Sexual dimorphism in the neuro-endocrine regulation of bicycle ergometric test parameters in untrained individuals with dysfunction of the neuro-endocrine-immune complex

Sofiya V. Ruzhylo1, Oksana A. Fihura1, Nataliya R. Zakalyak1, Galyna Y. Kovalchuk1, Xawery Žukow2, Dariya V. Popovych3

1Ivan Franko Pedagogical University, Drohobych, Ukraine doctor-0701@ukr.net
2Medical University of Białystok, Białystok, Poland xawerryzukow@gmail.com
3IY Horbachevs’kyi National Medical University, Ternopil’, Ukraine darakoz@yahoo.com

Abstract

Background. Ergometric physical working capacity (PWC) testing has a long tradition in occupational medicine. PWC can be tested, using performance indicators like VO₂ max or the mechanical power. However, the calculated by bicycle ergometry PWC in reality reflects the reaction of the autonomic nervous system to muscle load, which, in turn, is strong, but still not absolutely complete, correlates with VO₂ max as a real indicator of cardiorespiratory fitness. The purpose of this study is to clarify the relationship between PWC, calculated based on the result of two-stage bicycle ergometry, and the parameters of neuro-endocrine regulation as well as sexual differences in such relationships.

Materials and Methods. The object of observation were 30 women 29-76 (49,4±11,0) years and 30 men 24-69 (47,4±12,0) years without a clinical diagnosis, but with the deviations from the norm in a number of parameters of the neuro-endocrine-immune complex as a manifestation of maladaptation. For estimation of PWC a two-stage bicycle ergometry used. Parameters of EEG, HRV and adaptation hormones levels registered twice with an interval of 4 or 7 days. Results. In men, PWC correlates negatively with plasma levels of cortisol (r=-0.52) and triiodothyronine (r=-0.47), but positively with levels of calcitonin (r=0.25) and testosterone (r=0.22). The coefficient of multiple correlation R=0.705. In women, the correlation of the twice lower PWC with cortisol and calcitonin is weaker (r=-0.31 and 0.18, respectively), and is absent with testosterone and triiodothyronine, instead it was found in relation to aldosterone (r=-0.24); R=0.394. The PWC regression model for men includes 6 HRV and 11 EEG parameters (R=0.846), while for women only the mode HRV (r=-0.56) and two EEG parameters (R=0.608). Conclusion. PWC levels in men are generally downregulated by cortisol, triiodothyronine, sympathic tone, and 0-rhythm generating neurons, but upregulated by testosterone, calcitonin, vagal tone, and related α-rhythm generating neurons. In women, PWC levels are borderline downregulated by cortisol and aldosterone, but significantly upregulated by circulating catecholamines and β-rhythm generating neurons.

Keywords: bicycle ergometry, EEG, HRV, adaptation hormones, relationships, sexual dimorphism.
INTRODUCTION

Ergometric physical working capacity (PWC) testing has a long tradition in occupational medicine for assessing whether a sufficiently high level of physical performance for coping with the daily work requirements is given [33,36]. PWC can be tested maximally or submaximally, using performance indicators like VO₂ max [6] or the mechanical power [11,46]. In the case of submaximal PWC testing measuring the mechanical power, the achieved power at a given heart rate serves as performance indicator. There are age- and sex-specific norm values [37] that can be used to judge whether differences or changes are within the normal range or can be considered significant. In addition, cardiorespiratory fitness is considered an attribute of health in general and non-specific resistance in particular [2,9,12,15], and is also an important target of adaptogenic agents [21,27,30,48-50].

However, it has been known for a long time that although the calculated submaximal PWC is considered as an indicator of cardiorespiratory fitness [13], in reality it reflects the reaction of the autonomic nervous system to muscle load, which, in turn, is strong, but still not absolutely complete, correlates with VO₂ max as a real indicator of cardiorespiratory fitness. By the way, the correlation is significantly affected by the use of adrenergic and/or cholinergic blockers, as well as autonomic dysfunction as a manifestation of maladaptation [16,22,28].

The purpose of this study is to clarify the relationship between PWC, calculated based on the result of two-stage bicycle ergometry, and the parameters of neuro-endocrine regulation and sexual differences in such relationships.

MATERIAL AND RESEARCH METHODS

The object of observation were employees of the clinical sanatorium "Moldova" and PrJSC "Truskavets’ Spa": 30 women 29-76 (49,4±11,0) years and 30 men 24-69 (47,4±12,0) years. The volunteers were considered practically healthy (without a clinical diagnosis), but the initial testing revealed deviations from the norm in a number of parameters of the neuro-endocrine-immune complex (details follow) as a manifestation of maladaptation, which actually prompted them to participate in the study with the hope of recovery.

