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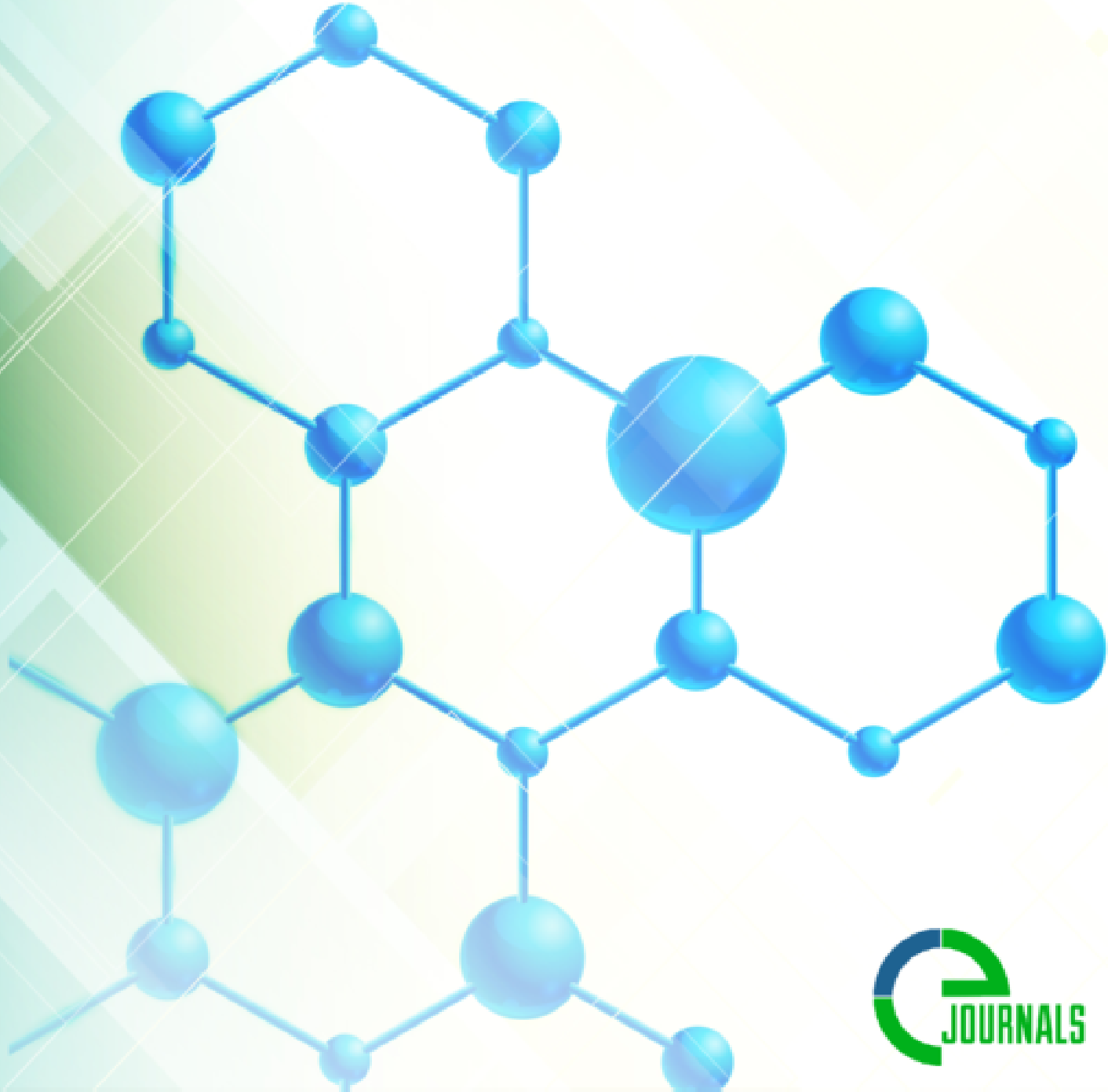

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# CLINICAL FEATURES OF CKD5D PATIENTS AND SYMPTOMATIC INTRADIALYSIS HYPOTENSION

