class I with regard to heart failure classification.

All patients were treated with at least one antiarrhythmic drug: 16 patients (94%) received amiodarone, 6 patients (41%) were using amiodarone plus mexiletine, and one patient received mexiletine only. All but one patient were treated with carvedilol or metoprolol CR/XL. One month before the procedure, the mean number of VT episodes was 25±23 (range 3–64), and the clinical VT cycle length was 331±47 ms.

Electrophysiological Findings and Mapping

All patients underwent endo-epicardial bipolar mapping during baseline rhythm with a cycle length of 965±100 ms and QRS_{peak}-QRSend interval of 90±42 ms. Endocardial and epicardial point sampling was similar (331±148 versus 393±141 points/map; P=0.13). Myocardial scarring (<0.5 mV) was present in all patients. These confluent areas were mainly observed in the posterolateral basal segments of the LV (n=14), whereas anteroapical scarring was found in only 3 patients.

Endocardial scars were identified in 15/17 (88%) patients, whereas epicardial scars were identified in all patients (Table 2). Combined endo-epicardial maps showed a confluent area of low-voltage electrograms in 15 patients, suggesting a transmural scar. Two other patients (patients 2 and 5) showed only an abnormal

Table 1. Clinical Characteristics of Patients Before Catheter Ablation

Pts*	Age (y)	Sex	LVEF (%)	ICD	AAD	Amio dose (mg/d)	ß-blocker	VT cycle length (ms)	VT†
1	66	M	45	No	Amio+mexil	600	Yes	300	3
2	49	F	51	No	Amio	400	Yes	320	5
3	60	M	34	Yes	Amio+mexil	800	Yes	300	54
4	56	M	33	Yes	Amio+mexil	600	Yes	380	27
5	60	F	40	Yes	Mexil*	…	No	250	6
6	64	M	42	Yes	Amio	400	Yes	330	56
7	53	F	45	Yes	Amio	400	Yes	280	10
8	61	M	32	No	Amio	400	Yes	440	4
9	55	M	38	Yes	Amio+mexil	600	Yes	340	53
10	48	M	32	Yes	Amio	400	Yes	360	22
11	53	M	24	Yes	Amio+mexil	600	Yes	350	60
12	48	F	48	Yes	Amio	600	Yes	260	3
13	68	M	45	Yes	Amio+mexil	400	Yes	320	64
14	52	M	28	Yes	Amio	600	Yes	385	4
15	41	M	38	Yes	Amio	600	Yes	340	41
16	51	M	30	Yes	Amio	400	Yes	360	3
17	55	F	35	No	Amio	600	Yes	320	10
All	55±7	…	37±7	…	…	494±175		331±47	25±23

Values are expressed as absolute value or mean±SD. AAD indicates antiarrhythmic drug; Amio, amiodarone; F, female; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; M, male; mexil, mexiletine; Pts, patients; and VT, ventricular tachycardia.

*Patient 5 did not use amiodarone (amio) or ß-blockers (carvedilol or metoprolol).

†Number of VT episodes in 1 month prior to VT ablation.

voltage in the epicardium. Endocardial dense scarring areas (median, 20.7 cm^2; IQR, 16.3–42.1 cm^2) were statistically similar to epicardial scars (median, 23.5 cm^2; IQR, 18.2–68.4 cm^2; P=0.17); however, individual values of epicardial scars were greater than those of scars on the endocardium in 13 of 17 patients (Figure 5).

Areas exhibiting LPs were found in 14/17 (82%) patients in the endocardial mapping and in 16/17 (94%) in the epicardial mapping (Table 2). All LAZ were observed within the densely scarred areas: 14/15 endocardial scars and 16/17 epicardial scars. Patients 10 and 17 presented 2 nonconfluent LAZs within a region of myocardial scarring in the LV endocardium. Three patients had 2 (patients 7 and 8) or 3 (patient 16) nonconfluent LAZs in the epicardial scar, and there were 2.1±0.8 LAZs per patient (Table 2).

Sixteen endocardial and 20 epicardial nonconfluent LAZs were observed (1.00±0.61 versus 1.24±0.66 LAZ per patient; P=0.3). The average extension of these areas was larger on the epicardium than on the endocardium (8.1±5.8 versus 13.4±9.5 cm^2; P=0.05). In other words, LAZs occupied 23±15% of the endocardial area and 33±12% of the epicardial area of the scar (P=0.04). Individually, the epicardial LAZ area was larger than the endocardial LAZ area in 11 of 17 patients (Figure 5). In a based on mixed effect model, the percentage of LAZ occupying the epicardial scar was 7.7% superior than the endocardium (CI95%, 0.28–15.14%; P=0.04). However, there were no differences between the scar or LAZ areas comparing the endocardium with the epicardium in the mixed model (Table 3).

A total of 2512 electrograms (1289 endocardial and 1223 epicardial) were recorded in the low-voltage area (<1.5 mV): 620/1289 (48%) were endocardial LPs, and 753/1223 (61%) were epicardial LPs (Table 4). These delayed electrograms were more prevalent in the dense scar than in the border zone (1201/1695 [70%] versus 172/817 [21%]; P<0.001). The type of LP (isolated or fragmented) was similar in the dense scar (IDP, 663/1695 [39%] versus LFP, 538/1695 [31%]; P=0.54), but isolated potentials were significantly less frequent in the border zone than in the dense scar (IDP-border zone, 28/817 [3%] versus IDP-dense scar, 663/1695 [39%]; P<0.001). Additionally, the prevalence of LP types was different in the LAZ sectors; IDPs were more frequent in the core than in the EZ (594/865 [68%] versus 97/542 [18%]; P<0.001) and, conversely, FPs were more prevalent in the EZ than in the CZ (411/542 [76%] versus 271/865 [31%]; P=0.001). LP fragmentation was significantly greater in the dense scar than in the border zone (5.0±2.8

Table 2. Endo-Epicardial Substrate Mapping

Pts	Baseline rhythm	EPI-ENDO scar	LV segment of scar	Points/map		ENDO			EPI		
				ENDO	EPI	Scar area, cm^2	LAZ area, cm^2	LAZ number	Scar area, cm^2	LAZ area, cm^2	LAZ number
1	SR	Both	P+B+L	200	320	3.0	1.2	1	10.3	5.6	1
2	SR	Epi	P+B+L	118	425	…	…	0	21.6	6.6	1
3	SR	Both	P+B+L	289	326	18.3	9.5	1	7.2	5.4	1
4	SR	Both	P+B+L	309	394	16.7	2.8	1	20.5	9.9	1
5	SR	Epi	P+B+L	266	287	…	…	0	25.8	6	1
6	SR	Both	P+B+L	298	228	20.7	9.4	1	16	8.5	1
7	SR	Both	Apex	462	534	10.1	…	0	18.9	5.4	2
8	SR	Both	P+B+L	210	408	18.5	2.1	1	75.5	26.1	2
9	SR	Both	P+B+L	258	561	21.6	6.9	1	28.7	10.4	1
10	SR	Both	P+B+L	669	509	55.4	12.4	2	70.1	7.3	1
11	VP	Both	Apex+A+L	594	720	295.4	23.3	1	176	34.8	1
12	SR	Both	Apex	261	289	16.3	3.9	1	17.5	…	0
13	SR	Both	P+B+L	288	388	25.6	5.2	1	44.5	20.4	1
14	SR	Both	P+B+L	446	352	35.4	14.9	1	23.5	7.3	1
15	SR	Both	P+B+L	182	320	10.8	6.7	1	21.2	11.7	1
16	VP	Both	P+B+L	305	495	42.1	9.5	1	98.1	26.3	3
17	SR	Both	P+B+L	468	124	50.3	5.6	2	66.8	1.6	1
All	…	…	…	331±148	393±141	20.7 (16.3–42.1)	8.1±5.8	1.0±0.6	23.5 (18.2–68.4)	12.1±9.5	1.2±0.6

Values are expressed as absolute values, mean±SD or median (P_{25}–P_{75}). A indicates anterior; B, basal; ENDO, left ventricle endocardium; Epi, ventricular epicardium; L, lateral; LAZ, late activation zone; LAZ, late activation zone; P, posterior; Pts, patients; SR, sinus rhythm; and VP, ventricular pacing rhythm.