In the morning in basal condition we recorded simultaneously electrocardiogram (ECG) and electroencephalogram (EEG). ECG recorded during 7 min in II lead to assess the parameters of heart rate variability (HRV) (hardware-software complex "CardioLab+HRV", "KhAI-Medica", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected. Baevskiy’s parameters: heart rate (HR), the mode (Mo), amplitude of mode, the variation scope (MxDMn) [3]. Temporal parameters (Time Domain Methods): the standart 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 then 50 ms (pNN50), triangular index (TNN). Spectral parameters (Frequency Domain Methods): absolute (msec²) and relative (%) power spectral density (PSD) bands of HRV: high-frequency (HF, range 0,40÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,040÷0,015 Hz) and ultra low-frequency (ULF, range 0,015÷0,003 Hz) [5,18,34]. Calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index (CI)=(VLF+LF)/HF, Baevskiy’s Stress Index.

EEG recorded during 25 sec a hardware-software complex “NeuroCom Standard” (KhAI Medica, Kharkiv, Ukraine) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref on the earlobes. Among the options considered the average EEG amplitude (µV), average
frequency (Hz), frequency deviation (Hz), index (%), absolute (μV²/Hz) and relative (%) PSD of basic rhythms: β (35±13 Hz), α (13±8 Hz), θ (8±4 Hz) and δ (4±0.5 Hz) in all loci, according to the instructions of the device. In addition, calculated coefficient of Asymmetry (As) and Laterality Index (LI) for PSD each Rhythm using formulas [19]:

As, % = 100•(Max – Min)/Min; LI, % = Σ [200•(Right – Left)/(Right + Left)]/8.

We calculated for HRV and each locus EEG the Entropy (h) of normalized PSD using Popovych’s IL [16,31] formulas based on classic Shannon’s CE [35] formulas:

hHRV = -(SPHF•log2SPHF+SPLF•log2SPLF+SPVLF•log2SPVLF+SPULF•log2SPULF)/log24;

hEEG = -(PSDα•log2PSDα+PSDβ•log2PSDβ+PSDθ•log2PSDθ+PSDδ•log2PSDδ)/log24.

At last in portion of venous blood determined plasma levels of major hormones of adaptation [8,14,22-24,29]: Cortisol, Testosterone, Aldosterone, Triiodothyronine and Calcitonin (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).

For estimation of physical working capacity (PWC) a bicycle ergometer “Tunturi” (Finland) is used. The power of the first load was 0.5 W/kg (HR±SD: 100±11 beats/min) at a pedaling frequency of 60-75 rpm. The power of the second load (after 3 min) was 1.5 W/kg (131±15 beats/min). This corresponded to the recommendations for ergometer testing in occupational medicine, particular for patients with maladaptation [2,7,13,41]. Calculated submaximal PWC150 with the mechanical power in Watt per kilogram body weight (W/kg) as indicator of cardiorespiratory fitness [13].

Testing was performed twice with an interval of 4 or 7 days.

Reference values of hormones and HRV are taken from the instructions for the kits and the device, respectively. Instead, EEG reference values due to their absence in the instructions are taken from the database of the Truskavetsian Scientific School of Balneology (n=112).

Results processed using the software package "Statistica 6.4".

RESULTS AND DISCUSSION

Both cohorts were almost identical in terms of age and body mass index (Table 1). The latter slightly exceeded the norm (by 8% in men and by 11% in women). Aldosterone and triiodothyronine plasma levels were equally normal, and cortisol levels were equally reduced (by 19% in men and by 18% in women). The actual levels of calcitonin did not differ, however, taking into account the significant sexual dimorphism (males/females average ratio is 2.76), it was found to be reduced by 25% in men and increased by 76% in women. A similar excess of the average norm (by 62%) in the latter was also found for testosterone, while in men its level corresponded to the age norm.
Table 1. Comparative characteristics of antropometric parameters and levels of adaptation hormones in men and women

| Variable                  | Males (n=59) | Females (n=59) | Reference (n=30) | t/p for sexes | t/p for M reference | t/p for F reference |
|---------------------------|--------------|----------------|------------------|---------------|---------------------|---------------------|
| Age, years                | 47,4         | 1,6            | 49,4             | 1,7           |                     |                     |
| Hight, cm                 | 178,2        | 0,7            | 163,8            | 1,1           |                     |                     |
| Weight, kg                | 83,0         | 0,7            | 71,5             | 1,3           |                     |                     |
| Body mass index, kg/m²    | 26,2         | 0,3            | 26,8             | 0,6           | 0,94 ns             | 2,99 ns             |
| Aldosterone, pM/L         | 226          | 222            | 238              | 238           | -0,68 ns            | -1,9 ns             |
| Triiodothyronine, nM/L    | 2,02         | 0,12           | 2,16             | 0,12          | 0,86 ns             | -1,22 ns            |
| Cortisol, nM/L            | 299          | 16             | 303              | 14            | 0,20 ns             | -2,77 ns            |
| Calcitonin, ng/L          | 10,51        | 8,87           | 13,95            | 5,05          | -1,31 ns            | -2,24 ns            |
| Testosterone, nM/L        | 13,1         | 0,8            | 14,4             | 0,5           | -10,6               | -1,46 ns            |

