ORIGINAL RESEARCH

Submitted: 20.9.2018; Accepted: 15.10.2018; Published online: 21.11.2018

The prospects for applications of cardiometric approach in evaluation of cardiotoxicity under Anthracyclines therapy in patients with breast cancer

Alla I. Shikhlyarova[1*], Lyubov Y. Vladimirova[1], Natalia M. Tikhanovskaya[1], Yulia Y. Arapova[1], Tatiana P. Protasova[1], Elena A. Sycheva[1], Lyudmila A. Ryadinskaya[1], Aza A. Lyanova[1], Irina L. Popova[1], Natalia A. Abramova[1], Kristina A. Novoselova[1], Anna E. Storozhakova[1], Maria O. Ezhova[1], Yuliana S. Shatova[1], Aleksandr E. Lisutin[1], Viktoria V. Pozdnyakova[1], Irina R. Dashkova[1], Stella M. Babieva[1]

[1] Rostov Research Institute of Oncology, Ministry of Healthcare of the Russian Federation
Russia, 344037, Rostov-on-Don, 14th Line st. 63

[*] Corresponding author:
e-mail: shikhliarova.a@mail.ru, phone: +7 (905) 431-92-67

Aims

The aim is to study the action and effects of antitumor polychemotherapy (PCT) with Anthracyclines on the cardiovascular system performance in primary oncological patients with breast cancer (BC).

Materials and methods

The study involved 21 females (49.8 ± 0.5 years) diagnosed with BC. PCT has been conducted in a neoadjuvant regimen in 18 patients and in an adjuvant one with Doxorubicin (60 mg/m2) and Cyclophosphamide (600 mg/m2) in 3 patients. The cardiovascular system functional state has been evaluated during six courses of PCT with the use of the Cardiocode device. At the same time, the conditions of the cardiovascular system have been assessed before PCT and during the fourth course using EchoCG and ECG.

Results and conclusions

Against the background of PCT with Anthracyclines noted are the cumulative changes in the blood vessel hemodynamics as reduced blood volumes ejected from the left ventricle and the atria and as alterations in the Rheogram signal. Observed is predominance of exchange of anaerobic energy over the aerobic one, characterized by a high level of the lactate concentration and accompanied by a decrease in the oxygen concentration on course 3, an increase in the phosphocreatine level on course 4 and its decrease during courses 5 and 6 of PCT. By the end of course 6 of PCT, a decline in adaptation functions and a disorder in compensatory processes in the myocardium against the background of development of uncompensated distress have been detected. Thus, the application of the cardiac cycle phase analysis method, along with the conventional methods for monitoring of the cardiovascular system performance, allows revealing disorders in its performance at early stages that is important for prevention of cardiovascular pathology, which may result from PCT.

Keywords

Cardiotoxicity, Chemotherapy, Anthracyclines, Breast cancer, Cardiometric approach, Electrocardiogram, Myocardial metabolism, Baevsky index

Imprint

Alla I. Shikhlyarova, Lyubov Y. Vladimirova, Natalia M. Tikhanovskaya, Yulia Y. Arapova, Tatiana P. Protasova, Elena A. Sycheva, Lyudmila A. Ryadinskaya, Aza A. L'yanova, Irina L. Popova, Natalia A. Abramova, Kristina A. Novoselova, Anna E. Storozhakova, Maria O. Ezhova, Yuliana S. Shatova, Aleksandr E. Lisutin, Viktoria V. Pozdnyakova, Irina R. Dashkova, Stella M. Babieva. The prospects for applications of cardiometric approach in evaluation of cardiotoxicity under Anthracyclines therapy in patients with breast cancer. Cardiometry; Issue 13; November 2018; p.15-21; DOI: 10.12710/cardiometry.2018.13.1521; Available from: http://www.cardiometry.net/issues/no13-november-2018/cardiotoxicity-under-anthracyclines-therapy

Introduction

In reference literature we can find data on adverse actions and effects of antitumor therapy methods on various organs and systems in the organism, including the cardiovascular system, but unfortunately these data and materials are not quite concrete [1-3].

