Electroanatomic Left Ventricular Mapping in the Porcine Model of Healed Anterior Myocardial Infarction
Correlation With Intracardiac Echocardiography and Pathological Analysis

David J. Callans, MD; Jian-Fang Ren, MD; John Michele, BS; Francis E. Marchlinski, MD; Stephen M. Dillon, PhD

Background—Catheter ablation for ventricular tachycardia in healed infarction is limited to patients with inducible, tolerated arrhythmias. Strategies that would allow mapping during sinus rhythm might obviate this limitation.

Methods and Results—Two sets of experiments were performed in adult pigs to refine a new technique for left ventricular mapping. First, detailed endocardial maps were done in 5 normal pigs and 7 pigs 6 to 10 weeks after left anterior descending coronary artery infarction to characterize electrograms in normal and infarcted tissue by electroanatomic mapping (CARTO, Biosense). Electrogram recording sites were verified by intracardiac echo (ICE, 9 MHz) and grouped by location: infarct (area of akinesis by ICE), border (0.5-cm perimeter of akinetic area), and remote. Compared with remote sites, electrograms from infarct sites had smaller amplitudes (1.2±0.5 versus 5.1±2.1 mV, P<0.001), longer durations (74.2±26.3 versus 36.3±6.4 ms, P<0.001), and more frequent notched or late components. Border zone electrograms were intermediate in amplitude and duration. Second, infarct characterization by electroanatomic mapping was compared with pathological (exclusion of triphenyltetrazolium chloride staining) and ICE measurements. Infarct size by pathology correlated with the area defined by contiguous electrograms with amplitude ≥1 mV (r=0.98, P<0.0001). Infarct size by ICE imaging correlated with the area defined by contiguous electrograms with amplitude ≥2 mV (r=0.95, P<0.0016).

Conclusions—Electroanatomic mapping during sinus rhythm allows accurate 3D characterization of infarct architecture and defines the relationship of electrophysiological and anatomic abnormalities. This technique may prove useful in devising anatomically based strategies for ablation of ventricular tachycardia. (Circulation. 1999;100:1744-1750.)

Key Words: mapping □ myocardial infarction □ tachyarrhythmias □ electrophysiology

At present, catheter ablation is feasible in only a limited number of patients with ventricular tachycardia (VT). Present techniques require lengthy mapping during VT, which precludes ablation therapy in patients who do not have inducible, tolerated VT. Initial attempts at mapping VT on the basis of the characteristics of sinus rhythm electrograms in anticipation of surgical ablation were unsuccessful. These studies demonstrated that analysis of electrogram characteristics was not sufficiently specific to guide discrete ablation at individual sites. However, preliminary experience in humans suggests that more extensive ablation, deployed anatomically with reference to the infarct zone as determined by electrogram characteristics in sinus rhythm, may result in successful ablation without mapping during VT. Refinement of linear ablation techniques will require more detailed understanding of the spatial relationship of the electrophysiological and the anatomic substrates for VT.

The purpose of the present study is 2-fold. First, endocardial mapping was performed in normal and infarcted animals with the CARTO system to characterize the spatial distribution of normal and abnormal electrograms. Second, the accuracy of electroanatomic voltage mapping in determining infarct size and location was compared with the “gold-standard” methods of pathological analysis and intracardiac echocardiography (ICE) in a porcine model of healed anterior infarction.

