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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Anthracycline chemotherapy impairs the structure and diastolic function of the left ventricle and induces negative arterial remodelling

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Abstract

Background: Anthracycline affects various cell lines, which may contribute to left ventricular (LV) dysfunction and vascular remodelling.

Aim: To assess the complex influence of anthracycline chemotherapy on the echocardiographic parameters of LV systolic and diastolic function and indices of vascular function and structure.

Methods: 35 women (age 50 ± 9 years old) with breast cancer scheduled for standard anthracycline chemotherapy were enrolled into the study. Examinations were performed at the baseline and six months after the last dose of anthracycline with a clinical follow-up of 9–12 months. LV systolic and diastolic function were assessed by: ejection fraction, transmitral flow, isovolumetric relaxation time, Tei index, mitral ring movement velocity and E/E′ ratio. Vascular parameters, including flow-mediated dilatation, intima–media thickness (IMT), aortic compliance, common carotid artery (CCA) compliance, and stiffness indices β were measured.

Results: None of the patients revealed any cardiovascular symptoms during follow-up. LV systolic function parameters remained normal. However, LV end-diastolic diameter (46 ± 3.5 vs. 48 ± 4 mm, $p = 0.004$) and LV end-diastolic volume (101 ± 25 vs. 112 ± 26 mL, $p = 0.01$) increased. The diastolic function changed — the Tei index increased (0.49 ± 0.09 vs. 0.54 ± 0.1, $p = 0.04$) and E′ ($p = 0.049$), A′ ($p = 0.02$) and S ($p = 0.01$) decreased. The E/E′ index increased ($p < 0.0001$) within the LV lateral wall. We observed an increase in carotid IMT ($p < 0.0001$), a decrease in aortic compliance ($p = 0.042$) and CCA compliance ($p = 0.004$), and an increase in aorta as well as the CCA stiffness indices ($p = 0.046$, $p = 0.003$, respectively).

Conclusions: Standard-dose anthracycline chemotherapy is associated with LV dilatation and diastolic dysfunction, regardless of the preserved global systolic function. It coexists with negative structural arterial remodelling.

Key words: anthracycline, cardiomyopathy, aortic stiffness, intima–media thickness, cardiovascular risk

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INTRODUCTION

Anthracycline antibiotics belong to the antineoplastic group of drugs whose major mechanism is exerted by embedding and hindering topoisomerase II, an enzyme related to both DNA and RNA synthesis in replicating cells [1]. Cardiotoxicity is one of the side effects of anthracycline therapy with acute, chronic or delayed types of symptoms. While acute cardiotoxicity may occur within a few days after the first dose during drug administration [1, 2], delayed cardiotoxicity may be observed without any time limits after the completion of antineoplastic therapy [1].

Chronic cardiotoxicity, which is related to the maximum cumulative drug dose, is the most important clinical problem and can lead to heart failure symptoms resulting from

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left ventricle (LV) systolic dysfunction within the first year of chemotherapy [1]. There are several risk factors of chronic anthracycline cardiotoxicity, including age > 65 years, arterial hypertension, a history of radiotherapy within the mediastinum or left lung area, liver dysfunction or coadministration of other cardiotoxic drugs, primarily trastuzumab [1, 3].

Echocardiography is the recommended method in a routine cardiological evaluation during anthracycline therapy. The aim of recent studies has been to identify patients with a high post-anthracycline cardiological risk. However, data on anthracycline-related complications within the vascular system, which often precede myocardial dysfunction, is limited. Therefore, our aim was to assess the influence of anthracycline-based chemotherapy on LV systolic and diastolic function as well as on the ultrasound indices of vascular function and remodelling in females suffering from breast cancer.

METHODS

Thirty-five women (35–68 years old) diagnosed with breast cancer and scheduled for anthracycline chemotherapy (doxorubicin or epirubicin) were prospectively enrolled into the study. All patients were given one of the following treatment schemes depending on their clinical symptoms, stage of advancement or progression risk factors:

1. epirubicin:

- **FEC** — fluorouracil 500 mg/m^2 i.v. day.1; epirubicin 75 mg/m^2 i.v. day.1; cyclophosphamide 500 mg/m^2 day.1 every 21 days — 14 patients;
- **EC —** epirubicin 90 mg/m^2 i.v. day.1; cyclophosphamide 600 mg/m^2 day.1 every 21 days — four patients;

2. doxorubicin:

- **FAC** — fluorouracil 500 mg/m^2 i.v. day.1; doxorubicin 50 mg/m^2 i.v. day.1; cyclophosphamide 500 mg/m^2 day.1 every 21 days — 13 patients;
- **TAC** — docetaxel 75 mg/m^2 i.v. day.1; doxorubicin 50 mg/m^2 i.v. day.1; cyclophosphamide 500 mg/m^2 day.1 every 21 day — four patients.

