

The utility of NT-proBNP and various echocardiographic methods in the determination of doxorubicin induced subclinical late cardiotoxicity

Ayşe Yıldırım¹, F. Sedef Tunaoglu², Kenan Kanburoglu³, F. Guclu Pinarlı⁴

¹Department of Paediatric Cardiology, Kartal Kosuyolu Training and Research Heart Hospital, Istanbul, Turkey

²Department of Paediatric Cardiology, Gazi University Medical Faculty, Ankara, Turkey

³Department of Neonatology, Fatih University Medical Faculty, Ankara, Turkey

⁴Department of Paediatric Oncology, Gazi University Medical Faculty, Ankara, Turkey

Abstract

Background and aim: Our aims were to investigate the utility of plasma N terminal-pro B-type natriuretic peptide (NT-proBNP) level and find the most beneficial echocardiographic parameters to detect subclinical cardiotoxicity in childhood-cancer survivors treated with doxorubicin.

Methods: The study included 23 patients with a mean age of 17.1 years, who had received doxorubicin therapy with a mean cumulative dose of 241.1 mg/m² with a median time period of 10.5 years since the last dose of doxorubicin. The control group consisted of 19 healthy volunteers matched for age, sex, and weight.

Results: The serum NT-proBNP levels of the patient group were higher than the control group. The measurements of myocardial performance index (MPI), tissue Doppler mitral septal annulus systolic (S's) and early diastolic (E's) velocities, ratio of early mitral flow velocity (E) to E's (E/E's), left ventricular diastolic volume (LVDV), tricuspid early diastolic velocity (TE) and percentage of left ventricular posterior wall thickness (%LVPWT) were found to be significantly different from the control group. MPI values were significantly correlated with NT-proBNP levels and cumulative doxorubicin doses.

Conclusions: Elevated MPI values, associated with high NT-pro BNP levels and high cumulative doxorubicin doses, could be a useful indicator of subclinical cardiotoxicity. NT-proBNP could be an effective marker in the long-term follow up of subclinical cardiotoxicity.

Key words: cardiotoxicity, NT-proBNP, echocardiography

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INTRODUCTION

Anthracyclines, especially doxorubicin, are commonly used for the treatment of childhood cancers, leading to a growing population of long-term cancer survivors. However, its use is limited by cardiotoxicity and chemotherapy related complications that can markedly affect the patients' quality of life. Increasingly, survivors and their clinicians are realising the importance of continual monitoring after cancer therapy. Early detection of anthracycline cardiotoxicity is critically important for successful management [1].

Serum N terminal-pro B-type natriuretic peptide (NT-proBNP) is a prohormone released from the cardiac ventricles in response to increased ventricular wall stress in association with pressure overload, elevated diastolic pressure and increased pulmonary capillary wedge pressure [2–5].

Only a little information is available about the utility of NT-proBNP as a marker of late anthracycline cardiotoxicity in long-term survivors of childhood cancers [6]. Therefore, in this study we aimed to determine the role of serum NT-proBNP level in a long-term follow up of these patients. Mo-

Address for correspondence:

Dr Ayşe Yıldırım, Kartal Kosuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Denizler Caddesi Cevizli Kavsagi No:2, Postal code: 34846, Istanbul, Turkey, tel: 090 216 4594440-1036-1060, fax: 0 90 2164 596321, e-mail: ayildirimmd@yahoo.com

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reover, we investigated the most beneficial echocardiographic parameters to evaluate subclinical cardiotoxicity by standard and tissue Doppler echocardiography. We also investigated the correlation between serum NT-proBNP level and echocardiographic parameters in patients and in an age- and gender-matched control group.

