
# THE ROLE OF INFLAMMATORY MARKERS, C-REACTIVE PROTEIN AND PRO-INFLAMMATORY CYTOKINES IN THE DEVELOPMENT AND PROGRESSION OF POST-INFARCTION HEART FAILURE

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Achievements in the field of immunology and molecular biology indicate the important role of immune activation and systemic inflammation in the new theory of CHF pathogenesis [47,52,74,72,81]. At present, the pathogenesis of CHF should be considered in the light of modern concepts in the field of cardiology, endocrinology, immunology, and molecular medicine. One of the latest achievements of modern cardiology is the establishment of the role of activation of the cytokine system in the pathogenesis of CHF [23,49].

In patients with CHF I-II FC, there is an increase in the blood content of pro-inflammatory cytokines. It is believed that their excessive expression stimulates the processes of blood hypercoagulation, the development of acute coronary syndromes, the formation of endothelial and myocardial dysfunction, and the progression of muscular dystrophy. Increased blood levels of pro-inflammatory cytokines associated with LV dysfunction and progressive CHF are considered by many researchers as a factor in endothelial damage and severe immune suppression with a high risk of secondary immunodeficiency [114, 146].

The concept of the formation of pathophysiological mechanisms of CHF remains not fully understood. At present, the pathogenesis of CHF should be considered in the light of modern concepts in the field of cardiology, endocrinology, immunology, and molecular medicine. One of the latest achievements of modern cardiology is the establishment of the role of activation of the cytokine system in the pathogenesis of CHF [59, 65, 66]. One of the latest achievements of modern cardiology is the establishment of the role of activation of the cytokine system in the pathogenesis of CHF [56].

This mechanism is based on the concept of nonspecific activation of macrophages and monocytes in the interstitial fluid as an inducer of the synthesis of pro-inflammatory cytokines that determine the evolution of left ventricular (LV) dysfunction of the heart [61,130,147].

Cytokines are a class of soluble peptide mediators of the immune system necessary for its development, functioning and interaction with other body systems [55,56]. At present, extensive information has been accumulated on cytokines involved in many physiological and pathological processes, through which character is regulated. severity, duration of inflammation and immune response. Cytokines, which are a system of homeostatic regulation of cellular functions common to the body, are secreted and synthesized by activated cells of the immune system, fibroblasts, epithelium, endothelium, bone marrow stromal cells into the extracellular space in an active form. By means of cytokines, the nature, depth and duration of inflammation and the body's immune response are regulated.

The most important class of biologically active substances that have an immunoinflammatory effect are pro-inflammatory cytokines. Among them, only a few are related to the formation and progression of CHF, affecting the cardiovascular system through various mechanisms. They have a negative inotropic effect, stimulate protein synthesis, increase capillary permeability, promote the progression of myocardial hypertrophy and participate in left ventricular remodeling processes [1,44,50].

**Purpose of the study:** to study the role of inflammatory markers, C-reactive protein and proinflammatory cytokines in the development and progression of postinfarction heart failure

Material and methods: In our study, when studying the content of pro-inflammatory cytokines in peripheral venous blood: TNF-α and interleukins 1β and interleukin 6 in patients with functional classes I-IV of chronic heart failure, 60 patients aged 41 to 70 years who had previously undergone AMI were examined. with CHF according to the classification of the New York Heart Association (NYHA).

The group of patients with CHF I FC consisted of 18 patients. CHF II FC - 24 patients, CHF III FC - 11 and CHF IV FC - 7 patients, respectively. The control group consisted of 20 practically healthy people comparable in sex and age with the study group.

