Samoilova E. V., Korotaeva A. A., Zhirov I. V.,
Aksenova Yu. O., Nasonova S. N., Tereshchenko S. N.
Chazov National Medical Research Center of Cardiology, Moscow, Russia

Interleukin 6 Signalling in Heart Failure With Preserved and Reduced Ejection Fraction

Aim	Identification of interleukin-6 (IL-6) signaling pathways in patients with chronic heart failure (CHF).
Material and methods	The diversity of IL-6 effects is due to the presence of classical signaling and trans-signaling pathways. The study included 164 patients with CHF hospitalized for acute decompensated heart failure (ADHF), of which 129 had reduced left ventricular ejection fraction (HFrEF), and 35 had preserved ejection fraction (HFpEF). Blood concentrations of IL-6, soluble IL-6 receptor (sIL-6R), soluble transducer protein gp130 (sgp130), and high-sensitivity C-reactive protein (hsCRP) were measured.
Results	Patients with HFpEF had lower concentrations of IL-6 (6.15 [2.78, 10.65] pg/ml) and hsCRP (11.27 [5.84, 24.40] mg/ml) than patients with HFrEF (9.20 [4.70; 15.62] pg/ml and 17.23 [8.70; 34.51 mg/ml], respectively). In contrast, concentrations of rIL-6R were higher in HFpEF (59.06 [40.00; 75.85] ng/ml) than in HFrEF (49.15 [38.20; 64.89] ng/ml). Concentrations of sgp130 were not significantly different. In patients with HFrEF, positive correlations were found between the concentrations of IL-6 and hsCRP, IL-6 and rIL-6R, and IL-6 and sgp130, while in patients with HFpEF, there was a correlation only between IL-6 and hsCRP, which appeared stronger than in patients with HFrEF (r=0.698; p<0.001 and r=0.297; p<0.05, respectively).
Conclusion	Classical IL-6 signaling and trans-signaling are expressed to different degrees in patients with HFrEF and HFpEF in ADHF. The results of the study supplement the existing knowledge about the pathogenesis of inflammation in CHF and may contribute to the development of new methods and approaches to the treatment of the disease.

Keywords	Chronic heart failure; left ventricular ejection fraction; interleukin-6; signaling
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Corresponding author Samoilova E. V. E-mail: erihter@mail.ru

Introduction

Chronic heart failure (CHF) is a serious medical, social, and economic problem of modern society, being one of the leading causes of high morbidity, frequent repeat hospitalizations, and reduced quality and duration of patients' lives [1, 2]. The wide heterogeneity of patients with multiple CHF etiologies, phenotypes and comorbidities leads to significant variation in response to therapy, and universal approaches to the treatment of CHF are not always effective. Symptoms and prognosis are improving in heart failure with reduced left ventricular ejection fraction (HFrEF), but mortality remains high in heart failure with preserved ejection fraction (HFpEF). [3, 4]. In this context, personalized approaches tailored to the patient profile are expected to significantly improve the quality of care. The optimization of existing methods and the development of new effective treatment options for patients with CHF is possible through in-depth study of the fundamental mechanisms of disease pathogenesis.

Most researchers believe that HFrEF and HFpEF are caused by different pathogenic mechanisms. Changes in cardiomyocytes and extracellular matrix after myocardial injury are responsible for cardiac remodeling in patients with HFrEF [5]. The structural and functional changes in the myocardium in HFpEF are heavily influenced by the systemic inflammation caused by comorbidities [6, 7].

It is generally accepted that inflammation is an important factor in the development and progression of CHF [8, 9]. Acute decompensated heart failure (ADHF) is associated with marked inflammatory progression. Inflammation is currently considered a novel therapeutic target for treating cardiovascular diseases [10]. Interleukin-6 (IL-6) has attracted particular attention due to the abundant evidence of its role in the development of cardiovascular complications [11, 12]. The combined effects of IL-6 may influence the pathogenesis of HF [13, 14].

IL-6 is a pleiotropic cytokine that has both pro-inflammatory and anti-inflammatory properties. The presence

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of different signaling pathways is responsible for the multidirectional effects of IL-6. In classical signaling, IL-6 binds to the membrane receptor IL-6R; in trans-signaling, IL-6 binds to the circulating soluble receptor sIL-6R. The transducer protein gp130, which is present on almost all cell types, transduces signals in the cell through both pathways. The soluble form of the transducer protein sgp130 is able to inhibit the IL-6 trans-signaling pathway without interfering with classical signal transduction. The anti-inflammatory activity of IL-6 is thought to be mediated to a greater extent by classical signaling, whereas trans-signaling predominantly mediates pro-inflammatory effects [15]. Since virtually all cells in the body respond to IL-6 signaling, targeting a specific IL-6 signaling pathway may provide an opportunity for selective therapeutic intervention.

