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Radionuclide Patterns of Ischemia in Acute Occlusive Diseases of Main Arteries of Lower Extremities

N.Y. Kudryashova*, O.G. Sinyakova, I.P. Mikhaylov, E.V. Migunova, O.V. Leshchinskaya

Department of Diagnostic Radiology
N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Healthcare Department
3 Bolshaya Sukharevskaya Square, Moscow 129090, Russian Federation

*** Contacts:** Natalia Y. Kudryashova, Dr. Med. Sci., Chief Researcher of the Department of Diagnostic Radiology, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department. Email: numedsklif@mail.ru

RELEVANCE The problem of diagnosing and treating patients with acute ischemia of the extremities against the background of thrombosis and atherosclerotic lesions of the main arteries remains very complex task and requires the use of various diagnostic methods, and the leading one is radiation diagnostics.
THE AIM OF THE STUDY. The development of radionuclide patterns of acute lower limb ischemia and assessment of the treatment efficacy in angiosurgical patients using three-phase scintigraphy.
Material and methods The radionuclide method was performed to examine 264 patients with acute thrombosis of the main arteries against the background of atherosclerotic lesions of the lower extremities arteries and clinical signs of acute ischemia of the lower extremities of I-III degree according to the classification of I.I. Zatevakhin.
RESULTS We defined quantitative and visual signs of acute ischemia, designed radionuclide semiotics, which allowed to detail the damaged tissue of lower extremities and evaluate the efficacy of the conservative or surgical treatment. The study contains clinical examples of patients with varying degrees of acute limb ischemia.
CONCLUSION The developed radionuclide patterns of acute ischemia in thrombosis of main arteries of the lower extremities allowed to determine the level of arterial occlusion and the degree of acute ischemia, identify the areas of lack of blood supply and necrosis with no clinical signs at an early stage of formation and optimize the treatment strategy.

Key words: radionuclide method, occlusive diseases of the main arteries, acute lower limb ischemia, three-phase scintigraphy
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Affiliations

Natalia Y. Kudryashova	Dr. Med. Sci., Chief Researcher of the Department of Diagnostic Radiology, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, https://orcid.org/0000-0003-1647-1635
Olga G. Sinyakova	Cand. Tech. Sci., Scientific Consultant of the Department of Diagnostic Radiology, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, https://orcid.org/0000-0003-1686-6952
Igor P. Mikhaylov	Dr. Med. Sci., Head of the Scientific Department of Emergency Vascular Surgery, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, https://orcid.org/0000-0003-0265-8685
Ekaterina V. Migunova	Cand. Med. Sci., Senior Researcher of the Department of Diagnostic Radiology, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, https://orcid.org/0000-0001-7521-487X
Olga V. Leshchinskaya	Radiologist of the Department of CT and Nuclear Medicine, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department

CT — computed tomography
CRA — coefficient of relative accumulation
EI — excretion index
MR-angiorgaphy — magnetic resonance angiography
RI — ratio index
RP — radiopharmaceutical
TLT — thrombolytic therapy

INTRODUCTION

Despite the technical advances in surgical treatment and management of the postoperative period, the diagnosis and treatment of patients with acute ischemia remain among the most difficult and least solved tasks of emergency vascular surgery. The mortality rate due to acute ischemia reaches 15–20% [1, 2]. Even with the widespread use of the latest endovascular techniques, thrombolytic therapy (TLT), and vasoactive drugs, most authors report 15–20% of amputations within 30 days of acute thrombosis [1, 2].

The main instrumental methods for diagnosing damage to the main arteries of the lower extremities are ultrasound dopplerography, radiopaque angiography, computed tomography (CT) and magnetic resonance angiography (MR-angiography). Each method has its advantages and limitations. The ultrasound method is a screening method and has proven its high diagnostic efficiency, but it does not allow the anatomy of the arteries to be fully characterized, has limited accuracy in the tortuous, calcified segments of the arteries, when visualizing the aortic-iliac segment (obesity, gas formation), vascular prostheses and with "normalization of the pulse" distal to stenosis. The limitations of this method also include the high dependence on the device and operator, subjectivity in the interpretation of images, and low reproducibility of the results [1, 3]. X-ray studies (contrast angiography, CT angiography) are used with water-soluble iodine-containing contrast agents, have a high information content, but these methods are unsafe for the patient, especially with renal dysfunction and allergic reactions, have low sensitivity to tibial arteries and arteries of the foot and have a large radiation load. MR-angiography has limited accuracy in stenosis (it is possible to overestimate the degree of stenosis), in the area of stents, it is contraindicated in the presence of metal structures in the patient's body, or in patients with claustrophobia [1–5].

