Combined Epicardial and Endocardial Electroanatomic Mapping in a Porcine Model of Healed Myocardial Infarction

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Background—Substrate mapping of post–myocardial infarction ventricular tachycardia involves electroanatomic delineation of scarred tissue on the basis of electrogram characteristics during sinus rhythm. A percutaneous transthoracic technique was recently described that allows catheter mapping of the epicardial surface of the heart. This study sought to determine whether the epicardial extent of a myocardial infarct could be defined during sinus rhythm.

Methods and Results—In a porcine model of healed anterior wall myocardial infarction (n=13 animals), detailed in vivo left ventricular endocardial and ventricular epicardial electroanatomic mapping was performed. Catheter access to the pericardial space was achieved by subxyphoid puncture under fluoroscopic guidance. Bipolar electrogram amplitude and duration characteristics of normal tissue were established on the basis of in vivo epicardial mapping data in 8 additional normal animals. With the use of these criteria, radiofrequency lesions (4 to 11 per animal) were placed along the endocardial and epicardial scar borders as defined by the electroanatomic map. The area of epicardial scar defined by abnormal bipolar voltage correlated well with the dimensions measured on pathological examination. The size and location also correlated well with the scar dimensions defined by electrogram duration criteria. Late potentials were noted in the border zones of both surfaces of the scar. During pathological examination, the radiofrequency lesions were situated at the borders of the epicardial scar.

Conclusions—A 3-dimensional construct of the infarcted myocardium can be rendered by combined epicardial and endocardial electroanatomic mapping. This experimental protocol is propaedeutic to future clinical studies incorporating endocardial and epicardial substrate mapping into catheter ablation strategies to treat post–myocardial infarction ventricular tachycardia. (Circulation. 2003;107:3236-3242.)

Key Words: ablation ■ electrophysiology ■ mapping ■ myocardial infarction ■ pericardium

The approach to catheter ablation of scar-related ventricular tachycardia (VT) has undergone a paradigm shift. It is now widely recognized that electroanatomic mapping during normal sinus rhythm can facilitate the identification and elimination of VT circuits.1–3 This substrate mapping approach can guide catheter ablation of hemodynamically stable as well as unstable VT. However, even this ablation strategy may be unsuccessful in the presence of epicardial tachycardia circuits.4 These epicardial circuits appear to be of relevance for VT related to both healed myocardial infarction (MI) and chronic Chagas disease.5

To this end, Sosa and colleagues6–9 have pioneered a percutaneous subxyphoid puncture technique to permit epicardial mapping and ablation from the pericardial space. Using activation and entrainment mapping techniques, they have demonstrated the utility of this approach in eliminating hemodynamically stable epicardial VT circuits related to both post-MI and Chagas disease. Because of the relative ease of catheter manipulation in the pericardial space, certain VT circuits can be more easily and quickly mapped and ablated than with the use of traditional endocardial techniques. However, the substrate mapping approach has not yet been applied to eliminate hemodynamically unstable epicardial VT circuits.

In this study, we sought to determine whether substrate mapping can characterize the epicardial extent of a myocardial infarct. Using a porcine model of healed MI, sinus rhythm electroanatomic mapping of both the left ventricular (LV) endocardial and ventricular epicardial surfaces of the heart was performed. The ability of either electrogram bipolar...
voltage amplitude (BV) or duration (DUR) criteria to define the epicardial extent of the scar was then assessed, as well as to guide the placement of radiofrequency (RF) ablation lesions at the epicardial scar border zone. These data provide the experimental groundwork for performing combined endocardial and epicardial substrate ablation—a strategy that may allow elimination of any monomorphic VT regardless of its location or hemodynamic effect.

Methods
This protocol was approved by the Massachusetts General Hospital Subcommittee of Research Animal Care and was performed according to institutional guidelines.

