Electromechanical Mapping Versus Positron Emission Tomography and Single Photon Emission Computed Tomography for the Detection of Myocardial Viability in Patients With Ischemic Cardiomyopathy

Henrik Wiggers, MD, PhD,* Hans Erik Bøtker, MD, PhD,* Peter Søgaard, MD, PhD,* Anne Kaltoft, MD, Flemming Hermansen, MD,† Won Yong Kim, MD, PhD,* Lars Krusell, MD,* Leif Thuesen, MD, PhD* Aarhus, Denmark

OBJECTIVES
We compared catheter-based electromechanical mapping (NOGA system, Biosense-Webster, Haifa, Israel) with positron emission tomography (PET) and single photon emission computed tomography (SPECT) for prediction of reversibly dysfunctional myocardium (RDM) and irreversibly dysfunctional myocardium (IDM) in patients with severe left ventricular dysfunction. Furthermore, we established the optimal discriminatory value of NOGA measurements for distinction between RDM and IDM.

BACKGROUND
The NOGA system can detect viable myocardium but has not been used for prediction of post-revascularization contractile function in patients with ischemic cardiomyopathy.

METHODS
Twenty patients (19 males, age [mean ± SD] 60 ± 16 years, ejection fraction [EF] 29 ± 6%) underwent viability testing with NOGA and PET or SPECT before revascularization. Left ventricular function was studied at baseline and six months after revascularization.

RESULTS
The EF increased to 34 ± 13% at six months (p < 0.05 vs. baseline). The 58 RDM and 57 IDM regions differed with regard to unipolar voltage amplitude (UVA) (9.2 ± 3.9 mV vs. 7.6 ± 4.0 mV, p < 0.05), normalized UVA (106 ± 54% vs. 75 ± 39%, p < 0.05), and tracer uptake (76 ± 17% vs. 60 ± 20%, p < 0.05). The NOGA local shortening did not distinguish between RDM and IDM (6.4 ± 5.8% vs. 5.4 ± 6.6%). By receiver operating characteristic curve analysis, myocardial tracer uptake had better diagnostic performance than UVA (area under curve [AUC] ± SE: 0.82 ± 0.04 vs. 0.63 ± 0.05, p < 0.05) and normalized UVA (AUC ± SE: 0.70 ± 0.05, p < 0.05). Optimal threshold was defined as the value yielding sensitivity = specificity for prediction of RDM. Sensitivity and specificity were 59% at a UVA of 8.4 mV, 65% at a normalized UVA of 83%, and 78% at a tracer uptake of 69%.

CONCLUSIONS
The NOGA system may discriminate RDM from IDM with optimal discriminatory values for UVA and normalized UVA of 8.4 mV and 83%, respectively. However, the diagnostic performance does not reach the level obtained by PET and SPECT in patients with severe heart failure. (J Am Coll Cardiol 2003;41:843–8) © 2003 by the American College of Cardiology Foundation

Catheter-based electromechanical mapping (1,2) can detect viable myocytes in dysfunctional myocardium of patients with ischemic heart disease and mildly reduced left ventricular (LV) function (3–5). In these patients, measures of regional electrical and contractile function correlate with myocardial metabolic activity, membrane integrity, and perfusion as assessed by positron emission tomography (PET) and single photon emission computed tomography (SPECT) (3–6). Electromechanical mapping can also predict recovery of contractile function after revascularization of infarct zones in patients with nearly normal LV function (6). The advantage of electromechanical mapping is the potential use in the catheterization laboratory allowing ad hoc percutaneous coronary intervention (PCI) guided by viability assessment. The drawbacks of the method are its invasive nature with the potential risk of embolization of LV thrombus material and of hemorrhagic pericardial effusion, as well as the variability of measurements that complicates distinction between viable and nonviable myocardium (7).

In patients with severely reduced LV function, we have previously found that absolute and normalized unipolar voltage amplitude (UVA) levels distinguish between myocardial regions with and without evidence of viable myocytes as assessed by PET (7). However, the diagnostic performance of electromechanical mapping for prediction of reversible myocardial dysfunction has not been compared with PET and SPECT by post-revascularization follow-up. Furthermore, the optimal discriminatory value of electromechanical mapping measurements for the distinction between reversibly dysfunctional myocardium (RDM) and irreversibly dysfunctional myocardium (IDM) has not been established.

