UDC 616.12-008.46:616.61-008.64-07-08

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CARDIORENAL SYNDROME IN PATIENTS WITH CHRONIC HEART FAILURE AS A STAGE OF THE CARDIORENAL CONTINUUM (PART I): DEFINITION, CLASSIFICATION, PATHOGENESIS, DIAGNOSIS, EPIDEMIOLOGY

Abstract

The combination of heart failure and renal failure is called cardiorenal syndrome. It is a stage of the cardiorenal continuum and, possibly, a small part of the cardiorenal-cerebral-metabolic axis. Despite the fact that the phrase "cardiorenal syndrome" and its five types have become a part of the medical lexicon, many aspects of this problem are still not clear. Cardiorenal syndrome can be diagnosed in 32–90.3% of patients with heart failure. Cardiorenal syndrome type 1 or 2 develops in most cases of heart failure: cardiorenal syndrome presents with the development of chronic kidney disease in patients with chronic heart failure and acute kidney injury in patients with acute heart failure. Impaired renal function has an unfavorable prognostic value. It leads to an increase in the mortality of patients with heart failure. It is necessary to timely diagnose the presence of cardiorenal syndrome and take it into account when managing patients with heart failure. Further researches are needed on ways to prevent the development and prevent the progression of kidney damage in patients with heart failure, to which the efforts of the multidisciplinary team should be directed. The first part of this review examines the current definition, classification, pathogenesis, epidemiology and prognosis of cardiorenal syndrome in patients with heart failure.

Key words: *cardiorenal continuum, cardiorenal syndrome, acute heart failure, chronic heart failure, chronic kidney disease, acute kidney injury, glomerular filtration rate, albuminuria, prognosis, mortality, survival, pathogenesis*

For citation: Reznik E. V., Nikitin I. G. CARDIORENAL SYNDROME IN PATIENTS WITH CHRONIC HEART FAILURE AS A STAGE OF THE CARDIORENAL CONTINUUM (PART I): DEFINITION, CLASSIFICATION, PATHOGENESIS, DIAGNOSIS, EPIDEMIOLOGY. The Russian Archives of Internal Medicine. 2019; 9(1): 5-22. [In Russian]. DOI: 10.20514/2226-6704-2019-9-1-5-22

DOI: 10.20514/2226-6704-2019-9-1-5-22

BP — blood pressure, ACE — angiotensin converting enzyme, ARC — active oxygen radicals, IAP — intra-abdominal pressure, PCWP — pulmonary capillary wedge pressure, RRT — renal replacement therapy, CAD — coronary artery disease, IL — interleukin, IM — myocardial infarction, CRS — cardiorenal syndrome, LV — left ventricle, CRCA — cardiac rhythm and conduction abnormalities, NUP — natriuretic peptides, ADHF — acute decompensated heart failure, ATN — acute tubular necrosis, ACS — acute coronary syndrome, AKI — acute kidney injury, AHF — acute heart failure, RF — renal failure, RAAS — renin-angiotensin-aldosterone system, SAS — sympathoadrenal system, CO — cardiac output, DM — diabetes mellitus, GFR — glomerular filtration rate, HF — heart failure, CRP — C-reactive protein, CVD — cardiovascular diseases, TIN — tubulointerstitial nephritis, PE — pulmonary embolism, EF — ejection fraction, TNF — tumor necrosis factor, FF — filtration fraction, CKD — chronic kidney disease, CHF — chronic heart failure, CVP — central venous pressure, UAE — urine albumin excretion

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The understanding of the development of cardiovascular disease (CVD) is currently based on the concept of the cardiovascular, cardio-cerebral and renal continuum (Figure 1) [73–75, 82].

The cardiovascular continuum is a chain of interrelated changes in the cardiovascular system from exposure to risk factors (hypertension, diabetes mellitus (DM), dyslipidemia, obesity, smoking, etc.) through the gradual emergence and progression of endothelial dysfunction, atherosclerosis, left ventricular (LV) hypertrophy, coronary artery disease (CAD), myocardial infarction (MI) to the development of heart failure (HF) and fatal outcome [3]. This is accompanied by brain damage from exposure to risk factors through the development of encephalopathy to stroke, cognitive impairment, dementia and fatal outcome.

Concurrently with these processes, in most cases, kidney pathology develops and progresses from risk factors, most of which are common for cardiovascular and renal diseases, through the appearance of albuminuria of varying severity (A1, A2, A3, A4 levels), a decrease in glomerular filtration rate (GFR) to the development of end-stage renal failure (RF) and fatal outcome [35].

Over the past 10 years, there has been more discussion on the issue of the "double epidemic" of heart and kidney failure [141], because many patients have both manifestations of these two clinical conditions, which has led to the ever-growing use of the concept of "cardiorenal syndrome" [4, 19, 23, 28].

Definition of CRS

Cardiorenal syndrome is the simultaneous presence in the patient of cardiac and renal dysfunction/failure [43, 46, 87, 160]. Initially, a patient with cardiorenal syndrome may have kidney pathology, leading to the development of RF, and then cardiovascular complications and HF. Conversely, primary heart disease can lead to HF, which can lead to the development of dysfunction and damage to the kidneys and end-stage RF [23].

Classification of CRS

There are 5 types of cardiorenal syndrome (Table 1) [144, 145, 147, 149, 150].

Type 1 — acute cardiorenal syndrome — is the development of acute kidney injury (AKI) in acute

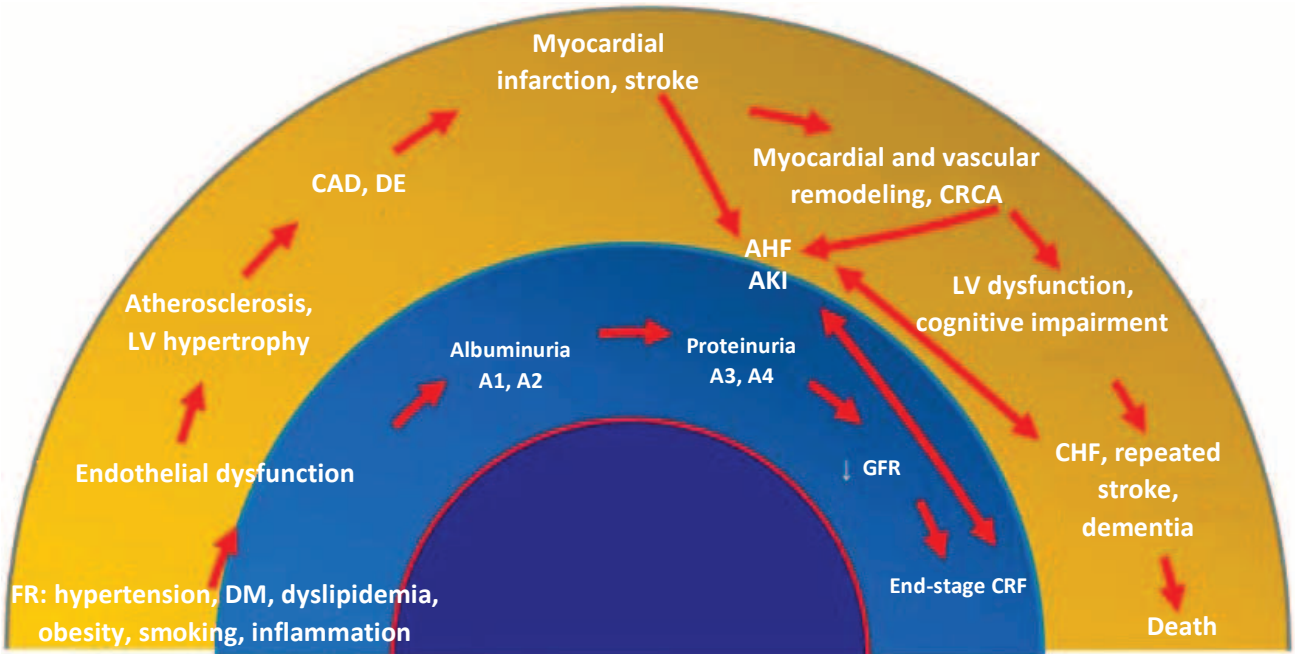

Figure 1. Cardiovascular, cardio-cerebral and renal continuum, with changes according to [Dzau et al. Circulation. 2006;114:2850–2870]. FR — risk factors, LV — left ventricle, DM — diabetes mellitus, CAD — coronary artery disease, DE — dyscirculatory encephalopathy. GFR — glomerular filtration rate, AKI — acute kidney injury, CRF — chronic renal failure, AHF — acute heart failure, CHF — chronic heart failure, CRCA — cardiac rhythm and conduction abnormalities

Figure 1. *Cardiovascular, cardio-cerebral and renal continuum, with changes according to [Dzau et al. Circulation. 2006; 114: 2850–2870].*

Table 1. *Classification of cardiorenal syndrome [146, 147]*

Type	Title	Clinical situations
1	Acute cardiorenal syndrome	Acute kidney injury in acute coronary syndrome, acute heart failure, decompensation of chronic heart failure, pulmonary embolism, after coronary angiography, cardiac surgery
2	Chronic cardiorenal syndrome	Chronic kidney disease in chronic heart failure due to coronary heart disease, hypertension, cardiomyopathies, valvular heart diseases and other
3	Acute renocardiac syndrome	Hypertension, acute coronary syndrome, acute heart failure, cardiac rhythm and conductivity abnormalities in acute kidney injury
4	Chronic renocardiac syndrome	Cardiovascular diseases (hypertension, left ventricular hypertrophy, cardiac calcification, valvular heart disease, myocardial infarction) in chronic kidney disease
5	Secondary cardiorenal syndrome	Systemic diseases with lesions of the heart and kidneys

cardiovascular conditions: acute coronary syndrome (ACS), pulmonary embolism (PE), acute heart failure (AHF), and decompensation of chronic HF (ADHF) [27, 35, 95, 97, 148].

Type 2 — chronic cardiorenal syndrome — is the development of chronic kidney disease (CKD) in chronic HF (CHF) [100].

Type 3 — acute renocardiac syndrome — is the development of acute cardiovascular pathology (hypertension, ACS, AHF, cardiac rhythm and conductivity abnormalities (CRCA)) secondary to acute pathology of the kidneys (renal ischemia, acute glomerulonephritis, etc.) [56].

Type 4 — chronic renocardiac syndrome — is the development of LV myocardial hypertrophy, calcification of heart structures, cardiovascular events, LV systolic and diastolic dysfunction in patients with CKD [94].

Type 5 — is secondary cardiorenal syndrome, which develops in systemic diseases such as diabetes mellitus (DM), rheumatic diseases (systemic vasculitis, systemic lupus erythematosus, systemic scleroderma, etc.), amyloidosis, sepsis, which simultaneously affect both the heart and kidneys, leading to the development of their dysfunction [165]. Based on this classification, kidney damage in most patients with HF is cardiorenal syndrome of type 1 or 2 [14, 15].

