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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*

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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

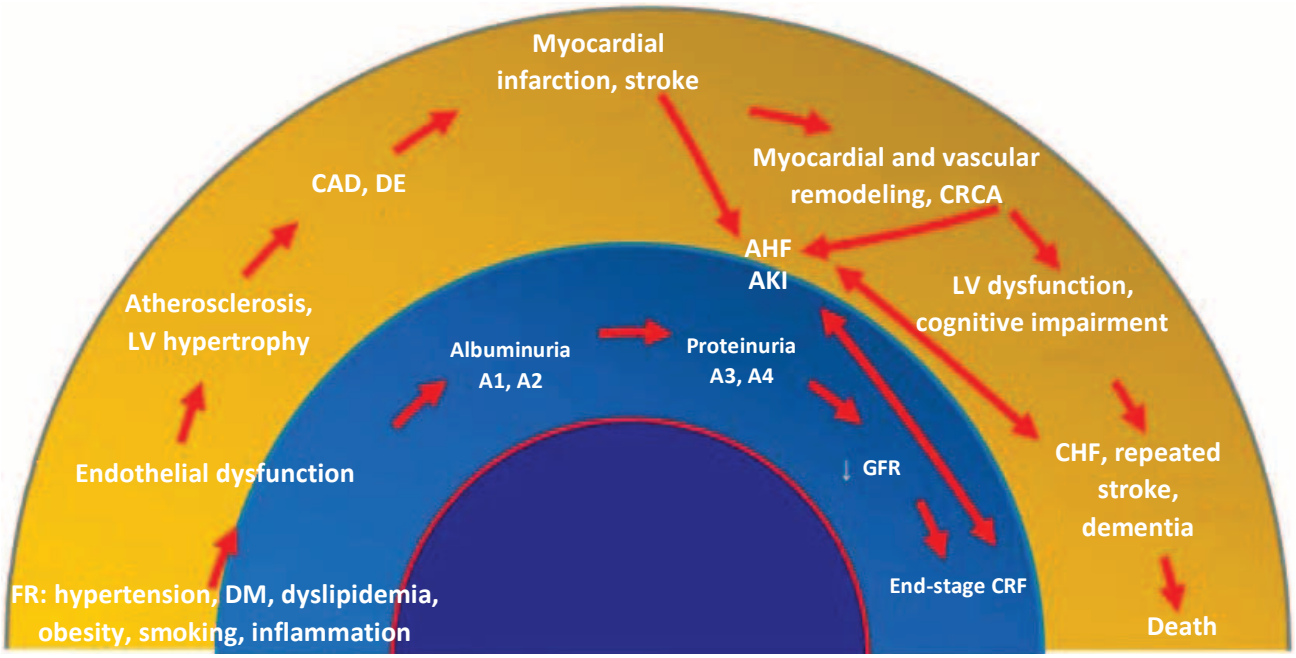

Figure 1. Cardiovascular, cardio-cerebral and renal continuum, with changes according to [Dzau et al. Circulation. 2006;114:2850–2870]. FR — risk factors, LV — left ventricle, DM — diabetes mellitus, CAD — coronary artery disease, DE — dyscirculatory encephalopathy. GFR — glomerular filtration rate, 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].

