Left Ventricular Electromechanical Mapping to Assess Efficacy of \( \text{phVEGF}_{165} \) Gene Transfer for Therapeutic Angiogenesis in Chronic Myocardial Ischemia

Peter R. Vale, MD; Douglas W. Losordo, MD; Charles E. Milliken, MA; Michael Maysky, MD; Darryl D. Esakof, MD; James F. Symes, MD; Jeffrey M. Isner, MD

Background—NOGA left ventricular (LV) electromechanical mapping (EMM) can be used to distinguish among infarcted, ischemic, and normal myocardium. We investigated the use of percutaneous LV EMM to assess the efficacy of myocardial gene transfer (GTx) of naked plasmid DNA encoding for vascular endothelial growth factor (\( \text{phVEGF}_{165} \)), administered during surgery by direct myocardial injection in patients with chronic myocardial ischemia.

Methods and Results—A total of 13 consecutive patients (8 men, mean age 60.1±2.3 years) with chronic stable angina due to angiographically documented coronary artery disease, all of whom had failed conventional therapy (drugs, PTCA, and/or CABG), were treated with direct myocardial injection of \( \text{phVEGF}_{165} \) via a minithoracotomy. Foci of ischemic myocardium were identified on LV EMM by preserved viability associated with an impairment in linear local shortening. Myocardial viability, defined by mean unipolar and bipolar voltage recordings ≥5 and ≥2 mV, respectively, did not change significantly after GTx. Analysis of linear local shortening in areas of myocardial ischemia, however, disclosed significant improvement after (15.26±0.98%) versus before (9.94±1.53%, \( P=0.004 \)) \( \text{phVEGF}_{165} \) GTx. The area of ischemic myocardium was consequently reduced from 6.45±1.37 cm² before GTx to 0.95±0.41 cm² after GTx (\( P=0.001 \)). These findings corresponded to improved perfusion scores calculated from single-photon emission CT–sestamibi myocardial perfusion scans recorded at rest (7.4±2.1 before GTx versus 4.5±1.4 after GTx, \( P=0.009 \)) and after pharmacological stress (12.8±2.7 before GTx versus 8.5±1.7 after GTx, \( P=0.047 \)).

Conclusions—The results of EMM constitute objective evidence that \( \text{phVEGF}_{165} \) GTx augments perfusion of ischemic myocardium. These findings, together with reduction in the size of the defects documented at rest by serial single-photon emission CT–sestamibi imaging, suggest that \( \text{phVEGF}_{165} \) GTx may successfully rescue foci of hibernating myocardium.

(Circulation. 2000;102:965-974.)

Key Words: mapping ■ coronary disease ■ angiogenesis ■ ischemia

Preclinical studies performed in animal models of limb and myocardial ischemia\(^1-5\) have documented that certain cytokines, including vascular endothelial growth factor (VEGF) and fibroblast growth factor-1 and -2, administered as recombinant protein or cDNA, may promote neovascularization of ischemic tissues. More recently, preliminary clinical trials have established that the results of these animal studies may extend to human subjects with limb\(^6-8\) and myocardial\(^9-12\) ischemia.

Earlier studies performed in our laboratory documented that symptomatic improvement in patients with myocardial ischemia was associated with improvement in the outcome of single-photon emission CT (SPECT)-sestamibi myocardial perfusion imaging\(^10\), not only was there a reduction in the perfusion deficits associated with pharmacological stress, but large defects detected at rest were often resolved as well. These findings constituted objective evidence of improved myocardial perfusion after therapeutic neovascularization, including the possibility that foci of hibernating myocardium might be successfully rescued.

