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Modern scintigraphic methods for assessing myocardial blood flow and reserve

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ABSTRACT

Background. Today, myocardial perfusion scintigraphy is an informative and accessible method for evaluating ischemic changes in the heart. However, this method has limitations, which are more connected with a semi-quantitative assessment of the study results. Currently, there is a class of specialized gamma cameras with cadmium zinc telluride detectors, which allow for quantitative analysis of scintigraphic data on coronary hemodynamics, i.e. evaluate indicators of coronary blood flow and reserve.

The aim of the review was to present and summarize the information about the coronary circulation under physiological and pathological conditions, as well as the possibilities of modern radionuclide methods in assessing coronary blood flow and reserve.

Materials and methods. In the process of preparing the review article, "PubMed", "Web of Science", "ScienceDirect", and "Elibrary" research databases were used. Search requests included such key words as: coronary artery disease, myocardial blood flow, coronary (myocardial) flow reserve, single photon emission computed tomography, cadmium-zinc-telluride, positron emission tomography.

Results. The review includes information on the state and methods of regulating coronary hemodynamics under normal conditions and against the background of pathological changes. It also includes information about radionuclide methods for assessing coronary hemodynamics which were used in the past, are currently being used, and promising ones,including dynamic single photon emission computed tomography.

Conclusion. The potential of dynamicsingle photon emission computed tomography as a method for quantification of coronary blood flow and reserve is high. This technique can become a simple and affordable alternative to the existing methods for assessing coronary (myocardial) blood flow and reserve. This will increase the information content of radionuclide diagnostics in assessing the severity of coronary insufficiency for more accurate risk stratification and determination of appropriate treatment strategy for cardiac patients.

Key words: dynamic single photon emission computed tomography, myocardial blood flow, coronary (myocardial) flow reserve, coronary artery disease, coronary artery atherosclerosis.

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Современные сцинтиграфические методы оценки миокардиального кровотока и резерва

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РЕЗЮМЕ

Введение. Перфузионная сцинтиграфия миокарда на сегодняшний день является информативным и доступными методом оценки ишемических изменений сердца. Однако эта методика, как и любая другая, имеет ряд определенных ограничений, которые в большей степени связаны с полуколичественной оценкой результатов исследования. В настоящее время существует класс специализированных гамма-камер с детекторами на основе кадмий-цинк-теллура, позволяющих проводить количественный анализ сцинтиграфических данных о состоянии коронарной гемодинамики, т.е. оценивать показатели коронарного кровотока и резерва.

Цель обзора – представить и обобщить сведения о физиологии кровообращения сердца в норме и при патологии, а также возможностях современных радионуклидных методов в оценке коронарного кровотока и резерва.

Материалы и методы. В процессе подготовки обзорной статьи использовались научные базы данных PubMed, Web of Science, ScienceDirect, Elibrary. Поисковый запросы включали ключевые слова: coronary artery disease, myocardial blood flow, coronary (myocardial) flow reserve, single-photon emission computed tomography, cadmium-zinc-telluride, positron emission tomography, ишемическая болезнь сердца, миокардиальный кровоток, однофотонная эмиссионная компьютерная томография, позитронная эмиссионная томография, резерв коронарного (миокардиального) кровотока.

Результаты. Обзор включает в себя сведения о состоянии и способах регуляции коронарной гемодинамики в условиях нормы и на фоне патологических изменений, радионуклидных методах оценки состояния коронарного русла, имеющих историческое значение, использующихся в настоящее время и перспективных, в том числе динамической однофотонной эмиссионной компьютерной томографии.

Заключение. Потенциальные возможности динамической однофотонной эмиссионной компьютерной томографии как метода количественной оценки коронарного кровотока и резерва высоки. Эта методика может стать простой и доступной альтернативой существующим способам оценки коронарного (миокардиального) кровотока и резерва, что позволит повысить информативность радионуклидной диагностики в оценке тяжести коронарной недостаточности, а значит будет способствовать более точной стратификации риска и определению походящей тактики лечения кардиологических пациентов.

