Detection of Myocardial Viability and Stunning

Electromechanical Mapping for Determination of Myocardial Contractility and Viability

A Comparison With Echocardiography, Myocardial Single-Photon Emission Computed Tomography, and Positron Emission Tomography

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OBJECTIVES
The purpose of this study was to validate electromechanical viability parameters with combined myocardial perfusion and metabolic imaging and echocardiography.

BACKGROUND
The NOGA System is a catheter-based, non-fluoroscopic, three-dimensional endocardial mapping system. This unique technique allows accurate simultaneous assessment of both local electrical activity and regional contractility.

METHODS
The results of NOGA, myocardial single-photon emission computed tomography (SPECT), positron emission tomography, and echocardiography in 51 patients with coronary artery disease and a pathologic SPECT study were transcribed in a nine-segment bull’s-eye projection and compared.

RESULTS
The local shortening of normally contracting segments, as shown by echocardiography, was 9.2 ± 5.1%, which decreased to 6.6 ± 5.0% and 4.1 ± 5.2% in hypokinetic and akinetic segments. The highest unipolar voltage (11.2 ± 5.0 mV) and local shortening (8.2 ± 5.0%) characterized normally perfused segments. Fixed perfusion defects with normal or limited 18-fluoro-2-deoxy-D-glucose uptake indicating viability had a significantly higher unipolar voltage than did scar tissue (7.25 ± 2.7 vs. 5.0 ± 3.1 mV, p = 0.029).

CONCLUSIONS
Electromechanical parameters sufficiently defined the viability state of the myocardium and showed good concordance with the findings by nuclear perfusion and metabolism imaging and echocardiography. The NOGA technique provides all the relevant information immediately after coronary angiography and enables the physician to proceed with therapy in the same setting. (J Am Coll Cardiol 2002;40:1067–74) © 2002 by the American College of Cardiology Foundation

Patients with reduced left ventricular (LV) performance due to viable but hibernating myocardium will show a substantial survival benefit after revascularization (1). Nuclear perfusion and metabolism imaging techniques are the golden standard for predicting functional recovery after revascularization (2–7), but they cannot be performed at the time of coronary angiography, which may lead to an inherent time delay between the diagnostic angiographic procedure and the interventional or surgical therapy.

The NOGA three-dimensional electromechanical endocardial mapping system, a non-fluoroscopic method that allows simultaneous assessment of both local electrical activity and regional contractility, offers this in-laboratory diagnostic potential. The system has been validated in animal models (8–11) and in a preliminary clinical study comparing the electromechanical features of infarcted areas with those of regions remote from the area of infarction (12).

The hypothesis that viable myocardium can be distinctly characterized by an electromechanical mismatch (or dissociation), defined as preserved electrical activity with decreased mechanical activity, was recently proven in a hibernation model (13). A comparison in human patients of NOGA results with thallium myocardial scintigraphy showed good concordance with respect to the identification of viable and non-viable myocardium (14).

The purpose of this study was to validate NOGA electromechanical viability parameters with combined myocardial perfusion and metabolism imaging by comparing the NOGA results with the results of technetium-99m (99mTc) tetrofosmin single-photon emission computed tomography (SPECT), metabolic imaging with 18-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET), and echocardiography.

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Abbreviations and Acronyms

FDG = 18-fluoro-2-deoxy-D-glucose
FI = fragmentation index
LLS = linear local shortening
LV = left ventricle, left ventricular
PET = positron emission tomography
SPECT = single-photon emission computed tomography
\(^{99m}\)Tc = technetium-99m
UV = unipolar voltage

METHODS

Patient population and selection. The study population consisted of 51 consecutive patients with proven coronary artery disease (35 men and 16 women; mean age 61 ± 9.7 years). Forty-two patients had a previous Q-wave MI (n = 24) or non-Q-wave myocardial infarction (n = 24). The mean ejection fraction was 51 ± 14%. In all patients, echocardiography and nuclear imaging were performed within eight days of the NOGA procedure. Thirty-one patients with a fixed perfusion defect on SPECT were also examined by PET. No clinical events or changes in medication occurred between the studies. Written, informed consent was obtained, and the study was approved by the Freiburg Ethical Committee and carried out in accordance with the Helsinki II Declaration.