Pathogenesis of cardiorenal syndrome in patients with HF

Hemodynamic disorders, neurohumoral activation, endothelial dysfunction, atherosclerosis, inflammation, oxidative stress, kidney embolism and other mechanisms are involved in the development of cardiorenal syndrome (CRS) in patients with HF (Figure 2) [1, 16, 22, 24, 45, 62, 70, 163].

Hemodynamic mechanisms of CRS pathogenesis

Hemodynamic mechanisms for the development of cardiorenal syndrome in HF include a decrease in cardiac output (CO), the development of venous stagnation and increased intra-abdominal pressure (IAP). For a long time it was believed that the main cause of kidney injury in HF is decreased cardiac output (CO), which leads to a decrease in renal blood flow, hypoxia, ischemia, kidney injury and their reduced functional ability [48, 98]. 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) often develop [38, 134]. Hence, a decrease in CO, hypoperfusion and ischemia of the kidneys alone may not explain kidney injury in patients with HF.

Great importance in the decline of kidney performance in recent years is given to venous stagnation and an increase in central venous pressure (CVP). These lead to a decrease in the filtration pressure in the capillaries of the glomeruli and contribute to a decrease in the glomerular filtration rate (GFR) [105, 110]. Also, an increase in CVP and renal venous pressure leads to an overgrowth of the venules around the distal nephron, which contributes to the compression of the tubules, increased pressure in the tubules and reverse flow of filtrate into the interstitial. Renal venous congestion can lead to interstitial hypoxia, inflammation and nephron damage, deterioration of kidney function, proteinuria and tubular dysfunction [8, 130].

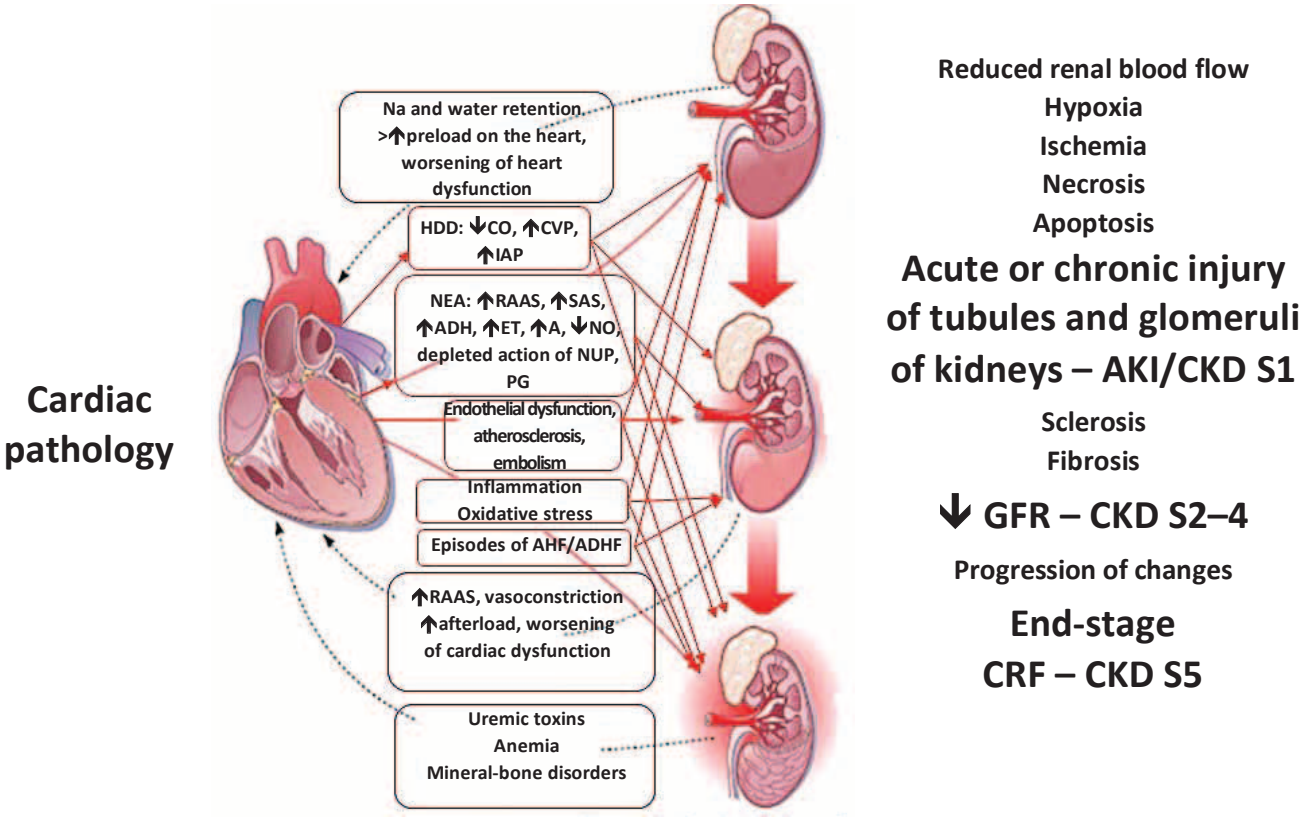

Figure 2. Cardiorenal syndrome pathogenesis, with changes according to [Ronco, C., Haapio, M., House, A.A. et al., *Cardiorenal syndrome.* //J Am Coll Cardiol, 2008. Vol. 52 (19): P. 1527–39]. A — adenosine, ADH — antidiuretic hormone, IAP — intra-abdominal pressure, HDD — hemodynamic disorders, NUP — natriuretic peptides, NEA — neuroendocrine activation, ADHF — acute decompensation of chronic heart failure, AKI — acute kidney injury, AHF — acute heart failure, PG — prostaglandins, RAAS — renin-angiotensin-aldosterone system, SAS — sympathoadrenal system, CO — cardiac output, GFR — glomerular filtration rate, CVP — central venous pressure, CKD — chronic kidney disease, CRF — chronic renal failure, ET — endothelium

Figure 2. *Pathogenesis of cardiorenal syndrome, with changes according to [Ronco, C., Haapio, M., House, A.A. et al., Cardiorenal syndrome. // J Am Coll Cardiol, 2008. Vol. 52 (19): P. 1527–39]*

Increased IAP is also associated with impaired renal function [128, 131]. Even healthy individuals had significantly reduced GFR, secondary to abdominal compression with increased IAP >20 mm Hg [135]. This can be explained by the compression of renal veins and parenchyma outside, which leads to a decrease in filtration pressure and GFR [135]. It was shown that the elevated CVP and IAP contribution to reducing GFR in HF is greater than that of the reduction of systemic blood pressure (BP), reduction of CO and increase in pulmonary capillary wedge pressure (PCWP) [110].

Neuroendocrine mechanisms of CRS pathogenesis

Neuroendocrine mechanisms involved in CRS development in HF are activation of renin-angiotensin-aldosterone (RAAS), sympathoadrenal system (SAS), excess production of endothelin, vasopressin (ADH), etc. Products of activation of all these systems lead to vasoconstriction, including narrowing of renal vessels, and, consequently, contribute to the reduction of renal blood flow, the development of chronic hypoxia, ischemia and kidney damage with a decrease in their functional abilities [156, 158]. In addition, vasoconstriction leads to an increase in afterload, which can contribute to the worsening of myocardial dysfunction [116].

The role of renin–angiotensin–aldosterone system in CRS pathogenesis

It is known that the effect of RAAS on the kidneys is diverse. Angiotensin II increases sodium reabsorption (Na^+) [34, 84, 116], which contributes to water retention and the development of edema, which increases preload on the heart and exacerbates its dysfunction.

In addition, angiotensin II leads to a spasm of the glomerular arterioles, wherein the narrowing of efferent arterioles prevails over the narrowing of afferent ones (Figure 3). Therefore, in the early stages of CHF, despite the decrease in renal blood flow, renal perfusion pressure and filtration fraction (FF) increase, which contributes to the preservation of normal values of GFR [116, 158].

On the one hand, this mechanism contributes to the maintenance of GFR. On the other hand, hyperfiltration can lead to damage to renal glomeruli: increased permeability of the basal membrane and loss of its negative charge. In addition, hyperfiltration helps to reduce hydrostatic pressure and to increase oncotic pressure in the peritubular capillaries. This leads to increased reabsorption of water and edematous syndrome, increased preload on the heart and aggravation of its dysfunction [116]. With the progression of CHF and further decrease in CO, renal blood flow decreases so much that renal perfusion pressure and FF fall, which leads to a decrease in GFR [14, 25, 37, 92, 118].

Angiotensin II also contributes to the development of albuminuria and proteinuria by increasing the intraglomerular pressure, the permeability of the basal membrane of the glomeruli and the loss of its negative charge. Excessive flow of plasma proteins into the lumen of the tubules leads to an increase in their reabsorption by epithelial cells of the proximal tubules, the accumulation of proteins in the cytoplasm of tubular cells, which ultimately leads to swelling and destruction of lysosomes, rupture of the basal membranes of the tubules, tubular dysfunction and the flow of plasma proteins in the interstitial. This causes activation of inflammatory and vasoactive genes, secretion of inflammatory mediators. They attract monocytes and T-lymphocytes to the interstitial space, which in turn leads to the activation of fibroblasts, synthesis of extracellular matrix and the development of interstitial fibrosis and nephrosclerosis — morphological substrate for the development of RF [6]. 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, which increases the synthesis of extracellular matrix components, which leads to the development of glomerulosclerosis [103, 119].

