Use of a Novel Endoscopic Catheter for Direct Visualization and Ablation in an Ovine Model of Chronic Myocardial Infarction

Brian P. Betensky, MD; Miguel Jauregui, MD; Bieito Campos, MD; John Michele, BS; Francis E. Marchlinski, MD; Leslie Oley, MS; Bryan Wylie, MS; David Robinson, BS; Edward P. Gerstenfeld, MS, MD

Background—Defining the arrhythmogenic substrate is essential for successful ablation of scar-related ventricular tachycardia. The visual characteristics of endocardial ischemic scar have not been described in vivo. The goal of this study was (1) to quantify the visual characteristics of normal tissue, scar border zone, and dense scar in vivo with the use of a novel endoscopic catheter that allows direct endocardial visualization and (2) to correlate visual attributes of myocardial scar with bipolar voltage.

Methods and Results—Percutaneous transient balloon occlusion (150 minutes) of the mid left anterior descending coronary artery was performed in an ovine model. Animals survived for 41.5±0.7 days. Detailed bipolar voltage maps of the left ventricle were acquired with the use of NavX. Video snapshots of the endocardium were acquired at sites distributed throughout the left ventricle. Visual tissue characteristics of normal (>1.5 mV), border (0.5–1.5 mV), and dense scar (<0.5 mV) were quantified with the use of image processing. Radiofrequency lesions (10–20 W, 30 seconds) were delivered under direct visualization. Mean white-threshold pixel area was lowest in normal tissue (189 969±41 478 pixels²), intermediate in scar border zone (255 979±36 016 pixels²), and highest in dense scar (324 452±30 152 pixels²; P<0.0001 for all pairwise comparisons). Tissue whiteness, characteristic of scar, was inversely correlated with bipolar voltage (P<0.0001). During radiofrequency lesions, there was a significant increase in white-thresholded pixel area of the visual field after ablation (average increase, 85 381±52 618 pixels²; P<0.001).

Conclusions—Visual characteristics of chronic infarct scar in vivo observed with the use of a novel endoscopic catheter correlate with bipolar electrogram voltage. Irrigated radiofrequency lesions in normal endocardial tissue and postinfarction zone can be visualized and quantified with the use of image processing. This technology shows promise for visually based delivery of radiofrequency lesions for the treatment of scar-based ventricular tachycardia.

Key Words: ablation • animal model • catheter ablation • myocardial infarction • ventricular tachycardia

M apping of poorly tolerated ventricular tachycardia (VT) combines reconstruction of cardiac anatomy and scar with the use of electroanatomic voltage mapping and pace mapping to locate VT exit sites.1,2 Ablative therapy involves an anatomic approach of lesion delivery in a linear fashion through the infarct border zone and may include ablation of late and fractionated potentials presumed to represent zones of slow conduction capable of sustaining VT.3–6 Despite the advent of these “substrate modification” techniques that allow ablation of VT that is not tolerated hemodynamically, the long-term result of VT ablation remains suboptimal. In the recent randomized Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) study, the 2-year success rate after ablation of VT in patients with ischemic cardiomyopathy was 47%.7 In addition to an evolving substrate, some of the limitations of substrate-based ablation include indirect localization of myocardial scar with the use of voltage mapping, poor catheter-myocardial contact during radiofrequency delivery, difficulty in delivering contiguous lesions, and challenges in achieving adequate lesion depth in dense scar.

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Given the largely anatomic approach to ablation of poorly tolerated VT in many centers, direct visualization of the myocardium may offer advantages to the indirect visualiza-
tion offered by current electroanatomic voltage mapping systems. These advantages include direct visualization of infarct heterogeneity and location, catheter stability, lesion development, and lesion contiguity. A novel endoscopic catheter (IRIS cardiac ablation catheter; Voyage Medical Inc, Redwood City, CA) allows direct visualization of endocardial tissue during mapping and delivery of irrigated radiofrequency ablation. Using this catheter in an ovine model of myocardial infarction, we hypothesized that (1) we could quantify and differentiate the visual characteristics of normal endocardium, infarct border zone, and dense scar; (2) scar characteristics defined by visual assessment would correlate with bipolar voltage recorded from the catheter tip; and (3) we could visualize and quantify ablative lesions delivered to normal tissue, infarct border zone, and scar. We also assessed the size of ablative lesions delivered with this novel catheter at different power settings.