Ключевые слова: динамическая однофотонная эмиссионная компьютерная томография, миокардиальный кровоток, резерв коронарного кровотока, ишемическая болезнь сердца, атеросклероз коронарных артерий.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Today, quantitative analysis of myocardial perfusion is believed to be the most informative method in assessing ischemic changes in the heart [1]. The main quantitative indicators reflecting the state of coronary hemodynamics are myocardial blood flow (MBF) and coronary flow reserve (CFR) [2]. However, methods for determining MBF and CFR are complex, expensive, and, therefore, are prac- tically not used in clinical practice. A new type of cadmium zinc tellurium (CZT) gamma cameras allows to perform dynamic single photon emission computed tomography, which was previously unavailable. This technology makes it possible to assess the MBF and CFR scintigraphic parameters.

The aim of this review was to present the normal and pathological physiology of cardiac circulation, as well as capabilities of advanced radionuclide methods in assessing parameters of coronary hemodynamics, i.e. assessment of MBF and CFR.

"PubMed", "Web of Science", "ScienceDirect", and "Elibrary" research databases were used in preparing as coronary artery disease (CAD), myocardial blood flow, coronary (myocardial) flow reserve, single photon emission computed tomography (SPECT), cadmium-zinc-telluride, positron emission tomography (PET); acronyms were also used, such as CAD, CFR, MBF, MFR, SPECT, CZT, PET.

The review includes information on the state and methods of regulating coronary hemodynamics under normal conditions and against the background of pathological changes, as well as on radionuclide methods for assessing myocardial perfusion which are of historical significance, are currently being used and promising ones, including dynamic single photon emission computed tomography (SPECT).

PHYSIOLOGICAL AND PATHOLOGICAL FOUNDATIONS OF CORONARY CIRCULATION

Understanding the physiology and pathophysiology of coronary circulation and such terms as coronary autoregulation, MBF, CFR (relative and absolute), and microvascular resistance is necessary for a correct clinical interpretation of a quantitative analysis of MBF and CFR.

Anatomy and physiology of coronary circulation

Approximately 5% of the circulatory minute volume flows into coronary arteries (CA) during the diastole phase. This is approximately 250 ml / min for a 300 gram heart muscle at functional rest. Thus, myocardial blood flow may vary from 0.3 to 0.8 ml / min / g.

Epicardial arteries, having low resistance, determine only ~5% of vascular resistance at rest [3, 4]. Arterioles outnumber arteries and determine 60% of vascular resistance [4]. Coronary capillaries account for ~25%, while venules and veins account for the remaining 10% [4].

According to the Hagen – Poiseuille equation, the pressure gradient that provides blood flow is inversely proportional to the vessel diameter in the fourth power. Thus, it means that even minimal reduction of vessel internal diameter leads to a significant decrease in the pressure gradient. Considering that proximal (i.e. epicardial) coronary arteries have a diameter of 3–4 mm [5], they represent lower resistance to blood flow than arterioles, the diameter of which is 20–200 μm [6].

Coronary arterioles are the main resistant vessels and determine myocardial blood flow conditions. [7]. The arteriole muscular wall allows for coronary autoregulation and metabolic vasodilation. Coronary autoregulation describes the capacity of the heart to maintain steady myocardial perfusion across a range of perfusion pressure [8, 9].

Capillaries are the smallest components of the heart vasculature (5–10 μm). However, this vascular structure provides 25% of vascular resistance, and at any given time it may contain up to 90% of the total blood volume of the heart muscle. Therefore, the functional condition of the capillaries determines myocardial blood flow to a greater extent than the tone of arterioles.

MECHANISMS REGULATING CORONARY VASCULAR TONE

The main mechanisms that regulate vascular tone include: 1) metabolic; 2) myogenic; 3) endothelium-dependent [8]. These three groups of factors affect arterioles depending on their diameter. [6].

Metabolic factors affect small arterioles (< 40 μm) [10, 11]. An increase in myocardial metabolism leads to an increase in the concentration of adenos-

ine [12], carbon dioxide [11], as well as in the level of acidosis [13, 14]. These metabolites penetrate into the interstitial space and interact with smooth muscle cells [15]. This interaction leads to arteriole vasodilation and increased myocardial perfusion.

The myogenic mechanism prevails in regulating the tone of arterioles with medium diameters (40–100 μm) [16, 17]. Calcium channels of smooth muscle cells (SMC) open in response to increased distension. Increasing intravascular blood pressure leads to vasoconstriction, and vice versa, when the intravascular blood pressure decreases, the intracellular Ca^{2+} concentration falls, leading to relaxation of the SMC and vasodilation. This form of myogenic control maintains stable arterial tension and is one of the mechanisms of vascular tone control [16].

