Article

Study of heart rate and corticosterone variability in the simulation of experimental rhino-surgical interventions.

Stepan Shilin[1], Iana Emets[1], Jun Hyun June[1], Irina Pinighina[1], Irina Uvartseva[1], Aleksandr Chernoyarov[1], Alexander Timoshenko[1], Alexander Markushin[1], Al Khatib Nashwan[1,2], Igor Kastyro [1,*], Igor Ganshin[1], Valentin Popadyuk [1]

1 RUDN University;
2 University Clinical Hospital, Damascus, Syria;
* Correspondence: ikastyro@gmail.com;
9060965527@mail.ru, https://orcid.org/0000-0003-2080-608X (S.S)
emets.yah@yandex.ru, https://orcid.org/0000-0003-3538-3737 (I.E)
gaginmuler@gmail.com, https://orcid.org/0009-0005-0749-8387 (J.H.J)
PNG.i@inbox.ru, https://orcid.org/0000-0003-4977-4202 (I.P)
irina.uvartseva@mail.ru, https://orcid.org/0000-0002-0049-6523 (I.U)
steshartist@mail.ru, https://orcid.org/0009-0007-1167-0164 (A.C)
dr.timoshenko@gmail.com, https://orcid.org/0009-0002-2281-2889 (A.T)
markuschin17@gmail.com, https://orcid.org/0000-0003-3860-8348 (A.M)
dr.nashwan.kh@gmail.com, https://orcid.org/0009-0004-6412-6750 (A.K.N)
ikastyro@gmail.com , https://orcid.org/0000-0001-6134-3080 (I.K)
gibdoc@yandex.ru, https://orcid.org/0000-0001-5766-9416 (I.G)
lorval04@mail.ru, https://orcid.org/0000-0003-3309-4683 (V.P)

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Abstract. Aims: to assess changes in the time range of heart rate variability (HRV) and plasma corticosterone concentration in rats after simulating septoplasty. Materials and methods: a septoplasty was simulated in 30 mature male Wistar rats weighing 210-290 g. An ECG was recorded with subsequent analysis of the time domain of HRV, as well as blood sampling for changes in the concentration of corticosterone in the blood plasma. Results: SDNN significantly increased in comparison with the control on days 2 and 3 ($p < 0.001$), but decreased on days 4-5 ($p < 0.001$) and 6 days ($p < 0.01$). rMSSD changed in waves with two irregular peaks on days 1 and 6. SDNN / rMSSD, in comparison with the 1st day of the postoperative period, increased on the 2nd day and continued to grow ($p < 0.05$), and on the 4th day it began to decrease ($p < 0.01$). The total power of HRV was low throughout the postoperative period ($p < 0.001$), except for the 3rd day, when it was equal to the control data. The increase in the total power indicator fell on the 3rd day after the operation ($p < 0.01$), after which its decline occurred again. The concentration of corticosterone in the blood plasma in rats was significantly higher than before ($p < 0.001$). From the 2nd to the 4th postoperative day, its plateau was determined. Conclusion: Simulation of septoplasty leads to changes in the time range of HRV, an increase in the concentration of corticosterone in the blood plasma in rats with its maximum at the time of surgery and after 24 hours, the formation of a "plateau" from the 2nd to the 4th postoperative days, which coincides with changes of HRV.

Keywords: septoplasty, heart rate variability, corticosterone, stress

1. Introduction

The most common surgical intervention for a deviated nasal septum is still septoplasty [1, 2] and can be performed under local or general anesthesia [3]. Using biological models, we have previously shown that modeling septoplasty leads to the development of an anxiety-like state [4] as a result of swelling of the nasal mucosa, inflammatory phenomena [5], and the development of an imbalance in the autonomic nervous system (ANS) [6], which manifested by a change in the behavior of rats in an open field [4]. It was also shown that in this case, the indicators of the frequency range of heart rate variability (HRV), which characterized the shift of the ANS towards sympathicotonia, change [6]. These physiological phenomena were supported by the results of morphological studies of the hippocampus in rats. Thus, after provoking surgical inflammation on the nasal septum, the number of dark neurons and p53-positive neurons increases [7-9]. The importance of studying physiological stress reactions in biological objects is determined by the development of stress reactions and pain syndrome in patients

2. Purpose of the study

Evaluate changes in heart rate variability and corticosterone during modeling of rhinosurgical interventions in biological objects.