Objective

Identify IL-6 signaling pathways in CHF patients. Since the relationship between the concentrations of IL-6, sIL-6R, and sgp130 is a determinant for initiating either the classical or trans-signaling pathway, we analyzed the levels of these components in patients with HFpEF and HFrEF in ADHF.

Material and Methods

The study included 164 patients with CHF who were hospitalized for ADHF. HFrEF (LVEF < 40%) was identified in 129 patients, and HFpEF (LVEF ≥ 50%) was identified in 35 patients. The Simpson method was used to determine this indicator in all cases. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Academician Chasov National Medical Research Center for Cardiology. All patients signed a specially designed informed consent form. The study excluded patients with malignant neoplasms, patients with left ventricular outflow tract obstruction, patients with acute inflammatory heart disease requiring antiviral therapy, immunomodulators, glucocorticoids (myocarditis, pericarditis), patients with restrictive heart diseases (restrictive pericarditis, restrictive cardiomyopathy), patients with severe renal impairment, patients with hepatic impairment (more than 3-fold increase in transaminase levels compared to the reference value), patients with clinically significant acute and chronic inflammatory diseases requiring specific therapy that may affect the parameters being studied. Patients underwent standard general clinical examinations (Table 1).

Central Illustration. Interleukin 6 Signalling in Heart Failure With Preserved and Reduced Ejection Fraction

