The Role of Echocardiography in Chemotherapy

Angelo Antunes Salgado[1,2,3,4], Celso Dias Coelho Filho[1,2], Camila Aparecida de Souza Segrégio Reis[1]

Hospital Universitário Pedro Ernesto - UERJ[1], Hospital Procardíaco[2], Instituto Nacional de Cardiologia[3], Clínica Amacor[4], Rio de Janeiro - RJ - Brazil

Introduction

With the increased survival of the population, and the widespread use of early detection campaigns, there was a substantial increase in the early detection of several types of neoplasias[1].

The evolution of cancer treatment, both in relation to chemotherapy as radiotherapy, have not diminished the importance of cardiac monitoring of these patients, since the potentially cardiotoxic drugs usually employed as anthracyclines (doxorubicin, epirubicin, idarubicin) and alkylating agents (cyclophosphamide, ifosphamide) are well know and potentially lethal[1,2]

The importance of early detection of cardiotoxic action of these drugs, when the suspension can still avoid heart damage and even restore normalcy, is already very well established in echocardiography [1.3.]

Cardiotoxicity caused by chemotherapy days after infusion, even after several years may occur, demonstrating the importance of long-term cardiac follow-up in these patients, which may be acute, subacute or chronic and characterized mainly by electrocardiographic, myocarditis changes, pericarditis and also by cardiac insufficiency.[2]

Cardiotoxicity depends on the type of infused agent (anthracyclines with agents that cause more dysfunction), usually occurring more at the extremes of age (<4 years and>60 years) in female patients with previous cardiac dysfunction and a history of associated mediastinal radiation. The cumulative dose of the chemotherapeutic agent is directly related to the degree of cardiac injury, being more evident dysfunction with cumulative anthracycline dose above 400mg/m² and infusion bolus[2, 4.]

The incidence of cardiotoxicity caused by anthracycline ranges from 18% to 26% and may reach 36% in patients receiving cumulative doses above 600mg/m². In some cases heart failure can occur up to 20 years after the administration of the pharmaceutical drug.[5]

More recently it has been shown that a new immunomodulatory agent trastuzumab used for the treatment of breast cancer in patients with severe expression of the human epidermal growth factor type 2 (HER-2) receptor may also have damage to cardiomyocytes. Despite the myotoxic effect is unknown, it has the ability to reverse cardiac dysfunction after its suspension, which does not occur with anthracyclines and alkylating agents. However, the use of trastuzumab in patients who have previously made use of anthracyclines, increases the incidence of cardiac disorders [2.5.]

The more usual assessment methods of pre-chemotherapy cardiac ventricular function are echocardiography and radionuclide ventriculography. These methods are very sensitive in the detection of cardiotoxicity. But their values are not interchangeable, i.e., if the initial analysis was made by echocardiography, evolution must also be made by this method. MRI is considered the gold standard in the analysis of ventricular function can also be used. But its unavailability in the public service and the very high cost limit its utilização[6].

Echocardiography therefore presents itself as one of the tests of choice for evaluating patients undergoing chemotherapy with cardiotoxic drugs, especially for its practicality, low cost and high definition. Echocardiography can define the onset of cardiac dysfunction through the ejection fraction, the assessment of myocardial performance index and more modern techniques, such as strain, strain rate and two-dimensional strain [1.6].

Assessment Of Cardiotoxicity By Echocardiography

Ejection fraction

The ejection fraction is a parameter commonly used for the assessment of cardiac function has been widely used to identify and monitor cardiotoxicity. However, the measurement of ejection fraction of the left ventricle by Teichholz method, is only based on dimensional analysis of systolic and diastolic movements of the middle segments of the septal wall and posterior wall, not taking into account the contractile state of the other walls, making the analysis of the ejection fraction by these methods, incomplete and subject to criticisms.[5,6]

The use of the analysis of ejection fraction by Simpson's method partially solved this problem, and for the acquisition, analysis of ventricular endocardial borders in systole and diastole, and two separate, perpendicular cuts between them is required, increasing the accuracy in obtaining the ventricular volumes and as a consequence the ejection fraction. However, this calculation cannot be performed in patients in whom endocardial border definition is not possible or is not clear. In addition, the failure to obtain an image in which the apical region of the left ventricle is well documented 5.7 can cause false results.[5,7]

Keywords

Echocardiography; Drug Therapy; Antineoplastic Agents; Cardiotoxins; Ventricular Dysfunction.