The purposes of the present study were to: 1) compare the ability of electromechanical mapping and PET and SPECT to discriminate between myocardium with and without...
Wiggers et al.
Electromechanical Mapping for Viability Assessment

post-revascularization recovery of function in patients with severe heart failure, and 2) identify the optimal threshold value of electromechanical mapping measurements for the prediction of post-revascularization myocardial function.

METHODS

Patients. We studied 20 patients with ischemic heart disease verified by significant coronary artery obstruction by coronary angiography and an ejection fraction (EF) <40%. Exclusion criteria included peripheral vascular disease, aortic stenosis, unstable ischemic syndrome, and LV thrombus on echocardiography or magnetic resonance imaging (MRI). Informed consent was obtained from all patients. Six patients were previously included in a study evaluating the NOGA system (Biosense-Webster, Haifa, Israel) mapping versus PET (7). The local ethics committee approved the study.

Study protocol. Before revascularization, the patients underwent viability assessment by NOGA electromechanical mapping and 18F-fluorodeoxyglucose (FDG) PET or 99mTc-sestamibi SPECT. Regional and global LV function were assessed before and six months after revascularization by paired three-dimensional echocardiographic or MRI studies.

Electromechanical mapping. The electromechanical mapping system NOGA has been described in detail previously (1,2,7). We used a direct retrograde left-sided approach through the femoral artery. The mapping catheter was advanced under fluoroscopic guidance to the LV. Points outlining the boundaries of the LV (apex, aortic outflow, mitral inflow) were acquired with fluoroscopic guidance. These hallmarks minimized rotational and horizontal misalignment in the construction of the polar maps that were used for comparison between the different imaging modalities. Unipolar signals filtered at 0.5 to 400 Hz were recorded in this study, and maps of UVA were obtained by displaying the peak-to-peak amplitudes. From the mechanical data, regional contractility was obtained by the use of the linear endocardial local shortening (LS) formula: LS(p) = \[\frac{\sum (L_{i(ED)} - L_{i(ES)/L_{i(ED)}})}{100}\], where LS (p) denotes the weighted average LS of a point (p) relative to all its endocardial neighboring points, and L_{i(ED)} and L_{i(ES)} are the distances of an index point from its neighbors at end-diastole and end-systole, respectively. The LS(p) value is a ratio that becomes smaller or even negative if regional contractility is reduced or becomes paradoxical. We acquired points only when the catheter tip was stable on the endocardium using location stability, loop stability, and cycle-length stability as specified by the manufacturer (1,2,7). Subsequently automatic editing was performed to remove internal points and points with unsatisfactory stability using moderate filtering. The UVA and linear endocardial LS were registered as previously described (7). Endocardial sites were in total divided into nine segments for comparative analysis with echocardiographic and PET imaging data (7). Normalized UVA were obtained as the percentage of the mean value of all control segments in each patient. This could not be performed in four patients who had no regions with normal wall motion score.

Nuclear cardiologic methods. We determined regional myocardial tracer uptake by FDG PET (11 patients) and 99mTc-sestamibi SPECT (9 patients). The PET studies were conducted under a hyperinsulinemic, euglycemic (5 mmol/l) clamp (Actrapid; Novo Nordisk, Gentofte, Denmark) with 40 mU/min/m² body surface area starting 1.5 h before the FDG scan. All subjects were scanned in two dimensions with an ECAT EXACT HR whole-body scanner (CTI/Siemens, Knoxville, Tennessee) with an axial field of view of 15 cm. A volume of 370 MBq FDG was injected, and 50 min later a static 10-min frame was acquired (7,8). Nine regions were defined to match the echocardiographic and the electromechanical regions (7). The FDG image was scaled to give the value of 100% in the region with maximal tracer uptake.

99mTc-sestamibi (700 MBq ± 10%) was injected after the patient had been resting for 30 min, and image acquisition was started 30 min after radioisotope injection. The SPECT acquisition was performed using a dual-headed rotating gamma camera (ADAC, Milpitas, Connecticut) with a high-resolution, parallel-holed collimator. Sixty-four projections of 25 s each were obtained over a non-circular 180° arc, extending from the 45° right anterior oblique to the 45° left posterior oblique position. No attenuation or scatter correction was used. Images were analyzed with the automatic quantitative program AutoQUANT (Cedars-Sinai Medical Center, Los Angeles, California) (9) and matched to the echocardiographic and the electromechanical regions. Images were scaled to give the value of 100% in the region with maximal tracer uptake. The PET and SPECT images were reoriented and aligned to MRI and echocardiographic studies by using the insertion of the right ventricle as a landmark.

