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## THE STATE OF THE VEGETATIVE PROVISION OF CARDIAC PERFORMANCE IN PATIENTS WITH HIV-INFECTION

**Abstract.** Investigation of the heart rate variability (HRV) is one of the available and noninvasive method of stratification of the cardio-vascular risk, however, the rhythm and strength of cardiac contractions react to any stress influences very keenly.

A decrease of the heart rhythm variability, mainly at the expense of a vagus modulation decrease of the cardiac rhythm, to a less degree – sympathetic one, which becomes dominating, is observed in HIV-infected patients already on early stages of infection. A decrease of the functional state of the vegetative nervous system in HIV-infected patients is combined with the development of the vegetative imbalance in bicsympathicotonia. The degree of the vegetative disorders correlates with the extent of immunodepression and the level of viral loading. Such changes testify to an increased degree of the risk development of unfavorable cardiovascular events in HIV-infected individuals, for indicate to the reduction of activity of the parasympathetic part of VNS and heart "defense" from the rise of life threatening arrhythmias.

**Key words:** HIV-infection, vegetative provision, cardiac performance.

**Introduction.** HIV-infected patients belong to the group of increased risk of cardio-vascular diseases, in particular, the development of asymptomatic ischemic heart disease [1.2]. This dictates the necessity to find prognostic and diagnostic methods for early verification of the cardio-vascular system involvement.

Investigation of the heart rate variability (HRV) is one of the available and noninvasive method of stratification of the cardio-vascular risk, however, the rhythm and strength of cardiac contractions react to any stress influences very keenly [3]. In this connection, cardiac rhythm change is a universal body reaction in response to different media influences what represent the result of numerous regulatory effects on cardiovascular system. The heart rhythm, at such approach, is considered to be as not only a pacemaker activity index of the sinus node, but to the greater degree, as integrated index of interaction of three factors regulating the cardiac rhythm: sympathetic, parasympathetic and humoral-metabolic [4]. Estimation of the state of the organism regulatory systems gives valuable information about a degree of their

intensity in regulating the heart rhythm, and also allows forecasting the risk of the development of pathological conditions. This provides a significant interest to practical use of the assessment methodology of VCR in HIV-infected patients.

**Objective:** to study the state of the vegetative support of cardiac activity in patients with HIV infection.

**Materials and methods.** 136 patients with HIV-infection and staying under conditions of the outpatient observation during 2013-2014 years in the regional centre of prophylaxis and combating Aids in the town of Chernivtsi have been examined. Among the indicated patients there were 66 (48.5%) men and 70 (51.5%) women aged 19-42 years. The middle age of the patients was (28.4±0.4) years.

Diagnosis of HIV-infection was made up on the basis of epidemiological anamnesis, clinical data and confirmed by detection of specific antibodies to HIV in reaction of immune-enzyme analysis and in the reaction of immunoblotting.

Among the examined patients there were 44(32.4%) patients with clinical stage I, 48(35.3%) – stage II, 23(16.9%) – stage III,

21(15.4%) – clinical stage IV.

Clinical-epidemiological data and the results of the laboratory methods of investigation: serological and immunological were taken into consideration making the diagnosis (including the content determination of CD4 – lymphocytes). The level of CD4 – lymphocytes was investigated after the disappearance of the symptoms of concomitant acute infectious disease (not less than in 4 weeks).

HIV-infection duration was counted from the moment of registering in a dispensary. 86(63.2%) patients were HIV-infected during not more than 5 years at the moment of the 1<sup>st</sup> inspection, 50(36.8%) patients – over 5 years.

All examined persons with clinical stages III-IV of HIV infection were receiving schemes of highly active antiretroviral therapy of the 1<sup>st</sup> line, recommended in Ukraine.

The group of comparison consisted of 30 healthy persons who, as to sex and age, were completely compared with the representatives of the groups under study.

All patients were examined according to the Order of MPH of Ukraine 55 dated 12.07.2010 “Clinical report of antiretroviral therapy of HIV-infection in adults and teenagers” [5].

The condition of the vegetative regulation of the heart rhythm was determined by means of computer cardiointervalometry using monitoring of the arterial pressure and electrocardiosignals of daily SDM23. Investigations of the heart rhythm variability were conducted in morning hours, fasting, following 15 minutes of the patient’s staying in clinostasis. ECG was recorded during 5 minutes. HRV evaluation was carried out according to the standard reports, calculating the time and spectral parameters as to the International dimension standards, physiological interpretation of the clinical use, developed by the working group of the European society of cardiologists and Northern American society of cardiac stimulation and electrophysiology [6].