Mapping procedure. The three-dimensional navigation-technology (Biosense Webster) mapping procedure was described in detail previously (9–14).

Briefly, under fluoroscopic guidance, the mapping catheter was introduced from the right femoral artery and advanced across the aortic valve into the LV. Three initial mapping points—the apex, inflow tract, and outflow tract—were acquired to generate the initial three-dimensional image. The remaining points (100 on average) were acquired without fluoroscopy. To verify the stability of the catheter tip with regard to the endocardium, four parameters—location stability, local activation time stability, cycle length stability, and loop stability—were calculated at each site. The average mapping time was 49 ± 14 min, and the average fluoroscopy time was 185 ± 26 s. The mapping procedure was followed by an automatic filtering process eliminating points that did not meet the aforementioned quality parameters as well as points not representing the LV endocardial surface (i.e., inner points). Only maps with at least 40 contact points and a reconstruction volume >50 ml were included in the analysis. Segments with less than three acquired points were excluded and regarded as empty.

Electrical data. The local unipolar voltage (UV) and bipolar voltage electrograms from the 2-mm tip electrode and a closely spaced (0.5 mm) 1-mm ring electrode were recorded at each point. The electrical information was presented as peak-to-peak amplitude UV maps in a color-coded fashion.

In addition, a quantitative description of the unipolar QRS complex fragmentation was similarly presented. The fragmentation index (FI) is independent of the signal’s amplitude; it is merely dependent on the number and relative amplitude of the fragments. For an unfragmented signal, FI = 1, whereas an index >1 represents a fragmented signal. The algorithm is fully described in the Appendix.

Mechanical data. Regional contractility was assessed by calculating the linear local shortening (LLS). This function has been previously described and validated: briefly, the algorithm calculates the fractional shortening of the regional endocardial surface at end systole (11,14).

Segmental analysis. For an analysis comparing NOGA with the other three-dimensional techniques, the NOGA endocardial surface was divided into nine segments, and the data were presented in a regional map (bull’s-eye projection). The long axis was defined as the line connecting the apex and the automatically calculated center of the ellipsoid that envelops the reconstructed LV. The length of the ventricular long axis was divided into three segments: apex (20%), mid-ventricle (40%), and base (40%). The mid-ventricle and base circumference were further divided into four regions: anterior (80°), septal (120°), inferior/posterior (80°), and lateral (80°) (Fig. 1).

Echocardiography. Regional contractility was assessed by echocardiography (Hewlett Packard model 2500) using standard views and divisions according to the guidelines of the American Society of Echocardiography. For comparison with NOGA LV maps, two experienced independent cardiologists who were blinded to the NOGA and nuclear imaging results reviewed the echocardiographic results and applied an additional nine-segment scoring system. Segmental contractility was assessed using a semiquantitative scoring system (1 = normal; 2 = hypokinetic; 3 = akinetic; 4 = dyskinetic) and was compared with the LLS results.

Myocardial SPECT. The SPECT studies were performed customarily (Sophycamera DS 7, Sopha Medical Vision), using optimized imaging, acquisition, and processing protocols according to the imaging guidelines of the American Society of Nuclear Cardiology, with \(^{99m}\)Tc tetrofosmin (Myoview) (15–17). The tracer (500 to 600 MBq) was injected intravenously at peak stress. In patients who were not able to cycle, 0.56 mg/kg of dipyridamole was administered intravenously. The examination at rest was performed on the following day using 500 to 600 MBq of \(^{99m}\)Tc tetrofosmin.

A semiquantitative analysis was performed by two experienced readers who were blinded to the NOGA and echocardiographic results. The results were transcribed into a nine-segment bull’s-eye projection using the following scoring: 1 = normal; 2 = perfusion deficit; 3 = perfusion defect; a = reversible; b = partially reversible; c = fixed.

