CARDIORENAL SYNDROME IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND BONE-MINERAL DISORDERS

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ABSTRACT

Chronic kidney disease (CKD) is a risk factor with an independent significance for the development and progression of cardiovascular diseases and mortality. In recent years, great attention has also been paid to the type of heart and blood vessel involvement in CKD. The cardiorenal syndrome occurs with a disruption of the healthy relationship between the kidney function and the heart, maintaining hemodynamics and maintaining organ perfusion. The dysfunction of one organ creates prerequisites for an altered function of the other target organ. A common finding in advanced kidney failure is mitral, aortic sclerosis and calcinosis. Clinical thinking of the physician for cardiovascular syndrome and understanding of its pathophysiological characteristics will significantly improve prognosis and quality of life in patients with cardiovascular and chronic kidney disease.

Keywords: chronic kidney disease, cardiovascular syndrome, heartbeat

INTRODUCTION

The term “cardio renal syndrome” was introduced in 2004 year, by leading experts at the US National Heart Lung Blood Institute as a „condition where therapy to relieve congestive heart failure symptoms is hampered by further deterioration of renal function. Cardiorenal syndrome occurs with a disruption of the healthy relationship between the kidneys and the heart, while preserving haemodynamics and maintaining organ perfusion. The dysfunction of one organ creates dysfunctions of the other. Chronic Kidney Disease (CKD) is a risk factor with an independent significance for cardiovascular disease and mortality. In recent years, too much attention has been paid to the type of heart and vessel involvement in CKD. The aim is to determine the basic parameters of the calcium-phosphorus metabolism and the impairment of the target organs (heart and vessels) by a sonographic method. Calcium-phosphorus metabolism has long been the focus of studying changes in chronic obstructive disease, but recently there have been a number of stud-
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Cardiorenal syndrome (CRS) is classified into 5 subtypes:  
- Type 1 CRS: also called acute CRS, is characterized by acute renal impairment as a result of acute heart failure, both of which are de novo.
- Type 2 CRS: also called chronic CRS, is characterized by progressive chronic kidney disease secondary to chronic heart disease.
- Type 3 and 4 CRS: also called acute and chronic renal cardiac syndrome, in which, contrary to previous forms, cardiac dysfunction is the result of primary kidney disease.
- Type 5 CRS: combined heart and kidney dysfunction resulting from acute or chronic systemic disease (3,14).

Cardiac disorders have multiple negative effects on renal function, and renal dysfunction can significantly impair cardiac function. Therefore, the direct and indirect effects of any dysfunctional organ can initiate and contribute to the progression of the combined disease of both organs through a complex combination of multiple neurohormonal feedback mechanisms. That is why the cardiovascular syndrome (CRS) is classified into 5 subtypes:

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The interaction between these factors leads to the phenotypic transformation of smooth muscle cells into osteoblasts. In addition to this active process, the oversaturation of the extracellular fluid with high serum concentrations of calcium and phosphorus results in deposition of calcium apatite in the vascular walls and myocardial structures. The impairment may be predominantly of the atherosclerotic type or the arteriosclerotic type. Both types are associated with increased cardiovascular morbidity or mortality. Their determination is important for clinical practice with a view to refining the therapeutic behavior. A common finding in congestive renal failure is mitral and aortic sclerosis and calcinosis. Most often, mitral valve involvement leads to mitral regurgitation, and aortic valve calcifications - to aortic stenosis that progresses rapidly in cases of terminal renal failure. Hyperphosphatemia is a major predictor of valve calcification. Metastatic calcifications in the heart occur as well. Myocardial calcium deposition is associated with a significant increase in the incidence of cardiac arrhythmias, coronary events, and sudden cardiac death.

