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Department of Nuclear Medicine, Department of Cardiology
Medical University of Lublin

ANNA TARKOWSKA, WITOLD CHOLEWIŃSKI,
TERESA WIDOMSKA-CZEKAJSKA, BOGUSŁAW STEFANIAK,
EWA PONIATOWICZ-FRASUNEK, MAREK WYPYCH,
BEATA CHRAPKO

The influence of nitroglycerin on myocardial 99mTc-Tetrofosmin uptake defects in coronary artery disease

Nitroglycerin (Ntg) is known to increase blood flow to the hypoperfused myocardial area and thus to reduce regional ischaemia of the heart muscle in coronary artery disease (CAD) (2). The mechanisms responsible for this effect include dilatation of stenotic vessels and enhancement of collateral flow to the territories distant to, and supplied by, the occluded artery (6, 11). It has been shown that nitrates alter distribution of myocardial perfusion by preferential increase of blood flow to the ischaemic areas with no significant changes in the total blood flow through the heart muscle (6). The reduction of regional myocardial ischaemia after application of Ntg has been demonstrated in numerous observations by myocardial scintigraphy with 201Tl-Thallium chloride (2, 12). Based on these observations it has been suggested that myocardial perfusion imaging performed using 201TlCl in combination with Ntg administration can be useful for assessing myocardial viability (12). Similar reduction of radiotracer uptake defects after nitrate administration has been found in myocardial perfusion images obtained with such technetium labeled compounds as MIBI (12, 15), and Teboroxime (3).

Recently, the relatively newly developed perfusion agent 99mTc-Tetrofosmin has also been shown to be useful in detecting increase in regional coronary blood flow to the underperfused areas resulting from nitrate administration (5, 7, 17).

The aim of this study was to assess the effect of a therapeutic dose of Ntg on 99mTc-Tetrofosmin uptake defects occurring in patients with coronary artery disease (CAD) in myocardial SPECT at rest.

MATERIAL AND METHODS

STUDY POPULATION

Thirty-four patients (pts) (32 men and 2 women aged 41-70 years, mean 56.9 years), with angiographically confirmed coronary artery disease (CAD) were studied. All patients selected for the study had > 60% reduction in luminar diameter of at least one major coronary artery as defined by coronary angiography and at least one radiotracer uptake defect in myocardial scintigraphy at rest. There were 9 subjects with one-vessel disease, 13 with two-vessel disease and 12 with three-vessel disease. LVEF measured at rest by gated blood pool study (GBP) ranged from 10% to 71%, with an average value of 45.3% ± 18.0%. Using the same method, regional wall motion abnormalities (RWMA) were found in 24 patients, all of whom had hypokinesis and 8 of whom had, additionally, dyskinesis. In the remaining 10 subjects no pathologic changes in regional contraction were observed. Twenty-three patients had a history of myocardial infarction 5 months to 19 years (on average 4.8 ± 5.25 years) before the study. Ten subjects underwent revascularization procedures (7 pts PTCA, and 3 pts CABG) 3 months to 5 years (on average 1.2 ±1.5 years) prior to the examination. None of the patients had congestive heart failure nor arrhythmia resulting from atrial flutter or atrial fibrillation. The majority were symptomatic, presenting with episodes of angina.

Radionuclide studies were performed after withdrawal of all medications that influence myocardial perfusion, myocardial contractility and heart rate. All patients gave informed consent to the examinations.

STUDY PROTOCOL

All patients underwent myocardial perfusion SPECT at rest, using two-day protocol.

First day: Baseline SPECT examination

740 MBq (20 mCi) 99mTc-Tetrofosmin (Myoview, Nycomed Amersham) was injected intravenously as a bolus, at rest, after overnight fast. Myocardial SPECT was started 1 h. after injection and performed using a rotating, double head, large field of view gamma camera (Varicam, GE Medical Systems), connected to a dedicated computer (XPert, GE Medical Systems). Both of the detectors were equipped with low energy, all purpose, parallel hole collimators and positioned at an angle of 90^0 in relation to each other. Data were acquired in 60 projections, 30 s. each, by both detectors jointly (30 projections by each of them) in step-and-shoot mode over a 180^0 circular orbit modified by body contouring, from the 45^0 RAO to the 45^0 LPO view. The activity measurements were performed using gated technique, with the cardiac cycle divided into 8 sequences. A 20% symmetric energy window, centered on the 140 keV peak was used. Data were acquired with a zoom factor of 1.28 and stored in a 64 x 64 computer matrix. During data process-

ing, filtered back-projection was performed using a Butterworth filter with a cutoff frequency of 0.4 cycles/pixel, order 2.5, according to the recommendations of the manufacturer. Attenuation and scatter corrections were not applied. Sets of short axis (oblique), vertical long axis (sagittal) and horizontal long axis (coronal) tomograms as well as 3D cine presentation of the left ventricle (LV) were constructed as a result of the examination.

