Endocardial Unipolar Voltage Mapping to Detect Epicardial Ventricular Tachycardia Substrate in Patients With Nonischemic Left Ventricular Cardiomyopathy

Mathew D. Hutchinson, MD; Edward P. Gerstenfeld, MD; Benoit Desjardins, MD, PhD; Rupa Bala, MD; Michael P. Riley, MD, PhD; Fermin C. Garcia, MD; Sanjay Dixit, MD; David Lin, MD; Wendy S. Tzou, MD; Joshua M. Cooper, MD; Ralph J. Verdino, MD; David J. Callans, MD; Francis E. Marchlinski, MD

Abstract

Background—Patients with nonischemic left ventricular cardiomyopathy (LVCM) and ventricular tachycardia (VT) have complex 3-dimensional substrate with variable involvement of the endocardium (ENDO) and epicardium (EPI). The purpose of this study was to determine whether ENDO unipolar (UNI) mapping with a larger electric field of view could identify EPI low bipolar (BIP) voltage regions in patients with LVCM undergoing VT ablation.

Methods and Results—The reference value for normal ENDO unipolar voltage was determined from 6 patients without structural heart disease. Consecutive patients undergoing VT ablation over an 8-year period with detailed (≥100 points) LV ENDO and EPI mapping and normal LV ENDO BIP voltage were identified. From this cohort, we compared patients with structurally normal hearts and normal EPI BIP voltage (EPI+, group 1) with patients with LVCM and low LV EPI BIP voltage regions present (EPI−, group 2). Confluent regions of ENDO UNI and EPI BIP low voltage (EPI−, group 1) were measured. The normal signal amplitude was >8.27 mV for LV ENDO UNI electrograms. Detailed LV ENDO-EPI maps in 5 EPI− patients were compared with 11 EPI+ patients. Confluent ENDO UNI low-voltage regions were seen in 9 of 11 (82%) of the EPI− (group 2) patients compared with none of 5 EPI− (group 1) patients (P<0.001). In all 9 patients with ENDO UNI low voltage, the ENDO UNI low-voltage regions were directly opposite to an area of EPI BIP low voltage (61% ENDO UNI-EPI BIP low-voltage area overlap).

Conclusions—EPI arrhythmia substrate can be reliably identified in most patients with LVCM using ENDO UNI voltage mapping in the absence of ENDO BIP abnormalities. (Circ Arrhythm Electrophysiol. 2011;4:49-55.)

Key Words: catheter ablation ▪ ventricular tachycardia ▪ electrophysiology mapping ▪ cardiomyopathy

The value of bipolar (BIP) electroanatomic mapping in patients with nonischemic left ventricular cardiomyopathy (LVCM) and scar-related ventricular tachycardia (VT) has been well established. The heterogeneous and often complex substrate distribution present in patients creates unique challenges for catheter-based VT therapy.

Although the true prevalence of epicardial substrate in the LVCM population remains unknown, many LVCM patients have more sizeable bipolar low-voltage regions on the epicardium (EPI) than the endocardium (ENDO). We have also found a limited number of LVCM patients presenting with VT of EPI origin to have completely normal ENDO BIP voltage characteristics. Limitations in the field-of-view of BIP electrograms in the setting of complex, nontransmural substrate may be responsible for the inability to detect these EPI abnormalities with BIP ENDO mapping. The utility of unipolar (UNI) ENDO electrogram recordings, which have a larger field of view to identify an epicardial substrate, has not been assessed in this population.

The purpose of this study was to evaluate whether ENDO UNI mapping can identify the presence and location of EPI low BIP voltage regions in patients with LVCM undergoing VT ablation who do not demonstrate endocardial bipolar voltage abnormalities.

Methods

Study Population

We examined consecutive patients undergoing VT ablation at the University of Pennsylvania from June 2002 to June 2010. All procedures were performed following the institutional guidelines of the University of Pennsylvania Health System, and all patients provided written informed consent. Patients undergoing detailed (≥100 points) ENDO and EPI electroanatomic mapping with complete sampling of all LV segments were included. The decision for an epicardial approach was made based on either (1) the character-
istics of the Vт on the surface 12-lead ECG; (2) the presence of epicardial substrate on imaging studies (CT, magnetic resonance, intracardiac echocardiography); and/or (3) the failure of prior endocardial ablation procedure.6

From the total cohort, we examined patients with normal LV ENDO BIP voltage. We then identified 2 study groups from the initial cohort: (1) patients with structurally normal hearts and normal EPI BIP voltage (EPI−, group 1) and (2) patients with LVCM and LV EPI BIP low-voltage regions present (EPI+, group 2).

