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A.I. Abdrahmanova*[1,2], N.B. Amirov[3,4], N.A. Cibulkin[5]

[1] — Kazan (Volga Region) Federal University, Department of Fundamental Foundations of Clinical Medicine, Kazan, Russia

[2] — Interregional Clinical Diagnostic Center, Department of Cardiology, Kazan, Russia

[3] — Kazan State Medical University, Ministry of Health of Russia, Department of Polyclinic Therapy and General Medical Practice, Kazan, Russia

[4] — Medical sanitary unit of the Ministry of Internal Affairs of Russia in the Republic of Tatarstan, Kazan, Russia

[5] — Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Department of Cardiology, X-ray Endovascular and Cardiovascular Surgery, Kazan, Russia

Application of Perfusion Single Photon Emission Computed Tomography of the Myocardium in Pain-Free Myocardial Ischemia

Abstract

This literature review provides data on the use of single-photon emission computed tomography of myocardium in silent myocardial ischemia. The presence of silent myocardial ischemia increases the risk of cardiovascular complications several times and may be the first manifestation of coronary heart disease. Assessing the state of morphofunctional processes in the myocardium is the main goal of diagnostic imaging using single-photon emission computed tomography of the myocardium. This allows to get three-dimensional image of left ventricle with information about distribution of perfusion volume across myocardium, makes it possible to more accurately differentiate such condition as silent myocardial ischemia. Conducting single-photon emission computed tomography in ECG synchronization mode allows you to visualize the kinetics of the myocardial walls in different phases of the cardiac cycle and thereby simultaneously assess the functional state of the left ventricular myocardium. Indicators of contractile function of the left ventricular myocardium in areas of transient hypoperfusion can be predictors of cardiac events after myocardial infarction and independent predictors of perioperative cardiac events in patients undergoing cardiac surgery. Performing single-photon emission computed tomography in ECG-synchronization mode allows visualizing kinetics of myocardial walls in different phases of cardiac cycle and thereby simultaneously assessing functional state of left ventricle myocardium. In combination with physical exercise and pharmacological tests, it helps to identify coronary stenosis among patients with silent myocardial ischemia. Perfusion single-photon emission computed tomography of myocardium is a necessary tool for stratification and assessment of prognosis of cardiac diseases in asymptomatic patients.

Key words: *silent myocardial ischemia, perfusion scintigraphy*

Conflict of interests

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*Contacts: Alsu I. Abdrakhmanova, e-mail: alsuchaa@mail.ru

ORCID ID: https://orcid.org/0000-0003-0769-3682

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CA — coronary artery, CAG — coronary angiography, CHD — coronary heart disease, ECG — electrocardiography, Echo-CG — echocardiography, EF — ejection fraction, ESV — end-systolic volume, LV — left ventricle, MI — myocardial infarction, PA — physical activity, SMI — silent myocardial ischemia, SPECT — single-photon emission computed tomography

Life-threatening conditions associated with the occlusion of coronary arteries (CAs), primarily, myocardial infarction (MI) and sudden cardiac death, are common signs of atherothrombotic vascular diseases. Silent myocardial ischemia (SMI) increases the risk of sudden cardiac death 10-fold, the risk of cardiac arrhythmias — 2-fold, the risk of MI and congestive heart failure — 1.5-fold [1–3]. Damage caused by myocardial ischemia leads to several pathological processes; among these, perfusion disorder is a more accurate and early marker of ischemia than ECG changes or dyssinergia determination [4]. Assessment of the state of morphofunctional processes in the myocardium (contractility, perfusion, sclerosis, ischemia, hibernation, innervation) is the primary goal of diagnostic imaging with radionuclide methods [5] that have high reproducibility, which enables to evaluate the dynamics of these processes [6]. Single-photon emission computed tomography (SPECT), the "gold" standard for assessing transient myocardial ischemia, allows assessing myocardial blood supply at the microcirculation level and defining the degree of damage to cardiomyocytes. The distribution of radiopharmaceuticals in the myocardium depends on perfusion and the integrity of the sarcolemma of cardiomyocytes. Drugs used for this method are based on the short-lived form of technetium-99m (99mTc-MIBI and 99mTc-tetrafosmin) and are distributed in the myocardium in proportion to the blood flow, thus reflecting perfusion, on the one hand, and, on the other hand, as lipophilic cations, they penetrate the cell membrane by passive diffusion (by electrochemical gradient). Then they bind to the mitochondrial membrane more stably and, thus, demonstrate the viability of the cell's energy chain, being its markers [7].