Angiotensin II enhances the synthesis and release of aldosterone [116, 158], which promotes sodium reabsorption at the level of distal tubules and collecting tubes and the development of edematous

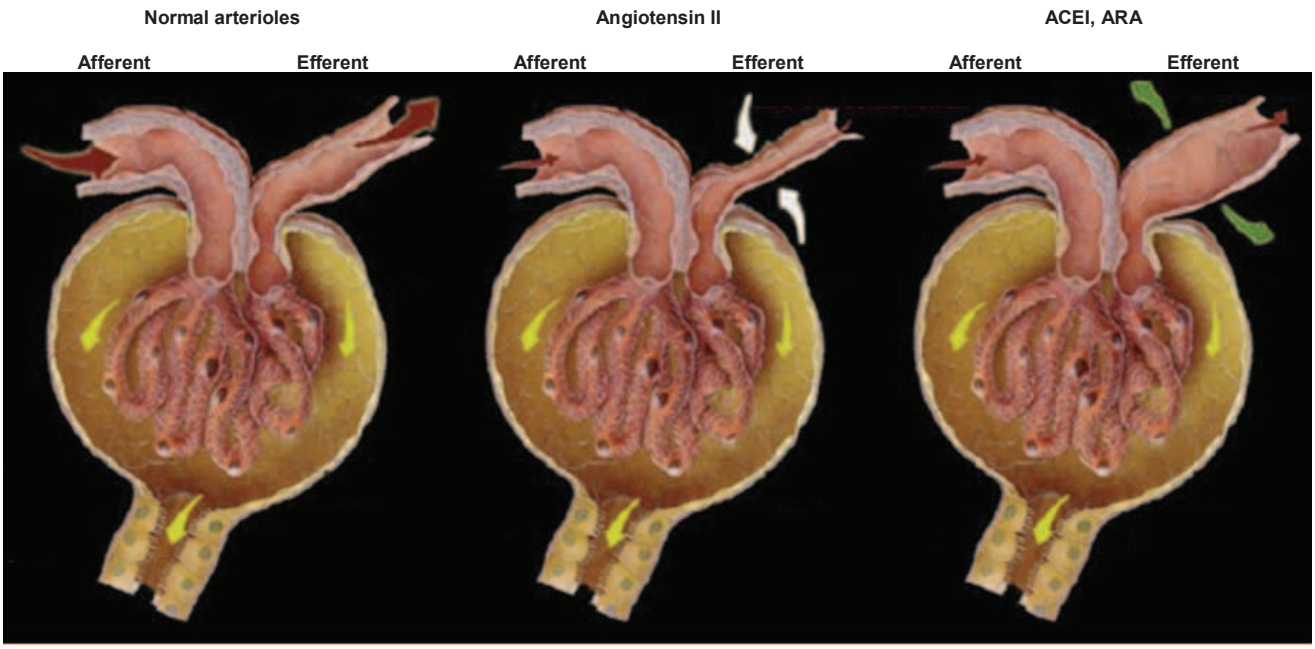

Figure 3. Effect of ATII on the glomerulus

Figure 3. *Effect of angiotensin II on the glomerulus. APF – angiotensin-converting enzyme, ARA – angiotensin receptor antagonists*

syndrome [25, 70]. In addition, aldosterone promotes connective tissue growth in patients with CHF, which contributes to the development of renal fibrosis and glomerulosclerosis [143].

The role of sympathoadrenal system in CRS pathogenesis

Activation of the sympathoadrenal system (SAS) also contributes to the development of renal dysfunction in patients with CHF [50]. Activation of α-adrenoreceptors in the basal membrane of the proximal tubules leads to an increase in sodium and water reabsorption [25]. Stimulation of α_1-adrenoreceptors in afferent and efferent arterioles leads to a narrowing of these vessels and, consequently, a decrease in renal blood flow. Stimulation of β_1-adrenoreceptors in the cells of the juxtaglomerular apparatus increases the release of renin and increases the activity of RAAS [70, 116].

Other aspects of neuroendocrine activation in the genesis of kidney damage in CHF

Antidiuretic hormone (ADH, vasopressin, arginine-vasopressin), endothelins and adenosine, the concentration of which increases with CHF, lead to vasoconstriction, and, consequently, to a decrease in renal blood flow, as well as an increase in water reabsorption, an increase in preload on the heart and venous stagnation [34, 116, 164, 165]. This contributes to the development of damage to the glomeruli and renal interstitium [36, 41], and to reduced GFR [25, 81, 85, 110, 168].

That is, it seems that compensatory neurohumoral mechanisms are not sufficiently adaptive in the long term. Vasoconstriction leads to the development of ischemia, damage to kidney structures. Retention of sodium and water by the kidneys, mediated by neurohumoral activation, leads to the progression of cardiac dysfunction, and this, in turn, contributes to more pronounced renal dysfunction. The vicious circle closes leading to the progression of CHF and the development of kidney damage [43].

The adverse effect of neurohumoral activation products in the early stages of CHF is prevented by a number of nephroprotective substances. These include endogenous vasodilating factors: natriuretic peptides (NUP), prostaglandins E2 and I2, nitric oxide [1, 24, 25, 37, 92, 116, 118, 156-158].

Natriuretic peptides: atrial (aNUP, ANP), brain (bNUP, BNP), C-natriuretic peptide (CNP) and urodilatin — dilate afferent and narrow efferent arterioles, increasing renal blood flow and GFR [13, 164, 165]. Also NUP inhibit sodium and water reabsorption, reduce the secretion of renin and aldosterone [116]. In the initial stages of CHF, this contributes to the preservation of kidney function, but then, despite NUP production, the phenomenon of escaping from its action develops. Resistance to NUP may be due to a decrease in sodium flow into the collecting tubes due to a drop in GFR or an increase in proximal sodium reabsorption [116, 158]. In addition, resistance to NUP may be associated with its destruction by the proximal endopeptidase, including neprilysin.

Prostaglandins E2 and I2, the production of which increases in a compensatory manner in CHF in response to an increase in the plasma concentration of vasoconstrictors, have a vasodilating effect, increase renal blood flow and natriuresis [25, 164, 165, 167].

Nitric oxide (NO, endothelium relaxant factor) is an even stronger vasodilator than prostaglandins E2 and I2. NO plays an important role in the regulation of the volume of extracellular fluid by the kidneys through vasodilation, natriuresis and desensitization of the tubulointerstitial feedback mechanism. It is shown that in patients with CHF, the activity of NO-synthase may decrease, which leads to a decrease in the production of NO [164, 165]. The dysregulation of NO is considered a major factor of endothelial dysfunction in patients with HF. Keilstein et al. have shown that there was a relationship between decreased renal perfusion, impaired NO-mediated endothelial vasodilation and a high concentration of endogenous NO-synthase inhibitor — asymmetric dimethylarginine in patients with CHF [35]. An increase in the activity of NADPH oxidase under the action of angiotensin II leads to NO inactivation. This is another potential mechanism of endothelial dysfunction in HF [42]. In addition, an increase in tumor necrosis factor (TNF) in CHF and CKD can lead to a decrease in the activity of NO-synthetase and an increase in the rate of endothelial cell apoptosis [87].

Over time, the nephroprotective effect of NUP, prostaglandins and NO is depleted, which contributes to the progression of renal hemodynamic disorders and reduced functional state of the kidneys [25, 37, 92, 118].

Oxidative stress, inflammation, apoptosis

Along with hemodynamic and neuroendocrine mechanisms, the main links involved in the development of kidney damage during HF are oxidative stress, activation of the inflammatory system and apoptosis (Figure 2) [46, 87, 88]. The development of oxidative stress can contribute to the activation of RAAS, as angiotensin II activates NADPH oxidase, which leads to the formation of active oxygen radicals (ARC) [46]. Also, according to experimental studies, increased production of ARC can contribute to the activation of SAS [33].

Adverse effects of oxidative stress are associated with damage to cardiomyocytes, endotheliocytes and renal tubular cells [127, 172]. In addition, ARCs lead to the proliferation of cells of intrarenal blood vessels and, consequently, the progression of renal blood supply disorders, and also launch a proapoptotic cascade in the cells of the proximal tubules [39, 40, 46]. Oxidative damage to the tubules and interstitial inhibit feedback mechanisms involved in the secretion of renin [46]. This may contribute to increased RAAS activity and its adverse effects on the kidneys. In addition, ARCs under oxidative stress in rats *in vivo* and *in vitro* increase the activity of pre-ganglion sympathetic neurons and, consequently, contribute to the increase of SAS activity [112, 161]. That is, oxidative stress can contribute to altered functional state of the kidneys, both directly and by activating neurohumoral systems [46].

In addition to oxidative stress, inflammation leads to kidney damage during HF [46, 62, 173, 174]. In an environment of mechanical overload and ischemia, cardiomyocytes are able to produce a large number of cytokines and provide an immune response [57]. In addition, venous stagnation increases the absorption of toxins in the intestine, increasing the inflammatory response [58]. Patients with CHF were found to have elevated levels of such markers of inflammation as C-reactive protein (CRP), interleukin-1 (IL-1), IL-1β, IL-6, IL-18, cell adhesion molecules, tumor necrosis factor alpha (TNF-α) and its soluble receptors in plasma and myocardium, as well as the relationship of these markers with the severity and progression of the disease [47, 62, 170]. Elevated levels of proinflammatory cytokines are associated with the activation of apoptosis, which is observed not only in cardiomyocytes, but also in smooth muscle cells of the vascular wall, renal tubular cells and glomeruli [8].

ARCs also lead to the activation of the inflammation system. They contribute to the production of pro-inflammatory cytokines, attraction and activation of leukocytes [45, 46].

In addition, the products of neurohumoral activation contribute to the development of inflammation. Angiotensin II increases tissue level of activated nuclear factor kappa B (NF-κB), induces expression of TNF-α, IL-6, chemoattractant protein of monocytes (MSR-1) [46, 154]. SAS can also lead to the activation of the inflammation system through norepinephrine-mediated production of cytokines in the liver and heart and neuropeptide Y [45, 46], a high level of which is found in patients with CHF. It is involved in long-term vasoconstriction, acts as a factor of vascular proliferation, can lead to increased hypoxia and activation of inflammation [46, 129].

Oxidative stress and inflammation can contribute to structural damage and fibrosis in the kidneys, although direct evidence is currently insufficient [62, 77, 111, 114]. Further research is required to obtain said evidence [46].

Anemia

Anemia can develop in CHF due to inhibition of erythropoiesis (due to relative or absolute deficiency of erythropoietin) and due to increased content of hepatic peptide hepcidin, which reduces iron absorption in the intestine and reduces the release of iron from hepatocytes and macrophages [87, 175]. Anemia contributes to the development of chronic hypoxia, ischemia and damage to the structures of the heart and kidneys [104]. Further studies are needed to prove the importance of anemia in the pathogenesis of kidney damage in CHF.

Other possible pathogenetic mechanisms of kidney damage in HF

Episodes of acute decompensation of HF are also considered a factor that predisposes to the progression of HF and kidney damage [62]. The frequency of CHF decompensation is independently related to the development of CKD [166]. This is due to the frequent development of AKI in ADHF, which may not result in complete recovery of kidney structure and function and may therefore contribute to the development and subsequent progression of CKD [55, 62].

Another pathogenetic link involved in the development of kidney damage in HF can be atherosclerosis. On the one hand, kidney disease and reduced functional ability are known risk factors for atherosclerosis. On the other hand, atherosclerosis can lead to impaired blood supply, damage and dysfunction of the kidneys and in some cases to ischemic kidney disease. In this regard, atherosclerosis and kidney disease can mutually reinforce each other and contribute to the progression of cardiorenal syndrome [87].

In some studies, dyslipidemia, impaired coagulation and vascular-platelet hemostasis are also listed among the mechanisms of renal dysfunction in CHF [71, 124].

Forms of cardiorenal syndrome type 1 in patients with HF

CRS of type 1, which is the development of AKI with initially normal renal function or with pre-existing CKD, may be prerenal, renal and less often — postrenal in nature [18].

Prerenal AKI in CRS of type 1

The following conditions can lead to the development of prerenal AKI in HF.