Positron emission tomography. Thirty-one patients with fixed SPECT perfusion defects underwent a PET study (UGM, PENN-PET). After overnight fasting, the patients received an insulin and glucose infusion. Thirty minutes later, FDG was administered. Positioning of the heart was assessed by a 12-min transmission scan. Image acquisition
was delayed for 30 min after the administration of FDG (250 MBq) to allow transportation of the tracer into the myocardium and phosphorylation in the cytosol. Then, a 20-min static emission scan and an iterative reconstruction were performed. The segment with the highest uptake of $99m$Tc tetrofosmin was regarded as having 100% FDG uptake. The results were transcribed into a nine-segment bull’s-eye projection using the following scoring: 1 = normal; 2 = limited uptake; 3 = no uptake.

**Statistical analysis.** The statistical analysis was based on a logistic regression model. As data derived from the comparative techniques were available at the segmental level (9 segments per patient), the NOGA parameters were averaged over segments. The ventricular ellipsoid was delineated by a mesh or grid composed of rectangles (Fig. 2). The net ∼1,000 grid points per LV map produced by this smooth reconstruction algorithm was used to compute mean segmental values and the standard deviation of the values of

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**Figure 1.** A zone map demonstrating the transcription of the three-dimensional NOGA map (right anterior oblique view) into a regional bull’s-eye projection. Each of the nine segments is colored differently (i.e., the apical zone is red). A = anterior; L = lateral; P = posterior; S = septal.

**Figure 2.** A grid composed of rectangles. After an initial flexible distortion, the model was matched to the sampled points and final smoothing was obtained by applying a surface convolution and matching a grid node for each sample and moving that node to the sample location. Each grid point then received a value proportional to its distance from the neighboring points and their values, using color interpolation and smoothing.
NOGA functions (mean ± SD). The segments were arranged into different groups according to the parameters of SPECT, PET, and echocardiography. Groups were compared using the nonparametric test of Kruskal and Wallis.

Analysis was performed by using the customary SAS/STAT software, version 7.0 (SAS Institute, Cary, North Carolina). To perform the logistic regression, the viability status of the myocardium, as defined by nuclear imaging (SPECT and PET) and echocardiography, was defined as a “binary response” (response variables: viable or non-viable). The parameters of the electromechanical mapping (UV, LLS, and FI) were used as dependent (explanatory) variables. On the basis of estimated logistic regression models, both sensitivity and specificity values were calculated. Receiver-operating characteristic curve analysis allowed the evaluation of trade-offs between sensitivity and specificity associated with different values of the test result. The thresholds for the various combinations of sensitivity and specificity were thus computed.

As the main goal was to try to establish universal, preferably patient-independent, thresholds, inter-patient as well as intra-patient effects were not introduced into the statistical model. Inclusion of these effects would have resulted in an undesired marked reduction of the model’s quality and validity.

RESULTS

Comparison between NOGA and echocardiography. Of 459 segments (9 segments per patient), 10 had no NOGA points and an additional 13 could not be interpreted by echocardiography. Hence, 436 segments were available for comparison: 246 were normal, 73 were hypokinetic, 81 were akinetic, and 36 were defined as dyskinetic by echocardiography.

Comparative regional contractility assessment. Conservative scoring (4 scores: normal, hypokinetic, akinetic, and dyskinetic) was initially evaluated. The average LLS of the normal segments was 9.2 ± 5.1%, which decreased to 6.6 ± 5.0% and 4.1 ± 5.2% in hypokinetic and akinetic segments, respectively. The median LLS of the dyskinetic segments was 3.7 ± 4.4%, which was not significantly lower than that of the akinetic segments. The LLS could therefore readily differentiate between normally contracting segments and segments with either akinesia or dyskinesia by echocardiography (p = 0.0001) (Fig. 3).

