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EFFECT OF RENAL DYSFUNCTION ON THE CARDIAC-VASCULAR SYSTEM. THE POSSIBILITIES OF EARLY DIAGNOSIS OF THE RENAL DYSFUNCTION

Abstract

The review is devoted to the discussion of modern concepts of the role of renal dysfunction in the development of chronic myocardial dysfunction in the context of cardio-renal syndrome (RVC) type 4. At the beginning of the review, the definition of cattle is given, general questions of pathogenesis and diagnosis of the disease are addressed. It is indicated that in patients with the initial stage of CKD, cardiovascular disorders are already registered which in the late stages of development of renal dysfunction are the leading causes of death and the true severity of the disease in patients with renal dysfunction is associated with an increased risk of cardiovascular events, rather than an achievement terminal renal failure and requiring renal replacement therapy. The progression of renal pathology leads to damage to the heart through various mechanisms and factors, both traditional and non-traditional, some of which, at the culmination of the renal continuum, are the result of the dialysis procedure itself in patients with terminal renal dysfunction. Mechanisms for the development of congestive heart failure in type 4 cattle include pressure overload (arterial hypertension) and volume (anemia, edematous syndrome), which increase in proportion to the decrease in renal function. Increase in blood pressure, changes in intracardial hemodynamics, deterioration of arterial compliance contribute to the acceleration of cardiovascular events. The role of laboratory predictors of renal dysfunction in the progression of cardiovascular disorders is discussed. The general approaches of echocardiographic visualization of the heart cavities and its importance in the diagnosis of cardiovascular diseases are discussed. Special attention is paid to the development of pulmonary arterial hypertension, changes in the left and right ventricle of the myocardium with renal dysfunction.

Key words: *renal dysfunction, cardio-renal syndrome, diagnosis, survival*

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25-OH-D_3 — vitamin D; RRT — renal replacement therapy; CHD — coronary heart disease; CRS — cardiorenal syndrome; PAH — pulmonary arterial hypertension; PAP — pulmonary arterial pressure; LV — left ventricle; UA — uric acid; RV — right ventricle; RAAS — renin-angiotensin system; GFR — glomerular filtration rate; HF — heart failure; CKD — chronic kidney disease; CKD-MBD — mineral and bone disorders in CKD; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol

The functions of the heart and kidneys are closely connected. Their interaction can be defined as a complex of biological relations between distant organs, which are mediated by cellular, molecular, nervous, endocrine and paracrine factors. Under physiological conditions, this connection helps to maintain homeostasis and the optimal functioning of the human body. Deterioration of the function

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of one of these organs causes a vicious circle of events leading to multiple organ failure. Although an impairment of renal function is well known in patients with heart disease [1–3], it remains unclear whether renal dysfunction is a passive response to cardiac failure. The term "cardiorenal syndrome" (CRS), i.e. the coexistence of cardiac and renal pathology in the same patient, has been widely used in clinical practice for more than 13 years. The clinical characteristics of CRS are based chiefly on primary organ dysfunction. Classification criteria have recently been reviewed by the ADQI working group (Acute Dialysis Quality Initiative) [4–8]. Thus, CRS type 4, or chronic cardiorenal syndrome, was defined as "chronic kidney disease leading to an impairment of cardiac function" and implies an extreme risk of cardiovascular disease in patients with chronic kidney disease (CKD) [9, 10]. However, little is known about whether specific renal disorders, such as mineral and bone disorders in CKD (CKD-MBD), endothelial dysfunction, fluid retention or activation of the renin-angiotensin (RAAS) and neuroendocrine systems, can contribute to the right ventricle (RV) dysfunction [11–13]. Studies of recent years found that cardiovascular disorders, which in the late stages of the renal dysfunction development are the leading causes of death, are already recorded in patients with initial stage CKD [14–16]. The accumulated data indicate that the true severity of the disease in patients with renal dysfunction is associated rather with an increased risk of cardiovascular events than with the development of end-stage renal disease requiring renal replacement therapy (RRT). According to modern data, the risk of kidney failure exceeds the risk of cardiovascular events only in patients with advanced CKD (C4) [17, 18].

Discussing the renal risk factors for cardiovascular disorders in CKD, it should be noted that dyslipidemia and chronic inflammation place an additional burden on the myocardium and endothelium of the vessels [19]. In patients with impaired renal function and significant proteinuria, the lipid profile becomes atherogenic, in part because of dysfunction of high-density lipoprotein cholesterol (HDL-C) and excessive oxidation of low-density lipoprotein cholesterol (LDL-C) [20]. In addition, chronic inflammation is one of the pathogenetic factors that can contribute to the development and progression of cardiovascular diseases, as has been confirmed in studies that showed a significant increase in C-reactive protein in patients with CKD with significant positive correlation with the renal arterial resistive index and feedback with the glomerular filtration rate (GFR) [21–23].

There is an independent association between the severity of renal dysfunction and adverse cardiac outcomes. A recent meta-analysis [24] described the exponential relationship between the severity of renal dysfunction and the risk of all incidences of death. The prevalence of cardiovascular events accounting for more than 50% of total mortality was demonstrated [7].

