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Radionuclide assessment of lower limb perfusion using ^{99m}Tc-MIBI in early stages of atherosclerosis

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Abstract

BACKGROUND: The aim of the work was a scintigraphic evaluation of regional blood supply of thigh and calf muscles using ^{99m}Tc-MIBI as a radiopharmaceutical, in early stages of atherosclerosis revealed during ultrasonographic examination of lower limbs, in patients without typical clinical symptoms of chronic ischaemia of lower limbs and with preserved normal Doppler spectrum of blood flow. Moreover, basic relations between early signs of lower limb atherosclerosis and abnormal myocardial perfusion, as well as asymptomatic hypoperfusion of lower limbs, were analysed.

MATERIAL AND METHODS: Stress and rest radionuclide study of lower limb muscles and myocardium using ^{99m}Tc-MIBI was performed in 47 men, who were divided into two groups based on ultrasonography results. The first group (group I) comprised 22 patients with early atherosclerotic changes in peripheral vessels and the second (group II) comprised 25 people with normal arteries. For the purposes of quantification of study results normal values of regional blood supply and indices of asymmetry at levels of thighs and calves, as proposed by Segall et al., were applied. Myocardial scintigrams were evaluated according to widely accepted rules (visual and semi quantitative — normative analysis).

RESULTS: Mean values of stress and rest perfusion indices of thighs as well as calves in gr. I were statistically significantly lower ($p < 0.001$) than in gr. II. Incidence of asymmetry in the stress perfusion of calves and thighs was statistically significantly higher ($p = 0.04$) in patients with atherosclerotic changes as compared with the control group. Abnormal myocardial perfusion was found in 77% of patients from group I and in 28% from group II ($p = 0.001$). Reversible, stress induced ischaemia was found in 59% and 16%, resp. ($p = 0.01$).

CONCLUSIONS: 1. Radionuclide study revealed a reduced stress as well as rest perfusion of lower limb muscles in clinically asymptomatic patients with atherosclerotic changes of lower limb vessels of low degree and a preserved normal Doppler blood flow spectrum. 2. Presence of early atherosclerotic changes in lower limb vessels implies a higher probability of asymptomatic hypoperfusion of lower limbs as well as coronary artery disease.

Key words: chronic hypoperfusion of lower limbs, atherosclerosis, perfusion scintigraphy of lower limbs, ^{99m}Tc-MIBI

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Introduction

The intensive development of high frequency ultrasonography has enabled detection of slightly advanced atherosclerotic changes in walls of superficial arteries of limbs and neck. Communications based on clinical and sectional studies confirm a higher intensity of atherosclerosis in patients with documented coronary artery disease or/and chronic hypoperfusion of lower limbs in comparison with people without symptoms of that disease. Advancement of atherosclerotic changes in peripheral arteries accessible to ultrasonographic studies is a good indicator of the

intensity of this disease in the whole circulation system and therefore can indirectly provide evidence of the condition of arteries practically inaccessible to non-invasive morphological examinations, i.e. calf vessels or distal parts of coronary arteries [1–5]. Only several communications on the effects of early atherosclerotic changes on the perfusion of organs and tissues are available at present. Scintigraphic studies using radionuclide labelled complexes — radiopharmaceuticals - enable such analysis. The aim of this work was the scintigraphic evaluation of perfusion of thigh and calf muscles using ^{99m}Tc-MIBI as the radiopharmaceutical, in early stages of atherosclerosis revealed in arteries of lower limbs by means of ultrasonography, in patients without typical clinical symptoms of chronic hypoperfusion of lower limbs and with normal Doppler blood flow spectra.

This work also tries to determine the relationship between early, asymptomatic stages of atherosclerosis of lower limbs and perfusion of left ventricular myocardium as well as asymptomatic hypoperfusion of lower limbs.

Material and methods

The study was carried out in 47 men with confirmed (11 patients) or suspected (36 patients) coronary artery disease, referred to have a myocardial perfusion study, who agreed to be additionally subjected to ultrasonography of lower limb arteries and imaging of distribution of the radiopharmaceutical in the whole body. The group included only patients with preserved foot pulse, a normal biphasal blood flow in Doppler ultrasonography and normal rest values of ankle-brachial index.

Typical symptoms of hypoperfusion of lower limbs were found in none of the studied patients.

Ultrasonography

Ultrasonographic study of lower limbs was carried out using an HDI 3000 device with a colour Doppler blood flow facility.

