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ORIGINAL ARTICLE

Right Ventricle Function Assessment in Doxorubicin Treated Children (Value of Dobutamine Stress Echocardiography, Tissue Doppler Imaging)

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Background Doxorubicin cardiotoxicity remains a significant clinical problem that requires a preventive strategy of early diagnosis. This study aimed to evaluate the feasibility of Doppler tissue imaging (DTI) and stress DTI as early screening tests in assessing the right ventricular systolic and diastolic functions.

Methods This study included 19 asymptomatic patients aged 4.9+2 1 years with normal systolic function who were receiving doxorubicin chemotherapy (Cumulative dose= 122.4+59.9 mg/m2). They were compared to 20 controls. They were subjected to Doppler-echocardiographic and DTI examination of the right ventricle (RV). All patients underwent low-dose (10 ug/kg/min) dobutamine stress echocardiography (DSG) and stress DTI.

Results RV systolic & diastolic functions [Assessed by Doppler study tricuspid inflow, and myocardial performance index (MPI) were impaired in patients compared with controls (P<0.05). DTI study confirmed and disclosed such impairment in RV systolic [decreased tricuspid annulus systolic (Sa) velocity and diastolic functions [Decreased early diastolic tricuspid (Ea) velocity in patients compared with controls (P <0.05). During DSE RV systolic functions and MPI showed significant improvement (p <0.05) while the diastolic parameters showed blunted changes compared with rest (p >0.05). This was confirmed by dobutamine stress DTI that showed significant improvement in tricuspid Sa (p <0.050) and non significant changes in the diastolic parameters (p >0.05). Patients with DTI-derived tricuspid Sa <7.5 cm/sec, MPI >4, E/A ratio <l cutoff values exhibited significantly different percent changes in all the DSE and dobutamine stress DTI right systolic, diastolic parameters as well as the MPI compared with the remaining patients (p <0.05).

Conclusions DTI confirmed and disclosed abnormal RV systolic and diastolic functions reported by conventional Doppler-echocardiography in asymptomatic doxorubicin-treated children. DSE and stress DTI showed improved RV systolic parameters and blunted changes in diastolic parameters compared with rest data. The combined new DTI-derived velocities, Doppler-derived indices (MPI) could discriminate patients with more worsened DSE and stress DTI results.

Keywords Tissue Doppler, Right Ventricle, Dobutamine.
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INTRODUCTION

With the development of anticancer drugs, radiotherapy, and the increased opportunity for bone marrow or hematopoietic stem cells transplantation, more than 2/3 of pediatric patients with leukemia or solid tumors survive long-term. The side effects following treatment, especially acute and chronic cardiac side effects after anthracycline infusion, have received considerable attention (1).

The cumulative and definitive nature of cardiotoxicity of anthracyclines requires a preventive strategy of early diagnosis (2) which is of great importance in oncological treatment (3). For early detection of this cardiotoxicity, several noninvasive techniques for evaluation of left ventricular (LV) systolic and diastolic function have been devised (4, 5) especially in long-term survivor after doxorubicin chemotherapy (6-8). However, these

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Abbreviations and Acronyms

DTI	: Doppler tissue imaging
DSG	: Dobutamine stress echocardiography
MPI	: Myocardial performance index
Sa	: Peak tricuspid annular systolic velocity
Ea	: Peak tricuspid annular early diastolic velocity
Aa	: Peak tricuspid annular late diastolic velocity
Tr	: Tricuspid
E	: Peak early filling velocity
A	: Peak atrial phase filling velocity
IVRT	: Isovolumic relaxation time

techniques do not always improve sensitivity and specificity for detecting this cardiotoxicity (9).

Tei, et al. described an echocardiography index (MPI) as a reliable assessment of both systolic and diastolic function of the LV& RV. It is the summation of the lsovolumetric contraction and relaxation times divided by the ejection time. It is also independent of loading conditions and heart rate (10, 11).

The risk of congestive heart failure in children has been reported to increase at cumulative doses >550 mg/m2 (12). Little has been published on the effects of small or moderate doses of anthracyclines on myocardial function in clinically asymptomatic children treated for malignant neoplasms (13). So, this study aimed to investigate the additive value of DTI and low-doses DSE or stress DTI to conventional Doppler-echocardiography in early detection of subclinical or clinical cardiotoxicity in asymptomatic children treated with doxorubicin chemotherapy and to evaluate their feasibility as early screening tests in assessing the right ventricular systolic and diastolic functions in such patients. The additive impact of Tei index on improving diagnosis was also assessed.