In men, the level of PWC is significantly negatively correlated with plasma levels of cortisol (Fig. 1) and triiodothyronine (Fig. 2), on the other hand, at the limit of significance (for a sample of n=59, critical module r=0,26) positively with levels of calcitonin and testosterone (Table 2) in the complete absence of correlation with aldosterone (r=-0,03).

![Fig. 1. Scatterplot of correlation between plasma cortisol level (line X) and PWC (line Y) in men](image-url)
Fig. 2. Scatterplot of correlation between plasma triiodothyronine level (line X) and PWC (line Y) in men

Judging by the coefficient of multiple correlation, this hormonal constellation determines the level of PWC by 49.7% (Table 2 and Fig. 2).

Table 2. Regression Summary for PWC_{150} (W/kg) in men

| N=59 | Beta | St. Err. of Beta | B   | St. Err. of B | t(54) | p-level |
|------|------|-----------------|-----|---------------|-------|---------|
| Variables | r     | Intercept       | 5.446 | 0.275 | 19.8 | 10^{-6} |
| Cortisol, nM/L | -0.52 | -0.376 | 0.1037 | -0.0019 | 0.0005 | -3.63 | 0.001 |
| Triiodothyronine, nM/L | -0.47 | -0.432 | 0.0998 | -0.3179 | 0.0735 | -4.33 | 10^{-4} |
| Calcitonin, ng/L | 0.25 | 0.160 | 0.1014 | 0.0147 | 0.0094 | 1.58 | 0.121 |
| Testosterone, nM/L | 0.22 | 0.262 | 0.0982 | 0.0282 | 0.0106 | 2.67 | 0.010 |

R=0.705; R^2=0.497; \chi^2(4)=38; p<10^{-6}; A Prime=0.503

Fig. 2. Scatterplot of canonical correlation between hormonal variables (X-line) and PWC (Y-line) in men

As a result of the regression analysis with stepwise exclusion of variables until reaching the maximum value of Adjusted R^2, 6 HRV and 11 EEG parameters were included in the
model (Table 3). The first 4 parameters of HRV are generally recognized markers of vagal tone, and Baevsky's stress index is a marker of sympathetic tone. The first 4 parameters of HRV are generally recognized markers of vagal tone, while Baevsky's stress index is a marker of sympathetic tone. The physiological interpretation of the VLF band remains a matter of debate.

### Table 3. Regression Summary for PWC_{150} (W/kg) in men

| Variables                        | Beta | St. Err. of Beta | B     | St. Err. of B | t(41) | p-level |
|----------------------------------|------|------------------|-------|---------------|-------|---------|
| Triangular index, units          | 0.45 | 0.976            | 0.304 | 0.1475        | 0.0459| 3,21    | 0.003  |
| MxDMN, msec                      | 0.41 | 0.578            | 0.349 | 0.0043        | 0.0026| 1,66    | 0.105  |
| SDNN, msec                       | 0.38 | 0.990            | 0.369 | 0.0287        | 0.0107| 2.68    | 0.010  |
| RMSSD, msec                      | 0.28 | -1.043           | 0.240 | -0.0428       | 0.0098| -4.35   | 10^{-4}|
| P3-α PSD, %                      | 0.33 | -0.938           | 0.296 | -0.0269       | 0.0085| -3.16   | 0.003  |
| P3-α PSD, µV^{2}/Hz              | 0.32 | 1.749            | 0.497 | 0.0027        | 0.0008| 3.52    | 0.001  |
| P4-α PSD, µV^{2}/Hz              | 0.32 | -1.375           | 0.610 | -0.0022       | 0.0010| -2.25   | 0.030  |
| T5-α PSD, %                      | 0.32 | -0.280           | 0.208 | -0.0088       | 0.0066| -1.34   | 0.187  |
| O2-α PSD, µV^{2}/Hz              | 0.31 | 0.898            | 0.407 | 0.0011        | 0.0005| 2.20    | 0.033  |
| Amplitude α, µV                  | 0.31 | -1.118           | 0.595 | -0.0610       | 0.0325| -1.88   | 0.067  |
| O1-α PSD, %                      | 0.30 | 0.305            | 0.264 | 0.0082        | 0.0071| 1.16    | 0.253  |
| T6-α PSD, %                      | 0.29 | 1.024            | 0.223 | 0.0321        | 0.0070| 4.59    | 10^{-4}|
| Laterality β, %                  | 0.29 | 0.279            | 0.107 | 0.0043        | 0.0017| 2.60    | 0.013  |
| VLF PSD, %                       | -0.41| -0.156           | 0.109 | -0.0055       | 0.0039| -1.43   | 0.161  |
| O2-0 PSD, %                      | -0.36| -0.377           | 0.108 | -0.0524       | 0.0150| -3.49   | 0.001  |
| Stress index, In units           | -0.32| 1.316            | 0.357 | 1.0556        | 0.2866| 3.68    | 0.001  |
| T3-0 PSD, µV^{2}/Hz              | -0.31| -0.179           | 0.117 | -0.0058       | 0.0038| -1.53   | 0.135  |