Methods

Study Design
The study was performed in an ovine model after creation of a myocardial infarction by transient balloon occlusion of the left anterior descending coronary artery. This study was approved by the University of Pennsylvania Institutional Animal Care and Use Committee and was performed within University Laboratory Animal Resources institutional guidelines.

Catheter Description
The IRIS catheter is designed for visualization of anatomic structures within the heart, cardiac mapping, and delivery of radiofrequency energy to myocardial tissue for the treatment of cardiac arrhythmias. The catheter is an open irrigation, direct visualization catheter consisting of a steerable 12.5F catheter with a distal self-expanding flexible hood (6.8 mm), an open aperture in the center of the hood face (3 mm), and an integrated high-resolution flexible fiberscope and illumination bundle (Figure 1). The catheter has 4 electrodes (2-mm interelectrode bipolar spacing) on the hood surface and an additional 8 electrodes on the outside of the hood to allow for localization of the catheter with the use of an impedance-based mapping system. With the hood in contact with the endocardium, a constant saline flush (5–10 mL/min) is used to keep the hood free of blood and allows for direct visualization of the endocardial surface. The video images are displayed on a monitor in the laboratory and recorded by an external system for digital archive and review. Brightness settings and camera focus were calibrated at the start of each experiment to optimize tissue clarity. The catheter handle contains a steering device that combines a primary unidirectional curve of up to 180 degrees with a 4-way steering mechanism that allows for fine movements of the catheter tip in 3 dimensions.

The hood contains a 2.7-mm electrode; when radiofrequency energy is delivered to the electrode, the saline serves as a medium to conduct current to the tissue (ie, a “virtual” radiofrequency electrode). This allows irrigated ablation from the 6.8-mm diameter catheter hood without direct electrode contact with the endocardium, with the effective “electrode” area being the 3-mm hood aperture. During ablation, saline irrigation is maintained at up to 25 mL/min with the use of an irrigation pump.

Myocardial Infarction Protocol
All animals were placed under general anesthesia. After induction with ketamine and buprenorphine, all animals were intubated and placed under general anesthesia with inhaled isoflurane 1% to 2% and mechanically ventilated. Vascular access was obtained through the femoral artery and vein with the use of standard hemostatic sheaths. Temperature was maintained at >37 °C with the use of a warming blanket and warmed saline. An intracardiac echo catheter...
left ventricle. After initial mapping was performed, the intracardiac echocardiography catheter was exchanged for a right ventricular quadripolar pacing catheter positioned at the right ventricular apex to perform programmed electric stimulation.

The 8 electrodes located on the hood exterior allowed catheter tip localization with the NavX mapping system (St. Jude Medical, Minnetonka, MN), and the 4 electrodes on the IRIS hood were used to simultaneously record bipolar voltage. A left ventricular geometry was created, and then a detailed bipolar voltage map was superimposed on the left ventricular geometry (Figure 2). Dense scar (<0.5 mV), border zone (0.5–1.5 mV), and healthy tissue (>1.5 mV) were defined with previously described voltage cutoffs. Individual recording sites were distributed throughout the left ventricle at points of stable apposition of the catheter hood with the myocardium. At each site, a video image was captured, the location was tagged, and electrograms were recorded on the NavX system for offline analysis. Mean bipolar electrogram voltage was calculated by averaging the 4 bipolar electrode pairs (1,2; 2,3; 3,4; 4,1) on the catheter tip and was correlated with the simultaneous visual snapshot of the myocardium at each site (Figure 3).

