MEDICAL SCIENCES

STUDY OF METHODS FOR ASSESSING VASCULAR RIGIDITY AND PREDICTING CARDIORENAL COMPLICATIONS IN PATIENTS WITH ISCHEMIC HEART DISEASE AND TYPE 2 DIABETES AFTER MYOCARDIAL REVASCULARIZATION

Nazarova G.
Junior Researcher, Republican Specialised Scientific and Practical Medical Centre for Therapy and Medical Rehabilitation
Alyavi A.
Doctor of Medical Sciences, Academician, Head of the Cardiology Laboratory, Republican Specialised Scientific and Practical Medical Centre for Therapy and Medical Rehabilitation
Tulyaganova D.
Doctor of Medical Sciences, Head of the Cardiology Department of the Republican Specialised Scientific and Practical Medical Centre for Therapy and Medical Rehabilitation
Khan T.
Junior Researcher, Republican Specialised Scientific and Practical Medical Centre for Therapy and Medical Rehabilitation
Razhabova D.
Junior Researcher at the Republican Specialised Scientific and Practical Medical Centre for Therapy and Medical Rehabilitation
State Institution "Republican Specialised Scientific and Practical Medical Centre for Therapy and Medical Rehabilitation" Tashkent, Uzbekistan
https://doi.org/10.5281/zenodo.17942884

Abstract
Despite improvements in methods of restoring coronary perfusion, a significant proportion of patients continue to have or develop new structural and functional myocardial abnormalities, including left ventricular remodelling, diastolic dysfunction, decreased contractility, increased vascular wall stiffness, and impaired microcirculatory coronary blood flow. There is a need for a more in-depth pathophysiological analysis of the mechanisms that prevent complete functional rehabilitation of the myocardium after revascularisation in patients with IHD and T2DM.

Keywords: coronary heart disease, diabetes mellitus, interleukin-6, echocardiography

Introduction. Ischemic heart disease (IHD) continues to be one of the leading causes of death and disability worldwide, remaining a key medical and social problem. [1]. The combination of CHD and type 2 diabetes mellitus (T2DM) is of particular clinical significance, as metabolic disorders in diabetes contribute to accelerated progression of atherosclerosis, increased thrombotic activity, chronic systemic inflammation, and endothelial dysfunction. Such patients experience earlier development of coronary insufficiency, more severe angina pectoris, and a high risk of recurrent coronary events, even after successful myocardial revascularisation (PCI or CABG). [2].

Despite improvements in methods of restoring coronary perfusion, a significant proportion of patients continue to have or develop new structural and functional myocardial abnormalities, including left ventricular remodelling, diastolic dysfunction, decreased contractility, increased vascular wall stiffness, and impaired microcirculatory coronary blood flow. There is a need for a more in-depth pathophysiological analysis of the mechanisms that prevent complete functional rehabilitation of the myocardium after revascularisation in patients with IHD and T2DM.

In recent years, increasing attention has been paid to cytokines and markers of endothelial dysfunction, which reflect chronic inflammation and impaired regulation of vascular tone. The most informative biomarkers include: Interleukin-6 (IL-6) — a key mediator of the inflammatory cascade that enhances atherogenesis and myocardial remodelling; Endothelin-1 (ET-1) — a potent vasoconstrictor that determines endothelial dysfunction and coronary vasospasm; Vascular endothelial growth factor (VEGF) — a regulator of angiogenesis and reparative processes in the myocardium.

Changes in the levels of these biomarkers indicate incomplete restoration of endothelial function and persistent inflammation, which may hinder reverse remodelling of the heart after revascularisation and determine the prognosis in patients with IHD complicated by DM2. However, a comprehensive assessment of the relationship between structural and functional parameters of the myocardium and levels of IL-6, ET-1, and FRS in patients who have undergone revascularisation has not been sufficiently studied and requires further clarification.

In this regard, the study is of considerable scientific and practical importance, as it allows us to identify the pathogenetic mechanisms underlying adverse cardiac remodelling in the comorbid course of IHD and T2DM and to determine biomarkers that are potentially applicable for prognosis, monitoring and personalised therapy.

In view of the above, the aim of our study was to investigate the relationship between structural and functional myocardial disorders and the content of IL-6, ET-1 and FRS in the blood of patients with IHD, exertional angina pectoris with concomitant type 2 diabetes mellitus who had previously undergone myocardial revascularisation.

