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Nuclear imaging of chemotherapy-induced cardiotoxicity

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The high efficiency of modern chemotherapy has made it possible to achieve great success in the treatment of cancer. Cardiovascular adverse effects are a major disadvantage of anticancer therapy, often requiring low and less effective doses or even drug withdrawal. Nuclear imaging techniques are the most sensitive in early detection of left ventricular damage and dysfunction during chemotherapy. This review presents modern data on the potential of nuclear imaging of cardiotoxicity.

Keywords: cardiotoxicity, cardio-oncology, anthracyclines, heart failure, nuclear imaging.

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Over the past several decades, early diagnosis and the development of new anticancer drugs have significantly improved the prognosis of cancer patients. Unfortunately, many of these drugs have a number of cardiac side effects, in particular related to the so-called cardiotoxicity. Its early detection and treatment are one of the tasks of modern cardio-oncology, and the solution of this task not only reduces the incidence of cardiovascular complications, but also provides better treatment for the underlying disease [1]. The most common cardiotoxic effects are caused by drugs such as anthracyclines, cyclophosphamide, monoclonal antibodies, and tyrosine kinase inhibitors. Unfortunately, the available knowledge about the pathophysiology of cardiotoxicity is not exhaustive, resulting in detecting it in most cases already at the stage of manifestation of cardiovascular disease. Irreversible cardiotoxic effects are caused by the production of free radicals in cells, impaired adrenergic functions and, ultimately, the death of cardiomyocytes due to calcium overload. Among the cardiovascular complications of chemotherapy are not only the development of left ventricular (LV) systolic dysfunction and heart failure (HF), but also myocarditis, arrhythmias, thrombosis, coronary, pericardial and valvular pathology [2]. However, it is the decrease in LV contractility that is the most frequently observed manifestation of cardiotoxicity, and it is associated with increased mortality during and after chemotherapy [3]. Chemotherapy-induced cardiotoxicity is defined as a decrease in LV ejection fraction (EF) due to hypokinesia (diffuse or more pronounced in the interventricular septum), with the appearance of congestive HF symptoms. A decrease in LVEF by at least 5%, or to a value <55% with the appearance of congestive HF signs and symptoms, or by at least 10% or to a value <50% without HF symptoms is considered significant from baseline values [4]. A decrease in EF by more than 10% or to a value of <50% is a clinical reason for discontinuation of the prescribed anticancer drug [5].

Thus, it is the assessment of LVEF in dynamics that is most important for identifying criteria for cardiotoxicity. In this case, the most accurate assessment of changes in LVEF plays a special role, that imposes significant requirements on the quality of images and intra-/inter-operator reproducibility [6]. It should be emphasized that with different research methods, the norm is a different value of LVEF [7-9]. Echocardiography (EchoCG) and magnetic resonance imaging (MRI) are the most commonly used imaging methods for non-invasive assessment of LV contractility. Two-dimensional echocardiography is the most accessible method, but its accuracy is low due to geometric assumptions, and the variability in measuring LVEF is about 10%, therefore, the possibility to reliably record a decrease in EF in dynamics by 5-10% by this method is considered doubtful [6]. Three-dimensional echocardiography is a more accurate method for measuring LV volume and function [10]. Nevertheless, echocardiography can be performed with sufficient accuracy only in 60% of patients with limited acoustic window, in particular, after mastectomy [11]. A more accurate method for assessing the functional parameters of the heart is MRI due to the low variability of LVEF measurement (from 2,4% to 7,3%), the absence of deficiencies in echocardiography and the possibility

of structural assessment of the myocardium, including edema and fibrosis [12]. Currently, the assessment of LVEF in dynamics using MRI is most often used as a verification method in assessing the effectiveness of cardioprotective drugs [13, 14]. The disadvantages of MRI are the duration of the study (10-20 min), the limitations in patients with claustrophobia and the presence of implanted devices, as well as the high cost, especially given the need for several repeated studies.

Radionuclide diagnostic (RND) methods such as: scintigraphy, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) also play an important role in the assessment and follow-up of cancer patients who have been prescribed potentially cardiotoxic chemotherapy. The main advantage of RND methods, which plays a special role in these cases, is the proven high reproducibility and operator independence due to fully automatic data collection [7, 15]. Moreover, in addition to the possibility of an accurate assessment of EF and a sensitive assessment of its dynamics, RND has a number of other indicators for non-invasive assessment of earlier biological processes preceding anatomical and even more functional damage to the myocardium [16].