Standard complex of time and spectral indices was estimated among HRV parameters, physiological nature of which is similar, however, there are some distinctions. SDNN and TP are integral HRV indices depending upon the

activity of both parts of the vegetative nervous system (VNS) and characterizing the state of vegetative regulation in general. Change of these indices is indicative of the vegetative displacement into the preference side of one part of the VNS. Specifically, a decrease shows the involvement of all functional reserves of the organism under the influence of the central regulation of hypothalamohypophysial level, an increase – to activation of autonomous control levels situated below. LF/HF (the ratio of low-frequency and high-frequency constituents of the spectrum) also reveals the balance of the sympathetic and parasympathetic VNS parts. rMSDD, pNN50 and HF represent the influence of the parasympathetic part of VNS and the evidence of sinus arrhythmia. LF represents mainly the influence of the sympathoadrenal system on cardiac activity. VLF characterizes the influence of higher vegetative centers upon the cardiovascular subcortical center; represents the state of neurohumoral and metabolic levels of regulation [3, 6-8].

**Results and discussion.** Frequency of cardiac contraction in a state of rest was  $(74.10 \pm 0.69)$  per minute in all HIV-infected patients under study, what reliably exceeded indices in the group of practically healthy persons  $(68.50 \pm 0.81)$  per minute ( $p < 0.05$ ), and accordingly statistically lower RRNN indices among patients in comparison with the control group. Specifically, this index in HIV-infected patients was  $(879.60 \pm 7.27)$  mc, what is reliably less of norm –  $(879.80 \pm 10.10)$  mc ( $p < 0.050$ ). This may be connected with a decrease of parasympathetic modulation of the cardiac rhythm and/or with the highest sympathetic tonus of the vegetative nervous system (VNS) in HIV-positive persons.

The data of our investigation indicate to a decrease of the heart rhythm variability, mainly at the expense of lowering the cardiac rhythm vagal simulation, in a less degree – sympathetic, which become the dominant one. The activity balance of the sympathetic and parasympathetic parts of the vegetative nervous system shifted to the side of the low-frequency component of the spectrum, that is, sympathicotonia is observed in the examined

cohort of patients. The indicated changes are the most significant in HIV-positive patients with deep immunodeficiency. Thus, all HRV time parameters under investigation of patients with I-II clinical stages of HIV infection statistically considerably differed from the corresponding indices of the patients with III-IV clinical stages of illness – SDNN parameter of the patients of group I was  $(96.18 \pm 1.22)$  mc while in group II –  $(85.14 \pm 1.44)$  mc ( $p < 0.05$ ), rMSSD –  $(34.26 \pm 0.57)$  mc against  $(27.66 \pm 0.88)$  mc ( $p < 0.05$ ), pNN50 –  $(18.43 \pm 0.66)$  % and  $(13.36 \pm 1.01)$  % according to the corresponding stages ( $p < 0.05$ ). Comparative analysis of the spectral HRV indices in patients of the groups I-II has shown, that deepening the immunodepression degree is accompanied by more significant changes of the functional state of the vegetative nervous system at the expense of further depression force of the general spectrum of vegetative regulation (TP) –  $(2192,0 \pm 53.9)$  mc in HIV –infected persons with I-II clinical stages against  $(1874.3 \pm 37.4)$  mc in persons with III-IV clinical stages ( $p < 0.05$ ) and essential decrease of contribution of both low-frequency (LF) – with  $(773.3 \pm 22.6)$  mc in patients of group I till  $(617.6 \pm 28.8)$  mc in patients of group II ( $p < 0.05$ ), and in highly frequent fluctuations (HF) – from  $(504.4 \pm 22.3)$  mc till  $(367.5 \pm 25.6)$  mc ( $p < 0.05$ ), as well as waves of a very low frequency (VLF) – from  $(742.5 \pm 21.8)$  mc in HIV-positive persons of group I to  $(607.1 \pm 28.7)$  mc in patients of group II ( $p < 0.05$ ). VLF amplitude is closely connected with psychoemotional tension and functional state of the cerebral cortex. Power of VLF fluctuations of HRV is a sensitive indicator of the metabolic processes' control and their low level reflects energy deficiency states. Constant psychoemotional tension is observed in HIV-infected patients, particularly with III-IV clinical stages, what may deepen energy-deficient state because of emaciation of the hypothalamus-hypophyseal-adrenal system.

Shifting of the sympathovagal balance to sympathicotonia is observed in the examined patients and indicative of it are statistically reliable increase of LF norm index from  $(58.52 \pm 0.51)$  n.o. at I-II clinical stages of illness to  $(62.14 \pm 0.59)$  n.o. at III-IV clinical stages

( $p < 0.05$ ), HF norm decrease to  $(41.48 \pm 0.51)$  n.o. in group I of patients to  $(37.86 \pm 0.59)$  n.o. in group II ( $p < 0.05$ ) and, accordingly, increase of the vegetative balance index (LF/HF) from  $(1.45 \pm 0.06)$  in HIV-positive persons with I-II clinical stages to  $(1.68 \pm 0.09)$  in patients with III-IV stages of the disease ( $p < 0.05$ ). Taking into consideration the aforesaid, obviously, the risk of the development of the life threatening ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) increases if there is a greater degree of immunodepression.

