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The interleukin value-10 in patients with coronary artery disease, hypertension and chronic heart failure

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Abstract
This article reviews the role of interleukin-10 (IL-10) in the pathogenesis and course of Coronary Artery Disease (CAD), hypertension and chronic heart failure (CHF). IL-10 is a key anti-inflammatory cytokine that plays an important role in regulating the immune response and reducing inflammation. In the context of cardiovascular diseases (CVD), inflammation is one of the leading mechanisms of their development and progression. Studies show that IL-10 levels can be altered in patients with CAD, hypertension and CHF, which indicates its potential participation in protective or adaptive responses of the body. The mechanisms by which IL-10 may influence endothelial function, vascular and myocardial remodeling, and the course of atherosclerosis are reviewed. The prognostic value of IL-10 levels for assessing the risk of complications and severity of CVD is discussed. The tasks of the study was to determine the activity of hc-CRP and pro-inflammatory cytokines (interleukins 1β,-6 and anti-inflammatory cytokine (IL-10) in patients with coronary artery disease, Permanent Atrial Fibrillation (AF) and without AF in a population-based comparison with healthy volunteers. The study shoved, that in patients with coronary artery disease combined with hypertension and permanent AF, a more pronounced (p<0.05) activity of anti-inflammatory IL-10 by 127.9% is observed compared to patients without AF. Elevated serum levels of IL-10 ≥ 23.0 pg/ml increase the chances of developing AF by 12.4 times in patients with coronary artery disease and hypertension, which can be used as additional criteria for diagnosing and predicting AF in this category of patients.

Keywords: Interleukin-10, coronary heart disease, arterial hypertension, chronic cardiovascular failure, inflammation, cytokines, biomarkers

Introduction
Cardiovascular disease (CVD) remains the leading cause of death worldwide. Although classical risk factors such as hypertension, dyslipidemia, diabetes, and smoking play a key role in the pathogenesis of CVD, there is growing interest in the immunoinflammatory component as an important mechanism in the development and progression of these diseases. Interleukin-10 (IL-10), a potent anti-inflammatory cytokine with immunoregulatory effects, has been the focus of research and has the potential to be a biomarker and therapeutic target in CVD [1]. Interleukin-10 is an anti-inflammatory cytokine produced by a variety of cells, including monocytes, macrophages, dendritic cells, T helper type 2 (Th2), regulatory T cells (Treg), B cells, and NK cells. Its main function is to inhibit the synthesis of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines, and MHC class II on the surface of antigen-presenting cells [2].

The role of IL-10 in coronary disease (CHD)
As is known, atherosclerosis is the main cause of CAD, in particular stable angina pectoris. According to modern theories, atherosclerosis is considered a chronic inflammatory vascular disease, where the imbalance between pro-inflammatory (high-sensitivity C-reactive protein, IL-1β and IL-6) and anti-inflammatory mediators is a major factor in the formation of atheroma. In coronary artery disease (CAD), it is able to modulate numerous cellular processes that play an important role in the emergence, progression and stabilization of atherosclerotic plaque, as well as in the regulation of cholesterol metabolism in macrophages [3]. IL-10 inhibits the release of lysosomal enzymes by neutrophils and monocytes, their production of metalloproteinases, the synthesis of pro-inflammatory cytokines (tumor necrosis factor α-TNF-α, IL-1, IL-6) and chemokines, disrupting the translocation of the transcription factor NF-κB.

This cytokine is able to significantly inhibit oxidation products, enhance the synthesis of no by activated macrophages, enhance the expression of the receptor for platelet activating factor by neutrophils and monocytes, prevents programmed cell death-apoptosis, promotes the growth and differentiation of monocytes into macrophages [4]. IL-10 expression has been identified both in the early stages of atherogenesis and in progressive human plaque, where it is able to limit local inflammatory reactions. For the most part, the concentration of IL-10 is determined in blood serum. However, its content in immunocompetent cells, which characterizes the degree of their activation and participation in the pathogenesis of the pathological process, has not been studied sufficiently [3].

The role of IL-10 in acute myocardial infarction (MI)

As is known, myocardial infarction is an acute condition that occurs as a result of a sudden cessation or significant reduction in blood supply to a part of the heart muscle (myocardium), which leads to necrosis (death) of this area [5]. After this, an acute phase of inflammation is triggered, which helps to clear the affected area of dead cells, but at the same time, an excessive or prolonged immune response causes additional damage and remodeling of the heart muscle. That is why anti-inflammatory mechanisms, in particular IL-10, play a critical role in protecting heart tissue:

- **Protective effect:** IL-10 reduces the infiltration of macrophages and neutrophils, limiting necrosis and apoptosis of cardiomyocytes [6].
- **Modulation of myocardial remodeling:** IL-10 inhibits fibrosis, reduces the expression of metalloproteinases (MMPs), which prevents excessive remodeling after infarction.
- **Anti-apoptotic effect:** IL-10 induces the expression of Bcl-2 in cardiomyocytes, thereby protecting them from ischemic injury [7].