Our exclusion criteria included: clinical or echocardiographic (ejection fraction < 50%) evidence of heart failure, symptoms of acute cardiotoxicity during chemotherapy, severe or uncontrolled arterial hypertension, diabetes, coronary artery disease, left-side chest wall radiation in the patient's medical history, active smoking, abnormalities in the ECG (e.g. abnormal rhythm, bundle branch blocks), autoimmune or endocrine diseases and infections.

Two examinations (medical history, physical examination, routine laboratory tests, transthoracic echocardiography and ultrasound vascular parameters) were performed before the first dose (initial evaluation) and six months after the last dose of anthracycline (post-treatment evaluation). All patients were followed-up for 9–12 months.

Thirty-one patients (of the 35 included) completed our observation: one patient died from the primary cancer, two patients had their chemotherapy changed (metastases), and one patient withdrew her consent to further observation.

Sixteen patients were given epirubicin (FEC — 13 patients, EC — three patients) and 15 patients were given doxorubicin (FAC — 11 patients, TAC — four patients). The cumulative dose of doxorubicin was 100–300 mg/m^2 (mean 278 ± 55 mg/m^2) and epirubicin 150–630 mg/m^2 (mean 414 mg/m^2). In the FEC and FAC treatment schedules, cyclophosphamide and fluorouracil were used in bioequivalent doses.

Final treatment included mastectomy in most cases (27 patients). Ten patients needed further chest radiotherapy: five patients in the doxorubicin group (left-side chest radiation — two patients) and five patients in the epirubicin group (left-side chest radiation — two patients). Six patients were given an additional therapy with trastuzumab (three patients from each of the groups) without radiotherapy. Eighteen (58%) patients were treated with tamoxifen in a standard dose.

Twenty women were in a menopause at baseline, but amenorrhoea was observed in all patients during the chemotherapy.

Transthoracic echocardiography

Left ventricular systolic function. We evaluated all of the standard parameters including: end-diastolic diameter (EDD), end-systolic diameter (ESD), interventricular septum thickness (IVS) and posterior wall thickness (PW) in an end-diastolic period in the parasternal long axis view. Left ventricular mass (LVM) was calculated using the Deveraux formula. Left ventricular mass index (LVMI) was calculated as the quotient LVM over body surface area (BSA) [4]. BSA was calculated using the Mostseller formula [4].

$$LVM\ [g] = [1.04 \times (EDD + IVS + PW)^3 - EDD^3] \times$$
$$\times\ 0.8 + 0.6 \text{ (variables in [cm])}$$
$$LVMI\ [g/m^2] = LVM\ [g]/BSA\ [m^2]$$

Left ventricular ejection fraction (LVEF) with stroke volume (SV) and cardiac output (CO) was assessed in an apical four-chamber view (Simpson's formula). Finally, segmental systolic function was estimated in all cases [4].

Left ventricular diastolic function. The peak velocities of early rapid filling (E), late filling (A) and E/A ratio were evaluated in an apical four-chamber view (the Doppler sample placed at the tips of opened mitral leaflets). Isovolumic contracting time (IVCT), isovolumic relaxation time (IVRT) and ejection time (ET) were also obtained using continuous Doppler visualisation.

Propagation of mitral inflow early filling wave: time [ms] and slope [mm Hg/s] were assessed in an apical four-chamber view with a colour Doppler in an M-mode visualisation (sample 4 cm above mitral ring).

Additionally, tissue Doppler imaging (TDI) of the mitral annulus in an apical four-chamber view (basal segments of IVS and lateral wall) was performed. Waves velocity: systolic (S),

early filling (E'), late filling (A') and E/E' ratio were obtained and an average from three heart cycles was obtained [4].

Myocardial performance index (MPI). The Tei index was calculated using the following formula:
Tei index = (IVCT + IVRT)/ET [ms] [4].

Ultrasound vascular system examination. The examinations were performed in the morning in a room at 22°C after a 15-min rest and an overnight fast. Smoking cigarettes was not allowed for 24 h prior to the examination. The subjects were lying supine with their heads slightly raised. All measurements of the brachial arteries were performed with a sphygmomanometric cuff on the proximal portion of the arm above the antecubital fossa on the longitudinal plane. The right brachial artery was scanned at rest, during reactive hyperemia, and following the administration of sublingual nitroglycerine (0.5 mg). Reactive hyperemia was induced by inflating the sphygmomanometer cuff to 200 mm Hg to occlude arterial inflow for 3 min. Brachial artery diameter and blood flow were obtained within 50–60 s of the cuff's deflation. Blood flow was measured from the pulsed Doppler signal and arterial diameters were taken from the anterior to the posterior 'M' line at the end diastole. Images were acquired with an ECG gating, with the end of the diastole corresponding to the onset of the R wave. The baseline and after-cuff deflation measurements were used in calculating flow mediated dilatation (FMD) (percentage increase of the artery diameter compared to the baseline results). Vascular response to sublingual nitroglycerine (0.4 mg) was assessed after 15 min based on nitroglicerine mediated dilatation (NMD) [5].

