Xenon effect on electrophysiological markers in oncology patients with postcastration syndrome during early postoperative period: pilot studies

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Abstract
Breast cancer (BC) takes a leading position among all malignant neoplasms in women. One of the critical aspects of the radical treatment of BC is the development of post-castration syndrome (PCS) in patients of reproductive age, who as a rule reach physiological, social and professional maturity, competence and status in the period up to 45 years of age. Traditionally used hormone replacement therapy, despite its high efficiency, has a number of contraindications and side effects. Therefore, it is urgent to develop and implement in clinical practice the effective methods of rehabilitation of patients with PCS. One of the main areas of research is the study of the prospects for the use of therapeutic xenon-oxygen mixtures in restorative medicine, as it has a pronounced anti-stress, hormone-modulating, antidepressant and sedative effect. Accordingly, the aim of the present paper is to study the effect of xenon on cardiovascular system markers, brain bioelectric activity and psycho-emotional state in oncology patients with hormone-positive breast cancer in the stage of surgical castration. 8 female oncology patients have been examined: the main group consists of women who received inhalations with a xenon-oxygen mixture on the fifth day after the surgery, and the reference group are the patients with the main course of treatment only. The electrocardiogram and electroencephalogram recording and the 8-color Lüscher test have been performed before, after surgery (ovariectomy) and after the completion of therapy. It has been established that the use of xenon-oxygen mixture in the main group of patients allows reducing the manifestation of somatic and psycho-emotional changes peculiar to PCS. After the course completion no stress of regulatory systems has been observed in patients, a tendency to normalization of myocardial metabolism, positive changes in bioelectrical activity and an improvement in the psychoemotional state have been revealed.

Keywords
Postcastration syndrome, Xenon, EEG, ECG, Psycho-emotional state

Imprint

Introduction
Breast cancer (BC) takes a leading position among all malignant neoplasms in women [1]. One of the critical aspects of the radical treatment of BC is the reproductive age of patients, who as a rule reach the physiological, social and professional maturity, competence and status in the period up to 45 years of age. The carried out hormone-reducing operations necessarily deprive young patients of their priorities for quality of life, health, development and self-realization.

Total ovariectomy is performed at the stage of surgical castration in case of hormone-dependent breast cancer after radical mastectomy. Already during the first hours and days after the moment of castration, significant violations of the hypothalamic, endocrine, neurovegetative, hemodynamic regulatory systems are revealed, as well as deep neuropsychic disorders [2, 3]. The consequences of postcastration syndrome (PCS) development in patients of reproductive age after performing radical surgery are unpredictable and complex for correction [3]. Nowadays drugs for hormone replacement therapy are used for PCS therapy. Despite their high effectiveness, they have a number of contraindications and side effects, which allows using them only as a short-term therapy [4].

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Therefore, it is urgent to develop and implement in clinical practice the effective methods of rehabilitation of patients with PCS. One of the main areas of research is the study of the prospects for the use of therapeutic xenon-oxygen mixtures in restorative medicine [5, 6]. The therapeutic effect of xenon is determined by high sensitivity of cardiovascular [6-8] and nervous system [6] to it. Xenon improves the processes of metabolism and the cerebral tissues oxygenation [9]. Xenon has a pronounced anti-stress, hormone-modulating, anti-depressant and sedative effect and is promising in the treatment of PCS [5].

Accordingly, the aim of the present paper is to study the effect of xenon on cardiovascular system and brain bioelectric activity indices and psychological state in oncology patients with hormone-positive breast cancer during the stage of surgical castration.

Materials and methods

8 female patients of reproductive age (under 45 years of age, mean age 36.4 ± 0.5) with the diagnosis of hormone-positive breast cancer, being at the stage of surgical castration (ovariectomy) after mastectomy and chemotherapy have been examined. The patients received comprehensive treatment at the FGBU RRIO over the 2016 to 2017 period. All examination protocols have been prepared in accordance with the Helsinki Declaration (1964) ethical standards and approved by the university committee on ethics.

Five procedures of xenon-oxygen inhalations every other day in the morning have been prescribed to the main group of patients on the fourth day after the surgical intervention (ovariectomy) [5]. The supply of xenon-oxygen mixture has been carried out through the face mask creating a hermetic closed circuit. A comfortable for the patient percentage of xenon in the gas mixture, usually 18–20 vol. %, has been established. The gas flow rate under conditions of hermeticity of the circuit is on average 1.8–2 liters. Duration of the inhalation is 12–17 minutes (saturation time, 5 minutes before the appearance of gas action signs, then breathing in a closed circuit, with additional portion oxygenation, for leveling the possible signs of hypocapnia, namely nausea, vomiting, redness of the skin, etc.). After inhalation the patients stayed in a state of superficial sleep, which resulted in the increase in duration of the recovery period, a comfortable state without external factors. During the procedure the parameters of hemodynamics and gas exchange have been monitored interactively. The reference group of patients received only the main therapy.

