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Possibilities of immunological diagnostics of chronic heart failure in patients with rheumatoid arthritis

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Abstract

Cardiorheumatology is one of the most pressing fields in current medical research, with numerous unresolved issues. Systemic inflammation contributes to the progression of atherosclerosis, alterations in the morphofunctional characteristics of the myocardium, an increase in recurrent hospitalizations, and a worsened prognosis.

Methods. This review presents modern categories of immunological biomarkers, including those indicating direct myocardial injury, secondary angiogenesis, myocardial fibrosis, and general vascular risk markers, which hold significant potential for assessing the progression of chronic heart failure in the context of rheumatoid arthritis.

Results. The presented groups of markers are not currently included in clinical guidelines for the management of chronic heart failure. However, they demonstrate meaningful associations with established parameters such as natriuretic peptides, left ventricular ejection fraction, and indicators of diastolic dysfunction, thereby offering practical value in daily clinical decision-making.

Conclusion. Immunological diagnostics in evaluating cardiovascular diseases associated with comorbid conditions is an emerging and actively evolving field. This approach is particularly relevant for patients with chronic heart failure and rheumatoid arthritis, given the strong pathophysiological link between autoimmune inflammation and heart failure development. Markers such as galectin-3, pentraxin-3, transforming growth factor-beta, γ-carboxyglutamate-containing matrix protein), neopterin, and vascular endothelial growth factor may help predict early signs of CHF decompensation.

Keywords: chronic heart failure, rheumatoid arthritis, galectin-3, pentraxin-3, transforming growth factor-beta, vascular endothelial growth factor.

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Introduction

Chronic heart failure (CHF) and rheumatic diseases are among the most common chronic non-communicable conditions that lead to persistent disability, deteriorate patients' quality of life, and negatively affect prognosis. The global prevalence of CHF is estimated to be between 1–2% [1]. Among individuals aged over 65, the prevalence increases sharply, exceeding 10%. Precise estimation of CHF prevalence remains difficult due to varying inclusion criteria in different registries, significant heterogeneity in clinical presentations depending on disease stage and left ventricular ejection fraction (LVEF), and differences in patient adherence to regular follow-up for disease monitoring. According to pooled data from various registries, the global number of patients with CHF is estimated to range between 23 and 37.7 million [2]. In the Russian Federation, the average number of patients with CHF has increased from 8 to 12.3 million over the past decade [3]. This growing burden poses a significant challenge to national healthcare systems.

The increase in CHF cases is primarily driven by a high prevalence of arterial hypertension (AH), coronary heart disease (CHD), obesity, and type 2 diabetes mellitus. AH is the leading cause of CHF in 95.5% of cases, followed by CHD in 69.7% [4]. Valvular heart diseases have become less common as a cause of CHF (only 4.3%) due to the advancement of surgical treatment methods.

Rheumatic diseases — comprising over 80 nosological entities — have a well-established role in contributing to long-term disability, declining health status, and increased risk of cardiovascular complications. Numerous studies and meta-analyses confirm that rheumatic conditions significantly contribute to the development of myocardial infarction, stroke, thrombosis, and the progression of AH, CHF, and atherosclerosis [5]. Among the most frequently encountered rheumatic disorders with an autoimmune inflammatory basis is rheumatoid arthritis (RA), which is also commonly associated with cardiovascular disease. In the Russian Federation, the prevalence of RA is approximately 610 cases per 100,000 population [6]. However, the exact prevalence of CHF among RA patients is difficult to determine, as most registries and studies focus on clinically overt CHF, particularly in hospitalized patients with decompensation.

Estimates suggest that the coexistence of CHF and RA ranges from 2.6% to 11.6% in the general population. Notably, early-onset RA has been associated with an increased risk of both ischemic and non-ischemic CHF compared to individuals without RA [7]. Prospective studies indicate that patients with both CHF and RA have higher all-cause mortality than those without RA [8]. Interestingly, preserved LVEF in CHF is more frequently observed in patients with RA than in those without, possibly due to the beneficial impact of anti-inflammatory therapy on myocardial structure and function, although this remains a subject of ongoing debate [9]. According to registry data, mortality rates among CHF patients with RA are twice as high compared to CHF patients without RA [10].