Within the diversity of the antitumor therapy complications, cardiotoxicity is of the greatest concern. As opposed to the tissues with intensive proliferative capacity, the cardiac muscle consists of myocardiocytes having a limited proliferative and regenerative potential that determines development of persistent manifestations of toxicity, as a rule. [4]. According to the practical recommendations of the Russian Society of Clinical Oncologists (RUSSCO), "cardiotoxicity" is a term that includes various undesired phenomena associated with the cardiovascular system against the background of drug therapy in cancer patients [5].

Concomitant pathology should be taken into account, when selecting specific therapy, treatment schedules and regimens as well as predicting possible undesired side effects.

Issues of tolerability of special methods for breast cancer (BC) treatment attract attention of not only oncologists, but also doctors of related specialties: therapists, cardiologists, anaesthesiologists, and others. How well the organism tolerates the stress associated with the malignant disease and its treatment depends on the available functional reserves in the organism. Unfortunately, there are no reliable tests or criteria which can make possible to evaluate the true interrelation between a growing cancerous tumor and an organism: some peculiarities of the macroorganism life may considerably affect the prognosis [2,3].

It has given a rise to our studies devoted to the peculiarities of changes in the cardiovascular system state in breast cancer patients at the stage of the antitumor chemotherapy application. Anthracycline antibiotics, Alkylating agents, Taxanes,Fluoropyrimidines and Trastuzumab have the most damaging effect on the cardiovascular system. According to the EWER classification, all cytostatic drugs are divided, depending on the type of the damaging effect on the cardiovascular system, into type I (with irreversible myocardial dysfunction due to myocardiocyte death (Anthracyclines)) and type II (with reversible dysfunction of myocardiocytes due to mitochondrial and protein damage (Trastuzumab)) [6].

There are a number of factors contributing to the appearance of early chronic cardiotoxicity: age under 4 years or over 65 years, female sex, thoracic radiation therapy, combined cytotoxic therapy, left ventricular ejection fraction (LVEF) less than 55%, the presence (in anamnesis) of compensated cicatricial myocardial changes, arterial hypertension, diabetes mellitus, ischemic heart disease, obesity [7].

Prior to the antitumor therapy, the following examination procedure is recommended: collection of complaints and anamnesis, physical examination with arterial pressure (AP) measurement, echocardiography (EchoCG) for LVEF assessment, the standard 12 lead electrocardiography (ECG), biochemical blood test, study of cardiac biomarkers, especially in patients with a high risk of developing left ventricular (LV) dysfunction. Certain algorithms exist for managing patients receiving antitumor therapy associated with development of the LV dysfunction in heart failure (HF) [5].

The Cardiocode device is a Russian portable cardio-analyzer of a new generation, developed by NTO "Cardiocode", Taganrog. The Cardiocode software provides immediately a single-stage noninvasive assessment of electrophysiological, metabolic and bio-adaptation parameters of the myocardium in combination with a prognosis of the cardiovascular system functional potential. The original examination algorithm includes recording of an extended spectrum (up to 10) of phases in each cardiac cycle, calculation of stroke blood volumes in different phases of the cardiac cycle, delivery of estimated parameters of the oxygen, lactate and phosphocreatine concentration in arbitrary units and stress index of the cardiac regulation systems.

Mentioned are the following capabilities of the Cardiocode technology: express diagnostics "here-and-now", noninvasive measurement of phase-related blood volumes, an assessment of heart life expectancy (for the first time in the world), an evaluation and a prediction of the cardiovascular system functional conditioning (for the first time in the world), detection of the sudden cardiac death signs, monitoring of population. The prompt identification of cardiovascular disorders in the terms of the phase analysis determines the unique possibility to adequately assess the damaging cardiotoxic effect of antitumor therapy and effectiveness of rehabilitation measures.

In accordance with the above, the aim herein is to study the action and effects of antitumor polychemotherapy (PCT) with the use of Anthracyclines on the cardiovascular system performance in cancer primary patients suffering from breast cancer (BC).

Materials and methods

The study involved 21 females (49.8 ± 0.5 years) diagnosed with primary BC, exposed to polychemotherapy (PCT) at the Rostov Research Institute of Oncology (RRIO) in 2018. The criteria for including patients in the study are the following:

– primary patients with BC scheduled for neo/adjuvant chemotherapy;

– use of Doxorubicin;

– the presence of cardiovascular system pathologies and other concomitant diseases (under satisfactory ECG and echocardiography parameters) is not a criterion for excluding patients from this study.