Patients were divided into two groups on the basis of presence or absence of atherosclerotic changes in femoral (common and superficial) and popliteal arteries. Group I consisted of 22 patients, in whose lower limb arteries several (two or more) atherosclerotic plaques or calcifications in walls of arteries, of total length not shorter than 10 cm (at least in one limb) were detected.

Group II (control) comprised 25 individuals without atherosclerotic changes in arteries of lower limbs, accessible to ultrasonography.

Exercise study protocol

All patients were subjected to a stress treadmill test according to a Bruce protocol. ECG, blood pressure and heart rate were continuously monitored. Stress test was finished when a maximum heart rate limit was attained or substantial fatigue or coronary pain were noted. Lower limb pain did not occur in any of the patients.

Radionuclide study of lower limbs

A complex of ^{99m}TC-MIBI was administered intravenously at a dose of 740–1110 MBq. A two-day study protocol was applied, typical for a stress — rest heart perfusion study. For the first time, radiopharmaceutical (Rph) was administered during a stress treadmill test when a maximum heart rate limit was attained. The patient continued walking for about 1 min. A rest lower limb examination was performed 3 days later. In both studies acquisition began 10 minutes after injection of Rph, using a VariCam gamma camera (Elscint, Haifa, Israel). Whole body scintigrams were acquired in posterior projection. Scan speed and acquisition time were 20 cm/min and 10 min, respectively; 1.5–2 million counts were collected.

In order to assess distribution of the Rph quantitatively, first regions of interest were drawn on scintigrams, containing whole body image, site of injection, thighs and calves. Next, indices of stress (I_s) and rest (I_r) perfusion were calculated as ratios of total counts in respective regions of interest and counts in the whole body image (after subtraction of the part of counts originating from the site of injection).

A stress perfusion symmetry was evaluated by comparison (ratio) of counts collected in left and right limb regions (I_{sym} — index of symmetry). Normal ranges (between 0.9 and 1.1) proposed by Segall et al [6] were applied.

Radionuclide myocardial perfusion study

A SPECT study was performed in the supine position 40-60 min after injection of Rph, using a dual-head gamma camera VariCam (Elscint, Haifa, Israel) equipped with a low energy high resolution collimator. Myocardial scintigrams were evaluated according to widely accepted rules (visual and semiquantitative — normative analysis).as normal or abnormal — presenting permanent or reversible perfusion abnormalities. Scintigram analysis was made by two experienced physicians and a final result was reached by consensus.

Statistical analysis

Comparison of distribution of quantitative variables was made with a non-parametric Mann-Whitney test.

For analysis of associations between qualitative variables a χ^2 test of independence for contingency tables was applied. Relations between quantitative variables were evaluated with Pearson's correlation coefficient.

For the assessment of 2 factors interaction a multi-way analysis of variance was used.

In all calculations differences were considered statistically significant for $p \leq 0.05$.

All the calculations were made by means of a Statistica 5.0 software package.

Results

Both patient groups were homogeneous with respect to age, incidence of hypertension, diabetes of type II, elevated lipids level and smoking of cigarettes. The only statistically significant difference between both groups was noted in distribution of body mass index, which was higher in the control group.

Parameters of distributions of demographic and clinical data in both patient groups are presented in Table 1.

Since in both groups body mass index was the only variable differing significantly, its possible effect on perfusion indices has been analyzed. Two-factor analysis of variance was applied for the purpose of comparison of stress perfusion indices, assuming

Table 1. Distribution parameters of demographic and clinical data in patients with atherosclerotic changes (group I) and a control group (group II) along with significance level of inter-group differences

	Group I	Group II	Significance level
Number of patients	22	25	
Age (mean ± SD)	53.5 ± 4.0	51.0 ± 5.0	NS (0.08)
BMI (mean ± SD)	27.0 ± 2.6	29.1 ± 3.0	0.02
Number of patients with arterial hypertension	10 (45%)	13 (52%)	NS (0.6)
Number of diabetic patients	3 (14%)	3 (12%)	NS (0.9)
Number of patients with history of myocardial infarction	7 (32%)	4 (16%)	NS (0.1)
Number of patients with hyperlipidaemia	9 (41%)	14 (56%)	NS (0.3)
Number of patients cigarette smokers	11 (50%)	10 (40%)	NS (0.5)

SD — standard deviation; NS — non-significant; BMI — body mass index

Table 2. Distribution parameters of lower limb regional perfusion indices and incidence of myocardial perfusion abnormalities in patients with atherosclerotic changes (group I) and control group (group II) along with significance level of inter-group differences