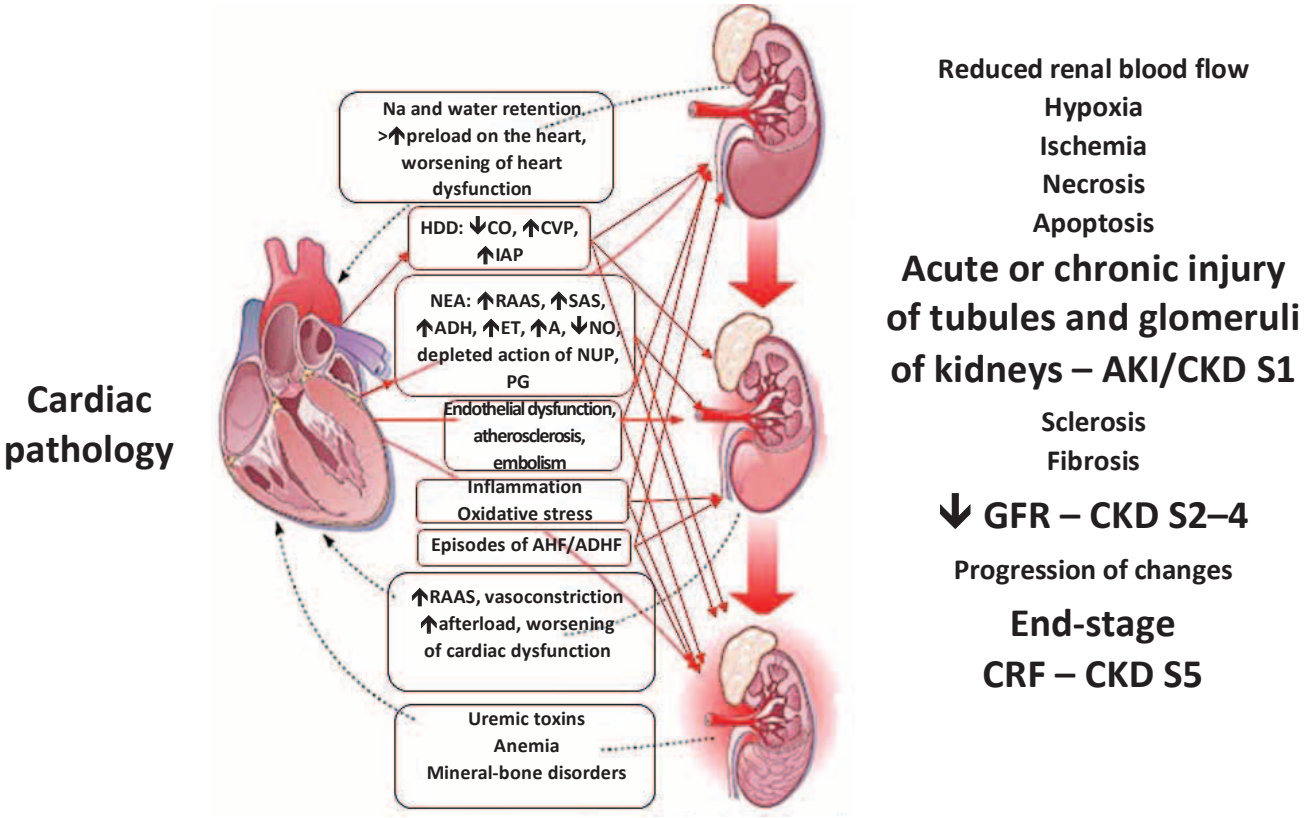

Figure 2. Cardiorenal syndrome pathogenesis, with changes according to [Ronco, C., Haapio, M., House, A.A. et al., *Cardiorenal syndrome.* //J Am Coll Cardiol, 2008. Vol. 52 (19): P. 1527–39]. A — adenosine, ADH — antidiuretic hormone, IAP — intra-abdominal pressure, HDD — hemodynamic disorders, NUP — 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

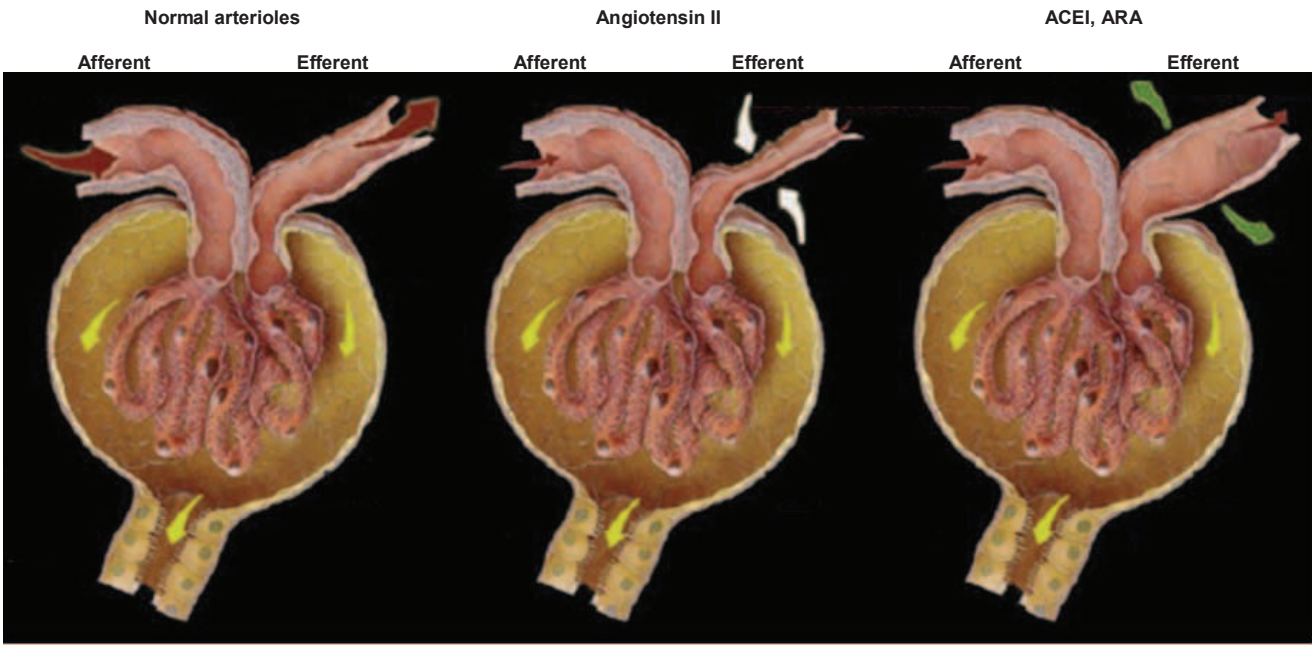

Figure 3. Effect of ATII on the glomerulus

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.

