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Evaluation of cardiac functions by tissue Doppler echocardiography method in long-term follow-up of pediatric Hodgkin lymphoma patients

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Summary

Aim: Treatment-associated cardiomyopathy which is one of the side effects of treatment can be asymptomatic in Hodgkin lymphoma patients. The aim of this study was to find out whether tissue Doppler echocardiography was superior to conventional echocardiography in determining potential cardiac problems in the patients diagnosed with Hodgkin lymphoma.

Material and Method: A total of 17 Hodgkin lymphoma patients (12 males, 5 females) who were being followed-up with disease-free status and without cardiac symptoms and whose treatment had been stopped for at least 4 years, and a control group of 14 healthy persons (8 males, 6 females) were included in the study. The cardiac functions of the patients were evaluated by M-mode, 2 dimentional, colour Doppler, CW Doppler and pulse Doppler techniques. Data analyzes were evaluated by program of Statistical Package for Social Science for Windows 11.5, and Shapiro Wilk, Student's t testi, Mann Whitney U, Fisher's exact chi square tests, respectively. Hospital ethics committee consent was received for the study (07.05.2007/no:5639).

Results: There was no statistical difference between the two groups (p: 0.302 and p: 0.860 respectively) when both groups were evaluated in terms of ejection fraction and fraction shortening by conventional echocardiography technique. Evaluation of both groups for the left ventricular isovolumic contraction time revealed a statistically significant longer time in the patient group compared to the control group (p: 0.038). The results were found longer in the patient group compared with the control group when both groups were evaluated in terms of myocardial performance index parameters and the left ventricular isovolumic contraction time parameters (p: 0.029 and p: 0.049, respectively).

Conclusions: We concluded that the left ventricular isovolumic contraction time, the left ventricular isovolumic acceleration time and myocardial performance index tests are important parameters for the early detection of cardiac pathologies that may develop in relation to chemotherapy. *(Turk Arch Ped 2011; 46: 220-5)*

Key words: Anthracycline, cardiotoxicity, Hodgkin lymphoma, side affect, tissue Doppler echocardiography.

Introduction

Marked advances have been observed in treatment of pediatric Hodgkin lymphoma disease in recent years in developing countries (1). However, side effects related to the medications and radiotherapy used for the primary disease constitute an important problem. Cardiomyopathy which develops with combined use of radiotherapy and anthracycline group medications is one of these problems. Combined use of these two therapies as well as each therapy method individually has potential cardiotoxic effect. Studies demonstrated cardiac side effects with a high rate in Hodgkin lymphoma patients who received only chemotherapy (2). Anthracyline group of medications included in the chemotherapeuticals used is an important negative factor for occurrence of this picture.

Even if Hodgkin lymphoma patients who survive for long-term appear complaint-free and problem-free, the actual rate of cardiac problems is higher than expected (3,4). This rate reaches a high level of 57% in some series and factors including total anthracycline dose (especially values higher than 250-300mg/m^2), anthracycline treatment at an early or advanced age, female gender, radiation therapy, high

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dose treatments have been proposed to play an important role in the occurence of this problem (3,5). The most commonly used test to determine this cardiac complication is uninterventional two-dimension echocardiography which measures left ventricular ejection fraction and shortening fraction. There are studies reporting that tests including stress echocardiography with low or high dose dopamin, measurement of myocardial tension with echocardiography, evaluation of exercise electrocardiogram, measurement of blood atrial natriuretic hormon and cardiac MR give better results for evaluation of cardiac side effects which may develop in long-term compared to classical echocardiography (6-9). However, in spite of all these studies, there is still no appropriate test which can early determine cardiomyopathy which may develop in long-term (10). Tissue Doppler echocardiography is a new technique which measures the acceleration process of the movements of the cardiac wall muscles. The main advantage of this test is the fact that it is not affected by age, blood pressure and cardiac rate. Tissue Doppler echocardiography can prematurely determine cardiac pathologies which may lead to mortality (11,12). Studies reported that tissue Doppler echocardiography evaluated long-term side effects with various subvariables in patients with pediatric malignencies and determined the picture of cardiomyopathy earlier compared to traditional methods (12,23,24,26,27). In this study, it was aimed to investigate if tissue Doppler echocardiography was superior to traditional echocardiography in determining long-term cardiac side effects of chemotherapeuticals in pediatric Hodgkin lymphoma patients who had not received radiotherapy.