Mailing Address: Angelo Antunes Salgado •
Rua Magalhães Couto, 237, Apt.101, 20735-180, Méier, Rio de Janeiro RJ - Brazil.
E-mail: angeloasalgado@gmail.com
Manuscript received July, 3rd, 2013; accepted October, 14th, 2013

DOI: 10.5935/2318-8219.20140004

With the introduction of three-dimensional methodology, analysis of ventricular volumes and ejection fraction, became much more reliable and reproducible, showing excellent correlation with volumes measured by magnetic resonance imaging. However the high cost of these devices and technical difficulties in the acquisition and processing of images, still considerably limit the use of that method.

Before the start of chemotherapy, values of the fraction of ejection fraction lower than 50% are considered as unsuitable for administration of cardiotoxic drugs with high power, should be careful in the administration of these drugs and prefer, if possible, drugs with less power cardiotoxic**.**

During chemotherapy, with the use of anthracyclines, if there is a drop in ejection fraction greater than 10% of the initial value, i.e., the pre-treatment assessment, reassessment of the use específico1 that chemotherapy is recommended.[1]

However, because chemotherapy causes permanent injury, usually no normalization of ejection fraction after this suspension, and not infrequently is usually rapid functional deterioration. With the exception of certain antineoplastic agents, such as monoclonal antibodies, where the incidence of cardiac dysfunction is low (2%), and the suspension of their administration can cause reversal of left ventricular dysfunction [1.3.]

Myocardial Performance Index (Index Tei)

It is defined as the sum of isovolumetric contraction with the isovolumetric relaxation time divided by ejection time, reflecting the combination of systolic and diastolic cardiac function, and has been associated with morbidity and mortality in patients with cardiac amyloidosis, dilated cardiomyopathy (idiopathic or ischemic) and primary pulmonary arterial hypertension. The myocardial performance index is easily obtained, reproducible, independent of pre and post loads, relatively independent of heart rate and does not depend on endocardial border definition, which makes it ideal for the analysis of cardiac function in longitudinal studies. Values above 0.45 are indicative of dysfunction ventricular[5].

This rate may be increased after therapy with anthracyclines due to prolongation of the isovolumic contraction and shortening of the ejection time, even in patients with low cumulative doses, given that its prognostic value in patients undergoing chemotherapy, has not been definido[8]

Diastolic Parameters

Changes in diastolic parameters as increased isovolumic LV relaxation, reduced velocity of early filling (E wave velocity) and decreased E/A ratio may occur in the presence of cardiotoxicity (Figures 1 and 2).