All these methods of radiation diagnostics are able to characterize in detail the state of the great vessels and collateral circulation of the limb, but they do not allow for an objective assessment of the state of the microvasculature of the ischemic limb and identify the focus of muscle necrosis at an early stage of its formation.

It should be noted that currently there are reports on the possibility of using dynamic contrast magnetic resonance imaging (MRI) to assess muscle perfusion in response to the load in patients with chronic lower limb ischemia, which allows you to judge upon the severity of collateral circulation indirectly, especially against conservative treatment aimed at stimulating the growth and/or development of collateral vessels in ischemic muscle [6]. However, there are no reports of the use of this method in routine clinical practice.

It is possible to obtain complete information about the blood supply of tissues during acute arterial occlusion backbone using the three phase scintigraphy of limbs with osteotropic radiopharmaceutical (RP) Pyrphotech^{99m}Tc [7-14].

We introduced a radionuclide technique for assessing the degree of acute ischemia into clinical practice at the N.V. Sklifosovsky Research Institute for Emergency Medicine, which makes it possible to objectively assess not only the state of the microvasculature of the ischemic limb, but also to identify the focus of aseptic muscle necrosis at an early stage of its formation [15–20].

Aim of study: to develop radionuclide semiotics of acute lower limb ischemia and evaluate the efficacy of treatment in angiosurgical patients with three-phase scintigraphy.

MATERIAL AND METHODS

We examined 264 patients (212 men and 52 women aged 38 to 91 years, mean age 62.5±9.3 years) with acute thrombosis of the main arteries (terminal aorta, iliac, femoral and popliteal arteries) on the background of atherosclerotic lesions of the lower extremities arteries and with clinical signs of acute ischemia of the lower extremities of the 1-3 degree according to the classification of I.I. Zatevakhin. The study did not include patients with irreversible tissue damage (3B stage), who had external signs of gangrene, which did not cause doubts in determining the degree of ischemia for angiosurgeons.

According to the location of thrombosis, patients were divided as follows: 24 (9.1%) patients with thrombosis of the terminal aorta, 41 (15.5%) patients with thrombosis of iliac arteries, 159 (60.2%) patients with thrombosis of femoral arteries, and 40 (15.2%) patients with thrombosis of popliteal arteries. Of these, 34 patients were examined again after treatment: 15 after surgical treatment, and 19 against the background of conservative therapy. Among the operated patients there were 13 men and 2 women aged 30 to 84 years (mean age 59.4±12.5 years). Against the background of conservative treatment (rheological, antiplatelet therapy, hyperbaric oxygenation), 19 patients with acute prolonged thrombosis, in some cases repeated and bilateral atherosclerotic lesions of the iliac, femoral and popliteal arteries, were examined with a radionuclide method: 15 men and 4 women aged 32 to 32 76 years (mean age 58.3±11.5 years). These patients were treated conservatively due to the inability to perform surgical intervention.

We analyzed scintigraphy in 60 patients (control group) with acute thrombosis of different location (iliac, femoral artery, femoropopliteal prosthesis, popliteal artery, aortofemoral and femorotibial prosthesis) and clear clinical signs of acute lower extremities ischemia of 1-3A degree for the development of radionuclide ischemia semiotics. These patients were considered as the basis for choosing the most informative indicators for scintigraphy .

A radionuclide study was performed after ultrasound and/or radiopaque angiography on day 1-2 of hospitalization to assess the initial state of the microvasculature. Repeated scintigraphy was performed in the early postoperative period (up to 7 days). Three-phase lower limb scintigraphy was performed with an osteotropic radiopharmaceutical Pyrphotech^{99m}Tc (Diamed, Russia), which is a phosphate complex that binds to hydroxyappatite crystals and immature collagen in the patient's body after intravenous administration. This radiopharmaceutical is included in healthy bone tissue, and accumulates in myocytes only with ischemia and necrosis due to increased capillary permeability, damage to cell membranes and active transport of calcium ions into the cell and extravascular space [13–15].

