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Assessment of Left Ventricular Function using a Two-Dimensional Speckle Tracking Echocardiography in Asymptomatic Survivors of Hodgkin's Lymphoma in Long-Term Follow-Up

Kür Sağlanan Hodgkin Lenfoma Hastalarının Uzun Dönem Takibinde Sol Ventrikül Fonksiyonlarının İki Boyutlu Strain Ekokardiyografi ile Değerlendirilmesi

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ABSTRACT

Introduction: Two-dimensional speckle tracking echocardiography (2D-STE) is sensitive in the assessment of left ventricular (LV) systolic function and may aid in diagnosis of late cardiac effects in asymptomatic Hodgkin's lymphoma (HL) survivors in long-term follow-up.

Methods: This is a cross-sectional study of 21 HL survivors previously treated with anthracyclines, with (8/21) or without-mediastinal (8/21) radiotherapy and no recurrence at least 3 years after treatment compared to age-matched 43 healthy volunteers. To assess long-term cardiac complications, we performed 12-lead electrocardiography and 2D transthoracic echocardiography. In addition to conventional echocardiographic parameters, we used tissue Doppler echocardiography for LV diastolic functions and 2D-STE for evaluating the global longitudinal strain (GLS) of the LV myocardium.

Results: The mean age of the HL survivors was 40±15 years and the female sex was predominant (11/21). The average PR interval of the HL survivors was significantly longer (154.7±19.6 ms vs 133.8±13.9 ms, p<0.001) while the QTc interval was significantly shorter (383.8±18.7 ms vs 402.4±11.7 ms, p<0.001) than the control group. HL survivors had significantly impaired GLS compared to the control group (-19.3±2.6 vs -22.6±1.6, p<0.001). Thirteen of the HL survivors (61%) with normal LV ejection fraction had impaired GLS. The frequency of left ventricular diastolic dysfunction (LVDD) in the HL survivors group was significantly higher than that of the control group (52% vs 26%, p=0.015). Therefore, LVDD was detected in 61.5% of patients with a GLS <-20%.

Conclusion: 2D-STE could be used in predicting late-onset subclinical cardiac side effects following treatment in asymptomatic HL survivors for long-term follow-up.

Keywords: Cardiomyopathy, cardiotoxicity, cardio-oncology, diastolic dysfunction, Hodgkin's disease, strain echocardiography

ÖZ

Amaç: İki boyutlu strain ekokardiyografi (2D-STE) sol ventrikül (SV) sistolik fonksiyonlarının ölçümünde hassas bir ölçüm yöntemidir. Hodgkin lenfoma (HL) hastalarının takibinde ortaya çıkabilecek geç kardiyak yan etkilerin değerlendirilmesinde kullanılabilir.

Yöntemler: Bu çalışma antrasiklin (n=21) ± mediasten (8/21)/mediasten dışı (8/21) ışın tedavisi alan, en az 3 yıl takipte nüks saptanmamış 21 HL hastası ve yaşları eşleştirilmiş 43 sağlıklı bireyin karşılaştırıldığı kesitsel çalışmadır. Bireylerin kardiyak komplikasyonları 12 derivasyonlu elektrokardiyografi ve konvansiyonel ekokardiyografi ile değerlendirildi. SV diyastolik fonksiyonu için doku Doppler ekokardiyografi, SV miyokardiyumun global longitudinal strain (GLS) değerlendirmesi için 2D-STE kullanıldı.

Bulgular: HL hastalarının ortalama yaşı 40±15 saptandı ve çoğunlukla kadındı (11/21). HL hastalarında kontrol grubuna göre ortalama PR mesafesi anlamlı derecede artmış (154,7±19,6 ms vs 133,8±13,9 ms, p<0,001), QTc mesafesi azalmış (383,8±18,7 ms vs 402,4±11,7 ms, p<0,001) saptandı. HL hastalarında GLS değerleri kontrol grubuna göre anlamlı derece azalmış (-19,3±2,6 vs -22,6±1,6, p<0,001) saptandı. SV sistolik fonksiyonları normal olan 13 hastanın (%61,9) strain değerleri azalmış saptandı. Sol ventrikül diyastolik disfonksiyon (SVDD) sıklığı HL hastalarında kontrol grubuna göre anlamlı derecede yüksek saptandı (%52 vs %26, p=0,015). GLS'si azalmış saptanan 13 hastanın 8'inde (%61,5) SVDD saptandı.

Sonuç: HL hastalarında geç başlangıçlı kardiyak yan etkilerin saptanmasında 2D-STE kullanılması önerilir.

