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CARDIORENAL SYNDROME: ETIOLOGY AND PATHOGENESIS

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Summary. Cardiorenal syndrome can be diagnosed in 32-90.3% of patients with heart failure. In most cases, cardiorenal syndrome of type 1 or 2 develops: in patients with chronic heart failure, cardiorenal syndrome is represented by the development of chronic kidney disease, in patients with acute heart failure - acute kidney injury. Impaired renal function has an unfavorable prognostic value: it leads to increased mortality in patients with heart failure. It is necessary to promptly diagnose the presence of cardiorenal syndrome and take its presence into account when managing patients with heart failure. Further study of ways to prevent the development and progression of kidney damage in patients with heart failure is required, which should be the focus of a multidisciplinary team.

Keywords: cardiorenal continuum, cardiorenal syndrome, chronic kidney disease, acute kidney injury, glomerular filtration rate, albuminuria, pathogenesis

Currently, the understanding of the development of cardiovascular diseases (CVD) is based on the concept of the cardiovascular, cardio-cerebral and renal continuum [1].

The cardiovascular continuum is a chain of interconnected changes in the cardiovascular system from the effects of risk factors (arterial hypertension (AH), diabetes mellitus (DM), dyslipidemia, obesity, smoking, etc.) through the gradual emergence and progression of endothelial dysfunction, atherosclerosis, left ventricular (LV) hypertrophy, coronary heart disease (CHD), myocardial infarction (MI) to the development of heart failure (HF) and death [2]. This is accompanied by brain damage from exposure to risk factors through the development of encephalopathy to stroke, cognitive impairment, dementia and death.

In parallel with these processes, in most cases, kidney pathology develops and progresses from risk factors, most of which are common to cardiovascular and renal diseases, through the appearance of albuminuria of varying severity (levels A1, A2, A3, A4), a decrease in glomerular filtration rate (GFR) until the development of end-stage renal failure (ESRD) and death [3].

Over the past 10 years, there has been increasing talk about the problem of a "double epidemic" of heart and kidney failure [4], since many patients simultaneously have manifestations of these two clinical conditions, which has led to the widespread use of the concept of "cardiorenal syndrome" [5].

Cardiorenal syndrome is the simultaneous presence in a patient of dysfunction/failure of the heart and kidneys [6]. Initially, a patient with cardiorenal syndrome may have kidney pathology, leading to the development of PN, and then cardiovascular complications and HF. Conversely, primary cardiac pathology can lead to HF, which can lead to the development of kidney dysfunction and damage and terminal renal failure [7].

The development of cardiorenal syndrome (CRS) in patients with HF involves hemodynamic disturbances, neurohumoral activation, endothelial dysfunction, atherosclerosis, inflammation, oxidative stress, embolism in the renal vessels and other mechanisms [8].

Hemodynamic mechanisms for the development of cardiorenal syndrome in HF include a decrease in cardiac output (CO), the development of venous stasis and an increase in intra-abdominal pressure (IAP). It has long been believed that the main cause of kidney damage in HF is a decrease in cardiac output (CO), which leads to a decrease in renal blood flow, hypoxia, ischemia, kidney damage and a decrease in their functional capacity [9]. However, in HF with preserved left ventricular (LV) ejection fraction (EF) and normal CO, as in CHF with reduced LVEF, acute kidney injury (AKI) and chronic kidney disease (CKD) also often develop [10]. Therefore, it is impossible to explain kidney damage in patients with HF solely by a decrease in CO, hypoperfusion, and renal ischemia.

In recent years, great importance in the development of a decrease in the functional capacity of the kidneys has been attributed to venous stagnation and an increase in central venous pressure (CVP). They lead to a decrease in filtration pressure in the glomerular capillaries and contribute to a decrease in glomerular

filtration rate (GFR) [11]. Also, an increase in central venous pressure and renal venous pressure leads to overstretching of the venules around the distal nephron, which contributes to compression of the tubules, increased pressure in the tubules and backflow of filtrate into the interstitium. Renal venous congestion can lead to interstitial hypoxia, the development of inflammation and nephron damage, deterioration of renal function, the development of proteinuria and tubular dysfunction [12].

