Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 21, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.01.041

QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Characterization of the Arrhythmogenic Substrate in Ischemic and Nonischemic Cardiomyopathy

Implications for Catheter Ablation of Hemodynamically Unstable Ventricular Tachycardia

Shiro Nakahara, MD, PHD, Roderick Tung, MD, Rafael J. Ramirez, PHD, Yoav Michowitz, MD, Marmar Vaseghi, MD, Eric Buch, MD, Jean Gima, RN, MN, NP, Isaac Wiener, MD, Aman Mahajan, MD, PHD, Noel G. Boyle, MD, PHD, Kalyanam Shivkumar, MD, PHD

Los Angeles, California

Objectives The purpose of this study was to compare the characteristics and prevalence of late potentials (LP) in patients with nonischemic cardiomyopathy (NICM) and ischemic cardiomyopathy (ICM) etiologies and evaluate their value as targets for catheter ablation.

Background LP are frequently found in post-myocardial infarction scars and are useful ablation targets. The relative prevalence and characteristics of LP in patients with NICM is not well understood.

Methods Thirty-three patients with structural heart disease (NICM, n = 16; ICM, n = 17) referred for catheter ablation of ventricular tachycardia were studied. Electroanatomic mapping was performed endocardially (n = 33) and epicardially (n = 19). The LP were defined as low voltage electrograms (<1.5 mV) with onset after the QRS interval. Very late potentials (vLP) were defined as electrograms with onset >100 ms after the QRS.

Results We sampled an average of 564 ± 449 points and 726 ± 483 points in the left ventricle endocardium and epicardium, respectively. Mean total low voltage area in patients with ICM was 101 ± 55 cm^2 and 56 ± 33 cm^2, endocardial and epicardial, respectively, compared with NICM of 55 ± 41 cm^2 and 53 ± 28 cm^2, respectively. Within the total low voltage area, vLP were observed more frequently in ICM than in NICM in endocardium (4.1% vs. 1.3%; p = 0.0003) and epicardium (4.3% vs. 2.1%, p = 0.035). An LP-targeted ablation strategy was effective in ICM patients (82% nonrecurrence at 12 ± 10 months of follow-up), whereas NICM patients had less favorable outcomes (50% at 15 ± 13 months of follow-up).

Conclusions The contribution of scar to the electrophysiological abnormalities targeted for ablation of unstable ventricular tachycardia differs between ICM and NICM. An approach incorporating LP ablation and pace-mapping had limited success in patients with NICM compared with ICM, and alternative ablation strategies should be considered. (J Am Coll Cardiol 2010;55:2355–65) © 2010 by the American College of Cardiology Foundation

Catheter ablation of hemodynamically unstable ventricular tachycardia (VT) relies on substrate mapping of sites critical for re-entry. Late potentials (LP), commonly seen in post-infarction scars, reflect areas of myocardium where conduction is slowed and interrupted by fibrosis (1,2). Although LP are not specific for critical isthmuses, they are highly sensitive as a guide for targeting ablation in patients with ischemic cardiomyopathy (ICM) (3–5). The prevalence and value of LP as ablation targets in patients with nonischemic cardiomyopathy (NICM) remains unknown.

Analysis of human explanted hearts with dilated cardiomyopathy has revealed fibrosis, myocyte disarray, and membrane abnormalities (6,7). Fractionated electrograms in patients with NICM have been attributed to lines of activation block from fibrosis, resulting in nonuniform conduction (8). However, scar in NICM differs from infarct scar with less confluence, a basal predilection, and less endocardial involvement (9–11). The purpose of this study was to compare the characteristics and prevalence of LP within scar tissue in patients with NICM and ICM and to assess their value as ablation targets.

From the University of California, Los Angeles, Cardiac Arrhythmia Center, David Geffen School of Medicine, Los Angeles, California. Supported by the National Heart, Lung, and Blood Institute (R01-HL084261 and R01-HL067647 to Dr. Shivkumar). Dr. Shivkumar's institution has received support from St. Jude Medical and Biosense Webster; this support is unrelated to the current study. Drs. Nakahara and Tung contributed equally to this work.

Manuscript received October 19, 2009; revised manuscript received January 5, 2010, accepted January 11, 2010.

JACC Vol. 55, No. 21, 2010
May 25, 2010:2355–65

Abbreviations and Acronyms

BZ = border zone
DS = dense scar
ICM = ischemic cardiomyopathy
LP = late potentials
mLP = moderate late potentials
NICM = nonischemic cardiomyopathy
TCL = tachycardia cycle length
TLV = total low voltage
vLP = very late potentials
VT = ventricular tachycardia

Methods

Patient selection. Electroanatomic data were obtained from 33 patients with structural heart disease referred for catheter ablation of VT from August 2004 to April 2006, and November 2007 to April 2009. Eleven patients with incomplete data were excluded (2006 to 2007). The diagnosis of NICM was based on the absence of coronary artery disease (>75% stenosis), prior myocardial infarction, or significant valvular abnormality. The diagnosis of ICM was established by prior myocardial infarction with Q waves, focal wall motion abnormality, or fixed perfusion defect correlated with >75% coronary stenosis. All studies were done under general anesthesia after pre-procedural transesophageal echocardiography excluded intracardiac thrombus. All patients underwent endocardial mapping; epicardial mapping was performed at the discretion of the operator. Written informed consent was obtained from all patients. The institutional review board approved review of these data.

Electroanatomical mapping and electrogram analysis. Endocardial mapping was performed through a trans-septal approach. An activated clotting time goal of ≥300 s was maintained throughout the procedure with intravenous heparin. Pericardial access was obtained by subxiphoid puncture as previously described (12,13), before heparinization. Epicardial access was performed surgically in patients with previous thoracotomy (n = 5), as described previously (14). Electroanatomic voltage mapping was performed during baseline rhythm using CARTO (Biosense-Webster, Diamond Bar, California) or NavX (Ensite, St. Jude Medical, St. Paul, Minnesota) systems. Bipolar electrograms were recorded with CARTO using irrigated or nonirrigated Navi-Star catheters (3.5- or 4-mm tip electrode, Biosense-Webster). Multipolar mapping with NavX was performed with a duodecapolar catheter (Livewire, 2-2-2 mm, St. Jude Medical). All points >8 mm from the geometry were considered to represent insufficient contact and were excluded. Three-dimensional bipolar electroanatomic maps were displayed with dense scar (DS) defined as ≤0.5 mV, border zone (BZ) from 0.51 to 1.50 mV, and total low voltage area (TLV) as ≤1.5 mV. During creation of the voltage map, LP sites were tagged. The areas TLV, BZ, and DS were measured offline using the incorporated software in both commercial systems. Bipolar electrograms were filtered from 30 to 300 Hz, displayed at 100 mm/s. Electrogram timing was measured manually offline.

