Methods of Detecting the Reduction of Myocardial Contractility in Patients with Oncohematological Profile in the Course of Polychemotherapy

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Abstract: The article is devoted to the modern representation of methods of diagnostics of subclinical myocardial contractile dysfunction in oncohematological patients in the course of chemotherapeutic treatment. Taking into account that the possibilities of standard echocardiographic examination not always allow to identify the subclinical dysfunction of the left ventricle (LV) myocardium, it is necessary to use more sensitive diagnostic strategies for the monitoring of myocardial function. The aim of this literature review is to present problems and prospects for detecting early, subclinical changes in the contractility of the LV myocardium in oncohematological patients who have undergone chemotherapeutic treatment, and to assess their significance as predictors of late chemotherapeutic cardiotoxicity. Echocardiography to assess global longitudinal strain (GLS), stress echocardiography (SE) with determination of the contractile reserve (CR) have a predictive role in the diagnosis of changes in myocardial contractility at early stages and the use of these methods in the examination of oncohematological patients will improve their quality of life and increase its duration.

Key Words: echocardiography, ejection fraction, global longitudinal strain, stress echocardiography, left ventricular contractile reserve.

Introduction:
Globally, 12.7 million people are diagnosed with cancer each year, and morbidity is predicted to increase by 40% in high income countries between 2008 and 2030 [1]. Cardiovascular diseases now account for about 32% of deaths worldwide, a significant proportion of which are previously treated with chemotherapy [2]. The latest recommendations of the European Society of Cardiology have subdivided cardiovascular complications into nine categories, including myocardial dysfunction, coronary heart disease, valve pathology, arrhythmias and pericarditis [3]. The cardiotoxicity of some groups of chemotherapeutic agents, such as anthracyclines (e.g. doxorubicin) [4] and alkylating agents (e.g. cyclophosphamide) [5], is well known. The effects of other groups of drugs on the cardiovascular system, such as monoclonal antibodies and immune response checkpoint inhibitors, are being actively studied. The positive clinical effects of new combinations of chemotherapeutic, immunotherapeutic agents and targeted drugs are balanced by the increased risk of acute and long-term toxicity to many organs and systems [6]. Toxicity to the cardiovascular system is one of the most formidable remote complications of chemotherapy, leading to a marked decline in quality of life of the patient and a decrease in life expectancy in this group of patients [7]. Standard echocardiographic changes, such as a reduction in the left ventricular ejection fraction (LVEF), are usually observed when myocardial damage has already occurred and in most cases is irreversible [8]. Sensitive and non-invasive methods for determining myocardial contractility, such as the determination of GLS and left ventricular contractile reserve (LVCR) are essential for patients undergoing chemotherapy [9]. SE with dobutamine makes it possible to estimate the LVCR and is widely used in patients with cardiovascular pathology [10], and the results of the use of SE to assess the LVCR in oncohematological patients, who received chemotherapeutic treatment according to various schemes performed to detect subclinical dysfunction of the LV...
myocardium, were demonstrated in several studies with inconsistent results. This may be due to the fact that GLS is more sensitive to early and subclinical changes in the contractility of the LV in onc hematological patients who have undergone chemotherapy treatment, and to assess their significance as predictors of late chemotherapeutic cardiotoxicity. We searched for the results of clinical studies on the contractility of the LV myocardium in cancer patients undergoing chemotherapy drugs from different groups in the PubMed database from January 1, 2004 to March 1, 2019 (over the past 15 years), based on the following terms: echocardiography, LVEF, GLS, LV, SE with dobutamine, LVCR, LV myocardial contractility, cardiotoxicity, cardiovascular events, anthracyclines, and GLS in onc hematological patients undergoing chemotherapy treatment in childhood. Approximately 6% of the patients who were treated with anthracyclines or pertuzumab may have decreased LV systolic function, found in the study of Yu et al., it was noted that a significant proportion of patients with cancer, having studied the frequency of reduction of GLS after chemotherapy treatment, the treatment with chemotherapeutic agents, such as doxorubicin, iphophonamide or pertuzumab, is correlated with a decrease in GLS [22]. In the study of Yu et al., it was noted that a significant proportion of adults receiving chemotherapy in childhood, adolescence and young age, have abnormal LV systolic function, found in the measurement of GLS, despite the presence of a normal fraction of LVEF (abnormal GLS (=16%) was observed in almost one quarter of the study participants, a corresponding decrease in the LVEF < 55% in 6.0%) [23].

A clinically significant change in the GLS is a relative decrease in this index by more than 15% of the baseline [11]. Moon et al. estimated GLS after anthracycline administration and this index turned out to be on the average 7.4% lower in the studied group of patients in comparison with the control [21]. In the routine determination of GLS among patients with cancer, the working group led by Laufer-Perl concluded that a significant decrease in this parameter is often observed among patients with cancer, having studied the frequency of reduction of GLS after chemotherapy treatment, the treatment with chemotherapeutic agents, such as doxorubicin, iphophonamide or pertuzumab, is correlated with a decrease in GLS [22]. In the study of Yu et al., it was noted that a significant proportion of adults receiving chemotherapy in childhood, adolescence and young age, have abnormal LV systolic function, found in the measurement of GLS, despite the presence of a normal fraction of LVEF (abnormal GLS (=16%) was observed in almost one quarter of the study participants, a corresponding decrease in the LVEF < 55% in 6.0%) [23].

