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**ORIGINAL ARTICLE**

# Diagnostic and Prognostic Role of Cardiotrophin-1 in Patients with Heart Failure

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## ABSTRACT

The review is devoted to the diagnostic and prognostic role of cardiotrophin-1 (CT-1) in patients with acute and chronic heart failure (CHF). The article provides information on the main regulatory effect of CT-1 in relation to the processes of cardiovascular remodeling. We considered the prospects of monitoring the plasma concentration of CT-1for the individualization of the assessment of cardiovascular risk in patients with CHF at various stages of the cardiovascular continuum.

**MeSH words:** heart failure, cardiotrophin-1, hypertrophy, fibrosis, cytokines.

## INTRODUCTION

In evolution, the human myocardium acquired the adaptation to stress and overload using hypertrophic growth, a process that can be "useful" (physiological hypertrophy) or pathological. An important distinguishing feature of pathological hypertrophy is mismatch between the increase in the thickness of the myocardial wall and the increase in contractile function. The mechanisms responsible for this or that type of hypertrophy interact closely and constantly compete with each other. So, almost all the mechanisms leading to pathological hypertrophy are compensatory in nature and at a certain stage in the development of the cardiovascular continuum can improve cardiac activity. However, these same mechanisms can ultimately lead to fibrosis, which plays a special role in the development and progression of chronic heart failure (CHF) [1, 2]. There is an increasing number of studies indicating that the development of CHF (especially in patients with preserved ejection fraction) begins with a phase of systemic and cardiac inflammation, leading to an increase in the deposition of extracellular matrix and the accumulation of collagen in the interstitial and perivascular spaces [3, 4]. This process is associated with increased left ventricular (LV) stiffness, diastolic and systolic dysfunction, and is also associated with a higher risk of hospitalization and cardiovascular death [5, 6].

One of the proteins that regulate the physiological growth and vascularization of the myocardium is cardiotrophin 1 (CT1), which is a protein with a molecular weight of 21.5 kDa. The coding region of CT-1 is located on three exons of the human chromosome 16p11.1-16p11.2. The similarity of these amino acid compositions indicates that CT-1 is a member of the cytokine family. According to modern concepts, it belongs to the interleukin-6 (IL-6) superfamily, has pronounced promitotic and proliferative properties, the ability to induce hypertrophy and hyperplasia of cardiomyocytes both in vivo and in vitro.

It is known that IL-6 is an intercellular interaction protein (cytokine) secreted during inflammation [7]. Its secretion is regulated according to the principle of positive feedback by catecholamines, the concentration of which in the blood of patients with CHF is significantly increased due to the activation of the sympathoadrenal system. The interaction of IL-6 with transmembrane receptors promotes homodimerization of another receptor, gp130, which triggers a signal transduction cascade.

The function of CT-1 is realized in a different way, which is capable of activating gp130 without prior interaction with other receptors (which are absent in cardiomyocytes). Ultimately, intracellular signaling mechanisms are activated in myocardial cells that implement all the biological effects of CT-1 [8,9]: mitogen-activated protein kinases – MAPK, dual specificity kinases - MEK1 and MEK5, the Janus kinase system / signal transducer and activator of transcription - JAK / STAT, nuclear transcription factor - Nf-kB To date, it has been established that the antiapoptic effect of CT-1 is achieved mainly due to the activity of p38 and p42/44 subunits of MAPK, while stimulation of cell growth and hypertrophy of cardiomyocytes is carried out with the involvement of alternative mechanisms, such as JAK / STAT, NF-κB or MEK- kinase / kinase c-Jun NH2-terminal protein [10,11,12,13]. Thus, CT-1 is capable of initiating myocardial hypertrophy and hyperplasia, as well as exerting an antiapoptic effect on cardiomyocytes. The main goal of the listed physiological effects of CT-1 is a cardioprotective effect at the initial stages of CHF formation in various pathological conditions of the heart muscle. However, the expression of the gp130 ligand for CT-1 on the surface of cardiomyocytes is regulated according to the "up and

down-regulation" mechanism, the principle of which is based on the cell's ability to independently change the number of receptors on it in response to the content of biologically active substances in the blood. All this is a reflection of the potential for "switching" the direction of intracellular signaling intensification from cardioprotective effects to stimulation of excessive remodeling [14]. Based on this, all intracellular signaling mechanisms mediated by regulatory enzymes such as MAPK, MEK1 and MEK5, JAK / STAT and Nf-kB cannot be called cardioprotective without a doubt [15, 16].

When inducted the physiological hypertrophy, CT-1, both in vitro and in vivo, caused predominantly an increase in the length of cardiomyocytes. The effect of CT-1 on the myocardium is carried out through limited activation of caspase 3 and caspase 9 (not maximally pronounced). In turn, the activation of these caspases leads to an increase in the transcriptional response of Mef2-, NF-κB- and STAT3-dependent signal transmitters. It is STAT3, in contrast to STAT1, that is responsible for the anti-inflammatory effect and promotes the survival of myocardial cells [17]. The above signaling pathways are elements of a cascade triggered by cell apoptosis, but their limited activation leads to favorable remodeling.

The administration of human CT-1 in animal models made it possible to establish that CT1 is responsible for reversible physiological hypertrophy and reversible angiogenesis. When the administration of this protein is stopped, these parameters of the myocardium return to their previous state. These results suggest that CT1 promotes the secretion of angiogenic factor by cardiomyocytes [18].

