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1.3 Pathogenetic aspects of chronic heart failure treatment

The aim of the work is a literature review of published clinical studies on the effects of hyperuricemia on the course of chronic heart failure (CHF).

Results. High levels of uric acid (UA) in people with cardiovascular disease (CVD) may be the result of decreased glomerular filtration rate, renal vasoconstriction, tissue ischemia, oxidative stress, and oxidative stress and / or diuretic treatment. On the other hand, many studies have shown that elevated UA are an independent risk factor for CVD and mortality. In CHF, the synthesis of enzymes that participate in the processes of lipid peroxidation, in particular xanthine oxidase, the main source of reactive oxygen species, increases. Impaired oxidative metabolism in hyperuricemia due to increased release of reactive oxygen species is directly involved in the development of hypertrophy and myocardial fibrosis, pathological remodeling of the left ventricle and myocardial contractility, which leads to the development and progression of CHF.

Conclusions. Studies show that uric acid is associated with cardiovascular disease, and hyperuricemia is common in patients with CHF. Hyperuricemia is associated with impaired peripheral blood flow and decreased vascular dilatation, which is closely correlated with clinical status and reduced physical ability. Recent studies also suggest a close correlation between uric acid levels and myocardial diastolic function and, more importantly, uric acid is determined by a strong, independent prognostic predictor in patients with CHF. Current experimental and clinical studies have shown that inhibition of xanthine oxidase causes significant beneficial pathophysiological changes. Proof of this effect suggests that myocardial energy metabolism, endothelial dysfunction, and exercise tolerance are improved by reducing markers of oxidative stress, so reducing serum uric acid levels is a promising therapeutic target for improving the treatment of patients with CHF.

Key words: uric acid, hyperuricemia, chronic heart failure.

Introduction. Hyperuricemia (HU) is a common pathological metabolic disorder among patients with chronic heart failure (CHF) and a significant independent predictor of mortality and re-hospitalization due to worsening of the disease course [19, 20, 21, 22]. Research by Q. Sanikidze et al. 2021 demonstrated that elevated uric acid (UA) levels in patients with CHF correlate with more severe systolic and diastolic myocardial dysfunction, poorer 6-minute test scores, and worse prognosis [23].

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Results and their discussion.

UA is the final product of purine metabolism catalyzed by xanthine oxidase (XO) from hypoxanthine or xanthine [24]. The normal serum UA level is usually 420 μmol/L (6.8 mg/dL) for men and 360 μmol/L (6 mg/dL) for women. An elevated level of UA in blood serum occurs in 2–18% of the population, varying depending on age, gender and many other factors [25, 26]. A high level of UA in blood serum was determined in hypoxic conditions, for example, in obstructive lung disease [27], neonatal hypoxia [28], acute [29] or CHF. Hypoxia and impaired oxidative metabolism contribute to an increase in UA levels. Hypoxia leads to the accumulation of its precursors, hypoxanthine and xanthine, activation of xanthine dehydrogenase (XDH) and xanthan oxidase (XO) [30]. UA may increase in patients with cardiovascular disease (CVD) due to increased synthesis, decreased excretion, or a combination of the above two mechanisms [31-33]. There are several possible mechanisms of increased UA synthesis in CHF, including increased XO levels and activity, enhanced conversion of XDH to XO, or increased XO levels as a result of enhanced breakdown of adenosine triphosphate (ATP) to adenosine and hypoxanthine [33, 34, 35]. A decrease in renal perfusion also leads to an increase in the level of UA. Since the progression of CHF leads to tissue hypoxia and increased serum lactate levels, UA renal clearance is impaired because lactate competes with urate in the proximal tubules of nephrons [36].

Although the liver is the main source of UA, the endothelium also contributes to its synthesis. In the heart, XO is localized exclusively in the endothelium of capillaries [37]. Therefore, UA generated in hypoxic conditions originates from capillary endothelial cells rather than from the myocardium, and GU in CHF is a reflection of the metabolic effect of hypoxia on the microvascular system [38]. A clinical study showed that there is an inverse relationship between the concentration of UA in the blood serum and the indicators of functional tests in patients with CHF [39]. It has been established that CHF is associated with chronic inflammation, as evidenced by an increased level of circulating cytokines, their soluble receptors, and soluble adhesion molecules [40, 41]. GU correlates with the level of circulating markers of inflammation in patients with CHF [42] and free radicals originating from XO, their synthesis is associated with increased expression of adhesion molecules by leukocytes [43].

