Original Article

EFFECTS OF CARDIOTOXIC CHEMOTHERAPEUTIC AGENTS ON VASCULAR STIFFNESS AND OSCILLOGRAPHIC EVALUATION

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Abstract

B Background: Several clinical studies have demonstrated that arterial stiffness is an early indicator of cardiovascular events. Our study aimed to detect the potential cardiovascular changes using arterial stiffness parameters and compare these changes with echocardiographic aortic stiffness parameters in cancer patients treated with cardiotoxic chemotherapeutics.

Methods and Results: Our study is a prospective case-control study. A total of 70 subjects between the ages of 18 and 50 years were included into our study. 30 of them were newly diagnosed cancer patients and 40 were age- and sex-matched control group. Baseline oscillometric arterial and echocardiographic aortic stiffness parameters were measured in all patients. In cancer patients, all of these parameters were measured again one month after chemotherapy protocol was completed. Mean age of the cancer patients was 41.4 ± 5.9 years and mean age of the control group was 39.6 ± 6.6 years (p=0.258). Before chemotherapy, marterial and aortic stiffness parameters were similar between the study and the control groups. After chemotherapy, oscillometric pulse wave velocity parameter increased compared to the control group and to the pre-chemotherapy values (p=0.004 and p<0.001, respectively). After chemotherapy, augmentation index parameter increased compared to the control group (p=0.013). Conclusion: In newly-diagnosed cancer patients treated with cardiotoxic chemotherapeutics, considerable impairment occurs in some of the oscillometric arterial stiffness parameters while there is no substantial effect on echocardiographic aortic stiffness. Arterial stiffness parameters in these patients might be useful in evaluating subclinical cardiovascular damage.

Keywords: Cardiotoxicity, chemotherapy, cancer, arterial stiffness, pulse wave velocity.

INTRODUCTION

Cancer diagnoses have increased due to the development of imaging devices with high temporal and spatial resolutions, widespread use of these imaging devices, and standardization of screening tests[1]. Diagnosed patients can survive for many years thanks to the diversification and activation of newly-developed therapeutic options[2]. However, with increased survival, long-term adverse effects of agents used for treatment of patients have appeared, and increased morbidity and mortality related to these adverse effects have become an important health issue[3]. Agents used for treatment of cancer affect cells of many organs and systems along with tumor cells. Cardiovascular system is one of the most affected systems[4[. Therefore, cardiovascular diseases are one of the most frequent reasons of treatment-induced morbidity and mortality increase in patients treated for cancer [5]. Recent studies have shown that chemotherapy-induced cardiotoxicity may occur up to 26% in a dose-dependent manner [6]. Of these, 98% develop within the first year, however, most of them are asymptomatic [7]. Studies have shown that, the earlier cardiotoxicity caused by chemotherapeutics is detected and the earlier appropriate protective treatment is initiated, the more rapid and effective is the clinical improvement, and restoration of cardiac functions [8].

Echocardiographic imaging alone is insufficient for early detection of cardiotoxicity. This makes using additional methods for the monitorization of cardiac functions of patients receiving chemotherapy and for early detection of cardiac adverse effects an obligation [9]. Several studies have shown that reduced dilation ability of great arteries against pulse pressure and increased

stiffness are associated with later cardiovascular morbidity and mortality [10, 11]. It was detected that 1 m/sec increase at aortic pulse wave velocity is associated with a 15% increase in the risk of cardiovascular events [12]. In this study, we aimed to detect potential cardiovascular changes using oscillometric arterial stiffness parameters and compare these changes with echocardiographic aortic stiffness parameters in cancer patients treated with cardiotoxic chemotherapeutics.

METHODS

Patient Selection and Study Design

Our study included 30 cancer patients who admitted to Municipal Cancer Center, Almaty, Kazakhstan Outpatient Clinic between December 2018 and January 2020, were planned to undergo cardiotoxic chemotherapy for the first time, and met the inclusion and exclusion criteria. The control group included 40 subjects who admitted to Turkestan Regional Oncological Outpatient Clinic for routine examination, did not have a known chronic disease, and had similar age and sex characteristics with the study group.

Exclusion criteria were history of chronic systemic disease, active tobacco use, previous chemotherapy/radiotherapy, decreased left ventricle ejection fraction (<50%) before treatment, advanced-stage valvular heart disease, history of cardiovascular disease, and morbid obesity.