PATIENTS AND METHODS:

Patients:

This study included 19 patients (13 boys and 6 girls aged 2 to 9 years (Mean age= 4.9±2.1 years) who were receiving Doxorubicin treatment for hematological malignancies in Oncology Department, and were assessed at Cardiac Department, Tanta University Hospital (Group I). Sixteen patients have been diagnosed as having acute lymphoblastic leukemia, 2 as having acute myeloid leukemia and one as having leukemic phase of lymphoma. Their weight ranged from 6 to 25 Kg (Mean= 16.2±5.0 Kg) and their body surface area (BSA) ranged from 0.33 to 0.83 m2 (Mean= 0.62+0.12 m2)

The mean cumulative dose of administered doxorubicin was 122.4±59.9 mg/m2 (Range from 41.5 to 250 mg/m2) (Low to moderate cumulative dose of doxorubicin).

The control group (Group II) consisted of 20 age-, sex- and BSA-matched healthy disease-free children (13 boys and 6 girls), aged 4.7±2.3 years (Range= 2-l0 years) with BSA= 0.64±0.14 m2.

Exclusion criteria:

Patients with blood hemoglobin concentration <8 g/dl, those with congenital or acquired heart disease including rheumatic heart disease and cardiomyopathy, were excluded from the study. Patients with renal hepatic on chest disorders were also excluded.

Methods:

All patients and controls were subjected to full history taking and thorough clinical examination, 12-lead ECG, M mode, 2-D and color Doppler echocardiographic examination and pulsed-wave mode of DTI. In addition, all patients underwent DSE and dobutamine stress DTI.

All subjects had their pulse, blood pressure and body surface area (BSA, m2) recorded immediately before echo-cardiographic study.

Doppler-echocardiographic examination:

The echocardiographic examination was done for all individuals in the left lateral decubitus position with a 4 MHz sector probe using a commercially available Sonos 5500 Hewlett-Packard phased-array system equipped with DTI technology.

Al least three consecutive beats were measured and averaged for each echocardiographic, Doppler or DTI parameter.

An electrocardiogram was simultaneously recorded for each patient.

Similarly, Doppler tricuspid flow pattern was determined and peak early phase filling velocity (E) and peak atrial phase filling velocity (A) were measured. The E/A ratio was also calculated. Doppler time intervals were measured form tricuspid inflow and RV outflow Doppler tracing with calculation of RV MPI (Tei index) (14). Right ventricular IVRT was also estimated.

Pulsed-wave Doppler tissue imaging:

Tricuspid annular velocity: On the apical 4-chamber view, the pulsed wave DTI cursor was placed at the tricuspid annulus at the RV free wall in such a way that the tricuspid annulus moved along the sampling line the filter setting and gains were adjusted to obtain the optimal clear tissue signal with minimal background noise and to exclude high frequency signals. Nyquist limit was adjusted to a velocity range of -30 to 30 cm/sec. The peak systolic and diastolic velocities were measured at a sweep speed of 50 mm/sec. The ECG was connected and traced simultaneously to define the systolic and diastolic waves (15, 16). The peak systolic (Sa) velocity was quantified It was measured at the peak phase which is corresponding to the T-wave of the ECG. A peak early diastolic wave (Ea) and late diastolic

wave (Aa, which occurred after the P wave of the ECG) were also measured. The peak systolic and diastolic major velocities were also recorded [A positive systolic velocity (Tricuspid Sa) and 2 negative diastolic velocities (Tricuspid Ea and tricuspid Aa) (17).

Low-dose dobutamine stress echocardiography (DSE): Dobutamine infusion was administered at 5 ug/Kg/min for 4 minutes then increased to 10 ug/Kg/min without sedation (18). Blood pressure and ECG were recorded at the beginning of each stage. Tow-dimensional echocardiogram was continuously monitored. Conventional Doppler-echocardiographic and pulsed DTI examinations were performed before (Rest study) and 4 minutes after infusion of 10 ug/Kg/min (Top of the low-dose dobutamine stress test).

Statistical Analysis:

The collected data was organized, tabulated and statistically analyzed using SPSS soft ware statistical computer package version 10 For quantitative data, the mean and standard deviation were calculated. The difference between two means was statistically analyzed using the paired or unpaired students (t) test. Chi square test was used when appropriate. Significance was adopted at p <0.05 for interpretation of results of tests of significance.

RESULTS

Basal evaluation

The study was preformed in 19 patients, results were compared with 20 age-, sex-and BSA-matched controls.

