STATE OF CENTRAL HEMODYNAMICS AND ENDOTHELIAL FUNCTION IN PATIENTS WITH ISCHEMIC HEART DISEASE AND TYPE 2 DIABETES MELLITUS

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Abstract

There was investigated the state of central hemodynamics and endothelial dysfunction in coronary heart disease (CHD) patients depending on the presence of type 2 diabetes mellitus (DM). Eighty-three patients with stable angina pectoris of FC II-IV were examined. It was found that biomarkers of endothelial dysfunction were significantly higher in patients with CHD associated with DM2. The presence of DM2 was associated with greater degree and area of ischemia, significantly greater dilatation of left heart chambers, decreased total contractility and higher score of left ventricle regional contractility impairment.

Keywords: ischemic heart disease, diabetes mellitus, systolic function, diastolic function, left ventricle, endothelin, vascular endothelial growth factor, interleukin 6.

Relevance. Cardiovascular diseases (CVDs), including coronary heart disease (CHD), remain one of the leading causes of mortality in the world according to the World Health Organization (WHO). They have a significant impact on people's health and quality of life, as well as a major economic burden on the health care system [1,2].

WHO reports that CVDs are the leading cause of death in the world, taking more than 17 million lives annually. Of these, approximately 7.4 million deaths are attributed to CHD, making it the most common type of cardiovascular disease. (WHO, 2019) [3].

The effectiveness of treatment of patients with ischemic heart disease largely depends on the degree of endothelial dysfunction and the functional state of central hemodynamics. In such cases, it is advisable to carry out a number of diagnostic measures to assess endothelial function and indicators of central hemodynamics in the treatment of patients with ischemic heart disease against the background of type 2 diabetes mellitus. Assessment of central hemodynamic parameters and endothelial activity in patients with CHD against the background of diabetes mellitus is important not only to determine the treatment tactics, but also to prevent possible complications and is one of the urgent problems of modern cardiology.

The role of endothelial dysfunction and functional state of central hemodynamics in the development of complications and worsening of its course and prognosis is undoubted, as there is a large number of studies concerning this issue [4]. But the studies aimed at a comprehensive study of clinical manifestations, endothelial dysfunction, functional state of central hemodynamics in patients with coronary heart disease against the background of diabetes mellitus are not numerous in the available literature.

In CHD against the background of type 2 diabetes mellitus there is a persistent endothelial dysfunction [5]. Assessment of endothelial activity using inflammatory biomarkers and central hemodynamic parameters in patients with coronary heart disease against the background of type 2 diabetes mellitus is of great importance in determining treatment tactics, which is reflected in the improvement of prognosis and quality of life of the patient.

According to the conducted scientific studies and analysis of the available literature, it can be concluded that it is necessary to conduct studies aimed at optimizing diagnosis by determining the severity of the disease and endothelial dysfunction using laboratory and instrumental tests in patients with CHD against the background of type 2 diabetes mellitus. In this regard, it is relevant to study the significance of inflammatory factors and biomarkers in the severity of the disease, optimization of treatment tactics and prediction of complications.

Purpose of the study. To study the state of central hemodynamics and to reveal endothelial dysfunction in CHD patients depending on the presence of type 2 DM.

Materials and methods. There were examined 83 patients (mean age 63,4±3,8 years) with CHD (stable angina pectoris FC II, III) who had undergone myocardial revascularization in anamnesis.

All patients were divided into two groups depending on the presence of type 2 DM. The first group consisted of 41 patients with type 2 DM. The second group consisted of 42 patients without DM.

The control group consisted of 20 patients (mean age 53.2±3.5 years) without cardiovascular pathology and severe chronic diseases.

All patients underwent a comprehensive study including: anthropometric parameters (body weight, kg; height, cm; body mass index - BMI, kg/m2), BP measurement and laboratory tests (fasting glycemia, mmol/L; blood lipids, mmol/L).

Endothelial dysfunction was studied by determining the blood levels of endothelin-1 (ET-1), interleukin 6 (IL-6), vascular endothelial growth factor (VEGF) by enzyme-linked immunosorbent assay on a solid-phase analyzer "Humareader Single" (Germany). ELISA

method is based on the use of antibodies or antigens labeled with enzymes, which allows to register the process of formation of antigen-antibody complex by enzymatic activity. ELISA is characterized by high specificity, its sensitivity in many cases exceeds the sensitivity of other immunological methods.

From instrumental methods all patients underwent ECG in 12 leads, echocardiography, tissue Dopplerography. Electrocardiography was performed on the first day of the patient's admission to the hospital. A stationary electrocardiograph "Bioset" (Germany) was used.