S. D. Anker et al. demonstrated that there is also a strong inverse relationship between serum SC concentration and peak peripheral blood flow velocity in patients with CHF [44]. This inverse correlation between the UA level and peripheral blood flow can be explained by the harmful effect of XO derivatives - free radicals on vascular function [44]. GU, especially in cachectic patients, in whom protein and muscle degradation leads to increased UA synthesis, correlates with increased postischemic vascular resistance [45].

To date, there are several main predictors of cardiovascular mortality in CHF - hemodynamic disorders, functional capacity, and neurometabolic imbalance, including neuroendocrine and immunological disorders [46, 47, 48]. S. D. Anker and A. J. Coats proposed a metabolic functional and hemodynamic staging system to assess prognosis in CHF [47]. Subsequently, S.D. Anker et al. suggested that UA levels in blood serum can be a metabolic marker [48]. The researchers evaluated the relationship between serum UA concentration and survival. The predictor of mortality in CHF was determined to be a UA limit of more than 565 mmol/l (9.50 mg/dL) (regardless of age, dose of diuretic, sodium, creatinine, and urea; $P = 0.0001$) [48].

The conducted studies demonstrated the role of the metabolic pathway of XO in the pathophysiology of CHF and other CVD [46, 48]. Blocking the accumulation of XO-generated radicals is a promising new therapeutic model of treatment for the prevention of the accumulation of oxygen radicals and their pathological effects on the human body. A number of studies have demonstrated the positive effects of reducing UA levels on the course of cardiovascular diseases [49, 50, 51].

In a study by N. Engberding et al. it was established that the expression and activity of XO, determined by electron spin resonance spectroscopy, significantly increases during an acute ischemic event [52]. The formation of reactive oxygen species (ROS) increased after myocardial infarction (MI), but significantly decreased after treatment with allopurinol [52]. Treatment with allopurinol significantly reduced left ventricular cavity dilatation and myocardial dysfunction after MI, assessed by echocardiography, and markedly reduced myocardial hypertrophy and interstitial fibrosis. The results of this study demonstrated a positive effect of allopurinol on the processes of remodeling of the left ventricle and the functional capacity of the myocardium, which can probably be explained, at least in part, by the suppression of myocardial XO and the reduction of ROS production [52].

Similarly, V. Mellin et al. compared the effects of allopurinol treatment on hemodynamics, function and structure of the left ventricle in rats with established CHF [53]. They found that allopurinol administration improved myocardial hemodynamics and function and prevented left ventricular remodeling. Researchers attribute this positive effect to the reduced formation of ROS and the improvement of redox mechanisms [53].

Assuming that dilated cardiomyopathy is characterized by an imbalance between the functional capacity of the left ventricle and myocardial energy consumption, T.P. Cappola et al. used intracoronary allopurinol to analyze the effects of XO inhibition on left ventricular function in nine patients with this disease [54]. The results of the study demonstrated that increasing the activity of XO can contribute to disturbances in energy metabolism in cardiomyopathy. A number of

studies [55, 56] evaluated the effects of XO inhibition with allopurinol on endothelial function and peripheral blood flow velocity - all showed improvements in peripheral vasodilation capacity and blood flow, both locally and systemically. W. Doehner et al. studied endothelium-dependent (EDVD) and endothelium-independent vasodilatation (EIVD) in 10 patients with CHF with a normal level of UA in the blood (315+42 mmol/l) and 9 patients with an elevated level of UA (535+54 mmol/l) [57]. Infusion of allopurinol (600 mg/min) improved EDVD ($p=0.05$), but did not affect EIVD in patients with GU [57].