Second day: SPECT after Ntg administration

After overnight fast, the patient was given 0.5 mg Ntg (Nitroglycerinum, Unia, Poland) sublingually, and 5 min later, 740 MBq 99mTc-Tetrofosmin was injected intravenously, as a bolus, at rest conditions. Further procedures were performed according to the same protocol as that used in the baseline studies above.

Regional tracer uptake in corresponding slices of baseline and Ntg studies were assessed visually and compared by two independent observers. The 99mTc-Tetrofosmin myocardial distribution was classified as abnormal if one or more areas of decreased count density, manifested by a change in color scale, were visually identified by both independent observers in consensus in at least two consecutive slices obtained in at least two perpendicular axes: the short axis and one or both long axes. Additionally, the 3D left ventricular cine images and the polar maps were inspected to comparatively assess 99mTc-Tetrofosmin myocardial distribution in both examinations. Only those cases in which both observers were in agreement were included in the study. No quantitative approach was applied to measure the degree or size of the ischaemic areas at baseline conditions or their changes after Nitroglycerin administration. However, to check the correlation between uptake defect changes after Ntg and certain other parameters, a 3-point score system was applied, with arbitrarily selected values: 3 – for improvement of regional perfusion, 1 – for deterioration, and 2 – for no change. The tracer defects were located according to the anatomically defined areas of the left ventricular myocardium (walls of the left ventricle). No segmental subdivision of the myocardium was performed.

On the day directly preceding the baseline SPECT, each patient underwent GBP study at rest and from the data acquired both the global and the regional function of the left ventricle were measured. For better evaluation of local LV wall motion, GBP was performed in two projections: LAO (with individual detector angle selection) and left lateral. To assess contraction abnormalities, regional amplitudes and phases were calculated and displayed. Quantification of amplitude abnormalities was performed using the procedure by Weller et al. (18). By the above methods, RWMA were detected and located with respect to the same anatomically defined areas as those used to locate 99mTc-Tetrofosmin uptake defects and thus a direct comparison between these two phenomena was performed.

The changes in 99mTc-Tetrofosmin uptake defects after Ntg were compared with the results of coronary angiography. This comparison included definition of stenotic artery in question, its path, degree and location of lumen diameter stenosis on the one hand and

the localization of tracer uptake defect in the territory supplied by the above artery on the other.

Statistical analysis

For numerical data, mean values ±SD were calculated. Differences in the mean values were assessed by Student's t-test for unpaired data. Differences in frequency of the symptoms under study were evaluated using Mann-Whitney U test. Correlation analysis was applied to assess relationships between uptake defect changes after Ntg, defined using the three-point score system described above, and other parameters. In all statistical comparisons, probability values <0.05 were considered significant.

RESULTS

Myocardial SPECT images obtained at baseline conditions revealed altogether 78 99mTc-Tetrofosmin uptake defects in all 34 pts. One area with reduced tracer accumulation was found in 8 subjects, 2 areas in 14 subjects, and 3 or more areas in 12 cases. Areas with reduced tracer accumulation showed various localization in the left ventricular myocardium (Table 1), but in the majority of patients decreased Tetrofosmin uptake was observed in the posterior wall of the left ventricle. The most infrequent localization of this abnormality was the apical area of the myocardium.

Table 1. Localization of 99mTc-Tetrofosmin uptake defects at baseline conditions

LV area	n
Anterior	16
Apical	8
Lateral	12
Posterior	28
Inferior	14

n – number of patients, LV – left ventricle

After Ntg administration, decrease, no change and increase of 99mTc-Tetrofosmin uptake defects were observed (Table 2). Improved regional perfusion with increase of 99mTc-Tetrofosmin accumulation (Im) in SPECT images (Fig. 1) was observed in 33/78 (42.3%) uptake defects detected in 18/34 (52.9 %) subjects, but a complete normalization of tracer distribution was found in only one patient. This patient was a 41-year-old female with mild angina, one-vessel disease (DIA 1) diagnosed by coronary angiography, no history of MI nor any revascularization procedure, normal global as well as regional function of the LV, and singular tracer uptake defect in the anteroseptal area at baseline