Anahtar Kelimeler: Kardiyomiyopati, kardiyotoksisite, kardiyo-onkoloji, diyastolik disfonksiyon, Hodgkin lenfoma, strain ekokardiyografi

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Introduction

Approximately 8,000 new Hodgkin's lymphoma (HL) patients are diagnosed in the United States annually (1). Cardiac complications constitute the most important non-malignant cause of mortality in HL survivors. Increased mortality rates due to cardiac related-events point to an inadequate screening of cardiac toxicity following treatment.

Patients with cardiotoxicity often have left ventricular diastolic dysfunction (LVDD) with preserved left ventricular systolic function (2). Left ventricle ejection fraction (LV-EF) measurements may not be sufficient for the evaluation of subclinical LV systolic dysfunction. Meanwhile, a two-dimensional speckle tracking echocardiography (2D-STE) enables a more detailed assessment of the LV myocardium with longitudinal strain measurements (3). However, its role in detecting late cardiotoxicity is unclear (4).

Thus, we aimed at examining long-term cardiac functions in asymptomatic HL survivors following treatment with adriablastin, bleomycin, vinblastine, dacarbazine (ABVD) protocol [with/without radiotherapy (RT)] and had no relapse for at least 3 years of follow-up.

Methods

Between 1999 and 2013, 21 HL survivors were evaluated in our study, which was conducted in the İstanbul University, İstanbul Faculty of Medicine, Department of Hematology. We included 43 healthy volunteers as controls and treated 213 HL patients in our clinic; however, patients without a follow-up file (n=140), those with relapsed Hodgkin's disease (n=5), those receiving non-ABVD chemotherapy (CT) or RT alone (n=34), and those who refused to participate in the study (n=13) were excluded (Figure 1).

The study included patients treated using the ABVD protocol (with or without RT) and had complete remission with no recurrence at follow-up for at least three years after remission.

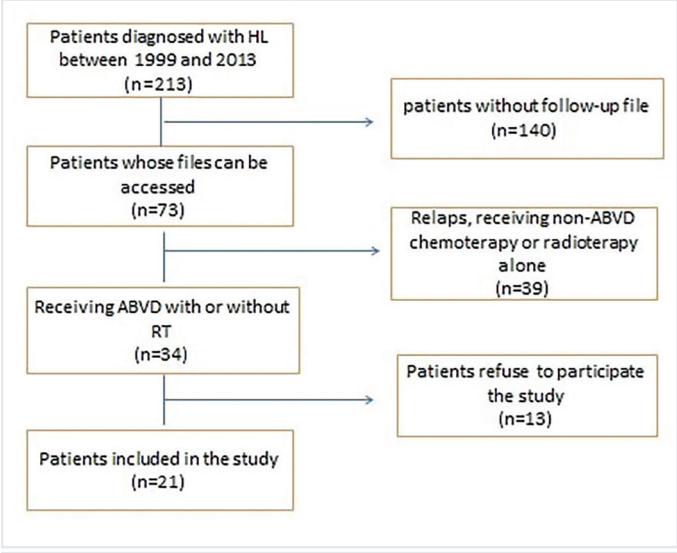

Figure 1. Distribution of patients with Hodgkin's lymphoma

ABVD: Adriablastin, bleomycin, vinblastine, dacarbazine protocol, HL: Hodgkin's lymphoma, RT: Radiotherapy

All patients were interrogated about complaints of shortness of breath, angina pectoris, syncope, or palpitation. Moreover, attending physicians conducted a thorough investigation of any history of heart failure or cardiomyopathy, ischemic heart disease, coronary angiography or angioplasty, pacemaker implantation or electrophysiologic study/ablation, pericardial disease, valvular heart disease, cardiac surgery, stroke or cerebrovascular disease.

The Eastern Cooperative Oncology Group (ECOG) performance scores of all participants were recorded. Levels of glucose (mg/dL), triglyceride (mg/dL), and low-density lipoprotein (LDL) cholesterol (mg/dL) were measured using blood samples.

Participants underwent 12-lead electrocardiography (ECG) after a 30-minute rest. All ECGs were taken at a rate of 25 mm/s and an amplitude of 10 mm/mV. QT, QTc, and PR intervals of all subjects were evaluated (5). All patients underwent two-dimensional transthoracic echocardiography (2D-TTE) using an iE33 echocardiography system (Philips Medical Systems, Andover, Massachusetts) through an X5-1 (1–5 MHz) transducer. All views were recorded and analyzed. A modified Simpson's method was used to calculate the LV-EF. Moreover, the apical 4-chamber view was used to document the mitral in-flow velocity pattern. The E/A ratio was equally evaluated. E' velocity and a' velocity were assessed using tissue Doppler image analysis. LVDD was defined as having an abnormal result in more than half of the four main parameters (>50% positive): Left atrial volume index >34 mL/m^2, septal e' <7 cm/sec or lateral e' <10 cm/sec, peak TR velocity >2.8 m/sec, average E/e' >14 (6).

