UDC 613.9: 378.172
DOI: 10.21668/health.risk/2020.4.17.eng

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Research article

STRESS BEFORE EXAMS AS A RISK FACTOR CAUSING FUNCTIONAL DISORDERS IN THE CARDIOVASCULAR SYSTEM IN STUDENTS WITH DIFFERENT METABOLIC STATUS

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Students who attend a medical HEE often face strain in their adaptation mechanisms when preparing for exams; it can create substantial preconditions for functional deregulation in body systems. The articles outlines some results obtained via examining heart rate variability (HRV) in students of the 2nd and the 3rd year attending the North Ossetia State Medical Academy who had different metabolic status in a period prior to exams.

Our research goal was to assess the state of the vegetative nervous system and regulatory systems in students with different metabolic status (BMI < 25; BMI=25–29.99; BMI=30–34.99.) who had to face excess stress during preparation to exams. Heart rate intervals were registered during five minutes in an examined person being at rest. HRV parameters were analyzed in time and frequency domains.

We revealed that medical students had elevated activity of the sympathetic section in their vegetative nervous system (VNS) during a period prior to exams; in particular, it was apparent for the regulation system of the vasomotor center (PLF = 48.4 %). Students' bodies had apparent strain in their regulatory systems (SI=177.5 a.u.). Total activity of the regulatory system was significantly elevated (TP=2,293 msec^2) due to central regulation levels. As students' BMI grew, there was a decrease in activity of the parasympathetic component in vegetative regulation and heart rate management became more centralized (IC=3.2–4.5 a.u.). Students with Class 3 obesity had the maximum spectrum power of the superlow component in heart rate variability (PVLF=29.3 %). HRV parameters analysis allows estimating whether adaptation processes in students' bodies are adequate during preparation to exams; it can be done in screening mode and provides an opportunity to perform timely prevention activities.

Key words: *stress, adaptation, risk factor, vegetative nervous system, heart rate variability, metabolic status, autonomous regulatory contour, central regulatory contour.*

Studying in a HEE involves permanent psychoemotional strain, hypokinesia, improper labor, nutrition, and leisure regime; all this allows assigning HEE students into a specific social group with elevated health risks. Necessity to master new materials and fulfill learning tasks in rather short time, a wish to get high ratings, and exam-related stresses are risk factors for most students that cause deregulatory disorders in functional activity of body systems [1]. Homeostatic systems are permanently strained, especially when a student is getting prepared for his or her exams, and it creates certain preconditions for diseases occurrence and hidden pathologies becoming apparent. Outer stressor impacts result in specific and non-specific reactions being mobilized in a body which are primarily regulated by the vegetative nervous system (VNS). A lot depends on its functional state including adaptation reserves capacity, efficiency and choice on adaptation strategy, working abilities and success in studies [1]. Anxiety that usually occurs in students during pre-exams time naturally makes for adaptation processes mobilization; however, in case

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it is too intense and long-term, adaptation mechanisms fail and it leads to growing strain in regulatory systems and a decrease in functional reserves ultimately resulting in dysregulation [2]. A lot of authors mention that depressions are widely spread among medical students [3–7]. It is becoming a serious problem for medical educational establishments in many countries [8, 9].

A concept on the cardiovascular system being a significant indicator of body adaptation reactions was formulated more than half a century ago. Heart rate variability (HRV) analysis is a procedure for assessing overall activity of regulatory mechanisms that support cardiovascular homeostasis, nuerohumoral heart regulation, and balance between sympathetic and parasympathetic sections in the VNS. HRV parameters allow estimating body adaptation abilities as well as using them for diagnosing and predicting various states: normal, pre-nosology, or pathology. Adaptation mechanisms overstrain and vegetative nervous system dysfunction underlie pre-nosology state of multiple somatic pathologies [10]. Heart is a very sensitive indicator showing all events and processes that occur in a body. Heart rate that is regulated via sympathetic and parasympathetic sections in the vegetative nervous system keenly reacts to any stress factors. Students' adaptation to studies in HEE is a serious medical and social problem. Irrational nutrition, hypodynamia, and great stresses are basic predictors of a life style typical for medical students; it leads to metabolic disorders and failures in regulatory systems functioning and creates significant risks of cardiovascular pathology occurrence. Educational process is an extreme factor for many students as it changes dynamic stereotype of physiological processes in regulatory systems; it can be a predecessor of hemodynamic, metabolic, and energetic health disorders and requires detecting at a pre-nosology stage.