We administered 500 MBq of Pyrphotech^{99m}Tc bolus injection into the cubital vein, the radiation load was 2.85 mSv. The radionuclide study was carried out in 3 stages: the first phase of the main blood flow, the dynamic recording immediately after the bolus injection of the radiopharmaceutical in the mode of 60 images of 1 s/image; the area of interest — "terminal aorta — iliac arteries — femoral arteries — popliteal arteries" (field detector view); the second phase blood supply phase (tissue), recording in the static mode 300 s/images 10 min after the introduction, the areas of interest"hip", "lower leg", "foot"; third phase (bone) post in static mode 300 sec/image 3 hours after administration, the areas of interest "thigh", "lower leg", "foot".

RESEARCH RESULTS

We have been using relative accumulation coefficient (CRA) for 10 years to assess the state of soft tissues in the tissue and bone phases, which calculation is based on a comparison of the intensity of radiopharmaceutical accumulation in the affected and healthy muscle tissue of the contralateral zone of the opposite limb [8, 13, 15]:

$CRA = N_{path} / N_{norm}$,

where N_{path} is the average count of pulses in the region of interest of the affected limb; N_{norm} is the average count of pulses in the region of interest of a healthy limb.

A significant limitation of this method for assessing ischemia is bilateral damage to the main arteries, which is most common in patients with multifocal atherosclerosis.

Based on the fact that the above method for assessing ischemia of limb tissues is unacceptable for bilateral arterial damage, we suggested two new indicators calculated for soft lower leg tissues for the objective assessment of the degree of ischemia in patients with acute thrombosis and atherosclerosis of the main arteries of both lower extremities: excretion index and ratio index in conjunction with two visual signs such as an area of lack of blood supply to limb segments and an area of radiopharmaceutical hyperfixation, corresponding to the local aseptic necrosis. Lower leg muscles were chosen as the main areas of interest for determining these indices, since blood supply to the muscles on the hips was often compensated due to anatomical features (the presence of a deep femoral artery), and it was not possible to isolate soft tissues in the bone phase on the feet.

The RP excretion index (EI) from the lower leg muscle tissue was calculated as the ratio of the average count of pulses in the muscle in the tissue phase (N_{tp}) to the average count of pulses in the muscle in the bone phase (N_{bp}):

$EI = K \cdot N_{tp} / N_{bp}$,

where K is the coefficient taking into account the decay of ^{99m}Tc (half-life 6.0058 h, decay constant λ=0.00192 min^{-1}) and the correction for bringing the value of EI to the interval of 3 h (180 min) between the time of investigation into tissue and the bone phase (t in min), since it is not always possible to strictly observe the three-hour interval between the 2nd and 3rd phases of the study;

$K = e^{-\lambda t} \cdot 180/t$.

The ratio index (RI) of the accumulation of radiopharmaceuticals in the muscle and the accumulation in the leg bone in the bone phase is calculated as the ratio of the average count of impulses in the leg muscle in the bone phase (N_m) to the average count of impulses in the leg bone in the bone phase (N_b):

$RI=N_m/N_b$.

To obtain mormal figures, we examined 10 patients referred to scintigraphy of the skeleton with suspected cancer (20 lower extremities) who hadn't any diseases of the main arteries of the lower extremities. Normally, EI and RI with adequate blood supply to the legs, taking into account the decay of the radiopharmaceutical and corrections for the time of recording the bone phase, were 2.40 ± 0.17 and 0.50 ± 0.02, respectively.

When analyzing the results of three-phase scintigraphy in 60 patients of the control group with clear clinical signs of ischemia, it was noted that in conditions of impaired blood flow and existing limb ischemia, RI increases and EI decreases in proportion to the severity of the disease. In this case, the growth of RI is more evident with increasing ischemia, and EI does not change or changes slightly starting from 2B degree, which is associated with impaired bone blood flow in this stage of the disease. The indicators were: RI=0.68±0.04; EI=1.56±0.17 in acute grade 1 ischemia; 0.70±0.04 and 1.54±0.11, respectively, in ischemia 2A; 0.88±0.06 and 1.36±0.18 in ischemia 2B; 0.93±0.14 and 0.93±0.27 in ischemia 2C; 0.93±0.04 and 0.82±0.18 in ischemia 3A. When analyzing the values of these indicators in patients with various clinical degrees of ischemia at the tibia level, a significant difference was observed between the indicators and the normal references, as well as between the groups: 1 and 2C, 1 and 3A, 2A and 2C, 2A and 3A, 2B and 2C (p<0.05).