To determine whether the implications of SPECT imaging could be confirmed by an independent diagnostic technique, we used a novel strategy of catheter-based electromechanical assessment of myocardial perfusion (NOGA system, Biosense-Webster, Johnson & Johnson). This system uses electromagnetic field sensors to combine and integrate real-time information from percutaneous intracardiac electrograms acquired at multiple endocardial locations. The result-

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ing interrogations can be used to distinguish between infarcted and normal myocardium\textsuperscript{13} and thus permit online assessment of myocardial function and viability.\textsuperscript{14}

In the present study, NOGA electromechanical mapping (EMM) was prospectively performed in 13 consecutive patients with chronic myocardial ischemia before and 60 days after gene transfer (GTx) of naked DNA encoding for the 165–amino acid isoform of VEGF-1 (phVEGF\textsubscript{165}), administered during surgery by direct myocardial injection. The results of the present study constitute additional objective evidence that phVEGF\textsubscript{165} GTx augments perfusion of ischemic myocardium, and the results also support the notion that phVEGF\textsubscript{165} GTx may successfully rescue foci of hibernating myocardium.

**Methods**

**Patient Selection**

All patients described in the present report participated in a phase-1 clinical trial of direct myocardial phVEGF\textsubscript{165} GTx initiated in February 1998. Eligibility and exclusion criteria have been previously published.\textsuperscript{10} Contraindications to EMM included aortic valve prosthesis, recent myocardial infarction with significant wall thinning, or evidence of left ventricular (LV) aneurysm and/or thrombus. NOGA EMM was initiated at St. Elizabeth’s Medical Center in July 1998. Since that time, all patients entered into this protocol have undergone prospective EMM before and after GTx with one exception: one patient was excluded from EMM (but not intraoperative GTx) on the basis of a mechanical aortic valve prosthesis.

**LV Electromechanical (NOGA) Mapping**

Subjects underwent LV EMM in conjunction with cardiac catheterization and coronary angiography <1 month before and 60 days after GTx. The NOGA system produces 3D electromechanical maps of the heart by analyzing parameters generated from intracardiac electrograms acquired at multiple endocardial locations that characterize mechanical, dynamic, and electrical LV functions. The mapping and navigation system comprises a locator pad, a reference catheter, a mapping catheter, and a processing unit with a graphics computer (Silicon Graphics) and has been previously described in detail.\textsuperscript{15}

To construct an electromechanical map, the mapping catheter (Biosense-Webster), a 7F fused-tip catheter with a miniature passive magnetic field sensor embedded within its distal tip that determines the position and rotation of the distal catheter segment, is introduced via a femoral arterial puncture and advanced to the LV. Three points (high septum, high lateral wall, and apex) are obtained with fluoroscopic guidance to generate the initial 3D image of the LV. An icon of the mapping catheter is displayed superimposed on the 3D map, thus enabling catheter manipulation in relation to the map. At each point, 3 electrophysiological parameters are monitored to determine the stability of endocardial contact with the catheter tip: location, cycle length, and local activation time. The reconstruction was updated in real time with the acquisition of each new point.

Local functional analysis (wall motion) is based on linear local shortening (LLS), a parameter that calculates the fractional shortening of regional endocardial surfaces at end systole. Unipolar (UpV) and bipolar (BpV) endocardial potentials are recorded from the tip electrode, and measurements that are based on these local intracardiac signal amplitudes formulate a guide to myocardial viability. The combination of these 2 data sets permits assessment of electromechanical function that identifies foci of myocardial ischemia. For example, for a given region of interest, UpV $\geq$5 mV (suggesting viable myocardium) and normal (±12%) LLS (suggesting normal contraction) would indicate normal myocardium. In contrast, UpV <5 mV and abnormal (±4%) LLS (signifying severe regional hypokinesis or akinesia) would indicate a site of LV infarction. Alternatively, UpV $\geq$5 mV and abnormal LLS of 4% to 12% (indicating mild to moderate impairment of contractility) would suggest a site of ischemic hibernating myocardium.\textsuperscript{13,16}

To quantify the degree of myocardial perfusion demonstrated visually by the mapping images, the long axis of the heart was divided into 4 regions: anterior, inferoposterior, septal, and lateral. Mean values for LLS, UpV, and BpV were calculated for ischemic myocardium (area of electromechanical uncoupling on NOGA mapping). In addition, for comparative analysis with nuclear imaging, LLS and voltage values from ischemic regions were compared with the corresponding perfusion score on the resting SPECT-sestamibi perfusion study. To quantify the area of ischemia, a 2D algorithm was used to calculate both the area of ischemia and the total surface area in the view depicting maximal ischemia.