Our research goal was to assess the vegetative nervous system and regulatory systems in students with different metabolic states during a pre-exam period.

Data and methods. We conducted a single cross-study of heart rate variability in 217 medical students attending the North Ossetia State Medical Academy (NOSMA) with different metabolic status in spring and summer 2019. Our examined group was made up of 166 female students (average age was 20.3 ± 0.1) and 51 male students (average age was 20.8 ± 0.2). HRV was recorded during 5 minutes (short-term recordings) with «Varikard 2.51» hardware-software complex. RR-intervals sequence was automatically analyzed in order to detect artifacts and arrhythmia with their subsequent exclusion from the analysis. According to the standards fixed by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology we examined two groups of HRV parameters, namely those from Time Domain and Frequency Domain[1]. We analyzed the following basic time domain HRV parameters: heart rate (strokes per minute); the root mean square of successive differences between normal heartbeats (RMSSD, msec); the standard deviation of NN intervals (SDNN, msec); % of heart intervals pairs that differed from each other by more than 50 ms from overall number in the total measured data (pNN50, %); coefficient of variation (CV, %). All differences to a certain extent reflect activity of the parasympathetic section in the vegetative nervous system and belong to autonomous regulatory contour. We also analyzed stress index (SI) that showed intensity of strain in regulatory systems and prevalence of central regulation mechanisms over autonomous ones. As for frequency parameters, we analyzed total power of HRV range (TP, $msec^2$); power of high frequency (0.15–0.4 Hz) component in the range (HF,

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[1] Guidelines: Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *European Heart Journal*, 1996, vol. 17, pp. 354–381 (in Russian).

msec^2); power of low frequency (0.04–0.15 Hz) component in the range (LF, msec^2); power of superlow frequency (≤0.04 Hz) component in the range (VLF, msec^2); LF/HF and VL/HF ratios that characterized ratio between central and autonomous regulation activity; time of high frequency (THF, sec) and low frequency (TLF, sec) component in the range; index of centralization (IC) that allowed estimating to what extent heart rate was regulated with centralized mechanisms; power of high frequency (PHF, %), low frequency (PLF, %), and superlow frequency (PVLF, %) components in heart rate variability given in % from the total power of HRV range and characterizing activity of different sections in regulation. To perform integral quantitative assessment of body functional state, we analyzed regulatory systems activity index (RSAI) calculated according to a specialized algorithm developed by R.M. Baevskiy; this parameter characterizes functional reserves with relation to adaptability to the environment [11]. HRV parameters obtained in our research were compared with parameters formulated with «OutWind» software program and given in a table with their standard ranges for typicality assessment being created automatically depending on a patient’s age. Since our study was a single and a cross one, and all the examined students were practically of the same age, standard ranges for assessing parameters typicality were applicable for the whole sampling.

We determined body mass index (BMI) for each student bearing in mind his or her age, height, and body mass. Average body mass amounted to 58.8 ± 0.93 kg (BMI = 21.5 ± 0.30) among girls; 77.47 ± 2.96 kg (BMI = = 24.4 ± 0.85) among boys. To analyze dynamics of HRV parameters in medical students with different body mass, we ranked all the data as per BMI gradations take as follows: «lower than 25» was normal body mass (183 students); «25–29.99», overweight (28 students); «30–34.99», obesity I degree (6 students).