КЛАСИФИКАЦИЯ

Класификацията на кардиопатии и бъбречна дисфункция (КБД) се основава на следните параметри: артериалната клапна калциноза - до аортна стеноза, която бързо прогресира при терминална бъбречна недостатъчност. Хиперфосфатемията е главен предиктор за развитие на клапна калциноза. Не рядко се установяват и метастатични калцификати в сърдечните съдове. Отлагането на калций в миокарда е свързано със значително увеличение на честотата на сърдечните аритмии, коронарните инциден- 

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• Type 1 Cardiorenal Syndrome (Acute Cardiac Arrhythmias Syndrome or Acute Worsening of the Cardiac Function Leading to Acute Deterioration of Renal Function)

The greatest attention in this pathological relationship should be paid to the interactions between heart and kidney failure. According to ESC4 recommendations, acute heart failure is defined as a rapid or gradual change in the symptoms of renal failure leading to the need for emergency therapy and/or hospitalization to alleviate the symptoms. Dynamic changes in the symptoms of heart failure are a critical component of the clinical manifestation of acute heart failure. Regardless of etiology, almost universal evidence is the presence of pulmonary and/or systemic stagnation due to increased chamber filling pressures with/without decrease in cardiac output. The most common acute heart failure occurs as a decompensation of chronic heart failure. Acute heart failure may develop in the following variants (some of which may overlap): 1) worsening or decompensation of chronic heart failure (with peripheral edema/stagnation); 2) pulmonary edema; 3) hypertensive heart failure [elevated systemic arterial pressure, fluid retention (congestion) and often conserved left ventricular ejection fraction]; 4) cardiogenic shock (with evidence of tissue hypoperfusion induced by heart failure after adequate correction of preload); 5) right heart failure; 6) heart failure in the course of
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In patients with Type 1 cardiorenal syndrome, pre-morbid chronic renal dysfunction is common and predisposes to the development of acute renal impairment. The mechanisms in which the onset of acute heart failure or acute decompensated chronic heart failure lead to acute renal impairment are multiple and complex (Fig. 1).

In acute heart failure acute renal impairment is more severe in patients with left ventricular ejection fraction than in patients with left ventricular function, which is observed at about 70% of patients with cardiogenic shock. Importantly, the diagnosis of cardiovascular syndrome is the discovery of new biomarkers of acute renal impairment. With the use of complement-DNA genes and screening techniques, several genes can be detected whose expression is activated several hours after renal damage (1,2).

Another potential detrimental factor for renal function in the heart disease axis is the use of a contrast agent for imaging the heart. This issue requires detailed consideration. In general, high-risk patient groups require adequate prophylaxis of contrast-induced nephropathy. Given that patients with Type 1 cardiac arrhythmias have a high mortality, a careful, systematic, multidisciplinary approach involving a number of specialists - cardiologists, nephrologists, emergency doctors, is required (5).

Type 2 Cardiorenal Syndrome (Chronic Cardiovascular Syndrome or Chronic Disorders of the Cardiovascular System Leading to Progressive and Permanent Chronic Renal Disease)

Coronary heart disease and hypertension are the most common causes of chronic heart failure followed by valvular heart disease and cardiomyopathies. Renal dysfunction is common in patients with heart failure and is strongly associated with increased morbidity and mortality. More than 50% of patients with heart failure have at least moderate impairment of renal function and the incidence increases with the severity of heart failure, age, a history of hypertension or diabetes mellitus. Kidney dysfunction is just one of the effects of heart failure, but can play a key role in the pathophysiology of heart failure. In all patients with heart failure, renal function should be monitored regularly by measuring the serum creatinine level and/or degree of glomerular filtration (9,10).

The study of congestive heart failure and pulmonary catheterization effectiveness showed no relationship between pulmonary hemodynamic parameters and serum creatinine levels in patients. The only dependence is on the right ventricular pressure, indicating that kidney congestion may be more important than...
Hyperperfusion itself cannot explain renal dysfunction at this time. Further research is needed to clarify the mechanisms of renal dysfunction and its therapeutic response. Neurohormonal disorders are caused by excessive production of vasocostrictors (noradrenaline, angiotensin, endothelin) and change in sensitivity, and/or secretion of endogenous vasodilator agents (natriuretic peptides, nitric oxide).

**Type 3 Cardiorenal Syndrome (Acute Renal Cardiac Syndrome)**

Type 3 cardiovascular syndrome is characterized by sudden and primary worsening of renal function (acute renal failure, ischemia or glomerulonephritis) resulting in acute cardiac dysfunction (heart failure, arrhythmia, ischemia).

