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Risk Factors in Progressive Arterial Hypertension (Systemic Analysis)

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Abstract

The present research aimed to access the significance of arterial hypertension risk factors and their relationships in the high-mountain villages of the Elbrus region (2100–3500 m above the sea level). For this, 260 patients were examined in total, 190 with arterial hypertension (hereinafter AH) of the 1, 2 and 3 degrees and 70 healthy individuals.

***Methods**. All the participants underwent complex examination: echocardiography; assessment of nitric oxide (NO) metabolites in the blood; heart rate variability (HRV); blood plasma lipid spectrum. Microsoft Statistica v. 10.0.1 software package was used for statistical processing. Multiple regression equations reflected the dynamics of relationships of three or more parameters (significant differences at p <0.05).*

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Results. *AH patients showed a progressive decrease in NO, an increase in sympathetic and HRV indicators, in left ventricular (LV) myocardial mass and atherogenic plasma index. The dependence of HRV indicators, LV morphofunctional parameters, hemodynamics, plasma lipid profile on NO level was revealed.*
Decreased significance of modifiable risk factors and increased lesions of 'target organs' with the progression of arterial hypertension were found; this explains complexity of prevention and possible therapeutic strategies.

Key-words: Arterial Hypertension, Risk Factors, Endothelial Dysfunction, Hemodynamics; Highlands.

1. Introduction

Endothelial dysfunction (ED) is the key factor in the occurrence and development of hypertension and comorbid diseases [1, 2]. Its main cause is a chronic deficiency of nitric oxide (NO) production. ED and NO deficiency are early and obligate precursors of cardiovascular pathology [3]. NO deficiency provokes morphological changes in the myocardium and blood vessels, and in atherosclerosis, accelerates the cycle of plaque development [4]. NO significantly contributes to the regulation of blood flow, coagulation, synaptic and neurohormonal activity, and regulates heart rate and hemodynamics. Decreased NO is the main risk factor for hypertension and its complications [5, 6].

Heart rate variability (HRV) reflects the total effect of regulation on the heart rate, their relationship with each other, with segmental and suprasegmental structures of the CNS and the effect of cortical inhibition on them [7, 8].

ED is accompanied by oxidative stress – free radicals damaging cell membranes, subcellular and nuclear structures [9].

Under hypoxic conditions, NO production increases due to the activation of NO synthases, nitrite reductase activity of hemproteins and enzymes, erythrocytosis, etc. [10].

At present, few researches focus on the significance of risk factors and their relationship in the development and course of ED in hypertension in different environmental conditions.

The present research aimed to assess the significance of risk factors and their relationship in patients with AH during its progression under different environmental conditions.

2. Materials and Research Methods

260 patients were examined (residing in the Elbrus region, 2100–3500 m above the sea level) in total, of them 190 patients with varying degrees of AH:

Group 1: 60 patients (25 male, 35 female) aged 47.2 ± 2.8, AH 1st degree;

Group 2: 65 patients (35 male, 30 female), aged 53.3 ± 2.4, AH 2nd degree;

Group 3: 65 patients (31 male, 34 female), aged 57.1 ± 2.5 years, AH 3rd degree;

Control group: 70 healthy individuals (33 male, 37 female), aged 46.5 ± 2.7 years.

The study was performed in accordance with Good Clinical Practice standards; all the patients were acquainted with the research methods and gave their informed consent. The survey protocol was approved by the local Ethics Committee. The diagnosis of hypertension was verified based on data from clinical, instrumental and laboratory studies. Overall risk stratification was determined in accordance with the recommendations of the Working Group on the Treatment of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology (ESH / ESC) 2018 [11].

The study included patients with AH (SBP> 140 and DBP> 90 mm Hg), risk factors, and no associated clinical conditions in the anamnesis. Exclusion criteria were as follows: symptomatic hypertension; metabolic, endocrine, inflammatory diseases; drug therapy that affects the concentration of nitrites, nitrates and lipids in the blood.