An assessment of the tumor incidence rate, localization and histological analysis of the tumor in the patient population has shown the following: the tumor

Table 1. Tumor incidence rate according to the TNM classification

Stage of disease	Absolute quantity	Relative quantity
T2-4N0M0	9	42,9%
T2-4N1M0	10	47,6%
N N2M0	1	4, 75%
N N3M0	1	4, 75%

Table 2. Occurrence of molecular-biological subtypes of breast tumors in the cohort under studies

Molecular-biological subtype	Absolute quantity	Relative quantity
Luminal subtype A	11	52,4%
Luminal subtype B	6	28%
Triple negative subtype	4	19%

incidence rate according to the TNM classification in the examined patients corresponds to T2-4N0M0 in 9 patients (42.9%), T2-4N1M0 in 10 patients (47.6% %), T2N2M0 in 1 patient (4.75%) and T2N2M0 in 1 patient (4, 75%) (see Table 1 herein).

The left breast has been affected by BC in 11 patients (52.4%); the right breast cancer has been found in 9 patients (42.8%), and bilateral synchronous breast cancer has been detected in 1 patient (4.8%). According to the histological examination data, the following molecular-biological subtypes of tumors have been identified in the above patients: luminal subtype B in 11 patients (52.4%), luminal subtype A in 6 patients (28%)and triple negative subtype in 4 patients (19 %) (see Table 2 herein).

According to the level of marker Ki67, the distribution of the patients is as follows: Ki67 ≥ 20% (15 patients, 71.4%), Ki67 ≤ 20% (6 patients, 26.8%). The HER2/Neu overexpression has not been detected in patients (see Table 3 herein).

The following concomitant diseases have been revealed: arterial hypertension of degree1-2, AH0-1, with risk of 2-4, in 9 patients (42.8%); chronic heart failure of stage 1, FC 2, in 6 patients (28.6%); hyperalimentation of degree 1-3, in 1 patient (4.8%); autoimmune thyroiditis in 1 patient (4.8%); myocardial dystrophy in 3 patients (14.2%); exertional angina pectoris, FC2, in 3 patients (14.2%); heart rhythm disorders in the form of transient ventricular extrasystole in 1 patient (4.8%); type 2 diabetes mellitus at the compensation stage in 1 patient (4.8%); migraine in 1 patient (4.8%). Six patients (28.6%) have been recorded to be free of concomitant diseases.

PCT has been performed in a neoadjuvant regimen in 18 patients, and an adjuvant therapy with the use of Doxorubicin (60 mg/m2) and Cyclophosphamide (600 mg/m2) has been completed in 3 patients. As an accompanying therapy, according to the indications, the patients have been prescribed omeprazole, prednisolone, ademetionine, inosine, famotidine.

The cardiovascular system has been monitored before course 1 and before course 4 of PCT on the basis of ECG and EchoCG data. The cardiovascular system functional state has been monitored on each of the six PCT courses with the Cardiocode device: before the beginning of course 1 (the background state), a day before the beginning of course 2, before course 3, etc. An ECG and a Rheogram (a Rheo) have been synchronously recorded with the use of the normal ECG electrodes for 30 seconds in the sitting position and 30 seconds in the standing position employing the cardiometric device Cardiocode. The electrodes for ECG and Rheogram recording have been located in the area of the aorta and the heart apex, while the upper electrode has been fixed to the bone zone in the aortic area; the lower one below the xiphoid process on the soft tissues; the additional electrodes used for the Rheography aside from the signal electrodes, and the ground electrode in the lower part of the body surface

With the application of the Cardiocode software, an analysis of the measured blood phase volumes, the Baevsky tension index (TI) evaluation for R-R intervals and an assessment of the myocardial metabolic processes have been conducted.

According to the durations of the cardiac cycle phases, stroke blood volumes (SV, ml), minute volumes (MV, l/ml), volumes of blood flowing into the ventricle during the early diastole (PV1, ml) and the atrial systole (PV2, ml), blood volumes ejected by the ventricle during rapid (PV3, ml) and slow ejection (PV4, ml) have been calculated noninvasively using the hemodynamic equation by G. Poyedintsev - O. Voronova [8].

