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Increased Arterial Stiffness in Children Treated with Anthracyclines for Malignant Disease

Vesna Herceg-Čavrak[1], Vladimir Ahel[2], Maja Batinica[1], Lana Matec[1] and Danijel Kardoš[3]

[1] University of Zagreb, »Sestre milosrdnice« University Hospital Center, Zagreb Children's Hospital, Department of Pediatrics, Cardiology Unit, Zagreb, Croatia
[2] University of Rijeka, Rijeka University Hospital Center, Kantrida Department of Pediatrics, Cardiology Unit, Rijeka, Croatia
[3] Valpovo Health Center, Valpovo, Croatia

ABSTRACT

Survivors of childhood cancer have a significantly higher late morbidity and mortality from cardiovascular diseases. The aim of this study was to determine whether anthracyclines used in childhood could increase arterial stiffness, a well-known independent predictor of cardiovascular diseases. The study included 53 children and adolescents aged 6–20 years having completed anthracycline treatment for a malignant disease according to various protocols at least a year before. The patients were free from clinical or laboratory signs of the underlying disease or cardiac disease. Control group consisted of 45 age- and sex-matched healthy children. Arterial stiffness was determined by measuring aortic pulse wave velocity (PWVao) using oscillometric method (Arteriograph TensioMed device). PWVao value was significantly increased (6.24±1.34 m/s vs. 5.42±0.69 m/s; p<0.001) in patients having received anthracyclines as compared to control group. Increased arterial stiffness was present irrespective of the following parameters: age, sex, body mass index, systolic and diastolic blood pressure, mean arterial pressure and heart rate. It is possible that the effect of anthracycline on increased cardiovascular morbidity and mortality in long-term childhood cancer survivors is associated not only with cardiotoxicity, but also with increased arterial stiffness.

Key words: *anthracyclines, arteries, drug effects, child, neoplasms, drug therapy, oscillometry*

Introduction

Anthracycline cardiotoxicity is one of the most serious complications of cancer therapy and could manifest as cardiomyopathy, pericarditis and congestive heart failure[1–3]. Today, more than 75 percent of children treated for childhood cancer can be cured[4]. For long-term survivors, the possible late effects of treatment are a major concern. Cardiac complications may appear long after the end of anthracyclines treatment and are the leading cause of morbidity and mortality in long-term survivors of childhood cancer[5]. Mortality related to cardiac causes in long-term survivors is tenfold that in control group[6]. The mechanism of anthracycline cardiotoxicity is not entirely clear, but oxidative stress plays an important role in myocardial and vascular damage in patients treated with anthracyclines[7].

Increased stiffness of central arteries has been shown to have an independent predictive value for cardiovascular events in adult population[8]. Since changes in blood vessels occur much earlier than clinically developed disease can be observed, arterial stiffness is a significant marker in the development of future cardiovascular changes.

Arterial stiffness increases normally during lifetime, but could be further enhanced by atherosclerotic process and diseases like hypertension, diabetes, dyslipidemia[9], and it is a marker of vascular disease. Arterial stiffness in childhood is influenced by classic risk factors for cardiovascular disease (obesity, metabolic syndrome, familial hypercholesterolemia, diabetes, physical inactivity)[10–11] and additionally by prenatal growth retardation, vasculitis, vasculopathy, and congenital heart disease[12]. There are several different methods to determine arterial stiffness, but to determine the stiffness of central arteries, measurement of aortic pulse wave velocity (PWVao) is the one most commonly used[13]. PWVao is the speed at which the forward pressure or flow wave is transmitted from aorta through the arterial tree. Age, height, and

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mean arterial pressure (MAP) were found to be major determinants of PWVao[14].

Little is known about the possible impact of anthracycline to increased arterial stiffness as a potential risk factor for later cardiovascular diseases[15].

The aim of our study was to determine whether the children having completed anthracycline treatment for a malignant disease a year or more before, have an increased central arterial stiffness measured by PWVao as compared to age- and sex-matched healthy children. The occlusive oscillometric method using Arteriograph is a new, easy-to-use and time-effective method for assessing arterial stiffness.