NO production was assessed by the content of nitrite-anion (NO_{2-}) and nitrate-anion (NO_{3-}) in blood plasma filtrates. NO_{2-}concentration was determined by the spectrophotometric method (SPh-4-A) using the Greiss reagent. NO_{3-}content was determined using brucine reagent. NO_{3-}content was calculated using a calibration curve made for sodium nitrate ($NaNO_3$) solutions [12].

Structural and functional parameters of the left ventricle (LV) were assessed by echocardiographic method using an Acuson Antares by Siemens Medical Solutions, (USA) in accordance with the recommendations of the American Echocardiographic Society. Additionally, the total and specific peripheral vascular resistance (SPVR = TPVR, dyn*s/cm^3/m^2), LV myocardial mass (LVMM), and myocardial mass index (LVMMI, g/m^2) were calculated. Relative wall thickness index of the left ventricle (iRWT, units) was determined; compliance functional index (CFI, units) – ratio (SV/LVMM, ml/g); myocardial tension index (MTI) – ratio (SBP/FSV, mm Hg/ml); arterial stiffness index (ASI, units), as a ratio (SI/PAP, ml/mm Hg), where PAP is pulse arterial pressure [13].

ECG and BP were recorded with portable daily monitors 'DMS-SOYUZ' and 'DMS – Advanced Technologies' (Russia). HRV analysis calculated the following (5-minute recording intervals):

- SDNN – standard deviation of the number of normal cardio intervals (CI);
- RMSSD – standard deviation of the absolute increments of CI duration;
- pNN50% - percentage of CI the duration of which differed by 50 ms or more.

The following parameters were also determined:

- Mo (sec) – value of CI duration corresponding to the middle of the modal class (50 ms wide);
- MoA% (mode amplitude) – percentage of CI that fall into the modal class;
- (RSAI = SDNN/RMSSD, units) – relative sympathetic activity index;
- SDR = (SBP + DBP * MoA/HR, units) – systemic dynamic response;
- RMI = (0.5 * RMSSD / RRNN * 100%) – respiratory modulation index.

Baevsky R.M. indicators were also calculated:

- stress index SI = MoA/(2*dRR*Mo, units);
- regulatory mechanisms functions indicators – functional reserve (FR, units),
- regulatory systems tension degree (TD, units).

The equations were as follows:

FR = 0.112*HR + 1.006*SI + 0.047*pNN50 + 0.086*HF;

TD = 0.14*HR + 0.165*SI + 1.293*pNN50 + 0.623*HF [14].

In the HRV frequency domain, the following was determined:

- total spectrum power – TP;
- power of all normal R-R intervals (ms^2);
- power in the range of very low, low and high frequencies (VLF, LF, HF, ms^2);
- vagosympathetic balance indicators (LF/HF, units);
- spectrum centralization (LF + VLF/HF, units);
- activity of subcortical nerve centers (VLF/LF, units) [15].

Plasma total cholesterol (TC), high density lipoprotein cholesterol (HDL), triglycerides (TG) were determined using a Cholestech LDX analyzer (USA). Very low density lipoprotein cholesterol (LDLP TC) and low density lipoprotein cholesterol (LDL cholesterol) were determined on a Prima semi-automatic photometer (Italy). The atherogenic coefficient (AC) was calculated as the ratio CS – cholesterol-HDL/cholesterol-HDL, units; atherogenic plasma index (API) as the ratio TG/HDL-C, units.

3. Statistical Analysis

The obtained results were processed with Statistical v. 10.0.1 software package by Stat Soft Inc, (USA). The mean values, their standard mean errors (M ± m) and the 95% confidence interval were calculated. The hypothesis of mean values equality was assessed using Student's t-test and Wilcoxon's test. The equations of multiple regression, reflecting the dynamics of the relationships of three or more studied parameters, were calculated. To exclude multicollinearity, Pearson correlations were analyzed between all the indicators (statistically significant differences at $p < 0.05$).

