Electromechanical Mapping Identifies Improvement in Function and Retention of Contractile Reserve After Revascularization in Ischemic Cardiomyopathy

Habib Samady, MD; C. Joon Choi, MD, PhD; Michael Ragosta, MD; Eric R. Powers, MD; George A. Beller, MD; Christopher M. Kramer, MD

Methods and Results—Eighteen patients with severe ischemic left ventricular dysfunction underwent EMM and dobutamine (D) cardiac magnetic resonance imaging (CMR) followed by revascularization. Four months after revascularization, all patients underwent a repeated D-CMR, and at 35 months, a subgroup (n=6) underwent a third CMR. Of 120 dysfunctional segments, 60 segments had improved rest function (IRF) and 60 did not. Twenty-eight of 60 segments (47%) that did not improve RF demonstrated postrevascularization contractile reserve (CR), and 32 of 60 segments (53%) that demonstrated neither IRF nor CR were persistently dysfunctional (PD). CR segments recovered significantly greater late function compared with IRF or PD: 14±12% vs 2±5% and 4±7%, respectively; P<0.05. EMM ratio, defined as the unipolar voltage divided by linear shortening, was significantly higher in IRF segments compared with segments that did not improve RF: 2.4±4.5 vs 0.7±3.5, P<0.05. Unipolar voltage was stepwise lower in normal, IRF, CR, and PD segments (10.5±4.7, 9.3±3.9, 8.8±3.2, and 7.4±2.3 mV, respectively; P<0.01 for trend).

Conclusions—Almost half of dysfunctional myocardial segments in chronic ischemic heart disease that do not improve RF early after revascularization demonstrate early CR and delayed functional recovery. EMM parameters can identify segments that improve RF and retain CR early after revascularization. (Circulation. 2004;110:2410-2416.)

Key Words: mapping ■ magnetic resonance imaging ■ cardiomyopathy ■ infarction ■ ischemia

An important goal of myocardial revascularization in patients with ventricular dysfunction and coronary artery disease (CAD) is improvement in resting function (RF). However, patients who do not improve RF early after revascularization can derive symptomatic and prognostic benefits similar to patients who recover function. These benefits may result from revascularization of myocardium with either subendocardial scar or profound hibernation with cytostructural changes that do not improve RF early after revascularization. We postulated that such segments might demonstrate postrevascularization improvement in contractile reserve (CR), which may be a marker for late recovery of ventricular function.

Left ventricular (LV) electromechanical mapping (EMM) is a catheter-based technique that measures regional electrical and mechanical myocardial function and has been proposed for assessment of myocardial viability in the cardiac catheterization laboratory. Experimental and clinical data suggest that unipolar voltage (UpV), a parameter assessed by EMM, can distinguish scar from viable myocardium. Recently, UpV has also been shown to distinguish subendocardial from transmural scar as defined by delayed hyperenhancement on contrast-enhanced cardiac magnetic resonance imaging (CMR).11 Accordingly, we hypothesized that in patients with severe LV dysfunction and CAD undergoing revascularization, (1) the ratio of UpV to linear shortening (LS) will be higher among dysfunctional segments that recover RF than those that do not; (2) a substantial number of segments that do not improve RF after revascularization demonstrate preserved CR, a surrogate for late functional recovery; and (3) UpV will be stepwise lower in normal myocardium, segments that improve RF, those that do not improve function but demonstrate CR, and those that neither improve RF nor demonstrate contractile reserve (persistently dysfunctional [PD]).

References

Because tagged rest and dobutamine CMR (D-CMR) quantitatively assesses subendocardial and transmural myocardial function and contractile reserve, we used D-CMR to evaluate whether EMM-derived UpV is related to baseline CR and subsequent improvement in rest and recruitable function.

Methods

Study Design

Twenty-two patients with >70% stenoses in 2 or more major epicardial vessels and severe ischemic LV dysfunction (ejection fraction [EF] <40% by contrast ventriculography) were enrolled. All patients underwent both EMM ( Biosense Webster) and tagged D-CMR on a 1.5-T Siemens Vision scanner. The study group consisted of all patients who completed baseline EMM and D-CMR and underwent clinically indicated revascularization and follow-up D-CMR 4 months after revascularization. All were contacted to return for a third CMR 3 years after revascularization. Exclusion criteria included significant peripheral vascular disease, aortic stenosis, acute myocardial infarction (MI), unstable ischemic syndromes, atrial fibrillation, LV thrombus, and contraindications to MR imaging, including pacemakers or defibrillators. The Investigational Review Board of the University of Virginia approved the protocol, and all patients provided written, informed consent.