**Results and discussions:** The results obtained indicate that in all observation groups the concentration of pro-inflammatory cytokines, namely TNF-α, IL-1β and IL-6, as well as CRP, were increased and significantly differed from those of the control group ($p<0.01$). Analysis of individual values of CRP in patients with chronic heart failure showed that among patients with FC I CHF, the minimum level was 1.7 mg/l, and the maximum was 15.4 mg/l, and averaged (5.8±0.92) mg / l. The level of TNF-α in patients with chronic heart failure ranged from 24.8 pg/ml to 636.7 pg/ml and on average corresponded to (177.9±35.7) pg/ml. The content of IL-1β was also increased significantly and varied from 14.8 pg/ml to 967.2 pg/ml with an average value of (178.4±35.3) pg/ml. In addition, the content of IL-6 was increased, which ranged from 45.2 pg / ml to 348,

Consequently, changes in the parameters of the cytokine system and CRP, inflammation activity, in patients with chronic heart failure were characterized by a significant increase in the content of CRP by more than 5.2 times compared with healthy individuals, TNF-α by more than 4.9 times, interleukin-1β in 7 times and IL-6 up to (163.1±32.2) pg/ml (with a norm of 49.6±7.3) pg/l or 3.2 times.

Table 1

**Mean levels of inflammatory markers in patients with postinfarction CHF (M±SD)**

| Persons examined | Markers of inflammation | | | |
|---|---|---|---|---|
| | CRP, mg/l, n=39 | TNF-α, pg/ml n=45 | IL-6, pg/ml n=42 | IL-1β, pg/ml n=39 |
| Patients with CHF | 5.8±0.92* | 177.9±35.7* | 163.1±32.2* | 178.4±35.3* |
| Healthy faces n=21 | 1.2±0.29 | 37.1±13.7 | 49.6±7.3 | 26.2±5.4 |

Note: * - $p<0.01$ compared to the control group

This increase in the content of CRP and pro-inflammatory cytokines indicates the

activation of inflammation processes, in the mechanism of induction, in the formation of which endothelial dysfunction and hypoxia of peripheral tissues may play a role.

The change in the content of CRP and pro-inflammatory cytokines depending on the severity of chronic heart failure revealed that in FC I CHF, the level of CRP was in the range from 1.6 mg/l to 8.4 mg/l and averaged (3.5±5 .7) pg/l (p<0.05 compared to control) (Table 2).

table 2

**The content of CRP and pro-inflammatory cytokines in patients with postinfarction heart failure depending on the functional class of postinfarction CHF (M±SD)**

| FCCHF | Markers of inflammation | | | |
|---|---|---|---|---|
| | CRP, mg/l | TNF-α, pg/ml | IL-6, pg/ml | IL-1β, pg\|ml |
| I FC CHF | 3.5±5.7*<br>n=18 | 129.1±20.9*<br>n=10 | 106.1±20.7*<br>n=7 | 127.2±41.1*<br>n=7 |
| II FC CHF | 6.4±2.8°°*<br>n=22 | 186.1±24.4*<br>n=20 | 131.1±18.8*<br>n=24 | 137.1±29.2<br>n=16 |
| III FC CHF | 5.8±0.8°°*<br>n = 11 | 201.9±27.9*<br>n = 9 | 164.1±29.3*<br>n = 11 | 337.8±61.1°°*<br>n = 11 |
| IV FC CHF | 6.3±2.4°°*<br>n=7 | 171.8,±23.6*<br>n=6 | 99.4±24.8*<br>n=3 | 399.2±72.9°°*<br>n=5 |
| Referenced values | 1.2±0.29 | 37.1±13.7 | 49.6±7.3 | 26.2±5.4 |

Note: * - p<0.01 compared with control °° p<0.05 compared with patients with CHF I-II FC

The second functional class of heart failure was characterized by the same high level of C-reactive protein. It ranged from 0.8 to 13.9 mg/l and on average corresponded to (6.4±2.8) mg/l, which significantly (p<0.01) differed from the level of healthy individuals and patients with CHF-1FC . With III and IV functional classes of CHF, the content of CRP in the blood was in the range of 1.5-17.1 mg/l and averaged in CHF III FC (5.8±0.8) mg/l and (6.3± 2.4) mg/l, respectively, significantly (p<0.001) differing from the control group and (p<0.01) patients with CHF I FC. Comparison of the level of CRP depending on the functional class of heart failure indicates an almost identical increase in its content in patients with FC II and more severe CHF. Analyzing the overall content of CRP in patients with CHF due to coronary heart disease, it should be indicated that an increase in the level of CRP took place, starting with patients with FC I CHF. The maximum increase occurred in patients with II and III FC CHF.

