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Potential usefulness of diastolic parameters measured by strain imaging echocardiography in the early prediction of chemotherapy-induced cardiotoxicity

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Abstract

Over the past decades, chemotherapy has significantly increased the overall prognosis and survival of several patients diagnosed with cancer. However, the usefulness of some chemotherapeutic agents has been hindered by a collateral dose-dependent cardiotoxicity. To date, although extensive efforts have been directed to the early detection of subclinical toxicity in patients treated with these drugs, it remains unclear which approach would be best in order to prevent chemotherapy-induced cardiotoxicity (CIC). For many years, conventional echocardiography has been among preferred noninvasive imaging modality to monitor left ventricular ejection fraction (LVEF) in patients undergoing chemotherapy. Unfortunately, a significant reduction in LVEF is not recognized early on after chemotherapy-induced myocardial damage. Moreover, delayed recognition has been associated with poor recovery potential and poor clinical outcome. Thus, there is a critical need to identify early, reliable parameters of subclinical injury. Myocardial deformation imaging, also known as strain imaging echocardiography (SIE), is becoming readily available for advanced routine echocardiography and has shown value in detecting subclinical ventricular dysfunction in several clinical scenarios. Abnormalities in systolic deformation parameters have been identified as early manifestation but left ventricular diastolic properties remain less well defined. We hypothesize that onset as well as progression of cardiotoxicity not only should disturb deformation curves of myocardial contraction, but also relaxation. Hence, SIE may detect subtle myocardial changes in diastole that could be of potential benefit in the early prediction of CIC. If this premise is proven correct, the use of a standardized advanced echocardiographic imaging protocol using both, systolic and diastolic strain imaging, will prove to be a powerful noninvasive tool as baseline and follow-up of these patients. Furthermore, it will foster the developing of more effective screening strategies in at risk cancer survivor populations, or identify the best time to start cardioprotective therapy to prevent CIC. Also, this experience might be extrapolated to other non-oncologic patient population in need of a surveillance tool to early recognize cardiac injury secondary to the use of cardiotoxic medications.

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Conflict of interest

This article content has no conflict of interest.

Keywords

Diastolic function; Strain imaging; Echocardiography; Chemotherapy; Cardiotoxicity

Background

Antitumor drugs have decreased mortality and improved survival rates in many patients with cancer. However, some of these drugs have serious cardiotoxic effects that may lead to irreversible cardiac injury and act against the overall benefit. This dilemma has raised a challenge to both, Cardiologist and Oncologist to establish an effective strategy to either reduce or prevent cardiac damage and its consequences.

Chemotherapy-Induced Cardiotoxicity represents the leading cause of morbidity and mortality in cancer survivors with up to 60% of mortality rate in a 2-year period after established the disease [1,2]. According to the Cardiac Review and Evaluation Committee of Trastuzumab-Associated Cardiotoxicity (CREC); cardiotoxicity is defined as a left ventricular ejection fraction (LVEF) reduction from baseline of 5% to <55% in patients with symptoms or 10% to <55% in asymptomatic patients [3]. In 2010, the European Society for Medical Oncology (ESMO) re-defined the concept as a reduction in LVEF of 20% from baseline despite normal function or a LVEF <50% [4]. However, current guidelines for recommendations and pre-treatment of chemotherapy-induced cardiotoxicity are not specific and differ among cardiovascular and oncology societies [5]. Among chemotherapeutic agents involved in cardiac toxicity, there has been placed an emphasis on Anthracyclines, Trastuzumab and Cyclophosphamide. When used in combined chemotherapeutic regimens, they all increase the risk of LV systolic dysfunction and in the case of anthracyclines-induced cardiotoxicity, the cardiac damage is irreversible.

Conventional echocardiography has been the gold standard noninvasive imaging modality to assess left ventricular systolic function in patients undergoing chemotherapy, based on measures of ejection fraction (LVEF). However, most of echocardiographic reports describe LVEF based on subjective visual estimates, failing to identify subtle changes in LV function in patients with “adequate” LV function. Consequently, the American Society of Echocardiography has recommended the use of objective measures to standardize echocardiographic reading and early detect serial changes in LVEF that could be crucial in the prognosis and prediction of chemotherapy-induced cardiotoxicity [6].