Additional information indicating decompensation of blood circulation was the presence of visual scintigraphic signs of soft tissue damage in the form of areas of lack of blood supply and areas of necrosis, and there was a significant hyperfixation of radiopharmaceuticals with accumulation in the bone phase in case of muscle necrosis with the presence of blood flow in the damage area.

This method of radionuclide assessment of the degree of ischemia allowed finding the level of occlusion in examined patients with acute thrombosis of the main arteries of the lower extremities, evaluation of mycrocirculatory state of extremities in detail and the degree of ischemia, identification of areas of doubtful tissue viability and selection of an appropriate therapeutic tactic.

In all 264 patients, the level of arterial occlusion was determined in the phase of the main blood flow (radionuclide aortoarteriography), and the scintigraphy data completely coincided with the data of other radiation methods, which showed the adequacy of radionuclide aortoarteriography in assessing the main blood flow. Studies have shown that this technique may be used if contrast angiography is not possible (Fig. 1).

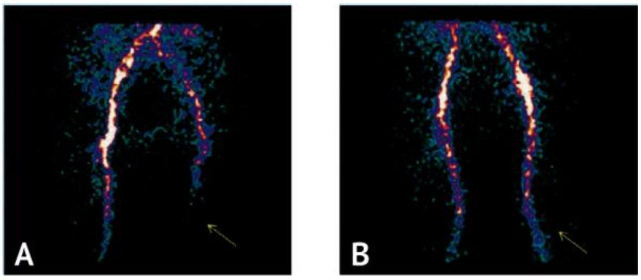


Fig. 1. Radionuclide angiography of aorta and arteries in a patient with acute thrombosis of the left femoral artery: A — prior to the operation, the area starting with the thrombosis is not visualized (an arrow); B — after thrombectomy; restoration of the main blood flow (indicated by an arrow)

The next two phases of scintigraphy characterized the state of the microvasculature of lower extremities at the cellular level. In case of muscle necrosis with preserved blood flow in the damage zone, focal hyperfixation of the radiopharmaceutical with increased accumulation was noted in the bone phase (Fig. 2). In this area, CRA was determined. The area of lack of blood supply to tissues was visualized as the absence (defect) of radiopharmaceutical accumulation (Fig. 3).

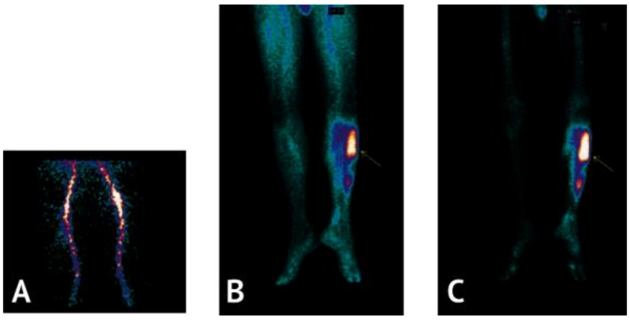


Fig. 2. The condition after thrombectomy of the left femoral artery. Scintigrams of the main blood flow (A), anterior projection of the lower leg in the tissue (B) and bone (C) phases of the study. The focus of aseptic necrosis of the anterolateral muscle group of the left lower leg (arrows). The growth of coefficient of relative accumulation (CRA) in the necrosis area is 6.5 to 22.0