All the data were statistically processed with Statistica 6.1 software package. We analyzed dynamic series of heart rate intervals and revealed that HR, SI, and PLF parameters were distributed normally. Accordingly, to describe these parameters, we applied average sample values and their errors; median, upper and lower quartiles were applied to analyze the remaining parameters. Statistical analysis included descriptive procedures, comparison between two independent samplings as per Mann-Whitney, comparison between several samplings with dispersion rank and factor analysis.

Results and discussion. We analyzed basic parameters of heart rate intervals obtained for medical students; the analysis revealed prevailing sympathetic VNS impacts during a pre-exam period. When examining Time Domain parameters, we established that heart rate (HR) was significantly higher in medical students (85.9 ± 12.0 strokes per minute) that physiological standards (55–80 strokes per minute) (Table 1).

When students are studying for their exams, their regulatory systems are strained and the central regulation mechanisms prevail as it is indicated by group stress index (SI) value being 177.5 ± 158.9 arbitrary units and it is higher than upper boundary of standard typicality assessment (150 arbitrary units).

Having analyzed basic HRV parameters in Frequency Domain, we revealed that the total power (TP) of heart rate variability range, a parameter that characterized total activity of regulatory systems, was significantly higher than physiological standard, 2,293.7 (1,424.0; 3,413.3) msec^2 against 1,500 msec^2. Regulatory systems activity depends on functional state of a body. Regulatory systems in students were obviously under stress and moved from «control» stage that was typical for ordinary living conditions to «regulation» and «centralization» stages that were activated due to necessity to spend more energy under stress and overloads during a pre-exam period.

We established that the main contribution into elevated total power of the range was made by power of low frequency (PLF) component in heart rate variability which reflected elevated activity of the sympathetic section;

Table 1

Descriptive statistics of basic HRV parameters in medical students

HRV parameters	Average	-95 % CI	+95 % CI	Median	Lower quartile	Upper quartile	Dispersion	Standard deviation (SD)	Standard error of the mean (m)
HR, str/min	85.9	84.3	87.5	86.3	78.0	93.9	143.2	12.0	0.8
Mean, msec	713.4	698.6	728.3	695.1	638.8	768.9	12,195.7	110.4	7.5
RMSSD, msec	41.0	37.4	44.7	34.0	24.3	49.7	729.8	27.0	1.8
pNN50, %	14.9	12.9	17.0	9.6	4.2	21.7	235.2	15.3	1.0
SDNN, msec	56.1	53.1	59.1	52.6	41.1	65.8	490.5	22.1	1.5
CV, %	7.8	7.4	8.1	7.5	6.1	8.9	6.0	2.5	0.2
SI	177.5	156.1	198.9	131.9	75.0	223.4	25,268.3	158.9	10.9
TP, msec^2	2,882.9	2,534.4	3,231.4	2,293.7	1,424.0	3,413.3	6,690,135.6	2,586.5	176.8
HF, msec^2	1,012.5	789.6	1,235.5	522.2	282.0	1,068.1	2,738,052.5	1,654.7	113.1
LF, msec^2	1,107.6	1,008.5	1,206.7	960.2	582.8	1,437.0	540,696.4	735.3	50.3
VLF, msec^2	446.2	390.1	502.3	332.8	180.8	541.0	173,294.7	416.3	28.5
ULF, msec^2	316.5	264.6	368.5	210.8	108.3	413.5	148,677.7	385.6	26.4
PHF, %	32.6	30.4	34.7	28.2	20.6	41.4	247.6	15.7	1.1
PLF, %	48.4	46.6	50.2	49.2	40.0	58.7	175.1	13.2	0.9
PVLF, %	19.1	17.9	20.2	17.7	13.0	24.3	74.3	8.6	0.6
LF/HF	2.1	1.9	2.3	1.8	1.0	2.7	2.2	1.5	0.1
VLF/HF	0.8	0.7	0.9	0.6	0.3	1.1	0.5	0.7	0.0
IC	2.9	2.6	3.2	2.5	1.4	3.9	4.1	2.0	0.1
ПАРС	4.8	4.6	5.1	5.0	4.0	6.0	3.0	1.7	0.1