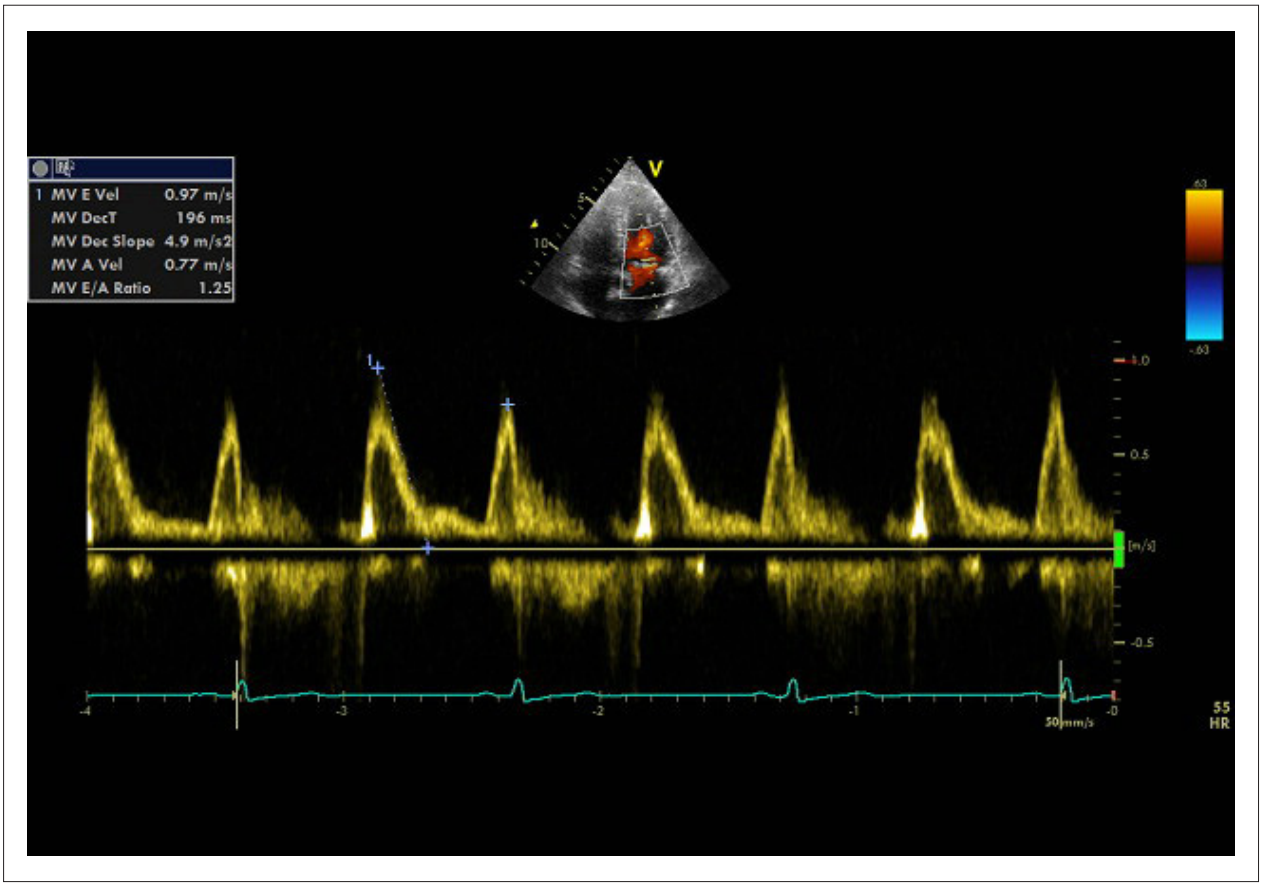

Figure 1 - *Patient pre-chemotherapy with daunorubicin. Note the E/A ratio 1.25 and the TDE of 196ms.*