Material and Method

17 Hodgkin lymphoma patients (12 male and 5 female) who were diagnosed between 1994 and 2003 in Dr.Sami Ulus Children's Hospital, had not received radiotherapy, had discontinued their treatment at least for four years and followed up as disease-free patients and had traditional echocardiograms taken with regular intervals during treatment and 14 healthy individuals (8 male and 6 female) as the control group were included in this study. Echocardiographic investigation was done using Vivid Pro7 device and 3 MHz probe. Dimensions of the right ventricle and left ventricle, outlets, valve failures, stenoses were evaluated using M-mod, two dimension, colored Doppler, CW Doppler and pulse Doppler.

The process was conducted in association with electrocardiographic monitorization. Tissue Doppler investigation was performed using 3 MHz probe. Apical four chamber position was selected as the test position. To obtain clean, residue-free vision Doppler "gain" was considered. Fitler format of echocardiography device was used. Doppler signals were recorded at a rate of 100 mm/sec. Isovolumic relaxation time and isovolumic contraction time from the basal part of the left ventricle, myocardial rate during the systole, myocardial rate during the erly diastole, the rate during the late diastole, ejection time, isovolumic contraction acceleration and acceleration of the ventricle at the time of isovolumic contraction were measured.

After treatment was ended, median follow up time was found to be 108 (54-174) months. Patients with previous cardiac problems were excluded from the study whether symptomatic or asymptomatic. Staging was done according to Ann-Arbor staging system. Five of the patients who were diagnosed as Hodgkin lymphoma were treated with adriablastine, belomycine, vinblastine, dacabazine, six were treated with cyclophosphamide, oncovin, procarbazine and prednisolone and six were treated with successive adriablastine, bleomycine, vinblastin, dacarbazine-cyclophosphmide, vincristin, procarbazine and prednisolone. Six cycles of cyclophosphamide, oncovin, procarbazine and prednisolone or adriablastine, bleomycine, vinblastin and dacarbasine were given to the patients in the early stage (stage 1-2). 12 cycles of successive therapy with adriablastine, bleomycine, vinblasatin, dacarbazine-cyclophosphamide, vincristin, procarbazine and prednisolone were given to the patients in the advanced stage (stage 3-4). Total doses of anthracycline and alkalinizing agents given to the patients with a diagnosis of Hodgkin lymphoma were calculated. No patient received radiotherapy. Clinical information about the patients are summarized in table 1.

Approval from the Hospital Local Ethics Committee and informed consent from all patients or relatives of the patients were obtained for this study (05.07.2007/number: 5639).

Statistical analysis

Analysis of the data was done using SPSS (Statistical Package for Social Science) for Windows 11.5 package program. Shapiro Wilk test was used to examine if the distribution of continious variables was close to normal. Descriptive statistical values were shown as mean±standard deviation or median (range between quarters) for continious variables and as number of cases and (%) for numerical variables. Student's t test was used to determine if there was a statistically significant difference between the groups in terms of mean values and Mann Whitney U test was used to evaluate the statistical significance in terms of median values. Nominal variables were examined by Fİsher's exact qui-square test. A p value of <0.05 was considered to be statistically significant.

Results

A total of 31 individuals were included in this study. 17 of them had Hodgkin lymphoma and 14 constituted the control