In a double-blind cross-over study, 14 hyperuricemic (558+21 mmol/L) patients with CHF were randomly assigned to allopurinol at a dose of 300 mg/day or placebo for 1 week [58]. Treatment reduced UA levels by 120 mmol/L in all patients (mean reduction 217 + 15 mmol/L, $p=0.0001$). Compared with placebo, allopurinol improved peak blood flow velocity as determined by venous occlusion plethysmography. Endothelium-dependent flow improved by 58% ($p = 0.011$), and had a direct relationship with a decrease in UA levels [58].

In a retrospective cohort study of A.D. Struthers et al. [59] investigated whether allopurinol treatment was associated with a change in mortality or hospitalization in patients with CHF, suggesting that high urate concentrations were independently associated with mortality and a fourfold increase in the risk of death [59]. The study results demonstrated that long-term high-dose (300 mg/day) allopurinol was associated with significantly better survival than long-term low-dose allopurinol (relative risk 0.59, 95% CI 0.37-0.95). Scientists concluded that the high risk associated with long-term GU is adequately reduced only by long-term use of high doses of allopurinol [59]. This may mean that high doses of allopurinol can completely reverse the negative effects of urate and improve survival [59].

Hyperuricemia increases the risk of heart failure, and higher levels of serum uric acid are seen in patients who have worse ventricular function, functional capacity, and prognosis. Heart failure is also accompanied by an upregulation of xanthine oxidase, the enzyme that catalyzes the formation of uric acid and a purported source of reactive oxygen species. However, the available evidence does

not support the premise that either uric acid or the activation of xanthine oxidase has direct injurious effects on the heart in the clinical setting. Xanthine oxidase inhibitors (allopurinol and oxypurinol) have had little benefit and may exert detrimental effects in patients with chronic heart failure in randomized controlled trials, and the more selective and potent inhibitor febuxostat increases the risk of cardiovascular death more than allopurinol. Instead, the available evidence indicates that changes in xanthine oxidase and uric acid are biomarkers of oxidative stress (particularly in heart failure) and that xanthine oxidase may provide an important source of nitric oxide that quenches the injurious effects of reactive oxygen species. A primary determinant of the cellular redox state is nicotinamide adenine dinucleotide, whose levels drive an inverse relationship between xanthine oxidase and sirtuin-1, a nutrient deprivation sensor that exerts important antioxidant and cardioprotective effects. Interestingly, sodium-glucose cotransporter 2 inhibitors induce a state of nutrient deprivation that includes activation of sirtuin-1, suppression of xanthine oxidase, and lowering of serum uric acid. The intermediary role of sirtuin-1 in both uric acid-lowering and cardioprotection may explain why, in mediation analyses of large-scale cardiovascular trials, the effect of sodium-glucose cotransporter 2 inhibitors to decrease serum uric acid is a major predictor of the ability of these drugs to decrease serious heart failure events.

Screening for CVD in patients with elevated levels of UA and treatment of GU in patients with cardiovascular risk are discussed in detail in the "Consensus of multidisciplinary experts on the diagnosis and treatment of patients with hyperuricemia and high cardiovascular risk" [60]. According to experts, the target level of UA should be below 360 μmol/L (6 mg/dl) in patients with GU or below 300 μmol/L (5 mg/dl) in patients with GU and a high probability of cardiovascular complications (with at least two six risk factors: hypertension, dyslipidemia, diabetes, chronic kidney disease, myocardial infarction, or history of stroke) [60].

Conclusions. Studies have shown that uric acid is associated with cardiovascular disease, and hyperuricemia is common in patients with CHF. Hyperuricemia is associated with a violation of peripheral blood flow and a decrease

in the dilatation capacity of blood vessels, which is closely correlated with the clinical status and reduced physical capacity. Recent studies also suggest a strong correlation between uric acid levels and myocardial diastolic function and, more importantly, uric acid is a strong, independent prognostic predictor in patients with CHF. Modern experimental and clinical studies determine that inhibition of xanthine oxidase causes significant beneficial pathophysiological changes. Demonstration of this effect suggests that myocardial energy metabolism, endothelial dysfunction, and exercise tolerance are improved by reducing markers of oxidative stress, so reducing serum uric acid levels is a promising therapeutic target for improving the treatment of patients with CHF.