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Оценка показателей глобальной продольной деформации левого предсердия в диагностике кардиотоксичности

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АННОТАЦИЯ

Широкий спектр крайне эффективных химиотерапевтических препаратов обладает негативным влиянием на сердечно-сосудистую систему, нивелируя успехи онкологического лечения. В связи с этим ранняя диагностика кардиотоксичности имеет крайне важное значение, позволяя вовремя применять профилактические и лечебные мероприятия.

Определение фракции выброса левого желудочка с помощью эхокардиографии — базовый неинвазивный инструментальный метод оценки сердечной функции и главный ориентир в вопросах диагностики сердечной дисфункции на фоне химиотерапии. Однако при субклиническом поражении показатель долго может оставаться нормальным, а также иметь выраженную межоператорскую вариабельность и зависимость от объёмной нагрузки. Специалисты постоянно находятся в поиске оптимальных эхокардиографических параметров, позволяющих диагностировать сердечную дисфункцию на ранних стадиях. Анализ глобальной продольной деформации левого предсердия представляется перспективным методом для данных целей. Большое количество накопленных данных позволяет говорить о том, что левое предсердие является не просто камерой-кондуитом, а отражает давление наполнения левого желудочка, являясь чувствительным маркером его систолической и диастолической дисфункции.

В обзоре представлен анализ имеющихся на настоящий момент исследований по применению методики оценки глобальной продольной деформации левого предсердия в диагностике сердечной дисфункции на фоне применения кардиотоксичных препаратов.

Ключевые слова: левое предсердие; кардиоонкология; кардиотоксичность; стрейн; эхокардиография; сердечная дисфункция; антрациклины.

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Left atrial longitudinal strain analysis in diagnostic of cardiotoxicity

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ABSTRACT

A wide range of extremely effective chemotherapy drugs has a negative effect on the cardiovascular system, leveling oncological treatment success. Early diagnosis of cardiotoxicity is very important, allowing timely application of preventive and therapeutic measures. Left ventricular ejection fraction evaluation using echocardiography is the basic non-invasive instrumental method to assess cardiac function and the main guideline in cardiac dysfunction diagnosis during chemotherapy. However, if dysfunction is subclinical, the ejection fraction can remain normal for a long time, and also has a pronounced inter-operator variability and dependence on volumetric load. Specialists are constantly in search of optimal echocardiographic parameters that allow early-stage cardiac dysfunction diagnosis. Analysis of the global longitudinal deformation of the left atrium seems to be a promising method for these purposes. A large amount of accumulated data suggests that the left atrium is not just a conduit chamber, but a reflection of the filling pressure of the left ventricle, being a sensitive marker of its systolic and diastolic dysfunction. This review presents an analysis of currently available studies on applying the methodology for assessing global longitudinal deformation of the left atrium in cardiac dysfunction diagnosis in the use of cardiotoxic drugs.

Keywords: left atrial function; transthoracic echocardiography; cardiotoxic agent; left ventricular dysfunction; anthracycline.

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左心房整体长轴应变参数在心脏毒性诊断中的评价

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简评

一系列极其有效的化疗药物对心血管系统有负面影响，从而找平了癌症治疗的成功。因此，心脏毒性的早期诊断非常重要，可以及时采取预防和治疗措施。

使用超声心动图测定左心室射血分数是评估心脏功能的基本无创仪器方法，也是化疗期间诊断心功能不全的主要指南。然而，在亚临床病变中，该指数可能在很长一段时间内保持正常，并且还具有明显的操作者间变异性和对体积负荷的依赖性。专家们一直在寻找最佳的超声心动图参数，以便在早期阶段诊断出心功能失调。左心房整体长轴应变的分析似乎是对于这些目的的有前途的方法。大量积累的数据表明，左心房不仅仅是一个导管，而是反映了左心室的充盈压力，是其收缩和舒张功能障碍的敏感标志。