METHODS

The study design was prospective; it included 23 patients, long-term survivors treated with anthracycline for childhood cancer, and 19 healthy volunteers. Cancer types treated with anthracycline in the patient group were lymphoma, angiosarcoma, hepatoblastoma, rhabdomyosarcoma, Wilms tumour and ganglioneuroblastoma. Inclusion criteria were: 1) Taking the last doxorubicin dose eight years ago (i.e. minimum period between the end of the chemotherapy and the moment of evaluation of NT-proBNP and echocardiographic parameters of eight years); 2) Receiving only one type of cardiotoxic chemotherapeutic agent; and 3) Having a cumulative dose of anthracycline < 450 mg/m². Exclusion criteria were: 1) Taking mediastinal radiotherapy; and 2) Having cardiovascular symptoms such as chest pain, effort dyspnoea, palpitation, easy fatigue, syncope etc. The physical examinations of both study groups were carried out. Their cardiac function evaluation was made by plasma NT-proBNP level, electrocardiogram (ECG) and echocardiography. The indicators of subclinical cardiotoxicity were accepted as significantly increased or decreased echocardiographic parameters (tissue Doppler imaging [TDI], M-mode and Doppler echocardiography) in the patient group compared to the control group. After recording the blood pressure and heart rate values of the patients, blood samples were taken for NT-proBNP. The institutional ethics committee approved the study. Patient and control groups gave their written informed consent.

Echocardiography

Echocardiographic evaluation was done with Philips IE33 equipment by 5 MHz transducer. Transthoracic echocardiography was administered to the patients in a supine, or in a left lateral, position. Parasternal long axis, parasternal short axis, and apical four-chamber views were recorded. Mean values of these measurements recorded from three consecutive views were used for statistical analysis. Standard M-mode recordings of the left ventricle (LV) were obtained. Interventricular septum thickness at end systole and diastole (IVSs and IVSd), LV posterior wall thickness at end systole (LVPWs) and at end diastole (LVPWd), and LV dimension at end systole (LVSD) and at end diastole (LVDD) were measured. LV end diastolic and systolic volumes (LVDV and LVSV) were calculated using "Recommendations for chamber quantification" (modified Simpson's rule) [7]. Fractional shortening (FS) and ejection fraction (EF) were calculated according to the formula [FS: (LVDD – LVSD)/LVDD] × 100 and

EF: [(LVDV – LVSV)/LVDV] × 100. Mitral early and late diastolic peak velocities (ME and MA) and tricuspid early and late diastolic velocities (TE and TA), mitral acceleration time (AT) and mitral deceleration time (DT) were measured. The percentage of LV posterior wall thickness (%LVPWt) and LV flow myocardial performance index (MPI) were calculated as previously described [8–11]. The tissue Doppler of mitral septal and lateral annulus from an apical four-chamber view was used to measure systolic velocity (S's and S'l), early diastolic velocity (E's and E'l), and late diastolic velocity (A's and A'l). We calculated the ratio of early diastolic mitral flow velocity (E) to tissue Doppler early diastolic velocity of the mitral septal annulus (E/E's). We also calculated the ratio of early diastolic mitral flow velocity (E) and tissue Doppler mitral lateral annulus (E/E'l). Descriptions of normal values of the echocardiographic parameters were used as previously described [8–12].

Measurement of NT-proBNP

EDTA-anticoagulated blood (3 mL) was collected by venous puncture. The whole blood was centrifuged for ten minutes (3,500 rpm) immediately; 100 µL of centrifuged plasma was assayed by immunoassay analyser (Siemens, Advia Centaur®). NT-proBNP assay was performed using the Triage NT-proBNP kit (Biosite Diagnostic, San Diego, CA, USA). NT-proBNP plasma level was quantitatively measured by chemiluminescence technology in which the normal maximal value was 100 pg/mL.

Statistical analysis

All data was entered in a Windows SPSS 15.0 software program; quantitative parameters were presented as mean ± SD and median; qualitative parameters were presented as frequency distribution and percentage. Mann-Whitney U test was used to compare the differences between the groups. Spearman correlation tests were used to examine the correlations between the echocardiographic parameters and factors in question i.e. cumulative anthracycline dose, NT-proBNP, age of the patients at diagnosis, and elapsed time after the last doxorubicin dose. Spearman correlation test were used between elapsed time after the last doxorubicin dose and NT-proBNP. Positive or negative correlations between these parameters found by Spearman tests were then re-examined by linear regression analysis. Statistical significance was defined as p < 0.05.

