

# Postictal disorders of heart rate regulation and functional capabilities of heart in status epilepticus

M.L. Mamalyga<sup>1</sup>, L.M. Mamalyga<sup>2</sup>, V.V. Sychev<sup>3</sup>

<sup>1</sup>Bakulev Scientific Center of Cardiovascular Surgery, Moscow, Russia

<sup>2</sup>Department of Anatomy and Human and Animal Physiology of Institute Biology Chemistry of Moscow State University of Education, Moscow, Russia

<sup>3</sup>Ryazan State Medical University named after academician I.P. Pavlov, Ryazan, Russia

## ABSTRACT

**The objective** of the study was to investigate the mechanisms of the autonomic regulation of heart and its functional capacity at different periods after the status epilepticus, and to assess the risk of life-threatening arrhythmias.

**Methods.** The work was carried out on male Wistar rats, weighing 280–320 g. The following methods were used to study: telemetry monitoring ECG and EEG, echocardiography, functional tests.

**Results.** Analysis of changes in autonomic regulation of heart after SE revealed the inadequacy of compensatory mechanisms that fail to prevent cardiac dysfunctions that reduce the functional capacity of heart and increase the risk of fatal ventricular arrhythmias, which are predictors of sudden cardiac death.

**Conclusions.** High degree of seizure activity of brain in SE predetermines secondary postictal complications in the form of prolonged disorders of autonomic regulation of heart, which increases its vulnerability, limits restorative capacity and can become a pathogenetic basis for severe cerebrocardial disorders.

**Keywords:** status epilepticus, ECG, functional capabilities of heart, heart rate variability, arrhythmias

## INTRODUCTION

Status epilepticus (SE) is one of the most severe life-threatening neurological disorders, since the epileptic seizures that occur are so frequent and prolonged that each subsequent one occurs before the patient has time to completely emerge from the previous seizure. Disorders that occur after SE are not limited to changes in the brain, causing severe vegeto-visceral dysfunctions, provoking, among others, an intricate complex of cardiovascular dysfunctions (1-4). The situation is aggravated by the fact that increased muscular activity during the status epilepticus greatly increases the load on the heart, the functional capabilities of which largely depend on the state of the regulation systems (2,3), so their disorder can lead to decompensation and the prenosologic status.

According to clinical studies and WHO data, the risk of sudden cardiac death in people suffering from epilepsy is 2 to 3 times higher than that of the general population (5). Given that the reorganization of the neuronal networks of the central nervous system continues for a long time after the status epilepticus (6,7), then in this period, one should expect characteristic changes in the autonomic regulation of heart and its functional capabilities. Although the causal relationship between the brain and the heart has become a long-known fact (2,3,8,9), however, the mechanisms provoking disruptions of the autonomic regulation of heart and its functional capacity at different times after SE, as well as their role in the occurrence of the risk of life-threatening arrhythmias, remain poorly investigated. Since SE is a disorder requiring emergency

Corresponding author:

M.L. Mamalyga MD, PhD

E-mail: mamalyga83@mail.ru

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therapy, stopping of seizure activity without taking into account the specifics of autonomic regulation of heart and its functional capacity in the ictal and postictal periods can be one of the serious causes of aggravation of cerebrocardial dysfunction (10-13).

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## EXPERIMENTAL SECTION

### Materials and methods

Studies were carried out in the autumn-winter period on white Wistar male rats weighing 300-320 g. The animals were placed in the vivarium in amount 5 rats per a cage, under natural lighting conditions (day/night), with free access to water and food. All studies were conducted in strict accordance with the basic bioethical “Rules of work with the use of experimental animals” and ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines (14).

*Modeling of status epilepticus.* Epileptic status in animals was caused by intraperitoneal administration of an increasing subconvulsive dose of pentylenetetrazole (PTZ, corazole, “Sigma” USA). The required duration of SE was achieved by first administering the drug at a dose of 40 mg/kg, then 10 minutes later – 20 mg/kg, and then 10 mg/kg and this dose was administered every 10 minutes before the onset of SE (15,16). This procedure allowed us to maintain status epilepticus for 2 hours. It was characterized by long recurring episodes of tonic-clonic seizures, interrupted by short phases of postictal depression, loss of postural control, without return to normal posture and consciousness. After this seizure activity was stopped with paraldehyde (0.6 ml/kg 10% solution, intraperitoneally), which is usually used for immediate intervention in the treatment of epilepsy. Animals of the control group received equivalent volumes of natural saline. Pentylenetetrazole and paraldehyde have no direct effect on the cardiovascular system (17). The effect of pentylenetetrazole is associated with a decrease in the activity of the GABA<sub>A</sub> receptor complex, which causes an increase in the excitation of neurons (15,18). All studies were performed after