Methods

Experimental Myocardial Infarction
The closed-chest infarction procedure, adapted from Eldar et al., was performed in 80- to 85-lb male pigs. After an overnight fast and premedication with ketamine 22 mg/kg, acetylpromazine 1.1 mg/kg, and atropine 0.05 mg/kg IM, pigs were intubated and ventilated with 60% oxygen/40% N₂O. General anesthesia with inhaled isoflurane was initiated and maintained. Arterial blood gas analysis was

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From the Arrhythmia Research Laboratory of the Allegheny University Hospitals, Hahnemann Division, Philadelphia, Pa.
Correspondence to David J. Callans, MD, Hospital of the University of Pennsylvania, Cardiology, 9 Founders Pavilion, 3400 Spruce St, Philadelphia, PA 19104. E-mail callansd@mail.med.upenn.edu
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performed throughout the procedure when clinically indicated. The animals were warmed with a water-circulating heating pad, and intravenous fluids were administered. A 9F sheath was placed percutaneously in the left femoral artery by the Seldinger technique to monitor blood pressure and to allow arterial access. An 8F AL 1 or 2 guide catheter was placed at the ostium of the left anterior descending coronary artery (LAD), and a 2- to 2.5-mm angioplasty balloon was advanced to the distal LAD at the site of the second diagonal branch. Thirty seconds after balloon inflation (6 atm), 300 µL of agarose gel beads (diameter of 75 to 150 µm; Biopad Laboratories) diluted in 1.5 mL saline was injected through the balloon lumen. The balloon was deflated and the catheter withdrawn. The evolving anterior infarction was assessed by continuous ECG and hemodynamic monitoring. The animal was maintained under general anesthesia until the arterial sheath was removed 30 minutes after the infarction procedure, and buprenorphine 0.3 mg IM was given to alleviate discomfort on awakening. After extubation, the animal was observed until able to walk without assistance.

Endocardial Mapping

After 6 to 10 weeks of infarct healing (infarct group), animals were subjected to left ventricular (LV) endocardial mapping after preparation with the same premedication, general anesthetic regimen, and procedural monitoring as above. Venous and arterial access was obtained by surgical cutdown to the carotid arteries and the external jugular veins; the femoral vessels were accessed percutaneously by the Seldinger technique. LV endocardial mapping was performed with the CARTO system (Biosense Inc), which has been described in detail. Briefly, the system creates a low-intensity (0.02- to 0.5-G) magnetic field that allows localization of the mapping catheter in space with 6 degrees of freedom, ie, position in the x, y, and z planes and rotation (roll, pitch, and yaw). The physical reference for the mapping catheter was a reference catheter sutured in place to the anterior chest wall directly over both the heart and the center of the magnet elements. The accuracy of this system has been estimated at 0.8 mm and 5°. Bipolar electrograms were recorded between the 4-mm tip distal electrode and the 2-mm third electrode; the interelectrode spacing was 1 mm. The electrograms were sampled at 1000 Hz and recorded after bandpass filtering at 10 to 400 Hz. Bipolar signals were displayed at variable gain, and peak-to-peak amplitude was measured automatically. The mapping catheter was introduced to the LV by a retrograde transaortic approach via the femoral and/or carotid arteries. Computer graphics imagery rendered a “cast” of the LV endocardial geometry using several boundary points under fluoroscopic guidance. Thereafter, the mapping catheter was manipulated primarily by the CARTO system, with fluoroscopy used only secondarily. Mapping catheter location was verified by ICE (see below), with special reference to defining the boundaries of the infarct. Mapping points were acquired until the entire ventricle had been sampled (contiguous color display at a triangle fill threshold of ≤40); high-density mapping was performed in the region of the infarct and the infarct border zone. The endocardial maps were displayed as voltage maps (Figure 4, A and B) representing a geometrically correct 3D representation of the LV endocardial surface in addition to presenting bipolar electrogram voltage at each site on the map. After completion of the voltage map, a series of radiofrequency lesions (30 to 50 W, 120 seconds) were delivered, guided by CARTO (electrogram voltage between 1 and 2 mV) and ICE imaging (adjacent to the area of akinesia) to tag the medial aspect of the infarct border zone. This tagging was used for orientation in comparing electroanatomic and pathological assessment of the infarct architecture.