When additional intermediate scores of contractility were introduced (7 scores: normal, mildly hypokinetic, hypokinetic, mildly akinetic, akinetic, mildly dyskinetic, dyskinetic), the LLS function could significantly differentiate even between normal or mildly hypokinetic segments and truly hypokinetic segments (9.2 ± 5.0% and 6.2 ± 5.0%, respectively). The rest of the poorly contracting segments had a median LLS of 3.9 ± 5.0%.

A LLS threshold of 4% identified significant regional contractility disturbances of akinetic or dyskinetic segments, with a specificity of 85%. A LLS threshold of 9% defined a normally contracting segment, with a sensitivity of 90%.

Correlation between electrical activity and regional contractility. The average UV significantly decreased from 12.2 ± 5.2 mV in normal segments to 8.3 ± 3.9 and 8.0 ± 3.7 mV in hypokinetic and akinetic segments, respectively. Dyskinetic segments had the lowest median UV (6.7 ± 2.5 mV). The FI was almost the same in normal and hypokinetic segments (11.5 ± 0.18 and 11.6 ± 0.19, respectively) but increased significantly to 1.26 ± 0.25 and 1.25 ± 0.25 in akinetic and dyskinetic segments, respectively (Fig. 3).

Comparison between NOGA and nuclear imaging. Correlation between electromechanical assessment and SPECT perfusion imaging. For the comparison between NOGA and SPECT, 406 segments were available. Of these, 332 segments were normally perfused at rest (282 were normal at both rest and stress and 50 segments had reversible deficits or defects), and 74 had fixed perfusion defects.

Both electrical and mechanical NOGA parameters were highly correlated with SPECT scores. The highest UV (11.2 ± 5.0 mV) and LLS (8.2 ± 5.0%) characterized normally perfused segments. Reversible segments were not significantly different at UV and LLS values of 11.7 ± 4.7 mV and 7.6 ± 7.3%, respectively. Fixed perfusion defects were clearly distinguished by low values of 6.3 ± 3.0 mV.
and 3.5 ± 4.0%, respectively, and were significantly different from both normal and reversible segments (p = 0.001) (Fig. 4).

A high FI (1.28 ± 0.23) was characteristic of fixed perfusion defects and was significantly higher (p = 0.001) than that of normal and reversible segments (1.15 ± 0.18 and 1.19 ± 0.24, respectively) (Fig. 4).

The overall concordance between UV and SPECT was 0.81. However, when the calculation was carried out separately for the apex plus mid-ventricle and for the base, the concordances were 0.83 and 0.9, respectively.

A threshold of UV of 6 mV (Fig. 5), LLS of 4%, or FI >1.5 each identified a fixed perfusion defect, with a specificity of 90%. A threshold of UV of 10 mV (Fig. 5), LLS of 9%, or FI <1.1 defined a normally perfused segment, with a sensitivity of 90%.

CORRELATION BETWEEN NOGA AND FDG-PET IMAGING. The PET results of 66 segments with a fixed perfusion defect were available for comparative analysis with NOGA results. Of these, 47 had normal (n = 28) or limited (n = 19) FDG uptake, indicative of viability, whereas 19 had no uptake, indicating non-viable scar tissue. Tissue with preserved glucose metabolism had a significantly higher UV (7.25 ± 2.7 and 6.47 ± 2.6 mV for normal and limited uptake, respectively), as compared with scar tissue (5.0 ± 3.1 mV, p = 0.029). As expected, all fixed perfusion segments did not differ significantly in their LLS values (3.1 ± 4.9%, 4.3 ± 4.0%, and 4.3 ± 4.5% for normal, limited, and no uptake, respectively).

When applying the aforementioned thresholds to define segments with NOGA parameters indicating fixed defects, 46 segments with UV <6 mV and FI >1.1 had available PET results. Of these, 34 had normal (n = 25) or limited (n = 9) uptake and 12 were non-viable. The UV was significantly higher in the viable segments (4.5 ± 0.9 mV) than in the non-viable segments (3.5 ± 1.0 mV, p = 0.0088). A high FI was similarly characteristic of non-viable segments

Figure 4. Correlation between NOGA parameters and single-photon emission computed tomography (SPECT) perfusion results. Data are expressed as the mean value ± SD. FI = fragmentation index; LLS = linear local shortening; UV = unipolar voltage.