3. Materials and methods

3.1. Method of surgical damage:

The study involved modeling septoplasty in 30 mature male Wistar rats weighing 210-290 g. The operation was performed under general anesthesia with a solution of Zoletil 100, which was injected into the tail vein. After the animal's motor reactions died out, a zigzag scarification of the mucous membrane of the nasal septum was carried out with a metal probe - from bottom to top and from back to front (Fig. 1).

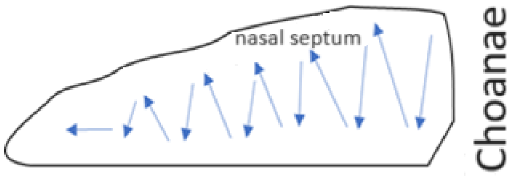

Figure 1. Scheme of modeling of septoplasty in rats - scarification of the nasal mucosa.

3.2. Electrocardiogram and heart rate variability:

Two days before the surgical intervention, all rats, under general anesthesia with a solution of Zoletil 100, were sutured with metal half-rings with capitate ends in three places - two in the back and one in the withers (Fig. 2 a, b). On the day of surgery, before the intervention itself, a control ECG recording was performed for 15 minutes on a Biopac M30-B research polygraph (California, USA). At the same time, the rats were in a free state. After the operation, the ECG was also recorded for 15 minutes daily for 6 days.

Figure 2. Scheme of applying (a) piercing (b) in rats for recording ECG on a Biopac M30-B polygraph (California, USA) (c).

From all recordings, fragments without artifacts were isolated and analyzed in the Biopack student lab 4.1 program. Recording fragments were selected 7.5 minutes (450 seconds) after the start of recording. This was due to the fact that after installing the electrodes, in the first 5-7 minutes the rat on the table got used to them and calmed down. The length of each segment was a minimum of 90 seconds for each rat. The average length of the processed ECG segments was 115±22 s.

Next, heart rate variability was analyzed according to R.M. Baevsky [11] in the Kubios HRV program (Fig. 3). Among the parameters of the HRV temporal spectrum, the following were studied: the standard deviation of R-R intervals (SDNN) between normal QRS complexes, the square root of the sum of squares of the difference in the values of successive pairs of normal R-R intervals (rMSSD), the ratio SDNN/rMSSD and total power (Total power, ms2).

Figure 3. Example of ECG data processing in Kubios HRV.

3.3. Determination of corticosterone concentration

To analyze blood plasma for the concentration of corticosterone in rats, blood was taken after recording an ECG from the tail vein before surgery, at the time of surgery, and 1-6 days after surgery. The blood obtained was immediately centrifuged [12, 13]. Blood samples were immediately centrifuged and plasma was stored at −20°C until analysis. Plasma corticosterone concentrations were quantified using ELISA. A commercial corticosterone enzyme immunoassay kit (Assay Designs Inc., Ann Arbor, Mich., USA) was used according to the manufacturer's instructions.

3.4. Statistical processing of results

Data were processed in Microsoft Exel, MATLAB, STATISTICA 12.6, JASP 0.14.0.0 software. When comparing group data before and after surgery, the Wilcoxon test was used. For each comparison, its own level of significance was determined ($p <$ from 0.001 to 0.05).