In addition, LV endocardial mapping was performed in 5 normal pigs to obtain a reference standard for electrogram amplitude and duration. Arterial access for this procedure was via the femoral artery by a percutaneous approach. Mapping was performed with fluoroscopic and CARTO guidance; ICE imaging was not used in this group.

Postprocedural analysis of the CARTO voltage maps included the following: (1) construction of isovoltage lines to evaluate infarct location; (2) deletion of individual points that were intracavitary; and (3) measurement of electrogram duration, defined as the earliest electrical activity to the onset of the decay artifact, at each site by use of electronic calipers. Data were compiled on the following electrogram characteristics: amplitude (unipolar and bipolar), duration of the bipolar electrogram, amplitude/duration, and presence of late (persisting after the surface QRS offset) and/or notched components. Sites were characterized by location relative to the infarct zone, determined by ICE, as infarct (area of scar or akinesia), border (within a 5-mm perimeter of the area of akinesis), and remote. Electrograms were further characterized as normal and abnormal on the basis of the 95% CIs for electrogram amplitude and duration for data collected in the noninfarcted pigs. Fractionated electrograms were defined as electrograms that were >1 SD from the mean values of abnormal electrograms in at least 2 of 3 characteristics: amplitude, duration, and the amplitude/duration ratio.

Intracardiac Echocardiography

ICE imaging was performed with a 9-MHz rotating ultrasound transducer, mounted at the distal end of a 9F, 110-cm catheter (Boston Scientific). Images were acquired with a Sonos Intravascular Imaging System (Hewlett-Packard). The system provides a maximal radial imaging depth of up to 10 cm and an optimum axial resolution of ≈0.2 to 0.3 mm. The imaging catheter was advanced to the LV via a retrograde aortic approach with a long 11F sheath placed via cutdown to the left carotid artery. ICE images are displayed as cross-sectional views 10° oblique to the vertical axis of the LV (Figure 4). The echocardiographic extent of the infarct was defined as the LV endocardial area of akinesia and/or scar. The maximal vertical and axial dimensions were measured, and the area was determined as an ellipse, for purposes of comparison with other modalities (see below).

Pathological Analysis

After completion of the mapping study, animals were euthanized by induction of ventricular fibrillation while a surgical plane of anesthesia was maintained. After death, the heart was resected immediately, and infarct areas (maximal height and width, area measured as an ellipse) were measured with hand calipers after staining in 1% tetrazolium chloride for 30 minutes.

Statistical Analysis

Data are presented as mean±SD, where appropriate. As mentioned above, infarct areas were estimated as ellipses, calculated from the maximum width and height measurements. Infarct areas determined by ICE, CARTO voltage mapping, and pathological analysis were compared by Student’s paired t test. Continuous electrogram characteristics (amplitude, duration, amplitude/duration, notched, late) recorded in different locations with reference to the infarct (infarct, border, remote, normal) as assessed by ICE were compared by ANOVA with Bonferroni’s correction for multiple comparisons. Categorical electrogram characteristics (normal versus abnormal, late or notched components) recorded in different locations were compared with contingency table testing with Bonferroni’s correction for multiple comparisons. A value of P≤0.05 was considered statistically significant.