Acute renal impairment may affect the heart in several ways (Fig. 3) and the hierarchy is not defined. Overflowing with liquids can lead to the development of pulmonary edema. Hyperkalemia may lead to arrhythmias and cardiac arrest. Untreated uremia affects myocardial contractility by accumulation of substances suppressing myocardial function and pericarditis. Acidity causes pulmonary vasoconstriction, which is a significant factor in the development of a right-sufficiency. Acidemia has a negative inotropic effect and, together with electrolyte imbalance, can lead to an increased risk of developing arrhythmia. Kidney ischemia can in turn trigger inflammation and apop...
Type 3 cardiorenal syndrome is also leading to bilateral renal artery stenosis.
(or unilateral stenosis of a single kidney). Patients with this condition develop acute or decompensated heart failure due to diastolic dysfunction associated with chronic elevation of arterial pressure following excessive activation of the renin-angiotensin-aldosterone system, renal dysfunction with water and sodium retention and acute myocardial ischemia due to increased oxygen demand for myocardium associated with intense peripheral vasoconstriction. If acute renal impairment is severe and renal replacement therapy is required, cardiovascular instability resulting from rapid fluid and electrolyte infusion may lead to hypotension, arrhythmias and myocardial ischemia (4).

Type 4 Cardiorenal Syndrome (Chronic Cardiorenal Syndrome)
Type 4 cardiorenal syndrome is characterized by primary chronic kidney disease (e.g., chronic glomerular disease) associated with decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of cardiovascular events (Fig. 4). Chronic kidney disease is differentiated into five stages, based on the severity of renal impairment and the degree of glomerular filtration (7).

In large studies (SOLVD, TRACE - Survival and Ventricular Enlargement, VALIANT - Valsartan in...
ексцессивна продукция на вазоконстриктори (норадреналин, ангиотензин, ендотелии) и промяна на чувствителността и/или секрецията на ендогенните вазодилататорни фактори (натриуретични пептиди, азотен оксид) (11,12).

Кардиоренален синдром тип 3 (остър ренокардиален синдром)

Кардиореналният синдром тип 3 се характеризира с внезапно и първично влошаване на бъбречната функция (остро бъбречно нарушение, исхемия или глюмерулонефрит), което води до остра сърдечна дисфункция (сърдечна недостатъчност, аритмия, исхемия).

Острото бъбречно увреждане може да засегне сърцето по няколко механизма (Фиг. 3), чиято

Acute Myocardial Infarction), in which patients with baseline serum creatinine level were not included 2.5 mg/dL (221 μmol/L), decreased renal function was associated with significant mortality and high incidence of cardiovascular events. Adverse cardiovascular events in patients with kidney disease are associated with the plasma levels of specific biomarkers. Troponins, asymmetric dimethylarginine, plasminogen activator type 1, homocysteine, natriuretic peptides, C-reactive protein, serum amyloid A, hemoglobin, and ischemically-modified albumin are markers that correlate with cardiovascular outcome in patients with chronic renal disease. These observations provide mechanistic dependence between chronic subclinical infections, accelerating athero-

Fig. 4. Type 4 cardiorenal syndrome.
Pathophysiological interactions between the heart and the kidney in Type 4 cardiac arrest or chronic cardiorenal syndrome (chronic renal disease, e.g., chronic glomerular disease leading to a decrease in cardiac function, cardiac hypertrophy or an increased risk of cardiovascular events)
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Type 5 Cardiorenal Syndrome (Secondary Cardiorenal Syndrome)

Type 5 cardiorenal syndrome is characterized by the presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders (Fig. 5). It is known that some acute and chronic diseases can affect both organs simultaneously and that the disease of one organ can affect the other and vice versa. Examples are conditions such as sepsis, diabetes, amyloidosis, systemic lupus erythematosus and sarcoidosis. The onset of functional myocardial depression and inadequate cardiac output may further reduce renal function as in Type 1 cardiogenic syndrome, and the development of acute renal impairment may affect cardiac function as in type 3 cardiogenic syndrome. Renal ischemia may also induce myocardial damage to a vicious circle that damages both organs (15).