The advent of speckle tracking strain imaging, allowed measurements to be made along the entire myocardium using offline analysis of standard B-mode cine images without the limitations of TDI [7]. Speckle tracking strain analysis has been previously used to demonstrate diastolic abnormalities at rest, as well as exercise induced diastolic stunning [8]. Unfortunately, an easy to use and automated imaging approach to assess diastole has not been developed. Since echocardiography is so readily available and speckle-tracking imaging is now widely accessible with advanced imaging protocols, bedside analysis systolic deformation can be rapidly determined during routine cardiac imaging. However, diastolic deformation is somewhat more complex as it involves early filling, diastasis and late diastolic filling after atrial contraction. Therefore, this analysis is best performed off-line

not only to measure rate of relaxation but also excluding the development of abnormalities in left ventricular compliance.

To date, some authors have explored whether myocardial deformation parameters could be appropriate in detecting early myocardial injury and forecast ventricular dysfunction or better known as cardiotoxicity in patients receiving cancer therapy, being mainly focused on systolic parameters [9]. In this context, a recent systematic review has reported some optimistic results [5]. In a large data involving a total of 1504 patients, peak systolic global longitudinal strain (GLS) appeared to be the best measure in detecting early myocardial changes during therapy. They found that 10% to 15% early reduction in GLS by STE during therapy was the best predictor of cardiotoxicity, defined as a development of heart failure or drop in LVEF. Additionally, in late survivors of cancer with normal LV function determined by conventional echocardiography, measures of global radial and circumferential strain were consistently abnormal. Florescu et al., reported similar results in 14 patients with breast cancer that developed Epirubicin-Induced Cardiotoxicity [10]. Likewise, GLS has shown to be an important predictor of mortality in routine follow-up of cancer patients with normal ejection fractions receiving chemotherapy [11]. Most recently, Right Ventricle strain parameters were determined in a cohort of 35 breast cancer patients and RV longitudinal strain declined over the time and was significantly associated with dyspnea [12]. Unfortunately, diastolic strain parameters have been relegated, if considered, to collateral less important measurements. Moreover, the limited reported data is contradictory in evaluating its effectiveness in the diagnosis and prediction of CIC.

The hypothesis

Given that critical information regarding the development of subclinical CIC is crucial not only to institute prompt and effective therapy, but also to alter the infusion of the offending chemotherapeutic agent -as these interventions are linked with long term outcomes-we speculate that using speckle tracking imaging technology, subtle changes in diastolic strain parameters can be detected earlier than systolic strain abnormalities, and these changes can predict further development of CIC.

Hypothesis discussion

Assessment of diastolic dysfunction has been relegated until recently when magnetic resonance imaging, and gated single-photon emission computed tomography/positron emission tomography (SPECT/PET), have attempted to identify abnormalities in diastolic dysfunction in patients with ischemia. The introduction of tissue Doppler imaging (TDI) was first used to assess changes in diastolic velocities after ischemia/reperfusion in a dog model, and was subsequently applied during dobutamine stress echocardiographic examination. Additionally, relaxation time as measured by TDI after dobutamine stress has been proposed as a novel marker for ischemia [13]. Unfortunately, the overall utility of TDI is limited by angle dependency, artifact from cardiac movement, and small areas of myocardial interrogation.

Diastolic abnormalities not only have been shown to be critical in differentiating abnormalities in myocardial perfusion during the development of ischemic cascade, but also in the development of left ventricular diastolic dysfunction associated with incident heart failure, particularly abnormalities in LV diastolic stiffness and detection of subclinical cardiac disease [14]. Since abnormalities in systolic deformation have been clearly identified and confirmed as early manifestations in a significant number of cancer patients receiving certain chemotherapeutic agents and if systolic and diastolic cardiac mechanics are so dependent with one another to attain optimal cardiac performance; it is only reasonable that the next step needed is to examine left ventricular diastolic properties in these patients. Particularly when diastole not only is more sensitive to both metabolic and electrical myocardial abnormalities; but also when diastolic dysfunction is always present when systolic dysfunction is known to occur.

