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Technetium-99m labelled somatostatin analogue myocardial uptake in subacute and "old" myocardial infarction: initial experience

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Background. It has been shown that prognosis following acute myocardial infarction (MI) strongly correlates with intensity of inflammatory reactions in response to myocardial injury. Thereby diagnostic methods for myocardial post-infarction inflammation (PII) monitoring are needed. Scintigraphy with somatostatin receptor targeted radiotracers has prospects for PII imaging, but its clinical value is poorly studied.

Methods. Six patients with ST-segment elevation anterior myocardial infarction (STEMI) were examined by chest SPECT/CT with ^{99m}Tc-Tektrotyd and rest myocardial perfusion scintigraphy (MPS) at subacute and remote (8th month) period of the disease. Parameters of both scintigraphic methods were estimated.

Results. In subacute stage of MI myocardial perfusion defects were revealed in all 6 patients (mean SRS 11.83 ± 8.89), ^{99m}Tc-Tektrotyd uptake in myocardium was revealed in 3 of 6 patients. At remote period intense uptake of ^{99m}Tc-Tektrotyd was found only in 1 patient. This uptake was more spread and clears, comparing with accumulation in subacute stage of AMI.

Conclusion. Myocardium scintigraphy with ^{99m}Tc-Tektrotyd allows identifying overexpression of somatostatin receptors in areas of recent and old myocardium infarction. In some patients the radiopharmaceutical uptake may expands to a remote period of the disease. Further larger studies and histological validation of scintigraphic results are needed.

Keywords: ^{99m}Tc-Tektrotyd, scintigraphy, acute myocardial infarction

Conflict of interest. The authors declare no conflict of interest. The study had no sponsorship.

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Использование меченного технецием-99m аналога соматостатина у больных с подостром инфарктом миокарда и в отдаленном периоде: первый опыт

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Введение. Показано, что прогноз после острого инфаркта (ИМ) имеет сильную корреляционную взаимосвязь с интенсивностью воспалительной реакции в ответ на повреждение миокарда. В связи с этим для мониторинга постинфарктного воспаления требуются новые диагностические подходы. Сцинтиграфия с меченными технецием-99m аналогами сомастостатина является перспективным методом визуализации постинфарктного воспаления, однако ее клиническое значение мало изучено.

Материал и методы. В исследование включено 6 пациентов с передним ИМ с подъемом сегмента *ST*. Всем пациентам была проведена ОФЭКТ-КТ грудной клетки ^{99m}Tc-тектротидом и перфузионная сцинтиграфия миокарда в состоянии покоя в подостром и отдаленном (8 мес) периоде.

Результаты. В подостром периоде дефекты перфузии миокарда были выявлены у всех пациентов (SRS 11.83 ± 8.89). В то же время накопление ^{99m}Tc-тектротида в миокарде было выявлено у 3 пациентов из 6 обследованных. В отдаленном периоде интенсивное накопление ^{99m}Tc-тектротида отмечалось только у 1 пациента из 6 и носило более распространенный характер по сравнению с подострым периодом ИМ.

Заключение. Сцинтиграфия миокарда с ^{99m}Tc-тектротидом позволяет выявить сверхэкспрессию рецепторов соматостатина у пациентов, перенесших ИМ как в подостром, так и в отдаленном периоде.