**SPECT Myocardial Perfusion Study**

Subjects underwent a Persantine SPECT-sestamibi study. The acquisition of the poststress SPECT image began 10 minutes after the end of the stress period. Redistribution images were recorded either before or at least 4 hours after stress with the subject at rest. Redistribution and reinjection data were reconstructed in short-axis, vertical, and longitudinal long-axis views. Perfusion scores were calculated for each patient on the basis of the Cedars-Sinai 20-segment short-axis system.\textsuperscript{17} On day 60, subjects underwent repeat nuclear perfusion testing; stress protocol and isotope were identical to those used at baseline.

**Plasmid DNA (phVEGF\textsubscript{165})**

The VEGF plasmid administered to all patients in the present study is a eukaryotic expression vector encoding the 165–amino acid isoform of the human VEGF gene\textsuperscript{18} transcriptionally regulated by the cytomegalovirus promoter/enhancer (phVEGF\textsubscript{165}).\textsuperscript{6,7}

**Direct Myocardial phVEGF\textsubscript{165} GTx**

A left lateral minithoracotomy was used to expose the heart, after which direct myocardial GTx was performed with a 25-gauge needle under continuous transesophageal echocardiographic monitoring.\textsuperscript{19} A total dose of 250 μg (n=5) or 500 μg (n=8) was divided into 4 aliquots, each delivered in 2.0 mL of normal saline to the lateral, anterior, or septal LV wall. Injection sites were selected according to the areas of ischemia identified by prior NOGA and sestamibi imaging.

**Evaluation of Gene Expression**

Evidence of successful GTx was documented by ELISA (R&D Systems) performed on serial samples of plasma obtained from each patient at predetermined time points as previously described.\textsuperscript{7}

**Statistical Analysis**

Data are reported as mean±SEM. Comparisons between paired variables were performed by Student t test with a significance level of P<0.05. For comparison between variables, the Pearson correlation coefficient was used. Post hoc testing was performed by using Fisher r to z analysis (for probability value). A value of P<0.05 was required for assumption of statistical significance.

**Results**

**Patients**

Clinical data regarding the 13 patients (mean age 60.1±2.3 years) treated with direct myocardial injection of phVEGF\textsubscript{165} and studied by EMM are listed in Table 1. All patients had $\geq$2 cardiovascular risk factors. Antiangiinal therapy included nitrates, calcium channel antagonists, and β-blockers. All patients had had previous bypass surgery, and all had a history of at least one prior myocardial infarction. Angioplasty was performed in 12 patients an average of 1.5 times. All patients were Canadian Cardiovascular Society functional class 3 or 4.
no significant changes in mean heart rate or blood pressure. EMM was associated with transient ventricular ectopic activity, but neither sustained ventricular arrhythmias nor other arrhythmias were observed. In all patients, NOGA maps were reliably reproduced after GTx in terms of the number of points, end-diastolic volume, end-systolic volume, and average loop stability (data not shown). The LV ejection fraction, calculated on the basis of algorithms incorporated in the NOGA system, increased from 31.3 ± 2.7% before GTx to 36.9 ± 2.3% after GTx (P = 0.023).

Foci of ischemic myocardium, identified by preserved viability associated with impaired LLS, ie, electromechanical uncoupling, were demonstrated in all patients before GTx. Foci of ischemia involved the anterior (n = 1), anteroseptal (n = 1), lateral (n = 1), inferolateral (n = 2), posterior (n = 3), posterolateral (n = 2), septal (n = 2), and inferoseptal (n = 1) walls. Mean UpV and BpV recordings ≥ 5 mV and ≥ 2 mV, respectively, defining myocardial viability in the ischemic zone, did not change significantly after GTx (Table 2). Mean LLS in areas of myocardial ischemia, however, improved significantly from 9.94 ± 1.53% before phVEGF165 GTx to 15.26 ± 0.98% after phVEGF165 GTx (P = 0.004). The area of ischemic myocardium was consequently reduced from 6.45 ± 1.37 cm² before phVEGF165 GTx to 0.95 ± 0.41 cm² after GTx (P = 0.001, Table 2). Examples of NOGA maps showing septal, lateral, anterior, and inferior ischemic zones before GTx with improvement after GTx are shown in panel A of Figures 1 through 5.

