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The Journal of Clinical Physiology and Pathology provides timely information for physicians and scientists concerned with human diseases

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The Journal of Clinical Physiology and Pathology is dedicated to the rapid publication of high-quality articles of interest to specialists in clinical and theoretical medicine, as well as specialists in biological areas, whose research contributes to the development of high-quality diagnosis, treatment and prevention of human diseases…

Given the variety of specialized journals, the JCPP publishes clinical, experimental, translational, and population health research across a range of disciplines. We prioritize rigorous study design that accurately defines the boundary of the normal state of the body and the onset of pathological processes, the etiology and pathogenesis of human diseases, evaluates diagnostic strategies and distinguishes between treatment options and outcomes.

Our aims are to (1) publish original materials that will improve clinicians' understanding of disease onset and help prevent disease in a timely manner; (2) to formulate a strategy for the prevention, diagnosis and treatment of diseases through clinical and translational research, including human genome research and new imaging techniques; (3) address issues of the relationship between experimental results and their application in clinical practice; (4) provide expert reviews of topics that keep our readers up to date on real advances; (5) to serve as a forum for general clinical and theoretical problems in the development of pathology; (6) provide helpful criticism that enables authors to improve their submissions. We believe this approach to editorial policy epitomizes the JCPP's commitment to providing important information that is easily interpreted by its diverse readership.

Article

The effect of olfactory analyzer deprivation in rats on the response of the autonomic nervous system

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Abstract: The effect of modeling septoplasty and modeling sensory deprivation of the olfactory analyzer in rats on changes in the frequency domain of heart rate variability was compared. Bulbectomy provokes more pronounced changes in heart rate variability in rats, compared with septoplasty simulation. After bulbectomy, the high frequencies, low frequencies, very low frequencies, and the LF/HF ratio increase.

Keywords: septoplasty, stress, bulbectomy, heart rate variability.

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1. Introduction

The olfactory analyzer plays an important role in the normal life, not only of humans, but also animals. Violation of its function could provoke development of a number of stress reactions. [1, 2].

Impaired olfactory function is observed in various diseases of the nasal cavity and paranasal sinuses, among which one of the most common is the deviation of the nasal septum (DNS) [3]. Also, dysfunction of the peripheral part of the olfactory analyzer is noted in the early postoperative period in patients after septoplasty [4], which is performed in patients with DNS [5, 6].

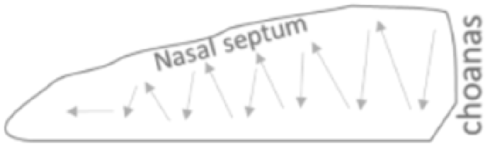
It is believed that heart rate variability reflects the affective physiological cognitive and behavioral aspects of the pain syndrome [7, 8], as well as a number of infectious diseases [9–11], that is, the presence of a particular intensity of the inflammatory process in the body. According to modern data, the central autonomic neural network is a functional integrated model involved in tonic, reflex and adaptive control of autonomic functions [12]. Obviously, HRV can be one of the objective methods for monitoring the response of the body's neurohumoral regulatory system to various stress factors that impair the function of the olfactory analyzer [13].

The purpose of the study: to compare the degree of stressfulness of bulbectomy in rats, as a model of sensory deprivation of the olfactory analyzer, with the simulation of septoplasty based on the analysis of heart rate variability.

2. Patients and Methods

The work was carried out on 20 mature male Wistar rats weighing 205.25±10.15 g. 3 days before surgery, all animals were under local anesthesia with 2% lidocaine solution and general anesthesia with Zoletil 50 solution (tiletamine hydrochloride and zolazepam hydrochloride) (3 mg per 100 g of rat body weight), 3 metal half-rings with rounded tips were installed for subsequent fixation of the electrodes. Three days later, an electrocardiogram (ECG) was recorded, and then surgical interventions were performed on the same day. To assess the state of the ANS, a spectral analysis of heart rate variability (HRV) was performed in rats before surgery, on days 1–6 after septoplasty modeling, and in the bulbectomy group, the indicated period corresponded to days 15–19 after surgery. The influence of humoral and supra-segmental levels of HRV regulation was assessed using the analysis of very low frequency (VLF), and the state of the PNS and SNS - using the high-frequency component of the heart rate (HF) and the low-frequency component of the heart rate (LF), respectively, as a percentage of each frequency indicator from their sums were also evaluated for the LF/HF ratio (vagosympathetic index).

Septoplasty. Zoletil 50 solution was intraperitoneally injected 10 minutes before surgery for general anesthesia at a dosage of 15 mg/kg. Modeling of septoplasty (Group 1, n=10) was performed by the standard method by zigzag scarification of the nasal mucosa (Fig. 1a) [1, 2, 7].



(a)

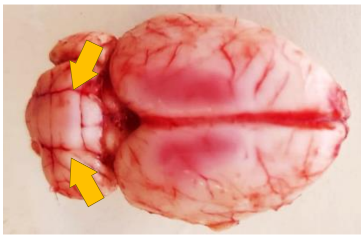

(b)

Figure 1. The result of bulbectomy in rats (yellow arrows indicate the sites of bulbectomy) (a) scheme of septoplasty simulation (b). The arrows indicate the direction of scarification of the nasal septum mucosa.

Bulbectomy. Bilateral bulbectomy (Fig. 1b) was performed (group 2, n=10) according to the protocol [14]. After the administration of Zoletil 100 solution at the above dosage, the head was shaved and over the olfactory bulbs in the skull, holes of 2 mm in size were made with a microborer for a needle anterior to the bregma on both sides at a distance of 2 mm from the midline of the frontal bone lying above the olfactory bulbs. Animals were excluded from the study if the bulbs were not completely removed or the frontal cortex was damaged [14]. It was important not to damage the frontal cortex. A hemostatic sponge was used to prevent bleeding from the burr holes. The antibiotic ceftriaxone powder was applied to the wound until they were closed with 7.5 mm surgical clamps. To assess the differences in the results before and after the operation, the Wilcoxon test was used, as well as between the groups, the Mann-Whitney test. Animal studies were carried out in accordance with the requirements of the "Regulations for Conducting Work Using Experimental Animals" (1984) and the " European Convention for the Protection of Vertebrate Animals used for Experimental or other Scientific Purposes" (1986). The studies were approved by the ethics committee of the RUDN MU on September 18, 2020 (protocol №1)

3. Results

Low frequency component. The bulbectomy group had significantly higher LF values throughout the follow-up period compared to the septoplasty group ($p<0.001$) (Fig. 2a).

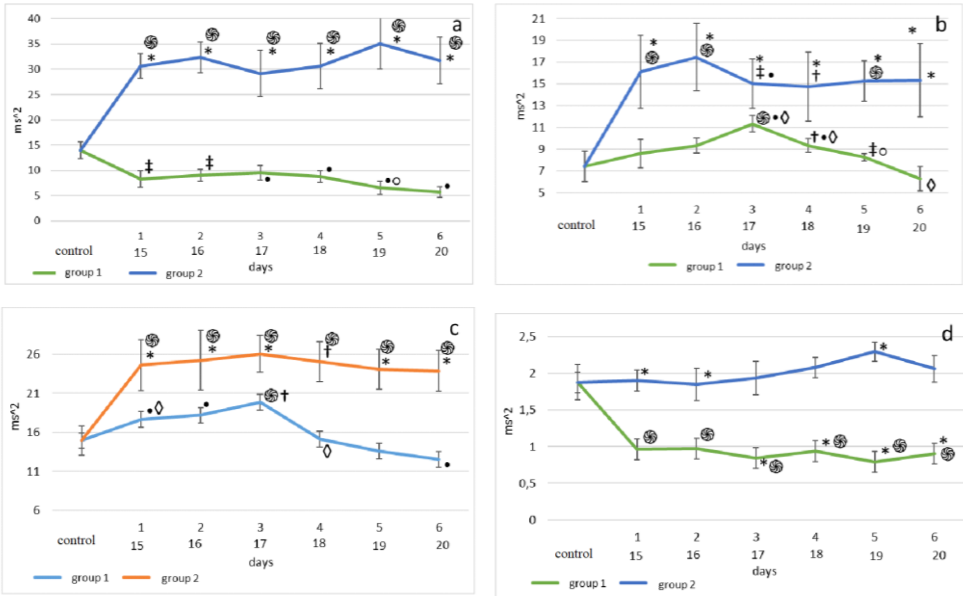


Figure 2. Changes in HRV frequency domain parameters after sensory deprivation simulation: LF (a), HF (b), VLF (c), LF/HF (d). Note: ֍ - significant differences between the experimental groups and the control group at p<0.001; ● – significant differences between the experimental groups and the control group p<0.01; * - significant differences between the experimental groups at p<0.001; † – significant differences between the experimental groups at p<0.01; ‡ - significant differences between the experimental groups at p<0.05; ◊ - significant differences between the terms within the experimental groups; p<0.001 ○ - significant differences between the terms within the experimental groups p<0.01.

High frequency component. Compared with the 1st group, HF of the 2nd group was significantly higher than the 1st 2nd, 5th, 6th days (p<0.001), 3rd day (p<0.05), 4th day (p<0.01) (Fig. 2b).

The Mann-Whitney test showed that the very low-frequency component of the 2nd group was significantly higher than in the 1st group on days 1st-3rd, 5th-6th (p<0.001) and day 4th (p< 0.01). (Fig. 2c).

Vagosympathetic index. According to the Mann-Whitney test, one day after surgery, the highest LF/HF was observed in the animals of the 2nd group, compared with the 1st group and control (p<0.001). 48 hours after modeling the effects on the olfactory analyzer in group 2, a similar picture was observed (p<0.001), however, the lowest values of the vagosympathetic index in this segment of its assessment were noted in group 1. In the third observation period, the highest values were found in the 2nd group, compared with the 1st (p<0.001). At the 4th, 5th and 6th time points for assessing the vagosympathetic index, the situation was the same as in the previous period. But on the 5th day of observation, the LF/HF of the 2nd group was significantly higher than in the 1st (p<0.001) (Fig. 2d).

4. Discussion

Surgical manipulations in the maxillofacial area lead to changes in heart rate variability [15].

Traditionally, frequency domain analysis of HRV reveals two or more peaks, a lower frequency (<0.15 Hz) and a higher frequency peak (>0.15 Hz), which are generally correlated with sympathetic and parasympathetic effects on cardiac activity, respectively. The decrease in HF compared to LF and the increase in VLF, which are observed simultaneously with changes in the behavior of rats under stress [8, 13], can be explained by the effect of post-surgical inflammation. High LF values in the bulbectomy group indicate a decrease in the activity of the SNS in the regulation of cardiac activity against the background of deprivation of the central part of the olfactory analyzer. It is known that fluctuations in the HF component are closely associated with the release of pro-inflammatory cytokines into the bloodstream an hour after exposure to a stress factor [11].

In addition, it has been shown that an anesthetic benefit that does not correspond to the volume of surgical intervention provokes vagotonia, which affects the regulation of cardiac activity [16]. In the early stages after septoplasty in the nasal cavity, inflammatory reactions are accompanied by mucosal oedema, and this leads to narrowing of the nasal passages and subsequent hypoxemia, which, in turn, increases PNS activity, which explains the increase in HF in the second group [15]. However, when modeling septoplasty in the first days after surgery, there was a drop in HF, probably due to the development of a classic stress response and the development of a depressive-like state. [17]. It is known that the VLF amplitude is closely related to emotional stress, and VLF can also show the regulation of metabolism [18]. The close connection of this HRV component with metabolism is confirmed by the relationship between diurnal changes in the concentration of the adipocyte hormone leptin in blood serum and diurnal changes in the VLF component of HRV [19]. The obtained difference between the groups can be explained by the fact that under conditions of complete deprivation of the olfactory analyzer, rats develop an anxiety state, and motor activity increases, since the olfactory analyzer in these animals is the leading one in cognition of the environment [8].

The vagosympathetic index (LF/HF) shows the ratio of the interaction between the SNS and PNS [20]. However, there is an opinion that this indicator does not quite accurately reflect the sympatho-vagal balance due to the fact that earlier many authors did not take into account its multifactorial nature of LF and HF [21]. There are other data showing that the vagosympathetic index can still reflect the state of balance of the autonomic nervous system. Thus, in fibromyalgia, an increase in LF/HF corresponds to a shift in the ANS to the dominance of the sympathetic division or to a decrease in the role of the parasympathetic, which is quite consistent with the nature of the autonomic function in fibromyalgia [22]. Septoplasty, in comparison with other models of operations in the maxillofacial region, in itself provokes an increase in the vagosympathetic index, which is due to the large area of the surgical field, a decrease in nasal passages, and sensory deprivation of the olfactory analyzer [1, 2, 7]. In the bulbectomy group, this figure is even higher, which can be explained by the complete absence of the function of the olfactory analyzer [8]. Previously, it was shown that modeling septoplasty in rats provokes the appearance of an anxiety-depressive state, which is manifested by changes in the behavior of animals [8, 23]. It is also known that surgical alteration in the maxillofacial region leads to changes in the cytoarchitectonics of the hippocampal pyramidal layer, an increase in neuronal apoptosis in the ammonium horn of the hippocampus [2], pronounced local inflammatory reactions of the depressive state, which is manifested by changes in the behavior of animals [15]. In addition, modeling of septoplasty in the early postoperative period provokes an increase in the activity of the sympathetic nervous system [8, 23], which is consistent with the data obtained in this study. Comparative characterization of the cytoarchitectonics of the hippocampus under conditions of sensory deprivation in various models remains to be studied [25-30].