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*Abstract: The study included 82 patients with CKD5d, the inclusion criterion was the presence of a risk of developing symptomatic intradialytic hypotension according to the Rice scale of SIH developed by our group. This sample of patients was randomly divided into 3 comparison groups: food deprivation, levocarnitine infusion, and midodrine administration immediately before the hemodialysis session. The study compared the groups by the incidence of SIH and other complications of the procedure. In patients with CKD5d at risk of SIH, the use of midodrine before HD can reduce the severity of the decrease in blood pressure and reliably prevent the development of SIH in 39% of patients. Food deprivation and a single levocarnitine infusion did not have a significant effect on the dynamics of SBP and the incidence of SIH.*

*Keywords: hemodialysis, chronic kidney disease, intradialytic hypotension, levocarnitine , midodrine , food deprivation.*

Relevance: Symptomatic Intradialytic hypotension (IDH) is one of the most common and clinically significant complications of hemodialysis in patients with chronic kidney disease stage 5d (CKD5d). IDH is associated with a deterioration in quality of life, an increased risk of hospitalization, and a decrease in life expectancy of patients. In this regard, the development and implementation of effective guidelines for the prevention of IDH is critical to improving clinical outcomes and optimizing care for patients with CKD5d.

The pathogenesis of hypotension during dialysis is a complex and poorly understood process in which, under the influence of factors associated with both the patient (e.g., LVH, diastolic dysfunction of the ventricle, arrhythmia, coronary heart disease, heart valve and myocardial pathology, anemia, protein and metabolic disorders, inflammatory markers, etc.) and the hemodialysis procedure (changes in the rate and volume of ultrafiltration, underestimation of the dry weight; low levels of sodium and calcium in the dialysate, high temperature of the dialysate, as well as bioincompatibility of the dialysis membrane, activation of the complement system, etc.), there is a decrease in plasma volume and disruption of cardiovascular regulatory mechanisms [1, 2, 3]. IDH occurs as a result of changes in the factors responsible for maintaining hemodynamic stability: slow movement of fluid from the extravascular space into the vessels ( refilling ), a decrease in systemic vascular resistance and cardiac output.

Patients with CKD 5d included in the first stage of the study did not differ from healthy volunteers (CG) in weight, despite the fluid retention syndrome typical of the terminal stage of CKD (Table 1). This phenomenon is possibly associated with sarcopenia observed in patients with terminal stage organ failure. The examination conducted before the HD procedure showed that patients with CKD had higher BP (both SBP and DBP, Fig. 3.1). At the same time, SBP recorded during the orthostatic test in both compared cohorts was comparable, reflecting the phenomenon of orthostatic hypotension in patients with CKD 5d. This phenomenon was registered in 1 representative of the CG (5%) and in 30 patients with CKD 5d (60%, chi square 2x2=17.69, p <0.001).

**Table 1**
**Clinical features of patients with CKD5d**

| indicator | KG (n=20) | CKD5d, stage 1 (n=50) |
|---|---|---|
| Age, years | 49.55 ± 2.91 | 43.42 ± 1.97 |
| duration of main disease, years | | 18.22 ± 1.12 |
| length of service as a State Duma member, months | | 5.90 ± 0.57 |
| weight before GD, kg | 81.25 ± 1.80 | 85.22 ± 1.50 |
| estimated target weight, kg | | 80.96 ± 1.42 |
| residual diuresis, ml/ day | | 127.90 ± 10.09 |

Note: Differences between groups are not significant.

Laboratory examination showed that patients with CKD, compared to the control group, had an increased concentration of blood creatinine (which reflects the essence of the pathology, $p < 0.001$), as well as a decrease in the concentration of total blood protein ( $p < 0.001$), an increase in the concentration of parathyroid hormone and phosphorus, which reflects a violation of bone-mineral metabolism characteristic of CKD5d ( $p < 0.001$ for both molecules, Table 3.2). These disorders are based on a violation of the renal excretion of small and medium molecules, which include parathyroid hormone, resulting in the development of osteoporosis and hyperphosphatemia .