implantation of control and experimental animals with transmitters for telemetric online registration of video ECG-EEG. Animals were investigated 5 and 10 days post SE. Every experimental and control group included no less than 12 animals. Among the experimental rats, 11.7% of cases of lethality were observed.

*Telemetry monitoring of ECG and EEG.* Recording of the video ECG-EEG was performed in free-moving animals online using the wireless telemetry system ML880B106 by ADInstruments (Australia), which allows to conduct multi-day monitoring without the slightest concern and stress of animals. The signal was transmitted by the transmitter (TR40BB) implanted into the abdominal cavity of the rat. The telemetric transmitter was implanted in each experimental and control animal two weeks before the study. For ECG recording, one of the electrodes of the first pair of the transmitter was fixed to the xiphoid process, the other was fixed to the sternohyoid muscle, which corresponds to the III standard lead. To monitor the total electrical activity of the neocortex (EEG), one of the electrodes of the second pair was implanted epidurally over the sensory motor region of the cortex, and the second (reference) was placed above the cerebellum. Only those spike-wave complexes, whose duration was at least 3 s, were taken into account. The operation was performed under general anesthesia with a mixture of zoletil, romethal (intraperitoneally at a dose of 20 and 10 mg/kg, respectively), observing the rules of asepsis and antiseptics. After the operation, each animal was kept in a separate cage. During the first 7 days, gentamicin and ketonal were administered to the animals.

Registration, recording and analysis of ECG and EEG parameters were performed using the LabChart 7 software for rats. The following was performed to test heart rate variability (HRV):

1) Time analysis: heart rate (HR), standard deviation (SDNN);

2) Spectral analysis: total spectrum power (TP), spectrum power of high frequency (HF), low frequency (LF) and very low frequency (VLF) components with a frequency range of 0.75-3 Hz, 0.02-0.75 Hz, <0.02 Hz, respectively, as well as the sympathetic-vagal index (LF/HF). The accuracy of measuring the R-R intervals was 1 ms, the sampling frequency was 1,024 Hz. In addition, the du-

ration of left ventricular repolarization (QTc) was analyzed by ECG.

**Functional test.** 5 days and 10 days after SE in animals, the functional capabilities of the myocardium were determined using a common stress EchoCG test with dobutamine (19). It was administered in a state of mild sedation intravenously by drop infusion with the help of an infusomat (Braun Perfusor Compact, Germany) according to the protocol of administration 10→20→30→40→50→60→70 µg/kg/min. The duration of administration of each dose of dobutamine was 5 minutes. During the entire period of drug administration (prior to recording of myocardial ischemia on the ECG), an online ECG was recorded and the heart rate variability was assessed.

**Statistical analysis** of the results of the study was carried out using the STATISTICA 10 software package. There were used the conventional methods of parametric and nonparametric statistics. In the case of independent samples, the mean values were compared according to Student's t-test, Mann-Whitney U-test, Wald-Wolfowitz runs test, and in the case of dependent ones - according to the Wilcoxon test. In addition, an analysis of the differences between the experimental and control groups was carried out using a single-factor analysis of variance, followed by an evaluation of differences between groups using the Newman-Keyles and Dunn criteria. The verification of the belonging of the samples to the normal distribution was carried out using the Kolmogorov-Smirnov test. The results of the study are presented in the form  $M \pm SEM$  (mean  $\pm$  standard error of mean). Results with a confidence level of at least 95% were considered statistically significant.

## RESULTS AND DISCUSSION

According to clinical data, 90% of deaths due to cardiac dysfunction occurring in the background of SE occur not during seizures or even the first 24 hours, but during more than 30 days after SE (10-12). This suggests that the functional heart disorders that occur in the status epilepticus can be chronically aggravated in the postictal period and increase the risk of life-threatening arrhythmias – one of the main causes of sudden cardiac death. At present, there is no consensus on the fundamental mechanisms of these disorders.