	Group I	Group II	Significance level
Number of patients	22	25	
I_s calf (mean ± SD)	5.8 ± 0.8	6.8 ± 0.7	$p < 0.0001$
I_r calf (mean ± SD)	3.0 ± 8.4	4.1 ± 1.1	$p < 0.0001$
I_s thigh (mean ± SD)	6.4 ± 1.2	7.4 ± 0.9	$p < 0.0001$
I_r thigh (mean ± SD)	4.2 ± 1.1	5.4 ± 1.1	$p < 0.0001$
Stress loading in MET (mean ± SD)	10.3 ± 2.3	12.1 ± 2.1	$p < 0.004$
Incidence of abnormal I_{sym} in stress study (calf or thigh)	7 (32%)	2 (8%)	$p = 0.04$
Incidence of myocardial perfusion abnormalities	17 (77%)	7 (28%)	$p = 0.001$
Incidence of stress induced myocardial perfusion abnormalities	13 (59%)	4 (16%)	$p = 0.01$

I_s — index of stress perfusion; I_r — index of rest perfusion; I_{sym} — index of perfusion symmetry; SD — standard deviation; NS — non-significant

adherence to particular group and body mass index as differing factors (with BMI ≤ 30 as a limit value).

The analysis confirmed the significance of the difference between mean perfusion indices in both patient groups ($p < 0.0001$) and did not reveal any interaction between adherence to a particular group and the value of BMI ($p = 0.4$). This result excludes any effect of a higher BMI in the control group on perfusion indices.

Although mean stress loading in the control group was significantly ($p < 0.004$) higher (Table 2), parameters a of stress test, according to Segall et al [6], may significantly affect perfusion of lower limb muscles only when the duration of the test is less than 2 minutes (so stress loading is very low). In our study all patients were subjected to a stress test lasting at least 6 minutes.

Statistical analysis of results obtained by means of quantification of lower limbs perfusion scintigrams (Table 2) showed that in the group of patients with atherosclerotic changes mean values of stress and rest perfusion indices of thighs as well as calves were statistically significantly lower ($p < 0.001$) than in the control group. Incidence of asymmetry (according to criteria proposed by Segall et al [6]) in the stress perfusion of calves and thighs was statistically significantly higher ($p = 0.04$) in patients with atherosclerotic changes as compared with the control group.

Abnormal myocardial perfusion was found in 77% of patients from group I and in 28% from group II ($p = 0.001$). Reversible, stress induced myocardial uptake defect, typical for ischaemia, was found in 59% and 16%, respectively ($p = 0.01$).

Detailed analysis of the results is presented in Table 2.

Discussion

Doppler ultrasonography is the gold standard used in diagnosis of persistent hypoperfusion of lower limbs. It provides information about vessel morphology complemented with analysis of blood flow velocity curve. Abnormalities of blood flow curve revealing significant limb hypoperfusion usually appear in the stage of significant loss of vascular patency. This is why patients with atherosclerotic vascular changes and a normal blood flow spectrum can be met in a clinical practice. Perfusion scintigraphy of skeletal muscles enables evaluation of lower limb perfusion at the level of a micro-circulation (in fact at a cellular level). Several communications on its practical use in diagnosis of chronic hypoperfusion of lower limbs as well as in the assessment of effectiveness of therapy are available [7–12].

A few methods of quantitative assessment of scintigraphic study have been proposed [13–15]. In this work we applied our own modification of a method presented by Hamanaka et al [16] based on the calculation of regional indices of perfusion. However, Segall et al [6] revealed the effect of such factors as sex, age, stress loading (only when duration of a stress test is shorter than 2 minutes) and body mass on the results of the study, so those parameters of a control group should not differ from a studied group of patients. In our work only men within a relatively narrow age range were studied and mean values of age in both groups were close to each other. Although mean stress loading was statistically significantly higher in the control group ($p < 0.004$), pa-