Echocardiography with tissue Doppler was performed on a Samsung medison ultrasound device "Accuvix.V20" (Korea) using a sector transducer with color mode and pulse-wave, continuous-wave mode with a frequency of 2-4 MHz in standard echocardiographic positions in M- and B-modes according to the recommendations of the American Society of Echocardiography (ASE) (Schiller N.B. et al., 1989).

As structural parameters of remodeling were recorded:

- LV end-diastolic volume (Simpson method) indexed to body surface area (EDV index);
- left atrial end-systolic volume (Simpson method) indexed to the body surface area (LA index);
- right ventricular end-diastolic area (planimetric method in the apical 4-chamber position), indexed to the body surface area (RV index);
- right atrial end-systolic area (planimetric method in the apical 4-chamber position), indexed to body surface area (RA index);
- diastolic thickness of the interventricular septum (parasternal position along the long axis of the left ventricle, IVS);
- diastolic thickness of LV posterior wall (parasternal position along the long axis of the left ventricle, LVAD);
- LV myocardial mass (shell method, apical position) indexed to the body surface area (MMLV index);
- sphericity index - the ratio of LV short diameter to cavity length (SI).

Functional characteristics of myocardial state:

- LV ejection fraction (LVEF) - the ratio of LV stroke volume (difference between LV EVC and LV end-systolic volume determined by Simpson's method) to LV EVC;
- index of regional LV contractility impairment (LV contractility index) - average values of the regional contractility score using the 17-segment scheme. Assessment of segment contractility is five-point (0 - hyperkinesis - systolic thickening more than 100%, 1-normokinesis - systolic thickening 50-100%, 2 - hypokinesis - systolic thickening less than 50%, 3 - akinesis - absence of systolic thickening, 4 - dyskinesis - systolic bulging of myocardial segment);
- shortening fraction of RV area (SFA) - ratio of the difference of end diastolic and end systolic area of LV measured by planimetric methods in apical 4-chamber position to end diastolic area of LV;
- stroke index (SI) - LV stroke volume indexed to the body surface area;
- minute index (MI) - product of MI by heart rate;
- type of myocardial diastolic filling (Dopplerography of transmittal and transtricuspidal blood flow, classification of diastolic filling types according to the Canadian classification of diastolic dysfunction, DD);
- integral index of myocardial function (Tei) - ratio of the duration of closed valve periods to the period of ejection (Doppler blood flow);
- mean pulmonary artery pressure (MPAP) - determined by the ratio of the duration of the period of acceleration of ejection flow to the total duration of the ejection period on the pulmonary artery valve.

Statistical processing of the obtained results was carried out using methods of variation statistics recommended for biomedical research on IBM PC AT Pentium IV. The results were processed using Microsoft Excel 2002 and Statistica 6.0 programs under Windows XP. The indicators are presented as the arithmetic mean of the variation series and its standard error ($M \pm m$). The reliability of differences in mean values was assessed using Student's t-criterion. The level of statistical reliability was taken as $p < 0.05$.

Results of the study. According to the inclusion criteria, 83 people were selected for the study. The first group consisted of 42 (50.6%) patients without the presence of type 2 DM. The second group consisted of 41 (49.4%) patients with type 2 DM. All patients had previously undergone myocardial revascularization.

Also, all patients included in the study signed informed voluntary consent. The conduct of the study was approved by the local ethical committee of the Republican specialized scientific practical medical centre of therapy and medical rehabilitation. The study participants were thoroughly informed about all goals and objectives of the study and its methods.

Table 1. Clinical characteristics of patients participating in the study.

Patient Characteristics	**1st group (without DM2)**	**2nd group (with DM2)**
Number of patients	42 (50,6%)	41 (49,4%)
Age, years	66,3± 1,42	61,5± 2,03
Sex composition (men; women)	 26 16	 27 14
BMI (kg/m2)	29,48±0,63	32,43±1,56
History of myocardial infarction (number of patients)	14	18

Both groups of patients were completely comparable in terms of the leading clinical and demographic parameters: sex, age, and BMI, but patients in the comparison group had a slightly higher body weight. Pa-

tients of both groups were also comparable in such clinical characteristics as the frequency of complaints of dyspnea, heart pain and the presence of other (except for CHD) cardiac pathology and comorbidities, except for myocardial infarction in the history, which was significantly more frequent in the group of patients with CHD + type 2 DM (p = 0.024).

Since there are currently no generally accepted normal values of endothelin-1 content, we determined normal and borderline reference values of these parameters using the data obtained in the control and comparison groups. Determination of the normal reference value seems to be necessary for further comparison of the values of the studied parameters in different groups of patients.