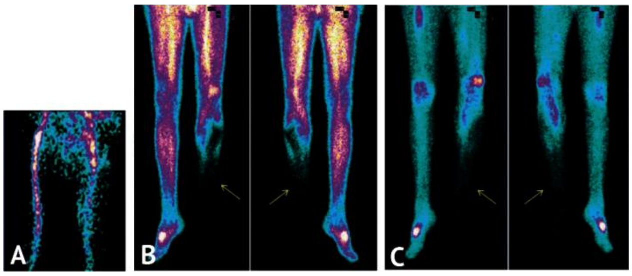
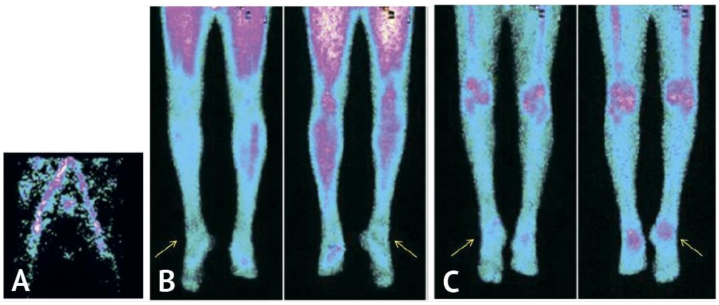


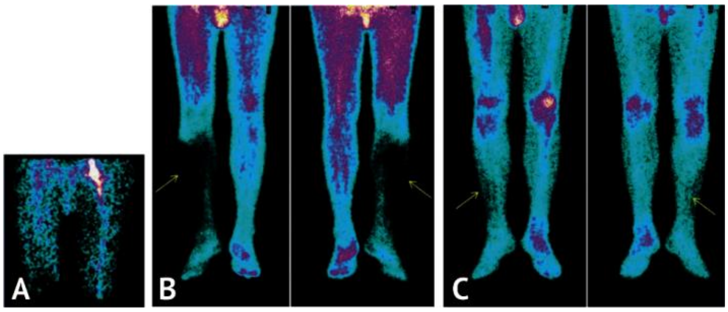
Fig. 3. Retrombosis of the right femoral artery. Scintigrams of the main blood flow (A), tissue (B — anterior and posterior projections) and bone (C — anterior and posterior projections) phases of the study. The area of lack of blood supply to the muscles of the left lower leg (indicated by arrows)

Areas of lack of blood supply to limb segments were identified in the affected limb, starting from grade 2B ischemia, and areas of necrosis we revealed starting from grade 2C. There were no signs of a lack of blood supply and areas of necrosis in ischemia of 1 and 2A degreesand no significant differences in EI and RI were obtained (p>0.05), so these degrees were combined (Fig. 4). In ischemia of 2B degree, areas of absence of radiopharmaceutical accumulation in the lower leg muscles and/or tissues of the foot in the tissue phase were visualized (Fig. 5); in 2C ischemia, there was a lack of radiopharmaceutical accumulation in the limb segments in the tissue phase in combination with focal necrosis (Fig. 6); in ischemia of 3A degree, there was a lack of blood supply to the muscles of the leg and foot tissues in both the tissue and bone phases in combination with necrotic changes in areas with preserved blood flow (Fig. 7). As a rule, a small area of necrosis was detected in 2C degree ischemia, and an extended necrosis involving one or more muscle groups was detected in ischemia of 3A degree. Scintigraphic criteria for ischemia in acute occlusive lesions of the arteries of the lower extremities by two quantitative indicators and two visual signs are presented in the table.



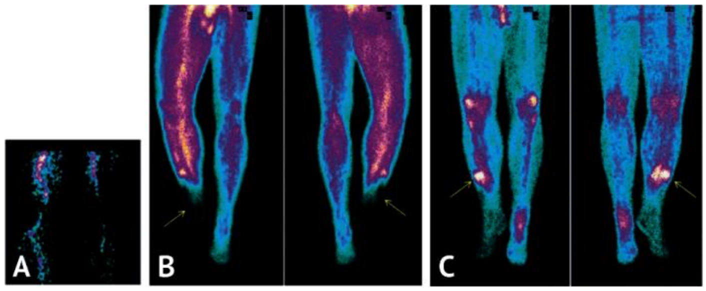
Lower leg muscles	Elimination index	Ratio index	Foci of necrosis	Areas with the lack of blood supply
Left lower limb	2.4	0.55	no	no
Right lower limb	1.55	0.64	no	no

Fig. 4. Acute thrombosis of the right femoral artery. Scintigrams of the main blood flow (A), tissue (B — anterior and posterior projections) and bone (C — anterior and posterior projection) phases of the study. Scintigraphic signs of acute ischemia of the right lower limb of grade 1–2A (indicated by arrows). No signs of ischemia of the left lower limb