本综述分析了目前关于使用心脏毒性药物诊断心脏功能障碍的左心房整体长轴应变的现有研究。

关键词： 左心房； 心脏肿瘤学； 心脏毒性； 心肌劳损； 超声心动图； 心功能不全； 蒽环类药物

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INTRODUCTION

Advances in modern oncology care have significantly increased the survival of cancer patients over recent decades. New chemotherapy drugs continue to be actively developed and introduced into clinical practice. The methods for detecting and diagnosing early cancer are improving. However, the short-term and long-term side effects of chemotherapy, such as death from heart and vascular diseases, have a significant effect on cancer mortality [1]. According to epidemiological studies, in patients successfully treated for cancer, the risk of cancer recurrence is eventually outweighed by the risk of cardiovascular diseases and their complications [2]. Cardiovascular mortality in childhood cancer survivors increases significantly after the age of 60 yr, which indicates a delayed effect of both the disease itself and treatment consequences [3]. Therefore, this patient population is the increasing focus of general practitioners and cardiologists. This is related to the general population aging as well as the fact that most cancer patients are in the age group of 65 yr and older [4]. As a result, both patients and healthcare systems have an increased burden, including financial [5].

It is now clear that this population requires a multidisciplinary approach. Cardio-oncology is a relatively new therapeutic area that focuses on patients receiving various types of cancer treatments that carry potential risks to the cardiovascular system. The systematic approach of this rapidly developing healthcare field is focused on screening, risk stratification, prevention, follow-up, and treatment of patients receiving chemotherapy and radiological treatment [6]. Cardiotoxicity is not limited to damage to the left ventricle (LV). It can be manifested by rhythm disturbances, damage to the pericardium and heart valves, coronary arteries, as well as arterial and pulmonary hypertension [7]. Simultaneously, some chemotherapy drugs cause rapid and early damage to the cardiovascular system, while side effects of other drugs appear only in many years [8]. Studies demonstrate the significance of the early detection of heart dysfunction (HD) signs, which in turn helps initiate timely treatment and prevent irreversible cardiac damage [9]. Echocardiography (Echo) plays a leading role in the diagnosis of this condition.

ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF CARDIOTOXICITY

Echocardiography is the basic diagnostic method in cardio-oncology. Measuring left ventricular ejection fraction (LVEF) using two-dimensional echocardiography remains one of the main tools in diagnosing cardiotoxicity signs and symptoms due to its availability and safety. It does, however, have some limitations, such as the inter-operator variability and the effect of image quality on the result. The ejection fraction (EF) is a volume-dependent parameter, and this often becomes critical for cancer patients, who are often hypovolemic due to vomiting, diarrhea, and loss of appetite [10]. LVEF does not change until the complete exhaustion of compensation mechanisms and significant myocardial damage, which makes it difficult to diagnose early cardiotoxicity using only this parameter [11].

The two-dimensional speckle-tracking Echo with global longitudinal strain (GLS) evaluations of the LV improves the diagnosis of HD, including the subclinical form, by diagnosing even minimal changes in LV function [12]. However, this parameter is also dependent on preload [13]. The LV strain is well reproducible in serial measurements and can be useful in identifying risk groups for heart damage, watchful waiting, and early decision-making on the initiation of cardioprotective therapy [12, 14].

Currently, there is the concept of a strain-oriented strategy in oncological cardioprotection [15]. A randomized, controlled, multicenter study (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) [10] was conducted from 2014 to 2019 and included 331 patients treated with anthracyclines. The results of this study were inconsistent. In the group of strain-oriented and conventional cardioprotective strategies, the EF was not statistically significantly different at the end of the study, so the primary endpoint was not reached. The subgroup sub-analysis revealed that LV strain-guided cardioprotective treatment significantly reduced a meaningful fall of LVEF to the abnormal range [16]. These results highlight the need for further research to determine whether the LV strain may be better than EF in identifying selected patient populations who would benefit from cardioprotective treatment to prevent cancer therapy-associated HD [10].

In 2021, the British Society of Echocardiography and the British Cardio-Oncology Society defined the following Echo criteria for cardiotoxicity: a decline in LVEF by >10% (absolute percentage points) from baseline to a value <50% (LVEF of 50 up to 54% is considered borderline and requires further information to decide if there is HD). When it comes to LV strain, a decline of <15% is considered abnormal, while only one episode of such decrease should be interpreted considering the whole clinical picture, as well as additional data, such as laboratory markers and results of other imaging techniques [17]. The authors of these guidelines emphasize that there are “grey zones” that can be seen in both the subclinical HF and normal condition, despite the integral Echo assessment of contractile function.

DIASTOLIC FUNCTION AND CARDIOTOXICITY

The measurement of diastolic function is also recommended in patients receiving cardiotoxic treatment, but its prognostic role is still unclear. Diastolic dysfunction, which is characterized by increased LV filling pressure, significantly increased the risk of cardiovascular events in the general population [18]. Studies in cancer patients demonstrate

inconsistent results and are often limited by a small sample size and a high heterogeneity of chemotherapy regimens.