In the control group, including relatively healthy people without established diseases, normal levels of circulating markers of endothelial dysfunction were calculated, which amounted to 26.8 pg/ml for endothelin. The obtained results were taken as optimal threshold values characterizing normal endothelial status in practically healthy individuals.

We conducted a comparative study of endothelin-1 levels in CHD patients with and without concomitant type 2 DM. The results of the study are presented in Table 2. Analysis of the obtained data showed that the content of endothelin-1 in CHD patients with type 2 DM is significantly higher than in the group of CHD patients without DM and the control group. The increase of ET-1 level was more determined in 83% of patients in the group of CHD patients with type 2 DM, whereas in the group of CHD patients without DM the level of ET-1 was elevated in 54,7% of cases. In the control group, only 2 participants (10%) demonstrated an increase in ET - 1 concentration.

Endothelin-1 is known to be the main form of endothelin, which is formed only in vascular endothelial cells and plays the most important role in the regulation of vascular tone, cardiac output and vascular channel permeability. ET-1 significantly increases myocardial contractility, causes vasoconstriction of coronary vessels, which leads to increasing ischemia and arrhythmia [7].

Thus, it was found that ET-1 concentration tends to increase slightly, whereas in patients with CHD associated with type 2 DM this indicator reaches a high level.

Table 2. Indices of endothelial dysfunction (VEGF, ET-1) and inflammatory factor (IL 6)

Indicators	**CHD with DM2 (n=41)**	**CHD without DM2 (n=42)**	**p**
IL-6, pg/mL	67,68±3,27	47,73±2,82	0,04
Endothelin-1, pg/mL	286,54±53,62	158,45±14,27	0,14
Vascular endothelial growth factor (VEGF), pg/mL	1138,24±65,71	684,49±58,63	0,05*

Note - * difference with the comparison group p < 0.05

When analyzing such parameters as VEGF and IL-6, a slight increase in their concentration in blood is noted in the group of CHD patients, and in the group of patients with CHD associated with type 2 DM there are higher unreliable figures compared to the main group.

Analysis of ECHOCG parameters in CHD patients showed some changes in cardiac geometry within ischemic remodeling: increase of chamber volumes (increase of LA volume index, EDV index, LV ICDO, RV diameter p<0,05 in comparison with control group), spherical deformation of LV cavity (increase of MMLV index, p<0,05). At the same time, comparison of indices of patients with CHD + type 2 DM showed that the size of left heart chambers and MMLV index were significantly larger than in CHD patients without DM. The right ventricular (RV) size was comparable regardless of the presence of DM.

Disturbances of ventricular systolic and diastolic function were also revealed: LV EF in CHD patients on average remained within normal values, but was significantly lower than in control group (p<0.05). A more detailed analysis showed that overall 51% of patients had heart failure (LV EF< 55%). At the same time, reduced LV EF in CHD patients was associated with the presence of DM.

Another index of LV myocardial systolic function, the index of regional contractility impairment, was assessed using the 17-segment LV model. More than half of the patients (53.6%) were found to have impaired regional contractility. At that, regional dyskinesis, as well as reduced total contractility, was associated with the presence of background DM (p<0.05).

Integral systolic LV remodeling index - an index combining parameters of LV structural and functional systolic remodeling, representing the ratio of LV EF to sphericity index, in patients included in the study was significantly lower than in the control group (p<0,05).

This is associated with both a decrease in LVEF and an increase in the sphericity index and changes in LV cavity geometry. Spherical remodeling of LV cavity itself disturbs the funnel-shape of ejection flow, reducing its efficiency and making an additional contribution to the impairment of total LV contractility. The lowest index was found in CHD patients with DM (compared to the CHD group without DM).

The analysis of LV diastolic function revealed a reliable tendency to impairment of processes of active diastolic relaxation of LV myocardium, which was manifested by a decrease of E/A ratio determined in the process of tissue Dopplerography of the lateral edge of mitral annulus (p<0,05, compared to control). Comparison of CHD patients with and without DM revealed a greater degree of diastolic dysfunction in patients with background DM. The analysis confirms the described regularities: the highest incidence of diastolic dysfunction is observed in the group of patients with CHD associated with type 2 DM.

Integral index of myocardial functional state Tei, reflecting the ratio of the sum of “closed valve” periods (isometric tension and isometric relaxation periods) to

ejection time, in patients included in the study was significantly higher than the control index ($p<0.05$). The highest value was observed in patients with background DM ($p<0,05$ in comparison with patients without DM). The consequence of LV functional state impairment, especially its diastolic dysfunction, is an increase in pulmonary artery occlusion pressure (PAOP), reflecting postcapillary pulmonary hypertension. In our study, in patients with CHD, especially with the presence of DM, PAOP was higher than in the control group, although on average for the groups remained within normal values ($p<0.05$, comparison of CHD patients with and without DM and control group).