Porcine Infarct Generation
As previously described, a closed-chest infarction procedure was performed in 25- to 35-kg pigs. After an overnight fast and premedication with 1.4 mg/kg Telazol, 1.1 mg/kg acetylpromazine, and 0.05 mg/kg IM atropine, the animals were intubated and ventilated with O2. General anesthesia was maintained with inhaled 1.5% to 2.5% isoflurane. Arterial access was obtained, and a JR4 guide catheter was placed in the left main coronary artery. A 2.5- to 3.5-mm PTCA balloon was advanced to the mid left anterior descending coronary artery (LAD), and the balloon was inflated to 4 atm. Twenty seconds after balloon inflation, 60 to 80 μL dry volume of Contour 75 to 150 μm emboli (Boston Scientific) diluted in 4 mL of sterile saline was injected through the central lumen of the PTCA catheter. Continuous ECG and hemodynamic monitoring was performed during the infarction and during recovery. After extubation, the animals were observed and monitored for 1 to 3 hours until able to ambulate without assistance. The pigs were housed in the animal facility for a minimum of 4 weeks before the follow-up electrophysiology study.

Pericardial Access
A catheter was placed into the pericardial space by means of the nonsurgical transthoracic puncture approach, as previously described. Briefly, the pericardial space is entered by means of a subxyphoid approach, with the use of a 17-gauge Tuohy needle (98.4-mm overall length, 1.5-mm OD, Arrow International, Inc). Under fluoroscopic guidance, small amounts of contrast media are injected through the needle as it is advanced into the pericardial space. Once this space is entered, a guide wire is passed through the needle, over which an introducer sheath is advanced. The mapping catheter is passed through the sheath and maneuvered within the pericardial space.

Electrophysiology Study
Studies were performed on 8 normal control pigs and 13 pigs with chronic MI. The animals were premedicated, intubated, and anesthetized as above. Intravascular introducer sheaths were placed in the femoral artery and vein and into the pericardial space. After the administration of systemic intravenous heparin, a 4-mm-tipped mapping catheter (Navistar, Biosense-Webster, Inc) was advanced into the left ventricle by means of the retrograde aortic approach. The CARTO electroanatomic mapping system has been described in detail. It allows for precise 3-dimensional electroanatomic mapping, using a low-intensity magnetic field that can localize the mapping catheter with 6 degrees of freedom.

During sinus rhythm, the LV endocardium and ventricular epicardium were fully mapped to achieve a fill threshold <15 mm or <20 mm, respectively. Because the electroanatomic map is a collection of finite points in space, the CARTO system extrapolates the data between electrograms to create a smooth gradation between adjacent points. Using a fill threshold <15 mm means that no gaps are present on the map when the CARTO points are <15 mm apart. In addition, particular attention was paid to fully define the borders of the scar. The ventricular epicardium was mapped to the atroven-

tricular junction, as defined by both atrial and ventricular signals consistent with this location. Maps were made on the CARTO system by using both electrogram BV amplitude and DUR characteristics. Electrograms were filtered from 10 to 400 Hz, and the peak-to-peak BV was automatically calculated on the CARTO system. With the use of the “double annotation” feature, DUR was calculated by use of the automatically gained bipolar electrogram. Electronic calipers were used to measure from the earliest onset of electrical activity to the onset of the decay artifact.

Normal values for electrogram BV and DUR were derived from analysis of the epicardial electrograms from the 8 healthy control pigs. The thresholds were determined by averaging the individual 95th percentile values obtained for the animals. Late potentials, defined as electrical activity extending beyond the end of the surface QRS complex, were identified and tagged on the map. Using a Stockert generator (Biosense-Webster, Inc), RF lesions (60 seconds, 65°C) were placed along the endocardial or epicardial scar borders as defined by BV mapping.

Pathological Analysis
At the conclusion of the procedure, the animals were killed and the heart was immediately explanted and examined. The borders of the infarcted myocardium were easily visualized on gross inspection; selected specimens were also stained with 1% tetrazolium chloride to verify the location/size. The size of the infarct was measured by using surgical calipers on the endocardium. The infarct area as defined by BV criteria, DUR criteria, or gross pathology was estimated assuming an elliptical shape (Area = π × Length/2 × Width/2). The accuracy of the bipolar voltage maps for delineating the scar was also confirmed by correlating the location of the RF lesions placed on the scar border by using the voltage maps with the location of the lesions relative to the scar on the explanted heart.