Clinical Outcome
Clinically, these 13 patients reported significant reduction in anginal episodes per week (48.1 ± 4.9 versus 2.0 ± 0.8, P = 0.0001) and in weekly consumption of nitroglycerin tablets (55.0 ± 7.1 versus 1.9 ± 0.8, P < 0.0001). Standard Bruce protocol exercise tolerance testing was performed in all patients at days 90 and 180 after GTx (Table 3). The mean duration of exercise increased from 272 to 453 seconds (P = 0.001) up to 180 days after GTx. LV ejection fraction remained the same (n = 5) or increased (n = 8, mean increase 5%) up to day 180 after GTx (mean ejection fraction 53.5 ± 3.7% before GTx versus 58.1 ± 3.8% after GTx, P = 0.004).

SPECT Myocardial Perfusion Study
The results of EMM corresponded to improved perfusion scores calculated from SPECT-sestamibi myocardial perfu-

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**TABLE 1.** Demographics and Clinical Data Before Gene Transfer

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.1 ± 2.3</td>
</tr>
<tr>
<td>Sex (male/female), n/n</td>
<td>8/5</td>
</tr>
<tr>
<td>Past smoking</td>
<td>9 (70)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Background diabetic retinopathy</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Prior PTCA/stent</td>
<td>12 (92)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>13 (100)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Ca²⁺ antagonists</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Angina, episodes/wk</td>
<td>48.1 ± 4.9</td>
</tr>
<tr>
<td>NTG, tablets/wk</td>
<td>55.0 ± 7.1</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>53.5 ± 3.7</td>
</tr>
<tr>
<td>Exercise capacity, s</td>
<td>272 ± 37</td>
</tr>
</tbody>
</table>

*Values are mean±SEM or n (%). MI indicates myocardial infarction; NTG, nitroglycerin; and LVEF, LV ejection fraction.

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**TABLE 2.** Objective Evidence of Improved Myocardial Perfusion

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stress</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 60</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 60</td>
</tr>
<tr>
<td>LLS, %</td>
<td>9.94 ± 1.53</td>
<td>15.26 ± 0.98*</td>
</tr>
<tr>
<td>Ischemic area, cm²</td>
<td>6.45 ± 1.37</td>
<td>0.95 ± 0.41†</td>
</tr>
<tr>
<td>UpV, mV</td>
<td>11.91 ± 1.25</td>
<td>10.75 ± 1.39</td>
</tr>
<tr>
<td>BpV, mV</td>
<td>3.15 ± 0.49</td>
<td>3.25 ± 0.41</td>
</tr>
<tr>
<td>Perfusion score</td>
<td>7.4 ± 2.1</td>
<td>4.5 ± 1.4‡</td>
</tr>
<tr>
<td></td>
<td>12.8 ± 2.7</td>
<td>8.5 ± 1.7*</td>
</tr>
</tbody>
</table>

*Values are mean±SEM.

