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Cardiorenalic Syndrome: Classification, Principles Diagnostics and Treatment

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Annotation: Cardiorenal syndrome (CRS) is a cardiorenal relationship in which acute or chronic dysfunction of one organ leads to acute or chronic failure of another. The primacy of kidney and cardiovascular diseases is conditional (cardiorenal or renocardial syndrome). The number of patients with comorbid cardiovascular and renal lesions has a steady upward trend in the world and is associated with high overall and cardiovascular mortality. The article presents current issues of cardiorenal relationships from the standpoint of modern concepts of the cardiorenal continuum, the commonality of risk factors and pathogenetic mechanisms, as well as the prognostic role of renal and cardiac pathology, and discusses the principles of diagnosis and treatment of clinical variants of CRS.

Keywords: cardiorenal syndrome, acute cardiac failure sufficiency, acute kidney injury, chronic kidney disease, chronic heart failure.

Introduction

The number of patients with comorbid cardiovascular and renal lesions has a steady upward trend. Modern cardiology and nephrology are closely integrated with each other on issues related to common risk factors for kidney and cardiovascular diseases, universal pathogenetic mechanisms, mutually aggravating prognosis and interrelated therapeutic strategies for nephro- and cardioprotection.

Definition and classification

A characteristic feature of cattle is the commonality of risk factors and pathogenesis of the processes of maladaptive remodeling of renal tissue, vascular wall and myocardium, which are built according to a feedback mechanism and are continuous in nature.

According to the proposed definition, CRS is a pathological interdependent condition involving the heart and kidneys, developing as a result of acute or chronic dysfunction of one of the organs with subsequent acute or chronic dysfunction of the other.

Thus, CRS include acute and chronic disorders in which the primarily affected organ can be either the heart or the kidney [1].

In 2008, at the ADQI consensus conference in Venice, C. Ronco et al. proposed a definition and classification of cattle, in which they identified five types [2].

Type 1 - acute bovine.Acute cardiac dysfunction (cardiogenic- (acute shock, acute decompensation of chronic heart failure - CHF) significantly reduces cardiac output and increases venous pressure. Renal perfusion and filtration capacity decrease, which leads to acute kidney injury (AKI), and subsequently to the development of chronic kidney disease (CKD). AKI in acute coronary syndrome occurs in 9-19% of cases, and in cardiogenic shock - in 70% of cases.

Acute heart failure (AHF) and acute decompensation of CHF are complicated by the development of AKI in 24-45% of patients with high overall and cardiac mortality. In AHF and acute decompensation of CHF, mortality is inversely proportional to the glomerular filtration rate (GFR) and left ventricular ejection fraction (EF).

The risk of adverse outcomes increases significantly with decreasing glomerular filtration rate (GFR) and even with a modest increase in serum creatinine concentration (by 0.3 mg/dL or 26.6 pmol/L). Resistance to diuretic therapy often develops: the use of high doses or combinations of diuretics may

be an additional iatrogenic mechanism for the progression of AKI. In this clinical situation, it is necessary to optimize cardiac output and use extracorporeal ultrafiltration. The presence of AKI with or without hyperkalemia limits the use of angiotensin-converting enzyme inhibitors (ACE), angiotensin II receptor antagonists (ARBs), and aldosterone antagonists in patients with CHF and myocardial infarction, which may negatively affect the outcome of the disease.

Type 2 - chronic bovine.Characterized by the presence of chronic cardiac pathology, primarily CHF, leading to the development or progression of CKD. Renal dysfunction in patients with CHF is detected in 45.0-63.6% of cases. Systolic and diastolic dysfunction of the left ventricle (LV) lead to prolonged renal hypoperfusion against the background of micro- and macroangiopathies, severe neurohormonal disorders: increased production of vasoconstrictors (adrenaline, angiotensin II, endothelin), changes in the sensitivity and release of endogenous vasodilators (natriuretic peptides, nitric oxide). A combination of cardiovascular risk factors (arterial hypertension, dyslipidemia, hyperuricemia) increases the likelihood of developing CKD.