1) Decrease in CO (with ADHF, AHF of different etiology, including cardiogenic shock, arrhythmias, conduction disorders, PE, cardiac tamponade, etc.).
2) Hypovolemia (excessive loss of extracellular fluid with a decrease in intravascular volume due to bleeding, vomiting, diarrhea, as well as burns and forced diuresis). Randomized DOSE study (n=308, ADHF) demonstrated that the administration of high (2.5 times higher than maintenance dose) compared with low (equal to maintenance) doses of loop diuretics led to a more rapid decrease in stagnation, but a greater reduction in GFR [79]. In this regard, it is recommended to administer diuretics in the minimum effective doses that do not cause excessive reduction of intravascular volume to avoid hypotension and AKI [7].
3) Peripheral vasodilation (hypoxemia, sepsis, etc.) with a decrease in systemic BP.
4) Spasm of renal vessels in shock, hypercalcemia, inhibition of prostaglandin synthesis (including during treatment with non-steroidal anti-inflammatory drugs — NSAIDs).
5) Administration of angiotensin-converting enzyme inhibitors (ACE) / sartans [18]. Under the influence of these drugs, afferent glomerular arterioles are mainly dilated (Figure 3), which may contribute to a decrease in renal perfusion pressure and FF [70, 120, 133] and, consequently, a decrease in GFR [29, 70]. In most patients with CHF, despite dilatation of efferent arterioles, GFR with ACE inhibitors / sartans remains stable due to increased renal blood flow resulting from dilation of arterioles [70, 120]. The development of prerenal AKI under the influence of ACE inhibitors / sartans in most cases is associated with a drop in systemic BP. To prevent this, it is necessary to start treatment with low doses, administer the first dose at night, slowly perform dose titration, avoid simultaneous administration of NSAIDs [120].

In most cases, prerenal AKI is accompanied by hypotension (SBP <90 mm Hg). Without adequate treatment, hypoxic nephron damage develops, which leads to progressive tubular dysfunction and, in some cases, ischemic acute tubular necrosis.

Renal AKI in CRS of type 1

The main types of renal AKI in HF are: 1) acute tubular necrosis (ATN); 2) acute tubulointerstitial nephritis (TIN); 3) occlusion of renal vessels [18].

Acute tubular necrosis (ATN, tubular necrosis) may be ischemic and toxic. As mentioned above, ischemic ATN can develop without adequate treatment of prerenal AKI (in this case, AKI will have a combined nature: prerenal and renal). Toxic tubular necrosis may occur as a result of the influence

of drugs (including massive doses of diuretics, contrast agents, anesthetics, etc.), exo- and endogenous toxins (including organic pigments myoglobin and hemoglobin). After cessation of exposure and excretion of the nephrotoxic agent, renal function is usually restored. Intratubular deposits in acute urate nephropathy, multiple myeloma, severe hypercalcemia and primary hyperoxaluria may be regarded as more rare causes of ATN [18].
The causes of acute TIN can be drugs, infectious diseases, uric acid salts, etc. [18, 146].
Occlusion of renal vessels may occur in thrombosis of the renal veins, thrombosis or embolism of the renal arteries [18]. Renal thrombosis with the development of AKI is often observed in disseminated intravascular coagulation. Atheroembolism (embolism with small fragments of atherosclerotic plaques) of the renal arteries develops quite rarely. It can be spontaneous, provoked by injuries and interventions such as angiography, angioplasty, intra-aortic balloon counterpulsation, vascular surgery and thrombolysis. Obstruction of small renal arteries leads to the development of ischemia, inflammatory reaction around emboli, hypertension and AKI. More than half of the inflammatory infiltrate cells are eosinophils, because cholesterol crystals of atherosclerotic plaque fragments have a direct chemotactic effect on them. The development of acute TIN exacerbates renal dysfunction in atheroembolism of the renal arteries. This condition is often undetected. The possible atheroembolism of the renal arteries is evidenced by the presence of systemic atherosclerosis, marble pattern of the skin, embolism with cholesterol crystals of the retinal arterioles (bright yellow Hollenhorst plaques), petechiae and ischemia of the toes with a preserved pulse on the rear artery of the foot. Laboratory examination often reveals eosinophilia of blood and eosinophiluria, hypercomplementemia, elevated levels of lactate dehydrogenase, erythrocyte sedimentation rate (ESR), leukocytosis. The diagnosis is confirmed by a kidney biopsy, in which cholesterol crystals are found in arterioles. Changes in the kidneys caused by atheroembolism of the renal arteries are often irreversible [23].

Postrenal AKI in CRS of type 1
The causes of postrenal AKI in HF may be acquired obstructive nephropathy due to nephrolithiasis, acute uric nephropathy or other causes that violate the passage of urine through the ureters; tumors (prostate, uterus, large intestine, etc.); endometriosis; retroperitoneal fibrosis (posttraumatic, secondary to aortic aneurysm, iatrogenic, idiopathic), etc. [18]. Diagnosis is based mainly on the results of imaging methods of examination.

Diagnosis of cardiorenal syndrome type 1 in patients with HF

For the diagnosis of CRS type 1 in patients with AHF/ADHF, it is advisable to use modern recommendations for the diagnosis of AKI, according to which AKI should be diagnosed in the presence of at least 1 of 3 criteria: 1) increase in creatinine by >26.5 μmol/l for 48 hours; 2) increase in creatinine by 1.5 times for 7 days; 3) decreased diuresis <0.5 ml/kg/h for 6 hours [9]. The approach to diagnosis of AKI severity is presented in Table 2.

Table 2. *The severity of acute kidney injury*

Stage	Serum creatinine	Diuresis, ml/kg/h
1	1.5–1.9 times increasing from the baseline OR 0.3 mg/dL (26.5 μmol/L) increase	<0.5 during >6 <12 hours
2	2.0–2.9 times increasing from the baseline	<0.5 during >12 <24 hours
3	3.0 times increasing from the baseline OR 4.0 mg/dL (353.6 μmol/L) increase OR Initiation of renal replacement therapy OR In patients younger than 18 years old, a decrease in glomerular filtration rate <35 ml/min/1.73 m^2	<0.3 during 24 hours OR Anuria during 12 hours

Biomarkers for the diagnosis of early stages of AKI may be cystatin C, KIM-1, L-FABR-liver type of fatty acid binding protein, IL-18-interleukin 18, NGAL [146]. Said biomarkers are being actively studied and may soon be introduced into the standards for the diagnosis of AKI, including in HF. In ultrasound examination in AKI, kidneys are usually of normal or enlarged size with preserved cortical-medullary ratio, and in color Doppler there is increased resistive index (RI) >0.8 cm/s [86, 96, 146].

Diagnosis of cardiorenal syndrome type 2 in patients with HF

For the diagnosis of cardiorenal syndrome type 2 in patients with CHF, it is advisable to use modern recommendations for the diagnosis and treatment of CKD [21]. CKD should be diagnosed in all patients with 1 or more markers of kidney damage for 3 months or more, regardless of glomerular filtration rate (GFR) and/or in patients with GFR values <60 ml/min/1.73 m^2 for 3 months or more, regardless of the presence of markers of kidney damage. The "3 months or more" interval during which decrease in GFR or markers of kidney damage should be detected is due to the fact that the acute variants of renal dysfunction during this period result in recovery, or lead to the emergence of CKD symptoms. The use of GFR <60 ml/min/1.73 m^2 as a diagnostic criterion is due to the fact that such a decrease in GFR corresponds to a loss of 50% of the mass of active nephrons, which is clinically significant.

For calculation of GFR, the latest and most accurate CKD-EPI formula should be used. Calculations can be made using the on-line calculator of the National Kidney Foundation, available on the website http://www.kidney.org/professionals/kdoqi/gfr_calculator.

In accordance with modern recommendations on CKD, the degree of decline in GFR is divided into 5 stages of kidney damage (Table 3) [9, 21].

Markers of kidney damage that should be considered in the diagnosis of CKD include:

1. Albuminuria/proteinuria (urine albumin excretion (UAE) ≥10 mg/24 h, or the urine albumin to creatinine ratio ≥10 mg/g (≥1 mg/mmol)
2. Changes in urinary sediment: erythrocyturia (hematuria), cylindruria, leukocyturia (pyuria)
3. Tubular dysfunction: glucosuria in the absence of hyperglycemia, phosphaturia, etc.
4. Histological changes in kidney biopsy (specific signs of kidney disease, nephrosclerosis)
5. Structural changes in imaging methods (renal developmental abnormalities, cysts, hydronephrosis, changes in kidney size, thinning of the cortical layer, the decrease in cortical-medullary ratio, increased echogenicity of the parenchyma)
6. History of kidney transplantation [21].

For the diagnosis of CKD a marker of kidney injury must be identified at least 2 times with an interval of 3 months or more. Histological changes in the kidneys or irreversible structural changes in imaging methods can be detected once [21].

Quantification of UAE (albuminuria) should be made in daily urine or in the first morning portion

Table 3. *Stages of CKD [9, 21]*

Stage	Description	Glomerular filtration rate, ml/min/1.73 m^2
C1	Kidney damage with normal or increased GFR	90–120
C2	Kidney damage with mild decreased GFR	60–89
C3a	Moderately decreased GFR	45–59
C3b	Moderately decreased GFR, with or without other evidence of kidney damage	30–44
C4	Severe decrease of GFR, with or without other evidence of kidney damage	15–29
C5	Terminal chronic renal failure, renal replacement therapy is necessary (dyalisis/transplantation)	<15

Note: GFR — glomerular filtration rate

of urine to determine albumin/creatinine ratio. In accordance with modern recommendations, there are 5 levels of albuminuria [20]:

A0 — optimal albuminuria: <10 mg/day, or mg/g creatinine;

A1 — increased albuminuria, formerly known as high normal, albuminuria: 10–29 mg/day, or mg/g creatinine;

A2 — high albuminuria, formerly known as microalbuminuria: 30–299 mg/day, or mg/g creatinine;

A3 — very high albuminuria, formerly called macroalbuminuria/proteinuria: 300–1,999 mg/day, or mg/g creatinine;

A4 — nephrotic albuminuria: ≥2,000 mg/day, or mg/g creatinine [9, 21].

The prevalence of decreased GFR in patients with HF

According to the national register of patients with AHF and ADHF ADHERE [32], which includes about 100,000 patients of different ages and with various comorbidities hospitalized in 270 US hospitals, the mean GFR calculated by the Cockroft-Gault formula was 48.9 ml/min/m^2 in men and 35.0 ml/min/m^2 in women [37, 89].