4. Results

4.1. Heart rate variability

● Standard deviation of R-R intervals. SDNN significantly increased compared to normal data on days 2 and 3 after septoplasty simulation ($p<0.001$), but decreased on days 4-5 ($p<0.001$) and 6 ($p<0.001$). 01). On days 2-3 of the postoperative period, there was a significant decrease in SDNN compared to day 1 ($p<0.01$). However, on days 4-6 there was a significant decrease ($p<0.001$) compared to the previous observation period (Table 1, Fig. 4a).

● RMSSD. The Wilcoxon test showed that the square root of the sum of the squares of the difference in the values of successive pairs of normal R-R intervals, compared with control data, one day after surgery significantly increased ($p<0.01$), but on the 2nd-5th ($p<0.001$) and on the 6th ($p<0.01$) day it was significantly below normal. The dynamics of changes in rMSSD had a wave-like character with two uneven peaks on days 1 and 6 (Table 1, Fig. 4b). Moreover, on the 4th day its minimum average value was recorded for the entire observation period after modeling septoplasty.

● SDNN/rMSSD. The nature of changes in the average values of this indicator was different from rMSSD. Thus, compared with preoperative values, it was significantly higher on days 2-5 ($p<0.001$), and significantly lower one day after the septoplasty simulation ($p<0.001$). Compared to the 1st day of the postoperative period, on the 2nd day there was an increase in the STDNN/rMSSD ratio ($p<0.001$). On the third day it also continued to increase ($p<0.05$), on the 4th day it decreased ($p<0.01$) compared to the previous day, and continued to significantly decrease only on the 6th day after surgery ($p< 0.05$) (Table 1, Fig. 4c).

● Total HRV power. An assessment of the overall power showed that modeling septoplasty led to a significant decrease in power throughout the entire postoperative period ($p<0.001$), except for the 3rd day, when no significant difference was found compared to the control. The increase in the total power indicator occurred on the 3rd day after surgery ($p<0.01$), after which it decreased again ($p<0.01$) (Table 1, Fig. 4d).

Table 1. Dynamics of changes in time domain parameters and total power of heart rate variability after modeling septoplasty in rats

HRV parameters	Control data	Postoperative period					
		1 day	2 day	3 day	4 day	5 day	6 day
SDNN (ms)	4,76±0,24	4,52±0,25	5,27±0,26	5,1±0,15	4,01±0,26	4,21±0,28	4,41±0,15
rMSSD (ms)	3,96±0,22	4,28±0,34	3,36±0,35	2,94±0,17	2,73±0,25	2,91±0,26	3,41±0,33
SDNN/ rMSSD (ms)	1,2±0,11	1,06±0,11	1,57±0,14	1,73±0,14	1,47±0,13	1,45±0,11	1,29±0,11
Total power (ms2)	27,19±2,95	19,14±2,06	18,49±3,09	24,96±3,23	15,08±3,37	16,75±2,67	18±2,27

