International Journal of
Health Systems and Medical Sciences

ISSN: 2833-7433
Volume 1 | No 4 | Oct-2022

# Chronic Heart Failure and Cytokines

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**Abstract** Chronic heart failure (CHF) is considered as a global non-communicable pandemic. In the pathogenesis of CHF, many factors are considered, including inflammatory cytokines. Cytokines is a group of soluble peptide mediators of the immune system, which is necessary for its development, functioning and interaction with other body systems.

TGF-β1 is a member of the group of multifocal cytokines. Many studies have shown the roles of TGF-β1 activation in the development of CVD, such as hypertension, cardiac hypertrophy and cardiac fibrosis leading to heart failure, as well as restenosis after coronary intervention and atherosclerosis. An analysis of the results of the studies performed indicates the direct involvement of TGF-β1 and its genetic structure in the processes of myocardial remodeling in heart failure, and also substantiates the need for further research in this direction.

**Keywords:** Chronic heart failure, cytokines, TGF-β1, cardiac fibrosis, hypertrophy

According to current literature, chronic heart failure (CHF) is considered as a global non-infectious pandemic, which primarily affects the elderly and senile. “CHF is not only a medical but also a social problem due to its significant prevalence, high mortality rate and high costs for the treatment of patients. CHF dramatically reduces the quality of life of patients and increases the risk of death by 4 times ... "[1]. In recent decades, modern medicine has made great advances in the treatment of cardiovascular diseases, but despite this, the prevalence of CHF continues to increase. According to world statistics, the prevalence of CHF increases with age, doubling every decade from the age of 50. At the same time, in people older than 65 years, its prevalence reaches 6-15%, while in younger people it is 2.2% [2].

The high prevalence in the population and a significant impact on the quality of life of patients indicate that many different aspects of CHF remain unresolved problems in medicine, as a result of which research in this area continues to be relevant for modern medicine. To date, a number of scientific studies are underway in the world, which are aimed at studying the pathogenetic foundations of the progression of CHF and methods of influencing them, as well as achieving high efficiency in the treatment of patients with CHF. In particular, it seems important to study the relationship between the severity of chronic heart failure and the severity of systemic endothelial dysfunction (ED), with the level of cytokines, etc. In this regard, the study of the course of CHF in a certain group of patients, and the development of methods for optimizing their treatment are urgent tasks facing specialists in this field.

Cytokines are a group of soluble peptide mediators of the immune system, which is necessary for its development, functioning and interaction with other body systems, and they are divided according to their mechanisms of action into pro-inflammatory, anti-inflammatory and immunoregulatory groups:

1. Pro-inflammatory cytokines that ensure the implementation of the inflammatory response: interleukins (IL) 1, 2, 6, 8, α-tumor necrosis factor (α-TNF), interferon-γ.
2. Anti-inflammatory cytokines that limit inflammation: IL-4, IL-10, transforming growth factor β.
3. Regulators of cellular and humoral immunity (natural or specific), with their own effector properties (antiviral, cytotoxic) [3].

Some pro-inflammatory cytokines 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 [4,5]. According to the scientific literature, the cytokine system is activated in 17.5-46% of patients with CHF. Information explaining the reason for the activation of the cytokine system is different, there is information about the stimulation of cytokine production by the sympathoadrenal system, the renin-angiotensin-addosterone system, and chronic hypoxia.

TGF-β1 is a member of the group of multifocal cytokines and was isolated from platelets in 1990. It can be produced by many cells, including cardiomyocytes, in response to metabolic stress. Normally, TGF-β1 is responsible for cell proliferation, differentiation, apoptosis, immune response, and extracellular matrix remodeling. In various CVDs, TGF-β1, by its inherent mechanism, can cause chronic inflammation, neovascularization, and myocardial fibrosis [6,7,8]

Many studies have shown the roles of TGF-β1 activation in the development of CVD, such as hypertension, cardiac hypertrophy and cardiac fibrosis leading to heart failure, as well as restenosis after coronary intervention and atherosclerosis [9]. TGF-β1 is an independent predictor of LV hypertrophy. Due to the fact that hypertrophy and interstitial fibrosis of the LV myocardium, as a rule, are detected during histological examination of the myocardium of patients with CHF LV EF, an increase in the level of TGF-β1 in the blood may reflect the severity of the disease in this category of patients. TGF-β1 also causes the progression of experimental kidney disease, and associations have been shown between serum TGF-β1 levels and risk factors for the progression of clinically significant kidney disease in humans [10].