5. Conclusions

Surgical traumatization of the nasal septum and upper jaw in rats in the early postoperative period causes a shift of the autonomic nervous system towards its sympathetic component. This indirectly indicates the occurrence of an acute stress response, the presence of a depressive-anxiety state, an increase in the mobilization of higher autonomic centers and an increase in the influence of neurohumoral and metabolic levels of regulation. The degree of stressfulness of bulbectomy in rats in the early postoperative period is more pronounced.

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Author Contributions: Conceptualization, A.M., V.P.; methodology M.K., I.G. and V.P.; software, A.I.; validation, P.M., A.K.; formal analysis, A.K.; investigation, A.K. and V.P.; resources, S.S.; data curation, P.M.; writing—original draft preparation, A.M.; writing—review and editing, M.K., I.G. and V.P.; visualization, P.V.; supervision, A.K.; project administration, S.S. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Complications of tracheoesophageal bypassing with prosthetics after laryngectomy

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Abstract: Laryngectomy for laryngeal cancer is the treatment of choice in these patients. Rehabilitation of patients with voice impairment is not an easy task. For the purpose of rehabilitation, tracheoesophageal bypass (TEB) is performed. When examining patients with TPS, medical personnel must be protected by personal protective equipment. Patients with PSI are at high risk for aspiration pneumonia. In the context of the COVID-19 pandemic, patients after laryngectomy with tracheoesophageal bypass surgery with prosthetics need to be given special attention. When infected with SARSCoV-2, these patients are at a special risk group. They need special conditions in the clinic – special care and rehabilitation.

Keywords: keywords. laryngectomy, rehabilitation, tracheoesophageal bypass, COVID-19, SARSCoV-2

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1. Introduction.

The main method of treating patients with tumors of the upper respiratory tract is usually surgery [1]. Laryngectomy for laryngeal cancer is the treatment of choice in these patients [2]. However, this type of surgery is disabling as patients lose their voice. Rehabilitation of patients with impaired voice function is not an easy problem [3-6]. For the purpose of rehabilitation, tracheoesophageal bypass surgery (TEB) is performed [7].

2. TEB patients & COVID-19.

When performing TEB with prosthetics after laryngectomy, a number of complications are possible associated with the displacement of the prosthesis and / or its course [8]. Usually, these problems can be corrected on an outpatient basis. But in the context of coronavirus infection and with an increased risk of SARS-COV-2, the patient and staff should be as safe as possible. Optimally, if in the examination room, forced ventilation with negative pressure and HEPA-filters are installed, which minimizes the risk of infection transmission [9].

3. TEB complications.

If the patient has a leak around the prosthesis, there is a risk of developing aspiration pneumonia, which can even have lethal consequences for the patient in the context of COVID-19. In the case of displacement of the prosthesis towards the trachea or esophagus, this can be diagnosed by X-ray, as well as using gastro- or tracheoscopy. It is advisable to start the study with standard X-ray images, and, if necessary, perform computed tomography (CT). Aspiration of the prosthesis into the airway is an absolute indication for urgent endoscopic intervention (regardless of the patient's COVID-19 status). It is prudent to treat all such patients as potentially infectious and to take all precautions to minimize the transmission of aerosol particles. When transporting to the operating room, it is necessary to cover the tracheostomy with a napkin, mask. Any attempt to use a filter or trachea tube in such a situation can further aggravate the cough and worsen the patient's condition.

When the patient's condition is stabilized, it is necessary to eliminate the complication as quickly as possible and, if possible, test for COVID-19. If there is a leak through the prosthesis, the patient should try to cope on his own at home. There are special plugs for the prosthesis ("like a key to a lock"), with which it is possible to block the lumen of the prosthesis. The flow will stop immediately, but the patient will not be able to talk (aphonia will occur). The patient may be advised to eat thicker food, which can also reduce aspiration.

If the voice prosthesis has completely fallen out, then at home the patient can temporarily insert a rubber catheter or a special dilator into the shunt in order to stop aspiration (the patient should be taught these procedures in advance or informed about the possibility of their own implementation). After that, the patient, in a stable condition and in safety, can already see a doctor on an outpatient basis.

In the clinic, the patient should be tested for COVID-19. Before receiving the test results, it is better to let the patient go home, and in case of a negative result, after 48 hours, invite again and replace the prosthesis.

If the test for COVID-19 is positive, then such a patient should stay at home as long as possible and undergo special antiviral treatment. Only after complete recovery from infection is it recommended to carry out procedures for replacing the prosthesis. When working with COVID-positive patients, all staff and all procedures are advised to wear a PARP respirator. If this is not possible, then use at least a respirator No. 95 and personal protective equipment (dressing gown, glasses, shoe covers).

4. Conclusions.

In the context of the COVID-19 pandemic, patients after laryngectomy with tracheoesophageal bypass surgery with prosthetics need to be given special attention. When infected with SARSCoV-2, these patients are at a special risk group. They need special conditions in the clinic - special care and rehabilitation.

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Article

The structure of arrhythmias in patients after septoplasty

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Abstract: In the present study, an attempt was made to study and evaluate the structure of cardiac arrhythmias in men and women using septoplasty under general anesthesia. Among all types of cardiac arrhythmias, premature atrial complexes and premature ventricular complexes extrasystoles (PAC and PVC) were most often found and were detected in all patients. Atrial tachycardias (AT) in men were significantly more likely to occur in the periods before surgery, during and after it, than in women. PACs at night was significantly more common in women. Ventricular arrhythmias (VA) were significantly more common in women than in men. Moreover, PVCs in women were detected significantly more often in all periods of observation. ATs and VAs in men were significantly more common after surgery. VAs in women were significantly more likely to occur before surgery than after it. Thus, the results of the study showed that of the considered cardiac arrhythmias during septoplasty under general anaesthesia much more frequently in men and women at all stages of the survey found PVCs, and the women of their significantly higher than in men. Cardiac arrhythmias (PAC and PVC) predominated mainly in the postoperative period with the exception of PVCs in women, which was higher in the preoperative period. Reducing the number of arrhythmias observed during operation, possibly due to the impact of drugs for general anaesthesia.

Keywords: septoplasty, arrhythmia, stress, general anaesthesia.

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1. Introduction

Septoplasty is a powerful surgical stressor [1-3]. After surgical interventions in the nasal cavity in animals, stress reactions occur due to an increase in predominantly nociceptive impulses that occur at the site of injury [4, 5]. As a rule, patients experience various types of cardiac arrhythmias and chronic hypoxia [6]. During surgical correction of deviated of nasal septum (septoplasty), which are a powerful stress factor, can cause arrhythmias [3, 5].

In the present study, an attempt was made to study and evaluate the structure of cardiac arrhythmias in men and women using septoplasty under general anesthesia.

2. Patients and Methods

For the period from June to October 2019, septoplasty was performed for 38 patients (20 men and 18 women, 18-55 years old) about the deviated of the nasal septum. Surgery was performed under general anesthesia using sol. Phentonyli (30 mkg / ml), sol. Midozolami (5 mg / ml), sol. Propofoli (150 mg), sol. Nimbexi (6 mg), sol. Traneksami (1000 mg), sol. Atropini (0.5 mg), sol. Ketonali (100 mg), sol. Cerucali (10 mg). Patients underwent holter ECG monitoring using a MT-101 Shiller (Switzerland) Halter, which began two hours before surgery and lasted for 24 hours. According to the results of the study, an analysis of the types of rhythm disturbances in each patient was carried out.

3. Results

Among all types of cardiac arrhythmias, premature atrial complexes and premature ventricular complexes extrasystoles (PAC and PVC) were most often found and were detected in all patients. Atrial tachycardias (AT) in men were significantly more likely to occur in the periods before surgery, during and after it, than in women. PACs at night was significantly more common in women. Ventricular arrhythmias (VA) were significantly more common in women than in men. Moreover, PVCs in women were detected significantly more often in all periods of observation. ATs and VAs in men were significantly more common after surgery. VAs in women were significantly more likely to occur before surgery than after it (tabl. 1).

Tables 1. Type of arrhythmia in men and women during septoplasty. *- more than other sex (p<0.01); † - more than before septoplasty (p<0.01); ‡ - less than before septoplasty (p<0.01).

		men				women			
		before surgery	surgery	after surgery	night	before surgery	surgery	after surgery	night
Atrial tachycaedias	PAC	8,25±2,4*	2.9±1.3‡	29.7±8.1†	11.6±4.1	4.6±1.4	3.1±1.4†	23.4±4.9†	19±5.6*†
	Couplet	0,4±0,13	2.1±1.2*†	3.6±1.7†	1.7±0.6†	1.4±0.6*	0.5±0.4†	2±0.6	3.4±2
	Triplet	0	0.1±0.1	2.9±1.7*†	0.6±0.2†	0	0.1±0.13	1.1±0.8†	2.9±2.4†
	SVTach	0,25±0,16*	0.3±0.2*	0.6±0.41	0.1±0.1	0	0	1.4±1†	0
	Bigem	0,06±0,05*	0	0.1±0.07	0.1	0	0.25±0.26	0.5±0.5	0
Ventricular ar-	PVC	16.9±3,6	21.6±5.7	35.25±11†	18.75±7.8	90.4±10.6*	46.9±5.6*‡	72.5±12.4*†	38.9±10.9*‡
	Couplet	1.25±0,5	2.4±1.34	3.06±1.7†	0.9±0.6	8.6±3.5*	3±1.14‡	4.25±1.8‡	1.5±0.8‡
	Triplet	0.06±0,05	0.4±0.25†	0.56±0.3†	0.25±0.1†	2.4±0.9*	1±0.45*‡	0.75±0.5‡	0.25±0.26‡
	VTach	0.25±0.12	0.13±0.1†	0.19±0.15	0.06±0.05†	1.6±0.75*	0.5±0.28*‡	0.13±0.13‡	0‡
	Bigem	0.13±0.07	0.06±0.07	0.06±0.05†	0.06±0.05†	0.25±0.17	0.25±0.17*	0.5±0.3*	0.5±0.4

4. Discussion

The nasal cavity contains the afferent section of many reflex arcs, which, passing through the autonomic nervous system, end in the heart [2-4]. Thus, manipulations in the nasal cavity can lead to dysregulation of cardiac activity and cause various kinds of arrhythmias [7, 8]. In experimental studies on the septoplasty simulation, it was shown that the application of trauma to the nasal septum mucous membrane entails an imbalance in the autonomic nervous system [9, 10], which is provoked by surgical damage in the maxillofacial region [10, 11]. The involvement of the central nervous system during stress reactions in the regulation of cardiac activity after septoplasty is also confirmed by morphological and physiological studies of the hippocampus formation [12-14]. To prevent the development of such complications of cardiac activity as arrhythmias, it is necessary to carefully assess the intraoperative risks, comorbidities of patients with deviated nasal septum, especially from the cardiovascular system [2, 3, 15], and also clearly determine the presence of predictors of the development of postoperative pain syndrome [15].

5. Conclusions

Thus, the results of the study showed that of the considered cardiac arrhythmias during septoplasty under general anaesthesia much more frequently in men and women at all stages of the survey found PVCs, and the women of their significantly higher than in men. Cardiac arrhythmias (PAC and PVC) predominated mainly in the postoperative period with the exception of PVCs in women, which was higher in the preoperative period. Reducing the number of arrhythmias observed during operation, possibly due to the impact of drugs for general anaesthesia.

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Article

Treatment COVID-19 virus-positive patients after laryngectomy in a hospital

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Abstract: The coronavirus pandemic is spreading rapidly around the world. The health systems of all countries faced extraordinary problems in terms of the creation and distribution of medical resources, including the re-equipment and creation of new hospital beds, and the provision of personal protective equipment. The patients who undergo a laryngectomy are a special category. Given the fact that during the operation they have a separation of the upper and lower respiratory tract, in the context of the COVID-19 pandemic, such patients require special attention from oncologists and otorhinolaryngologists. Purpose of the study is to review the characteristics of patient management after a laryngectomy in a COVID-19 pandemic. Laryngectomy patients represent a unique contingent in conditions of coronavirus infection SARS-COV-2, it is advisable to focus on providing them with protective equipment. This will significantly reduce the risk of infection with their virus, which can be a deadly threat to them. Infected patients during an epidemic represent a potential source of infection for medical personnel, which requires special protective measures. All procedures associated with the replacement of the prosthesis, endoscopic manipulations, it is advisable to postpone until the normalization of the epidemiological situation. If carrying out such operations is vital, then they should be carried out, observing all necessary precautions for both the patient and medical personnel.

Keywords: coronavirus pandemic, COVID-19, laryngectomy

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1. Introduction

COVID-19 is caused by the SARS-CoV-2 (Severe acute respiratory syndrome-related coronavirus 2) coronavirus, which is genetically related to the SARS family and the Middle East Respiratory Syndrome (MERS) virus and is a recombinant virus between bat coronavirus and an unknown coronavirus. The genetic sequence of SARSCoV-2 is similar to the SARS-CoV sequence by at least 79% [1, 2].

