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Cardiometry in oncology: new digital possibilities for analyzing the cardiovascular system state in cancer patients

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Abstract

The new high-tech era begins not with supply of an innovative product to the market, but rather with an intellectual leap in the field of open issues in fundamental engineering, healthcare and education. In the present essay, an example of the successful translation of mathematical, physics- and engineering-related philosophy into the digital platform of Cardiometry is discussed. The theory of hemodynamics, the laws of axiomatics, logic and adaptation can be expressed in terms of mathematics. The original analytical software used in PC-assisted device Cardiocode allows carrying out a phase analysis of the hemodynamics within an extended range. Pilot studies conducted by us in cancer patients at the stages of multi-course chemotherapy have revealed abnormalities and disorders in hemodynamics, energy exchange and adaptation expectancy of the heart at early stages of cancer treatment that is of prognostic significance. Pronounced processes of destabilization in hemodynamics, a suppressed energy exchange and a degradation of adaptation capabilities by the end of the chemotherapy courses involves the appearance of cardiotoxic effects. Based on records covering the specific frequencies discovered in ECG & Rheogram, the R-R interval scatter plots, the metabolic parameters and the Baevsky stress index, we have demonstrated cardioprotective influence made by xenon as a possible solution of the indicated problem. Thus, the Cardiocode technology supports diagnostics by offering an original cardiometric approach, significantly broadening the notion of cardio-oncology from the perspective of the cardiotoxicity pathogenesis under the cancer development conditions and in treatment thereof.

Keywords

Cardiometry, Oncology, Hemodynamics, Cardiometric approach, Cardiotoxicity pathogenesis, Prediction, ECG, Rheogram, Metabolic parameters, The Baevsky stress index, Cardiac cycle phase analysis

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In the reference literature on cardiology and oncology, many common reference marks for pathogenesis of these most common and dangerous human diseases can be found. Indeed, the multilevel mechanisms of the control and regulation of the homeostasis in biological systems, from a genome to an organism as a whole, are designed and work according to the same unique principle of the cause-effect determination. The integrity of the process design makes it possible to clearly identify the key stones marking pathogenetic alterations in the cardiovascular system against the background of the development of cancer or, on the other hand, detect abnormalities and disorders in rhythm genesis, metabolism and adaptive heart capabilities induced by tumor growth and toxogenic effect of drugs and radiation therapy. There is a similarity in the potential risk factors for both diseases: an acute or chronic inflammation, metabolic disorders and hypodynamia, which may accompany a human individual from adolescence to adulthood [1-7].

An important thesis should be emphasized that at the present stage of high speed development of strategies and technologies in cancer treatment it is crucial to preserve and use the fundamentals and discoveries of the laws governing the control and regulation in living systems in the most expedient manner. But, unfortunately, sometimes we can see that some large-scale theoretical concepts and promising conceptual ideas cannot find their applications in practice. This is a barrier to further development and transformation of medicine into a science supported by a fundamentally new methodology.

As noted by A.I. Semenova from the N.N. Petrov Oncology Research Institute, St. Petersburg, Russia, the current knowledge on pathogenesis and risk factors for cardiotoxicity has allowed developing and implementing a number of effective techniques aimed at its prevention and early detection: radionuclide ventriculography, echocardiography, serial myocardial biopsy, an identification and an analysis of plasma markers in cardiac dysfunction [8].

We should mention that the leading technology for the functional cardiovascular system diagnostics remains electrocardiography (ECG). Modern in-hospital and portable cardio-analyzers are indispensable at any medical institution, because they make possible to immediately obtain informative parameters of heart failure and select the most adequate cardiotropic therapy for any nosology, including cases if oncological diseases.

Nowadays, it should be stated that issues associated with developing a supplementary cardiometric analysis, based on a fresh mathematical approach, have become the biggest challenge.

So, the cardiometric analysis deserves our attention. The existing cardiographic devices should be furnished with a new option to use a supplementary digital technology based on cardiometry, the feasibility of which stems from the needs of outer space exploration, as it has been mentioned more than once by Sergey Korolev, the Architect of the Soviet Space Program. In this context, it has been expected that the new mathematical approach thereto is capable of identifying and analyzing fluctuations, variability and changes in the performance of the cardiovascular system under functional loads both on the Earth and in space, including pathological processes, in particular, oncopathology.