Figure 5. Analysis of fixed perfusion defects by positron emission tomography (PET). A desired specificity of 90% defines a lower threshold of 4.5 mV for PET and 6 mV for single-photon emission computed tomography (SPECT). Thus, the unipolar voltage can differentiate between viable and non-viable fixed perfusion defects.
A threshold of UV of 4.5 mV (Fig. 5, 6) and FI both identified non-viable tissue, with a specificity of 90% and a sensitivity of 65%. To identify scar tissue with a high sensitivity (>90%) and to exclude scar tissue with a high specificity (>90%) in areas with a fixed perfusion defect during SPECT, there may be a gray zone of the UV between 4.5 and 10 mV, which can make individual interpretation difficult.

CORRELATION OF NOGA PARAMETERS WITH SIZE OF INFARCTED AREA. Eighteen patients had no fixed defect; 24 had between one and four fixed defects; and seven patients had up to seven segments with a perfusion defect.

The entire ventricle’s mean UV highly correlated with the size of the fixed perfusion defect (p = 0.0001). The mean UV decreased from 12.9 mV in patients who had no fixed defect to 5.9 mV in patients with fixed defects in seven segments. The entire ventricle’s mean LLS decreased similarly from 9% to 3% (p = 0.001).

Although the mean UV in the normally perfused territories decreased accordingly (from 12.9 to 5.5 mV), the UV within the pathologic zones varied less and was relatively stable (8.7 to 5 mV; mean 6.3 mV). The LLS in the pathologic zones, however, decreased according to the extent of the fixed defect (from 7.6% in ventricles with a single-segment fixed defect to 2.5% in ventricles with perfusion defects in 7 segments).

DISCUSSION

Hypothesis. The results of this study confirm the hypothesis that electromechanical assessment in ischemic cardiomyopathy can differentiate viable from scarred myocardium.
Our study focuses on the relationship between electromechanical mapping and combined perfusion and metabolism imaging. Unipolar voltage does not only differentiate normally perfused myocardium from fixed perfusion defects, but it also identifies non-viable zones within the perfusion defects, in accordance with the findings of PET glucose utilization. The “hybrid” imaging approach using ⁹⁹mTc tetrofosmin SPECT and FDG-PET has been validated with regard to the determination of myocardial viability and prediction of functional outcome (18). Only patients with a mismatch between SPECT (indicating a perfusion defect) and PET (indicating viability) demonstrated an improved regional wall motion and a significant reduction of cardiac events after revascularization. Thus, electromechanical mapping may be helpful in identifying patients who benefit most from revascularization. However, this study had not been designed to answer that question.

Reversible ischemia. The UV of normally perfused segments and segments with reversible ischemia was identical. This indicates that areas with reversible ischemia cannot be identified by peak-to-peak UV amplitude measurements, which is not surprising, because NOGA electromechanical mapping was performed only at rest. The inability to differentiate normal perfusion from reversible ischemia is further supported by identical LLS values in both normally perfused segments and segments with reversible ischemia.

These observations are in contrast to the findings of Kornowski et al. (14), who compared the NOGA electromechanical mapping function only with perfusion imaging in 18 patients. In this study, there was a significant difference in the UV of normally perfused segments and reversible defects, which showed reduced perfusion only during stress but normal perfusion at rest. Electromechanical mapping under some form of stress (i.e., dobutamine, dipyridamole, or even handgrip exercise), as well as a more sophisticated assessment of local electrical activity, could shed more light on this unsolved issue.

Kornowski et al. (14) reported a mild reduction in endocardial voltage potentials and LLS in segments with reversible perfusion defects, as well as a profound electromechanical impairment in segments with fixed defects.