Prior to the surgical intervention (1st stage of the study), on the third day after the operation (stage 2) and after the therapy completion (stage 3), the electrocardiogram (ECG), the electroencephalogram (EEG) of calm wakefulness and the 8-color test by M. Lüscher [10] have been recorded.

ECG has been recorded using a single lead placed on a bone in the aortic area during 30 seconds in the lying position with the help of Cardiocode device (Taganrog, Russia). Heart hemodynamic parameters, the tension index of the regulatory systems by Baevsky, metabolism of myocardium (oxygen, lactate and phosphocreatine quantity) have been calculated using the Cardiocode software. Heart hemodynamic indicators have been evaluated using the data on blood phase volumes calculated noninvasively by means of substitution of cardiac cycle phase durations into the G. Poyedintsev – O. Voronova equation of hemodynamics [11]:

- SV – stroke volume of blood, ml;
- PV1 – blood volume entering the ventricle during early diastole, ml;
- PV2 – blood volume entering the ventricle during atrial systole, ml;
- PV3 – blood volume ejected from the ventricle during rapid ejection, ml;
- PV4 – blood volume ejected from the ventricle during slow ejection, ml;
- PV5 – blood volume pumped by the ascending aorta during systole, ml.

According to the variation pulsometer results the regulatory systems tension index (TI) by Baevsky has been calculated: 100–500 conventional units is a norm, more than 500 c.u. is overtension, less than 100c.u. is a weak state of the regulatory systems [11]. The stability of state has been evaluated by the RR-intervals and blood stroke volumes (SV) scatterograms. The changes in myocardium metabolism has been evaluated by the oxygen, lactate and phosphocreatine quantity, calculated indirectly with the help of Cardiocode software. A parameter value within the range of 0.7…0.85, 0.6…0.65, 0.5…0.55 has been considered as a norm for aerobic process; 3.0…7.0 for anaerobic-glycolitic process and 2.0…4.0 for anaerobic-allocatic one [11].

The EEG has been recorded in 19 monopolar leads (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2), placed according to the 10-20 sys-
tem, using the electroencephalograph-recorder “Encephalan-EEGR-19/26” (Medikom MTD, Taganrog). Calculated has been the spectral capacity of EEG in a state of calm wakefulness with closed eyes in frequency range 0.5–18.0 Hz using the Fourier transformation (FFT). Artifacts have been excluded from the analysis. The data have been processed with the use of software package Statistica10. A statistical analysis of changes in the sum of EEG spectral capacity during different treatment stages has been carried out with the help of the Kolmogorov-Smirnov nonparametric test (p < 0.05).

The following parameters have been evaluated by the Lüscher 8-color test [10]: the level of anxiety, the prevailing emotional background and the state of the organism energetic balance. The level of anxiety has been interpreted depending on location of four main colors of the test according to the method [10]. The stable emotional background of an individual has been determined using the rate of the total deviation from the autogenous norm calculated according to A.I. Yuriev’s formula [10]. The organism energetic balance has been characterized by the vegetative coefficient for the Lüscher test proposed by K. Shiposh, and the vegetative balance coefficient [10]. The coefficient values differ from 0.2 to 5 points and are interpreted in the following way: chronic overstrain, compensated state of fatigue, optimal efficiency and superexcitation.

The study results have been processed with the use of Statistica10 software package.

**Results**

The basic heart hemodynamic parameters calculation in patients of the main and reference group has allowed detecting absence of their disorders at different stages of the study. Each parameter value is presented in Table 1.

The calculation of the regulatory systems TI and the analysis of the RR intervals and stroke blood volumes scatterograms in the reference group patients before ovariectomy and after the therapy completion has showed the absence of regulatory systems tension (TI = 472 (SD = 23.2) conventional units and TI = 397 (SD = 46.2) conventional units, respectively). But this state has been unstable (Fig. 1А and 1С). After the ovariectomy (Fig. 1В) in this group patients a mean-stable state of the regulatory system tension (TI = 919 (SD = 33.8) conventional units) has been detected.

Evaluation of the parameters of myocardial metabolism in patients of the reference group has demonstrated low oxygen values (0.37 (SD = 0.02) conventional units and 0.14 (SD = 0.02) conventional units, respectively), high lactate indices (0.8 (SD = 0.04) conventional units and 1.4 (SD = 0.04) conventional units, respectively) with a normal content of phosphocreatine (3.3 (SD = 1.2) conventional units and 2.6 (SD = 0.6) conventional units, respectively) at the first and second stages of the study. At the third stage of the study after the therapy completion with a reduced quantity of oxygen (0.11 (SD = 0.04) conventional units), the quantity of phosphocreatine has decreased below normal (0.48 (SD = 0.03) conventional units), the quantity of lactate has normalized (4.2 (SD = 0.4) conventional units).