The development of hypertensive nephrosclerosis in arterial hypertension (AH) is a common cause of CKD and is significantly accelerated by hyperuricemia, hyperglycemia and dyslipidemia. Moderate decrease in SCF in essential AH leads to a doubling of the risk of death. At different time periods of the disease, transformation of acute and chronic CRS (types 1 and 2) is possible.

Type 3 Cattle-acute renocardial syndrome.Characterized by primary, sudden deterioration of renal function (e.g., acute glomerulonephritis or pyelonephritis, acute tubular necrosis, acute urinary tract obstruction), which leads to acute cardiac dysfunction (ACI, arrhythmias, ischemia). AKI is often observed in hospitalized patients and in patients in the intensive care unit, in 9 and 35% of cases, respectively. The prevalence of AKI in coronary angiography (contrast-induced nephropathy) and cardiac surgery ranges from 0.3 to 29.7% and is associated with high mortality.

AKI affects the functional state of the heart through several mechanisms. Hypervolemia can lead to the development of AHF, hyperkalemia can lead to the development of arrhythmias and cardiac arrest, uremic intoxication reduces the inotropic function of the myocardium and leads to the development of pericarditis. Acidosis developing in renal failure, contributing to the development of pulmonary vasoconstriction and right ventricular failure, has a negative inotropic effect and, in addition to electrolyte disorders, increases the risk of developing arrhythmias. In addition, renal ischemia itself can provoke inflammation and apoptosis of cardiomyocytes.

A special form of this type of CRS is renal artery stenosis. Blockade of the renin-angiotensin-aldosterone system (RAAS) is a necessary component of therapy for such patients, but in case of bilateral renal artery stenosis or stenosis of the artery of a single kidney, the use of these drugs can lead to decompensation of renal failure. In case of severe AKI requiring renal replacement therapy (RRT), hypotension, rhythm and conduction disturbances, and myocardial ischemia caused by rapid movement of fluid and electrolytes during dialysis can develop [3].

Type 4 Cattle-chronic renocardial syndrome.This is a situation- when primary CKD leads to cardiac dysfunction (ventricular hypertrophy, diastolic dysfunction or increased risk of adverse cardiovascular events). The main cause of kidney damage is diabetes mellitus (DM) type 2 and hypertension, a significant role is played by atherosclerosis, CHF and obesity. In patients with pre-dialysis CKD, the prevalence of cardiac pathology, overall and cardiac mortality correlate with the severity of renal dysfunction. As the severity of CKD increases, there is progression of left ventricular hypertrophy, development of systolic or diastolic dysfunction, “acceleration” of atherosclerosis, and calcification of the vascular bed [4].

The prevalence of cardiovascular diseases in the population of patients with reduced renal function is 64% higher than in individuals with preserved function. An independent inverse relationship was found between SCF <60 ml/min/1.73 m2and an increased risk of death, cardiovascular complications, and hospitalization [5]. The incidence of new cardiovascular complications is 4.8% in patients with stage 2 CKD and almost doubles in stages 3-4. The risk of developing adverse cardiovascular

outcomes in patients on dialysis or in kidney transplant recipients is tens of times higher than in the general population.

Anemia in CKD

The study of the pathogenetic role of relative or absolute erythropoietin deficiency (anemia) in CKD continues.

Anemia is detected in the vast majority of patients with CKD. A persistent decrease in hemoglobin has been recorded in at least 80% of patients with creatinine clearance of no less than 25 ml/min [6,7]. Anemia is often detected even at lower serum creatinine values: among patients with moderate hypercreatininemia, its frequency was 50% [7].

The development of anemia in CKD is determined by several components. With “large” proteinuria, significant losses of erythropoietin, transferrin, and ionized iron are sometimes recorded in the pool of proteins excreted in the urine. As renal failure progresses, the structures that produce erythropoietin are gradually replaced by fibrous tissue, which is accompanied by the loss of their hormone-producing properties [7]. Hypoperfusion of renal tissue is of primary importance in the development of anemia. Increasing ischemia of endothelial cells of peritubular capillaries and fibroblasts localized in the tubulointerstitium causes a decrease in their production of erythropoietin.