Table 2. 99mTc-Tetrofosmin uptake defect changes (TUDC) induced by Ntg

TUDC		No of pts		No of defects	
		n	%	n	%
Total		34	100.0	78	100.0
Improvement (Im)		18	52.9	33	42.3
No change (NC)		7	20.6	29	37.2
Deterioration (De)		9	26.5	16	20.5
Significance	Im *vs* NC	$p < 0.01$		ns	
	Im *vs* De	$p < 0.05$		$p < 0.01$	
	NC *vs* De	ns		$p < 0.05$	

ns – not significant, vs – versus

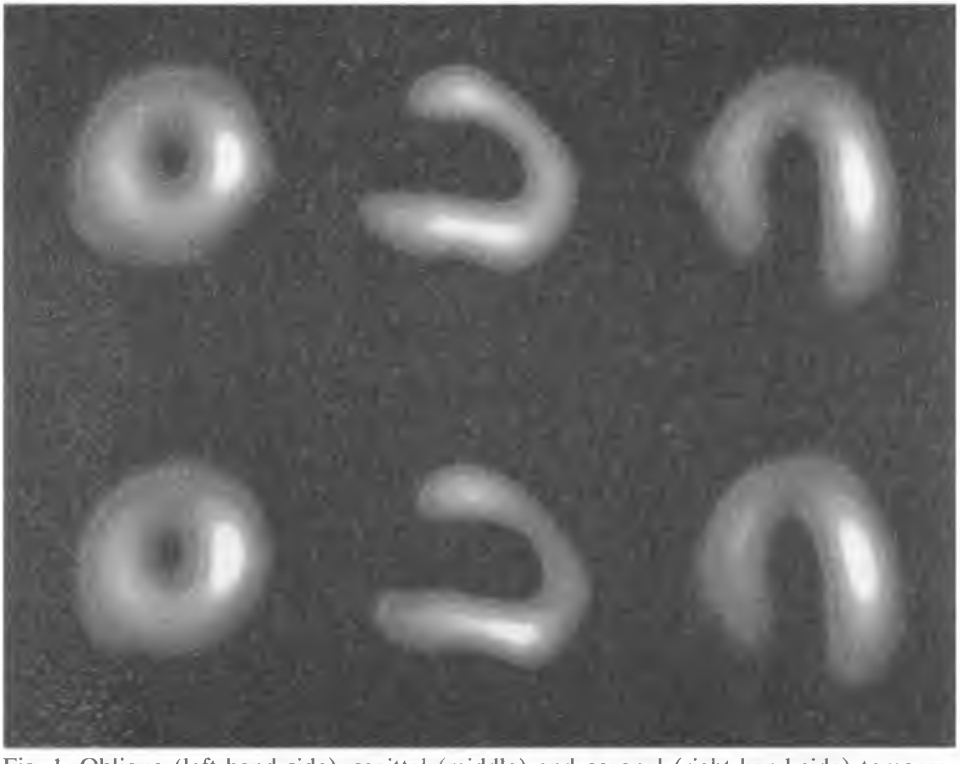

Fig. 1. Oblique (left-hand side), sagittal (middle) and coronal (right-hand side) tomographic slices in a patient with 99mTc-Tetrofosmin uptake defect in the anteroseptal area at baseline conditions (bottom row). Corresponding slices after Ntg (top row) show distinct improvement of tracer uptake, manifested as decrease of defect size and increased count density

conditions. Twenty-nine out of 78 (37.2%) defects in 7/34 (20.6 %) cases did not change after Ntg administration (NC) (Fig. 2). The remaining 16/78 (20.5%) uptake defects in 9/34 (26.5 %) patients showed worsening after Ntg administration (Dc), with increase in size and more expressed reduction of tracer accumulation (Fig. 3). In 3 of the subjects under study additional appearances of underperfused areas were found, which were not visible at baseline conditions. These were 42,- 54- and 70-year-old males, all of whom had three-vessel disease, and history of myocardial infarction. One of them underwent CABG 8 months prior to the study. LVEF was normal in 2 of these patients and decreased, with a value of 37%, in 1 patient. Two of these subjects had regional hypokinesis, in the third no local wall motion abnormalities were observed. In all of these the additional tracer uptake defect was localized in the posterior wall of the LV.