Therapeutic Approaches

Considering that, on the one hand, limited renal function reduces the ability to effectively correct the volume load in heart failure and, on the other hand, heart failure further aggravates renal function, the therapy of cardiorenal syndrome requires dynamic...
нужди на миокарда, а това води до интензивната периферна вазоконстрикция. При остро бъбречно нарушение се изисква необходимост от бъбречно-заместителна терапия, като сърдечно-съдовата нестабилност води до хипотония, аритмии и миокардна иксемия (4).

**Кардиоренален синдром тип 4 (хроничен ренокардиален синдром)**

Кардиореналният синдром тип 4 се характеризира с първично хронично бъбречно заболяване (напр. хронична гломерулна болест), асоциирано с понижена сърдечна функция, камерна хипертрофия, диастолна дисфункция и/или повишен риск за сърдечно-съдови инциденти (Фиг. 4). Хроничната бъбречна болест се диференцира в пет стадия, въз основа на тежестта на бъбречното увреждане и степента на гломерулната филтрация (7).

Патофизиологически взаимодействия между сърцето и бъбрека при кардиоренален синдром тип 4 или „хроничен ренокардиален синдром“ (хронична бъбречна болест, напр. хронична гломерулна болест, водеща до понижение на сърдечната функция, сърдечна хипертрофия или повишен риск за сърдечно-съдови инциденти) В някои големи проучвания (SOLVD – Studies Of Left Ventricular Dysfunction, TRACE – Trandolapril Cardiac Evaluation, SAVE – Survival And Ventricular Enlargement, VALIANT – Valsartan in Cardiac Evaluation, SAVE – Survival And Ventricular Dysfunction, TRACE – Trandolapril Cardiac Evaluation, и др.) са придобити ценни информация относно риска за сърдечно-съдови инциденти у пациенти с хронична бъбречна болест. Независимо от това, пациентите с хронична бъбречна болест имат значителен риск за сърдечно-съдови инциденти и това е свързано с пренасянето на риска за инциденти за неблагоприятните клинични резултати.

**ACE Inhibitors**

They have a pronounced nephroprotective effect, as, in addition to arterial pressure, intra-adrenal pressure decreases. This is done by significantly reducing the resistance of the v. afferens of the glomerular capillaries. Reduced proteinuria as a result of this leads to retention of renal function.

**Angiotensin 2 Receptor Blockers**

Their function is related to nephroprotection, they do not outperform ACE inhibitors and are used only in case of intolerance.

**Direct Renin Blockers (Aliskiren)**

They reduce intra-adrenal pressure and proteinuria.

**Calcium Antagonists**

Dihydropyridines such as nifedipine deregulate v. afferens regulation, increase intraglomerular pressure and increase proteinuria. Calcium antagonists that block third generation T and L channels - amiodipin and lacipidin favorably influence intramolecular pressure, reduce proteinuria, do not stimulate sympathetic system, which is one of their most important qualities. Calcium antagonists of the verapamil lineage have a beneficial effect on intraglomerular pressure, reduce proteinuria, and lead to retention of renal function.

**Beta Blockers**

In renal failure, the sympathoadrenal system is one of the four cardiorenal connectors and the effect on it is important for the prognosis.

**Diuretics**

They are most commonly used as first-line medication for volume burdens for patients with heart failure. Sometimes they cause a temporary rise in the body’s nitrogen, and this causes concern. Although blocking an important pathogenetic region, aldosterone antagonists should be given cautiously in renal insufficiency, in reduced doses, under strict laboratory control. Under conditions of renal insufficiency, their co-administration with ACE inhibitors and angiotensin receptor blockers should be avoided.