Let us consider an example of the successful implementation of the multidisciplinary approach using the theory of hemodynamics, the laws of axiomatics and logics for an expanded cardiac cycle phase analysis. Probably, it would be beneficial to demonstrate new capabilities of cardiometry in oncology, show the prospects and the reliability of the metabolic marker assessment of the efficiency of the cardiovascular system performance under development and treatment of malignant tumors, as well as the capability to predict a heart life expectancy in cancer patients.

Adhering to the above philosophy, a joint pilot research project has been conducted by the Rostov Research Institute of Oncology, the Russian Ministry of Healthcare, and Russian New University (ROSNOU, Moscow, Russia).

Before we proceed further let us discuss: what are the basic components of a new digital cardiometric platform?

Firstly, the translation of the complex mathematical model of hemodynamics by G.M. Poyedintsev - O.K. Voronova into practice has become possible because of the discovery and the proper mathematical description of the law of blood flow in large vessels, when blood moves along the vessels in the regime of elevated fluidity. This regime is called the "third flow regime" in contrast to the laminar and turbulent flows, and it is characterized by minor friction losses due to the unique ring pattern made by alternating layers of blood elements and plasma [9].

Secondly, M.Yu. Rudenko and V.A. Zernov have experimentally established and mathematically substantiated the previously unknown law of generation of a stable interference of arterial pressure waves in blood vessels within the areas of the local rise in the waves' impedance. At the same time, under an occlusive blood flow, at an effective impedance of the vessel, the phenomenon of the stable interference is naturally manifested only for one portion of the reflected wave, the magnitude of which is directly proportional to the increase in the impedance of the vessel, and the other portion of the wave travels unchanged [10].

Thirdly, the mathematical model of hemodynamics with the digitized law of arterial pressure wave interference, established considering the characteristics of the energy and adaptation potential of the cardiac muscle and the blood vessels, has been embodied in a brilliant design idea of simultaneous recording of the hemodynamics phase structure and the cardiac performance data. The above mentioned phase structure covers an extended range of the phases of each cardiac cycle (up to 10), the blood stroke volume in different phases of the cycle, the calculated parameters of some metabolites (oxygen, lactate, phosphocreatine) according to the technique by S.A. Dushanin; it also allows identifying the wave ranges of the cardiac rhythm genesis for an identifi-