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A CASE OF SPONTANEOUS CORONARY ARTERY DISSECTION (REVIEW AND CASE REPORT)

Abstract

The article presents a literature review on the problem of spontaneous coronary artery dissection (SCAD) — tearing of its wall, not associated with atherosclerosis, trauma or iatrogenic effects, leading to blood penetration between vessel layers of the artery. The consequence of this dissection is obstruction of the coronary artery due to the formation of intramural hematoma or intima damage and myocardial ischemia with development of acute coronary syndrome, myocardial infarction or sudden cardiac death. Information on the epidemiology, pathophysiology and etiology of the disease is presented in the paper. It highlights a role of arteriopathies, inflammatory diseases, pregnancy and female sex hormones, genetic causes as well as initiating and stress factors in SCAD development. The clinic picture and diagnosis of the disease are described. It was emphasized that in addition to clinical manifestations, the traditional electrocardiogram and coronary angiography remain the standard for diagnostics of the dissection. In the treatment of SCAD, percutaneous coronary intervention with stenting of the affected artery, coronary artery bypass graft and medications are used, with preference of conservative drug therapy. A special attention is paid to the features of diagnostic and therapeutic measures in pregnant and breast-feeding patients. The article also presents a clinical case of large-focal myocardial infarction complicated by cardiogenic shock in a young woman in the postpartum period without any risk factors for coronary heart disease, which was caused by SCAD. Diagnosis was accompanied by certain difficulties. An urgent percutaneous coronary intervention with stenting of the infarct-related coronary artery allowed to rapidly improve and stabilize the patient's condition.

Key words: *spontaneous coronary artery dissection, myocardial infarction, cardiogenic shock, diagnosis, coronary angiography, treatment, pregnancy, postpartum period*

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CABG — coronary artery bypass graft, SCAD — spontaneous coronary artery dissection, MI — myocardial infarction, IMH — intramural hematoma, LV — left ventricle, ACS — acute coronary syndrome, FMD — fibromuscular dysplasia, PCI — percutaneous coronary intervention, ECG — electrocardiogram

Introduction

Spontaneous dissection (rupture) of the coronary artery (SCAD) is a tear of its wall, not associated with atherosclerosis, trauma or iatrogenic effects, leading to the penetration of blood between the vessel membranes (tunica intima, tunica media and tunica externa). The consequence of such dissection is coronary artery obstruction due to the formation of intramural hematoma (IMH) or damage to intima and myocardial ischemia with development of acute coronary syndrome (ACS), myocardial infarction (MI) or sudden cardiac death [1].

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SCAD was described for the first time in 1931 [2], but in recent years, due to the rapid development of endovascular technologies, this problem has become particularly relevant [3].

Epidemiology

The true incidence of SCAD is unknown because of the difficulties with its diagnosis and the lack of experience among clinicians. However, it is believed that SCAD may cause ACS and MI in 1 to 4% of cases in the general population, in 35% of women aged under 50 years [4] and in 43% of pregnant women [5]. The left coronary artery is the most often affected (32–50%), and multiple SCAD occurs in 23% of cases [6].

Pathophysiology

SCAD is characterized by spontaneous formation of IMH within the coronary artery wall. This is confirmed by both intracoronary images and serial histopathological observations [4]. There are two theories for the development of SCAD. The first suggests that the primary pathological event is damage to the vascular wall (intima tear), which allows blood to leave the true channel of the vessel and create a false one. According to the second theory, spontaneous hemorrhage from own small artery vessels (vasa vasorum) within the vascular wall is considered to be the primary initiating event [7].

In the analysis of serial optical coherence tomography scans in patients with SCAD, it was noted that the site of intima damage can not always be found by this technique, which supports the second theory of pathogenesis [8]. In cases where it is possible to detect the site of damage to the intima, it remains unclear whether this is the initiating event or the consequence of increased pressure in the false channel, or the impact of the instrumental procedure on the coronary artery. The presence of an inflammatory cell infiltrate surrounding the dissection site can be used to recognize SCAD and to distinguish it from an iatrogenic one [9].

Etiology

The nature of SCAD seems to be multifactorial: hereditary or acquired arteriopathies, systemic inflammatory diseases, genetic defects, hormonal influences and their combinations with initiating stressful situations [10].

Arteriopathy

Among all arteriopathies, association of SCAD with multifocal fibromuscular dysplasia (FMD) is the most common (17–86%) [11]. This dysplasia, which affects any arterial bed, can manifest in the form of arterial stenosis, aneurysm, tortuosity or dissection. Multifocal FMD is its most frequent type and angiographically looks like zones of intermittent stenoses, dilations and aneurysms; the focal variant (<10% of cases) angiographically manifests itself as a single concentric or tubular narrowing. Currently, FMD is associated with conditions in which the fragility of arterial vessels is genetically mediated. Reports on typical histological and angiographic findings of FMD in the coronary arteries, including patients with previous events of SCAD, gave reason to believe that it can be a manifestation of a specific "coronary form" of FMD [12].

Pregnancy and female sex hormones

SCAD is the most common cause of MI in pregnant or postpartum female patients (approximately 1.81 cases per 100,000 pregnancies) [3]. The majority of its cases develop in the third trimester or early postpartum period, but there is evidence of SCAD in earlier gestation periods [13].

