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Research Article / Araştırma Makalesi

Evaluation of Anthracycline Related Arterial Stiffness in Childhood Cancer Survivors

Çocukluk Çağı Kanser Sağ Kalanlarında Antrasiklin İlişkili Arteriyel Sertliğin Değerlendirilmesi

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Abstract

Childhood cancer survivors have a significantly increased risk of cardiovascular morbidity and mortality. Improved screening methods are needed for early detection of cardiotoxicity. The aim of the study is to evaluate arterial stiffness as an indicator of vascular damage by oscillometric pulse wave analysis in childhood cancer survivors. A total of 38 patients and 25 age and gender matched healthy volunteers were included in this cross-sectional single centre study. All participants, underwent evaluation of arterial stiffness through non-invasive measurement of hemodynamic parameters such as pulse wave velocity (PWV) and central systolic blood pressure (c-SBP) with the Mobil-O-Graph® pulse wave analysis device. Left ventricular ejection fraction (LVEF) and left ventricular mass index (LVMI) were obtained by M-mode echocardiography. The median age of the childhood cancer survivors was 12.5 (4.25-18) and the median duration time after end of chemotherapy was 36 (12-116) months. Both groups were statistically similar in age, body mass index, LVEF and LVMI. Childhood cancer survivors had significantly lower peripheral systolic blood pressure compared to controls. Average c-SBP and PWV were similar between groups. Childhood cancer survivors > 15 years old also had similar PWV value with those < 15 years old. There were no signs of arterial stiffness in childhood cancer survivors late after chemotherapy according to the ambulatory oscillometric PWA. Longer follow-up duration may be required to determination of subclinical vascular damage

Keywords: anthracyclines, arterial stiffness, cardiotoxicity, pulse wave velocity, vascular toxicity

Özet

Çocukluk çağı kanser sağ kalanlarının kardiyovasküler morbidite ve mortalite riski önemli ölçüde artmıştır. Kardiyovasküler toksisitenin erken tespiti için gelişmiş tarama yöntemlerine ihtiyaç vardır. Çalışmanın amacı, çocukluk çağı kanseri sağ kalanlarında osilometrik nabız dalga analizi ile vasküler hasarın bir göstergesi olan arteriyel sertliği değerlendirmektir. Bu kesitsel, tek merkezli çalışmaya toplam 38 hasta ve 25 yaş ve cinsiyet uyumlu sağlıklı gönüllü çalışmaya dahil edildi. Tüm katılımcılar Mobil-O-Graph® marka nabız dalga analizi cihazı ile nabız dalga hızı (PWV) ve merkezi sistolik kan basıncı (c-SBP) gibi hemodinamik parametrelerin invazif olmayan ölçümü yoluyla arteriyel sertliğin değerlendirmesine tabi tutuldu. Sol ventrikül ejeksiyon fraksiyonu (LVEF) ve sol ventrikül kitle indeksi (LVMI) M-mod ekokardiyografi ile ölçüldü. Çocukluk çağı kanseri sağ kalanlarının medyan yaşı 12,5 (4,25-18) ve kemoterapi bitiminden sonraki medyan süresi 36 (12-116) aydı. Her iki grup da yaş, vücut kitle indeksi, LVEF ve LVMI açısından istatistiksel olarak benzerdi. Çocukluk çağı kanseri sağ kalanları, kontrollere kıyasla daha düşük periferik sistolik kan basıncına sahipti. Ortalama c-SBP ve PWV gruplar arasında benzerdi. Onbeş yaşından büyük çocukluk çağı kanseri sağ kalanları, 15 yaşından küçüklerle benzer PWV değerine sahipti. Ambulatuar osilometrik PWA ile çocukluk çağı kanseri sağ kalanlarında kronik dönemde subklinik arteriyel sertlik bulgusu tespit edilmedi. Subklinik vasküler hasarın tespiti için daha uzun takip süresi gerekli olabilir.

Anahtar Kelimeler: antrasiklinler, arterial stiffness, kardiyak toksisite, nabız dalga hızı, vasküler toksisite

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1. Introduction

Anticancer treatments, including anthracyclines, alkylating agents, and vascular endothelial growth factor inhibitors, are associated with direct vascular damage and an increased risk of adverse vascular outcomes that can occur after the first treatment and persist into survival (1,2). Therefore, recent reports in the field of vascular cardio-oncology highlighted the critical need for continuous monitoring of vascular health during treatment and in survivors. Thus, primary and secondary treatment strategies can be developed to prevent vascular side effects. However, there are no systematic reports evaluating current clinical strategies that have been used to monitor vascular toxicity. This reflects a serious gap in our current knowledge of anthracycline-associated vascular injury and the need to identify potential imaging approaches.