Table 2

Results obtained via rank dispersion analysis of HRV parameters

HRV parameters	Kruskal-Wallis test	*p*	Median test (common median)	χ^2	*p*
HR, str/min	59.98	0.0000	86.31	50.46	0.0000
Mean, ms	59.98	0.0000	695.1	50.5	0.0000
RMSSD	55.76	0.0000	30.02	48.11	0.0000
pNN50 %	68.6	0.0000	9.63	60.95	0.0000
SDNN	31.87	0.0000	52.62	23.51	0.0000
CV, %	18.24	0.0004	7.50	14.12	0.0027
SI	44.79	0.0000	131.98	37.12	0.0000
TP, ms^2	28.61	0.0000	2,293.6	28.24	0.0000
HF, ms^2	54.68	0.0000	522.19	43.57	0.0000
LF,ms^2	12.62	0.0055	960.16	10.11	0.0179
VLF, ms^2	23.12	0.0000	332.75	17.60	0.0005
ULF, ms^2	11.84	0.0079	210.79	11.89	0.0078
IC	46.65	0.0000	2.54	31.46	0.0000

the parameter was equal to 48.4 ± 13.2 %. This result indicates there is growing activity of sympathetic section in the VNS, in particular, vasomotor center regulation system.

Complex HRV assessment allowed establishing that medical students had apparently activated regulatory systems in a body since group median of regulatory systems activity index (RSAI) was equal to 5 (4; 6) scores with physiological standard being 1–3 scores; it corresponds to apparent strain in regulatory systems, including elevated activity of the sympathicoadrenal system and hypophysis-adrenals system. It can be caused by a stress occurring due to increased mental and emotional loads and chronic lack of proper sleep during a pre-exam period [12]. As it was shown by S.Y. Dong, M. Lee et al., when examined people were tested with mental arithmetic, it resulted in growing low frequency components R-R and SBP, that is, sympathetic activity markers, and in declining high-frequency component in R-R interval changeability, a parasympathetic activity marker [13].

In order to determine HRV parameters that were most closely related to intensity of regulatory systems strain, we analyzed the whole data array with rank dispersion analysis; as a result, we managed to establish HRV parameters that were the most informative and had significant discrepancies depending on RSAI value (Table 2).

As an example, we made a figure that illustrated dynamics of heart rate (HR) depending on RSAI value (Figure 1).

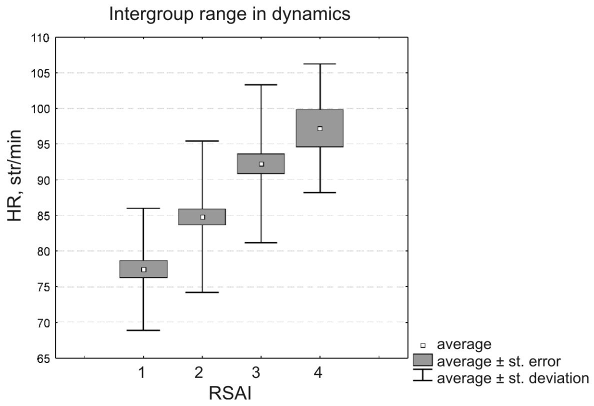

Figure 1. Correlation between heart rate (HR) and RSAI (1 is physiological standard; 2 is pre-nosology; 3 is pre-morbid state; 4 is adaptation failure)

We analyzed HRV parameters in medical students with different body mass; the analysis revealed that there were discrepancies in HRV parameters depending on BMI gradation (Figure 2).