Results

Characteristics of Normal Endocardial Electrograms

LV endocardial electrograms (n=374) were recorded from distinct sites in 5 normal pigs (77 to 100 per animal) (Table). Electrograms recorded from normal animals were sharp, with single, rapid deflections. No electrograms were late, and only 0.5% had notched upstrokes. The mean unipolar electrogram amplitude was 12.4±6.1 mV; 95% of all electrograms recorded in noninfarcted pigs had an amplitude of >4.6 mV. The mean bipolar electrogram amplitude was 5.2±2.2 mV; 95%
of all electrograms recorded in noninfarcted pigs had an amplitude of $\geq 2.5$ mV. The correlation between unipolar and bipolar electrogram amplitudes recorded from the same site was poor ($r^2=0.04$, $P=0.0001$), and as in previous studies,3,8 bipolar amplitude was used for further analysis. The mean bipolar electrogram duration was 31.4±6.4 ms; 95% of all electrograms had durations of $\geq 42$ ms. The ratio of amplitude and duration was 0.178±0.102 mV/ms; 95% of all electrograms had ratios of $>0.076$ mV/ms. Normal electrograms were defined by all characteristics within the 95% values; abnormal electrograms had $\geq 1$ of the following: amplitude $<2.5$ mV, duration $\geq 42$ ms, amplitude/duration ratio $\leq 0.076$ mV/ms, presence of notching or fractionation, or duration later than the surface ECG QRS offset (late electrograms). Of the electrograms recorded from noninfarcted animals, 7.8% were classified as abnormal. In the noninfarcted animals, sites with abnormal electrograms were noncontiguous and randomly distributed throughout the LV.

### Characteristics of Electrograms Recorded in Infarcted Animals

There were significant differences in all electrogram characteristics when recording sites were grouped by location relative to the infarct as determined by ICE imaging (Figure 1, Table). Electrograms recorded from within the infarct zone had significantly lower bipolar amplitude (1.2±0.5 mV) and longer duration (74.2±26.3 ms) than electrograms recorded from border and remote areas ($P<0.001$ for all comparisons). Of the electrograms recorded from the infarct area, 100% were classified as abnormal, compared with 91.3% in the border area and 23.5% of remote electrograms ($P<0.001$ for all comparisons). Electrograms from the infarct area frequently demonstrated notching on the upstroke (84%; $P=NS$ compared with border zone, $P<0.001$ compared with remote) and late components (57%; $P<0.001$ compared with border and remote electrograms).

The characteristics of electrograms recorded from sites in the infarct border zone (as determined by ICE imaging) were also distinct from remote and infarct electrograms, although there was more overlap than observed with infarct zone electrograms. Border zone electrograms were smaller in bipolar amplitude (2.8±0.9 versus 5.1±2.1 mV, $P<0.001$), longer in duration (52.8±15.1 versus 36.3±7.4 ms, $P<0.001$), more likely to be abnormal (91.3% versus 23.5%, $P<0.001$), and more likely to demonstrate notched components (73.8% versus 15.2%, $P<0.001$) than electrograms recorded from remote sites. Post hoc criteria of electrogram amplitude between 2 and 3.5 mV and the presence of a notch was only 47.6% sensitive but was 98.7% specific for border zone location.

Fractionated electrograms were defined as electrograms that were $\geq 1$ SD from the mean values of the abnormal electrogram group in $\geq 2$ of the 3 electrogram characteristics (amplitude, duration, amplitude/duration).3 By this definition, fractionated electrograms were those with amplitude $<0.8$ mV, duration $>84$ ms, and/or an amplitude/duration ratio of $\geq 0.01$. Forty-six electrograms met the criteria for being fractionated. The mean characteristics for fractionated electrograms were an amplitude of 0.7±0.3 mV, a duration of 99.5±25.1 ms, and an amplitude/duration ratio of 0.007±0.003. Of the fractionated electrograms, 100% were located within the infarct zone.

### Endocardial Voltage Mapping: Correlation With ICE and Pathological Analysis

Seven pigs were studied a mean of 8 weeks (range, 6 to 10 weeks) after LAD infarction. Infarcts were typically teardrop-shaped when viewed from the epicardium and centered over the intraventricular septum with LV greater than right ventricular involvement (Figure 2). Mean LV epicardial infarct size was larger than endocardial infarct size ($8.4\pm5.6$ versus $2.6\pm2.3$ cm$^2$, $P=0.038$). For the purposes of subsequent analysis, the LV endocardial extent of the infarct was considered.