RESULTS

The study group included 23 anthracycline treated patients (16 male, seven female) and 19 control subjects (13 male, six female). All patients had received only doxorubicin therapy. The mean cumulative doxorubicin dose they had been exposed to was 241.1 ± 125.9 (median: 200: 86–330) mg/m² and the mean elapsed time since the end of chemotherapy was 10.5 ± 4.0 (median: 10.4: 8–14) years. The physical exams and ECG results of both study groups were normal.

Table 1. Demographic data and haemodynamic parameters of the patient and control groups

	Patient	Control	P
Age [years]	17.1 ± 3.2	17.6 ± 4.0	NS
Weight [kg]	66.9 ± 9.5	60.8 ± 9.4	NS
Height [cm]	165.1 ± 6.4	167.3 ± 7.1	NS
NT-proBNP [pg/mL]	45.3 ± 39.7	21.5 ± 11.5	0.01
SBP [mm Hg]	113.5 ± 12.1	111.7 ± 11.1	NS
DBP [mm Hg]	66.5 ± 10.6	65.4 ± 7.3	NS
Heart rate [/min]	85.0 ± 18.7	81.4 ± 16.6	NS

SBP — systolic blood pressure; DBP — diastolic blood pressure

The age, sex, weight, height, serum NT-proBNP level and haemodynamic parameters of the patients are set out in Table 1. Serum NT-proBNP levels of the patient group were higher than the control group. The echocardiographic parameters of the patient and control groups are set out in Table 2. TDI mitral septal systolic and early diastolic velocities of the patient group were significantly lower, and E/E's values of the patient group were significantly higher, than the control group. MPI values and LVDV of the patient group were significantly higher than the control group, and %LVPWt measurements of the patient group were slightly lower than the control group ($p = 0.049$). Tricuspid E velocities of the patient group were also significantly lower than the control group.

Correlation

In Spearman correlation analysis, a positive correlation was found between serum NT-proBNP level and parameters such as MPI ($r: 0.68$, $p: 0.006$), LVDD ($r: 0.65$, $p: 0.001$), and LVDV ($r: 0.42$, $p: 0.045$). A negative correlation was found between NT-proBNP level and parameters such as mitral deceleration time (MDT) ($r: -0.45$, $p: 0.035$), TA ($r: -0.57$, $p: 0.005$). Those variables positively correlated (LVDD, LVDV and MPI) and negatively correlated (MDT and TA) with NT-proBNP according to the Spearman analyses were re-evaluated by linear regression analysis. In linear regression analysis, the model was significant ($R: 0.91$, $R\text{square}: 0.84$, $F: 20.5$, $p: 0.000$); only the MPI ($p: 0.15$) value remained significantly correlated with NT-proBNP, whereas all other variables were eliminated (Fig. 1). Finally, a positive correlation was found between the cumulative doxorubicin dose and MPI in both Spearman correlation test and linear regression analysis in the patient group. (Spearman test — $p: 0.001$, $r: 0.74$; regression analysis — $R: 0.78$, $R\text{square}: 0.62$, $F: 9.8$, $p: 0.09$, Fig. 2). Correlation was not present between the elapsed time from the last doxorubicin dose and the echocardiographic parameters and NT-proBNP levels in Spearman correlation test. There was no significant difference between the results of correlation analysis tests after excluding the three patients with

NT-proBNP level > 100 ng/mL. There was no correlation between the NT-proBNP levels and echocardiographic parameters in the control group.