Akselrod S et al [1] in pioneering experiment illustrated that after parasympathetic blockade the amplitude of the VLF peak is reduced; β-sympathetic blockade tends to reduce the VLF peak’s amplitude, but this effect is not consistent because of the low tonic level of sympathetic activity in the resting dog. Increasing the activity of either the sympathetic or parasympathetic nervous system augments the area under the VLF peak. Therefore, both SNS and PSNS may mediate the VLF fluctuations. Selective blockade of renin-angiotensin system (by converting enzyme inhibitor) lead to 2-4.5-fold increase in the area under the VLF peak. Although VLF power has been correlated with low levels of testosterone, while cortisol have not [17,39]. In the cohort of men observed by us, the relative PSD of VLF band correlates negatively with markers of vagal tone (r=-0.44÷-0.54), but positively with the stress index (r=0.27) and AMo (r=0.31), as well as cortisol (r=0.44) in the complete absence of a connection with both aldosterone (r=-0.05) and testosterone (r=-0.03). So, in this specific situation, the relative PSD of VLF band acts as a marker of sympathetic tone and cortisol.
Among the EEG parameters included in the regression model, the activity of the α-rhythm generating neural structures, which project to the temporal, parietal and occipital both right and left loci of the scalp, are positively correlated with PWC.

Judging by the scheme of Winkelmann T et al [45], on the P3/P4 loci is projected supramarginal gyrus, on the T5/T6 loci transverse temporal cortex, and on the O1/O2 loci lingual gyrus of left/right hemisphere, the thickness of which are positively correlated (r=0.43 for P3; 0.51 for T6 and 0.47 for O2 respectively) with vagally mediated HRV (HF band and RMSSD). This is in excellent agreement with our data on vagal upregulation of PWC. At the same time, the activity of θ-rhythm-generating neurons of right lingual gyrus (O2) and left superior temporal gyrus (T3) makes down regulation of PWC. Taken together, neurogenic influences determine the level of PWC in men by 71.7% (Table 3 and Fig. 3).

![Scatterplot](image)

R=0.846; R²=0.717; χ²(16)=58; p=10⁻⁶; Λ Prime=0.307

Fig. 3. Scatterplot of canonical correlation between EEG&HRV variables (X-line) and PWC (Y-line) in men

In women, the neuro-endocrine regulation of PWC differs from that in men both quantitatively and qualitatively. In particular, downregulation on the part of cortisol and upregulation on the part of calcitonin are weaker, and on the part of triiodothyronine and testosterone they come to nothing (r=-0.13 and -0.04 respectively), instead there is a weak downregulation on the part of aldosterone, absent in men. Accordingly, the measure of hormonal determination is very weak (15.5%), but statistically significant (Table 4 and Fig. 4).

Table 4. Regression Summary for PWC₁₅₀ (W/kg) in women

| Variables      | Beta | St. Err. of Beta | B   | St. Err. of B | t(55) | p-level |
|----------------|------|-----------------|-----|---------------|-------|---------|
| Cortisol, nM/L | -0.31| -0.263          | 0.128| -0.000        | -2.06 | 0.045   |
| Aldosterone, pM/L | -0.24| -0.219         | 0.125| -0.002        | -1.76 | 0.085   |
| Calcitonin, ng/L | 0.18 | 0.118          | 0.128| 0.003         | 0.92  | 0.361   |
Among the HRV parameters, the connection with the mode (Fig. 5), which is an inverse marker of the level of circulating catecholamines [3], turned out to be the most significant. A significant positive correlation was also found with the sympathetic tone marker LFnu (r=0.30) and P3-β PSD (0.27), but these parameters were formally outside the model. Instead, PSD entropy at the P3 locus and T5-β PSD were included in the model. As a result, the measure of neurogenic determination of PWC turned out to be very strong (37.0%), but significantly weaker than that in men.

