Published in final edited form as:

Heart Rhythm. 2010 March ; 7(3): 389–395. doi:10.1016/j.hrthm.2009.11.023.

DISTINGUISHING EPICARDIAL FAT FROM SCAR: ANALYSIS OF ELECTROGRAMS USING HIGH DENSITY ELECTROANATOMIC MAPPING IN A NOVEL PORCINE INFARCT MODEL

Roderick Tung, MD*,

UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine at UCLA, Los Angeles, CA

Shiro Nakahara, MD PhD*,

UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine at UCLA, Los Angeles, CA

Rafael Ramirez, PhD,

UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine at UCLA, Los Angeles, CA

Chi Lai, MD,

Department of Pathology & Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA

Michael C. Fishbein, MD, and

Department of Pathology & Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA

Kalyanam Shivkumar, MD PhD FHRS

UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine at UCLA, Los Angeles, CA

Abstract

Background—The presence of epicardial fat can confound the quantification of scar during transpericardial electroanatomic mapping. The electrogram (EGM) characteristics of epicardial fat have not been systematically compared with infarct scar using gross and histopathologic analysis as a gold standard.

Methods—A closed-chest infarction was created in 40–50 kg pigs by occlusion of the circumflex artery for 150 minutes using an angioplasty balloon. This artery was chosen to minimize any potential overlap of epicardial fat with infarct and to spare any septal involvement. After 4–12 weeks of infarct healing, epicardial mapping was performed. EGMs in low voltage regions (<1.5mV) were analyzed and bipolar amplitude, duration, number of deflections, and the presence of late potentials were recorded. Statistical analysis was performed using unpaired t-test and chi square analysis. Gross and histopathologic examination was used to confirm areas of fat and infarct scar.

Results—Seven porcine hearts were analyzed after high-density epicardial mapping (364±92 points) was performed 48±19 days after infarction. The mean bipolar EGM amplitude was similar

© 2009 Published by Elsevier Inc on behalf of The Heart Rhythm Society.

Address for Correspondence: Kalyanam Shivkumar MD PhD FHRS, UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine at UCLA, Ronald Reagan UCLA Medical Center, 47-123 CHS, 10833 Le Conte Avenue, Los Angeles CA 90095-1679, Phone: 310 206 6433, Fax: 310 794 6492, kshivkumar@mednet.ucla.edu.

*These authors contributed equally to this work.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

in fat and scar (0.77 ± 0.34 vs 0.75 ± 0.38 mV; $P = \text{NS}$). The mean EGM duration was longer in scar than fat (68.8 ± 18.9 vs 50.1 ± 11.6 ms; $P < 0.0001$) and exhibited more fractionation (8.5 ± 3.1 vs 4.7 ± 1.8 deflections; $P < 0.0001$). The presence of late potentials was 99% specific for scar. Further, areas of fat > 4 mm in thickness registered low voltage bipolar EGMs.

Conclusion—Scar from healed myocardial infarction exhibits more fractionation and longer EGM duration when compared to fat. Late potentials are highly specific for locating infarct scars.

Keywords

Epicardial; fat; infarction; electrogram; late potential

Percutaneous epicardial mapping has become an important strategy for mapping and ablation of ventricular tachycardia (VT) in the presence of structural heart disease.¹ Reentrant circuits have been shown to involve the epicardium in the setting of healed infarct scars, nonischemic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and Chagas disease.^{2–6} The principles of endocardial electroanatomic mapping to identify areas of low voltage to guide substrate-based ablation have been applied to epicardial mapping. However, the presence of epicardial fat confounds the diagnosis of myocardial scar, as both are represented by low voltage signals.^{3,7} This overlap is particularly relevant in the setting of ischemic cardiomyopathy when perivascular fat may be adjacent to the infarct area and in nonischemic cardiomyopathy, where scars have been demonstrated to have a basal perivalvular predilection.^{8,9} Additionally, the presence of epicardial fat interposed between the ablation catheter and epicardial surface can impact lesion formation. Thus, an accurate distinction between fat and epicardial scar is essential for defining the arrhythmogenic substrate for successful ablation of VT. To date, the electrogram (EGM) characteristics of epicardial fat have not been systematically compared with those of infarct scar tissue.

In this study, we sought to examine the EGM characteristics of epicardial fat and scar using gross and histopathologic analysis. We used a novel circumflex model of healed myocardial infarction to create a scar anatomically distinct from interventricular and periannular epicardial fat, to minimize the potential for superimposed fat on scar.