The stability of the state of the regulatory systems has been determined on the basis of the TI values, and the TI values ranged from 100 to 500 arbitrary units have been considered as the norm; the TI values exceeding 500 have been classified as overtension, and the TI indicators less than 100 have been interpreted as a weak state of the regulatory systems [8].

The cardiac metabolic processes have been assessed according to the parameters of the oxygen, lactate and phosphocreatine concentrations, calculated

Table 3. Data on cancer marker indicators in the group under studies

Level of expression	Absolute quantity	Relative quantity
Ki67≥ 20%	15	71,4%
Ki67 ≤ 20%	6	26,8%
HER2/Neu overexpression	0	0

by the method offered by S.A. Dushanin [9] that has been translated into the Cardiocode software. As to the aerobic process, the parametric values varying in the ranges 0.7 ... 0.85, 0.6 ... 0.65, 0.5 ... 0.55 have been taken as the norm; the norm for the anaerobic-glycolytic process is assumed to be within the range 3.0 ... 7.0; and we have adopted the indicative values 2.0 ... 4.0 as the normal values for the anaerobic allocate process, respectively [8].

The statistics data have been analyzed with the Statistica 10.0 software (StatSoft, USA). The comparison of the cardiovascular activity parameters at different stages of PCT has been carried out using the Student's criterion. Taking into account the Bonferroni correction, it has been assumed that the values $p<0.017$ are significantly reliable.

The study has been carried out in accordance with the ethical principles for medical research involving human subjects (the Declaration of Helsinki, Finland, 1964).

Results

The cardiovascular system state evaluation in patients before the beginning of PCT has demonstrated that the hemodynamic characteristics (see Table 4 herein) and the conditions of the regulatory systems according to the TI classes have corresponded to the norm (see Figure 1), that the myocardial energy state according to the concentrations of oxygen (0.6 arbitrary units, Figure 2) and phosphocreatine (2.5 arbitrary units, Figure 2) are within the normal limits, the level of lactate (at a norm of 2.0 - 4.0 arbitrary units) is equal to 8.2 arbitrary units (see Figure 2) and indicates an accumulation of the latter. In accordance with the EchoCG recorded before the PCT examination, 25% of the patients have initial atherosclerotic alterations in the aortic valve cusps and the aortic base, 30% of the patients have suffered from a physiological relative mitral tricuspid valve insufficiency of the first degree, and in 27% of the cases initial signs of left ventricular hypertrophy have been found.

Upon the completion of course 1 of PCT, observed has been a decrease in volumes of blood ejected by the ventricle during the rapid (PV3), up to 26.28 ml, and slow, to 18.01 ml, ejection (PV4) phases (see Table 4 herein). Pronounced is an increase in the TI values up to 329,6 arbitrary units (Figure 1) and the lactate content up to 11, 0 arbitrary units (Figure 2B) that is above the norm, the upper limit of which is 4.0 arbitrary units. The phosphocreatine concentration in this case is recorded to be 3.7 arbitrary units: it corresponds to the highest limit of the norm (Figure 2C).

On course 1 of PCT, noted has been a decrease in the volume of blood entering the ventricle during the atrial systole down to 16.8 ml (PV2), against the background of the reduced PV3 (26.4 ml) and PV4 (18.06 ml) parameters, remaining at the same level (see Table 1 herein). The TI value increases up to 484.6 arbitrary units (see Figure 1 herein). The phosphocreatine level sharply increases ($p<0.017$) and corresponds to its maximum value of 6.8 arbitrary units that exceeds the background values by 36.8% and are higher than the norm (see Figure 2C herein). The oxygen level, decreased on course 3 down to 0.5 arbitrary units, the lower limit of the norm, has reached the level of 0.7 arbitrary units on course 4 of PCT (see Figure 2A herein).

Beginning with course 4 of PCT, in 75% of the patients the Rheogram has demonstrated some signal delays in the form of a "step" (marked off by arrows in Figure 3 herein), which is a marker of hemodynamic disorders in the coronary arteries [8].