Thus, the influence of RA on the course of CHF is a topic of increasing clinical and scientific relevance. Key areas of interest include early detection of CHF progression, the effects of anti-inflammatory therapy for RA in CHF patients, and the ability to predict the risk of heart failure decompensation.

Methods

A non-systematic review of domestic and international literature on the research topic was conducted using comprehensive sampling in the databases PubMed, RSCI (Russian Science Citation Index), and eLibrary. The search was performed using the following keywords and their combinations: arterial hypertension, coronary heart disease, chronic heart failure, rheumatoid arthritis, nonsteroidal anti-inflammatory drugs (NSAIDs), as well as combined queries such as chronic heart failure and rheumatoid arthritis, coronary heart disease and rheumatoid arthritis, arterial hypertension and rheumatoid arthritis, chronic heart failure and NSAIDs. The review included analysis of data from literature reviews, original research articles, and meta-analyses. In total, 65 sources were analyzed. The search depth covered an 8-year period from 2014 to 2023.

Results and discussion

The role of systemic autoimmune processes in the progression of chronic heart failure

Chronic autoimmune inflammation is a well-established factor contributing to the destabilization of cardiovascular diseases, significantly worsening both disease prognosis and overall survival. Persistently elevated levels of C-reactive protein, interleukin-1, and interleukin-6 promote endothelial dysfunction

and accelerate the progression of atherosclerosis. It has been demonstrated that patients with rheumatoid arthritis (RA) have a higher incidence of atherosclerotic processes compared to the general population [11]. The inflammation exerts direct cytotoxic effects on myocardial cells and microcirculation, thereby accelerating myocardial remodeling. As is known, the synovial membrane is the primary target of the immune process in RA. The immunological cascade characteristic of RA leads to sustained high concentrations of pro-inflammatory cytokines and mononuclear cells in the bloodstream. Cellular and interstitial changes in the myocardium associated with RA are believed to be contributors to the development of CHF.

Key pathophysiological changes identified by researchers include: myocardial cellular and interstitial remodeling, hypertrophy, enlargement of the left atrium, ventricular dilation, alterations in collagen structure, and interstitial fibrosis [12]. One of the central mechanisms in the development of CHF in RA is the overproduction of matrix metalloproteinases (MMPs), a process activated by tumor necrosis factor-alpha (TNF-α). Dysregulation of MMP activity promotes collagen synthesis and left ventricular dilatation [13].

Prolonged systemic inflammation also exerts a detrimental impact on endothelial function, arterial intima structure, and the balance of vasodilatory and vasoconstrictive mediators, significantly increasing the risk of systemic atherosclerosis progression. These changes substantially elevate the likelihood of acute cardiovascular events in this patient group [14].

Several small-scale prospective studies have shown that even in patients with RA and arterial hypertension (AH) who receive maximally tolerated doses of antihypertensive therapy, there is progressive worsening of arterial stiffness, increased intima-media thickness, and elevated peripheral vascular resistance [15]. Taken together, these pathophysiological mechanisms are expected to negatively impact disease prognosis in patients with CHF, particularly when heart failure arises due to coronary heart disease (CHD) and AH in the context of RA.

Systemic autoimmune inflammation has been shown to contribute to the development of cardiac arrhythmias in patients with CHF and RA, representing yet another destabilizing factor in the progression of CHF within this comorbid context. According to the Danish National Registry data published in 2017, the incidence of atrial fibrillation (AF) in patients with RA was 40% higher compared to the control group [16, 17]. Several studies have supported the existence of a strong link between systemic inflammation and the development of AF [18, 19]. Researchers suggest that the primary mechanisms responsible for arrhythmogenesis in these patients include the influence of circulating autoimmune complexes, which interfere with potassium and L-type calcium currents, as well as M2-muscarinic cholinergic and beta-adrenergic receptor function [20, 21].

Another critical factor exacerbating CHF in the context of systemic autoimmune disease is the presence of chronic pain syndrome. Persistent pain stimulates the production of numerous pro-inflammatory mediators, such as prostaglandins, interleukins, and tumor necrosis factor-alpha (TNF-α), which have detrimental effects on cardiovascular function. Meta-analyses have shown that chronic pain associated with rheumatic diseases significantly increases the risk of CVD in the general population. Moreover, a statistically significant association between chronic pain syndrome and increased mortality has been demonstrated [22].