In all patients, the global longitudinal strain (GLS) of the LV was assessed using 2D-STE. For deformation analysis, the CMQ mode of the Philips IE33, QLAB 10.8.5 software was used. At 42-56 times per second, 3 consecutive cardiac periods were videotaped from the apical 4-, 3- (long axis), and 2-chamber views. For each view, three points were placed at the end of diastole (two at the base of the LV and one at the apex). The software finally traced the endocardial and epicardial borders automatically. The operator adjusted measurements where necessary. Each LV wall was divided into 3 equal parts (base, mid, and apical), and 17 segmental strain curves were collected. Peak systolic strain was designed to compare the values of all segments at the time of aortic valve closure. Decreased GLS was described as GLS-20% (7).

The ECG recordings, 2D-TTE examinations, and laboratory tests of HL patients before ABVD treatment were extracted from patient files and recorded.

Before the study, all patients provided written informed consent in accordance with the Helsinki Declaration. The İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee approved the study (approval number: 343, date: 10.02.2015).

Statistical Analysis

The descriptive statistics were computed using the NCSS 2007 Statistical Software (Utah, USA). Continuous data were expressed as the mean ± standard deviations, and categorical data as percentages. When the distribution was normal, Pearson correlation analysis was used to assess the relationships between parameters; when the distribution

was not normal, the Spearman correlation analysis was used. The chi-squared test (when the variables were categorical) or the Independent samples t-test (when variables were continuous) were used to determine significant differences between groups. To compare differences in median values between patient groups, the Mann-Whitney U test was used. A p-value of <0.05 was considered statistically significant.

Results

Patient Group

The mean age of the HL survivors was 40±15 years, and at the time of diagnosis was 35±19 years. The female gender was predominant (52.3%). The average time after HL diagnosis was 7±2.4 years. The most common HL subtype detected was nodular sclerosis (47.6%).

ECOG performance scores of all patients were "0". No significant changes in plasma glucose (p=0.711), serum LDL cholesterol (p=0.084), serum triglyceride levels (p=0.622), systolic (p=0.964) and diastolic (p=0.563) blood pressures, and heart rate (p=0.611) were detected in patients before treatment.

The patients were treated with an average of 6.3 cycles (4-12 cycles) of ABVD protocol. Average doses of chemotherapeutic drugs administered were 319.7 mg/m^2 (200-600 mg/m^2) for adriamycin, 112.4 mg/m^2 (60-180 mg/m^2) for bleomycin, 72.5 mg/m^2 (40-120 mg/m^2) for vinblastine, 4721 mg/m^2 (2800-8400 mg/m^2) for dacarbazine. Eight patients received only non-mediastinal RT, five patients received only mediastinal RT, and three received both with a median dose of 25 Gy (18-36 Gy). Eight of twenty-one patients received mediastinal RT in our study.

Comparison of Patient Group and Control Group

In HL survivors and the control group, the mean age and sex ratio were similar (p=0.874, p=0.927, respectively). There were no significant differences in plasma glucose, LDL, and triglyceride levels between the two groups (p=0.126, p=0.08, p=0.165, respectively). The heart rates of the HL survivors were significantly higher than those in the control group (82±18 vs 73±10, p=0.049). The systolic and diastolic blood pressures were similar between the two groups (p=0.348, p=0.760, respectively).

Demographic characteristics and laboratory analysis of HL survivors and the control group are shown in Table 1.

Electrocardiogram

The PR interval in patient groups was significantly longer than those in control group (154.7±19.6 ms vs 133.8±13.9 ms, p<0.001). Nevertheless, the PR interval was not >200 ms (first degree AV block) in any patient. The patient group QTc interval was significantly shorter than that of the control group (383.8±18.7 ms vs 402.4±11.7 ms, p<0.001).

Echocardiography

There were no critical differences in LV volumes, diameters, wall thickness, and EF between the groups.

LVDD was significantly higher in the HL group than in the control group (52% vs 26%, p=0.015). Additionally, GLS was impaired considerably in HL patient group than in the control group (-19.3±2.6 vs -22.6±1.6, p<0.001).

Table 2 presents the conventional echocardiographic parameters of LV systolic and diastolic functions and ECG parameters for both patient and control groups.