A control examination of the cardiovascular system on the PCT course 4 using EchoCG and standard ECG has shown that after the four courses of PCT, 22% of the patients have suffered from sinus tachycardia; in 77.8% of the cases found have been atherosclerotic alterations in the aortic valve cusps and the aortic base; in 55,6% of the patients detected have been initial signs of left ventricular hypertrophy; 55.6% in the patients cohort have demonstrated a reduction in myocardial recovery processes in the posterior lower portions of the left ventricle; in 22.2% revealed has been slowing of atrial myocardial conduction and signs of myocardial hypoxia.

On courses 5 and 6 of PCT, the values of PV1, PV2, PV3 and PV4 continued to decrease ($p<0.017$): on course 6 the PV1 parameter has been recorded to be 40% below the background values and is equal to 14.4 ml; PV2 is 80% less than the background parameters and has reached 17, 6 ml; PV3 is identified to be 21.8

Table 4. The main characteristics of heart hemodynamics during six courses of PCT

Parameters		SV	MV	PV1	PV2	PV3	PV4
Course of PCT	1	50,8±2,2	3,96±0,1	36,13±0,8	22,94±1,2	32,7±2,1	22,41±1,1
	2	45,6±0,8	3,56±0,2	23,87±01,2	20,4±0,8	26,28±1,8*	18,01±0,6*
	3	43,1±0,2	3,54±0,13	24,37±1,3	19,58±0,4	26,08±0,6	17,87±2,3
	4	44,9±0,5	3,24±0,1	27,62±0,3	16,8±0,5*	26,4±2,1	18,06±0,5
	5	42,6±1,1	3,56±0,24	20,75±0,6*	18,2±0,2*	25,09±1,8	17,02±0,1
	6	36,78±0,1	3,75±0,1	14,5±0,3*	17,6±0,6*	21,8±0,9	14,05±0,1*

Note: * significantly reliable variances at p<0,01.

ml, i.e. 66.7% below the respective background values, PV4 has been detected to be 14.05 ml, 62.7% less than the background parameters, respectively (see Table 4 herein). The tension index continued to increase and has reached 530.7 and 558.8 arbitrary units on course 5 and 6 of PCT, respectively (see Figure 1 herein). The lactate level has increased by more than 50% in comparison with the respective background value and is above the norm (p <0.017). On course 5 detected has been the maximum increase in lactate up to 15.9 arbitrary units (p <0.017) (see Figure 2B). The phosphocreatine level has decreased to the lowest value of the norm: 2.7 and 2.5 arbitrary units (see Figure 2C).

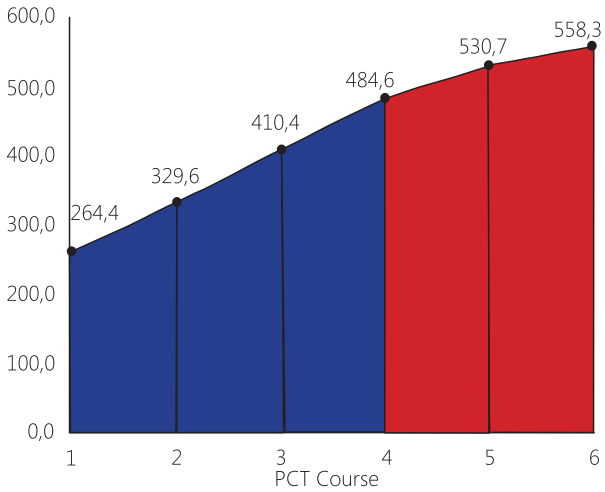

Figure 1. The Baevsky tension index during six courses of PCT

Discussions

The cardiovascular complications arising from the cardiotoxic effect of antitumor therapy are one of the main causes of mortality growth in cancer patients [10]. Despite an intensive progress of cardio-oncology, addressing studying the mechanisms of the antitumor therapy, the cardiotoxic actions and effects, we have to solve one of the key problems of cumulative PCT: it is prediction of development of possible cardiovascular disorders, their early diagnostics and effective therapy [11, 12].