Although specific studies examining the direct impact of chronic pain on CHF in patients with RA remain limited, several investigations have highlighted a significant deterioration in quality of life among patients with CHF who experience persistent pain [23].

Taken together, these comorbid pathophysiological mechanisms considerably worsen the course of CHF in patients with RA (Figure 1). This underscores the need for the identification and clinical implementation of early diagnostic markers of CHF decompensation in the setting of RA, with the aim of preventing disease progression and improving patient outcomes.

Immunological markers for the diagnosis of chronic heart failure in the presence of rheumatoid arthritis

To date, a significant number of immunomodulatory cytokines have been identified that may serve as diagnostic tools in CHF. These biomarkers reflect various stages of the inflammatory process and, depending on their properties, can provide insight not only into the presence and severity of CHF, but also into specific pathological changes occurring in the myocardium. Such markers, according to experts, may

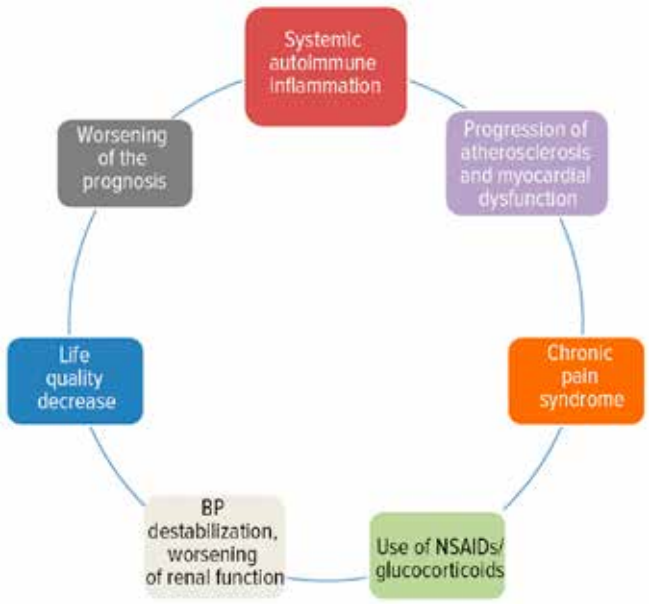

Fig. 1. Cascade of pathogenetic processes in patients with chronic heart failure and rheumatoid arthritis

pave the way for novel therapeutic strategies targeting disease progression.

Figure 2 presents several groups of biomarkers that are not currently included in major clinical guidelines but are considered promising indicators of myocardial dysfunction in CHF.

Cytoplasmic fatty acid-binding proteins (FABPs) are an emerging class of biomarkers indicative of myocardial injury. These proteins play a key role in fatty acid metabolism and regulation. Six isoforms of heart-type FABPs (Heart-FABPs) are known to be sensitive to myocardial damage. Upon myocardial injury, Heart-FABPs are rapidly released into the bloodstream, reaching peak concentrations approximately three hours after an acute myocardial infarction. This makes them useful for the early detection of myocardial injury [24]. Beyond acute coronary syndromes, preliminary data suggest that H-FABPs may also serve as predictive markers for worsening CHF, myocardial ischemia, impaired renal function, and overall prognosis in heart failure patients [25]. There are no data yet on the use of this marker in patients with RA, but given the mechanisms of this association, studying its properties in RA may be promising.

Excessive lipid peroxidation, particularly of the atherogenic low-density lipoprotein (LDL) fraction, is a critical factor in atherosclerotic plaque formation. Given the well-documented impact of systemic inflammation on atherogenesis, investigating oxidative stress markers may offer valuable insight into the studied comorbidity. Oxidized LDL are taken up by macrophages and smooth muscle cells in the vascular wall, leading to the formation of foam cells—key components of early atherosclerotic lesions. These modified lipoproteins elicit an immune response, resulting in the production of autoantibodies to oxidized LDL (oLAB) [26].