An improvement of regional perfusion was the most frequent reaction to Ntg in patients with one-vessel disease (6/9) and with two-vessel disease (8/13) (Fig. 4). In these subjects, increased reduction of tracer uptake was observed in 2/9 and in 1/13 cases, re-

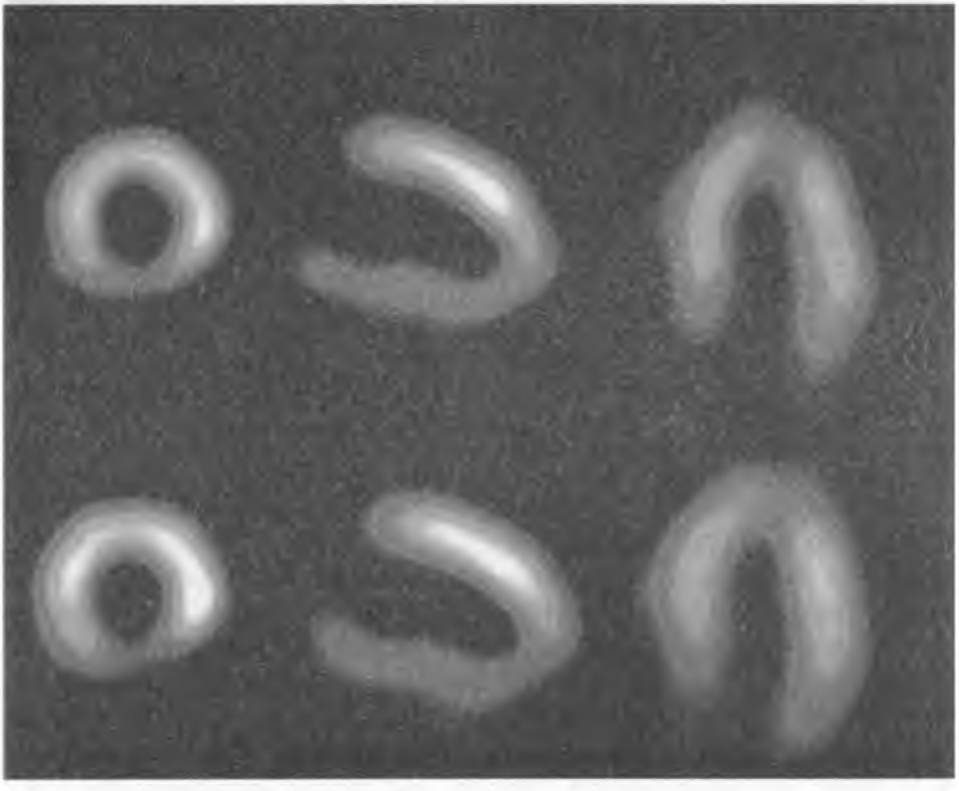

Fig. 2. Oblique (left-hand side), sagittal (middle) and coronal (right-hand side) tomographic slices in a patient with 99mTc-Tetrofosmin uptake defect in the posterior wall at baseline conditions (bottom row). Administration of Ntg did not induce any changes in myocardial tracer distribution (top row)