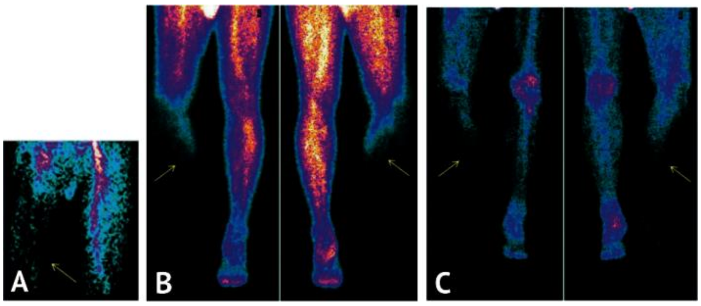
Lower leg muscles	Elimination index	Ratio index	Foci of necrosis	Areas with the lack of blood supply
Left lower limb	2.12	0.56	no	no
Right lower limb	-	0.86	no	in the tissue phase (lower leg)

Fig. 5. Acute thrombosis of the right branch of the aorto-femoral prosthesis. Scintigrams of the main blood flow a (A), tissue (B— anterior and posterior projection) and bone (C — anterior and posterior projection) phases of the study. The lack of blood supply to the right lower leg in the tissue phase with its partial restoration in the bone phase (indicated by arrows). Scintigraphic signs of ischemia of the right lower limb correspond to grade 2B



Lower leg muscles	Elimination index	Ratio index	Foci of necrosis	Areas with the lack of blood supply
Left lower limb	1.80	0.58	no	no
Right lower limb	0.95	0.98	yes	in the tissue phase (lower leg and foot)

Fig. 6. Acute thrombosis of the right popliteal artery. The condition after femoral-popliteal autologous bypass grafting. Scintigrams of the main blood flow (A), tissue (B — anterior and posterior projection) and bone (C — anterior and posterior projection) phases of the study. The lack of blood supply to the distal third of the right lower leg and foot in the tissue phase (indicated by arrows) with its partial restoration in the bone. Focus of aseptic necrosis of the anterior-lateral group of lower leg muscles (indicated by the arrows). Scintigraphic signs of acute ischemia of the right lower limb, grade 2B



Lower leg muscles	Elimination index	Ratio index	Foci of necrosis	Areas with the lack of blood supply
Left lower limb	1.65	0.64	no	no
Right lower limb	-	-	-	in the tissue and bone phases (lower leg and foot)

Fig. 7. Acute thrombosis of the right femoral artery. Scintigrams of the main blood flow (A), tissue (B — anterior and posterior projection) and bone (C — anterior and posterior projection) phases of the study. The lack of blood supply to the right lower leg and foot in the tissue and bone phases. Scintigraphic signs of acute ischemia of the right lower limb, grade 3A

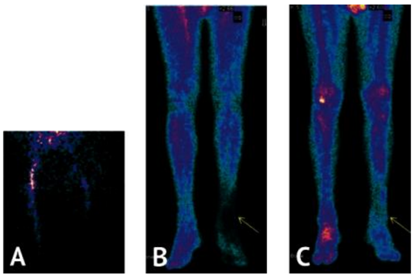
Table

The assessment of the degree of lower limb ischemia by the radionuclide method

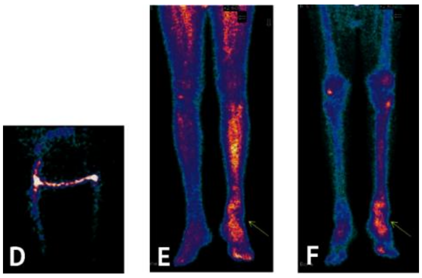
Degree of ischemia	Elimination index	Ratio index	Areas with the lack of blood supply	Foci of aseptic necrosis
1 - 2A	1.54±0.17	0.68±0.04	no	no
2B	1.36±0.18	0.88±0.06	in tissue phase	no
2C	0.93±0.27	0.93±0.14 (or not determined)	in tissue phase	yes
3A	0.82±0.18	0.93±0.04 (or not determined)	in tissue and bone phases	yes