Abbreviations and Acronyms

- AUC = area under curve
- EF = ejection fraction
- FDG = 18F-fluorodeoxyglucose
- IDM = irreversibly dysfunctional myocardium
- LS = local shortening
- LV = left ventricle/ventricular
- LVEF = left ventricular ejection fraction
- MRI = magnetic resonance imaging
- PCI = percutaneous coronary intervention
- PET = positron emission tomography
- RDM = reversibly dysfunctional myocardium
- ROC = receiver operating characteristic
- SPECT = single photon emission computed tomography
- UVA = unipolar voltage amplitude

March 5, 2003:843–8
Assessment of regional and global LV function. Evaluation of regional and global LV function was done with echocardiography (11 patients) and MRI (9 patients). We performed transthoracic three-dimensional echocardiography by apical rotation with tissue harmonic imaging using a 2.5-MHz transducer mounted in a hand-held rotation device (Vingmed System Five, GE-Vingmed Ultrasound, Horten, Norway) (10). The resulting two-dimensional, long-axis images were stored as digital cine loops in a computer for off-line analysis and generation of a three-dimensional image (Echo-Pac software, GE-Vingmed Ultrasound, Horten, Norway).

The MRI investigation was performed on a 1.5-T whole body system (Gyroscan ACS-NT 15, Philips Medical Systems, Best, The Netherlands). The subjects were examined in the supine position. A breath hold fast echo sequence with echo planar imaging was used to acquire a stack of eight to nine parallel and equidistant short-axis images that included the LV from base to apex. The slice selection was defined from an arbitrary starting point (10).

The LV volumes were calculated according to echocardiography and MRI by manual tracing of endocardial borders at end-diastole and end-systole as previously described (10). Wall motion analysis using a nine-segment model was performed by consensus of two observers who were blinded to the viability data. Myocardial regions were graded as follows: 1) control regions with normal wall motion score before revascularization; 2) reversibly dysfunctional regions with recovery of function at follow-up by ≥1 wall motion score; or 3) irreversibly dysfunctional regions without recovery of function at follow-up. Coronary angiography. Coronary angiography was performed through the femoral artery. We assessed location of stenoses and graded mean luminal diameter stenosis visually (diameter stenosis ≥50% was considered significant). Follow-up six months after revascularization did not identify any occluded target vessels.

Statistical analysis. Data are presented as mean ± SD or median (25th to 75th percentile) unless otherwise indicated. We used the statistical software program SPSS 10.0 (SPSS Inc., Cary, North Carolina) for statistical analyses. The Kolmogorov–Smirnov test was used as a test of normality and was used to compare characteristics of reversibly and irreversibly dysfunctional regions. Comparison of left ventricular ejection fraction (LVEF) and volumes before and after revascularization was done by paired t test. Student t test was used to compare wall motion scores at baseline in segments with and without recovery and patient characteristics between patients undergoing PET and SPECT. Receiver operating characteristic (ROC) curve analysis was performed to compare the diagnostic performance of the different modalities studied for discrimination between RDM and IDM (11). Area under curves (AUC) were compared as described by Hanley and McNeil (11) using the statistical software program GraphROC (GraphROC, Turku, Finland). A value of p < 0.05 was considered significant.

RESULTS

Patient characteristics. Among the 20 patients studied, 19 were males with mean age of 60 ± 16 years. The EF was 29 ± 6% (range 15% to 40%). Three patients had no clinical history of previous acute myocardial infarction, but they all displayed severe wall motion abnormalities on echocardiography. The median time interval from infarction to revascularization was 1 year (range 2 months to 20 years). Two patients had previously undergone revascularization. Five patients had one- vessel disease, 3 had two- vessel disease, and 12 had three- vessel disease. Left main coronary artery disease was present in two patients. Revascularization was performed by coronary artery bypass grafting in 11 patients and PCI in 9. Median time interval from NOGA and PET/SPECT to revascularization was 24 and 54 days, respectively. No cardiac events occurred between inclusion in the study, viability tests, revascularization, and follow-up at 184 ± 69 days. The EF increased to 34 ± 13% at follow-up (p < 0.05 vs. baseline), whereas LV end-diastolic volumes did not differ (202 ± 42 ml vs. 209 ± 59 ml, p = 0.51).

There were no differences between patients undergoing PET and SPECT with regard to age (60 ± 8 years vs. 63 ± 7 years), LVEF (30 ± 7% vs. 28 ± 7%), extent of coronary artery disease (2 [2 to 3] vs. 3 [2 to 3] diseased vessels), or co-morbidities.

