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Relationships between geomagnetic Ap-index and HRV and endocrine parameters in patients with dysfunction of the neuroendocrine-immune complex

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Abstract
Background. Recently, on the example of two cohort of patients, we found that disturbances of the geomagnetic field cause a significant immediate modulating effect on the level of immune parameters in the blood. The data available in the literature give grounds for assumptions about the **direct** effect of disturbances of the geomagnetic field on immunocytes, and **indirectly**, through immunotropic neurotransmitters and hormones. Our hypothesis is as follows. Disturbances of the geomagnetic field are perceived by acupuncture points. The information obtained is transmitted to neurons and endocrinocytes, the mediators of which, in turn, affect immunocytes. The purpose of this study is to test this hypothesis. **Material and methods**. The object of observation were 21 men (24-63 y) and 20 women (30-72 y) with neuroendocrine-immune complex dysfunction. Each patient was tested twice with an interval of 4 days. Retrospectively we recorded the geomagnetic Ap-Index on the day of testing and during the previous 7 days, using resource https://www.spaceweatherlive.com/. Recorded the heart rate variability (HRV) parameters, determined the plasma level of cortisol, triiodothyronine and testosterone. **Results**. During the week, the average level of Ap-index ranged from 7 to 13 nT. Maximum coefficients of multiple correlation with HRV&Hormonal parameters were detected for Ap-index on 2 (R=0,506) and 7 (R=0,403) days before testing. The canonical correlation between Ap-indices for 7 days before and on the day of testing, and the HRV&Hormonal parameters is 0,766. In turn, the immune parameters are closely related to the HRV&Hormonal parameters (R=0,714). **Conclusion**. Disturbances of the geomagnetic field (Ap-index) causes a significant immediate modulating effect on the immune, HRV and endocrine parameters, apparently through acupuncture points as polymodal receptors of the ecoceptive sensitivity system.

Key words: geomagnetic Ap-index, HRV, cortisol, triiodothyronine, testosterone, relationships, humans.

Introduction

Recently, on the example of two cohort of patients, we found that disturbances of the geomagnetic field cause a significant immediate modulating effect on the level of immune parameters in the blood (Popovych et al, 2021; Tserkovniuk et al, 2021). The data available in the literature give grounds for assumptions about the **direct** effect of disturbances of the geomagnetic field on immunocytes, and **indirectly**, through immunotropic neurotransmitters and hormones. Accepting Lymansky's hypothesis (Lymansky, 1990; Gulyar et Limansky, 2003), we assumed that disturbances of the geomagnetic field are perceived by acupuncture points (AP). The information obtained is transmitted to neurons and endocrinocytes, the mediators of which, in turn, affect immunocytes. The purpose of this study is to test this hypothesis.

Material and methods

Participants. The object of observation were 21 men (24-63; 44±12 y) and 20 women (30-72; 49±12 y) with neuroendocrine-immune complex dysfunction: increased level of HRVs-markers of sympathetic tone and decreased markers of vagal tone, moderate hypocortisolemia in both sexes and hypertestosteronemia in women, decreased parameters of phagocytosis by neutrophils of gram-negative and gram-positive bacteria as well as the level of T-helpers, but increased levels of NK- and B-lymphocytes, Igg G and M.

Procedure / Test protocol / Skill test trial / Measure / Instruments. Each patient was examined twice with an interval of 4 days. Observations were carried out on 09.06. and 13.06. 2015 (13 men and 3 women), 14.09. and 18.09. 2015 (1 man and 4 women), 27-28.03. and 04-05.04. 2018 (3 men and 7 women), 28.01 and 01.02. 2019 (4 men and 6 women). Retrospectively we recorded the geomagnetic Ap-Index, i.e. the average value of deviation of the geomagnetic field strength from normal in this region (range on Earth: 35-65 μT) on the day of testing and during the previous 7 days, using a publicly available information resource https://www.spaceweatherlive.com/.