In a large cohort study, Armstrong et al. assessed the LVEF, global longitudinal and circumferential myocardial deformities in 1820 patients who underwent chemotherapeutic treatment in childhood. Approximately 6% of the patients underwent a decrease in the LVEF below 50%. However, about 1/3 of the patients with a normal LVEF showed signs of cardiac disease in the form of abnormal parameters of global longitudinal and circumferential myocardial deformities [24]. These observations indicate that the prevalence of LV systolic dysfunction among long-term chemotherapeutic patients may be significantly underestimated when only the LVEF is used in diagnosis. Taking into account that the Paterucha et al. study found that the decrease in GLS preceded the decrease in the LVEF among adolescents receiving treatment regimens including anthracyclines [25], it is very important to use the assessment of GLS at reversible stages of cardiotoxic complications. All of the above data indicate the absolute need to determine the GLS in onc hematological patients undergoing chemotherapy or who have completed treatment as an auxiliary tool, but the long-term prognostic significance of abnormal GLS is currently in the process of research to determine the correlation between the reduction of this indicator and the development of heart failure, as it will be extremely important for clinical decision-making in cardiology.

**SE with assessment of LVCR as a method of diagnostics of polychemotherapy complications**

SE is widely used as a diagnostic tool in cardiology to diagnose coronary heart disease and assess the LVCR, but it is not not the only option for this technique for today. Low-dose SE
with dobutamine (5-10 µg/kg/min), which detects myocardial contraction reserve without developing a chronotropic effect, can also be assessed in practice as a safe and sensitive method to assess the reduction of myocardial contractility in patients receiving chemotherapy treatment. Clinical use of this method may contribute to early detection of subclinical myocardial dysfunction in patients without myocardial dysfunction at rest by increasing myocardial contractility and evaluating the functional reserve of the heart against pharmacological load [26]. The LVCR is a measure of the internal contractility of the LV. SE with dobutamine to determine the LVCR is a useful strategy for identifying myocardial viability and early detection of patients who may develop late cardiac dysfunction after chemotherapy treatment. The presence of a preserved CR for SE identifies a myocardium with higher peak stress values and a smaller end-systolic volume of the LV. The absence of a CR is due to lower peak force values and a higher end-systolic volume of the LV. Reduced LVCR contains information about the volume of the LV, systolic arterial pressure, regional anomalies of wall motion [27].

The LVCR for the first time in the course of chemotherapy (before and after) was studied in the prospective Civelli et al. study and proved to be a very sensitive method for identification of patients at high risk of cardiotoxicity. In this study, 8 out of 47 (17%) patients showed a significant decrease in the LVEF in the 18 months after chemotherapy, and in the same cohort there was no LVCR prior to treatment. We would like to note that diastolic dysfunction in patients in this study was detected no earlier than 4 months after the discovery of changes in the LVCR and did not predict systolic dysfunction [26]. At the same time, at the Nippon Medical School in Tokyo, it was found that subclinical cardiotoxicity detection in the treatment of anthracyclines with cumulative dose≥200 mg/m² is possible in low-dose SE with dobutamine [28]. In 2007, a team of researchers led by M. Jarfelt found that adult patients with acute lymphatic leukemia who received doxorubicin treatment on average 21 years after remission were found to have subclinical heart dysfunction in 50% of the SE study without any clinical manifestations [29]. These results demonstrate that SE under peak loads can reveal systolic dysfunction not diagnosed by other methods. The data obtained in the Gallucci et al. research show that there is no increase in the LVEF after pharmacological load in patients with anthracycline treatment and this blunted myocardial response, in their opinion, is associated with cardiomyocyte damage after infusion of drugs from the anthracycline group [30], taking into account the absence of a clinical picture in the patients under study, the data obtained may serve as an important marker for the diagnosis of LV subclinical dysfunction. De Caro et al. studied 55 patients with childhood anthracyclines for oncohematological disease (control group - 63 healthy individuals) and it was found out that 30% of 55 patients showed signs of LV subclinical dysfunction, either a decrease in the size of the LV posterior wall or an increase in systolic tension of the LV wall [31]. Burdick et al. confirms that SE with dobutamine and CR assessment contributes to the detection of myocardial dysfunction in chemotherapy earlier than normal echocardiographic parameters or radial and circumferential myocardial deformities of the LV [32]. Despite the conflicting results of the use of SE to assess the LVCR, this technique is of great interest to researchers around the world and is likely to occupy a place among the methods for diagnosing contractile LV myocardial dysfunction.

**Conclusion**

Diagnostic approaches to a patient suffering from oncohematological pathology are often very complex, as one of the most important moments is the timely detection of adverse events from the cardiovascular system. In this review, we highlighted the role of imaging techniques and biomarkers to detect subclinical cardiac dysfunction. The possibility of early detection of a group of patients at high risk of LV contractile dysfunction is a promising strategy for both oncohematologists and cardiologists. The information obtained about the presence or absence of subclinical LV dysfunction will enable oncohematologists to reduce doses or completely stop chemotherapy, on the other hand, it can allow cardiologists to maintain heart function or prevent myocardial dysfunction of the LV with the help of cardioprotectors. This topic is of the most important among oncohematological patients, in whom the presence of cardiac dysfunction, even asymptomatic, adversely affects clinical outcomes and severely limits therapeutic strategies. Echocardiography with determination of GLS, SE with the definition of the LVCR have predictive role in the diagnosis of such changes in the early stages. Thus, understanding the relationship between the biological processes under study, the markers and methods used to diagnose them, and the clinical outcomes is essential to improving the quality of life of patients and increasing its duration.

**Conflict of interests**: Authors declare lack of the possible conflicts of interests.

**References**