Detailed medical history was taken from all patients. Age, sex, height, weight, body mass index, and body surface area values were recorded.

Arteriographic Evaluation

Cancer patients were evaluated by measurement of arterial stiffness, central cardiovascular parameters, and arterial pressure using Mobil-O-Graph 24 h ABPM NG® (Stolberg, Germany) arteriography device before chemotherapy and one month after treatment protocol was completed. The control group were also evaluated using the same device. Before evaluation, the patients were taken into a quiet room that was not disturbingly lighted for measurements using Mobil-O-Graph 24 h ABPM NG® (Stolberg, Germany) arteriography device. After at least 10 minutes of resting in this room, at least two measurements were taken from the brachial artery region using a suitably sized cuff in sitting position. The measurement side was the opposite of mass side in patients with breast cancer to allow measurement from the same side after surgical procedure, and right brachial artery in other patients. It was ensured that patients did not eat or consume caffeine-containing substances three hours before measurement time, and they were asked not to speak during measurement[13].

During oscillometric measurement with arteriographic device, cuff is inflated up to a level which is at least 35 mmHg above the measured systolic arterial pressure value to completely block brachial arterial blood flow. A membrane forms over the brachial artery at the upper edge of inflated cuff where blood flow is blocked[14]. Waves occurring as a result of pressure changes in the central arterial system are detected by sensitive pressure sensors in the cuff at this membrane level and conveyed into special tonometer of the device. Waves recorded by tonometer are transferred to a computer and evaluated by HMS Client Server 5.2® software developed for Mobil-O-Graph 24 h ABPM NG device. The following parameters have been evaluated at oscillometric measurements performed by the Mobil-O-Graph 24 h ABPM NG device (Figure)

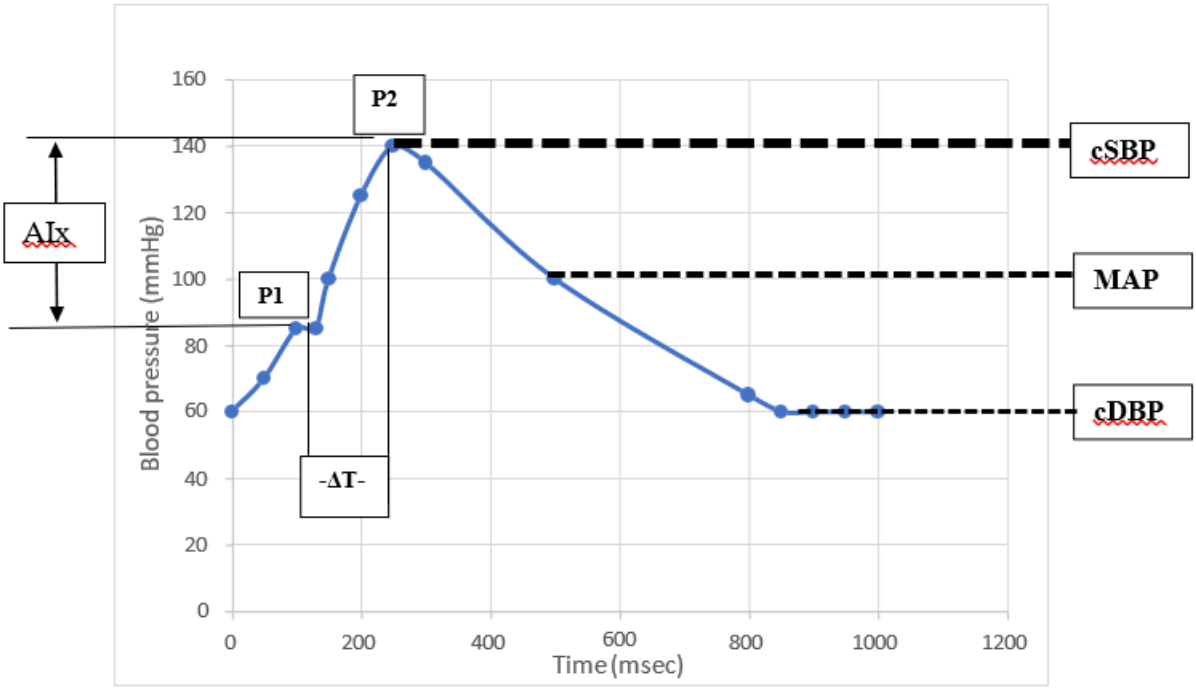

Figure 1: Graphical representation of the pulse wave

AIx: augmentation index, P1: early systolic wave, P2: reflected wave, ΔT: pulse wave transit time, cSBP: central systolic blood pressure, cDBP: central diastolic blood pressure, MAP: mean arterial pressure