In the last two years, the SARS-CoV-2 (Severe acute respiratory syndrome-related coronavirus 2) pandemic has been taking place. The transmission of infection is carried out by airborne droplets, airborne dust and contact routes [3]. The leading route of transmission of SARS-CoV-2 is airborne, which is realized when coughing, sneezing and talking at a close (less than 2 meters) distance. The contact route of transmission is carried out during handshakes and other types of direct contact with an infected person, as well as through food, surfaces and objects contaminated with the virus tem, activation of the hypothalamic-pituitary-adrenal and adrenergic systems, changes in behavioral reactions, as well as the occurrence of anxiety state [4-12]. At the same time, the morphological causes of such reactions are not fully understood [13-14].

2. Features of examination of patients after laryngectomy under covid-19 epidemic

The defeat of the pharynx and larynx by a tumor process leads to disabling consequences [4-6]. Moreover, the rehabilitation of such patients is an extremely difficult process [7-10].

Given the presence of a high viral load in the upper respiratory tract, all ENT procedures are high-risk procedures, and otorhinolaryngologists are at risk for COVID-19 infection.

The most common symptoms of coronavirus infection are cough (dry or with little sputum) in 80% of cases; shortness of breath (55%); fatigue (44%); a feeling of congestion in the chest (> 20%).

Testing for COVID-19 is most often done by swabbing the oropharynx and nasopharynx. But given that the breathing of patients after laryngectomy is carried out through a tracheostomy, it is advisable to consider testing for SARS-COV-2 by detecting the virus in tracheal aspirates and from the nasal cavity, which is consistent with the WHO recommendations.

Any diagnostic and therapeutic procedures in the upper respiratory and digestive tracts, as a rule, cause coughing and should be considered as potentially dangerous in terms of aerosol transmission for medical personnel [3]. To limit the transmission of COVID-19 and to maximize the safety of medical personnel, it is shown to use personal protective equipment (PPE), and, if possible, even to cancel or postpone a dangerous procedure (AAO-HNS).

Taking into account the peculiarities of the anatomy, as well as the volume of laryngectomy [3, 5, 9], which is associated with the formation of a tracheoesophageal fistula and voice prosthetics, all medical recommendations should be organized in such a way as to minimize the possibility of transmission of the SARS-COV-2 virus from the patient to the medical staff. In this case, the use of personal protective equipment is relevant.

In patients after laryngectomy, there is no nasal breathing and untreated air through the tracheostomy directly enters the respiratory tract, which, as a rule, is accompanied by severe cough. At the same time, aerosol transmission of viral particles can significantly increase, compared with an ordinary person, when the protective function of the nose is preserved [5, 9]. So, during the outbreak of the SARS epidemic in 2003, a significant concentration of viral particles was determined in tracheal aspirates. Therefore, the issue of care and contact with the patient after laryngectomy, both in inpatient and at home, is extremely important. Based on this, we recommend that any patient after laryngectomy be considered as potentially dangerous and infected with COVID-19.

We recommend a standard set of personal protective equipment for staff in contact with COVID patients to prevent infection of medical personnel when examining all patients after laryngeal surgery. It should be noted that the use of respirator No. 95 and a protective screen for the face in 100% of cases effectively protects the employee from infection [3].

In the case when an in-person consultation is absolutely necessary (examination after surgery, complications, suspicion of a relapse of the disease), it is important to "screen" these patients even before visiting the clinic. It is advisable to take a thorough history and conduct an examination for COVID-19.

It is important to note that a patient with a tracheostomy must use a respiratory heat exchanger with a viral-bacterial hygroscopic filter and cover the tracheostomy with a mask, scarf or clothing during a visit to the clinic [11].

3. Treatment of patients with the COVID-19 virus in a hospital.

When a patient is admitted to a hospital and planning treatment, it is extremely important that all medical workers of the department understand the surgical anatomy of the airways in a patient after laryngectomy. The attention of the personnel should be emphasized that the use of oxygen masks and nasal catheters in such a patient will be useless, since the upper respiratory tract is "turned off" from breathing as a result of the operation, and oxygenation occurs only through the tracheostomy. Under ideal conditions, it is advisable to test all incoming patients for COVID-19.

However, if testing is not possible, all patients should be treated as potentially infected and all feasible remedies should be used. It is extremely important for patients to use heat exchangers with viral or bacterial filters attached to the tracheostomy area.

In case of severe coughing and profuse sputum secretion, special tracheotubes with powerful HEPA-filters can be used. And such a patient can be placed in a room with negative pressure and / or a closed ventilation system in order to prevent the spread of viral particles to other rooms. In some cases, it is advisable to use mechanical ventilation in auxiliary modes in order to provide a closed breathing circuit for the patient (even if his oxygenation does not suffer greatly). It is also important to use mechanical barriers over the tracheostomy (transparent blocks with holes for the doctor's hands), which is especially important at the time of intubation and extubation, when caring for the tracheotomy tube. The main thing in this situation is to prevent the spread of aerosol particles of the virus by any possible means.

Each patient after laryngectomy in the ward should have an individual suction, which the patient should be trained to use even before the operation. When caring for such patients, strict use of PPE is necessary, at least until negative tests for COVID-19 are obtained.

In case of a negative COVID-19 status for patients, it is still recommended to use HME with viral and bacterial filters from the very first hours after the operation, as well as wear a mask on the face and neck (which will provide a mechanical obstacle to the spread of the virus).

The patient should be explained that it is not necessary to touch the tracheostomy unnecessarily, and after all hygiene measures have been taken, hands should be thoroughly washed. Caring for the skin around the tracheostomy is very important to reduce airway contamination.

After laryngectomy, self-contamination (contamination with viral particles of one's own airways) is also possible during the use of a voice prosthesis and when closing the tracheostomy with a finger, therefore it is so important to focus the patient's attention on frequent hand washing. During an epidemic, the use of HANDS-FREE systems becomes extremely relevant, which allow the patient after laryngectomy not to touch the tracheostomy with a finger at all during speech load.

4. Conclusions

Considering the fact that patients after laryngectomy are a unique contingent in conditions of SARS-COV-2 coronavirus infection, it is advisable to focus on providing them with protective equipment (filters and heat exchangers). This will significantly reduce their risk of contracting the virus, which could pose a lethal threat to them.

In addition, already infected patients themselves during an epidemic represent a potential source of infection for medical personnel, which requires the use of special protective measures.

It is advisable to postpone all procedures related to the replacement of the prosthesis, endoscopic manipulations until the epidemiological situation normalizes. If the conduct of such operations is vital, then they should be carried out, observing all the necessary precautions for both the patient and the medical staff.

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Article

Heart rate variability after craniofacial surgery simulation

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Abstract: Each article is accompanied by a summary. The summary should be extended and contain no more than 450 words. The summary of the original article should be structured as follows: the purpose of the study; material and methods; results; conclusion. The summary of the review article should contain a summary and be consistent with the structure of the article.
A summary of the Clinical Case article includes relevance, description of the clinical observation, and conclusion. The resume is followed by keywords (when choosing keywords, we recommend using the MeSH keyword dictionary).

Keywords: HRV, rats, septoplasty, anesthesia, ECG, autonomic nervus system, stress..

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1. **Introduction**

Septoplasty is a powerful surgical stressor [1-3]. After surgical interventions in the nasal cavity in the body of animals, stress reactions occur [4-6], due to an increase in predominantly nociceptive impulses that occur at the site of injury [7, 8]. Aims: to evaluate the heart rate variability after simulation of septoplasty in rats under various general anesthesia schemes.

2. **materials and Methods**

The study was carried out on system (ANS), an analysis of heart rate variability (HRV) was carried out in rats before surgery (control data) and on the second, fourth and sixth days after surgery. All rats were divided into two groups of 12 animals each. In group 1, phthorothane was used for anesthesia and in group 2, zoletil was used. The operation was performed by 2-sided zigzagscarification of the nasal septum mucosa. Interpreted 30-second fragments of records containing an average of 189 RR intervals without artifacts. Isolation of a 30 second fragment took place in the Biopac Student Lab 4.1 software. After that, the parameters of spectral analysis were calculated in the Kubios HRV program.The spectral component of heart rate variability was assessed using the Wilcoxon test for connected samples.

3. Aims

Aims to evaluate the heart rate variability after simulation of septoplasty in rats under various general anesthesia schemes.

4. Results

In both groups, STD RR increased slightly (group 1 (5.12 ± 0.56 ms) (p› 0.05); group 2 (5.27 ± 0.57 ms) (p› 0.05). day STD RR increased in group 1 (6.38 ± 0.74 ms) (p ‹0.01), while in group 2 it decreased (4.0 ± 0.39 ms) (p ‹0.01), compared with control (4.76 ± 0.5). On the sixth day in both groups, STD RR returned to preoperative values (4.32 ± 0.77 ms and 4.31 ± 0.72 ms, respectively) (p› 0.05). On the second day, Mean HR increased in groups 1 and 2 (411.35 ± 9.89 bpm and 411.23 ± 10.32 bpm, respectively) (p ‹0.001). On the fourth day, Mean HR in group 2 increased (423.04 ± 11.56 beats / min) (p‹0.001), and in group 1 Mean HR decreased, but still remained above the control (396.88 ± 11.02 beats /min) (p ‹0.01). On day 6, Mean HR in both groups increased (428.11 ± 12.31 bpm and 437.95 ± 10.81 bpm, respectively) (p ‹0.05). On the second day after surgery, RMSSD increased in group 1 (5.28 ± 0.7 ms) (p ‹0.001), while in group 2 RMSSD decreased (3.36 ± 0.35 ms) (p ‹0, 05). On the fourth day, positive dynamics was noted in group 1 (6.59 ± 0.65 ms) (p ‹0.05), and in group 2, negative dynamics of changes in RMSSD (2.73 ± 0.25 ms) (p ‹0.001). In group 1, on the sixth day, RMSSD decreased (5.25 ± 0.77 ms) (p ‹0.05), and in group 2, RMSSD decreased (3.41 ± 0.69 ms) (p ‹0.01), reaching the values before the surgery.

5. Discussion

Experimental work on the nasal septum in rats is carried out to study the effect on the surrounding tissues of grafts replacing the cartilage of the septum, new methods of hemostasis and prevention of postoperative nosebleeds, in order to develop manual skills of the surgeon [9, 10, 11], etc. Despite these facts, the simulation of septoplasty in small rodents, as classical experimental animals, on a non-deviated nasal septum can show the role of traumatic as well as surgical damage in the manifestation of stress reactions. In previous studies, we have shown that surgical damage to the nasal such traumatization is sensory deprivation of the olfactory analyzer, which, in turn, can cause changes in the cytoarchitectonics of the hippocampus [12, 13].

6. Conclusions

The use of phthorothane is preferable and gives a more pronounced increase in the tone of the parasympathetic division of the ANS, in comparison with zoletil. This helps to reduce stress- related hyperactivation of the sympathetic nervous system in the postoperative period.

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Conflicts of Interest: The authors declare no conflict of interest.

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Article

Rapid diagnosis of laryngeal cancer using Raman fluorescence spectroscopy

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Abstract: Aims: to provide a scientific and practical justification for the use of Raman fluorescence spectroscopy in the early express-diagnostics of laryngeal cancer. Patients and methods. A total of 83 patients with a diagnosis of laryngeal cancer were examined. The spectra of the intact mucous membrane of the larynx, the anatomical structures of the larynx in cancer and precancer were analyzed. The individual features of the bands of Raman scattering of light and fluorescent signals in intact tissues, in case of dysplasia, and squamous cell carcinoma of the larynx were evaluated. To compare the data of Raman fluorescence spectroscopy, the histological method was used in this study. The study evaluated the sensitivity and specificity of the method. To take the spectra, a laser setup was used using both fluorescent and Raman components, with a wavelength of 532 nm. Measurements were taken immediately after removal of the laryngeal tissue (1-5 seconds) involved in the malignant process. Results. In this study, using Raman fluorescence spectroscopy, individual spectral characteristics of the tissues of the larynx were obtained in intact tissues and in laryngeal cancer, as well as in dysplasia (precancer). In this study, in the above groups there are differences both in fluorescence signals and in Raman scattering bands. This information can be useful in the early diagnosis of laryngeal cancer for the clinicians. Conclusions. In the future, Raman fluorescent medical technologies can be used for the purpose of early express diagnostics of tumor diseases of the larynx. Clinical Medicine and Public Health and Healthcare in general need the development of technologies of this kind in order to improve the quality and efficiency of diagnosing and treating diseases at the stage of their initiation.

Keywords: Raman-fluorescence medical technologies, laryngeal cancer, squamous cell carcinoma of the larynx, early diagnosis of cancer, tumor diseases of the ENT-organs..

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1. Introduction

More than 600,000 of new of malignancies cases are registered in Russia annually, and there are approximately 300 thousand deaths from this nosology every year [1]. Laryngeal cancer is one of the most common types of squamous cell carcinoma of the head and neck [2-6]. According to statistics, 13,000 of new cases are expected annually in the USA with a 70% survival rate [7]. Laryngeal cancer ranks 20th in the structure of the most common types of malignant neoplasms, more than 150,000 of new cases are detected every year in the world [8]. Moreover, this type of cancer occurs in one third of cases of malignant neoplasm of head and neck with squamous cell transformation [9]. Optimal treatment of this pathology requires an interdisciplinary approach with the participation of different medical specialists [10].