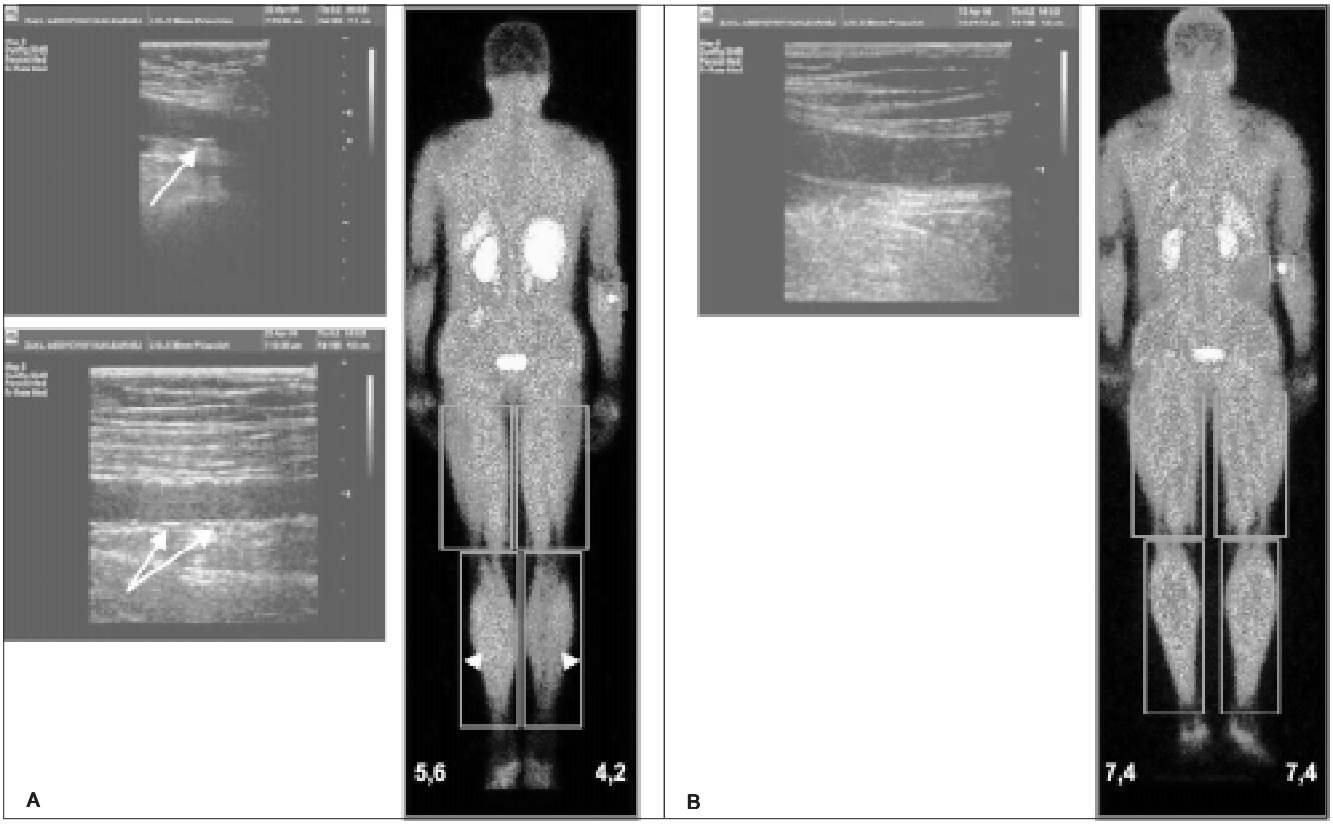

Figure 1A. Whole body scintigrams with regions of interest and ultrasonographic images of a femoral superficial artery with (group I) atherosclerotic changes; **B.** Whole body scintigrams with regions of interest and ultrasonographic images of a femoral superficial artery without atherosclerotic changes; long arrows show calcifications and atherosclerotic plaque in intima-media of artery. Short arrows — asymmetry in Rph uptake in calf muscles. Values of stress perfusion indices are shown at the bottom of scintigrams.

rameters a of stress test, according to Segall et al. [6], may significantly affect perfusion of lower limb muscles only when the duration of the test is less than 2 minutes (so stress loading is very low). In our study all patients were subjected to a stress test lasting at least 6 minutes, so higher stress loading in the control group could not have affected study results. The only parameter that differed significantly in both studied groups was body mass index. However, its effect on study results has been excluded, so a comparison of results has in fact been carried out in homogeneous patient groups that differed only with respect to the presence or absence of morphological atherosclerotic changes in ultrasonography, a factor deciding upon inclusion to a particular group.

Circulatory insufficiency or diseases leading to the atrophy of muscles (neurological or muscle-skeletal system disorders) that might affect study results were not diagnosed in any of the patients.