Perfusion SPECT in ECG synchronization mode enables to visualize the kinetics of myocardial walls in different phases of the cardiac cycle and, therefore, to simultaneously assess the functional status of the left ventricular (LV) myocardium [8]. Contractility is evaluated simultaneously with the main perfusion protocol, without increasing the duration of the study. However, the obtained data on LV contractility are quite accurate and reproducible [9, 10].

The combination of SPECT with physical activity (PA) or pharmacological tests helps to detect coronary stenosis in patients with SMI, since in cases of coronary stenosis of less than 85%, in most cases there is no decrease in blood flow under functional rest conditions, and almost 70% of acute coronary events are the result of coronary damage without significant hemodynamics changes [11, 12]. Triggered heterogeneity of blood flow is visible on scintigrams as defects in myocardial perfusion of different severity. Perfusion disorders are usually divided into stable and transient: persistent perfusion defects may correspond to necrosis zones or myocardial scarring; transient perfusion defects usually represent reversible myocardial ischemia [13]. The onset of stress-induced perfusion defects in patients with coronary insufficiency is usually accompanied by impaired LV contractility. Most patients demonstrate a rapid restoration of cardiac contractility after stopping physical activity. However, in about 30–35% of cases, inotropic function impairment persists for an hour after stress test. Such long stress-induced LV dysfunction is considered an early predictor of coronary thrombosis and can be used as a non-invasive marker of vascular lesion severity [14]. Parameters of the LV myocardial contractile function in the zones of transient hypoperfusion can be predictors of cardiac events after previous MI. The most accurate parameters for disease prognosis in patients with MI are LV ejection fraction (EF) and end-systolic volume (ESV): mortality among patients with MI with LVEF 45% and/or ESV 70 ml is significantly lower compared with patients with MI with

LVEF < 45% and/or ESV > 70 ml [14, 15]. Low LVEF (<30%) and severe perfusion defects are a predictor of death from cardiac events. Identification of transient perfusion defects adds no negative prognostic value to low LVEF (less than 30%) due to the high risk of sudden cardiac death in such patients [3, 15]. The state of the LV contractile function after acute MI can be one of the main determinants of prognosis. Analysis of the results of ECG-synchronized SPECT in post-infarction patients confirmed the high prognostic value of this method in the stratification of the risk of cardiac events: a decrease in LVEF to 40% or less increases the risk of cardiac events by a factor of three [10, 14]. Parameters of the cardiac contractile function are independent predictors of perioperative cardiac events in patients undergoing cardiac surgery. The assessment of volumetric parameters and LVEF is especially important for patients with normal myocardial perfusion. The sensitivity and specificity of scintigraphy with stress test are on average 85–90% and 70–75%, respectively [11, 12, 16].

Studies in the group of asymptomatic patients after coronary artery bypass surgery prove the special prognostic value of SPECT in the first six years after surgery. The detection of perfusion defects, either stable or reversible, is associated with a higher risk of death and the risk of non-fatal MI [2]. Myocardial perfusion SPECT is also used to stratify and assess the prognosis of myocardial diseases. An earlier diagnosis of asymptomatic myocardial ischemia gives an accurate identification of the culprit vessels, preventing unnecessary interventional treatment. In certain population groups, non-invasive imaging using SPECT can significantly improve cardiovascular risk assessment and increase adherence to treatment when preventive interventions match the magnitude of the risk [1].

SPECT is considered one of the main non-invasive methods for diagnosing obstructive CA lesions in patients with an intermediate result of preliminary tests for CHD. This method has a fairly high sensitivity (90–91%) and specificity (75–84%). SPECT also allows risk stratification in patients with CHD. A direct correlation was demonstrated: an increase in the spreading area of ischemia on SPECT resulted in an annual increase in the frequency of deaths from cardiac causes and MI. SPECT allows selecting patients for myocardial revascularization, i.e., in the case of myocardial ischemia of up to 10% according to SPECT, the risk of death for cardiac reasons during myocardial revascularization is higher than from drug treatment, and in the case of ischemia of over 10%, myocardial revascularization improves survival compared to conservative therapy [3, 17, 18].