Statistical Analysis
Sinus rhythm epicardial electrogram characteristics were defined by means of electroanatomic mapping in 8 control animals with structurally normal ventricles. With the use of these data, the mean and 95% cutoff for normal electrogram characteristics were calculated for each animal. The average of the 8 values was then calculated. Statistical analysis was carried out with SAS software (SAS Institute, Inc). A probability value of <0.05 was considered to be statistically significant. The correlation analyses were performed and a simple regression model was constructed to assess the relation between the different scar area determinations. At other points, the data are typically represented as mean±SD.

Results
Normal Reference Values for Epicardial Ventricular Electrograms
The ventricular epicardial electrograms were recorded from distinct sites in 8 normal pigs (99±38 points per animal; range, 57 to 179). The epicardial ventricular “chamber” volume was calculated to be 310±109 mL. The mean BV was 4.0±1.2 mV (range, 0.5 to 19.9 mV), and 95% were >1.4 mV. The mean DUR was 39.3±2.3 ms (range, 21 to 72 ms), and 95% were <49.0 ms. Normal parameters were based on the 95th percentile of values: that is, the BV value above which were 95% of the points, and the DUR value below which were 95% of the points. Sites with BV values that were outside of this 95th percentile were concentrated toward the base of the heart, where epicardial fat is typically thickest (Figure 1). It is important to note that despite the fact that the pericardial space is a potential space, catheter-tissue contact was not assured by the catheter simply being in the pericardial space (Figure 1, E and F).
Epicardial Mapping of the Porcine Infarct

Thirteen pigs with chronic anterior wall MI underwent combined LV endocardial and ventricular epicardial electroanatomic mapping 68±25 days after MI (range, 34 to 112 days; Figure 2). The endocardial and epicardial electrograms were recorded from 167±54 (range, 70 to 318) and 205±67 (range, 143 to 390) distinct sites per animal, respectively. Late potentials were noted on the epicardial surface of the scar in all animals. The area of infarcted tissue as determined by BV <1.5 mV was 25.9±11.1 cm² (range, 10.0 to 45.6 cm²) and by gross pathology, 26.6±10.8 cm² (range, 9.2 to 45.2 cm²). The scar area as defined by this BV isobar corresponded well to the gross pathologic analysis (r=0.96, P=0.0001; Figure 3).

As previously described, the endocardial BV map is capable of guiding the placement of RF lesions along the endocardial border zone of the scar (Figure 2, A through C). To determine whether electroanatomic mapping could similarly guide catheter ablation to the scar’s epicardial border zone, epicardial RF lesions were placed guided solely by the BV map. As shown in Figure 3, on gross pathological examination, the lesions were uniformly situated at the epicardial borders of the scar.

Electrogram DUR Epicardial Mapping of the Porcine Infarct

In 9 of the animals, a DUR map was also generated by manually annotating each of the electrograms to define its beginning and end. The area of the infarction as defined by DUR ≥50 ms was 28.0±9.7 cm² (range, 15.8 to 45.6 cm²; Figure 4). The area bounded the DUR isobar of 50 ms corresponded well to the scar as defined by BV criteria.
...of the infarction, often in close proximity to the atrioventricular groove. Gross pathological analysis revealed these areas to be healthy myocardium but frequently with large amounts of overlying epicardial fat (up to 1 cm thick). However, the corresponding DUR values at these sites were <50 ms and therefore were correctly identified as normal myocardium (Figure 4).