A total of 618 endocardial sites were sampled from the 7 infarcted animals (range, 62 to 134 per animal). The area bounded by contiguous bipolar electrograms with isovoltage values of 1 mV during endocardial mapping correlated well with infarct size determined by pathological analysis ($r^2=0.96$, $P=0.0001$; Figure 3A). In addition, CARTO volt-
age mapping described infarct location and border zone geometry accurately compared with pathological analysis (Figure 4). Tagged RF lesions placed in the border zone as defined by CARTO and ICE imaging were consistently adjacent to the area of dense infarction defined by pathological analysis. The area bounded by contiguous electrograms with isovoltage values of 2 mV during endocardial mapping correlated well with infarct size determined by ICE ($r^2 = 0.89$, $P = 0.0016$; Figure 3B). CARTO voltage mapping also correlated well with ICE in terms of infarct geometry and the assignment of individual points to the infarct border zone (Figures 4 and 5). Isovoltage lines constructed with unipolar electrograms were not as helpful in defining infarct anatomy and had less consistent relationships with infarct size as determined by ICE or pathology.

**Discussion**

Several important features of the porcine closed-chest chronic infarction model closely parallel healed anterior infarction in human patients. Previous studies have demonstrated that the pathology of the infarct and the border zone resembles that observed after transmural anterior infarction in humans. In addition, uniform sustained VT can be induced with programmed stimulation, and sudden, presumably arrhythmic death has been observed to occur spontaneously. This study demonstrated several points that are important for the development of anatomically based VT ablation procedures in this representative experimental model. First, normal and abnormal bipolar electrograms were characterized in a quantitative manner; this information establishes guidelines for future mapping studies using this system. Interestingly, the threshold values for determination of normal versus abnormal electrograms in this study were very similar to that demonstrated in human hearts by use of the same recording system. Second, it was demonstrated that electroanatomic voltage mapping accurately determines 3D infarct anatomy and correlates with measurements derived from LV ICE imaging and pathological analysis, techniques that are not available for use in human studies. Contiguous areas described by isovoltage lines of 1 mV during CARTO mapping correlated with the area of dense scar demonstrated by pathological analysis. In addition, contiguous areas bounded by an isovoltage line of 2 mV correlated well with the area of akinesis by ICE imaging. The area of akinesis determined by ICE was consistently greater than the area determined by pathological analysis; whether this represents a unique characteristic of this model, perhaps due to the tethering effect of the larger area of epicardial infarct, is unknown. Although previous studies have validated the spatial accuracy of the CARTO system in more simplistic situations, this is the first demonstration of its high degree of accuracy in 3D representation of diseased myocardium. Both lines of investigation enhance understanding of the spatial relationship between the electrophysiological and the anatomic substrates for arrhythmogenesis, a necessary prerequisite for anatomically based ablation procedures.

Two previous studies have reported on the feasibility of LV electroanatomic mapping. Both studies have used a
Figure 4. Assessment of infarct size and location by electroanatomic mapping compared with pathological analysis and ICE. A, Electroanatomic voltage map performed in a normal pig is shown in right anterior oblique 30° view. A 3D "cast" of endocardial surface of LV is evident, with color-coded information representing bipolar electrogram voltage at each site. In this normal heart, all sites had electrogram voltages >2 mV and are depicted in purple. B, Electroanatomic map from an animal 6 to 10 weeks after LAD embolization. Sites with electrograms ≤1 mV are denoted in red, those >2 mV in purple, and those 1 to 2 mV by intervening colors. Maximum height, width, and infarct area inscribed by an isovoltage line of contiguous points with electrogram amplitudes ≤1 mV are 3.5 cm, 2.7 cm, and 7.4 cm², respectively. This correlates well with measurement of dense infarction determined by pathological analysis, as shown in C, which presents endocardial surface infarct facing after lateral wall was opened (~10° left anterior oblique). D, Midcavity systolic (top) and diastolic (bottom) ICE image from same experiment. Infarct area, denoted by solid arrows, is akinetic, with thinning of myocardium and increased echo density. c denotes shadowing artifact from mapping catheter. Maximum height, width, and infarct area measured by ICE imaging are 5.2 cm (not shown, determined from sequential cross-sectional views), 3.7 cm, and 15.1 cm², respectively. This correlates well with area inscribed by an isovoltage line of 2 mV on electroanatomic map in B; maximum height, width, and infarct area by this technique are 5.1 cm, 3.9 cm, and 15.6 cm², respectively.