Intima–media thickness (IMT). All measurements were performed in the common carotid arteries 1 to 2 cm proximally to the carotid bulb. The common carotids were studied in longitudinal planes using the anterior and lateral approaches. IMT was measured on the posterior wall of the artery [6]. An average of ten measurements was used to calculate IMT.

Arterial stiffness parameters

Pulse wave velocity (PWV) assessment. Two pulse waves were obtained transcutaneously at the base of the neck for the right common carotid artery and over the right femoral artery. Transit time was measured as the time between the foot of the pulse wave and the foot of the R wave. Pulse transit time was determined as the average of ten consecutive beats. Time delay (t) was calculated as the difference between these two transit times. The distance (d) travelled by the pulse wave was measured over the body surface as the distance between two recording sites. PWV was calculated as PWV = d [m]/t [s] [6].

Arterial diameter and cross-sectional area changes. The right common carotid artery (CCA), CCA cross-sectional systolic and diastolic areas (As and Ad) and aortic (Ao) systolic and diastolic diameters (Ds and Dd) were measured. The following parameters of arterial stiffness were analysed [6]:

- pulse pressure (PP = SBP – DBP): brachial pulse pressure (PP) was calculated as the difference between sphygmomanometric systolic (SBP) and diastolic blood pressure (DBP).
- compliance C = $\Delta V/\Delta P$: compliance was defined as the volume change to pressure ratio.

Total arterial compliance (TAC) was determined as the left ventricular SV to PP ratio (TAC = SV/PP [mL]/[beat × mm Hg]).

CCA and Ao compliance were calculated using the following formula: C = (Dd – Ds)/PP [mm/mm Hg] where Dd — diastolic (maximal) artery diameter (heart systolic period), Ds — systolic (minimal) artery diameter (heart diastolic period).

CCA C = (Ad – As)/PP [cm^2/mm Hg] was calculated where Ad — diastolic (maximal) CCA cross sectional area (heart systolic period), As — systolic (minimal) and CCA cross sectional area (heart diastolic period).

- stiffness index β = ln (SBP – DBP)/[(Dd – Ds)/Ds]: stiffness index β, an indicator of the intrinsic mechanical wall properties, was calculated using the following formula: β = ln (SBP – DBP)/[(Dd – Ds)/Ds].

The stiffness indices were obtained for Ao and CCA. Echocardiography and vascular ultrasound measurements were performed by experts using a Toshiba Aplio ultrasound system equipped with a 3.5 MHz sector probe and a 7–10 MHz linear probe. The intra- and inter-observer coefficients of variation were 7.1% and 10.2% for echocardiography, and 16.0% and 18.5% for vascular ultrasound measurements, respectively.

The study was approved by the Local Ethics Committee. All subjects were informed about the nature of the study and signed informed consent forms.

Statistical analysis

All text and table results were expressed as means ± standard deviation or number and percentage. A p value < 0.05 was considered statistically significant. Logarithmic transformation was used for continuous variables if necessary. A paired samples t-test was used to compare the paired observations for continuous variables and a McNemar's test was used to compare the paired observations for categorical variables. Pearson's correlation was used to analyse the degree of association between two variables. Multivariable logistic stepwise regression was used to assess independent predictors of changes in the LV indices. Statistical tests were performed using MedCalc version 9.0.1.1.

RESULTS

Clinical characteristics

The mean age of our study population was 50 ± 9 years. None of the patients experienced any cardiovascular clinical symptoms during the follow-up period. Sixteen patients had well-controlled arterial hypertension, and new cases of hypertension were not noted during the observation. A diagnosis

Table 1. Selected clinical parameters before the first anthracycline dose (initial evaluation) and six months after the last anthracycline dose (post-treatment evaluation) in the study population

Parameter	Initial evaluation		Post-treatment evaluation		P
	Mean	SD	Mean	SD	
BMI [kg/m^2]	26.0	4.8	25.8	4.6	0.68
SBP [mm Hg]	136	21	135	14	0.78
DBP [mm Hg]	83	9	83	9	0.67
HR [bpm]	79	14	72	11	0.041
Hb [g/dL]	13.1	0.9	12.1	0.96	0.0001
HCT [%]	38.1	2.5	35.9	2.6	< 0.0001
WBC [K/μL]	6.8	1.6	6.0	1.8	0.008
PLT [K/μL]	279	62	317	77	0.004
Glucose [mg/dL]	97.5	23	102.7	19	0.012
Creatinine [μmol/L]	56.2	10.2	60.3	12.2	0.012
ALAT [U/L]	18.7	12.9	26.3	14.2	0.009
ALP [U/L]	65.6	14.7	67.8	20.4	0.395
Bilirubin [mg/dL]	0.53	0.18	0.40	0.14	0.0001
GFR [mL/min]	117.5	33	110.8	33	0.058

The table presents mean values and standard deviations; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; Hb — haemoglobin; HCT — haematocrit; WBC — white blood cells; PLT — platelets; ALAT — alanine aminotransferase; ALP — alkaline phosphatase; GFR — glomerular filtration rate

of hypertension was based on blood pressure (BP) levels (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) or a previously documented diagnosis and current antihypertensive treatment.