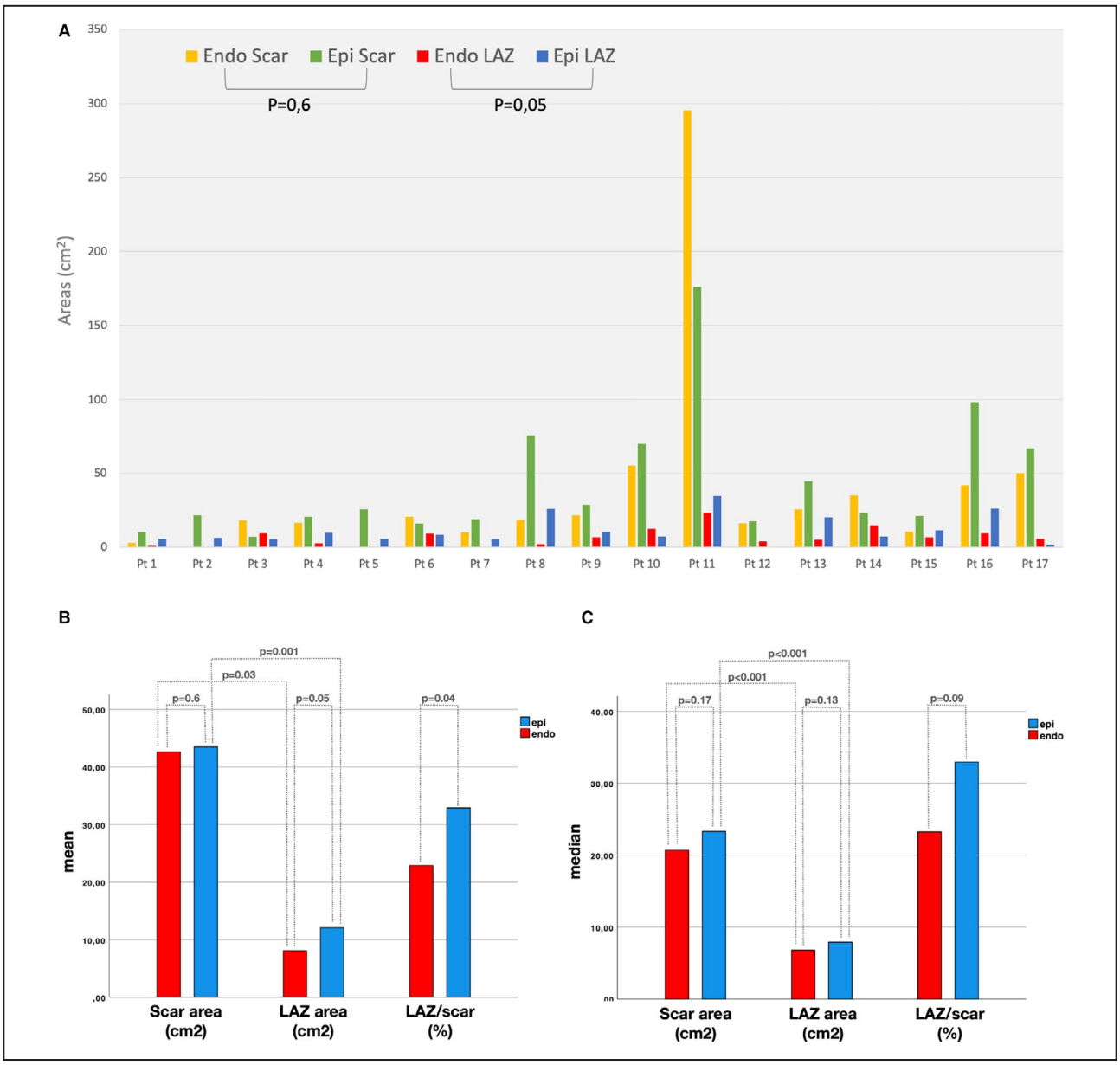

Figure 5. Comparison of endocardial and epicardial areas of the chagasic substrate.
Scar and LAZ areas measured in each patient (A). The mean (**B**) and median (**C**) were showed to compare scar area (*), LAZ area and percentage of LAZ related with the scar (LAZ/scar) between the endocardium (endo) and epicardium (epi). LAZ indicates late activation zone; and Pt, patient. *Scar areas were a non-normally distributed data.

versus 3.3±0.5; *P*<0.001) and in the epicardium than in the endocardium (5.0±3.1 versus 4.2±1.4; *P*<0.001). Additionally, the fragmentation was more pronounced in the core than in the entrance of the LAZ (6.6±3.1 versus 3.4±0.5; *P*<0.001). Finally, amplitudes of LPs were significantly greater in the epicardium than in

Table 3. Comparison Between the Endocardial and Epicardial Mapping According to the Scar and LAZ

Comparison	Variable dependent	Results (average)	CI 95%	*P* value
Endo vs Epi	Areas (cm^2)	−3.31	−19.81 to 13.18	0.69
Endo vs Epi	Scar area (cm^2)	−7.90	−42.86 to 41.27	0.97
Endo vs Epi	LAZ area (cm^2)	−3.98	−10.00 to 2.04	0.18
Scar vs LAZ	Areas (cm^2)	33.74	17.55 to 49.90	<0.0001
Epi vs Endo	Rate of LAZ in the scar (%)	7.7	0.28 to 15.14	0.04

Endo indicates left ventricle endocardium; Epi, ventricular epicardium; and LAZ, late activation zone.

Table 4. Distribution and Characteristics of Bipolar Electrograms

2512 electrograms	Surface mapped		*P* value*	LVA (<1.5 mV)		*P* value†	LAZ (PT area)		*P* value‡
	ENDO	EPI		DS (<0.5 mV)	BZ (0.5–1.5 mV)		Core	Entrance	
N (%)	1289/2512 (51)	1223/2512 (49)	0.18	1695/2512 (67)	817/2512 (32)	<0.001	865/2512 (34)	545/2512 (22)	<0.001
Volt, mV	0.38±0.23	0.36±0.26	0.07	0.25±0.10	0.65±0.20	<0.001	0.25±0.12	0.35±0.15	<0.001
Dur, ms	67±41	72±33	<0.001	82±41	45±10	<0.001	108±40	60±10	<0.001
LPs (n)	620/1289 (48)	753/1223 (61)	0.001	1201/1695 (70)	172/817 (21)	<0.001	865/865 (100)	508/545 (93)	0.26
LPs volt, mV	0.18±0.09	0.20±0.10	0.001	0.18±0.09	0.31±0.10	<0.001	0.17±0.08	0.25±0.10	<0.001
QRS_{end}-LP, ms	43±41	43±19	0.92	47±35	15±9	<0.001	60±32	14±9	<0.001
IDPs (%)	297/1289 (23)	394/1223 (32)	0.12	663/1695 (39)	28/817 (3)	<0.001	594/865 (68)	97/542 (18)	<0.001
LFPs (%)	323/1289 (25)	359/1223 (29)	0.14	538/1695 (31)	144/817 (17)	0.001	271/865 (31)	411/542 (76)	<0.001
Fragmentation§	4.2±1.4	5.0±3.1	<0.001	5.0±2.8	3.3±0.5	<0.001	6.6±3.1	3.4±0.5	<0.001

Values are expressed as absolute values (n), percentages (%), or means±SDs. BZ indicates border zone (0.50–1.50 mV); DS, dense scar (amplitude <0.50 mV); dur, duration of bipolar electrogram; ENDO, left ventricle endocardium; EPI, ventricular epicardium; IDPs, isolated diastolic potentials; LAZ, late activation zone; LFPs, late fragmented potentials; LPs, late potentials; LPs Volt, near-field voltage; LVA, low-voltage area (<1.50 mV); QRS_{end}-LP, interval between the end of QRS and LP; and volt, voltage of bipolar electrogram.