The causes of pregnancy-associated SCAD are not fully clear, although it is assumed that hormonal changes occurring during this period violate the architecture of the arterial wall, contribute to its rupture, the appearance of IMH and the onset of clinical symptoms [14]. The accumulation of these changes over several pregnancies may explain the increased risk of SCAD in women with multiple births. This is also facilitated by the presence of hypertension, lipid disorders, chronic depression, migraine, as well as age-related motherhood and infertility treatment in history [14].

Women with pregnancy-associated SCAD have a worse prognosis than other patients, and it is unclear why pregnancy-related disease is characterized by more aggressive widespread dissection and why it does not develop in most of them [15].

Inflammatory diseases

There are reports describing SCAD in patients with various systemic inflammatory processes, including systemic lupus erythematosus, inflammatory bowel disease, nodular periarteritis, sarcoidosis, and cryoglobulinemia secondary to hepatitis C [3].

Heredity and genetics

SCAD sometimes develops in individuals with hereditary arteriopathies and connective tissue dysplasia. Cases in patients suffering from Ehlers-Danlos vascular syndrome, Marfan and Loeys-Dietz syndromes, and also with polycystic kidney disease were described [16]. It is possible that there is a gene with a defect that increases the risk of SCAD, and studies are being conducted to identify it.

Initiating and stressful factors

Most often, SCAD is preceded by the release of catecholamines due to physical (24%) or emotional (40%) stress (as in stress-induced cardiomyopathy — Takotsubo syndrome). Emotional stress is more often observed in women, and physical stress — in men [17]. Hormonal changes associated with pregnancy, menopause, use of oral contraceptives, hormonal therapy, infertility treatment or high doses of corticosteroids also play a role [18].

Clinical picture

As a rule, in patients with SCAD there is almost always a picture of ACS and increased cardiac enzymes. Cardiogenic shock is seen in 2–5% of patients, the picture of ST-elevated MI – in 26–87%, without elevation — in 13–69%. Ventricular arrhythmias or sudden cardiac death develop in 3–11% of patients with SCAD [19].

Diagnosis

Diagnostic errors are often made in patients with SCAD, partly due to the young age of patients and the lack of risk factors for atherosclerosis. In case of suspected SCAD, it is **necessary to perform ECG** and coronary angiography as quickly as possible, especially when detecting ST segment elevation on the ECG [20]. Intravascular ultrasonography and optical coherence tomography provide a more detailed visualization of the vascular wall, which facilitates the diagnosis of SCAD, but they are not always available. Therefore, **traditional ECG and coronary angiography remain the standard for diagnosis of SCAD** [3].

Coronary angiography

According to J. Saw angiographic classification [12], type 1 SCAD is a classical manifestation of multiple radiolucent areas or defects in filling of arterial walls. Type 2 is characterized by the presence of diffuse stenosis which varies in severity and length (usually >20 mm): 2A variant is a diffuse narrowing of the artery, limited proximally and distally from IMH by normal segments, and 2B variant is a diffuse narrowing extending to the distal end of the artery. In case of type 3 there is focal or tubular stenosis, usually <20 mm in length, which mimics atherosclerosis. Naturally, intracoronary imaging allows to confirm IMH and SCAD.

It is shown [19] that the pattern of diffuse uniform stenosis (type 2) was the most frequent (67.5%) angiographic manifestation of SCAD, type 1 occurred in 29.1%, type 3 — in 3.4% of cases. It should be remembered that special care should be taken when performing coronary angiography in patients with SCAD, given the fragility of the coronary arteries and the risk of iatrogenic dissection.

Other imaging methods

Intravascular ultrasonography and optical coherence tomography are also used for diagnosis of SCAD, providing additional information, but have certain potential risks — aggravation (provocation) of coronary dissection by a probe or catheter, catheter-induced occlusion of the true artery lumen and hydraulic expansion by injection of false contrast [21].

Therefore, intracoronary imaging should only be performed when coronary angiographic diagnosis is unclear (type 3 or unknown injury) and when the vessel diameter is large enough for intracoronary imaging. Computer tomographic coronary angiography may also be a promising method for SCAD diagnosis [22].

Treatment

Although current guidelines for the management of patients with ACS of atherosclerotic origin recommend an early invasive strategy with revascularization of revealed disorders, there are no randomized studies with the results of revascularization in SCAD yet. Their necessity is crucial, since the mechanism of vascular obstruction, acute vascular response to balloon dilation and the natural outcome of conservatively treated catastrophes in SCAD differ significantly in comparison with ACS of atherosclerotic nature [3].

Conservative treatment

Despite the absence of comprehensive prospective studies, there is evidence that angiographic recovery of SCAD disorders is observed in the majority of patients (70–97%) who were re-examined weeks and months after their conservative management [21]. Persistent dissection was found in the minority of patients and it is unclear why it persisted. The length of recovery is also unclear, but there is evidence that it may take several days or weeks [17].

It should be remembered that early complications of recurrent MI associated with SCAD may develop in 5–10% of conservatively treated patients, mainly associated with increased dissection during the first week after an acute episode [14].

In high-risk patients with ongoing ischemia and dissection of the left coronary artery trunk or hemodynamic instability, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) may be used.