**Table 5. Regression Summary for PWC150 (W/kg) in men**

R=0.608; R²=0.370; Adjusted R²=0.336; F(3,6)=10.8; p=10⁻⁵; SD=0.14 W/kg

| Variables            | Beta  | St. Err. of Beta | B     | St. Err. of B | t(55)  | p-level |
|----------------------|-------|------------------|-------|--------------|--------|---------|
| Mode HRV, msec       | -0.56 | -0.523           | 0.109 | -0.0007      | -4.80  | 10⁻⁵    |
| P3 PSD Entropy       | 0.24  | 0.1825           | 0.108 | 0.2169       | 1.69   | 0.097   |
| T5-β PSD, µV2/Hz     | 0.23  | 0.136            | 0.109 | 0.0002       | 1.26   | 0.214   |
R=0.608; R²=0.370; χ²(3)=26; p=10⁻⁵; Λ Prime=0.629

Fig. 6. Scatterplot of canonical correlation between EEG&HRV variables (X-line) and PWC (Y-line) in women

It is very interesting that in the already cited study of Winkelmann T et al [45] a negative correlation (r=-0.45) was found between the thickness of the isthmus cingulate cortex LH, which also projects to the P3 locus, and vagally mediated HRV. This suggests that the β-rhythm generating neurons of this area of the cortex, as well as of transverse temporal cortex RH (T6) are responsible for increasing the sympathetic tone and/or the level of circulating catecholamines through medullary sympathoexcitatory neurons [43,44] and other structures of the central autonomic network [4,20,25,26,32,40,42]. The described sexual dimorphism in the neuro-endocrine regulation of PWC is visualized in the form of profiles of correlation coefficients (Fig. 7).
Fig. 7. Profiles of correlation coefficients between EEG&HRV parameters and PWC in men and women

The sexual dimorphism in the neuro-endocrine regulation of PWC is manifested against the background of the absence of significant differences in the HRV parameters involved, with the exception of a 9% higher sympathetic tone in men, which, in turn, exceeded the norm in both sexes in combination with a decrease in vagal tone and an increase in the level of circulating catecholamines (Table 6).

Among the EEG parameters (Table 7), the PSD of the θ-rhythm in the T3 locus was found to be more than two times lower in men than in women, as well as a 32% lower PSD of the β-rhythm in the T5 locus, which, however, did not differ from the average norm, and in women exceeded it by 84% and 35%, respectively.

In addition, males had 16-20% lower than normal PSDs of the α-rhythm at all 4 loci, while females only at the P3 locus.

Table 6. Comparative characteristics of HRV parameters correlated with PWC

| Variable           | Males (n=59) | Females (n=59) | Reference (n=118) | t/p for sexes | t/p for M reference | t/p for F reference |
|--------------------|-------------|----------------|-------------------|---------------|---------------------|---------------------|
| Mode, msec         | 775         | 778            | 870               | 0,44          | -4,24 <0,001        | -4,24 <0,001        |
| MxDMN, msec        | 209         | 232            | 245               | 1,58 >0,05    | -2,88 <0,01         | -1,15 ns            |
| Stress index, units| 203         | 232            | 245               | -0,97 ns      | 2,86 <0,01         | 1,53 >0,05          |
| Stress index, ln units| 5,01       | 4,83           | 4,89              | -1,28 ns      | 0,85 ns             | -0,49 ns            |
| Triangular index, units| 10,8        | 11,7           | 11,2              | 1,09 ns       | -0,65 ns            | 0,80 ns             |
| SDNN, msec         | 44,2        | 48,7           | 56,2              | 1,19 ns       | -3,21 <0,01         | -2,12 <0,05         |
| RMSSD, msec        | 22,9        | 27,5           | 30,1              | 1,48 ns       | -2,94 <0,01         | -1,01 ns            |
| LFnu PSD, %        | 81,7        | 74,8           | 64,4              | -3,10 <0,01   | 8,44 <10^{-4}       | -4,24 <0,001        |
| VLF PSD, %         | 47,2        | 43,4           | 53,6              | -1,18 ns      | -2,19 <0,05         | -4,24 <0,001        |
Table 7. Comparative characteristics of EEG parameters correlated with PWC