Clinical parameters, including body mass index, SBP, DBP and PP obtained at the initial and on the post-treatment evaluation were comparable. However, the mean heart rate on the second examination was significantly reduced compared to the first examination (79 ± 14 vs. 72 ± 11; $p < 0.05$).

The following pharmacotherapy of arterial hypertension was used: beta-blockers (35.5%), angiotensin-converting enzyme inhibitors (ACEI, 19.4%), calcium-channel blockers (9.7%) or diuretics (9.7%). Clinical evaluation and laboratory tests did not confirm anaemia, diabetes, liver or kidney failure; however it did reveal some dysfunction in those organs (Table 1).

Transthoracic echocardiography

Left ventricular systolic function. LV segmental systolic function and global systolic function estimated by EF ($p = 0.95$) and CO ($p = 0.895$) remained similar. However, mean LV EDD ($p = 0.004$) and LV EDV ($p = 0.01$) increased significantly without changes in LV ESD or LV ESV, which resulted in an increase in LV SV ($p = 0.005$). A comparison of the initial and post-treatment LV EDD and LV EDV measurements revealed a significant increase in these parameters in 20 (64.5%) patients.

Additional analysis revealed reductions in IVS ($p = 0.036$) and PW ($p = 0,045$) diameter, although LVM and LVMI on the post-treatment evaluation were comparable with the initial exam (Table 2). We also found a shortening of the mean ET (313 ± 45 vs. 288 ± 42 ms; $p = 0.03$) and a reduction in the S wave velocity assessed in the TDI (lateral wall).

Left ventricular diastolic function. E-wave and A-wave velocity, E/A index and deceleration time remained similar in all individuals. However, we found a prolongation of the mean IVRT ($p = 0.17$). Colour Doppler evaluation revealed a prolongation of the time ($p = 0.047$) and a reduction of the slope of flow propagation velocity ($p = 0.046$).

TDI showed a reduction in E' ($p = 0.049$), A' ($p = 0.02$), and an increase in the E/E' index ($p < 0.0001$) assessed for the lateral wall. Similar parameters assessed within IVS did not change significantly (Table 3). A comparison of the initial and post-treatment measurements in individual patients revealed a significant increase of the E/E' index in 26 (83.8%) and a significant decrease of E' in 20 (64.5%) patients.

Myocardial performance index (MPI). A significant increase of the Tei index was observed in 18 (58%) individuals (Fig. 1).

Ultrasound vascular function and structure. Ultrasound parameters of vascular function: FMD, NMD and FMD/NMD were comparable between the initial and the post-treatment (after six months) evaluations (Table 4). Nevertheless, 23 (74%) individuals revealed a significant carotid IMT increase ($p < 0.0001$) (Fig. 2).

Analysis of the parameters of the large arteries showed a decrease in compliance with an increase in the stiffness

Table 2. Selected left ventricular systolic and diastolic parameters before the first anthracycline dose (initial evaluation) and six months after the last anthracycline dose (post-treatment evaluation) in the study population

Parameter	Initial evaluation		Post-treatment evaluation		P*
	Mean	SD	Mean	SD	
LVEDD [mm]	46	3.5	48	4.0	0.0001
LVESD [mm]	30	4.0	31	5.0	NS
IVS [mm]	10	1.4	9,6	1.3	0.03
PW [mm]	8.8	0.9	8.4	1.2	0.04
LVM [g]	156	33	152	36	NS
LVMI [g/m^2]	89	16	87	17	NS
LVEDV [mL]	101.0	25	112.0	26	0.003
LVESV [mL]	38	12	41	16	NS
SV [mL]	63	16	71	16	0.005
LVEF [%]	63.0	6.0	63.0	5.0	NS
LVCO [l/min]	5.0	1.6	5.1	1.3	NS

*After adjusting for baseline haematocrit, glomerular filtration rate and chemotherapy schemes; the table presents mean values and standard deviations; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; IVS — interventricular septum; PW — posterior wall; LVM — left ventricular mass; LVMI — left ventricular mass index; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular systolic volume; SV — stroke volume; LVEF — left ventricular ejection fraction; LVCO — left ventricular cardiac output