Structural heart disease was excluded in the EPI− patients with transthoracic echocardiography and stress testing (if >30 years old). The diagnosis of LVCM was established by the absence of significant (>70% stenosis) coronary artery disease, documented prior myocardial infarction, or significant primary valvular abnormalities. Other likely causes of dilated cardiomyopathy were also excluded, including arrhythmogenic right ventricular dysplasia cardiomyopathy, cardiac sarcoidosis, and alcoholic cardiomyopathy. All study patients had a history of spontaneous sustained monomorphic Vт documented either by surface ECG or stored intracardiac electrograms from an implanted cardioverter-defibrillator.

Sinus Rhythm Electroanatomic Mapping
Electroanatomic mapping of the endocardium and the epicardium during the baseline rhythm was performed during the same procedure using the CARTO system (Biosense Webster Inc, Diamond Bar, CA). Either a 4-mm distal-tip/2-mm ring electrode ablation catheter (NaviStar, Biosense Webster Inc) or a 3.5-mm distal-tip irrigated catheter (Navistar Thermocool, Biosense Webster Inc) was used as the mapping catheter. Bipolar signals were recorded between the tip of the ablation catheter (cathode) and Wilson central terminal and were filtered at 1 to 240 Hz and displayed at 200 mm/s. All electrograms were visually reviewed for the presence of noise or pacing artifact. Electroanatomic points that were clearly internal to the 3-dimensional surface were excluded. All quantitative electro-anatomic data were acquired using a fill threshold of 20 on the CARTO mapping system.

A retrograde, transaortic approach was used to access the LV ENDO in all cases. Access to the pericardial space and epicardium was obtained using the technique described by Sosa et al. Briefly, under general anesthesia, a Tuohy needle was introduced via a subxiphoid approach to gain access for sheath and ablation catheter placement. A value of 1.5 mV defined normal LV endocardial bipolar electrogram amplitude. Our recent work defined normal LV EPI BIP signal amplitude to be >1.0 mV (after excluding the regions within 1.5 cm of the coronary vasculature).5

Reference Values for Voltage Abnormality With Electroanatomic Mapping
We determined the reference value for endocardial LV UNI electrogram voltage by examining the voltage characteristics in a separate cohort of 6 patients without structural heart disease who underwent electrophysiological testing for symptomatic premature ventricular contractions. Detailed (>100 points) electroanatomic mapping was performed in each patient. Structural heart disease was excluded in these patients with transthoracic echocardiography and stress testing (if >30 years old).

A 4-mm, distal-tip/2-mm ring electrode ablation catheter (NaviStar, Biosense Webster Inc) was used as the mapping catheter. Unipolar signals were recorded between the tip of the ablation catheter (cathode) and Wilson central terminal and were filtered at 1 to 240 Hz and displayed at 200 mm/s. All electrograms were visually reviewed for the presence of noise or pacing artifact. Electroanatomic points that were clearly internal to the 3-dimensional surface were excluded. Catheter contact at each site sampled was verified using a combination of fluoroscopic assessment as well as temporal stability of the recorded electrograms. Normal LV ENDO UNI signal amplitude was defined as that exceeded by 95% of all electrograms.

Quantitative Assessment of Confluent Low-Voltage Regions
Confluent regions of ENDO UNI and EPI BIP low voltage (>2 cm²) were measured using the standard surface area measurement tool on

Table 1. Baseline Patient Characteristics

<table>
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<th>LVEF, %</th>
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<th>No. of Prior Procedures</th>
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</tr>
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<tr>
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LVEF indicates left ventricular ejection fraction; AAD, antiarrhythmic drugs; ICD, implantable cardioverter-defibrillator; SMVT, sustained monomorphic ventricular tachycardia; and PVC, premature ventricular complex; Proc, procainamide; Mex, mexilitine; Dofet, dolefïlite; quin, quinidine.
the CARTO system (software version 9.0.34). When multiple areas of confluent low voltage were present, the aggregate area from individual regions of interest was calculated. We also measured the surface area of direct spatial overlap between the ENDO UNI and EPI BIP low-voltage areas using the mesh feature on the CARTO software and reported a percentage overlap (ENDO UNI and EPI overlap area/total ENDO UNI area).

The low-amplitude EPI BIP regions were considered abnormal if confluent signal amplitude was \(<1.0\) mV and \(>20\%\) of sites also demonstrated any of the following abnormal electrogram characteristics: (1) wide, \(>80\) ms in duration; (2) split, 2 or more distinct components with \(>20\) ms isoelectric segment between peaks of individual components; or (3) late, distinct electrograms with onset after the end of the QRS complex. Areas within \(1.5\) cm of the major coronary arteries were excluded from the low-voltage assessment.\(^5\)

When assessing confluent ENDO UNI low-voltage regions, areas within \(1\) cm of the mitral and aortic valve annuli were excluded from the measurement. This was done to prevent overestimation of the UNI low-voltage area around the valve, which may record low voltage because of the absence of myocardium within the area of the valve annulus.