Heart rate variability is a unified method that allows not only to evaluate autonomic regulation of heart and its functional state, to reveal the reserves of regulation systems, but also to trace the dynamics of pathogenesis in certain conditions of the organism (20). According to the generally accepted opinion (2,20,21), the autonomic status of the organism is largely determined by the contribution of each of the three functional parameters (HF, LF, VLF) to the formation of common HRV taking into account the absolute power of the spectra.

Analysis of the results shows that SE leads to a disruption of autonomic regulation of heart, which persists for a long time after the status epilepticus. Thus, 5 days after SE, a statistically significant decrease in the total spectrum power and SDNN by 35% and 33% occurs (Table 1). At the same time, spectral analysis of HRV revealed multidirectional changes in high- and low-frequency components of HF and LF waves. Since the spectral power of the low frequency component is considered the criterion for evaluating the sympathetic effects on the heart rate, a statistically significant increase in LFms<sup>2</sup>, LF% (by 35%, and 106%, respectively) 5 days after SE reflects an increase in sympathetic tone. In this case, the fraction of the very low frequency component (VLF%) in the total power of the spectrum decreases in comparison with the control by 80% ( $P < 0.001$ ), which indicates a predominant violation in the neurohumoral link of autonomic regulation.

**TABLE 1.** Changes of heart rhythm variability in different periods post epileptic status

| Heart rhythm variability | Control          | After 5 days         | After 10 days       |
|--------------------------|------------------|----------------------|---------------------|
| HR                       | 262 $\pm$ 17.04  | 336 $\pm$ 26.71 *    | 297 $\pm$ 23.7      |
| RMSSD                    | 7.71 $\pm$ 0.37  | 4.01 $\pm$ 0.37 ***  | 6.97 $\pm$ 0.57     |
| SDNN                     | 15.37 $\pm$ 0.67 | 10.34 $\pm$ 0.74 *** | 8.8 $\pm$ 0.71 ***  |
| TP, mc2                  | 87.1 $\pm$ 6.44  | 57.1 $\pm$ 4.74 **   | 60.1 $\pm$ 5.47 **  |
| HF, mc2                  | 10.48 $\pm$ 0.74 | 6.52 $\pm$ 0.62 **   | 11.05 $\pm$ 0.93    |
| LF, mc2                  | 33.12 $\pm$ 3.42 | 44.71 $\pm$ 3.61 **  | 47.1 $\pm$ 3.23 **  |
| VLF, mc2                 | 43.5 $\pm$ 3.19  | 5.87 $\pm$ 0.51 ***  | 3.89 $\pm$ 0.35 *** |
| HF, %                    | 12.03 $\pm$ 0.91 | 11.42 $\pm$ 1.04     | 18.39 $\pm$ 1.41 ** |
| LF, %                    | 38.03 $\pm$ 2.46 | 78.30 $\pm$ 5.87 *** | 78.3 $\pm$ 6.14 *** |
| VLF, %                   | 49.9 $\pm$ 3.77  | 10.28 $\pm$ 0.87 *** | 6.47 $\pm$ 0.58 *** |
| LF/HF                    | 3.16 $\pm$ 0.23  | 6.86 $\pm$ 0.59 ***  | 4.27 $\pm$ 0.33 **  |
| IC                       | 7.31 $\pm$ 0.62  | 7.75 $\pm$ 0.65      | 4.44 $\pm$ 0.33 **  |
| SI                       | 7.5 $\pm$ 0.62   | 10.37 $\pm$ 0.76 **  | 11.74 $\pm$ 0.99 ** |

Note (here and in Table 2). \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$

Simultaneous decrease of HF ms<sup>2</sup> waves and RMSSD by 38% and 48% respectively reflects a decrease in the activity of the parasympathetic link of autonomic regulation contributing to a shift in the balance of autonomic regulation of heart toward the predominance of sympathetic influences. This is confirmed by more than 2-fold increase (in comparison with the control) of sympathetic-vagal index (LF/HF). All this is accompanied by an increase of 38% (P<0.01) of the stress index (SI).