The tone of large arterioles (more than 100 μm), as well as coronary arteries, is regulated mainly by the endothelium. The interaction between the blood flow and endothelial cells triggers the process of NO synthesis from L-arginine via endothelial NO synthase [18]. Then, NO diffuses into the underlying layer of smooth muscle cells of the vascular wall and activates soluble guanylate cyclase, which, in turn, converts guanosine triphosphate into cyclic guanosine monophosphate (cGMP). As a result, cGMP gives a signal to the smooth muscle cells to relax, thus vasodilation occurs.

The implementation of these mechanisms leads to the fact that the coronary blood flow increases by 4–5 times at stress and is equal to 5–6 ml / min / g. Therefore, an adequate level of myocardial blood supply is maintained [19].

MBF at rest depends on cardiac oxygen demand and myocardial contractility. Cardiac oxygen demand is determined by the heart rate and blood pressure, as well as myocardial contractility. It has been proven that women have higher MBF. In addition, it is known that taking medications, such as beta-blockers, can affect MBF, even at functional rest. The myocardial blood flow value also depends on age, the presence of endothelial dysfunction, left ventricular fibrotic changes, and anemia. [20].

The main factors which affect the magnitude of stress-induced MBF include submaximal coronary dilation, anatomical remodeling of the macro- and microcirculatory bed, increased microvascular resistance, fibrotic changes, heart denervation, systemic inflammation, and risk factors (diabetes, arterial hypertension, smoking, hypercholesterolemia). In addition, the use of caffeinated products can reduce coronary vasodilation [21].

AUTOREGULATION IN CORONARY ARTERY STENOSIS

Experimental studies by K.L. Gould and L. Lipscomb showed that myocardial blood flow remained stable until the narrowing of the coronary artery to ~85% of the diameter [22]. This was determined by great possibilities of coronary autoregulation. Further narrowing of the coronary artery could lead to a decrease in MBF at rest. One of the drawbacks of this study was the inability to assess the effect of microcirculatory dysfunction. This is explained by fact that the animals used are, as a rule, young and do not yet have disorders at the microvascular bed level.

The results obtained by K.L. Gould and K. Lipscomb were confirmed in a clinical study evaluating the impact of coronary autoregulation mechanisms in patients with coronary artery disease [23, 24]. The IDEAL study showed that patients with more severe atherosclerotic lesions had an increase in the transtenotic pressure gradient, but the MBF did not change. This was due to a decrease in microvascular resistance.

These experimental and clinical data indicate that in moderate stenosis, it is coronary autoregulation that ensures the stability of myocardial perfusion due to processes occurring at the microvasculature level. For this reason, these kinds of stenosis do not cause myocardial ischemia at rest and such patients remain asymptomatic. However, under conditions of increased loads on the cardiac muscle, compensatory mechanisms at the microcirculation level are depleted, and the epicardial artery stenoses become a limiting factor that prevents adequate MBF.

CORONARY BLOOD FLOW RESERVE

The ratio of stress-induced MBF to blood flow under functional resting is described as coronary flow reserve (CFR) [20]. CFR depends on the following factors: 1) MBF at rest; 2) perfusion pressure in arterioles; 3) extravascular coronary resistance; 4) cross-sectional area of arterioles per unit volume of myocardium [20].

CFR is a relative index and is determined by the total capacity of the coronary arteries in hyperemia

and at physiological rest and reflects the hemodynamics of the micro- and macrocirculation [20]. This distinguishes CFR from the fractional flow reserve (FFR), which is defined during invasive coronary angiography using a specialized transducer as the more distal to stenosis / more proximal to stenosis pressure ratio against the background of pharmacologically induced hyperemia. Thus, using FFR, it is possible to assess only the blood flow decrease in large epicardial arteries.

RADIONUCLIDE METHODS FOR ASSESSING CORONARY BLOOD FLOW AND CORONARY FLOW RESERVE

One of the first methods for assessing MBF and CFR was myocardial scintigraphy with ^{131}I-labeled macroaggregated albumin (^{131}I–MAA) [25]. The method consists in injecting a radiopharmaceutical (RP) with ^{131}I–MAA directly into the left ventricle and temporary embolization of the capillary bed of the coronary arteries [25]. Heymann et al. played the most significant role in the development, validation, and implementation of myocardial scintigraphy with ^{131}I-MAA [25]. In the experimental work of these authors, the scintigraphic data were compared with results of invasive measurement of MBF. A strong correlation between MBF velocity and the distribution of microspheres was shown [25].