Rank dispersion analysis of HRV parameters and students' ranked BMI values allowed establishing that as body mass grew, there was a decline in activity of parasympathetic section in vegetative regulation, as it was indicated by RMSSD drop from 34.7 msec (25.8; 50.3) among students with normal BMI to 20.7 (17.5; 27.8) among those with obesity I degree; drop in power of high frequency component (PHF) from 28.2 (26.5; 41.4) to 18.2 (12.7; 27.4); and an increase in time of high frequency component (THF) from 4.9 (3.4; 5.7) to 6,2 (5.8; 6.6). Index of centralization (IC) is another important parameter that reflects an extent to which non-respiratory components in sinus arrhythmia prevail over respiratory ones. The index is calculated basing on power of high- and low frequency components in HRV and allows making quantitative assessment of ratio between central and autonomous heart rate regulatory contours. Autonomous regulatory contour is related to respiratory component in sinus arrhythmia and parasympathetic regulation; however, the more actively centralized regulatory contour participates in heart rate management, the greater is a decrease in respiratory waves range, and vegetative homeostasis is shifted towards sympathetic regulation prevalence. In our research students tended to have a growth in centralized heart rate regulation as their BMI grew since index of centralization (IC) increased from 2.5 (1.4; 3.8) among students with normal BMI to 4.5 (2.9; 6.8) among those with obesity I degree. PostHoc analysis revealed that RMSSD, PHF, THF, and IC were authentically different among students with normal BMI and obesity I degree ($p \leq 0.05$). We revealed that VLF/HF ratio also grew as BMI increased (Figure 3) and amounted to 0.54 (0.32; 1.01) among students with normal BMI; 0.87 (0.53; 1.56), among students with overweight; 1.87 (1.00; 3,02), among students with obesity I degree.