In the present study, in order to improve effectiveness of an early detection of cardiovascular disorders, when conducting PCT with the use of Anthracyclines, the standard methods for monitoring cardiovascular function (EchoCG, ECG) together with the new cardiac cycle phase analysis technology, offering the "here and now" express diagnostics, have been used. As a result, against the background of PCT, revealed have been the following cumulative changes in the cardiovascular system hemodynamic parameters, indicating insufficient blood flow to the heart: we have noted that, upon course 1 of PCT, the blood volumes, ejected by the left ventricle, have been reduced, and upon course 3, the blood volumes, entering the left ventricle, have been decreased. Despite the fact that the numerical values of the volumes are within the limits of the norm, the revealed tendency can be recognized as a predictor for disorders and abnormalities in the cardiac performance. The Rheogram data also indicate the presence of the disorders in coronary vessel hemodynamics after three courses of PCT. The assessment of the myocardial energy state has shown that, against the background of PCT, the anaerobic energy exchange processes predominate, as evidenced by the high level of lactate. The observed sharp increase in the phosphocreatine concentration on course 4 and the lactate level on course 5 of PCT is a response to a decrease in the level of oxygen at the third level of PCT, i.e. we have observed a compensation of the anaerobic energy exchange at the expense of the anaerobic allocate one. In passing, it should be noted that the dynamics of changes in the level of oxygen, lactate and phosphocreatine concentrations during six courses of PCT bears witness to a decline in energy supply to the myocardium. The TI system parameter also is an indicator of the intensity in the cardiovascular system performance: until course 4

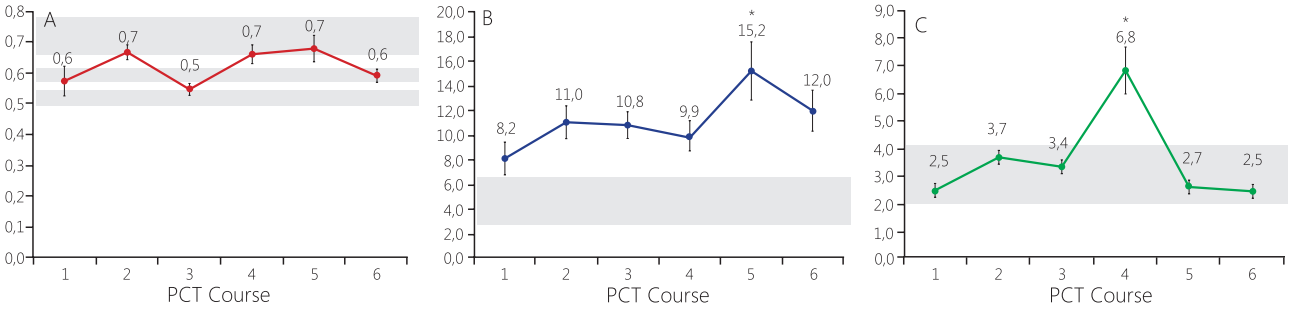

Figure 2. Assessment of metabolic processes in the myocardium during six courses of PCT: A – oxygen level , B – lactate level , C – phosphocreatine level.

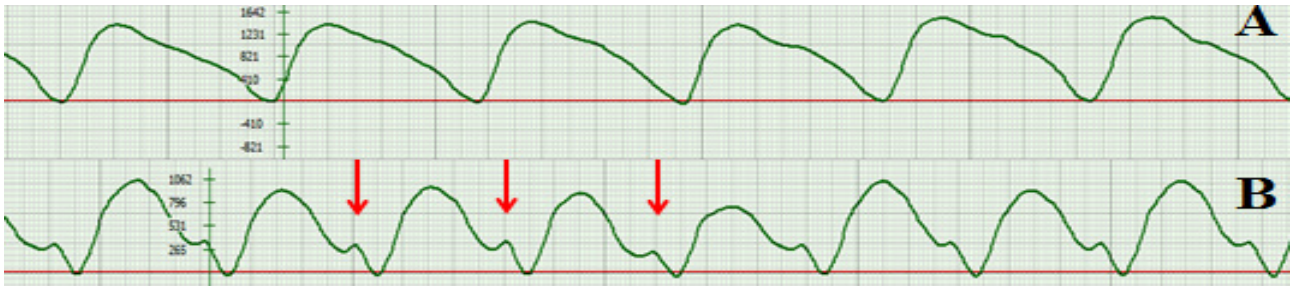

Figure 3. The Rheo curve before the beginning of PCT (A) vs. the Rheo curve on PCT course 4 (B)

the system has been found in the state of compensated distress; on course 5 and 6 of PCT the system passes into uncompensated distress that indicates a crisis in the functioning of the adaptation systems.