The LP were defined as low voltage electrograms (≤1.5 mV) with a distinct onset after the QRS, showing double or multiple components separated by a very low amplitude or isoelectric interval of >20 ms (3,5). Very late potentials (vLP) were electrograms with onset >100 ms after the QRS (15). Moderate late potentials (mLP) were electrograms with onset <100 ms after the QRS. The same definition was applied across patients with intrinsic and paced complexes (Fig. 1). Electrogram duration was measured from the onset to the offset of the local electrogram. The LP were quantified both as total number and percentage of sampled points.

We verified catheter stability and electrogram reproducibility by sampling repeatedly (up to 9 preceding electrograms) at each location. The morphology and timing were analyzed by 2 observers and determined by consensus.

Catheter ablation. Programmed stimulation was performed with up to triple ventricular extrastimuli testing, drive cycle lengths 600 and 400 ms, 10 ms decrement down to 200 ms or refractoriness. After VT was induced, a second induction was performed to assess for reproducibility or a second distinct morphology. Induced VTs were stored as a template for pace-mapping, and a targeted VT was defined as: 1) similar to 12-lead of presenting VT, if available; 2) similar in tachycardia cycle length (TCL) seen on implantable cardioverter-defibrillator interrogation; or 3) reproducibly

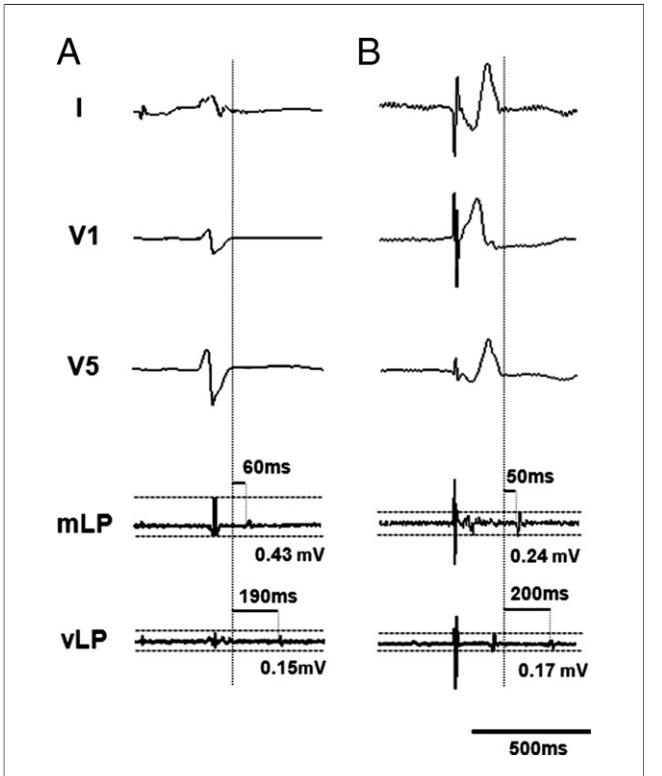

Figure 1 Examples of mLP and vLP

Examples of moderate late potentials (mLP) and very late potentials (vLP): recordings from left ventricular mapping sites during **(A)** atrial pacing rhythm and **(B)** biventricular pacing rhythm.

inducible. Ventricular fibrillation was not counted as a VT morphology.

Ablation was performed at pace-mapping sites that showed perfect (12 of 12 match) and good matches (10 of 12 match) for the targeted VT. Additional ablation was delivered at tagged sites with LP within and around the DS. These lesions were connected within the DS, and lesions were extended to the BZ. If the mitral annulus was within 2 cm of the TLV area, an ablation line to connect the two was created (n = 2). Radiofrequency energy (50 W maximum) was delivered through a 3.5-mm tip open-irrigation catheter (ThermoCool, Biosense Webster), 4-mm tip closed-irrigation catheter (Chilli II, Boston Scientific, Natick, Massachusetts), or 8-mm tip Navistar catheter (n = 4).

At the end of the ablation procedure, programmed electrical stimulation was repeated in the same fashion as pre-ablation induction. In cases where hemodynamic instability was present, testing was not performed. Acute procedural success was defined as complete noninducibility after ablation. Partial success was defined as inducibility of a non-targeted VT. Recurrence of VT after hospital discharge was assessed by interrogation of the implantable cardioverter-defibrillator (n = 30 of 32) and patient interview.

Statistical analysis. All continuous data are presented as mean ± SD, compared using unpaired Student *t* test. Comparison of proportions was performed by chi-square test or Fisher exact test. Examination of normal quantile plots and the Shapiro-Wilk goodness-of-fit statistic showed that the distribution of vLP, mLP, and total LP did not always follow a Gaussian distribution. Therefore, we report medians and quartiles, and use the Mann-Whitney *U* test to compute p values of NICM versus ICM. A value of $p < 0.05$ was considered statistically significant.

Table 1 Baseline Characteristics

Patient #	Etiology	Age (yrs)	Sex	LVEF (%)	ICD	Antiarrhythmic Drugs	No. of Prior Procedures	Map	No. of Induced MVTs	Epicardial Access
1	Nonischemic	52	M	35	Yes	Amio	2	Epi and Endo	1	Puncture
2	Nonischemic	56	F	15	Yes	Amio	0	Epi and Endo	1	Puncture
3	Nonischemic	64	M	20	Yes	Amio	0	Epi and Endo	2	Puncture
4	Nonischemic	38	F	55	Yes	Amio, procain	0	Endo	2	
5	Nonischemic	68	M	20	Yes	Amio	1	Epi and Endo	5	Puncture
6	Nonischemic	54	M	35	Yes	Amio	1	Epi and Endo	3	Puncture
7	Nonischemic	48	F	30	Yes	Amio	1	Epi and Endo	2	Puncture
8	Nonischemic	50	M	25	Yes	Amio+Mex	1	Epi and Endo	1	Puncture
9	Nonischemic	70	M	30	Yes	Amio	1	Endo	5	
10	Nonischemic	75	M	20	Yes	Amio	0	Epi and Endo	3	Puncture
11	Nonischemic	60	M	20	Yes	Amio	1	Endo	2	
12	Nonischemic	70	M	45	No	Sota+Lido	1	Endo	2	
13	Nonischemic	50	M	20	Yes	Amio	2	Epi and Endo	2	Puncture
14	Nonischemic	50	M	10	Yes	Mex	1	Epi and Endo	6	Puncture
15	Nonischemic	76	M	20	Yes	Amio	0	Epi and Endo	3	Puncture
16	Nonischemic	58	M	25	Yes	Amio	0	Epi and Endo	1	Puncture
Mean ± SD		59 ± 11	—	27 ± 12	—	—	0.8 ± 0.7	—	2.6 ± 1.6	—
17	Ischemic	73	M	10	Yes	Amio+Sota+Mex	3	Endo	2	
18	Ischemic	74	M	25	Yes	Amio	0	Endo	3	
19	Ischemic	59	M	15	Yes	Amio	2	Epi and Endo	2	Surgical
20	Ischemic	75	M	30	Yes	Amio	0	Endo	2	
21	Ischemic	53	M	25	Yes	Amio+Mex	0	Endo	3	
22	Ischemic	70	M	20	Yes	Amio+Mex	0	Endo	2	
23	Ischemic	61	M	20	Yes	Amio+Mex	0	Epi and Endo	2	Puncture
24	Ischemic	71	M	25	Yes	Amio+Mex	0	Endo	2	
25	Ischemic	65	M	35	Yes	Amio	1	Epi and Endo	2	Surgical
26	Ischemic	81	M	35	Yes	Amio	0	Epi and Endo	1	Puncture
27	Ischemic	76	M	10	Yes	Amio	0	Endo	2	
28	Ischemic	75	M	20	Yes	Amio	0	Endo	2	
29	Ischemic	71	M	20	Yes	Amio	0	Endo	3	
30	Ischemic	64	M	20	Yes	Amio	0	Epi and Endo	2	Surgical
21	Ischemic	75	F	25	Yes	Amio	0	Endo	3	
32	Ischemic	67	M	15	Yes	Sota	1	Epi and Endo	2	Surgical
33	Ischemic	71	M	15	Yes	Amio	1	Epi and Endo	3	Surgical
Mean ± SD	—	69 ± 7	—	21 ± 7	—	—	0.5 ± 0.9	—	2.2 ± 0.6	—