*P < 0.05, †P = 0.001, and ‡P < 0.01 vs baseline.
sion scans recorded at rest (7.4±2.1 before GTx versus 4.5±1.4 after GTx, \(P=0.009\)) and after pharmacological stress (12.8±2.7 before GTx versus 8.5±1.7 after GTx, \(P=0.047\); Table 2). A positive correlation existed between the change in rest perfusion score for ischemic myocardium and the reduction in ischemic area as measured by NOGA mapping (\(P=0.042, r=0.567\)). Shown in panel B of Figures 1 through 5 are selected perfusion images showing improvement after GTx, corresponding to the NOGA maps shown in panel A of Figures 1 through 5.
Figure 2. A, NOGA LV EMM performed in 58-year-old man. NOGA images in left anterior oblique projection before GTx show UpV and LLS maps using same color scale as in Figure 1A; red zone on LLS map (top right) and preserved viability (purple/pink/blue/green) on UpV map (top left) constitute a focus of electromechanical uncoupling that suggests ischemic or hibernating myocardium (arrow) in lateral LV wall. UpV and LLS maps in same projection constructed 60 days after GTx (bottom left and right, respectively) disclose near-complete resolution of lateral wall ischemic zone (8.08 cm² before GTx vs 0.16 cm² after GTx) corresponding to changes observed on SPECT scan (panel B). Vertical and horizontal axes (x, y, and z) are presented as white lines. B, Perfusional SPECT-sestamibi myocardial perfusion scanning. Selected short-axis and horizontal-axis stress and resting images that used same color scale as in Figure 1B were taken before and after plhVEGF165 GTx in same patient as shown in panel A. Pre-GTx scans (top) show large partially reversible lateral wall defect (arrows) and moderate reversible septal wall defect (arrowheads). Post-GTx scans (bottom) show almost complete normalization of resting perfusion and marked improvement in stress images.
Figure 3. A, NOGA LV EMM. UpV and LLS NOGA images (same color scale as in Figure 1A) in anteroposterior projection (top left and right, respectively) of 55-year-old man before phVEGF165 GTx showing an area of electromechanical uncoupling suggestive of ischemic or hibernating myocardium that involves the anterior region (arrow). Sixty days after GTx, UpV and LLS images (bottom left and right, respectively) show complete resolution of ischemia (ischemic area 5.29 cm² before GTx vs 0.00 cm² after GTx) that corresponds to changes observed on SPECT scan (panel B). Red line represents long axis through apex. Vertical and horizontal axes (x, y, and z) are presented as white lines. B, Persantine SPECT-sestamibi myocardial perfusion scanning. Selected short-axis and vertical-axis stress and resting images (same color scale as in Figure 1B) were taken before and after phVEGF165 GTx in same patient as shown in panel A. Pre-GTx stress scans (top) show fixed anterior defect (arrowheads) at rest and reversible anteroseptal defect (arrow) that appears with stress. Post-GTx scans (bottom) show normalization of resting perfusion.
Discussion
The patients in the present study comprise a consecutive series of 13 patients treated with direct myocardial GTx of phVEGF165 as part of a phase-1, dose-escalating, open-label clinical study for symptomatic myocardial ischemia.

The collated electrical and mechanical results of percutaneous EMM provide both an assessment of myocardial viability (ie, the presence of normal versus reduced voltage) and wall motion (presence of normal versus reduced fractional shortening). Validation of intracardiac signal recording

Figure 4. A. NOGA LV EMM. UpV and LLS NOGA images (same color scale as in Figure 1A) in right anterior oblique projection (top left and right, respectively) of 48-year-old man before phVEGF165 GTx. There is an area of electromechanical uncoupling suggestive of ischemic or hibernating myocardium involving the inferoseptal region (arrow). Sixty days after GTx, UpV and LLS images (bottom left and right, respectively) show complete resolution of ischemia (10.08 cm² before GTx vs 0.00 cm² after GTx) that corresponds to changes observed on SPECT scan (panel B). Red line represents long axis through apex. Vertical and horizontal axes (x, y, and z) are presented as white lines. B. Persantine SPECT-sestamibi myocardial perfusion scanning. Selected short-axis and vertical-axis stress and resting images (same color scale as Figure 1B) were taken before and after phVEGF165 GTx in same patient as shown in panel A. Pre-GTx scans (top) show reversible inferoseptal defect (arrows). Post-GTx scans (bottom) show complete normalization of resting perfusion and perfusion after pharmacological stress.
Figure 5. A, NOGA LV EMM. UpV and LLS NOGA images (same color scale as in Figure 1A) in left anterior oblique projection (top left and right, respectively) of 53-year-old woman before phVEGF165 GTx showing area of electromechanical uncoupling suggestive of ischemic or hibernating myocardium that involves the inferolateral region (arrow). Sixty days after GTx, UpV and LLS images (bottom left and right, respectively) show complete resolution of ischemia (1.39 cm² before GTx vs 0.00 cm² after GTx) that corresponds to changes observed on SPECT scan (panel B). B, Persantine SPECT-sestamibi myocardial perfusion scanning. Selected short-axis and horizontal-axis stress and resting images (same color scale as in Figure 1B) were taken before and after phVEGF165 GTx in same patient as shown in panel A. Pre-GTx scans (top) show a reversible inferolateral defect (arrows). Post-GTx scans (bottom panel) show complete normalization of resting perfusion.
and location accuracy has been previously established, both in vitro and in vivo. Clinical investigations have demonstrated that the mapping capabilities of the NOGA system may be used to distinguish between infarcted and normal myocardium. Gepstein et al found significantly lower LLS (<4%) and bipolar voltages (<2 mV) in infarcted versus noninfarcted myocardium. Furthermore, comparison with pathological specimens confirmed that the location and extent of infarction could be accurately defined by EMM. These earlier findings were confirmed by Kornowski and colleagues, who showed that patients with prior myocardial infarction had reduced UpV (7.2 ± 2.7 mV) and BpV (1.4 ± 0.7 mV) recordings compared with patients without prior infarction (19.7 ± 4.4 and 5.8 ± 1.0 mV for UpV and BpV, respectively) and that these patients had reduced local endocardial shortening compared with patients without prior infarction. Moreover, Kornowski et al demonstrated that mean voltage and LLS values are highest when measured in myocardial segments with normal perfusion and lowest when measured from segments with fixed perfusion defects; intermediate LLS (4% to 12%) and voltage (≥5 mV) recordings were documented for myocardial segments with reversible perfusion defects.