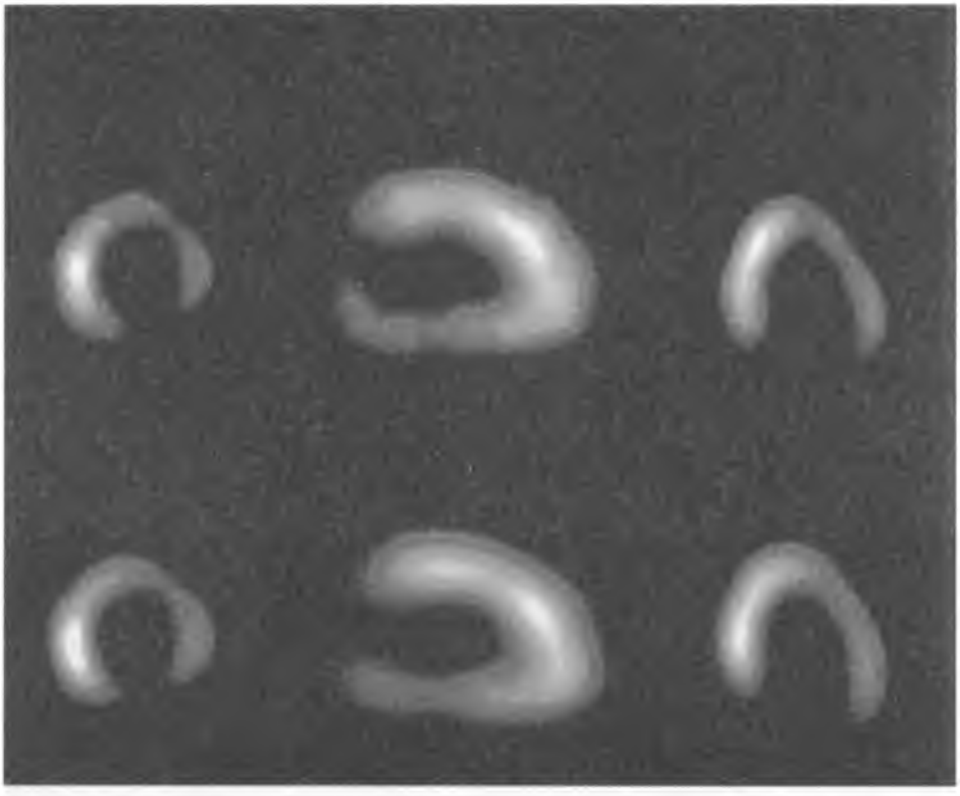

Fig. 3. Oblique (left-hand side), sagittal (middle) and coronal (right-hand side) tomographic slices in a patient with 99mTc-Tetrofosmin uptake defect in the postero-lateral area at baseline conditions (bottom row). Corresponding slices obtained after Ntg (top row) reveal deterioration of regional perfusion manifested as increase in defect size, more decreased count density, and appearance of a new hypoperfused area in the anterior wall

spectively. In subjects with three-vessel disease improved Tetrofosmin accumulation in underperfused areas was seen in 4/12 cases, which was less frequent than deterioration of regional blood flow (6/12). No change in tracer distribution after Ntg was observed more frequently in subjects with two-vessel disease (4/13 pts) than in those with one-vessel disease (1/9 pts) and with three-vessel disease (2/12 pts). Statistical comparison between the 3 subgroups constructed according to the above CAD subdivision revealed significantly more frequent deterioration of Tetrofosmin uptake defects in patients with three--vessel disease (6/12) than in those with two-vessel disease (1/13) ($P<0.02$). All the remaining differences in frequencies of the three observed reactions to Ntg, observed between patients with various numbers of involved main coronary arteries were statistically non-significant ($p>0.05$). Similarly, no significant relationships were found between changes in Tetrofosmin uptake after Ntg and the number of involved vessels, although this number, expressed as a quotient of stenotic arteries per patient, was the greatest in

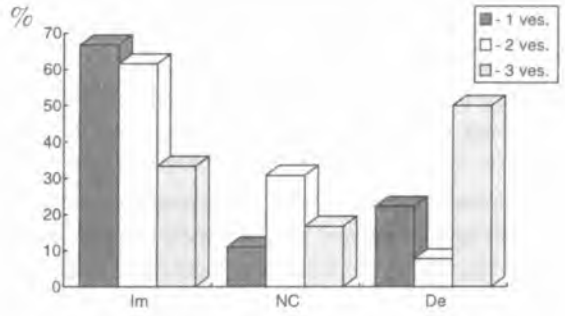

Fig. 4. Comparison of 99mTc Tetrofosmin uptake defect changes after Ntg in patients with one-vesel disease (red bars), two-vessel disease (blue bars), and three-vessel disease (yellow bars). Improvement of regional perfusion was the most frequent reaction to Ntg in pts with one- and two-vessel disease. In subjects with three-vessel disease deterioration of tracer uptake defect was observed most frequently. The frequencies of the defect changes were calculated as percentages of the total number of pts in each given subgroup and represented by the bar heights. Im = improvement of tracer uptake, NC = no change, De = deterioration of regional perfusion defect

Table 3. Relationship between 99mTc-Tetrofosmin uptake defect changes (TUDC) and number of involved vessels

TUDC	No of patients	No of involved vessels	No of involved vessels / pts	
			$\bar{x}$	SD
Total	34	71	2.08	0.78
Im	18	34	1.94	0.70
NC	7	15	2.14	0.63
De	9	22	2.44	0.83
Significance		Im *vs* NC	ns	
		Im *vs* De	ns	
		NC *vs* De	ns	

Im – improvement, NC – no change, De – deterioration, ns – not significant, x – mean, SD – standard deviation, vs – versus

cases with deterioration and the smallest in those with improvement (Table 3). Also, no statistically significant relationship existed between reaction of regional Tetrofosmin distribution to Ntg administration and the degree of coronary artery stenosis. An analysis performed after dividing the clinical material into 3 subgroups, according to the narrowing of the luminal diameter of stenotic vessels of, respectively, $\leq$ 79%, 80%-89%, and $\geq$ 90%, revealed that in each of these subgroups frequencies of improvement, no change and deterioration were similar, but with slightly more frequent improvement in patients

with coronary artery stenosis ≤ 79% and slightly more frequent deterioration in subjects with stenosis 80%–89% than in the other subgroups (Fig. 5).