### Measurement of Endocardial to Epicardial Distance

To prevent potential confounding of voltage measurements related to variable distances between the ENDO and EPI (ENDO-EPI) electroanatomic mapping surfaces, the ENDO-EPI distance was calculated using the standard distance measurement tool on the CARTO software. The perpendicular ENDO-EPI distances were measured in each patient at 2 separate sites (typically the basal and mid lateral LV segments) adjacent to the low-voltage region; a mean distance value was reported.

### Statistical Analysis

All electroanatomic measurements were tested using the 1-sample Kolmogorov-Smirnov test against a normal distribution. Continuous data are expressed as a mean±SD or a range, as appropriate. When comparing continuous variables, a Student \(t\) test was used for normally distributed data; the Mann–Whitney \(U\) test was used for data that were not normally distributed. The McNemar test was used to compare dichotomous variables. A probability value of \(\leq0.05\) was considered statistically significant.

### Results

#### Reference Values for Voltage Abnormality With Electroanatomic Mapping

The reference population consisted of 6 patients (5 males, 1 female), with a mean age of 36±18 years. A total of 683 LV electrograms were analyzed (range, 100 to 168 points per patient). Ninety-five percent of LV ENDO unipolar signals had an amplitude \(>8.27\) mV (mean, 19.6±6.9 mV), defined as the value of normal LV ENDO UNI signal amplitude.

### Patient Characteristics

The clinical characteristics of the study patients are displayed in Table 1. Of the 1517 patients undergoing ablation for VT at our institution between June 2002 and June 2010, 168 had a combined ENDO-EPI procedure. Of these patients, 16 had detailed mapping of the ENDO and EPI with normal ENDO BIP voltage. From this group of 16 patients, 5 had structurally normal hearts and normal BIP EPI voltage (EPI–) and
underwent mapping and ablation of idiopathic VT/ventricular premature depolarization. Eleven additional patients had LVCM and VT with confirmed epicardial origin with a confluent region (>2 cm²) of EPI BIP low voltage present (EPI+).

**Electroanatomic Mapping**

The characteristics of the electroanatomic maps from the EPI+ patients are shown in Table 2. The mean number of electroanatomic points on the ENDO and EPI maps was similar between EPI+ and EPI− patients (ENDO maps: 188±57 versus 166±67, P=0.3; EPI maps: 491±178 versus 361±206, P=0.1). The mean ENDO UNI voltage was significantly lower in the EPI+ versus EPI− groups (10.5±3.2 versus 14.7±2.6 mV, P=0.04). In contrast, there was no difference in ENDO BIP voltage between the EPI+ and EPI− patients (4.1±0.6 versus 4.3±0.8 mV; P=0.9).

Confluent ENDO UNI low-voltage regions (>2 cm²) were seen in 9 of 11 (82%) of the EPI+ patients compared with none of 5 of the EPI− patients (Figure 1). In the EPI+ group, the mean EPI BIP low-voltage area was significantly larger than the corresponding ENDO UNI area (49.1±38.4 cm² versus 19.2±28.2, P=0.02). In all 9 patients with ENDO UNI low-voltage regions, at least 1 of the ENDO UNI regions was directly opposite to an area of EPI BIP low voltage (Figure 2). Of the total ENDO UNI low-voltage area, 61% directly overlapped EPI BIP low-voltage regions. The mean LV ENDO UNI voltage within the low-voltage areas in the EPI+ patient cohort was 5.5±1.7 mV.

**Endocardial to Epicardial Distance**

The mean overall distance from ENDO-EPI as assessed by electroanatomic mapping was 15.7±4.0 mm. There was no difference in the ENDO-EPI distance in the EPI+ versus EPI− patients (16.0±3.0 versus 15.0±5.4 mm, P=0.5).

**Discussion**

The present study describes the detection of EPI substrate in LVCM using ENDO electroanatomic mapping in patients with normal endocardial bipolar voltage maps. Our data reveal regions of low LV ENDO UNI voltage in 82% of patients with confirmed epicardial scar as indexed by confluent area of low bipolar voltage with fractionated and late electrograms. Furthermore, the findings appeared to be specific in that the 5 patients with idiopathic ventricular premature depolarization or VT and normal EPI and ENDO bipolar voltage maps did not demonstrate any ENDO unipolar electrogram abnormalities. The close spatial correlation of the ENDO UNI and EPI BIP low-voltage regions in the absence of ENDO BIP attenuation suggests that the UNI ENDO signals characterize tissue more remote from the ENDO.