Ключевые слова: ^{99m}Tc-тектротид, сцинтиграфия, острый инфаркт миокарда

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Abbreviations

MI – myocardial infarction

STEMI – ST-segment elevation myocardial infarction

LV EF – left ventricular ejection fraction

SSTR-t – somatostatin receptor targeted

TTE – transthoracic echocardiography

MPS – myocardial perfusion scintigraphy

^{99m}Tc-MIBI – ^{99m}Tc-sestamibi

Introduction

Despite of the significant improvement in acute myocardial infarction (MI) diagnosis and treatment, it remains one of the main causes of disability and mortality worldwide [1]. The reperfusion therapy with primary percutaneous coronary intervention is a method of choice in patients with *ST*-segment elevation myocardial infarction (STEMI) within 12 h of symptom onset, limiting infarct size, preserving left ventricular ejection fraction (LVEF), and improving clinical outcomes [2]. However, about 22% of STEMI patients develop post-infarct heart failure, which is largely determined by infarct size resulting from both myocardial ischemia and reperfusion injury [3]. Also it has been shown that acute myocardial damage causes local and systemic inflammatory reactions, which intensity strongly correlates with prognosis following an acute MI [4]. In this connection the impact of anti-inflammatory therapeutic strategies, including inhibition of interleukin-1β by the monoclonal antibody canakinumab and inhibition of leucocyte tubulin polymerization by colchicine, on cardiovascular outcomes in patients with previous MI was studied in several randomized controlled trials [5–8]. However, there results have not fully proven the rationale for the use of anti-inflammatory drugs in MI patients, possibly due to the absence of specific methods to control an inflammation in the myocardium [9]. Recently, the applicability of somatostatin receptor targeted (SSTR-t) radiotracers for post-ischemic myocardial inflammation imaging using PET and SPECT [10–13] has been shown on several clinical cases and the possibility of using them for image-guide anti-inflammatory therapy in MI patients was discussed. In our pilot study we have attempted to expand this initial experience and to estimate the ability of technetium-99m SSTR-t radiotracer ^{99m}Tc-Tektrotyd to accumulate in the myocardium in the early and late period after MI.

Methods and materials

From October 2020 to October 2021 a total of 6 patients with anterior STEMI (the average age of 57.83 ± 10.72 years, 5 males), which were treated in the Cardiac Emergency Department of Cardiology Research Institute Tomsk NRMC, were included in the study.

The following inclusion criteria were defined.

Patients over 18 years with primary anterior STEMI [14], signed informed consent.

Exclusion criteria were the following:

1. Patients with re-infarction;

2. Patients with non-ST elevation myocardial infarction;

5. Myocarditis, infective endocarditis, infiltrative cardiomyopathy;

8. Prior therapy with somatostatin analogues;

9. Patient refusal to participate in the study.

All patient underwent primary percutaneous coronary intervention (PCI) with stenting of left anterior descending artery (LAD) (with or without preliminary thrombolysis) and medical treatment according to current guidelines [14].

Besides conventional diagnostic procedures [14] on the 7th day after MI onset (the time of M2 macrophages peak accumulation in acute MI area according to "Timeline of the inflammatory response cascade" presented by Krenning B.J 2020 [15]) all patients underwent SPECT/CT with ^{99m}Tc-HYNIC-[D-Phe^{1}, Tyr^{3}-oktreotide (^{99m}Tc-Tektrotyd) and on the 9th day – myocardial perfusion scintigraphy (MPS) at rest, using ^{99m}Tc-sestamibi (^{99m}Tc-MIBI).

At 8th months after AMI, patients who demonstrated any accumulation of ^{99m}Tc-Tektrotyd in the myocardium were re-examined with transthoracic echocardiography (TTE), ^{99m}Tc-Tektrotyd and ^{99m}Tc-MIBI SPECT/CT at rest (an interval between scintigraphic examination was of 2 days).

All scintigraphic procedures were performed on SPECT/CT scanner GE Discovery NM/CT 570c (GE Healthcare, Milwaukee, WI, USA) equipped with solid state cadmium-zinc-telluride (CZT) detectors. Both ^{99m}Tc-Tektrotyd and MPS scans were acquired using low-energy multi-pinhole collimator and 19 stationary detectors simultaneously imaging 19 different views without detector rotation. Each detector contained 32 × 32 pixelated (2.46 × 2.46 mm) CZT elements. 20% energy window at 140 keV was used. All patients were imaged in the supine position with arms placed over their heads. The acquisition time was 7 min.

Cardiac SPECT/CT study was performed at 1 and 3 hours after intravenous injection of 370 MBq of ^{99m}Tc-Tektrotyd.

Myocardial perfusion scintigraphy (MPS) was performed at 60 min after injection of 5 MBq/kg of ^{99m}Tc-MIBI in rest condition. Image acquisition and reconstruction was performed according to EANM procedural guidelines for myocardial perfusion scintigraphy using cardiac centered gamma-cameras [16].

To obtain attenuation map and anatomical heart imaging, low-dose unenhanced CT scan without ECG triggering and breath-hold was performed in all patients with the following parameters: tube voltage of 120 kV, tube current of 20 mA, rotation time of 0.8 s, helical pitch 0,969:1, slice thickness of 5 mm, and interstice interval of 5 mm for both ^{99m}Tc-Tektrotyd and rest MPS scans [17].

