NOGA-Guided Analysis of Regional Myocardial Perfusion Abnormalities Treated With Intramyocardial Injections of Plasmid Encoding Vascular Endothelial Growth Factor A-165 in Patients With Chronic Myocardial Ischemia Subanalysis of the EUROINJECT-ONE Multicenter Double-Blind Randomized Study

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Background—The aim of this substudy of the EUROINJECT-ONE double-blind randomized trial was to analyze changes in myocardial perfusion in NOGA-defined regions with intramyocardial injections of plasmid encoding plasmid human (ph)VEGF-A165 using an elaborated transformation algorithm.

Methods and Results—After randomization, 80 no-option patients received either active, phVEGF-A165 (n=40), or placebo plasmid (n=40) percutaneously via NOGA-Myostar injections. The injected area (region of interest, ROI) was delineated as a best polygon by connecting of the injection points marked on NOGA polar maps. The ROI was projected onto the baseline and follow-up rest and stress polar maps of the 99m-Tc-sestamibi/tetrofosmin single-photon emission computed tomography scintigraphy calculating the extent and severity (expressed as the mean normalized tracer uptake) of the ROI automatically. The extents of the ROI were similar in the VEGF and placebo groups (19.4±4.2% versus 21.5±5.4% of entire myocardium). No differences were found between VEGF and placebo groups at baseline with regard to the perfusion defect severity (rest: 69±11.7% versus 68.7±13.3%; stress: 63±13.3% versus 62.6±13.6%; and reversibility: 6.0±7.7% versus 6.7±9.0%). At follow-up, a trend toward improvement in perfusion defect severity at stress was observed in VEGF group as compared with placebo (68.5±11.9% versus 62.5±13.5%, P=0.072) without reaching normal values. The reversibility of the ROI decreased significantly at follow-up in VEGF group as compared with the placebo group (1.2±9.0% versus 7.1±9.0%, P=0.016). Twenty-one patients in VEGF and 8 patients in placebo group (P<0.01) exhibited an improvement in tracer uptake during stress, defined as a ≥5% increase in the normalized tracer uptake of the ROI.

Conclusions—Projection of the NOGA-guided injection area onto the single-photon emission computed tomography polar maps permits quantitative evaluation of myocardial perfusion in regions treated with angiogenic substances. Injections of phVEGF A165 plasmid improve, but do not normalize, the stress-induced perfusion abnormalities. (Circulation. 2005;112[suppl I]:I-157–I-165.)

Key Words: angiogenesis mapping gene therapy perfusion scintigraphy

Cell- and gene-based therapies involving the intracoronary or intramyocardial delivery of pluripotent cells or genes encoding vascular growth factors have the aim of clinical cardiac therapeutic angiogenesis for patients not amenable to conventional revascularization.1–8 Several small phase I/II gene-based nonrandomized and randomized clinical studies in which the intramyocardial application mode was used suggested benefit through improvements in angina pectoris symptoms, exercise capacity, and regional myocardial perfusion.5,6,9–12 The scintigraphic images in these studies were
mainly analyzed visually. As the therapy mode differs from the coronary revascularization, however, this new method indicates a need for standardization of image analysis to enhance the usefulness of single photon emission computer tomography (SPECT) perfusion imaging in intramyocardial therapeutic angiogenesis studies.13

The EUROINJECT-ONE study is the largest randomized placebo-controlled multicenter trial studying the improvement of regional myocardial perfusion by NOGA 3-dimensional guided endocardial injections of plasmid encoding plasmid human (ph)VEGF-A165 in no-option patients with stress-induced myocardial ischemia who are not amenable to conventional revascularization.14 The main results, the baseline and follow-up data of the EUROINJECT-ONE study, the procedural and safety data, and the 3- and 6-month clinical outcomes were recently reported.14

The present subanalysis of the EUROINJECT-ONE study was initiated because visual analysis of the perfusion scintigraphy (the primary end point of the study) clearly demonstrated that the NOGA-defined treated areas do not and cannot completely overlap the scintigraphic reversible ischemic areas (Figure 1). Although the main inclusion criterion for the EUROINJECT-ONE study was significant perfusion defects on adenosine 99m-Tc-sestamibi myocardial perfusion scintigraphy, and the area of treatment was directed toward that ischemic area, the direct method with which the treatment area, the region of interest (ROI), was delineated involved 3D NOGA maps of unipolar voltage (UV) and local linear shortening (LLS). Because the 2 images furnish different information concerning the functional status of the myocardium (the NOGA endocardial UV and LLS provide information on viability and resting myocardial mechanical function, respectively, whereas perfusion scintigraphy yields data on resting and stress-induced perfusion abnormalities), a comparative interpretation of the images is difficult, with the result that the usual artery-driven segmental quantitative analysis of perfusion scintigraphy in such intramyocardial therapy studies might be inadequate.