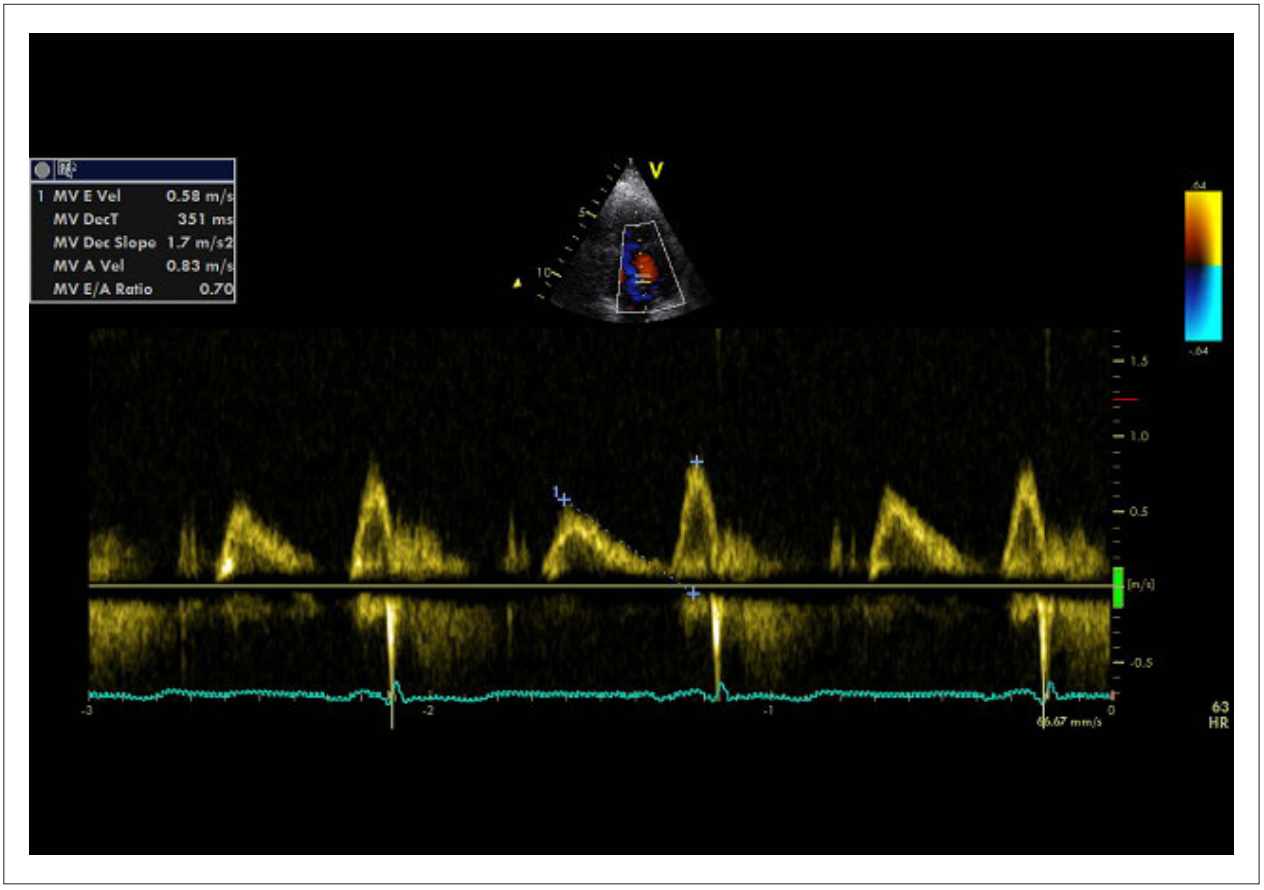

Figure 2 - *The same patient of Figure 1 after 3 months of treatment. Despite the maintenance of ejection fraction, worsening of diastolic parameters, with E/A ratio of 0.7 and TDE of 351ms. After 2 months, the patient with systolic dysfunction, indicative of cardiotoxicity.*

Changes in diastolic function may precede changes in systolic cardiomyopathy induced by chemotherapy. However, studies to define the role of diastolic changes in chemotherapy are few single-center and representative. Furthermore, although the Doppler be used for the assessment of compliance and relaxation of the left ventricle is subject to their evaluation of cardiac filling conditions, and heart rate.

Study of 43 patients receiving anthracycline and trastuzumab for breast cancer therapy has not demonstrated the importance of changes in diastolic parameters to predict cardiotoxicidade.[10]

In a study of 26 patients, Stoddard et al.11 showed that the prolongation of the isovolumic relaxation time (IRT) preceded the development of systolic dysfunction in the presence of anthracycline therapy, however the low number of patients studied and the lack of prospective studies restrict the use of TRIV in detecting early cardiomyotoxicity.[11]

All these diastolic variables are highly influenced by preload and after load [11].Portanto, larger, multicenter studies need to be conducted to better define the role of diastolic dysfunction in the setting of chemotherapy cardiotoxicity.

Strain And Two-dimensional Strain

With the evolution of echocardiography, new processes are being incorporated into the analysis method, which is still poorly defined its prognostic relevance in the study of various diseases. Among these new procedures highlights the two-dimensional strain technique that demonstrates the deformity of myocardial tissue in their layers, longitudinal, radial and circumferential variables. This process presents excellent correlation with, gold standard MRI, and has the ability to demonstrate a deficit of deformation in contractility walls still preserved in the evaluation of other parameters. Unlike the calculation of ejection fraction measurement of strain is not altered by cardiac geometry, and may be performed in circumstances in which the endocardial borders are not well visualized and can estimate both systolic function and diastólica[12].