The comparison between patients with previous MI and those without history of this complication also revealed no significant differences in reaction of Tetrofosmin uptake defects to Ntg (Fig. 6).

An analysis of the relationship between LV global function on the one hand and effect of Ntg on Tetrofosmin uptake defects on the other, showed slightly higher LVEF values in subjects with De than in pts with Im but these differences were not significant

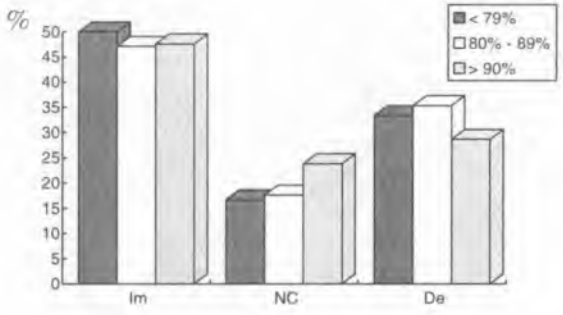

Fig. 5. Comparison of 99mTc-Tetrofosmin uptake defect changes after Ntg in pts with coronary artery lumen diameter stenosis ≤ 79% (green bars), 80%-89% (yellow bars), and ≥ 90% (red bars). Improvement of regional perfusion after Ntg was observed in the majority of pts in each of the above three subgroups. Frequencies of improvement, no change and deterioration were similar in these subgroups. Im=improvement of tracer uptake; NC = no change; De = deterioration of regional perfusion defect

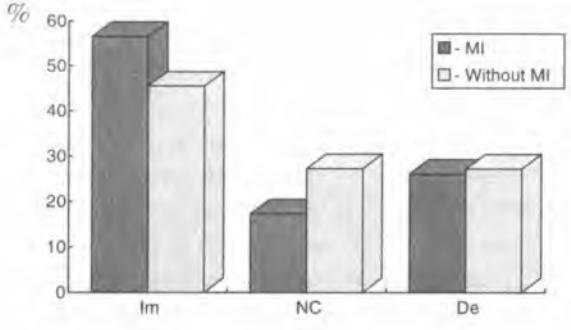

Fig. 6. Comparison of 99mTc-Tetrofosmin uptake defect changes after Ntg administration in pts with and without history of myocardial infarction (MI). Improvement (Im) of regional perfusion after Ntg was somewhat more frequent in subjects with MI (blue bars) than in those wthout MI (red bars). Deterioration (De) occurred in both subgroups with very similar frequency. No change (NC) in tracer uptake defects was slightly more frequent in pts with MI than in those without MI

Table 4. Relationship between LVEF at baseline conditions and 99mTc-Tetrofosmin uptake defect changes (TUDC)

TUDC	Total	LVEF	
	n	$\bar{x}$	SD
Total	34	45.3	17.9
Im	18	43.6	19.1
NC	7	45.6	13.9
De	9	48.2	19.7
Significance			
Im *vs* NC		ns	
Im *vs* De		ns	
NC *vs* De		ns	

Im – improvement, NC – no change, De – deterioration, ns – not significant, $\bar{x}$ – mean, SD – standard deviation, vs – versus

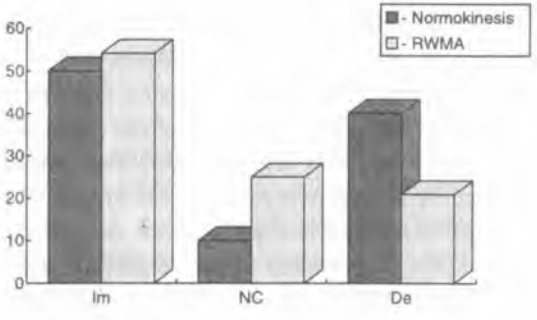

Fig. 7. Comparison of 99mTc-Tetrofosmin uptake defect changes after Ntg in pts with normokinesis (red bars) and in those with RWMA (green bars). Improvement (Im) or no change (NC) of regional perfusion were more frequent and deterioration (De) more scarce in subjects with RWMA than in the other subgroup

(Table 4). There were also no significant differences in reaction to Ntg between patients with normokinesis and those with RWMA but in subjects with RWMA improvement or no change of regional perfusion were observed more frequently and deterioration more rarely than in the other subgroup (Fig. 7).