Materials and methods. A total of 116 patients with IHD, exertional angina pectoris FC 2, and a history of myocardial revascularisation were observed. The average age of all patients was 65 years [45; 87]. Depending on the presence of type 2 diabetes mellitus, patients were divided into two groups. The first group consisted of 56 patients without type 2 diabetes mellitus. The second group included 60 patients with type 2 diabetes mellitus. All patients were comparable in terms of clinical, anthropometric, and haemodynamic parameters.

The blood levels of IL-6, ET-1, and FRS were measured by solid-phase enzyme immunoassay using the VEGF-IFA-BEST reagent kit manufactured by Vector-Best CJSC (Russia, reference range in blood serum -0-10 pg/ml

Echocardiography with tissue Doppler imaging was performed using a Samsung Medison Accuvix.V20 ultrasound machine (Korea) using a sector probe with colour mode and pulse wave and continuous wave modes 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).

Results. When studying the initial indicators of IL-6, ET-1, and FRES, a significant increase (p=0.008, <0.001, <0.001, respectively) was revealed in the main group.

When performing echocardiography in our study, no statistically significant differences were found in the assessment of indexed parameters in both groups, the values of which were within the normal range.

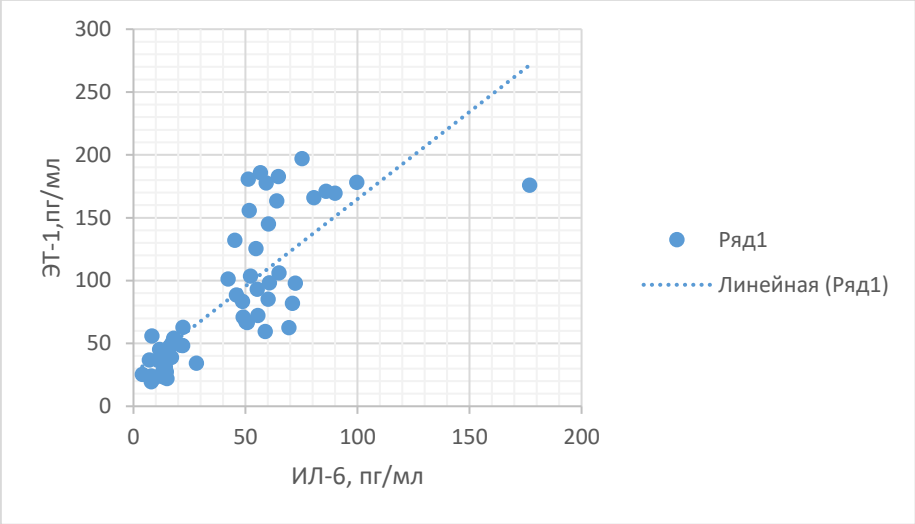

Figure 1 Correlation between IL-6 and ET-1 in patients with IHD associated with type 2 diabetes mellitus

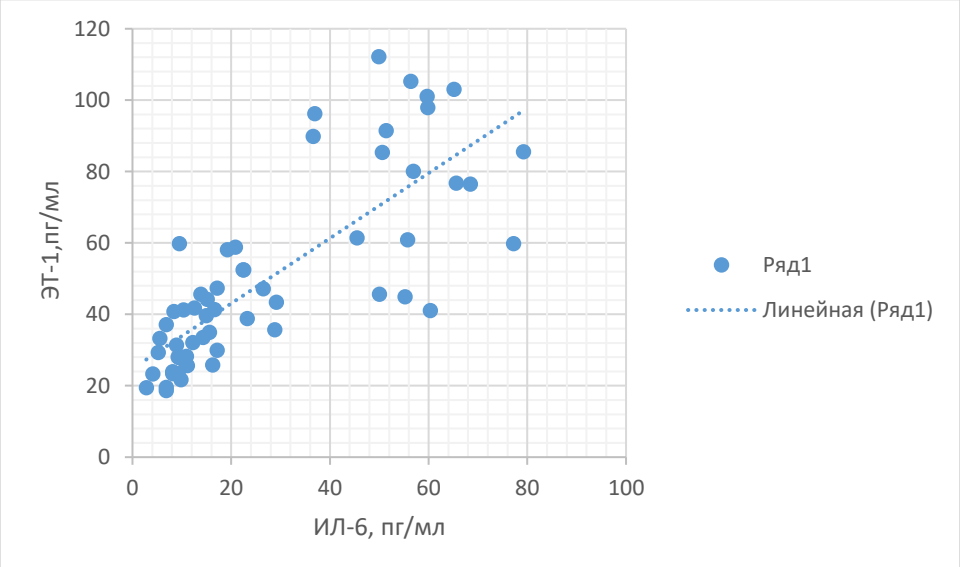

Figure 2. Correlation between IL-6 and ET-1 in patients with IHD, without association with type 2 diabetes mellitus

When performing a correlation analysis in the main group and in the comparison group, a similarly strong direct correlation with ET-1 was found depending on the IL-6 level (r=0.79 vs r=0.78, p<0.05) Fig. 1 and Fig. 2.