DISCUSSION

The myocardium is made up of cells with limited regeneration capacity. Doxorubicin is a well known cardiotoxic agent that induces myocardial degeneration. Once injured, the myocardium shows progressive dysfunction that may result in congestive heart failure. Standard 12-lead ECG or echocardiography may not be able to show minimal myocardial changes [12–16]. Increased serum NT-proBNP level as a result of elevated ventricular volume and pressure reflects LV dysfunction. Only a limited number of studies have investigated NT-proBNP as a marker or predictor of late-cardiotoxicity to date [14–19]. Urbanova et al. [16] revealed that NT-proBNP levels of an anthracycline treated group (mean dose: 221 mg/m^2) were higher than a control group (NT-proBNP: 35.1 vs. 9.6 pg/mL). In our study, the NT-proBNP levels of 23 patients who had received a mean doxorubicin dose of 241.1 mg/m^2 with a mean elapsed time of 10.5 years since the last chemotherapy were found to be higher than the control group (NT-proBNP: 45.3 vs. 21.5 pg/mL). Even though the mean NT-proBNP levels of the patient group in our study were normal, they were significantly higher than the control group ($p < 0.05$). Therefore it may be accepted that NT-proBNP is an early cardio-marker of subclinical cardiotoxicity.

There have been a few studies into the relationship between the serum NT-proBNP level and echocardiographic parameters. In the study by Germanakis et al. [14], higher NT-proBNP levels were associated with reduced LV mass in asymptomatic children treated with anthracycline. In another study, abnormal NT-proBNP levels were found to be significantly related to the end-diastolic LV internal diameter [14]. In the study by Aggarwal et al. [18], plasma NT-proBNP was significantly higher and multiple echocardiographic parameters were abnormal in patients with cardiac dysfunction. In the study by Brouwer et al. [19], abnormal FS and/or abnormal diastolic function were present in 43% of adult childhood-cancer survivors. Their NT-proBNP levels were higher in association with increased wall motion score index. In contrast to these studies, Urbanova et al. [16] could not reveal any echocardiographic changes in anthracycline treated patients with high NT-proBNP levels. In our study, high serum NT-proBNP levels were associated with increased MPI values. Such differences among several studies are acceptable because there are various factors affecting the degree of cardiotoxicity, such as cancer type, cumulative anthracycline doses exposed, the age of the patient at the time of diagnosis, the time since the last chemotherapy, additional cardiotoxic medication and history of mediastinal radiotherapy. Therefore, depending on the degree of myocardial injury, different correlations may be found between NT-proBNP levels and

Table 2. Echocardiographic parameters of the patients and control groups enrolled in the study

	Patient	Control	P
Left ventricular systolic function			
Ejection fraction [%]	69.6 ± 4.4	72.0 ± 6.7	NS
Fractional shortening [%]	37.3 ± 7.1	41.2 ± 6.2	NS
TDI S's [cm/s]	7.9 ± 2.3	9.1 ± 1.4	0.01
TDI S'l [cm/s]	8.3 ± 2.2	8.9 ± 1.4	NS
Left ventricular diastolic function			
ME [cm/s]	114 ± 0.1	116 ± 0.1	NS
MA [cm/s]	66 ± 0.1	69 ± 0.1	NS
E/A	1.7 ± 0.3	1.6 ± 0.2	NS
TDI E's [cm/s]	13.5 ± 4.1	15.2 ± 1.2	0.002
TDI E'l [cm/s]	16.8 ± 4.5	18.1 ± 1.9	NS
TDI A's [cm/s]	6.8 ± 2.3	6.5 ± 1.6	NS
TDI A'l [cm/s]	6.6 ± 2.2	6.2 ± 1.5	NS
E/E's	6.6 ± 1.8	5.3 ± 1.1	0.01
E/E'l	5.7 ± 1.7	5.4 ± 0.9	NS
MAT [s]	66.3 ± 17.4	64.3 ± 13.7	NS
MDT [s]	103.7 ± 21.1	94.3 ± 12.5	NS
Left ventricular systolic and diastolic function			
Myocardial performance index	0.39 ± 0.4	0.33 ± 0.0	0.00
Left ventricular volume and diameter			
LVDV [cm ³]	90.6 ± 18.2	80.3 ± 13.8	0.04
LVSV [cm ³]	30.2 ± 8.0	27.3 ± 3.0	NS
LVDD [cm]	4.39 ± 0.3	4.21 ± 0.2	NS
LVSD [cm]	2.57 ± 0.3	2.41 ± 0.2	NS
Left atrial diameter			
Left atrium [cm]	2.6 ± 0.4	2.58 ± 0.5	NS
Left ventricular thickness			
IVSs [cm]	1.04 ± 0.1	1.21 ± 0.2	NS
IVSd [cm]	0.77 ± 0.1	0.91 ± 0.1	NS
LVPWs [cm]	1.18 ± 0.1	1.27 ± 0.1	NS
LVPWd [cm]	0.71 ± 0.1	0.79 ± 0.0	NS
LVPWt [%]	42.7 ± 18.1	54.3 ± 6.9	0.04
Right ventricular diastolic function			
Tricuspid early diastolic velocity [cm/s]	85 ± 0.1	94 ± 0.1	0.03
Tricuspid late diastolic velocity [cm/s]	59 ± 0.1	53 ± 0.1	NS