**Nesiritide**

It is a recombinant brain natriuretic peptide that is used more in the United States and less in European countries. In acute heart failure, there are no advantages over nitroglycerin, but there are proven advantages over placebo. Improves heart function, but does not improve kidney function, even in patients who have significant diuresis and natriuresis. A number of studies have shown that patients with cardiogenic syndrome often have episodes of hypotension and even cardiogenic shock with oligonucleosis and this requires the inclusion of inotropic drugs.
CONCLUSION

In acute and chronic conditions, the interaction between the heart and the kidneys in dysfunction of both organs has an important clinical significance. Calcium-phosphorus metabolism deteriorates as the renal insufficiency progresses and improves after transplantation. The incidence of calcifications of the myocardial structures becomes significantly greater with the progression of kidney disease and decreases after transplantation, with a stronger dependence on serum phosphorus. Changes can be explained with predominantly arteriosclerotic type vascular involvement in the progression of renal failure and impact on baroreflex sensitivity.

The complexity of these conditions and the need for adequate therapy require a multidisciplinary approach and involvement of various specialists - cardiologists, nephrologists, emergency doctors. Randomized controlled trials are needed to investigate interventions aimed at reducing the incidence of mortality in cardiovascular syndrome. Addressing cardiovascular syndrome and understanding its pathophysiological characteristics can significantly improve the prognosis of patients.

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Lacidipine, повлияват благоприятно на вътрешнолекулното налягане, намаляват протеинурията, без да стимулират симпатика, като това е едно от най-важните им качества.

Калициевите антагонисти от верапамиловия ред имат позитивен ефект върху вътрегломерулното налягане, намаляват протеинурията и подобряват бъбречната функция.

**Бета блокери**

При бъбречна недостатъчност симпатико-адреналната система е една от четирите кардио-ренина конектори и въздействието върху нея има важно значение за прогнозата и изхода на заболяванията.

**Диуретици**

Най-често се използват диуретиците като първа линия медикаменти при обемно обременяване на пациенти със застойна сърдечна недостатъчност. Понякога причиняват временно покачване на азотните тела, което предизвиква безпокойство. Въпреки че блокират важно патогенетично звено, антагонистите на алдостерона трябва да се предписват внимателно при пациенти с бъбречна недостатъчност – в намалени дози при стриктен лабораторен контрол. При установена бъбречна недостатъчност и ХБЗ трябва да се избягва съчетанието им с АСЕ инхибитори и ангиотензин рецепторни блокери (АРБ).

**Nesiritide**

Той е рекомбинантен мозъчен натриуритичен пептид, който се използва предимно в САЩ и по-малко в европейските страни. При остра сърдечна недостатъчност Nesiritide няма предимства пред нитроглицерин, но има доказан приоритет спрямо плацебо. Подобрява сърдечната функция, но не повлиява бъбречната дейност, дори при пациенти, които имат значителна диуреза и натриуреза.

Редица проучвания демонстрират, че пациентите с кардиоренален синдром нерядко имат епизоди на хипотония и дори кардиогенен шок с олиоанурия, като това налага определено включване на инотропни медикаменти.

**ЗАКЛЮЧЕНИЕ**

При остри и хронични състояния взаимодействието между сърцето и бъбреците при дисфункция и на двата органи има важно клинично значение. Калициево-фосфорният метаболизъм се влошава в напредването на бъбречната недостатъчност и се подобрява след бъбречна трансплантация. Честотата на калцификатите на миокардните структу-


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ри става сигнификантно по-голяма с напредването на бъбречното заболяване и намалява след трансплантация, като по-силна е зависимостта с нивото на серумния фосфор. Промените могат да се объяснят с предимно артериосклеротичния тип съдово засягане при напредването на ХБЗ и въздействие върху барорефлекторната чувствителност.

Комплексността на тези състояния и необходимостта от адекватна терапия изискват мултидисциплинарен подход и участие на различни специалисти – кардиолози, нефролози, рентгенолози, съдови хирури. Необходимо е провеждането на рандомизирани контролирани проучвания, в които да бъдат прилагани интервенциите, имащи за цел понижение на заболеваемостта и смъртността при доказан кардиоренален синдром. Клиничното мислене за кардиореналния синдром и разбирането на патофизиологичните му характеристики ще подобри значително прогнозата и качеството на живот при пациентите със сърдечно-съдови и хронични бъбречни заболявания.

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