| Variable                  | Males (n=59) | Females (n=59) | Reference (n=112) | t/p for sexes | t/p for M reference | t/p for F reference |
|---------------------------|--------------|----------------|-------------------|---------------|---------------------|---------------------|
| T3-θ PSD, µV^2/Hz         | 26.4         | 55.4           | 30                | 3.51          | <0.01               | ns                  |
|                           | 2.5          | 7.9            | 3                 | -0.92         | ns                  | <0.01               |
| T5-β PSD, µV^2/Hz         | 65           | 96             | 71                | 2.20          | <0.05               | ns                  |
|                           | 5            | 13             | 5                 | -0.81         | ns                  | >0.05               |
| P3-α PSD, %               | 35.7         | 35.3           | 42.7              | -0.09         | ns                  | <0.05               |
|                           | 2.8          | 2.7            | 2.0               | -0.23         | <0.05               | <0.05               |
| O1-α PSD, %               | 33.5         | 36.7           | 42.0              | 0.78          | ns                  | <0.05               |
|                           | 3.0          | 2.7            | 2.0               | -2.35         | <0.05               | >0.05               |
| T6-α PSD, %               | 28.6         | 31.8           | 35.5              | 0.92          | ns                  | <0.05               |
|                           | 2.6          | 2.4            | 1.7               | -2.25         | <0.05               | ns                  |
| T5-α PSD, %               | 28.6         | 32.7           | 35.1              | 1.16          | ns                  | <0.05               |
|                           | 2.6          | 2.4            | 1.7               | -2.10         | ns                  | <0.05               |
| P3-β PSD, %               | 20.4         | 20.1           | 22.7              | -0.18         | ns                  | <0.05               |
|                           | 1.5          | 1.4            | 1.1               | -1.21         | <0.05               | >0.05               |
| Laterality β, %           | -4           | -6             | -1                | -0.35         | ns                  | <0.05               |
|                           | 5            | 4              | 3                 | -0.53         | ns                  | ns                  |
| P3 PSD Entropy            | 0.79         | 0.80           | 0.80              | 0.10          | ns                  | <0.05               |
| Amplitude α, µV           | 16.3         | 18.3           | 17.4              | 0.93          | ns                  | <0.05               |
|                           | 1.5          | 1.6            | 1.0               | -0.67         | ns                  | ns                  |
| P3-α PSD, µV^2/Hz         | 279          | 326            | 287               | 0.56          | ns                  | ns                  |
|                           | 53           | 67             | 36                | -0.13         | ns                  | ns                  |
| O2-α PSD, µV^2/Hz         | 292          | 332            | 301               | 0.42          | ns                  | ns                  |
|                           | 65           | 67             | 43                | -0.12         | ns                  | ns                  |
| O2-0 PSD, %               | 7.4          | 8.0            | 7.1               | 0.71          | ns                  | 1.26                |
|                           | 0.6          | 0.6            | 0.4               | 0.41          | ns                  | ns                  |

Identified deviations from the norm are, apparently, a manifestation of dysfunction of the neuro-endocrine-immune complex and maladaptation [16,23,28].

CONCLUSION

PWC levels in men are generally downregulated by cortisol, triiodothyronine, sympathetic tone, and θ-rhythm generating neurons, but upregulated by testosterone, calcitonin, vagal tone, and related α-rhythm generating neurons. In women, PWC levels are borderline downregulated by cortisol and aldosterone, but significantly upregulated by circulating catecholamines and β-rhythm generating neurons.

ACKNOWLEDGMENT

We express sincere gratitude to administration of clinical sanatorium “Moldova”, “Truskavets’ Spa” and “Truskavets’kurort” as well as coworkers Babelyuk VE, Korolyshyn TA and Kikhtan VV for help in recording tests. Special thanks to the volunteers.

ACCORDANCE TO ETHICS STANDARDS

Tests in patients are carried out 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.

REFERENCES

1. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science (NY). 1981; 213(4504): 220-222.

2. Amosov MV, Bendet YaA. Physical activity and heart [in Russian]. Kyiv. Zdorovya; 1989: 215.

3. Baevskiy RM, Ivanov GG. Heart Rate Variability: theoretical aspects and possibilities of clinical application [in Russian]. Ultrazvukovaya i funktsionalnaya diagnostika. 2001; 3: 106-127.

4. Benaroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993; 68(10): 988-1001.

5. Bernston GG, Bigger JT jr, Eckberg DL, Grossman P, Kaufman PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, Van der Molen MW. Heart Rate Variability: Origins, methods, and interpretive caveats. Psychophysiology. 1997; 34: 623-648.

6. Bugajska J, Makowiec-Dabrowska T, Bortkiewicz A, Gadzicka E, Marszalek A, Lewandowski Z, Konarska M. Physical capacity of occupationally active population and capability to perform physical work. Int J Occup Saf Ergon. 2011; 17: 129–138.

7. Chatterjee M, Schmeißer G. Aktualisierter Leitfaden für die Ergometrie im Rahmen arbeitsmedizinischer Untersuchungen. Arb. Soz. Umweltmed. 2017; 52: 913–921.

8. Chrousoos GP. Stressors, stress and neuroendocrine integration of the adaptive response. The 1997 Hans Selye memorial lecture. In: Stress of life: from molecules to man / Ed by P Csermely. Ann NYAS. 1998; 851: 311-335.