An additional factor contributing to the formation of anemia is the mii hyperproduction of tumor necrosis factor-alpha (TNF-a), having a depressant effect on the production of erythropoietin, bone marrow erythropoiesis and the release of iron from the cells of the reticuloendothelial system.

Anemia can be significantly aggravated by long-term use of aspirin and other non-steroidal anti-inflammatory drugs, especially in high doses, since this significantly increases the likelihood of gastrointestinal bleeding, including “subclinical” bleeding that remains undetected for a long time.

Anemia largely determines the high risk of cardiovascular complications, primarily myocardial contractility disorders, an increase in the mass of the LV myocardium in CKD. The administration of drugs that stimulate erythropoiesis to patients with CHF, CKD and anemia leads to an improvement in the functional state of the heart, a decrease in the size of the LV and a decrease in the level of brain natriuretic peptide [8].

Type 5 cattle - secondary cattle.Characterized by the presence of a combined renal and cardiac pathology due to acute or chronic sys- systemic diseases, in which the dysfunction of one organ affects the functional state of another, and vice versa. Such diseases are sepsis, diabetes, amyloidosis, systemic lupus erythematosus, sarcoidosis. Data on the prevalence of type 5 CRS are scarce due to the large number of acute and chronic predisposing conditions.

Sepsis can lead to AKI, simultaneously causing myocardial depression, the mechanisms of development of these conditions are not fully understood. The prevalence of AKI in sepsis is 11-64%, and the frequency of increased troponins is 30-80%, their combination is associated with an increase in mortality compared with the presence of only one of the conditions. In this case, the development of functional myocardial depression and inadequate cardiac output lead to further deterioration of renal function, as in type 1 CRS, and AKI affects the functional state of the heart, as in type 3 CRS, resulting in a vicious circle.

Prevention and treatment of cardiorenal syndrome

In accordance with the pathogenetic mechanisms of development of cardiorenal syndrome, modern recommendations for the management of patients with heart failure, chronic kidney disease, acute kidney injury, to prevent the development and progression of cardiorenal syndrome, the main principles of the therapeutic strategy have been formulated [9]. Nephroprotective and cardioprotective effects have a number of common mechanisms of implementation and target indicators: reduction of proteinuria, normalization of blood pressure (BP), dyslipidemia, compensation of anemia, phosphorus-calcium metabolism, insulin resistance, hypersympathicotonia, hyperuricemia.

The main requirements for drugs for the treatment of patients with CKD and heart disease should be metabolic neutrality, dual elimination pathway (hepatic and renal), improvement of endothelial function, and proven presence of nephroprotective and cardioprotective properties.

To achieve nephro- and cardioprotection, the following approaches are recommended:

1. Episodes of acute decompensation of chronic heart failure accuracy (ADHF) predispose to the development of AKI, the emergence and progression of CRF. For the purpose of nephroprotection, it is extremely important to prescribe competentdrug therapy for heart failureaccording to modern recommendations in order to prevent and reduce the frequency of decompensation [10]. In most patients, it should include ACE inhibitors/angiotensin receptor antagonists, beta-blockers, diuretics, and mineralocorticoid receptor antagonists. If the specified combination is ineffective with systolic BP>100 mmHg, it is possible to replace ACE inhibitors or angiotensin receptor antagonists with sacubitril/ valsartan, with sinus rhythm with HR>70 - adding ivabradine, with QRS >130 ms - discussion of cardiac resynchronization therapy. At the same time, in order to prevent episodes of hypovolemia and hypotension that contribute to the development of AKI, it is necessary to start drug therapy therapy with minimal doses, slowly titrate the dose and adjust according to the SCF [11].

2. Diet.To prevent the progression of CKD, the effectiveness of the effectiveness of a diet with a low salt content (salt <6 g/day, sodium <2.4 g/day), protein (1 g/kg/day at stages 1-2 of CKD and 0.6-0.8 g/kg/day at CKD stages 3a-4), replacement of animal proteins with plant proteins, which have less stress on the kidneys (soy proteins have no less negative impact on renal hemodynamics and have nephro-, cardio-protective and anti-sclerotic effects), low potassium content (>4 g/day at CKD stages 1-2 and 2-4 g/day at CKD stages 3a-4), low phosphate content (1.7 g/day at CKD stages 1-2 and 0.8-1.0 g/day at CKD stages 3a-4) [12].