DISCUSSION

Tetrofosmin is a lipophilic cationic diphosphine which labelled with Technetium 99mTc has been developed for myocardial perfusion imaging (13). It has been demonstrated that distribution of 99mTc-Tetrofosmin in the heart muscle is proportional to the blood flow (16), and that regional uptake defects of this tracer are related to the severity of coronary artery stenosis (4, 16).

The results obtained by Glover et al. (10) in experimental studies performed in canine models indicate that the myocardial uptake of 99m-Tetrofosmin is dependent not only on blood flow but on myocyte viability as well.

Recently, several observations have been reported showing that administration of nitrates prior to 99mTc-Tetrofosmin injection enhances the detection of perfusion defect reversibility (5, 7) and that resulting increase in the radiotracer uptake is in good agreement with improvement of LV global and regional function (7, 17). Moreover, it has been demonstrated that nitrate – Tetrofosmin SPECT may be useful in predicting reversibility of regional wall motion abnormalities after successful revascularization (8). In connection with the above findings it has been suggested that perfusion imaging with 99mTc-Tetrofosmin in combination with nitrates may be useful for identification of myocardial viability (4, 5, 17) similarly to the application of nitrates with Thallium (5, 12, 17).

In this study the test group comprised 34 pts with CAD showing various degrees of perfusion abnormalities and various LV function conditions.

Only visual assessments of tracer uptake defects were performed in this study without applying any quantitative approach to determine myocardial count density distribution at baseline conditions and its changes after ntg administration. Despite some limitations, this procedure, if performed by an experienced team, has proved to yield reliable results (1), which are comparable to those obtained using various methods of data quantification.

In this study 33/78 (42.3%) Tetrofosmin uptake defects in 18/34 (52.9%) subjects showed improvement after Ntg administration, 29/78 (37.2%) defects in 7/34 (20.6%) patients had no change, and 16/78 (20.5%) in 9/34 (26.5%) cases showed deterioration. The first two findings, indicating improvement or no change in Tetrofosmin distribution, agree with results obtained by some other authors (4, 7, 17).

Deterioration of regional Tetrofosmin uptake after Ntg, observed in this study in 9/34 subjects is a somewhat unusual finding. Similar changes were reported also by Flotats et al. (7), who found a worsening of tracer uptake in 6/73 (8%) myocardial segments with severely reduced baseline Tetrofosmin uptake, as well as by Maurea et al. in a study with 99mTc-SESTAMIBI imaging after Ntg (15). But none of these authors payed any particular attention to these findings.

The mechanisms responsible for this phenomenon are not clear. As previously mentioned, nitrate administration is known to increase coronary blood flow by dilating the stenotic vessels and enhancing collateral flow distal to the occluded coronary artery (2, 6, 11). However, based on observations by Ganz et al. (9) and Liu et al. (14) it might be

presumed that the worsening of Tetrofosmin uptake defects observed in this study may result from inadequate or even from lack of dilatation of the stenotic vessels due, for example, to abnormal metabolism of the ischaemic tissue. As another factor one may consider insufficiently developed collateral circulation distal to the occluded coronary artery (12). Finally, it is possible that sometimes the nitrate effect may be greater in adjacent territories, resulting in a relative decrease in regional uptake in underperfused areas (7).

In our study no explicit relationship was found between 99mTc-Tetrofosmin uptake changes after Ntg administration on the one hand and the number of narrowed vessels and degree of coronary artery stenosis detected by coronary angiography, history of myocardial infarction nor left ventricular function on the other. Despite the absence of statistical confirmation, the obtained results might to some degree suggest a tendency indicating that improvement of regional perfusion defects after Ntg occurs predominantly in patients with lower numbers of involved vessels, and more impaired LV contractility. Ntg-augmented improvement of 99mTc-Tetrofosmin uptake in underperfused areas in subjects with regional wall motion abnormalities of the left ventricle at baseline was observed also by Flotats et al. (7). On the other hand, Ntg induced deterioration of regional Tetrofosmin uptake might be considered to occur predominantly in patients with higher numbers of stenotic vessels (those with three-vessel disease first of all), narrowing of coronary artery lumen diameter $\leq$ 89%, and relatively good LV function. However, the results of assessment of the relationships between Ntg-induced changes in Tetrofosmin uptake defects and condition of left ventricular perfusion and function should be considered with caution – firstly because the observed tendencies are weak, and secondly – because the relatively small numbers of patients in the subgroups (created according to perfusion and functional conditions of the LV) could influence the statistical comparisons between them. Hence, the above suggestions should be verified on a larger study population. Further studies are necessary to identify mechanisms responsible for different reactions of ischaemic myocardium to nitrate administration and thus to evaluate whether some still unknown factors do not influence the value of 99mTc-Tetrofosmin SPECT with Ntg in assessing myocardial viability.