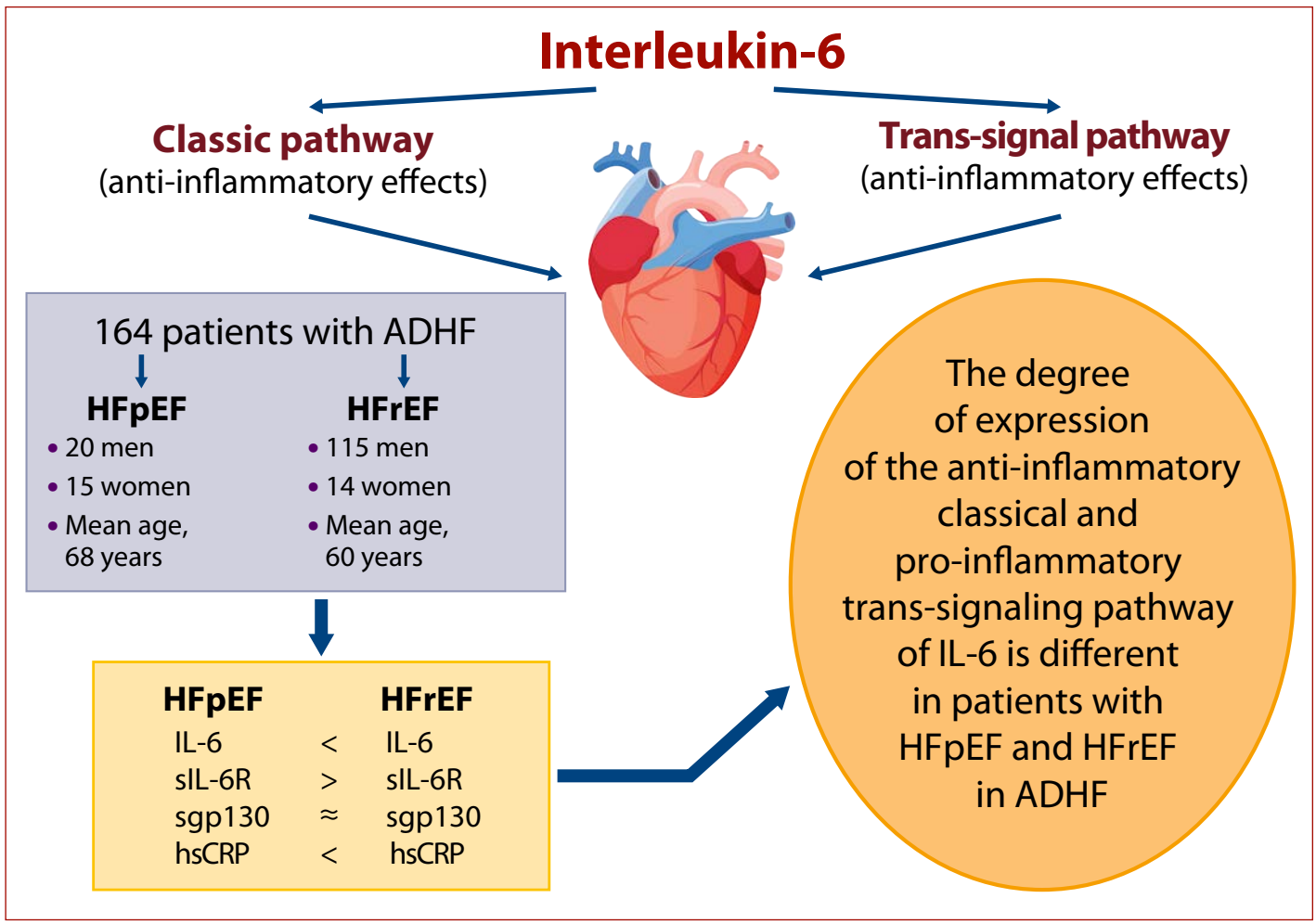

Table 1. General characteristics of patients with CHF according to LVEF

Parameter	Patients with HFpEF (n = 35)	Patients with HFrEF (n = 129)
Age, years	68 [60; 74]	60 [52; 67]
Male/female, n (%)	20 (57)/15 (43)	115 (89)/14 (11)
Hypertension, n (%)	34 (97)	85 (66)
CAD, n (%)	12 (34)	67 (52)
HR, bpm	87 [72; 109]	80 [70; 98]
SBP, mm Hg	130 [115; 150]	118 [105; 130]
DBP, mm Hg	80 [70; 86]	75 [70; 80]
DM, n (%)	9 (26)	32 (25)
BMI, kg/m²	31.00 [26.75; 35.00]	30.00 [26.00; 34.00]
Smoking, n (%)	11 (31)	78 (60)

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index.

Venous blood samples were obtained on admission prior to surgery. Plasma and serum samples were stored at –70 °C until assayed.

IL-6, sgp130 and sIL-6R levels were determined by enzyme-linked immunosorbent assay (ELISA) using R&D Systems reagent kits. High-sensitivity C-reactive protein (hsCRP) concentrations were determined using Vector-Best (Russia) reagent kits.

The levels of the IL-6/sIL-6R/sgp130 ternary complex, expressed in nmol/L, were calculated from the plasma concentrations of IL-6, sIL-6R and sgp130 [16].

Statistical processing of the data obtained was performed using the IBM SPSS Statistics 23.0. For non-normally distributed indicators, results are presented as medians and interquartile ranges [25th percentile; 75th percentile]. The nonparametric Mann-Whitney test for independent samples was used to quantitatively compare groups. Correlation analysis using Spearman's rank correlation was used to evaluate the relationship between the parameters studied. Results were considered statistically significant at $p<0.05$.

Results

Differences were found between the levels of IL-6 pathway components in patients with HFpEF and those with HFrEF. Patients with HFrEF had significantly higher levels of IL-6 than patients with HFpEF. However, sIL-6R levels were lower in patients with HFrEF than in patients with HFpEF. Plasma levels of sgp130 were higher in patients with HFrEF than in patients with HFpEF, but the differences between groups were not statistically significant (Table 2).

IL-6 is a major inducer of CRP synthesis. We have shown that the levels of hsCRP are higher in patients with HFrEF than in patients with HFpEF (see Table 2).

Correlation analysis of IL-6, sIL-6R, sgp130 and hsCRP showed correlations between IL-6 and hsCRP, IL-6 and sIL-6R, IL-6 and sgp130, and between sIL-6R and sgp130 in patients with HFrEF (see Figure 1; Table 3). Only a correlation between IL-6 and hsCRP levels was observed in patients with HFpEF (see Figure 1). Notably, the correlation between IL-6 and hsCRP was stronger in patients with HFpEF.

Because IL-6, sIL-6R, and sgp130 interact in blood on a molar basis, the levels of IL-6/sIL-6R/sgp130 ternary complexes (nmol/L) were calculated and found to be higher in patients with HFpEF (0.1211 [0.1126; 0.1273] nmol/L) compared with patients with HFrEF (0.1166 [0.1097; 0.1253] nmol/L; $p < 0.05$).