4. Results and Discussion

Table 1 gives the analysis of stable metabolites NO-NO_2 and NO3 of their sum in the blood. Blood NO_2 concentration is reduced in Group 1 by 4%, and in Groups 2 and 3 by 35% and 80%, respectively. Blood NO_3 concentration is reduced in Group 1 by 4% and significantly decreases in Groups 2 and 3 – by 30% and 1.3 times, respectively. Total blood NO is reduced in Group 1 by 4% and in Groups 2 and 3 by 40% and 1.3 times, respectively, in comparison with the control group.

Table 1 - Dynamics of Stable Nitric Oxide Metabolites Blood Levels in Patients with AH of Varying Degrees and in Healthy Individuals (M ± m)

Groups / Parameters	Healthy individuals (Control group) (n=70)	AH 1 degree (Group 1) (n=60)	AH 2 degree (Group 2) (n=65)	AH 3 degree (Group 3) (n=65)
NO_2^-, mcmol/L	18.3±1.2	17.9±1.1	13.6±0.9*#	10.2±0.8*#
NO_3^-, mcmol/L	114.6±1.5	109.3±1.4	91.7±1.5*#	87.6±1.4*#
NO, mcmol/L	132.9±1.3	127.2±1.2	105.3±1.4*#	97.8±1.2*#

Notes: * - the differences are reliable between 1, 2 and 3 groups and control group ($p < 0.05$).

- differences are reliable between 1, 2 and 3 groups ($p < 0.05$). Abbreviations: NO_2 – nitrites; NO_3 – nitrates; NO – total concentration of nitrites and nitrates in the blood.

According to the data, the concentration of NO metabolites in the blood of patients with AH (as well as nitrites, nitrates and ED) progressively decreases.

Table 2 - Parameters of Intracardial Hemodynamics and Morphofunctional Structure of the LV in Patients with AH of Varying Degrees and in Healthy Individuals (M ± m)

Groups / Parameters	Healthy individuals (Control group) (n=70)	AH 1 degree (Group 1) (n=60)	AH 2 degree (Group 2) (n=65)	AH 3 degree (Group 3) (n=65)
APm, mmHg	88.7±1.3	109.5±1.2*	122.6±1.5*	125.3±1.3*#
FDPI, ml/m^2	60.9±0.9	61.1±0.8	62.7±1.1*	64.5±1.3*#
SI, ml/m^2	39.6±0.9	39.9±0.9	40.1±1.2	41.4±1.2
SPVR, dyn c/cm^3/m^2	89.,5±9.46	948.5±10.6*	1212.6±11.2*	1263±12.2*#
LVMMI, g/m^2	86.9±1.2	97.6±1.3*	118.3±1.4*#	128.9±1.6*#
SI/LVMMI, units	0.45±0.002	0.39±0.003*	0.32±0.002*#	0.31±0.002*#
LVRWTI, units	0.36±0.001	0.38±0.001*	0.42±0.002*#	0.44±0.002*#
SBP/FSV, units	3.59±0.03	4.78±0.04*	5.98±0.04*#	6.78±0.05*#
EF %	65.1±0.9	63.4±1.1	60.1±0.8*	59.1±0.9*#
RC %	34.7±0.4	32.6±0.3	30.3±0.4*	29.6±0.7*#
SI/PAP, units	0.99±0.05	1.03±0.05	1.68±0.03*#	2.38±0.02*#

Notes: * - differences between control group and Groups 1, 2 and 3, $p < 0.05$.

* # - differences between groups, $p < 0.05$.

The table shows that FDPI increased in Groups 2 and 3 compared to the control group by 12%. SI is slightly higher in AH patients (by 3-4%). SPVR increased in Groups 2 and 3 (35-40%). The LVMM index increased in all the AH patients (by 20-48%). FIS is reduced in AH patients (by 18-45%) in comparison with the control group. LV RVWTI is higher in AH patients (by 8-23%). SBP/FSV index increased in Groups 2 and 3 (1.5 and 1.9 times). EF and RC indicators are reduced in Groups 2 and 3 (8-10%). The SI/PAP index increased in Groups 2 and 3 (by 40-55%).