Further studies demonstrated reliability of the ^{131}I-MAA method and recommendations for its clinical use [26–28]. Additionally, the safety of myocardial scintigraphy with ^{131}I-MAA was demonstrated in a clinical study by W.L. Ashburn et al. [29].

There are very few works by Russian authors devoted to the assessment of MBF using ^{131}I-MAA. The main contribution to the study of this quantitative assessment method of left ventricular myocardial perfusion was the research of a scientific group led by A.Z. Eventov [30]. In the works of this group, the fundamental possibility of using ^{99m}Tc for the labeling of human serum albumin microspheres was demonstrated. The method was validated, and its diagnostic capabilities were shown.

Positron emission tomography (PET) has been named the "gold standard" for evaluating MBF and CFR [31]. The fundamental possibility and validation of this method for MBF and CFR evaluation have been shown in a large number of experimental and clinical studies [1, 2, 32–34]. In particular, it was shown that only $[^{15}O]H_2O$ has a direct linear correlation between the extraction fraction value and MBF. Based on this, we can conclude that PET with $[^{15}O]H_2O$ is the most accurate method for estimating MBF and CFR. Other PET tracers (Rb, NH_3), due to the peculiarities of pharmacokinetics, describe the change in the dynamics of the MBF value worse, and the results of studies using these radionuclides are approximate [33].

However, due to the greater availability of radiopharmaceuticals, PET with Rb or ^{13}N is more commonly used in clinical practice. In addition, it should be noted that $[^{15}O]H_2O$ is not available for the practical use in the USA.

Wide diagnostic capabilities in the MBF and CFR assessment in patients with various cardiac pathologies were also demonstrated in a large number of different types of studies. The article by A. Kaufmann et al. proves the advantage of quantitative data analysis over visual evaluation of PET results. A large number of studies [34–37] demonstrated the prognostic significance of quantitative myocardial PET perfusion in assessing the risk of unfavorable cardiac events. A decrease in CFR < 1.5 is associated with a 16-fold increase in the cardiac death risk. [38].

However, the use of PET in cardiology practice is limited by such factors as the unavailability of PET scanners, radiopharmaceutical synthesis systems, as well as injection equipment. According to the European Commission for Health and Consumer Protection, PET accounts for about 6–7% of all radioisotope studies [39]. Therefore, SPECT is still the most common method of radionuclide diagnostics.

The first scientific research in MBF and CFR determination using SPECT was based on collected data of the first RP bolus passage through the cardiac cavities and ventricular myocardium and the calculation of the global retention index in the planar mode. This method made it possible to determine the global retention index of the tracer. Therefore, the CFR value was calculated based on the retention index, taking into account the activity of the RP in the pulmonary artery [40].

A strong correlation of the obtained indicator with the FFR value was demonstrated (r = 0.85, p < 0.001) [40, 41]. Yoshinori et al. [42] compared the CFR evaluated by SPECT with ^{99m}Tc-Sestami-

bi and PET with [^{15}O]H_2O. However, the SPECT method lowered CFR values in comparison with PET [42].

Thus, a tomographic mode was used to estimate the regional values of MBF and CFR by fast rotating the gamma-camera detectors. Using this recording technique, Cuocolo et al. [43] showed a strong correlation ($r = 0.85$, $p < 0.001$) between the scintigraphic CFR index and intracoronary Doppler data: 1.36 ± 0.43 vs. 1.39 ± 0.42, respectively.

Similar results were obtained by Hsu et al. [44]. The authors did not find significant differences between MBF and CFR determined by SPECT with ^{99m}Tc-Sestamibi and PET with ^{13}N-ammonium. There were no significant differences in the studied parameters: MBF at rest was 0.78 ± 0.14 ml / min / g vs. 0.78 ± 0.22 ml / min / g ($p = 0.929$), MBF against the background of the stress test was 2.80 ± 0.39 ml / min / g vs. 2.83 ± 0.54 ml / min / g ($p = 0.766$), CFR was 3.58 ± 0.47 vs. 3.67 ± 0.47 ($p = 0.472$) in the group of healthy volunteers; CFR at rest was 0.83 ± 0.24 ml / min / g vs. 0.74 ± 0.31 ml / min / g ($p = 0.088$), CFR against the background of the stress test – 1.95 ± 0.66 ml/min/g vs. 1.93 ± 0.78 ml/min/g ($p = 0.813$), CFR was 2.4 ± 0.78 vs. 2.53 ± 0.72 ($p = 0.601$) in coronary artery disease (CAD) patients for PET and SPECT, respectively. As in the previous work, there was an insignificant downward shift in the MBF and CFR indices determined by SPECT compared to PET. In addition, the authors demonstrated high inter-and intra-operative reproducibility of quantitative SPECT results.