A significant increase in the concentration of inflammatory markers - CRP and interleukin 6 ( $p < 0.001$ for both markers) was also noted.

Complete blood count demonstrated a decrease in blood hemoglobin concentration typical of CKD5d ( $p < 0.001$), associated with both a decrease in the expression of erythropoietin by the kidneys against the background of renal parenchymal fibrosis and with chronic systemic inflammation and the use of iron stores for the synthesis of matrix metalloproteinases . The number of leukocytes in patients with CKD5d was increased compared to the CG ( $p < 0.001$), but was within the reference norm, which confirms the absence of an acute inflammatory reaction or pronounced exacerbation of chronic inflammatory diseases. The high concentration of proinflammatory cytokines reflects low-intensity chronic inflammation induced by both terminal renal failure and hemodialysis itself, in particular the dialyzer membrane (contact inflammation).

The concentration of platelets in the peripheral blood of patients was significantly reduced compared to representatives of the control group ( $p < 0.01$), which is probably associated with both a decrease in the hematopoietic activity of the megakaryocytic lineage and with the mechanical destruction of platelets during HD.

**Table 2**

**Laboratory parameters in patients with CKD5d in the predialysis period and in the CG**

| indicator | avg KG (n=20) | Wed 1 stage (n=50) |
|---|---|---|
| Creatinine, μmol /l | 64.55±2.08 | 308.44±14.60*** |
| total protein, g/l | 69.60±1.71 | 45.84±1.28*** |
| Parathyroid hormone, pg /ml | 35.30±2.23 | 330.08±18.72*** |
| Calcium, mmol/l | 2.31±0.05 | 2.19±0.07 |
| Phosphorus, mmol/ | 1.05±0.03 | 2.29±0.06*** |
| CRP, ng /ml | 1.38±0.16 | 7.66±0.58*** |
| IL-6, pg /ml | 2.25±0.47 | 9.90±0.60*** |
| Hemoglobin, g/l | 133.85±4.24 | 92.02±1.64*** |
| Leukocytes, *10(9)/l | 6.03±0.27 | 8.83±0.27*** |
| Platelets, *10(9)/l | 282.00±13.64 | 222.90±11.41** |

Note: * - reliability of intergroup differences: two signs - $p < 0.01$, three signs - $p < 0.001$.

ECG study revealed that 3 patients with CKD5d had a disturbance of heart rhythm in the form of permanent atrial fibrillation, while in the CG, sinus rhythm was registered in all. In terms of heart rate, sinus tachycardia was registered in the CKD5d group (95.50±1.94 beats per min, versus 66.65±2.60 beats per min, $p < 0.001$), which is associated with both redistributive sideropenia and myocardial remodeling , which is a marker of the risk of developing heart failure.

Evaluation of the ECG curve shape revealed in the CKD5d group an expansion of the QRS complex to an average of 100.70±2.36 msec (versus 83.40±1.71 msec in the CG, $p < 0.001$). This change may be associated with both a disturbance of intraventricular conduction due to myocardial hypertrophy or the development of intermyocardial fibrosis, and with a disturbance of electrolyte balance , in particular hyperkalemia, which is also characteristic of the terminal stage of CKD.

Pathological Q wave was recorded in 8 patients with CKD5d (16%), which is associated with both myocardial hypertrophy and intermyocardial fibrosis, and with ischemic myocardial necrosis. In the CG, pathological Q wave was not recorded in any case. Also, in the CKD group, changes in the repolarization phase (chi square 2x2 = 4.55, $p < 0.05$), signs of LVH (chi square 2x2 = 4.86, $p < 0.05$) and ventricular extrasystole (chi square 2x2 = 6.70, $p < 0.01$) were observed significantly more often than in the CG . These findings reflect the processes of pathological myocardial remodeling in patients with CKD5d in response to both metabolic and hemodynamic changes.