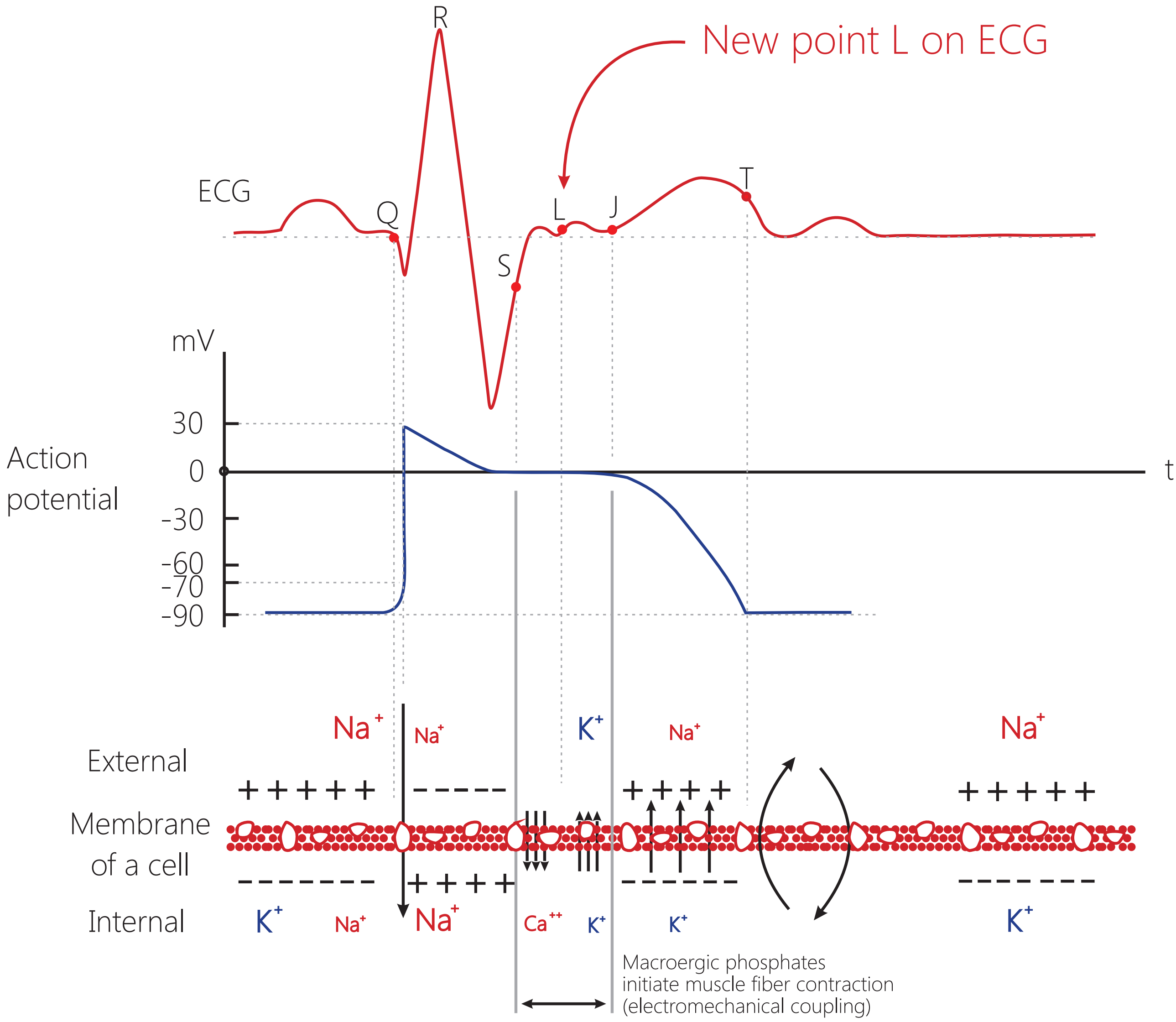


Figure 1. Improved scheme of the mechanism of electromechanical coupling of the activation of ion channels, the energy supply processes and the cardiac performance actuation

cation of the adaptation reactions by the Garkavi system method [11] and determining the Baevsky index [12].

Thus, on the basis of the laws of mathematics, physics, chemistry and the theory of living systems adaptation, the original complex analytical software for Cardiocode, a PC-assisted device of a new generation, has been developed. This device is designed to deliver noninvasively hemodynamic data and assess the hemodynamic performance of the heart and the coronary vessels upon recording synchronously a single lead ECG and RHEO in the aortic area for 30 seconds in sitting position and 30 seconds in standing position followed by further processing. The small sizes of the device makes it possible to immediately obtain most informative parameters of hemodynamics and provide an express diagnostics under the most unfavorable conditions, with ensuring at the same time the reliability of the calculated phase analysis multi-parametric criteria. A high level of the novelty of the offered Cardiocode technology implies also realization of the capabilities for evaluating the phase-related biochemical processes, which are responsible for the quality of the heart muscle contractility, taking into account the electrochemical ion processes of generation of the Action Potential (AP) and the electromechanical coupling between the contraction and hemodynamic processes (see Figure 1 herein).

From point S to j, the cardiac performance is governed by electromechanical coupling (EMC). The S-L phase of tension pictures the aortic valve opening. The action potential (AP) is equal to zero, the calcium ions begin entering the muscle fiber cells, and due to EMC the contraction takes place under anaerobic conditions with lactate production. At time L, the aortic valve starts its opening and opens fully at point j. Segment L-j is a rapid ejection phase. EMC continues its work. The AP value is equal to zero, the K ions start leaving the cells for the intercellular space. This is an aerobic process, when phosphocreatine undertakes a significant role. At point j the first part of the slow ejection phase starts and ends at the beginning of the Tн wave generation. The AP returns to its initial value, the tension decreases, and the available blood amount reduces the pressure on the muscle fibers of the heart ventricles. Due to a difference in the pressures, blood enters the aorta, expands the latter and increases the pressure on the baroreceptors, which generate AP, so than the T wave, indicating the aorta expansion, on an ECG curve is generated.