METHODS

Experimental Myocardial Infarction

A closed-chest infarction procedure was performed in 40–50 kg pigs.¹⁰ After an overnight fast and premedication with ketamine, pigs were intubated and ventilated on oxygen. General anesthesia with inhaled isoflurane was initiated and maintained. Heparin was bolused intravenously at 10,000 IU and then 5,000 IU hourly. Premedication with lidocaine (50 mg) and esmolol (50 mg) was administered via right femoral artery access. An obtuse marginal branch of the circumflex artery was occluded for 150 minutes using an angioplasty balloon (2.25×8 mm) via retrograde aortic approach using an AL1 sheath from the right femoral artery. Evolving infarction was confirmed and assessed by continuous ECG monitoring. Lidocaine and esmolol were rebolused if recurrent ventricular ectopy was seen, typically 30 minutes into infarction. After extubation, the animal was observed for 1–3 hours until able to walk and feed without assistance. All studies and protocols were approved and were performed in accordance with the Animal Research Committee at UCLA.

Epicardial Mapping

After 4–12 weeks of infarct healing, animals were subjected to left ventricular epicardial mapping after preparation with the same premedication and general anesthesia as described above. The pericardium was accessed by subxiphoid approach, with the use of 17 gauge

Touhy needle prior to heparin administration, as previously described.¹ Briefly, under fluoroscopic guidance, contrast media was injected to define the pericardium and a small amount was injected to confirm entry into the pericardial space. A guidewire was passed through the needle, over which an SLO sheath (St. Jude Medical, Minnetonka, MN) was placed into the pericardial space. The mapping catheter is introduced through the sheath and maneuvered in the pericardial space.

The left ventricle was mapped using CARTO system electroanatomic system (Biosense-Webster, Diamond Bar, CA) and NaviStar 4mm catheter during sinus rhythm to achieve a fill threshold of <15mm. High-density mapping was performed in the regions of low voltage, border zone, along the valve annulus, and interventricular septum. Scar was defined as <1.5mV and dense scar was <0.5mV during acquisition of data points. Valve annulus points were defined as sites with 1:1 ratio of atrial and ventricular EGM amplitudes.

Pathologic Analysis

After completion of mapping, animals were euthanized. The heart was resected immediately. The gross specimens were photographed and epicardial infarct area and regions of epicardial fat were delineated. The hearts were then serially sectioned parallel to the atrioventricular groove, from apex to base, into slices one centimeter thick. These sections were incubated in formalin until fully fixed and then photographed. Each slice was totally embedded in sequential sections of the entire slice of tissue. After routine processing, embedding, and cutting, histologic sections from each paraffin block were stained with hematoxylin and eosin or trichrome/elastic staining.

Electrogram analysis

Three dimensional electroanatomic maps acquired in sinus rhythm were displayed by bipolar voltage with dense scar defined as <0.5mV, scar border zone (BZ) from 0.51mV to 1.5mV, and low voltage area as <1.5mV. Amplitude was the voltage difference between the highest and lowest deflections in a given EGM. Bipolar EGMs were filtered at 30–400Hz and duration was measured in all low voltage areas at 400 mm/s speed, using electronic calipers from the onset of the earliest local deflection to the point of return to the baseline. Late potentials were defined as an EGM with a distinct onset after the terminal deflection of the QRS complex.

The number of deflections of each EGM was counted at 400 mm/s. This was determined by counting the number of turning points (positive to negative and vice versa) in each EGM.¹¹ (See Figure 1, sample EGMs) Three observers independently counted deflections for each EGM in the analysis. In situations where there was discrepancy, any agreement between two of the independent observers was taken as the final number of deflections. On the rare occasion where all three numbers were different, the median number was chosen.

Normal values for amplitude, duration, and fractionation were derived from sampling epicardial points with bipolar voltage >1.6mV anatomically distinct from the area of infarction and perivascular fat. Forty points were sampled from each porcine subject. With use of this data, the mean values for normal EGMs were calculated.

Statistical analysis

All values are expressed as mean±standard deviation. For comparing continuous variable, unpaired Student's T-test was used and for non-continuous variable, Chi-square test was used. A p-value of <0.05 was considered significant. Sensitivity for the identification of scar was defined as true positives for a given criteria (duration, deflection, or presence of late

potential) in the presence of scar/ all positives (scar). Specificity for scar was defined as true negatives identified for a criteria in the presence of fat/all negatives(fat).

RESULTS

Seven porcine subjects with healed inferolateral infarction underwent high-density epicardial mapping 48±19 days (range, 32–88 days) after induction of myocardial infarction. Low voltage areas correlating with epicardial fat on gross pathologic examination were seen in five out of seven electroanatomic maps. Epicardial fat predominated in two major areas: 1.) the basal portion of the interventricular course of the LAD up adjacent to the left atrial appendage (see Figure 2). 2.) the AV groove from the basal portion of the posterior interventricular septum, or crux of the heart, to the basal lateral wall.