Amio = amiodarone; Endo = endocardial; Epi = epicardial; ICD = implantable cardioverter-defibrillator; Ischemic = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; Lido = lidocaine; Mex = mexiletine; MVT = monomorphic ventricular tachycardia; Nonischemic = nonischemic cardiomyopathy; Sota = sotarol.

JACC Vol. 55, No. 21, 2010
May 25, 2010:2355–65

Results

Patient characteristics. Baseline patient characteristics of 33 patients (16 NICM, 17 ICM) are shown in Table 1. The majority of patients were male (88%), with mean age 64.2 ± 10.5 years, mean ejection fraction 23.9 ± 9.8%. Most patients (97%; 32 of 33) had an implantable cardioverter-defibrillator; mean number of prior ablation attempts per patient was 0.6 (median 0, range 0 to 3). All patients were previously treated with at least 1 antiarrhythmic drug.

All patients had inducible monomorphic VT with endocardial programmed stimulation, and most VTs (87%; 69 of 79) were hemodynamically unstable. The mean number of induced VTs was 2.4 ± 1.1 (2.6 ± 1.6 in patients with NICM and 2.2 ± 0.6 in patients with ICM). The mean TCL was shorter in NICM patients than in the ICM group (421 ± 88 ms and 488 ± 104 ms, respectively; p = 0.003).

Electroanatomic mapping. The findings on electroanatomical mapping are shown in Table 2. The majority of maps were created using the NavX system (76%; 25 of 33). Detailed endocardial mapping was performed in all patients, and epicardial mapping in 58% (19 of 33: 12 in NICM, 7 in ICM). The average number of points sampled was 564 ±

Table 2 Electrogram and Electroanatomical Mapping Data

	NICM Patients	ICM Patients	p Value
EAM (NavX/Carto)	12/4	13/4	>0.999*
Underlying rhythm (non-V pace/BIV/RV)	10/6/0	10/6/1	0.616†
CLBBB	1	2	>0.999*
QRS duration	159 ± 42	167 ± 30	0.538‡
Mean number of mapped EGMs			0.104‡
Endo	432 ± 389	687 ± 476	0.104‡
Epi	659 ± 507	759 ± 484	0.677‡
TLV ≤1.5 mV area, cm^2			
Endo	55 ± 41	101 ± 55	0.012‡
Epi	53 ± 28	56 ± 33	0.796‡
DS ≤0.5 mV area, cm^2			
Endo	26 ± 21	63 ± 39	0.002‡
Epi	26 ± 19	33 ± 21	0.442‡
BZ 0.51–1.5 mV area, cm^2			
Endo	30 ± 28	38 ± 22	0.367‡
Epi	27 ± 21	23 ± 15	0.698‡
DS as percent of TLV area, %			
Endo	41 ± 24	61 ± 17	0.009‡
Epi	47 ± 27	55 ± 17	0.501‡
TLV sampling density, patients/cm^2			
Endo	5.3 ± 3.3	5.4 ± 3.0	0.961‡
Epi	10.8 ± 6.8	9.2 ± 5.1	0.606‡
No. of vLP			
Endo	3.0 (0.5, 6.5)	21.0 (9.5, 31.5)	<0.0001§
Epi	4.5 (0, 13.5)	29.0 (11, 29.8)	0.0169§
No. of mLP			
Endo	7.0 (4.5, 10.5)	12.0 (4.8, 14.3)	0.4064§
Epi	6.5 (2, 27.5)	10.0 (8.5, 29)	0.5818§
No. of TLP			
Endo	9.5 (5.0, 19.5)	32.0 (19.3, 45.3)	0.0013§
Epi	13.0 (2.5, 45.5)	39.0 (19, 51)	0.3513§

	Non-V Pace	V Pace	p Value	Non-V Pace	V Pace	p Value
No. of vLP						
Endo	3.0 (1.0, 3.0)	3.0 (0, 10.0)	NS§	23.0 (10, 31)	20.0 (8.5, 31.5)	NS§
Epi	5.0 (0, 13.0)	4.5 (0, 14.0)	NS§	21.0 (5.3, 27.0)	29.5 (20.0, 36.0)	NS§
No. of mLP						
Endo	8.0 (6.0, 11.0)	6.0 (3.0, 8.0)	NS§	6.5 (5.0, 13.0)	12.0 (6.0, 21.3)	NS§
Epi	5.0 (0, 26.0)	9.5 (4.0, 29.0)	NS§	10.0 (2.5, 25.0)	10.5 (9.0, 20.0)	NS§
No. of TLP						
Endo	9.5 (8.0, 20.0)	8.5 (5.0, 17.0)	NS§	30.5 (20.0, 39.0)	32.0 (18.3, 45.8)	NS§
Epi	10.0 (0, 44.0)	14.0 (4.0, 47.0)	NS§	39.0 (9.8, 48.0)	40.0 (29.0, 56.0)	NS§

Values are expressed as mean ± SD, or median (quartiles). *Fisher exact test was used. †Chi-square test was used. ‡Unpaired Student *t* test was used. §Nonparametric Mann-Whitney *U* test was used. BIV = biventricular; BZ = border zone area; CLBBB = complete left bundle branch block; DS = dense scar area; EAM = electroanatomical mapping system; EGM = electrogram; mLP= moderate late potentials; NS = nonsignificant; RV = right ventricular; TLP= total late potentials; TLV = total low-voltage area; V = ventricular; vLP= very late potentials; other abbreviations as in Table 1.

