Assessing Myocardial Viability and Infarct Transmurality With Left Ventricular Electromechanical Mapping in Patients With Stable Coronary Artery Disease Validation by Delayed-Enhancement Magnetic Resonance Imaging

Emerson C. Perin, MD; Guilherme V. Silva, MD; Rogerio Sarmento-Leite, MD; Andre L.S. Sousa, MD; Marcus Howell, MD; Raja Muthupillai, PhD; Brenda Lambert, RN; William K. Vaughn, PhD; Scott D. Flamm, MD

Background—This study was designed to define myocardial viability and establish practical cut-off values for differentiating normal myocardial tissue from subendocardial and transmural scar tissue by using electromechanical mapping (EMM). We validated our results by delayed-enhancement cardiac MRI (DE-MRI).

Methods and Results—We prospectively studied 15 ambulatory patients with stable coronary disease who were candidates for cardiac catheterization. Within 48 hours of EMM, DE-MRI was performed. Using EMM software, we created a bull’s eye precisely matched to that generated by DE-MRI. Segment by segment, we compared the MRI results to the corresponding unipolar voltage value for that same segment in the EMM bull’s eye. Of 300 total segments, 275 were compared. The segments were divided into normal (n=110), subendocardial scar (n=49), and transmural scar (n=15). We found that subendocardial (6.8±2.9 mV) and transmural (4.6±1.9 mV) scar segments had significantly less unipolar voltage than normal (11.6±4.5 mV) segments (P<0.05 for each comparison). When normal myocardium was compared with myocardium with subendocardial scar, the threshold for differentiating between the two areas was 7.9 mV (sensitivity, 80%; specificity, 80%). Comparison of normal tissue to transmural scar yielded a threshold of 6.9 mV (sensitivity, 93%; specificity, 88%).

Conclusions—Our results demonstrate that normal myocardium can be accurately distinguished from myocardium with subendocardial or transmural infarcts on the basis of unipolar voltage values obtained through EMM. This is the first study to validate these results by using cardiac DE-MRI in humans. (Circulation. 2002;106:957-961.)

Key Words: coronary disease ■ magnetic resonance imaging ■ myocardium

Functional myocardial recovery after revascularization is directly related to the presence and degree of scar tissue in the myocardium. Therapies aimed at enhancing the vascularity or cellularity of the myocardium rely on the evaluation of the underlying target tissue. Therefore, defining and quantifying myocardial viability is of great interest in cardiology today. Methods that can identify and differentiate normal myocardial tissue from scar tissue include SPECT, PET, and MRI. MRI is rapidly evolving, and its cardiovascular applications range from the assessment of hemodynamic and functional variables (left ventricular mass and volume) to the study of myocardial perfusion and metabolism. The inherently superior soft-tissue contrast offered by MRI allows effective discrimination between the normal and diseased states of the cardiovascular system. In addition, MRI is noninvasive, imposes no radiation burden to the patient, and often offers better spatial resolution than competing diagnostic modalities, such as nuclear medicine. The combination of these characteristics makes MRI an attractive tool for the assessment of cardiovascular anatomy and physiology. Recently, the introduction of delayed-enhancement MRI technique (DE-MRI) has made it possible to evaluate the presence and extent of irreversibly injured myocardium. Given the submillimeter spatial resolution capabilities of MRI, it is possible to discriminate the extent of myocardial injury as subendocardial or transmural, a capability unmatched by other competing modalities.

Several studies have suggested that left ventricular electromechanical mapping (EMM) can also be used to assess myocardial viability on the basis of myocardial voltage. The ability of EMM to distinguish between infarcted and...
TABLE 1. Patient Demographics

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Mean age, y</td>
<td>62±11</td>
</tr>
<tr>
<td>Men</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Prior myocardal infarction</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (40)</td>
</tr>
<tr>
<td>II</td>
<td>1 (7)</td>
</tr>
<tr>
<td>III</td>
<td>5 (33)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Prior percutaneous intervention</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Prior coronary artery bypass grafting</td>
<td>10 (67)</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%).

healthy myocardium has been corroborated by SPECT and PET imaging. Also, the ability of EMM to provide 3D, real-time images makes it possible to guide and deliver direct myocardial therapies using an integrated injection system, such as delivery of vascular endothelial growth factors. However, precise definition of myocardial viability using EMM relies on establishing accurate EMM thresholds. So far, no such thresholds have been established.