To assess the parameters of heart rate variability (HRV) recorded during 7 min electrocardiogram in II lead (software and hardware complex "CardioLab+HRV", KhAI-MEDICA, Kharkiv). For further analysis the following parameters HRV were selected. Temporal parameters (Time Domain Methods): the standard deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater than 50 msec (pNN_{50}); Triangular Index (TNN). Spectral parameters (Frequency Domain Methods): power spectral density (PSD) bands of HRV - high-frequency (HF, range 0,4÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,04÷0,015 Hz) and ultralow-frequency (ULF, range 0,015÷0,003 Hz). Calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF). Baevsky's parameters. Heart rate (HR), Mode (Mo), the Amplitude of Mode (AMo), Variational Sweep (MxDMn), Vegetative Balance Index (VBI=AMo/MxDMn), Stress Index (BSI=AMo/2•Mo•MxDMn) as well as Baevsky's Activity of Regulatory Systems Index (BARS) (HRV, 1996; Berntson GG et al, 1997; Baevsky, Ivanov, 2001).

Among hormones determined major adaptation hormones Cortisol, Testosterone and Triiodothyronine (by the ELISA with the use of analyzer "RT-2100C" and corresponding sets of reagents from "Алкор Био", XEMA Co., Ltd and DRG International Inc.).

Data collection and analysis / Statistical analysis. Results processed by using the software package "Statistica 64".

Results

During the week before testing, the average level of Ap-index was in the range of 7÷13 nT (Fig. 1).

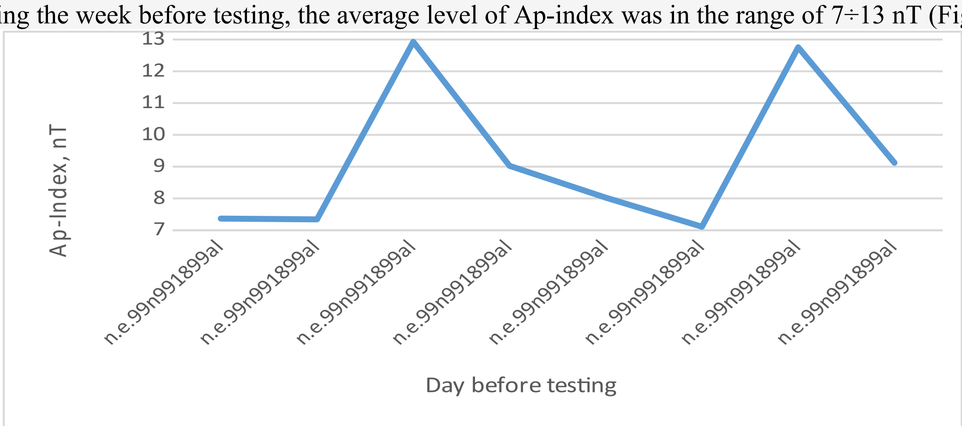


Fig. 1. Values of Ap-Index (M±SE) on the day of testing and during the previous 7 days

The matrix of correlations between Ap-Indices and HRV&Endocrine parameters was created (Table 1).

From the above it seems that geomagnetic disturbances with a lag of 7-5 days cause a sympathotonic shift of the autonomic balance due, first of all, to a decrease in vagal tone and, to a lesser extent, an increase in sympathetic tone and circulating catecholamines (marked by 1/Mode ratio). With a two-day delay, ULF band (the physiological essence of which still remains as terra incognita) upregulated by geomagnetic disturbances, while plasma testosterone levels (not relevant, but standardized by sex and age of patients) downregulated. Triiodothyronine and cortisol downregulated by geomagnetic disturbances on the day of blood collection.