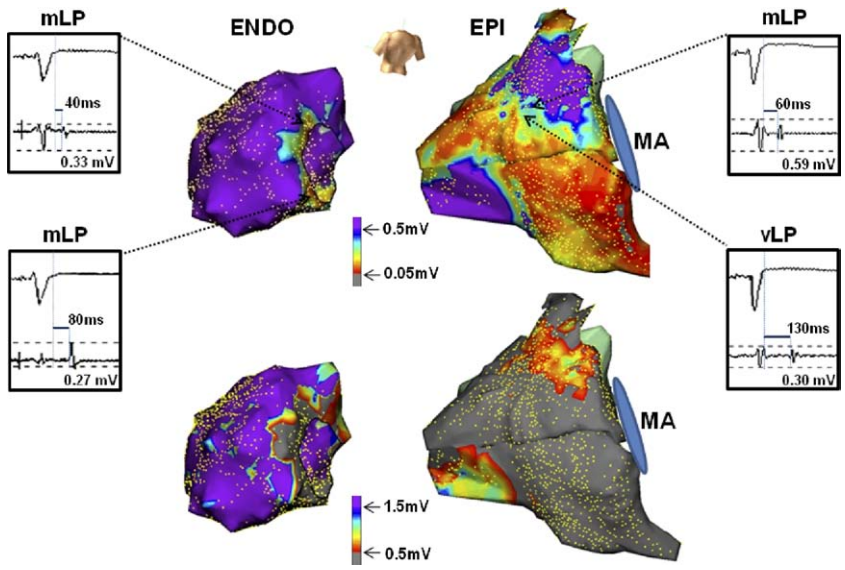

Figure 2 **Endocardial and Epicardial Electroanatomical LV Voltage Maps From a Representative Patient With Nonischemic Cardiomyopathy**

Posteroanterior view of the endocardial (ENDO) and epicardial (EPI) left ventricular (LV) voltage maps showing basal regions of dense scar at 2 voltage threshold scales. Among late potentials (LP) seen, moderate late potentials (mLP) outnumbered very late potentials (vLP). MA = mitral annulus.

449 and 726 ± 483 in the left ventricular endocardium and epicardium, respectively. Concealed entrainment was performed and demonstrated in 2 VTs.

Figure 2 shows a typical combined map in a patient with NICM demonstrating a patchy basal region of low voltage area on endocardial mapping with significantly greater epicardial scar area. In 15 of 16 patients with NICM (94%), low voltage areas were demonstrated on endocardial mapping (Table 2). A basal predilection was observed in 93% (14 of 15) of cases. Similarly, 10 of 12 patients (83%) who underwent epicardial mapping demonstrated epicardial low voltage areas, with a basal location in 90%, typically involving the corresponding inferolateral free wall. In patients with NICM, the TLV areas were comparable on the endocardium and epicardium (55 ± 41 cm^2 and 53 ± 28 cm^2, respectively; p = NS).

Figure 3 shows a typical combined map for a patient with ICM with inferolateral infarction. In all patients with ICM, low voltage areas were identified on endocardial maps. In patients with ICM, endocardial infarcts were located anteriorly in 24% (4 of 17), inferiorly in 52% (9 of 17), and inferolaterally in 24% (4 of 17). All 7 ICM patients (41%) who underwent epicardial mapping demonstrated evidence of epicardial scar extension. Anterior 29% (2 of 7), inferior 43% (3 of 7), and inferolateral 29% (2 of 7) locations were observed in these patients. The mean TLV area (≤1.5 mV) in patients with ICM was larger in the endocardium than epicardium (101 ± 55 cm^2 vs. 56 ± 33 cm^2) (Table 2, Fig. 4A).

Mean TLV in the endocardium was significantly larger in the ICM group than the NICM group (101 ± 55 cm^2 vs. 55 ± 41 cm^2, respectively; p = 0.012) (Table 2, Fig. 4A). A similar difference was observed with DS areas (63 ± 39 cm^2 vs. 26 ± 21 cm^2; p = 0.002). The DS occupied a larger percentage of the TLV in patients with ICM compared with NICM (61 ± 17% vs. 41 ± 24%; p = 0.009) (Table 2). No differences were observed in BZ areas between patients with NICM and ICM on epicardial mapping (23 ± 22 cm^2 vs. 23 ± 15 cm^2, respectively; p = nonsignificant) or endocardial mapping (30 ± 28 cm^2 vs. 38 ± 22 cm^2, respectively; p = nonsignificant). Additionally, no differences were seen in epicardial scar area between patients with ICM and NICM (TLV 56 ± 33 cm^2 vs. 53 ± 28 cm^2, and DS 33 ± 21 cm^2 vs. 26 ± 19 cm^2, respectively).

LP. Multiple LP were identified in all patients on both endocardial and epicardial maps, with one exception. There was no difference in sampling density between the NICM and ICM groups on endocardial and epicardial surfaces (Table 2). Figure 5 shows a histogram of the total number of LP sorted by voltage amplitude. Eighty-three percent of all LP analyzed were identified within DS on both epicardial and endocardial surfaces in both NICM and ICM groups.

With regard to the total number of LP, patients with NICM had significantly fewer endocardial LP than did patients with ICM (median 9.5 vs. 32.0; p = 0.0013) (Table 2). This difference was driven by a larger proportion of vLP seen in patients with ICM (median 21.0 vs. 3.0, p < 0.0001). Although no difference in total LP was seen between NICM and ICM groups on epicardial maps, NICM patients had significantly fewer vLP compared with ICM patients (median 4.5 vs. 29.0; p = 0.0169) (Table 2, Fig. 4B). Patients with paced complexes were analyzed separately from patients with intrinsic ventricular com-

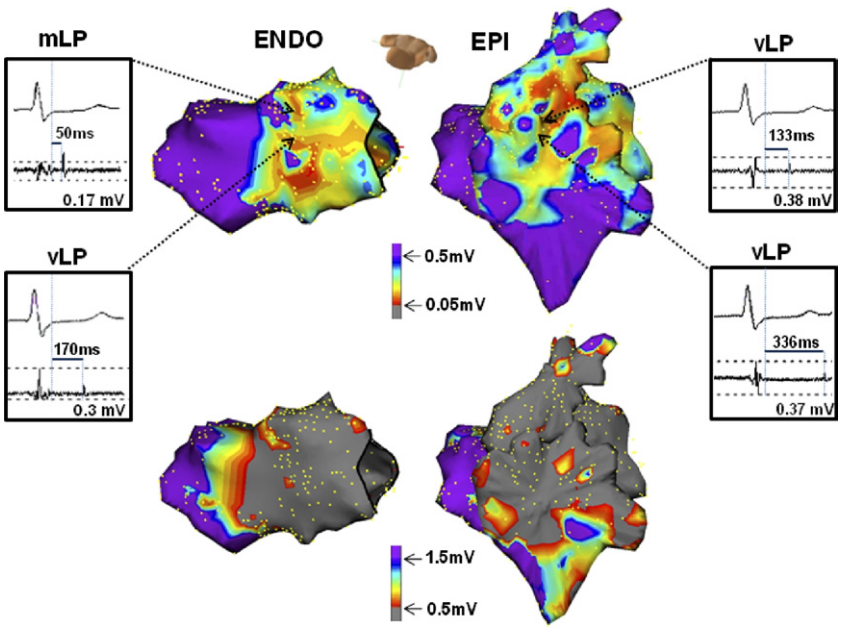

Figure 3 **Representative Endocardial and Epicardial Maps From a Patient With Ischemic Cardiomyopathy**

Inferior view of the LV voltage maps showing inferolateral infarction on both ENDO and EPI surfaces at 2 voltage threshold scales. Among LP seen, vLP outnumbered mLP. Abbreviations as in Figure 2.

plexes, and we found no significant differences in the number of total LP and vLP between these groups in patients with ICM and NICM (Table 2).