**Image Processing**

Video snapshots of each region were acquired offline with the use of Corel VisualStudio 12. Bitmap images were imported into the Fiji Package for ImageJ, an open-source Java-based image processing application developed by the National Institutes of Health. Individual color images were contrast enhanced and color thresholded to best approximate red-white tissue borders. Thresholding parameters were preset to default mode with an HSB color space. Saturation and brightness were initially fixed at 0 to 255. Hue was the first parameter assessed by setting the color range to 0 to 15. The upper limit was then decreased in a stepwise fashion until red regions appeared to break through between the black regions and the white regions. Once this was established, the saturation parameter was adjusted to avoid counting the 4 white electrodes. The image was then converted to an 8-bit format for particle analysis. Images were
analyzed in a random chronological order. Pixel measurement settings were standardized for ensuring consistent particle analysis measurements. All images with blood in view were excluded so that tissue whiteness was not falsely affected.

**Radiofrequency Lesion Delivery**
After completion of geometric and voltage data acquisition, a series of radiofrequency lesions were delivered to regions of healthy, border, and dense scar tissue for 30 seconds each at powers of 10, 15, and 20 W. During radiofrequency, energy delivery irrigation was maintained at 25 mL/min. Constant power delivery was maintained for each lesion; no attempt was made to titrate power delivery on the basis of visual findings in order to determine a histopathological correlation to the different power settings. Local bipolar electrograms were recorded before and immediately after radiofrequency delivery. The time to tissue blanching, defined as the time until the field of view through the central 6-mm aperture was completely white, was recorded by 2 independent observers. It was hypothesized that this measure, reflective of scar formation during ablation, would differ among normal myocardium, border zone, and dense scar.10,11

**Gross Anatomy and Histopathology**
At the conclusion of the mapping and lesion study, while under a deep plane of anesthesia, sheep were euthanized, and the hearts were explanted. The hearts were then incised posteriorly to provide a posteroanterior view of the endocardial surface. Scar distribution and radiofrequency lesions were visually inspected and then marked with colored sutures to denote power delivery for each lesion. The hearts were then immersed in 10% buffered formalin. After fixation, the radiofrequency lesions were identified and grossly trimmed, and the width and depth of each lesion were measured with a hand caliper. Trimmed sections were embedded in paraffin, cut 4 mm thick, and stained with Masson’s trichrome (Histo Tec Laboratory, Hayward, CA). Histology slides were evaluated with a light microscope, and histopathological findings were recorded.

**Statistical Analysis**
To accommodate the repeated measurements on each animal, linear mixed models were used to compare tissue types and assess the association of tissue whiteness and voltage. Pairwise comparisons between groups were corrected for multiple testing with the use of the Sidak method. The Kenward-Roger approximation was used to account for small sample sizes, and sensitivity to the assumed variance-covariance structure was checked with the use of robust standard errors. Voltage was log transformed to linearize the relationship to whiteness. The significance of the overall tissue whiteness change from before to after ablation as well as lesion width and depth were also assessed with the use of mixed model analyses, as described above. The analyses included terms for tissue type, power, and their interaction. Analyses were performed with the use of SPSS version 16.0 statistical software (SPSS, Chicago, IL) and SAS version 9.2 (SAS Institute, Cary, NC).

**Results**
Eight male Hunter-Dorset sheep were included in this study. Animals survived for a mean of 41.5±0.7 days after infarct creation. Detailed bipolar endocardial voltage maps were acquired in each animal. In the 8 animals, visual images and mean bipolar voltage were examined and compared at 148 sites: normal tissue (n=75), border zone (n=49), and dense scar (n=24). At an additional 60 sites (normal=32, border=20, dense scar=8), bipolar voltage and image analyses were performed before and after radiofrequency ablation.