Given the well-known intricate architecture of the myocardium based on the circumferential muscle mass fiber composition mainly dominated by transverse and oblique helical fiber arrangement on the inner and outer walls of the heart; it is now more reasonable to explain how the heart fills and empties. In this context, during ejection the circumferential fibers continue to shorten together with the oblique fibers in the right and left-handed helices (or descending and ascending apical segments) that co-contract to shorten and thicken to empty the heart. The circumferential fibers produce a horizontal counterforce that accentuates narrowing throughout ejection. Furthermore, these contracting transverse circumferential fibers provide a “buttress” to counteract the outward forces generated by the twisting and shortening oblique muscle of the inner right- and left-handed helical segments and thereby prevent an outward explosion at the cardiac base during ejection. The twisting segments move in clockwise and counterclockwise directions. In contrast, the suction phase or rapid diastolic filling occurs after the ventricular pressure falls below atrial pressure and is associated with a further rapid accentuation of untwisting of the apex in a clockwise direction. Specifically, 40% of untwisting occurred before the rapid filling phase. Continued untwisting is caused by elastic recoil of compressed titin coils within the left-handed helix fibers, in a manner similar to circumferential muscle (basal loop) widening and recoil for clockwise rotation during the isovolumic phase. Although the recoil mechanism is responsible for rapid filling, the vital role of active and unopposed left-handed helix contraction to cause straightening during the isovolumic phase is an important component because suction is impeded or avoided if this motion is opposed by prolonged descending contraction. As the contractile phase dissipates and all the muscle segments become relaxed, the rapid titin-related “unwinding” of the apex to its original position creates the suction required to cause rapid ventricular filling, which occurs as the ventricular pressure drops below the atrial pressure. Further widening and lengthening develop from the hydraulic effects resulting from rapid and then passive filling after the apical reciprocal twisting action has stopped.

Since not only both left ventricular systolic and diastolic mechanical events are so anatomically and functionally linked; but also their deformation curves so intricately related; it is only natural to hypothesize that onset as well as progression of cardiotoxicity should disturb deformation curves of myocardial contraction and relaxation. However, no echocardiography studies at the moment have shown that changes in diastolic parameters

can predict subsequent cardiotoxicity. In addition, although controversial, several studies report that changes in systolic strain parameters occur prior to, or in the absence of changes in traditional diastolic parameters [15,16].

Given that critical clinical information regarding the development of subclinical heart failure symptoms is crucial not only to institute prompt and effective therapy, but also to alter the infusion of the offending chemotherapeutic agent as these interventions are linked with long term outcomes; it would be interesting to assess whether left ventricular diastolic abnormalities, if present, might adversely contribute to worse clinical outcomes or diminish the efficacy of instituting standard heart failure therapy. If this premise is proven correct, the use of a standardized advanced echocardiographic imaging protocol using both, systolic and diastolic strain imaging will prove to be a powerful noninvasive tool as baseline and follow-up of these patients. Furthermore, it will promote the developing of more effective screening strategies in at risk cancer survivor populations, or identify the best time to start cardioprotective therapy to prevent CIC. Likewise, although our hypothesis is focused on oncologic patient population, any possible finding could be useful to other populations in need of a surveillance tool to early recognize cardiac injury secondary to the use of cardiotoxic agents.

Conclusion

Much remains to be understood about the importance of speckle tracking imaging in the prediction and further management of chemotherapy-induced cardiotoxicity. Studies are encouraged to define left ventricular diastolic curves of myocardial relaxation and determine if abnormalities occur, and if so in which part of diastole and the extent of these abnormalities. Whether diastolic mechanical changes precede the onset of abnormalities in systolic deformation needs to be distinguish. Finally, a characterization of the systolic-diastolic profile of cancer patients that develop cardiotoxicity must be better explored. This information might be essential not only to develop more effective screening strategies in at risk cancer survivor populations, but identify the best time to start cardioprotection therapy to prevent the development of chemotherapy-induced cardiotoxicity.

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