In a study by F. Besli et al., patients with CHF exhibited significantly elevated levels of oLABs compared to controls, with a strong correlation between oLAB concentrations and NT-proBNP levels [27]. Similarly, B. Nowak et al. reported increased oLAB levels in a cohort of 37 patients with RA relative to healthy individuals. Furthermore, oLAB levels were positively correlated with RA disease activity, carotid intima-media thickness, SCORE index, erythrocyte sedimentation rate (ESR), and disease duration [28].

These findings suggest not only the prognostic utility of oLABs but also reinforce the mechanistic links underlying the comorbid relationship between CHF and RA. The integration of such immunological markers into clinical practice may offer new opportunities for early risk stratification, diagnosis, and targeted intervention.

Chronic myocardial and vascular damage in the context of systemic autoimmune disease triggers secondary (pathological) angiogenesis, a phenomenon observed in various pathological conditions.

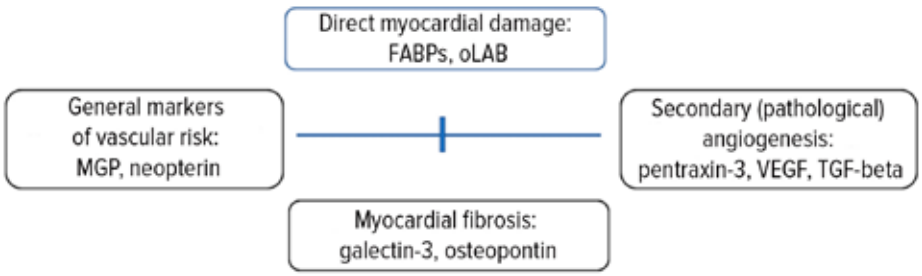

Fig. 2. Markers of systemic autoimmune inflammatory processes

Currently, secondary angiogenesis is known to develop in CHF, cancer and metastasis, RA, bronchial asthma, obesity, psoriasis, and age-related macular degeneration, among others [29]. Investigating this process in patients with CHF has become one of the most relevant areas of modern cardiology. More than 30 immunological biomarkers of pathological angiogenesis have been described. One of the most significant among them is Pentraxin-3, a protein synthesized locally at the site of inflammation. Pentraxin-3 has been identified as a potential prognostic marker of adverse outcomes in patients with CHF [30]. Its elevated levels, particularly values above 3.64 ng/mL, have been associated with a higher risk of disease progression and mortality in CHF patients [31–33].

Another important angiogenic factor is vascular endothelial growth factor (VEGF). VEGF proteins are key regulators of capillary formation and oxygen delivery in hypoxic tissues. Several studies have demonstrated that measuring VEGF levels alongside NT-proBNP enhances diagnostic accuracy in identifying CHF decompensation in patients presenting with dyspnea [34]. Meta-analyses have shown that VEGF levels are significantly elevated in patients with RA compared to healthy controls and correlate with disease activity indices [35]. According to S. Dai, VEGF may serve as a therapeutic target for evaluating the effectiveness of anti-inflammatory treatment in RA [36].

The transforming growth factor beta (TGF-ß) is another immunomodulatory cytokine of interest, known to indirectly influence multiple biological processes such as myocardial hypertrophy, fibrosis, apoptosis, cellular differentiation, and angiogenesis. TGF-ß production is induced in response to inflammatory stimuli. Small-scale cross-sectional studies have demonstrated significantly elevated TGF-β levels in CHF patients compared to healthy individuals [37]. TGF-ß is being explored as a potential target in RA therapy,

The culmination of the cascade of immune responses, chronic metabolic disturbances, and microcirculatory dysfunction is the development of myocardial fibrosis. The most extensively studied immunological biomarker associated with this process is Galectin-3, a beta-galactoside-binding lectin involved in vascular fibrosis, atherosclerosis, and myocardial remodeling. A circulating level above 17.8 ng/mL is associated with an increased risk of adverse outcomes in patients with CHF. According to experts, Galectin-3 has the highest diagnostic utility among cardiovascular biomarkers not yet included in current clinical guidelines for CHF management [38].

In patients with cardiovascular diseases and RA, multifactorial analyses have demonstrated a significant association between Galectin-3 levels and parameters such as pulse wave velocity, stroke volume, and LVEF [39–41]. In our own study of patients with concomitant CHF and RA, elevated Galectin-3 levels were found to correlate with worsening dyslipidemia, declining renal function, and increased blood pressure [42].

