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**THE DEPENDENCE OF THE ENDOTHELIAL FUNCTION ON COMORBID STATES IN PATIENTS WITH ASTHMA**

**WPŁYW FUNKCJI ŚRÓDBŁONKA NA CHOROBY WSPÓŁWYSTĘPUJĄCE U PACJENTÓW Z ASTMĄ**

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**ABSTRACT**

**Introduction:** the purpose of the research consisted in the study of the functional state of the endothelium in patients having persistent asthma (A) with an uncontrolled coursein combination with diabetes mellitus type 2 (DM2T) and obesity (O)

**The aim:** on the basis of a complex study of nitric oxide metabolites (nitrosothiols, S-NO), von Willebrand factor (VWF) and endothelin-1 (EТ-1).

**Materials and methods:** The study involved 90 A patients with comorbid states, who were divided into 3 groups. Group 1 included patients with A, group 2 consisted of Awith DM2T (A+DM2T), group 3 was composed of A and obesity (A+O); the control group had 21 persons.

**Results:** Lower S-NO levels in patients from groups 2 and 3 and an increase of ET-1 in these groups versus the control one demonstrate an imbalance of the indices, whichproduce an effect on the vascular tone. Statistically, the activity of VWF as the marker of an endothelial damage was significantly higher: it was 169.0 (147.0;178.50) in cases from group 2 and 156.0 (142.75;165.0) in those from the group of A+O. Thus, indices of a disrupted endothelial function were more expressed in patients from group 2. Positive relations of ET-1 with VWF and negative ones with S-NO.

**Conclusions:** The conducted study has proved that the endothelial function in patients with A+DM2T and A+O is characterized by a disturbed relationship between relaxingand constricting endothelial factors. The obtained data make it possible to receive an opportunity to correct the above impairments in future.

**KEY WORDS:** asthma, comorbidity, endothelin-1, von Willebrand factor, nitric oxide metabolites.

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**INTRODUCTION**

The study of the functional state of the vascular endothe-lium in pathology of different organs and systems is an active subject of discussions [1;2]. An activation and/or damage of the endothelium are known to be present in a wide spectrum of pathological processes, including the respiratory system [3;4;5]. Studies conducted during recent years have revealed that endothelial dysfunction acts as an onset of vascular complications and asthma [6;7]. But the problem of the state of the endothelial function in asthma (A) remains unsolved.

Participation of the endothelium in regulation of the sys-temic and pulmonary vascular tone takes part by means of formation and release of vasodilating and vasoconstricting substances, including endothelin-1 (EТ-1) and the endo-thelium-dependent relaxing factor, nitric oxide (NO) [8;9]. A metabolic disturbance of NO plays a leading part in the endothelial dysfunction.

The researches, conducted by foreign and Ukrainian authors, convincingly prove that the vasoregulatory dys-function of the endothelium is revealed even before an organic damage and in the absence of any clinical and instrumental signs of a disruption of the pulmonary func-tion [10;11;12]. Besides, it is possible to detect the degree

of severity of the pathological process and predict a fur-ther course and outcome of the disease proceeding from the degree of expression of the endothelial dysfunction [13;14;15]. These circumstances necessitate study of new methods, which make it possible to assess the state of the vascular endothelium, particularly in patients ill with A.

**THE AIM**

To study the functional state of the vascular endothelium in patients having persistent A with an uncontrolled course in combination with diabetes mellitus type 2 (DM2T) and obesity on the basis of a complex study of nitric oxide metabolites (nitrosothiols, S-NO), von Willebrand factor (VWF) and endothelin-1 (EТ-1).

**MATERIALS AND METHODS**

The study involved 90 A patients with comorbid states and an uncontrolled course. The above cases were divided into 3 groups. Group 1 included patients with isolated A, group 2 consisted of A with DM2T (A+DM2T), group 3 was composed of A and obesity (A+O); the control group had 21 persons. The patients underwent a general clinical

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**Table I.** Laboratory values of the functional state of the endothelium in the studied groups.