As a compromise, in addition to the semiquantitative visual analysis of the ROI, a quantitative global perfusion analysis of the EUROINJECT-ONE data was performed without separation of the treated and nontreated areas. It did not reveal significant difference between the VEGF and placebo groups with regard to the follow-up rest- and stress-induced global perfusion abnormalities.14 Accordingly, the aim of the present substudy was to develop an algorithm with which the NOGA-defined injected area can be delineated automatically on the 2D NOGA and SPECT image polar maps, making feasible a comparative quantitative analysis of the myocardial perfusion in the exact regions treated with intramyocardial injections of phVEGF-A165 or placebo plasmid.

**Methods**

**Patients**

The detailed study design, inclusion and exclusion criteria, and baseline characteristics of the patients were published recently.14 Briefly, 80 no-option patients with stable angina pectoris and adenosine-induced ischemia revealed by 99m-Tc sestamibi/setroforsmin myocardial perfusion scintigraphy were included in the
study in 6 European centers. The patients were randomized centrally by the hospital pharmacy at the Karolinska University Hospital to receive either active pHVEGF-A165 (VEGF group, n=40) or inactive (placebo group n=40) plasmid. We requested that all patients attend the 3-month follow-up for clinical, angiographic, and scintigraphic control and diagnostic NOGA mapping. The study was approved by the national ethical committees and Medical Products Agencies, and informed consent has been obtained from all patients.

The primary end point of the study was the efficacy of the intramyocardial gene transfer, measured by change in myocardial perfusion defects at rest and under pharmacological stress between inclusion and 3-month follow-up SPECT. The secondary end points were the safety, changes in NOGA-derived UV values, changes in local wall motion assessed by contrast ventriculography and NOGA endocardial mapping (expressed in LLS values), and the clinical end points. Current medication was not changed until follow-up was completed.

**NOGA Endocardial Mapping for Manual Delineation of the Region of Interest and Intramyocardial Injections**

The electroanatomical mapping was performed in a standardized mode as described previously. After automatic inner point and base point filtering, the surface points of the final 3D NOGA map were transferred to the 2D polar map (corresponding internal, middle, and outer circles for apex, middle part, and base of the left ventricle) using conventional mathematical software converting Cartesian (rectangular) x, y, and z coordinates to polar (r and theta) coordinates, with a theta value of 0 for anterior wall border. The r value represents the distance between the point and apex along the long axis of the heart, and the theta value represents the angle between the actual point and the center of the image. Both the online 3D and the online polar maps were constructed automatically with the NOGA software.

The intramyocardial injections were given immediately after diagnostic NOGA mapping. Based on the localization of the stress-induced ischemic region assessed primarily by myocardial SPECT and secondarily by NOGA mapping (UV values >6 mV, and LLS >4%), the ROI was delineated on the 3D NOGA map, and the injection catheter was navigated into this area. A total dose of 0.5 mg pHVEGF-A165 or placebo plasmid was administered in 10 intramyocardial injections (0.3 mL each) within the delineated area, as previously described. The plasmid contained a cytomegalovirus promoter/enhancer to drive the VEGF-A165 expression. The placebo plasmid did not contain VEGF DNA.

**Perfusion Scintigraphy**

SPECT studies were conducted according to a 2-day stress-rest protocol (500 to 700 MBq 99mTc-sestamibi or tetrofosmin in each study) using adenosine infusion over 4 to 6 minutes (0.14 mg·kg⁻¹·min⁻¹ by infusion pump) for the pharmacological stress study. The stress tests at inclusion and at follow-up were performed with identical tracers, exercise loads, and cumulative adenosine doses.