Another biomarker currently under discussion for its prognostic potential in CHF is osteopontin. Physiologically, osteopontin plays a regulatory role in the expression of a number of key cytokines, including interleukins-3, -10, -12, interferon-gamma, integrin avB3, and macrophage activity. It contributes to the remodeling and repair of damaged tissues. Literature sources increasingly highlight its value as a predictor of CHF progression. Studies have shown significantly elevated osteopontin levels in CHF patients compared to healthy individuals [43], with a proportional increase in both osteopontin and circulating T-lymphocytes as CHF severity increases and LVEF decreases [44]. A similar pattern has been observed in RA patients, making osteopontin a promising biomarker in individuals with coexisting CHF and RA.

In the context of examining individual pathogenetic pathways involved in the comorbid association of CHF and RA, as well as the immunological markers that characterize these processes, the search for novel biomarkers that reflect overall cardiovascular risk remains highly relevant. Among such markers, particular attention has been given to matrix Gla protein (MGP), a vitamin K–dependent protein synthesized by vascular smooth muscle cells. MGP plays a critical role in the regulation of vascular calcification, including within atherosclerotic plaques, as well as in various other tissues and organs. According to current research, elevated levels of MGP are associated with both the onset and progression of CHF, as well as cardiac arrhythmias [45]. Furthermore, experimental studies have demonstrated a relationship between MGP expression and inflammatory and degenerative processes within bone and cartilage structures in patients with osteoarthritis [46].

Irreversible myocardial changes resulting from ischemia, prolonged metabolic disturbances, or

apoptosis, which contribute to an increased risk of acute cardiovascular events, may also be predicted through the measurement of neopterin. Neopterin is a pteridine derivative produced by monocytes and macrophages in response to interferon-gamma stimulation. While currently utilized primarily in the diagnosis of viral, bacterial (notably tuberculosis), and parasitic infections [47], growing evidence supports its use as a prognostic marker in cardiovascular diseases.

Elevated neopterin concentrations have been shown to correlate with the severity and extent of atherosclerotic disease, including degree of stenosis and calcification. Increased neopterin levels have also been observed in patients with CHF of both ischemic and non-ischemic origin, with a moderate inverse correlation with LVEF ($r = –0.33$; $p = 0.017$), and a positive correlation with end-systolic left ventricular volume ($r = 0.32$; $p = 0.024$) [48]. Given its connection to both infectious and autoimmune inflammation, neopterin may serve as a promising biomarker in assessing cardiovascular risk in patients with CHF and concomitant RA.

The number of patients with CHF and RA is likely to increase, primarily due to rising life expectancy among individuals with CHD and AH. A current clinical reality is the growing population of patients with CHF with preserved or mildly reduced LVEF — a population whose true size remains uncertain. Another driver of the increased prevalence of this comorbid association is systemic autoimmune inflammation, which contributes to CHF development through a cascade of mechanisms, including cytokine-mediated myocardial and coronary artery damage, vascular stiffness, and cardiac and vascular remodeling.

Based on the analyzed data, it becomes evident that the pathogenesis of this comorbidity is not a simple linear cause-and-effect relationship but rather a complex interplay of interconnected processes. This complexity likely accounts for the wide variety of immunological markers proposed for the diagnosis and monitoring of CHF in the context of RA. The primary challenge in managing this condition lies in predicting episodes of CHF decompensation in patients with RA and developing evidence-based strategies to prevent such outcomes. We believe that priority should be given to the investigation of broad cardiovascular risk biomarkers in large-scale, long-term prospective studies, with the aim of integrating these markers into routine clinical practice.

Conclusion

Patients with CHF and RA require particular attention from both internists and cardiologists due to their markedly elevated risk of CHF decompensation. A critical feature of this association is the development of irreversible myocardial changes at pre-symptomatic stages under the influence of ongoing autoimmune inflammation. From this perspective, an urgent clinical objective is the implementation of immunological screening protocols aimed at identifying high-risk patients early and adjusting therapeutic strategies to mitigate adverse cardiovascular outcomes.

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