^{99m}Tc-Tektrotyd data processing and analysis

Hybrid SPECT/CT images were reconstructed on the dedicated workstation (Xeleris 4.0; GE Healthcare, Haifa, Israel) into axial, sagittal, and coronal planes, using Corridor 4DM SPECT (GE Healthcare, Haifa, Israel) software. The reconstructed fused SPECT/CT images were viewed in multiplanar projections by two nuclear medicine physicians. A positive finding (presence of uptake) was defined as the observation of radioactivity relatively higher than uptake in adjacent tissues and LV cavity.

The intensities of ^{99m}Tc-Tektrotyd uptake in the myocardium and in the LV cavity were quantitatively assessed using Volumetrics MI software (GE Healthcare, Haifa, Israel). All circular ROI were measured at one slice and had equal size of 1 cm^2; average count was used for further calculations. After that, myocardium / LV-cavity ratio was calculated.

Myocardial perfusion scintigraphy data processing and analysis

All MPS images were interpreted by two experienced nuclear cardiology physicians. CZT images were reconstructed on the dedicated workstation (Xeleris 4.0; GE Healthcare, Haifa, Israel) using maximum-penalized-likelihood iterative reconstruction (60 iterations; Green OSL Alpha 0.7; Green OSL Beta 0.3) to acquire perfusion images in standard cardiac axes (short axis, vertical long axis, and horizontal long axis). The software Myovation for Alcyone (GE Healthcare, Haifa, Israel) was used for image reconstruction, and Butterworth post-processing filter (frequency 0.37; order 7) was applied to the reconstructed slices. The reconstruction was performed in 70 × 70 pixels matrix with 50 slices.

Rest images were analyzed with a commercially available software package Corridor 4DM (University of Michigan, Ann Arbor, MI, USA). The calculation of MPS parameters was performed based on uncorrected and attenuation corrected image analysis. Perfusion in each of 17 segments was visually classified as 0 = normal, 1 = mild reduction, 2 = moderate reduction, 3 = severe reduction or 4 = absent perfusion, and the segmental scores were summed rest (SRS) images. MPS studies were considered abnormal in the presence of SRS ⩾ 4 [18].

Results

Baseline characteristics of the enrolled patients are presented in a Table 1. Most of them were men (5 of 6), mean age was 58.17 ± 10.34 years. Three of six patients had moderately reduced LV EF, three others – preserved or normal LV EF (51.17 ± 6.55 %).

Table 1. Baseline characteristics of the enrolled patients

Characteristics	Patient No 1	Patient No 2	Patient No 3	Patient No 4	Patient No 5	Patient No 6
Age	51	63	56	72	43	64
Sex	male	male	male	female	male	male
Hypertension stage	III	III	III	III	III	III
Diabetes mellitus	no	no	no	no	no	no
Dyslipidemia	yes	yes	yes	yes	yes	yes
Obesity	yes	no	yes	yes	no	no
Smoking	no	yes	yes	no	yes	yes
Family history of CVD	yes	no	no	no	yes	no
Pre-CHF	no	no	no	no	no	no
Hemoglobin (g/L)***	146	155	157	145	162	168
Glucose (mmol/L)***	5.01	5.68	6.4	6.36	4.87	4.72
Creatinine (mcmol/L) ***	71.00	85.00	95.00	85.00	80.00	80.00
Troponin I (ng/ml) *	3.81	0.02	35.07	2,07	10.66	14.16
Troponin I (ng/ml) *	5.1	0.87	120.44	87.42	25.00	25.00
CRP (mg/L)***	5.1	2.9	10,4	12,3	7,9	3.2
LV EF (%)	44	54	47	53	62	47
LV EDV (ml)	124	91	108	107	93	99
LV ESV (ml)	70	42	57	50	35	52
Culprit lesion	LAD	LAD	LAD	LAD	LAD	LAD
Total ischemic time (min)	1110	215	274	946	937	214

Note: * – in admission; ** – peak value; *** – on 7th day after acute myocardial infarction onset; CVD – cardio-vascular disease, CHF – chronic heart failure, CRP – C-reactive protein, LV EF – left ventricular ejection fraction, LV EDV – left ventricular end diastolic volume, LV ESV – left ventricular end systolic volume.