Determination of tumor diseases biomarkers is one of the most important tasks in clinical practice [11-12]. Late diagnosis and a significant decrease in the life quality of patients with cancer of different localization serve as an additional motivation for the development of early methods for diagnosing cancer. Early express diagnostics of tumor diseases of the ENT organs is no exception [8,13,14]. In particular, the search for markers of the oncological process in laryngeal cancer deserves close attention [15]. Among other things, in laryngeal cancer strict adherence to the boundaries of tumor tissue resection during surgery is very important in order to avoid the recurrence of the pathological process, so it is necessary to develop an accurate and rapid intraoperative determination of the boundaries of prevalence malignancy in laryngeal cancer [16,17]. Recent scientific articles describe the use of Raman scattering in combination with deep irradiation and related hardware and software systems in relation to the identification of laryngeal squamous cell carcinoma [18]. The question of increasing the sensitivity and specificity of methods for early indication of the pathological process in laryngeal cancer remains in demand due to the increasing frequency of cases with the relapse of the disease [19]. Despite the use in practice such methods as histological [20], immunohistochemical [14], and polymerase chain reaction [21], scientists around the world are faced with the important issue of accelerating the process of identifying the oncological process - the implementation of its immediate determination in real time. Patients with this pathology visit doctor at an advanced stage, when treatment may be either completely ineffective or insufficiently effective. Accordingly, doctors faced a difficult task - to conduct high-quality, highly sensitive and specific, fast, non-invasive diagnosis of cancer at an early stage, even before clinical manifestations. Accordingly, doctors are faced with a difficult task - to conduct a high-quality, highly sensitive, highly specific, fast, non-invasive diagnosis of cancer at early stage, even before clinical manifestations. Histological examination, despite its accuracy, very often takes a lot of time, and also, often, is carried out at an advanced stage of larynx cancer, given the peculiarities of routing and patient referral, which is a separate challenge. The search for modern methods for the early detection of oncological diseases, including laryngeal cancer, using highly sensitive, highly specific, accurate, fast, non-invasive diagnostic methods is one of the most important tasks of public health and healthcare [22-24]. Raman fluorescent medical technologies have proven themselves as such diagnostic methods [25-30]. Currently, Raman scattering is used in the diagnosis of tumor diseases of the ENT organs, including laryngeal cancer [31-32].

Today there are certain difficulties for using in clinical practice these methods, such as the high cost of equipment, the lack of doctors who can do this technology and, accordingly, training in this area; insufficient development of algorithms for diagnosing tumor and inflammatory diseases of the ENT organs, including cancer of the larynx, as one of the most common types of oncological pathology in the practice of otorhinolaryngologist and oncologist. In connection with the above, the purpose of the study was set.

The aim of the study: to provide a scientific and practical justification for the use of Raman fluorescence spectroscopy in the early express-diagnostics of laryngeal cancer.

2. Patients and Methods

A total of 83 patients with a diagnosis of laryngeal cancer were examined. The spectra of the intact mucous membrane of the larynx, the anatomical structures of the larynx in cancer and precancer were analyzed. The individual features of the bands of Raman scattering of light and fluorescent signals in intact tissues, in case of dysplasia, and squamous cell carcinoma of the larynx were evaluated. To compare the data of Raman fluorescence spectroscopy, the histological method was used in this study. The study evaluated the sensitivity and specificity of the method. To take the spectra, a laser setup was used using both fluorescent and Raman components, with a wavelength of 532 nm.

Measurements were taken immediately after removal of the laryngeal tissue (1-5 seconds) involved in the malignant process.

In this study we used the WHO classification accepted in Paris in 2005, according to which 3 stages of laryngeal intraepithelial neoplasia of squamous epithelium (LIN) are distinguished: LIN 1, LIN 2, LIN 3: mild dysplasia, moderate dysplasia, severe dysplasia, and cancer in situ.

3. Results.

The main distinguishing feature of the intact tissue surrounding the tissue of the larynx involved in the tumor process in squamous cell carcinoma, as shown in Figure 1, is that in this case there are no peaks at wavenumbers of 1100 cm -1 and 1500-1650 cm -1, which registered at all stages of the course of squamous cell carcinoma of the larynx, including at the stage of LIN 3-dysplasia, grade 3.

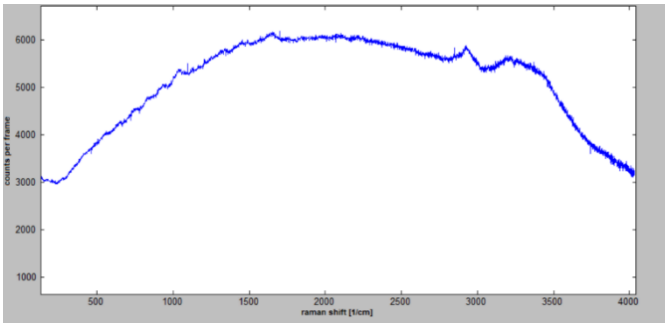

Figure 1. Spectrum of intact laryngeal tissue not involved in the tumor process, surrounding larynx squamous cell carcinoma. On the abscissa axis - the magnitude of the wave numbers in reciprocal centimeters (cm -1), along the ordinate axis - the intensity of fluorescence (in relative units - OE).

A total of 24 patients were examined, 24*20=480 spectra. As we can see, there is a small peak at 2900 cm -1, after which an additional rise in fluorescence is recorded. In 11 patients with squamous carcinoma of the larynx (undifferentiated type, with an average degree of keratinization), 220 spectra were analyzed from the surface of the tissues of the larynx. In this case, Raman peaks were registered at 1250, 1400, 1900/cm. 2 rises in fluorescence were registered with maximum peaks at 11500 and 12100 relative units (RU) (maximum fluorescence intensity was visualized).

In 12 patients, 240 spectra were analyzed. As noted in Figure 2, 2 fluorescence signals are recorded with a maximum at 1200 cm -1 (8500 OU), 2100/cm (12000 OU). When this is visualized Raman peaks on the values of the wave numbers: 1200 cm -1, 2900 cm -1.

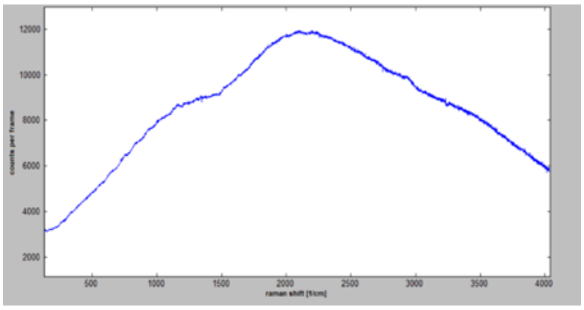

Figure 2. Spectrum of squamous cell carcinoma of the larynx, poorly differentiated, non-keratinizing type of tumor.

In 22 patients, 440 spectra were analyzed. According to Figure 3, the main peaks are recorded at wave numbers 1100 cm -1, 1500 cm -1, 2900 cm -1, additional peaks are recorded at 800, 900, 1000, 1250, 1400, 1600, 1700, 2700 cm -1. The first maximum is at 13200 OE, the second maximum is at 13000 OE, the third maximum (main peak) is at 9000 OE.

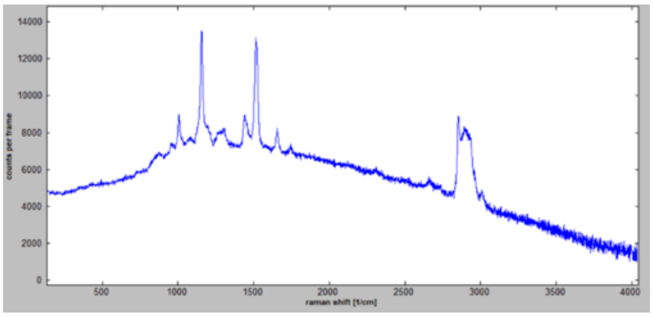

Figure 3. Spectrum of squamous cell carcinoma of the larynx with metastasis in regional lymph nodes.

Figure 4 shows that the intensity of the main peaks is lower, their configuration is less pronounced, with smoother transitions, however, these peaks stand out against the general background of the generalized fluorescence signal. There are peaks at 1100, 1500, 2900 cm -1, with a maximum fluorescence intensity at 6500, 6900 and 4800 cm -1. In 14 patients, 280 spectra were recorded.

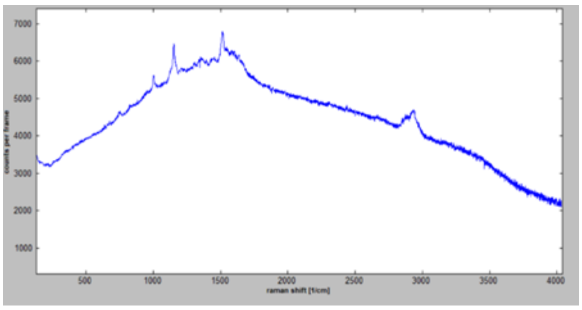

Figure 4 Spectrum of tumor tissue during the formation of squamous cell carcinoma of the larynx (LIN 3 with the transition to cancer in situ), a highly differentiated type of tumor tissue.

As noted in the course of the study, the more highly differentiated type of squamous cell carcinoma, the more the spectrum correlates with the spectrum of intact laryngeal tissue, and vice versa, with a low-differentiated type, a smoother spectral curve is noted, a more powerful fluorescence signal.

Also, important acquires the process of keratinization in squamous cell carcinoma of the larynx. In squamous cell carcinoma of the larynx without keratinization and with keratinization, spectral differences are noted, which in the future can be used to determine the type of tumor.

4 Discussion

The obtained results correlate with the world literature data. Thus, the use of transnasal Raman spectroscopy for differentiation of tumor and intact tissue during endoscopic examination in the "real time" mode (in the range of wave numbers 2800-3020 cm -1) in the region of the anatomical structures of the larynx is described.

This study showed that Raman spectroscopy has the potential for non-invasive diagnosis and real-time detection of laryngeal cancer at the molecular level [33]. Raman spectra in the range of 800-1800 cm -1 from various tissue sites, taken immediately after surgery for 5 seconds, can illustrate the changes occurring in the tissue with a diagnostic sensitivity of 88.0% and a specificity of 91.4% in relation to the identification of malignant neoplasms larynx [34].

Conducting fiber-optic Raman spectroscopy in the range of 800-1800 cm -1 for the diagnosis of cancer of the larynx in vivo in the course of an endoscopic study has demonstrated effectiveness in differentiating tissues of the larynx in cancer and normal. The Raman spectra of intact and tumor tissues of the larynx differ significantly, which may be due to different amounts and ratios of proteins, lipids, nucleic acids, and the content of bound water in the cells of the anatomical structures of the larynx [35].

The literature describes the state of the art in optical techniques, with particular attention paid to the combined intraoperative use of fluorescence imaging and Raman spectroscopy for targeted imaging during resection of tumor tissue within an intact area with well-defined margins [36].

When using Raman light scattering (wavelength 785 nm) and registration of excitation in the range of wave numbers 50-1500 cm -1, it seems possible to determine the types of biomolecules of each group of tissues under study (phospholipids, amides, tyrosine, phenylalanine, collagen, etc.) [37].

The technology of surface-enhanced Raman scattering of light has shown promise in diagnosis of cancer of various organ locations in vivo. Ordinary Raman signals are extremely weak and are easily distorted by fluorescence. The sensitivity and specificity of the combined method, according to some authors, were 99.2% and 98.4%, respectively (for the identification of intact and tumor tissues) [31].

Thus, clinical practice today requires the development of accurate methods for diagnosing cancer in situ and rapid identification during surgical intervention for the purpose of resection of a malignant neoplasm, which is the key to reducing cancer morbidity and mortality. To date, there are many diagnostic methods, however, none of them has a sufficient level of specificity, sensitivity, spatial and temporal resolution, speed and accuracy. In addition, most methods cannot provide information on the molecular composition of the tissue.

In this case, Raman fluorescence spectroscopy is of particular interest in the differentiation of resection margins of tumor tissue within intact tissue in "real time" mode [25]. The Raman spectrum illustrates the internal "molecular imprint" of the tissue, and any biochemical change associated with an inflammatory or tumor state of the tissue is reflected in this "spectral imprint". Currently, Raman spectroscopy systems in combination with modern hardware and software systems and machine learning methods can serve as additional diagnostic and treatment tools in oncological practice [38-40]. Raman measurements in vivo have been made possible by recent technological advances in Raman endoscopy and signal amplification facilities [41].

As a result of the study, it was noted that the method of Raman fluorescence spectrometry in the future can be used to expressly identify the tumor and pre-tumor process in laryngeal cancer, in particular, in squamous cell carcinoma of the larynx at its various stages and with various types of tumors. Given that the tissue spectra in normal and laryngeal cancer differ, the clinician needs a database of spectra that allows identifying malignant growth even at the initiation of the precancerous process, since at this stage, patients, as a rule, do not go to the doctor yet, but can be examined as part of a medical examination.

5. Conclusion

Summarizing the above, it should be noted that in the development of a special algorithm for combined diagnostics, Raman fluorescence spectroscopy can be used as a screening technique for the purpose of early rapid identification of larynx cancer with subsequent application in clinical practice, which is the goal of further research.

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Conflicts of Interest: The authors declare no conflict of interest.

