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Right Ventricular Global Longitudinal Strain and Its Role in the Prediction of Chemotherapy-Induced Cardiovascular Toxicity

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ABSTRACT

Chemotherapy-induced cardiovascular toxicity (CTR-CVT) poses a substantial risk to cancer patients, predominantly affecting the left ventricle (LV). However, recent insights underscore the right ventricle's (RV) vulnerability to these deleterious effects. This paradigm shift has prompted a burgeoning interest in systematically evaluating the RV in cancer patients undergoing chemotherapy and radiotherapy. Notably, the RV may manifest signs of dysfunction preceding those in the LV, necessitating meticulous monitoring and early intervention. Over the past few years, studies have increasingly emphasized the importance of scrutinizing the RV in the context of cancer treatments. The early detection of RV dysfunction emerges as a critical factor in preventing progressive damage and enhancing overall cardiac function. The focus on diligent monitoring and timely intervention in the right ventricle highlights a paradigmatic shift in cardio-oncology practices. This abstract underscore the current landscape in which right ventricle dysfunction (RVD) has become a pivotal area of focus within cardio-oncology. By recognizing the susceptibility of the RV to chemotherapy-induced toxicity, clinicians can implement proactive measures to mitigate potential cardiac complications. As the understanding of these dynamics evolves, this heightened awareness promises to shape future strategies for the comprehensive care of cancer patients, emphasizing preserving both left and right ventricular function throughout treatment.

Keywords: Chemotherapy-related cardiovascular toxicity (CTR-CVT); chemotherapy-related cardiac dysfunction (CTRCD); global longitudinal strain (GLS); left ventricular ejection fraction (LVEF); right ventricle dysfunction (RVD).

INTRODUCTION

Worldwide, cancer and cardiovascular diseases (CVD) are the major public health issues and the leading causes of death.[1] With improvements in cancer diagnosis and treatment, the incidence of anticancer therapy-related cardiotoxicity and complications of cancer survivors has increased.[2] Modern oncological treatment regimens often incorporate chemotherapy, radiotherapy, and immune checkpoint inhibitors, whose deleterious cardiac effects might be additive or synergistic.[3,4] Anthracyclines are the most extensively studied chemotherapeutic agents associated with myocardial injury. The complex of anthracycline-Top (topoisomerase) IIβ-DNA is a leading mechanism of irreversible DNA damage and mitochondrial dysfunction in cardiomyocytes, which contributes to myocardial energetic depletion, oxidative stress, and apoptotic cell death.[5,6] Trastuzumab (tyrosine-protein kinase erbB-2 pathway receptor inhibitor) was the first monoclonal antibody studied in detail for the treatment of cancer. While erbB-2 is present in cardiac myocytes, it is also involved in some pathways that promote cardioprotection that regulate apoptosis, hypertrophic growth, mitotic growth, cell elongation, intercellular adhesion, angiogenesis, and sensitivity to adrenergic signaling. Therefore, an interruption of these cellular pathways may be potentially harmful to the heart.[7] There are two types of cardiotoxicities:

Type I: Prototype Anthracycline treatment; The degree of damage depends on the received dosage, leading to cell apoptosis and irreversible damage at the cell level. Early detection of complications and timely treatment is therefore essential to prevent left ventricular remodeling and, consequently, heart failure.

Type II: Prototype Trastuzumab treatment; It does not depend on the drug dosage, does not cause apoptosis, and is often reversible.[8]

The increasing awareness of chemotherapy-induced cardiomyopathy has led to the development of screening and intervention protocols to reduce cardiac risk. The field is advancing to predict better and identify biomarkers of chemotherapy-related heart dysfunction (CTRCD) in cancer patients.[9]

Diagnosis of chemotherapy-induced cardiotoxicity

Echocardiography is the cornerstone for diagnosing chemotherapy-induced cardiotoxicity (CTRCD). In the emerging field of cardio-oncology, experts usually focus on evaluating left ventricular function. In chemotherapy-induced cardiotoxicity, the left ventricular ejection fraction (LVEF) is reduced by> 10% and/or <55% below (2-dimensional echocardiography).[10] LVEF is a robust prognostic predictor for assessing left ventricular function, though it exhibits low sensitivity to subtle changes in contractile function.