Table 2. Scintigraphic and echocardiographic parameters of enrolled patients

Characteristics	Patient No 1	Patient No 2	Patient No 3	Patient No 4	Patient No 5	Patient No 6
^{99m}Tc-Tektrotyd uptake on 7th day after MI onset (localization/focus to LV cavity ratio)	Apex, anterior wall / 2.1	Absence of uptake/ 1.7	Septum, anterior, lateral wall / 2.5	Anterior wall / 2.6	Absence of uptake / 1.5	Absence of uptake / 1.7
^{99m}Tc-Tektrotyd uptake on 8th months after MI onset (localization/focus to LV cavity ratio)	Absence of uptake/ /1.6	NP	Septum, anterior, apical lateral wall 2.4	Absence of uptake / 1.06	NP	NP
Rest MPS on 9th day after MI onset (SRS)	10	4	23	23	5	6
Rest MPS on 8th months after MI onset (SRS)	8	NP	32	23	NP	NP
LV EF (%), baseline / 8th months after MI onset	44/48	54/NP	47/46	52/54	62/NP	47/NP
LV EDV (ml), baseline / 8th months after MI onset	124/143	91/NP	108/150	107/120	93/NP	99/NP
LV ESV (ml), baseline / 8th months after MI onset	70/75	42/NP	57/81	50/55	35/NP	52/NP

Note: NP – not performed, MI – myocardial infarction, LV – left ventricle, MPS – myocardium perfusion scintigraphy, SRS – summed rest score, LV EF – left ventricular ejection fraction, LV EDV – left ventricular end diastolic volume, LV ESV – left ventricular end systolic volume.