The meta-analysis by M. Nagiub et al. [19] studied the predictive ability of diastolic parameters in the detection of doxorubicin-induced cardiomyopathy and showed that Doppler parameters E (p = 0.003), E/A ratio (p < 0.0001), lateral e' (p < 0.005), and s' (p = 0.01) were significantly associated with the systolic function worsening in this group of patients over a long follow-up period. However, the authors highlighted that only 4 of the 17 studies included in the meta-analysis were optimally designed and had all serial diastolic measurements.

A prospective study by J.N. Upshaw et al. (n = 362) [20] also studied changes in diastolic parameters during treatment with anthracyclines with/without trastuzumab. Study participants demonstrated a persistent diastolic function deterioration with decrease in the E/A ratio, lateral and septal e' velocity, and increase in the E/e' ratio E/e' (p < 0.01) by Month 6. The abnormal diastolic function was observed in 60% of cases after 1 yr, 70% after 2 yr, and 80% after 3 yr. The impaired function was associated with a subsequent decrease in LVEF and progressive longitudinal deformity of the LV. The authors concluded that comprehensive breast cancer therapy is associated with a moderate persistent deterioration in diastolic function with a low risk of the subsequent HD.

A meta-analysis of 13 studies (n = 892) by R.I. Mincu et al. [21] demonstrated that in patients without pre-existing heart disease who received anthracyclines, treatment had a modest effect on the E/A ratio (p < 0.001) with no change in e' and E/e'. The authors of this meta-analysis point to multiple limitations of studies and their heterogeneity with the high risk of bias, so randomized trials are required with large samples using new echocardiographic parameters (such as diastolic strain).

The aforementioned studies of diastolic function in patients receiving cardiotoxic treatment indicate the need for more careful monitoring of cancer patients and identifying an abnormal diastolic profile. Further research is also needed.

To sum up, we can say that there are still some questions, gaps, and "grey zones" related to the echocardiographic diagnosis of HD associated with the use of cardiotoxic drugs with a focus on its early signs, which should be detected to prevent irreversible myocardial damage.

LEFT ATRIUM FUNCTION AND CARDIOTOXICITY

Cardiac imaging professionals are constantly looking for available reproducible techniques and parameters that can be routinely used in clinical practice for the consistent serial evaluation with minimal inter-operator variability and maximum angle- and volume-independence. It is important to note the growing interest of researchers in the function of the left atrium (LA). Large studies have demonstrated an independent predictive value of LA size in patients with heart failure, so this parameter can be considered a possible global prognostic indicator of the population [22, 23]. After developing the invasive techniques, such as 3D and speckle tracking Echo, it became clear that the LA is not just a conduit chamber for filling the LV. The close dynamic relationship between the LV and the LA makes it a kind of mirror reflecting the function of the LV and modulates its filling pressure through the reservoir, conduit, and contractile phases [24, 25]. The LA adapts to changes in the LV compliance by changing its own function and mechanics [26]. Over the past decade, there has been a rapid increase in publications on using speckle-tracking Echo for LA strain assessment. These data are used to assess both diastolic and atrial functions [27, 28]. The method demonstrates a good correlation with computed tomography and magnetic resonance imaging of the heart as well as with invasive measurements [29–31]. Although the deformation of the LA is not completely independent of the preload, its conditions appear to have less effect on the deformation of the LA than on its volume [32]. Simultaneously, different phases of LA contraction have some specific characteristics. For example, reservoir and contractile functions decrease until the symptoms of heart failure occur, the LA dilates, and non-invasive LV filling pressure increases, which allows to diagnose the diastolic dysfunction at the preclinical stage [33]. Evidence has been obtained during the past 10 yr in favor of using changes in parameters of the GLS of the LA as the only marker of LV diastolic dysfunction [28, 34]. We can say that LA deformity, indicating LV compliance, can be used as a significant indicator of LA dysfunction and an early marker of diastolic dysfunction when general echocardiographic parameters are still normal [35]. A meta-analysis by F. Pathan et al. [36], which included 30 studies (with 2,038 healthy volunteers), demonstrated the following normal levels of global longitudinal LA strain parameters: reservoir strain (ƐR) 39% (95% confidence interval (CI) 38–41), contractile strain (ƐCT) 18% (95% CI 16–19), and conduit strain (ƐCD) 23% (95% CI 21–25).