Table 3. Selected left ventricular diastolic function parameters before the first anthracycline dose (initial evaluation) and six months after the last anthracycline dose (post-treatment evaluation) in the study population

Parameter	Initial evaluation		Post-treatment evaluation		P
	Mean	SD	Mean	SD	
Mitral flow:					
E wave [m/s]	0.77	0.14	0.75	0.21	0.61
A wave [m/s]	0.66	0.17	0.62	0.15	0.14
E/A	1.2	0.33	1.2	0.54	0.81
DT [ms]	172	31	181	42	0.35
IVRT [ms]	89	15	94	15	0.17
Tei index	0.49	0.09	0.54	0.1	0.04
E wave propagation time [ms]	93	29	106	24	0.047
Flow propagation — slope [mm Hg/s]	479	168	406	113	0.046
TDI–IVS:					
S wave [cm/s]	8.1	2.0	7.5	1.8	0.14
E' wave [cm/s]	9.9	2.7	9.4	2.8	0.39
A' wave [cm/s]	9.5	2.8	9.6	2.7	0.91
E/E'	8.4	3.2	8.6	2.9	0.86
TDI–LW:					
S wave [cm/s]	8.1	1.7	7.4	1.5	0.01
E' wave [cm/s]	11.6	3.1	10.5	1.5	0.049
A' wave [cm/s]	9.6	2.6	8.2	2.0	0.02
E/E'	6.99	2.0	10.5	3.3	< 0.0001

The table presents mean values and standard deviations; DT — deceleration time; IVRT — isovolumic relaxation time; TDI — tissue Doppler imaging; IVS — interventricular septum; LW — lateral wall

Table 4. Selected ultrasound vascular parameters before the first anthracycline dose (initial evaluation) and six months after the last anthracycline dose (post-treatment evaluation) in the study population

Parameter	Initial evaluation		Post-treatment evaluation		P
	Mean	SD	Mean	SD	
FMD [%]	26	15	24	11	NS
NMD [%]	39	20	40	17	NS
Carotid IMT [mm]	0.59	0.1	0.74	0.11	0.001
PWV [m/s]	16.7	11.8	14.9	8.4	NS
PP [mm Hg]	53	15	52	13	NS
TAC [mL/bpm × mm Hg]	1.3	0.4	1.4	0.5	NS
Ao C [mm/mm Hg]	0.061	0.04	0.046	0.03	NS
CCA C diameter [mm/mm Hg]	0.12	0.07	0.08	0.05	0.002
CCA C area [cm^2/mm Hg]	0.1	0.05	0.07	0.05	0.03
Ao stiffness index β	6.47	0.62	6.76	0.72	0.05
CCA stiffness index β	6.47	0.66	6.82	0.62	0.003

*After adjusting for baseline haematocrit, glomerular filtration rate and chemotherapy schemes; the table presents mean values and standard deviations; FMD — flow mediated dilatation; NMD — nitroglycerine mediated dilatation; IMT — intima-media thickness; PWV — pulse wave velocity; PP — pulse pressure; TAC — total arterial compliance; Ao — aortic; CCA — common carotid artery; C — compliance

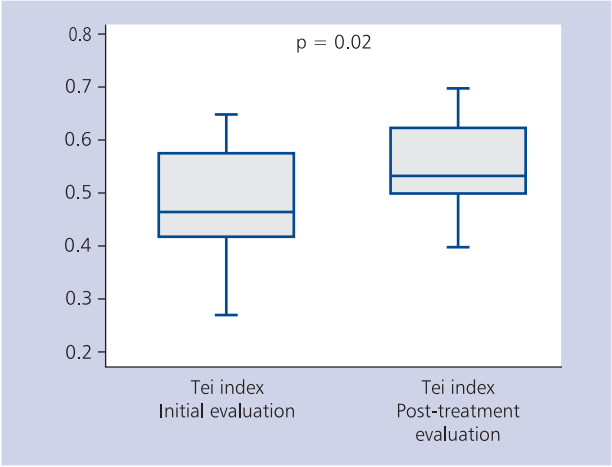

Figure 1. Tei index before the first anthracycline dose (initial) and six months after the last anthracycline dose (post-treatment) in the study population

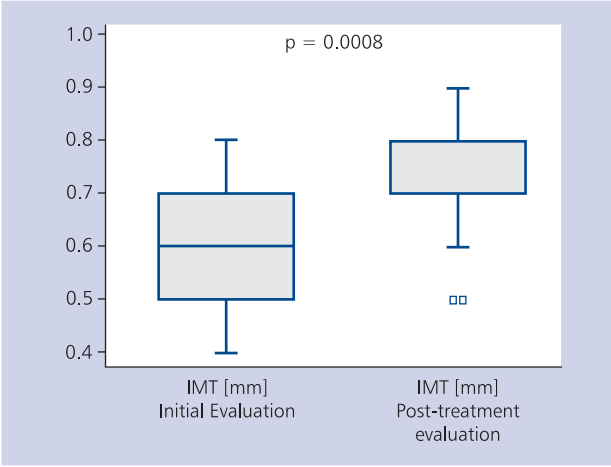

Figure 2. Intima-media thickness (IMT) before the first anthracycline dose (initial) and six months after the last anthracycline dose (post-treatment) in the study population

index during our observation. However, PWV and TAC evaluated six months after the last dose of anthracycline were comparable to the initial data (Table 4, Fig. 3).