According to the Medicare information system, decreased GFR calculated by the formula MDRD <60 ml/min/1.73 m^2 was detected in 60.4% of patients who were on inpatient treatment with a diagnosis of CHF [123]. According to Bruch et al., MDRD GFR below 60 ml/min/1.73 m^2 for 3 months was observed in 50.2% of patients with CHF [51]. In a study by de Silva et al., MDRD GFR <60 ml/min was noted in 57% of patients [68]. In other studies, the prevalence of decline in GFR <60 ml/min/1.73 m^2 among patients hospitalized with ADHF was also 50–70% [72, 78, 121, 122, 125, 164].

A retrospective analysis of CONSENSUS, SOLVD, DIG, CIBIS-II, COMET, CHARM, CARE-HF databases of large clinical studies revealed that a decrease in creatinine clearance calculated by Cockroft-Gault formula or a decrease in GFR calculated by MDRD formula of <60 ml/min/1.73 m^2 was revealed in 32–50% of patients with CHF [125].

According to Russian researchers, a decrease in MDRD GFR of <60 ml/min/1.73 m^2 was found in 77.1%, CKD of different stages — in 90.3% of patients with CHF with low LVEF [15].

In a large population-based study called NHANES III, it was shown that among the US population over 20 years of age, stage 1 of CKD was in 3.3%, stage 2 — in 3.0% and stage 3 — in 4.3% of the population [30, 31, 101]. Clearly, the prevalence of GFR reduction in patients with CHF is many times higher than that in the general population.

Urine albumin excretion in patients with CHF: epidemiological and pathogenetic aspects

In 1992 Eiskjaer et al. for the first time showed that in 13 patients with CHF the rate of UAE was higher than in 13 healthy individuals from a control group (12 μg/min compared to 2.8 μg/min, p<0.01) [76]. Then during the assessment by Van de Wal et al. of albumin/creatinine ratio in a random urine sample, microalbuminuria (A2) was detected in 32% (95% CI 22–42%) of 94 outpatients with a stable course of CHF of III–IV FC according to NYHA [169]. Jackson et al. revealed microalbuminuria (A2) in 30% and macroalbuminuria (A3) in 11% of patients with CHF among CHARM program participants. Moreover, UAE increase was similar in patients with reduced and preserved LVEF [99]. Orea-Tejeda et al. showed the presence of microalbuminuria in 40% of 30 patients with diastolic and 24% of 42 patients with systolic CHF with LVEF <45% [137], with about half of the patients having concomitant DM [99, 137].

According to Russian researchers, in assessing albumin/creatinine ratio in morning urine, microalbuminuria (A2) was detected in 58.6% (95% CI 45.7–71.5), a high normal level of albuminuria (A1) — in 10.0% of patients. In daily urine, microalbuminuria (A2) was detected in 67.1% (95% CI 54.7–79.5), high normal level (A1) — in 22.9%, macroalbuminuria (A3) — in 5.7% of patients [17]. The higher level of UAE, as well as the lower values of GFR in the Russian Federation, seems to be due to the fact that UAE was determined not in a random single sample, but in the first morning and daily urine. It may also be due to ethnic differences, greater clinical symptoms, systolic dysfunction, and less adherence to therapy.

It should be noted that the incidence of albuminuria in patients with CHF is much higher than its

prevalence in the general population, in patients with diabetes and hypertension, which is 6.6–8.3%, 16–32% and 11–40%, respectively [26, 52, 67, 83, 93].

There is currently no clear answer to the question on the reason for increased UAE and the development of albuminuria in HF. On the one hand, albuminuria may be a manifestation of kidney damage: altered function of the semi-permeable glomerular filter and increased intraglomerular pressure [138]. On the other hand, the increased permeability of the glomerular filter for albumin may reflect the presence of generalized endothelial dysfunction [4, 139] and be associated with capillaropathy secondary to atherosclerosis [69, 91, 93].

In diabetic nephropathy at early stages, the development of albuminuria is associated with a change in the charge of anionic components of the glomerular basal membrane. Then, in these patients, the pore size in the glomerular basal membrane increases, which can lead to the progression of albuminuria and the development of macroalbuminuria. In patients with CHF, albuminuria is possibly also first associated with charge-mediated, and then with structural changes in glomerular basal membrane [14].

It was previously assumed that albumin molecules in the process of filtration and passage through the tubules remained unchanged. Then it was found that in patients with DM, before the development of albuminuria, 90–95% of the filtered albumin is destroyed in the tubules to small fragments with a molecular weight of 1–15 kDa, which are not determined by standard immunochemical methods. As kidney damage progresses, the fragmentation of albumin in the tubules decreases, which contributes to the development of albuminuria [138].

In addition, the filtered albumin can be reabsorbed by the cells of the proximal tubules via receptor-dependent endocytosis. Disruption of this process can also contribute to the improvement of UAE and the development of albuminuria [14].

In patients with DM, the relationship of microalbuminuria with changes in Willebrand factor, fibrinogen, thrombomodulin and plasminogen activator inhibitor 1 was revealed. This suggested that disruption of the coagulation and fibrinolytic systems in CVD also contributes to the development of albuminuria [90].

New biomarkers of kidney function and damage

New markers of kidney dysfunction and damage include cystatin C (CysC), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and quiescin 6 [60, 61, 65, 136, 167]. In many studies, levels of these markers were moderately elevated in patients with CHF compared to the control group, even in patients with normal GFR [62].

Cystatin C is an inhibitor of serine proteases with a low molecular weight (13 kDa), which is released from various nucleated cells at a relatively constant rate, is freely filtered by glomeruli, not secreted, slightly reabsorbed. Unlike creatinine and blood urea nitrogen, it does not depend on protein intake, muscle mass and catabolic processes [135]. Serum cystatin C was supposed to be a more sensitive marker of glomerular filtration disorders than creatinine [109]. However, cystatin C did not demonstrate specificity with respect to kidney function. Its level varies with age [159], may depend on immunosuppressive therapy [80], the presence of diabetes, thyroid function [151, 155]. To increase its diagnostic value, formulas have been developed for calculating GFR based on the concentration of this substance, as well as on its combination with creatinine.

Recently, blood cystatin C has been shown to be an independent predictor of mortality, heart transplantation, and hospitalizations for HF [167]. A close relationship between blood cystatin C and myocardial damage, the level of NT-pro-BNP and ventricular dysfunction was revealed [107, 108, 113, 167]. The relationship between the level of cystatin C and the duration of hospitalization in patients with CAD, CHF and AHF was not revealed [53]. However, patients with elevated cystatin levels had an increased risk of death and death/re-hospitalizations [54]. And cystatin has shown itself as a predictor, stronger than the usual markers of kidney function [107, 117, 132]. In combination of cystatin C with NT-Pro-BNP, the predictive value increased [53][20][8].

Another new marker of kidney damage is lipocalin, which is associated with neutrophil gelatinase (NGAL). It is a protein with a molecular weight of 25 kDa, which is produced and secreted by immune

cells, hepatocytes and renal tubular cells in various pathological conditions [115]. Experimental and clinical studies have shown that the expression of NGAL increases in the heart in HF and myocarditis, as well as in atherosclerotic plaques. In clinical studies, blood and urine levels of NGAL were correlated with creatinine or GFR, as well as with clinical and biochemical markers (e. g., NUP) and in some, but not all, studies with the severity of HF [61]. Blood NGAL levels have also been linked with increased mortality and the frequency of hospitalizations for HF [44, 62, 162].

Similar results are published for KIM-1 and NAG. KIM-1 is a glycoprotein expressed by proximal tubules in kidney injury. It is referred to as "renal troponin". Its presence in patients with HF and its correlation with NT-proBNP indicates that kidney injury is present in many patients with severe HF [59]. The level of KIM-1 in urine increases compared to the control in clinically apparent HF [102]. Levels of KIM-1 and NAG were correlated with severity of HF and were predictors of total mortality and hospitalizations for HF [63–66].

Quiescin 6 (QuiescinQ6, QSOX1) is a protein involved in the formation of disulfide bonds. According to the results of large-scale genomic studies, it (along with BNP) was associated with ADHF. Its biological significance and feasibility of clinical use is currently being studied [49, 126, 140].

Renal hemodynamics

Early diagnosis of CRS in patients with CHF can be facilitated by imaging technology [86]. Renal hemodynamics can be studied by duplex scanning of renal arteries [2]. At the same time, patients with CHF compared with the norm showed a decrease in peak systolic (Vps) and final diastolic blood flow (Ved) rates [171], an increase in pulsation (PI), resistive (RI) indices, systolic-diastolic ratio (S/D), and decrease in renal blood flow parameters [11–14, 17, 171].

Changes in parameters of renal hemodynamics in patients with CHF may be associated with edema of interstitial tissue and changes in the intrarenal vascular bed, such as renal arteriolar hyalinosis and fibroplastic thickening of the intima of small arteries [92, 152, 153], which are typical for nephrosclerosis, which develops in severe CHF. Renal hemodynamic disorders in patients with CHF are similar to changes detected in kidney pathology of another etiology. This may be due to the common mechanisms underlying renal hemodynamic disorders in these diseases, which determines the common approaches to nephroprotection [10, 14, 17].

Doppler characteristics of renal blood flow in patients with CHF are interrelated with the generally recognized manifestations of renal dysfunction: serum creatinine concentration, GFR and UAE [14, 17]. A similar relationship between doppler ultrasonography at different levels of the renal arterial tree with serum creatinine concentration, creatinine clearance and GFR is indicated in patients with hypertension and CRF, secondary to chronic glomerulonephritis, DM and chronic pyelonephritis [14]. The relationship of RI and PI with the level of albuminuria was revealed in patients with hypertension [5].

According to B. Krumme, intrarenal resistance indices are not so much specific markers of kidney damage, as a complex indicator of compliance, pulsation and peripheral resistance of the entire arterial vascular bed. The change in compliance and peripheral resistance of the arterial vascular bed is accompanied by similar changes in renal vessels, which contributes to a decrease in GFR and an increase in UAE [106].

