https://doi.org/10.38109/2225-1685-2019-4-122-132



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# THE EFFECT OF COMBINED CHEMOTHERAPY IN WOMEN WITH BREAST CANCER ON THE STIFFNESS OF THE COMMON CAROTID ARTERY AND PULSE WAVE PARAMETERS STUDIED BY ECHO TRACKING

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**SUMMARY**

The aim of the study was to study the effect of combined chemotherapy in women with breast cancer (BC) on arterial stiffness and pulse wave by ultrasound examination of the common carotid artery (CCA) using echo tracking technology.

**Materials and methods.** 40 women with triple negative breast cancer aged 27 to 75 years (47.5±12.0) were examined initially and after chemotherapy with the inclusion of anthracyclines (doxorubicin), taxanes (paclitaxel) and platinum derivatives (cisplatin). Arterial stiffness parametres (β-stiffness index, Ep-elastic modulus, AC-arterial compliance, PWV-pulse wave velocity) and AI – augmentation index were studied in the distal CCA at a distance of 2 cm from bifurcation on an Aloka ProSound α7 ultrasound machine using echo tracking technology.

**Results.** After combined chemotherapy the parameters β, Ep, PWV not significantly changed (9,3±4,3 vs 8,9±4,5, p=0,63 ;128,73±65,9 vs 119,0±69,5 кПа, p=0,29 ; 6,7±1,5 vs 6,3±1,5 m/s, p=0,24 respectively). Statistically significant decrease in AI from 14, 5±11.3 to 11.1±10.6% (p=0.009) and an increase in AC from 0.72±0.25 to 0.87±0.3 $mm^2$ / kPa (p=0.004) were demonstrated as well as decrease in systolic blood pressure (SBP) from 129.5±14.0 to 118.5±14.5 mm Hg (p=0.0001) and an increase in heart rate from 67.9±10.7 to 76.6±12.1 bpm (p=0.0004), lower the level of hemoglobin from 129.6±20.4 to 102.2±16.3 g / l (p=0.00001) and red blood cells from 4.7±0.4 to 3.3±0.6 1012 / l (p=0.00001).

**Conclusion:**

In women with breast cancer in the early period after combined chemotherapy with the inclusion of anthracyclines (doxorubicin), taxanes (paclitaxel) and platinum derivatives (cisplatin), there were no increased stiffness of the common carotid artery. Pseudo-positive changes in the form of an increase in the extensibility of the vascular wall and a decrease in the augmentation index are explained by general hemodynamic changes in the form of a decrease in the SBP, an increase in heart rate, as well as anemia during chemotherapy.

**Keywords:** *arterial stiffness, pulse wave, echo tracking, chemotherapy, breast cancer*

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**For citation:** Заирова А.Р., Рогоза А.Н., Авалян А.А., Ощепкова Е.В. Влияние комбинированной химиотерапии у женщин больных раком молочной железы на жесткость общей сонной артерии и показатели пульсовой волны по данным эхо-трекинга. Евразийский кардиологический журнал. 2019, Ноябрь 25; 4: 122-127 [Trans. into Eng. ed.: Zairova A.R., Rogoza A.N., Avalyan A.A., Oshchepkova E.V. The effect of combined chemotherapy in women with breast cancer on the stiffness of the common carotid artery and pulse wave parameters studied by echo tracking. Eurasian heart journal. 2019, November 25; 4:128-132]

Cardiovascular complications following the drug and radiation therapy conducted in oncological patients have initiated the development of a multidisciplinary approach and a new specialty design at cardio-oncology medical treatment [1]. By now, various aspects of the problem has been systemized and analyzed and relevant recommendations have been worked out [1-3]. However, there are still many pending problems on the way to optimized efficiency and safety of oncological patients' treatment [4-6].

Many research papers address cardiotoxicity of the drugs used, search, and identification of early markers of cardiac involvement with heart failure development [7-9]. The current absence of any generally recognized and instrumentally detectable similar markers for vasotoxicity makes it necessary to search them therefor [10-13].