Further study also revealed a positive correlation of moderate strength between IL-6 and iCDO in the main group and in the comparison group (rr0.30 vs r=0.39, p<0.05) (Fig. 3, 4).

Despite improvements in methods of restoring coronary perfusion, a significant proportion of patients continue to have or develop new structural and functional myocardial abnormalities, including left ventricular remodelling, diastolic dysfunction, decreased contractility, increased vascular wall stiffness, and impaired microcirculatory coronary blood flow. There is a need for a more in-depth pathophysiological analysis of the mechanisms that prevent complete functional rehabilitation of the myocardium after revascularisation in patients with IHD and T2DM.

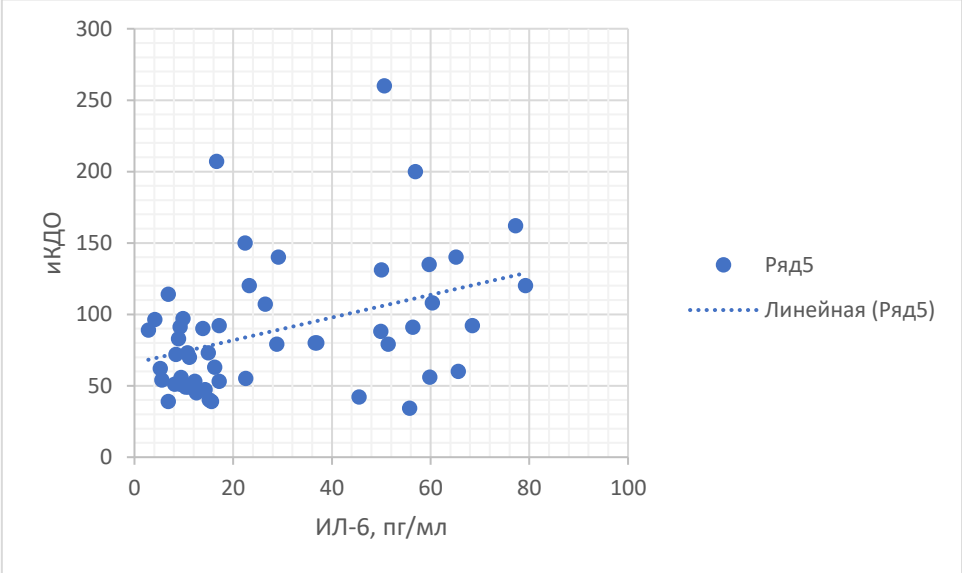

Figure 3 Correlation between IL-6 and iCDO in a group of patients with IHD associated with type 2 diabetes mellitus.