Table 1. Matrix of correlations between Ap-Indices and HRV&Endocrine parameters

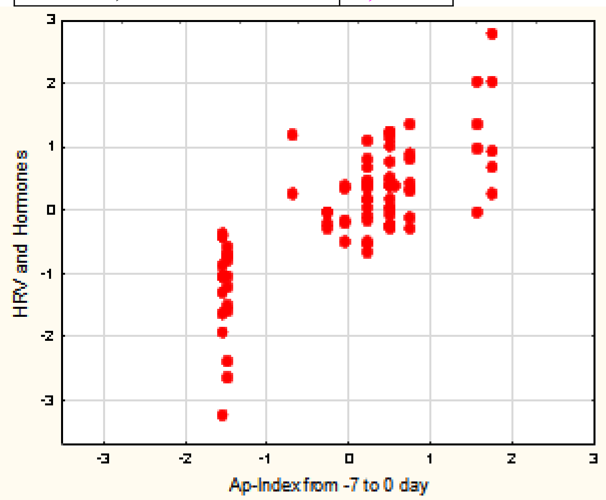
HRV/Hormones	**Ap-7**	**Ap-6**	**Ap-5**	Ap-4	**Ap-3**	**Ap-2**	Ap-1	**Ap0**	**Z±SE**
AMo/MxDMn Index	**0,36**	0,16	-0,00	-0,02	0,13	-0,04	-0,03	0,08	**2,30±0,48**
AMo	**0,32**	**0,22**	-0,05	-0,02	0,12	-0,12	-0,07	0,05	**0,38±0,13**
Triangular Index	**-0,23**	**-0,21**	-0,08	-0,04	-0,16	0,15	0,16	0,04	0,03±0,19
MxDMn	**-0,23**	**-0,19**	-0,10	-0,06	-0,19	0,10	0,17	0,05	**-0,35±0,12**
SDNN	**-0,19**	-0,17	-0,04	-0,01	0,03	**0,20**	0,08	-0,09	**-0,30±0,09**
LF band PS	**-0,19**	**-0,20**	-0,03	0,02	-0,01	**0,22**	0,14	-0,08	**0,91±0,30**
HF band PS	-0,10	-0,14	-0,17	-0,05	-0,13	0,08	0,11	0,01	**-0,36±0,17**
LF/(LF+HF)	-0,10	-0,05	**0,27**	0,12	**0,20**	0,17	0,08	-0,07	**1,22±0,10**
LF/HF	-0,10	-0,10	**0,24**	0,01	0,06	0,06	0,10	0,02	**1,71±0,30**
1/Mode	0,10	0,03	**0,21**	0,08	0,12	0,07	-0,11	-0,01	**-1,21±0,14**
Baevsky's ARS Index	0,15	-0,04	**0,21**	0,03	**0,17**	0,15	0,03	0,02	**3,31±0,28**
VLF band PS	-0,07	-0,05	-0,00	-0,02	**0,16**	0,13	-0,01	-0,14	-0,13±0,44
ULF band PS	-0,08	-0,10	-0,03	0,10	0,05	**0,36**	0,01	-0,08	**1,56±0,69**
ULF/TP	-0,10	-0,08	-0,01	0,07	-0,01	**0,19**	-0,05	-0,10	**0,55±0,24**
Testosterone standard	0,14	0,09	0,07	0,07	-0,01	**-0,30**	-0,13	0,04	
								M	-0,15±0,20
								F	**1,43±0,44**
Triiodothyronine	-0,09	-0,15	-0,11	-0,05	0,02	0,03	-0,15	**-0,27**	-0,34±0,20
								M	-0,50±0,27
								F	-0,16±0,29
Cortisol	0,09	0,15	0,01	0,11	0,15	0,00	-0,18	**-0,21**	**-1,04±0,04**
								M	**-1,12±0,06**
								F	**-0,95±0,06**
Multiple correlation R	**0,412**	**0,381**	**0,332**	0,177	**0,314**	**0,506**	0,286	**0,293**	

Note. For hormones, Z-scores are given in general, as well as separately for men and women.

According to the canonical correlation analysis, geomagnetic perturbations on the day of testing and for seven days before it determines the HRV&Endocrine parameters by 59% (Table 2 and Fig. 1).

Table 2. Factor Structure Matrix for Canonical Roots of Ap-Indices and HRV&Endocrine parameters

Left set	**R**
Ap-2, nT	**0,641**
Ap-5, nT	**0,203**
Ap-3, nT	**0,165**
Ap-7, nT	**-0,151**
Ap-6, nT	**-0,025**
Ap-0, nT	**-0,104**
Right set	**R**
ULF band, $msec^2$	**0,429**
ULF/TP, %	**0,311**
VLF band, $msec^2$	**0,257**
Baevsky's ARSI, units	**0,197**
LF/(LF+HF), %	**0,161**
LF/HF	**0,150**
1/Mode, $msec^{-1}$	**0,090**
Testosterone, Z-score	**-0,789**
AMo, %	**-0,146**
Vegetative Balance Ind, un	**-0,076**
SDNN, msec	**0,258**
Triangular Index, units	**0,139**
MxDMn, msec	**0,089**
LF band, $msec^2$	**0,086**
Triiodothyronine, nM/L	**0,336**
Cortisol, nM/L	**0,200**