TDI — tissue Doppler imaging; S's — mitral septal annular systolic velocity; S'l — mitral lateral annular systolic velocity; E's — mitral septal annular early diastolic velocity; E'l — mitral lateral annular early diastolic velocity; A's — mitral septal annular late diastolic velocity; A'l — mitral lateral annular late diastolic velocity; ME — mitral early diastolic velocity; MA — mitral late diastolic velocity; MAT — mitral acceleration time; MDT — mitral deceleration time; LVDV — left ventricular diastolic volume; LVSV — left ventricular systolic volume; LVDD — left ventricular diastolic diameter; LVSD — left ventricular systolic diameter; IVSs — interventricular septum systolic thickness; IVSd — interventricular septum diastolic thickness; LVPWs — left ventricular posterior wall systolic thickness; LVPWd — left ventricular posterior wall diastolic thickness; LVPWt — left ventricular posterior wall thickness

echocardiographic parameters. In this study, patients taking a high cumulative anthracycline dose, having cardiac symptoms, taking multiple cardiotoxic agents and mediastinal radiotherapy were excluded from the study. Even if a small number of patients were included in the study, we got a rather uniform group in terms of the elapsed time since the end

of chemotherapy (range 8–14 years), which allowed us to make more reliable comments in long-term follow-up.

Monitoring of anthracycline cardiotoxicity is most simply accomplished using echocardiographic parameters, including FS and EF. However, these parameters are not sensitive enough to detect cardiotoxicity. Several sophisticated echocar-

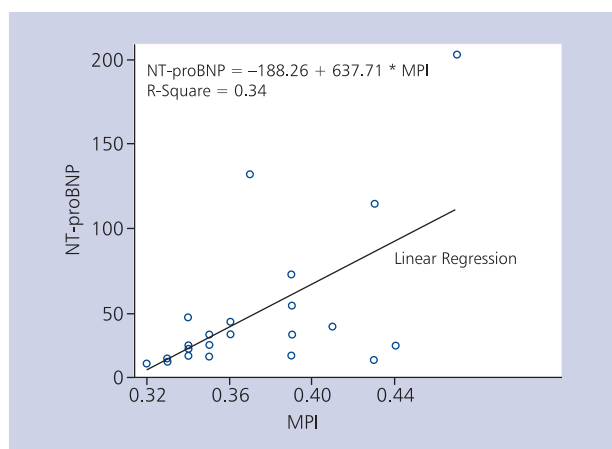


Figure 1. Correlation between NT-proBNP and myocardial performance index (MPI) in linear regression analysis