In this study, we sought to determine EMM unipolar voltage thresholds for defining myocardial viability and to establish practical cut-off values for differentiating normal tissue from subendocardial and transmural scar tissue. Cardiac DE-MRI was used as the gold standard because of its high spatial and contrast resolution images, which can distinctly differentiate the degree of infarct transmurality.

Methods

Patients

This prospective study involved 15 ambulatory patients with stable coronary artery disease who were candidates for cardiac catheterization. All EMM studies were performed before diagnostic angiography. The group included 10 men and 5 women, whose ages ranged from 35 to 75 years (mean, 62±11 years). Table 1 shows the patients’ demographics. Within 48 hours of EMM, cardiac DE-MRI was performed.

Inclusion Criteria

EMM procedures and cardiac DE-MRI were performed only on patients who were clinically stable. Patients with severe peripheral vascular disease, atrial fibrillation, aortic stenosis, a suspected left ventricular thrombus, or acute coronary syndromes were excluded. Patients were also excluded from the protocol if they had any of the standard contraindications to MRI, such as the presence of a pacemaker, implantable defibrillator, and intracerebral aneurysm clips. St Luke’s Episcopal Hospital Institutional Review Board approved the study protocol, and informed consent was obtained from all patients on enrollment.

Imaging Protocols

Electromechanical Mapping

To construct an electromechanical map of the left ventricle, we acquired a series of points at multiple locations on the left ventricular endocardial surface by using the NOGA mapping system (Biosense Webster). The procedure has been described elsewhere. In this study, we used a filling threshold of 15 mm. After the desired number of points had been acquired, we removed poor data points from the original map by using an automatic software filter at the moderate setting. The following points were removed: those located in the interior of the left ventricular cavity, those that did not fit the standard stability criteria (location stability <4 mm; loop stability <6 mm; cycle length <10%), those obtained during ST-segment elevation, and those unrelated to the left ventricular cavity (eg, in an atrial location).

Mapping Procedure Protocol

After biplane left ventricular angiography was completed, each patient was given 70 U/kg of heparin. The mapping catheter curve (B, D, or F) was selected on the basis of the left ventricular size. Under fluoroscopic guidance, the 7F-mapping catheter was advanced to the descending thoracic aorta, where the catheter tip was fully deflected. The catheter was then advanced around the aortic arch and across the aortic valve into the left ventricle. Then the deflection was relaxed, and the catheter tip was oriented to the left ventricular apex. The initial data point was acquired at the apex. One point each was also acquired at the base of the septum and the lateral wall, thereby completing an initial triangle that defined the borders of the left ventricle. Subsequent points were acquired until all of the endocardial segments had been uniformly sampled; ideally, 3 points were acquired in each of 12 segments, as recommended by the NOGA Mapping Excellence Program. (The NOGA Mapping Excellence Program was created by Biosense Webster to assure the quality of the maps. It has been developed and implemented by the authors in conjunction with Biosense-Webster.) Using the above-described parameters, each data point was filtered online immediately after acquisition and during the postprocessing analysis. Figures 1A and 1B show a completed unipolar voltage map with an area of inferobasal scar.

MRI

Cardiac MRI was performed during the same hospital admission, within 48 hours after EMM. Personnel performing and interpreting the cardiac MRI were blinded to the results of the EMM procedure.
A 1.5 Tesla commercially available MRI scanner (Philips NT-Intera, Best) with a cardiac software package was used for imaging. A peripheral intravenous line (20-gauge) was inserted, vectorcardiogram (VCG) leads were placed according to standard protocol, and a 5-element, phased-array surface coil was used for enhanced signal to noise ratio. After localization of the heart, ECG-gated cine images were obtained in the following orientations: 2-chamber-long axis, 4-chamber-long axis, and a short axis stack covering the entirety of the left ventricle from the base to apex. Gd-DTPA (0.2 mmol/kg) was administered intravenously, and, after a 15-minute delay, images were obtained in the same orientations using a breath-hold 2D inversion-recovery, T1-weighted gradient-echo sequence (DE-MRI). The DE-MRI sequence had the following acquisition parameters: TR/TE/α = 7 ms/3 ms/15 degrees; voxel size = 1.2×1.2×10 mm; 32 lines of k-space collected for each R-R interval in end diastole; acquisition time, 16 heart beats; NSA = 2. The inversion time was modified iteratively to obtain maximal nulling of remote normal left ventricular myocardium, with an average value of 225 ms.