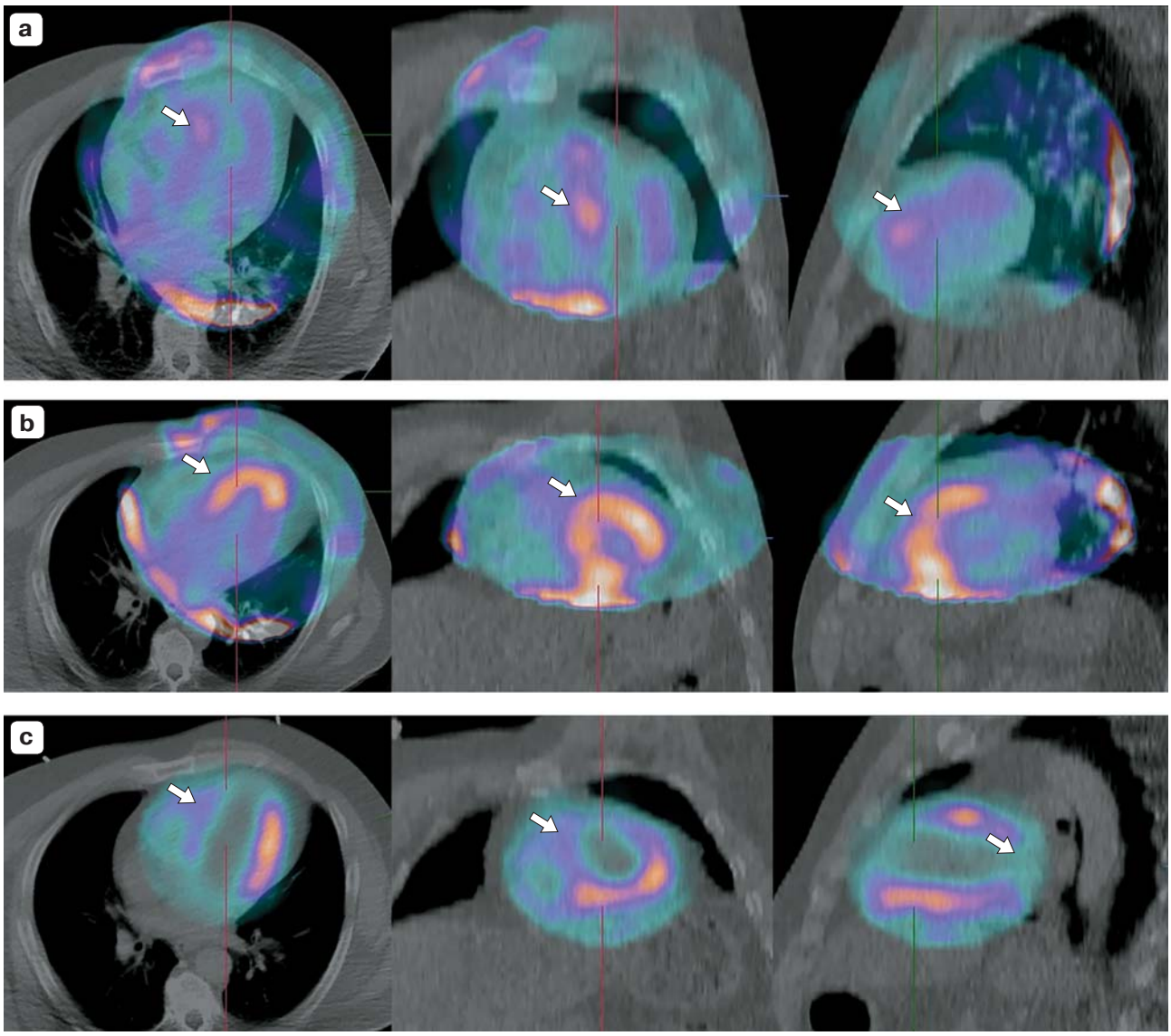

Fig. 1. a – Cardiac ^{99m}Tc-Tektrotyd SPECT/CT which was performed in subacute stage of the myocardium infarction shows increased local uptake of the tracer in apical and intermediate anterior wall, septum and lateral wall of the left ventricular (pointed with arrows). **b** – In the same patient cardiac ^{99m}Tc-Tektrotyd SPECT/CT performed in remote period of myocardium infarction (8 months) shows expanded and clearer uptake of the tracer. **c** – Rest myocardium perfusion scintigtraphy with ^{99m}Tc-sestamibi performed in remote period of myocardium infarction (8 months) shows areas of hypoperfusion matched with areas of ^{99m}Tc-Tektrotyd uptake.

Accumulation of ^{99m}Tc-Tektrotyd in myocardium was revealed in 3 of 6 patients on the 7th day after MI onset (Table 2, Fig.1). In all cases the uptake was localized in the apex and anterior area of LV, and in 1 case additionally in the septum and lateral wall of LV. Images of patient №1 were previously presented by Sazonova S.I. et al. [12].

Rest myocardium perfusion scintigraphy performed on the 9th day after MI onset revealed perfusion defects in all 6 patients (mean SRS 11.83 ± 8.89), located predominantly in the apex and anterior wall of the LV (Table 2).

At 8 months after MI onset TTE, rest MPS and myocardium scintigraphy with ^{99m}Tc-Tektrotyd were performed in 3 patients, who showed positive findings in subacute stage of STEMI (Table 2). Among them intense uptake of ^{99m}Tc-Tektrotyd was found only in 1 patient No3. This uptake was more spread and in-