EchoCG study revealed signs of myocardial remodeling in patients with CKD5d ( Table 3.3). Thus, the LV volume in patients with CKD was significantly increased compared to the CG ( $p < 0.001$) and compared to the reference norm. The LV myocardial mass was also increased ( $p < 0.001$ compared to the CG), but the TCS index did not differ in both compared groups, indicating balanced parallel processes of LVH and dilation. Thus, on average, LV remodeling by the type of eccentric LVH with dilation is recorded in the CKD5d group. LV remodeling with dilation is associated with spherical reorganization of the cavity, an increase in the area of myocardial fibrosis and a decrease in the optimality of systolic contraction. As a result, the efficiency of systole decreases, which in the present study was manifested by a decrease in the LVEF index

in the CKD5d group compared to the CG ( $p < 0.01$), although it remained on average within the reference norm of 50% in the group. The IRRS, reflecting the regional contractile function, demonstrated a significant increase in patients with CKD5d ( $p < 0.01$), which may be associated with ischemic damage, intraventricular dyssynchrony against the background of LBBB block or intramyocardial fibrosis.

Also in the CKD5d group, LA dilation was observed ( $p < 0.001$ comparison of LA with CG), which may explain the appearance of AF in this group of patients.

One of the urgent problems of renocardial syndrome is pulmonary hypertension, in particular, in patients receiving treatment with program hemodialysis, the syndrome of CHF with high output develops due to blood shunting in the AV fistula. In the present study, dilatation of the RV ( $p < 0.001$) and pulmonary systolic hypertension PASP ( $p < 0.001$) were detected .

The disruption of the structure and architecture of the myocardium during remodeling increases tissue rigidity, resulting in disruption of the optimal active diastolic relaxation of the myocardium and development of diastolic dysfunction of the LV with a decrease in the ratio of early and atrial filling velocities ( $p < 0.01$ compared to CG). Reactive amplification of atrial systole is one of the mechanisms for the development of its dilation.

**Table 3**
**EchoCG parameters in patients with CKD5d and representatives of the CG**

| indicator | avg KG (n=20) | Wed 1 stage (n=50) |
|---|---|---|
| iEDVO LV, ml/m2 | 59.75±2.98 | 93.68±2.80*** |
| iMMLV , g/m2 | 77.90±3.01 | 107.50±2.40*** |
| OTC, rel ed | 0.35±0.01 | 0.36±0.01 |
| LVEF, % | 62.50±1.16 | 58.22±0.95** |
| INRS, score | 1.01±0.01 | 1.07±0.02** |
| ILP , ml/m2 | 26.65±1.03 | 41.00±1.13*** |
| RV , mm | 22.15±1.02 | 32.94±1.01*** |
| NPV, mm | 15.65±0.41 | 20.72±0.57*** |
| PASP , mmHg | 23.65±0.68 | 34.46±1.07*** |
| E/A LV, rel. ed | 1.27±0.05 | 1.00±0.06** |

Note: * - reliability of intergroup differences: two signs - $p < 0.01$, three signs - $p < 0.001$.

remodeling is largely a response to hemodynamic stress, but metabolic changes characteristic of CKD also affect the CVS tissues. Thus, in patients with CKD, calcification of the heart valves is recorded , which reflects a violation of bone-mineral metabolism with the formation of extraosseous calcification. Thus, in patients with CKD5d, calcification of the valves occurs in 17 patients (34%), against 1 case (5%) in the group of healthy peers (chi square $2x2 = 6.70$, $p < 0.01$). The aortic valve (AV) is predominantly affected, as it is subject to the greatest hemodynamic stress due to high-speed flow. Valve calcification leads to the formation of regurgitation (26 patients in the CKD group - 52%) and stenosis (44 people - 88%). In the CG, regurgitation was observed in 25% (5 people, chi square $2x2=4.35$, $p < 0.05$), stenosis - in no case. However, all the described disorders of the heart valve function in the present study were hemodynamically insignificant and did not require surgical interventions.

Thus, a comparison of patients with CKD5d and CG showed the presence of hemodynamic and metabolic shifts that change the structural and functional state of the cardiovascular system and are associated with deterioration of vascular regulation.

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