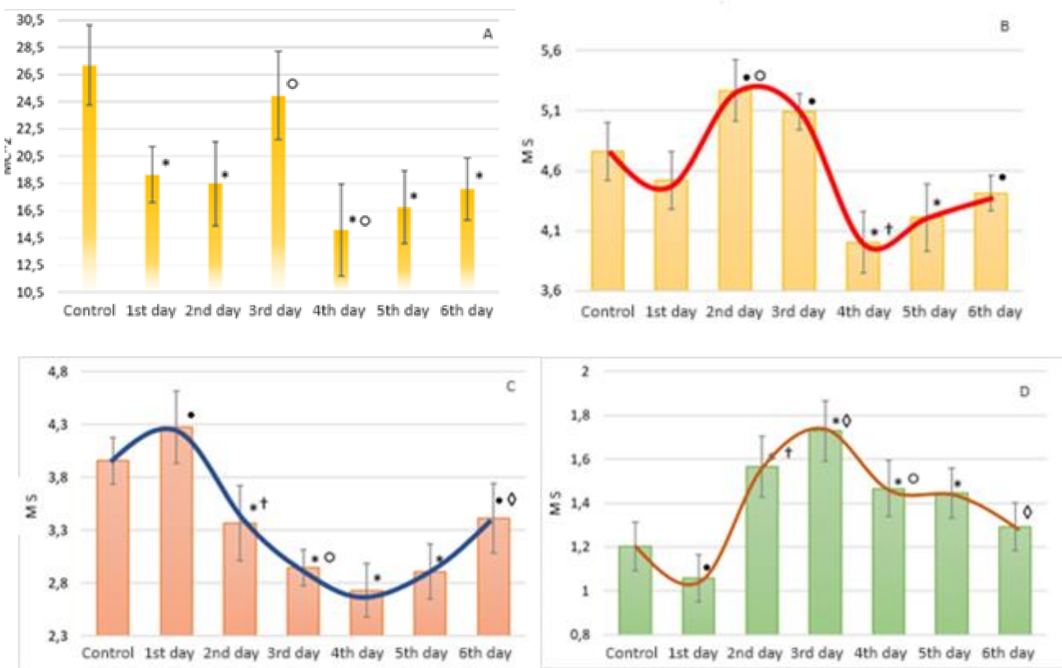

Figure 4. Changes in HRV after modeling septoplasty in the time spectrum: a-standard deviation of R-R intervals (SDNN) between normal QRS complexes; b-rMSSD (the square root of the sum of the squares of the difference in values of consecutive pairs of normal R-R intervals); c – the ratio STDNN/rMSSD; d – total power. Note: * - significant difference between preoperative data (control) and postoperative data at $p<0.001$; ● - significant difference between preoperative data (control) and postoperative data at $p<0.01$; † - significant difference between follow – up periods after surgery at $p<0.001$; o – significant difference between follow-up periods after surgery at $p<0.01$; ◊ - significant difference between follow-up periods after surgery at $p<0.05$.

4.2. Corticosterone

According to the Wilcoxon test, at the time of septoplasty modeling and throughout the entire postoperative period, the concentration of corticosterone in the blood plasma of rats was significantly higher than before it ($p<0.001$). The maximum level of the hormone of the adrenal cortex was noted at the time of the operation itself; a day later its concentration decreased significantly ($p<0.001$), and from the 2nd to the 4th postoperative day its plateau was determined (Fig. 3.6). But from the 5th day, the concentration of corticosterone in the blood plasma in rats continued to decrease ($p<0.01$) (Table 2).

Table 2. Corticosterone concentration values in rats after septoplasty simulation.

	control	operation	1 day	2 day	3 day	4 day	5 day	6 day
ng/ ml	38,57±2 ,12	195,77±4, 43	159,87± 7,89	121,05±6,7 5	122,55±5, 38	118,4±5, 7	102,7±5, 3	61,7±4, 46

5. Discussion.

SDNN represents rapid changes associated with parasympathetic activity. Although SDNN is considered to be a measure of overall HRV power and is sensitive to both sympathetic and parasympathetic input, it is, however, more reflective of parasympathetic tone [14, 15]. Low overall HRV, defined by low SDNN values, reflects decreased parasympathetic and/or increased sympathetic activity [16]. Thus, it was previously shown that an increase in SDNN values corresponded to high activity of the vagus nerve [17]. It is known that SDNN corresponds to the high-frequency component of the HRV frequency domain and characterizes vagal activity [18]. After septoplasty, an increase in SDNN occurred on days 2-3, which corresponded to an increase in plasma corticosterone levels in rats. Consequently, sympathicotonia was observed during this period, since it is known that an increase in the level of glucocorticoids in the blood plasma under conditions of acute or chronic stress occurs against the background of sympathicotonia [19], but against the background of depletion of the sympathoadrenal system under conditions of desynchronosis, its level may decrease [20]. However, on days 1 and 4-6 after surgery, the power of SDNN was either equal to or lower than control data against the background of a persistent increase in the concentration of corticosterone levels in the blood of animals. It can be concluded that, indeed, both the sympathetic and parasympathetic nervous systems contribute to changes in SDNN, and SDNN in some cases cannot be interpreted unambiguously.