Patients and Methods

The study design was a case-control trial including 53 children and adolescents aged 6 to 20 years (34 (64.2%) male and 19 (35.8%) female) having received an anthracyclines (doxorubicin, epirubicin, daunorubicin) for the treatment of malignant disease more than a year before (cases), and 45 age- and sex-matched healthy controls. Study patients were free from clinical and laboratory signs of the underlying disease or cardiac disease. Anthracycline chemotherapy was applied according to different chemotherapy protocols. Participants receiving cancer treatment were diagnosed with osteosarcoma and Ewing sarcoma (n=17), Hodgkin and non-Hodgkin lymphoma (n=9), Wilms tumor (n=4), neuroblastoma (n=4), synovial sarcoma (n=3), rhabdomyosarcoma (n=3) and other tumors (n=13).

Doxorubicin, epirubicin and daunorubicin were administered as part of various chemotherapy protocols in a total dose of 75–375 mg/m^2 (212±93 mg/m^2).

Cyclophosphamide, another possibly cardiotoxic drug[16], was administered in a dose of 7–42 mg/kg /day (18.54±14,74), total dose of 0.70–7.20 g/m^2 (4.37±3.00 g/m^2). Additional chemotherapeutics included in different protocols were antimetabolite methotrexate, alkaloid vincristine, and the alkylating agent cisplatin. None of the study patients received radiotherapy in the mediastinal and abdominal area.

Exclusion criteria were patients with arrhythmia, known renal, endocrine, cardiovascular or other chronic disease, and course of corticosteroids or antihypertensive therapy. Median time elapsed from the last chemotherapy dose was 2 (range 1–16) years.

Control subjects were 45 healthy children and adolescents aged 6 to 20 years (25 (55.6%) male and 20 (44.4%) female), referred to cardiologist because of innocent heart murmur and healthy volunteers. Sample size was computed by power analysis for Mann-Whitney U test: minimum total 94 subjects would make around 47 subjects *per* group, with the parameter level of significance $\alpha=0.05$, estimated effect size d=0.6, power 0.80 (G*Power for Windows 3.1.2; available from: http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/).

All relevant information including both personal and family history regarding the symptoms and signs associated with cardiovascular abnormalities were collected using a questionnaire administered to study subjects and their parents.

Children and adolescents underwent physical examination with special attention paid to symptoms and signs associated with cardiovascular abnormalities. Anthropometric measurements (body height and weight, waist and hip circumference) were performed according to standard procedures: waist circumference (cm) was measured in midline between the edge of lower rib cage and iliac crest; hip circumference (cm) was measured at the point of maximal width. Body mass index (BMI) was calculated according to the equation: body weight (kg)/body height^2 (m^2). Distance between the jugulum and symphysis (J-Sy) (cm) was measured from the upper edge of manubrium sterni to the upper edge of symphysis, ensuring that we measured the shortest distance between these two points. The measurements were performed twice and the mean values were used.

Blood pressure (BP; mm Hg) was measured in supine position after 10-minute rest, with appropriate cuff, using the oscillometric device Philips Patient Monitor M 3926A. Each measurement was performed twice and the mean value was used in further calculations.

Standard 12-chanel ECG was performed with Agilent Pagewriter 100.

Echocardiography

Echocardiography was performed on HP SONOS 4500 machine with 4 MHz transducer. Complete examination included two-dimensional echocardiography (2D), motion mode echocardiography (M-mode) and Doppler technique. The left ventricular (LV; cm) internal dimension, interventricular septal thickness (IVS; cm) and LV posterior wall thickness (LVPW; cm) were measured during diastole and systole according to the methods established by the American Society of Echocardiography[17]. Measurements for each parameter were performed twice and the mean value was used in further calculations. Fractional shortening (FS; %), left ventricle mass (LVM; g) and left ventricle mass index (LVMI; g/m$^{2.7}$) were calculated according to the previously published and standard techniques[18].

Arteriograph

The occlusive oscillometric method for measuring PWVao by Arteriograph (TensioMed Ltd., Budapest, Hungary; Software Arteriograph for Windows 2000) is based on plethysmography recording of pulse wave oscillations detected on the upper-arm cuff by a special high fidelity sensor.