TGF-β1 in its active state stimulates the growth of cardiomyocytes and proliferation of myofibroblasts, and at the same time has an anti-apoptotic effect on them. The development of interstitial fibrosis, a decrease in the elasticity of the heart muscle and blood vessels are associated with the action of TGF-β1.

TGF-β is considered a predictive biomarker for many cardiovascular diseases: in patients with coronary artery disease, elevated serum levels of TGF-β1 are significantly associated with increased survival with reduced rates of coronary events and interventions [11]. On the contrary, after angioplasty there is a greater risk of restenosis in patients with a higher level of TGF-β 1 in the blood at 15 minutes, 24 hours and 2 weeks after the procedure [12]. Patients will benefit from additional interventions to prevent restenosis. Overexpression of TGF-β1 in transgenic mice leads to cardiac hypertrophy, which is characterized by both interstitial fibrosis and hypertrophic growth of cardiomyocytes [13]. The study showed that accelerated TGF-β1 signaling leads to a decrease in the diameter of the arterial lumen with a subsequent increase in vascular resistance and hypertension [14].

In patients with CHF, a high level of TGF-β1 is associated with the development of vascular stenosis due to increased fibrosis processes and is characterized as an important component of the inflammatory response, contributing to the development of CHF with preserved ejection fraction [15]. Data on the role of TGF-β1 in the pathogenesis of CHF were also confirmed in an experimental study on animals (rabbits), F. Zhang et al. revealed an increase in the level of TGF-pi with an increase in the severity of heart failure [16].

According to the results of the analysis, a statistically significant increase in the level of transforming growth factor beta 1 was found in all patients with chronic heart failure, regardless of the ejection fraction, compared with the control group. It was found that the level of transforming growth factor

beta 1 in all patients with chronic heart failure increased with subsequent functional class, with the exception of patients with low ejection fraction of functional class IV. This trend was more pronounced in patients suffering from chronic heart failure with preserved ejection fraction [17].

There are some conflicting results in the literature, Y. Izumiya et al. positive correlations between TGF-β1 and BNP were found in patients with CHF LV EF [18]. Whereas in the works of Boyko A.M. et al. no significant correlation was established between TGF-β1 and BNP, which is the "gold standard" for determining CHF [19]. However, the results of recent studies [20, 21] indicate that the blood levels of BNP are significantly higher in CHF patients with reduced LV EF than in patients with HF LV EF. Boyko A.M. and co-authors also showed that in patients with CHF LV EF, the serum level of TGF-β1 significantly correlates with the values of the thickness of the posterior LV wall, the mass of the LV myocardium and the thickness of the interventricular septum, as well as with the serum level of the tissue inhibitor of metalloproteinases (1 (TIMP(1) and matrix metalloproteinase 3 (MMP(3) in patients with CHF LV EF. In this study, correlations between TGF-β1 and LV myocardial mass, LV myocardial mass index, E and A ratio (E/A) , volume of the left atrium, which is not consistent with the data of the observational study DIAST-CHF [19].

According to recent studies, a significant increase in TGFβ-R1 expression was found in hypertensive patients with severe LVH, and a positive correlation was found between TGFβR1 expression and cardiomyocyte hypertrophy. Two missense mutations were identified, one of which was discovered for the first time, two synonymous substitutions, and a polymorphic variant of the splicing site [22, 23, 24].

An analysis of the results of the studies performed indicates the direct involvement of TGF-β1 and its genetic structure in the processes of myocardial remodeling in heart failure, and also substantiates the need for further research in this direction.

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