The imaging data (after attenuation and scatter correction) were submitted to the Core Laboratory of Department of Cardiology, University of Vienna. Transaxial files of the baseline and follow-up rest and stress SPECT images (provided in DICOM format from all centers) were transferred to an image-analysis workstation (Onyx, SGI), and polar maps were constructed by using Munich-Heart software in a way similar to that used for the NOGA polar maps. Care was taken to achieve correct spatial normalization of myocardial SPECT images after the exclusion of blood pool and background activities (mean blood pool activities measured in the lumen of the left ventricle: baseline rest, 7.3%; stress, 8.4%; follow-up rest, 6.3%; stress, 8.3%; mean background activities: baseline rest, 1.2%; stress, 3.1%; follow-up rest, 1±1%; stress, 2±1% in relation to the peak heart activity).

**NOGA-Guided Analysis of Regional Myocardial Perfusion Abnormalities in the Injected Areas**

From the x, y, and z coordinates of the acquired point list of the NOGA mapping, an offline 3D image was reconstructed by using JMP program (JMP 3.0 version, SAS Institute) to compare and control the injection sites with the original NOGA 3D maps (Figure 2). For transposition of the ROI from the NOGA polar maps to the SPECT polar maps, an off-line NOGA polar map was reconstructed from the corresponding polar coordinates (r and theta) of each point from the point list by using Deltagraph (Deltapoint Inc) to allow measurements of the size of the injected area and mean normalized tracer uptake of the ROI. The injection points were then flagged on the reconstructed NOGA polar map and connected so as to encircle the treated territory as the best convex polygon. Based on the supposition that the effect of VEGF production is not limited strictly to the injection points, the encircled area was enlarged proportionally by 10%, delineating an extended effective treated area (Figure 3).

The NOGA-guided extended effective treated area was determined individually for each patient, and the modified r and theta polar coordinates of the extended effective treated areas were transferred to the corresponding baseline and follow-up rest and stress semiquantitative polar maps (Figure 4). The extent of the treated area was calculated automatically from the scintigraphic polar maps and expressed as a percentage of the entire myocardium. The severity of the perfusion abnormality of the delineated treated area was calculated as the mean normalized tracer uptake at rest and stress at baseline and follow-up (Figure 4) (normal values >70%, moderate defect between 51% to 70%, severe defect ≤50%). The reversibility of the perfusion defect was calculated as the difference between stress and rest normalized tracer uptake within the delineated area.

For analysis of the tracer uptake within the manually treated area, the injection points and the diagnostic mapping points within the manually encircled area on the 3D map were transferred to the polar map delineating the manually derived ROI (Figure 3). The size and form of the automatically delineated extended treated area were compared with those of the prospectively manually delineated treated area (Figure 3), and the extent and severity of perfusion defects of the manually delineated area were calculated as described above.

The size and severity of the perfusion defects of the automatically and manually delineated areas were repeatedly calculated by 2 observers for the determination of interobserver variability. Linear regression analysis resulted in a regression coefficient of r=0.999 (P<0.001) both for size and severity of defect with the automatic method, and of r=0.71 (P<0.001) for size and r=0.69 for severity (P<0.001) with the manual method. The differences were due to the manual corrections for included/excluded internal points by the construction of the best polygon with both methods.

**Visual Analysis of the SPECT Images**

To validate the results of the elaborated algorithm, the usual semiquantitative visual interpretation of the global perfusion was performed with the 20-segment score system, and a summed score during stress (SSS) and rest (SRS) and the difference between stress and rest (summed difference score, SDS) at baseline and at follow-up was calculated.

**Statistics**

Data from the 2 groups are presented as mean±standard deviation. Differences between the groups were tested by using Student t test for continuous parameters, and χ² test for categorical variables. Correlation between the normalized tracer uptake (severity of perfusion defect) and the visual segmental score was tested using linear regression analysis. A difference was considered statistically significant at P<0.05.

To determine the cut-off point for significant change in stress-induced perfusion abnormality within the NOGA-derived area, receiver operating characteristics analysis was performed, which presented the cut-off points with corresponding predictive accuracies (area under the curve). As no data are available on the individual
significant changes in quantitative perfusion between baseline and follow-up within the intramyocardially treated region, we used the 20-segment score system data as reference, indicating significant improvement in SSS at the follow-up. The statistical analyses were performed with the standard SAS package and the CLABROC and LABROC computer software.