The developed radionuclide semiotics of the degrees of ischemia was used in examination of all angiosurgical patients with acute ischemia. It was shown that the radionuclide method allows the state of the microvasculature of lower extremities to be objectively assessed, identifying areas of lack of blood supply to the muscles and areas of aseptic necrosis in the early stages of their formation, and the degree of impaired leaching of the radiopharmaceutical from the muscle in the delayed (bone) phase of the study directly depends on the severity of ischemia tissues. Taking into account the data of three-phase scintigraphy in 25% of patients (66 out of 264), the degree of ischemia was clarified with a tendency to its increase due to the identification of areas of aseptic necrosis that did not have clinical signs. With an unfavorable outcome and the development of gangrene in a number of patients, amputation level was determined taking into account scintigraphy data.

Among the operated patients, positive dynamics was recorded in 12 patients (80%) out of 15. Pronounced positive dynamics with increased blood supply at the microcirculatory level: a decrease in the degree of ischemia, restoration of main blood flow, an increase in EI (from 65 to 100%) and a decrease in RI (from 45 to 25%), was noted in 5 patients with thrombosis of the terminal aorta, iliac and femoral arteries (Fig. 8). They underwent aorto-femoral bifurcation replacement (1), femoral-femoral bifurcation replacement (1), femoral-femoral bypass surgery from right to left (1) and loop endarterectomy from the iliac and femoral arteries on the left (1). Positive dynamics with an increase in EI (by 15–28%) and a decrease in RI (up to 25%) was observed in 7 patients after ileofemoral prosthetics (2), lumbar sympathectomy (3), rheolytic thromboextraction and thrombectomy from the femoral, popliteal and tibia arteries (2) (Fig. 9).

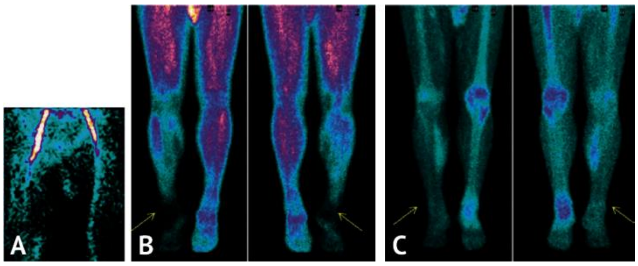


Lower leg muscles	Elimination index	Ratio index	Foci of necrosis	Areas with the lack of blood supply
Left lower limb	1.30	0.88	no	in the tissue phase (lower leg and foot)
Right lower limb	1.55	0.68	no	no

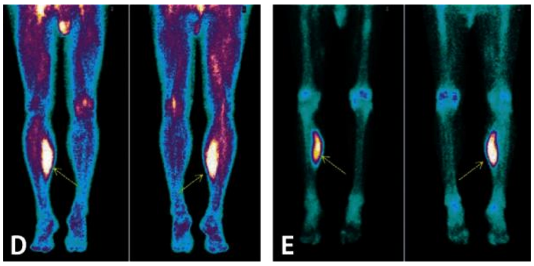


Lower leg muscles	Elimination index	Ratio index	Foci of necrosis	Areas with the lack of blood supply
Left lower limb	2.60	0.31	no	no
Right lower limb	1.65	0.58	no	no

Fig. 8. Thrombosis of the left external iliac artery, the condition after crossover femoral-femoral bypass from right to left. Scintigrams of the phase of the main blood flow: A — before surgery; D — after surgery. Scintigrams before surgery in the anterior projection in the tissue (B) and bone (C) phases of the study. Decreased blood supply to the distal third of the left lower leg and foot in the tissue phase with partial restoration in the bone (indicated by arrows). Scintigraphic signs of acute ischemia of the left lower limb, grade 2B. Scintigrams after surgery in the anterior projection in the tissue (E) and bone (F) phases of the study. Increased blood supply to the left lower limb with the restoration of blood supply to the left lower leg and foot (indicated by arrows). Significant positive dynamics



Lower leg muscles	Elimination index	Ratio index	Foci of necrosis	Areas with the lack of blood supply
Left lower limb	1.54	0.63	no	no
Right lower limb	1.38	0.89	no	in the tissue phase (lower leg and foot)