Thus, cardiorenal syndrome is a natural and integral part of the cardiorenal continuum. It may be only a small part of the cardiorenal-metabolic axis [142]. Cardiorenal syndrome is the development of chronic kidney disease in patients with chronic and acute kidney injury in patients with acute heart failure. Cardiorenal syndrome can be diagnosed in 32–90.3% of patients with HF. Impaired renal function has poor prognostic value: it leads to increased mortality in patients with HF. It is necessary to timely diagnose the presence of cardiorenal syndrome and take this into account in the management of patients with HF. It is necessary to further study ways to prevent the development and progression of kidney damage in patients with heart failure, which should be the focus of the efforts of a multidisciplinary team.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Arutyunov G.P. Pathophysiological processes in the kidneys in patients with CHF. Journal of heart failure. 2008; 9(5): 234-249 [In Russian].
2. Glazun L.O., Mitkov V.V., Polukhina E.V. Doppler assessment of intrarenal hemodynamic disorders in patients with chronic renal failure. Ultrasound and functional diagnostics. 2003; 4: 21-27 [In Russian].
3. Karpov Yu.A., Gendlin G.E. Efficiency of angiotensin receptor blockers at different stages of the cardiovascular continuum — focus on valsartan. Atmosphere. News of Cardiology. 2012; 2: 27-31 [In Russian].
4. Kobalava ZH.D., Dmitrov T.B. Cardiorenal Syndrome. Russian Medical Journal. 2003; 11(12): 699-702 [In Russian].
5. Konechnaya E.Ya., Nanchikeeva M.L., Gladkaya A.A., The value of indicators of intrathecal renal hemodynamics in patients with essential hypertension. Ultrasound and Functional Diagnostics. 2001; 2: 83-89 [In Russian].
6. Kutyrina I.M. Nephroprotective properties of blockers for the synthesis of angiotensin II: the effect of renitec on proteinuria. Heart Failure. 2000; 1(3): 92-93 [In Russian].
7. Mareev V.Yu., Ageev F.T., Arutyunov G.P. National recommendations of OSSN, RKO and RNMOT for diagnosis and treatment of chronic heart failure (fourth revision). Journal of Heart Failure. 2013; 14(7): 379-472 [In Russian].
8. Medvedeva E.A., Shilyaeva N.V. Cardiorenal syndrome in chronic heart failure: pathogenesis, diagnosis, prognosis and treatment options. Russian Journal of Cardiology. 2017; 141(1): 136-141 [In Russian].
9. Moiseev V.S., Mukhin N.A., Smirnov A.V. Cardiovascular risk and chronic kidney disease: cardio-nephroprotection strategies. Russian Journal of Cardiology. 2014; 112(8): 7-37 [In Russian].
10. Nazarenko G.I., Khitrova A.N., Krasnov T.V. Doppler research in uronephrology. Modern medical technology. Medicine: Moscow. 2002; 152 p. [In Russian].
11. Olkhova E.B., Zarubina S.A., Bykovsky V.A. Echographic assessment of renal hemodynamics in children of different ages. Ultrasound diagnosis in obstetrics, gynecology, pediatrics. 1999; 3: 212-218 [In Russian].
12. Poleschuk L.A. Characteristics of renal hemodynamics in children with kidney disease (Literature Review). Nephrology and dialysis. 2006; 8(3): 225-231 [In Russian].
13. Reznik E.V. State renal hemodynamics and renal function in patients with chronic heart nedostatochnostyu. Dissertatsiya for the degree of candidate of medical sciences. Moscow. 2007; 161 p. [In Russian].
14. Reznik E.V. Kidneys as a target organ for chronic heart failure. Lamber. 2011; 188 p. [In Russian].
15. Reznik E.V., Gendlin G.E., Guschina V.M. Chronic kidney disease in patients with chronic heart failure (Literature review). Nephrology and dialysis. 2010; 12(1): 13-24 [In Russian].
16. Reznik E.V., Gendlin G.E., Storozhakov G.I. Renal dysfunction in patients with chronic heart failure: pathogenesis, diagnosis and treatment. Journal of Heart Failure. 2005; 6(6): 45-50 [In Russian].
17. Reznik E.V., Gendlin G.E., Khripun A.I. Renal function, urinary albumin excretion and renal hemodynamics in patients with chronic heart failure. Nephrology and dialysis. 2010; 12(4): 275-286 [In Russian].
18. Smirnov A.V., Dobronravov V.A., National Recommendations. Acute kidney damage: the basic principles of diagnosis, prevention and treatment. http://nonr.ru/wp-content/uploads/2013/11/STROJE- DAMAGE- MENS- BASIC-PRINCIPLES- DIAGNOSTICS- PROPHYLA- TYPE- THERAPY.pdf, 2015 [accessed 2018 Oct 15] [In Russian].
19. Smirnov, A.V., Dobronravov, V.A., Kayukov, I.V., Cardiorenal Continuum: The Pathogenetic Basis of Preventive Nephrology. Nephrology 2005; 9(3): 7-15 [In Russian].
20. Smirnov, A.V., Shilov, E.M., Bobkova, I.N. et al., NATIONAL RECOMMENDATIONS CHRONIC KIDNEY DISEASE: BASIC TERMS, DEFINITION, DIAGNOSTIC, SCRININIG, APPROACHES TO PREVENTION AND TREATMENT. Nephrology 2012; 16(1): 89-115 [In Russian].
21. Smirnov, A.V., Shilov, E.M., Dobronravov, V.A. et al., National guidelines. Chronic kidney disease: the basic principles of screening, diagnosis, prevention and treatment approaches. Lefty: St. Petersburg. 2012; 51p. [In Russian].
22. Storozhakov G.I., Gendlin G.E., Reznik E.V. The main directions in the treatment of patients with chronic heart failure: a guide for general practitioners, general practitioners. Moscow: Miklos. 2008; 137-149 [In Russian].
23. Storozhakov G.I., Gendlin G.E., Reznik E.V. The heart is ill — the kidneys suffer: cardiorenal syndrome in chronic heart failure. Medical business. 2009; 1: 27-36 [In Russian].
24. Tereshchenko S.N. Modern aspects of cardiorenal syndrome. Journal of Heart Failure. 2008; 9(5): 226-230 [In Russian].
25. Tereshchenko S.N., Demidova I.V. Renal Function in Chronic Heart Failure in Patients of Elderly and Elderly Age. Heart. 2002; 1(5): 251-256 [In Russian].
26. Shabalin V.V., Grinshtein Yu.I., Hypertensive nephrosclerosis (hypertensive nephropathy). Rostov-on-Don, Krasnoyarsk: Fenix, Publishing projects. 2006; 41-66 [In Russian].
27. Shilov E.M., Kutyrina I.M., Novikova M.S. Therapeutic strategies for treating cardiorenal syndrome. The attending physician. 2012; 1: 8-13 [In Russian].
28. Shutov A.M., Mashina T.V., Marder N.Ya. Chronic heart failure in patients with chronic kidney disease. Nephrology and dialysis. 2005; 7(2): 140-144 [In Russian].
29. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991; 325 (5): 293-302.
30. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39 (2 Suppl 1): S1-266.
31. NKF takes the next step in K/DOQI process with guidelines for CKD. Nephrol News Issues. 2002; 16 (4): 52-53.
32. Adams K.F., Jr., Fonarow G.C., Emerman C.L. et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005; 149 (2): 209-16.
33. Amin J.K., Xiao L., Pimental D.R. et al. Reactive oxygen species mediate alpha-adrenergic receptor-stimulated hypertrophy in adult rat ventricular myocytes. J Mol Cell Cardiol. 2001; 33 (1): 131-9.
34. Askoxylakis V., Thieke C., Pleger S.T. et al. Long-term survival of cancer patients compared to heart failure and stroke: a systematic review. BMC Cancer. 2010; 10: 105.

35. Bagshaw S.M., Cruz D.N., Epidemiology of cardiorenal syndromes. Contrib Nephrol. 2010; 165: 68-82.
36. Bakris G.L., R, R.N. Endothelin modulates angiotensin II-induced mitogenesis of human mesangial cells. Am J Physiol. 1993; 264 (6 Pt 2): F937-42.
37. Bellomo R., Ronco C. The kidney in heart failure. Kidney Int Suppl. 1998; 66: S58-61.
38. Bhatia R.S., Tu J.V., Lee D.S. et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006; 355 (3): 260-9.
39. Bianchi P., Seguelas M.H., Parini A. et al. Activation of pro-apoptotic cascade by dopamine in renal epithelial cells is fully dependent on hydrogen peroxide generation by monoamine oxidases. J Am Soc Nephrol. 2003; 14 (4): 855-62.
40. Bleeker M.W., De Groot P.C., Pawelczyk J.A. et al. Effects of 18 days of bed rest on leg and arm venous properties. J Appl Physiol. 2004; 96 (3): 840-7.
41. Bleumink G.S., Schut A.F., Sturkenboom, M.C. et al. Genetic polymorphisms and heart failure. Genet Med. 2004; 6 (6): 465-74.
42. Bock J.S., Gottlieb S.S., Cardiorenal syndrome: new perspectives. Circulation. 2010; 121 (23): 2592-600.
43. Boerrigter G., Lapp H., Burnett J.C., Modulation of cGMP in heart failure: a new therapeutic paradigm. Handb Exp Pharmacol. 2009; 191: 485-506.
44. Bolignano D., Basile G., Parisi P. et al. Increased plasma neutrophil gelatinase-associated lipocalin levels predict mortality in elderly patients with chronic heart failure. Rejuvenation Res. 2009; 12 (1): 7-14.
45. Bongartz L.G., Braam B., Gaillard C.A. et al. Target organ cross talk in cardiorenal syndrome: animal models. Am J Physiol Renal Physiol. 2012; 303 (9): F1253-63.
46. Bongartz L.G., Cramer M.J., Doevendans P.A. et al. The severe cardiorenal syndrome: 'Guyton revisited'. Eur Heart J. 2005; 26 (1): 11-7.
47. Bozkurt B., Mann D.L., Deswal A., Biomarkers of inflammation in heart failure. Heart Fail Rev. 2010; 15 (4): 331-41.
48. Braam B., Cupples W.A., Joles J.A. et al. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. Heart Fail Rev. 2012; 17 (2): 161-75.
49. Braunwald E., Heart failure. JACC Heart Fail. 2013; 1 (1): 1-20.
50. Bristow M.R. Treatment of chronic heart failure with beta-adrenergic receptor antagonists: a convergence of receptor pharmacology and clinical cardiology. Circ Res. 2011; 109 (10): 1176-94.
51. Bruch C., Rothenburge, M., Gotzman, M. et al, Chronic kidney disease in patients with chronic heart failure--impact on intracardiac conduction, diastolic function and prognosis. Int J Cardiol. 2007; 118 (3): 375-80.
52. Bruno G., Pagano G. Low prevalence of microalbuminuria in young Italian insulin-dependent diabetic patients with short duration of disease: a population-based study. Piedmont Study Group for Diabetes Epidemiology. Diabet Med. 1996; 13 (10): 889-93.
53. Butler J., Chirovsky D., Phatak H. et al. Renal function, health outcomes, and resource utilization in acute heart failure: a systematic review. Circ Heart Fail. 2010; 3 (6): 726-45.
54. Campbell C.Y., Clarke W., Park H. et al. Usefulness of cystatin C and prognosis following admission for acute heart failure. Am J Cardiol. 2009; 104 (3): 389-92.
55. Chawla L.S., Kimmel P.L. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int. 2012; 82 (5): 516-24.
56. Chuasuwan A., Kellum J.A., Cardio-renal syndrome type 3: epidemiology, pathophysiology, and treatment. Semin Nephrol. 2012; 32 (1): 31-9.
57. Colombo P.C., Ganda A., Lin J. et al. Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome. Heart Fail Rev. 2012; 17 (2): 177-90.
58. Colombo P.C., Onat D., Sabbah H.N. Acute heart failure as "acute endothelitis"-Interaction of fluid overload and endothelial dysfunction. Eur J Heart Fail. 2008; 10 (2): 170-5.
59. Comnick M., Ishani A. Renal biomarkers of kidney injury in cardiorenal syndrome. Curr Heart Fail Rep. 2011; 8 (2): 99-105.
60. Cruz D.N., Fard A., Clementi A. et al. Role of biomarkers in the diagnosis and management of cardio-renal syndromes. Semin Nephrol. 2012; 32 (1): 79-92.
61. Cruz D.N., Gaiao S., Maisel A. et al. Neutrophil gelatinase-associated lipocalin as a biomarker of cardiovascular disease: a systematic review. Clin Chem Lab Med. 2012; 50 (9): 1533-45.
62. Cruz D.N., Schmidt-Ott K.M., Vescovo G. et al. Pathophysiology of cardiorenal syndrome type 2 in stable chronic heart failure: workgroup statements from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2013; 182: 117-36.
63. Damman K., Masson S., Hillege H.L. et al. Clinical outcome of renal tubular damage in chronic heart failure. Eur Heart J. 2011.
64. Damman K., Masson S., Hillege H.L. et al. Tubular damage and worsening renal function in chronic heart failure. JACC Heart Fail. 2013; 1 (5): 417-24.
65. Damman K., Van Veldhuisen D.J., Navis G. et al. Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. Heart. 2010; 96 (16): 1297-302.
66. Damman K., van Veldhuisen D.J., Navis G. et al. Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure. Eur J Heart Fail. 2008; 10 (10): 997-1000.
67. de Jong P.E., Hillege H.L., Pinto-Sietsma S.J. et al. Screening for microalbuminuria in the general population: a tool to detect subjects at risk for progressive renal failure in an early phase? Nephrol Dial Transplant. 2003; 18 (1): 10-3.
68. de Silva R., Nikitin N.P., Witte K.K. et al. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. Eur Heart J. 2006; 27 (5): 569-81.
69. Deckert T., Yokoyama H., Mathiesen E. et al. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. BMJ. 1996; 312 (7035): 871-4.
70. Delles C., Schmieder R.E. The kidney in congestive heart failure: renal adverse event rate of treatment. J Cardiovasc Pharmacol. 2001; 38 (1): 99-107.
71. Dobre D., Rossignol P., Metra M. et al. Can we prevent or treat renal dysfunction in chronic heart failure? Heart Fail Rev. 2012; 17 (2): 283-90.