Results
At follow-up, no changes in parameters influencing the scintigraphic results (body mass index, lipid profile, resting blood pressure, and heart rate) were detected. During stress imaging, comparable hyperemia was achieved at baseline and at follow-up (heart rate 96 ± 17 and 97 ± 21 bpm, peak stress systolic blood pressure 149 ± 29 and 145 ± 27 mm Hg, respectively) without difference between the VEGF and placebo groups. Similarly, no differences were recorded between baseline and follow-up resting heart rate and blood pressure during the NOGA procedure.

The treated ischemic areas were anterior (in 18% and 23%), lateral (in 25% and 15%), posterior (in 33% and 30%), septal (in 13% and 13%), and mixed (in 11% and 19%) in the VEGF and placebo groups, respectively. Five patients in the placebo and 1 patient in VEGF group were excluded from the scintigraphic analysis because of death during follow-up (1 in the placebo group) and poor image quality (4 in the placebo group and 1 in the VEGF group).

Results of the NOGA-Guided Analysis of Myocardial Perfusion in the Injected Areas
The extents of the NOGA-injection guided treated area (extended effective treated area) were similar in the 2 groups (19.4 ± 4.2% versus 21.5 ± 5.4% of the entire myocardium in the VEGF versus placebo groups, respectively), and differed significantly (P < 0.01) from those of the manually delineated treated areas (34.0 ± 7.1 versus 36.6 ± 9.9% in the VEGF and placebo groups, respectively), which included larger border areas in NOGA and SPECT images. The baseline mean normalized SPECT perfusion tracer uptakes (severity of the defect) at rest and at stress and the reversibility in the ROI did not differ between the VEGF and placebo groups (Figure 5).

At the 3-month follow-up, the mean resting tracer uptakes of the treated area did not differ from baseline and did not differ between the groups (Figure 5), and were near normal in both groups, both at baseline and at follow-up. A strong trend (P = 0.072) toward less severe perfusion defect at stress was observed in the patients who received VEGF treatment as compared with the placebo group (Figure 5). The mean amount of tracer uptake of the ROI at stress was increased significantly in the VEGF group (P = 0.043), although it did not reach normal values; no change was observed in the placebo group. The reversibility of the perfusion defect decreased significantly in VEGF group (P = 0.022) and was

Figure 2. Part of the “point list” retrieved from the NOGA mapping, containing the x, y, and z coordinates of the points acquired during the NOGA mapping, and the r and theta polar coordinates of the points for construction of the polar map (upper). From the point list, the reconstructed 3D image of the left ventricle with the injection points (red X) (similar to the NOGA 3D map) (bottom left) and the reconstructed polar map similar to the NOGA polar map (bottom right) are presented.
significantly better than that in the placebo group (Figure 5). No differences were observed between the groups, and no changes within the groups were seen with regard to the tracer uptakes at rest and stress at baseline and follow-up in the remote myocardial areas (Figure 6).

Comparison of the NOGA-Guided Perfusion With the Visual Analysis

The visual analysis of the global myocardial perfusion revealed no differences at baseline. SSS was 21.8±10.5 versus 22.5±8.5 in the VEGF versus placebo groups, and SDS was 8.7±8.7 versus 7.1±6.0, respectively. At follow-up, trends toward better SSS (18.9±10.3 versus 23.4±8.7, respectively, P=0.068) and SDS (5.7±5.8 versus 9.3±8.6, respectively, P=0.063) were observed in VEGF group. The mean normalized tracer uptake within the automatically delineated treated area correlated significantly (P<0.001) with the results of the visual global perfusion score (between SRS and resting defect severity: r=0.715 and r=0.716; and between SSS and stress defect severity: r=0.733 and r=0.692, at baseline and at follow-up).

Receiver operating characteristics analysis revealed a cut-off value of 5% for the mean tracer uptake within the treated area predicting individual improvement at the follow-up, with a predictive accuracy of 0.815 (P<0.001) (standard error of 0.056, 95% confidence interval of 0.705 to 0.925), and a common sensitivity/specificity of 76%.