Regression analysis

Regression analysis did not reveal any correlations between the type, cumulative dose or dose per cycle of anthracycline and the echocardiographic or ultrasound parameters.

Concomitant medication — tamoxifen

The only significant difference when comparing the subgroup with or without tamoxifen therapy (18 vs. 13 patients; 54% vs. 46%) was the degree of change in LV EDD. Patients receiving tamoxifen therapy had a significantly smaller increase of LV EDD (0.7 ± 0.9 vs. 2.8 ± 2.4 mm, p = 0.03). In multivariate regression analysis, tamoxifen use (r = –0.200) and initial haematocrit (r = –0.047) were both independent factors predicting a change in LV EDD (F = 5.79, p = 0.008).

Concomitant disease — systemic hypertension

Statistical analysis did not reveal any relationship between the diagnosis of systemic hypertension and anthracycline-induced changes in the echocardiographic or ultrasound parameters.

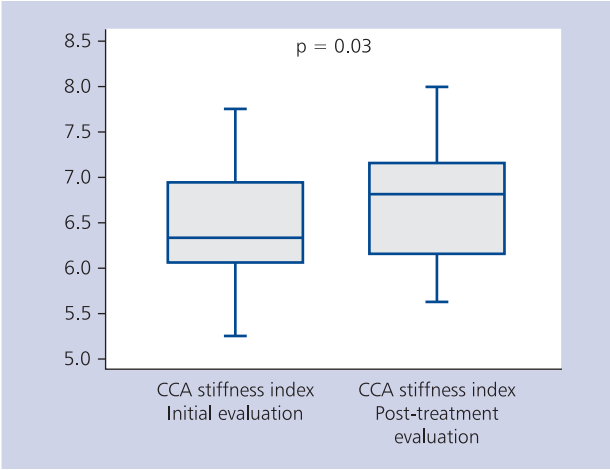

Figure 3. Common carotid artery (CCA) stiffness index before the first anthracycline dose (initial) and six months after the last anthracycline dose (post-treatment) in the study population

DISCUSSION

Cardiotoxicity occurring during or after anthracycline therapy is one of many potential complications that may limit the use of these effective antineoplastic drugs. Unfortunately, anthracyclines act on both cells that undergo rapid divisions (e.g. endothelium cells, fibroblasts) and those that are highly differentiated (e.g. cardiomiocytes) [1, 7, 8].

In our study, we assessed the influence of breast cancer anthracycline-related chemotherapy on the function and structure of the cardiovascular system. Anthracycline-based chemotherapy was not accompanied by overt heart failure symptoms or a simultaneous decrease in LVEF. A reduction in S' wave velocity in TDI was the only parameter indicating a worse LV systolic function. However, increases in LV EDD and LV EDV were observed, which resulted in an increased ejection volume and preserved LVEF. The above-mentioned changes were noticed after a relatively short (six months) observation after the treatment was completed.

LV dilatation concomitant with a decrease in LV wall thickness and progression to dilated cardiomyopathy related to anthracycline use has been observed in previous, long-term studies [9].

Simultaneously, implementation of anthracyclines significantly affected LV diastolic function. We found a reduction in the velocity of the E' and A' wave of the mitral ring movement, as well as an increase in the E/E' index, while mitral flow Doppler parameters remained unchanged when evaluating the lateral part of the mitral valve ring. However, the changes in the TDI and mitral flow Doppler parameters were not significant. The E wave propagation time and flow propagation velocity changed, as did diastolic function, which might also be related to the LV dilatation.

Our findings are consistent with previous studies [10–13]. A decrease in E wave velocity and an increase in A wave velocity, as well as changes in the TDI parameters similar to our results, are the most frequent observations. The degree of LV diastolic dysfunction as well as its prevalence increases over time from the last dose of anthracyclines [14, 15]. Our evaluation was performed six months after the anthracycline chemotherapy, which was long enough for chronic cardiotoxicity. However, a further clinical and echocardiographic follow-up of potentially delayed cardiotoxicity should be performed.

A Doppler evaluation revealed an increase in the LV Tei index while the mean LV ET was shortened. Similarly, mitral inflow deceleration time was comparable. These results are similar to the literature data and suggest a prolongation of isovolumetric systole and diastole with a simultaneous shortening of ET [10, 11, 16, 17]. It should be emphasised that during this study no tendency toward tachycardia was detected, and that the mean heart rate decreased. Optimal anti-hypertensive therapy and the LV changes described above could explain this finding.