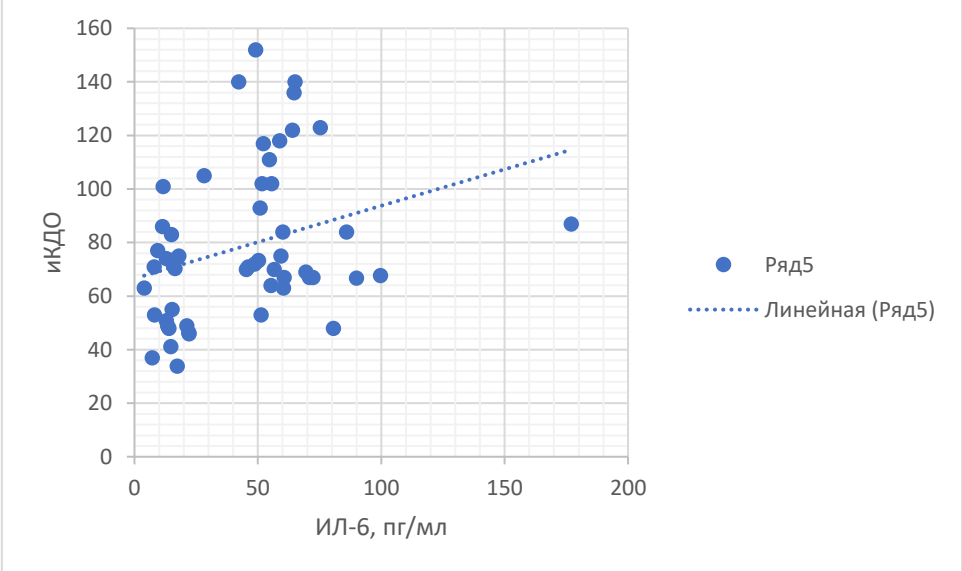

Figure 4 Correlation between IL-6 and iCDO in a group of patients with IHD not associated with type 2 diabetes mellitus.

In the correlation analysis of iPJ and IL-6, the strength of the correlation reached an average level and amounted to r=-0.33 in the group of patients with type 2 diabetes mellitus. Meanwhile, in the group of patients without association with diabetes mellitus, the strength of the correlation amounted to r=-0.40.

It Is noteworthy that in the analysis of INRS with IL-6, the strength of the correlation was inversely strong and amounted to r=-0.54 in the main group. An inverse correlation was also observed in the comparison group, but it was of medium strength (r=-0.39).

Discussion. Our study revealed the prognostic significance of elevated serum IL-6 levels for the development of diabetes, highlighting the key role of interleukins in initiating or exacerbating inflammatory processes associated with diabetes.

Inflammation and oxidative stress interact in the pathogenesis of diabetes and together drive disease progression [9]. This bidirectional relationship reminds us that the prognostic value of interleukins in the development of diabetes highlights the potential for developing biomarker-based screening tools. Furthermore, translating these findings into clinical practice requires longitudinal studies to confirm the efficacy and reliability

of cytokine levels as prognostic biomarkers for diabetes and its complications.

A large number of studies have confirmed that IL-6 exerts both pro-inflammatory and anti-inflammatory effects through various IL-6Rs. IL-6 receptor complexes consist of IL-6R or soluble IL-6R and gp130. It appears that the pro-inflammatory effect mainly depends on trans-signalling mediated by IL-6R, while the anti-inflammatory effect mainly depends on membrane-bound IL-6R (3–6). 4IL-6 induces Th17 differentiation, suppresses Treg differentiation, and stimulates M2 macrophage polarisation (7–9). Lymphocytes, monocytes/macrophages, adipocytes, as well as haematopoietic and endothelial cells are cellular sources of IL-6 (10). The gp130 protein is expressed in virtually all tissues (11).

Cardiac fibrosis is characterised by excessive deposition of extracellular matrix (ECM) proteins, leading to enlargement of the cardiac interstitium, which is a common pathophysiological companion of most myocardial diseases. This is associated with cardiac dysfunction, arrhythmogenesis, and adverse outcomes (12,13). HF is a complex clinical syndrome caused by structural or functional impairment of ventricular filling or blood ejection (14). Proinflammatory cytokines trigger a series of pathological reactions, such as oxidative stress, endothelial dysfunction, induction of myocyte apoptosis, and hypertrophy, which ultimately leads to cardiomyocyte dysfunction (15).

An experimental study has shown that IL-6 plays a central role in myocardial fibrosis, which depends on the activation of the MAPK and CAMKII-STAT3 pathways. IL-6 is a downstream signal of hypoxia-induced mitogenic factor (HIMF), and its inhibition can prevent fibroblast activation (16). In addition, IL-6 overexpression enhances TGF-β1-mediated MMP2/MMP3 signalling to induce proliferation, differentiation, and fibrosis of myofibroblasts (17). Mice with IL-6 knockout showed a lower degree of cardiac fibrosis. Thus, anti-IL-6 may be a potential therapeutic target for reducing cardiac fibrosis.

The regional contractility impairment index based on peak systolic deformation coefficient (Ecc) data is inversely related to plasma IL-6 levels and reflects a decrease in the contractile function of LV regions, especially the septum and lower wall, with an increase in interleukin-6.

Conclusion. Thus, selective inhibition of trans-signalling, rather than global inhibition, may be a future therapeutic strategy. Cytokines influence the progression of cardiac pathology by regulating complex signalling networks. We have illustrated the link between IL-6 and ischaemic heart disease after revascularisation in patients with and without type 2 diabetes mellitus. Further research is needed to identify potential therapeutic targets and biomarkers for cardiovascular disease.

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