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Mean arterial pressure (MAP)
- Pulse
- Pulse pressure (NB)
- Central systolic blood pressure (cSBP)
- Central diastolic blood pressure (cDBP)
- Augmentation Index (AIx)
- Pulse Wave Velocity (PWV)

After left ventricular systole, pumping of blood from the ascending aorta causes dilation of the aorta and creates a pulse wave that spreads to arterial system at certain speeds.

This pulse wave comprises of three different wave forms:

- The first wave spreading from heart during systole (P1)

- Reflected wave from distal to heart during diastole, especially arising from vascular bifurcations (P2)

- Diastolic reflected wave occurring around aortic root

As the latter two wave forms overlap and complete each other, they may be assessed as a single reflected wave. The first wave (systolic wave, P1) depends on arterial stiffness and left ventricle ejection performance. The second wave (diastolic wave, P2) depends on site of reflection and stiffness of the arterial system(15).

The velocity of waves formed in arterial system is called pulse wave velocity (PWV). PWV is the ratio of distance travelled by arterial pulse wave from one end of vessel to other end to time(16). Its formula is:

$$PWV=\Delta d\ (meter)/\Delta t\ (second)$$

As arterial stiffness increases, velocity of both direct wave and reflected wave increases. Reflected wave which would normally reach to aortic root in early diastole reaches to aortic root in late diastole and contributes to direct wave. The assessment method which numerically shows this contribution of reflected wave to main wave is called augmentation index (AIx)(17). It is calculated by dividing the difference between two pulse waves by pulse pressure (PP) and multiplying with 100(18). Its formula is:

$$AIx\ (\%) = (P2 - P1) / PP \times 100$$

Augmentation index depends on the velocity, intensity and distance to the reflection point of spreading wave, heart rate, and cardiac contractility(19). Thus, it is seen as another important parameter in the evaluation of arterial stiffness and calculation of cardiovascular risk

Transthoracic Echocardiographic Evaluation

Cancer patients were assessed by transthoracic echocardiography (TTE) before chemotherapy was initiated and one month after treatment protocol was completed. The control group also underwent the same echocardiographic assessment. In all patients, Vivid E9 (GE Vingmed Ultrasound, Horten, Norway)

echocardiography device and M5S (1.5-4.5 MHz) ultrasound probe were used for TTE. Parasternal long axis, parasternal short axis, apical 4-chamber, apical 2-chamber, apical 5-chamber, and subcostal windows were used for TTE. Systolic and diastolic diameters of the ascending aorta, anteroposterior diameter of left atrium, interventricular septum thickness, posterior wall thickness, and left ventricle end-diastolic and end-systolic diameters were measured. Left ventricular mass and mass index were calculated using Devereux formula(20). Valvular functions were evaluated using Color Doppler. Transmitral early and late diastolic flow velocities (E and A waves), and pulmonary artery systolic pressure were measured using 2D Doppler, and early and late diastolic velocities of mitral annulus (e' and a' wave) using tissue Doppler. Subsequently, E/A and E/e' ratios were calculated. Left ventricle ejection fraction value was measured by modified Simpson's rule using apical 4-chamber and apical 2-chamber views. Using ascending aorta diameter measurements, aortic elasticity parameters were calculated using the following formulas(21);

Aortic strain (%) = (aorta systolic diameter-aorta diastolic diameter)/aorta diastolic

diameter

Aortic stiffness index = log(SBP-DBP)/aortic strain

Aortic distensibility ($cm^2.dyn^{-1}.10^{-6}$) = 2*aortic strain/(SBP-DBP)

Elastic modulus (mmHg) = (SBP-DBP)/aortic strain

Statistical Analysis. Study data were evaluated by using "SPSS (Statistical Package for Social Sciences) for Windows 21.0 (SPSS Inc, Chicago, IL)" (spss.int.omu.edu.tr-Network Lisans) software provided by Ondokuz Mayis University, Department

of Information Technology. Descriptive statistics were presented as mean ± standard deviation, frequency distribution, and percentage. Chi-Square Test and Fisher's Exact Test were used for the evaluation of categorical variables.