The pathophysiological background for complications following the drug therapy of oncological diseases such as CHD, which are related with myocardial ischemia cardiac rhythm disorders, stroke and peripheral artery involvement are considered such mechanisms of vasotoxicity as endothelial damage, vasospasm, pro-thrombogenic status and arterial thrombosis, as well as accelerated development of both atherosclerosis and arteriosclerosis [1-5,10-13].

The instrumental vascular remodeling research implies the need for assessing arterial stiffness and pulse wave indices [14]. Currently, some studies showing an increase of aorta and magistral arteries stiffness and also of reflected wave indices in response to chemotherapy. [12,15-19]. Some authors consider the CCA local stiffness as a biomarker for vascular involvement caused by radiation therapy [20]. However, the studies which assess the CCA local stiffness in response to chemotherapy are rather sporadic [21].

The purpose of the study is to analyze the effect of combined chemotherapy in women with breast cancer (BC) on local arterial stiffness and pulse wave through analysis of ultrasound examination result of the common carotid artery (CCA) using echo tracking technology.

## MATERIALS AND METHODS

40 women aged from 27 to 75 years (47.5±12.0 years) with histologically proven triple negative BC phenotype (negative estrogen, progesterone, HER2 receptors) were engaged in the study. The patients have received combined chemotherapy with the use of anthracyclines (doxorubicin), taxanes (paclitaxel) and platinum derivatives (cisplatin).Chemotherapy duration (8 cycles in total) depended on the disease stage (primary resectable (T1-3N0-1M0) – 22 women – 1st subgroup) and primary non-resectable BC (T4N any M0 and T3N2-3M0) – 18 women –2nd subgroup) amounted 8 (chemotherapy cycles conducted once a week) or 16 (chemotherapy cycles conducted once every two weeks) weeks respectively [22]. Thus, the cumulated dose of doxorubicin, paclitaxel and cisplatin for the entire treatment period amounted to 200, 800 and 240 mg/m$^2$ in the 1st subgroup and 320; 1,200 and 400 mg/m$^2$ in the 2nd subgroup of patients.

The arterial stiffness and pulse wave indices were studied through Aloka ProSound $\alpha$7 ultrasound apparatus using echo-tracking technology, both initially and immediately after chemotherapy, i.e. after 2-4 months. The following data were assessed and analyzed:

$\beta$ – stiffness index: $\beta$=ln (Ps / Pd) / [(Ds – Dd) / Dd]; Ep – Peterson's elastic modulus: Ep=(Ps – Pd) / [(Ds – Dd) / Dd ] (kPa), AC – compliance (flexibility): AC=(Ds – Dd) / [4 (Ps – Pd)] (mm$^2$/kPa), PWV $\beta$= (local) pulse wave velocity (m/s), AI – augmentation index: AI=$\Delta$P / PP (%), where Ps is SBP level, Pd is DBP level, Ds is arterial diameter at end systole, Dd is arterial diameter at end diastole, $\Delta$P is reflected wave-related pressure rise, PP is pulse pressure.

According to the study protocol after BP recording, 3 consecutive measurements were conducted in each of the right and left CCA distal segments, at 1.5-2 cm from bifurcation when synchronizing with an ECG. The wall portamonitoring were set at the boundary between the intima media and the anterior and posterior wall adventitia. Mean values for 10-12 cardiac cycles were calculated during each measurement. Thereafter, mean values of all the studied indices were calculated for both CCAs (Fig. 1).

The statistical analysis was carried out using Statistica software, version 10.0. The individual groups' data are expressed as M±STD (tables) and M±SE (graphs). The dynamic changes and intergroup differences were analyzed using non-parametric Wilcoxon and Mann-Whitney criteria. The differences were considered statistically significant at $p<0.05$. The correlation analysis was carried out using Spearman's rank correlation.

## RESULTS

The clinical and laboratory data of studied women with BC are shown in Table 1.