3. Quitting smokingdue to the fact that it is dose dependent a risk factor for decreased SCF and the development of microalbuminuria [12].

4. Limit alcohol consumption[12].

5. Elimination or minimization of the effects of modifiable risk factorsdevelopment and progression of CKD. It should be avoided the use of nephrotoxic drugs, including non-steroidal anti-inflammatory drugs (NSAIDs), nephrotoxic antibiotics, radiocontrast agents, nutritional supplements (including Thai herbs, “fat burners”, nutritional mixtures for building muscle mass), which can adversely affect kidney function.

The use of even small doses of acetylsalicylic acid (ASA), like other NSAIDs, in patients with CHF is associated with worsening of the outcome, since this drug blocks the synthesis of prostaglandins, which prevent the negative impact of neurohumoral activation, and weakens the effect of drugs for the treatment of CHF - ACE inhibitors, diuretics, spironolactone, carvedilol. The prescription of ASA is associated with a higher frequency of hospitalizations due to worsening of CHF [13]. This indicates the need to avoid prescribing NSAIDs for CHF (with the exception of prescribing ASA in the early period up to 8 weeks after myocardial infarction), especially in the presence of renal dysfunction. If antiplatelet therapy is necessary, replacing ASA with clopidogrel may be indicated [13]. It is necessary to take into account that, starting from CKD stage 3b, the effectiveness of thiazide diuretics decreases and the risk of their side effects increases, in connection with which preference should be given to loop diuretics. In addition, with SCF<30 ml/min/1.73m2due to the risk of worsening renal dysfunction and the development of hyperkalemia, aldosterone antagonists are absolutely contraindicated, and with a SCF of 30-60 ml/min/ 1.73m2They should be used with caution at a dose of no more than 25 mg/day and the level of potassium and creatinine in the blood should be carefully monitored during therapy 7 days after the start of therapy and the dose change, then weekly for up to 1.5 months, then once every 4 months [14].

Cardiac glycosides should be administered to patients with CRS with great caution, only in the presence of atrial fibrillation.

When prescribing digoxin, the SCF should be taken into account, since digoxin excretion decreases with decreasing SCF, and serum digoxin concentrations should be maintained at <0.8 ng/mL. For safety reasons, in patients with CRS, it is not recommended to initiate treatment with loading doses; low doses of 0.125 mg, possibly every other day, should be used as maintenance doses [14].

6. Maintenancebody mass index(BMI) within 20-25 kg/m2for by adjusting the caloric content of the diet and sufficient physical activity (30 minutes of aerobic exercise at least 4-5 times a week), since an increase in BMI >25 kg/m2even in young healthy people is associated with an increased risk of developing terminal CRF [15].

7. Strict blood pressure control.Target blood pressure level <140/90 mmHg at optimal urinary albumin excretion (UAE) <10 mg/g (A0), with a higher degree of albuminuria (A1-A4) <130/80 mmHg. In this case, it is very important to avoid a decrease in systolic blood pressure <120 mmHg to prevent a decrease in renal blood flow [16].

8. Strict glycemic control. Target level of glycated he- MobA1c depends on age and existing complications; in most patients it is <7%.

9. PurposeACE inhibitors/ARB/ARNI. Nephroprotective The action of ACE inhibitors and ARBs is associated with the fact that they increase renal blood flow due to dilation of afferent arterioles and increase in cardiac output and block the adverse effects of angiotensin II on the kidneys, including proliferation and hypertrophy of mesangial cells. With long-term use of ACE inhibitors/ARBs, dilation of efferent arterioles prevents hyperfiltration and reduces albuminuria [17]. All this leads to a slowdown in the progression of CKD and a reduction in the risk of developing terminal CRF.