Percutaneous coronary intervention

There is evidence that PCI in the treatment of SCAD is associated with an increased risk of complications and worse results due to the fragility of the arteries [17]. They are more susceptible to iatrogenic dissections, and coronary catheters often fall into the false lumen of the vessel and overlap the true one. Balloon dilation and stent placement may also increase the risk of vascular wall damage. In addition, the length of dissections is often extensive, which may require the use of longer coronary stents, which in turn increases the risk of subsequent intra-stent restenosis and thrombosis. In addition, SCAD most often affects the distal coronary segments, which may be too small or too remote for stent placement [23].

Therefore, in order to improve the outcomes of PCI in the case of SCAD, refrain from deep insertion of a catheter, non-coaxial placement of its tip, wetting the catheter, and a large injection of contrast agent. Instead of radial access, femoral access is preferred, which reduces the risk of catheter-induced iatrogenic dissection three times [19].

It is believed that for patients with SCAD in PCI the following are safer: (1) implantation of long drug-eluting stents that extend proximally and distally by 5–10 mm out of IMH areas to ensure their compression; (2) direct stenting without prior balloon dilation to avoid additional risks of IMH expansion; (3) isolated balloon angioplasty to restore coronary blood flow without stenting; (4) scoring balloon fenestration of IMH for decompression of blood portion from the false lumen to true one; (5) a multi-stent approach with initial stent sealing of the distal and proximal ends before stenting of median site in order to minimize IMH spreading; and (6) the use of bioresorbable stents to provide a temporary framework [23].

Naturally, after successful PCI, double antiplatelet therapy should be prescribed corresponding to stent implantation.

Coronary artery bypass graft

Published data on CABG in SCAD are limited to case descriptions, small series of observations, and retrospective analysis with a small sample size. CABG is described as a therapeutic strategy for SCAD in patients with dissection of the common left coronary artery trunk or the proximal segments of the arteries after a technical failure of attempt in case of PCI. At the same time, both arterial and venous shunts are used, although the long-term results of surgeries are not very comforting [20].

In summary, conservative therapy is generally the preferred strategy for the management of patients with SCAD who are clinically stable and have no objective signs of current ischemia, and this approach is generally associated with favorable outcomes. A conservative strategy is also appropriate in patients with distal vascular occlusion, which cannot be corrected in PCI [3].

Therapy after discharge from the hospital

Patients with SCAD who have undergone coronary revascularization should certainly receive *antiplatelet agents*, although there are no studies to assess its optimal duration and nature. Some experts recommend double antiplatelet therapy for at least a year, others — for a few months (1–3), followed by monotherapy with aspirin, which is taken for at least a year or indefinitely (if there are no contraindications) [24].
The use of *β-blockers* should be considered in patients with SCAD who have left ventricular (LV) dysfunction, arrhythmia, or hypertension, although some experts support the mandatory and long-term use of β-blockers [14].
Angiotensin-converting enzyme inhibitors or *angiotensin receptor blockers* should be prescribed if MI due to SCAD is complicated by LV dysfunction [25] or in concomitant hypertension. At the same time, women of reproductive age should be warned about the teratogenicity of antagonists of the renin-angiotensin system. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated during gestation because their treatment in the 2nd and 3rd trimesters has been shown to be associated with toxic effects on the fetus (impaired renal function, oligohydramnios, decreased cranial vault, and sometimes fetal renal failure and even death) [26].
Statin therapy in SCAD is generally not used if there is no dyslipidemia, atherosclerosis or diabetes, and in the presence of anginal pain, nitrates, calcium channel blockers or ranolazine are used [3].

Spontaneous coronary artery dissection and pregnancy

Most pregnancy-associated SCAD cases occur in the first month after delivery, but they can develop in any gestational period [27]. The management of SCAD in such patients requires the interaction of cardiac and obstetric services [28]. However, despite the special situation in pregnancy, the principles of SCAD management are basically the same as without pregnancy, and in case of doubt in diagnosis and strategy, it is necessary to conduct early and careful angiography (with modern technologies, radiation for the fetus is relatively low [29]).
It should also be remembered that clopidogrel is not recommended for women who are breastfeeding, and small doses of aspirin are safe during pregnancy and breastfeeding. Despite the fact that β-blockers are associated with fetal growth restriction, they are often prescribed during pregnancy for the treatment of hypertension. Labetalol is preferred, especially in the early stages of pregnancy, and metoprolol and atenolol can result in reduced fetal weight and cause bradycardia in newborns during breastfeeding [30].
We have seen a case of SCAD in a young woman.

Case report

The patient, 35 years old, without any medical history, was delivered to the clinic by an ambulance team on 8.05.2018 with complaints of weakness, breathlessness and intense constricting pain in the upper chest, which abruptly occurred about 5 hours ago after a family dispute. On March 19, 2018, 50 days before the present deterioration, the patient gave birth to a healthy boy (cesarean section); the pregnancy period proceeded without complications.
Relatives of the patient first referred to the district doctor, who regarded these symptoms as manifestations of nervous and emotional stress and osteochondrosis and recommended the use of Valerian and ointment with diclofenac. But since the patient's condition did not improve, the relatives called an ambulance, and this doctor suspected her of acute coronary syndrome.
On admission: critical condition, adynamic, lethargic, responds to questions in monosyllables, with difficulty. She had normosthenic constitution The skin is pale, covered with cold sweat. Pulse is of small volume, arrhythmic, 106 min^{-1}, BP 80/40 mm Hg, the boundaries of the heart are normal, its tones are muffled, tachycardia, frequent premature beats. The thorax is painless during palpation, evenly participates in the act of breathing, pulmonary sound during percussion is normal throughout the surface, breathing is vesicular, 26 min^{-1}, there are no rales. The abdomen is soft, painless, from the navel to the pubis postoperative scar is seen. The lower edge of the liver is located at the line of costal arch; segments of the intestine are of normal properties.