**Visual Characterization of Tissue Types**
Visually, there were clear differences among the tissue types under direct visualization, with healthy myocardium appearing pink/red, dense infarct appearing white, and infarct border zone showing red/white intermingled fibers (Figure 3). These qualitative findings were quantified by counting the whiteness of each visual field after white-thresholding. The mean white-thresholded pixel area (range, 97 569–398 002 pixels\(^2\)) was significantly different among healthy endocardium, border zone, and dense scar (Figure 4A; \(P<0.0001\) for all pairwise comparisons). Mean peak-to-peak bipolar voltage (range, 0.16–19.64 mV) was inversely correlated with mean white-thresholded pixel area. With each doubling of voltage, white-thresholded pixel area was estimated to decrease by \(\approx 62 100\) pixels \((P<0.001)\) (Figure 4B).

**Visual Characterization of Radiofrequency Lesions**
Delivery of radiofrequency lesions (n=60) was visualized in real time with the use of the IRIS catheter (Figure 5; and Movie I in the online-only Data Supplement). Radiofrequency lesions were marked by an initial quiescent period, followed by marked, rapid tissue whitening starting at the center of the visual field and radiating outward. Small microbubbles could be seen developing during higher-power energy delivery. At the highest power (20 W), an inaudible steam “pop” was observed only once during radiofrequency delivery. Microbubbles were visualized and increased in volume before the steam pop occurred. Endocardial coagulum or thrombi were not observed during ablation. After each lesion was delivered, the catheter could be navigated around the lesion borders, which were clearly demarcated in vivo. Each lesion was delivered individually, separate from the others, to allow for later histological analysis of lesion size.
There was a significant increase in white-thresholded pixel area of the visual field both within each tissue type ($P<0.001$ for each type) and overall (average increase, $85.381\pm52.618$ pixels$^2$; $P<0.001$) after ablation. Visually, even lesions appearing in dense scar were readily apparent.

Despite the subjective appearance of more robust visual field whitening during the highest power (20-W lesions), the time to tissue blanching was not significantly correlated with tissue type when all lesions were grouped together (dense scar, $16.3\pm10.4$ seconds; border zone, $12.6\pm7.0$ seconds; normal, $14.7\pm4.8$ seconds; $P=0.339$).

**Histopathology of the Left Ventricle and Radiofrequency Lesions**

Sections of the ventricle had large regions of chronic infarct scar tissue, as well as regions that had acute coagulative necrosis of the myocardial fibers. The scar tissue (infarct) was represented by regions of fibrous connective tissues mixed with a collagenous matrix. Zones of persisting normal myocardial fibers were interspersed within the chronic scar. The acute ablation foci were well demarcated, consisting of swollen and dark myocardial fibers with loss of cellular detail along with interstitial edema and congestion/hemorrhage (Figure 6). Ablation lesions were either individually localized and separated by zones of healthy myocardial tissue or adjacent to and within infarct scars. In the latter case, radiofrequency application targeted the surviving myocardial fibers still persisting in previously infarcted tissue. These isolated sheets of myofibers sustained complete thermal necrosis (Figure 6).

Of the 62 lesions delivered, 45 lesions were identified during histopathological examination. Sizable lesions were achieved across all tissue types (width, $6.5\pm2.0$ mm; range, 2.0–16.0 mm; depth, $5.2\pm1.9$ mm; range, 2–10 mm). Lesion width (for 10 versus 15 versus 20 W, adjusted mean±SEM=5.2±0.8 versus 6.1±0.6 versus 8.1±0.6 mm; $P=0.01$) and depth (2.9±0.7 versus 5.4±0.6 versus 5.8±0.6 mm; $P=0.0003$) increased with increasing power (Figure 7).