A group of authors from Japan, led by T. Tsukamoto [45], compared the CFR values determined by dynamic SPECT with ^{99m}Tc-MIBI and PET with [^{15}O]H_2O. As a result, a strong correlation between MBF and CFR values estimated by these methods was shown ($r = 0.84$, $p < 0.0001$). However, the MBF values according to the SPECT data were significantly lower compared to the PET results. The authors pointed out that the modification of the formula for calculating MBF values could improve the accuracy of the SPECT method for quantitative analysis of myocardial perfusion.

However, it must be noted that a significant disadvantage of the conventional SPECT is the inability to perform dynamic data collection in the tomographic mode. In addition, Anger-type gamma cameras are significantly inferior to PET in terms of temporal and spatial resolution [46].

Today, there is a new generation of gamma cameras with cadmium zinc telluride (CZT) detectors, as well as a subclass of specialized cardiac devices. Such gamma cameras have high sensitivity and resolution [48]. Tomographic three-dimensional images are generated during data collection. This, in combination with new algorithms for reconstruction of scintigraphic images, makes it possible to perform dynamic SPECT and evaluate the MBF and CFR indicators [49].

One of the fundamental works on assessing the capabilities of CZT gamma cameras to evaluate MBF and CFR is a study by Ruddy et al. [50]. In the experiment on large animals, the authors compared the MBF and CFR values determined by SPECT with three radiopharmaceuticals: ^{201}Tl, ^{99m}Tc-Tetrofosmin, and ^{99m}Tc-Sestamibi. Scintigraphy with ^{99m}Tc-MAA was chosen as a reference method. A strong correlation between tracers and the reference method was found. Thus, MBF values correlated better with ^{201}Tl ($r = 0.81$) and to a lesser extent with ^{99m}Tc preparations with 0.56 (Tetrofosmin) and 0.38 (Sestamibi). However, according to the RCC indicator, a strong correlation was found with all investigated RPs: ^{201}Tl ($r = 0.81$), ^{99m}Tc-Tetrofosmin ($r = 0.82$), ^{99m}Tc-Sestamibi ($r = 0.8$) [50].

One of the first clinical studies was a work of a scientific group led by S. Ben-Haim from the Institute of Nuclear Medicine, University College London [51]. The authors demonstrated the practical possibility of evaluating MBF and CFR using dynamic SPECT and showed high reproducibility of the results. Additionally, it was shown that the CFR value was statistically significantly lower in the group of patients with angiographically significant coronary artery stenoses, compared to patients without them. In addition, CFR significantly decreased as the degree of coronary artery stenosis increased. However, the authors emphasize the need for further clinical validation of this method.

A study by B. Bouallègue et al. [52] compared the global and regional CFR values determined by dynamic SPECT with the results of invasive coronary angiography and FFR in patients with severe multivessel coronary artery disease. According to the data obtained, the global CFR determined

for the entire left ventricle significantly correlated with the number of vessels with stenosis ($r = 0.70$, $p < 0.001$); and its regional value (determined for the coronary artery pool) was associated with both the degree of stenosis and the FFR value. At the same time, ROC analysis showed that the sensitivity, specificity, and diagnostic accuracy of this indicator for assessing the hemodynamic significance of coronary artery stenoses were 89%, 82%, and 85%, respectively.

It should be noted that, in contrast to MBF, the FFR value does not reflect the microcircular conditions. Comparison of the two methods does not contradict logic; however, certain inaccuracies will inevitably arise in the results of such an analysis. Based on the foregoing, a direct comparison of PET and dynamic SPECT data is more correct from the point of view of the coronary microcirculation physiology.

Nikoulou et al. performed such kind of comparative analysis between the results of dynamic SPECT with ^{99m}Tc-tetrofosmin and PET with ^{13}N-ammonium. The authors did not find differences for MBF at rest, but dynamic SPECT lowered the stress-induced MBF values compared to PET [53]. The sensitivity, specificity, and diagnostic accuracy of dynamic SPECT in identifying ischemia with a cut-off CFR value of 1.26 were 70, 78, and 75%, respectively. The authors emphasize that the CFR determination on CZT cameras can be used in clinical practice as an alternative to PET.