**TABLE 2.** ECG parameters in different periods post status epilepticus

| Parameter                                | Control       | 5 days post SE   | 10 days post SE |
|--|---------------|------------------|-----------------|
| Interval R-R, ms                         | 229 ± 18.7    | 178 ± 16.7       | 202 ± 15.8      |
| Interval P-R, ms                         | 50.7 ± 4.46   | 48.1 ± 4.58      | 53.4 ± 3.38     |
| P, ms                                    | 23.8 ± 1.7    | 19.5 ± 1.6       | 22.4 ± 1.47     |
| Interval QRS, ms                         | 22.1 ± 1.65   | 24.3 ± 1.56      | 25.2 ± 2.17     |
| Interval QT, ms                          | 64.8 ± 3.62   | 66.2 ± 5.09      | 82.1 ± 5.73 *   |
| Interval QTc, ms                         | 124 ± 9.95    | 156 ± 10.40 *    | 182 ± 13.17 **  |
| The number of intervals QTc > 220 ms (%) | 0.74 ± 0.08   | 11.37 ± 0.92 *** | 2.77 ± 0.33 *** |
| Interval Tpeak – Tend, ms                | 15.8 ± 1.01   | 20.2 ± 1.45 *    | 24.2 ± 1.93 **  |
| The amplitude of the segment ST, mB      | -0.08 ± 0.009 | -0.05 ± 0.005    | -0.07 ± 0.007   |

In addition, the imbalance in the autonomic regulation of heart that occurs 5 days after SE is accompanied by a statistically significant increase in the QTc and TpeakTend intervals (Table 2), which are the predictors of life-threatening heart rate disturbances. An analysis of the ST segment depression allowed us to exclude transient ischemic injuries. There were no violations of depolarization in the atria and ventricles, as well as atrioventricular conduction, as evidenced by the normal duration of intervals PR, QRS and P-wave.

Attention is drawn to the results of spectral analysis of HRV 10 days after SE, which revealed statistically significant differences in the spectral power level of the high frequency (HR) component of HRV, as well as the level of change in the sympathovagal index (LF/HF) from similar indices that occurred 5 day after SE. So, after 10 days the power of the spectrum of the high-frequency component (HFms<sup>2</sup>) and RMSSD increases to the control level, which reflects an increase in activity of the parasympathetic link of autonomic regulation. Despite the fact that 10 days after the status epilepticus, the LF/HF sympathovagal index is 35% higher

than the control, its value is 38% (P <0.01) lower than the one observed 5 days after SE, and the number of QTc intervals over 220 ms is 4.1 times smaller. The increase in the fraction of the high-frequency component of HRV in autonomic regulation of heart 10 days after SE reflects the increase in vagal activity, which, apparently, indicates a compensatory reaction.

This is consistent with clinical and experimental studies that have found the protective effect of vagal activity. Thus, vagotonia increases coronary perfusion, improves autonomic regulation of heart rate and weakens heart failure in seizure conditions (22,23), while a decrease in vagal activity in epilepsy correlates with an increased risk of sudden cardiac death (21,24).

However, an increase in SI detected 10 days after the SE indicates that the compensatory processes are achieved at the cost of a significant tension of the regulatory mechanisms. The decrease in TP and SDNN, as well as the increase in QTc and TpeakTend indicate that the compensatory mechanisms can not only increase the level of regulatory system activity and autonomic regulation of blood circulation, but also prevent the occurrence of fatal ventricular arrhythmias that are the predictors of sudden cardiac death (25,26). This is confirmed by the results of monitoring the number of QTc intervals over 220 ms at 5 days and 10 days after SE, which revealed their multiple increase (15.4 and 3.7 times, respectively). According to the opinion of R.M. Bayevsky (20), a decrease in the level of activity of regulatory systems (TP, SDNN), reflects the low adaptive capacity of the cardiovascular system.