72. Dries D.L., Exner D.V., Domanski M.J. et al. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000; 35 (3): 681-9.
73. Dzau V., Braunwald E. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. Am Heart J. 1991; 121 (4 Pt 1): 1244-63.
74. Dzau V.J., Antman E.M., Black H.R. et al. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part I: Pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). Circulation, 2006; 114 (25): 2850-70.
75. Dzau V.J., Antman E.M., Black H.R. et al. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part II: Clinical trial evidence (acute coronary syndromes through renal disease) and future directions. Circulation. 2006; 114 (25): 2871-91.
76. Eiskjaer H., Bagger J.P., Mogensen C.E. et al. Enhanced urinary excretion of albumin in congestive heart failure: effect of ACE-inhibition. Scand J Clin Lab Invest. 1992; 52 (3): 193-9.
77. Entin-Meer M., Ben-Shoshan J., Maysel-Auslender S. et al. Accelerated renal fibrosis in cardiorenal syndrome is associated with long-term increase in urine neutrophil gelatinase-associated lipocalin levels. Am J Nephrol. 2012; 36 (2): 190-200.
78. Ezekowitz J., McAlister F.A., Humphries K.H. et al. The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. J Am Coll Cardiol. 2004; 44 (8): 1587-92.
79. Felker G.M., Lee K.L., Bull D.A. et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011; 364 (9): 797-805.
80. Ferrannini M., Vischini G., Di Daniele N. Cystatin C: a promising misunderstood biomarker for the diagnosis of acute kidney injury. Kidney Int. 2008; 74 (12): 1623; author reply 1623-4.
81. Funaya H., Kitakaze M., Node K. et al. Plasma adenosine levels increase in patients with chronic heart failure. Circulation. 1997; 95 (6): 1363-5.
82. Garcia-Donaire J.A., Ruilope L.M. Cardiovascular and Renal Links along the Cardiorenal Continuum. Int J Nephrol. 2011; 975782.
83. Garg J.P., Bakris G.L., Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. Vasc Med. 2002; 7 (1): 35-43.
84. Garvin J.L. Angiotensin stimulates bicarbonate transport and Na+/K+ ATPase in rat proximal straight tubules. J Am Soc Nephrol. 1991; 1 (10): 1146-52.
85. Giannessi D., Del Ry S., Vitale R.L. The role of endothelins and their receptors in heart failure. Pharmacol Res. 2001; 43 (2): 111-26.
86. Grande D., Terlizzese P., Iacoviello M., Role of imaging in the evaluation of renal dysfunction in heart failure patients. World J Nephrol. 2017; 6 (3): 123-131.
87. Hatamizadeh P., Fonarow G.C., Budoff M.J. et al. Cardiorenal syndrome: pathophysiology and potential targets for clinical management. Nat Rev Nephrol. 2013; 9 (2): 99-111.
88. Heymes C., Bendall J.K., Ratajczak P. et al. Increased myocardial NADPH oxidase activity in human heart failure. J Am Coll Cardiol. 2003; 41 (12): 2164-71.
89. Heywood J.T. The cardiorenal syndrome: lessons from the ADHERE database and treatment options. Heart Fail Rev. 2004; 9 (3): 195-201.
90. Hillege H., Van Gilst W., de Zeeuw D. et al. Renal function as a predictor of prognosis in chronic heart failure. Heart Fail Monit. 2002; 2 (3): 78-84.
91. Hillege H.L., Fidler V., Diercks G.F. et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002; 106 (14): 1777-82.
92. Hillege H.L., Girbes A.R., de Kam P.J. et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000; 102 (2): 203-10.
93. Hillege H.L., Janssen W.M., Bak A.A. et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med. 2001; 249 (6): 519-26.
94. House A.A. Cardio-renal syndrome type 4: epidemiology, pathophysiology and treatment. Semin Nephrol. 2012; 32 (1): 40-8.
95. House A.A., Anand I., Bellomo R. et al. Definition and classification of Cardio-Renal Syndromes: workgroup statements from the 7th ADQI Consensus Conference. Nephrol Dial Transplant. 2010; 25 (5): 1416-20.
96. Iacoviello M., Leone M., Antoncecchi V. et al. Evaluation of chronic kidney disease in chronic heart failure: From biomarkers to arterial renal resistances. World J Clin Cases 2015; 3 (1): 10-9.
97. Ismail Y., Kasmikha Z., Green H.L. et al. Cardio-renal syndrome type 1: epidemiology, pathophysiology, and treatment. Semin Nephrol. 2012; 32 (1): 18-25.
98. Iyngkaran P., Schneider H., Devarajan P. et al. Cardio-renal syndrome: new perspective in diagnostics. Semin Nephrol. 2012; 32 (1): 3-17.
99. Jackson C.E., Solomon S.D., Gerstein H.C. et al. Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet. 2009; 374 (9689): 543-50.
100. Jois P., Mebazaa A., Cardio-renal syndrome type 2: epidemiology, pathophysiology, and treatment. Semin Nephrol. 2012; 32 (1): 26-30.
101. Jones C.A., Christensen A.L., Salihu H. et al. Prediction of individual probabilities of livebirth and multiple birth events following in vitro fertilization (IVF): a new outcomes counselling tool for IVF providers and patients using HFEA metrics. J Exp Clin Assist Reprod. 2011; 8: 3.
102. Jungbauer C.G., Birner C., Jung B. et al. Kidney injury molecule-1 and N-acetyl-beta-D-glucosaminidase in chronic heart failure: possible biomarkers of cardiorenal syndrome. Eur J Heart Fail. 2011; 13 (10): 1104-10.
103. Kagami S., Border W.A., Miller D.E. et al. Angiotensin II stimulates extracellular matrix protein synthesis through induction of transforming growth factor-beta expression in rat glomerular mesangial cells. J Clin Invest. 1994; 93 (6): 2431-7.
104. Khan S.S., Xue J.L., Kazmi W.H. et al. Does predialysis nephrology care influence patient survival after initiation of dialysis? Kidney Int. 2005; 67 (3): 1038-46.
105. Kishimoto T., Maekawa M., Abe Y. et al. Intrarenal distribution of blood flow and renin release during renal venous pressure elevation. Kidney Int. 1973; 4 (4): 259-66.