**Discussion**

We found that a novel endoscopic catheter allows real-time visualization of the left ventricular endocardium during mapping and irrigated radiofrequency ablation. Direct visualization allowed the operator to differentiate among electrogram-defined dense scar, border zone, and normal tissue in an ovine model of chronic myocardial infarction. The difference in tissue characteristics among these regions was readily apparent visually, and these visual findings could be quantified with the use of image processing, demonstrating a direct inverse correlation between visual field whiteness and bipolar electrogram voltage. Direct visualization was also performed during irrigated radiofrequency ablation, with qualitative and quantitative whitening of the visual field occurring during ablation. Radiofrequency lesion visualization was most pronounced in normal tissue but also readily apparent in dense scar. Microbubble formation was rarely seen at higher powers and in one case presaged a steam pop.

These findings introduce a new paradigm in catheter ablation. Initially, catheter ablation was guided indirectly by fluoroscopy and electrograms recorded from the electrode tip. The advent of electroanatomic mapping allowed one to construct a virtual geometry and, with computed tomographic or magnetic resonance image registration, an indirect representation of the cardiac chamber anatomy and catheter.
Intracardiac ultrasound provided the first real-time feedback of anatomy during ablation; however, the anatomic rendering was limited by the resolution and field of view of ultrasound. Now, direct visualization of the endocardial surface is feasible during mapping and ablation. This has many important implications. Many arrhythmias are targeted with the use of a combination of electric and anatomic information, including atrial fibrillation, atrial flutter, papillary muscle VT, and VT in ischemic cardiomyopathy. Ablation of VT that is poorly tolerated hemodynamically is performed with a combination of pace mapping and linear ablation through the scar border zone. Some have advocated scar “homogenization,” with ablation of all portions of electrically active scar or late potentials that might harbor future VT circuits. The IRIS endoscopic catheter can be used to rapidly construct a voltage map that identifies the location of scar and border zone. Ablation can then be performed through regions of border zone with direct visual confirmation. In addition, ablation of other areas of presumably viable tissue throughout the scar can be performed empirically. There may be other advantages to direct visualization during ablation. Visualization ensures catheter contact during ablation because one cannot visualize the endocardium until contact is achieved and the saline flush clears blood from the field of view. This will likely enhance the depth and consistency of ablative lesions. Furthermore, tissue blanching during radiofrequency delivery actually confirms that the tissue has reached an adequate temperature for irreversible thermal necrosis. It has been demonstrated previously that tissue optical properties change as the tissue is heated on the basis of increased light scattering from denatured proteins and changes to mitochondria (observed by us as blanching). These visual/optical changes have been found to occur in the 50°C to 60°C range.

Visual feedback during ablation also may prevent complications via early visualization of thrombus and avoidance of steam pops due to downward titration of power when aggres-
sive microbubbles appear. Linear, contiguous lesions may also be secured by visually connecting individual lesions. Previous lesions can also be revisited quite easily should the catheter be repositioned. Contact with certain challenging anatomical structures, such as the papillary muscle, can be confirmed before ablation. Furthermore, ablation through the virtual electrode saline irrigant may also have advantages over ablation with the use of contact electrodes. Energy delivery is more uniform and efficient because the radiofrequency energy is delivered directly to the myocardium in the field of view. This is in contrast to contact irrigated catheter ablation, in which energy delivery may vary significantly depending on catheter orientation as a result of the variable electrode/myocardial interface and loss of energy to the surrounding blood pool. Finally, the flat 6-mm distal hood surface is also less likely to lead to cardiac perforation; we have never seen a perforation despite aggressive catheter manipulation in this animal model.

Prior Work
Two visualization catheters have been described previously, including the CardioFocus endoscopic ablation system (CardioFocus Inc, Marlborough, MA) and the FLEXview system (Boston Scientific Cardiac Surgery, Santa Clara, CA). CardioFocus uses a small endoscope to allow visualization through a balloon placed in the pulmonary vein ostium. This system is designed specifically for pulmonary vein isolation, and such a balloon cannot be maneuvered around a cavity such as the left ventricle. The FLEXview system is a gastroenterology endoscopy catheter that was adapted for use in epicardial visualization. This catheter did not have the ability to perform fine mapping, recording of electric signals, or ablation. None of these studies addressed scar-based models of VT.