**Correlation of the Endocardial and Epicardial Surfaces of the Infarcted Myocardium**

The calculated volumes of the LV endocardial and ventricular epicardial chamber constructs were 190±127 mL (range, 85 to 233 mL) and 488±130 mL (range, 303 to 718 mL), respectively. When both chambers were displayed simultaneously, the relation of the endocardial and epicardial aspects of the scar is seen (Figure 5). As expected, the extension of the scar onto the septum can only be seen on the LV endocardial map. The surface areas of the epicardial and endocardial extent of the scarred tissue were 26.8±11.1 cm² and 29.5±13.5 cm², respectively. There was a reasonable correlation between the magnitudes of these scar surface areas (r=0.81, P=0.0007; Figure 5E).

**Discussion**

The major findings of this study include: (1) The subxyphoid pericardial access approach can be used in concert with traditional transvascular catheter mapping to render a realistic 3-dimensional construct of the endocardial and epicardial surfaces of the left ventricle, (2) epicardial substrate mapping based on sinus rhythm bipolar electrogram criteria—voltage amplitude and duration—can reliably localize infarcted epicardial tissue, and (3) substrate mapping can guide the placement of RF ablation lesions to the epicardial borders of a myocardial infarct.

**Substrate-Based Ablation Strategy**

The concept of substrate-based catheter mapping and ablation of VT takes its origin from the surgical experience with post-MI VT management. Initially, this was dependent on detailed intraoperative catheter mapping to identify the tachycardia circuits. However, it later became apparent that knowledge of the location of the infarcted substrate was sufficient to guide the surgical resection/transection procedure. Although a purely anatomic approach to catheter ablation of post-MI VT is not currently feasible, the concept of substrate mapping has been extended to the interventional electrophysiology field. Endocardial substrate mapping is now widely performed in concert with other electrophysiological maneuvers (entrainment mapping, pace mapping, and activation mapping) to guide catheter ablation of post-MI VT.1–3

Sosa and colleagues recently demonstrated that a subxyphoid puncture approach to the pericardial space can be performed safely even in the absence of a pericardial effusion. Furthermore, they demonstrated that hemodynamically stable post-MI VT circuits can be both mapped and eliminated by epicardial RF ablation. However, most VT circuits are hemodynamically unstable, and the concept of substrate mapping and ablation has not been applied to epicardial VT circuits. Accordingly, this study was initiated to develop a...
more 3-dimensional understanding of the scarred myocardium in a porcine model of healed MI. To our knowledge, this work represents the first description of systematic catheter-based endocardial and epicardial substrate mapping in an in vivo situation.

**Electrogram Criteria for Epicardial Substrate Mapping**

The epicardial mapping studies in the initial series of control animals were important to establish “normal” epicardial electrogram criteria. These values were similar to those obtained for the porcine endocardium in the same model system (1.5 mV and 50 ms for BV and DUR, respectively). This raises the possibility that the endocardial threshold values currently used in patients may also apply for epicardial mapping. However, this needs to be verified in epicardial mapping studies of patients with normal ventricular function.

Most clinical studies that use endocardial substrate mapping have used BV criteria for infarct localization. However, we have previously noted that DUR values can also be used for endocardial substrate mapping. Consistent with the endocardial mapping data, in the current study, both BV and DUR criteria were able to effectively delineate the epicardial extent of the porcine infarct. This relation persisted over a range of myocardial scar dimensions.

As with endocardial DUR mapping, epicardial DUR mapping must be interpreted with the understanding that the electroanatomic mapping system used in this study displays the ECGs with variable gain. This has the potential to overestimate the electrogram DUR at sites of low BV value. Further studies will be required to determine if DUR mapping is merely complementary to BV mapping or if it can provide unique information to better localize critical portions of the VT circuit. It is also important to note that the DUR values were calculated manually in a post hoc fashion. The time required for generating the DUR map may therefore preclude its clinical utility—until automated electronic annotation algorithms are developed.