Lower leg muscles	Elimination index	Ratio index	Foci of necrosis	Areas with the lack of blood supply
Left lower limb	1.58	0.60	no	no
Right lower limb	1.71	0.51	yes	no

Fig. 9. Acute thrombosis of the right branch of an aortic femoral prosthesis. The condition after thrombectomy. Scintigrams before surgery of the main blood flow (A), tissue (B — front and rear projection) and bone (C — front and rear projection) phases of the study. 1. The lack of blood supply to the right foot and the portion of the posterior group of muscles of the right lower leg in the tissue phase with a partial restoration of blood supply to the right foot in the bone phase (indicated by arrows). Scintigraphic signs of ischemia of the right lower limb, grade 2B. Scintigrams after surgery of tissue (D — anterior and posterior projection) and bone (C — anterior and posterior projection) phases of the study. The focus of aseptic necrosis of a portion of the posterior muscle group of the right lower leg (indicated by arrows). The restoration of blood supply to the right lower limb. Positive postoperative dynamics. CRA=3.6/18

In 3 patients with long-term ischemia on the background of thrombosis of the femoral-popliteal prosthesis, TLT was performed without effect, and then thrombectomy was performed. Surgical intervention was also ineffective. Repeated scintigraphy showed an increase in ischemia (from 2C to 3A degree) with a decrease in EI and an increase in RI by 30–40%, and an extended area of necrosis of the leg muscles was revealed.

A positive effect of conservative treatment was observed in 12 patients (63.2%) of 19: increased microcirculation, a tendency to an increase in EI (by 10–40%) and a decrease in RI (by 10–20%), a decrease in the area of soft tissue infiltrative changes, and, therefore, a decrease in the degree of ischemia. One patient (out of 12) with acute thrombosis of the leg arteries after stenting of the popliteal artery showed a marked improvement in blood supply in the course of TLT: EI increased by 89% (from 0.9 to 1.7), indicating a high efficiency of TLT.

In 7 patients with prolonged ischemia of the lower extremities of 3A degree, the positive dynamics wasn't observed in the course of conservative therapy. The indicators of EI and RI remained at the same level, areas of aseptic muscle necrosis increased in area and depth (increase in CRA in the bone phase). These patients subsequently resolved the issue of reconstructive surgery to reduce the level of amputation or amputation, which level was determined taking into account scintigraphy data (Fig. 10).

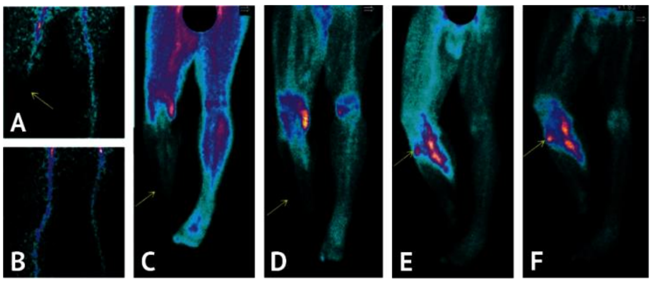


Fig. 10. Acute thrombosis of the right popliteal artery. The condition after thrombectomy. Scintigrams of the phase of the main blood flow: A — before surgery, B — after surgery. Scintigrams before surgery in the anterior projection in the tissue (C) and bone (D) phases of the study. The blood supply to the right lower limb is absent starting from the level of the knee joint (indicated by arrows). Scintigrams after thrombectomy in the anterior projection in the tissue (E) and bone (F) phases of the study. The restoration of blood supply to the posterior group of muscles of the right lower leg with the formation of an aseptic necrosis area (indicated by arrows). CRA 4.0/8.0. The lack of blood supply to the lower third of the right lower leg and foot

FINDINGS

1. The developed radionuclide semiotics of ischemia in acute occlusion of the main arteries of the lower extremities allowed us: a) to determine the level of arterial occlusion; b) to determine the degree of acute ischemia of lower extremities; c) to identify areas of lack of blood supply and necrosis for selection of adequate treatment tactics.

2. In patients with acute occlusive lesion of the arterial bed, this study detailed and specified the type of clinical manifestations of lower limb ischemia in connection with revealed aseptic necrosis areas with no clinical signs upon scintigraphy.

3. Control scintigraphy in angiosurgical patients made it possible to objectively evaluate the result of the treatment.

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