At rest, systolic and diastolic blood pressure exhibited non significant differences between patients and controls (112±13 Vs 105±15 mmHg and 70±5 Vs 67+18 mmHg, p >0.05 respectively). The heart rate reported similar non significant differences between patients and controls (93±15 Vs 85+14 beats/minute, p <0.05).

RV Tei index showed significant increase compared with controls p <0.05).

Conventional Doppler-echocardiographic data (Table 1 and Figure 1):

Conventional echo-Doppler examination of the right ventricle revealed evident diastolic abnormalities with significantly decreased tricuspid E wave velocity, elevated A wave velocity and decreased E/A ratio in patients compared with controls(P <0.05).

DTI Study (Table 2):

DTI examination of the tricuspid annular velocities revealed reduced peak tricuspid Sa wave velocity in patients compared with controls (P <0.05). Meanwhile, the DTI examination further disclosed the right ventricular diastolic dysfunction with significantly decreased tricuspid peak Ea velocity (P <0.05) and decreased tricuspid Ea/Aa ratio (yet, P >0.05) in patients compared with controls.

Two patients with Doppler tricuspid E/A ratio >1 reported abnormal Ea/Aa <1.

Table 1: RV. Doppler echocardiography at rest in patients, controls and dobutamine stress echocardiography in patients:

	Controls at rest	Patients at rest	Dobutamine stress
Variables	**Mean+ SD**	**Mean+ SD**	
Conventional Doppler			**DSE**
Tricuspid E (m/sec)	0.54±0.10	0.67±0.12*	0.72±0.22
Tricuspid A (m/sec)	0.38±0.05	0.59±0.15*	0.66±0.19
Tricuspid E/A	1.43±0.21	1.18±0.31*	1.12±0.44
Tricuspid IVRT (msec)	58.97±6.99	74.36±12.98*	64.13±18.24
RV Tei index	0.30±0.05	0.38±0.11*	0.33±0.14#

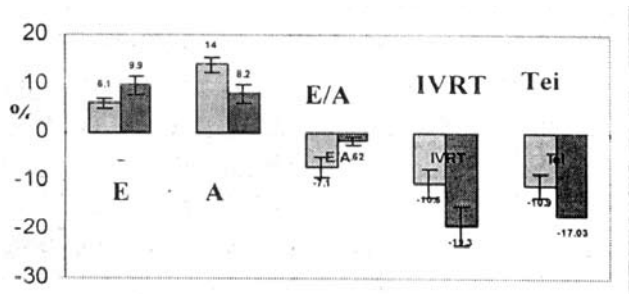

Figure 1: Doppler-echo RV diastolic parameters and Tei index. *E*= peak early filling velocity, *A*= peak atrial phase filling velocity, *IVRT*= isovolumic relaxation time.

Table 2: RV DTI. at rest in patients, controls and dobutamine stress DTI. In patients:

	Controls at rest	Patients at rest	Dobutamine stress
Variables	**Mean+SD**	**Mean+SD**	
DTI			***Dobutamine stress DTI***
Tricuspid Sa (cm/sec)	15.17±1.61	13.42±3.17*	16.62±5.64#
Tricuspid Ea (cm/sec)	17.63±1.58	15.58±2.04*	17.67±4.32
Tricuspid Aa (cm/sec)	13.29±2.46	13.75±4.30	16.00±7.97
Tricuspid Ea/Aa	1.32±0.13	1.22±0.36	1.20±1.39

* Significant p <0.05 when comparing patients to controls.
# Significant p <0.05 when comparing DSE and Dobutamine stress DTI to rest values.
E= peak early filling velocity, *A*= peak atrial phase filling velocity, *IVRT*= isovolumic relaxation time, *Sa*= peak tricuspid annular systolic velocity, *Ea*= peak tricuspid annular early diastolic velocity, *Aa*= peak tricuspid annular late diastolic velocity.

DSE (Table 1):

No major side effects were recorded; except one patient who developed a self-limiting run of supraventricular tachycardia with a heart rate of 145 beats/min at the end

of the dobutamine infusion dose of 10 ug/kg and were completely asymptomatic. The systolic blood pressure and heart rate were significantly increase during DSE compared with their values at rest (136±24 Vs 112±13 mm Hg, and 97±17 Vs 93±15 beats/minute, p <0.05) while the diastolic blood pressure showed non significant changes (72±6 Vs 70±5 mm Hg, p >0.05).