**Role of Epicardial Fat in Substrate Mapping**

The role of epicardial fat on electrogram characteristics is important to address. In a preliminary study, electrogram amplitudes were obtained in patients undergoing CABG surgery from areas with and without epicardial fat (Andre d’Avila, MD, Mauricio Scanavacca, MD, and Eduardo Sosa, MD, personal communication, 2002). The peak-to-peak BV amplitude was not modified by the epicardial fat, except in areas with epicardial fat >5 mm in thickness. In the current study, the areas of low BV were concentrated at the bases of the control ventricles—the regions where epicardial fat is thickest, measuring up to 10 mm at some points. Although thinner layers of fat are typically present over other aspects of the epicardium (such as over the LAD), the BV values were predominantly >1.5 mV at these regions in this study. On the
other hand, the DUR values were typically normal regardless of the thickness of the epicardial fat. Although further systematic studies on the role of epicardial fat on substrate mapping are clearly warranted, these data do suggest that BV criteria can accurately reflect the health of the epicardial tissue—except in those situations in which the overlying fat is >5 mm. In these situations, the DUR criteria may serve as a good confirmatory parameter.

**Technical Aspects of Epicardial Substrate Mapping**

Epicardial substrate mapping is technically different from endocardial mapping. On the one hand, there are few obstacles to catheter movement in the pericardial space overlying the ventricles; therefore, it is often easier to reach any particular area. However, the fact that the pericardium is a virtual space does not ensure catheter contact with the myocardium. During epicardial mapping, the catheter must be deflected toward/against the myocardial tissue, and one must be vigilant in identifying falsely low BV values caused by poor contact. To this end, the DUR values may again be particularly helpful: a low BV value of an otherwise “normal-looking” ECG—that is, not fractionated, and of normal DUR—may indicate poor contact rather than abnormal myocardium.

**Combined Endocardial-Epicardial Substrate Mapping**

The electroanatomic mapping system permits simultaneous display of the LV endocardial and ventricular epicardial surface constructs of the heart. The ability to realize a more realistic 3-dimensional understanding of the myocardial infarct location raises the interesting possibility that the endocardial map might be able to guide epicardial ablation without...
the generation of an epicardial map. To this end, it was interesting to note that during combined endocardial-epicardial mapping, the scar borders of the two surfaces were closely situated (Figure 5). However, it is important to note that this strategy is likely to be applicable only to transmural myocardial infarcts. Also of note, even combined endocardial-epicardial mapping may not be able to identify truly intramural tachycardia circuits.

Limitations
In this report, epicardial mapping of only anterior wall MI was evaluated. Although no significant differences are expected, one cannot rule out the possibility that epicardial mapping of MI at other locations may be different. Furthermore, it should be noted that this infarct model may in itself have limitations that preclude its generalization. For example, because this infarct model most closely resembles that of an acutely occluded vessel with little to no coronary reflow, these results may not be applicable to patchier infarct morphologies. Also, the use of a 2-dimensional ellipsoid for the calculation of the scar area ignores the 3-dimensional endocardial chamber geometry. Furthermore, such a simplified estimation may not be applicable to scars with irregular shapes, such as patchy scars, those located at the ventricular basal regions, or scars resulting from nonischemic heart disease.

The electrograms for normal ventricular epicardium were analyzed in aggregate without regard for whether the sites were acquired over the left or right ventricle. Although these electrogram characteristics did not appear to be particularly different, it is important to note that the difference between the RV and LV wall thickness is less in the porcine heart than in humans. Accordingly, when normal values are established for humans, a more careful examination of the potential differences between the two chamber surfaces should be undertaken.

It is important to note that although this study suggests that epicardial substrate mapping is feasible in humans, there are few data that speak to the safety of applying multiple/linear RF ablation lesions to the ventricular epicardium. More work is required to establish the safety and efficacy of epicardial substrate ablation.

Conclusions
These data represent the first reported experimental evidence of the feasibility of epicardial substrate mapping. Furthermore, the data establish the proof-of-principle that epicardial substrate mapping can guide the placement of RF lesions at the epicardial borders of an infarct. They provide an experimental basis for further studies in epicardial substrate mapping and ablation of VT. The feasibility of epicardial substrate mapping also raises the possibility of using this methodology to guide other cardiovascular applications, such as the injection of genetic therapeutic agents, or cardiomyocyte progenitor stem cells into scarred myocardium for the treatment of congestive heart failure.

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