The *strain* has emerged as a quantitative method to estimate the function and contractility by assessing the deformation. The strain is given in percentage terms as on the deformation of the segment studied with respect to their size original[8, 13].

It is important to remember that the *strain* is a measure of review of deformation and, as the entire deformation is dependent on volume. Moreover, obtaining the strain in different brands of apparatus does not enable a comparison

of the values, since manufacturers use different algorithms for obtaining the value of the strain. Such that, for comparison of abnormal myocardial deformation of patients undergoing chemotherapy, it is essential that the values are coming from the same device.

At the same time two-dimensional strain detects spontaneous intra-myocardial echoes (speckles) and evaluates these speckles movement along the cardiac cycle, thereby calculating the deformation. It is a quick and easy method of acquisition, with less inter and intra observer variability than conventional strain, and that, unlike the latter, be independent angle. The strain evaluates only the longitudinal deformation, while the two-dimensional strain also evaluates the radial and circumferential strain, enhancing the assessment of cardiac function [12].

The evaluation of myocardial longitudinal deformation may be considered as a more sensitive marker to detect early cardiac dysfunction that the global assessment of cardiac radial contractile function (M mode) or cardiac global (Simpson) [5].

Sawaya et al. [10] found no correlation between change in ejection fraction or diastolic function in early detection of cardiotoxicity. In this study, comprising 43 patients, factors related cardiotoxicity were decreased cardiac global longitudinal strain and elevated troponin I in the 3rd month of the study. This study indicates that these two parameters can serve as early markers of toxicity, and serve to show that chemotherapy can have its continued administration safely or not (Figures 3 and 4). Analyzing separately the longitudinal strain measured in the 3rd month, its drop > 10% it is inferred sensitivity of 78% and specificity of 79% and negative predictive value of 93% to show cardiotoxicity in the 6th month after the beginning of the treatment. Changes in ejection fraction and diastolic function in the 3rd month showed no early diagnosis of dysfunction cardíaca[10].

Park et al.[14] with review of 13 children undergoing chemotherapy with anthracycline also showed a decrease in radial and longitudinal strain after the first dose, while the fall in ejection fraction occurred only after the second chemotherapy session, demonstrating the early changes of deformation in relation to the changes of classic contractility. There was also an increase of isovolumic LV relaxation and reduced amplitude of early diastolic mitral flow (E wave) [14].

In another study in which 35 patients with breast cancer were treated with trastuzumab, 18 patients (51%) showed significant reduction of longitudinal strain, demonstrating subclinical myocardial dysfunction, even before the fall of the fraction of ejeção.[15]

Despite promising studies, the real role of two-dimensional strain aiding in the detection of cardiac dysfunction is to be set, still requiring wider multicentre studies.

Conclusion:

Ejection fraction and fractional shortening of the LV are important predictors of morbidity and mortality in patients receiving cardiotoxic chemotherapy parameters and should still be used as markers of cardiotoxicity, according to current guidelines. The decrease in ejection fraction still works as aspirational for detecting cardiotoxicity by chemotherapy, with larger decrease of 10% as an indicator of disruption in the administration of this drug. However, the changes in these parameters during treatment, as well as changes of the LV diameters, left ventricular mass and wall thickness, are found in the later course of therapy and often appear only when myocardial lesions are already irreversible. The presence of early markers of dysfunction, such as strain and two-dimensional strain may be useful for detecting subclinical myocardial dysfunction of this tool and can serve as an alert for possible early termination of therapy exchange for or less cardiotoxic drugs[16].