Am J Cardiol. 1993;87:363–372.


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Figure 5. Relationship of ICE and electroanatomic mapping in assigning individual sites to infarct border zone. Electroanatomic map is displayed as in Figure 4B. Points that were collected when catheter was determined by ICE to be on infarct side but near border of akinetic area are displayed as orange dots. Note that shape and position of 2-mV isovoltage line closely reflect distribution of orange dots.

Related system (NOGA, Biosense Inc) that provides data on regional ventricular function (local fractional shortening) as well as electroanatomic mapping. Kornowski et al demonstrated the feasibility of electroanatomic mapping in a canine model and in human patients. They described areas in which electrical and functional data matched (normal or infarct zones) and mismatched (presumably stunned or hibernating myocardium) that were located in distributions predictable from knowledge of the coronary anatomy. Gepstein and coworkers validated a slightly different voltage mapping strategy and accurately defined the location and extent of the infarct in a canine model of chronic LAD occlusion compared with pathological analysis. We believe that the present study extends these studies in 2 important ways. First, electroanatomic voltage mapping was validated not only by comparison with pathological analysis but also by ICE imaging. Because ICE imaging is assuming an increasing role in monitoring interventional electrophysiology procedures, demonstrating interdependence between the 2 techniques is particularly important. Second, this study extends the use of electroanatomic mapping to an animal model more representative of healed infarction in human patients with VT.

Limitations

Although the porcine chronic infarction model appears to reproduce important features of clinical postinfarction VT and its substrate, there are almost certainly as yet undefined differences between the model and the human condition. Another possible limitation is that the standards presented for electrogram characteristics and isovoltage values for infarct mapping are recording-system-specific; that is, their usefulness may be limited to mapping studies using the CARTO system and the above-specified filter settings. This limitation could be offered for any specific recording system or technique. Furthermore, these observations demonstrate that independent of specific voltage cutoff values, the infarct area can be recognized by the progression of isovoltage lines from abnormal to normal as distance from the infarct increases. Another system-specific limitation is the automatic gain amplifier system used for voltage information processing. Ideally, electrogram durations would be determined at a fixed gain to prevent overestimation of the duration at low-amplitude sites. Nonetheless, validation of the CARTO system was important, because it may be useful for anatomically based ablation of ventricular arrhythmias just as it has been for atrial flutter and atrial fibrillation.

Although the success rates for VT ablation have been steadily improving, there are several important limitations to existing techniques. The most appropriate patient for VT ablation by currently available strategies has a single or at most a few morphologies of well-tolerated, sustained VT that can be reproducibly induced with programmed stimulation. The proportion of patients that meet these requirements has been estimated to be ~10% of all patients with VT who were referred to a specialized center with an interest in VT ablation. Recent studies in our own laboratory using an intention-to-treat analysis have demonstrated that in nonselected patients with a history of well-tolerated VT, ablation is successful in only 58% of procedures in which it was planned. One half of the failures were caused by inability to successfully ablate VT by use of a point ablation paradigm despite adequate conditions for mapping. Most of the remaining procedural failure was attributable to inability to induce sufficiently well-tolerated VT to allow prolonged mapping. An anatomic paradigm for ablation using mapping information that could be collected without inducing VT may be able to reduce the incidence of ablation failure caused by both of these problems. The information acquired in this study, validating the method of identifying the infarct border zone by electroanatomic voltage mapping, may be helpful in devising anatomically based ablation strategies.

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