The aim herein is to determine the clinical value of the offered supplementary cardiometric analysis as a new noninvasive technology used for identification of the cardiotoxicity signs at early and late stages of chemotherapy and assess the predictive capabilities of the Cardiocode device and technology.

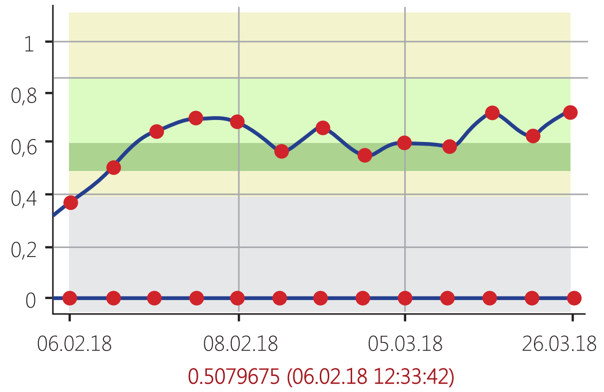
Materials and methods

Twenty-one female patients with breast cancer T2-4N1M0 (90.5%) on PCT with the use of Doxorubicin at a dose of 60 mg/m2 per 1 course (6 courses in total) have been enrolled into our studies. 126 recoding cases within the framework of ECG and Rheo monitoring have been treated employing the Cardiocode phase analysis technology. In parallel, conventional standard clinical laboratory methods, involving the generally accepted medical equipment for examination (BC, CBC, IBS, US, EchoCG), have been applied according to standard schedules. At the same time, psychological testing of anxiety level, emotional background and energy balance (Lüscher-Test) have been carried out. The types of the integral adaptation reactions by the organism according to the concept by L. Kh. Garkavi have been identified, and the Baevsky index has been computed in the patients of the above mentioned cohort.

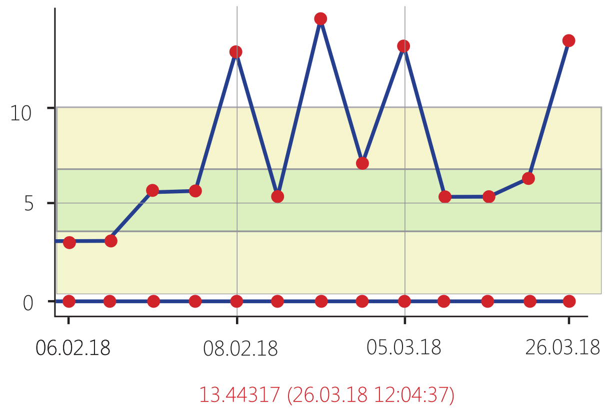
Results

The results of our studies on the cardiotoxic actions and effects, detected upon completion of 3 courses of PCT in breast cancer treatment, have shown first and foremost abnormalities and disorders in the fundamental metabolic processes affecting the energy resources of the heart (see Figure 2 herein).

As follows from the calculated data, already after the first course of PCT observed is a compensatory rise in the oxygen concentration, with the maintenance of this elevated level under its weak fluctuating dynamics. The lactate quantity increases, especially upon completion of the second course of PCT that finally indicates an increase in loading on the heart (see Figure 3 herein).



A) Aerobic processes



B) Anaerobic glycolytic processes

Figure 2. Dynamics of oxygen saturation (A) and lactate production (B) at the initial stages of PCT in patients with breast cancer