Average values. In our larger study, the average UV in all three SPECT perfusion categories (normal, reversible, and fixed perfusion defects) was lower than that in Kornowski’s study (14). Because we have shown that there is an inverse relationship between the size of the perfusion defect and the UV in normally perfused myocardium, we assume that our patients had a higher incidence of large defects. In fact, in Kornowski’s study, only patients with an ejection fraction >40% were included. In contrast, in our study, there was no limitation regarding the ejection fraction.

Study limitations. The results of electromechanical mapping, nuclear perfusion and metabolic imaging, and echocardiography have been transcribed into a nine-segment bull’s-eye projection. For each patient, four nine-segment models were generated for comparison. The main disadvantage of this segmental approach is a possible malalignment or “segmental shift” when comparing it with defined segments of other modalities. In addition, two-dimensional echocardiographic interpretation of regional wall motion abnormalities is critically dependent on the reviewer’s ability to distinguish between segmental myocardial motion and that motion generated by the translational and rotational movement of the heart. Wall thickening is an important parameter in analyzing myocardial contractility by echocardiography. This parameter was not taken into account by the LLS function. As LLS describes the movement of a point on the endocardial surface, it does not exactly reflect contractility and cannot distinguish between active and passive movement.

The difference between the electrical activity measured in normally perfused regions and that in fixed perfusion defects decreases as the size of the defect increases. As a consequence, a “smearing effect” might occur in LVs with large perfusion defects. This makes it more difficult to correctly determine the accurate borders of the defect. In addition, the UV within the perfusion defect is lower in extended than in small defects. This could lead to an underestimation of viability when a fixed threshold is used.

This study describes the correlation between electromechanical mapping, myocardial SPECT, and PET. Although the predictive value of combined perfusion and metabolism imaging for functional recovery has been proven in many studies, a combined NOGA and angiographic follow-up after successful revascularization is needed to further confirm the correlation between electromechanical parameters and myocardial recovery.

Conclusions. The NOGA endocardial electromechanical mapping system is a suitable tool for on-line viability assessment. Its electromechanical parameters show good concordance with the combined findings of nuclear perfusion and metabolic imaging. A single diagnostic catheterization procedure consisting of routine coronary angiography followed immediately by NOGA mapping allows the assessment of coronary morphology, LV function, and myocardial viability in the same session. Patients with reversible myocardial dysfunction due to hibernation could be revascularized in the same session. However, this issue needs further investigation.

References

APPENDIX

Algorithm for calculating FI. First, the time boundaries $b_1$, $b_2$ of a given unipolar intracardiac QRS $V(t)$ were defined. Then, the QRS complexes were isolated and the baseline drift removed.

$$S(t) = V(b_1) - t \cdot \frac{V(b_2) - V(b_1)}{b_2 - b_1}, \text{ re}[0,1]$$  \[1\]

where $b_1$ and $b_2$ are time moments. For discrete time, it will be translated into

$$S(i) = V(b_1 + i) - i \cdot \frac{V(b_2) - V(b_1)}{b_2 - b_1}, i = 0K b_2 - b_1$$  \[2\]

where $I$, $b_1$, and $b_2$ are time indexes.

The absolute values of the isolated QRS complex derivatives were computed as:

$$D(t) = \frac{|dS(t)|}{dt}$$  \[3\]

or, in discrete form, as:

$$D(i) = |S(i + 1) - S(i)|$$  \[4\]

The integral curve of the absolute derivative curve was computed as:

$$R(t) = \int_0^t D(\tau)d\tau$$  \[5\]

or, in the discrete form, as:

$$R(k) = \sum_{i=0}^{i=k} D(i)$$  \[6\]

The final value $R(b_2)$ was used to compute the FI as:

$$F = 0.5 - \frac{R(b_2)}{\max(S) - \min(S)}$$  \[7\]

Hence, the FI is independent of the signal’s amplitude and is merely dependent on the number and relative amplitude of the fragments. The minimal possible value for $F$ is 1. For two equal fragments, the value is 2, etc.