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Article

General anesthesia methods and their influence on HRV and pain syndrome after rhinosurgery

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Abstract: Aims: to evaluate various methods of anesthesia during septoplasty for changes in heart rate variability (HRV) and acute pain syndrome in the early postoperative period. Patients and methods. All patients received local anesthesia with 2% procaine solution. In group 1(105 people) premedication was used with 2% promedol solution and 60 mg of ketorolac in the evening, in group 2 (108 people) - fentanyl, propofol, cisatracuria besylate, tranexamic acid, atropine and metoclopramide, in group 3 (78 people) - atracuria besylate, sodium thiopental, nitrous oxide and halothane. In groups 2 and 3, 100 mg of ketoprofen was administered intramuscularly in the evening on the day of surgery. The frequency domain of HRV was estimated per day. Pain was assessed using a visual analogue scale (VAS). Results. ULF and LF were significantly higher in groups 2 and 3 than in the local anesthetic group. VLF in the second group was significantly lower than in groups 1 and 3. Groups 2 and 3 had low HF. The VHF of group 2 was significantly lower than in groups 1 and 3, which also differed from each other - the VHF values in group 1 were higher than in group 2. Total power in group 2 was significantly lower than in groups 1 and 3. Pain syndrome was less pronounced in group 2. Conclusion. The following scheme may be less stressful when performing septopalstics for general anesthesia: fentanyl, propofol, cisatracuria besylate, tranexamic acid, atropine and metoclopramide.

Keywords: septoplasty, stress, HRV, anesthesia.

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1. Introduction

A nasal septum deviation (NSD) can cause reduced airflow in the nasal cavity, chronic irritation of the mucous membranes and postnasal dript [1]. The association between upper airway obstruction and cardiovascular disease has previously been investigated in relation to cardiac arrhythmias, pulmonary vascular reactivity and cardiac mortality. The mechanisms underlying this relationship have been attributed to increased oxidative stress and increased sympathetic nervous system (SNS) tone [2].Septoplasty is still the most common surgical procedure for NSD [3]. The choice of septoplasty as a treatment method for patients with nasal septum deviation is beyond doubt. So, over the next 6-12 months, septoplasty leads to an improvement in nasal breathing and, as a result, to an improvement in the quality of life. At the same time, the general antioxidative status of patients improves.

In our previous studies on experimental septoplasty simulation in rats, the degree of its stressfulness was shown. Thus, in the first two days in animals, a depressive-like state develops[4] changes in the cytoarchitectonics of the pyramidal layer of the hippocampus and there is an increase in p53-positive neurons in it[5] as a result of local inflammatory reactions and narrowing of the common nasal passages in response to damage to the nasal septum, and also the subsequent severe imbalance of the autonomic nervous system (ANS) [6].

Surgical interventions in the human nasal cavity lead to changes in the balance of ANS [1], as well as to the occurrence of cardiac arrhythmias [7]. When performing septoplasty, it is important to use both local and general anesthesia with sedation, since severe pain can cause a decrease in heart rate due to the predominance of the tone of the parasympathetic nervous system (PNS) over the sympathetic (SNS), which, in turn, lowering the pulse, and leads to a dangerous drop in blood pressure. These side effects can be monitored using a daily recording of a Holter electrocardiogram and an analysis of heart rate variability (HRV).

HRV is a physiological parameter influenced by the balance between SNS and PNS [8]. A decrease in HRV with short ECG records is a manifestation of the reactions of normal adaptability of the body, but with daily monitoring of the ECG, such rigidity is a sign of a violation of the adaptive reactions of the body [9].

Although there are several studies in the literature investigating the relationship between HRV and NSD [10], as well as the effect of septoplasty on postoperative HRV [1], however, to date, there are no studies that have evaluated the effect of anesthesia choice during septoplasty on stress responses in the early postoperative period - imbalance of the autonomic nervous system and acute pain syndrome. In the present study, an attempt was made to determine the least stressful method of anesthesia during septoplasty based on the assessment of heart rate variability and acute pain.

2. Patients and Methods

In the period from 2014 to 2021. The study involved 291 people with NSD who underwent septoplasty. We studied the three most popular methods of anesthesia in clinics in Moscow (Russia) (Table 1).

Table 1. Study Design.

	1st group		2nd group		3rd group	
Number of patients	n=105		n=108		n=78	
Age (years)	18-44		18-45		17-42	
Sex	men	women	men	women	men	women
	n=58	n=47	n=62	n=46	n=44	n=34
Premedication	sol. Promedolum 2% 1ml.		no			
Local infiltration anesthesia	sol. Procaini 1% (250 mg), sol. Epinephrini 0,1% (10 mg)					
General anesthesia	no		sol. Phentanyli (30 mkg/ml), sol. Propofoli (150 mg), sol. Nimbexi (6 mg), sol. Traneksami (1000 mg), sol. Atropini (0,5 mg), sol. Cerucali (10 mg)		sol. Tracriumi (20 ml), sol. Thiopentali sodiumi (750 mg), Nitrogenium oxydulatum (1 л/ч), Phthorothanum 1 об/%	
Analgesic therapy on the day of surgery at 20-22 pm	sol. Ketorolaci (60 mg)		sol. Ketoprofeni (100 mg)			
Patient examination methods	Holter ECG 24-hour monitoring VAS					

164 men and 127 women (from 18 to 45 years old) were operated on. The study included only those women who had surgery during the periovulatory period (endometrial proliferation phase) of the menstrual cycle, since it was previously shown that it is during this period of the ovarian-menstrual cycle that the risk of nosebleeds is minimal when performing surgical interventions in the nasal cavity.

2.1. Exclusion criteria.

The study excluded patients with severe chronic diseases of the cardiovascular system, lungs, kidneys, cancer patients, mental illness, with concomitant nasal and paranasal sinus pathologies (polypous rhinosinusitis, hypertrophy of the inferior turbinates, papillomas, chronic sinusitis, paranasal sinus cysts).

2.2. Perioperative anesthesia and pain management.

Patients were randomly assigned to groups according to the type of anesthetic aid. In the first group (105 people), septoplasty was performed under local anesthesia. Local infiltration anesthesia was also used in both other groups using 2% procaine solution, and to reduce the risk of intraoperative nosebleeds - 0.1% epinephrine solution. Ketarolac (60 mg) was used intramuscularly as an anesthetic in this group in the evening (Table 1).

In the second group (108 patients), in addition to local anesthesia, fentanyl, propofol, cisatracuria besylate (nimbex), tranexamic acid (tranexam), atropine and metoclopramide (cerucal) were used. 78 patients of the 3rd group received atracuria besylate, sodium thiopental, nitrous oxide and halothane (fluorothane) as general anesthesia. As a non-steroidal anti-inflammatory drug in patients of groups 2 and 3, 100 mg of ketoprofen was used intramuscularly in the evening hours on the day of surgery (Table 1). For all patients for anterior nasal tamponade, foam tampons with a rubber glove were used. In the 1st and 2nd groups, the operated surgeons removed the tampons two days after the operation, and in the second - one day later.

2.3. Heart rate variability.

40-60 minutes before the surgical intervention, the Schiller MT-210 (Schiller, Switzerland) daily Holter ECG monitoring system was installed for 24 hours. To assess the state of the vegetative system, the parameters of the HRV frequency range were evaluated: ultra-low-frequency component (ULF), very low-frequency component (VLF), low-frequency component (LF), high-frequency component (HF), very high-frequency component (VHF), as well as total power.

2.4.Assessment of the intensity of pain syndrome.

The severity of acute pain after septoplasty was assessed using a visual analogue scale (VAS) (Fig. 1).

Figure 1. Visual analogue scale (100 mm).

Patients were asked to mark with a vertical line the place of the scale that, in their opinion, corresponded to the pain experienced. The gradation of pain intensity was as follows. From 0 to 25 mm pain was assessed as mild or absent, from 26 to 50 mm pain was considered moderate, severe pain corresponded to the range 56-75 mm, and very severe and unbearable pain - 76-100 mm. VAS was offered to patients 1, 3, 6, after surgery. One day and two days after the operation, the pain intensity was assessed 1 hour after the removal of the anterior nasal tampons.

*2.**5**. Statistics.*

The data were processed using Exel 2019, JASP 0.14.0.0, Schiller MT-210 programs. With a uniform distribution of the data sample, the Student's t test was used to determine the reliability of differences, and the Mann-Whitney test was used for an uneven distribution.

The study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects of World Medical Association Declaration of Helsinki; Federal Law No. 323-FZ "On the Basics of Health Protection of Citizens in the Russian Federation"; Order of the Ministry of Health of the Russian Federation No. 200n "Rules for Good Clinical Practice"

3. Results. HRV.

According to Student's test, the ultra-low-frequency component of HRV in the groups with general anesthesia was significantly higher than in the group with local anesthesia ($p < 0.01$) (Table 2, Fig. 2a).

Table 2. Frequency Analysis Of HRV In Patients After Septoplasty

	ULF (Hz)	VLF(Hz)	LF (Hz)	HF (Hz)	VHF (Hz)	Total power
1st group	0,0005±0,00006	0,01±0,0003	0,08±0,00082	0,2±0,003	0,5±0,006	0,04±0,004
2nd group	0,0005±0,00005	0,01±0,0002	0,09±0,001	0,2±0,002	0,5±0,01	0,03±0,002
3rd group	0,0006±0,00006	0,01±0,0003	0,09±0,001	0,2±0,002	0,007	0,04±0,002

Similar data were obtained when analyzing the low-frequency component ($p < 0.01$) (Table 2, Figure 2b). The very low-frequency component, according to the Mann-Whitney criterion, in the second group was significantly lower (p ‹0.01), compared with groups 1 and 3, which did not differ from each other (Table 2, Fig. 2b). Comparison of the high-frequency component, according to Student's t-test, showed that the groups with general anesthesia had significantly low HF HRV (p ‹0.001), compared with the group of local anesthesia, and did not differ between themselves (Table 2, Figure 2d). The very high frequency component of group 2 was significantly lower than in groups 1 and 3 (p ‹0.001, Mann-Whitney test), which also differed among themselves – the VHF values in the first group were higher than in the second (p‹0,01, Student's test) (Table 2, Figure 2e).

The total power spectrum, according to the Mann-Whitney test, in the second group was also significantly lower (p ‹0.001) than in groups 1 and 3. However, the total power of the 3rd group was significantly higher than that of the 1st group (p ‹0.01) (Table 2, Figure 2f).

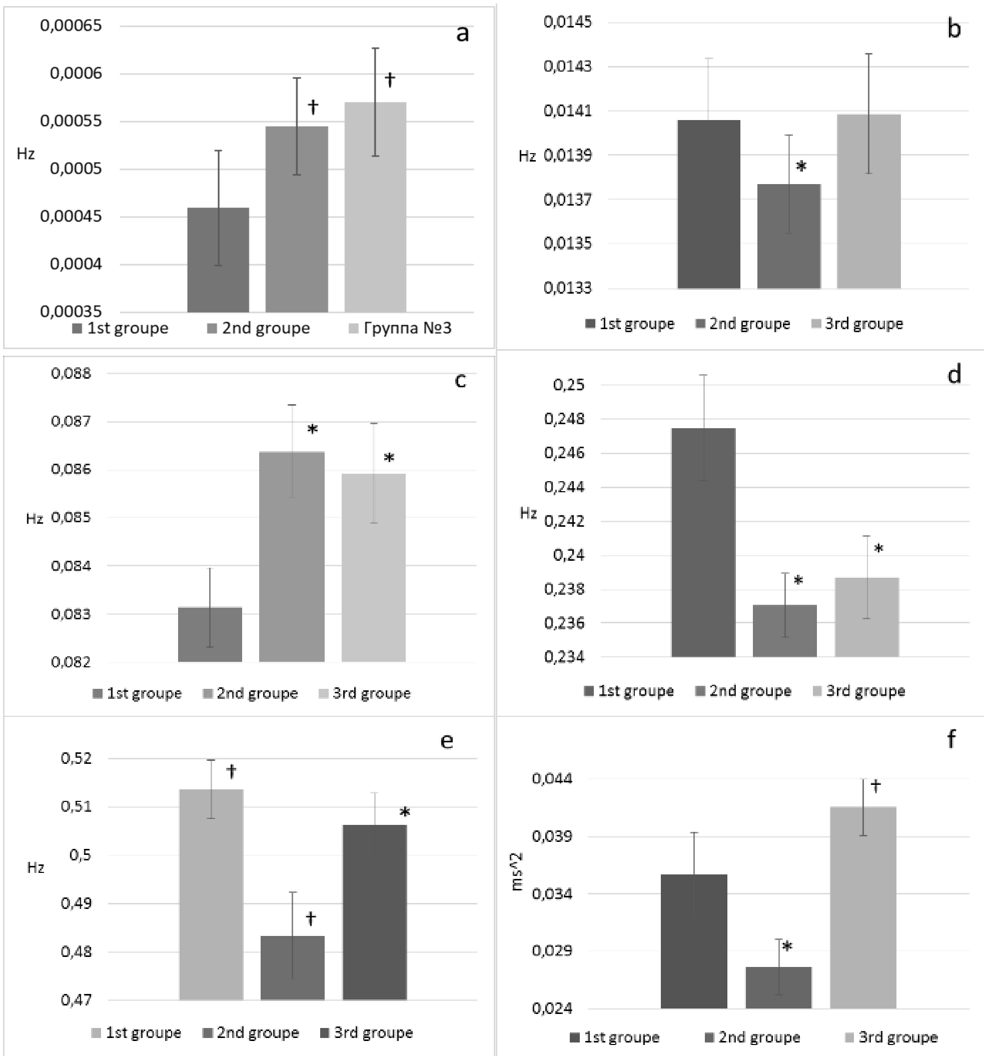

Figure 2. Changes in HRV in the frequency spectrum after septoplasty: a - ultra low frequency component (ULF), b - very low frequency component (VLF), c - low frequency component (LF), d - high frequency component (HF), e - very high frequency component (VHF), e - total power spectrum. * - significant differences between groups at p ‹0.01; † - significant differences between groups at p ‹0.05 (explanations in the text).