*Comparison between ENDO and EPI.

†Comparison between dense scar and border zone.

‡Comparison between core and entrance of LAZ.

§Fragmentation represents the number of positive deflections of the LFPs.

the endocardium (0.20±0.10 versus 0.18±0.09 mV; *P*=0.001) and the delay between the latest QRS recorded and inscription of LP (QRS_{end}-LP interval) was similar between the endocardial and epicardial mapping (43±41 versus 43±19 ms; *P*=0.92).

A total of 63 sustained monomorphic VTs with a cycle length of 382±68 ms were induced in 17 patients (3.7±2.6; range 1–11), with one patient having only 1 induced VT and the remaining 16 patients having ≥2 induced VTs. Unmappable VTs were considered in 41 (65%) of the induced arrhythmias due to hemodynamic collapse. Therefore, activation and entrainment mapping were possible in only 22 well-tolerated VTs. The cycle length of stable VTs was significantly slower than that of nonmappable VTs (420±75 ms versus 361±55 ms, *P*<0.001).

A total of 31 sites within the VT circuit were identified by entrainment mapping; 1 entrance/inner loop, 10 mid-isthmus, 16 exit-isthmus, 1 bystander, and 3 outer loop sites were identified (Table 5). All mid-isthmus sites (100%) were mapped in the CZ of the areas exhibiting LPs and were located within the dense scar, with a signal amplitude <0.50 mV. Conversely, 13 of the 16 exit sites (81%) were located in the EZ of the LAZ, most commonly found in the scarred myocardium (<0.50 mV). The other 3 exit sites were recorded in the border zone (0.5–1.5 mV) but outside of the LAZ (in other words, without LPs). Sites defined as bystander or entrance/inner loop of reentry were located inside the dense scar and presented LPs during baseline rhythm. The outer loop sites were mapped outside of the LAZ, with signal amplitudes between 0.5 and 1.5 mV (border zone).

Pacemapping was performed at 110 sites in the endocardium and 100 sites in the epicardium (Table 6). All pacemapping sites were located in the low-voltage area (<1.5 mV). One hundred sixty-nine (80%) of these 210 sites had LPs recorded during the baseline rhythm. Seventy-two percent (122/169) of the sites displaying LPs had significantly higher matching pace maps (≥10/12) than pacing at sites (23/210) with low voltage and the absence of LPs (72 versus 10%, *P*<0.001). All pace maps generated within the core of the LAZ (105±41 ms) and densely scarred (94±40 ms) areas presented S-QRS intervals >50 ms; however, pace maps presented shorter S-QRS intervals at sites in the EZ of the LAZ (105±41 ms versus 56±27 ms, *P*<0.001) and voltage border zone (94±40 versus 40±24 ms, *P*<0.001).

Sites meeting these prespecified criteria of putative channels were identified by pacemapping in 55 of 63 VTs and by entrainment in 22 of 63 VTs. Accordingly, endocardial and epicardial critical isthmuses were presumed in 19 (30%) and 36 (57%) of the sustained VTs, respectively.

Table 5. Characteristics of Electrograms Recorded in the Sites of Reentrant Circuits Defined by Entrainment of Stable VT

Sites of reentry circuit	Entrained sites (n, 31)	VT		Baseline rhythm						
							Type of electrogram			
		S-QRS (ms)	Volt (mV)	Volt (mV)	Dur (ms)	QRS_{end}-LP (ms)	IDPs	LFP	FP	NP
Isthmus	10	177±48	0.17±0.06	0.16±0.04	121±29	78±24	6	4	0	0
Exit	16	89±19	0.31±0.11	0.35±0.11	76±35	33±21	7	6	2	1
Outer loop	3	191±163	0.52±0.11	0.55±0.08	45.7±4	…	0	0	0	3
Inner L/ent	1	249	0.23	0.26	72	42	0	1	0	0
Bystander	1	160	0.11	0.16	104	62	1	0	0	0

Values are expressed as value absolute (n) or mean±SD. dur indicates duration of bipolar electrogram; FP, fragmented but not late potentials; IDPs, isolated diastolic potentials; Inner L/ent, inner loop or entrance; LFPs, late fragmented potentials; NP, low-voltage electrogram, with short duration (<50 ms); QRS_{end}-LP, interval between the end of QRS and LP; S-QRS, interval between stimulus artifact and earliest QRS complex of VT by entrainment; volt, bipolar voltage; and VT, ventricular tachycardia.

Catheter Ablation and Immediate Results

Endocardial and epicardial catheter ablation was performed aiming for complete LP elimination in all patients (Table 7). The procedure and fluoroscopic times were 332±68 and 83±37 minutes, respectively. Thirteen of 22 mappable VTs terminated in 12/17 patients during RF application guided by entrainment, and ablation was continued with complete elimination of LPs in 15 of 17 patients (88.2%). A mean of 16±10 and 29±15 RF applications were necessary to eliminate all late LPs in the endocardium and epicardium (P=0.04), respectively. The total RF time was 31±15 minutes (13±8 minutes for endocardial and 22±10 minutes for epicardial ablation; P=0.03). Epicardial ablation was not performed in one patient (patient 17) because the LPs recorded initially in the epicardial mapping disappeared after successful endocardial ablation. Additionally, catheter ablation was performed only in the endocardium (patient 12) or epicardium (patients 5 and 7) due to the single surface location of LAZ in 3 patients.

Ablation failure occurred in 2 (11.8%) patients. In one patient (patient 10), abolishment of LPs was only partially achieved because phrenic nerve capture and the marginal branch of the circumflex artery were within 1 cm of the epicardial LAZ, avoiding epicardial radiofrequency energy delivery. The other patient (patient 2) had pericardial tamponade requiring interruption of the procedure and surgical repair due to laceration of the posterior interventricular vein.

Long-Term Follow-Up

A minimum of 24 months of follow-up was conducted for all surviving patients who underwent ablation (Figure 6 and Figure S2). Fourteen of 17 patients (82%) had no VT during a follow-up of 39±11 months (range 24–56.5). Fourteen of 15 patients with complete LP elimination were free of VT (free VT rate=93.3%). In this group, only one VT recurrence occurred in the 23rd month of follow-up (patient 14); this patient presented a single and self-limited episode of slow VT (126 bpm) without ICD therapy. A low dose of amiodarone (200 mg/day) was restarted, and no further VT episodes were recorded by ICD. Unsuccessful patients (patients 2 and 10) had new VT episodes requiring appropriate ICD therapy (antitachycardia pacing). Table 7 summarizes the results of clinical follow-up.

Amiodarone was reduced in 10 patients and discontinued in 7 patients during follow-up (Figure S1). After 12 months, the amiodarone dosage was reduced from 494±175 to 159±128 mg/day (P<0.001). One patient restarted amiodarone because of inappropriate ICD therapy due to atrial fibrillation (patient 12), and another restarted amiodarone because of VT recurrence (patient 14).

Two patients died from noncardiac causes 24 months after the procedure (Figure S3). Both patients (8 and 11) presented clinical impairment due to sepsis in the 36th and 25th months of follow-up but without VT recurrence. For all patients, LVEF measured by TTE at the 24-month follow-up was not significantly different from the baseline measure (38±7% versus 37±7%; P=0.67).