Clinical Data

Baseline, periprocedural, and follow-up clinical data were gathered prospectively. Angina and heart failure scores were determined with the Canadian Cardiovascular Classification Society (CCCS) and New York Heart Association (NYHA) classification schemes, respectively. All other clinical characteristics and discharge and follow-up medications were documented by patient interview, physical examination, and telephone interviews.

Electromechanical Mapping

EMM was performed within 1 week of the D-CMR. The EMM system has been previously described in detail. At the end of cardiac catheterization, the femoral sheath was exchanged for a 45-cm 8F sheath. Systemic heparin (70 U/kg) was administered. The mapping catheter was advanced into the LV, where points were acquired when the catheter tip was stable on the endocardium, after documentation of local activation time stability, location stability, loop stability, and cycle-length stability. The unit processes information on electrical properties of the LV from the mapped points in real time on a Silicon Graphics workstation, constructing simultaneous 3-dimensional UpV and LS maps, with an interpolation threshold of 40 mm between adjacent points.

Figure 1. Data from 69-year-old male (patient 17 from Table 1). A, Right anterior oblique view (upper panel) of his EMM map, demonstrating preserved UpV (8.5±1.7 mV) in anteroseptal myocardium (green/blue) and severely diminished UpV (4.0±0.3 mV) in apex (red); lower panel shows corresponding bull’s-eye, demonstrating segmental quantitative UpV. B, D-CMR end-systolic images, midventricular short-axis slice on top, and apical short-axis slice below. Baseline rest images are shown on left, and images obtained after 10 μg·kg⁻¹·min⁻¹ dobutamine are at center. Follow-up rest images 4 months after coronary artery bypass graft (CABG) are shown on right. Midventricular images (top) show severe dysfunction at baseline, with dyskinesis in anteroseptum (9 to 12 o’clock position on image) and hypokinesis in anterolateral wall (12 to 3 o’clock position). Mean transmural %S was 2.9% in these regions, which improved to 12.9% with dobutamine (center) and to 17.2% at follow-up (right). Note improved tag deformation in anteroseptum and anterolateral myocardium, as well as reduced end-systolic cavity area. Apex (bottom) demonstrates severe dysfunction at rest (mean %S, 4.4%), absent CR (%S with dobutamine, 6.7%), and PD at follow-up (%S, 6.6%). Lack of improvement at apex is noted, despite reduced end-systolic cavity area. However, LVEF by CMR increased from 14% to 29% between baseline and follow-up after CABG. Abbreviations are as defined in text.
When all endocardial regions were represented on the reconstructed map, the catheter was removed from the LV.

Analysis
For each patient, color-coded UpV and LS maps with corresponding “bull’s-eye” maps were generated (Figure 1A). The long axis was divided into 3 segments: apex, midventricle, and base, consisting of 20%, 40%, and 40% of the long-axis length, respectively. Thus, the longitudinal location of each endocardial site was determined on the basis of its projection on the long axis. EMM images were thus divided into 12 segments (4 apical, 4 midventricular, and 4 basal, with each short-axis slice divided into anteroseptal, anterolateral, inferolateral, and inferoseptal; Figure 1B). Therefore, 36 longitudinal measurements were made per patient: 3 transmural measurements per region (4 regions per slice in each of 3 slices). These were then matched by region to the EMM data. Prerevascularization and postrevascularization tagged images were matched by location from landmarks in the right ventricular insertion site and papillary muscles. Both subendocardial and averaged transmural data (subendocardial, midwall, and subepicardial) in 4 regions were used to calculate the EMM ratio for each segment as UpV divided by LS. Segments with <3 data points were excluded from analysis. The global UpV-EMM ratio was calculated for each patient by averaging each of the 12 segments per patient.

Cardiac MR Imaging
Breath-hold, short-axis, gradient-echo cine MR imaging was performed on a Siemens 1.5-T Vision scanner. Imaging parameters included a repetition time of 100 ms with view sharing; 50-ms temporal resolution; echo time of 4.8 ms; flip angle 20°; slice thickness 7 mm; field of view 30 cm; matrix 256 × 256, and 15 heartbeats and was performed in short-axis slices from apex to base. Breath-hold tagged, gradient-echo cine MR imaging (repetition time of 90 ms with view sharing; 45-ms temporal resolution; echo time of 4 ms; 8-mm tag line separations; 128 × 256 matrix interpolated to 256 × 256; field of view 30 cm) was performed in 3 short-axis slices at the apical, middle, and basal LV. After baseline tagged gradient-echo cine images were obtained, low-dose dobutamine infusion starting at 5 μg · kg\(^{-1}\) · min\(^{-1}\) and then increasing to 10 μg · kg\(^{-1}\) · min\(^{-1}\) was administered intravenously for 5 minutes each. During each level of infusion, tagged gradient-echo cine MR imaging was repeated in the same 3 slices. After revascularization, the same MR techniques were repeated, including cine MR and tagged cine MR imaging at rest and with dobutamine (Figure 1B). Of the patients contacted regarding a late follow-up CMR, 8 agreed to return, but 2 had received devices in the interim (pacemaker or defibrillator) that precluded repeated CMR.