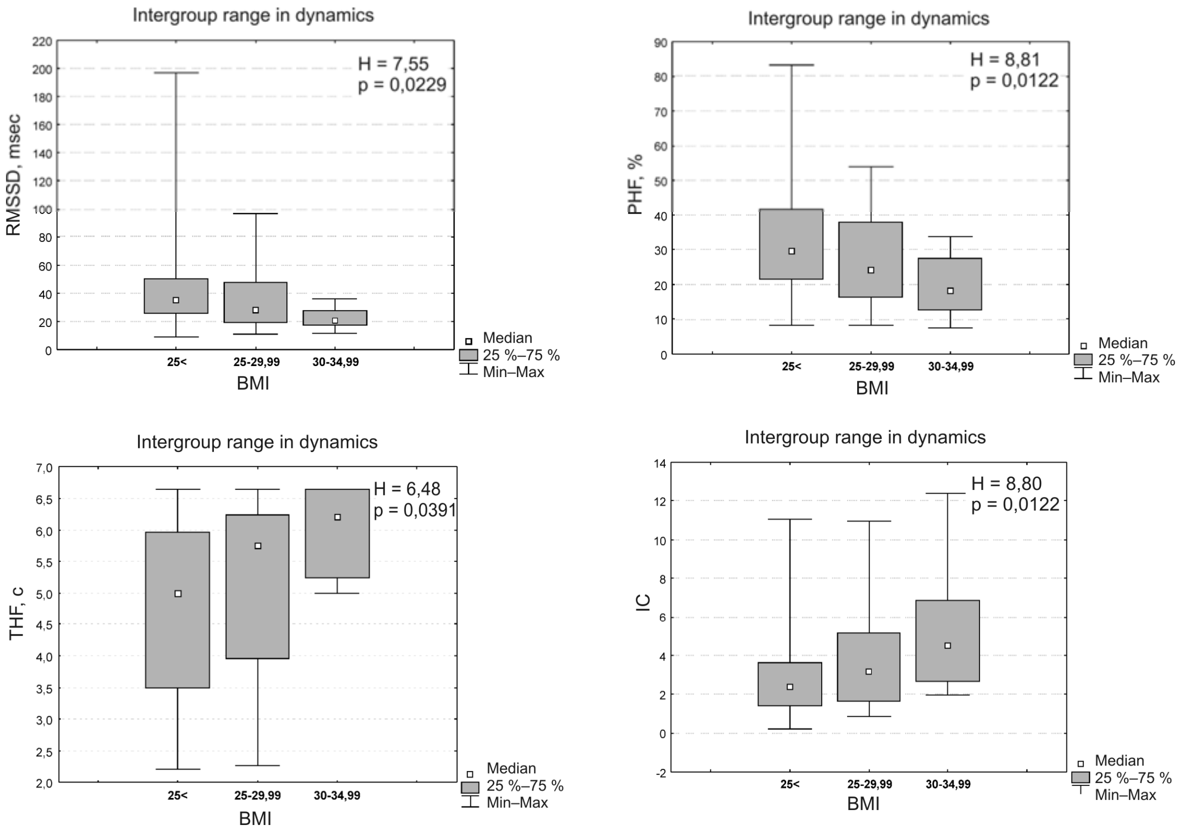

Figure 2. Heart rate variability parameters (RMSSD, PHF, THF, IC) taken in dynamics depending on BMI

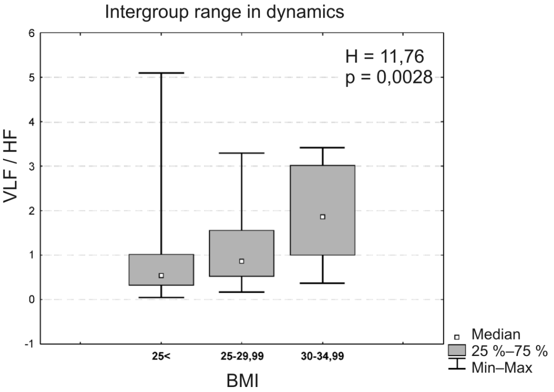

Figure 3. VLF/HF dynamics depending on BMI

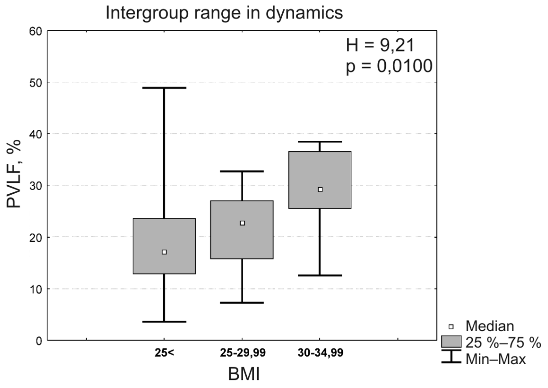

Figure 4. Power of superlow frequency component in heart rate variability (PVLF, %) taken in dynamics depending on BMI

This VLF/HF dynamics indicates that central heart rate regulatory contour is becoming more active against autonomous one. Since autonomous regulatory contour is actually a parasympathetic one, growing centralization in regulation means that vegetative homeostasis is shifted towards sympathetic regulation prevalence.

We revealed that students with BMI that corresponded to obesity I degree had maximum power of superlow frequency component in heart rate variability (PVLF, %) that was equal to 29.3 % (25.6; 36.5) against 22.7 % (15.8; 27.04) among students with overweight and 17.2 % (12.9; 23.5) among students with normal body mass (Figure 4). PVLF characterizes relative activity of sympathetic section in regulation and thermal regulation processes, but apart from that it can be also used as a marker showing intensity of relation between autonomous (segmental) circulation regulation with above-segmental one including hypophysis-hypothalamus and cortical regulation. Moreover, it is a good indicator reflecting regulation over metabolic processes [14–16].