Pulse wave velocity (PWV)

The technique is based on the fact that during systole, the blood volume ejected into the aorta generates a pulse wave, so-called 'early systolic peak' (P_1). As this pulse

wave runs down, it reflects from the bifurcation of the aorta, creating a second wave, so-called 'late systolic peak' (P_2). Return time (RT) is calculated as the difference in milliseconds between the first and the reflected systolic wave. *Aortic pulse wave velocity (PWVao)* is calculated from the return time and the distance traveled by the pulse wave from the jugulum (sternal notch) to the pubic symphysis, which is closest to the real length of the aorta. This distance was measured on the body surface using calibrated scale. PWVao is then calculated as distance/time (m/s).

$$\text{PWVao(m/s)} = \frac{\text{Jug} - \text{Sy(m)}}{\text{RT}/\,2\text{(s)}}$$

Standard deviation (SD_{PWVao}) (m/s) indicates the quality of measurement, i.e. dispersion of PWVao values of particular cardiac cycles. SD_{PWVao} is calculated for PWVao of each individual pulse wave. A mean of $SD_{PWVao} > 1.1$ m/s indicates unsatisfactory measurement and it should be repeated. In the present study, it was less than 0.5 (m/s).

Besides PWVao, augmentation index (AIx), central aortic systolic pressure (SBPao) aortic pulse pressure (PPao) (mm Hg), mean arterial pressure (MAP) (mmHg) and peripheral blood pressure (BP) are also determined by use of Arteriograph.

Augmentation index (AIx) is a complex parameter that provides information on systemic arterial stiffness because it depends on peripheral resistance and pulse wave velocity. There is strong correlation between augmentation index of brachial artery (AIx br) and of aorta (AIxao) (r=0.94; $P<0.001$)[19]. Augmentation index (AIx) is on a decrease in children until age 15, then it rises. It was not analyzed in this study.

$$\text{AIx} = \frac{(P_2 - P_1)}{\text{PP}} \times 100\ (\%)$$

(P1, early systolic peak; P2, late systolic peak; PP, pulse pressure)

Central systolic blood pressure (SBPao) (mmHg) could be automatically calculated by direct analysis, without the use of transfer function[19], on the basis of peripheral (brachial) pressure (BP) and brachial augmentation index (AIxbr), which correlates strongly with central augmentation index (AIxao) (r=0.94; $P<0.001$).

Aortic pulse pressure (PPao) (mmHg)

$$\text{PPao (mmHg)} = \text{SBPao–DBPao;}$$

(SBPao, aortic systolic blood pressure; DBPao, aortic diastolic blood pressure)

Mean arterial pressure (MAP) (mmHg)

$$\text{MAP(mmHg)} = \text{DAP} + \frac{(\text{SAP} - \text{DAP})}{3};$$

(SAP, brachial systolic pressure; DAP, brachial diastolic pressure)

In recent years, three studies have been published that compared the known noninvasive methods to determine arterial stiffness parameters: piezoelectronic method (Complior), applanation tonometry (SphygmoCor) and oscillometric method (Arteriograph)[20–22]. Carotid-femoral PWV, a method used by SphygmoCor, is considered a 'gold standard'. There was no significant difference among the three methods in time measurements (transit time = RT/2), whereas PWV differed due to the mode of distance (pathway) measurement[20]. There was significant correlation of PWV values obtained by Arteriograph and SphygmoCor (r=0.67; p<0.001), and Complior (r=0.69; p<0.001).

High correlation was found between AIx determined by Arteriograph and SphygmoCor (r=0.92; p<0.001)[21]. The PWV and AIx values recorded by Arteriograph correlated well with those obtained by use of Complior (r=0.60; p<0.001) and SphygmoCor (r=0.89; p<0.001)[22]. The advantage of occlusive oscillometric method by Arteriograph over other methods is its simple use.

The latest study by Horvath et al.[19] including 93 patients showed excellent correlation of PWVao values determined by Arteriograph and an invasive method. There was strong correlation between aortic AIx measured invasively and brachial artery AIx measured noninvasively, by oscillometric method (Arteriograph) (r=0.94; p<0.001). A comparable level of correlation (r=0.95; p<0.001) was found between invasively measured and noninvasively (Artreiograph) calculated central pressure (SBPao). Significant correlation (r=0.91; p<0.001) was recorded between invasively measured aortic PWV and PWV measured noninvasively by use of Arteriograph.