Characterization of Patients With Significant Treatment Effect After Intramyocardial Injection of phVEGF-A165

Twenty-one patients (53%) in the VEGF group and 8 patients (20%) in the placebo group (P<0.01) exhibited a major improvement in the severity of stress defect, defined as a ≥5% increase of the normalized tracer uptake of the ROI. In the
VEGF group, patients with significant treatment effect exhibited a trend to more severe perfusion abnormalities at stress at baseline (mean tracer uptake of ROI: 59.2±15.3% and 67.7±8.7%, P=0.079; and SSS: 24.6±12.8 and 18.4±5.5, P=0.100 in patients with and without treatment effect, respectively). The treated area was located more often in posterior/lateral regions (P=0.06), and more patients had experienced a previous myocardial infarction (P=0.027), characterized by an SRS of 3 or 4 in at least 2 segments. The size of the ROI, age, and sex did not differ between the patients with and without treatment effect. No differences could be observed between the patients with (n=8) or without (n=32) significant improvement in the placebo group with regard to the qualitative and quantitative scintigraphic data and clinical parameters.

Comparison of the Results of the Manually and Automatically Delineated Treated Areas

The results of the manually delineated treated area as illustrated in Figure 3 indicated nonsignificantly higher tracer uptakes of the treated areas both at baseline and at follow-up.
under rest and stress conditions. Additionally, the resting mean normalized tracer uptake reached the normal range both at baseline (73.4 ± 12.2% versus 71.4 ± 10.7%, respectively) and follow-up (73.4 ± 11.8% versus 72.4 ± 10.1%, respectively) in both the VEGF and placebo groups. No difference was found between the groups with regard to the baseline stress-induced perfusion defect severities (63.1 ± 11.0% versus 63.4 ± 9.8% in VEGF and placebo groups) and the reversibility (10.4 ± 9.9% versus 7.9 ± 7.7%, respectively). The comparison of the amount of stress tracer uptakes (68.9 ± 9.2% versus 64.9 ± 8.3%, *P* = 0.081, respectively) led to results similar to those observed using the automatic method but without difference between the groups with regard to the reversibility (5.9 ± 9.0% versus 7.3 ± 7.2%, respectively).

**Discussion**

The transformation of the injection area to the scintigraphic images permits the first exact quantitative analysis of the myocardial perfusion of the NOGA-derivative-injected areas in patients treated with intramyocardial gene therapy. The present algorithm allows a detailed quantitative analysis of the extent and severity of a specifically treated area, and thus it furnishes more information than the global or the usual segmental artery-driven quantitative evaluation or the visual semiquantitative evaluation of SPECT images. NOGA-guided analysis of myocardial perfusion of the intramyocardially injected areas resulted in a strong trend toward better perfusion under pharmacological stress in patients receiving phVEGF-A165 as compared with patients receiving inactive plasmid. The severity and reversibility of the SPECT perfusion abnormality decreased significantly in the VEGF group at the 3-month follow-up, and the improvement was statistically significant as compared with the placebo group. Despite the significant increase in tracer uptake at stress in the entire VEGF group, the perfusion abnormality did not reach the normal values, and only 53% of the patients in the VEGF group exhibited an individual significant improvement in stress-induced defect severity on myocardial scintigraphy. These data are in accordance with the results of the previously published NOGA and contrast ventriculography data of the EUROINJECT-ONE study with regard to the improved but not normalized local wall motion in the injected area.14

The manually delineated area on the diagnostic NOGA map (before intramyocardial injection) was significantly larger than the actually treated area (extended effective treated area); however, it was similar in magnitude to the overall extent of the stress-induced moderate perfusion defects, as published by the EUROINJECT-ONE Study Group.14 The comparative analysis of the manual and automatic methods for delineation of the treated areas revealed higher tracer uptakes in the manually derived territories, resulting in misleading normal resting tracer uptakes, probably because of the involvement of border zones between ischemic and normally perfused areas. Moreover, it turned out that the whole extent of the area intended to be treated that was delineated online by the investigator was not used, as only ≈ 60% of the area intended to be treated was injected.

Previous studies have reported significant improvement in stress-induced perfusion abnormalities on semiquantitative assessment of the overall perfusion after intramyocardial injection of phVEGF-A165 or phVEGF-C9–12 or the intracoronary delivery of genes encoding growth factors2 in no-option patients. The fully quantitative segmental analysis of myocardial perfusion after intracoronary delivery of adenoviral fibroblast growth factor-4 in the Angiogene Gene Therapy trial resulted in a significant improvement in the treated group, with a trend toward better perfusion in the treated patients as compared with placebo4 similar to that in the EUROINJECT-ONE study. The reason for the differences between the promising results of the myocardial perfusion (as an objective hard clinical end point) in the small nonrandomized and randomized studies and the largest randomized study, the EUROINJECT-ONE, is not completely clear, even if the different modes of analysis of the perfusion abnormalities might explain some features. The patients included in the EUROINJECT-ONE study displayed near normal resting perfusion and a moderately decreased perfusion during stress in a large portion (30%) of the myocardium. This constellation with normal or near normal viability in the NOGA voltage map23 would be ideal for intramyocardial gene therapy. Most of our included patients, however, had mul-
tivessel disease with previous myocardial infarctions and decreased perfusion at stress even in the remote myocardium, which might also influence the outcome of our study. To avoid the influence of confounding factors on the assessment of the perfusion studies, as our analysis indicates, a quantitative exact analysis of the myocardial perfusion in the injected area might be required in gene- and cell-based therapies.