Obesity is known to be a significant risk factor causing diseases occurrence and development. A correlation between high BMI values and overall mortality is confirmed with results obtained via meta-analyses that describe a J-like functional correlation between this factor and mortality and stratify its low risks at BMI varying from 20.0 kg/m^2 to 25 kg/m^2 [17, 18]. And here cardiovascular pathology takes the first rank place among nosologies associated with overweight and obesity since more than two thirds of deaths related to high BMI all over the world are deaths due to cardiovascular diseases [19]. Dependence between HRV parameters that characterize vegetative regulation and metabolic disorders has been described by V.A. Nevzorova and E.A. Abramov, given that there were no discrepancies in the structure of carbohydrate metabolism disorders between the examined groups [20]. Vegetative dysfunction detected in patients with metabolic syndrome is thought to be related to obesity degree and it is also predicted that further metabolic disorders development will result in diabetic vegetative neuropathy occurrence. It should be noted that a concept of metabolic syndrome (MS) as a cluster of risk factors causing type 2 diabetes and cardiovascular diseases (CVD) has undergone certain evolutionary changes over recent years. In particular, S.I. Kseneva, E.V. Borodulina et al. revealed that frequency of cardiac vegetative neuropathy reached 37.5 % due to MS [21]. It was also noted that vegetative nervous system dysfunction (just as resistance to insulin) was a primary reason for MS development. Integration of vegetative dysfunction in MS pathogenesis provides an opportunity to include certain nosologies into MS cluster [22]. Despite there are multiple scores for assessing CVD risks occurrence (the Framingham Risk Score, PROCAM, SCORE, UKPDS, ULSAM, and others), none of them allows precise prediction of CVD risks for young people aged 18–35 without any clinical signs of atherosclerosis; however, there have been multiple attempts to adapt some of predictive models for assessing risks of CVD occurrence among young people [23]. Given that there is usually low probability that cardiovascular events might occur in the nearest future and less apparent risk factors, it is more difficult to assess absolute CVD risks for young people. Young males in general are more susceptible to risks of CVD occurrence than young females since stresses result in changes in lipid blood structure in them towards atherogenicity and increased blood pressure [24, 25]. Apart from this, obesity among young males is a predictor that determines occurrence of atherosclerosis in coronary arteries in 15 % cases [26].

An existing problem related to proper CVD risks stratification among young people makes it necessary to develop a predictive model that should include new criteria and be able to detect young people who run high CVD risks with significant precision. It is vital for further examinations and timely preventive activities and it will allow preventing CVD-related morbidity and mortality at an older age. Given that, it is necessary to further examine HRV parameters as biomarkers in predicting CVD risks occurrence among students involving greater numbers of participants.

Conclusions. We performed a complex assessment of HRV in medical students during a period prior to exams; the assessment revealed that there was apparent strain in their regulatory systems due to elevated activity of the sympathico-adrenal system and hypophysis-adrenals system. Integral regulatory systems activity was significantly increased due to a drastic growth in central regulation activity.

Growing body mass was accompanied with the parasympathetic section in vegetative regulation being less active as it was indicated by a decrease in RMSSD, power of high frequency component, and growing time of high frequency component. And there was also a growth in centralization of heart rate regulation, and accordingly index of centralization and VLF/HF ratio also increased. Non-respiratory component in sinus arrhythmia prevailed over respiratory ones in cardiointervals array, and as respiratory waves range decreased, vegetative homeostasis was shifted towards sympathetic regulation prevalence. As metabolic disorders became more intense, there was a growth in power of superlow frequency component in heart rate variability, and it allowed using this parameter as an indicator of metabolic disorders that resulted in elevated risks of cardiovascular events.

Analysis of HRV parameters in students allows assessing adaptation processes adequacy as a response to stressors, such as mental and emotional loads in educational processes, obtaining data on VNS state, and using these data as a basis for preventive and recovery activities. It is necessary to further investigate HRV parameters as biomarkers predicting CVD risks for students involving greater numbers of participants and to implement these biomarkers in practical activities.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 20.02.2020
Accepted: 11.11.2020
Published: 30.12.2020