Table 1. Clinical properties of the patients

Age at the time of diagnosis months)	Gender	Subgroup	Stage	Total dose of alkalinizing agent (m2)	Total dose of anthracycline (m2)	Time passed after the end of treatment (months)
101	E	LY	II	CTX: 6000 mg, PRO: 9000 mg	-	150
36	E	KH	II	CTX: 6000 mg PRO: 9000 mg	-	132
92	E	NS	II	CTX: 3000 mg, PRO: 4500 mg	ADM: 450 mg, BLEO: 180 U	60
84	E	KH	II		ADM: 300 mg, BLEO: 120 U	108
36	E	NS	III	CTX: 3000 mg, PRO: 4500 mg	ADM: 450 mg, BLEO: 180 U	60
87	E	KH	III	CTX: 3000 mg, PRO: 4500 mg	ADM: 450 mg BLEO: 180 U	66
113	K	LZ	II	CTX: 6000 mg, PRO: 9000 mg	-	126
151	K	NS	II	CTX: 6000 mg, PRO: 9000 mg		87
106	K	KH	II	CTX: 6000 mg, PRO: 9000 mg		132
65	E	NS	II		ADM: 3000 mg BLEO: 1200 U	108
114	K	KH	III	CTX: 3000 mg, PRO: 4500 mg	ADM: 450 mg, BLEO: 180 U	54
48	E	KH	II		ADM: 300 mg, BLEO: 120 U	63
96	K	KH	II	CTX: 6000 mg, PRO: 9000 mg		84
42	E	LZ	II	CTX: 1000 mg, PRO: 1500 mg	ADM: 300 mg, BLEO: 120 U	144
126	E	LZ	II		ADM: 300 mg, BLEO: 120 U	115
58	E	KH	II		ADM: 300 mg, BLEO:120 U	66
84	E	KH	III	CTX: 3000 mg, PRO: 4500 mg	ADM: 450 mg BLEO: 180 U	55

Abbreviations: ADM: Adriablastine, BLEO: Bleomycine, CTX: Cyclophosphamide, M: Male, MC: Mixed cell, F: Female, LD: Lymphocyte Deficient, LR: Lymphocyte Rich, mg: Miligram, NS: Nodular Sclerosing , PRO: Procarbazine, U: Ünit

group. Men age of the patients with Hodgkin lymphoma was 180.1±48.6 months; the mean age of the control group was 184.3±28.9 months (p=0.766). 12 of the patients with Hodgkin lymphoma were male and 5 were female. 8 of the healthy group were male and 6 were female (p=0.477). When the two groups were comapred in terms of ejection fraction and shortening fraction by traditional echocardiography technique, no statisticlly significant difference was observed (p=0.302 and p=0.860, respectively). When the two groups were compared in terms of tissue Doppler echocardiography measurements, left ventricular isovolumic contraction time (LVBICT) in the Hodgkin lymphoma group (150.12±44.72 ms) was found to be lower than the control group (118.57±39.86 ms). The statistical difference between these two groups was found to be at the borderline (p=0.049). Left ventricular isovolumic acceleration time (LVBIVA) was found to be lower in the Hodgkin lymphoma group (2.73±0.69 m/s^2) compared to the control group (3.45±1.05 m/s^2). Statistical significant difference was found between the values of these two groups (p=0.038). Myocardial performance index (MPI) was found to be 1.06 (0.63) in the Hodgkin lymphoma group and 0.77 (0.33) in the control group. A statistically significant difference was found between these values (p=0.029).

Table 2. Evaluation of the clinical and demographical properties of the groups

Variables	Patient group (s=17)	Control group (s=14)	p
Age	180.1±48.6	184.3±28.9	0.766[a]
Gender M/F	12/5	8/6	0.477[b]
LVBS	0.09±0.02	0.09±0.02	0.951[a]
LVBE	0.20±0.03	0.22±0.04	0.177[a]
LVBA	0.08 (0.02)	0.08 (0.03)	0.570[b]
LVBICT	150.12±44.72	118.57±39.86	0.049[a]
LVBSS	208.00±37.67	231.50±33.81	0.081[a]
LVBES	120.76±20.16	111.50±18.27	0.195[a]
LVBAS	61.59±17.22	61.57±11.37	0.998[a]
LVBIRT	70.18±12.75	68.64±19.70	0.804[a]
LVBIVA	2.73±0.69	3.45±1.05	0.038[a]
LVBSA	0.96±0.39	0.91±0.30	0.659[a]
LVBEA	3.85±0.80	3.87±1.00	0.941[a]
LVBAA	2.10 (1.68)	2.65 (2.40)	0.279[b]
EF	70.77±7.86	68.06±6.11	0.302[a]
FS	39.00 (11.50)	36.00 (7.50)	0.860[b]
TEI	1.06 (0.63)	0.77 (0.33)	0.029[b]