Epicardial scar was seen in four of seven porcine subjects. Infarctions from an occlusion of obtuse marginal branch tended to have a linear configuration and extended from the apex to the base on the inferolateral wall and was anatomically distinct from periannular fat. (See Figure 3) On sectioning, subendocardial infarction was confirmed in all seven subjects.

The mean number of points mapped in the epicardium was 364±92 per subject. The mean low voltage area on CARTO for fat was 18.6±16.6 cm² and the mean area for scar was 12.1±9.9 cm². The mean number of points sampled in fat was 35±29 and the mean number of points sampled in scar was 35±21.

Amplitude and duration

The mean bipolar EGM amplitude was similar in fat and scar (0.77±0.34 vs 0.75±0.38mV; P=NS). Among points sampled in normal myocardium, the mean bipolar voltage was 5.9±3.5mV and unipolar voltage was 10.4±4.6.

The mean EGM duration was longer in scar than fat (68.8±18.9 vs 50.1±11.6 ms; P<0.0001). (See figure 4) The mean EGM duration sampled from normal myocardium was 50.0±6.7. The area under the receiver operating characteristic curve was 0.78, p<0.0001. (Figure 5) A cut-off point of >50 ms was 80% sensitive and 52% specific for scar. An EGM duration of >80 ms was 99% specific for scar.

Late potentials

Late potentials were observed in 39.1% of total EGMs (54/138 points) analyzed within scar. In contrast, late potentials were rarely seen (0.8%) in areas of epicardial fat (2/248 points). These two points were confirmed to overly normal myocardium on gross and histopathologic analysis. This difference in LP frequency between scar and fat was statistically significant (p<0.0001). The presence of late potentials had a specificity of 99% for scar.

Deflections and fractionation

EGMs examined within scar exhibited more fractionation compared with fat (8.5±3.1 vs 4.7±1.8 deflections; P<0.0001). Amongst points sampled within normal myocardium, the mean number of deflections was 4.8±1.4. A cutpoint of five deflections was 95% sensitive for scar had only 52% specificity. Only 7.7% of EGMs within fat had 8 or more deflections compared to 58.7% within scar, resulting in a sensitivity 59% and specificity of 92% for scar. The area under the receiver operating characteristic curve was 0.86, p<0.0001. (Figure 5).

When combining deflections with duration, specificity for scar was significantly improved (Table 1). In contrast, sensitivity for scar was diminished by combining criteria.

Fat thickness

An anterior fat stripe consistent with the interventricular course of the LAD was seen in five of seven subjects. The extent to which this was represented by low voltage was variable. Comparison of the thickness of fat in those with minimal area with those with dense representation on electroanatomic mapping demonstrates a direct correlation with fat thickness. The range of fat thickness was 1–7 mm. In the two epicardial maps where an area of low voltage was not registered in the interventricular septum, the maximum fat thicknesses were 2 and 3 mm. Areas of low voltage ($<1.5\text{mV}$) were seen only in areas where the fat thickness was 4mm or greater. (See Figure 5)

DISCUSSION

The major findings of this study are: 1.) Epicardial fat can be distinguished from scar based on EGM duration and the degree of fractionation 2.) Late potentials are highly specific for myocardial infarct scar 3.) A critical thickness of fat must be present to register a low amplitude bipolar EGM. This is the first study, to our knowledge, to systematically analyze the specific EGM characteristics between epicardial fat and scar. While no criteria examined offered high sensitivity for the identification of scar within areas of low voltage, we report clinically relevant specific criteria for confirming the presence of scar.

As epicardial fat overlies and insulates myocardium when recording EGMs during epicardial mapping, low voltage amplitudes can be detected in areas of normal myocardium. An appreciation for the fact that epicardial fat can mimic scar is imperative to the interpretation of electroanatomic mapping via percutaneous subxiphoid approach. While preprocedural imaging and knowledge of infarct or scar location can be useful in discriminating expected areas of scar from fat, interpretation may be clouded when areas of scar are adjacent or superimposed with fat.¹² In cases of nonischemic cardiomyopathy, where scar predominates adjacent to the AV groove, and in ischemic cardiomyopathy, where an infarct-related artery may lie under perivascular fat, this remains a particular challenge. A real-time interpretation of EGM characteristics seen in low-voltage areas is invaluable.