CONCLUSIONS

1. Sublingual administration of Ntg may result in improvement as well as in deterioration of regional perfusion defects, assessed with 99mTc-Tetrofosmin in CAD.

2. The relationships between changes in uptake defects of this tracer on the one hand and conditions of LV function and severity of heart muscle perfusion abnormalities on the other are unclear and should be verified on a larger study population.

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SUMMARY

Nitroglycerin (Ntg) is known to increase blood flow to the hypoperfused myocardial area and thus to reduce regional ischaemia of the heart muscle in coronary artery disease (CAD). The aim of this study was to assess the effect of a therapeutic dose of Ntg on 99mTc-Tetrofosmin uptake defects occurring in patients (pts) with CAD in myocardial SPECT at rest. The study population comprised 34 pts with CAD. All subjects underwent myocardial perfusion SPECT at rest, using 2-day, protocol. On the first day 99mTc-Tetrofosmin was injected in baseline conditions and on the second day, after sublingual administration of 0.5mg Ntg. The baseline examination revealed altogether 78 Tetrofosmin uptake defects in all 34 pts. The SPECT after Ntg showed improved tracer uptake in 33/78 perfusion defects in 18/34 pts, no change in 29/78 defects in 7/34 cases and more reduced tracer uptake in 16/78 defects in 9/34 pts. No explicit, significant relationship was found between 99mTc-Tetrofosmin uptake changes after Ntg on the one hand and the number of involved vessels, degree of coronary artery stenosis, history of myocardial infarction and LV global and regional function on the other. It is concluded that sublinqual administration of Ntg may result in improvement as well as in deterioration of regional perfusion defects, assessed with 99mTc-Tetrofosmin in CAD. The relationships between Ntg-augmented changes in uptake defects of this tracer on the one hand and conditions of the LV function and severity of heart muscle perfusion abnormalities on the other are unclear and should be verified on a larger study population.

Wpływ nitrogliceryny na regionalne zaburzenia wychwytu 99mTc-Tetrofosminy w chorobie niedokrwiennej serca

Znanym działaniem nitrogliceryny jest zwiększanie przepływu krwi w niedokrwionych obszarach miokardium i przez to zmniejszanie regionalnej ischemii u pacjentów z chorobą wieńcową. Celem pracy była ocena wpływu terapeutycznej dawki nitrogliceryny na zaburzenia akumulacji 99mTc-Tetrofosminy w mięśniu serca w spoczynkowym badaniu perfuzji, wykonanym techniką SPECT. Badania przeprowadzono u 34 pacjentów z potwierdzoną chorobą niedokrwienną serca. U wszystkich badanych scyntygrafię perfuzyjną mięśnia serca techniką SPECT wykonano protokołem dwudniowym w spoczynku. Pierwszego dnia iniekcję 99mTc-Tetrofosminy wykonano w warunkach podstawowych, drugiego dnia – po podjęzykowym podaniu 0.5 mg nitrogliceryny. Badanie w warunkach podstawowych uwidoczniło łącznie 78 defektów perfuzji u wszystkich 34 pacjentów. W pomiarze po podaniu nitrogliceryny poprawę perfuzji stwierdzono w 33/78 obszarach u 18/35 pacjentów, brak istotnych zmian w 29/78 obszarach u 7/34 pacjentów oraz pogorszenie w 16/78 obszarach u 9/34 osób. Stwierdzono istotną zależność pomiędzy kierunkiem zmian perfuzji po podaniu nitrogliceryny z jednej strony a ilością zajętych naczyń, wielkością zwężenia naczynia, przebytym zawałem serca oraz globalną i regionalną funkcją komory lewej – z drugiej. Na podstawie uzyskanych wyników można stwierdzić, że u pacjentów z chorobą wieńcową podjęzykowe podanie nitrogliceryny może powodować zarówno zmniejszenie, jak i nasilenie regionalnych zaburzeń perfuzji, ocenianych techniką SPECT przy użyciu 99mTc-Tetrofosminy. Zależności pomiędzy zmianami perfuzji pod wpływem nitrogliceryny z jednej strony a stopniem upośledzenia funkcji i perfuzji z drugiej pozostają niejasne i wymagają weryfikacji na większym materiale klinicznym.