The distribution normality of parameters was examined using visual (histogram and probability charts) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk Test). For the normally distributed parameters, Student's T Test was used for statistical significance between two independent groups and Paired Sample T Test for statistical significance between two dependent groups. For non-normally distributed parameters, Mann-Whitney U Test was used for statistical significance between two independent groups and Wilcoxon Signed-Rank Test for statistical significance between two dependent groups. The correlation between parameters was evaluated using Pearson Correlation Analysis. For intra-observer

variability, 10 subjects were randomly selected from each group and measurements were repeated by the same operator after at least one month. For inter-observer variability, a second operator blinded to results of the first operator repeated measurements. Reproducibility was calculated by intraclass correlation coefficient. Statistical significance level was set at $p<0.05$. For intra-observer variability, eight subjects were randomly selected from each group and the measurements were repeated twice by the same operator within one month. For inter-observer variability, a second operator blinded to results of the first operator repeated the measurements.

RESULTS

Patients A total of 70 volunteers were included into our study, with the study group comprising of 30 individuals planned to undergo cardiotoxic chemotherapy and the control group comprising of 40 healthy individuals who were not followed up for any disease. There were 29 females (96.7%) and one male (3.3%) in the study group compared to 38 females (95%) and two males (5%) in the control group ($p=1.0$). While mean age of the study group was 41.4 ± 5.9 years, mean age of the control group was 39.6 ± 6.6 years ($p=0.258$). There was no significant difference between the patient and the control groups in terms of body mass index ($p=0.508$).

Twenty-eight of individuals in the study group (93.3%) had diagnosis of breast cancer. After pathological evaluation, 27 of these breast cancer patients were detected to have invasive ductal carcinoma and one to have invasive lobular carcinoma. One patient at the study group was squamous-cell lung cancer (3.3%) and another patient was diffuse large B-cell lymphoma (3.3%). Histological stage of cancer was detected to be 2 in 10 patients (33.3%), 3 in 19 patients (63.3%), and 4 in one patient (3.3%). During follow-up of the patients, 16 patients (53.3%) underwent breast conserving surgery, six patients (20%) underwent radical mastectomy, and eight patients (26.7%) did not undergo any tumor surgery.

In addition to chemotherapy, 16 out of 30 patients (53.3%) received radiotherapy and 15 (50%) received hormone therapy.

The median invasive tumor diameters measured by non-invasive imaging methods or at pathological examinations after surgery was 28 mm (15-90). When tumors were staged by diameter, six patients were at T1 stage, 17 at T2 stage, and six at T3 stage.

Table 1 shows the chemotherapeutics and their doses, and number of patients receiving these agents.

Table 1: Chemotherapy doses given to cancer patients

	Mean	St. Deviation	Median	Min.	Max.	N
Doxorubicin Dose (mg)	402.8	66.3	400	320	640	29
Cyclophosphamide Dose (mg)	4157.1	1171.7	4000	3200	9600	28
Paclitaxel Dose (mg)	1608.8	264.9	1560	1380	2460	16

Trastuzumab Dose (mg)		4594.5	960.6	4665	2560	6200	10
Carboplatin Dose (mg)		7680.0	---	7680	7680	7680	1
Adriamycin Dose (mg)		500.0	198.0	500	360	640	2
5-Fluorouracil (mg)	Dose	5100.0	424.3	5100	4800	5400	2
Docetaxel Dose (mg)		540.0	---	540	540	540	1

Arterial Stiffness Parameters

Table 2 shows results for oscillometric arterial stiffness parameters of the groups.