Abolition of LPs was achieved in 15/17 patients, and 2/15 (patients 14 and 16) kept inducible VT; these VTs had faster cycle lengths (250 and 280 ms) than those induced before substrate ablation. Only patient 14 had VT during follow-up. Patients with partial LP elimination (patient 10) or unsuccessful ablation (patient 2) continued to present inducible VT. During follow-up, the VT recurrence rate was 6.7% in patients with complete LP elimination (1/15 pts) and 100% (2/2 pts) in those with absent or partial abolition. Complete LP elimination had a positive predictive value of 94%, negative predictive value of 100%, sensitivity of 100%, and specificity of 67% for VT recurrence during follow-up (Table 8).

Table 6. Pace-Mapping Results

Substrate mapped	Paced sites n, 210 (%)	S-QRS (ms)	*P* value	Paced ECG match VT (%)		Baseline rhythm					
				<10/12	≥10/12	Volt (mV)	*P* value	Dur (ms)	*P* value	QRS_{end}-LP (ms)	*P* value
LAZ	169/210 (80)	84±43		47/169 (28)	122/169 (72)	0.32±0.10		96±34		50±35	
Entrance	68/210 (32)	56±27	<0.001*	14/68 (21)	54/68 (80)	0.37±0.10	<0.001*	62±14	<0.001*	17±13	<0.001*
Core	101/210 (48)	105±41		33/101 (33)	68/101 (67)	0.24±0.08		119±47		64±32	
Outside	41/210 (20)	35±12	<0.001†	18/41 (44)	23/41 (56)	0.62±0.20	<0.001†	43±11	<0.001†	…	<0.001†
LVA	210 (100)	75±43		65/210 (31)	145/210 (69)	0.35±0.17		86±47		50±35	
BZ	73/210 (35)	40±24	<0.001‡	23/73 (32)	50/73 (68)	0.61±0.16	<0.001‡	49±12	<0.001‡	11±6	<0.001‡
DS	137/210 (65)	94±40		42/137 (31)	95/137 (69)	0.25±0.07		105±47		58±33	
ENDO	110/210 (52)	68±44	0.01§	33/110 (30)	77/110 (70)	0.37±0.19	0.004§	79±54	0.02§	50±45	0.93§
EPI	100/210 (48)	83±42		32/100 (32)	68/100 (68)	0.31±0.12		93±36		50±25	

Values are expressed as absolute values, percentages (%), or means±SDs. BZ indicates border zone (0.50–1.50 mV); DS, dense scar (<0.50 mV); dur, duration of bipolar electrogram; ENDO, left ventricle endocardium; EPI, ventricular epicardium; LAZ, late activation zone; LPs volt, near-field voltage; LPs, late potentials; LVA, low-voltage area (<1.50 mV); QRS_{end}-LP, interval between the end of QRS and LP; and Volt, voltage of bipolar electrogram.

*Comparison of quantitative values (S-QRS interval; volt; dur; and QRS_{end}-LP interval) between the core and entrance of the LAZ.

†Comparison of quantitative values (S-QRS interval; volt; dur; and QRS_{end}-LP interval) between outside and the entrance of the LAZ.

‡Comparison of quantitative values (S-QRS interval; volt; dur; and QRS_{end}-LP interval) between dense scars and border zones.

§Comparison of quantitative values (S-QRS interval; volt; dur; and QRS_{end}-LP interval) between endo and epi.

Table 7. Results of Catheter Ablation and Clinical Follow-Up

Pts	Acute success	LPs ablation	Follow-up (mo)	VT recurrence	Time of recurrence (mo)	LVEF 24th mo (%)	Amio, last visit	Amio doses, last visit (mg/d)	VT events
1	Yes	ENDO+EPI	42	No	…	45	No	0	0
2*	No	No	56.5	Yes	27	43	Yes	400	2
3	Yes	ENDO+EPI	26	No	…	33	No	0	0
4	Yes	ENDO+EPI	35.5	No	…	36	Yes	200	0
5	Yes	EPI	35	No	…	40	No	0	0
6	Yes	ENDO+EPI	56	No	…	45	Yes	0	0
7	Yes	EPI	37	No	…	45	No	0	0
8	Yes	ENDO+EPI	36	No	…	28	Yes	200	0
9	Yes	ENDO+EPI	40.5	No	…	44	Yes	200	0
10†	No	ENDO	35	Yes	21	33	Yes	400	4
11	Yes	ENDO+EPI	25.5	No	…	28	Yes	400	0
12	Yes	ENDO	54.5	No	…	50	Yes	200	0
13	Yes	ENDO+EPI	53	No	…	39	Yes	200	0
14	Yes	ENDO+EPI	36.5	Yes	23	32	Yes	200	1
15	Yes	ENDO+EPI	42	No	…	40	Yes	200	0
16	Yes	ENDO+EPI	25	No	…	28	Yes	200	0
17‡	Yes	ENDO	24	No	…	40	No	0	0
All	…	…	39±11	…	…	38±7	…	165±145	0.41±1

Values are expressed as value absolute or mean±SD. Amio indicates amiodarone; CA, catheter ablation; ENDO, left ventricle endocardium; EPI, epicardium; LPs, late potentials; LVEF, LV ejection fraction; Pts, patients; and VT, ventricular tachycardia.

*Patient 2: development of cardiac tamponade before ablation (see text).

†Patient 10: only late potentials in ENDO.

‡Patient 17: epicardial LPs disappeared with endocardial ablation.