A more sensitive and relatively new imaging technique is the so-called speckle-tracking echocardiography, which can detect chemotherapy-induced cardiotoxicity or myocardial damage relatively early by measuring global longitudinal strain.[11,12] According to the most recent ESC guidelines on cardio-oncology, global longitudinal strain (GLS) is essential in diagnosing the cardiotoxicity of oncological therapy. The proposed cut-off point for suspecting subclinical heart impairment is a 15% relative drop in GLS during cancer treatment.[13] As a result, a new concept of cardiotoxicity has emerged: cancer therapy-related cardiovascular toxicity (CTR-CVT) with LVEF and GLS alterations.

All existing chemotherapy-induced cardiotoxicity studies are focused on left ventricular dysfunction and remodeling. However, the impact of chemotherapeutic agents on the right ventricle (RV) has yet to be thoroughly researched. Several preliminary reports on chemotherapy-related cardiac dysfunction (CTRCD) have shown that the right ventricle can also be affected by chemotherapy, as evidenced by right ventricular biopsies.[14]

Value of the right ventricular global longitudinal strain (RVGLS)

Right ventricular (RV) systolic dysfunction has been identified as an independent prognostic marker of many cardiovascular diseases.[14,15] However, due to its complex morphology (when compared to the LV's ellipsoidal shape, the RV appears triangular from the side and crescent-shaped in cross-section,[16] complex systolic motion, and prominent myocardial trabeculations, measuring RV systolic function is limited and difficult in routine clinical practice.[17,18] Although cardiac magnetic resonance offers more possibilities, such as accurate evaluation of RV volumes and function, the deficient availability and high level of competence necessary for this kind of imaging are the significant obstacles to its adoption in everyday clinical practice and thus, the preferred technique for analyzing RV mechanics remains 2D speckle tracking echocardiography (2DSTE). While most research has been dedicated to the utility of left ventricular global systolic strain, several studies demonstrated the usefulness and prognostic value of right ventricular (RV) systolic strain in various clinical scenarios. The three main parameters of RV strain are right ventricular global longitudinal strain (RVGLS), right ventricular free wall longitudinal strain (RVFWLS), and interventricular septal wall longitudinal strain (IVSLS)).[19] RVGLS is superior to standard parameters in assessing subtle right ventricle (RV) systolic dysfunction.[20,21] The RV wall is mainly composed of superficial and deep muscle layers, where the fibers of the superficial layer are arranged more or less circumferentially, and the deep muscle fibers are longitudinally aligned from base to apex. The deep muscle layers account for about 80% of RV contraction,[22] thus GLS allows us to assess the global systolic function of the RV. RVGLS measures the longitudinal contraction of the right ventricle, which is more significant than other traditional measures, such as TAPSE and tricuspid S' velocity. These latter parameters represent the displacement degree of the basal segment of the RV-free wall. They are, therefore, less prognostic than RV GLS.[23] RV longitudinal strain is the cornerstone of RV mechanics evaluation, with excellent repeatability and more significant predictive value in patients with diverse CV diseases.[24-27] Regional RV strain represents a potential means to assess myocardial contractility that is less load-dependent,[28] and may be applicable across a wide range of pathologies including arrhythmogenic RV dysplasia,[29] pulmonary embolisms,[30] pulmonary hypertension,[31] systemic right ventricles,[32] and amyloidosis.[33-35] Another significant advantage of 2D tracking methods is that they are not angle-dependent within the acquired imaging plane.[36] Despite the increasing evidence supporting the evaluation of RV longitudinal strain in most cardiovascular patients, it has not yet become a standard echocardiographic examination in most echocardiography labs.[37]

Role of RV in the prediction of chemotherapy-related cardiovascular toxicity

Cardiovascular complications caused by cancer therapy have become the second most significant threat to the long-term survival of patients.[38] Studies show that RV remodeling occurs concurrently with LV remodeling and that the deformation mechanics of the left and right ventricles follow similar temporal patterns and degrees of impairment during chemotherapy treatment,[39] thus RV remodeling should not be overlooked in the overall cardiac assessment of chemotherapy patients, particularly those receiving anthracyclines.[40] GLS has proven to be a crucial predictor of mortality during the routine follow-up of cancer patients with normal ejection fractions receiving chemotherapy.[41] RGVLS detects subclinical RV damage with higher sensitivity and specificity in patients with cardiomyopathies, cardiac amyloidosis, and cancer.[42-44] Alterations in right ventricle function, specifically global longitudinal strain (GLS), have been identified as a valuable prognostic indicator for predicting outcomes and mortality in patients with breast cancer. Several studies have examined the impact of breast cancer treatment on cardiac function, mainly focusing on the right ventricle.[45]