3.1. Pain intensity.

According to the Mann-Whitney criterion, the pain syndrome during the first two hours after septoplasty was significantly lower in the second group than in the other groups (p ‹0.001) (Fig. 3).

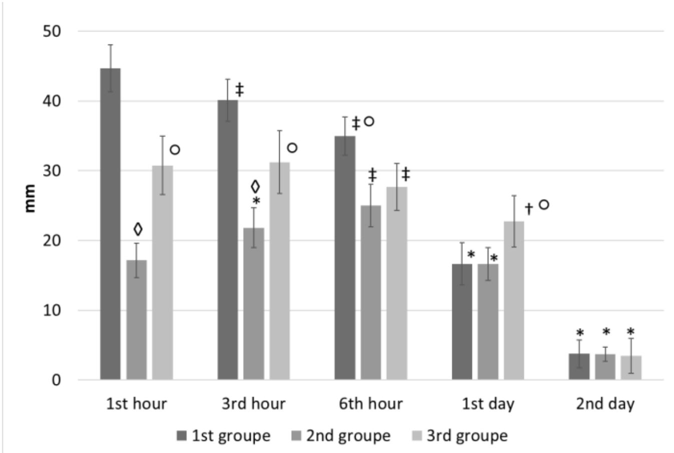

Figure 3. Comparison of pain syndrome in groups of patients with different anesthetic tactics using VAS: * - significant differences between the terms after surgery within the group at p ‹0.001; † - significant differences between the terms after surgery within the group at p ‹0.01; ‡ - significant differences between the terms after surgery within the group at p ‹0.05; ◊ - significant differences between groups at p ‹0.001; ○ - significant differences between groups at p ‹0.01; ● - significant differences between groups at p ‹0.05.

Table 3. Change In Pain Intensity (mm).

Time after septoplasty	1st hour	3rd hour	6th hour	1st day	2nd day
1st group	44,65±3,37	44,65±3,37	44,65±3,37	44,65±3,37	44,65±3,37
2nd group	17,15±2,47	17,15±2,47	17,15±2,47	17,15±2,47	17,15±2,47
3rd group	30,75±2,21	30,75±2,21	30,75±2,21	30,75±2,21	30,75±2,21

At the same time, the intensity of acute pain in the first group was significantly higher than in the third (p ‹0.01). 6 hours after surgery, pain in the groups with general anesthesia was significantly lower than in the group with local anesthesia and premedication (p ‹0.01), and did not differ among themselves. One day after septoplasty, the severity of pain in the first two groups was statistically the same, but in the third group the pain was more intense (p ‹0.01) (Fig. 3). Two days later, in all groups, the intensity of the pain syndrome was low or it was not statistically indistinguishable (Tab.3).

The dynamics of the severity of acute pain within the groups was as follows. In the first group, its significant growth was noted at the 3rd (p ‹0.01) and 6th (p ‹0.05) hours after the operation (Fig. 3). Then there was a significant decrease (p ‹0.001). A gradual decrease in pain severity was observed in group 1 after 1 and 3 hours (p ‹0.05), as well as on days 1 and 2 after septoplasty (p ‹0.001). In patients of group 3, a decrease in pain syndrome was noted only 6 hours after surgery (p ‹0.05) with its gradual regression (Tab.3).

4. Discussion

Septoplasty, if performed by experienced surgeons, is a daily surgery due to its short duration and relative ease of postoperative rehabilitation [11]. Due to the peculiarities of the innervation of the nasal septum, it is strongly recommended to carry out high-quality control and prevention of bleeding during surgery and effective postoperative analgesia [12]. In the present study, the examined patients did not have massive intraoperative bleeding, and those who had them were not included in the study, since this would most likely affect the HRV results. Also, all patients underwent standard analgesic therapy with non-selective blockers of cyclooxygenases 1 and 2.

In the early postoperative period after septoplasty, inflammation (pronounced edema, hyperemia of the nasal mucosa, abundant mucous discharge, hemorrhagic crusts) persist for up to two days, followed by a decrease until the 14th day after surgery. This can explain the more pronounced pain syndrome in 3 group, since the tampons were removed within a day after septoplasty, which corresponds to our other data obtained earlier [13].

HRV helps to identify changes in ANS, metabolism, hormonal status, exposure to stress factors, etc. Both SNS and PNS activity contributes to HRV and is highly correlated with the power of the ULF, VLF and LF bands as well as the total power [14].

ULF is often associated with circadian rhythms. An increase in values in all three groups indicates a failure of the circadian rhythms as a result of surgical trauma, especially in the groups with general anesthesia.

VLF also shows a state of hyperactivity, mobilization of energy and metabolic reserves, centralization of the regulation of adaptive mechanisms by increasing the influence of higher autonomic centers and mobilization of the hypothalamic-pituitary-adrenal axis. In the group with local anesthesia and in the group with the use of atracurium besylate, sodium thiopental, nitrous oxide and fluorothane, VLF was increased, which clearly indicates the transition of control over the autonomic regulation of the heart from the spinal to a higher level - the level of the autonomic centers of the brain.

HF shows the tone of the parasympathetic nervous system, while LF, according to some authors, can reflect both sympathetic (predominantly) and parasympathetic tone [15]. In the present study, LF was increased in the general anesthesia groups, which may indicate an increased sympathetic effect on the heart. The high-frequency component of HRV was significantly higher in the group with local anesthesia, which indicates an increase in PNS and the development of normal adaptive responses in this group.

The presence of activity in the VHF range can serve as a diagnostic test for vagus nerve denervation[16]. An increase in VHF in groups 1 and 3 indicates a decrease in control from the PNS, as well as an increase in the "centralization" of autonomic regulation, which is confirmed by an increase in VLF in these groups.

Total power is the sum of the energy in the ULF, VLF, LF, and HF bands in 24 hours[17]. This indicator can characterize the general vegetative activity, with sympathetic activity being the main factor [18]. The increase in total power was also observed in groups 1 and 3, but it was less in the group with local anesthesia.

The worst indicators are possessed by groups 1 and 3, in which reactions of centralization of autonomic control were observed, in comparison with group 2. In patients of group 1, on the first day after the operation, the tone of the parasympathetic nervous system dominated, over the sympathetic, which was not observed in the groups with general anesthesia. This can be regarded as a disruption of normal adaptive responses, since the SNS should first of all respond to stress[19]. Normal secondary activation of the sympathetic nervous system to secondary surgical stress occurred in the groups with general anesthesia, while in the second group it was less pronounced [20-25].

Among the presented schemes of anesthesia for septoplasty, the most preferable is the scheme for the use of fentanyl, propofol, cisatracurium besylate, tranexamic acid, atropine and metoclopramide, which is quite consistent with modern concepts of multimodal anesthesia [26]. The existing opinion about the best subjective indicators in patients after septoplasty with local anesthesia is not confirmed in this study.

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Conflicts of Interest: The authors declare no conflict of interest.

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Article

The effect of stress on the formation of p53-positive and dark neurons in the hippocampus in a model of septoplasty in rats

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Abstract: The aim of this study was to determine the role of surgical stress on the formation of p53-positive and dark neurons (DN) in the hippocampus, and to examine the parallelism of their formation in the pyramidal layer of the hippocampus.

Simulated septoplasty was performed on 20 Wistar rats. The hippocampus and dentate gyrus (DG) were examined, in which the number of DN and p53-positive neurons was determined at 2, 4 and 6 days after surgery.

Compared with the control group (n = 5), the number of DN and p53-positive neurons increased in experimental animals at all periods. A direct relationship was obtained between the increase in the number of DN and p53-positive neurons in the hippocampal formation.

Septoplasty simulation in rats results in the pathogenetic cascades onset, which, in its turn, changes the morpho-functional properties of neurons of the pyramidal layer of the hippocampus and contributes to their neuroplasticity.Activation of NMDS receptors of neurons during stress apparently, initiates two ways of neuron life – the beginning of p53 protein expression and the DN formation. Both ways can finally lead to apoptosis. The formation of dark neurons and the expression of the p53 protein in them are most likely to be interconnected and can probably provide neuroprotective mechanisms.

Keywords: septoplasty, stress, p53, dark neurons, hippocampus.

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1. Introduction

Simulated septoplasty in rats leads to the development of a powerful stress response. Few experimental data are available to determine the consequences of nasal surgery [1].

Various stressors lead to changes in the functional state of neurons with the development of subsequent morpho-physiological abnormalities [2]. The hippocampus receives special attention in stress because it is very sensitive to various damaging factors [3, 4]. In neuronal damage, as in damage to other cells, p53 protein is an activator of transcription of a specific set of target genes, a cell cycle inhibitory regulatory factor and an effector of cellular responses to damage, which include cell cycle arrest and apoptosis [5]. However, p53 has also been shown to be neuroprotective. For example, this has been shown in an in vivo model of tautopathy [6]. P53 controls the transcription of a group of genes involved in the synaptic function of neurons. The transcriptional control of p53 of these synaptic genes is conserved in mouse neurons and the human brain[6]. Morphologically altered neurons after exposure to stressors can have basophilia in their staining [3, 7]. Such neurons are usually referred to as dark neurons. They have specific morphological features: shrunken cytoplasm, karyopiknosis, corkscrew axon [3, 7]. Apoptosis is believed to occur in these neurons [8]. However, it is not excluded that dark neurons are capable of restoring their morpho-functional state under certain conditions [7].

However, no studies evaluating the parallelism of p53 protein expression in hippocampal neurons and the appearance of dark neurons there in have been performed in a septoplasty simulation in rats.

The aim of this study was to determine the role of surgical stress on the formation of p53-positive and dark neurons in the hippocampus, and to examine the parallelism of their formation in the pyramidal layer of the hippocampus.

2. Patients and Methods

In the study, 20 sexually mature male Wistar rats weighing 250±20 g were randomly divided into experimental (n=15) and control (n=5) groups. The rats were kept under controlled temperature (23±2.5°C), 12-hour illumination and free access to water and food. Anesthesia was administered with zoletil 100 solution (15 mg/kg) 10 min before surgery to 15 rats, which constituted the experimental group.

The animals were housed in a specially equipped room, access to which was limited. Intact animals were housed in cages for individual housing. In the experimental male rats were used no earlier than 2 weeks later – the period of adaptation to new conditions of detention. The rats received a standard diet once a day, with free access to water. All animals during the experiments were under the same conditions. The keeping of rats, modeling of surgical trauma – septoplasty, as well as the removal of animals from experience were carried out in accordance with the ethical standards set in the Geneva Convention "International Guiding principles for Biomedical Research Involving Animals" (Geneva, 1990).

Experimental procedure. 20 animals in the experimental group were simulated septoplasty using the standard method by zigzag scarification of the nasal cavity mucosa with a sharp probe in caudo-cranial direction (Fig. 1a)[9].

Tissue probe. In the experimental and control groups, euthanasia was carried out by administering toxic doses of zoletil 100 solution. In the experimental group the animals were slaughtered on the 2nd, 6th and 14th days postoperatively, 5 animals for each period. The brain was first perfused through the aorta with 0.9% sodium chloride solution, then with 10% formalin buffered solution, after which the brains were encased in paraffin blocks. Serial slices of the brain at the level of the bregma were taken with a microtome blade and 8 slices in the frontal plane, 4 μm thick, were obtained from each animal.

Staining. In each rat, 10 brain slices were stained with antibodies to p53 protein with Meyer's haematoxylin and 10 slices were stained with Nissl toluidine blue. Hippocampal subfields CA1, CA2, CA3 and dentate gyrus (DG) were studied (Fig. 1b, 1c).

Morphometry. In the pyramidal subfield layer, the absolute number of neurons that were nuclear antibody-positive to p53 protein was counted, as well as the number of dark neurons (Fig. 2).