She had childbirth by cesarean section 2 months ago in medical history (the child is not breastfeeding). There are no risk factors for coronary artery disease.

The patient's father had a dissecting aortic aneurysm, and the mother had two prior strokes.

On the ECG recorded by the doctor of the ambulance, there was elevated ST segment of 1 to 3 mm in leads V_2–V_5 (Fig. 1).

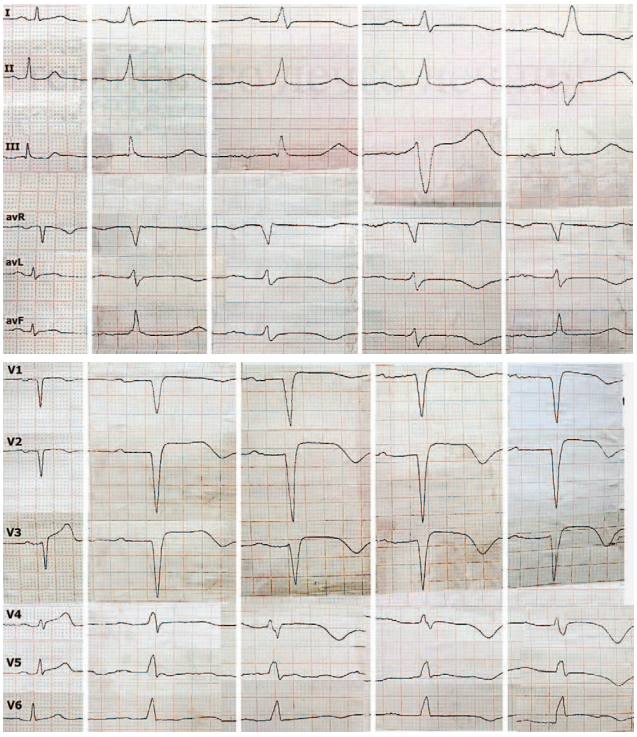
According to urgent echocardiography, there was akinesia of the apical anterior, apical septal, apical posterior; middle anterior septal LV segments, and hypokinesia of the middle anterior, middle posterior, septal LV segments.

Urgent coronary angiography (femoral access) revealed stenosis of up to 70% of the 1st portion of the anterior interventricular branch of the left coronary artery (left anterior descending artery, LAD) with transition to the ostium of diagonal branch and occlusion of the 2nd portion of LAD (acute thrombosis, TIMI flow grade 0) (Fig. 2).

During guidewire installation and balloon angioplasty, dissection of LAD (type 3 according to J. Saw angiographic classification) was found [12] (focal or tubular stenosis up to 20 mm in length, simulating atherosclerosis) (Fig. 3).

Stenting of LAD was performed (Fig. 4).

After PCI, the patient's condition immediately improved — pain in the chest disappeared, and blood pressure and pulse normalized (120/80 mm Hg). Subsequently, on the background of therapy with aspirin, clopidogrel, bisoprolol and lisinopril, it remained quite satisfactory. The patient well tolerated the expansion of the motor mode. Chest pain



On admission (paper speed 25 mm/sec)	1st day (50 mm/sec)	2nd day (50 mm/sec)	3rd day (50 mm/sec)	4th day (50 mm/sec)

Figure 1. *Dynamic electrocardiographic changes in a patient*

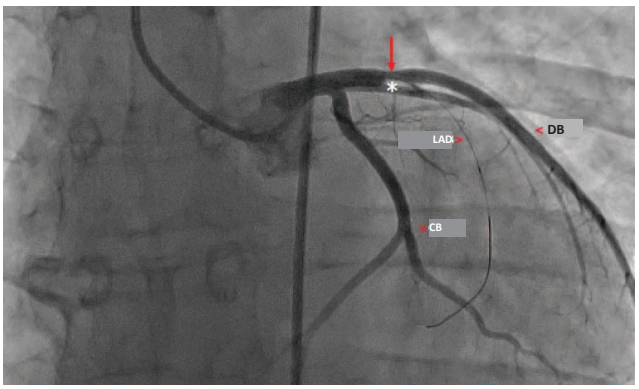


Figure 2. *Coronary angiography: stenosis of up to 70% of the 1st portion of the anterior interventricular branch of the left coronary artery (LAD) with transition to the ostium of diagonal branch (DB, marked by a red arrow) and occlusion (acute thrombosis type) of the 2nd portion of LAD (marked with a white asterisk), TIMI flow grade 0; a guidewire is seen in the artery (its line is marked by a small red arrow ">"); CB – circumflex branch*