There were no differences between the above listed data of women of the studied subgroups. When analyzing the existing main risk factors for CVD, increased TC and LDL cholesterol values in 23 women (58%), overweight in 11 women (28%) and adipose in 7 women (18%), hyperglycemia in 2 women (5%) in the general group as a whole were observed.

Increased BP level in 12 (30%) persons was observed. Before chemotherapy, anti-hypertensive therapy was either corrected (10 women) or prescribed for the first time (2 women) in those suffering AH (arterial hypertension).

The studied CCA arterial stiffness and pulse wave indices are provided in Table 2.

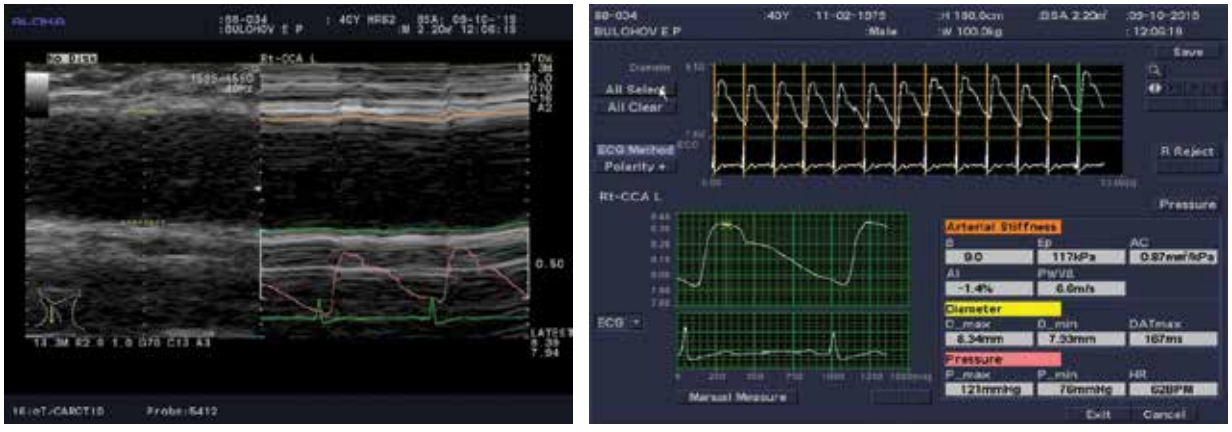


**Figure 1. CCA wall motion image and calculated local arterial stiffness and pulse wave indices on the screen, at Aloka ProSound $\alpha$7 ultrasound apparatus echo-tracking mode**

**Table 1. Clinical and laboratory data in-vivo of women with BC (initially, before treatment)**

| Data | General group n= 40 | 1st subgroup n= 22 | 2nd subgroup n= 18 | P (1-2 subgroups) |
|---|---|---|---|---|
| Age, years | 47,5±12,0 | 46,6±11,1 | 48.6±13,6 | no data |
| BWI, kg/m$^2$ | 26,2±5,2 | 26,0±5,7 | 26,6±4,7 | no data |
| SBP, mm Hg | 129,5±14,0 | 126,0±12,8 | 134,0±15,3 | no data |
| DBP, mm Hg | 79,6±7,2 | 78,2±5,8 | 81,3±8,4 | no data |
| Heart rate, beats per min | 68,0±10,7 | 65,4±7,8 | 70,1±13,0 | no data |
| TC, mmol/l | 5,5±1,1 | 5,6±1,0 | 5,4±1,2 | no data |
| TG, mmol/l | 1,2±0,6 | 1,1±0,6 | 1,3±0,7 | no data |
| HDL, mmol/l | 1,5±0,4 | 1,6±0,3 | 1,5±0,4 | no data |
| LDL, mmol/l | 3,4±1,0 | 3,5±1,0 | 3,3±0,9 | no data |
| Glucose, mmol/l | 5,4±0,5 | 5,4±0,4 | 5,3±0,6 | no data |
| Creatinine, mmol/l | 73,2±10,5 | 71,3±11,2 | 75,7±9,3 | no data |
| Hemoglobin, g/l | 129,6±20,4 | 126,3±23,6 | 133,0±15,6 | no data |
| Erythrocytes, $10^{12}$/l | 4,7±0,4 | 4,7±0,3 | 4,7±0,4 | no data |