Vascular damage results in an increase in the level of arterial stiffness defined as a decrease in the elastic property of the wall structure of the arteries. Arterial stiffness is a vascular biomarker describing the alterations of arterial properties which result in a reduction of the arterial wall elasticity, and therefore in a decrease of the buffering capacity of arteries to pulsatile cardiac ejection (3). Cancer patients and survivors have increased arterial stiffness more than the levels expected with aging (4,5). According to the results of the analysis of a total of 19 studies, the arterial stiffness level of cancer patients is higher both after treatment compared to baseline values and compared to healthy controls (6). Anthracyclines cause overexpression of inflammatory cytokines in endothelial cells and reduce production of endothelin and nitric oxide (NO) resulting in endothelial cells being more susceptible to apoptosis and the functional integrity of endothelium being compromised (7). All these mechanisms lead to a loss of the ability of endothelial cells to regulate the vascular smooth muscle tone and therefore arterial stiffness increases (3).

The gold standard method used for the assessment of arterial stiffness is pulse wave analysis (PWA). Non-invasive investigation of the PWV, via ultrasound or oscillometric methods, provides information on the elasticity of the vascular system and enables early recognition of damages in the vessels. Moreover, oscillometric PWA is a current and reliable method that has recently been used in children as well as in adults (8,9).

The aim of this study is to determine the subclinical evidence of anthracyclines related endothelial dysfunction by non-invasive ambulatory oscillometric PWA in childhood cancer survivors.

2. Methods

This is a cross-sectional and single-center study which was conducted with childhood cancer survivors who were received anthracycline chemotherapy and healthy controls. The control group consisted of healthy children, who were referred to the pediatric cardiology clinic and only diagnosed with innocent murmur and had no evidence of structural heart disease on echocardiography. Inclusion criteria were as follows; being older than six years old, having at least one year after chemotherapy, not having diabetes, hyperlipidemia, kidney, liver and structural heart diseases. This information was obtained from the parents and health records. All of the participants were evaluated in terms of structural and functional heart disease with two-dimensional and M-mode echocardiographic examination. The study protocol was approved by the Eskisehir Osmangazi University Ethics Committee (Approval number: E-25403353) and written informed consent was obtained from the parents of each child.

Echocardiographic examination

Transthoracic echocardiography was performed by one single experienced pediatric cardiologist using the commercially available equipment Affinity 70 (Philips Medical Systems, Bothell, WA, USA) with 2–4 and 4–8 MHz broadband probes. The participants were examined at rest while in the left lateral decubitus during sinus rhythm. Left ventricular internal dimensions (LVEDd), interventricular septum thickness (IVSDd), and posterior wall thickness (LVPWd) were measured at the end diastole using two-dimensional M-mode echocardiography

according to the pediatric guidelines of the American Society of Echocardiography (10). Left ventricular mass (LVM) was calculated according to the Devereux Formula and indexed to the heights. Left ventricular ejection fraction (EF) was calculated using the Teichholz formula (11,12).

Pulse wave analysis

Oscillometric PWA is an easy-to-apply, non-invasive and reliable method in the assessment of arterial stiffness and has been reported to be suitable for children (13). For pulse wave analysis and blood pressure monitoring, the Mobil-O-Graph (IEM, Industrielle Entwicklung Medizintechnik und Vertriebsgesellschaft mbH, Stolberg, Germany) device and ARCSolver pulse wave analysis software (AIT Austrian Institute of Technology GmbH, Vienna, Austria) were used. A 24-hour blood pressure monitoring was performed by connecting a cuff of a size appropriate for upper right arm circumference. As a result of the analysis, 24-hour peripheral and central blood pressure measurements, systolic and diastolic blood pressure loads, nighttime blood pressure reduction rates, pulse wave velocity and augmentation index measurements were obtained.

Statistical Analysis

The data were analyzed using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used for assessment of normal distribution. All normally distributed data was shown appropriately as mean ± standard deviation, otherwise they were presented as median with range. Data was adequately evaluated according to their distribution by T-test or Mann-Whitney-U-Test. Correlations between variables were analyzed with Pearson's correlation for normally distributed variables and Spearman's who for non-normally distributed data. P-values of <0.05 were indicated as statistically significant.

3. Results

Thirty-eight patients who were received anthracycline treatment between 2007 and 2019 with the diagnosis of a childhood cancer at Eskisehir Osmangazi University Pediatric Hematology Clinic and 25 healthy children were included in the study. There was no significant difference between patients and controls in terms of age, gender and anthropometric measurements (p>0.05) (Table 1). The characteristic features of cancer survivors are specified in Table 2.