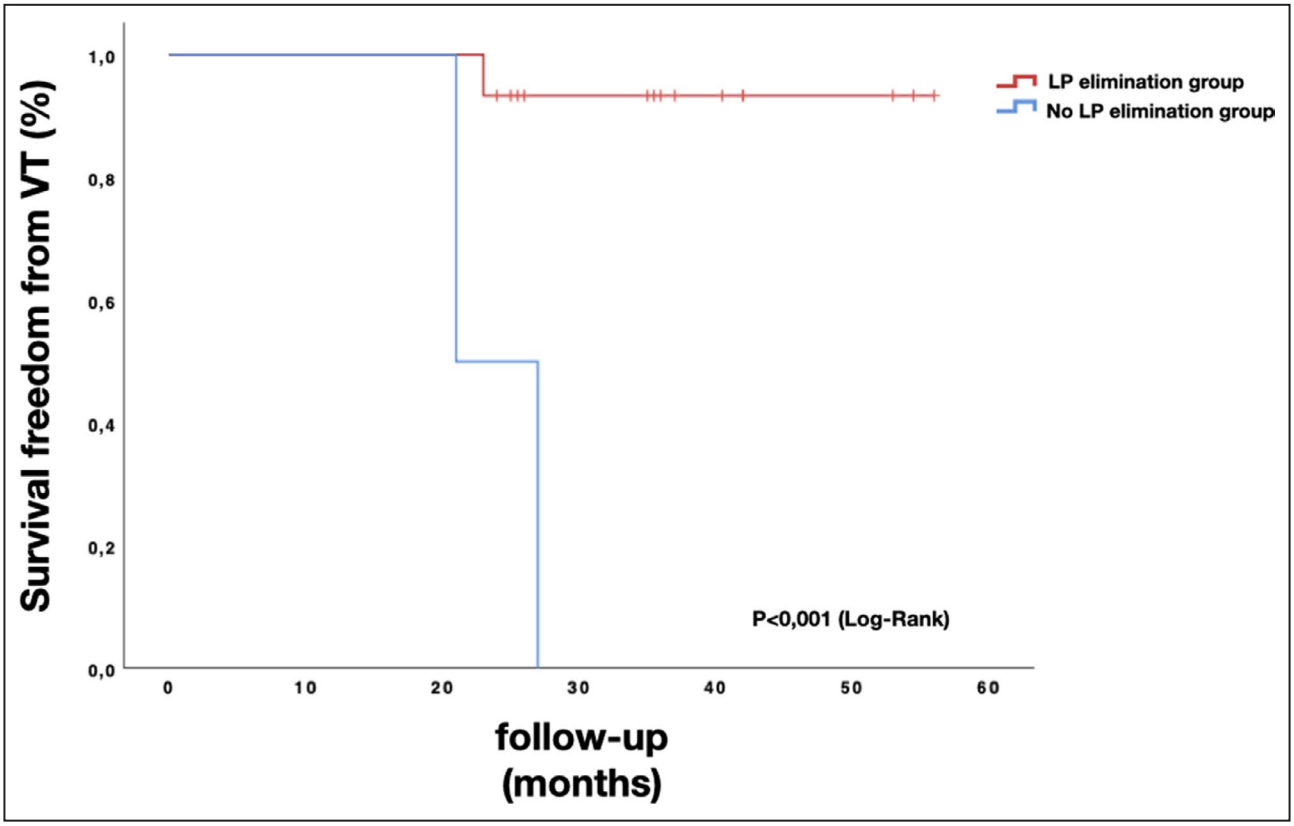

Figure 6. **Kaplan-Meier curve depicting freedom from recurrent ventricular tachycardia (VT) in chagasic patients submitted to substrate ablation with (red line) or without (blue line) elimination of late potentials (LP).**

DISCUSSION

Main Findings

To our knowledge, this is the first study reporting the importance of LPs recorded during sinus rhythm to the underlying substrate in patients with chronic Chagas cardiomyopathy and medically refractory ventricular tachycardia. The main result of this study was that complete abolition of LPs may constitute an effective end point with high acute success during VT ablation in chagasic patients and a low incidence of VT recurrence during long-term follow-up. Secondary findings obtained during endo-epicardial mapping revealed (1) the presence of confluent and transmural scars with a similar extension of myocardial scarring on both mapping surfaces; (2) epicardial scarred tissue was identified in all patients and was related to the majority of induced VTs (rate of 57%); (3) LPs were mainly encountered within these regions of myocardial scarring (<0.5 mV) and were identified by adjusting the latest activation of bipolar electrograms acquired by 3D mapping during baseline rhythm; (4) regions exhibiting LPs were important for the identification of slow conduction channels validated by entrainment and pacemapping during multiple induced VTs; and (5) complete LP elimination presented excellent accuracy to predict VT recurrence during extended follow-up.

Importance of Epicardial Substrate in Patients With Chagas Heart Disease

The pathogenesis of CCC is not entirely understood. Chagas heart disease is characterized by chronic myocarditis that promotes a unique arrhythmogenic substrate.[7] The main aspect of the disease is myocardial inflammation and the consequent necrotic and fibrotic lesions.[4,5,20–22] Microvascular damage or autonomic changes regulating tissue perfusion also contribute to impaired tissue blood flow with fibrotic scarring.[7,21] The inflammatory response also produces electrical decoupling between myocytes, damaging intercellular junctions and resulting in slow and discontinuous conduction.[23] Thus, fibrotic damage to myocardial tissue coupled with electrical conduction abnormalities promotes the substrate necessary for the development of reentrant circuits in chagasic patients.

The present study shows that arrhythmogenic substrate in patients with CCC is commonly found in the subepicardial myocardium with a preferential location in the posterolateral basal segments of the left ventricle,

Table 8. LP Elimination and VT Inducibility as End points of Catheter Ablation

Postablation end point	Pts with complete LP elimination		
	Yes	No	Total
Pts with VT inducibility			
Yes	2	2	4
No	11	0	11
Total	13	2	15

Value are expressed as absolute values. LPs indicates late potentials; Pts, patients; and VT, ventricular tachycardia.

*Postablation programmed ventricular stimulation not performed in 2 patients (excluded by accuracy analysis).

as described by other authors.[6,8,9] A confluent transmural extension of the scar compromising both the subendocardium and subepicardium was predominantly met in our patients, confirming the scarring pattern described in patients with CCC undergoing delayed enhancement cardiac resonance imaging.[24–26] Mello et al showed that an extensive area of transmural fibrosis occupying at least 2 coalescent segments of the LV was an important tool for identifying arrhythmogenic substrates of VT in patients with CCC.[24]

The confluent scarring tissue accounts for up to 25% of the endocardial or epicardial surface; endocardial scar areas were smaller than epicardial scar areas in the majority of our patients without reaching a significant difference. Previously, other authors reported larger epicardial scars than endocardial scars in patients who underwent voltage bipolar mapping to characterize the chagasic substrate.[8,9] Henz et al demonstrated that scars (<0.5 mV) found on the epicardial surface (56.8±40.6 cm^2) have a 2× greater extension than those found on the endocardium (22.5±15.8 cm^2).[8] Similarly, Soto-Becerra et al reported that the epicardial scar area (28 cm^2, IQR 20–36) has a greater distribution than that found in the endocardium (19 cm^2, IQR 15–26).[9] In our analysis, the scar distribution corresponded to an area of 20 cm^2 (IQR, 16–42) in the endocardium and 23 cm^2 (IQR, 18–68) in the ventricular epicardium.

The difference in the findings may have been due to the low number of points used to construct the 3-dimensional voltage map in the study published by Henz et al, in which a sample of 169±77 points/map was acquired in the endocardium and 201±94 in the epicardium.[8] In this way, less dense voltage maps were generated in relation to those outlined in our study in which the LV endocardium was mapped by a sample of 331±148 points and the ventricular epicardium by 393±141 points. In the study by Soto-Becerra et al, the surfaces of the LV were similarly mapped with a high density of points (EPI 452 points/map, 330–560 and ENDO 284, 226–442), which may explain the accordance of scar areas with those found in our population.[9]

In ischemic and nonischemic cardiomyopathy, abnormal conduction tunnels inside the scar are recognized by the presence of delayed electrical activity after the end of the QRS complex, called LPs.[11–13] These electrograms recorded in baseline rhythm have been correlated through electrophysiological mapping with critical points for scar-related VT.[11–13,27] In our study, the areas exhibiting the LPs, called LAZs, were found in all patients through the activation map by adjusting the color bar to include all abnormal ventricular activity recorded after the end of the QRS complex. Late activation mapping defined slow conduction channels of the arrhythmogenic substrate of our patients during baseline rhythm. Other authors have also reported that the activation map can locate areas exhibiting LPs and guide the substrate ablation of VT in patients with nonchagasic cardiomyopathies.[12,28,29]

The majority of LPs in our study were located within dense scars (amplitude 0.30±0.15 mV), accounting for up to 35% of the total myocardial scarring. These LAZs were predominantly confluent, but some patients uncommonly demonstrated nonconfluent areas of LPs on the same mapped surface, representing various abnormal regions within the same scar. The extension of confluent LAZs was higher in the epicardium (13.4±9.5 cm^2) than in the LV endocardium (8.1±5.8 cm^2), suggesting that these activation data may be of considerable importance for the arrhythmogenic scar tissue present in the subepicardial chagasic substrate. Although delayed electrograms are not able to differentiate the central isthmus from adjacent bystander sites, they can delineate and reduce the area of interest for the approach of the substrate in patients with complex VT.