**Table 2. CCA arterial stiffness and pulse wave indices in women suffering BC (initially, prior treatment)**

| Data | General group n= 40 | 1st subgroup n= 22 | 2nd subgroup n= 18 | P (1-2 subgroups) |
|---|---|---|---|---|
| β | 9,3±4,3 | 9,3±4,5 | 9,2±4,1 | no data |
| Ep kPa | 128,73±65,9 | 127,3±68,9 | 130,5±64,1 | no data |
| AC mm$^2$/kPa | 0,72±0,25 | 0,75±0,27 | 0,70±0,20 | no data |
| PWV m/s | 6,7±1,5 | 6,6±1,6 | 6,8±1,4 | no data |
| AI % | 14,5±11,3 | 13,6±10,3 | 16,1±12,6 | no data |

The obtained data analysis revealed that the studied indices β and Ep of age norms were increased in 14 patients (35%) in total, of which 9 patients (23%) demonstrated increase of independently of AP stiffness index β [23]. There were no statistically significant differences between the subgroups in the indices studied.

Generally known interrelations between the studied parameters and other clinical and laboratory data were confirmed [14,24] (Table 3).

It was detected that the most tight interrelation are between the local stiffness indices and age, SBP and LDL cholesterol values.

After chemotherapy cycles, during repeated examination of the women with BC it came under notice first of all that SBP levels decreased both in women with existing AH who received anti-hypertensive therapy – from 146.5±9.9 to 130.0±14.6 mm Hg (p<0.01), and in eutonic women who received no anti-hypertensive treatment – from 122.2±7.6 to 115.4±8.3 mm Hg (p=0.002) (Fig. 2).

The statistically significant SBP decrease was observed both in the general group and in the two studied subgroups at different chemotherapy modes (Fig. 3). No DBP level changes were observed in response to chemotherapy.

Similarly, both the general group and the two studied subgroups at different chemotherapy regimes generally demonstrated increased heart rates as compared to the initial values (Fig. 4).

After chemotherapy significant changes in laboratory findings were also observed. Significantly lower hemoglobin and RBC levels were observed (Fig. 5).

As for lipid exchange data, it was the other way round: both TC and LDL cholesterol with TG increased significantly (Fig. 6).

No significant differences in the laboratory findings shifts were observed between the two surveyed subgroups under different chemotherapy regimes.

The studied CCA local arterial stiffness and pulse wave parameters obtained after chemotherapy are provided in Table 4.

**Table 3. Interrelation between the CCA local stiffness and pulse wave indices and clinical and laboratory data in women suffering BC (initially, prior treatment)**

| Data | β | Ep kPa | AC mm$^2$/kPa | PWV m/s | AI % |
|---|---|---|---|---|---|
| Age | r=0,8 p<0001 | r=0,8 p<0001 | r=-0,67p<0001 | r=0,8p<0001 | r=0,45 p=003 |
| BMI | r=0,55 p=0003 | r=0,56 p=0002 | r=-0,37 p=02 | r=0,59p=0001 | r=0,4 p=01 |
| SBP (systolic blood pressure) | r=0,63 p<0001 | r=0,73 p<0001 | r=-0,8 p<0001 | r=0,7 p<0001 | r=0,46 p=002 |
| TC (total cholesterol) | r=0,46 p=004 | r=0,50 p=002 | r=-0,53p=0006 | r=0,56p=0002 | r=0,58p=0001 |
| LDL cholesterol | r=0,57 p=0003 | r=0,60 p=0001 | r=-0,61p=0001 | r=0,65p<0001 | r=0,62p=0001 |
| TG (tumor growth) | r=0,54 p=0005 | r=0,56 p=0004 | r=-0,55p=0004 | r=0,57p=0002 | no data |
| HDL | r=-0,3 p=06 | r=-0,3 p=07 | r=0,4 p=0,02 | r=-0,3 p=05 | no data |