9. Daniela M, Catalina L, Ilie O, Paula M, Daniel-Andrei I, Ioana B. Effects of Exercise Training on the Autonomic Nervous System with a Focus on Anti-Inflammatory and Antioxidants Effects. Antioxidants (Basel, Switzerland). 2022; 11(2): 350.

10. Del Valle-Mondragón L, Becerra-Luna B, Cartas-Rosado R, et al. Correlation between Angiotensin Serum Levels and Very-Low-Frequency Spectral Power of Heart Rate Variability during Hemodialysis. Life (Basel). 2022; 10(5): 3030-3039.

11. Farazdaghi GR, Wohlfart B. Reference values for the physical work capacity on a bicycle ergometer for women between 20 and 80 years of age. Clin. Physiol. 2001; 21: 682–687.

12. Fil V, Zukow W, Kovalchuk G, Voloshyn O, Kopko I, Lupok O, Stets V. The role of innate muscular endurance and resistance to hypoxia in reactions to acute stress of neuroendocrine, metabolic and ECGs parameters and gastric mucosa in rats. Journal of Physical Education and Sport. 2021; 21(Suppl. 5): 3002-3039.

13. Finger JD, Krug S, Gößwald A, Härtel S, Bös K. English Version: Kardiorespiratorische Fitness bei Erwachsenen in Deutschland. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1) Bundesgesundheitsbl. 2013; 56: 772–778.

14. Garkavi LKh, Kvakina YB, Kuz’menko TS. Antistress Reactions and Activation Therapy [in Russian]. Moskva. Imedis; 1998: 654.

15. Gozhenko AI. Essays on disease theory [in Russian]. Odesa; 2010: 24.

16. Gozhenko AI, Korda MM, Popadynets’ OO, Popovych IL. Entropy, Harmony, Synchronization and Their Neuro-Endocrine-Immune Correlates [in Ukrainian]. Odesa. Feniks; 2021: 232.

17. Hasson D, Theorell T, Liljeholm-Johansson Y, Canlon B. Psychosocial and physiological correlates of self-reported hearing problems in male and female musicians in symphony orchestras. Int J Psychophysiol. 2009; 74(2): 93-100.

18. Heart Rate Variability. Standards of Measurement, Physiological Interpretation, and Clinical Use. Task Force of ESC and NASPE. Circulation. 1996; 93(5): 1043-1065.

19. Newberg AB, Alavi A, Baim M, Pourdehnad M, Santanna J, d’Aquili E. The measurement of regional cerebral blood flow during the complex cognitive task of meditation: a preliminary SPECT study. Psychiatry Research: Neuroimaging Section. 2001; 106: 113-122.

20. Palma JA, Benaroch EE. Neural control of the heart: recent concepts and clinical correlations.
Neurology. 2014; 83(3): 261-271.

21. Panossian AG, Efferth T, Shikov AN, Pozharitskaya ON, Kuchta K, Mukherjee PK, Banerjee S, Heinrich M, Wu W, Guo DA, Wagner H. Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress- and aging-related diseases. Med Res Rev. 2021; 41(1): 630-703.

22. Popovych IL. Stresslimiting Adaptogene Mechanism of Biological and Curative Activity of Water Naftussya [in Ukrainian]. Kyiv. Computerpress; 2011: 300.

23. Popovych IL. The concept of neuro-endocrine-immune complex (review) [in Russian]. Medical Hydrology and Rehabilitation. 2009; 7(3): 9-18.

24. Popovych IL, Gozhenko AI, Korda MM, Klisheh IM, Popovych DV, Zukow W (editors). Mineral Waters, Metabolism, Neuro-Endocrine-Immune Complex. Odesa. Feniks; 2022: 252.

25. Popovych IL, Kozyavkina OV, Kozyavkina NV, Korolyshyn TA, Lukovich YuS, Barylyak LG. Correlation between Indices of the Heart Rate Variability and Parameters of Ongoing EEG in Patients Suffering from Chronic Renal Pathology. Neurophysiology. 2014; 46(2): 139-148.

26. Popovych IL, Lukovich YuS, Korolyshyn TA, Barylyak LG, Kovalska LB, Zukow W. Relationship between the parameters heart rate variability and background EEG activity in healthy men. Journal of Health Sciences. 2013; 3(4): 217-240.

27. Popovych IL, Ruzhylo SV, Ivassivka SV, Aksentiyuch BI (editors). Balneocardioangiology [in Ukrainian]. Kyiv. Computerpress; 2005: 229.

28. Popovych IL, Vis’tak (Markevych) HI, Humega MD, Ruzhylo SV. Vegetotropic Effects of Bioactive Water Naftussya and their Neuroendocrine-Immune, Metabolic and Hemodynamic Accompaniments [in Ukrainian]. Kyiv. UNESCO-SOCIO; 2014: 162.