Reliable correlations between the parameters of HRV and the level CD4 and RRNN ( $r = +0.39 \dots + 0.44$ ,  $p < 0.05$ ), CD4 and SDNN ( $r = +0.36 \dots + 0.40$ ,  $p < 0.05$ ); CD4 and rMSSD ( $r = +0.38 \dots + 0.43$ ,  $p < 0.05$ ); CD4 and TP ( $r = +0.34 \dots + 0.37$ ,  $p < 0.05$ ) confirm the role of changes of vegetative regulation in HIV-infection progress.

Investigation of the relation between viral loading and HRV parameters gave the possibility to establish statistically significant poor negative correlation with RRNN index ( $r = -0.31 \dots - 0.32$ ,  $p < 0.05$ ) and TP ( $r = -0.27 \dots - 0.29$ ,  $p < 0.05$ ).

None of the statistically reliable relation between the duration of HIV-infection and indices of the functional state of the vegetative nervous system in patients with HIV-infection was detected.

Not high values of correlation coefficient in the examined patients may be explained by a small per cent of patients – (15.4%) with the terminal stage of HIV-infection.

The data of our research agree with the researches of foreign scientists, devoted to the study and estimation of the vegetative disorders in HIV-infected patients using the analysis of HRV [7,9-12]. They also show the imbalance of the central subsegmental and autonomous segmental outlines regulation of the cardiac rhythm in HIV-infected persons. Thus, the American investigators at the head of Dominic C. Chow [7] examined 57 persons, from whom 31 persons were HIV-positive patients including 22 patients with the low level of viral loading and 26 patients made up the control group. Despite the fact that this research was limited by a small scale of selection, it showed essential decrease

of time parameters (SDNN, rMSSD and pNN 50) in HIV-infected persons in comparison with the control group in uncorrected model. And these differences remained significant when making functional tests – at deep breathing (parasympathetic activity modulation) and orthostatic test (sympathetic activity modulation), even after correction of age and sex. No essential differences in indices of time domain among HIV-infected participants of the research with different level of virological depression were observed. Analyzing spectral indices, the investigators revealed a tendency to power lowering of high frequency waves [HF] and, at the same time, to an increase of the vegetative index (LF/HF) in HIV-infected patients in comparison with healthy persons. So, changes of HRV indices in the examined patients were connected with significant decrease of parasympathetic and simultaneous increase of sympathetic influence upon rhythm. A weak negative correlation between the parameters of time HRV analysis and the level of viral loading was observed. The same relation was found with the indices of the parasympathetic modulation of the cardiac rhythm during a trial with the fixed rate of breathing. To counterbalance, in case of active orthostatic trial, a positive relation with vegetative balance coefficient was fixed. The authors reached a conclusion concerning possible relation between the vegetative degeneration and HIV-viremia.

Investigation, carried out by Compostella C. and co-authors has shown a significant decrease of all parameters of HRV and greater HCF in HIV-positive patients in comparison with healthy individuals. It should be indicated that more considerable sympathetic-parasympathetic imbalance was observed in patients with the level CD4 – lymphocytes lower 200cells/mcl. Poor degree of correlation has been revealed between the parameters of heart rate variability and immune status of patients.

Dominic C. Chow's investigation of the vegetative dysfunction in the patients with HIV-associated lipodystrophy [12], showed the evident disorders of the sympathetic-vagal heart rhythm modulation in the indicated cohort of patients. Thus, reliably lower indices of the heart

rate variability and apparent sympathicotonia in comparison with the group of HIV-infected individuals without the signs of lipodystrophy and healthy persons have been fixed in HIV-positive patients with lipodystrophy signs. This indicates to a considerable cardiovascular risk in such patients.

Somewhat earlier a number of Indian scientists [11] also carried out spectral analysis of ECG records and revealed a decrease of all HRV parameters including essential depression of index of the spectrum of general power of HIV seropositive individuals already on early stages without clinical manifestations of vegetative dysfunction. Such finding suggested an idea, that HRV changes might be early marker of coming sympatho-vagal imbalance and threat of the development of unfavorable cardiovascular events.

**Conclusions.** A decrease of the heart rhythm variability, mainly at the expense of a vagus modulation decrease of the cardiac rhythm, to a less degree – sympathetic one, which becomes dominating, is observed in HIV-infected patients already on early stages of infection. A decrease of the functional state of the vegetative nervous system in HIV-infected patients is combined with the development of the vegetative imbalance in bicsympathicotonia. The degree of the vegetative disorders correlates with the extent of immunodepression and the level of viral loading. Such changes testify to an increased degree of the risk development of unfavorable cardiovascular events in HIV-infected individuals, for indicate to the reduction of activity of the parasympathetic part of VNS and heart “defense” from the rise of life threatening arrhythmias.

**Perspectives of further investigations.** Subsequent investigations will consist of studying changes of indices of the functional state of the vegetative nervous system in HIV-infected patients depending upon the nozological forms of some of the most frequent attendant diseases.

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