As seen in previous studies, no differences in bipolar voltage recordings in areas of fat and scar were seen in our porcine subjects. With regards to duration, Reddy et al initially reported an EGM duration of 50 ms to be specific for epicardial scar, with an excellent correlation between gross anatomic scar and electroanatomic mapping derived only from EGM duration.³ No formal analysis between fat and scar was presented, although it was mentioned that areas of fat up to 10mm in thickness had normal EGM duration. Saba et al¹³ found no appreciable differences in EGM duration between normal LV epicardium and fat $>5\text{mm}$ (44.4 ± 7.4 vs. 45.8 ± 6.4 , $p=\text{NS}$). Our findings are consistent with these observations, although we found a cutpoint of 70 ms to be more specific for scar. The additional criteria of 6 deflections in EGMs with duration of >60 ms was specific as well. In a study of patients with nonischemic cardiomyopathy referred for epicardial mapping, Cano et al. found that EGMs that were split or had duration >80 ms were seen in only 2.3% of points mapped.⁹ In our study, we found a duration of >80 ms to be 99% specific for scar.

This is the first study to evaluate the impact of fractionation to differentiate scar from fat. Fractionated signals reflect areas of slow conduction with zig-zag propagation and are thought to be highly specific for diseased tissue.^{14–16} In the present analysis, a greater number of EGM deflections was observed more frequently in scar compared to fat. While the degree of fractionation was specific for scar, the addition of duration criteria allowed for

enhanced specificity for scar. Consistent with fat merely insulating myocardial potentials, late potentials were highly specific for scar. These findings are consistent with the observations of Cano et al, where late potentials were not seen in the AV groove in normal controls.

Our findings that a critical fat thickness of 4mm is required to result in a low bipolar voltage is consistent with previous observations.^{13,17} In one series intraoperative mapping studies, bipolar voltages were diminished only in areas where epicardial fat thickness exceeded 5 mm, where 31% of recordings were <0.5mV. Interestingly, these recordings had zero amplitude, which was not seen in our study. However, measurement after pathologic sectioning has advantages over intraoperative estimates for thickness accuracy. Reddy et al reported normal bipolar voltages in areas where fat thickness was less than 5mm.³

Limitations

In this study, only epicardial mapping of inferolateral infarctions were included. This infarct model which involves a branch occlusion of the circumflex marginal system results in smaller infarctions than previous models of anterior infarction. Due to the smaller size of infarct, less points within scar were available for analysis and comparison with fat. However, a balloon occlusion model more accurately simulates the pathophysiology of human infarction treated with reperfusion, which likely accounts for patchier scar when compared to models using alcohol or microspheres for infarct generation. As in human infarct, heterogeneity in scar extent was seen but the effect of a transmural infarction versus a patchy infarction with epicardial extension on electrograms registered during epicardial mapping is unknown. Specifically, the relationship between the extent of scar heterogeneity and electrogram voltage, duration, and deflections has not been systematically studied. A comparison of homogeneous transmural areas with models of patchier infarct areas to determine the virtual electrode of sensing or “field of view” will require precise means of registration i.e plunge needle electrodes. The generalization of the EGM differences between infarct and fat from the current porcine model to humans must be confirmed although immediate pathologic correlation is difficult to achieve in human cases.

Acknowledgments

This work was supported by the NHLBI (R01HL084261 and R01 HL067647 to Dr. Shivkumar).

REFERENCES

1. Sosa E, Scanavacca M, d'Avila A, et al. A new technique to perform epicardial mapping in the electrophysiology laboratory. *J Cardiovasc Electrophysiol*. 1996; 7:531–536. [PubMed: 8743758]
2. 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. [PubMed: 16399044]
3. Reddy VY, Wroblewski D, Houghtaling C, et al. Combined epicardial and endocardial electroanatomic mapping in a porcine model of healed myocardial infarction. *Circulation*. 2003; 107:3236–3242. [PubMed: 12796129]
4. Soejima K, Stevenson WG, Sapp JL, et al. Endocardial and epicardial radiofrequency ablation of ventricular tachycardia associated with dilated cardiomyopathy: the importance of low-voltage scars. *J Am Coll Cardiol*. 2004; 43:1834–1842. [PubMed: 15145109]
5. Sosa E, Scanavacca M, D'Avila A, et al. Radiofrequency catheter ablation of ventricular tachycardia guided by nonsurgical epicardial mapping in chronic Chagasic heart disease. *Pacing Clin Electrophysiol*. 1999; 22:128–130. [PubMed: 9990612]