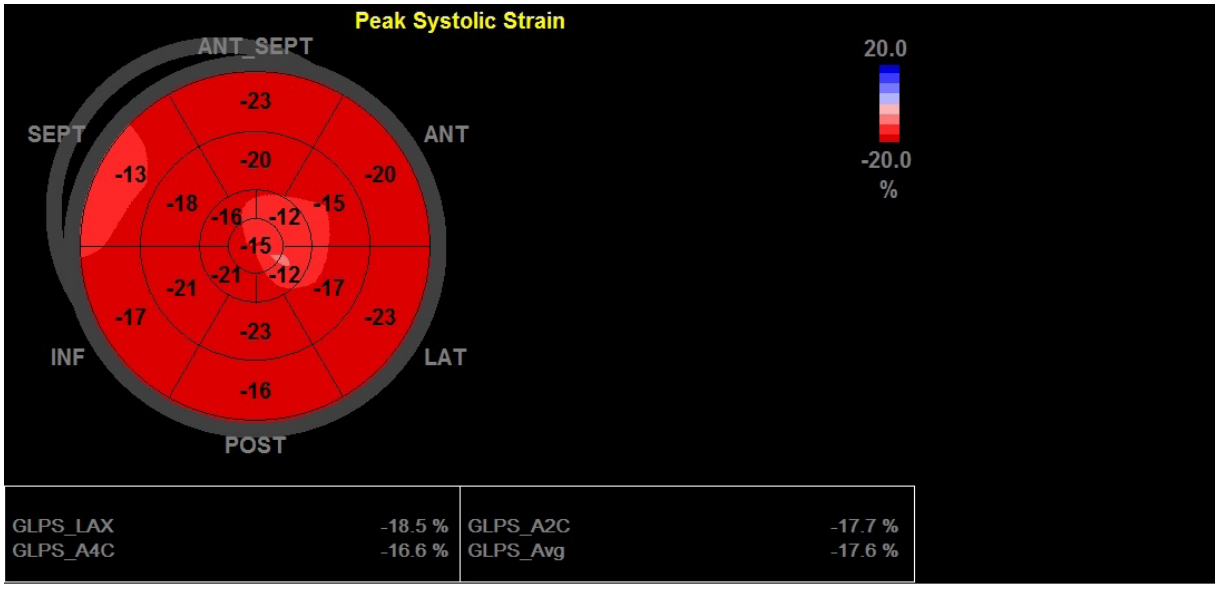

Figure 3 - *Longitudinal Strain two-dimensional pre-chemotherapy with daunorubicin. Note homogeneous myocardial deformation, with overall average value of -17.6%.*