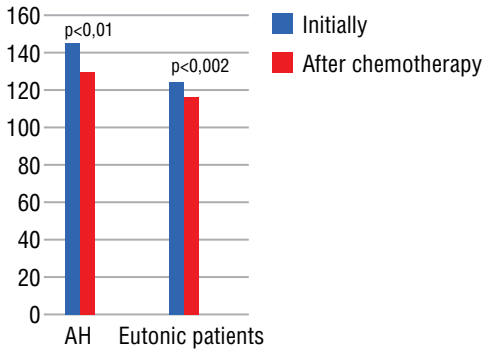


**Figure 2. SBP in mm Hg indices – prior and after chemotherapy – in AH (n = 12) and eutonic (n=28) women with BC (clinical BP measured during the CCA local arterial stiffness parameters analysis) (M±SE).**

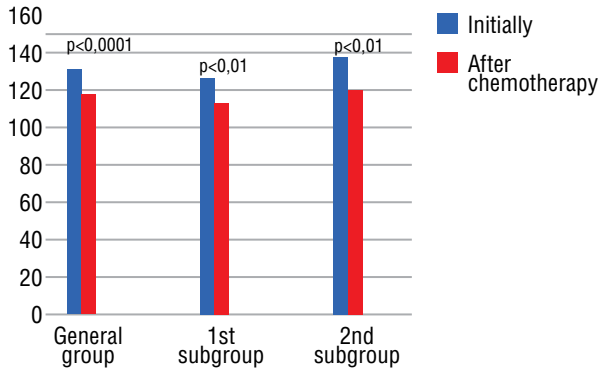


**Figure 3. SBP (mm Hg) indices dynamics in women with BC in response to chemotherapy (clinical BP measured during the CCA local arterial stiffness data analysis) (M±SE).**

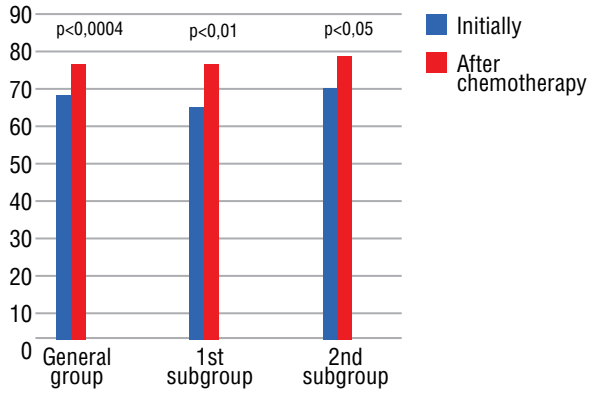


**Figure 4. Heart rate (beats per min) dynamics in women with BC in response to chemotherapy (heart rate recorded during CCA local arterial stiffness data study) (M±SE)**

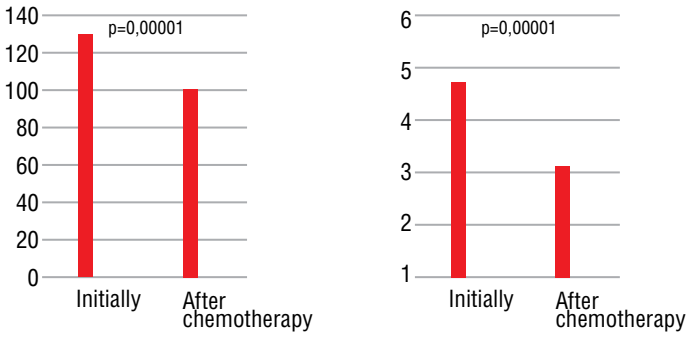


**Figure 5. Hb level (g/l) (A) and RBC (1012/l) (B) levels in women with BC – prior and after chemotherapy performed (in the general group). (M±SE)**