Data Analysis
End-diastolic and end-systolic volumes and EF were calculated from stacked short-axis, breath-hold, cine MR imaging slices from apex to base before and after revascularization with use of an Argus workstation (Siemens) and a modified Simpson’s rule. Percent circumferential transmural shortening (%S) was measured from breath-hold tagged, cine MR images at rest and at peak dobutamine (10 μg · kg\(^{-1}\) · min\(^{-1}\)) in the 3 short-axis slices both before and after revascularization.\(^5\)\(^-\)\(^8\) In each slice, %S was measured in the subendocardium, midwall, and subepicardium in 4 regions where tags were perpendicular to the endocardial surface (anteroseptal, anterolateral, inferolateral, and inferiorseptal; Figure 1B). Therefore, 36 measurements were made per patient: 3 transmural measurements per region (4 regions per slice in each of 3 slices). These were then matched by region to the EMM data. P4ererevascularization and postrevascularization tagged images were matched by location from landmarks in the right ventricular insertion site and papillary muscles. Both subendocardial and averaged transmural data (subendocardial, midwall, and subepicardial) were analyzed.

D-CMR Definitions of Segmental Characteristics
Normal segmental myocardial function was defined as %S ≥ 10% by tagged CMR, based on 2 standard deviations below the mean in normal volunteers.\(^14\) The presence of transmural or subendocardial CR in dysfunctional segments was defined as a ≥ 5% increase in transmural or subendocardial %S, respectively, with dobutamine compared with rest.\(^5\)\(^-\)\(^6\) A ≥ 5% increase in rest %S after revascularization in a given segment was defined as improved RF (IRF).\(^5\) Segments that did not improve RF but demonstrated a normal response to dobutamine (≥ 5% increase in %S with dobutamine
TABLE 2. CMR Volumetric Data Before and After Revascularization

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After Revascularization</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume, mL</td>
<td>166±58</td>
<td>153±59</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic volume, mL</td>
<td>124±58</td>
<td>97±57</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>53±23</td>
<td>65±21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33±14</td>
<td>44±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>268±80</td>
<td>263±84</td>
<td>NS</td>
</tr>
</tbody>
</table>

CMR indicates cardiac magnetic resonance; LVEF, left ventricular ejection fraction.

Results

Compared with rest) after revascularization were defined as preserved CR. Those segments that failed to improve RF or demonstrate contractile reserve after revascularization were termed PD.

Statistical Analysis

Continuous data are expressed as mean±SD. Data from matched EMM and D-CMR segments were compared. t Tests were used for univariate dichotomous comparisons. Categorical EMM and D-CMR variables were compared by ANOVA. When appropriate, a post hoc pairwise comparison was made with the Bonferroni modification. A probability value of <0.05 was considered significant.

Revascularization Procedures

Two patients underwent multivessel percutaneous revascularization. The remaining 16 patients underwent coronary artery bypass surgery, with a mean of 2.5±1 grafts per patient. Mean cardiopulmonary bypass and cross-clamp times were 117±58 and 70±29 minutes, respectively. There were no clinically apparent periprocedural MIs. Discharge medications included aspirin in 100%, lipid-lowering therapy in 67%, β-blockers in 56%, and angiotensin-converting-enzyme inhibitors in 72%.

Clinical Response to Revascularization

Clinical follow-up was performed 4±2 months after revascularization. At follow-up, all patients were on aspirin, 78% on lipid-lowering therapy, 61% on β-blockers, and 72% on angiotensin-converting-enzyme inhibitors. Mean CCS angina score improved from 2±1 to 0.4±1 (P<0.001), and mean NYHA heart failure score improved from 3±1 to 1±1 (P<0.001) in response to revascularization.

Early and Late Functional Response to Revascularization

Baseline and 4-month postrevascularization CMR volumetric data are shown in Table 2. End-diastolic volume did not change significantly (166±58 to 153±59 mL, P=NS). However, end-systolic volume decreased from 124±58 to 96±57 mL (P<0.05). Stroke volume increased from 53±23 to 65±21 mL (P<0.05), and LVEF increased from 31±9% to 44±12% (P<0.001).