A comparative analysis of the results of dynamic SPECT and cardiac magnetic resonance imaging in patients with known or suspected CAD was carried out in the work of Fang et al. According to the results obtained, stress-induced MBF, assessed using the above-described methods, showed a strong correlation ($r = 0.76$). The ROC analysis showed that, with a stress-induced MBF of 1.32 ml / g / min, the sensitivity, specificity, and diagnostic accuracy of dynamic SPECT in identifying obstructive coronary artery disease were 94%, 90%, and 93%, respectively. Scintigraphic assessment of CFR was not performed in this study.

A study by Miyagawa et al. [55] was devoted to the assessment of the coronary hemodynamics in patients with multivessel CAD. It showed that CFR correlated with left ventricular ejection fraction, FFR, and SYNTAX Score. The sensitivity and specificity of dynamic SPECT in the identification of multivessel coronary artery disease were 93.3% and 75.9%, respectively. The sensitivity and specificity of dynamic SPECT in the identification of multivessel coronary artery disease with a cut-off CFR value of 1.3 was 93.3 and 75.9%, respectively.

Significant results considering the dynamic myocardial SPECT technique were obtained by Wells et al. [56]. The authors investigated the effect of such factors as the attenuation correction, motion correction and binding of the tracer to red blood cells on CFR and MBF. According to the data obtained, corrections for the displacement of the patient's body and for the residual activity of RP in the blood pool increased the accuracy of the MC and RCC assessment using dynamic SPECT compared to PET. However, the correction of attenuation did not increase the accuracy of the scintigraphic technique. Additionally, the authors showed a correlation between the scintigraphic values of MBF and CFR and the PET data with $[^{15}O]H_2O$.

In 2018, the WATERDAY study [57] was carried out, aimed at assessing the MBF and CFR values based on dynamic SPECT data. The study included patients with stable ischemic heart disease. All patients underwent dynamic SPECT, PET with $[^{15}O]H_2O$, and invasive coronary angiography with FFR assessment. The authors showed high interoperable reproducibility of the scintigraphic method of MBF and CFR assessment. Also, a strong correlation between dynamic SPECT and PET data and the FFR value was found. Additionally, the sensitivity, specificity, accuracy, and positive and negative predictive values of the scintigraphic CFR were calculated for the identification of ischemia: 83.3%, 95.8%, 93.3%, 100% and 85.7%, respectively, and for the detection of hemodynamically significant stenosis (FFR $\leq$ 0.8): 58.3%, 84.6%, 81.1%, 36.8% and 93%, respectively.

In the work in the nonselective group of patients with an established diagnosis and suspicion of coronary artery disease, Zavadovsky et al. [58] showed a strong positive correlation between MBF, absolute and relative CFR, and FFR value: $p = 0.63$ ($p < 0.001$), $p = 0.66$ ($p < 0.01$), and $p = 0.73$ ($p < 0.01$), respectively (a cut-off CFR value $\leq$ 1.48). The sensitivity and specificity of dynamic SPECT with the assessment of quantitative myocardial perfusion indices for identifying

the hemodynamic significance of coronary artery stenosis were 69.2% and 93.3%, respectively. In another study, the same group of authors [59] showed a decrease in global CFR in patients with multivessel CAD compared to the control group: 1.39 (1.12; 1.69) and 1.86 (1.59; 2.2), $p < 0.001$. Thus, the sensitivity and specificity of dynamic SPECT in the identification of multivessel CAD were 81.8% and 66.7%, respectively.

CONCLUSION

Despite the technical differences between PET and SPECT, the methods used to evaluate MBF and CFR are largely similar. Moreover, these methods practically do not differ from one of the first methods for determining MBF and CFR – scintigraphy with 131I and ^{99m}Tc-MAA. The basic principle of the above-described methods is to evaluate the retention index of the radionuclide tracer and convert it to the myocardial blood flow value, using various mathematical algorithms and models. In the studies analyzed, various techniques were used for both dynamic SPECT and the processing of the results obtained (Table).

Most studies (62.5%) used a common radiopharmaceutical, ^{99m}Tc-MIBI. The bolus principle of RP injections was used in 75%. Therefore, short frames were more often used to construct the "activity-time" curve. In half of the studies, a one-compartment model was used to evaluate the dynamic myocardial SPECT data. This is determined by the fact that this model is more common and is the base model in processing PET data. At the same time, the Net Retention model has been used more recently.