Table 3 presents the results of HRV studies. SDNN, RMSSD and pNN50 indexes are reduced in Group 1 by 5-7%, in Group 2 by 20-85%, in Group 3 by 65% and 95% compared with the control group.

Table 3 - Indexes of HRV in Patients with AH and in Healthy Individuals (M ± m)

Groups / Parameters	Healthy individuals (Control group) (n=70)	AH 1st degree (Group 1) (n=60)	AH 2nd degree (Group 2) (n=65)	AH 3rd degree (Group 3) (n=65)
SDNN, ms	72.9±1.5	66.2±1.4*	60.7±1.3*	54.4±1.4*
RMSSD, ms	39.7±1.4	35,7±1,3*	29.4±1.1*	20.6±1.3*
pNN50, %	24.6±0.4	22.9±0.3	15.7±0.3*	12.3±0.5*
MoA, %	23.4±1.6	29.8±1.2*	33.6±1.7*	42.2±2.1*
SI, units	22.7±1.8	26.2±1.9*	40.4±2.2*	43.8±2.4*
TSPP, ms^2	3032.7±87.5	2664.7±73.8*	2135.5±78.6*	1992.7±73.2*
VLF, ms^2	1095.3±68.2	996.2±54.5*	924.5±63.4*	896.4±62.3*
LF, ms^2	927.8±42.2	833.7±45.8*	698.6±47.3*	658.7±43.3*
HF, ms^2	1009.6±43.4	834.8±32.7*	512.4±46.7*	437.6±41.2*
LF/HF, units	0.92±0.04	0.998±0.05	1.36±0.03*	1.51±0.04*
VLF+LF/HF, units	2.01±0.05	2.19±0.02	3.17±0.03*	3.55±0.03*
VLF/LF, units	1.08±0.05	1.19±0.04	1.32±0.02*	1.36±0.03*
VLF %	36.1±0.15	37.4±0.24	43.3±0.15*	44.9±0.14*
LF %	30.6±0.14	34.2±0.16	32.9±0.14*	33.2±0.13*
HF %	33.3±0.13	28.4±0.16	23.8±0.15*	21.9±0.14*
EF, units	42.4±1.2	51.2±1.3*	71.3±1.3*	75.2±1.5*
TD, units	69.5±1.3	54.6±1.3*	48.7±1.2*	39.7±1.6*
RSAI, ms	1.87±0.03	1.93±0.02	2.06±0.04*	2.68±0.06*
RMI %	60.1±1.1	48.2±1.2*	41.8±1.5	35.8±1.4*
SDR, units	84.1±1.2	112.8±1.3*	183.6±2.4*	207.8±2.1*

Notes: * - reliability of differences between the group of healthy individuals and groups of AH patients.

Indicators of variation pulsometry and Baevsky R.M. indicators were higher in Group 1 by 20-45%, in Group 2 by 48% and in Group 3 by 96%. In all the AH groups, TSP was lower by 27-66%. VLF range was reduced in Group 1 by 16% and in Groups 2 and 3 by 13-22%.

LF range was reduced in all the AH patients by 12-70%. HF range was reduced in Groups 2 and 3 (by 47% and 2.3 times). LF/HF index was higher in AH patients by 12-64%, VLF + LF/HF index by 20-85%, and VLF/LF index in Groups 2 and 3 by 17-24%. The percentage in the spectrum of HF range in AH patients was reduced (by 7-68%). FR increased in AH patients (by 32-90% and 1.4 times). SI was reduced in AH patients by 27-43% and 1.3 times, RMI was reduced in Groups 2 and 3 by 43-68%. RSAI increased in Groups 2 and 3 by 22-45%, and SDR increased 2-2.5 times in Groups 2 and 3 in comparison with control group.