Radionuclide (tomo)ventriculography. Planar ECG-synchronized ventriculography (MUGA) with labeled erythrocytes has been a proven method for over 40 years [17]. In this study, a series of summation images of the cardiac cavities is recorded at several (usually 16) stages of the cardiac cycle. This allows with high accuracy and reproducibility to assess the volume of the cavity and LVEF, including in cancer patients [18]. In a study involving patients with non-Hodgkin's lymphoma and doxorubicin therapy at a high cumulative dose, the method sensitivity was 90% and the specificity was 72% in predicting the development of chronic HF [19]. These data were supplemented with a study that showed that there can be significant discrepancies between clinical symptoms of HF and decrease in LVEF. Thus, in 66% of patients with a clinical picture of doxorubicin-induced HF, there was no significant decrease in LVEF according to planar MUGA [20]. It is obvious that patients with chronic HF and intact LVEF constitute a separate category that requires a deeper study of the myocardium than an assessment of only its contractile ability [21, 22].

The tomographic variant of radionuclide ventriculography — radionuclide tomoventriculography (RTVG) — allowed raising the sensitivity of assessing myocardial contractility disorders to a new level. It became possible to more accurately assess disorders of global and local contractility, systolic and diastolic function of both the LV and the right ventricle, which, according to some studies, made it possible to more accurately monitor and personalize therapy in patients with HF [20]. There is evidence that the EF values slightly underestimated in RTVG compared to radionuclide ventriculography (both equilibrium and first-pass) and EchoCG, however, in general, these methods have good cross-correlation [23]. At the same time, the maximum accuracy of calculating LVEF based on RTVG data depends on a number of factors, including on the number of images within the R-R interval (preferably 16) and the quality of the study protocol. New life for ventriculographic techniques can be given by the introduction of new models of single-photon tomographs based on cadmium-zinc-telluride (CZT) detectors [24].

Scintigraphy with ^{111}In-antimyosin. Antimyosin is a specific marker of myocardial cell damage and necrosis. It binds to intracellular myosin in violation of the integrity of the sarcolemma, causing irreversible damage to cells. The accumulation of ^{111}In-labeled antimyosin has been studied in myocardial infarction, myocarditis, heart transplant rejection, and anthracycline cardiotoxicity [25]. Scintigraphy and SPET with this radiopharmaceutical (RP) may play a role in the subclinical assessment of LV dysfunction [26]. In particular, after a cycle of courses of anthracycline chemotherapy in patients with breast cancer without cardiovascular risk factors or previous chemotherapy or radiotherapy of the mediastinum, the accumulation of labeled antimiosin was indicated, and the level of accumulation of this RP correlated with a subsequent decrease in LVEF. In patients with increased accumulation of this RP in the myocardium (heart/mediastinal accumulation ratio $\geqslant$1,9) with a cumulative dose of doxorubicin of 240-300 mg/m^2 a more pronounced decrease in LVEF (>10%) was developed with a subsequent cumulative dose of 420-600 mg/m^2 [25]. In addition, in patients with a persistent decrease in EF, the accumulation of ^{111}In-antimyosin was more pronounced compared with those in whom the decrease in EF was reversible — 1,83±0,37 vs 1,52±0,21 ($p<0,01$) [27]. Thus, scintigraphy with ^{111}In-antimyosin turned out to be useful as a marker of an increased risk of developing HF in patients who are on therapy with high doses of anthracyclines, including for identifying patients with a higher probability of developing irreversible LV dysfunction, which will require discontinuation of this drug.

Scintigraphy with ^{123}I-meta-iodine-benzylguanidine (MIBG). MIBG is a structural analogue of norepinephrine, but it does not undergo metabolism, accumulating in presynaptic adrenergic terminals and thus allowing them to be visualized. Chemotherapy activates the body's compensatory response in the form of an increase in the activity of the adrenergic and renin-angiotensin systems to preserve the blood supply to organs, namely, an increase in the release of norepinephrine is noted, which leads to the depletion of its deposits and a decrease in the activity of its carrier hNET1 [28]. This leads to a decrease in the capture of MIBG and an acceleration of its removal. A number

of studies have shown that a decrease in the relative accumulation of MIBG in the myocardium (H/M <1,9) is more often observed in patients taking a higher dose of doxorubicin, and is a predictor of a decrease in LVEF in the future [25].