Among all endocardial points sampled in the TLV (≤1.5 mV), 1.3% in NICM and 4.1% in ICM demonstrated vLP. In epicardium, 2.1% in NICM and 4.3% in ICM of all epicardial points sampled demonstrated vLP (Table 3). Additionally, local electrogram duration of all LP within TLV was longer in patients with ICM than in patients with NICM (endocardial 325 ± 106 ms vs. 240 ± 100 ms, respectively; $p < 0.0001$; epicardial 312 ± 105 ms vs. 203 ± 83 ms, respectively; $p < 0.0001$). In the ICM group, there were no differences in local electrogram duration of all LP within TLV between endocardium and epicardium (325 ± 106 ms vs. 312 ± 105 ms, p = NS). In the NICM group, local electrogram duration was longer in endocardium than epicardium (240 ± 100 ms vs. 203 ± 83 ms, respectively, $p < 0.0001$).

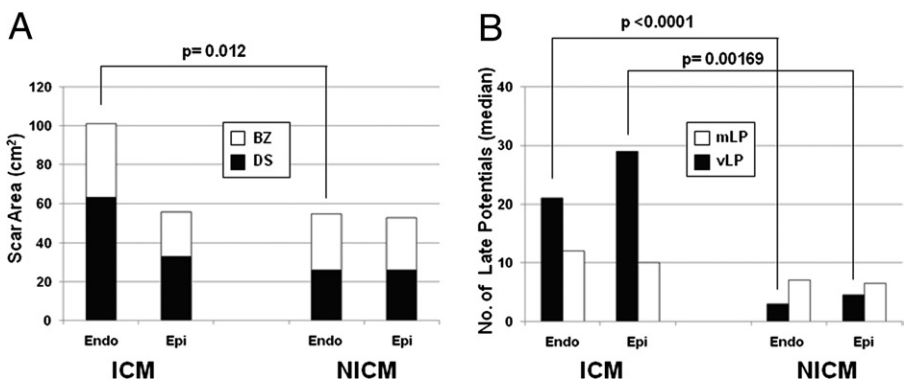

Figure 4 **Differences in Scar Area and LP Between NICM and ICM Substrates**

(A) Endocardial (Endo) scar area was twice the epicardial (Epi) scar area in patients with ischemic cardiomyopathy (ICM). Patients with nonischemic cardiomyopathy (NICM) in this cohort had equal extent of scar on the endocardium and epicardium. Less dense scar (DS) **(solid bars)** was observed in patients with NICM. **Open bars** indicate border zone (BZ). **(B)** Patients with ICM had more LP than did patients with NICM. This difference was driven by a greater number of vLP **(solid bars)** in ICM. **Open bars** indicate mLP. Abbreviations as in Figure 2.

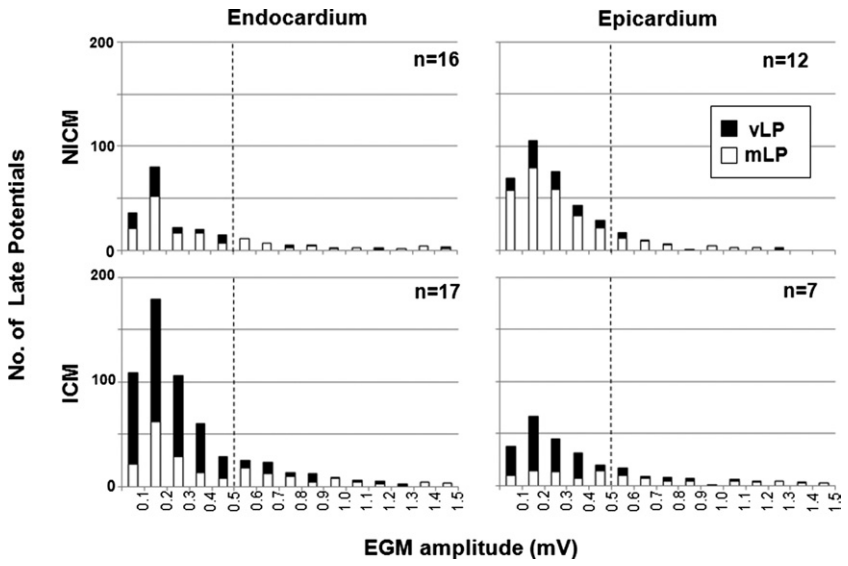

Figure 5 Endocardial and Epicardial LP Histograms

Endocardial and epicardial LP histograms in low voltage areas from patients with NICM **(upper panels)** and ICM **(lower panels)** with total number of LP plotted against electrogram (EGM) amplitude in 0.1 mV bin sizes. The **vertical dashed lines** delineate DS from BZ. **Solid bars** = vLP; **open bars** = mLP. Abbreviations as in Figures 2 and 4.

Pace-mapping and catheter ablation. Catheter ablation was performed epicardially and endocardially in 9 patients (NICM, n = 6; ICM, n = 3), endocardially in 22 patients (NICM, n = 9; ICM, n = 13), and epicardially only in 1 patient (NICM, n = 1). An LP-based ablation strategy combined with pace-mapping was feasible in all patients with ICM. Although all patients with NICM demonstrated LP, 3 patients had <5 total LP and pace-maps did not match the targeted VT at these sites.

Among ICM patients who underwent endocardial mapping, 14 of 17 (83%) had the best pace-map on the endocardium. Among patients who underwent epicardial mapping in the ICM group, 2 of 7 (29%) had either excellent or good pace-maps that matched the targeted VT better than endocardial pace-mapping. Ablation at these sites acutely rendered the VT noninducible and did not have recurrence in follow-up. Among NICM patients who underwent endocardial mapping, 7 of 16 (44%) had the best pace-map from the endocardium. Pace-maps from the epicardium were better than endocardium in 4 of 12 (33%) patients, and these patients did not have clinical recurrence after ablation at these sites. Among ICM patients, 6 perfect pace-map sites were identified (5 with LP), and 10 good pace-maps sites were identified (7 with