The data obtained indicate that in healthy individuals, rapid regulation of the heart rate prevails. In AH patients in Groups 2 and 3, regulation of the heart rate was shifted to the area of sympathetic, humoral and ergotropic influences of the suprasegmental structures of the CNS with a weakening influence of cortical inhibition on them.

Table 4 shows the results of plasma lipids in patients with AH of varying degrees and in healthy individuals. Total cholesterol in blood plasma in Groups 1, 2 and 3 is higher than in the control group by 3-8%. HDL cholesterol in plasma is reduced in Groups 2 and 3 by 38-66%. TG content in Groups 2 and 3 is reliably higher than in the control group by 20-65%, and VLDL cholesterol in Groups 2 and 3 by 11-45%. LDL cholesterol in Groups 2 and 3 is higher than in the control group by 12-20%.

Table 4 - Plasma Lipids in Patients with AH of Varying Degrees and in Healthy Individuals

Groups / Parameters	Healthy individuals (Control group) (n=70)	AH 1st degree (Group 1) (n=60)	AH 2nd degree (Group 2) (n=65)	AH 3rd degree (Group 3) (n=65)
TCL, mmol/L	3.99±0.11	4.12±0.12	4.82±0.14*	5.12±0.13*#
TCL HDLP	2.08±0.1	1.96±0.12	1.06±0.03*#	0.88±0.04*#
TCL LDLP	2.24±0.12	2.43±0.11	3.62±0.12*#	4.12±0.12*#
CL LPVLD	0.28±0.04	0.31±0.03*	0.43±0.06*#	0.51±0.05*#
TG, mmol/L	0.39±0.01	0.42±0.02*	0.56±0.02*#	0.73±0.03*#
AC, units	0.92±0.06	1.1±0.03	3.59±0.04*#	4.82±0.03*#
AIP, units	0.19±0.01	0.26±0.01*	0.62±0.002*#	0.72±0.003*#

Notes: * - differences are significant between Groups 1, 2, 3 and control group, $p < 0.05$.

- differences are significant between Group 1 and Groups 2 and 3, $p < 0.05$.

AC in AH groups is significantly higher by 19%, 3.9-5 times. AIP in AH groups was 35-65% and 3 times higher than in the control group.

Thus, changes in the plasma lipid profile begin in patients with AH 1st degree and progressively increase in patients with AH 2nd and 3rd degrees.

Multiple regression equations are presented as the dependence of variables: $\mathbf{Y = f(\beta X) + \varepsilon}$, where X = (X1, X2, .., Xn) is a vector of factors (explanatory) variables; β is a vector of parameters; Y is effective sign; ε is random error.

The empirical multiple regression equation is presented as:

Y = b0 + b1X1 + b2X2 + b3X3 + b4X4 + b5X5 + e / Ym where b0 is a free member determining Y value when all factorial signs Xi = 0. Relative specific coefficients of elasticity are determined by the formula Ei=(bi*(Xi_m/Y_m) where bi is the regression coefficient, Xi_m is the average value of the factor attribute, Ym is the average value of the effective attribute. Ei coefficient shows how much the effective attribute Y will change when the factor Xi changes by 1% from its average level with a fixed position of other factors. If Ei> 1, it has a significant impact on the effective indicator Y, and if Ei <1, it has little effect on the effective sign Y [15].

The equations of multiple regression for AH patients and healthy individuals to clarify dependencies were as follows:

Y(NO)=b1X1(ADm)+b2X2(SI)+b3X3(LVMM)+b4X4(PWV)+b5X5(SPVR);

Y(NO)=b1X1(SDNN)+b2X2(CH)+b3X3(RSAI)+b4X4(ΦP)+b5X5(SDR);

Y(NO)=b1X1(OXC)+b2X2(AIP)+b3X3(TΓ)+b4X4(XC LPLP)+b5X5(LF/HF);

Y(AD)=b1X1(NO)+b2X2(PWV)+b3X3(RVWT)+b4X4(LVMM)+b5X5(SPVR);

78 regression equations were calculated where individual indicators acted as effective indicators. Of these, the most significant factors were selected for the coefficients of elasticity (Ei).