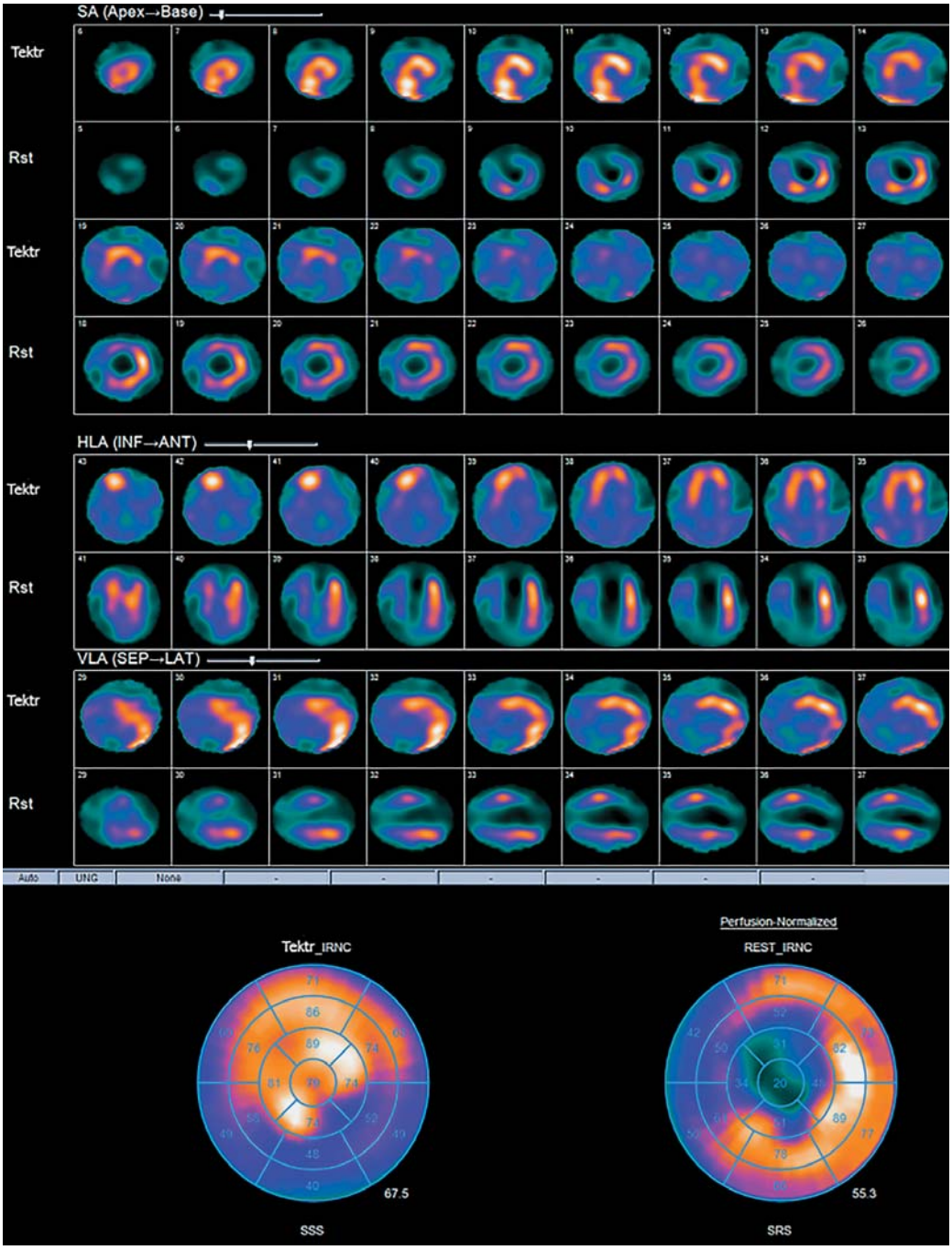

Fig. 2. Cardiac ^{99m}Tc-Tektrotyd (Tektr), ^{99m}Tc-sestamibi SPECT images at rest (Rst) and their polar maps shows «mirror» accumulation of tracers in patient with old myocardium infarction.

tensive, comparing with ^{99m}Tc-Tektrotyd accumulation, observed at 7th day after MI onset. Its localization was fully corresponded to the area of perfusion defect, detected by rest MPS (Fig 1, 2). Additionally, patient No3 underwent cardiac magnetic resonance imaging (MRI), which showed area of hyperenhancement on LGE images in the basal and middle anterior-septal wall as well as in the apical part of the inferior wall of the LV, corresponding to the old myocardial infarction region (Fig 3). No MRI signs of myocardial inflammation were revealed. The patient No3 was also different from the others in the largest SRS, troponin I and glucose level in subacute stage of STEMI, and had the largest increase of EDV (on 38%), ESV (on 42%) and SRS (on 39%) after 8 months.