Four of the 11 EPI+ patients had confluent regions of ENDO UNI low voltage that did not correlate with EPI BIP abnormalities. In fact, 2 EPI+ patients had larger ENDO UNI low-voltage areas compared with the corresponding EPI BIP voltage. Cardiac MRI was available in 2 of these 4 patients; both scans confirmed regions of midmyocardial delayed enhancement directly adjacent to the ENDO UNI abnormality.
Thus, the most likely explanation for the discordant ENDO UNI and EPI BIP low voltage is the presence of midmyocardial substrate, which is detected better with ENDO UNI mapping than with either ENDO or EPI BIP mapping. When we compared the mean ENDO UNI and BIP voltages in patients without structural heart disease with those with LVCM, only the UNI voltages differed significantly between the EPI+ and EPI− groups. It is likely that the UNI electrograms provide a larger “antenna” to detail a more complex 3-dimensional substrate pattern commonly present in the patients with NICM who have VT. It also suggests that the UNI voltage difference is more than simply a threshold effect of the applied cutoff voltage.

Use of Unipolar Mapping in Postinfarction Substrate
Several reports have examined the UNI voltage characteristics in chronic animal infarction models. Based on this previous work, the threshold values of unipolar voltage required to differentiate infarcted from normal tissue ranged between 6.2 and 10 mV. Our UNI voltage cutoff of 8.27 mV was determined in human subjects by examining voltage characteristics in normal hearts.

Field-of-View of Bipolar Voltage Mapping
Several publications as well as clinical experience have called into question the “field-of-view” of bipolar electrograms. One publication described that bipolar and unipolar electrogram amplitude reduction (<1.5 and <6.5 mV, respectively) were predictive of the presence of delayed enhancement on magnetic resonance in patients with infarct-related VT; however, neither was useful in predicting the degree of infarct transmurality. The same study found a >20% underestimation of the DE region on magnetic resonance from the bipolar voltage map in one-third of cases.

A separate report noted significant variability in BIP electrogram amplitude in postinfarction patients when the LV activation wave front was altered using differential pacing maneuvers. Bogun et al demonstrated enhanced representation of DE regions on magnetic resonance with combined EPI and ENDO bipolar mapping in patients with LV cardiomyopathy. These observations reinforce the importance of using adjunctive imaging modalities in characterizing nonischemic VT substrate.

Previous reports describing EPI substrate have focused on local BIP voltage characteristics that necessarily require epicardial access. Although epicardial mapping is often required when ablating LVCM-related VT, most operators do not empirically obtain percutaneous pericardial access in all cases. The UNI ENDO electrogram recording information may provide a valuable clue suggesting the presence of a probable epicardial substrate and the need to pursue epicardial mapping and ablation.
Limitations
This study includes a limited number of patients. We did not include patients with incomplete LV voltage maps both to avoid underestimation of low-voltage regions and to represent all LV segments equally. This sampling technique has been well established clinically for bipolar voltage mapping for more than a decade and has been correlated histopathologically with VT arrhythmia substrate. The distinction between normal and abnormal ENDO UNI voltages is less dramatic than seen with ENDO BIP electrograms; this may represent a composite 3-dimensional assessment of scar burden reflected by the unipolar electrogram. Additional investigation is warranted to correlate UNI electrogram characteristics with MRI in this patient population.

As indicated, an abnormal unipolar voltage map in the setting of normal bipolar voltage map does not guarantee the presence of an abnormal epicardial substrate. The presence of isolated midmyocardial scar would be anticipated to also create lower unipolar ENDO voltage.

Conclusions
Our results suggest that UNI ENDO voltage can provide an indication of epicardial VT substrate in patients with LVCM with normal bipolar endocardial voltage.

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Disclosures
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**CLINICAL PERSPECTIVE**

Ablation of ventricular tachycardia in patients with nonischemic left ventricular cardiomyopathy (LVCM) is a significant challenge. Partly because of complex 3-dimensional ventricular tachycardia substrate produced by scars that can be endocardial, epicardial, or intramyocardial. Bipolar voltage maps detect endocardial scar as low-voltage regions during endocardial mapping, but epicardial and midmyocardial scars require either percutaneous epicardial mapping or MRI for recognition. Because minimally filtered unipolar recordings have a greater field of view than bipolar electrograms, we evaluated their use for detecting the presence of epicardial scar during endocardial mapping. In patients with normal hearts, the reference value for the 95th percentile of unipolar voltage was found to be 8.27 mV, and this value was prospectively evaluated in 11 LVCM patients with normal endocardial bipolar voltage and large areas of epicardial low voltage found at epicardial mapping (mean, 49.1 ± 38.4 cm²). An endocardial region of low unipolar voltage below the epicardial scar region was seen in 82% of cases. Thus, in LVCM, analysis of endocardial unipolar electrograms can suggest the presence of epicardial low voltage regions consistent with scar. Unipolar endocardial voltage maps may facilitate the decision to expedite epicardial mapping and ablation in selected patients with LVCM.
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