Abbreviations: a: Student's t test, b: Fisher's exact qui-square test, c: Mann Whitney U test. , EF:Ejection Fraction (%), , FS: Shortening Fraction, LVBA: Left Ventricular Basal Amplitude A (m/s), LVBAA: Left Ventricular Acceleration A (m/s2 (%),LVBAS: Left Ventricular Basal Time A (ms), LVBE: Left Ventricular Basal amplitude E (m/s), LVBEA: Left Ventricular Acceleration E (m/s2), LVBES: Left Ventricular Basal time E (ms), LVBICT: Left Ventricular Isovolumic Contraciton Time (ms), LVBIRT: Left Ventricular Isovolumic Relaxation Time (ms), LVBIVA: Left Ventricular Isovolumic Acceleration Time (m/s2), LVBS: Left Ventricular Basal Amplitude S (m/s), LVBSA: Left Ventriular Acceleration S (m/s2), LVBSS: Left ventricular Basal Time S (ms), TEI:Tei index

Marked relation between myocardial performance index and total doses of medicine was observed. Evaluation of the variables is summarized in Table 2.

Discussion

In patients using anthracycline group of medicines, cardiotoxicity which develops both in short-term (during the first year of treatment) and in long-term follow up up to 20 years after treatment (chronic period) is well known. Free radicals which are released as a result of anthracycline treatment and apoptosis picture in myocytes which develops by stimulation of superoxides are thought to lead to this clinical pathology. While this effect may be independent of dose, it may increase in parallel to increased total doses of chemotherapeuticals (13). On the other hand, cardiotoxicity cases are reported in patients who use usual doses of alkalinizing agents, although cardiomyopathy is known to develop especially in patients with bone marrow transplant following treatment with high doses of alkalinizing agents (14). Stimulation of cell apopytosis in the heart by cyclophosphamide, reduction of serum carnitine level as a result of treatment and abnormalities in serum lipid levels are thought to be involved in the development cardiotoxicity (13,15,16). The majority of carciovascular problems developing in cancer patients who had used anthracycline group of drugs may be asymptomatic for a long period. In patients treated with alkalinizing agents and anthracyclines, monitoring of cardiomyopathy is done by traditional echocardiography technique measuring ejection fraction and shortening fraction. These investigations are done to evaluate systolic functions. However, diastolic functions are assumed to be disrupted firstly in patients who develop cardiomyopathy (5). Therefore, not only systolic, but also diastolic functions should be evaluated for early diagnosis and evaluation of cardiomyopathy in these patients. Tissue Doppler echocardiography technique is thought to be a more efficient technique compared to traditional echocardiography technique, since it gives information about both systolic and diastolic functions (4).

Myocardial performance index (MPI) which is also known as Tei index, since it was firstly determined by Tei (17) is a measure obtained by dividing the sum of isovolumic contraction and relaxation times to ejection time. Myocardial performance index is a simple, reproducible test independent of heart rate and blood pressure which are compatible with systolic and diastolic dysfunction of the myocardium (6). Myocardial performance index is thought to be a measure which can be used to demonstrate the effect of congenital cardiac diseases, heart failure, coronary heart disease, valvular diseases, pulmonary hypertension and drug-dependent cardiotoxicity on the heart at an early time (18). In a study performed by Santin et al. (19), MPI index was found to be significantly reduced in patients who received chemotherapy and radiotherapy compared to the control group, but no difference was found between the patients who only received chemotherapy and the control group. In contrary to these findings, MPI value was found to be significantly lower in the patient groups who received treatment protocols including both anthracycline and alkalinizing agents without radiotherapy compared to the control group in our study. In a previous study performed by Öcal et al (20) in our hospital in 35 pediatric patients with a diagnosis of pediatric malign disease, MPI index was shown to be significantly lower in patients who received anthracycline compared to the control group. However, there was no association between this lower value and the total dose of the chemotherapeutical drug. In a study performed by Larussi et al.(21) in patients with a diagnosis of pediatric Hodgkin lymphoma, left ventricular isovolumic shortening time (ICT) and MPI was found to be lower in patients who received chemotherapy compared to the control group in accordance with our study. There was no association between these lower values and anthracycline dose and

radiotherapy. In addition, in the study performed by Karakurt et al. (22) in patients with pediatric malignancy who received treatment protocols including anthracycline group of drugs and who did not receive mediastinal radiotherapy, MPI values were found to be statistically significantly lower compared to the healthy group and these lower values were found to be significantly parallel to the total anthracycline doses. Increased severity of cardiomyopathy is expected with increased dose of anthracycline or other cardiotoxic drugs. The fact that no statistically significant relation was found between total drug dose and cardiomyopathy in our study may be due to the low number of subjects. In a study performed by Yıldırım et al. (23) in pediatric patients who received treatment with a diagnosis of lymphoma and solid tumor, it was suggested that left ventricular flow MPI value was a better indicator for determining cardiomyopahty compared to left ventricular wall MPI value.