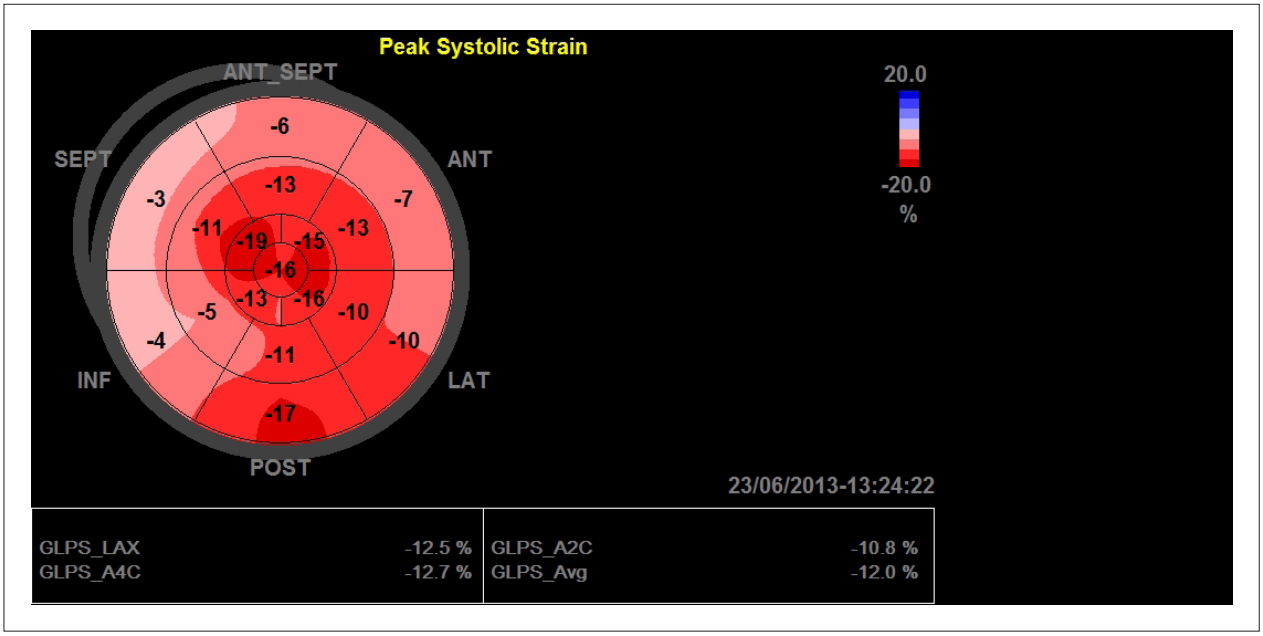

Figure 4 - *Dimensional Strain longitudinal after 6 months of chemotherapy in the same patient in the previous figure. Note heterogeneous myocardial deformation, more preserved in apical segments, with greater than 10% of the average overall value compared to baseline (-12%) drop.*

References

1. Kalil Filho R, Hajjar LA, Bacal F, Hoff P, Diz Mdel P, Galas FRB, et al; Sociedade Brasileira de Cardiologia. I Diretriz Brasileira de Cardio-Oncologia da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2011; 96(2 supl.1):1-52.
2. Geiger S, Lange V, Suhl P, Heinemann V, Stemmler HJ. Anticancertherapy induced cardiotoxicity: review of the literature. Anticancer Drugs. 2010;21(6):578-90.
3. Karanth NV, Roy A, Joseph M, de Pasquale C, Karapetis C, Koczwara B. Utility of prechemotherapyechocardiographical assessment of cardiac abnormalities. Support Care Cancer. 2011;19(12):2021-6.
4. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol. 2010; 7(10):564-75.
5. Eidem BW. Identification of anthracycline cardiotoxicity:leftventricular ejection fraction is not enough. J Am Soc Echocardiogr. 2008;21(12):1290-2.
6. Sociedade Brasileira de Cardiologia. Diretriz para Indicações e utilização da ecocardiografia na prática clínica Arq. Bras. Cardiol. 2004; 82 (suppl.2):11-34.
7. Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? J ClinOncol. 2008;26(8):1201-3.
8. Jassal DS, Han SY, Hans C, Shharma A, Fang T, Ahmadie R. Utility of tissue Doppler and strain rate imaging in the early detection of trastuzumab and anthracycline mediated cardiomyopathy. J Am Soc Echocardiogr. 2009;22(4):418-24.
9. Wu AH. Cardiotoxic drugs: clinical monitoring and decision making. Heart. 2008;94(11):1503-9.
10. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011; 107(9):1375–80.
11. Stoddard MF, Seeger J, Liddell NE, Hadley TJ, Sullivan DM, Kypeersmith J.. Prolongation of isovolumetric relaxation time as assessed by Doppler echocardiography predicts doxorubicin-Induced systolic dysfunction in humans. J Am Coll Cardiol.. 1992; 30 (1):62-9.
12. Stanton T, Leano R, Marwick TH. Prediction of All-Cause Mortality From Global Longitudinal Speckle Strain. Circ Cardiovasc Imaging.2009;2(3):356-64.
13. Sawaya H, Plana JC, Schereer- Crosbie M.. Newest echocardiographic techniques for the detection of cardiotoxicity and heart failure during chemotherapy. Heart Fail Clin. 2011; 7(3):313-21.
14. Park JH, Kim YH, Hyun MC, Kim HS. Cardiac functional evaluation using vector velocity imaging after chemotherapy including anthracyclines in children with cancer. Korean Circ J. 2009;39(9):352-8.
15. Hare JL, Brown JK, Leano R, Jenkins C, Woodward N, Marwick TH. Use of myocardial deformation imaging todetect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab. Am Heart J. 2009;158(2):294–301.
16. Porea TJ, Dreyer ZE, Bricker JT, Mahoney DH Jr. Evaluation of left ventricular function in asymptomatic children about to undergo anthracycline-based chemotherapy for acute leukemia: an outcome study. J Pediatr Hematol Oncol. 2001;23(7):420-3.

Review Article