Measurement

Examination should be performed in a quiet room, at temperature of about 22°C. The patient should avoid taking food and smoking for 3 hours and alcohol drinks for 10 hours before examination. At least 10-minute rest and mental relaxation should precede the examination. Measurement is performed in supine position, relaxed, with legs extended, but not sleeping. The method cannot provide reliable data in patients with arrhythmia and therefore it is not used in these patients. Upper arm cuff is placed and tightened firmly to produce the state of brachial artery occlusion by suprasystolic pressure value. Cuff contact with the patient's chest should be avoided. Arteriograph measures actual systolic and diastolic pressure first by oscillometric method, then the cuff is deflated. This is followed by cuff re-inflation, first to diastolic, then to suprasystolic pressure value (actual systolic pressure measured +35 mm Hg). Then the device registers and records signals at systolic and diastolic blood pressure values for 8–10 seconds. All signals recorded are processed by computer software designed for this purpose (1.10.0.1). Each of the measurements was performed twice and the mean value was used in further calculations.

The study was conducted following the principles of bioethical standards. The protocol was approved by the Children's Hospital Ethics Committee and Central Ethics Committee of Rijeka University School of Medicine. A

written informed consent was obtained from the parent or guardian of each child included in the study. Major adolescents signed informed consent by themselves.

Statistical analysis

Descriptive statistics was used to describe the basic characteristics of age, sex, BMI, anthropometric parameters (waist and hip circumference, jugulum-symphysis distance), BP and HR. Normality of data distribution was analyzed using the Kolmogorov-Smirnov test. The χ^2-test was used to estimate differences in the distribution of qualitative variables. Differences in quantitative variables between study groups were analyzed with the parametric *t*-test or nonparametric Mann-Whitney test, according to their distribution. Calculation of Pearson's *r* correlation coefficient was also performed for certain quantitative variables.

All statistical tests were performed at the 95% level of significance; difference between study groups was considered significant at $p<0.05$. MedCalc software for Windows version 11.3 (www.medcalc.be) was used for database management and statistical analysis.

Results

There was no significant difference between the patient group and control group according to age, sex, BMI, waist and hip circumference, jugulum-symphysis distance, HR and BP level (differences in variables were analyzed with independent t-test, except for sex, where χ^2-test was used) (Table 1).

There was a statistically significant difference in PWVao between the patient and control group. The subjects having received anthracyclines showed a higher PWVao than controls ($p<0.001$) (Table 2).

There was no correlation between the cumulative anthracycline dose and PWVao ($r=0.227$) in patient group. PWVao was not increased in patients having received higher doses of anthracyclines.

There was no significant difference in the mean PWVao between patients having (n=9) and having not (n=44) received cyclophosphamide (6.41±2.05 m/s *vs.* 6.21±1.17 m/s; $p=0.790$).

There was no sex difference in PWVao value in patient group (male 6.33±1.35 m/s *vs.* female 6.08±1.34 m/s;

TABLE 1
DEMOGRAPHIC DATA OF STUDY SUBJECTS: ANTHRACYCLINE RECIPIENTS AND CONTROL GROUP

Variable	Patients N=53	Control N=45	p
Sex (male/female)	M 34 (64.2%) F 19 (35.8%)	M 25 (55.6%) F 20 (44.4%)	0.386
Age (yrs): X±SD	13.59±4.44	12.21±3.03	0.081
BMI (kg/m^2): X±SD	20.16±4.63	18.98±3.48	0.162
Hip (cm): X±SD	82.63±17.09	79.87±12.21	0.368
Waist (cm): X±SD	72.18±15.05	67.81±9.94	0.100
Waist to hip ratio: X±SD	0.88±0.07	0.85±0.05	0.034
Jugulum-symphysis (cm): X±SD	47.02±7.45	45.98±5.53	0.441
Systolic BP (mm Hg): X±SD	109.76±16.13	114.44±11.31	0.105
Diastolic BP (mm Hg): X±SD	61.05±8.23	63.01±6.17	0.191
HR (beats/min): X±SD	76.09±14.47	74.49±12.00	0.556
Anthracycline dose (mg/m^2)	212±93	0	NA

BMI – body mass index; BP – blood pressure; HR – heart rate

TABLE 2
HEMODYNAMIC PARAMETERS MEASURED BY ARTERIOGRAPH IN STUDY SUBJECTS – ANTHRACYCLINE RECIPIENTS AND CONTROL GROUP

Variable	Patients N=53	Control N=45	p
PWVao (m/s): X±SD	6.24±1.34	5.42±0.69	<0.001
PPao (mm Hg): X±SD	37.81±6.13	35.66±5.41	0.079
SBPao (mm Hg): X±SD	99.10±10.50	97.91±8.71	0.556
MAP (mm Hg): X±SD	78.26±9.07	78.86±6.87	0.728