Figure 2 shows that at 4 months after revascularization, 60 of 120 (50%) of dysfunctional segments had IRF, 28 of 120 (23%) did not improve RF but demonstrated preserved CR, and 32 of 120 (27%) remained PD. Thus, 28 of 60 (47%) of baseline dysfunctional segments that did not have IRF after revascularization showed CR.

In the subgroup of patients who also underwent late CMR at 35±12 months, 40 of 72 myocardial segments were dysfunctional at baseline. Of these 40, 24 were in the IRF group, 9 in the CR group, and 7 in the PD group at 4 months after revascularization. At 35±12 months, segments in the CR group showed a significantly greater increase in shortening (14±12%) compared with the IRF group (2±5%) and the PD group (4±7%, P<0.05 for both comparisons; Figure 3).
Forty-five percent of CR segments showed a >15% further increase in shortening at 35 months compared with none in the IRF and PD groups.

EMM and Functional Response to Revascularization

Segmental Analysis

Unipolar Voltage

The percentage of segments with IRF was stepwise higher with increasing UpV (40% of segments with ≤5 mV, 54% of segments with 5 to 10 mV, and 68% of segments with ≥10 mV; P < 0.001). Similarly, the percentage of segments with either IRF or preserved CR was greater with increasing UpV (46% of segments with ≤5 mV, 73% of segments with 5 to 10 mV, and 90% with ≥10 mV, P < 0.001).

UpV was stepwise lower in normal, IRF, CR, and PD myocardial segments (10.5 ± 4.7, 9.3 ± 3.9, 8.8 ± 3.2, and 7.4 ± 2.3 mV, respectively; P < 0.01 for trend; Figure 4). Among dysfunctional segments, UpV tended to be higher in segments that showed IRF compared with those that did not after revascularization (9.3 ± 4.5 vs 8.1 ± 4.2, P = 0.09). UpV in segments that displayed either improvement in RF or preserved CR after revascularization was significantly higher than in PD segments (9.1 ± 4.0 vs 7.5 ± 2.3, P < 0.05).

Discussion

This study demonstrated that, in patients with ischemic cardiomyopathy undergoing revascularization, (1) the ratio of UpV to LS measured by EMM was significantly higher in segments that showed IRF; (2) the ratio of UpV to LS averaged per patient was significantly higher in patients with improved LVEF by 15%; (3) almost half of myocardial segments that do not improve RF demonstrated postrevascularization CR; (4) compared with segments that showed IRF or remained PD, segments that did not improve RF but retained CR appeared to demonstrate significant late functional improvement; and (5) UpV was stepwise lower in normal myocardium, dysfunctional myocardium with IRF, dysfunctional myocardium that did not improve RF but demonstrated CR, and myocardium that remained PD after revascularization.

UpV and Functional Recovery

A single study has previously explored the relation between UpV and postrevascularization recovery of regional function.7 However, that study evaluated patients after MI with a mean baseline EF of 49% undergoing revascularization, not patients with chronic severe ischemic cardiomyopathy with a mean baseline EF of 31%, as in our study. Furthermore, the study by Koch et al7 used contrast ventriculography to assess...
regional wall motion, which may be limited in its ability to quantify changes over time. To the best of our knowledge, this is the first demonstration of a relation between baseline UpV and functional response to revascularization in patients with severe ischemic cardiomyopathy.

Previous studies comparing EMM to noninvasive modalities of viability assessment have suggested that a UpV of <6 to 7 mV can identify nonviable myocardium. Yet this study found that almost 40% of the segments with a UpV <5 mV showed recovery of RF after revascularization. We believe that there may be 2 explanations for this observation. The first is that the relation between viability on prerevascularization assessment and subsequent functional recovery is not perfect, and most imaging modalities have limitations in their predictive value of functional recovery. The second explanation lies in the definition of improvement in function. Improvement in function is a continuum, yet many studies evaluate this either dichotomously or semiquantitatively on a visual scale. Improvement of function was defined in the present study as ≥5% improvement in regional shortening by tagged cine CMR. It may take more than this sensitive quantitative improvement in %S to translate into a visible improvement in wall thickening. Whereas as many as 40% of dysfunctional myocardial segments with UpV <5 mV improved RF (with our stringent definition), only 20% of such segments improved shortening by ≥10%, and just 8% improved shortening by ≥20% after revascularization. Therefore, the relation between prerevascularization viability and improvement in RF is complex, and the degree of functional improvement after revascularization represents a spectrum.