Data Analysis

EMM Analysis
Each map was displayed in a polar distribution format (bull’s eye). After postprocessing was completed, only segments with 2 or more points were considered for the final analysis. For each segment, we obtained a mean value for the unipolar voltage from the points within that segment.

MRI Analysis
Contiguous short-axis delayed-enhancement images covering the entire left ventricle were transferred to a commercially available postprocessing software (MASS, MEDIS software) for additional postprocessing. The endocardial and epicardial boundaries were manually drawn for each slice to isolate the myocardium. Each slice was additionally divided into 9 equi-angular segments, with the segments starting clockwise from the anterior insertion of the right ventricle into the septum. The following bull’s eye maps, reflecting the mean signal intensity of each segment, were generated: (1) endocardial bull’s eye: the mean signal intensity of the 50% of the myocardium bordering between the blood-pool boundary to the midmyocardium; and (2) epicardial bull’s eye: the mean signal intensity of the 50% of the myocardium starting from the midmyocardium to the epicardial boundary. The gray scale window and level were maintained at the same value for the bull’s eye maps for each patient, with black reflecting normal myocardium and the bright signal (signal intensity ≥ 2 SD above remote normal myocardium) reflecting irreversibly injured myocardium (Figure 1C).

The MRI myocardial segments were categorized into 3 groups: normal, subendocardial scar tissue, and transmural scar tissue. Normal tissue was defined by the absence of bright signal in both endocardial and epicardial bull’s eye. Subendocardial scar was defined to be present when bright signal was present in the endocardial bull’s eye and absent in the epicardial bull’s eye. Bright signal present in both endocardial and epicardial bull’s eyes defined the presence of transmural scar.

Comparative Analyses of EMM and Cardiac MRI Data

We analyzed the EMM and cardiac DE-MRI data using the bull’s eye representations. Using EMM software, we created a bull’s eye precisely matched to that generated by DE-MRI for comparative analysis. Segment by segment, the MRI results as delineated above were compared in a blinded fashion to the corresponding unipolar voltage (unIV) value for that same segment in the EMM bull’s eye. Voltage values were tabulated into 3 groups according to the DE-MRI analysis (normal, subendocardial scar, and transmural scar), and the unIV values (mean ± SD) for each group were obtained.

Table 2. Electrical Data in 275 Myocardial Segments Divided According to Characteristics of Cardiac DE-MRI

<table>
<thead>
<tr>
<th>DE-MRI</th>
<th>No. Segments</th>
<th>Unipolar Voltage, mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>211</td>
<td>11.6 ± 4.5*</td>
</tr>
<tr>
<td>Subendocardial scar</td>
<td>49</td>
<td>6.8 ± 2.9*</td>
</tr>
<tr>
<td>Transmural scar</td>
<td>15</td>
<td>4.6 ± 1.9*</td>
</tr>
</tbody>
</table>

*ANOVA: N vs S, N vs T, P < 0.05.

Results

A total of 64 ± 11 points were acquired for all of the maps (total mapping time, 34 ± 10 minutes). A total of 275 of 300 segments were analyzed. The segments were divided into 3 categories: normal (n = 211), subendocardial scar (n = 49), and transmural scar (n = 15). The subendocardial and transmural scar segments had significantly less unipolar voltage than the normal segments (P < 0.05 for each comparison) (Table 2).

When ROCs were constructed to compare normal myocardium and myocardium with subendocardial scar, the threshold was 7.9 mV (sensitivity, 80%; specificity, 80%) (Figure 2). Similarly, comparison of normal tissue versus transmural scar tissue yielded a threshold of 6.9 mV (sensitivity, 93%; specificity, 88%) (Figure 3). The comparison between voltage values in subendocardial scar segments and transmural scar segments did not reach statistical significance.