Isovolumic acceleration (IVA) value calculated using peak value of the rate measured at the time of isovolumic contraction and the time passed from the basal to the peak is a measure which provides evaluation of systolic functions without being affected by hemodynamic changes (24). In our study, although ejection fraction value in the group who received treatment and shortening fraction values in both groups were not significantly different, left ventricular isovolumic acceleration (LVBIVA) value was found to be significantly higher compared to the control group. This measure may be one of the first heralds of systolic dysfunction which occurs after diastolic dysfunction. There are studies reporting that ventricular isovolumic contraction and relaxation acceleration time values are good measures demonstrating systolic functions early without being affected by preload and afterload (25). In a study performed by Dorup et al. (5) in patients with pediatric Wilms tumor and acute lymphoblastic leucemia, diastolic early acceleration abnormalities were specifically found in subjects with a shortening fraction below 25%. In patients whose total anthracycline dose was 250 mg/m2, lengthening of ventricular relaxation time and shortening in acceleration time were observed and these findings were emphasized to indicate that diastolic dysfunction occurred before systolic dysfunction. In a study performed by Baysal et al (26) in 20 subjects with pediatric tumor, left ventricular isovolumic contraction time and left ventricular isovolumic relaxation time values were found to be longer in patients who received anthracycline treatment compared to the control group. Similarly, in a study performed by Öcal et al.(20), a significant difference in MPI value as well as lengthening of left ventricular isovolumic contraction time was demonstrated in cancer patients receiving chemotherapy. In our study group, only left ventricular isovolumic contraction time was found to be lenghtened at the borderline of significance. This difference may be caused by the relatively low number of patients who received anthracycline treatment and by the fact that a part of the patients of Baysal et al(26) received radiotherapy.

In our study, no difference was observed between the patients who received only anthracycline and the patients who received anthracycline and alkalinizing agent or the patients who did not receive anthracycline treatment and received only alkalinizing agent in terms of cardiotoxicity. This result may be caused by the low number of patients. Consequently, long-term follow up is necessary not only in patients who received anthracycline treatment, but also in patients who received alkalinizing agent in terms of cardiomyopahty. MPI measurement by tissue Doppler echocardiography technique which evaluates diastolic functions adequately may be a beneficial method to determine cardiomyopathy at an early time which may develop in these patients. There are limited number of studies in the literature about the clinical significance of left ventricular isovolumic contraction time which was found to be different at the borderline of significance (p=0.049) compared to the control group and left ventricular isovolumic acceleration time which was found to be statistically significantly different compared to the control group (p=0.038) in our study. The significant difference in terms of acceleration time in our study is remarkable. Therefore, evaluation together with MPI may be significant in terms of demonstrating cardiac affection. To obtain more adequate data about this subject large-scale prospective studies in which serial examinations will be performed by tissue Doppler echocardiography from the time of diagnosis are needed.

Limitation of the study:

The main limitation of our study is the small number of patients. In addition, absence of tissue Doppler records before and during treatment is another defect. Such defects can be prevented by planned, large-scale, prospective studies.

Conflict of interest: None declared.

References

1. Buyukpamukcu M, Varan A, Akyuz C, et al. The treatment of childhood Hodgkin lymphoma: improved survival in a developing country. Acta Oncol 2009; 48: 44-51.
2. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. J Natl Cancer Inst 2007; 99: 206-14.
3. Kremer LCM, Van Der Pal HJH, Offringa M, et al. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol 2002; 13: 819-29.
4. Adams MJ, Lipsitz SR, Colan SD. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 2004; 22: 3139-48.
5. Dorup I, Levitt G, Sullivan I, et al. Prospective longitudinal assessment of late anthracycline cardiotoxicity after childhood cancer: the role of diastolic function. Heart 2004; 90: 1214–21.
6. Hamada H, Ohkubo T, Maeda M, et al. Evaluation of cardiac reserved function by high-dose dobutamine-stress echocardiography in asymptomatic anthracycline-treated survivors of childhood cancer. Pediatr Int 2006; 48: 313-20.
7. Pınarlı FG, Oğuz A, Tunaoğlu FS, et al. Late cardiac evaluation of children with solid tumors after anthracycline chemotherapy. Pediatr Blood Cancer 2005; 44: 370-7.