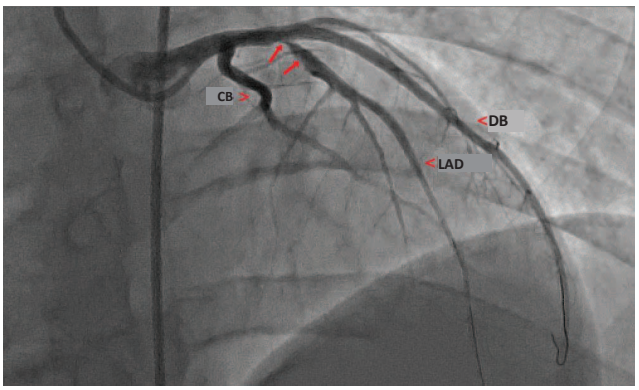


Figure 3. *The site of spontaneous coronary artery dissection after balloon angioplasty. Blood flow is partially restored along the anterior interventricular branch (LAD). Defects of the coronary artery wall are marked with red arrows. DB – diagonal branch; CB – circumflex branch*

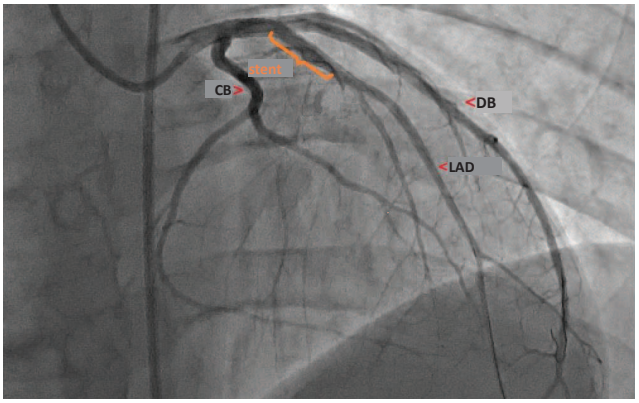


Figure 4. *Stenting of the anterior interventricular branch of the left coronary artery (LAD) with complete restore of blood flow. LAD stenting fragment is marked with an orange curly bracket. DB – diagonal branch; CB – circumflex branch*

and shortness of breath were not noted. On ECG series (Fig. 1) typical pattern, which is characteristic for acute large-focal anteroseptal LV MI, was observed. Two weeks later, the patient was discharged from the clinic with a recommendation to continue the therapy.

On the basis of clinical, anamnestic and ECG data, echocardiographic and angiographic studies, taking into account the course of the disease during treatment, the following diagnosis was made: Spontaneous dissection of the anterior interventricular branch of the left coronary artery. Acute large-focal MI in anterior and posterior septal segments and in the apex of the LV. Cardiogenic shock. Urgent PCI (balloon angioplasty and stenting of infarct-related artery) on 8.5.2018.

With control examination after 4 months: there were no complaints; in an objective status — without significant abnormalities. 6-minute walk test — 550 m.

Thus, in the young patient in the postpartum period, we observed acute large-focal LV MI caused by spontaneous dissection and thrombosis of LAD and the ostium of its diagonal branch, complicated by cardiogenic shock. Diagnosis was challenging. However, the clinical pattern, ECG recording and coronary angiography allowed to make the correct diagnosis, and urgent PCI quickly improved and stabilized patient's condition.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Protasova E.A., Furman N.V., Titkov I.V. Spontaneous coronary artery dissection as a cause of acute myocardial infarction. Cardiovascular Therapy and Prevention. 2014;13(5):70-73. doi: 10.15829/1728-8800-2014-5-70-73 [in Russian].
2. Pretty H.C. Dissecting aneurysm of coronary artery in a woman aged 42: rupture. Br Med J. 1931;1:667. doi: 10.1136/bmj.1.3667.667.
3. Hayes S.N., Kim E.S.H., Saw J., et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. Circulation. 2018;137(19):e523-e557. doi: 10.1161/CIR.0000000000000564.
4. Rogowski S., Maeder M.T., Weilenmann D., et al. Spontaneous coronary artery dissection: angiographic follow-up and long-term clinical outcome in a predominantly medically treated population. Catheter Cardiovasc Interv. 2017;89:59–68. doi: 10.1002/ccd.26383.
5. Elkayam U., Jalnapurkar S., Barakkat M.N., et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. Circulation. 2014;129:1695–1702. doi: 10.1161/CIRCULATIONAHA.113.002054.
6. Rashid H.N., Wong D.T., Wijesekera H., et al. Incidence and characterisation of spontaneous coronary artery dissection as a cause of acute coronary syndrome: a single-centre Australian experience. Int J Cardiol. 2016;202:336–338. doi: 10.1016/j.ijcard.2015.09.072.
7. Kwon T.G., Gulati R., Matsuzawa Y., et al. Proliferation of coronary adventitial vasa vasorum in patients with spontaneous coronary artery dissection. JACC Cardiovasc Imaging. 2016;9:891–892. doi:10.1016/j.jcmg.2015.11.030.
8. Alfonso F., Paulo M., Gonzalo N., et al. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. J Am Coll Cardiol. 2012;59:1073–1079. doi: 10.1016/j.jacc.2011.08.082.
9. Desai S., Sheppard M.N. Sudden cardiac death: look closely at the coronaries for spontaneous dissection which can be missed: a study of 9 cases. Am J Forensic Med Pathol. 2012;33:26–29. doi:10.1097/PAF.0b013e3181e29598.
10. Saw J., Ricci D., Starovoytov A., et al. Spontaneous coronary artery dissection: prevalence of predisposing conditions including fibromuscular dysplasia in a tertiary center cohort. JACC Cardiovasc Interv. 2013;6:44–52. doi: 10.1016/j.jcin.2012.08.017.