Scintigraphy with ^{111}In-trastuzumab. Anthracyclines therapy in cancer patients can increase the expression of human epidermal growth factor receptor 2 (HER2) by cardiomyocytes. In patients previously treated with anthracyclines, trastuzumab, a drug with a direct effect on HER2, can cause cardiotoxic effects by inhibiting not only HER2 tumor cells, but also cardiomyocytes, which activates apoptotic mechanisms and enhances anthracycline-induced oxidative stress. Thus, scintigraphy with ^{111}In-labeled trastuzumab (^{111}In-Tz) can be used to assess the level of HER2 expression by cardiomyocytes, and, therefore, the risk of LV dysfunction in patients receiving this drug [29]. In a study by Behr, et al. ^{111}In-Tz scintigraphy was performed in 20 patients with metastatic HER2/neu-positive breast cancer who were previously treated with anthracyclines and are scheduled for trastuzumab therapy. The accumulation of ^{111}In-Tz in the myocardium was noted in 7 patients, of whom 6 subsequently developed II-IV HF of functional class according to NYHA (New-York Heart Association), while none of the 13 patients without the accumulation of this RP had adverse cardiovascular events [30]. However, in a subsequent study [31], these results could not be repeated; in general, the rationale for using this RP in terms of predicting the development of trastuzumab-induced cardiotoxicity requires further substantiation.

Scintigraphy with ^{99m}Tc-annexin V. Apoptosis of cardiomyocytes plays a decisive role in the development of cardiomyopathies, and is observed in many ischemic, inflammatory and reactive conditions, including anthracycline-induced cardiomyopathy and myocarditis [32]. In cells that have triggered the apoptosis mechanism, proteases and sphingomyelinases are activated at an early stage, followed by exposure of phosphatidylserine molecules on the outer membrane of the cell. Annexin-V has a high affinity for phosphatidylserine and, thus, allows visualization of apoptotic processes in cells [33]. Studies of scintigraphy with labeled annexin V were carried out in animals; there was an increased accumulation of this RP in the myocardium in acute and chronic doxorubicin-induced cardiomyopathy with signs of apoptosis. At the same time, signs of oxidative stress were confirmed by histological analysis [34]. The clinical use of this RP requires further research.

Scintigraphy with^{123}I-fatty acid. Chemotherapy with drugs of the taxane class (docetaxel, paclitaxel) is used in the treatment of breast, lung and ovarian cancer. The use of these drugs is associated with the risk of ischemic and arrhythmic side effects with a certain probability of developing HF. In particular, taxanes have a damaging effect on the transport systems in cardiomyocytes, which leads to impaired storage of free fatty acids in the cytosolic lipid pool and a decrease in the level of mitochondrial absorption of free fatty acids for beta-oxidation. Scintigraphy with 123-iodine-labeled phenyl-methyl-pentadecanoic acid (^{123}I-BMIPP) is used to assess violations of the biochemical processes of oxidation of free fatty acids [35]. A number of studies have shown a decrease in the accumulation of ^{123}I-BMIPP in the myocardium during chemotherapy, including both doxorubicin and taxanes. At the same time, a decrease in the accumulation of this RP in the myocardium depends on the cumulative dose of doxorubicin and is associated with a more pronounced decrease in LVEF in the future [35].

PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). The use of PET in cardio-oncology looks promising, since the most common RP for PET, ^{18}F-FDG, has long won a solid position both for assessing the prevalence of a tumor process and response to therapy, and for assessing myocardial metabolism, which is an important step in assessing its viability. In addition, PET with ^{18}F-FDG is used to detect inflammation (for example, in myocarditis) [36], to monitor the therapeutic response in primary heart lymphoma, and to assess metastatic lesions of the pericardium [37]. However, chemotherapy does not cause significant disturbances in glucose metabolism in cardiomyocytes according to PET with ^{18}F-FDG; its level may even increase on the background of a decrease in fatty acid intake. This is probably due to the partial transition of myocardial metabolism towards aerobic glycolysis under conditions of the occurrence of hypoxic processes in the myocardium on the background of chemotherapy [38, 39]. PET with neurotropic RP (^{11}C-hydroxyephedrine) reveals a decrease in β-adrenergic receptor density in patients with HF and decreased LVEF, but these processes are not specific for chemotherapy-induced cardiotoxicity [40].