In a clinical study by Cavusoglu *et al*. (2006), it was shown that higher levels of IL-10 in plasma of patients with acute myocardial infarction were associated with a better prognosis and lower mortality [8]. Patients with acute MI who had elevated levels of IL-10 had fewer complications in the acute phase, including myocardial rupture and post-infarction heart failure [9].

The role of IL-10 in chronic heart failure

Chronic heart failure (CHF) is a clinical syndrome that occurs as a result of a structural or functional impairment of the heart's ability to provide adequate organ perfusion. The pathogenesis of CHF largely involves chronic systemic inflammation, which contributes to the progression of myocardial remodeling and the deterioration of the clinical condition of patients. In recent years, the study of anti-inflammatory cytokines has attracted attention, among which interleukin-10 (IL-10) plays a key role. CHF is characterized by chronic inflammation, which contributes to myocardial remodeling. IL-10 protects cardiomyocytes from apoptosis, reduces the level of fibrosis and modulates fibroblast activity [10]. However, in clinical settings, the data are contradictory: an increase in IL-10 in some patients with CHF may reflect a compensatory response to systemic inflammation, and does not always predict a better prognosis [11].

Roles of IL-10 in CHF

• Anti-inflammatory effect

In animal models of CHF, administration of recombinant IL-10 or induction of its expression was associated with a decrease in myocardial expression of pro-inflammatory cytokines, inhibition of fibroblast activation and reduction of intercellular fibrosis, improvement of ejection fraction and overall systolic cardiac function [12].

• Myocardial remodeling

In a study by Krishnamurthy *et al*. (2009), IL-10 was shown to reduce the expression of TNF-α in the heart, reduce left ventricular hypertrophy and improve survival in mice after experimental MI [13]. IL-10 also modulates the activity of matrix metalloproteinases (MMPs), reducing the degradation of the extracellular matrix, which is critical for limiting pathological remodeling in CHF [14].

IL-10 is also considered a powerful prognostic factor for cardiovascular disease. Higher levels of IL-10 are associated with better survival due to suppression of chronic systemic inflammation. However, in some studies, high concentrations of IL-10 are interpreted as a response to a severe systemic inflammatory state and are associated with a worse prognosis [14]. A study by Rauchhaus *et al*. (2000) demonstrated that patients with CHF and elevated levels of IL-10 and TNF-α had significantly higher mortality than patients with normal levels of both cytokines [10].

Given the described effects, IL-10 is considered a promising therapeutic target. Preclinical studies use recombinant IL-10, adenoviral vectors, and nanoparticles for targeted delivery of IL-10 to affected tissues [15]. However, the clinical application of IL-10 as a biologic is limited by its short half-life, immune side effects, and difficulty in delivering it to the site of injury. Therefore, future studies are aimed at creating modified forms of IL-10 or inducing its endogenous synthesis [16].

The administration of recombinant IL-10 or induction of its expression in animal models of MI reduces mortality, improves ejection fraction, and reduces the area of necrosis [17]. In animal models, the administration of recombinant IL-10 reduced the size of the post-infarction scar and improved systolic function [18].

Based on experimental data, the following approaches to the use of IL-10 in the treatment of CHF are considered:-

- **Gene therapy:** The use of adenoviral vectors for the expression of IL-10 in cardiac tissue [19];
- **Cell therapy:** The introduction of mesenchymal stem cells modified for the synthesis of IL-10 [20].
- **The use of nanotechnology:** Targeted delivery of IL-10 or its inducers using liposomes or nanoparticles [18]. However, none of these strategies has yet gone beyond preclinical or early clinical studies.

