

## SCIENTIFIC REVIEWS AND LECTURES

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## FEATURES OF THE COURSE AND MODERN DIAGNOSIS OF CHRONIC HEART FAILURE ON THE BACKGROUND OF COMORBID ASSOCIATIONS

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The review presents current information on the course of chronic heart failure on the background of comorbid associations. Special attention is paid to the peculiarities of the course of heart failure on the background of rheumatological diseases.

The authors evaluate epidemiological indicators, as well as the most relevant studies and meta-analyses devoted to this topic. Modern methods of diagnostics of myocardial morphofunctional parameters in this group of patients are presented, in particular, the possibilities of two-dimensional spectral-tracking echocardiography are presented.

The data of actual researches concerning the use of such immunological markers as galectin-3, pentraxin-3, adiponectin and cystatin-C are presented.

**Keywords:** chronic heart failure, comorbidity, modern diagnosis of CHF, prognosis.

Chronic heart failure is one of the most common cardiovascular diseases (CVD), and belongs to the category of so-called chronic noncommunicable diseases (CVD). The prevalence of CHF continues to grow steadily, naturally prompting new questions of diagnosis and therapy tactics. Due to the active development of pharmacological approaches in the treatment of CHF, including CHF, the life expectancy of patients is increasing. In this regard, practitioners have to deal with an increasing number of cases of associations of various diseases in one patient. This phenomenon inevitably leads to difficulties in the management of such a patient, as there is a significant number of factors and relationships leading to undesirable consequences, worsening the course of both the underlying disease and concomitant, increasing the number of re-hospitalizations. It is also worth noting the impact of this phenomenon on the health care system as a whole, as the combination of several diseases in one patient leads to an increase in the cost of its treatment.

This relationship is described in the literature as comorbidity. By this term, experts mean the coexistence of two or more diseases in one patient,

pathogenetically and genetically interrelated. It is necessary to emphasize that the term multimorbidity, used as a synonym, is often found. However, multimorbidity is a combination of several chronic diseases of various origins in one patient. In this case, no causal relationship is implied. Therefore, when describing this problem, it is logical to use the term comorbidity [5].

**Comorbidity and chronic heart failure.** Among the chronic non-communicable diseases having significant relevance in this matter it is necessary to highlight the cardiovascular disease. Cardiovascular diseases (CVD), despite the enormous advances in medicine and pharmacy, remain the most common pathology throughout the world, and are the first cause of death in developed countries. The classic ending of the most common CVD is chronic heart failure, the prevalence of which in Western countries reaches from 1 to 2% in the general population, reaching 10% in people over 70 years of age [19]. The absolute number of people with CHF has doubled in the last 20 years: from 7.18 to 12.35 million people [8]. This phenomenon is due, according to experts, oddly enough, modern advances in medicine in this area. However, an increase in the life expectancy of patients with CHF does not lead to an increase in the number of cases of repeated hospitalization, an increase in the financial burden on patient households and on the health care system as a whole. According to WHO, the global cost of treatment of CVDs is about 863 billion US dollars annually. Approximately 10% of this amount is due to heart failure. Experts predict a further increase in the financial burden due to

continued urbanization, increased life expectancy and population aging [24].

Cardiovascular comorbidity in the context of heart failure is a phenomenon with a high prevalence. For patients with CHF, this phenomenon is of particular relevance. It is quite difficult to specify specific numbers of the prevalence of certain comorbid conditions against a background of insufficiency, since it depends on many different factors: the level of medical care of a particular region or country, incomes of the population, the quality of tracking patients with these conditions. It is also necessary to take into account unregistered patients with asymptomatic heart failure [14].

The most complete and objective information on this issue is provided by experts from central Europe and the USA. According to the European register EHFSII which includes 3580 patients with CHF of all functional classes with an average age of  $70 \pm 13$  years, the most common comorbid associations in CHF are atrial fibrillation (AF) - 39%, type II diabetes mellitus - 33% and chronic kidney disease (CKD) III and IV stages - 17% [18].

However, compared with the ADHERE registry (USA) in patients with heart failure, the most common associated condition is anemia - 53%, then type II diabetes - 44%, AF and chronic obstructive pulmonary disease - 31% and CKD stage III and IV - 30% [12]. The high frequency of occurrence of anemia is associated with manifestations of cardiorenal syndrome.

It has been proven that the above-described conditions are the leading causes of worsening of the course of CHF, regardless of its etiology and stage,

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which inevitably leads to an increase in the number of repeated hospitalizations and a worsening prognosis. The described data demonstrate the dominance of diabetes among these states.

According to the meta-analyses of randomized clinical trials, SOLVD, RESOLVD, BEST, ALLHAT and others showed a significantly high frequency of repeated hospitalizations with CHF decompensation and renal function compared with patients without diabetes [15]. According to DIABHYCAR, the annual mortality rate of patients with CHF on the background of diabetes is 12 times higher [14].