The EchoCG and ECG examinations performed on course 4 of PCT also have demonstrated building-up of loading on the cardiac performance: noted are the atherosclerotic alterations in the heart blood vessels, left ventricular hypertrophy and diminished recovery processes in the myocardium.

According to the obtained results, the alterations traced in the cardiovascular system performance against the background of PCT are found to be cumulative. First of all, noted is the decrease in the cardiac hemodynamics that is further reflected in the tension of the cardiovascular system performance and its transition to the anaerobic energy exchange. The greatest changes in the parameters of cardiovascular hemodynamics and the energy state have been revealed on course 4 of PCT. Taking into account the decline in the adaptation functions and the disorder in myocardial compensatory processes, it is advisable to select an effective therapy capable of reducing the risk of developing cardiovascular disorders and abnormalities at the stage of PCT.

Conclusions

1. Against the background of PCT with the use of Anthracyclines we observe the cumulative alterations in the vessel hemodynamics, reflected in a reduction of the blood volumes ejected by the left ventricle and the atria as well as Rheogram signal changes.
2. We have revealed that there is predominance of the anaerobic energy exchange at the stages of PCT, the characteristic features of which are as follows: a high level of the lactate concentration, a decrease in the oxygen concentration on course 3, an increase in the phosphocreatine concentration on course 4 and a decrease of the latter on courses 5 and 6 of PCT.
3. PCT leads to a decline in the adaption functions and compensatory processes in the myocardium; it results in the development of uncompensated distress.
4. The application of the cardiac cycle phase analysis technology, along with the conventional methods for monitoring the cardiovascular system parameters, allows revealing disorders and abnormalities in the performance of the heart and blood vessels at early stages.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

All the authors read the ICMJE criteria for authorship and approved the final manuscript.

References

1. Demidov VP, Ostrovcev LD, Volkova MA. Mammary cancer. Combined and complex treatment of patients with malignant tumors: a guide for doctors. Moscow: Medicina; 1989. [in Russian].
2. Fauchi AS, Harrison BE. Principles of Internal Medicine. Moscow: Praktika; 2002. [in Russian].
3. Wood ME, Bunn PA. Hematology/Oncology Secrets. Moscow: Binom; 2000.
4. Semenova AI. Cardio-neurotoxicity of antitumor drugs (pathogenesis, clinic, prevention, treatment). Prakticheskaya onkologiya. 2009;10:168-76. [in Russian]
5. Moiseenko VM. Practical Recommend. for Medicinal Treatm. Malignant Tumors (RUSSCO). Mos.: Rossiyskoe obshhestvo klinicheskoy onkologii; 2017. [in Russian].
6. Ewer MS, Martin FI, Henderson C, et al. Cardiac safety of liposomal antracyclines. Semin. Oncol. 2004;31:161-81.
7. Von Hoff DD, Layard MW, Basa P. Risk factors for doxorubicin-induced congestive heart failure. Ann. Intern. Med. 1979;91:710-7.
8. Rudenko MYu, Zernov VA, Voronova OK, et al. Guide for "Cardiocode" Using the Method of the Analysis of the Phase of the Heart Cycle. Taganrog: IKM; 2015.
9. Dushanin SA, Beregovoj YV, Tsvetkova OA, et al. Multifactorial Express Diagnostics System for Functional Preparedness of Athletes under Current and Operational Medical Pedagogical Control. Kiev: Kievskaya knizhnaya fabrika «ZHovten'»; 1986. [in Russian].
10. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. Nat. Rev. Cardiol. 2015;12:620. doi: 10.1038/nrcardio.2015.65.
11. Cardiovascular Toxicity Induced by Chemotherapy and Target Drugs. Practical Recommendations. M.: RUSSCO; 2013. [in Russian].
12. Kit OI, Shikhlyarova AI, Turkin IN, et al. Use of physical factors of electromagnetic nature for decreasing complications in respiratory and cardiovascular systems in patients after surgical treatment of lung cancer. Cardiometry. November 2017;11:64–70; DOI: 10.12710/cardiometry.2017.11.6470.