RMSSD characterizes the activity of the parasympathetic division of the ANS [21], and it correlates well with the high-frequency component (HF) of the frequency domain of HRV [22]. In our study, the highest rMSSD values were observed 1 day after surgery, which can be explained by a disruption of normal adaptive processes, since under normal stress conditions the tone of the sympathetic nervous system prevails, along with activation of the hypothalamic-pituitary-adrenal axis [23]. These results are consistent with a drop in the overall power of HRV in the first two days after surgery, which may also indicate a breakdown in adaptive reactions in response to damage to the nasal septum and subsequent sensory deprivation of the peripheral part of the olfactory analyzer [5].

The ratio of SDNN to rMSSD can characterize vagosympathetic balance and is quite consistent with LF/HF (the ratio of the low-frequency component to the high-frequency component of the HRV frequency spectrum or the vagosipathic index) [24]. Moreover, in the absence of differences in SDNN and rMSSD, SDNN/rMSSD may show a difference between study groups [24]. For example, if SDNN/RMSSD is an appropriate expression of LF/HF, higher SDNN/RMSSD, for example in fibromyalgia, compared with healthy controls, characterizes a shift in the balance of the ANS towards the sympathetic component, which is consistent with other studies [25, 26]. Changes in SDNN/rMSSD confirm the idea that on the first day after septoplasty modeling in rats, disadaptation reactions develop, which are manifested by an increase in the activity of the parasympathetic nervous system against the background of an increase in corticosterone, as well as a decrease in the activity of rats in the open field [4, 6], and in the subsequent postoperative period, the body's response to surgical stress is characterized by an increase in the activity of the sympathetic nervous system with an increase in total power in the period 2-4 days, with a peak on the third day, which coincides with the maximum changes in the cytoarchitecture of the pyramidal layer of the hippocampus in almost all of its subfields [7-9], as well as with the formation of a "plateau" on the graph of corticosterone concentration (Fig. 5).

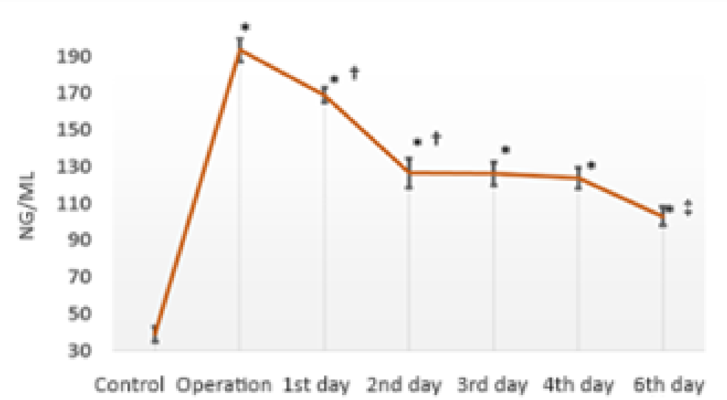

Figure 5. Dynamics of changes in the concentration of corticosterone in blood plasma in rats before and after the simulation of septoplasty. Note: * - significant differences between preoperative data (control) and post-operative data at p<0.001; † - significant difference between postoperative follow-up periods at p<0.001; ‡ – significant difference between postoperative follow-up periods at p<0.01.

6. Conclusions

The concentration of corticosterone in the blood plasma, SDNN/rMSSD and the total power of HRV most accurately characterize the developing responses of the body under conditions of surgical stress when modeling septoplasty in biological objects. Thus, modeling septoplasty in rats leads to the development of disadaptive processes on the first day, followed by normalization of adaptive processes in the period from the second to the fourth postoperative days.

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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