The available evidence on the cardio- and vasculotoxicity of anthracyclines therapy is limited [7, 18–20] and no studieshave included such a broad panel of vascular indices.

The results of our study suggest accelerated arterial remodelling. Carotid IMT increased significantly, but carotid IMT values were still within the 0.6–0.9 mm range. However, the observed carotid IMT increase was higher than we had expected since the mean increase of this complex was 0.0069 mm for women and 0.0075 mm for men [21]. Structural remodelling of the vascular system has important clinical implications. Carotid IMT thickening constitutes a well-known cardiovascular risk factor that has a potential unfavourable influence on LV diastolic function.

Our observations of a decrease in Ao compliance and CCA compliance, as well as an increase in the stiffness index, could also be considered as unfavourable arterial changes. Simultaneously, no increase in arterial BP, PP or PWV was found with a decrease in TAC. The results are in accordance with the recently published data by Chaosuwannakit et al. [20]. Those authors found a significant increase in aortic stiffness that occurred within four months of exposure to anthracycline.

Endothelial-function-related vascular reactivity did not change significantly six months after anthracycline therapy — FMD and NMD were comparable to the values obtained before the chemotherapy. The relatively long time period between the harmful stimulus and further examination could have a potential influence on the results. In some experimental studies, FMD decrease was observed just after the completion of anthracycline therapy [7].

An important fact for the evaluation of vascular parameters was that the women were examined in a menopausal period or that some of the patients experienced an absence of menstruation during the whole observation period, which was caused by the type of treatment. Secondary endocrine changes might have constituted an additional mechanism of unfavourable arterial remodelling. Moreover, some patients

received an additional tamoxifen therapy (SORM — a selective oestrogen receptor modulator), which acted as an agonist and antagonist of the oestrogen receptor simultaneously, and, interestingly, tamoxifen use prevented LV dilatation.

Associations between SORM therapy and the cardiovascular system in postmenopausal females with breast cancer have been reported. However, these reports only referred to a decrease in carotid IMT and an increase in FMD. Favourable changes were found after six months [18] or after more than 12 months of the therapy [17]. In our study, tamoxifen did not modify the negative vascular changes. We suspect that the anthracyclines negated the potentially beneficial effect of tamoxifen on the vessels in our study population. However, SORM effects are dependent on the age group and vascular protection was reported among postmenopausal women. Significant differences in age between our patients (50 ± 9 years) and the study population of Simon et al. [19] (61 ± 8 years) might also have affected the results. An interesting observation is that tamoxifen use was associated with the prevention of the anthracycline-dependent increase of LV EDD. An explanation of this phenomenon could be a cardioprotective effect, as was seen in the animal study by Daosukho et al. [22]. Higher manganese superoxide dismutase (mitochondrial antioxidant enzyme) levels were observed in cardiomyocytes in mice which were pretreated with tamoxifen compared controls after the administration of adriamycin.

Limitations of the study

There are some limitations of our paper. We present the results of a prospective, observational study. The study presents a real time-course of chemotherapy for breast cancer with other than anthracycline antineoplastic drugs used in compliance with the chemotherapy protocols. The most frequent were — fluorouracil and cyclophosphamide (at comparable dosages) — FAC and FEC and EC schemes and docetaxel. One should not exclude their potential unfavourable influence on the circulatory system, while the observed changes are not typical for the complications that have been described to date [23, 24].

The next limitation of the study was the treatment of arterial hypertension. Beta-blockers and ACEI were used in our study. Both agents have potential cardioprotective effects [25], but these were not observed in our data. The small number of patients in both subsets (11 and six patients, respectively) could be the cause of the lack of measurable cardioprotective effects on the parameters evaluated.

Despite the fact that some unfavourable changes of LV diameters, volumes, diastolic function and vascular parameters did not occur in all patients, predisposing factors have not yet been settled. It should be highlighted that no relationship between the type of anthracyclines, their cumulative doses or the doses per cycle (and potential cardiovascular toxicity) were found. The limited number of patients may explain the lack of significant associations. The changes were observed during the implementation of standard anthracycline therapy, which suggests that there is no safe dose of these drugs.

CONCLUSIONS

In multivariate regression analysis, not only tamoxifen use, but also haematocrit, was an independent factor predicting a change in LV EDD. This needs further evaluation before final conclusions are made.

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AG, KMS, MM, and MH carried out the study, data analyses and drafted the manuscript. AC participated in the study design and statistical analysis. WP and ZG participated in the study design and co-ordination. All authors read and approved the final manuscript.