Discussion

The ability of EMM to define areas of viable myocardium has been extensively studied using different perfusion techniques, such as FDG-PET and SPECT-thallium. Nonetheless, when using perfusion studies as a gold standard, unipolar voltage thresholds have proven to have suboptimal specificity and sensitivity to detect viable myocardium, leading to individual normalization to improve diagnostic accuracy. This study is the first to compare left ventricular EMM with cardiac DE-MRI in humans. Cardiac DE-MRI precisely delimits the presence and extent of myocardial scar tissue. The results demonstrated that normal myocardium is accu-
rately distinguished from subendocardial infarcts or transmural infarcts on the basis of unipolar voltage values. This additionally corroborates the finding of Wolf et al.\textsuperscript{37} that EMM can accurately predict the transmural extent of a myocardial infarction. Interestingly, in the canine model used by these researchers, the parameter associated with a higher sensitivity to infarction transmurality was bipolar voltage; however, unipolar voltage, unipolar voltage slew rate, and impedance could also determine the extent of infarcted myocardium. The design of the study by Wolf et al., using thorough mapping technique and a higher number of points per segment (obtainable with an animal model), allowed a more detailed analysis of transmurality of infarcts (<30%, 31% to 60%, and 61% to 100%).

Previous clinical studies\textsuperscript{22,28} using EMM have characterized normal myocardium as that having uniV values >12 mV. Clinical studies\textsuperscript{26–29,38} of electrical activity and myocardial viability found values for UniV ranging from 6.4 mV to 7.5 mV to define viable myocardium. In the present study, the finding of a threshold of 6.9 mV to detect transmural infarction is associated with higher sensitivity and specificity than has previously been obtained. Nonetheless, these findings are in concordance with previous viability studies and additionally validate UniV as an indicator of myocardial health.

To be classified as a subendocardial infarct, scar tissue had to involve <50% of the myocardial thickness by DE-MRI. Even with this more practical approach (fewer points per segment) and a less accurate assessment of local electrical activity (unipolar voltage) in comparison with the animal study mentioned above, endocardial EMM distinguished between normal and subendocardial scar tissue and between normal and transmural scar tissue in patients. However, EMM could not distinguish between subendocardial and transmural scar. More importantly, when ROC analysis was applied to our data, high specificity and sensitivity were obtained for thresholds differentiating normal from scarred myocardium. Thus, the present data confirm the utility of EMM as a valuable tool for diagnostic evaluation of myocardial viability in the invasive cardiology setting where clinical decisions involving high-risk revascularization procedures are frequently entertained on an immediate basis.

In addition, the present development of new techniques of direct myocardial therapy aiming toward angiogenesis or restoration of contractility either through cell transplantation with stem cells\textsuperscript{39} and myoblasts\textsuperscript{40,41} or growth factor injection\textsuperscript{42} holds the potential for significant advancement in the treatment of ischemic heart disease. Although cell transplantation for cardiac repair and angiogenesis shows great preclinical promise,\textsuperscript{43,44} its future will profoundly depend on conducting carefully controlled clinical trials with appropriate methods and end points. A critical issue in that regard is the mode of delivery of these therapies. In the cell-transplantation era, the endocardial mapping system might play an important role, because it is a less invasive approach with promising results.\textsuperscript{45} In light of the above, in the present study, the definition of practical unipolar voltage thresholds for assessment of viability may increase the accuracy of therapy delivery. In theory, the demarcation of appropriate target zones for treatment is one of the keys to the success of the procedure. Moreover, along the boundaries of the pre-defined target zone, each potential individual injection site could be interrogated before therapy delivery to ascertain delivery into viable myocardium. Conversely, delivery into a presumed region of nonviable tissue might be targeted if EMM interrogation reveals attractive voltage thresholds.

**Study Limitations**

This study has two primary limitations: a relatively small study population and lack of confirmation of functional recovery in segments classified as viable. Despite the small study population, EMM unipolar voltages could reliably differentiate both subendocardial and transmurally infarcted regions of myocardium based on DE-MRI findings. This finding adds to the body of knowledge validating the use of EMM. As noted previously, DE-MRI is an accurate predictor of functional recovery in myocardium without transmural scar formation and can be performed in a resting study without the need for radiation or potentially nephrotoxic contrast agent. As such, it provides a practical and reliable technique for predicting viability.

**Conclusions**

When compared with cardiac DE-MRI, electromechanical voltage maps can distinguish normal myocardial tissue from subendocardial and transmural scar tissue with high sensitivity and specificity. Electromechanical voltage maps may be useful in assessing the viability of myocardial tissue when considering the application of direct myocardial therapies and in other scenarios where immediate assessment of underlying viability in the catheterization laboratory is paramount to clinical success.

**References**

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