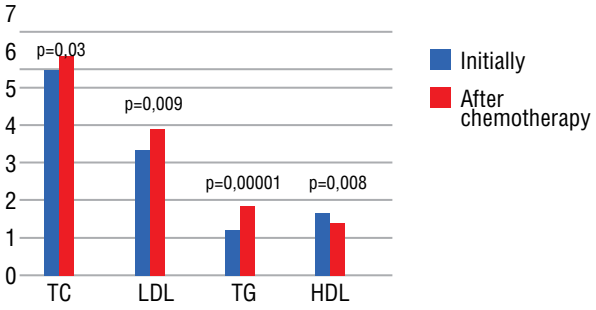


**Figure 6. Blood lipid exchange indices (mmol/l) in women with BC – prior and after chemotherapy performed (in the general group). (M±SE)**

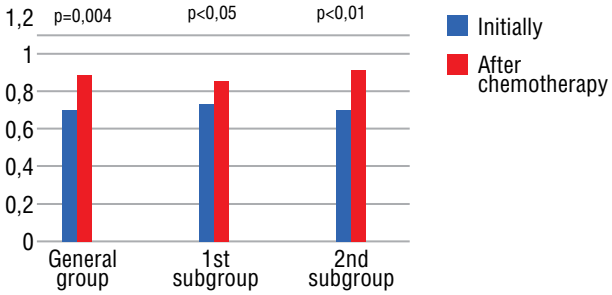


**Figure 7. CCA extensibility (AC mm²/kPa) in women with BC – prior and after chemotherapy. (M±SE)**

After chemotherapy, a tendency for lower local stiffness indices (β, Ep PWV) was observed (9,3±4,3 vs 8,9±4,5, p=0,63;128,73±65,9 vs 119,0±69,5 kPa, p=0,29; 6,7±1,5 vs 6,3±1,5 m/s, p=0,24 respectively), however, statistically significant dynamics were only demonstrated by AC (extensibility) (Fig. 7) and AI (augmentation index).

For the example of the general group, a significant increase in the CCA extensibility from 0.72 ± 0.25 to 0.87 ± 0.3 mm² / kPa (p = 0.004) can be regarded as pseudo-positive, based on the above formula for calculating the AC index, since it occurs against the background of a decrease in the level of SBP from 129.5 ± 14.0 to 118.5 ± 14.5 mm Hg (p = 0.0001).

**Table 4. CCA arterial stiffness and pulse wave indices in women with BC (after chemotherapy) (M±STD)**

| Data | General group n= 40 | 1st subgroup n= 22 | 2nd subgroup n= 18 | P (1-2 subgroups) |
|---|---|---|---|---|
| β | 8,9±4,5 | 9,5±5,0 | 8,2±3,7 | no data |
| Ep kPa | 119,0±69,5 | 125,5±76,7 | 111,0±60,9 | no data |
| AC mm²/ kPa | 0,87±0,3 | 0,86±0,4 | 0,89±0,4 | no data |
| PWV m/s | 6,3±1,5 | 6,3±1,5 | 6,3±1,5 | no data |
| AI% | 11,1±10 | 9,8±9,2 | 12,4±11,0 | no data |

After chemotherapy, the augmentation index (AI) in women with BC both in the general group (from 14.5 ± 11.3 to 11.1 ± 10.6%, p = 0.009), and in the two subgroups (from 13.6 ± 10.3 to 9.8 ± 9.2%, p<0.05 in the 1st) and (from 16.1 ± 12.6 to 12.4 ± 11.0%, p<0.01 in the 2nd) decreased significantly. Considering that inverse relationship between heart rate and AI [25] and significant heart rate increase in the women with BC in response to chemotherapy is known, an additional analysis, i.e. AI 75 (AI normalized to the heart rate = 75) was carried out. This analysis proved no significant AI 75 changes both in the general group and in the two subgroups, despite the fact that a tendency for reduction in this indicant (60% patients demonstrated lower AI 75 than initial values after chemotherapy) was observed.