Interestingly, only 53% of the patients in the VEGF group exhibited significant improvement in the amount of the tracer uptake (≥5% increase in normalized tracer uptake at stress within the treated area at follow-up). This is in full accordance with the published results of the semiquantitative score analysis. The reasons for the surprising relatively low rate (53%) of patients displaying a significant improvement in stress-induced perfusion defect severity are complex; they include the interpretation mismatch of the baseline scintigraphic and NOGA images and the local heterogeneously viable state of the myocardium in the treated areas.

The explanation of the significant improvement in the stress-induced defect in 8 patients in the placebo group remains unclear. This strong placebo effect, which has been seen previously in studies including no-option patients, might be explained by inflammation and scar formation after the NOGA procedure, an inflammatory reaction to the gene transfer vehicle, the special care and attention to no-option NOGA procedure, an inflammatory reaction to the gene transfer vehicle, the special care and attention to no-option patients included in a new therapy study, or the variability of the myocardial perfusion defects as discussed in the substudy of the Angina Treatments—Lasers and Normal Therapies in Comparison study.

Critique of the Method

The accuracy of the 3D NOGA unipolar voltage map depends on the number of sampling points and their distribution in 3D space. In the EUROIJECT-ONE study, the numbers of acquired points from the ROI in the VEGF and placebo groups were 18±1 and 22±5 (total mapping points 100±2 and 102±5, respectively), suggesting high accuracy. The determination of the apex of the left ventricle (as this point becomes the center of the polar map) is a crucial point for transfer of data from 3D to the polar map. The guiding of the NOGA catheter, however, is supported by fluoroscopy and contrast left ventriculography, methods that allow a highly accurate determination of the point representing the apex.

The reconstruction of the 3D NOGA map from the acquired x, y, and z coordinates and of the 2D polar map from the r and theta polar coordinates revealed minor differences from the original NOGA maps because of the additional algorithms of the original software for better visualization of the maps (eg, dependence of the 9- or 12-segment polar map analysis, different representations of the location, injection and diagnostic mapping points, etc). As we used the same reconstruction and analysis system for all patients, however, and as the locations of the injection points were similar to those for the original 3D NOGA map, systematic error can be excluded.

Further differences between the NOGA and scintigraphic polar maps might be caused by the different acquisition methods; records of endocardial mapping points are ECG-triggered, whereas nongated SPECT images reflect the tracer uptake averaged for the whole cardiac cycle.

Limitations

Enlargement of the polygonal ROI by 5% resulted in nonsignificant worsening, whereas enlargement by 20% resulted in a nonsignificant improvement of the defect severity (eg, exclusion or inclusion of more border zones), leading to opposite changes in sensitivity and specificity of the method. Further subanalyses will allow selection of the appropriate effective treatment area.

The present subanalysis focused on the perfusion defect severity, as the size of the treated area was constant between baseline and follow-up. As previously indicated, the usual visual and quantitative segmental analysis of the treated area considering the segmental changes in defect size might not be appropriate in a nonsegmental treatment mode. Accordingly, the global quantitative and global visual analyses of perfusion revealed only a trend toward improvement in stress-induced perfusion defect size in the VEGF group as compared with the placebo group. Further ongoing development of the presented method will permit an assessment of combined extent and severity of perfusion defect within the injected area after intramyocardial injection therapy.

In conclusion, the transformation algorithm for transfer of the NOGA-derived injected area to the scintigraphic images permits an exact evaluation of the myocardial perfusion in regions treated intramyocardially with angiogenic substances. Injections of phVEGF-A165 plasmid into a myocardial area with a reversible stress ischemia improve, but do not normalize, the stress-induced perfusion abnormalities.

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