In the main group patients at the first (Fig. 2А) and second (Fig. 2Б) stages of the study noted has been the unstable state of the regulatory systems tension (TI = 677 (SD = 35.2) conventional units and 533 (SD = 21.4) conventional units, respectively). At the third stage (Fig. 2С) no regulatory system tension

<table>
<thead>
<tr>
<th>Hemodynamic parameters</th>
<th>Reference group</th>
<th>Main group</th>
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<tbody>
<tr>
<td></td>
<td>Before operation</td>
<td>After operation</td>
</tr>
<tr>
<td>SV</td>
<td>59.2 (0.8)</td>
<td>57.2 (7.2)</td>
</tr>
<tr>
<td>PV1</td>
<td>38.8 (2.5)</td>
<td>32.7 (3.4)</td>
</tr>
<tr>
<td>PV2</td>
<td>20.5 (2.6)</td>
<td>24.6 (10.4)</td>
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<tr>
<td>PV3</td>
<td>35.2 (0.5)</td>
<td>33.9 (4.3)</td>
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<tr>
<td>PV4</td>
<td>24.1 (0.4)</td>
<td>23.4 (2.9)</td>
</tr>
<tr>
<td>PV5</td>
<td>8.8 (0.7)</td>
<td>8.48 (0.8)</td>
</tr>
</tbody>
</table>

Note: In the table the parameters’ mean values and their standard deviation are presented.
evaluation and this state has been moderate-stable.

Evaluation of the myocardium energetic state in the main group patients at the first and second stage of the study, before and after the ovariectomy, has demonstrated a low content of oxygen (0.25 (0.02) conventional units, 0.5 (SD = 0.02) and 0.42 (SD = 0.07 conventional units), respectively) and phosphocreatine (0.36 (SD = 0.01) conventional units and 0.4 (SD = 0.01) conventional units, respectively) with increased content of lactate (22.6 (SD = 2.5) conventional units and 18.3 (SD = 1.6) conventional units, respectively). At the third stage of the study after the therapy completion increased content of oxygen in myocardium has been revealed (0.51 (SD = 0.02) conventional units), when approaching the rates of lactate (8.5 (SD = 1.4) conventional units) and phosphocreatine (0.96 (SD = 0.3) conventional units) to the norm.

At all the experiment stages the patients in the reference group of EEG in the state of calm wakefulness with closed eyes have been characterized by irregular disorganized alpha-activity in a form of wave groups and low index (30–40 %), not modulated by the amplitude keeping the zone differences. Against the background of the polymorphic activity the separate groups of slow activity, low amplitude and low index (up to 25 %) are presented. Before the surgery and after the therapy completion beta-activity in the form of mean and high index (40–51 %) wave groups has also been noted. Figure 3 shows the localization of foci of the most pronounced activity of the EEG: at the first stage (3B) the focus of the alpha activity has been localized in the right parietal area, the beta activity focus has been localized in the right temporal area, the delta activity focus – in the left frontal-anteroposterior area. At the second stage (Figure 3C) the focus of the alpha activity shifted to the left temporal area, the delta activity focus shifted to the right frontal-anteroposterior area. At the third stage (Figure 3D) the focus of alpha activity has been localized in the central-parietal area, the beta activity focus has been localized in the right temporal area, and the delta activity focus – in the left temporal area.

The evaluation of the spectral capacity change (the Kolmogorov-Smirnov test, p < 0.05) as compared with the first stage has demonstrated reduction in the spectral capacity in the delta-rhythm range and retardation of alpha-rhythm at the second stage of the study. Decrease in the alpha-activity capacity is noted at the third stage of the study (Fig. 3A).
In the main group patients at the first stage of the study, irregular, insufficiently organized alpha-activity in the form of high amplitude and index rhythm (70–77%) with smoothed area differences has dominated on the EEG before the ovariectomy, the localization focus is in the right parietal area (Fig. 4B). Also pronounced is the beta-activity in the form of high index (39–43%), mean amplitude and low frequency rhythm, not localized. Demonstrated is slow activity of the mean index (up to 30) with amplitude up to 38 µV in the form of separate waves, localized in the left temporal area (Fig. 4B).