Doppler values of tricuspid inflow showed insignificantly increased E wave velocity during DSE compared with rest values (p >0.05). Similarly, the E/A ratio showed non significant decrease (p >0.05) and the IVRT showed non significant improvement (p >0.05) during DSE. The right ventricular Tei index reported significant improvement during DSE (p <0.05).

Dobutarnine stress DTI (Tables 2 and Figure 2):

Concerning the RV dobutarnine stress DTI, significant improvement in the tricuspid Sa wave peak velocity was observed compared with rest DTI values (p <0.05). Meanwhile, the tricuspid Aa and Ea waves peak velocities showed non significant changes (p >0.05). The tricuspid Ea/Aa ratio showed virtually no change compared with rest rafios (p <0.05).

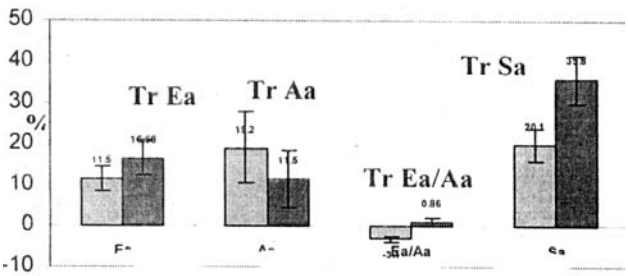

Figure 2: DTI RV systolic and diastolic parameters.
RV= right ventricle, *Tr*= tricuspid, *Sa*= peak tricuspid annular systolic velocity, *Ea*= peak tricuspid annular early diastolic velocity, *Aa*= peak tricuspid annular late diastolic velocity.

DSE and dobutarnine stress DTI were not conducted in controls for ethical reasons. So, changes in right ventricular systolic and diastolic function parameters were not compared in patients with changes in controls.

DISCUSSION:

Anthracyclines (Daunomycin, doxorubicin, epirubicin, idarubicin) are among the most effective antineoplastic drugs and have gained widespread use in the treatment of numerous solid tumors and hematological malignancies. These drugs belong to the class of antineoplastic antibiotics which interfere with cell replication, by acting on DNA at several levels showing an effect in every phase of the cell cycle.

Doxorubicin and daunomycin are the more commonly used anthracyclines in clinical practice; they are administered only by intravenous infusion and metabolized by the liver. Their main route of excretion is through bile, while urinary elimination accounts for approximately 1/6 of the total amount. Although anthracyclines exhibit a range of toxic effects including myelosuppression, mucositis and hair loss, cardiotoxicity may be permanent and progressive (19).

Therefore, the oncologist should take into account the risk of cardiac toxicity due to anthracyclines as a potential cause of severe morbidity in survivors of childhood cancers, as children will have a chance of long-term survival once cured from cancer (19).

The present study assessed 19 children aged 4.9+2.1 years receiving doxorubicin cumulative dose of 122.4+ 59.9 mg/m2 BSA (Range f rom 41.5 to 250 mg/m2) in addition to 20 age- sex- and BSA-matched controls. Evident diastolic abnormalities were reported with conventional Doppler echocardiography in patients compared with controls. DTI further disclosed RV systolic and diastolic dysfunction. During DSE, Doppler values of tricuspid inflow showed blunted changes while the RV Tei index reported significant improvement. Dobutamine stress DTI showed significant improvement in the tricuspid Sa wave while the tricuspid Aa and Ea and E/A showed non significant or virtually no changes compared with rest value.

Oberholzer, et al. previously studied left and right ventricular function using MRI in young cancer patients treated with cardiotoxic anthracyclines, Twenty-eight patients (Mean age 16.4 years) underwent cardiac MRI at 1.5 T. The study protocol consisted of morphologic T2-weighted images with fat suppression and cine steady-state free precession sequences (SSFP) for functional analysis. Seven patients were examined at the end of chemotherapy, two of them also repeatedly during therapy, and 21 patients following an average period of three years after finishing chemotherapy (Range one month--20 years), The end-systolic volume index increased and the ejection fraction of the left and right ventricle decreased during anthracycline therapy. Two of seven patients showed a myocardial edema at the end of the therapy. In 15 of all 28 patients, the left ventricular ejection fraction was reduced to less than 55% (Minimum 44%). No clinical signs of cardiac insufficiency or cardiomyopathy were observed.so they suggested that MRI is able to detect acute as well as chronic subclinical cardiotoxic effects of anthracyclines. Impairment of the right ventricular function should be considered in the diagnosis of anthracycline-induced cardiomyopathy (20).