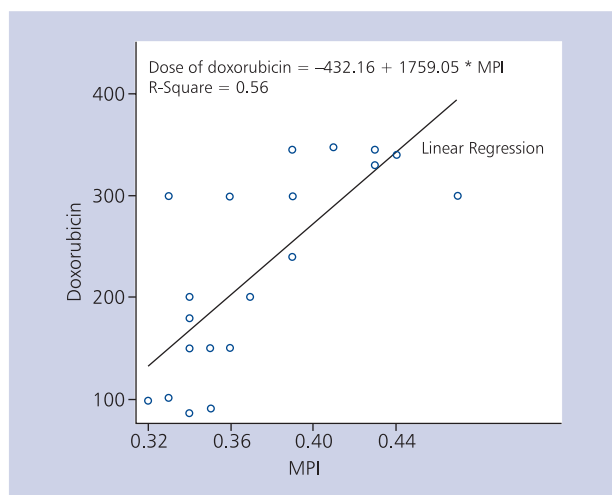


Figure 2. Correlation between cumulative doxorubicin doses and myocardial performance index (MPI) in linear regression analysis

diographic parameters have been used to detect early cardiotoxicity, most of which are technically difficult to apply to children [5, 10, 11, 13]. The parameters used in childhood cancer survivors should be reliable and easily applicable. In this study, there was no difference between the groups in standard LV systolic functions such as EF and FS. However, there were significant changes in tissue Doppler velocities, MPI, LVDV and TE measurements. Among these parameters, MPI is reliable and technically easily applicable to detect subclinical cardiotoxicity.

Tissue Doppler early diastolic velocity of the mitral annulus (E') reflects the rate of myocardial relaxation, and it has been postulated as a good indicator of LV myocardial diastolic function. TDI early diastolic velocity increases as transmitral gradient increases with exercise in normal subjects. The-

refore, E/E' at rest and during exercise ($E/E' < 8$) are similar. Decreased mitral annular E' is one of the earliest markers of diastolic dysfunction. In early diastolic dysfunction, TDI mitral septal annular early diastolic function is disturbed, whereas mitral early diastolic function remains normal [20, 21]. In their study, Hillis et al. [22] postulated that a diagnosis of acute myocardial infarction in adult patients with $E/E's > 15$ carried a significantly higher risk of mortality. The utility of E/E' measurement in the detection of diastolic dysfunction in doxorubicin treated childhood cancer survivors has not been investigated. In our study, although the tissue Doppler mitral septal annular late diastolic, mitral lateral systolic and diastolic functions and $E/E'I$ values of the patient group were normal, mitral septal annular early diastolic velocities were decreased, and mitral $E/E's$ values were increased ($E/E's = 6.6$, $E/E'I = 5.3$). We suggest that E/E' , an easily measurable quantitative parameter, may be used for the follow up of long-term survivors treated with doxorubicin.

Several echocardiographic parameters have been used for the early detection of subclinical cardiac anthracycline toxicity to date. Of these parameters, MPI has been found to be sensitive for both subclinical LV systolic and diastolic dysfunctions induced by anthracycline toxicity [23, 24]. In our study, LV systolic and diastolic functions of the patient group were normal (EF, FS, LVDD, LVSD, ME, MA) but the MPI values were significantly increased in the patient group compared to the control group. The MPI values were increased as the anthracycline dose and NT-proBNP were increased, which suggests MPI as a reliable indicator of subclinical cardiotoxicity, even if no systolic or diastolic dysfunction can be demonstrated by standard echocardiographic measurements. MPI can be used in a long-term follow up.

Increased MPI values show global LV dysfunction, but cannot show systolic or diastolic dysfunction separately. In TDI, we observed that systolic and diastolic functions were preserved at mitral lateral annulus, whereas they were impaired at mitral septal annulus due to the doxorubicin cardiotoxicity. Although the LV systolic and diastolic wall thicknesses were normal in the patient group, the %LVPWt values of the patient group were slightly decreased compared to the control group. The reason for such thinning may be the cardiotoxic effect of doxorubicin. The MPI, LVDV, %LVPWt, TE and TDI S's, E's, and $E/E's$ values of the patient group were significantly different from the control group. Therefore we assume that especially the changes in these parameters may be early signs of cardiotoxicity in childhood cancer survivors. These parameters also allow us to measure cardiac functions with various methods.