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Indices** | **Controls (n = 21) С** | **А (n = 35)** | **А+DM2Т (n = 30)** | **А+О (n = 31)** |  |
| **Group 1** | **Group 2** | **Group 3** |  |
|  |  |  |
|  |  |  | |  |  |
|  |  | **Me (Lq; Uq)** | |  |  |
|  |  |  |  |  |  |
| S-NO, | 0.590 | 0.810 \* | 0.230\* | 0.440\* |  |
| µmol/l | (0.540;0.625) | (0.770;0.840) | (0.200;0.270) | (0.360;0.510) |  |
|  |  | | | |  |
|  | **МWUTest: p1-2 = 0.0000; p1-3 = 0.0022; p2-3 = 0.4744; pс-1 = 0.0000; pс-2 = 0.0000; pс-3 = 68.500** | | | |  |
| VWF, % | 83.000 | 115.000\* | 169.000\* | 156.000\* |  |
|  | (82.000;86.000) | (100.000;127.000) | (147.000;178.500) | (142.750;165.000) |  |
|  |  | | | |  |
|  | **МWUTest: p1-2 = 0.0000; p1-3 = 0.0022; p2-3 = 0.000; pс-1 = 0.0000; pс-2 = 0.0000; pс-3 = 1105.5** | | | |  |
| ЕT-1, | 3.680\* | 3.980\* | 9.860\* | 6.240\* |  |
| µmol/ml | (3.450;3.995) | (3.670;4.120) | (8.950;12.030) | (5.880;6.870) |  |

**МWUTest: p1-2 = 0.0000; p1-3 = 0.0022; p2-3 = 0.000; pс-1 = 0.0000; pс-2 = 0.0000; pс-3 = 0.0000** 1. Ме – median, Lq – lower quartile, Uq – upper quartile;

1. \* The level of statistical significance versus the control group with р<0.001; МWUTest – nonparametric Mann-Whitney U criterion for a pair-wise comparison.

**Table II.** The index of a correlation analysis between the studied indices and ET-1



|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Index** |  | **A** |  | **А+DM2Т** |  | **А+О** |  |
|  |  |  |  |  |  |  |
| **r1** | **p1** | **r2** | **p2** | **r3** | **p3** |  |
|  |  |
| WC | 0.55 | 0.001 | 0.776 | 0.0001 | 0.37 | 0.007 |  |
|  |  |  |  |  |  |  |  |
| Years of disease | 0.232 | 0.05 | 0.772 | 0.0001 | 0.21 | 0.05 |  |
|  |  |  |  |  |  |  |  |
| VС, % | 0.12 | 0.1 | -0.27 | 0.005 | **-** 0.34 | 0.031 |  |
|  |  |  |  |  |  |  |  |
| FEF, 25 % | -0.31 | 0.012 | - 0.76 | 0.001 | - 0.29 | 0.06 |  |
|  |  |  |  |  |  |  |  |
| FEF, 50 % | -0.25 | 0.03 | - 0.75 | 0.001 | - 0.33 | 0.001 |  |
|  |  |  |  |  |  |  |  |
| FEF, 75 % | -0.34 | 0.001 | - 0.59 | 0.001 | - 0.62 | 0.009 |  |
|  |  |  |  |  |  |  |  |
| VWF, % | 0.13 | 0.36 | 0.78 | 0.001 | 0. 32 | 0.006 |  |
|  |  |  |  |  |  |  |  |
| S-NO, fmol/l | -0.25 | 0.043 | -0.63 | 0.002 | - 0.45 | 0.001 |  |
|  |  |  |  |  |  |  |  |

r1 – the relation of the indices in the group of А;

r2 – the relation of the indices in the group of А+DM2Т;

r3 – the relation of the indices in the group of А+О;

p1 – the probability of a correlation in the group of А;

p2 – the probability of a correlation in the group of А+DM2Т;

p3 – the probability of a correlation in the group of А+О.

examination, a physical examination, revealing of their anthropometric values: weighing, calculation of their body mass index (BMI), measuring of their waist circumference (WC) and hip circumference. Their respiratory function (RF) was assessed. The study of the endothelial function included revealing of nitrosothiols (S-NO), von Willebrand factor (VWF) and endothelin-1 (EТ-1). Determination of the level of ET-1 in plasma samples was made with help of an immunoenzymatic kit for quantification of endothelin (1-21) in biological fluids (Biomedica, Germany). Blood for ET-1 study was taken at morning hours from the ulnar vein into 5 ml cooled siliconized test tubes, which contained complexon K3. Fresh samples were immediately placed on ice. Plasma was separated by centrifugation at the rate of 3,000 rotations per minute during 5 minutes and put into silicon test tubes. The samples were frozen and delivered in a special refrigerator to the Central Research Laboratory

of Kharkiv National Medical University, where they were stored at the temperature of -70оС until being analysed. The concentration of stable metabolites of nitric oxide in blood serum (S-NO) was determined by the spectrophotometric method modified by Kovalova О.M. (2007) [16].