The other indices studied (BWI, glucose level, creatinine) demonstrated no significant changes after chemotherapy as compared to the initial data. We have separately analyzed dynamics of the studied local stiffness and pulse wave indices in AH and eutonic patient subgroups. This analysis revealed no significant differences between the subgroups.

## DISCUSSION

Toxicity mechanisms for the drug products used for treatment of the BC women, included in this study, are known. E.g., besides direct and indirect damaging impact on cardiotoxicity in the mechanism of anthracyclines (doxorubicin) the direct damaging action on the vascular endothelium is also confirmed, which in aggregate leads to the cardiomyopathy genesis and heart failure, as well as to vascular remodeling [1-4]. The background for toxicity of platinum derivatives (cisplatin), the use of which is associated with probable arterial or venous thrombosis, is also endothelial damage, decrease of NO bio availability and increase of platelet aggregation [1-5,10,11]. As for taxanes (paclitaxel), the key mechanism for myocardial ischemia clinical manifestation is considered to be coronary spasm a background for which is endothelial and smooth muscular damage, which additionally manifests itself as vascular-mediated peripheral nephropathy and increased vascular permeability[1-5,10,11].In terms of the effect duration, two types of vascular toxicity are distinguished: long-term (cisplatin, doxorubicin) and transitory (taxanes) increase in the risk of vascular complications [5,10].

Combination of chemotherapeutic agents is also known to cause significant increase in the toxicity-related complications. E.g., taxanes are proven to reduce the elimination of doxorubicin, which leads to increase in its plasma concentration and its degradation to more toxic metabolites in the myocardium [26]. Paclitaxel in combination with anthracyclines also increases cardiotoxicity of the latter [27], etc.

Thus, the group of BC women we studied was characterized by high probability of both cardio- and vasotoxicity manifestation. The manifestations of cardiotoxicity and its markers are described and analyzed in previous studies [9,22]. In this study, our aim was to study the changes in arterial stiffness and pulse wave parameters in the early period after chemotherapy. We supposed the possibility of identifying the sings of increased arterial stiffness, as exemplified by the CCA wall (elastic-muscular artery), since some authors described such changes [21].

However, as a result of our study and analysis of its data, we may claim the absence of any signs of the CCA arterial stiffness increase after the conducted combined chemotherapy. Moreover, pseudo-positive changes, such as increased CCA wall compliance and lower augmentation index were demonstrated. No differences in the studied parameters' changes were observed between subgroups differing in their chemotherapy regimens or BP levels. The obtained results may be explained by general hemodynamic changes, i.e. lower SBP, higher heart rate, and also by anemia development in response to the received treatment [25,28,29]. The similar changes, i.e. lower SBP level and also changes in such arterial stiffness indices as brachial-ankle and carotid-femoral pulse wave velocity (baPWV and cfPWV), in women with BC in response to combined treatment with anthracyclines, taxanes and trastuzumab were previously observed by other authors [30]. Probably, in the early period after the said types of combined chemotherapy such hemodynamic manifestations of vasotoxicity as lower vascular tone dominate, and the signs of arterial remodeling leading to increased arterial stiffness can be diagnosed in longer terms after the treatment.

## CONCLUSION

No signs of increased arterial stiffness of common carotid artery were revealed in women with breast cancer in the early period after combined chemotherapy with the use of anthracyclines (doxorubicin), taxanes (paclitaxel) and platinum derivatives (cisplatin). The pseudo-positive changes, i.e. increased artery wall compliance and lower augmentation index, may be due to such general hemodynamic changes as SBP decrease, heart rate increase and also anemia after chemotherapy. To assess vasotoxicity of the conducted antitumor therapy, it would be advisable to use complex instrumental evaluation of the arteries' structural and functional condition at various levels of the vascular bed both in the early and long dates after treatment.

## REFERENCES

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Accepted for publication: 31.10.2019