In the control group, the relationship was established between NO and AD, SDR (r = -0.485; -0.632; p <0.01); between SDNN and VLF, LF, RMSSD, HF (r = 0.779 - 0.923; p <0.01); between ADS with SDR, LF, LF / HF (r = 0.686 - 0.812; p <0.01). There were no statistically significant relationships between NO and indicators of morphofunctional structure, LV geometry, and HRV parameters.

In Group 1, the relationship was established between NO and AP, SDR, OPSS (r = -0.583 - -0.659; p <0.01); between NO and RMSSD, HDL cholesterol (r = 0.428; 0.523; p <0.01); between AP and SPVR, SDR, LF/HF (r = 0.638 - 0.785; p <0.01); between SDNN with VLF, TP, RMSSD (r = 0.438 - 0.913; p <0.01); between SDNN and OPSS, ADSr, SDR, LF/HF (r = -0.694 - -0.869; p <0.01).

In Group 2, relationships were established between NO and OPSS, LVMM, ADS, SDR, AIP (r = -0.484 - -0.765; p <0.01); between ADS and LVMM, OPSS, SDR, LF / HF (r = 0.556 - 0.793; p <0.01); between AP and SDNN, RMSSD, HF (r = -0.612– -0.885; p <0.01); between RMSSD and AP, SP, SI (r = -0.436 - -0.897; p <0.01).

In Group 3, relationships between NO and SPVR, AIP, LDL cholesterol, AP, SDR were established (r = -0.542 - -0.792; p <0.01); between AP and SI, SPVR, LVMM, SDR, LF/HF (r = 0.657 - 0.933; p <0.01) and the relationship between AP and SDNN, RMSSD, HF, NO

(r = -0.749 - -0.892; p < 0.01). Relationships between SDNN and AP, SI, LF/HF (r = -0.597 - -0.823; p <0.01).

An inverse relationship was found between age and NO in all patients; it was stronger in Groups 2 and 3 (r = -0.686 r = -0.732; p <0.01).

The regression analysis reveals that the key factors influencing NO blood concentration in healthy individuals are the level of AP and SDR.

Group 1 has a greater number of significant factors affecting NO: AP, SDR, SPVR, LDL cholesterol, and AIP.

In group 2, the list is more extensive: LDL cholesterol, SPVR, LVMM, AP, SDR, and AIP. With an increase in the number of interconnections, the strength between AP and indicators of the morphofunctional structure of the LV, and indicators of HRV and LP of the plasma spectrum increases.

Group 3 has the biggest number of significant factors. As the influence of AP and SPVR on the NO concentration weakens, the number and strength of connections between ADS and indicators of the morphofunctional structure and geometry of the LV, between AP and sympathetic indicators, and HRV indicators and parameters of the LP spectrum of plasma increases. The relationship between parasympathetic indicators, HRV and LDL indicators, AIP increases with weakening and/or loss of relationships between the parameters of the HRV time and frequency domain. Thus, in AH patients the dynamics of endothelial factors significance decreases and the significance of AH complications indicators increases – remodeling of the myocardium, vessels and lipid peroxide stress.

5. Conclusion

The results obtained show the emergence and dynamic increase of intersystem connections in AH patients. With the progression of hypertension, the relationship between NO and the parameters of hemodynamics and HRV decreases, and the relationship between AP and the structural and functional indicators of the LV, sympathetic HRV indicators and the LP spectrum of plasma increase.

AH patients in dynamics on the background of ED and of a progressive decrease in NO demonstrate centralized regulation of the HR and hemodynamics with the development of its ‘autonomy’. In Groups 2 and 3, the regulatory function of the endothelium decreases, risk factors are less significant, and the prevailing morphological changes in target organs come to the fore.

Thus, the significance of risk factors changes and the consequences associated with damage to target organs increase. Integration of the circulatory system with nitric oxide and regulation of the CNS cause cascade discrete changes in systemic relationships and are a key factor in AH course.

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