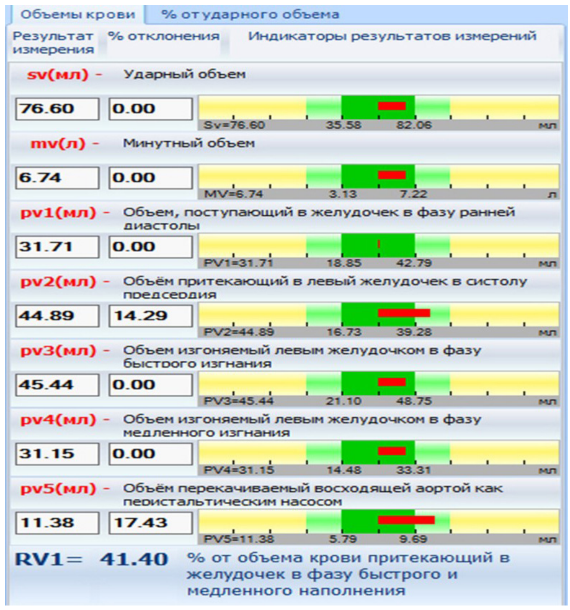


Figure 3. Hemodynamic parameters upon completion of 3 courses of PCT (screenshot)

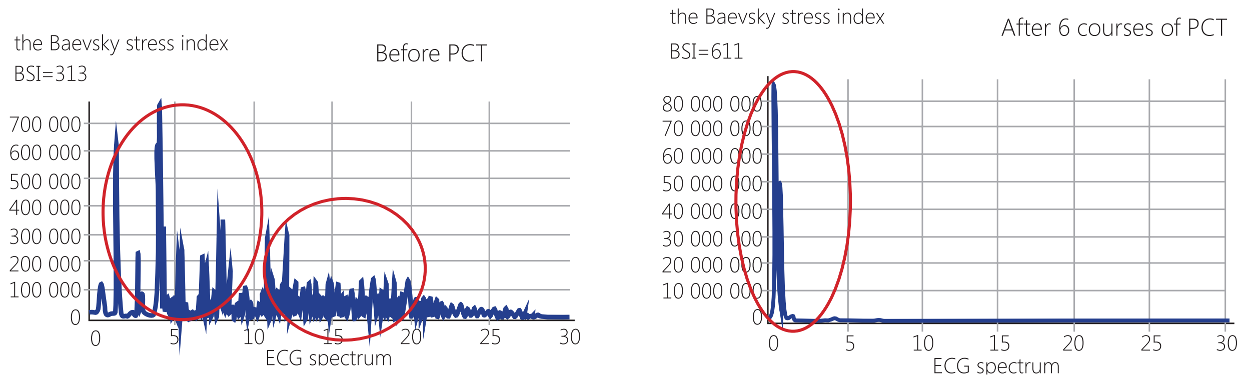


Figure 4. Evaluation of the cardiac rhythms frequency characteristics with the use of spectral analysis

Then, as scheduled, the phases of the ejection of blood to the aorta are recorded (L-j signifies the rapid ejection, and j-T refers to the slow ejection). The given data indicate that after the first course of PCT, suppression of the blood ejection to the aorta is found as the primary stress inducing effect. We have detected an increase in the load in the atrial systole (+ 14.29%) and building-up of the aorta pump function (+ 17.43%). After 3 courses of PCT, the partially compensated ejection function is diminished, that indicates an accumulated fatigue in the heart muscle fibers. These findings can also be supported by the rheographic curves, which are displayed on the monitor screen below the ECG curve.

The Rheo curves recorded in parallel with the ECG curves demonstrate that after course 4 of the administered PCT, a delay in the ejection manifests itself in the form of a "clear-cut step" on the curves that is a pronounced sign of hemodynamic abnormalities and disorders in the coronary arteries.

When evaluating the degree of tension in the systems responsible for the control and regulation of the cardiac activity during PCT, the distress syndrome is evidently manifested as one of the deepest integrative forms of the abnormalities in the physiological adaptation system. Pathogenetic mechanisms of distress development at a certain stage induce an increase in compensatory capabilities of CNS as well as the cardiovascular, endocrine, thymic-lymphatic and other systems in the organism. The phase of compensated distress is retained till course 3 of PCT, but the further growth of tension and energy expenditures contributes to a phase transition to a state of uncompensated distress and a crisis in the adaptation systems, as evidenced by real data obtained in the patients completing course 5 and 6 of the anticancer drug medication.