In cardio-oncological imaging, the LA function remained unstudied for a long time, since the focus was completely shifted to the LV. Its function (volume) was indirectly evaluated by examination of diastolic function. In recent years, the LA strain analysis has attracted the close attention of specialists involved in the diagnosis of cardiotoxicity.

The very first study of LA strain and cardiotoxicity was conducted in 2013 by I. Monteet al. [37] in a small sample of patients with multiple sclerosis (n = 20) treated with mitoxantrone. This prospective study showed a decrease in the global LA strain by the end of treatment (10 months vs. 0 months: 15.2 ± 12.5 vs. 20.2 ± 11.1, p < 0.05). Cardiotoxic anthracycline drugs and epidermal growth factor inhibitors were the main focus of the subsequent studies, but other groups have also been studied. For example, the study by A. Sonaglioni et al. [38] included patients (n = 28) receiving

bevacizumab (an inhibitor of the biological activity of vascular endothelial growth factor) for bowel cancer. Echo was performed before the start of treatment, then after 3 and 6 months with measuring positive and negative LA strain (ЄCD and ЄCT). After 6 months, no statistically significant changes in the parameters were observed. In subgroups of patients developing cardiotoxicity-associated HD, it was found that in patients with HD, basal echocardiographic characteristics indicating increased LV filling pressure were statistically significantly higher, including a higher E/e' ratio (p = 0.01) and lower baseline ЄCD (p = 0.007). Accordingly, the observed changes could be predictors of HD. Similar data were obtained in a prospective study by J. Meloche et al. (n = 51) [39]: In nine patients who achieved the cardiotoxicity criteria, treatment with anthracyclines and trastuzumab was associated with a lower basal ЄR (50.0% ± 9.6% vs. 45.6% ± 4.9%, p = 0.058) and ЄCT (30.1% ± 8.0% vs. 24.3% ± 4.6%, p = 0.008). Of them, seven demonstrated an increase in ЄCT, probably due to compensating the reduced LV function. At all phases of treatment, this group of patients showed an early decrease in LA function: ЄCT by Month 3 (29.5 ± 7.6 vs. 27 ± 8.5, p = 0.008), ЄR (49.7% ± 8.8% vs. 44.4% ± 10.4%, p < 0.001), and ЄCT (20.2% ± 4.6% vs. 17.3% ± 5.3%, p < 0.001) by Month 6.

R. Emerson et al. (n = 51) [40], M. Laufer-Perl et al. (n = 40) [41], S. Moustafa et al. (n = 68) [42], J. and Moreno et al. (n = 52) [43] showed a statistically significant decrease in LA strain during anthracycline therapy with or without the addition of trastuzumab. E. Setti et al. (n = 64) [44] found that ЄR and LA volumes can predict the EF trend during 6 months of trastuzumab treatment.

In contrast, S. Moustafa et al. (n = 56) [45] and Y. Anqi et al. (n = 40) [46] found no differences in parameters of LA function associated with chemotherapy. In the first study [45], this can be explained by using a tyrosine kinase inhibitor as a study drug, which does not have a direct toxic effect on the heart muscle and has rather toxic effects on vessels. In the second study [46], authors pointed out that anthracyclines were administered in low doses, although the decrease in LVEF (p < 0.05) and LV strain (p < 0.05) reached statistical significance. A.T. Timóteo et al. [47] (n = 77) also did not find any difference in the LA deformity. The most significant declining trend was observed in ЄCT, and this is consistent with the data of J. Meloche et al. [39] and M. Laufer-Perl et al. [41]. A retrospective study by H. Park et al. (n = 72) [48] included patients already treated with anthracyclines. They were subsequently divided into those who developed (n = 13) and did not develop (n = 59) HD. Basal echocardiographic findings were the same. At the end of chemotherapy, LV strain (p = 0.002) and ЄR (p < 0.001) decreased statistically significantly in both groups. In ROC analysis, 11.7% was the optimal ЄR reduction for predicting future HD, with sensitivity and specificity superior to LV strain. D. di Lisi et al. [49] (n = 102) assessed LA strain, and they were the first who determined index of LA stiffness (a new potential predictive index, which is the E/e' to ЄR ratio). None of the patients developed clinical signs of HD. However, 53% of the patients had subclinical dysfunction, so they were divided into two groups (with and without dysfunction). In both groups, an early increase in the index of LA stiffness (p < 0.0001) and a decrease in ЄR (p < 0.0001) were observed. The authors concluded that these parameters could detect the early subclinical HD more accurately than the LV strain [49], and their conclusions are consistent with the findings of H. Park et al. [48].