Discussion

In humans, a large proportion of IL-6 is present in the free state and does not form complexes with either sIL-6R or sgp130. This suggests that endogenous sgp130 is insufficient to block IL-6 trans-signaling via sIL-6R. Even at high blood levels of sIL-6R and sgp130, the relative ratio of free IL-6 and IL-6/sIL-6R complex allows simultaneous classical and trans-signaling [17].

Table 2. Levels of IL-6, sIL-6R, sgp130 and hsCRP according to left ventricular ejection fraction in patients with ADHF

Parameter	Patients with HFpEF (n = 35)	Patients with HFrEF (n = 129)	p
IL-6, pg/mL	6.15 [2.78; 10.65]	9.20 [4.70; 15.62]	0.004
sIL-6R, ng/mL	59.06 [40.00; 75.85]	49.15 [38.20; 64.89]	0.041
sgp130, ng/mL	479.65 [385.86; 634.01]	505.59 [421.37; 570.18]	0.689
hsCRP, mg/mL	11.27 [5.84; 24.40]	17.23 [8.70; 34.51]	0.032

IL-6, interleukin-6; sIL-6R, soluble IL-6 receptor; sgp130, soluble form of transducer protein; hsCRP, high-sensitivity C-reactive protein; ADHF, acute decompensated heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Table 3. Correlations between IL-6 levels and components of its pathways in HFpEF and HFrEF

Parameter	Patients with HFpEF (n = 35)	Patients with HFrEF (n = 129)
IL-6: sIL-6R	—	r = 0.262; p = 0.002
IL-6: sgp130	—	r = 0.362; p < 0.001
sIL-6R: sgp130	—	r = 0.442; p < 0.001

IL-6, interleukin-6; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; sIL-6R, soluble IL-6 receptor; sgp130, soluble form of transducer protein; r, Spearman's correlation coefficient; "–", no statistical significance.

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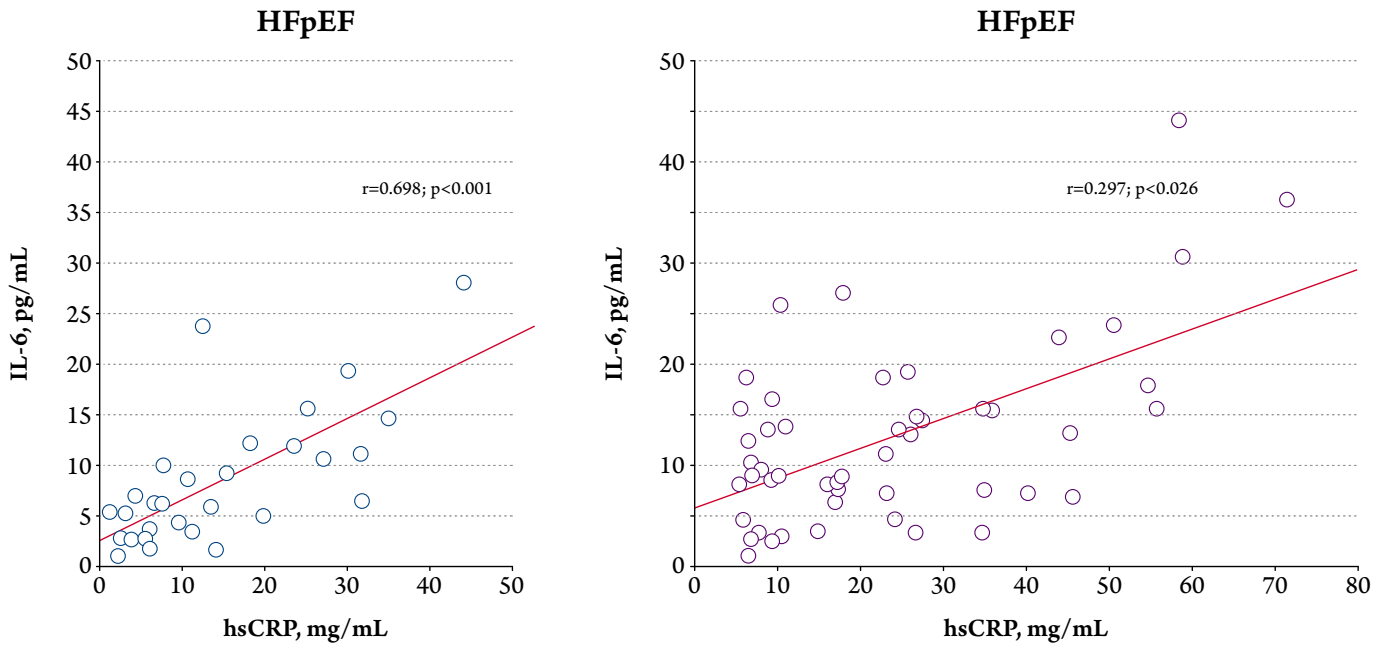
Figure 1. Correlation between the levels of IL-6 and hsCRP in HFpEF and HFrEF



IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. r, Spearman's correlation coefficient.

The differences in the levels of IL-6, sIL-6R, sgp130, and hsCRP between HFrEF and HFpEF found in this study, and the lack of correlations between the levels of IL-6 and components of the trans-signaling pathway in HFpEF as opposed to HFrEF may indicate that IL-6 signaling in HFrEF is different from that in HFpEF.

The higher levels of IL-6 and lower levels of sIL-6R, as well as the weak correlation between them in HFrEF compared to HFpEF, may be the result of increased binding of the IL-6/sIL-6R complex to gp130 on the cell membrane. This leads to a decrease in circulating sIL-6R levels. Low levels of IL-6/sIL-6R complex are sufficient to stimulate trans-signaling [17]. It can be hypothesized that, under these conditions, the trans-signaling of IL-6 is more pronounced in patients with HFrEF than in patients with HFpEF.

IL-6 is virtually the only cytokine that directly induces hsCRP synthesis in liver cells. Hepatocytes are one of the few cell types that express the IL-6R membrane receptor, which is involved in classical signal transduction. IL-6 and hsCRP levels were lower in patients with HFpEF, and the positive correlation between these parameters was stronger than in patients with HFrEF. It is likely that in addition to the classical IL-6 pathway, the IL-6 trans-signaling pathway is involved in CRP formation in patients with HFrEF. The presence of sIL-6R was shown to enhance the production of acute phase inflammatory proteins by liver cells [18].

Changes in sIL-6R and sgp130 levels largely regulate IL-6 trans-signaling. The levels of sIL-6R and sgp130 are generally regarded as a buffering system that can either promote IL-6 signaling through the formation of the IL-6/sIL-6R complex or inhibit signaling through the binding of sgp130 to the IL-6/sIL-6R complex [19]. The higher levels of IL-6/sIL-6R/sgp130 ternary complex observed in our study in patients with HFpEF compared to patients with HFrEF suggest that physiological inhibition of the IL-6 trans-signaling pathway is more pronounced in HFpEF.

A strategy of inhibiting IL-6 activity is used in clinical practice around the world for some diseases. There is no data on the use of this strategy in CHF. Currently used IL-6 inhibitors (siltuximab) or inhibitors of its receptor (tocilizumab, sarilumab) block both of the IL-6 signaling pathways. However, blocking the entire IL-6 signaling leads to pronounced side effects because IL-6 is essential for many vital functions. The ability to inhibit only one IL-6 pathway represents a clinically safer strategy. In a rat model of myocardial reperfusion infarction, administration of antibodies neutralizing IL-6 had no effect on infarct size, whereas sgp130Fc, an inhibitor of the IL-6 trans-signaling pathway, reduced infarct size by approximately 50% while preserving cardiac function [20]. A selective inhibitor of the IL-6 trans-signaling pathway, olamkicept, a variant of sgp130Fc, showed promising results in Phase II clinical trials in inflammatory bowel disease [21]. Olamkicept significantly reduced arterial wall inflammation in a female patient with high-risk coronary artery atherosclerosis [22]. Next-generation variants of sgp130 with increased affinity and selectivity for IL-6 trans-signaling are in development [23].

Limitations

The study is limited by the relatively small number of patients with HFpEF, which may have affected the statistical significance of the differences between groups and the strength of the correlations identified.

Conclusion

Thus, we found that the degree of expression of the classical and trans-signaling pathways of interleukin-6 is different in heart failure patients with reduced and preserved left ventricular ejection fraction in acute decompensated heart failure. The results of this study further contribute to the understanding of the mechanisms of inflammation in chronic heart failure with different left ventricular ejection fractions, which may contribute to the development of new therapeutic approaches for the treatment of the disease.

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