Table

Analysis of various techniques for conducting and processing the results of dynamic SPECT

Author	Gamma camera	Type/administration method of RP	Stress agent	Algorithm of reconstruction	Model of reconstruction	MC/AC	Research time	Protocol
Agostini D. et al., 2018	D-SPECT	MIBI/injector (bolus)	Regadenoson, 400 mg	32 frames 21 × 3 sec 1 × 9 sec 1 × 15 sec 1 × 21 sec 1 × 27 sec 7 × 30 sec	Net Retention	?/–	6 min	One-day
Fang Y.D. et al., 2017	GE Discovery NM 530c	MIBI/? (bolus)	Dipyridamole, 0.124 mg/kg/min	48 frames 48 × 30 sec	2-compartment model	?/–	5 min	One-day
Bouallègue F.B. et al., 2015	GE Discovery NM 530c	Tetrofosmin/? (bolus)	Dipyridamole, 0.75 mg/kg, 4 min	48 frames 30 × 3 sec 18 × 15 sec	1-compartment model	?/–	6 min	One-day
Nikoulou R. et al., 2016	GE Discovery CT/NM 570c	Tetrofosmin/? (bolus)	Adenosine, 140 mcg/kg/min	12 frames 6 × 10 sec 6 × 30 sec	1-compartment model	?/–	4 min	One-day
Miyagawa M. et al., 2017	GE Discovery NM 530c	MIBI, Tetrofosmin/? (bolus)	ATP, 160 mcg/kg/min, 5 min	200 frames 200 × 3 sec	1-compartment model	?/–	10 min	One-day
Ben-Haim S. et al., 2013	D-SPECT	MIBI/injector (bolus)	Adenosine, 140 mcg/kg/min, 6 min; Dipyridamole, 0.142 mg/kg/min, 4 min	60–70 frames	2-compartment model	?/–	6 min?	One-day, two-day
Wells R.G. et al., 2017	GE Discovery NM 530c	Tetrofosmin/ injector, 9 ml in 30 sec	Dipyridamole, 0.142 mg/kg/min, 5 min	19 frames 9 × 10 sec 6 × 15 sec 4 × 120 sec	1-compartment model	+/+	11 min	One-day
Zavadovsky K.V. et al., 2019	GE Discovery NM/CT 570 c	MIBI (bolus)	Adenosine, 140 mcg/kg/min, 4 min.	44 frames 40 × 4.5 sec 4 × 45 sec	Net Retention	+/+	6 min	One-day, two-day

Note. The study was carried out with correction of scintigraphy images – "+", without correction of scintigraphy images – "–"; data were not presented in the study – "?".

This model is less dependent on the pharmacokinetics of the radionuclide indicator as compared to one- and two-compartment models. This model is appropriate for tracers with a nonlinear dependence of retention and the blood flow, such as ^{99m}Tc-MIBI or ^{99m}Tc-tetrofosmin. It should be noted that most authors used a one-day study protocol for dynamic SPECT. This requires a correction parameter for the second study and complicates the mathematical processing of results.

Methods for improving the quality of scintigraphic images, such as attenuation correction (AC), motion correction (MC), and correction of heartbeat artifacts [60], were not used in most of the reviewed studies. Currently, there is no common opinion about the need to include such tools for processing dynamic SPECT data. However, the work of Ruddy et al. [56], devoted to the influence of various correcting factors on scintigraphic parameters of MBF and CFR, showed the need to use motion correction, while the use of attenuation correction alone did not significantly affect these indicators.

Dynamic SPECT is performed according to basic principles; however, there is a large number of technical differences that are listed above. Thus, the evolution of the dynamic SPECT method with MBF and CFR assessment is not complete, although it is at the final stage of conceptual and methodological research. This is confirmed by similar research results presented in this review and validation of the scintigraphic method with "gold standards" – PET and FFR [57, 58].

Currently there is an insufficient number of clinical trials in this area. However, the potential of dynamic SPECT as a method for quantification of coronary blood flow and reserve is high. This technique can become a simple and affordable alternative to existing methods for assessing MBF and CFR. This will increase the informative value of radionuclide diagnostics in assessing the severity of coronary insufficiency for more accurate risk stratification and determination of appropriate treatment strategy for cardiac patients.

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