The stepwise reduction in UpV from normal myocardium to that which improves RF early after revascularization, to myocardium that retains CR early and recovers function late after revascularization, to PD myocardium suggests that UpV reflects myocardial pathology and its subsequent response to revascularization.

EMM Ratio: UpV/LS and Functional Recovery

We found the EMM ratio of UpV/LS to be better than UpV alone for identifying myocardial segments that will improve RF. Indeed, UpV/LS was significantly higher in segments that improved function 4 months after revascularization compared with those that did not. Similarly, averaged values of UpV/LS per patient were significantly higher in patients who significantly improved global ventricular function. These data suggest that myocardium with severe dysfunction but preserved voltage is most likely to recover regional function and global RF.

Beyond Recovery of RF: Preserved CR After Revascularization

Although it is widely accepted that recovery of resting ventricular function signifies the presence of viability, some patients who do not recover resting ventricular function after revascularization derive symptomatic and survival benefit similar to those who improve RF. Indeed, many dysfunctional segments with subendocardial scar may not recover RF, despite revascularization. In addition, myocardium with profound hibernation or severe repetitive stunning with cyto-

structural myocyte changes may not fully recover function at an early time point but display late recovery of function. Beneficial effects of myocardial revascularization beyond improvement in early RF may include limitations of LV remodeling, prevention of lethal arrhythmias, reduction in recurrent ischemic events, and gradual repair of profound hibernating myocardium to allow late functional recovery.

We found that 47% of dysfunctional segments that did not improve RF after revascularization demonstrated CR and that UpV was preserved in such segments as in those that improved RF. Demonstration of CR after revascularization, in the absence of improvement in RF, may identify myocardium with subendocardial scar or profound hibernation that might benefit from revascularization. Late functional recovery (35 months) in myocardial segments that did not improve RF at 4 months after revascularization but retained CR suggests that those segments may have been profoundly hibernating and not subendocardial scar. Larger patient cohorts with long-term follow-up are needed to establish whether the demonstration of postrevascularization CR is an early surrogate marker of benefit from myocardial revascularization in patients with ischemic cardiomyopathy.

The study of Perin et al demonstrated the ability of UpV to discriminate between normal, subendocardial, and transmural scar as defined by hyperenhancement on CMR. However, the predictive value of 1% to 50% transmural hyperenhancement (subendocardial scar) for functional recovery after revascularization is suboptimal (between 40% and 60%). Functional responses with tagged D-CMR or UpV assessed by EMM in subendocardial infarction may be more predictive of functional recovery than an anatomic definition of scar alone.

The presence of contrast in the myocardium significantly impairs the ability to tag the myocardium by CMR, and therefore, tagging and delayed contrast-enhanced CMR cannot be used in concert. Correlative studies with tagging performed before contrast infusion would be helpful in this regard in the future.

Study Limitations

The first limitation of this study is its relatively small sample size. Despite this, we observed a relation between baseline UpV and improvement in RF and demonstrable CR after revascularization. As reported in studies comparing voltage to noninvasive viability modalities, we observed a significant overlap in voltage between segments that demonstrated a functional response to revascularization and those that did not. This overlap in voltage and EMM ratio of UpV/LS between segments that demonstrated a response to revascularization and those that remained PD made it difficult to obtain a clinically useful UpV or EMM ratio threshold for predicting functional improvement. This might reflect a biologic limitation of UpV to accurately predict functional response to revascularization, or it may have resulted from coregistration problems between EMM and D-CMR images, both 3-dimensional imaging modalities.

The second limitation is that coronary angiography was not performed routinely after revascularization. Therefore, subclinical bypass graft occlusion or in-stent restenosis in revas-
cularized vessels cannot be excluded. The third limitation of this study relates to the dobutamine protocol used for D-CMR. For detection of ischemia, dobutamine doses up to 40 μg/min are recommended. However, we have shown that low-dose dobutamine, 10 μg/min as used in this study, is adequate for defining CR. A substantial proportion of patients were on β-blocker medications. The effect of these medications on patients’ responses to dobutamine is unclear. Finally, this is the first study demonstrating the value of the ratio of UpV/LS; further studies evaluating this parameter are warranted.

Conclusions
In patients with severe ischemic cardiomyopathy undergoing revascularization, (1) the ratio of UpV to LS is higher in myocardium that improves regional and global function compared with that which does not; (2) almost half of the segments that did not improve RF after revascularization demonstrated preserved CR and late functional recovery; and (3) UpV is stepwise lower in normal myocardium, segments that improve RF, those that do not improve function but demonstrate CR, and PD segments.

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References
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