Table 2: Oscillometric arterial stiffness parameters and blood pressure parameters of the groups

		Control Group (n=40)	Pre-Treatment Cancer Patients (n=30)	Post-Treatment Cancer Patients (n=30)	p	p*	p**
PWV (m/sec)		5.96±0.71	6.23±0.83	6.5±0.81	0.144	**0.004**	**<0.001**
Augmentation Index (%)		24.45±8.8	28.17±9.66	29.67±8.1	0.098	**0.013**	0.293
Total Vascular Resistance (TVR) (sec*mmHg/mL)		1.22±0.13	1.23±0.11	1.22±0.12	0.642	0.912	0.407
SBP (mmHg)		120.3±13.3	121.3±14.8	125.7±16.7	0.77	0.137	**0.033**
DBP (mmHg)		75.25±10.4	77.53±11.8	80.1±13.5	0.137	0.094	0.187
Pulse (beat/mean)		79.2±11.37	86 ± 17.98	88.5±14.4	0.076	**0.004**	0.26
Mean Arterial Pressure (mmHg)		96.1±10.67	97.67±12.7	101±14.4	0.572	0.107	0.075
Pulse (mmHg)	Pressure	44.73±9.33	43.9 ± 7.99	45.6±8.59	0.699	0.689	0.177
cSBP (mmHg)		110±11.7	111.3±12.5	115.6±15.9	0.654	0.097	**0.033**

cDBP (mmHg)	77.23±10.4	79.1±11.96	81.73±13.6	0.493	0.12	0.165

p: The control group vs. the pre-treatment patient group p*: The control group vs. the post-treatment patient group
p**: The pre-treatment patient group vs. the post-treatment patient group
PWV: pulse wave velocity, SBP: systolic blood pressure, DBP: diastolic blood pressure,cSBP: central SBP, sDBP: central DBP

After chemotherapy, pulse wave velocity (PWV) parameter increased compared to the control group and the pre-chemotherapy values (p=0.004 and p<0.001, respectively).

Additionally, after chemotherapy, augmentation index increased compared to the control group (p=0.013).

After chemotherapy, systolic blood pressure and central systolic blood pressure values increased compared to the pre-chemotherapy values (p=0.033 and p=0.033, respectively).

After chemotherapy, pulse rate increased compared to the control group (p=0.004).

Echocardiographic Parameters

Table 3 shows standard transthoracic echocardiography parameters of the groups.

Table 3: Standardized transthoracic echocardiographic parameters of the groups

ControlGroup (n=40)		Pre-Treatmen tCancer Patients (n=30)	Post-Treatmen tCancer Patients (n=30)	p	p*	p**
LVEF (%)	62.88±2.82	61.4±3.24	59.27±4.18	0.046	**<0.001**	**0.002**
LVEDD (mm)	43.63±3.96	42.47±4.18	44.4±4.81	0.241	0.463	**<0.001**
LVESD (mm)	25.2±3.04	26.3±3.82	28.43±4.61	0.184	**0.002**	**<0.001**
IVS (mm)	9.58±1.36	9.73±1.53	10.07±1.55	0.649	0.163	0.057
PW (mm)	9.55±1.28	9.67±1.32	9.97±1.4	0.711	0.2	0.071
LA (mm)	30.6±2.8	29.4±3.47	30.53±3.33	0.114	0.928	**0.001**
E/A	1.38±0.23	1.23±0.29	1.12±0.35	0.022	**<0.001**	0.095
E/e	6±1.2	6.38±1.72	5.79±0.99	0.287	0.444	0.066
LVMI (gr/m²)	79.6±17.87	80.9±22.03	88.9±23.25	0.79	0.063	**<0.001**

p: The control group vs. the pre-treatment patient group p*: The control group vs. the post-treatment patient group
p**: The pre-treatment patient group vs. the post-treatment patient group
LVEF: left ventricle ejection fraction, LVEDD: left ventricle end-diastolic diameter, LVESD: left ventricle end-systolic diameter, IVS: interventricular septum, PW: posterior wall, LA:left atrium, LVMI: left ventricular mass index

After chemotherapy, LVEF value decreased compared to the control group and the pre-chemotherapy values (p<0.001 and p=0.002, respectively). After chemotherapy, left atrium diameter and LVMI value increased compared to the pre-chemotherapy values (p=0.001 and p<0.001, respectively). After chemotherapy, E/A ratio decreased compared to the control group (p<0.001).

When aortic stiffness parameters assessed by echocardiography were analyzed, no significant difference was detected between the groups in terms of aortic strain, aortic stiffness index, aortic distensibility, and aortic elastic modulus values (Table 4).