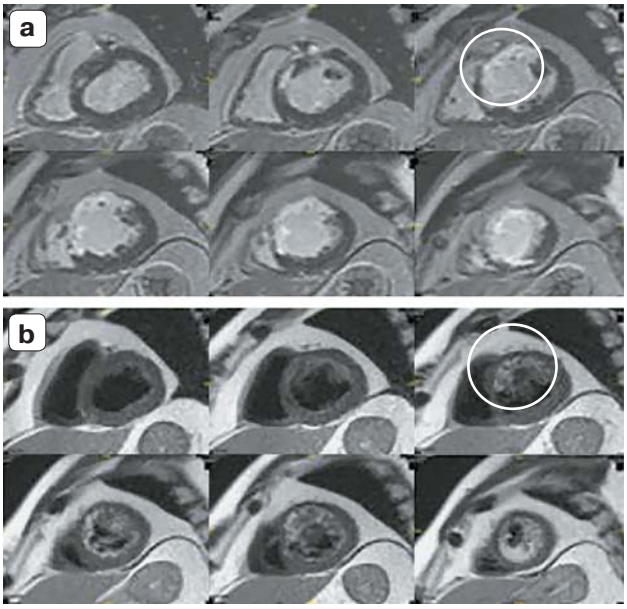

Fig. 3. Cardiac MRI images of the patient with ^{99m}Tc-Tektrotyd intense accumulation in the area of old MI: scar in the anterior-septal wall, no signs of inflammation. **a** – late gadolinium enhancement (LGE) images. Area of hyperenhancement corresponded to anteroseptal segments of left ventricular. **b** – T2-weihgted images. No signs of edema.
LGE visualizes postinfarction cardiosclerosis in the projection of the anterior septal wall in the basal and middle sections of the left ventricle and the inferior wall of the left ventricle in the apical section. This picture does not correspond to an acute infarction, because. an increase in the intensity of the MR signal (edema zone) on T2-WI is not visualized.

Discussion

In the present pilot study was shown the possibility of ^{99m}Tc-Tektrotyd to accumulate intensively in the site of recent myocardium infarction following by the expansion of the uptake area during the MI remote period, indicating overexpression of somatostatin receptors and increased number of activated macrophages in the scar and adjacent ischemic myocardial tissues [10–13]. Also few different variants of ^{99m}Tc-Tektrotyd accumulation in the myocardium of clinically similar patients with anterior STEMI were demonstrated: 1) the absence of uptake in subacute stage of AMI, 2) the presence of intensive local uptake in subacute stage of MI followed by the absence of uptake in the remote period, 3) the presence of intensive local uptake in subacute stage of MI followed by expansion of the uptake area. This demonstrates the individual inflammatory response to myocardial injury and its severity during myocardial healing. What is significant, is that ^{99m}Tc-Tectrotide uptake area in all cases was matched with areas of hypoperfusion, detected by rest MPS.

Our results are consistent with data, presented by Tarkin J.M. et al in 2019 [11]. The authors found that ^{68}Ga-DOTATATE (somatostatin receptor subtype-2 positron emission tomography ligand) can identify active inflammation in recently infarcted myocardium, as well as old ischemic injury. The pathophysiological explanation of these results, contradictions with experimental data in mice [19], and the necessity of histological validation of scintigraphic results are discussed in details in their paper [11].

The current data indicate the prospect of using scintigraphy with technetium labelled SSTR-t radiotracers to identify groups of post-MI patients who need anti-inflammatory therapy to prevent an adverse myocardium remodeling. Definitely, to assess the clinical value of the method, it is necessary to study many issues, including timing for images registration, definition of quantitative uptake criteria and association of SSTR-t scintigraphy results with adverse remodeling.

Limitations

The present study has several limitations, the most notable of which are small sample size and short follow-up period. This limits the full assessment of the ^{99m}Tc-Tektrotyd accumulation patterns in patients with acute MI. In addition, histological validation of scintigraphic results is necessary, but was not performed in current study.

New knowledge gained

Myocardium scintigraphy with ^{99m}Tc-Tektrotyd allows identifying overexpression of somatostatin receptors in areas of recent and old myocardium infarction. In some patients the area of the radiopharmaceutical uptake expands to a remote period of the disease.

Conclusion

Thus, in the presented study, it was shown the possibility of ^{99m}Tc-Tektrotyd to accumulate intensively both in sites of recent and old myocardium infarction, indicating overexpression of somatostatin receptors there. Herewith an intensity and distribution of the radiopharmaceutical uptake were individual in subacute and remote period of the disease. These results may

point to the prospect of using scintigraphy with technetium labelled SSTR-t radiotracers to identify groups of post-MI patients who need anti-inflammatory therapy to prevent an adverse myocardium remodeling. However, further larger studies of the clinical and prognostic value of the method and histological validation of scintigraphic results are needed.

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Authors' participation

Ilyushenkova J.N. – collection and analysis of data, analysis and interpretation of the obtained data, conducting research.

Syrkina A.G. – conducting research, responsibility for the integrity of all parts of the article.

Trusov A.A. – conducting research, collection and analysis of data.

Mishkina A.I. – collection and analysis of data.

Mochula O.V. – collection and analysis of data.

Sazonova S.I. – concept and design of the study, text preparation and editing, approval of the final version of the article.

Ryabov V.V. – participation in scientific design, approval of the final version of the article.

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