PWVao – aortic pulse wave velocity; PPao – aortic pulse pressure; SBPao – aortic systolic blood pressure; MAP – mean arterial pressure

TABLE 3
ECHOCARDIOGRAPHIC PARAMETERS OF STUDY SUBJECTS – ANTHRACYCLINE RECIPIENTS AND CONTROL GROUP

Variable	Patients N=53	Control N=45	p
IVSd (cm)	0.70±0.18	0.70±0.18	0.913
LVEDd (cm)	4.35±0.66	4.35±0.46	0.978
LVPWd (cm)	0.66±0.18	0.63±0.16	0.394
FS (%)	33.11±4.41	35.88±3.77	0.001
LVM (g)	103.94±64.96	98.47±54.53	0.656
LVMI ($g/m^{2.7}$)	30.34±10.68	29.12±8.35	0.535

IVSd – diastolic interventricular septal thickness; LVEDd – left ventricular end diastolic diameter; LVPWd – diastolic left ventricular posterior wall thickness; FS – fractional shortening; LVM – left ventricular mass; LVMI – left ventricular mass index

p=0.519) and control group (male 5.35±0.79 m/s *vs.* female 5.52±0.56 m/s; p=0.415).

In addition, there was no difference between the values of MAP (p=0.72), PPao (p=0.079), and SBPao (p=0.556) (Table 2).

Analysis of echocardiography results (Table 3) yielded no statistically significant difference in left ventricular parameters of IVSd, LVEDd, LVPWd (p>0.05), LVM (p=0.656) and LVMI ($g/m^{2.7}$) (p=0.535).

However, a difference was found in left ventricular FS (p=0.001), which was lower in patients as compared to control subjects.

Discussion

Children and adolescents treated with anthracyclines for a malignant disease had increased aortic stiffness when compared to the age- and sex-matched healthy group. In our study, increased aortic stiffness expressed as an increased PWVao value was found in the group of children and adolescents treated with anthracyclines at least a year after completion of chemotherapy.

Long-term survivors of childhood cancer become an increasing group with a significant risk of premature heart disease[1]. The Childhood Cancer Survivor Study, where 14,358 cancer survivors were compared to their siblings, has reported a higher risk of heart failure (relative risk [RR] 5.7), myocardial infarction (RR 4.9), atherosclerosis (RR 10.2), pericardial disease (RR 6.3) and valvular disease (RR 4.8) in these patients[23].

An increase in arterial stiffness causes a premature return of reflected pulse waves in late systole, increases central systolic pressure, pulse pressure, and afterload, causes heart muscle hypertrophy and reduces coronary perfusion[24]. Increased stiffness of central arteries has been demonstrated to have an independent predictive value for cardiovascular events in adult population[8]. In their study including 1207 adolescents, Arnett et al. found the systolic BP and arterial elasticity to be inversely proportional in this population[9]. Riley et al. report on reduction of arterial elasticity in children with elevated BP and cholesterol[10]. Children of hypertensive parents have been found to have increased arterial stiffness measured both in the aorta and in the carotid artery, suggesting the possible genetic component[11,12]. Only a few studies report data on normal PWVao values as a measure of arterial stiffness in children, but these measurements were performed in a small number of children and with different methods[25]. Reusz et al. report on a recent study of reference values of carotid-femoral PWV obtained in more than 1000 children[14]. Reference values of PWVao measured by Arteriograph have not yet been published.

The effect of anthracyclines on arterial stiffness could be explained with oxidative stress[1], structural changes in the vascular endothelial matrix, or disruption in the regulation of the arterial wall smooth muscle tone. Anthracycline increased the effect of inflammatory cytokines, which can cause damage to vascular endothelium[26].

If anthracyclines can cause increased arterial stiffness, they could possibly be an additional factor for the increased number of cardiovascular diseases in long-term survivors of childhood cancer.

To the best of our knowledge, there are no published data on arterial stiffness measurements in children treated with anthracyclines.