This study suggests that LP mapping could be used to identify specific regions of low voltage inside the diseased myocardium. In agreement with these findings, the importance of LPs has been demonstrated in nonchagasic substrates.[11,17,30] Arenal et al demonstrated that delayed electrograms extended by an area of 3.5±2.6 cm^2 in the postinfarction endocardial scar.[11] These areas were visualized mainly within the dense scar (<0.50 mV) and presented a bipolar amplitude of 0.26±0.11 mV. Similarly, Zeppenfeld et al found regions of low amplitude and abnormal activation (duration >40 ms) forming a 3.1±1.5 cm^2 area of endocardial scarring in patients with ischemic cardiomyopathy that represented a site of interest of VT ablation.[17] In nonischemic cardiomyopathy, Cano et al mapped the presence of 50% abnormally activated electrograms (>80 ms, 2 distinct components or isolated LP) in the low-voltage regions on the ventricular epicardium, with a prevalence of epicardial LPs of 25%.[30]

In this study, LPs were found in all patients with CCC and sustained VT, and their occurrence was

reported and compared with all mapped electrograms, with a prevalence of 54% of the low-amplitude signals (<1.50 mV) and 48% in the areas of dense scarring (<0.50 mV), without differences between the mapped surfaces. Furthermore, the signals recorded inside the CZ of LAZs and dense scarring presented lower amplitude, longer duration, more marked fragmentation and more pronounced latency between the end of QRS and LP (QRS_{end}-PT interval) than those electrograms recorded on the border zone but outside of the LAZ. These data are in agreement with the findings of Zeppenfeld et al in patients postinfarction[17] and Henz et al in chagasic patients, where the duration of electrograms (>46 ms) could be used to better characterize the low-voltage areas mapped in the ventricular epicardium.[8] All these abnormal activities recorded during baseline rhythm can be found inside the myocardial scar of the chagasic substrate of sustained VT.

Late Potentials and Conduction Channels

Late potentials are a marker of slow conduction and can be used to identify the isthmus of the reentry circuit of VT.[31] In our study, LPs that mapped within the confluent low-voltage areas were related to critical components of reentrant sustained VT. Entrainment techniques identified the isthmus of mappable VT inside the dense scar and the core zone of the LAZ; exit sites were mapped predominantly in the entrance of the LAZ at the edge of the border zone. The prevalence of LPs was 100% in the central isthmus and 80% in exit sites. Interestingly, the latency of these delayed electrograms (such as duration, fragmentation, and QRS_{end}-LP interval) was more pronounced in the sites defined as central isthmus than as the exit of stable VTs. These findings demonstrate that abnormal conduction channels of chagasic VT were associated with a high prevalence of LPs and that the critical points for reentry can be located within the dense scar, where electrical conduction abnormalities are more pronounced.

The definition of the central isthmus by entrainment has been described within postinfarction myocardial scarring.[32,33] Soejima et al and Hsia et al showed that these sites located in the critical pathway for sustained reentry had bipolar amplitudes of 0.32±0.16 and 0.33±0.15 mV recorded in the baseline rhythm, respectively.[32,33] These authors observed that in sinus rhythm, the amplitudes of exit signals were higher than those recorded into the central isthmus.[32,33] In contrast, the electrograms recorded during the non-VT rhythm of our chagasic patients showed amplitudes of 0.16±0.04 mV in the central isthmus and 0.35±0.11 mV in the exit sites defined by entrainment during VT. The lower voltage findings in our patients may be explained by the intensity and heterogeneity of these substrates, with slower and deeper channels located within the chagasic myocardium than in postinfarction tissue.

LPs have been described as components of the reentry circuit in patients with ischemic and nonischemic cardiomyopathy.[10,27] Bogun et al and Hsia et al observed that all sites of the central isthmus were located inside the dense scar (<0.50 mV), with a high prevalence of late potentials (>90%)[10,27] and that exit sites were found predominantly outside of the dense scar, with a signal amplitude between 0.50 and 1.50 mV and lower prevalence of LP (20%).[10] They also reported that the interval from the QRS to the isolated diastolic potential recorded in sinus rhythm was longer in the central isthmus than in the exit sites, emphasizing that LPs may be markers of putative channels of the reentry circuit.[10,27]

Additionally, abnormal conduction channels defined by pace mapping were able to indicate critical components in chagasic patients with unstable VT. Pace mapping from sites with LPs within the LAZ has a longer stimulus QRS interval and good or perfect matching with VT morphology. Similarly, Bogun et al showed that 65% of the pace mapping performed at sites displaying isolated potentials was associated with well- or perfectly matched VT compared to only 5% of sites without late electrograms.[27] Additionally, Brunckhorst et al reported that paced sites with an S-QRS interval ≥40 ms were found within the postinfarction scar and located in 79% of sites near the isthmus of the VT, which is considered a target of catheter ablation.[34] In contrast to findings in chagasic patients, these authors also reported that a paced site showing good or perfect matching with VT morphology did not improve the ability to locate the target of ablation since only 54% of these sites were near the isthmus of the reentrant circuit.[34]

Sites meeting prespecified criteria of putative channels were identified by pacemapping or entrainment in 55 of 63 induced VTs, with a predominantly epicardial channel in 57% of the sustained VTs. All conduction channels discovered by pacemapping were located inside of the LP areas, with more prolonged propagation of electrical impulses in the CZ than in the EZ of the LAZ. Importantly, this finding allows us to verify that the channels responsible for sustained reentry present exit at the edge of the scar border and the central isthmus inside the scar, where the highest prevalence of LPs is found. In agreement with this chagasic study, Nayyar et al performed pace mapping at multiple sites of the postinfarcted substrate to locate abnormal conduction channels and characterize those capable of perpetuating the VT reentry circuit.[35] Fifty-seven channels able to sustain VT were found, with 97% inside of a dense scar (0.10–0.50 mV) extending to the border zone in 48%.[35] Furthermore, the S-QRS interval (73 ms) within these low-voltage channels resembled those verified in

this chagasic study (75 ms), which also supports the arrangement and preferential conduction of channels in the chagasic substrate.

Chagasic substrate mapping during baseline rhythm was able to find confluent and individualized areas of LPs within the dense scar, allowing accurate clarification of the complex circuit of multiple VTs. These findings demonstrate the importance of a complete representation of the low voltage and abnormal activation regions to characterize the arrhythmogenic substrate of chagasic patients and to use an effective approach. As other authors have described, a high prevalence of the epicardial substrate justifies the concomitant endo-epicardial mapping.[8,9] Furthermore, the abnormal activation of electrograms recorded during baseline rhythm within low-voltage epicardial regions minimizes the influence of epicardial adipose tissue, which can reduce the signal amplitude without interfering with the duration.

Catheter Ablation and Outcomes

In this study, substrate-based ablation was performed for all chagasic patients targeting the complete elimination of LPs. Using this approach, we achieved excellent VT-free survival at least comparable to that reported in other studies in which similar substrate modifications were used in patients with ischemic or nonischemic cardiomyopathies.[11–13,36,37] Importantly, there was also an overall reduction in amiodarone doses without prejudice to the control of arrhythmic events, allowing us to minimize the adverse effects of the chronic use of the medication. These findings were reported by other authors, demonstrating a significant reduction in the need for amiodarone in the postablation substrate period to control VT in patients with chronic ischemic cardiomyopathy.[38]

The recurrence of VTs was continuously monitored with an ICD during an extended follow-up period. This reveals a significant long-lasting decrease in VT after substrate ablation in patients who had experienced frequent VT episodes. After acute procedural success, 88% of patients remained completely free from VT during at least 24 months of follow-up (39 months). In a single case of recurrence in this success group, VT was significantly slower and self-limited without ICD therapy.