CONCLUSIONS

NT-proBNP levels of 23 asymptomatic patients with a mean cumulative doxorubicin dose of 241.1 mg/m² and eight years having elapsed since the last doxorubicin dose were two ti-

mes higher than the control group. This finding may be accepted as an early sign of subclinical cardiotoxicity. The MPI of the patient group were significantly higher than the control group. Elevated MPI values, associated with high NT-proBNP levels and high cumulative doxorubicin doses, could be a useful indicator of subclinical cardiotoxicity. %LVPWt and TDI measurements used to assess the systolic and diastolic functions of different cardiac walls and E/E' calculation could also be useful parameters to detect subclinical cardiotoxicity. Early detection of doxorubicin cardiotoxicity is crucial for successful management of these patients and to give them a chance to plan their lives.

Conflict of interest: none declared

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Przydatność oznaczania NT-proBNP i różnych metod echokardiograficznych w określaniu subklinicznej późnej toksyczności spowodowanej doksorubicyną

Ayşe Yildirim¹, F. Sedef Tunaoglu², Kenan Kanburoglu³, F. Guclu Pinarli⁴

¹Department of Paediatric Cardiology, Kartal Kosuyolu Training and Research Heart Hospital, Istanbul, Turcja

²Department of Paediatric Cardiology, Gazi University Medical Faculty, Ankara, Turcja

³Department of Neonatology, Fatih University Medical Faculty, Ankara, Turcja

⁴Department of Paediatric Oncology, Gazi University Medical Faculty, Ankara, Turcja

Streszczenie

Wstęp i cel: Celem pracy była ocena przydatności osoczowego stężenia N-końcowego fragmentu propeptydu natriuretycznego typu B (NT-proBNP) i ustalenie echokardiograficznych parametrów najbardziej pomocnych w wykrywaniu subklinicznej kardiotoxyczności u dzieci, które przebyły leczenie doksorubicyną z powodu choroby nowotworowej.

Metody: Badaniem objęto 23 chorych w wieku średnio 17,1 roku, którzy otrzymywali doksorubicynę w średniej skumulowanej dawce 241,1 mg/m²; mediana czasu od przyjęcia ostatniej dawki doksorubicyny wynosiła 10,5 roku. Grupa kontrolna składała się z 19 zdrowych ochotników dopasowanych pod względem wieku, płci i masy ciała.

Wyniki: Stężenia NT-proBNP były wyższe w grupie leczonej niż w grupie kontrolnej. Wskaźnik wydolności mięśnia sercowego (MPI), określony na podstawie badania techniką doplera tkankowego, skurczowa (S's) i wczesnorozkurczowa prędkość pierścienia mitralnego (E's) w części przegrodowej, stosunek prędkości wczesnorozkurczowej napływu mitralnego (E) do E's (E/E's), objętość rozkurczowa lewej komory (LVDV), wczesnorozkurczowa prędkość pierścienia trójdzielnego (TE) i skurczowy przyrost grubości tylnej ściany lewej komory (LVPWt) różniły się istotnie między grupami. Stwierdzono istotne korelacje między wartościami MPI a stężeniami NT-proBNP i skumulowanymi dawkami doksorubicyny.

Wnioski: Podwyższone wartości MPI w połączeniu z wysokimi stężeniami NT-proBNP i dużą skumulowaną dawką doksorubicyny mogą być przydatnym wskaźnikiem subklinicznej kardiotoxyczności. Stężenie NT-proBNP może być stosowane jako skuteczny wskaźnik w długookresowej obserwacji subklinicznej kardiotoxyczności poantracyklinowej.

Słowa kluczowe: kardiotoxyczność, NT-proBNP, echokardiografia

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Adres do korespondencji:

Dr Ayşe Yildirim, Kartal Kosuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Denizler Caddesi Cevizli Kavsagi No:2, Postal code: 34846, Istanbul, Turkey, tel: 090 216 4594440-1036-1060, fax: 0 90 2164 596321, e-mail: ayildirimmd@yahoo.com

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