Table 4: Echocardiographic aortic stiffness parameters of the groups

ControlGroup (n=40)		Pre-Treatment Cancer Patients (n=30)	Post-Treatment Cancer Patients (n=30)	p	p*	p**
Systolic Diameter of The Ascending Aorta (mm)	29.2±3.03	28.27±3.3	28.77±3.14	0.237	0.584	**0.005**
Diastolic Diameter ofThe Ascending Aorta (mm)	27.23±3.1	26.33±3.2	26.85±3.03	0.243	0.617	**0.002**
Aortic Strain (%)	7.31±2.98	7.43±2.27	7.21±2.5	0.855	0.875	0.581
Aortic Stiffness Index	3.36±1.66	2.94±1.22	3.21±1.61	0.247	0.706	0.287
Aortic Distensibility ($cm^2.dyn^{-1}.10^{-6}$)	0.34±0.16	0.35±0.13	0.33±0.13	0.749	0.719	0.336
Aortic Elastic Modulus ($dyn.cm^{-2}.10^6$)	7.42±3.82	6.67±3.12	7.36±3.71	0.378	0.944	0.193

p: The control group vs. the pre-treatment patient group p*: The control group vs. the post-treatment patient group
p**: The pre-treatment patient group vs. the post-treatment patient group

Correlation Analysis. In the correlation analyses, strong positive correlation was detected between aortic distensibility and aortic strain (r=0.845, p<0.001), and strong negative correlation between these values and elastic modulus, and stiffness index (r= -0.877, p<0.001 and r= -0.838, p<0.001, respectively).

Furthermore, a weak negative correlation was observed between aortic distensibility and PWV (r= -0.285, p=0.017).

Variability Analysis.

The intra-observer and inter-observer intraclass correlation coefficients for echocardiographic parameters ranged from 0.69 to 0.99 ($p<0.05$ for all).

DISCUSSION.

In this study, while there was no substantial effect of cardiotoxic chemotherapeutics on echocardiographic aortic stiffness parameters in newly-diagnosed cancer patients, considerable impairment was detected in oscillometric arterial stiffness parameters such as pulse wave velocity and augmentation index.

Cardiovascular system is the leading organ system affected by chemotherapeutics [4]. It has been shown that early detection and treatment of cardiovascular damage developed after exposure to cardiotoxic chemotherapeutics stop the progression of damage, accelerate improvement, and even provide full functional restoration [7]. Thus, it is anticipated that revealing cardiovascular adverse effects of cancer treatment during subclinical period and treating them early would reduce rates of morbidity and mortality due to cardiovascular diseases[6]. Many studies in patients with hypertension, diabetes and chronic renal failure, and in elderly patients have shown that arterial stiffness is an independent indicator of development of cardiovascular disease[22]. In this study, we aimed to detect the potential cardiovascular changes by using oscillometric arterial stiffness parameters which may be useful in predicting early cardiovascular involvement and compare these changes with echocardiographic aortic stiffness parameters in cancer patients treated with cardiotoxic chemotherapeutics.

Many measurement methods are used for the assessment of arterial stiffness including invasive and non-invasive methods such as intrathoracic surgical approach, catheter angiographic approach, transthoracic Doppler's ultrasonography, MR angiography, and arteriography devices[23]. The efficacy and safety of Mobil-O-Graph 24 h ABPM NG® (Stolberg, Germany) arteriography device which we used for the assessment of arterial stiffness in this study have been shown in comparative studies with invasive methods and devices such as SphygmoCor system (AtCor Medical, Sidney, Australia)[24].