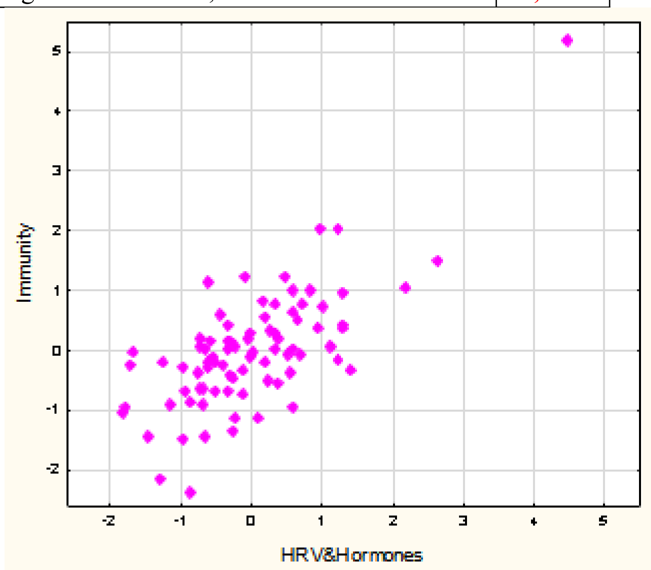
R=0,766; R^2=0,589; $\chi^2_{(120)}$=194; p<10^{-4}; Λ Prime=0,060

Fig. 2. Scatterplot of canonical correlation between Ap Geomagnetic indices before 7 days and on day testing (X-line) and HRV&Hormonal parameters (Y-line)

The next step was to analyze the canonical correlation between the HRV and endocrine parameters, on the one hand, and the immune parameters registered in a previous study (Tserkovniuk et al, 2021) - on the other hand. The degree of immunomodulation induced by circulating catecholamines, sympathetic and vagus nerves, and adaptation hormones was found to be quite noticeable: 51% (Table 3 and Fig. 2).

Table 3. Factor Structure Matrix for Canonical Roots of HRV&Hormonal and Immune parameters

Left set	**R1**
1/Mode as Circulating Cathecholamines, $msec^{-1}$	0,766
Testosterone standardized by sex&age, Z-score	0,426
AMo/MxDMn as Vegetative Balance Index, un	0,255
Amplitude of Mode as Sympathetic tone, %	0,199
Cortisol, nM/L	0,059
ULF/TP	-0,319
MxDMn as Vagal tone, msec	-0,281
Triangular Index as Vagal tone, units	-0,276
ULF band, $msec^2$	-0,201
SDNN as Vagal tone, msec	-0,166
Triiodothyronine, nM/L	-0,122
Testosterone actual, nM/L	-0,095
Right set	**R1**
Killing Index vs Staph. aureus, %	0,527
Microbial Count for E. coli, Bacteria/Phagocyte	0,403
Phagocytosis Index vs E. coli, %	0,375
Bactericidal Capacity vs Staph. aureus, 10^9 B/L	0,372
Bactericidal Capacity vs E. coli, 10^9 Bacteria/L	0,172
Phagocytosis Index vs Staph. aureus, %	0,148
0-Lymphocytes, %	0,323
$CD22^+$ B-Lymphocytes, %	-0,236
$CD3^+CD4^+$ T-helper Lymphocytes	-0,217
Killing Index vs E. coli, %	-0,206



R=0,714; R^2=0,510; $\chi^2_{(140)}$=164; p=0,049; Λ Prime=0,090

Fig. 3. Scatterplot of canonical correlation between HRV&Hormonal (X-line) and Immunity (Y-line) parameters

Discussion

The presented results fit into the concept that Solar-induced fluctuations in the ambient geomagnetic field have been correlated with a wide range of biological effects, including changes in EEG (Babayev and Allahverdiyeva, 2007; Mulligan et al, 2010; Novik and Smirnov, 2013) and HRV (Baevsky et al, 1997; McCraty et al, 2017) parameters in humans. Let's dwell in more detail on the research closest to ours in design.