Table 3 Distribution of LP in Low Voltage Area

	Endocardium			Epicardium		
	NICM (n = 16)	ICM (n = 17)	p Value	NICM* (n = 10)	ICM (n = 7)	p Value
DS (≤0.5 mV)						
vLP	1.8 (0, 2.9)	6.0 (4.8, 8.8)	<0.0001	2.2 (0.4, 6.3)	5.6 (4.8, 8.2)	0.057
mLP	2.9 (1.4, 6.1)	1.5 (1.0, 3.4)	0.188	6.2 (3.2, 12.8)	2.4 (2.0, 4.0)	0.082
Total LP	5.0 (4.1, 6.7)	9.6 (7.4, 11.5)	0.011	9.1 (5.8, 15.4)	8.9 (7.2, 10.4)	0.828
BZ (0.51–1.5 mV)						
vLP	0 (0, 0.2)	1.1 (0, 2.2)	0.0330	0.2 (0, 0.7)	0.2 (0, 5.7)	0.503
mLP	1.9 (0.8, 5.4)	1.2 (0, 4.4)	0.662	1.2 (0.4, 3.9)	1.2 (0.3, 4.7)	0.961
Total LP	2.3 (1.0, 5.4)	2.3 (1.3, 5.6)	0.539	2.8 (0.4, 4.2)	1.9 (0.7, 10.4)	0.660
Total low voltage area (≤1.5 mV)						
vLP	1.3 (0.3, 2.4)	4.1 (2.9, 7.6)	0.0003	2.1 (0.8, 3.4)	4.3 (3.4, 7.5)	0.035
mLP	3.7 (2.0, 5.4)	1.5 (1.1, 3.5)	0.072	4.0 (2.3, 7.0)	1.5 (1.2, 4.9)	0.261
Total LP	4.6 (3.1, 7.2)	7.7 (5.5, 10.3)	0.061	6.8 (2.8, 10.1)	7.1 (5.4, 10.4)	0.733

Results reported as percent of total electrograms sampled and displayed as median (quartiles). *In 10 nonischemic cardiomyopathy (NICM) patients, LP were assessed in the confluent abnormal low voltage areas away from vascular structures. All p values for comparing NICM to ischemic cardiomyopathy (ICM) used the nonparametric Mann-Whitney *U* test.

Abbreviations as in Table 2.

Table 4 Results of Mapping and Ablation

Patient #	Mapped Rhythm	Low Voltage Area (cm^2) Endo (DS/TLV)	Low Voltage Area (cm^2) Epi (DS/TLV)	Location Endo	Location Epi	Putative Isthmus Sites	Outcome Acute	Outcome Intermediate
Nonischemic								
1	Sinus	29/44	10/33	Basal-inferolateral	Basal-inferolateral	Epi	Failed	No Rec
2	Sinus	58/144	4/40	Basal-inferolateral-septum	Basal-mid-inferolateral	Endo	Complete	No Rec
3	Sinus	6/15	0/0	Basal-anterior	LV base	Epi + Endo	Partial	No Rec
4	Sinus	0/2.3	—	Basal-inferolateral	—	Endo	Partial	No Rec
5	A	41/66	47/55	Basal-inferolateral	Basal-mid-inferolateral	Epi + Endo	Complete	No Rec
6	A	14/26	29/53	Basal-inferolateral	Basal-mid-inferolateral	Epi + Endo	Complete	No Rec
7	BiV	48/117	40/73	Basal-septum, lateral	Basal-mid Inferolateral	Endo	Complete	No Rec
8	BiV	11/34	24/30	Basal-inferolateral-septum	Basal-inferolateral	Endo	Complete	No Rec
9	Sinus	11/33	—	Basal-septum	—	Endo	Partial	Rec
10	Sinus	16/40	0/0	Basal-septum	LV base	Endo	Partial	Rec
11	Sinus	54/74	—	Inferior	—	Endo	Partial	Rec
12	Sinus	53/68	—	Anteroseptal	—	Endo	Failed	Rec
13	BiV	10/39	55/73	Basal-inferolateral	Basal-mid Inferolateral	Epi + Endo	Complete	Rec
14	BiV	44/77	8/23	Basal-anteroseptal	Basal-mid Inferolateral	Epi + Endo	Partial	Rec
15	BiV	0/0	4/30	None	Inferoapical	Endo	Partial	Rec
16	BiV	15/108	34/115	Inferolateral	Basal-mid-inferolateral	Endo	Complete	Rec
Ischemic								
17	Sinus	36/52	—	Anteroseptal	—	Endo	Complete	No Rec
18	Sinus	87/146	—	Anterior	—	Endo	Complete	No Rec
19	Sinus	122/167	32/49	Inferolateral	Inferolateral	Epi + Endo	Complete	No Rec
20	Sinus	14/35	—	Inferior	—	Endo	Complete	No Rec
21	A	67/102	—	Inferior	—	Endo	Complete	No Rec
22	A	42/96	—	Anteroseptal	—	Endo	Complete	No Rec
23	A	9/51	2/10	Inferolateral	Inferior	Endo	Complete	No Rec
24	A	47/64	—	Inferior	—	Endo	Complete	No Rec
25	A	31/48	14/22	Inferior	Inferior	Epi + Endo	Complete	No Rec
26	BiV	93/127	42/89	Anteroseptal	Anterior	Endo	Complete	No Rec
27	BiV	152/220	—	Inferior	—	Endo	Complete	No Rec
28	BIV	108/200	—	Inferior	—	Endo	Partial	No Rec
29	BiV	75/92	—	Inferolateral	—	Endo	Complete	No Rec
30	RV	35/72	30/48	Inferolateral	Inferolateral	Epi + Endo	Complete	No Rec
31	Sinus	38/48	—	Inferior	—	Endo	Partial	Rec
32	BIV	67/96	66/92	Anteroseptal	Anterior	Endo	Complete	Rec
33	BiV	51/101	46/85	Inferior	Inferior	Endo	Partial	Rec

A = atrial pace; Complete = complete noninducible; LV = left ventricular; N/A = not available; Partial = partial-inducible for nontargeted ventricular tachycardia; Rec = recurrence; other abbreviations as in Tables 1 and 2.

LP). Among NICM patients, 2 perfect pace-map sites were identified (1 with LP), and 9 good pace-map sites were identified (4 with LP).

The ablation results are summarized in Table 4. The acute success rate (complete, noninducible) was 44% (7 of 16) in NICM and 82% (14 of 17) in ICM ($p < 0.05$). The intermediate success rate was 50% (8 of 16) in NICM patients (average follow-up of 15 ± 13 months), and 82% (14 of 17) in ICM patients (average follow-up of 12 ± 10 months).

Overall, there were no significant differences in LP duration between patients with or without VT recurrence, in both NICM and ICM groups. In the ICM group, no differences in the total number and percentage of total LP, mLP, and vLP were noted between patients who had recurrence and clinical success. Additionally, there were no significant differences in TLV and DS area. No differences in TCL were seen between patients who had recurrence and patients who did not, although patients with recurrence had more induced VTs (2.1 ± 0.6 vs. 3.0 ± 1.0, $p = 0.048$).