The content of pro-inflammatory cytokines in the blood, in particularTNF-α was also increased, starting from patients with FC I CHF, where its content ranged from 42.5 pg/ml to 343.9 pg/ml on average (129.1±20.9) pg/ml (p< 0.01 compared to control). With II FC CHF levelTNF-α was significantly elevated. ContentTNF-α was in the range from 49.9 pg/ml to 483.9 pg/ml with an average value of (186.1±24.4) pg/ml, which significantly exceeded both control values (p<0.001) and the previous group (p<0.05). In patients with III FC CHF, the average level of contentTNF-α was increased to the most significant extent and corresponded to (201.9±27.9) pg/ml with changes in individual values in the groups from 78.9 pg/ml to 681.3 pg/ml. in the group of patients with IV FC CHF levelTNF-α in blood plasma was also significantly increased compared to the control and averaged(171.8±23.6) pg/ml with a change in individual parameters from 17.9 pg/ml to 317.3 pg/ml, which was significantly

higher compared to the control" ($p<0.01$) and somewhat lower compared with patients III and IV functional class.

Analysis of the content of IL-6 in patients with chronic heart failure showed the following. At the initial degree of circulatory disorders, in patients with FC I CHF, the level of IL-6 was (106.1 ± 20.7) pg / ml with individual changes, in the group of examined from 44, 1 pg/ml to 178.9 pg/ml ($p<0.01$ compared to control). The second functional class of CHF was characterized by a slight increase in the content of IL-6 compared with the previous group, where its level was (131±18.8) pg/ml with individual fluctuations in the group from 41.0 pg/ml to 299.4 pg/ml . In patients with III FC CHF, there was a further unreliable increase in the content of IL-6 to (164.1±29.3) pg/ml ($p<0.001$ compared with the control) with a minimum value in the group of 63.1 pg/ml and a maximum of 317 .4 pg/ml. IV FC CHF was characterized by a decrease in the level of IL-6 when compared with the previous groups.

Thus, attention is drawn to higher levels of IL-6 in patients with II and III FC heart failure and a slight decrease in this indicator in patients with FC IV CHF. At the same time, a small number of observations in the last group does not give the right to assert this with certainty.

Changes in IL-1β in patients with chronic heart failure were characterized as follows. In patients with chronic heart failure FC I, the level of IL-1β was (127.2±41.1) pg/ml, with individual indicators in the group from 89.2 pg/ml to 187.7 pg/ml, which is significantly higher ($p< 0.01$) compared with control. The second functional class of chronic heart failure was characterized by a higher level of IL-1β, which averaged (137.1±29.2) pg/ml with individual values from 30.1 pg/ml to 298.1 pg/ml, which is significant higher than the control, but not significantly compared with the previous group. In patients with CHF III FC, the content of interleukin 6 was significantly ($p<0.01$) higher than in the previous groups. It averaged (337.8±61.1) pg/ml with individual values in the group from 61.2 pg/ml to 792, 7 pg/ml the highest content of IL-1β was in the group of patients with IV FC CHF. On average, in the group, it was (399.2±72.9) pg/ml, with individual values from 146.3 pg/ml to 917.7 pg/ml ($p<0.001$ compared with the control and $p<0.01$ according to compared to previous groups). Thus, the content of IL-1β is increased, starting from patients with FC I CHF

**Conclusions:** Analyzing the change in the content of inflammation indicators in the functional classes of heart failure (Table 2.), it should be noted an increase in the content of CRP in patients with CHF I FC by 2.9 times and 4.8-5.3 times in CLE II, III and IV FC. This indicates an increase in the processes of inflammation, starting with II FC CNC and maintaining this increase until the terminal stage of the disease.

As for TNF-α, IL-6, IL-1β, an increase in their content was noted, starting with patients with CNK FC I. This increase progressed to stage III CNC, for TNF-α and IL-6, and was expressed to a lesser extent compared with the indicators in patients with I-III FC CNC. The content of IL-1β, in contrast to TNF-α and IL-6, increased in accordance with the severity of chronic circulatory insufficiency and reached maximum levels in patients with IV FC CNK.

The study revealed a negative effect of TNF-α, IL-1β and IL-6 hypercytokinemia in patients with postinfarction CHF, which plays a key role in the pathogenesis and progression of LV remodeling.

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