Increased IAP is also associated with impaired renal function [13]. Even in healthy people with abdominal compression with an increase in IAP >20 mm Hg. GFR decreased significantly [14]. This can be explained by compression of the renal veins and parenchyma from the outside, which leads to a decrease in filtration pressure and GFR [15].

It has been shown that the importance of increased CVP and IAP in reducing GFR in HF exceeds that of a decrease in systemic arterial pressure (BP), a decrease in CO, and an increase in pulmonary capillary wedge pressure (PCWP) [16].

Neuroendocrine mechanisms involved in the development of CRS in HF are activation of the renin-angiotensin-aldosterone (RAAS), sympathoadrenal system (SAS), excess production of endothelin, vasopressin (ADH), etc. Activation products of all these systems lead to vasoconstriction, including h. constriction of renal vessels, and, therefore, contribute to a decrease in renal blood flow, the development of chronic hypoxia, ischemia and kidney damage with a decrease in their functional abilities [17]. In addition, vasoconstriction leads to increased cardiac afterload, which may contribute to worsening myocardial dysfunction [18].

It is known that the effect of the RAAS on the kidneys is diverse. Angiotensin II enhances sodium (Na+) reabsorption [19], which promotes water retention and the development of edema syndrome, which increases preload on the heart and aggravates its dysfunction.

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In addition, angiotensin II leads to spasm of glomerular arterioles, and the narrowing of the efferent arterioles prevails over the narrowing of the afferent arterioles, therefore, in the early stages of CHF, despite a decrease in renal blood flow, renal perfusion pressure and filtration fraction (FF) increase, which helps maintain normal GFR values [20].

On the one hand, this mechanism contributes to the maintenance of GFR. On the other hand, hyperfiltration can lead to damage to the glomeruli of the kidneys: increased permeability of the basement membrane and loss of its negative charge. In addition, hyperfiltration helps to reduce hydrostatic pressure and increase oncotic pressure in the peritubular capillaries. This leads to increased water reabsorption and edema syndrome, increased preload on the heart and aggravation of its dysfunction [21]. With the progression of CHF and a further decrease in CO, renal blood flow decreases so much that renal perfusion pressure and FF decrease, which leads to a decrease in GFR [1].

Also, angiotensin II, by increasing intraglomerular pressure, the permeability of the glomerular basement membrane and the loss of its negative charge, contributes to the development of albuminuria and proteinuria. Excessive intake of plasma proteins into the lumen of the tubules leads to increased reabsorption by the epithelial cells of the proximal tubules, accumulation of proteins in the cytoplasm of the tubular cells, which ultimately leads to swelling and destruction of lysosomes, rupture of the basement membranes of the tubules, tubular dysfunction and the entry of plasma proteins into the interstitium . This causes activation of inflammatory and vasoactive genes and the secretion of inflammatory mediators. They attract monocytes and T-lymphocytes into the interstitial space, which, in turn, leads to the activation of fibroblasts, the synthesis of the extracellular matrix and the development of interstitial fibrosis and nephrosclerosis - a morphological substrate for the development of PN [3]. Activation of fibroblasts is also promoted by vasoconstriction of peritubular vessels with the development of ischemia [6]. In addition, angiotensin

II causes hyperplasia of glomerular mesangial cells, stimulates their production of transforming growth factor b, under the influence of which the synthesis of extracellular matrix components increases, which leads to the development of glomerulosclerosis [22].

Angiotensin II enhances the synthesis and release of aldosterone [9], which promotes sodium reabsorption at the level of the distal tubules and collecting ducts and the development of edema syndrome [8]. In addition, aldosterone promotes the proliferation of connective tissue in patients with CHF, which contributes to the development of renal fibrosis and glomerulosclerosis [5].

Activation of the sympathoadrenal system (SAS) also contributes to the development of kidney dysfunction in patients with CHF [17]. Activation of α-adrenergic receptors in the basement membrane of the proximal tubules leads to increased reabsorption of sodium and water [12]. Stimulation of α1-adrenergic receptors in afferent and efferent arterioles leads to constriction of these vessels and, consequently, a decrease in renal blood flow. Stimulation of β1-adrenergic receptors in the cells of the juxtaglomerular apparatus increases the release of renin and increases the activity of the RAAS [21].

Thus, cardiorenal syndrome is a natural and integral part of the cardiorenal continuum. Perhaps it is only a small link in the cardiorenal-metabolic axis [6].

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