As mentioned previously, a chronic increase in the level of CT-1 in the plasma of patients with cardiovascular diseases (CVD) acquires the inverse significance for the prognosis. In the studies by Cottone S. et al., it was found that in patients with hypertension, accompanied by LV hypertrophy (LVH), the level of CT-1 was higher than in the control group of healthy people [19]. At the same time, on the background of antihypertensive therapy, a decrease in the level of CT-1 was noted, which could reflect the reverse development of LVH. Therefore, monitoring CT-1 in the management of patients with hypertension allows us to assess the cardioprotective effect of the treatment used [20, 21].

Moreover, increased levels of CT-1 are also determined in patients with hypertrophic and dilated cardiomyopathies, acute myocarditis, regardless of the severity of LVH and myocardial dysfunction [22, 19, 23]. It was found that a high value of CT-1 in blood plasma is associated with the existing of LVH, regardless of concomitant comorbid pathology: hypertrophic cardiomyopathy, dilated cardiomyopathy, hypertension, aortic stenosis and mitral regurgitation [24, 19, 23]. Based on these data, it can be concluded that the concentration of CT-1 can be considered as an independent marker of myocardial hypertrophy in cohorts of patients with various CVD [24].

Under conditions of biomechanical stress caused by pressure or volume overload, the synthesis of CT-1 increases, as a result of which myocardial defense mechanisms are activated. But excessive neurohumoral activation ultimately leads to maladaptive remodeling of the LV and, accordingly, the progression of CHF [25].

The connection between CT-1 and the processes of myocardial fibrosis is also worth nothing. Prolonged systemic hypertension leads to excessive deposition of type I and type III collagen fibers in the interstitium and perivascular region of the myocardium. This is partly due to hyperactivation of the renin-angiotensin-aldosterone and sympathoadrenal systems. They initiate the synthesis of CT-1 in cardiomyocytes, which has a profibrotic effect. In turn, myocardial fibrosis is one of the main factors in the development and progression of heart failure. At the same time, diastolic dysfunction, deterioration of contractility with the formation of systolic dysfunction, the development of cardiac arrhythmias and coronary blood flow impairment are observed [26].

In vitro and in vivo, it was confirmed that CT-1 stimulates not only the differentiation of cardiac fibroblasts into myofibroblasts, which is assessed by an increase in the expression of α-smooth muscle actin α-SMA, but also the expression of mRNA of type I and III collagen [27]. It was found that the concentration of CT-1 in the myocardium and blood plasma in patients with CHF was higher ($p < 0.001$) compared with the control group, as well as the volume fraction of collagen according to endomyocardial biopsy. In addition, the highest CT-1 values in the myocardium were obtained in patients with CHF with a reduced ejection fraction (CHFrEF), which correlated with the values of myocardial fibrosis biomarkers (PICP –carboxyterminal propeptide of type I procollagen and PIIINP - N-terminal propeptide of procollagen type III).

CT-1 is involved in the development of vascular endothelial dysfunction [28]. In the endothelium, biologically active substances are formed that participate in the regulation of blood coagulation, vascular tone and the development of the vascular wall. It was found that with the development of atherosclerosis, CT-1 initiates the synthesis of monocytic chemotactic protein-1 (MCP-1) by endotheliocytes, which promotes the activation and migration of leukocytes to the inflammation focus in the vascular wall. Atherosclerosis, in turn, is one of the most important causes of hypertension and coronary heart disease (CHD), which often lead to the development of CHF. At the same time, impaired endothelial function contributes to a further decrease in EF and progression of CHF [29]. Also, CT-1 stimulates TNF-α production by peripheral circulating monocytes. In turn, TNF-α supports the maintenance of the inflammatory process in the vascular wall even in the absence of antigenic stimulation and severe microcirculation disorders [30, 31]. The process of vascular remodeling is also regulated by phosphorylation of the aforementioned 42/44 and p38 MAPK subunits [32]. The result of this chemical transformations is proliferation, hypertrophy and an increase in the production of extracellular collagen matrix, an increase in systemic vascular resistance, as well as regulation of the growth and destabilization of atheroma. Thus, endothelial dysfunction in CHF serves as a marker of a negative clinical outcome [33].

In studies by Zolk et al, it was found that CT-1 significantly suppresses myocardial contractility in direct proportion to its concentration in blood plasma in patients

with CHF [34]. Therefore, the constantly increased synthesis and release of CT-1 accelerates the development of contractile dysfunction and the progression of CHF. At the same time Talwar et al. reported that the concentration of CT-1 in plasma in healthy people is ~ 10-50 pM and increases to 30-500 pM in patients with LV systolic dysfunction [35].

In a study by Tsutamoto et. al. [25], which involved 125 patients with CHF with LVEF<45%, a negative correlation was found between the level of CT-1 and LVEF. The concentration of CT-1 in plasma and soluble gp130 increased with the severity of CHF, which is confirmed by the studies of Zolk et al [13]

Thus, this literature review reflects the biological role of CT-1 in the regulation of hypertrophic growth and the development of cardiac fibrosis, as well as the possibility of its use as a diagnostic biomarker of the early stages of CHF, monitoring the effectiveness of treatment of hypertension, CHD and CHF.

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