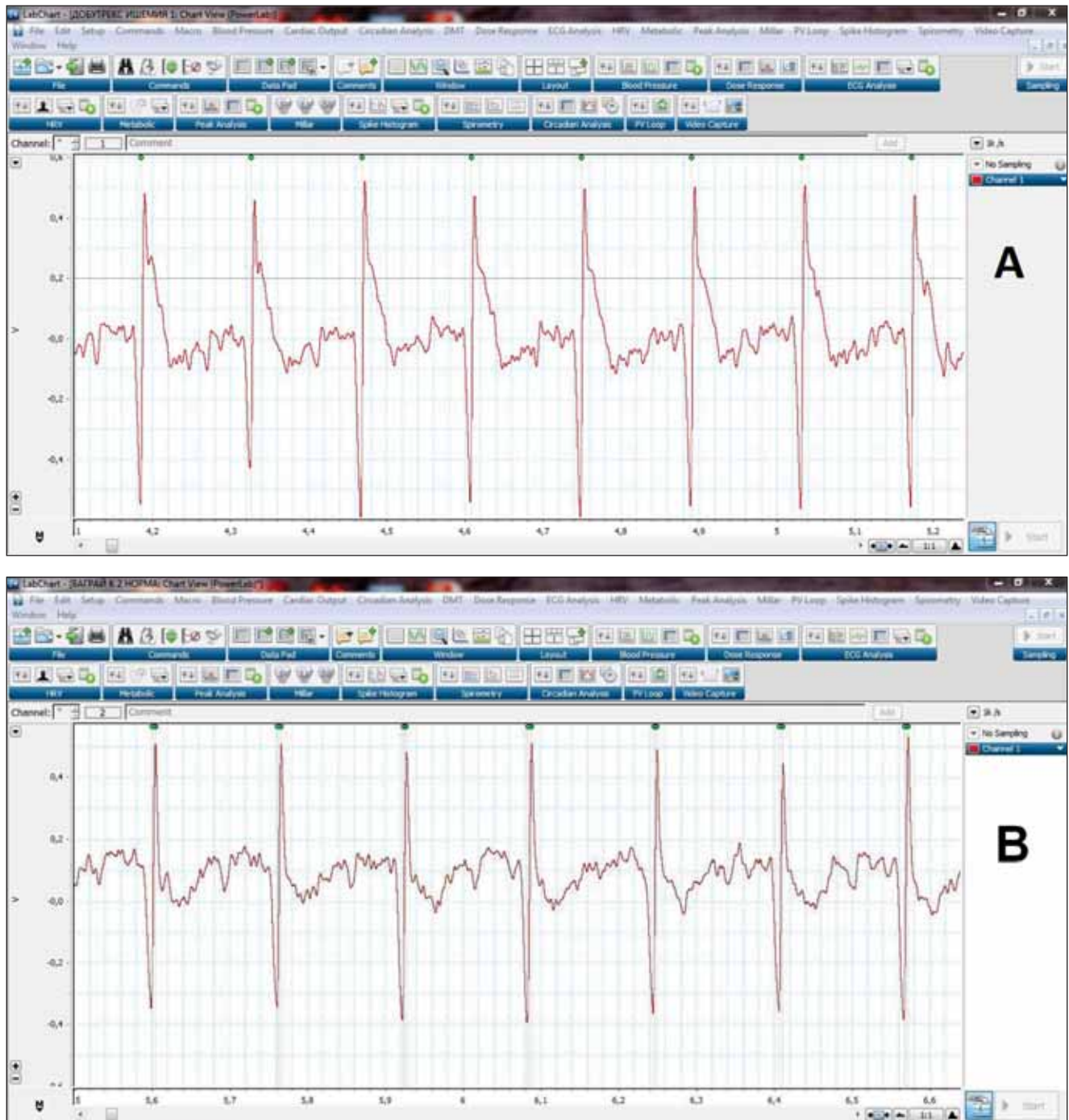
The obtained results suggest that the disorders of autonomic regulation of heart in the studied postictal periods can predetermine changes in its functional capabilities. Therefore, using the common stress test with dobutamine (19), we studied potential of heart 5 days and 10 days after SE. Diagnostic criterion of myocardial ischemia in stress-load was considered the ST segment elevation > 2 mm in the III standard lead. It was found that in animals of experimental groups, myocardial ischemia occurs with a lower load than in control, which reflects a decrease in compensatory mechanisms after SE. Thus, in the animals of control group, the ischemic changes in the myocardium were detected after a functional dose corresponding to a dobutamine



dose of  $80 \pm 5.95 \mu\text{g/kg/min}$ , whereas 5 days and 10 days after SE the ischemic changes (Fig. 1) were detected after dobutamine doses  $50 \pm 3.17 \mu\text{g/kg/min}$  and  $60 \pm 4.07 \mu\text{g/kg/min}$ , respectively, which is statistically significantly lower than the control by 38% ( $P < 0.001$ ) and 25% and ( $P < 0.01$ ), respectively. This is due to the fact that the functional load is accompanied not only by the mobilization of energy and plastic resources of heart, but also by the overstraining of the cardiac regulation system that

is disrupted after SE, which does not allow long-term maintenance of compensatory mechanisms with an increasing stress-induced load.