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Negatywny wpływ chemioterapii z zastosowaniem antracyklin na wielkość i funkcję rozkurczową lewej komory oraz przebudowę naczyń tętniczych

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Streszczenie

Wstęp: Upośledzenie funkcji skurczowej lewej komory jest znanym i dobrze udokumentowanym powikłaniem występującym w przebiegu chemioterapii raka piersi z zastosowaniem antracyklin. Brak specyficzności ich działania jest przyczyną uszkodzenia zdrowych komórek, np. fibroblastów, co może prowadzić do zaburzenia funkcji rozkurczowej i niekorzystnej przebudowy naczyń.

Cel: Celem pracy była kompleksowa ocena wpływu terapii z zastosowaniem antracyklin na parametry funkcji skurczowej i rozkurczowej serca oraz wskaźniki czynności i budowy naczyń.

Metody: Badaniem objęto grupę 35 kobiet w wieku 50 ± 9 lat, z rozpoznanym rakiem piersi kwalifikowanych do standardowej terapii zawierającej antracykliny. Epirubicynę otrzymywało (E) — FEC (E — 75 mg/m^2/cykl) 14 osób i EC (E — 90 mg/m^2/cykl) — 4 osoby, a doksorubicinę (A) — FAC (A — 50 mg/m^2/cykl) — 13 osób i TAC (A — 50 mg/m^2/cykl) — 4 osoby. Dawka kumulacyjna w przypadku epirubicyny wynosiła 150–630 mg/m^2, a doksorubiciny 100–300 mg/m^2. W schematach FEC i FAC stosowano 5-fluorouracyl i cyklofosfamid w dawkach biorównoważnych. Oceny echokardiograficznej i ultrasonograficznej naczyń dokonywano wyjściowo i 6 miesięcy po ostatniej dawce antracykliny. Obserwacja kliniczna pacjentów wynosiła 9–12 miesięcy. Funkcję skurczową i rozkurczową oceniano na podstawie frakcji wyrzutowej, rzutu minutowego serca, parametrów napływu mitralnego, czasu rozkurczu izowolumetrycznego, prędkości ruchu pierścienia mitralnego (E', A', S) mierzonej przy użyciu doplera tkankowego (TDI), wskaźnika E/E' i wskaźnika Tei. Ocieniano również następujące parametry naczyniowe świadczące o funkcji (rozkurcz naczynia zależny od przepływu dla tętnicy ramieniowej) i budowie naczyń: prędkość fali tętna, podatność aorty i tętnicy szyjnej wspólnej, wskaźnik sztywności β dla aorty i tętnicy szyjnej wspólnej, grubość kompleksu błona wewnętrzna–środkowa na ścianie tylnej tętnicy szyjnej wspólnej (IMT).

Wyniki: W trakcie obserwacji u żadnej chorej nie zaobserwowano objawów niewydolności serca. Funkcja skurczowa lewej komory pozostała prawidłowa. Stwierdzono natomiast znaczący wzrost objętości końcoworozkurczowej (101 ± 25 *vs*. 112 ± 26 ml; p = 0,01) i wymiaru końcoworozkurczowego (46 ± 3,5 *vs*. 48 ± 4 mm; p =0,004). Zaobserwowano również wydłużenie wskaźnika Tei (0,49 ± 0,09 *vs*. 0,54 ± 0,1; p = 0,04). Parametry oceniane przy zastosowaniu TDI w zakresie bocznej ściany lewej komory zmniejszyły się: E' (11,6 ± 3,1 cm/s *vs*. 10,5 ± 3,3 cm/m; p = 0,049), A' (9,6 ± 2,6 cm/s *vs*. 8,2 ± 2,0 cm/s; p = 0,02) i S (8,1 ± 1,7 cm/s *vs*. 7,4 ± 1,5 cm/s; p = 0,01), natomiast wskaźnik E/E' wzrósł (7,0 ± 2,0 *vs*. 10,5 ± 3,3; p < 0,0001). Analiza pomiarów naczyniowych wykazała istotny wzrost IMT ściany tylnej (0,59 ± 0,1 *vs*. 0,74 ± 0,11; p < 0,0001), spadek podatności aorty (p = 0,0042) i tętnicy szyjnej wspólnej (p = 0,004) oraz wzrost wskaźników sztywności β aorty i tętnicy szyjnej wspólnej (odpowiednio p = 0,046, p = 0.003).

Wnioski: Mimo dobrej tolerancji chemioterapii z zastosowaniem standardowych dawek antracyklin i zachowania funkcji skurczowej lewej komory zaobserwowano powiększenie lewej komory i pogorszenie funkcji rozkurczowej serca. Zmiany te współistnieją z cechami negatywnej przebudowy dużych naczyń tętniczych.

Słowa kluczowe: antracykliny, kardiomiopatia, grubość kompleksu błona wewnętrzna–środkowa, ryzyko sercowo-naczyniowe, sztywność aorty

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