It was proven that SPECT results were more important for the prognosis than the number of affected arteries during coronary angiography (CAG) because SPECT enables to determine myocardial viability. The signs of previous MI according to the results of functional methods combined with the occlusion of a culprit artery on CAG and no signs of myocardial viability according to the results of SPECT with a high probability indicate the presence of irreversible myocardial scarring in the area of previous MI and no indications for percutaneous coronary interventions [19]. At the same time, the intensity of radiopharmaceutical accumulation in the myocardium supplied by a culprit artery can be determined by the peculiarities of its metabolic disorder [20, 21]. It was shown that the mortality rate of patients with CHD increased in proportion to the area of the transient ischemia zone, reaching 6.5% per year with values of more than 20% of the total LV area. Moreover, perifocal ischemia (around the scar area after MI) is associated with a higher risk of cardiac death compared to ischemic zones not associated with the scar. One of the main diagnostic tasks of stress SPECT is the stratification of risk groups by the presence and severity of ischemia induced by physical activity, its localization, transient dilatation and LV dysfunction, and decreased LV ejection fraction [3, 15].

According to our data, comorbidities with SMI (diabetes mellitus, hypertension) have no effect on myocardial perfusion [22]. This is probably because perfusion disorder does not depend on the origin of atherosclerosis. Acute cardiovascular events of atherosclerotic etiology are not always associated with risk factors. Another reason for our data may be the small number of patients in the study group [22]. In the work by E. I. Denisenko-Kankiya et al. (2019), a significant decrease in myocardial perfusion during exercise according to SPECT results was detected in patients with a history of hypertension and diabetes mellitus [23].

MI worsens perfusion parameters both at rest and in stress but does not change stress-induced transient ischemia [22]. The difference in perfusion after previous MI is associated with the presence of nonperfusion scar areas.

The degree of worsening of perfusion does not depend on MI, since a viable myocardium responds equally to physical activity. This suggests that perfusion disorders occur in the living myocardium and are not associated with scar zones. Our data match the results obtained by other authors: in the work by A.A. Ansheles et al. (2012), 73 (94.8%) patients with MI had a stable perfusion defect in the area corresponding to ECG data [24].

According to our study, testing with physical activity increased EF in patients with SMI (regardless of MI) due to increased contractility of the viable myocardium [22]. In the work by A. A. Ansheles et al. (2012), 32% of patients showed a decrease in EF by more than 3% after exercise; in 53% it remained almost unchanged; and in 15% it increased by more than 3%. The first and second cases were interpreted as the absence of adequate increase in EF after exercise. The decrease in EF after exercise was thought to be associated with the degree of transient ischemia. However, despite the tendency (more severe ischemia leads to a more significant decrease in EF after exercise), a weak correlation was found between the parameters [24].

The stress test worsens perfusion parameters compared to the state at rest in nine segments (10, 11, 12, 13, 16, 17, 18, 19) out of 19. This pattern occurs primarily in the cases of left circulation type. Physical activity worsens perfusion in the lateral wall of LV and its adjacent segments due to the lack of possible compensatory blood supply from the right coronary artery. It can be assumed that pathological changes occur in most cases in the anterior interventricular artery system [22]. According to literature, a damaged anterior interventricular branch of the left coronary artery was determined in 46.1% if it was isolated and combined; and less often — in the circumflex branch of the left coronary artery (25.6%) [25].

The main indications and limitations for SPECT are presented in Table 1.

Determining the diagnostic significance and value of ECG-synchronized SPECT compared to other imaging methods is not always possible for assessing myocardial and coronary lesions in patients with SMI due to different detection principles.

Multispiral computed tomography and magnetic resonance imaging can give a lot of objective numerical data: diameter of vessels, size of cavities and other structures, while SPECT either does not allow obtaining these values, or gives them based on indirect data. However, despite their value, quantitative data do not allow full assessment of the state of the heart. For example, such an important parameter as myocardial viability is, at best, a semi-quantitative, and most often — an estimated, qualitative factor.

Positive stress-ECG test during SPECT in patients with CHD in 100% of cases indicates transient myocardial ischemia, while negative stress-ECG test shows the absence of ischemic signs only in 35% of cases. Tests that were doubtful or were not brought to diagnostic criteria affect the final diagnosis of myocardial perfusion according to SPECT, which requires a more detailed analysis of the obtained data [24].