Another important analytical aspect of assessing cardiotoxicity in cancer patients is the spectral analysis of the frequency characteristics of the cardiac rhythms in the patients (see Figure 4, left plot, herein). This is one of the most valuable informative approaches, which allows a better understanding of the priorities given by the autonomous nervous system control and regulation, when either the sympathetic or the parasympathetic subsystem is activated. The spectrogram segments indicating the initial state before PCT marked by the ovals (see Figure 4 left picture herein) are exemplary patterns of a well-balanced rhythm genesis, showing slow (respiratory) and rapid oscillations of different spectral densities. In contrast to this, upon completion of 6 PCT courses, found are a low-frequency spectrum only (see Figure 4, right plot, herein).

A significant predominance of slow waves in the cardiac rhythm on course 6 of PCT is a clear marker of the stress tension in the regulation systems, and a sharp decrease in the spectral density of the cardiac rhythm rapid oscillations, even in a calm state, indicates an unfavorable prognosis.

Such prognostic findings may be useful for the physician-chemotherapist and the cardiologist, when choosing the proper tactics in the restorative cardiotropic therapy. Often, not the monotherapeutic factor, but rather complex multisystem regulation medication can be chosen.

Another exemplary case to demonstrate the effectiveness of application of cardiometry is an assessment of restorative xenon therapy in cancer patients. It is well known that the development of postcastration syndrome at the stage of ovariectomy in patients of reproductive age with hormone-positive breast cancer is accompanied by a severe dysfunction of their regulatory systems, overtension and depletion of the metabolic and contractile processes in the myocardium. In 20 patients with hormone-dependent breast cancer, the cardioprotective effect of xenon has been