106. Krumme B. Renal Doppler sonography-update in clinical nephrology. Nephron Clin Pract. 2006; 103 (2): 24-8.
107. Lassus J., Harjola V.P., Sund R. et al. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. Eur Heart J. 2007; 28 (15): 1841-7.
108. Lassus J.P., Nieminen M.S., Peuhkurinen K. et al. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. Eur Heart J. 2010; 31 (22): 2791-8.
109. Laterza O.F., Price C.P., Scott M.G. Cystatin C: an improved estimator of glomerular filtration rate? Clin Chem. 2002; 48 (5): 699-707.
110. Lazzarini V., Bettari L., Bugatti S. et al. Can we prevent or treat renal dysfunction in acute heart failure? Heart Fail Rev. 2012; 17 (2): 291-303.
111. Lekawanvijit S., Kompa A.R., Zhang Y. et al. Myocardial infarction impairs renal function, induces renal interstitial fibrosis, and increases renal KIM-1 expression: implications for cardiorenal syndrome. Am J Physiol Heart Circ Physiol. 2012; 302 (9): H1884-93.
112. Lin H.H., Chen C.H., Hsieh W.K. et al. Hydrogen peroxide increases the activity of rat sympathetic preganglionic neurons in vivo and in vitro. Neuroscience. 2003; 121 (3): 641-7.
113. Linzbach S., Samigullin A., Yilmaz S. et al. Role of N-terminal pro-brain natriuretic peptide and cystatin C to estimate renal function in patients with and without heart failure. //Am J Cardiol, 2009. Vol. 103 (8): P. 1128-33.
114. Lu J., Wang X., Wang W. et al. Abrogation of lectin-like oxidized LDL receptor-1 attenuates acute myocardial ischemia-induced renal dysfunction by modulating systemic and local inflammation. Kidney Int. 2012; 82 (4): 436-44.
115. Maisel A.S., Mueller C., Fitzgerald R. et al. Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: the NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial. Eur J Heart Fail. 2011; 13 (8): 846-51.
116. Makaritsis K.P., Liakopoulos V., Leivaditis K. et al. Adaptation of renal function in heart failure. Ren Fail. 2006; 28 (7): 527-35.
117. Manzano-Fernandez S., Boronat-Garcia M., Albaladejo-Oton M.D. et al. Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. Am J Cardiol. 2009; 103 (12): 1753-9.
118. Marenzi G., Lauri G., Guazzi M. et al. Cardiac and renal dysfunction in chronic heart failure: relation to neurohumoral activation and prognosis. Am J Med Sci. 2001; 321 (6): 359-66.
119. Matsusaka T., Hymes J., Ichikawa I. Angiotensin in progressive renal diseases: theory and practice. J Am Soc Nephrol. 1996; 7 (10): 2025-43.
120. Maxwell A.P., Ong H.Y., Nicholls D.P. Influence of progressive renal dysfunction in chronic heart failure. Eur J Heart Fail. 2002; 4 (2): 125-30.
121. McAlister F.A., Ezekowitz J., Tonelli M. et al. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation. 2004; 109 (8): 1004-9.
122. McClellan W.M., Flanders W.D., Langston R.D. et al. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol. 2002; 13 (7): 1928-36.
123. McClellan W.M., Langston R.D., Presley R. Medicare patients with cardiovascular disease have a high prevalence of chronic kidney disease and a high rate of progression to end-stage renal disease. J Am Soc Nephrol. 2004; 15 (7): 1912-9.
124. McCullough P.A. Why is chronic kidney disease the "spoiler" for cardiovascular outcomes? J Am Coll Cardiol. 2003; 41 (5): 725-8.
125. McMurray J.J. Chronic kidney disease in patients with cardiac disease: a review of evidence-based treatment. Kidney Int. 2005; 68 (4): 1419-26.
126. Mebazaa A., Vanpoucke G., Thomas G. et al. Unbiased plasma proteomics for novel diagnostic biomarkers in cardiovascular disease: identification of quiescin Q6 as a candidate biomarker of acutely decompensated heart failure. Eur Heart J. 2012; 33 (18): 2317-24.
127. Miyata T., Sugiyama,S., Saito A. et al. Reactive carbonyl compounds related uremic toxicity ("carbonyl stress"). Kidney Int Suppl. 2001; 78: S25-31.
128. Mohmand H., Goldfarb S. Renal dysfunction associated with intra-abdominal hypertension and the abdominal compartment syndrome. J Am Soc Nephrol. 2011; 22 (4): 615-21.
129. Morris M.J., Cox H.S., Lambert G.W. et al. Region-specific neuropeptide Y overflows at rest and during sympathetic activation in humans. Hypertension. 1997; 29 (1 Pt 1): 137-43.
130. Mullens W., Abrahams Z., Francis G.S. et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009; 53 (7): 589-96.
131. Mullens W., Abrahams Z., Skouri H.N. et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol. 2008; 51 (3): 300-6.
132. Naruse H., Ishii J., Kawai T. et al. Cystatin C in acute heart failure without advanced renal impairment. Am J Med. 2009; 122 (6): 566-73.
133. Navis G., Faber H.J., de Zeeuw D. et al. ACE inhibitors and the kidney. A risk-benefit assessment. Drug Saf. 1996; 15 (3): 200-11.
134. Nohria A., Hasselblad V., Stebbins A. et al. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol. 2008; 51 (13): 1268-74.
135. Nunez J., Minana G., Santas E. et al. Cardiorenal Syndrome in Acute Heart Failure: Revisiting Paradigms. Rev Esp Cardiol (Engl Ed). 2015; 68 (5): 426-35.
136. Nymo S.H., Ueland T., Askevold E.T. et al. The association between neutrophil gelatinase-associated lipocalin and clinical outcome in chronic heart failure: results from CORONA*. J Intern Med. 2012; 271 (5): 436-43.
137. Orea-Tejeda A., Colin-Ramirez E., Hernandez-Gilsoul T. et al. Microalbuminuria in systolic and diastolic chronic heart failure patients. Cardiol J. 2008; 15 (2): P. 143-9.
138. Osicka T.M., Houlihan C.A., Chan J.G. et al. Albuminuria in patients with type 1 diabetes is directly linked to changes in the lysosome-mediated degradation of albumin during renal passage. Diabetes. 2000; 49 (9): 1579-84.
139. Pedrinelli R., Dell'Omo G., Di Bello V. et al. Microalbuminuria, an integrated marker of cardiovascular risk in essential hypertension. J Hum Hypertens. 2002; 16 (2): 79-89.

140. Piran S., Liu P., Morales A. et al. Where genome meets phenome: rationale for integrating genetic and protein biomarkers in the diagnosis and management of dilated cardiomyopathy and heart failure. J Am Coll Cardiol. 2012; 60 (4): 283-9.
141. Pokhrel, N., Maharjan, N., Dhakal, B. et al., Cardiorenal syndrome: A literature review. //Exp Clin Cardiol, 2008. Vol. 13 (4): P. 165-70.
142. Preeti J., Alexandre M., Pupalan I. et al. Chronic Heart Failure and Comorbid Renal Dysfunction — A Focus on Type 2 Cardiorenal Syndrome. Curr Cardiol Rev. 2016; 12 (3): 186-94.
143. Remuzzi G., Cattaneo D., Perico N. The aggravating mechanisms of aldosterone on kidney fibrosis. J Am Soc Nephrol. 2008; 19 (8): 1459-62.
144. Ronco C., Cardiorenal syndromes: definition and classification. Contrib Nephrol. 2010; 164: 33-8.
145. Ronco C., Cruz D. Cardio-renal syndromes: introduction. Semin Nephrol. 2012; 32 (1): 1-2.
146. Ronco C., Di Lullo L. Cardiorenal Syndrome in Western Countries: Epidemiology, Diagnosis and Management Approaches. Kidney Dis (Basel). 2017; 2 (4): 151-163.
147. Ronco C., Haapio M., House A.A. et al. Cardiorenal syndrome. J Am Coll Cardiol. 2008; 52 (19): 1527-39.
148. Ronco C., Maisel A. Volume overload and cardiorenal syndromes. Congest Heart Fail. 2010; 16 Suppl 1: Si-iv; quiz Svi.
149. Ronco C., McCullough P., Anker S.D. et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2010; 31 (6): 703-11.
150. Ronco C., McCullough P.A., Anker S.D. et al. Cardiorenal syndromes: an executive summary from the consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2010; 165: 54-67.
151. Roos J.F., Doust J., Tett S.E. et al. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children-a meta-analysis. Clin Biochem. 2007; 40 (5-6): 383-91.
152. Ruilope L.M. Kidney dysfunction: a sensitive predictor of cardiovascular risk. Am J Hypertens. 2001; 14 (6 Pt 2): 213S-217S.
153. Ruilope L.M., van Veldhuisen D.J., Ritz E. et al. Renal function: the Cinderella of cardiovascular risk profile. J Am Coll Cardiol. 2001; 38 (7): 1782-7.
154. Ruiz-Ortega M., Ruperez M., Lorenzo O. et al. Angiotensin II regulates the synthesis of proinflammatory cytokines and chemokines in the kidney. Kidney Int Suppl. 2002 (82): S12-22.
155. Rule A.D., Bergstralh E.J., Slezak J.M. et al. Glomerular filtration rate estimated by cystatin C among different clinical presentations. Kidney Int. 2006; 69 (2): 399-405.
156. Schrier R.W. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (1). N Engl J Med. 1988; 319 (16): 1065-72.
157. Schrier R.W. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (2). N Engl J Med. 1988; 319 (17): 1127-34.
158. Schrier R.W., Abraham W.T. Hormones and hemodynamics in heart failure. N Engl J Med. 1999; 341 (8): 577-85.
159. Shlipak M.G., Katz R., Kestenbaum B. et al. Rate of kidney function decline in older adults: a comparison using creatinine and cystatin C. Am J Nephrol. 2009; 30 (3): 171-8.
160. Shlipak M.G., Massie B.M. The clinical challenge of cardiorenal syndrome. Circulation. 2004; 110 (12): 1514-7.
161. Shokoji T., Nishiyama A., Fujisawa Y. et al. Renal sympathetic nerve responses to tempol in spontaneously hypertensive rats. Hypertension. 2003; 41 (2): 266-73.
162. Shrestha K., Borowski A.G., Troughton R.W. et al. Renal dysfunction is a stronger determinant of systemic neutrophil gelatinase-associated lipocalin levels than myocardial dysfunction in systolic heart failure. J Card Fail. 2011; 17 (6): 472-8.
163. Silverberg D.S., Wexler D., Blum M. et al. The interaction between heart failure, renal failure and anemia — the cardio-renal anemia syndrome. Blood Purif. 2004; 22 (3): 277-84.
164. Smilde T.D., Hillege H.L., Voors A.A. et al. Prognostic importance of renal function in patients with early heart failure and mild left ventricular dysfunction. Am J Cardiol. 2004; 94 (2): 240-3.
165. Soni S.S., Ronco C., Pophale R. et al. Cardio-renal syndrome type 5: epidemiology, pathophysiology, and treatment. Semin Nephrol. 2012; 32 (1): 49-56.
166. Tanaka K., Ito M., Kodama M. et al. Longitudinal change in renal function in patients with idiopathic dilated cardiomyopathy without renal insufficiency at initial diagnosis. Circ J. 2007; 71 (12): 1927-31.
167. Tang W.H., Van Lente F., Shrestha K. et al. Impact of myocardial function on cystatin C measurements in chronic systolic heart failure. J Card Fail. 2008; 14 (5): 394-9.
168. Vallon V., Miracle C., Thomson S. Adenosine and kidney function: potential implications in patients with heart failure. Eur J Heart Fail. 2008; 10 (2): 176-87.
169. van de Wal R.M., Asselbergs F.W., Plokker H.W. et al. High prevalence of microalbuminuria in chronic heart failure patients. J Card Fail. 2005; 11 (8): 602-6.
170. Vasan R.S., Sullivan L.M., Roubenoff R. et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. Circulation. 2003; 107 (11): 1486-91.
171. Vigna C., Russo A., Barbano F. et al. Color Doppler ultrasonography for the assessment of renal blood flow in heart failure. Chest. 1995; 108 (4): 912-8.
172. Witko-Sarsat V., Friedlander M., Capeillere-Blandin C. et al. Advanced oxidation protein products as a novel marker of oxidative stress in uremia. Kidney Int. 1996; 49 (5): 1304-13.
173. Witko-Sarsat V., Friedlander M., Nguyen Khoa T. et al. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. J Immunol. 1998; 161 (5): 2524-32.
174. Witko-Sarsat V., Nguyen Khoa T., Jungers P. et al. Advanced oxidation protein products: oxidative stress markers and mediators of inflammation in uremia. Adv Nephrol Necker Hosp. 1998; 28: 321-41.
175. Young B., Zaritsky J., Hepcidin for clinicians. Clin J Am Soc Nephrol. 2009; 4 (8): 1384-7.

Article received on 15.10.2018
Accepted for publication on 09.12.2018