Scintigraphy and SPET with ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin. Myocardial perfusion scintigraphy is the most demanded study in nuclear cardiology, it also has certain prospects for imaging signs of cardiotoxicity. The performance of this study with ECG-synchronization (S-SPET) is currently an integral part of the protocol of perfusion scintigraphy at rest and after exercise testing to assess transient myocardial ischemia in patients with suspected or established coronary artery disease. Initial acquisition of end-diastolic and end-systolic LV volumes in automatic mode, improvement of the quality of detecting systems and image processing programs led to the fact that the accuracy and reproducibility of perfusion S-SPET in assessing LVEF is not inferior to tomoventriculography [41]. Like RTVG, perfusion S-SPET in the modern version provides the speed and time parameters of the expulsion of blood from the LV into systole and its filling in diastole.

The most important advantage of ECG-synchronized studies with ^{99m}Tc-MIBI or tetrofosmin is the simultaneous comparison of LV myocardial contractility with its cellular perfusion [42]. The mechanism for assessing myocardial perfusion using these RP is based on the fact that they are both lipophilic cations that penetrate into the cardiomyocyte by passive diffusion (along an electrochemical gradient) in proportion to myocardial blood flow. The further fate of these two RPs inside the cell differs. While tetrofosmin predominantly accumulates in the cytosol, ^{99m}Tc-MIBI is more sensitive to differences in the potential of the outer membrane of the cardiomyocyte and the mitochondrial membrane, which has the greatest negative charge. As a result, ~90% of intracellular ^{99m}Tc-MIBI accumulates in intact mitochondria, thus reflecting the preservation of the cell's energy chains [43]. Toxic effects of anthracyclines, including associated with oxidative stress, cause direct damage to mitochondria and, as a consequence, a decrease in the uptake of ^{99m}Tc-MIBI by them [44]. This is manifested by the appearance of diffuse changes in the accumulation of RP in the myocardium, which can be reliably visualized at the current level of image quality. According to our own preliminary data, such initial changes in perfusion can occur during several courses of chemotherapy and be reversible; however, when they worsen, they are already visually interpreted as signs of diffuse fibrosis and become partially irreversible. At the same time, the severity of such diffuse perfusion disorders can be expressed in quantitative units, which, upon reaching a certain threshold, become an unfavorable prognostic sign in terms of the absence of an increase in EF after withdrawal or replacement of the polychemotherapy regimen [45].

A new direction in the assessment of cardiotoxicity using SPET with ^{99m}Tc-MIBI may be the assessment of the rate of its removal from the myocardium. This approach is borrowed from the biphasic radionuclide mammography method, which is widely used in the diagnosis and assessment of the response to breast cancer therapy. The principle of this method is that ^{99m}Tc-MIBI also accumulates in the mitochondria of some tumor cells, in particular, malignant tumors of the breast and lungs. In this case, the accumulation of ^{99m}Tc-MIBI in cancer cells depends not only on the activity of cell proliferation, but also on the presence of mechanisms for removing this RP from the cell. In particular, the presence of P-glycoprotein on the tumor cell membrane increases its protection, mediating the rapid elimination of foreign substances, including molecules of anticancer drugs. Thus, the acceleration of the removal of ^{99m}Tc-MIBI from the tumor focus, according to biphasic mammoscintigraphy, is an important sign of its drug resistance [46]. As applied to myocardial scintigraphy, this means that the accelerated removal of ^{99m}Tc-MIBI from cardiomyocytes is an earlier marker of mitochondrial damage, even at the stage of disrupting of energy chains work and reducing the potential of its matrix, i.e., before irreversible changes occur, which are already manifested by a decrease in the level of accumulation of RP [42, 47, 48].

In general, cardiotoxicity is one of the main and clinically and prognostically significant side effects of anticancer therapy. A decrease in LVEF is the most validated criterion for assessing the presence of myocardial damage during or after chemotherapy. However, a decrease in myocardial function occurs only when there is significant damage to it, and compensatory mechanisms are exhausted [49]. In this case, the time for taking cardioprotective measures is lost, since myocardial damage becomes irreversible and leads to the development of chronic HF [50]. Thus, in cardio-oncology there is a need for new non-invasive methods — inexpensive, more sensitive in terms of recognizing signs of cardiotoxicity at the subclinical stage, and providing prognostic information to reduce mortality in cancer patients. There are interesting prospects for early detection of myocardial damage by nuclear imaging using new molecular indicators that can help identify patients at high risk of developing LV dysfunction who are undergoing chemotherapy. Further experimental and clinical studies are required to implement these techniques and RP.

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