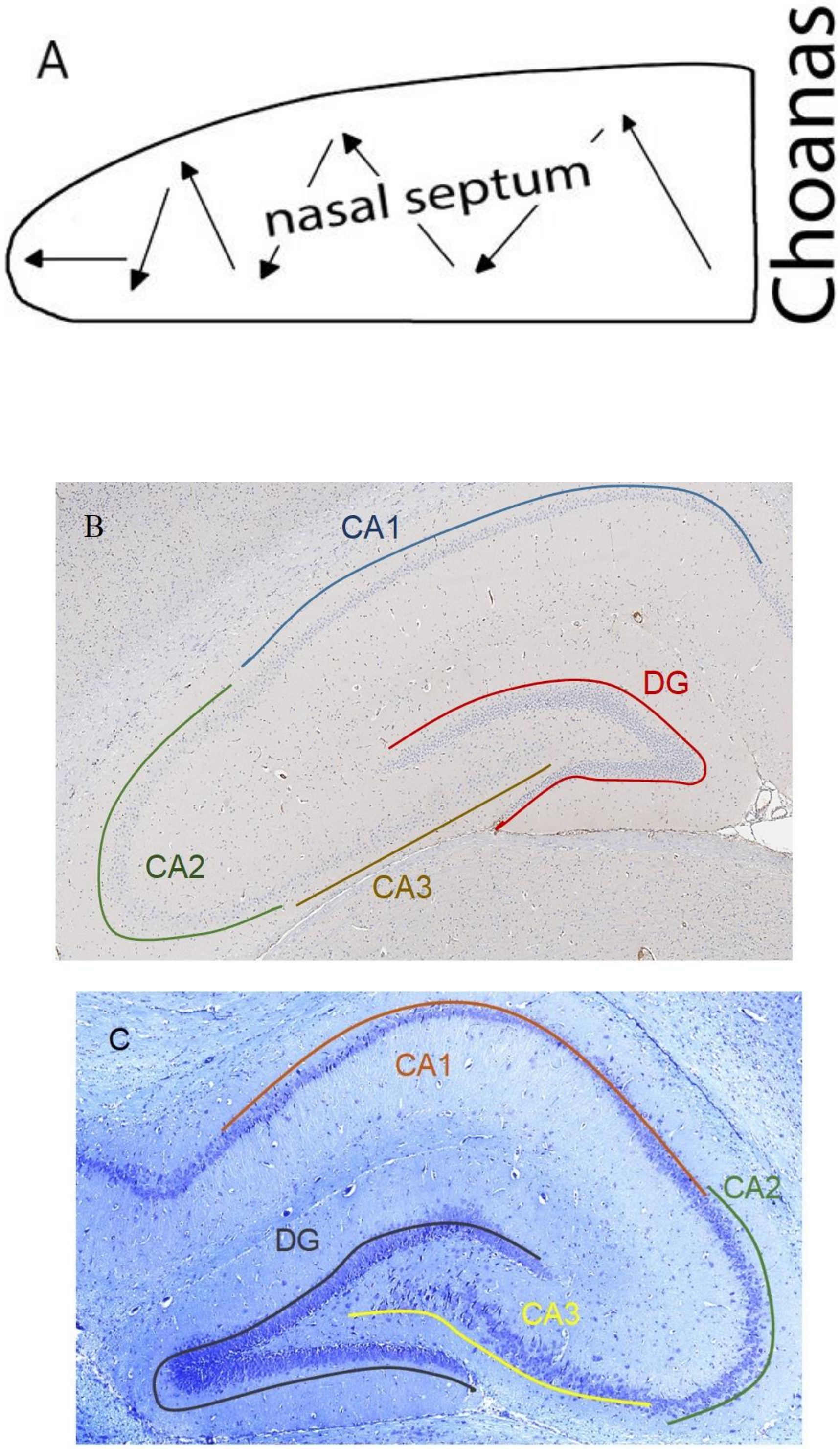


Figure 1. A. Scheme of the septoplasty simulation. Arrows indicate the direction of the nasal septum scarification. B. Location of the rat hippocampus subfields. Immunohistochemical reaction anti-p53. Staining with Mayer's hematoxylin. Magnification, x10. C. Location of the rat hippocampus subfields. Nissl staining. Magnification, x10

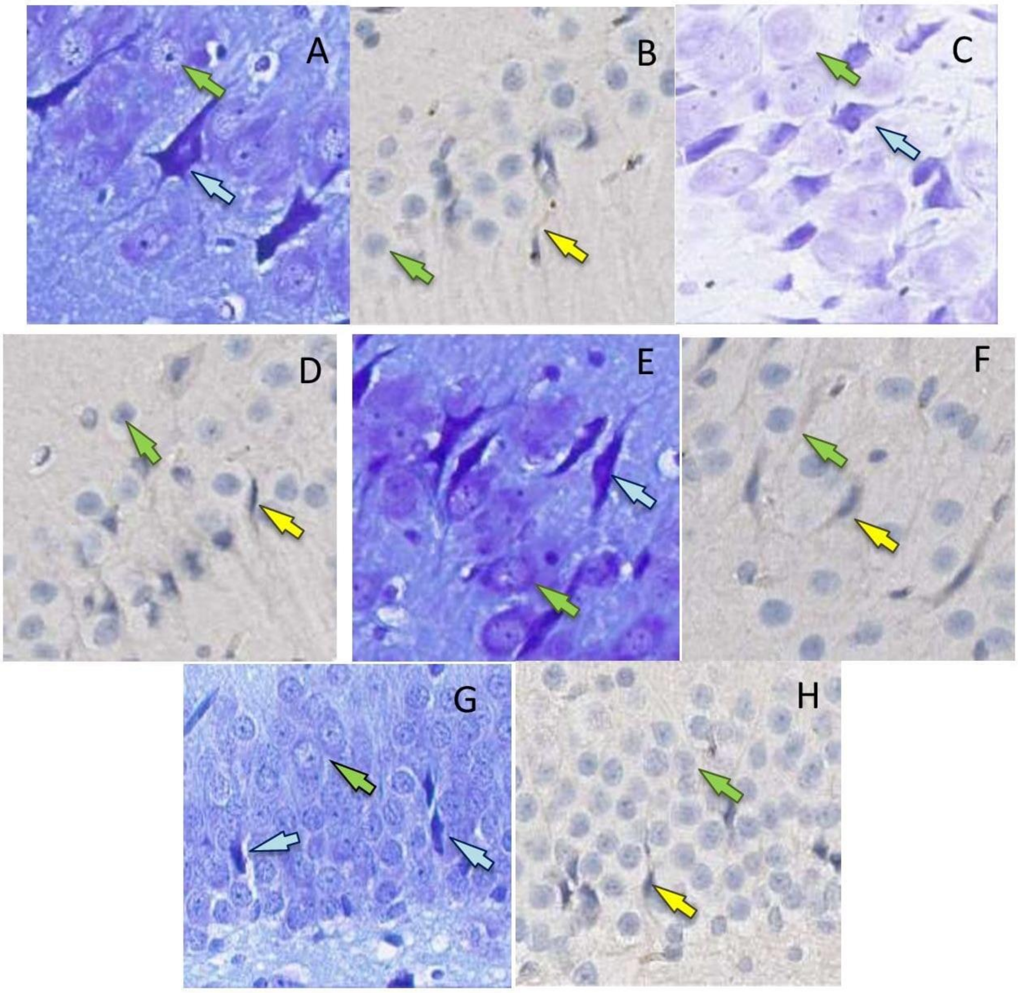


Figure 2. P53-positive neurons (b, d, f, h) (yellow arrows, surrounded by mouse monoclonal antibodies to p53 protein, x400) and dark neurons (a, c, d, g) (blue arrows, Nissl toluidine blue, x400) in the hippocampal formation in rats on the 2nd (a, b, g), 4th (c, d, h) and 6th days (e, f) after the septoplasty simulation. Green arrows indicate intact neurons. Subfield CA1 – a, d; subfield CA2 – b, c; subfield CA3 – e, f; DG – g, h.

The counting area in each subfield was 20934±1260 μm^2. Neurons are counted using the Aperio ImageScope program. For the histological specimen analysis, the ImageJ software was used.

Statistical analysis of the data. The data obtained using cell counting methods were presented as mean ± SE. Then, they were compared between both groups using a t-test SPSS 21software.

3. Results

Number of dark neurons. There was a non-Gaussian distribution in the number of THs in the pyramidal layer of the hippocampus both in the experimental and control groups. In CA1, the number of TNs on days 2 and 4 did not differ significantly from the control, but on day 6 postoperatively there was a decrease ($p<0.001$) (Fig.3b).