In cases of coronary heart disease (CHD) and heart failure (HF), the development of renal dysfunction and cardiac pathology may have the same or shared risk factors reflecting the prevalence of vascular and endothelial dysfunction and/or the toxic effect of uremia [25]. Data from more than 1.4 million people from several meta-analyses were analyzed [14, 15]. The risk of cardiovascular mortality changed slightly with GFR greater than 75 mL/min/1.73 m² after adjustment for traditional cardiovascular risk factors. It increases linearly with a GFR less than these rates [14, 15]. Cardiovascular mortality was almost twice as high in patients with CKD Stage 3 (GFR 30–59 mL/min/1.73 m²) and three times as high in Stage 4 (15–29 mL/min/1.73 m²) than in individuals with normal renal function [14, 15]. In case of upper limit of moderate albuminuria (30–299 mg/g), the risk of cardiovascular mortality rises more than twofold compared to that in individuals without albuminuria [14, 15]. Even a small increase in albuminuria requires clinical attention. In addition, CHD itself can contribute to the development of hemodynamically significant arrhythmias and congestive HF [26]. The progression of renal pathology damages the heart through various mechanisms and factors, both traditional and non-traditional, some of which, in the culmination of the renal continuum, are the result of the dialysis procedure itself in patients with terminal renal dysfunction [27, 28].

The mechanism of development of congestive HF in CRS type 4 includes pressure overload (hypertension) and volume overload (anemia, edematous syndrome); HF increases proportionally as renal function decreases. As noted, the increase in blood pressure, changes in intracardial hemodynamics, deterioration of arterial compliance, which may be, in part, a result of CKD-MBD, contribute to the acceleration of cardiovascular events [29].

In recent years, special attention has been paid to the role of phosphate retention and related disorders falling under the CKD-MBD section. Patients with renal dysfunction often develop a deficiency in vitamin D activity due to the lack of its precursor, the impairment of activity of the renal 1 -hydroxylase enzyme, which converts this precursor into an active hormone, or both [30]. As a result, phosphorus and calcium metabolism in tissues is disrupted and hyperphosphatemia occurs [31].

This disorder is characterized by early disruption of skeletal homeostasis, a decrease in the activity of vitamin D (25-OH-D_3), and the subsequent development of hyperparathyroidism. With regard to CRS type 4, this imbalance of bone and mineral metabolism is manifested by the calcification of blood vessels; the heart vasculature and valves are literally transformed phenotypically and begin to "ossify".

In particular, vascular smooth muscle cells undergo transformation into cells that have characteristic signs of osteoblasts. These cells express cell markers and products necessary for the production and maintenance of bone tissue [32].

In patients with CKD, a significant decrease in 25-OH-D_3 and a marked increase in intact parathyroid hormone and phosphorus are recorded already at an early stage of the disease. Given this, it can be assumed that atherosclerosis, endothelial dysfunction and CKD-MBD can determine changes in renal blood flow, pulmonary circulation, and also the geometry of the right heart with a decrease in the post-systolic excursion of the tricuspid valve (TAPSE / tricuspid annular plane systolic excursion) and increase of systolic pulmonary arterial pressure according to echocardiography (ePASP / estimated pulmonary artery systolic pressure).

Disrupted mineral metabolism, which is often observed in CKD, can promote the acceleration of the structural remodeling of the heart. Thus, experimental studies have shown that hyperparathyroidism and vitamin D deficiency can adversely affect the left ventricle (LV). The effects of mineral metabolism on the RV in renal dysfunction are also actively studied [33–35]. In particular, the signs of hyperparathyroidism, hyperphosphataemia, vitamin D deficiency and vascular calcification in association with CRS type 4 have been identified already in the early stages of CKD [13, 34].

Hyperuricemia can act pathogenetically as an initiating agent for oxidative stress, inflammation, endothelial dysfunction and the development of systemic atherosclerosis, but its role is still not fully understood. In patients with CKD, the level of uric acid (UA) significantly increases in comparison with healthy individuals. Hyperuricemia is common in CKD and is associated with LV hypertrophy, impaired renal function, and increased cardiovascular morbidity and mortality [36, 37]. However, the effect of hyperuricemia on the RV is still poorly understood. When the blood UA level increases, production of nitric oxide is suppressed, and the proliferation and migration of vascular endothelial cells increase. These effects can be partially associated with the activation of RAAS, which causes the development of LV hypertrophy and myocardial fibrosis, by direct exposure of angiotensin II and aldosterone to cardiomyocytes [38].

Other factors that increase cardiovascular risk in patients with CKD include an increase in activity of RAAS and the sympathetic nervous system. Angiotensin II stimulates production of superoxides, interleukin-6, and other proinflammatory cytokines. At the same time, the bioactivity of nitric oxide, which is involved in the contraction and growth of vascular smooth muscles and in platelet aggregation, as well as in leukocyte adhesion to endothelium, is decreased. The activity of the renalase, the enzyme responsible for catecholamine metabolism, is decreased in patients with CKD. Absolutely, all these vasoactive substances and multidirectional pathological changes prevent normal endothelium function [39, 40].