Thus, the obtained results **indicate that SE** initiates pathogenetic mechanisms provoking **the formation** of disorders of autonomic regulation of heart, which persist for a long time after the status epilepticus, which significantly reduces its functional capabilities. This is consistent with the current concept of the role of prolonged hyperactiva-



**FIGURE 1.** Myocardial ischemia of rats (ST segment elevation) 5 days after SE with a functional load corresponding to dobutamine dose  $50 \mu\text{g/kg/min}$  (A), no ECG changes in control animals with the same load (B).

tion of the sympathoadrenal system in the pathogenesis of cerebrocardial disorders (8). Since changes in the state of the cardiovascular system caused by convulsive seizures are mediated through the autonomic region of the hypothalamus (27), the disturbances of HRV in SE can be associated with prolonged or chronic changes in autonomic centers, which are continuously stimulated or blocked by repeated spike-and-wave discharge. This is supported by the results of studies indicating that SE in the ictal and postictal periods can cause degeneration of the CNS cellular structures, including degeneration in the autonomic region of the hypothalamus and the brain stem, which participate in the regulation of the functions of the cardiovascular system (28,29). Studies on different models of SE revealed the earliest postictal disorders in these parts of brain (30). Despite the fact that most degenerating cells die within the first week, damage to the brain cells, like generalized tonic-clonic seizures, was observed in rats for 3-5 months after SE (28). Moreover, transplantation of stem cells not exposed to the effect of SE increases GABA-ergic activity and suppresses spontaneous recurrent seizures (6). All this gives grounds to believe that one of the main reasons for prolonging the disorders of autonomic regulation of heart and reducing its functional capabilities, found in our studies, is structural and functional brain damage that occur during SE. They provoke a cardiac pathology, which is aggravated after the status epilepticus and contributes to the occurrence of life-threatening arrhythmias even against the background of low seizure readiness or its absence. This is consistent with the opinion of the authors on the possibility of a chronic change in the sympathovagal balance after SE (3).

It should be emphasized that a decrease in the reserve functionality of heart of animals after SE can be associated with structural and functional disorders of cardiomyocytes, which, in the opinion of some authors, arise because of high sympathetic activity (1). Thus, according to the results of molecular studies, ischemia and tachycardia due to high sympathetic activity in SE lead to damage to cardiac myofilament, with no gross structural dam-

age to heart (3). These results suggest that prolonged cardiac dysfunction that occurs after SE can be caused not only by a direct disorder of the autonomic regulation of heart, but also by the damage caused by it to the fine structural organization of cardiac myofilaments. Since the molecular changes in the organization of myofilaments are not always noticeable against the background of macrostructural disorders of heart, this issue is not always emphasized in describing the pathogenesis of cardiocerebral disorders.

Thus, the analysis of study results indicates that the high level of seizure activity of brain in SE predetermines secondary postictal complications in the form of prolonged disorders of autonomic regulation of heart, which increases its vulnerability, limits restorative capacity and can become a pathogenetic basis for severe cerebrocardial disorders. Moreover, analysis of changes in autonomic regulation of heart after SE revealed the inadequacy of compensatory mechanisms that fail to prevent cardiac dysfunctions that reduce the functional capacity of heart and increase the risk of **fatal ventricular arrhythmias**, which are predictors of sudden cardiac death. In this regard, in the treatment of SE, anticonvulsant therapy, apparently, should be carried out simultaneously with cardioprotective therapy. However, the solution of specific issues of this problem requires additional investigation.

## CONCLUSIONS

High degree of seizure activity of brain in SE predetermines secondary postictal complications in the form of prolonged disorders of autonomic regulation of heart, which increases its vulnerability, limits restorative capacity and can become a pathogenetic basis for severe cerebrocardial disorders. Therefore, when treating patients with SE, the physician should take into account the interdependence of cardiac and cerebral disorders and focus not only on the neurological condition, but also on the detection and prevention of concomitant cardiac pathology that may be the cause of sudden cardiac death even in the absence of seizure activity.

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