At the second stage of the study, after the ovariectomy, irregular, insufficiently organized alpha-activity in the form of a high amplitude rhythm, mean index (up to 64%), localized in the right occipital area, has been observed on the EEG (Fig. 4C). Delta-activity in the form of rhythm of 1.0 Hz frequency, mean amplitude, with the localization focus in the right anteriofrontal area has dominated. As compared with the first stage detected is decrease in capacity of alpha-activity (the Kolmogorov-Smirnov test, p < 0.05, Fig. 4A).

At the third stage of the study, after the therapy completion an irregular, insufficiently organized alpha activity in the form of a high amplitude rhythm, a high index (69–73%), dominated on the EEG, with smoothed zonal differences, the focus of localization being in the left parietal area (Fig. 4D). The delta-activity of mean index (up to 40%) in the form of separate waves, localized in the right anteriofrontal area (Fig. 2D) is also evident. As compared with the second stage identified is rise in the delta- and alpha-activity capacity. The delta-activity capacity is also higher compared with the first stage. Noted is decrease in the capacity of the low frequency alpha-activity and increase in the high frequency one (the Kolmogorov-Smirnov test, p < 0.05, Fig. 2A).

As a result of the Lüscher 8-color test the general features which describe psychological state of the reference and main group patients on each stage of the study have been separated. In the reference group patients at the first stage of the study the psychoemotional state has been characterized by the presence of anxiety, psychological adaptation and optimal working efficiency. Beginning with the second stage of the study, in some patients at the second and third stages of the study an actively-dependent position focused on the opinion of significant individuals, without manifestations of anxiety and stress, was pronounced. In another part of the patients at the second stage of the study a state of anxiety expressed in dissatisfaction...
with the situation, vulnerability, and compensated by sthenic type of reaction, active position, pronounced emotivity, has been detected. On the third stage the stress state manifestations, caused by the feeling of frustration and overtension of efforts aimed at obstacles overcoming are typical for the above mentioned patients. The stress state is compensated by means of a passively defensive position. Negative emotions, bad mood, unpleasant feelings and fatigue prevail.

In the main group patients at the first stage of the study moderately anxious state expressed in frustration, uncertainty, dependence, suspiciousness and fears for health, has been marked. In major cases the given state has been compensated by a passively-meditative position, control of the state and concern for health. Psychological adaptiveness, stable emotional state and optimal working efficiency have also been marked. At the second stage no manifestations of anxiety and stress have been detected in the patients. A need for bright feelings, self-confidence, positive emotions, optimism and optimal working efficiency have been marked. The vegetative coefficient index indicates the compensated state of fatigue. After the therapy completion, improvement in general condition and mood, reduction of pain in the area of the postoperative wound, normalization of night sleep, increase in attention concentration and activity, optimism and positive attitude toward continuing the treatment have been noted.

Discussion

On the basis of the obtained data we established that the post-castration syndrome in oncology patients during the early postoperative period in most cases is characterized by the presence of anxiety with prevalence of negative emotions, disorder in adaptation process, sleeping and general state, state of overstrain, that corresponds to literature data on cognitive function aggravation in patients with breast cancer after surgical treatment [12, 13]. Disorder in the neurohumoral background in the patients caused moderate change of bioelectric activity in brain mainly of a regulatory type due to regulating systems dysfunction [14], tension in the regulatory systems and disorders in the myocardium energetic state, indicating the system overtension and exhaustion.

In patients exposed to the course of xenon oxygen mixture inhalation additionally to the main therapy, also detected is absence of tension in the regulatory systems and a tendency to normalization of the myocardium metabolism. Thus, confirmed is the data on cardioprotective effect of xenon which consists in maintaining the cardiovascular stability [15]. At the
same time absence of the xenon effect on general hemodynamic parameters has been observed [16]. Detected are the changes in EEG consisting in increase in capacity of alpha-activity in high frequencies. This fact proves the data on the activating effect of xenon [17]. Absence of the beta-rhythm, the rhythm of tension is characteristic of the above mentioned EEG changes as well. At the same time in the reference group patients the EEG is characterized by slowdown in the alpha-rhythm and presence of beta-activity. Detected is improvement of psychological state. Thus, the positive effect of xenon in oncology patients in early postoperative period involved neurohumoral stabilization and functional state optimization of the patients’ state [15, 18]. The ability to prevent disorders associated with the post-castration syndrome will allow the patients to maintain their functional and social status, which is a prerequisite for a full life [19].

Conclusions
1. Application of xenon-oxygen inhalation in the early postoperative period in oncology patients with PCS has demonstrated decrease in the regulatory system tension (according to the TI data) and normalization of myocardium metabolism indicators with the absence of its effect on general hemodynamic parameters.
2. Against the background of taking the xenon-oxygen inhalations revealed have been the shifts in the amplitude-frequency markers of the EEG towards its activation and improvement in general psycho-emotional state of the patients.

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

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