When analyzing myocardial contractility, SPECT provides comprehensive quantitative data on the movement and thickening of LV walls in the form of compact polar maps. This approach allows detecting only repeated, reproducible, i.e., significant contractility disorders with their exact localization. This is the difference between SPECT and echocardiography and magnetic resonance imaging, where a cine loop from only one or several contractile cycles is analyzed. SPECT automatically gives values of systolic motion and thickening of LV walls in each of the segments, with an accuracy of 1–2 mm, which enables to set the normal criteria and discretize contractility disorders based on a scoring system similar to perfusion disorders. If EF is 20–70%, then when conducting ECG-synchronized SPECT, EF is, on average, 7–9 units lower than when assessed using EchoCG. These differences are due to different algorithms for calculating EF that lead to different normal EF values according to the two methods [15].

In most cases, the localization of stable and transient perfusion defects according to SPECT results reliably predicts the presence of lesions in each major CA. However, it was found that stenoses of up to 80% in 71.4% of cases do not cause transient

myocardial ischemia in their system area (except for the left coronary artery trunk and the proximal segment of the anterior descending coronary artery) [24]. This is probably because the achieved stress is not always sufficient to detect SMI. If there is a suspected hemodynamically significant CA lesion, a stress test should be performed with the maximum possible stress for the patient to assess myocardial ischemia using SPECT with a mandatory comparison of data with CAG results. The lowest sensitivity and specificity of SPECT for detecting CA stenosis of more than 70% was observed in patients with multivascular diseases [8, 12].

Thus, SPECT is a non-invasive imaging method that allows diagnosing the functional significance of atherosclerotic damage of CA, assessing local tissue perfusion, myocardial viability, determining the prognosis and risk stratification in patients. The informative value of this method increases when combined with tests with physical activity. Myocardial SPECT with a stress test for the diagnosis of SMI has the following advantages: the method is more effective since it allows establishing localization, severity of myocardial ischemia during exercise; determining the indications for surgical revascularization; identifying a microcirculatory form of ischemia. Myocardial SPECT with stress test has a higher sensitivity and specificity than ECG stress test and higher sensitivity than stress echocardiography. SPECT should be performed in patients with implicit "coronary" symptoms or patients with risk factors and negative results for coronary insufficiency [6, 10, 26].

A more detailed study of the diagnostic capabilities of SPECT in the assessment of biological processes in patients with SMI is needed today. This imaging method is a necessary tool for risk stratification and assessment of myocardial disease prognosis in asymptomatic patients.

Table 1. *Indications and limitations for ECG-synchronized single-photon emission computed tomography of the myocardium*

Indications for SPECT	Limitations for SPECT
Detection of myocardial perfusion defects in case of suspicion of significant coronary artery stenosis	Duration of the procedure
Selection of patients for coronary angiography	Difficulties in interpreting data in the posterior basal and lower parts of the interventricular septum
Assessment of the effect of the revealed atherosclerotic lesion and coronary artery stenosis on myocardial perfusion	
Assessment of the feasibility and volume of the planned percutaneous coronary intervention, determination of symptom-related coronary artery	Low sensitivity of the method in the presence of multiple lesions of the coronary arteries
Dynamic observation and assessment of the effect of drug therapy and interventions	An allergic reaction to radiopharmaceuticals
Prognosis and risk stratification in chronic coronary artery disease	
Suspicion of myocardial infarction (assessment of reperfusion, prognosis before further interventions in high-risk patients)	For children under 16 years of age
Assessment of the consistency of the heart function before complex cardiac and other operations	For women of reproductive age in the early stages of a diagnosed or possible pregnancy
Differential diagnosis between coronary and non-coronary etiology of myocardial damage	
Assessment of the state of perfusion and contractile function of the myocardium in heart failure	Technical restrictions on patient weight
Assessment of left ventricular contractility in case of questionable results of echocardiography	

Note: SPECT — single-photon emission computed tomography, ECG — electrocardiography

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

Abdrakhmanova A.I. (ORCID ID: https://orcid.org/0000-0003-0769-3682): concept and design development, review of Russian-language publications on the topic of the article, data analysis and interpretation, responsible for all aspects of the work

Amirov N.B. (ORCID ID: https://orcid.org/0000-0003-0009-9103): critical intellectual content review, final approval for manuscript publication

Tsibulkin N.A. (ORCID ID: https://orcid.org/0000-0002-1343-0478): concept and design development, review of English-language publications on the topic of the article, data analysis and interpretation

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