Two cross-sectional studies should be mentioned, which evaluated long-term effects of anthracycline therapy on LA function in childhood cancer survivors. VW Li et al. (n = 26) [50] included men who received anthracycline treatment in childhood (time without chemotherapy 14.2 ± 5.4 yr), and they were compared with age-matched healthy people. Cancer patients had statistically significantly lower maximum (p = 0.009) and minimum (p = 0.017) values of LA volume and ЄCT (p = 0.011). The authors suggested that LA remodeling, which is characterized by a decrease in its contractile function, was caused by LA fibrosis which was induced by anthracycline treatment in childhood.

R.W. Loar et al. [51] compared two groups of sex- and age-matched patients: cancer patients without chemotherapy for more than 1 yr (n = 45) and healthy individuals (n = 45). In the first group, there were statistically significantly lower ЄR values (p = 0.04) compared with controls. The sub-analysis identified 11 patients as the lowest quartile with the lowest ЄR values. In this group, all patients were statistically significantly older than the patients in top three quartiles (p = 0.001), who had no changes in diastolic function and LA strain, regardless of the duration of chemotherapy and doses of anthracyclines. Therefore, age was the only independent predictor of decreased LA function after cancer therapy (p < 0.001). A retrospective observational study by NR Patel et al. [52] showed the opposite results: Of 55 children, only those under 12 yr old had statistically significant differences in LA strain before/after chemotherapy (p = 0.01). As a result, the long-term effects of ongoing treatment on LA function have yet to be established, and this will require long-term observational studies.

In conclusion, we would like to present some data from a retrospective study by M. Tadic et al. (n = 92) [53], which showed a decrease in reservoir and conduit functions of the LA (p < 0.001) in cancer patients before the initiation of chemotherapy compared with a control group with comparable characteristics. The authors suggested that cancer itself may be associated with a decrease in LA function, regardless of other characteristics, and consider several hypotheses and potential mechanisms for this relationship, such as inflammation, activation of biohormonal systems, circulation of vasoactive peptides and cytokines, prevalence of smoking in this group, and disease-related changes in lifestyle (in particular, decreased activity).

To sum up, it can be noted that many studies predominantly involve women, whose initial population-based values of LA strain are higher than those of men [54]. The LA strain measurement itself has the following advantages: This is an angle-independent technique; visualization of the LA in the four-chamber position is less susceptible to lung lobe interference; and image artifacts and reverberation occur less frequently [55]. However, this method also has some limitations: The LA is a thin-walled chamber, which makes it difficult to trace the endocardium. Additionally, researchers often "cut off" the projection of the LA, shortening its longitudinal size. Remember that the dependence of the parameter on the frame rate and preload (but less than that of the LV and EF strain). Moreover, special software is required. However, simplicity and prognostic and diagnostic value of this method make it a useful tool for cardio-oncologists.

It is necessary to establish in which cases the serial measurement of the LA strain will provide the greatest advantage and complement echocardiographic findings: when used for the diagnosis of early subclinical cardiotoxicity or delayed effects of chemotherapy or for deciding on the initiation of therapy and monitoring its effectiveness. Answering these questions will require prospective controlled studies in large patient populations.

The active development of new chemotherapeutic drugs provides cardio-oncologists with new challenges. For example, an irreversible tyrosine kinase inhibitor ibrutinib is associated with a high incidence of atrial fibrillation. A recent study by A. Singh et al. [56] showed a good predictive value of LA strain in this population of patients.

Study limitations

In conclusion, limitations of the review should be noted. Most studies reported have small patient populations and are retrospective. In terms of chemotherapy regimens, they are quite heterogeneous. Some patients receive radiation therapy for the thoracic area, which may contribute to changes in echocardiographic parameters.

CONCLUSION

Therefore, currently available studies suggest the potential value of assessing LA deformity in patients receiving chemotherapy with a cardiotoxic effect.

The potential of Echo needs further research. The assessment of LA strain appears to be a promising and useful method in cardio-oncology.

ADDITIONAL INFORMATION

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