8. Mavikure-Groothuis AM, Weijers G, Groot-Loonen, et al. Interobsever, interobserver and intrapatient reliability scores of myocardial strain imaging with 2-D echocardiography in patients treated with anthracycline. Ultrasound Med Biol 2009; 35: 697-704.
9. Oberholzer K, Kunz RP, Dittrich M, et al. Anthracycline-induced cardiotoxicity: cardiac MRI after treatment for childhood cancer. Rofo 2004; 176: 1245-50.
10. Gharib MI, Burnett AK. Chemotherapy-induced cardiotoxicity: current practice and prospects of prophylaxis. Eur J Heart Fail 2002; 4: 235-42.
11. Mogelvang R, Sogaard P, Pedersen SA, et al. Cardiac dysfunction assessed by echocardiographic tissue Doppler imaging is an ndependent predictor of mortality in the general population. Circulation 2009; 119: 2679-85.
12. Nagy AC, Cserep Z, Tolnay E, et al. Early diagnosis of chemotherapyinduced cardiomyopathy: a prospective tissue Doppler imaging study. Pathol Oncol Res 2008; 14: 69-77.
13. Schimmel KJ, Richel DJ, Van Den Brink RB, et al. Cardiotoxicity of cytotoxic drugs. Cancer Treat Rev 2004; 30: 181-91.
14. Muller L, Kramm CM, Lawrenz W, et al. Recurrent atrial ectopic tachycardia following chemotherapy with ifosfamide. Pediatr Hematol Oncol 2004; 21: 307-11.
15. Fatani AG, Darweesh AQ, Rizwan L, et al. Carnitine deficiency aggravates cyclophosphamide-induced cardiotoxicity in rats. Chemotherapy 2010; 56: 71-81.
16. Mythili Y, Sudharsan PT, Sudhahar V, et al. Protective effect of DL-α- lipoic acid on cyclophosphamide induced hyperlipidemic cardiomyopathy. Eur J Pharmacol 2006; 543: 92-6.
17. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol 1995; 26: 396-404.
18. Lakoumentas JA, Panou FK, Kotseroglou VK, et al. The Tei Index of myocardial performance: applications in cardiology. Hellenic J Cardiol 2005; 46: 52-8.
19. Santin JC, Deheinzelin D, Junior SP, et al. Late echocardiography assessment of systolic and diastolic function of the left ventricle in pediatric cancer survivors after anthracycline therapy. J Pediatr Hematol Oncol 2007; 29: 761-5.
20. Ocal B, Oğuz D, Karademir S, et al. Myocardial performance index combining systolic and diastolic myocardial performance in doxorubicin- treated patients and its correlation to conventional echo/Doppler indices. Pediatr Cardiol 2002; 23: 522-7.
21. Larussi D, Pisacane C, Indolfi P, et al. Evaluation of left ventricular function in long-term survivors of childhood Hodgkin disease. Pediatr Blood Cancer 2005; 45: 700-5.
22. Karakurt C, Kocak G, Ozgen U. Evaluation of the left ventricular function with tissue tracking and tissue Doppler echocardiography in pediatric malignancy survivors after anthracycline therapy. Echocardiography 2008; 25: 880-7.
23. Yıldırım A, Tunaoğlu FS. Pınarlı FG, et al. Tissue and flow myocardial performance index measurements taken during dobutamine stress echocardiography for early diagnosis of late anthracycline cardiotoxicity. Pediatr Cardiol 2010; 31: 96-105.
24. Ozer N. Assessment of mitral stenosis with isovolumic myocardial acceleration. Turk Kardiyol Dern Arş 2008; 36: 395-6.
25. Hashimoto I, Bhat AH, Li X, et al. Tissue doppler-derived myocardial acceleration for evaluation of left ventricular diastolic function. J Am Coll Cardiol 2004; 44: 1459-66.
26. Baysal T, Koksal Y, Oran B, et al. Cardic functions evaluated with tissue doppler imaging in childhood cancers tretaed with anthracyclines. Pediatr Hematol Oncol 2010; 27: 13-23.