In the NICM group, patients who had recurrence had a fewer number of vLP compared with patients who did not have recurrence (4.9 ± 7.3 vs. 14.0 ± 9.3, $p = 0.047$). As a percentage of total sampled points, fewer vLP were also seen in patients who had recurrence, although this difference was not statistically significant. (1.1% vs. 3.0%, $p = 0.1$). There was no difference in total number and percentage of LP and mLP, TLV, and DS area between patients with NICM who had successful ablation and those who had recurrence. Although there was a trend toward more VTs induced in patients who had recurrence (2.1 ± 1.4 vs. 3.0 ± 1.7, $p = 0.27$), this was not statistically significant. The

TCL was shorter in patients with NICM who had recurrence compared with patients who did not (402 ± 67 ms vs. 457 ± 99 ms; p = 0.04).

Discussion

Main findings. The current study is the first to define the arrhythmogenic substrate in NICM by detailing the prevalence and characteristics of LP in comparison with patients who have ICM. Significantly fewer numbers of endocardial and epicardial vLP were recorded in patients with NICM than with ICM, both in absolute number and as a percentage of points sampled within TLV areas. An ablation strategy targeting LP and pace-mapping showed limited success in patients who have NICM compared with patients who have ICM.

When entrainment mapping cannot be performed because of hemodynamic instability, a strategy relying on electrogram characteristics and electroanatomic mapping is necessary for successful ablation of VT. Bogun et al. (16) demonstrated that vLP (200 ± 131 ms after QRS) were more predictive of critical conducting channels than mLP that closely followed (48 ± 30 ms) the QRS. Sites with perfect pace-maps within a VT circuit demonstrated vLP in 99% of cases, with a mean electrogram duration of 241 ± 83 ms (5). Arenal et al. (3) demonstrated that an ablation strategy aimed at abolishing all isolated LP combined with pace-mapping (>2 components separated by a 50-ms isoelectric interval, or >150 ms from right ventricle stimulus artifact) was effective in suppressing all but 1 clinical VT among 24 patients, with a 79% freedom from VT recurrence at 9 months. Our data are consistent with these previous studies of ICM-related VT and supports the concept that vLP are excellent targets for catheter ablation in ICM patients.

The finding of larger endocardial than epicardial scar area in patients with ICM is consistent with the ischemic wavefront of necrosis phenomenon (17). Endocardial areas of DS and TLV were larger in ICM patients than in NICM patients. Epicardial scar was observed in all 7 patients with ICM who underwent epicardial mapping, with an equivalent percentage of vLP seen on endocardial mapping (4.3% vs. 4.1%). Epicardial vLP were more frequent within TLV in ICM patients compared with NICM patients, supporting a complementary role of epicardial mapping and ablation in patients with ICM. However, the measurement of epicardial local electrogram onset may be longer than on the endocardium due to transmural conduction delay.

The electroanatomic substrate in patients with NICM referred for refractory monomorphic VT has been described previously (9). Our findings corroborate the published literature demonstrating a basal perivalvular predilection in NICM scar. In contrast to findings reported by Soejima et al. (18) and Cano et al. (19), we did not observe significant differences between epicardial and endocardial scar areas in patients with NICM. Our findings are more consistent with those of Bogun et al. (10), where epicardial scar area was greater than endocardial scar in 5 of 14 patients based on delayed contrast-enhanced magnetic resonance imaging, although 50% of patients with NICM did not have an identifiable scar. This may represent varying degrees of referral bias, as NICM patients in these previous studies had more prior endocardial ablation attempts than in the present study—Soejima et al. (18) 1.0 prior ablations, Cano et al. (19) 1.8 prior ablations, and present study 0.6 prior ablations—and may illustrate the heterogeneity of the nonischemic population.

The 50% success rate for NICM VT ablation at 15 months is consistent with previous studies (9,18). Among patients referred for epicardial mapping because of failed endocardial ablation, Cano et al. (19) recently reported a success rate of 71% at 18 months, which is higher than our experience. Patients with NICM in our cohort had fewer LP on the epicardium as a percentage of TLV points sampled (6.8% vs. 25.8% in Cano et al. [19]) despite higher sampling density in our study (659 ± 507 vs. 363 ± 147). Further studies are required to determine the impact of the number of mapped LP on ablation success and clinical outcomes. Although Cano et al. (19) set the low voltage threshold at <1.0 mV, differences in scar substrates from referral bias may account for differences between these cohorts.

In the present study, the mean number of VTs induced (2.4 ± 1.1) was fewer than what is reported in the literature: 3 ± 2 in the Euro-VT study (20), and 3 median in the ThermoCool trial (21). This is likely the result of our practice to perform the ablation procedure under general anesthesia and to limit pre-ablation induction to 2 programmed stimulations in most cases. The routine use of general anesthesia without hemodynamic support systems also likely accounts for the relatively higher prevalence of untolerated VTs in this cohort.

Implications. Early studies by Cassidy et al. (22), demonstrated fewer abnormal electrograms in patients who had cardiomyopathy compared with patients who had myocardial infarction. The cellular mechanisms responsible for differences in scar formation are unknown. As scar in NICM tends to be smaller and less confluent than in ICM, the re-entrant circuit may have different anatomic and functional properties that affect propagation. In contrast to DS with isolated surviving myocardial bundles, scar in NICM that is patchy may have fewer fixed boundaries and protected channels or isthmuses, which may alter the extent of local conduction slowing. Despite fewer LP and vLP in patients with NICM compared with ICM, the percentage of mLP was consistently higher within DS in patients who have NICM on both endocardial and epicardial mapping. Although these differences were not statistically significant, the trend of a higher mLP percentage in NICM than ICM supports a lesser extent of functional conduction slowing or less bordered conducting channels in NICM. The local electrogram duration was also much longer in patients with

ICM, in both endocardium and epicardium. These findings suggest that the scar and fibrosis resulting from nonischemic etiologies is distinctly different from post-infarct scar. Additionally, sites with vLP were usually clustered in 1 region (n = 6) or 2 regions (n = 10) in patients with ICM. In contradistinction, vLP in patients with NICM were distributed sporadically.

In this study, patients with NICM had shorter TCLs compared with those with ICM. Additionally, NICM patients with recurrence had shorter mean TCL and fewer vLP mapped than NICM patients without recurrence. The differences in cycle length may result from smaller scar areas and fewer targeted LP in NICM patients with recurrence. In the ICM group, no differences were observed in TCL between patients with recurrence and those without. The relative effects of antiarrhythmic therapy on conduction slowing in re-entrant circuits in NICM compared with ICM is not known.

At present, there is no consensus on the optimal ablation lesion set for a given scar with unmappable VT. Although no study to date has compared the efficacy of different ablation strategies, "scar homogenization" with ablation of all electrograms with delayed activation and late potentials has been proposed as an end point for ablation (3,23). In contrast, 1 prospective, randomized trial has shown that linear lesions that transect scar with circumferential T-shaped lesions at BZs reduce VT recurrence (24). In the current study, both the acute and intermediate success rates of VT ablation was lower in patients with NICM compared with ICM despite similar clinical characteristics. Since patients with NICM have fewer LP, a strategy targeting LP is inherently limited by fewer substrate targets. In these NICM patients, our study suggests that the ablation approach commonly employed in ICM substrates is likely to be insufficient, and alternative or adjunctive linear lesion strategies need to be considered.