Table 1. Demographics of patients and controls.

Variable	Patients (n=38)	Controls (n=25)	P value
Age	12.5 (4.25-18)	11 (6.5-17)	0.513
Gender (female/male)	19/19	13/12	0.541
Weight, kg	43.93±14.95	41.1±15.75	0.522
Height, cm	146.43±18.58	148.32±16.24	0.681
BMI, kg/m^2	19.87±3.84	18.05±3.73	0.068

BMI, body mass index

Table 2. Characteristics of patients

Diagnosis (n)	
Hodgkin disease	1
Non-Hodgkin lymphoma (Burkitt, NHL, T-NHL)	3
Acute lymphoblastic leukemia (PreB-ALL, T-ALL, C-ALL)	29
Myeloid leukemia (AML)	2
Wilms tumor	2
Renal cell carcinoma	1
Time off therapy (months)	36 (12-116)
Cumulative anthracycline dose, mg/m^2	240 (100-650)

The left ventricular morphological features and systolic functions determined by M-mode echocardiographic examination were similar in childhood cancer survivors and controls (p>0.005) (Table 3). Controls had higher all-day average systolic blood pressure value compared to cancer survivors (107.57±7.39 vs 111.88±7.56, p=0.029). However, the all-day average systolic blood pressure load and central systolic blood pressure were not significantly different between the two groups (23.57±20.2 vs 30.24±18.1, p=0.188, 96.36±6.63 vs 98.84±6.54, p=0.151). Average PWV and Aug@75 values were were not significantly different between childhood cancer survivors and controls (4.4 (4.1-5.2) vs 4.4 (4.1-5.1), p=0.379, 20.81±6.4 vs 21.56±6.46, p=0.655) (Table 4). When cancer survivors were divided into subgroups by age, cancer survivors older than 15 years had similar PWV as controls less than 15 years old (4.68±0.47 vs 4.7±0.29, p=0.639).

Table 3. Comprasion of echocardiographic measurments.

Measurments	Patients (n=38)	Controls (n=25)	P values
IVSDd, mm	7 (4-11.7)	6.5 (4.3-10)	0.386
LVEDd, mm	42.70±4.72	42.33±4.95	0.768
LVPWd, mm	6.27±1.45	6.82±1.19	0.120
LVMI, gr/m^2	63.82±15.03	65.2±14.72	0.721
EF, %	69.94±5.89	69.94±6.36	0.634

EF; ejection fraction, IVSDd; Interventricular septum diameter at end-diastol, LVEDd; left ventricular end-diastolic diameter, LVPWd;left ventricular posterior wall thicness at end-diastol, LVMI; left ventricular mass index.

Table 4. Comprasion of blood pressure and arterial stiffness measurments.

Measurments	Patients (n=38)	Controls (n=25)	P values
24-h average SBP, mmHg	107.57±7.39	111.88±7.56	**0.029**
24-h average DBP, mmHg	63.36±5.41	64.2±3.77	0.507
24-h average cSBP, mmHg	96.36±6.63	98.84±6.54	0.151
24-h average cDBP, mmHg	65 (53-76)	66 (60-74)	0.382
PWV, m/s	4.4 (4.1-5.2)	4.4 (4.1-5.1)	0.379
Aug@75, %	20.81±6.4	21.56±6.46	0.655
24-h SBP load	23.57±20.2	30.24±18.1	0.188
Diurnal systolic variation, %	9.4±5.53	7.77±6.01	0.258

Aug@75; augmentation index, cDBP; central diastolic blood pressure, cSBP; central systolic blood pressure, DBP; diastolic blood pressure, PWV; pulse wave velocity, SBP; systolic blood pressure

The time after chemotherapy completed was negative correlated with shortening fraction and positive correlated with central systolic blood pressure (r=-0.339, p=0.037, r=0.338, p=0.038, respectively).

4. Discussion

According to the current study, left ventricular systolic functions of patients who were received anthracycline for childhood cancer, evaluated at least one year after the end of treatment, were similar with their healthy peers. Central systolic blood pressure and pulse wave velocity examined for the level of arterial stiffness were also not significantly different from their healthy peers. However, cancer survivors, all of whom were normotensive, had lower peripheral systolic blood pressures compared to healthy children.