6. Sosa E, Scanavacca M, d'Avila A, et al. Nonsurgical transthoracic epicardial catheter ablation to treat recurrent ventricular tachycardia occurring late after myocardial infarction. *J Am Coll Cardiol*. 2000; 35:1442–1449. [PubMed: 10807445]
7. Dixit S, Narula N, Callans DJ, et al. Electroanatomic mapping of human heart: epicardial fat can mimic scar. *J Cardiovasc Electrophysiol*. 2003; 14:1128. [PubMed: 14521672]
8. Hsia HH, Callans DJ, Marchlinski FE. Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia. *Circulation*. 2003; 108:704–710. [PubMed: 12885746]
9. 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. [PubMed: 19695457]
10. Donahue JK, Sasano T, Kelemen K. Gene therapy approaches to ventricular tachyarrhythmias. *J Electrocardiol*. 2007; 40:S187–S191. [PubMed: 17993320]
11. Lellouche N, Buch E, Celigoj A, et al. Functional characterization of atrial electrograms in sinus rhythm delineates sites of parasympathetic innervation in patients with paroxysmal atrial fibrillation. *J Am Coll Cardiol*. 2007; 50:1324–1331. [PubMed: 17903630]
12. Abbata S, Desai JC, Cury RC, et al. Mapping epicardial fat with multi-detector computed tomography to facilitate percutaneous transepical arrhythmia ablation. *Eur J Radiol*. 2006; 57:417–422. [PubMed: 16434161]
13. Saba MM, Akella J, Gammie J, et al. The influence of fat thickness on the human epicardial bipolar electrogram characteristics: measurements on patients undergoing open-heart surgery. *Europace*. 2009; 11:949–953. [PubMed: 19546189]
14. de Bakker JM, van Capelle FJ, Janse MJ, et al. Slow conduction in the infarcted human heart. 'Zigzag' course of activation. *Circulation*. 1993; 88:915–926. [PubMed: 8353918]
15. 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; 27:1071–1078. [PubMed: 8609323]
16. Callans DJ, Ren JF, Michele J, et al. Electroanatomic left ventricular mapping in the porcine model of healed anterior myocardial infarction. Correlation with intracardiac echocardiography and pathological analysis. *Circulation*. 1999; 100:1744–1750. [PubMed: 10525495]
17. d'Avila A. Epicardial catheter ablation of ventricular tachycardia. *Heart Rhythm*. 2008; 5:S73–S75. [PubMed: 18456208]

Figure 1. Method of EGM analysis

Method for counting duration and deflections for electrograms analyzed.

Figure 2. Explanted heart demonstrating anatomically distinct region of scar from fat
A. Anteroposterior view of epicardial fat in the anterior interventricular groove (red dashed line) with inferolateral infarction (asterisk). B. Left anterior oblique view of inferolateral infarction (blue dashed line) adjacent to the obtuse marginal.

Figure 3. Electroanatomic map and gross pathologic correlation

Correlation of low voltage areas on CARTO (A) with gross pathologic examination (B) demonstrating epicardial fat in the posterior AV groove (red dashed line) and linear lateral infarction extending from base to apex (black dashed line). Late potentials were specific for scar amongst low voltage areas. Note myocardial contusion to the right of scar from epicardial puncture during pericardial access. Histopathologic confirmation (100x magnification) of epicardial scar (C) from transmural infarction and adipose tissue overlying normal myocardium (D).

Figure 4. Electrogram characteristics between scar and fat for number of deflections and electrogram duration

Differences in electrogram duration and number of deflections between scar and fat. Mean and standard error of mean are represented by line plot.

Figure 5. Receiver operating characteristics for deflection and EGM duration criteria. Test characteristics are shown for different cutoff points

Receiver operating characteristic curves demonstrating test characteristics of electrogram duration and number of deflections at various cutoff points.

Figure 6. Relationship of fat thickness with identification of low voltage area on electroanatomic mapping (anterior interventricular fat stripe)

Thickness of fat exceeds 4mm in a heart (6mm) that registers a large area of low voltage in the anterior interventricular groove (blue dashed line) compared to a heart that does not (3mm).

Table 1
Combined test characteristics of EGM duration (ms) and number of deflections for the identification of scar

Test characteristics for identification of scar using combined number of deflections with electrogram duration.

	Sensitivity (%)	Specificity (%)
EGM duration (ms) and deflections		
>50 and 6	74	79
>50 and 7	64	87
>50 and 8	55	93
>50 and 9	42	96
>60 and 6	62	90
>60 and 7	58	92
>60 and 8	52	95
>60 and 9	40	97
>70 and 6	48	95
>70 and 7	45	96
>70 and 8	42	97
>70 and 9	34	98
Late potential	39	99