There are a few publications focusing on electroanatomical substrate mapping and ablation in patients with CCC and VT.[8,9] Henz et al reported a low recurrence of VT (6 of 17 patients) but during a short follow-up period (<1 year).[8] By simultaneous endo-epicardial mapping, linear lesions guided by pace mapping or fractionated potential were used in 14 of 18 procedures differently from our study in that the success of substrate ablation was guided purely by a delayed electrogram approach.[8] In another publication, Soto-Becerra et al (69) also reported low recurrence (16%) in 19 chagasic patients who underwent endo-epicardial ablation with a different approach (as guided by activation and entrainment mapping or abnormal delayed electrograms during sinus rhythm) and were followed for 13 months.[9]

Highly effective ablation can be achieved by the abolition of multiple VT channels present in the complex substrate. In this study, we reached a rate of 3.6 induced VTs, which represents approximately double the rate found in the studies of Soto-Becerra et al (1.8 VTs/patient) and Henz et al (1.6 VTs/patient).[8,9] This finding can justify the excellent result of LP ablation, with efficacy demonstrated both during the procedure and clinical follow-up.

After LP abolishment, high-energy pacing inside the target region was performed to assure electrically unexcitable scarring and to minimize the influence of the far-field signal on substrate ablation. In agreement with this aspect, Baldinger et al reported postablation stimulation as a lesion creation indicator through abolition of local capture or prolongation of the S-QRS interval to >72%.[39] Refinement of the recognition of the residual substrate after ablation by response to local stimulation allows limiting the unnecessary extension of the ablation and subsequently increasing the time of the procedure.

Prior studies also showed that LPs can be used as targets of catheter ablation for VT in patients with nonchagasic cardiomyopathy.[11–13,36,37] In the study by Arenal et al, successful LP ablation was achieved in 19/24 patients (79.2%), with no VT recurrence during 9 months of follow-up.[11] Vergara et al described that complete LP abolition could be achieved in 84% of patients, with only 9.5% of this successful group presenting arrhythmia recurrence during follow-up.[12] In another study, Jaïs et al reported that patients with a complete absence of local abnormal ventricular activity (termed LAVA) at the end of the procedure had an arrhythmia-free survival rate (68%) higher than patients who did not reach this goal of catheter ablation (20%).[13] Other authors have also shown that the ablation of abnormal ventricular activity into the myocardial scarring by the technique of scar dechanneling or core isolation was associated with low recurrence rate (16.4% and 14%, respectively) for long-term clinical follow-up (21 and 17.5 months, respectively).[36,37]

The limitations of epicardial ablation precluded the complete elimination of LPs in 2 patients: (1) coronary vessels and the phrenic nerve near the target region of ablation and (2) vascular damage during pericardial access. Baldinger et al reported the reasons for the failure of epicardial ablation.[40] The main limitations of epicardial ablation include failure to identify a target for catheter ablation and proximity to coronary vessels or the phrenic nerve.[40] Furthermore, acute complications related to epicardial access occurred in 9% of cases,

with the most frequent being bleeding into the pericardial space.[40]

Interestingly, in this study, LPs recorded initially in the epicardial mapping disappeared after successful endocardial ablation in one patient, suggesting transmural connections or deeper radiofrequency lesions. Prior studies also reported this finding in patients who underwent catheter ablation for VT.[13,41] Komatsu et al reported the feasibility of an approach for the modification of subepicardial substrate by endocardial ablation, with this aspect being achieved more frequently in ischemic heart disease (28%) and right ventricular arrhythmogenic dysplasia (40%) than in nonischemic cardiomyopathy (8%).[41] The progression from the subendocardium to the epicardium in post-myocardial infarction and the lower thickness of the right ventricular myocardial wall in patients with arrhythmogenic right ventricular dysplasia (ARVD) were possible explanations for the results.[41] In contrast, arrhythmic substrates in nonischemic cardiomyopathy are located predominantly intramurally or subepicardially with minimal subendocardial scarring.[30] The possibility of interconnection between the endo-epicardial substrate can be explained by the unique aspect of scar formation that progresses predominantly from the subepicardium to the subendocardium in perivalvar segments of the LV of chagasic patients.

The study described the predictive value of complete LP elimination for assessing the results of VT ablation in chagasic patients. In this aspect, excellent accuracy in predicting an arrhythmia-free survival rate was found by endo-epicardial abolition of delayed activity of the LAZ. In agreement with these findings, prior reports showed the value of abnormal activity abolished by catheter ablation as an independent predictor of VT-free survival rate.[12,13] Other authors reported that ventricular programmed stimulation performed instantly or short-term postablation can be a relevant tool to assess the arrhythmia-free survival rate during clinical follow-up.[42,43]

The extended period of follow-up (39±11 months) showed an excellent reduction in VT burden and ICD discharges. The majority of the patients presented a good clinical prognosis, without clinical impairment of ventricular function. Two patients died from noncardiac causes. A prior report found frequent discharges of ICDs as an independent predictor of cardiovascular mortality in patients with CCC.[44] The reduction in burden ICD shocks has been related to the clinical improvement of patients with ischemic or nonischemic cardiomyopathy by decreasing cardiovascular mortality and hospitalization for heart failure.[42,45,46]

Study Limitations

The population of this study consisted of stringently selected patients who underwent VT catheter ablation but cannot represent all patients with CCC and VTs. However, the procedure indications represent a large proportion of patients referred for scar-related VT ablation in the setting of structural heart disease.[47]

Although it was conducted prospectively, the positive outcome reached by the target of catheter ablation could be influenced by the observational study coupled with potential bias in patient selection. The results demonstrate a promising ablation strategy and propose the need for clinical studies to assess whether the elimination of LPs definitively improves the clinical outcome in the chagasic population with sustained VT.

The potential difficulties of electrogram analysis with an 8 mm tip catheter were overcome by high-density mapping and complete filling of electrical signals in the substrate region. Importantly, the large tip catheter ensured deeper effective RF lesions to achieve the main end point in the study. An open-irrigated ablation catheter was instituted only in the last patient included in the study, making it impossible to compare the characteristics of the electrograms and parameters of RF energy delivery. Furthermore, substrate modification by catheter ablation could be related to more destruction of myocardial tissue than necessary to achieve clinical success, but this finding was minimized by adequate characterization and elimination of low-amplitude delayed electrograms of the chagasic substrate. Additionally, we used a <1.50 mV cutoff to characterize the low-voltage tissue during endo-epicardial mapping. Although this value may overestimate the low-voltage region, we defined an amplitude of <0.50 mV signal coupled with abnormal activity as the target of catheter ablation. Additionally, we demonstrated that the presence of LPs within regions of myocardial scarring increases the likelihood of finding arrhythmogenic channels critical for maintaining VT. In comparison with the HD Grid or Pentaray catheters which are the current standard tools for high density mapping, the use of an 8 mm ablation catheter for the substrate mapping was a limitation of the study.

CONCLUSIONS

Ventricular tachycardia in patients with chronic Chagas cardiomyopathy can be effectively treated by late potential ablation based on baseline rhythm electrogram mapping. Confluent regions exhibiting clusters of these low-voltage delayed electrograms were highly correlated with critical components of chagasic VT. Therefore, channels could be identified in all patients with chagasic VTs by adjusting the latest activation time of the bipolar late electrogram in the activation maps. Epicardial substrate involved in the VT circuit was commonly verified in chagasic patients, justifying a combined endo-epicardial approach. The low incidence of arrhythmic recurrences during extended

follow-up reinforces the importance of the complete recognition and ablation of arrhythmogenic substrates in chagasic patients.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Figures S1–S3