VWF was detected by the photoelectrocolorimetric method. The activity of VWF in the studied plasma was assessed by agglutination of the standardized preparation of thrombocytes [16].

The study findings were statistically processed with use of SPSS 19 program for Windows (IBM, USA). Quantitative variables were described by the following parameters: the median (Me) and the 25th and 75 percentiles (M [Q1; Q2]). In order to reveal differences between independent samples, the Mann-Whitney U test was used. The normality of data distribution was analysed with help of the Shapiro-Wilk test. Relations between the indices were

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studied with a correlation analysis using the Spearman’s rank correlation coefficient (r) and the Chaddock’s scale.

The age of the examined people was 48 (21; 56) years. Distribution of the groups by the gender sign revealed predominance of women – 68 %, men comprising 32 %. The age median was equal to 46 (23; 61) years in the women and 43 (20; 56) in the men. The median of disease duration was 12 (4; 29) years. The disease duration median in the men was 10 (3; 42) years, that of the women being 14 (5;

1. years. The patients’ diagnoses were as follows: there were 59 % of cases with a moderately severe persisting course of the disease and 41 % of patients with a severe persisting course.

The research was conducted in compliance with re-quirements of the Declaration of Helsinki (Br.Med J, 1964; p.177) the protocol was approved by the Ethics Committee of Kharkiv National Medical University; the patients’ in-formed consent was received.

**RESULTS AND DISCUSSION**

Indices of the functional state of the endothelium in pa-tients with A, A+DM2T and A+O significantly differed from the control group (Table I). Lower S-NO levels in patients from groups 2 and 3 and an increase of ET-1 in these groups demonstrate an imbalance of the indices, which produce an effect on the vascular tone. Statistically, the activity of VWF as the marker of an endothelial damage was significantly higher: it was 169.0 (147.0; 178.50) in cases from group 2 and 156.0 (142.75; 165.0) in those from the group of A+O. Thus, indices of a disrupted endothelial function were more expressed in patients from group 2. An increase of VWF in cases suffering from A with DM2T and obesity resulted in a higher thrombogenicity of the vascular wall against a background of the endothelial dysfunction.

A correlation analysis revealed relationships of the stud-ied indices of the functional state of their endothelium in patients from different groups (Table II).

Positive relations of ET-1 with VWF and negative ones with S-NO and basic indices of RF were demonstrated. The endothelial function was affected by duration of the disease and abdominal obesity, as it was confirmed by the correlations revealed (Table II).

Endothelin, produced by the cells of the respiratory epi-thelium and endothelium, is of paramount importance in the development of bronchospasm, including that caused by physical activity, as it contributes to the increase in the tone of smooth muscles and increased permeability of the microcirculatory channel [17]. S-NO is involved in the regulation of the tone and structure of vessels, promotes mucociliary clearance in the respiratory tract, participates in the processes of inflammation and immune defense

1. One of the main causes of activation of VWF is the destruction of endothelial cells and subendothelium, which, in the opinion of several authors, is important not only for assessing the degree of disturbance of its function as a predictor of endothelial dysfunction, but the severity and prevalence of vessels, but the severity and prevalence

of vascular injury [18]. The findings show that endothe-lial damages are an unfavourable pathogenetic factor in pulmonary vascular dystonia with resultant progression of bronchial obstruction and development of hypoxia, particularly in patients with a comorbid course. Our data coincide with literature ones. Having analysed statistical characteristics of all examined endothelial indices in our patients, we revealed a high reliability both in A and in A with comorbid states. The above fact entitles us to state that statistical characteristics of the corresponding indices in different groups reliably differed from one another and that the level of the examined parameters depended upon the patient’s belonging to a particular group. A sequential comparison of the above indices in the studied groups depending upon the degree of severity did not reveal any reliable differences.

**CONCLUSION**

The conducted study has proved that the endothelial func-tion in patients with A+DM2T and A+O is characterized by a disturbed relationship between relaxing and constric-ting endothelial factors, mainly by means of an intensified action of the constricting ones. When compared with the group of patients without any accompanying pathology, the largest changes were revealed in patients with A and DM2T from the side of activity indices of their coagulative and endothelial factors of relaxation. The obtained data make it possible to receive an opportunity to correct the above impairments in future.

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