The concentration of B-type natriuretic peptide (BNP) and inactive NT-proBNP peptide also significantly increases in patients with CKD compared with patients of the corresponding age and gender with normal renal function [41].

As the CKD stages progress and culminate in the onset of a condition that requires dialysis (one of the components of CKD stage 5), the associations between renal dysfunction and heart disease become complex and multilevel. It is expected that CRS type 4 can cause significant negative consequences, both at the individual and public levels, as the number of patients with CKD in the population steadily grows [28].

In individuals who are at the stage of hemodialysis therapy, the functioning arteriovenous shunt additionally contributes to a volume overload [29]. This increase in cardiac load leads to compensatory hypertrophy, and, accordingly, to excessive work of cardiac myocytes with an increase in the need for

oxygen delivery. Inevitably, the death and fibrosis of myocytes occur, leading to the dilation of the cardiac chambers and the development of systolic myocardial dysfunction [42, 43].

Clinico-epidemiological studies have established that the incidence of LV hypertrophy is already increasing at the initial stage of renal dysfunction. LV hypertrophy in CKD is characterized by myocardial fibrosis, which can result in a contractility disorder [44]. As noted above, both nephrogenic anemia [45] and an increase in vascular rigidity can play a role in the development of LV hypertrophy in addition to hypertension, which subsequently leads to a decrease in the coronary flow reserve [46]. The expression of endothelial nitric oxide synthase (eNOS) is suppressed, suggesting a possible mechanism of coronary endothelial dysfunction at the early stages of CKD [39].

The studies of Dini et al. [11] have shown that cardiovascular disorders are an important prognostic factor of poor survival in patients with CKD. Right ventricular HF also contributes to morbidity and mortality. In addition, the increase in RV mass was associated with cases of HF and cardiovascular mortality. It is appropriate to note that the left and right ventricles have a different embryological origin, geometry, and fiber orientation. The LV is known to originate from the primary layer of the heart, whereas the RV originates from the anterior section of the heart; the LV has an elliptical shape, whereas the RV is triangular. In addition, LV myocardium is thicker and has a greater mass than that of RV and, therefore, is better adapted to pressure overload, while a more compliant RV tolerates volume overload better [11–13].

The parameter of tricuspid annular plane systolic excursion (TAPSE), along with pulmonary arterial pressure (PAP), is one of the widely studied methods of Doppler echocardiography of the RV. It is associated with adverse outcomes [47]. Thus, high ePASP is an identified factor of cardiovascular risk in the general population, but little is known about systolic PAP at the early stages of CKD [48, 49]. The prevalence of ePASP was evaluated in two large cohort studies. Thus, the Olmsted County Study [50] and the Armadale Echocardiography Study [51] showed an ePASP level of about 5% in the first case and 9.1% in the second one. In patients in the last stages of CKD (stage C5) according to the KDOQI (Kidney Disease Outcomes Quality Initiative), the ePASP level significantly exceeds that of the general population, accounting for 9–39% among those receiving conservative treatment, 18.8–68.8% among the patients on hemodialysis [50], and 0–42% among those on peritoneal dialysis [33]. Pulmonary hypertension in CKD can be associated with several risk factors, such as anemia, apnea, increased sympathetic activity, inflammation, vascular calcification, and endothelial dysfunction, but the pathogenesis of pulmonary arterial hypertension (PAH) in patients with early stages of CKD remains unclear [13, 48].

In one study, TAPSE and ePASP were significantly different in patients with CKD from the control group of healthy subjects. In addition, ePASP negatively correlated with GFR, showing its progressive increase with impaired renal function, while there were no statistically significant differences between the two groups in pulmonary artery wedge pressure and the RV end-diastolic volume. In fact, hyperparathyroidism in experimental models (on dogs) was associated with calcification of pulmonary vessels and PAH, and with an increase in the PAH frequency. A relationship between PAH and hyperparathyroidism was also discovered in patients at the pre-dialysis stage as well as in those undergoing dialysis [33]. Insufficient activation of vitamin D receptors can also affect CRS type 4, which is manifested not only in damage to classic target organs, but also in damage to other nonclassical targets, including vessels, the heart, the immune system, endocrine organs, and the nervous system. Myocardium is an important target of vitamin D. Its deficiency leads to increased regulation of RAAS, hypertrophy of the LV and vascular smooth muscle cells, which was shown in experimental studies in mice with insufficient activation of vitamin D receptors. Overexpression of renin was detected and myocyte hypertrophy was discovered [53, 54]. Vitamin D deficiency is associated with an increase in cardiovascular morbidity and mortality, possibly due to changes of the structure and function of the heart, and while its effect on the LV has been carefully studied, little is yet known about its effect on the RV [13, 55, 56].

Therefore, a timely assessment of the bidirectional influence of the heart and kidneys is a key point in understanding the severity of such disorders. The mechanisms leading to multiple organ changes in the development of renal dysfunction require further study, and the implementation of treatment and prevention measures should be carried out while taking into account the multidisciplinary nature of the problem.

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

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