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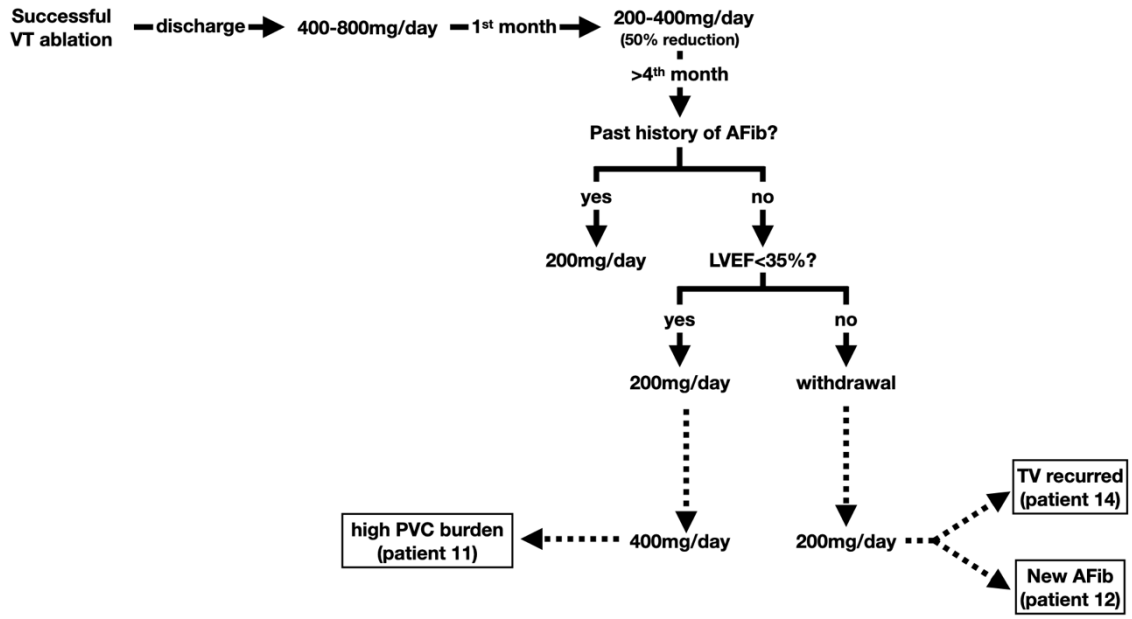
SUPPLEMENTAL MATERIAL

Figure S1. Protocol after the success ablation regarding decreasing or withdrawal of amiodarone.



After hospital discharge, the patients received amiodarone (400-800mg/day), which was reduced to 200-400mg/day (ie, reduced 50%) during the 1st month after ablation. After 4th month, amiodarone was again reduced to 200mg/day or completely withdrawal, depending of baseline left ventricle ejection fraction (LVEF) or past history of atrial fibrillation (AFib). In patients with a LVEF below 35% or AFib, amiodarone was maintained in the dose of 200mg/day. Otherwise, amiodarone was withdrawal in patients with LVEF above 35% or without AFib. After success ablation, three patients had to restart or increase amiodarone (dashed arrows): one because ventricular tachycardia (VT) recurred (patient 14); other patient due to AFib triggering an inappropriate ICD therapy (patient 12); and another patient (patient 11) had a high premature ventricular contraction (PVC) burden during the follow-up, which it was relieved with a higher dose (400mg/day).

Figure S2. Kaplan-Meier curve demonstrating event-free survival rate of 82% over a mean follow-up of 39±11 months in 17 patients who had presented for recurrent ventricular tachycardia and underwent substrate ablation (green line).

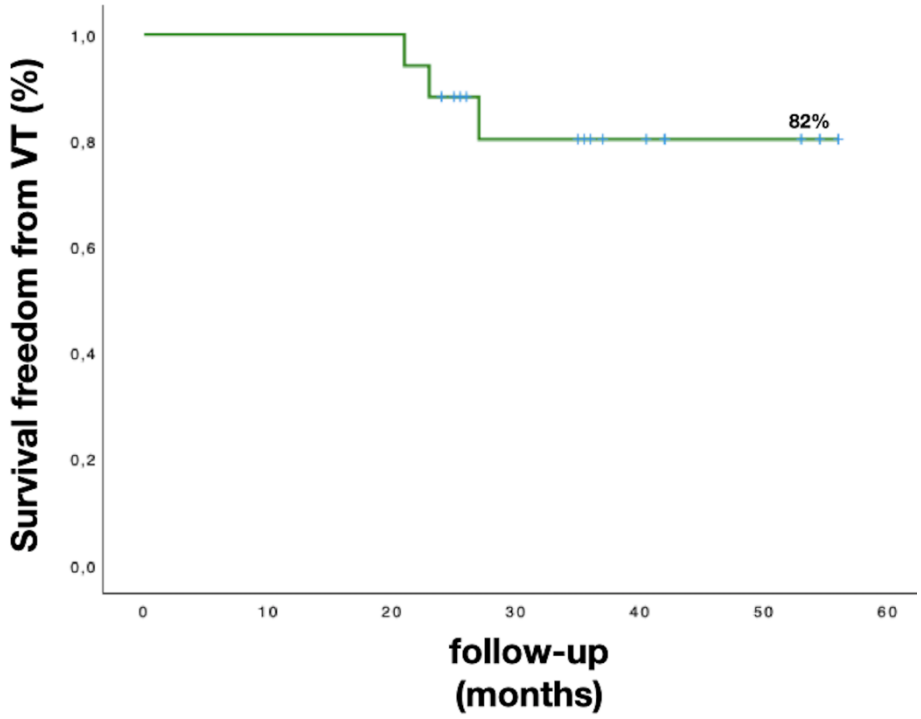
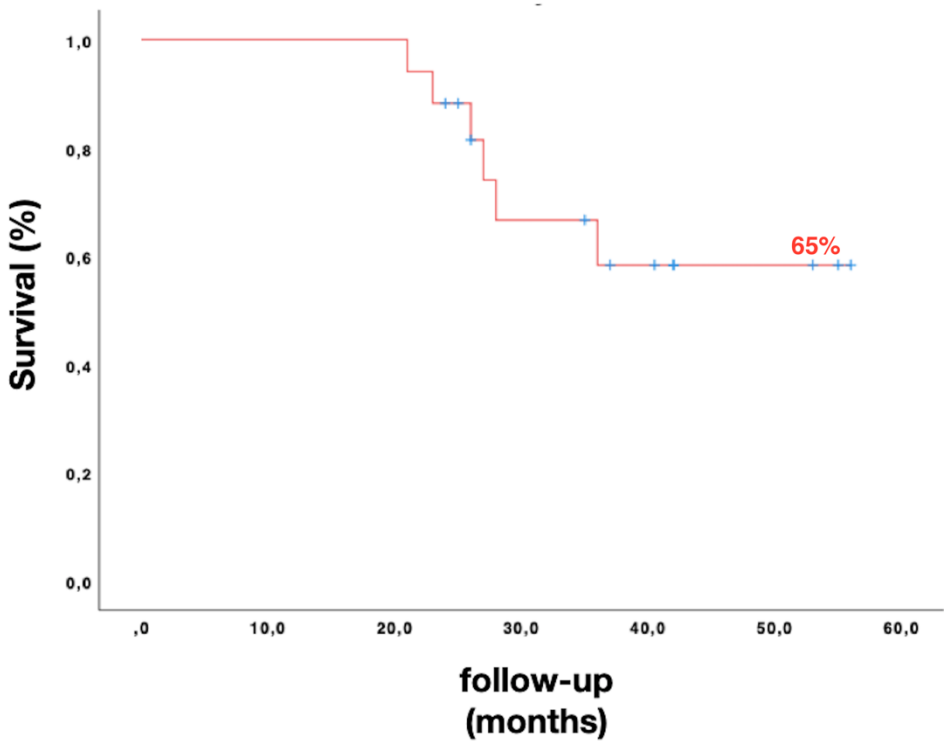


Figure S3. Kaplan-Meier curve estimates of composite clinical endpoint (all-cause mortality, heart failure hospitalization or ventricular tachycardia episode) in chagasic patients who were treated with substrate ablation.



During the follow-up, three patients presented VT; one patient was hospitalized due to heart failure; and 2 patients died.