29. Radchenko OM. Adaptation reactions in the clinic of internal diseases [in Ukrainian]. L’viv. Liga-Press; 2004: 232.

30. Ruzhylo SV, Tserkovnyuk AV, Popovych IL. Actotrophic Effects of Balneotherapeutic Complex of Truskavets spa [in Ukrainian]. Kyiv. Computerpress; 2003: 131.

31. Ruzhylo SV, Fihura OA, Zukow W, Popovych IL. Immediate neurotropic effects of Ukrainian phytocomposition. Journal of Education, Health and Sport. 2015; 5(4): 415-427.

32. Sakaki M, Yoo HJ, Nga L, Lee TH, Thayer JF, Mather M. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. Neuroimage. 2016; 139: 44-52.

33. Sammito S, Heblich F, Güttler N. Die Fahrradergometrie in der arbeitsmedizinischen Vorsorge. Zbl Arbeitsmed. 2020; 70: 240–246.

34. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health. 2017; 5: 258.

35. Shannon CE. A mathematical theory of information. Bell Syst Tech J. 1948; 27: 379-423.

36. Steinhelber B, Seibt R, Gabriel J, Brontsouj S, Muljono M, Downar T, Bär M, Bonsch R, Brandt A, Martus P, Rieger MA. Effects of Face Masks on Physical Performance and Physiological Response during a Submaximal Bicycle Ergometer Test. International journal of environmental research and public health. 2022; 19(3): 1063.

37. Stemper T. Gesundheit, Fitness, Freizeitsport: Praxis des Modernen Gesundheitssports. Köln. Bund; 1988: 144.

38. Taylor JA, Carr DL, Myers CW, Eckberg DL. Mechanisms underlying very-low-frequency RR-interval oscillations in humans. Circulation. 1998; 98(6): 547-555.

39. Theorell T, Liljeholm-Johansson Y, Björk H, Ericson M. Saliva testosterone and heart rate variability in the professional symphony orchestra after "public fainings" of an orchestra member. Psychoneuroendocrinology. 2007; 32(6): 660-668.

40. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev. 2009; 33: 81-88.

41. Trappe H-J, Lölgen H. Leitlinien zur Ergometrie. Z Kardiol. 2000; 89: 16.

42. Vanneste S, De Ridder D. Brain Areas Controlling Heart Rate Variability in Tinnitus and Tinnitus-Related Distress. PloS ONE. 2013; 8(3): e59728.

43. Verberne AJ, Lam W, Owens NC, Sartor D. Supramedullary modulation of sympathetic vasomotor function. Clin Exp Pharmacol Physiol. 1997; 24(9-10): 748-754.

44. Verberne AJ. Medullary sympathoexcitatory neurons are inhibited by activation of the medial
prefrontal cortex in the rat. Am J Physiol. 1996; 270(4Pt2): R713-R719.

45. Winkelmann T, Thayer JF, Pohlak ST, Nees F, Grimm O, Flor H. Structural brain correlates of heart rate variability in healthy young adult population. Brain Structure and Function. 2017; 222(2): 1061-1068.

46. Wohlfart B, Farazdaghi GR. Reference values for the physical work capacity on a bicycle ergometer for men - a comparison with a previous study on women. Clinical physiology and functional imaging. 2003: 23(3): 166–170.

47. Yoo HJ, Thayer JF, Greenig S, Lee TH, Ponzio A, Min J, Sakaki M, Nga L, Mater M, Koenig J. Brain structural concomitants of resting state heart rate variability in the young and old: evidence from two independent samples. Brain Structure and Function. 2018; 223(2): 727-737.

48. Zukow W, Fil VM, Kovalchuk HY, Voloshyn OR, Kopko IY, Lupak OM, Ivasivka AS, Musiyenko OV, Bilas VR, Popovych IL. The role of innate muscular endurance and resistance to hypoxia in reactions to acute stress of immunity in rats. Journal of Physical Education and Sport. 2022; 21(7): 1608-1617.

49. Zukow W, Flyunt I-S S, Ponomarenko RB, Rybak NY, Fil’ VM, Kovalchuk HY, Sarancha SM, Nahurna YV. Polyvariant change of step-test under the influence of natural adaptogens and their accompaniments. Pedagogy and Psychology of Sport. 2020; 6(2): 74-84.

50. Zukow W, Flyunt I-S S, Ruzhylo SV, Kovalchuk HY, Nahurna YV, Popovych DV, Sarancha SM. Forecasting of multivariant changes in step test under the influence of natural adaptogens. Pedagogy and Psychology of Sport. 2021; 7(1): 85-93.