Table 3: Indices of systolic and diastolic cardiac function

Indicators	**CHD with DM2 (n=41)**	**CHD without DM2 (n=42)**	**Control group (n=20)**
EDV index, ml/m^2	123,19±7,62	97,72±5,63	78,60 ± 10,58
LA index, ml/m^2	26,38±12,13	22,63±0,58*	19,4 ± 4,75*
MMLV index	134,73±22,31	125,64±19,04*	97,61±10,45*
SI	0,77±0,16	0,62±0,13	0,57 ± 0,14
LV EF, %	55,13±6,37	52,32±5.92*	64,85 ± 4,91
LV contractility index, points	1,33±0,12	1,31±0,11	1,00 ± 0,00
Integral systolic remodeling index, points	63,45±24,36	68,41±25,82	121,74±31,65
LV E/A	0,72±0,31	0,83±0,33	1,53±0,15
RV E/A	0,80±0,39	0,85±0,41	1,56±0,17
LV Tei	0,43±0,11	0,39±0,11	0,28 ± 0,06
RV Tei	0,37±0,11	0,35±0,10	0,23 ± 0,04
PAOP, mmHg	19,24±4,75	17,83±5,25	10,50±1,8
MPAP, mmHg	30,57 ±4,62	29,73±4,78	22,64±3,49

Note - difference with the comparison group $p < 0.05$

The level of systolic pressure in the pulmonary artery was also determined in combination with PAOP. It was found that in patients with CHD there is an unreliable increase in pressure in the small circle of circulation ($p<0.05$ compared to control group) with maximum effect in patients with CHD + DM2.

The integral index of myocardial functional state of LV (Thei LV), as well as the total integral functional index demonstrated the violation of ventricular functional state in CHD patients ($p<0,05$ with CGcontrol group), and more pronounced violations were associated with the presence of background DM in general in all patients included in the study ($p<0,05$).

Formation of myocardial dys- and asynergy zone, its extent significantly affect the course of the disease and prognosis for the patient's life. Assessment of myocardial structural and functional reorganization dynamics in CHD patients allows to verify more effectively the severity of the disease and possible complications, and also determines a rational approach to treatment tactics.

In patients with angina pectoris with the most severe functional classes against the background of myocardial mass growth and LV hypertrophy, some LV cavity expansion and decreased ejection fraction are revealed. Along with this, diastolic dysfunction by type 1 is noted. Progression of the disorder occurs with aggravation of functional class of stable angina pectoris and presence of complications. Thus, in patients with III-IV FC, complicated by CHF, development of diastolic dysfunction of both type 1 and type 2 (pseudonormalization), as well as predominance of eccentric LV hypertrophy was found. Early sensitive indicators of myocardial remodeling include an increase in end-systolic size and volume [6,7,8].

The severity of ischemic myocardial remodeling directly correlates with the incidence of adverse cardiovascular events. Echocardiographic parameters preceding the development of systolic, diastolic dysfunction and CHF, such as increased end-systolic size and end-systolic volume, myocardial stress, decreased diastolic peak filling and relaxation ratios are considered to be early predictors of LV remodeling [9,10,11,12].

Conclusion.

In conclusion, biomarkers of endothelial dysfunction such as endothelin-1, IL-6 and IL-6 and VEGF were significantly higher in patients with DM2-associated CHD. This indicates a high level of inflammation and vascular wall damage in this population. In addition, we observed a trend toward a progressive increase in disease severity compared with healthy subjects and CHD patients without type 2 DM.

In patients with CHD, angina pectoris with the most severe FC, complicated by CHF we revealed a tendency to insignificant structural and functional remodeling of not only left, but also right heart sections with increase not only in volumes of heart cavities, but also in myocardial mass, as well as impaired myocardial functional state, systolic and diastolic functions of both ventricles.

Background DM was associated with more pronounced abnormalities, i.e. greater degree and area of ischemia, and characterized in particular by significantly greater dilatation of left heart chambers, decreased total contractility and higher score of regional LV contractility impairment, higher values of pulmonary artery pressure, which can be explained by more widespread coronary lesions and greater degree and area of ischemia.

Thus, the study of functional state of cardiac hemodynamics and endothelial dysfunction in mechanisms of CHD development, determination of the role of proinflammatory markers for risk assessment of development and prediction of pathology course, as well as introduction of modern innovative technologies of diagnostics and prediction of cardiovascular complications in patients with CHD associated with type 2 diabetes mellitus, allow to identify groups of increased risk of development and determine effective tactics of prevention and treatment of this pathology, which, in the final analysis, will allow to identify groups of increased risk of development and determine effective tactics of prevention and treatment of this pathology.

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