Electromechanical mapping procedural characteristics. We sampled 74 ± 20 points per patient, of which 50 ± 18 points fulfilled the stability criteria after moderate filtering. In 13 regions, satisfactory mapping data were not available because <3 points were sampled during the procedure. Mapping time was 45 ± 10 min.

Regional characteristics. Among the 180 regions, 28 displayed normal wall motion score (control regions) and 152 were dysfunctional. We excluded 13 regions with missing electromechanical data and 24 regions that were unvascularized. Among 115 dysfunctional regions in the final analysis, recovery of function was observed in 58, whereas 57 were irreversibly dysfunctional. Among the 11 patients undergoing coronary artery bypass grafting, a total of 36 of 76 dysfunctional segments (47%) displayed reversible myocardial dysfunction. In the nine patients undergoing PCI, 22 of 39 dysfunctional segments (56%) recovered function at follow-up. There was no statistical difference in the likelihood of recovery in dysfunctional segments among the two groups (p = 0.37). Wall motion score before revascularization did not differ between segments with and without functional recovery (2.3 ± 0.6 and 2.5 ± 0.5, p = 0.18). Accordingly, LS was not different in the two types of regions (Table 1). Reversibly dysfunctional regions had higher UVA, normalized UVA, and tracer uptake than irreversibly dysfunctional regions, whereas LS was similar (Table 1). Control regions had higher LS than dysfunctional regions, and similar UVA, normalized UVA, and...
tracer uptake as in reversibly dysfunctional regions. There were no differences between FDG and \(^{99m}\)Tc-sestamibi uptake in control, reversibly dysfunctional or irreversibly dysfunctional regions (Table 1).

**Comparison between electromechanical mapping and PET/SPECT.** The ROC curve analysis showed that for prediction of functional outcome in dysfunctional myocardium after revascularization, myocardial tracer uptake (AUC \(\pm SE\), 0.76 \(\pm 0.05\)) was superior to UVA (AUC \(\pm SE\), 0.64 \(\pm 0.05\); \(p < 0.05\) vs. tracer uptake). In patients with control regions available for normalization of UVA, this approach tended to improve the diagnostic accuracy of electromechanical mapping compared with absolute UVA (Fig. 1) (AUC \(\pm SE\), 0.70 \(\pm 0.05\) vs. 0.63 \(\pm 0.05\); \(p = 0.09\)). Tracer uptake remained the best predictor of functional outcome after revascularization in these patients (AUC \(\pm SE\), 0.82 \(\pm 0.04\); \(p < 0.05\) vs. normalized UVA). Subgroup ROC curve analysis in patients studied with either PET or SPECT revealed similar AUC (AUC \(\pm SE\), 0.81 \(\pm 0.06\) vs. 0.84 \(\pm 0.07\)) for the two nuclear cardiologic methods.

The optimal cutoff value for distinction between RDM and IDM was 68% for FDG uptake and 71% for \(^{99m}\)Tc-sestamibi (\(p = NS\)).

**Prediction of recovery of LV function by electromechanical mapping and PET/SPECT at different threshold criteria for viability.** The sensitivity and specificity for the distinction between RDM and IDM are shown at various thresholds of UVA, normalized UVA, and tracer uptake in Figures 2A to 2C. The selection of the optimal threshold value depends on the consequences of false positive and false negative test results, but the proportion of correctly classified cases, efficiency, is often highest when sensitivity = specificity. Sensitivity and specificity was 59% at an UVA of 8.4 mV, 65% at a normalized UVA of 83%, and 78% at a tracer uptake of 69%.

## DISCUSSION

The present study establishes that catheter-based mapping of regional myocardial electrical function can discriminate between RDM and IDM in patients with severe LV dysfunction. However, the diagnostic performance of this modality does not reach the level obtained with PET and SPECT.