For a long time, ACE inhibitors were contraindicated at serum potassium levels above 5 mmol/L and creatinine above 220 pmol/L (2.5 mg/dL). Later, it was found that in patients over 65 years of age with systolic dysfunction LVEF <40%, the reduction in mortality within 1 year with ACE inhibitor treatment was more significant in patients with serum creatinine concentrations >265 pmol/L (3 mg/dL) than in patients with creatinine concentrations <265 mg/dL (37% and 16%, respectively). In this regard, “there is no specific creatinine level at which the use of ACE inhibitors is contraindicated” [18].

Most experts agree that ACE inhibitors or angiotensin II receptor antagonists can be used when serum creatinine is <6 mg/dL (528 pmol/L) and SCF is >20 mL/min, but renal artery stenosis should be excluded before starting treatment. In patients with SCF <30 mL/min/1.73 m2 Treatment should be initiated in a hospital where daily determination of creatinine, potassium and serum agents for the treatment of acute renal failure are used. In patients with SCF >30 ml/ min/1.73m2It is necessary to determine the concentrations of creatinine and potassium in the blood serum and SCF after 7 days from the start of treatment and increasing the dose, then weekly up to 1.5 months, then once every 4 months. If, during therapy, the creatinine concentration has increased by less than 50% and remains below 266 pmol / l, SCF is above 25 ml / min / 1.73 m2, potassium is below or equal to 5.5 mmol/l - no changes in therapy with ACE inhibitors or ARBs are required. With more pronounced changes in the concentration of creatinine and/or potassium in the blood - it is necessary to reduce the dose of the ACE inhibitor/ARB by 2 times and monitor creatinine and potassium after 1 week. With an increase in the concentration of potassium in the blood >5.5 mmol/l, an increase in creatinine by more than 100% or above 310 pmol/l, a decrease in SCF <20 ml/min/1.73m2RAAS blockers should be discontinued.

It is necessary to temporarily cancel ACE inhibitors and ARBs during planned administration of radiocontrast agents, preparation for colonoscopy, before major surgical interventions. The combination of an ACE inhibitor and an ARB reduces the excretion of EAM and BP better than the isolated administration of each of these groups of drugs, but does not prevent the development of a combined endpoint: doubling of the creatinine level, entry into dialysis, or death. In this regard, the combination of an ACE inhibitor and an ARB is currently not recommended. The composition of the drug of the new ARNIS group - sacubitril / valsartan includes an ARB and a neprilysin inhibitor. Neprilysin is a neutral endopeptidase that breaks down natriuretic peptides (NUP), bradykinin and

other peptides. Inhibition of neprilysin leads to an increase in the blood level of NUP, an increase in diuresis, natriuresis, vasodilation, improved myocardial relaxation, and a decrease in the secretion of renin and aldosterone.

10. Hypolipidemic therapy. To slow down the progression atherosclerosis and renal fibrosis, which contribute to the development of CKD, the use of statins is indicated. According to the results of studies, statins at various stages of CKD significantly reduced daily proteinuria, although they did not significantly affect the SCF. The positive effects of statins did not depend on the stage of CKD [19]. In accordance with current recommendations, due to the lack of effect of statins on hard endpoints, initiation of statin therapy in CHF is currently not recommended, although continuation of therapy is possible in patients with ischemic etiology of CHF.

11. Reduction of intra-abdominal pressure. In patients with ascites Paracentesis with fluid evacuation may be considered to relieve symptoms. This procedure, by reducing intra-abdominal pressure, may partially increase renal filtration pressure and SCF [20].

Conclusion

The primacy of kidney and cardiovascular diseases is conditional (cardiorenal or renocardial syndrome), since damage to one organ leads to the need to use

preventive and therapeutic measures in relation to another organ. The presence of CRS is currently a multidisciplinary problem requiring the efforts of clinicians of different specialties (cardiologist, nephrologist). This indicates the emergence of a new interdisciplinary field of science - cardionephrology.

Studying the causes and mechanisms of formation of types of CRS, early detection of biomarkers of damage and risk factors will help to determine optimal methods of CRS correction in order to improve survival, improve the quality of life of patients and determine approaches to preventive and treatment tactics.

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