The only study that examined the effect of anthracyclines on arterial stiffness in adults was the one by Chaosuwannakit et al.[15]. A significant increase in PWVao and decrease of aortic distensibility (AoD) from baseline values occurs 4 months after the administration of anthracycline. The measurement of PWV and AoD was performed by phase-contrast cardiovascular magnetic resonance (PC-CMR). In the study by Chaosuwannakit et al.[15], increased arterial stiffness was observed 4 months after initiation of anthracycline treatment. Presuming the possibility of reversible condition, it seems reasonable to measure it a year after chemotherapy completion or later, to prove the long-term persistence of its effects. In our study, the measurement of PWVao was performed in patients that have completed anthracycline therapy a year or more before.

PWVao values in our study were significantly higher (p<0.001) in the group of patients previously treated with anthracyclines than in the control group. The mean

PWV value was 6.24±1.34 m/s in patient group *versus* 5.42±0.69 m/s in control group. The values are comparable because the groups did not differ significantly according to age, sex, BH, BW, BMI or HR.

There was no difference in systolic, diastolic, mean BP and PPao value. Since PWVao measurement with oscillometric method by Arteriograph TensioMed has been introduced recently, reference or normal values for children have not yet been published.

In our study, there was no correlation of PWVao with the dose of anthracycline (r=0.227). Chaosuwannakit et al.[15] found the higher cumulative doses of anthracyclines to correlate positively with greater reduction of ascending thoracic AoD, but not with the increase in PWV.

Among other parameters monitored in the present study, FS was significantly lower in patient group than in control group, as also reported from other studies[27,28]. Other echocardiographic parameters (IVSd, LVEDd, LVPWd, LVM and LVMI) did not differ significantly between the groups of patients and healthy subjects.

The limitations of our study were as follows: a heterogeneous group of patients regarding anthracycline dose; inability to compare PWVao values according to anthracycline dosage due to a small number of patients; and the lack of follow up over time.

Conclusion

The children having completed treatment with anthracyclines at least a year ago have higher PWVao values, implicating the increased arterial stiffness as a known independent predictor of cardiovascular diseases. It could be a factor affecting the increased number of cardiovascular complications in late survivors of childhood cancer.

As we recorded an increased PWVao in patients at least a year after chemotherapy completion, it appears that structural and functional changes of arterial wall caused by anthracyclines can persist for at least one year. In conclusion, besides their cardiotoxicity, anthracyclines also increase arterial stiffness, thus additionally contributing to the increased risk of cardiovascular diseases in individuals treated for malignant diseases in childhood.

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V. Herceg-Čavrak

University of Zagreb, »Sestre milosrdnice« University Hospital Center, Zagreb Children's Hospital, Department of Pediatrics, Cardiology Unit, Klaićeva 16, 10000 Zagreb, Croatia
e-mail: vherceg@gmail.com

POVEĆANA KRUTOST ARTERIJA U DJECE LIJEČENE ANTRACIKLINIMA ZBOG MALIGNE BOLESTI

S A Ž E T A K

Osobe koje su preživjele malignu bolest u djetinjstvu imaju značajno veći pobol i smrtnost od kardiovaskularnih bolesti u odrasloj dobi. Cilj ove studije je bio odrediti mogu li antraciklini primijenjeni u djetinjstvu povećati krutost arterija, koja je dobro poznati nezavisni prediktor kardiovaskularnih bolesti. Pregledano je 53-oje djece i adolescenata dobi 6–20 godina, u kojih je liječenje maligne bolesti antraciklinima prema različitim protokolima završeno prije najmanje godinu dana. Bolesnici su bili bez kliničkih ili laboratorijskih znakova osnovne bolesti ili srčane bolesti. Kontrolnu skupinu sačinjavalo je 45-ero zdrave djece slične dobi i spola. Krutost arterija je određena mjerenjem brzine širenja pulsnog vala (PWV) oscilometrijskom metodom (uređajem Arteriograph TensioMed). U ispitanika koji su liječeni antraciklinima PWV je bio značajno veći u usporedbi s kontrolnom skupinom (6,24±1,34 m/s prema 5,42±0,69 m/s, $p<0,001$). Krutost arterija je bila povećana bez obzira na dob, spol, indeks tjelesne mase, sistolički i dijastolički arterijski tlak, srednji arterijski tlak i srčanu frekvenciju. Moguće je da učinak antraciklina na povećanje kasne smrtnosti u osoba liječenih u djetinjstvu zbog maligne bolesti nije povezan samo s kardiotoksičnosti, nego i s povećanom krutosti arterija.