Study limitations. The population studied is relatively small, but findings were consistent among patients. Patients in this series may have a referral bias as they all had VT requiring an intervention. The applicability of these findings to all patients with NICM may be limited, as this group represents a heterogeneous population.

The use of a multipolar catheter to achieve high-density mapping has not been systematically validated in the ventricle. By taking the most external points on an endocardial map (and the most internal points on an epicardial map), points >8 mm away from the initial geometry were excluded to minimize points without good catheter contact. As in the case of point-by-point mapping, catheter contact in our studies was also confirmed fluoroscopically.

Last, the relationship of LP to critical conducting channels or isthmuses cannot be ascertained by an approach based on LP and pace-mapping. Although perfect pace-map matches with long stimulus latencies have been interpreted as markers of isthmus locations, bystander pathways cannot be excluded without entrainment mapping. Because the majority of patients in this study had hemodynamically untolerated VT, termination of arrhythmia during radiofrequency could not be demonstrated in this cohort as proof of a critical site.

Conclusions

The contribution of scar to electrophysiological abnormalities targeted for ablation of unstable VT differs between ICM and NICM. Patients who have NICM have smaller endocardial scar and fewer LP within endocardial and epicardial scar compared with patients who have ICM. The relative paucity of vLP in patients who have NICM may partly account for the challenges in VT ablation for this population, and alternative ablative strategies should be considered.

Acknowledgments

The authors express their gratitude to Dr. Michael Laks for critical review of this manuscript, and to Dr. Jeffrey Gornbein for statistical assistance.

Reprint requests and correspondence: Dr. Kalyanam Shivkumar, UCLA Cardiac Arrhythmia Center, A2-237 CHS, 10833 Le Conte Avenue, Los Angeles, California 90095-1679. E-mail: kshivkumar@mednet.ucla.edu.

REFERENCES

1. de Bakker JM, van Capelle FJ, Janse MJ, et al. Slow conduction in the infarcted human heart. "Zigzag" course of activation. Circulation 1993;88:915–26.
2. Gardner PI, Ursell PC, Fenoglio JJ Jr., Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. Circulation 1985;72:596–611.
3. Arenal A, Glez-Torrecilla E, Ortiz M, et al. Ablation of electrograms with an isolated, delayed component as treatment of unmappable monomorphic ventricular tachycardias in patients with structural heart disease. J Am Coll Cardiol 2003;41:81–92.
4. Brunckhorst CB, Stevenson WG, Jackman WM, et al. Ventricular mapping during atrial and ventricular pacing. Relationship of multipotential electrograms to ventricular tachycardia reentry circuits after myocardial infarction. Eur Heart J 2002;23:1131–8.
5. Bogun F, Good E, Reich S, et al. Isolated potentials during sinus rhythm and pace-mapping within scars as guides for ablation of post-infarction ventricular tachycardia. J Am Coll Cardiol 2006;47:2013–9.
6. Unverferth DV, Baker PB, Swift SE, et al. Extent of myocardial fibrosis and cellular hypertrophy in dilated cardiomyopathy. Am J Cardiol 1986;57:816–20.
7. Sugrue DD, Holmes DR Jr., Gersh BJ, et al. Cardiac histologic findings in patients with life-threatening ventricular arrhythmias of unknown origin. J Am Coll Cardiol 1984;4:952–7.
8. de Bakker JM, van Capelle FJ, Janse MJ, et al. Fractionated electrograms in dilated cardiomyopathy: origin and relation to abnormal conduction. J Am Coll Cardiol 1996;27:1071–8.
9. Hsia HH, Callans DJ, Marchlinski FE. Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia. Circulation 2003;108:704–10.
10. Bogun FM, Desjardins B, Good E, et al. Delayed-enhanced magnetic resonance imaging in nonischemic cardiomyopathy: utility for identifying the ventricular arrhythmia substrate. J Am Coll Cardiol 2009;53:1138–45.

11. Roberts WC, Siegel RJ, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. Am J Cardiol 1987;60:1340–55.
12. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. J Cardiovasc Electrophysiol 1996;7:531–6.
13. Cesario DA, Vaseghi M, Boyle NG, et al. Value of high-density endocardial and epicardial mapping for catheter ablation of hemodynamically unstable ventricular tachycardia. Heart Rhythm 2006;3:1–10.
14. Soejima K, Couper G, Cooper JM, Sapp JL, Epstein LM, Stevenson WG. Subxiphoid surgical approach for epicardial catheter-based mapping and ablation in patients with prior cardiac surgery or difficult pericardial access. Circulation 2004;110:1197–201.
15. Haqqani HM, Kalman JM, Roberts-Thomson KC, et al. Fundamental differences in electrophysiologic and electroanatomic substrate between ischemic cardiomyopathy patients with and without clinical ventricular tachycardia. J Am Coll Cardiol 2009;54:166–73.
16. Bogun F, Bender B, Li YG, et al. Analysis during sinus rhythm of critical sites in reentry circuits of postinfarction ventricular tachycardia. J Interv Card Electrophysiol 2002;7:95–103.
17. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977;56:786–94.
18. Soejima K, Stevenson WG, Sapp JL, Selwyn AP, Couper G, Epstein LM. Endocardial and epicardial radiofrequency ablation of ventricular tachycardia associated with dilated cardiomyopathy: the importance of low-voltage scars. J Am Coll Cardiol 2004;43:1834–42.
19. Cano O, Hutchinson M, Lin D, et al. Electroanatomic substrate and ablation outcome for suspected epicardial ventricular tachycardia in left ventricular nonischemic cardiomyopathy. J Am Coll Cardiol 2009;54:799–808.
20. Tanner H, Hindricks G, Volkmer M, et al. Catheter ablation of recurrent scar-related ventricular tachycardia using electroanatomical mapping and irrigated ablation technology: results of the prospective multicenter Euro-VT-Study. J Cardiovasc Electrophysiol 2009 Jul 28 [E-pub ahead of print].
21. Stevenson WG, Wilber DJ, Natale A, et al. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter ThermoCool Ventricular Tachycardia Ablation Trial. Circulation 2008;118:2773–82.
22. Cassidy DM, Vassallo JA, Miller JM, et al. Endocardial catheter mapping in patients in sinus rhythm: relationship to underlying heart disease and ventricular arrhythmias. Circulation 1986;73:645–52.
23. Nault I, Maury P, Sacher F, Lellouche N, Deplagne A, Knecht S. Characterization of late ventricular potentials as ventricular tachycardia substrate and impact of ablation (abstr). Heart Rhythm 2009;6 Suppl:227.
24. Reddy VY, Reynolds MR, Neuzil P, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med 2007;357:2657–65.

Key Words: catheter ablation ■ ventricular tachycardia ■ myocardial infarct scars ■ late potentials.