In their study in 29 breast cancer patients treated with cardiotoxic chemotherapeutics and 12 healthy volunteers, Grover et al. evaluated patients using pre- and post-treatment MR images, and detected significant increase in PWV and significant decrease in aortic distensibility which is an indicatory of elasticity in the study group[25]. In a study again in cancer patients receiving anthracycline-based chemotherapy, PWV was increased when evaluated six months after treatment initiation compared to pre-treatment values[11]. In a study where 5960 patients were follow-up for a mean of 7.6 years, high augmentation index has been shown to be considerably associated with future cardiovascular events[26]. In a study in 24 females with breast cancer who received doxorubicin- and cyclophosphamide-based chemotherapy protocol, there was no difference detected between pre-treatment PWV, Aix, and conventional echocardiographic parameters and post-treatment values measured one week after treatment was completed [27]. In our study, while the PWV value of the control group was similar with pre-treatment PWV value of the study group, post-treatment PWV value increased significantly in the study group. Also, while baseline AIx values were similar between the control and the study groups, there was an increase in the study group after treatment. Moreover, a significant increase was detected in peripheral and central systolic blood pressure after treatment. These results support the hypothesis of our study that cardiotoxic chemotherapeutics increase arterial stiffness. With increasing stiffness, dilation capacity and elasticity of the aorta decrease. It has been shown that aortic distensibility and aortic strain values, which are elasticity parameters, decrease with increased arterial stiffness, and elastic modulus and stiffness index increase in line with PWV[28]. These values can be measured on the aorta using echocardiographic methods[29]. In our study, while aortic distensibility and aortic strain tended to decrease and elastic modulus and stiffness tended to increase after treatment, these changes were not statistically significant. This was interpreted as echocardiographic aortic stiffness parameters were insufficient compared to oscillometric arterial stiffness parameters in the early detection of cardiovascular involvement due to chemotherapeutics in our study group. What is the pathophysiological mechanism underlying the results in our study? Due to direct cytotoxic effects of chemotherapeutics on endothelium or due to nuclear degeneration, apoptosis occurs in the cells(30). As nitric oxide and vasodilator cytokines could not be released from dysfunctional endothelium, arterial elasticity decreases and arterial stiffness increases[31]. In the stiff arterial system, rapidly moving reflected waves which would normally reach to left ventricle at early diastole reach at late diastole and increase left ventricular systolic pressure load. Hypertrophy occurs and need for oxygen increases in the left ventricle which tries to overcome high systolic pressure [32]. Due to decreased pressure in diastole, coronary perfusion is impaired and myocardial ischemia occurs as increased oxygen demand of the left ventricle is not met [33]. Direct cytotoxic effects of cardiotoxic chemotherapeutics are well-known, and these effects are explained by free radical damage,

apoptosis through nucleus or cellular membrane degeneration, and fibrosis[4, 6]. Furthermore, endothelial dysfunction and wall stress due to increased stiffness in the systemic arterial system accelerate atherosclerotic process[34].

According to the consensus report issued by the European Society of Cardiology in 2016, 10% or more decrease in LVEF value measured by echocardiography below the normal values is accepted as cardiotoxicity[35]. However, the limitations of echocardiographic LVEF parameter include the effects of image quality and clinical status on the measurements, intra-and inter-observer variability, and insufficiency to predict possible future cardiovascular complications[36]. In their retrospective study in 356 patients with childhood cancer, Watts et al. detected that assessment of left ventricular systolic function by conventional echocardiography was insufficient in predicting cardiotoxicity and stated that alternative methods are needed[9].

Cardiotoxic chemotherapeutic agents may not only affect systolic functions measured by LVEF but also diastolic functions. In a prospective study in 35 women diagnosed with breast cancer and who are planned to undergo anthracycline-based chemotherapy, systolic and diastolic echocardiographic parameters of patients were measured before treatment and six months after treatment. While there was no considerable change in systolic functions, diastolic dysfunction was detected, and it was suggested that this was related to afterload and stress increase caused by increased arterial stiffness[10]. In their study comparing echocardiographic tissue Doppler findings between patients treated with anthracycline and healthy volunteers, Stapleton et al. detected that mitral E/A and E/e' values were lower in the anthracycline group[37].

In our study, post-chemotherapy LVEF value decreased compared to the control group and the pre-chemotherapy values; however, this decrease does not meet the cardiotoxicity criteria for LVEF in the current guidelines. Moreover, LVEDD and LVESD were detected to increase after chemotherapy, which indicates left ventricular dilation. The increase detected in LVMI was considered to be related with this dilation occurring without a change in wall thicknesses. Furthermore, E/A ratio was detected to be decreased with E/e ratio remaining unchanged after chemotherapy. These findings show that signs of systolic dysfunction caused by chemotherapy-induced myocyte damage and signs of diastolic dysfunction caused by increased arterial resistance in the patients were intertwined in our study.

CONCLUSION.

Significant impairment occurs in the oscillometric arterial stiffness parameters such as pulse wave velocity and augmentation index which are early indicators of cardiovascular events in newly-diagnosed cancer patients treated with cardiotoxic chemotherapeutics. Measuring arterial stiffness parameters is an easily accessible, non-invasive and inexpensive technique, and might be useful in the evaluation of subclinical cardiovascular damage in these patients.

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