According to the concept of “central autonomic network (CAN)” (Benarroch, 1993; Palma and Benarroch, 2014; Thayer and Lane, 2009) it include following cortical, subcortical, and medullary structures: the anterior cingulate, insular, orbitofrontal, and ventromedial cortices; the central nucleus of the amygdala; the paraventricular and related nuclei of the hypothalamus; the periaqueductal gray matter; the nucleus of the solitary tract; the nucleus ambiguous; the ventrolateral medulla; the ventromedial medulla and the medullary tegmental field. The primary output of the CAN is mediated through the preganglionic sympathetic and parasympathetic neurons, which exert control over the heart via the stellate ganglia and the vagus nerve, respectively. The interplay of sympathetic and parasympathetic influences on sinoatrial node pacemaker activity generates the complex variability that characterizes the healthy heart rate rhythm, which is called HRV. A fundamental principle of the neural control of the heart is its hierarchical organization, with cortical structures providing inhibitory control over limbic and brainstem sympathoexcitatory, cardioacceleratory circuits. Indeed, disruption of prefrontal activity leads to disinhibition of sympathoexcitatory circuits, with a resultant increase in heart rate and decrease in vagally-mediated HRV (Verberne, 1996; 1997). Furthermore, left-sided (dominant hemisphere) forebrain structures appear to be predominantly involved in vagal regulation, whereas homotopic right (non-dominant) forebrain regions seem to primarily control sympathetic tone and responses (Guo et al, 2016; Winkelmann et al, 2017). However, the lateralization model of autonomic control of the heart remains controversial (Thayer et al, 2012; Yoo et al, 2017; Carnevali et al, 2018).

Baevsky et al (1997) discovered during 1990-1994 the about 30% decrease in RMSSD of HRV in cosmonauts studied during a geomagnetic storm as compared to cosmonauts monitored on quiet days. McCraty et al (2017) a coupling between geomagnetic activity and the human nervous system's function identified by virtue of continuous monitoring of HRV and the time-varying geomagnetic field over a 31-day period in a group of 10 individuals who went about their normal day-to-day lives. A time series correlation analysis identified a response of the group's autonomic nervous systems to various dynamic changes in the solar, cosmic ray, and ambient magnetic field. Correlation coefficients were calculated between the HRV variables and environmental measures during three distinct time periods of environmental activity. There were significant correlations between the group's HRV and solar wind speed, Kp, Ap, solar radio flux, cosmic ray counts, Schumann resonance power, and the total variations in the magnetic field. In addition, the time series data were time synchronized and normalized, after which all circadian rhythms were removed. It was found that the participants' HRV rhythms synchronized across the 31-day period at a period of approximately 2,5 days, even though all participants were in separate locations. Overall, this suggests that daily autonomic nervous system activity not only responds to changes in solar and geomagnetic activity, but is synchronized with the time-varying magnetic fields associated with geomagnetic field-line resonances and Schumann resonances.

We also found a positive correlation of Ap-indices with HRV sympathetic/vagal balance indices as well as a negative correlation with HRV-markers of vagal tone, but with a shift of a few days. It appears that geomagnetic perturbation-induced inhibition of vagal nuclei and/or excitation of sympathetic nuclei of the brainstem occurs only after a few days.

If the disturbances of the Earth's magnetic field are an obvious causal factor, then we are tormented by doubts about its first target (acceptor). Accepting the hypothesis of Limansky (1990; 2003), we conclude that caused by geomagnetic disturbances multidirectional and asymmetric changes in the conductivity of a limited constellation of APs in one way or another (through afferent cutaneous nerves or liquid crystalline collagen fibers of the connective tissues (Ho et Knight, 1998; Langevin, 2006)) reach medullary, subcortical and cortical structures of CAN, exciting some neurons and inhibiting others, thus triggering well-studied mechanisms of neuro-immune, neuro-endocrine and endocrine-immune modulation (Tracey, 2007; Thayer et Sternberg, 2010; Popovych et al, 2013; 2014; 2018; Babelyuk et al, 2017; Kul'chyns'kyi et al, 2017; Gozhenko et al, 2019; 2021) documented in our study.

If we accept the paradigm of Eastern medicine, the information from APs enters the Chakras, which regulate the neuro-endocrine-immune complex. The reality of this assumption is evidenced by the parameters of GDV (biophotonics), registered in the same observed individuals. But this will be discussed in a separate article.