Childhood cancer survivors have a significantly increased risk of cardiovascular morbidity and mortality (14). Thus, the risk of death from cardiovascular disease in childhood cancer survivors is seven times higher than in the general population (15). Having anthracycline-containing

chemotherapy at an early age further increases this risk (16). Therefore, the screening guidelines of Children's Oncology Group recommended regularly echocardiographic evaluation for children exposed to anthracyclines or radiotherapy to detect early cardiac abnormalities that might be treated (17,18). In the study, left ventricular ejection fraction and shortening fraction were normal in childhood cancer survivors and there was no patient with evident myocardial dysfunction. One of the reasons for the lack of myocardial dysfunction was might be the average cumulative anthracycline dose which was less than 300 mg/m2. However, even children who have received low cumulative doses are known to be at high risk for long-term cardiotoxicity (19). Hence, there may be subclinical findings that cannot be detected by conventional echocardiography methods in childhood, while prominent myocardial systolic dysfunction with a significant decrease in left ventricular EF is diagnosed in long term of life. In addition, the negative relationship between the time remaining after the completion of chemotherapy and systolic functions also emphasizes the increased risk of cardiovascular damage over time.

Decrease in left ventricular mass and wall thickness, which is a precursor of significant systolic dysfunction, is also one of the findings that can be detected in the long-term follow-up of childhood cancer survivors (20). The absence of a decrease in left ventricular wall thickness and mass in childhood cancer survivors compared to controls, may support that morphological impairment in these patients is not a common finding in childhood, just like apparent myocardial dysfunction. In addition, determination of arterial stiffness and central blood pressure values at expected levels in our patients may suggested that there was no increase in central vascular resistance that may lead load dependent myocardial remodeling. Moreover, our finding that childhood cancer survivors had lower peripheral systolic blood pressure values than healthy controls is inconsistent with the literature. Indeed, high peripheral SBP and (pre) hypertension were defined as the late complications of cancer treatment regimens (21). One of the most conceivable explanation for our finding might be the sedentary lifestyle and lower physical activity levels of cancer survivors compared to their healthy peers. Limitations in motor ability due to drug neurotoxicity and developmental delay during long periods of hospital admission may lead to lower physical activity in childhood cancer survivors (22,23). Therefore, sedentary lifestyle habits may have tended to lower 24-hour blood pressure values compared to their more physically active peers. Similar with our results, Nováková et al. were also reported the lower values of systolic blood pressure in children, adolescents, and young adults previously treated with anthracyclines compared to healthy controls of the same age. Moreover, they stated that the age-dependent blood-pressure increase, which was present in healthy adolescents, was not found in cancer survivors (24). Impairment of the sympathetic nervous system caused by anthracycline toxicity, which was reported previously, may lead the lower blood pressure in CCSs (25).

The another issue that is known to be closely associated with long-term mortality in childhood cancer survivors and recommended to be taken into consideration in the follow-up of these patients is vascular damage. Although there are studies on vascular damage in cancer survivors using different methods for evaluation, any method has not yet been included in the guidelines as the standard recommended method. Therefore, the need for defining the most appropriate approach to early detection of anthracyclines-associated vascular damage is an important issue. Pulse wave analysis is a method that allows simple, painless and non-invasive detection of increased arterial stiffness, which is an important finding of vascular damage (26). In the present study, there was no increase in pulse wave velocities and therefore in arterial stiffness, according to the results of the oscillometric pulse wave analysis of the patients. The clearly defined endothelial damage, which is related to anthracyclines in cancer survivors, is closely related to age. Therefore, these patients should be followed for lifetime in terms of cardiovascular toxicity. Furthermore, another treatment modality associated with vascular damage in cancer survivors is radiotherapy (27,28). None

of the childhood cancer survivors included in the study were received radiotherapy, hence this might have been resulted with less vascular damage.

Limitations

The main limitations of our study is the small sample size and lack of long-term follow-up duration. Long-term follow-up of the patients, including their adulthood, will allow the detection of expected vascular damage and myocardial remodeling findings. This may had resulted in the absence of patients with a diagnosis of cardiomyopathy in the cohort of the study. The use of conventional echocardiography to examine cardiotoxicity may be inadequate in detecting findings of subtle cardiotoxicity. These subtle myocardial abnormalities might be demonstrated with further imaging methods such as tissue Doppler imaging, strain echocardiography, and cardiac magnetic resonance imaging. The strength of this study is; it is one of the few studies which arterial stiffness of cancer survivors was assessed by oscillometric pulse wave analysis (29).

5. Conclusion

The results of the present study show that there is no sign of marked deterioration in left ventricular morphology and systolic functions in patients who received anthracycline without radiotherapy due to childhood cancer and who have passed at least one year after the last dose of chemotherapy. According to 24-hour ambulatory blood pressure monitoring and oscillometric pulse wave analysis of these patients, mean systolic blood pressure was not elevated, pulse wave velocity and central blood pressure values were similar to healthy peers, and arterial stiffness was not increased. Longer follow-up duration and advanced imaging modalities may be required for determination of subclinical cardiovascular toxicity signs.

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