A special topic of active research in recent years has been the peculiarities of the course of CHF against the background of liver pathology, oncological diseases, in particular, issues of chemotherapy. For example, cardiotoxicity problems are actively discussed when using drugs of the anthracycline series [16].

According to experts, the systemic inflammatory process should be singled out among the actual mechanisms of development of CVD, in particular, CHF, as well as the causes of its decompensation. The relevance is CHF in combination with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), osteoarthritis (OA).

It has been shown that it affects the progression of heart failure. Interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- $\alpha$ ) and C - reactive protein (CRP). Patients with this association have an increased risk of developing cardiovascular events [7,20].

There are a number of specific mechanisms that significantly aggravate the course of heart failure. First of all, it is worth noting the decline in quality of life. For various numerous studies, the most informative questionnaires in this aspect are the SF-36 and Charlson questionnaires. There is a significant deterioration in the indices of physical activity, psychoemotional state, vital activity, and general health [2, 1].

**Current diagnostics of heart failure.** When analyzing the problems of diagnosing heart failure associated with various clinical conditions, the issue of timely diagnosis of CHF, as well as the identification of the morphological and functional features of the myocardium in this group of patients is relevant. Especially worth noting patients with intact of LVEF. In this category, basic diagnostic criteria do not provide a complete picture of clinical features. It is also necessary to understand that the detailed estimated specific morphofunctional parameters

can be used in models, according to the forecast for this category of patients.

Regarding echocardiography, it is worth noting two-dimensional spectral-tracking technology with the definition of global longitudinal strain. This indicator is a non-Doppler indicator, and, therefore, angle-independent, which allows increasing the objectivity of the results. In contrast to the pulse-wave mode, this technology allows you to determine the systolic longitudinal function, regional longitudinal systolic deformation of 17 segments at three levels (basal, medial and apical) with automatic formation of a map. According to experts, the value of systolic dysfunction with the definition of its depth and comparison with other morphofunctional parameters on the background of intact LV EF can be significant parameters for the formation of cardiac risk groups at the preclinical stage of disease development [22].

Absolutely absolute criterion for the diagnosis of heart failure today is the use of natriuretic peptides. To date, it has been established that an increase in these markers in the blood is associated with decompensation of CHF and a worsening prognosis for the disease. Also, the use of this marker allows for a detailed differential diagnosis [13].

Among the most common clinical associations with CHF is a link with metabolic syndrome and diabetes. In this regard, markers that regulate energy homeostasis, fibrosis and myocardial hypertrophy are of interest. These include adiponectin. It is believed that the development of diabetes mellitus type 2 and insulin resistance are associated with impaired secretion of adiponectin. The prognostic significance of adiponectin in patients with CHF is currently not well understood. However, according to some studies, it has been found that in patients with heart failure with CHD, a low level of adiponectin is associated with diastolic dysfunction [23].

Progressive deterioration of renal function is the most important prognostic factor for the adverse outcome of chronic heart failure [3, 5]. In this relationship, against the background of studying the dynamics of the natriuretic peptide, it is worth highlighting the role of cystatin C as a marker of the predictor of the development of chronic kidney disease and target organ damage [10].

The last few years have been actively discussing the mechanisms of the influence of chronic inflammation on the development, course and prognosis of heart failure. This relationship is particularly relevant for patients with heart

failure in the background of inflammatory diseases of the joints. In this aspect, it is worth highlighting such markers as galectin-3 and pentraxin-3. There is an opinion of experts about the possibility of using galectin-3 as a marker of the effectiveness of treatment of RA [16]. Observations of an increase in the level of galectin-3 in the presence of a positive antibody titer to cyclic citrulline peptide are described: 4.2  $\mu\text{g} / \text{ml}$  (3.6; 6.1) versus 3.8  $\mu\text{g} / \text{ml}$  (3.0; 4.8);  $p < 0.01$  in the control group [17]. In relation to pentaxin-3, data on the use of this protein in patients with autoimmune diseases have been published. In particular, in a meta-analysis (China) in 20 studies in patients with RA, systemic lupus erythematosus, ankylosing spondyloarthritis, and multiple sclerosis, a significant increase in pentaraxin-3 was observed compared with healthy individuals ( $p < 0.001$ ) [11]. There are no studies on the significance of this marker in patients with comorbid status in heart failure, however, given the high prevalence of the above diseases in CHF and the relevance of the subject of inflammation in CVD, this marker is likely to have significant interest in the future.

Among modern markers that are currently undergoing active research, it is worth highlighting the growth factor of differentiation (RDS-15), osteopontin, kopetin. Studies on these cytokines are local and do not have broad evidence. However, already now there is evidence that these markers have significantly greater specificity with respect to the myocardium compared to standard acute phase proteins, as well as inverse correlation with the parameters of myocardial contractility [21,25,26].

**Conclusion.** Today we can confidently assert that CHF is a pathology that needs a multidisciplinary approach from different specialists. Patients with the above clinical associated conditions should be examined not only within the framework of a clinical standard. Especially it concerns the assessment of morphofunctional parameters of the myocardium and prognosis of heart failure. In general, the problem described requires further research and development.

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