Although in ultrasonography no abnormalities have been observed, in a Doppler blood flow spectrum, in patients with low advancement of atherosclerotic changes, statistically significantly lower radiopharmaceutical uptake in thighs and calves have been found in scintigraphy, pointing to a lower perfusion of those regions. Damage to micro-circulation as a result or dysfunction of arterial endothelium and/or myocyte metabolism abnormalities are plausible causes of this phenomenon. These factors affect uptake of ^{99m}Tc-MIBI in myocyte cytoplasm and mitochondria through the change of their cell membrane potential [19].

In muscles of patients with chronic hypoperfusion of lower limbs Brass et al [20] and Bauer et al [21], analysing results of biopsy and magnetic resonance spectroscopy, found metabolic abnormalities referred to as acquired muscle myopathy, manifesting themselves with altered expressions of mitochondrial enzymes, increased accumulation of metabolic intermediates, higher incidence of mitochondrial DNA mutations, altered regulation of mitochondrial respiration and a lowered desaturation of haemoglobin in muscles. Pellegrini et al. [22] showed that the intensity of arterial endothelium dysfunction correlated with myocardial uptake of ^{99m}Tc-MIBI and restrained coronary flow reserve. Moreover, a lower uptake of the complex has been observed in patients with endothelium dysfunction in the course of hypertension or hyperlipidaemia [23]. However, the effect of both specified factors on ^{99m}Tc-MIBI uptake has not yet been fully clarified.

The present work confirmed observations made by Duet et al [10] and Tellier et al [12] concerning a potential usefulness of scintigraphy in the diagnosis of chronic hypoperfusion of lower limbs. This study revealed perfusion abnormalities earlier than a Doppler blood flow ultrasonography. The work should be continued aiming at clinical application of the method.

Siegel et al [24] proposed application of indices of symmetry of radiopharmaceutical uptake in calves and muscles. Comparing results of patients with arteriographically documented chronic hypoperfusion of lower limbs with the control group, the authors

determined the sensitivity and specificity of scintigraphy, which were 81% and 80%, respectively. Results of our earlier study also confirmed a diagnostic usefulness of stress indices of symmetry of ^{99m}Tc-MIBI uptake in muscles of lower limbs [8].

Several communications present similar normal ranges of this index. Cosson et al [25], applying those normal values, revealed a hypoperfusion in 42% of asymptomatic diabetic patients with abnormal lipid level in blood plasma, and Tellier et al — in 60% of also asymptomatic patients with coronary artery disease [26]. Our present study disclosed an unfavourable effect of early stages of atherosclerosis on muscle perfusion. Incidence of asymmetry (according to criteria proposed by Segall et al [6]) in the stress perfusion of calves and thighs was statistically significantly higher in patients with atherosclerotic changes compared with the control group.

Ultrasonography still remains the basic tool in the diagnosis of a chronic hypoperfusion of lower limbs. At present several methods of ultrasonographic assessment of atherosclerosis intensity are available. Practical applications of quantitative methods based on measurement of artery intima-media thickness are limited because of their insufficient precision and variability of the parameter among individuals. This is why, in the present work, a much simpler qualitative criterion based on the presence or absence of atherosclerotic changes in vessel walls has been used [27, 28].

In the present work we showed that detection of early atherosclerotic changes in ultrasonography such as plaques or calcifications in vessel walls implies, in spite of a still normal Doppler blood flow spectrum, not only lower limb hypoperfusion, but also, in patients with suspected or confirmed coronary artery disease, a higher incidence of regional myocardial perfusion abnormalities. This is especially true for stress induced myocardial hypoperfusion, which is prognostically unfavourable. This finding implies that ultrasonographic detection of even small atherosclerotic changes in walls of peripheral vessels of lower limbs should be treated as a warning signal for the intensification of diagnostic effort toward the detection of coronary artery disease as well as prevention of chronic hypoperfusion of the lower limbs. The low cost of ultrasonographic study, its high availability, non-invasiveness as well as simple criteria for evaluation of the extent of atherosclerotic changes justify a wider application of the method in the diagnosis of the advancement of atherosclerosis.

Conclusions

1. Radionuclide study revealed a reduced stress as well as rest perfusion of lower limb muscles in clinically asymptomatic patients with atherosclerotic changes of lower limb vessels of low degree and a preserved normal Doppler blood flow spectrum.
2. Presence of early atherosclerotic changes in lower limb vessels implies a higher probability of asymptomatic hypoperfusion of lower limbs as well as of coronary artery disease.

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