**Mapping of regional electrical function for prediction of contractile status after revascularization.** The potential of endocardial electromechanical mapping for the prediction of post-revascularization recovery of LV function in patients...
with ischemic cardiomyopathy has not previously been established by postoperative follow-up. Koch et al. (6) reported a sensitivity of 91% and a specificity of 71% for prediction of reversible myocardial dysfunction at an UVA threshold of 7.5 mV. In the present study, the same threshold yielded a sensitivity of 69% and a specificity of 52%. The different test characteristics may be explained by differences between the patient populations studied, because the subjects studied by Koch et al. (6) had preserved LV function with a mean EF of 49% and were predominantly one-vessel diseased. Extensive infarction, fibrosis, LV dilation, and remodeling affect the electrical properties of the myocardium (12) and can account for different electrical properties of RDM and IDM in patients with and without preserved LV function. Differences in regional electrical activities can be reduced by the far-field component of UVA (13); such differences could also explain why regional UVA in control regions were lower and the overlap between UVA in reversibly and irreversibly dysfunctional regions was greater in our patients than in patients with relatively preserved systolic function (3–6). The optimal discriminatory value of electromechanical mapping measurements for the distinction between RDM and IDM was higher than predicted from comparison with PET and SPECT in studies without postoperative follow-up (3–7), possibly because of the known overestimation of viability by nuclear techniques compared with functional recovery after revascularization (14). In the study by Botker et al. (7), optimal diagnostic thresholds of electromechanical mapping for the detection of PET-viable segments were 6.5 mV and 68%, but no follow-up data on LV function were available. The higher diagnostic threshold observed in the present study is likely due to the use of recovery of LV function as an outcome measure. Positron emission tomography and SPECT are sensitive but not specific for the prediction of post-revascularization recovery of LV function (8,14), and positive predictive values are on average 70% to 75% (14). This is due to a considerable part of PET/SPECT-viable segments not regaining contractile function after revascularization because of remodeling and subendocardial scarring (15).

Electromechanical mapping versus nuclear cardiologic methods in the prediction of RDM and IDM. The diagnostic performance of electromechanical mapping appeared less efficient than PET/SPECT as assessed by ROC curve analysis of UVA compared with tracer uptake. The difference between the areas under the ROC curves reflects a larger overlap of electrical activity than tracer uptake in regions with reversible and irreversible myocardial dysfunction. Measures to reduce the variability of electrical measurements, therefore, will increase the diagnostic accuracy of regional UVA. As previously suggested (7), normalization of UVA improved the diagnostic characteristics of electrical mapping. Even so, electromechanical mapping did not reach the same diagnostic performance as the nuclear cardiologic methods. Achievement of a higher point density by the sampling of more points may reduce variability and improve the diagnostic characteristics, but it requires a longer mapping time. Analysis of endocardial impedance and unipolar signal slew rate does not increase the ability of endocardial mapping to detect scar tissue (16). In its present form, the NOGA system is useful for regional viability assessment in patients without severe LV dysfunction (3–7), although this has limited clinical implications.
Mapping of linear endocardial LS. The LS obtained by the NOGA system has been reported to differ between regions with and without evidence of viable myocytes as assessed by PET or SPECT (3–6). In our study population of patients with severe LV dysfunction, wall motion scores and local mechanical function did not differ in reversibly and irreversibly dysfunctional regions, a common observation in patients with ischemic cardiomyopathy (8). Mapping of regional contractile function in these patients discriminated between regions with preserved and reduced contractility, and together with mapping of electrical function, this allows NOGA-guided therapeutic interventions (17). Thus, NOGA is an excellent intracardial navigation system, but its potential appears much greater for therapeutic than for diagnostic purposes.

Study limitations. Our comparison between NOGA and either PET or SPECT may be impaired by different diagnostic characteristics of the two nuclear cardiologic methods. However, subgroup ROC curve analysis in patients studied with either of these modalities revealed similar AUC, suggesting that the diagnostic characteristics did not differ. In addition, there were no differences between FDG and 99mTc-sestamibi uptake in control, reversibly did not differ. In addition, there were no differences between similar AUC, suggesting that the diagnostic characteristics methods. However, subgroup ROC curve analysis in patients discriminated between regions with preserved and reduced contractility, and together with mapping of electrical function, this allows NOGA-guided therapeutic interventions (17). Thus, NOGA is an excellent intracardial navigation system, but its potential appears much greater for therapeutic than for diagnostic purposes.

Conclusions. In patients with severe LV dysfunction, catheter-based mapping of regional UVA can differentiate between RDM and IDM. However, the diagnostic performance does not reach the level obtained by PET and SPECT which also have the advantage that they are non-invasive modalities with negligible complication risks.

Acknowledgments

We thank Karin Boisen, A. D. Blankholm, the staff at the PET Center, and the nurses at the catheterization laboratory for excellent technical assistance.

Reprint requests and correspondence: Dr. Henrik Wiggers, Department of Cardiology, Skejby Hospital, Aarhus University Hospital, DK-8200 Aarhus N, Denmark. E-mail: henrikwiggers@dadlnet.dk.

REFERENCES