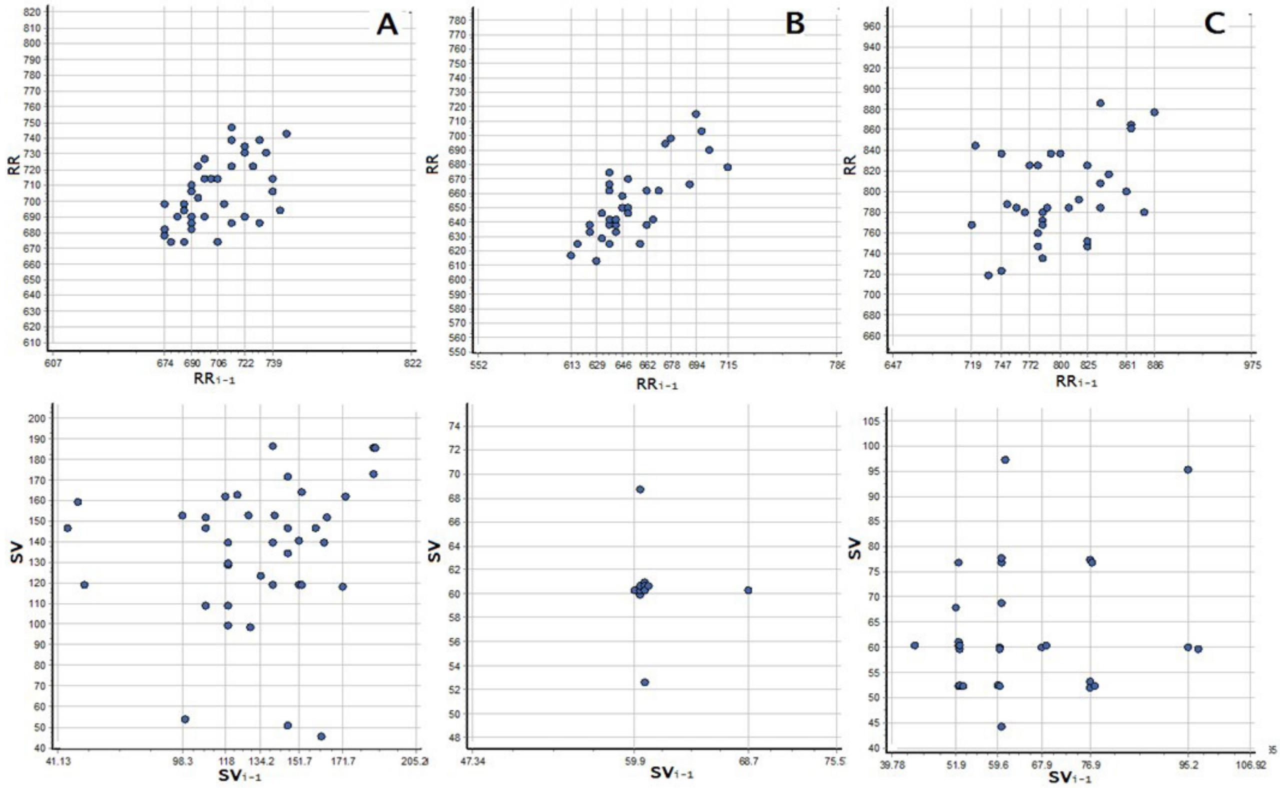


Figure 5. Assessment of the state stability in the form of the scatter plots of RR-intervals

studied in their complex therapy at the stage of surgical castration. The used clinical laboratory studies, examination techniques and equipment have been used the same in the xenon effect investigations as it is the case with the above mentioned cohort of the breast cancer patients.

The cardioprotective effectiveness of xenon is confirmed by the data upon phase analysis of hemodynamic parameter produced by processing of the respective ECG and Rheo curves. The obtained data bear witness to the cardiovascular stability and the absence of the regulatory system tension, when using xenon exposures. An assessment of the state stability in the form of the scatter plots of RR-intervals and stroke blood volumes with calculation of the stress index provided by the "Cardiocode" software is presented in Figure 5 herein.

Calculation of the concentrations of oxygen, lactate and phosphocreatine in the myocardium in patients with hormone-positive breast cancer after panhysterectomy and the use of the xenon-oxygen mixture in the early postcastration period have demonstrated that the oxygen level has been normalized, and the aerobic and anaerobic oxidation of substrates of mitochondrial energy, expressed as the ratio of phosphocreatine concentration and lactate concentration, has been balanced.

Conclusions

Thus, the applications of the Cardiocode technology for an analytical quantitative examination of the cardiovascular system performance should be viewed as an optional extra, which may be effectively added to the conventional electrocardiographic and ultrasound examinations to predict cardiotoxic effects in cancer treatment. The supplementary aspects of hemodynamic disorders, assessment of energy and adaptation resources, especially at the early stages of chemotherapy and in other types of cancer treatment, are identified and discussed in our studies. Taking into account the latest requirements for the use of digital technologies and devices in medicine (eHealth, e-technology), the cardiometric technology is based on the applications of mathematical analysis to dynamic biological systems. The principles and mathematical patterns inherent in this e-technology, as they first appear, may touch off a skeptical reaction in the scientific community, since an innovative technology does not deal with conventionally used substrates for the study of metabolism. However, the challenging issue on applications of the digital approach to be immersed in a new data world cannot be overestimated, where each accurately calculated, statistically valid, value is a key to understanding the top secrets of the control and regulation of the cardiovascular system performance in cancer patients, including the most severe cases of anti-cancer drug medication conditions.

From the above line of reasoning, we may conclude the following:

1. The complex study of development of the cardiotoxic effect processes at the stages of multi-course breast cancer polychemotherapy on the basis of the phase and spectral analysis of hemodynamics, the metabolic and adaptation status of the cardiovascular system performance, carried out by the Cardiocode software as an optional extra, effectively added to the conventional electrocardiographic and ultrasound examinations, represents a supplementary actual, prognostically significant, aspect of the cardiac diagnostics, testing and examination.

2. New resources of the cardiometric analysis may offer possibilities of conducting screening in cancer-treated patients to determine effectiveness of correcting measures to eliminate or even fully avoid cardiotoxic effects of aggressive methods of malignant tumor treatment, with the use of cardiotropic means both of the specific and nonspecific nature.

3. The study of correlative relations between analog models of experimental oncology, including biochemical, electrophysiological and other aspects of the mechanism of development and prevention of cardiotoxicity within the framework of the study of tumor-bearing animals, when conducting chemotherapy in combination with cardioprotective factors and measures, contributes to strengthening of the fundamentals of the cardiometry phase analysis in terms of hemodynamics, energy and adaptation in a living organism.

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.

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