Unlike the present study, Belham, et al. (21). studied the relative effect on left ventricular (LV) and right ventricular (RV) function of low-dose anthracycline-containing chemotherapy regimes, 23 patients (Mean age 48±20 years) underwent echocardiographic LV and RV function the change in LV Tei was significantly greater than the change in RV Tei (0.07±0.13 vs 0.01±0.09, P=

.044). So they concluded that Low-dose anthracycline administration has a significant negative impact on LV function but does not affect RV functionexaminations before any anthracycline had been administered and then after low-dose anthracycline (Doxorubicin 50-125 mg/m2). The Tei index was used to compare the relative effects on RV and LV function.their results showed that anthracycline administration was significantly associated with an increase in the LV Tei index (0.38±0.12 vs 0.46±0.16, P= .02). There was no significant change in the RV Tei index (0.19±0.10 vs 0.20±0.10, P= .72). Comparing the relative effect on global LV and RV function the change in LV Tei was significant greater than the change in RV Tei (0.07±0.13 vs 0.01±0.09, P= .044)

Cottin, et al. (22) reported no significant alterations in the RV functions assessed by radionuclide measurement in women one-year after moderate doses of Later, Lanzarini, et al. (23) reported that RV systolic function (the tricuspid annular plane systolic excursion) was comparable between patients and controls.anthracycline.

On the contrary, Barendswaard, et al. (24) found that 19.9% of segments showed abnormal wall motion by radionuclide ventriculography in 52 patients in the RV which was significantly higher than in the LV.

Moreover, Rumoroso, et al. (25) reported reversible right heart failure in 33 year women 15 days after receiving doxorubicin. Severe regional right ventricular wall motion abnormalities were appreciated through 2-D and Doppler-flow echocardiography while there was no evidence of impaired systolic or diastolic LV function. Later, Kapusta, et al. (26) reported decreased RV wall thickness in anthracycline-treated patients compared with controls.

CONCLUSIONS

Results of the present study suggested concomitant changes in RV myocardial systolic and diastolic functions in asymptomatic children who received low to moderate doses of doxorubicin for treatment of childhood hematological malignancies.

DTI data have enhanced this study. DT1-derived systolic and diastolic velocities confirmed and disclosed abnormal RV systolic and diastolic functions reported by conventional Doppler-echocardiography. DTI even permitted clearer differentiation of any true myocardial relaxation abnormalities and subsequent pseudonormalization. DTI velocities might be considered as a useful non invasive method that even added incremental value and are superior to the standard Doppler-echocardiography parameters alone.

DSE and stress DTI showed improved RV systolic parameters and blunted changes in diastolic parameters compared with rest data. So, DSE and stress DTI were proved to be sensitive approaches for confirming subclinical cardiac dysfunction.

The combined new DTI-derived velocities, Doppler derived indices (MPI) could discriminate patients with more worsened DSE and stress DTI results. Measurement of these parameters could add significant value to routine monitoring of systolic function alone during doxorubicin chemotherapy. Likewise, cardiotoxicity can be detected early by the repetitive measurement of these easily available parameters based on limited number of variables at rest. In addition, these parameters could add significant information that benefit in the clinical management and follow up of such patients. These information could therefore have therapeutic implications that would benefits from further exploration. The prognostic importance, of these variables for serial and prospective studies in the long term needs further investigations.

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REFERENCES

1. Jong HP, Yeo HK, Myung CH, et al. Cardiac functional evaluation using vector velocity imaging after chemotherapy including anthracyclines in children with cancer. Korean Circ J 2009; 39(9):352-8.
2. Tassan Mangina S, Brasselet C, Nazeyrollas P, et al. Intérêt du Doppler tissulaire pulse pour le dépistage précoce de l'altération de la fonction myocardique aux anthracyclines. [Value of pulsed Doppler tissue imaging for early detection of myocardial dysfunction with anthracyclines]. Arch Mal Coeur Vaiss 2002; 95(4):263-8.
3. Herth F, Schulz MR, Manegold C, et al. Durchfuhrbarkeit der stressechokardiographie zur fruherkennung der anthracyclin-induzierten kardiomyopathie. [Usefulness of stress echocardiography for early diagnosis of anthracycline-induced cardiomyopathy]. Pneumologie 2001; 55(8):385-9.
4. Massing JL, Caillot D, Mouhat T, et al. Détection précoce de la toxicité cardiaque des anthracyclines. Intérêt de l'étude isotopique. [Early detection of cardiotoxicity of anthracyclines. Value of isotopic method]. Arch Mal Coeur Vaiss 1996; 89(1):57-62.
5. Wilson GM, Rahko PS. The clinical utility of automatic boundary detection for the determination of left ventricular volume: A comparison with conventional off-line echocardiographic quantification. J Am Soc Echocardiogr 1995; 8(6):822-9.
6. Bu'Lock FA, Mott MG, Oakhill A, et al. Left ventricular diastolic function after anthracycline chemotherapy in childhood: Relation with systolic function, symptoms and pathophysiology. Br Heart J 1995; 73(4):340-50.
7. Lipshultz SE, Colan SD, Gelber RD, et al. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 324(12):808-15.
8. Lee BH, Goodenday LS, Muswick GJ, et al. Alterations in left ventricular diastolic function with doxorubicin therapy. J Am Coll Cardiol 1987; 9(1):184-8.