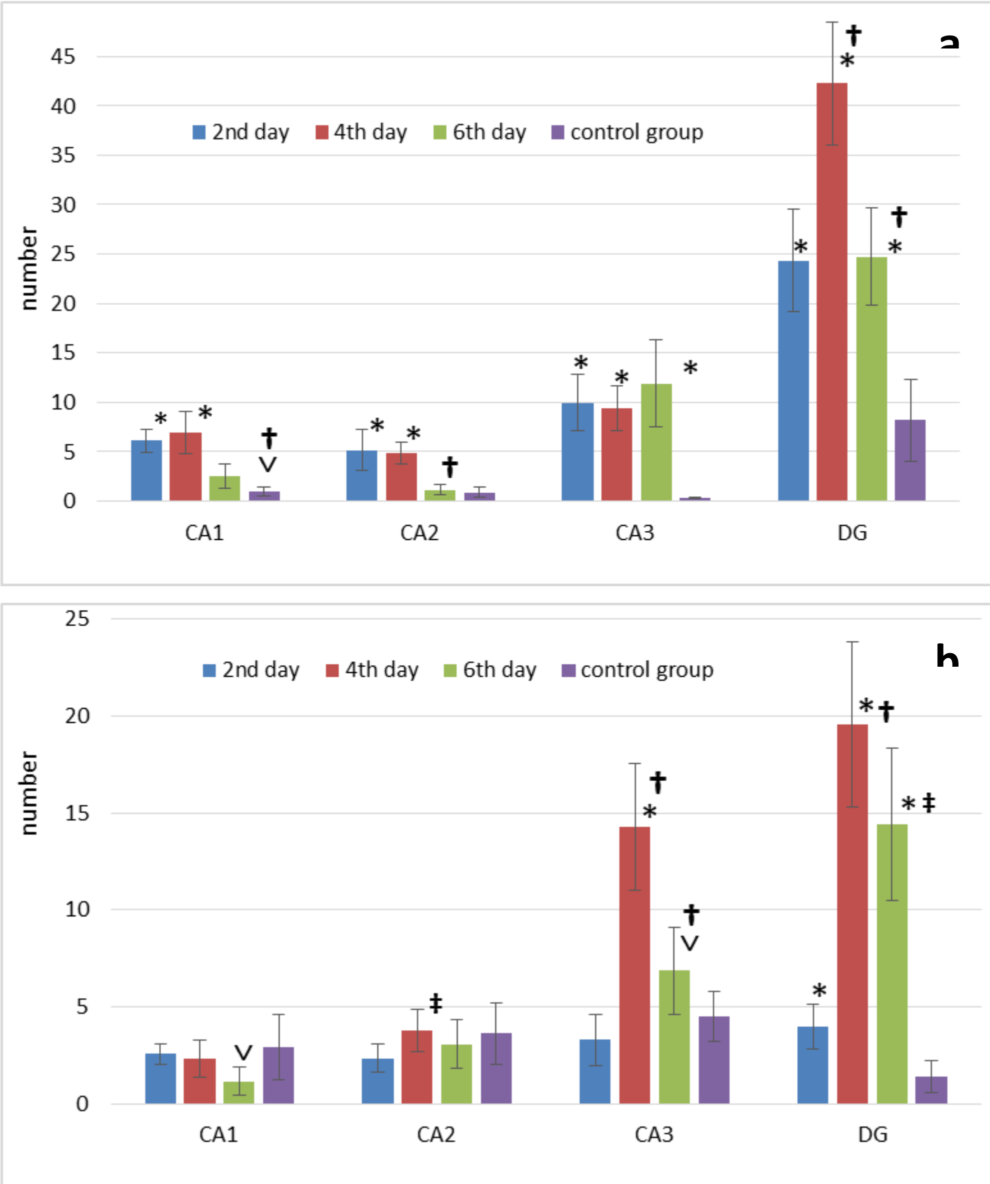


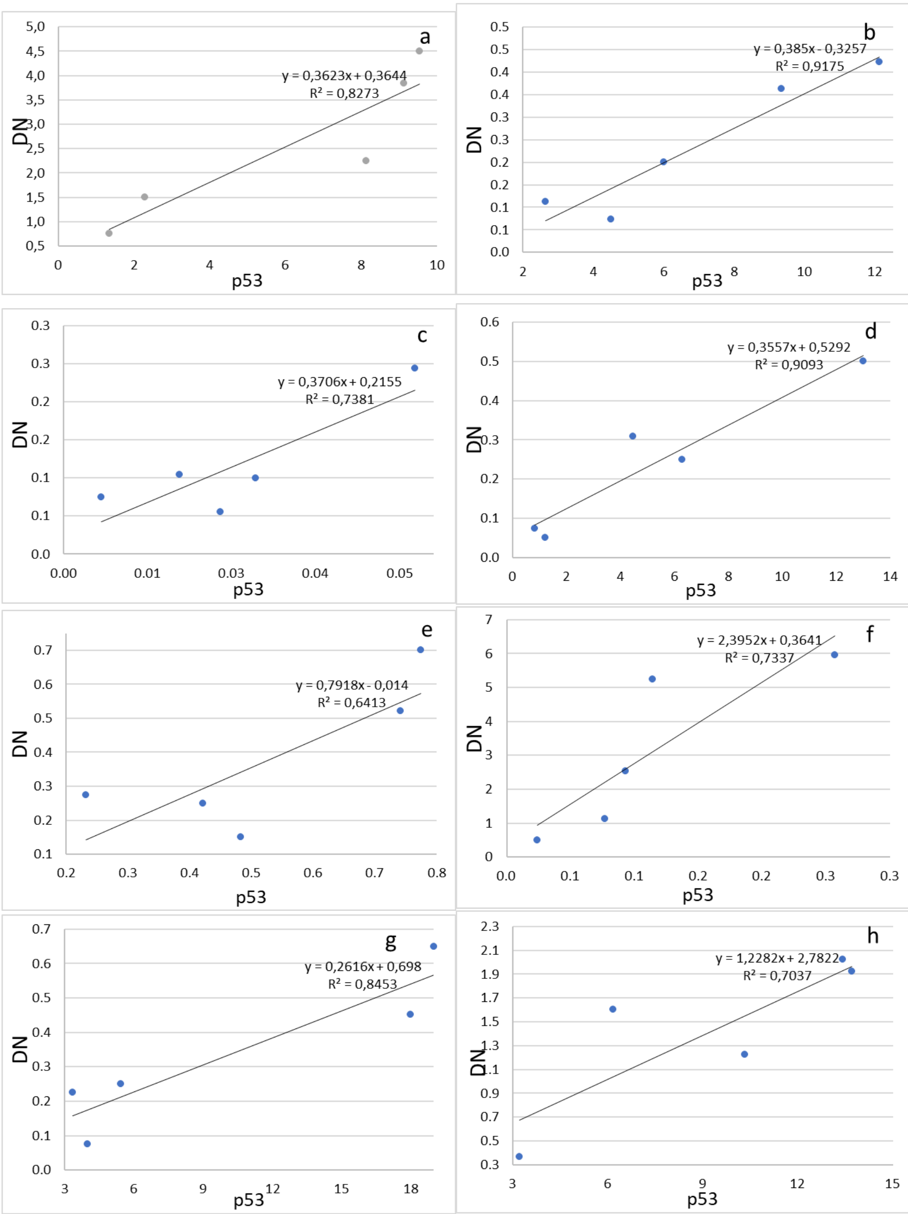
Figure 3. Changes in the number of p53-positive neurons (p53) (a) and dark neurons (b) in the septoplasty simulation. Note: * - significant differences between data of the control group and terms after operation (p<0.001); ˅ - significant differences between data of the control group and terms after operation (p<0.05); † - significant differences between terms after operation within experimental group (p<0.001); ‡ - significant differences between terms after operation within the experimental group (p<0.05).

There was no significant difference in CA2 between the experimental group and the control group. On day 2 postoperatively, there was a minimum of THs compared to day 4 (p<0.001). On day 4 postoperatively, there was the peak in number of THs in CA3 compared to the rest of the day (p<0.001). In the control group, the number of THs was not different from day 2, but it was significantly lower compared to day 4 (p<0.001) and day 6 (p<0.05) after surgery (Fig. 3b). In DG, similar results to CA3 were observed (Fig.3b).

Number of p53-positive neurons. According to Mann-Whitney test the number of p53-positive neurons in CA1 significantly increased on days 2, 4 ($p<0.001$) and 6 ($p<0.05$) after septoplasty compared to control group. Dynamically, the peak of increase in the p53 protein expression in the cytoplasm of CA1 and CA2 neurons of hippocampus occurred on days 2-4, and on day 6 the number of these neurons significantly decreased ($p<0.001$). On day 6, p53-positive neurons in CA2 did not differ from the control group (Fig.3a). In CA3 there was an increase in p53 protein expression at all time points after surgery compared to the controls ($p<0.001$).

In DG, compared to the controls, the number of p53-positive neurons was significantly higher at all time points of evaluation. The number of these cells peaked on day 4, compared to the other terms ($p<0.001$) (Figure 3a).

Comparing the number of neurons in which the p53 protein was expressed into the cytoplasm and the DN number, a positive strong correlation was found at all evaluation lines and in all hippocampal subfields (Fig.4).



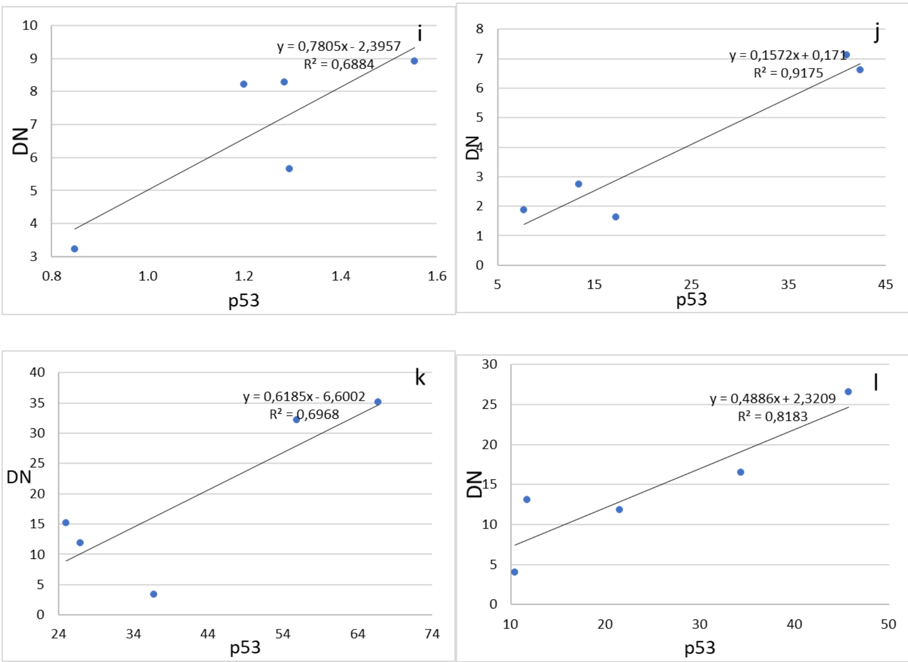


Figure 4. Correlation between the number of dark neurons (DN) and the number of p53-positive neurons (p53) in the hippocampal subfields CA1 (a-c), CA2 (d-f), CA3 (g-i) and DG (j-l) on the 2nd (a, d, g, j), 4th (b, e, h, k) and 6th (c, f, i, l) days after the septoplasty simulation.

The lowest coefficient of determination was found when evaluating the CA2 subfield on the 4th day after surgery (Table 1).

	Days after Septoplasty Simulation		
	2-d (R2)	4-th (R2)	6-th (R2)
CA1	0,80	0,94	0,71
CA2	0,92	0,60	0,73
CA3	0,88	0,70	0,61
DG	0,92	0,71	0,82

Table 1. Determination coefficients for comparing the number of dark neurons (TN) and the number of p53-positive neurons (p53) in the hippocampus after septoplasty simulation.

4. Discussion

The p53 protein is activated by cellular stress and DNA damage and, depending on the severity of stress and the specific cell type, can contribute to adaptive responses to stress or can trigger cell cycle arrest or its apoptosis [10]. When normal proliferating cells are DNA damaged, they may react in one of the two ways: cell cycle arrest r apoptosis, and p53 is engaged in both of those processes [11].

The p53 protein is an important component in the neuron apoptosis, for example, after ischemic event or excitotoxicity [12]. An increase in number of such neurons has been demonstrated in ischemia, traumatic brain injuries [13]. Some research studies have proved that p53 is part of the biochemical processes in the cell caused by the activation of NMDA-receptors (N-methyl-D-aspartate) and finally resulting to apoptosis [14].

The mechanisms of proapoptotic action are assumed to be realized through the induction of the TP53 gene (protein p53) expression, the regulation of which inhibits the passage of the cell cycle from G1 to S-phase, which blocks the division of cancer cells and tumor growth[15]. Except to the widely studied role of p53 as a regulator of apoptosis triggering, its neuroprotective role has also been demonstrated [16]. The main goal of neuroprotection is to prevent the death of neurons in the ischemic area, where apoptosis is one of the mechanisms of neuronal death. Bioenergetic processes are slowed down in the penumbra and neurons which have not died yet, remaining in them. In this regard, the absence of neurons in the hippocampus with obvious morphological signs of apoptosis in the analysis of the slices obtained by us, may indicate the presence of neuroprotective properties of the p53 protein. It has been shown that posttranslational modifications of p53 can contribute to the differentiation of neurons, as well as to the growth and regeneration of axons [17].

It was shown that p53 is a neuroprotector in an in vivo model of taupathy[18]. By analyzing the chromatin immunoprecipitation chip, it was determined, that p53 controls the transcription of a group of genes participated in providing synaptic function. Genetic manipulation of these genes changed the neurotoxicity of the tau- protein. The authors have found, that both in mice's neurons and in the human brain, transcriptional control of these synaptic genes is maintained due to p53. Thus, it has been suggested, that the provision of synaptic function, as a manifestation of neuroprotection, can be performed by p53 protein[18].

In addition to activating the TP53 gene, NMDA receptors participate in caspase-dependent apoptosis, increasing the level of calcium ions, boosting the enzyme caspase-3 activity. This enzyme, in turn, start the formation of dark neurons and their next degeneration. When inhibiting caspases with the pancaspase inhibitor FK011, a decrease in the changes characteristic of dark neurons has been achieved[19].

Previously, it was also shown, that dark neurons can both restore their morpho-functional state by increasing the cisterns of the granular endoplasmic reticulum with the formation of membrane curls, the transition of this process to astrocytic processes and, as a consequence, with a subsequent decline in the degree of structural compaction of the cell [7], and be a sign of the final necrotic decay of the cell regardless of the cause of neuron death, including various biochemical cascades of apoptosis [8]. There is an opinion, that dark neurons- are the result of oxidative stress. Thus, it has been shown, that the use of luteolin after brain injury in vivo reduces the number of dark neurons and oxidative stress in them in the hippocampus [20]. It has been shown, that the presence of regenerating dark neurons in the case of animal studies indicates the vulnerability of neuroprotective properties of neuroglia [21]. The presence of such phenomena, as cytoplasmic shrinkage and surface reduction in DN is compared by some authors with the manifestation of neuroplasticity characteristics [22,23]. In fact, plasticity refers to the unique ability of the brain (neuron) to change and reorganize in response to changes in the environment.

This property of neurons contributes to their viability and, consequently, the organism's survival [24].The most well-known examples of neuronal plasticity are the formation of new synapses, the proliferation of dendritic spines, the retraction and simplification of dendrites, and the reduction of dendritic spines under stressful conditions. Some studies have shown that endogenous or exogenous stressors are associated with a decrease in the surface and dendritic spike of neurons [25].

The high determination coefficients found in this study confirm the theory that presence of dark neurons in the hippocampus and dentate gyrus is most likely closely related to the expression of the p53 protein during surgical stress caused by septoplasty simulation in rats. This is probably due to the activation of NMDS receptors in neurons under the influence of surgical stress, as it has been shown that stress leads to an increase in the content of NMDA receptors in the dendritic spike apparatus[26]. In addition, exposure to a large amount of glutamate leads to functional changes in neurons and subsequent launch of the apoptosis program [27]. Stress is known to result in degeneration of hippocampal neuron dendrites [28]. In dark neurons, the dendrites are poorly developed or practically absent as a result of modulation of NMDA receptors. This was shown by the example of CA3 subfield neurons in the hippocampus [29]. In addition, chronic stress has been reported to cause atrophy of the pyramidal layer of the subfield CA1 [30, 31], decrease the long-term potentiation of neurons of the hippocampal CA1 subfield [32] and cause apoptosis of neurons, as well as a decrease in the density of dendritic spikes in neurons in the CA1 region of the hippocampus [33]. Thus, it can be assumed that there is a common mechanism that result to the start of two processes, discussed in this article – the expression of the p53 protein in the cytoplasm and the formation of dark neurons. The trigger of these pathways is probably the activation of NMDA receptors of neurons.

Morphological changes in the hippocamp are confirmed by our previous studies, which showed that septoplasty simulation in rats provokes the development of many stress reactions[34] and even a breakdown in adaptation[35]: an increase in the number of dark neurons[36], the expression of the p53 protein[3], a significant release of corticosterone into the blood plasma[37], and an increase in degranulation of mast cells[38], disturbances in the balance of the autonomic nervous system[39,40], changes in behavior when testing rats in an open field[9], the appearance of anxiety and a depressive-like state[41].

5. Conclusions

Septoplasty simulation in rat's results in the pathogenetic cascades onset, which, in its turn, changes the morpho-functional properties of neurons of the pyramidal layer of the hippocampus and contributes to their neuroplasticity. Activation of NMDS receptors of neurons during stress apparently, initiates two ways of neuron life - the beginning of p53 protein expression and the formation of dark neurons. Both ways can finally lead to apoptosis. The formation of dark neurons and the expression of the p53 protein in them are most likely to be interconnected and can probably provide neuroprotective mechanisms.

Compliance with Ethical Standards.

The keeping of rats, modeling of surgical trauma – septoplasty, as well as the removal of animals from experience were carried out in accordance with the ethical standards set in the

Geneva Convention "International Guiding principles for Biomedical Research Involving Animals" (Geneva, 1990).

Author Contributions: Conceptualization, G.K, V.P. and A.T.; methodology, G.K. and P.M.; software, M.K.; validation, Y.D.., S.S., O.M. and G.M.; formal analysis, V.A.; investigation, M.K. and G.K.; resources, A.T.; data curation, V.P..; writing—original draft preparation, G.K. and O.M.; writing—review and editing, V.P., P.M. and Y.D..; visualization, V.P.; supervision, O.M.; project administration, S.S . All authors have read and agreed to the published version of the manuscript.

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