Among the HL patient group, 52% (n=11) had LVDD, and 61% (n=13) had impaired GLS (<-20%). Eight patients with GLS <-20%, eight patients

Table 1. The demographic characteristics and laboratory parameter of HL survivors and control group

	Study group (n=21)	Control group (n=43)	p
Age	40.2±15	40.8±14.5	0.874
Sex			
Male	10 (47.6%)	21 (48.8%)	
Female	11 (52.4%)	22 (51.2%)	0.927
Glucose (mg/dL)	87±23	79±19	0.126
Lipid profile			
LDL (mg/dL)	127±52	103±53.5	0.088
Triglyceride (mg/dL)	127±65	104±58	0.165
Heart rate (bpm)	82±18	73±10	0.049
Systolic blood pressure (mmHg)	117±12	113±14	0.348
Diastolic blood pressure (mmHg)	77±8	76±7	0.760

P: Independent sample t-test, HL: Hodgkin's lymphoma, LDL: Low-density lipoprotein

Table 2. ECG and echocardiographic parameters of HL survivors and control group

	HL (n=21)	Control group (n=43)	p
LV-EF (%)	66±5	68±5	0.091
SV (mL)	67±17	62±18	0.360
ESV (mL)	33±11	36±14	0.475
EDV (mL)	101±26	99±22	0.781
LVEDD (cm)	4±0.52	4.6±0.44	0.822
LVESD (cm)	2.87±0.43	2.89±0.38	0.875
LAD (cm)	3.31±0.41	3.32±0.15	0.926
E (m/s)	73±22	86±17	0.017*
A (m/s)	68±18	67±16	0.793
e' (m/s)	9±4	9±2	0.295
a' (m/s)	8±2	7±2	0.064
E/A	1.14±0.44	1.36±0.49	0.089
e'/a'	1.2±0.72	1.49±0.72	0.134
LVDD	52 (%)	26 (%)	0,015*
GLS (%)	-19.3±2.6	-22.6±1.6	<0.001*
Electrocardiogram			
PR (ms)	154.7±19.6	133.8±13.9	<0.001*
QTc (ms)	383.8±18.7	402.4±11.7	<0.001*

E/A: Early diastolic transmitral flow/late diastolic transmitral flow, a': Late diastolic tissue velocity, e': Early diastolic tissue velocity, ESV: End systolic volume, EDV: End diastolic volume, GLS: Global longitudinal strain, LV-EF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, LAD: Left atrium diameter, LVDD: Left ventricular diastolic dysfunction, SV: Stroke volume, *: Significant p-value (<0.05), HL: Hodgkin's lymphoma, ECG: Electrocardiography

with LVDD, and five patients with both, were categorized in the mild-risk group for adriamycin toxicity dose (Table 3).

In both groups, only a mild valve regurgitation (mitral, aortic, tricuspid, or pulmonary) was detected.

Discussion

In general, half of the patients receiving anthracycline therapy developed cardiac toxicity (8). Cardiac side effects increase with the addition of RT to anthracycline-based CT in these patients. The risk of cardiac complications considerably increases 8-10 years after treatment (9,10). This suggests that screening for cardiac toxicity should be underwent many years for this population, especially in asymptomatic HL survivors. The National Comprehensive Cancer Network suggests the annual evaluation of cardiac complications in patients who received more than 300 mg of anthracycline-based therapy (11). Most (76.2%) patients received >300 mg anthracycline-based treatment in the current study.

ECG and TTE are the preferred screening tools for cardiac toxicity in asymptomatic patients (11,12). ECG abnormalities may be seen in early and late periods of CT treatment (12). QTc prolongation is a side effect of anthracycline therapy, with case reports of patients presenting with acute cardiotoxicity and heart failure (13). However, these were always in the setting of other co-existing conditions and concomitant use of other QTc-prolonging drugs. There is no increased incidence of torsade de pointes in patients using anthracyclines (14). In our study, QTc prolongation was not detected in any patient. On the contrary, QTc intervals were shorter in HL survivors than in those of the control group.

Several studies have found an increase in deaths due to myocardial infarction among patients treated for HL with mediastinal RT (15). In a retrospective study conducted in Florida, 10.4% (42/415) of survivors developed CAD at averagely 9 years after treatment. Notably, the only treatment-related factor associated with CAD development was the use of a radiation technique that targets a part of the heart (16). CAD was not detected in HL survivors of our study, perhaps due to the small number of patients treated with mediastinal RT (8 of 21 patients).