9. Hashimoto I, Ichida F, Miura M, et al. Automatic border detection identifies subclinical anthracycline cardiotoxicity in children with malignancy. Circulation 1999; 99(18):2367-70.
10. Djaiani GN, McCreath BJ, Ti LK, et al. Mitral flow propagation velocity identifies patients with abnormal diastolic function during coronary artery bypass graft surgery. Anesth Analg 2002; 95(3):524-30.
11. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol 1995; 26(2):135-6.
12. Haque A, Otsuji Y, Yoshifuku S, et al. Effects of valve dysfunction on Doppler Tei index. J Am Soc Echocardiogr 2002; 15(9):877-83.
13. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med 1996; 125(1):47-58.
14. Burgess MI, Bright Thomas RJ, Ray SG. Echocardiographic evaluation of right ventricular function. Eur J Echocardiogr 2002; 3(4):252-62.
15. McDicken WN, Sutherland GR, Moran CM, et al. Colour Doppler velocity imaging of the myocardium. Ultrasound Med Biol 1992; 18(6-7):651-4.
16. Sutherland GR, Stewart MJ, Groundstroem KW, et al. Color Doppler myocardial imaging: A new technique for the assessment of myocardial function. J Am Soc Echocardiogr 1994; 7(5):441-58.
17. Alam M, Wardell J, Andersson E, et al. Characteristics of mitral and tricuspid annular velocities determined by pulsed wave Doppler tissue imaging in healthy subjects. J Am Soc Echocardiogr 1999; 12(8):618-28.
18. Klewer SE, Goldberg SJ, Donnerstein RL, et al. Dobutamine stress echocardiography: A sensitive indicator of diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer. J Am Coll Cardiol 1992; 19(2):394-401.
19. Puma N, Ruggiero A, Ridola V, et al. Anthracycline-related cardiotoxicity: Risk factors and therapeutic options in childhood cancers. Signa Vitae 2008; 3(1):30-4.
20. Oberholzer K, Kunz RP, Dittrich M, et al. Anthracycline-induced cardiotoxicity: Cardiac MRI after treatment for childhood cancer. Rofo 2004; 176(9):1245-50.
21. Belham M, Kruger A, Pritchard C. The Tei index identifies a differential effect on left and right ventricular function with low-dose anthracycline chemotherapy. J Am Soc Echocardiogr 2006; 19(2):206-10.
22. Cottin Y, Touzery C, Coudert B, et al. Diastolic or systolic left and right ventricular impairment at moderate doses of anthracycline? A 1-year follow-up study of women. Eur J Nucl Med 1996; 23(5):511-6.
23. Lanzarini L, Bossi G, Laudisa ML, et al. Lack of clinically significant cardiac dysfunction during intermediate dobutamine doses in long-term childhood cancer survivors exposed to anthracyclines. Am Heart J 2000; 140(2):315-23.
24. Barendswaard EC, Prpic H, Van der Wall EE, et al. Right ventricle wall motion abnormalities in patients treated with chemotherapy. Clin Nucl Med 1991; 16(7):513-6.
25. Rumoroso JR, Montes PM, Garcia JC, et al. Insuficiencia ventricular derecha aguda reversible tras tratamiento con antraciclinas. [Acute right ventricular insufficiency reversible following anthracycline treatment]. Rev Esp Cardiol 1995; 48(3):205-7.
26. Kapusta L, Thijssen JM, Groot Loonen J, et al. Tissue Doppler imaging in detection of myocardial dysfunction in survivors of childhood cancer treated with anthracyclines. Ultrasound Med Biol 2000; 26(7):1099-108.