In the present clinical study, LV EMM was used in a serial fashion to provide an independent objective analysis of the impact of phVEGF165 GTx on myocardial perfusion. Foci of ischemic myocardium were identified by preserved viability associated with impaired LLS. Myocardial viability, defined by both mean UpV and BpV recordings of ≥5 and ≥2 mV, respectively, did not change significantly after GTx. Analysis of LLS in areas of myocardial ischemia, however, documented marked improvement after GTx. Consequently, the area of ischemic myocardium was reduced to a statistically significant extent.

These findings corresponded with improved perfusion scores calculated from SPECT-sestamibi myocardial perfusion scans recorded at rest and after pharmacological stress. Perfusion defects on the resting SPECT images were associated with ischemic characteristics on EMM. Sequential SPECT scans recorded before and after GTx demonstrated partial or complete resolution of fixed defects in 4 (33%) and 5 (43%) patients, respectively, in whom defects were present on the rest images.

Resolution of rest defects observed in these SPECT scans after GTx is particularly intriguing. In this population of severely disabled, so-called no-option, patients, the rest defects were presumed to represent sites of myocardial scar associated with the clinical history of myocardial infarction in 13 of 13 patients. Partial or complete resolution of these rest defects after GTx is consistent with the notion that these preexisting defects constitute foci of hibernating myocardium and may have been successfully resuscitated as the result of therapeutic neovascularization.

The corresponding NOGA maps likewise showed reduced evidence of ischemia after GTx. EMM provides separate assessments of viability (endocardial voltage recording) and function (LLS). Thus, those areas of the NOGA map that showed viable myocardium with impaired function before GTx versus viable myocardium with improved function after GTx support the notion that the defects that resolved on the SPECT scans constitute sites of hibernating myocardium that have been resuscitated as a result of myocardial neovascularization. These findings further confirm that LV EMM may represent an independent diagnostic tool that may be useful for defining the myocardial consequences of improved perfusion. In the present series of patients, EMM was used in all cases to identify the extent of myocardial ischemia before and after GTx administered via thoracotomy. Preliminary studies performed in swine with myocardial ischemia and more recently in patients suggest that mapping the extent of ischemia may also be used online to direct percutaneous myocardial GTx. Such an adjunct may be particularly advantageous for optimizing low-efficiency strategies, such as naked DNA GTx, in which EMM may direct the injection of naked DNA to ischemic muscle, which has been shown previously to yield higher levels of gene expression.

Acknowledgments

This study was supported in part by a grant from the E.L. Weigand Foundation, Reno, Nev; and the Peter Lewis Educational Foundation. Dr Vale is the recipient of a fellowship from Bracco Diagnostics Inc/Society for Cardiac Angiography and Interventions.

References


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_Circulation_. 2000;102:965-974
doi: 10.1161/01.CIR.102.9.965

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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