Table 3. Adriamycin doses and risk classification in patients with LVDD and GLS impairment

	Average dose (mg/m^2)	Risk group	(n=21)	%
GLS <-20%	333.7	Mild	8	38
		Moderate	4	19
		Severe	1	4
LVDD	303.5	Mild	8	38
		Moderate	3	14
		Severe	0	0
		Severe	1	4
GLS <-20%+ LVDD	317.3	Mild	5	23
		Moderate	3	14
		Severe	0	0

GLS: Global longitudinal strain, mild-risk: 300-450 mg/m^2, moderate risk: 450-550 mg/m^2, high (severe) risk: Cumulative dose limit >550 mg/m^2, LVDD: Left ventricular diastolic dysfunction

Thus, we concluded that LV-EF is not sensitive enough for the early diagnosis of cardiomyopathies caused by chemotherapeutics (17). When EF was normal, it was useful in detecting LVDD as an indicator of early cardiomyopathy (18). LVDD contributes to the onset of heart failure and precedes the development of systolic dysfunction (19). Some studies have examined the usefulness of diastolic parameters in detecting anthracycline-related cardiac injury (20). Moreover, LVDD prevalence was higher in HL survivors who received at least 35 Gy mediastinal RT (21). Consistent with these studies, the amplitude of the E-wave in HL patients was significantly lower than that of the control group (73±22 vs 86±17 p=0.017) as the onset of LVDD and 52% of patients had LVDD while LV-EF was normal. Two of 11 patients with LVDD received mediastinal RT.

Great developments in non-invasive myocardial mechanics and cardiac function evaluation have been made possible by 2D-STE. Current studies suggest that the detection of subclinical systolic dysfunction using 2D-STE could be the first sign of LV systolic dysfunction (22). GLS is regarded as the most promising 2D-STE parameter for estimating cardiotoxicity (23). A 10-15% relative decline in GLS throughout cancer treatment assigns patients at risk of subsequent LV-EF decrease or progression of congestive heart failure. It is thought to be an indicator of cardiotoxicity (24,25). The ASE/EACVI Expert Consensus recommends GLS-based follow-up of adults during and after cancer treatment (26). In many studies, subclinical systolic dysfunction was detected by 2D-STE after anthracycline therapy despite normal LV-EF (27,28). Also, GLS decline was associated with long-term survival and LV-EF long-term reduction (24,25). Otherwise, impaired GLS was associated with exposure to mediastinal RT and high doses of anthracyclines (29). In our study, GLS impairment was detected in 62% of patients (n=13) despite normal LV-EF. Four of them received mediastinal RT in our study. Furthermore, 25% of patients with both GLS <-20% and LVDD received mediastinal RT in our study. Adriamycin doses and risk classification for cardiac toxicity were accepted as mild-risk (300-450 mg/m^2), moderate risk (450-550 mg/m^2), and high risk (>550 mg/m^2) (30). Eight of thirteen patients with GLS <-20%; Eight of eleven patients with LVDD, and five of eight patients with both GLS <-20% and LVDD, were detected in the mild-risk group in terms of toxicity dose of Adriamycin (Table 3). According to our study, patients in the mild-risk group could be evaluated for cardiac toxicity as well.

RT regions and doses were different, and the number of participants was not sufficient for comparison; therefore, no comparison was made between patients receiving only CT and those receiving both CT and RT.

Study Limitations

There were some limitations in our study. The number of patients enrolled in the study was relatively small. Also, the predictive effect of impaired GLS on symptomatic heart failure or decreased LV-EF was not evaluated. Our study was a retrospective cross-sectional study, and we assessed LV functions only once after the evaluation before CT ± RT. Performing echocardiogram periodically in patients with HL may explain how GLS and LV-EF impairment progressed over time. Our recommendation is to conduct further studies on late-onset cardiac toxicity in HL survivors and determine the predictive role of STE in larger samples and over more extended follow-up periods.

Conclusion

Despite normal LV-EF, patients may have subtle late-onset changes of LV systolic function measured by STE. STE may detect subclinical LV systolic dysfunction and simplify long-term monitoring of asymptomatic HL survivors. Whether such subtle changes of LV systolic functions can predict the risk of developing heart failure should be investigated in further prospective studies.

Ethics Committee Approval: The İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee approved the study (approval number: 343, date: 10.02.2015).

Informed Consent: Before the study, all patients provided written informed consent in accordance with the Helsinki Declaration.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.A., A.A.; Concept - M.A., A.A., N.Ö., B.U., M.N.; Design - M.A., B.U., M.N.; Data Collection or Processing - M.A., P.K.Ö., A.A., R.B.; Analysis or Interpretation - M.A., P.K.Ö., A.A., R.B., N.Ö., B.U., M.N.; Literature Search - M.A., P.K.Ö., A.A., R.B., N.Ö.; Writing - M.A., P.K.Ö., R.B., N.Ö., B.U., M.N.

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