According to Nordmann et al (2017)**,** there are 3 prevailing proposals being weighed regarding how magnetic fields are sensed by animals. First is provocation of action potentials in neurons by electromagnetic induction; second is light-sensitive, chemical-based mechanism mediated by **cryptochromes** resulting in action potentials as nervous signals (Gegear et al, 2008; Zaporozhan et Ponomarenko, 2010; Foley et al, 2011; Hammad et al, 2020; Cifra et al, 2021; Wan et al, 2021); and third is magnetite-based **magnetoreceptors** mechanically spotting the magnetic field, leading to neuronal action potentials (Kirschvink et al, 2001; Winklhofer et Kirschvink, 2010; Gilder et al, 2018). Therefore, the brain can **directly** accept geomagnetic disturbances, without the mediation of APs, followed by neuro-endocrine and neuro-immune modulation.

Simko and Mattsson (2004) envisage that electromagnetic field (EMF) exposure can cause both acute and chronic effects that are mediated by increased free radical levels. Firstly, direct activation of, for example macrophages (or other cells) by short-term exposure to EMF leads to phagocytosis (or other cell specific responses) and consequently, free radical production. This pathway may be utilized to positively influence certain aspects of the immune response. Secondly, EMF-induced macrophage (cell) activation includes direct stimulation of free radical production. Rosado et al (2018) note, whereas the majority of the in vitro studies focused on monocytes/macrophages and fibroblasts, the effects of the exposure to EMF on other cell types are not well defined. In macrophages, the reduction in pro-inflammatory cytokines induced by EMF is associated with the activation of regulatory mechanisms induced by a moderate oxidative stress. However, in the case of neutrophils, activation of oxidative stress by EMF induces activation of NETosis.

However, this information is not entirely appropriate for our discussion, because the applied EMFs had a power **comparable** to that of the Earth's magnetic field or even **greater**. Only two studies of Selmaoui et al (1996; 2011) is noteworthy. The authors showed that exposure to 50-Hz magnetic fields (10 μT) significantly increases IL-6 when subjects were exposed to an intermittent magnetic field. However, no effect has been observed on interleukin IL-1β, IL-2, IL-1RA, and IL-2R. No significant differences were observed between sham-exposed (control) and exposed men for hemoglobin concentration, hematocrit, red blood cells, platelets, total leukocytes, monocytes, lymphocytes, eosinophils, or neutrophils. Immunologic variables (CD3, CD4, CD8, NK and B cells) were unaltered. Therefore, the **initial** acceptance of geomagnetic disturbances by **immunocytes** is possible, but unlikely.

Gorgo et al (2018) in recent study the monitoring of specific intensity of bacteria Photobacterium phosphoreum luminescence has been carried out for 2 months (September-October 2015) and it was compared to the daily values of activity of the geomagnetic field in the conditions of Kyïv, during the research of bioluminescence. Variation determination of the geomagnetic field was conducted from data of Space Environment Center, NOAA&U.S. Air Force. The inverse proportional reliable average correlation was defined between the values of specific bacterial luminescence and the Kp (r=-0,41) as well as Ap (r=-0,41) indexes of the geomagnetic field, and with the values of flux of Sun radiation at a wavelength 10,7 cm - reliable directly proportional correlation (r=0,305). Interestingly, the average values of Ap-indexes were close to those in our observations (in September 13,7±2,68 nT; in October 14,9±1,90 nT). Surprising is the proximity of the force of influence of the intensity of variations of the magnetic field on the day of testing (Ap0) both on the manifestation of bacterial activity (Gorgo et al, 2018) and phagocytic function of neutrophils against bacteria (Tserkovniuk et al, 2021). This, in our opinion, confirms the **direct** effect of the geomagnetic field disturbances on human neutrophils. The decrease in the level of T-helpers (r=-0,27) and B-lymphocytes (r=-0,19) reflects, in our opinion, the weakening of their expression of CD4 and CD22 receptors, respectively, as evidenced by the positive correlation of the Ap-index with the level of 0-lymphocytes (r=0,26).

Conclusion. Disturbances of the geomagnetic field (Ap-index) causes a significant immediate modulating effect on the immune, HRV and endocrine parameters, apparently through acupuncture points as polymodal receptors of the ecoceptive sensitivity system.

Acknowledgment

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Accordance to ethics standards

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

Conflict of Interest. For all authors any conflict of interests is absent.

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