One study by Calleja et al.[46] evaluated right ventricle parameters in young women diagnosed with HER-2+ breast cancer. The study found that some patients developed cardiotoxicity, which affected RV-GLS and RV-FWLS. Another study by Mustafa et al., found that trastuzumab treatment hurt the right ventricle's ability to contract and perform

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optimally, as evidenced by a significant decrease in RVGLS.[47]

In a study conducted by Boczar et al., HER-2-negative breast cancer patients were analyzed for changes in their cardiac function.[48] The results showed a decrease in left ventricular ejection fraction (LVEF) and a significant worsening in right ventricular fractional area change (RV-FAC) and right ventricular free wall longitudinal strain (RV-FWLS). These findings suggest that breast cancer treatment may impact cardiac function, although the clinical significance of these changes remains unclear.

Arciniegas et al. examined female patients newly diagnosed with breast cancer for changes in LVEF and RV GLS.[49] The study found a decrease in LVEF, indicating a potential risk for cardiotoxicity. Additionally, a decrease in RV GLS was observed, which had predictive value in determining the likelihood of cardiotoxicity.

Keramida et al., found that female breast cancer patients with HER-2 positivity experienced a decrease in LVEF, left ventricular global longitudinal strain (LVGLS), and right ventricular global longitudinal strain (RVGLS).[50] These findings highlight the potential impact of breast cancer on both left and right ventricular function.

Wang et al., evaluated the mechanical properties of the right ventricular myocardium in breast cancer patients who had undergone chemotherapy.[51] The study utilized 3D-STI to assess changes in RVGLS and RVGAS levels, which were closely correlated with other cardiac parameters. These findings suggest that RVGLS and RVGAS can serve as sensitive indicators for identifying the decline in right ventricular function.

XU et al., revealed that longitudinal strain analysis through 3D STE can help identify subclinical right ventricular dysfunction in cases where conventional indices of RV function are unaffected.[52] The research concluded that 3D RV FWLS was the most influential parameter in the early detection of cardiac toxicity-related cardiac dysfunction (CTRCD) in breast cancer patients undergoing epirubicin therapy.

Chang et al., assessed breast cancer patients undergoing epirubicin therapy and found that right ventricular longitudinal strain significantly declined after the first cycle and was associated with dyspnea development and the accumulating dose of epirubicin.[53] The study concluded that RVLS_FW sensitively predicts dyspnea development in breast cancer patients receiving epirubicin therapy, but further studies are needed to validate its role in long-term patient survival.

According to the study conducted by Gorgiladze et al., a substantial decrease in left and right ventricular global longitudinal strain (LV-GLS, RV-GLS) was seen from baseline to completion, regardless of the dosage of chemotherapy and the patient's cardiovascular risk.[54]

In summary, these studies highlight the importance of evaluating right ventricle function, particularly global longitudinal strain, in predicting outcomes and mortality in breast cancer patients. The findings suggest that breast cancer treatment may have an impact on cardiac function, emphasizing the need for close monitoring and early detection of cardiotoxicity to optimize patient care and outcomes.

CONCLUSION

There is a growing recognition of the importance of assessing cardiac parameters, mainly the right ventricle's function, in breast cancer patients. The studies suggest several key points:

- **Impact of the chemotherapy**: The studies collectively indicate that breast cancer treatment can affect both left (LVEF) and right ventricular (RV-FAC, RV-FWLS) function, suggesting a global impact on the heart
- **Use of Advanced Imaging Techniques**: Advanced imaging techniques such as 2D STE and 3D-STI are being utilized to asses changes in RVGLS and EVGAS, providing sensitive indicators for identifying declines in RV function. Longitudinal strain analysis through 3D STE is also highlighted as an effective method for detecting subclinical right ventricular dysfunction early.
- **Monitoring during chemotherapy:** Studies focusing on chemotherapy, such as those involving anthracycline therapy, emphasize the importance of closely monitoring right ventricular function, as changes in RV longitudinal strain were associated with dyspnea development and the accumulating dose of chemotherapy.
- **Clinical significance:** While changes in cardiac parameters were observed, the clinical significance of these alterations remains unclear. Further studies are needed to validate the role of these parameters in predicting long-term patient survival and to understand the overall impact on patient outcomes.

In conclusion, these findings underscore the importance of comprehensive cardiac assessment, especially evaluating RV function and global longitudinal strain, in breast cancer patients; regular monitoring and early detection of cardiotoxicity are highlighted as crucial aspects of patient care to optimize outcomes.[55]

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