Materials and Methods

In the period from 2018 to 2020, we also studied IL-10 levels in cardiology patients as part of the dissertation study "Prediction of the development of permanent atrial fibrillation and hospitalizations of patients with ischemic heart disease and in combination with arterial hypertension", which was conducted at the Department of Internal Medicine 3 of Dnipro State Medical University. One of the tasks of the dissertation study was to determine the activity of hc-CRP and pro-

inflammatory cytokines (interleukins 1β,-6 and anti-inflammatory cytokine (IL-10) in patients with coronary artery disease, permanent atrial fibrillation (AF) and without AF in a population-based comparison with healthy volunteers. To achieve the set goal, we examined 78 patients with hypertension, coronary artery disease, and CHF. The patients were hospitalized in the cardiology and therapeutic departments of the Dnipro City Clinical Hospital No 11 of the Dnipro City Council. The average age of the examined was 66.3±1.0 years, among them men prevailed-43 (55.1%) patients. The patients were divided into 2 groups. Group 1 (N=42) included patients with hypertension, CAD, CHF, and permanent AF (21 men and 21 women, average age-68.0 ± 1.2 years). Group 2 (N=36) consisted of patients with hypertension, CAD, and CHF without AF (22 men and 14 women, average age-64.3 ± 1.5 years). The control group consisted of a control group of 15 respondents, matched by age and sex.

The study did not include patients with chronic CHF II B or III stage/IV FC according to NYHA; acute coronary syndrome, myocardial infarction in the last 6 months; cardiomyopathies; hemodynamically significant heart defects, acute cerebrovascular accident, glomerular filtration rate (GFR) < 60 ml/min/1.73 m2; patients with cancer and individuals who abused alcohol and strong psychotropic substances.

Diagnostic Workup

At the stage of inclusion in the study, all patients underwent general clinical examinations: collection of complaints and anamnesis, physical examination, measurement of blood pressure upon admission to the hospital, calculation of body mass index (BMI) according to the Quetelet formula, determination of laboratory parameters (complete blood count and urine analysis, biochemical blood test). Additionally, the levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-10 (IL-10) were determined by enzyme-linked immunosorbent assay. 12-channel electrocardiography (ECG) was recorded, 24-hour ECG monitoring, and transthoracic echocardiography of the heart (Echo-CG) were performed.

Statistical processing of the obtained results was carried out using the statistical software packages Statistica v.6.1 (serial number AGAR909E415822FA) and MedCalc Statical Software v.11.5.0. (Free Trial). The hypothesis of normality of distribution of quantitative characteristics was tested using the Lilliefors and Shapiro-Wilk criteria. With normal data distribution, the arithmetic mean (M), standard error (m), Student's test (t) were used; with other distributions, the median (Me), quartiles (25%-75%), Mann-Whitney test (U). Comparison of relative values was carried out using the Pearson Chi-square test ($\chi 2$) and Fisher's exact test (TCF). The presence of relationships between the studied data was established using the results of correlation analysis with the calculation of Spearman's rank correlation coefficients (rs). The critical value of the statistical significance level (p) for all types of analysis was set at < 0.05 (5%).

Results and Discussions

According to the results of our study, in patients with coronary artery disease, hypertension and permanent AF (group 1), the activity of anti-inflammatory IL-10 significantly exceeded by almost 2 times and amounted to 33.04 pg/ml [15.91; 35.54] versus 14.50 pg/ml [6.49; 21.74], ($p < 0.001$) compared to patients without AF (group 2). At the same time, in the blood of respondents without cardiovascular diseases (N=15) the level of IL-10 was 9.94 [7.86; 11.65] pg/ml, which corresponds to the reference interval of "norm". In some cases, a high level of IL-10 is also considered as a marker of a compensatory response to systemic inflammation, and its interpretation should take into account the clinical context.

Correlation analysis between clinical and anamnestic indicators revealed a positive correlation in patients with permanent AF with an increase in IL-10 levels, which was most associated with BMI (r=0.56), angina pectoris (r=0.54), CVD (r=0.45), LDL (r=0.37), and an inverse relationship was also established between IL-10 levels and LVEF (r=-0.50) and LVMI (r=-0.51). In group 2 of patients with CHD combined with hypertension without AF, close correlations between IL-10 levels were observed only with Echo-CG indicators-EF (r=-0.50) and LVMI (r=-0.52).

Using ROC analysis, optimal cut-off points were determined for IL-10, which in combination with hc-CRP, IL-1β and IL-6 characterize the development of AF. It was found that the operating characteristics for prediction are an increase in serum IL-10 level ≥ 23.0 pg/ml (AUC=0.745; 95% CI 0.633-0.837; HR=66.7%; SD=86.1%).

Conclusion

- In patients with coronary artery disease combined with hypertension and permanent AF, a more pronounced ($p<0.05$) activity of anti-inflammatory IL-10 by 127.9% is observed compared to patients without AF.
- Elevated serum levels of IL-10 ≥ 23.0 pg/ml increase the chances of developing AF by 12.4 times in patients with coronary artery disease and hypertension, which can be used as additional criteria for diagnosing and predicting AF in this category of patients.

The obtained data expand and complement previous research data and clearly demonstrate the need to include laboratory determination of markers of chronic inflammation in the general diagnostic examination.

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