Limitations
There are several limitations to the endoscopic catheter system. Visualization requires endocardial contact; no visualization occurs when the catheter is manipulated inside the left ventricular cavity. We used an electroanatomic mapping system to guide catheter manipulation, localization, and rendering of the voltage map to define the location of endocardial scar. These combined modalities may increase the cost of the procedure; however, with additional use it is likely that the endoscopic catheter could be used without a mapping system. A large amount of saline is given throughout these procedures because a constant infusion is needed during both mapping and ablation. This may be reduced in future versions of the catheter.

The absolute value for tissue whiteness was determined offline. Further investigation is warranted to determine whether more automated software capable of real-time, online quantification for visually based mapping is feasible and to establish clinical reference values for different tissue types. Although visual blanching is the hallmark of lesion formation and progressively deeper lesions were achieved at higher powers, a statistically significant correlation between lesion depth and change in tissue whiteness before and after ablation or time to initial blanching was not observed in this study. Thus, further research is needed to develop visually based criteria that may help to predict lesion depth. Finally, we recognize that the optical properties of endocardial tissue vary between cardiac chambers and that there may exist species-specific differences in the whiteness of ventricular endocardium at baseline, potentially limiting the generalizability of our results to humans with chronic myocardial infarction.

Conclusions
A novel endoscopic catheter is capable of direct endocardial visualization during mapping and ablation in an ovine model of chronic myocardial infarction. Using this catheter, we were able to visualize and quantify differences in tissue characteristics among normal myocardium, border zone, and dense scar. Irrigated radiofrequency lesions were visualized during and after ablation in both normal tissue and dense scar. Integration of direct visualization with current mapping techniques may enable visually guided ablation of heterogeneous scar capable of supporting VT. This technology shows promise for visually based delivery of contiguous radiofrequency lesions for the treatment of scar-based VT.

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Disclosures
Dr Marchlinski is on the Scientific Advisory Board of Voyage Medical Inc. Wylie, L. Oley, and D. Robinson are employees of Voyage Medical Inc. Dr Gerstenfeld has an investigator-initiated research grant from Voyage Medical Inc and is on the Scientific Advisory Board of Voyage Medical Inc.

References
CLINICAL PERSPECTIVE

Substrate mapping of ventricular tachycardia typically uses indirect measures of identifying myocardial scar, including electroanatomic voltage mapping and intracardiac echocardiography. We describe a novel catheter capable of direct endocardial visualization during mapping and irrigated radiofrequency ablation. The catheter contains a small fiberscope capable of directly visualizing the endocardial surface through a clear hood on the catheter tip with a 6.8-mm field of view. Saline is constantly flushed through the catheter to clear blood from the hood and allow visualization of the endocardial surface. Electrograms can be recorded from 4 orthogonal electrodes on the catheter tip; irrigated radiofrequency ablation can be performed via an electrode proximal to the catheter tip that heats the saline irrigant. We tested whether this catheter could visually differentiate among dense scar, border zone, and normal myocardium in an ovine model of chronic myocardial infarction. With the use of image processing techniques, the visual whiteness in the field of view was quantified and correlated well with electrogram measures of scar. Irrigated ablation lesions were delivered and could be observed in both healthy myocardium and myocardial scar. This approach offers a new paradigm in catheter ablation. Advantages include confirmation of catheter contact with the endocardium, direct visualization of anatomic structures such as the papillary muscles and myocardial scar, improved efficacy and safety of catheter ablation through visualization of lesion formation, and the ability to visually confirm contiguity of lesions delivered in a linear fashion during catheter ablation.
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**Movie Legend**

**Movie 1**: Left panel: Electroanatomic voltage map of the swine left ventricle showing catheter position on the mid-septum. Right panel: Video of the scar border zone during radiofrequency ablation. Note the heterogeneous appearance of the scar tissue at baseline and the whitening that occurs during ablation.