11. Olin J.W., Gornik H.L., Bacharach J.M., et al. Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. Circulation. 2014;129:1048–1078. doi: 10.1161/01.cir.0000442577.96802.8c.
12. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. Catheter Cardiovasc Interv. 2014;84:1115–1122. doi: 10.1002/ccd.25293.
13. Codsi E., Tweet M.S., Rose C.H., et al. Spontaneous coronary artery dissection in pregnancy: what every obstetrician should know. Obstet Gynecol. 2016;128:731–738. doi: 10.1097/AOG.0000000000001630.
14. Saw J., Mancini G.B.J., Humphries KH. Contemporary review on spontaneous coronary artery dissection. J Am Coll Cardiol. 2016;68:297–312. doi: 10.1016/j.jacc.2016.05.034.
15. Cade J.R., Szarf G., de Siqueira M.E., et al. Pregnancy-associated spontaneous coronary artery dissection: insights from a case series of 13 patients. Eur Heart J Cardiovasc Imaging. 2017; 18:54–61. doi: 10.1093/ehjci/jew021.
16. Henkin S., Negrotto S.M., Tweet M.S., et al. Spontaneous coronary artery dissection and its association with heritable connective tissue disorders. Heart. 2016;102:876–883. doi: 10.1136/heartjnl-2015-308645.
17. Tweet M.S., Hayes S.N., Pitta S.R., et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. Circulation. 2012;126:579–588. doi: 10.1161/CIRCULATIONAHA.112.105718.
18. Nakamoto K., Matsuda M., Kanno K., et al. A case of a young, healthy woman with spontaneous coronary artery dissection associated with oral contraceptive use: long-term residual dissection of the coronary artery. J Cardiol Cases. 2013;8:179–182. DOI: 10.1161/CIR.0000000000000564.
19. Saw J., Aymong E., Sedlak T., et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. Circ Cardiovasc Interv. 2014;7:645–655. doi: 10.1016/j.jcin.2012.08.017.
20. Tweet M.S., Eleid M.F., Best P.J., et al. Spontaneous coronary artery dissection: revascularization versus conservative therapy. Circ Cardiovasc Interv. 2014;7:777–786. doi: 10.1161/CIRCINTERVENTIONS.114.001659.
21. Alfonso F., Paulo M., Dutary J. Endovascular imaging of angiographically invisible spontaneous coronary artery dissection. JACC Cardiovasc Interv. 2012 Apr;5(4):452-3. doi: 10.1016/j.jcin.2012.01.016.
22. Hollander J.E., Than M, Mueller C. State-of-the-art evaluation of emergency department patients presenting with potential acute coronary syndromes. Circulation. 2016;134:547–564. doi: 10.1161/CIRCULATIONAHA.116.021886.
23. Alkhouli M., Cole M., Ling F.S. Coronary artery fenestration prior to stenting in spontaneous coronary artery dissection. Catheter Cardiovasc Interv. 2016;88:E23–E27. doi: 10.1002/ccd.26161.
24. Tweet M.S., Gulati R., Hayes S.N. What clinicians should know about spontaneous coronary artery dissection. Mayo Clin Proc. 2015;90:1125–1130. doi:10.1016/j.mayocp.2015.05.010.
25. Jneid H., Anderson J.L., Wright R.S., et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2012;126:875–910. doi: 10.1161/CIR.0b013e318256f1e0.
26. Vatutin N.T., Taradin G.G., Popelnukhina L.G., et al. Treatment of peripartum cardiomyopathy. Archive of Internal Medicine. 2017; 7(5): 340-349. DOI: 10.20514/2226-6704-2017-7-5-340-349 [In Russian].
27. Vatutin N.T., Taradin G.G., Taratorina A.A., et al. Ischemic heart disease and pregnancy. Medical and Social Problems of Family. 2013; 18(4): 97-106 [in Russian].
28. Elkayam U., Goland S., Pieper P.G., Silverside C.K. High-risk cardiac disease in pregnancy, part I. J Am Coll Cardiol. 2016;68:396–410. doi: 10.1016/j.jacc.2016.05.048.
29. Regitz-Zagrosek V., Blomstrom Lundqvist C., Borghi C., et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147–3197. doi: 10.1093/eurheartj/ehr218.
30. Peacock W.F., Hilleman D.E., Levy P.D., et al. A systematic review of nicardipine vs labetalol for the management of hypertensive crises. Am J Emerg Med. 2012;30:981–993. doi: 10.1016/j.ajem.2011.06.040.

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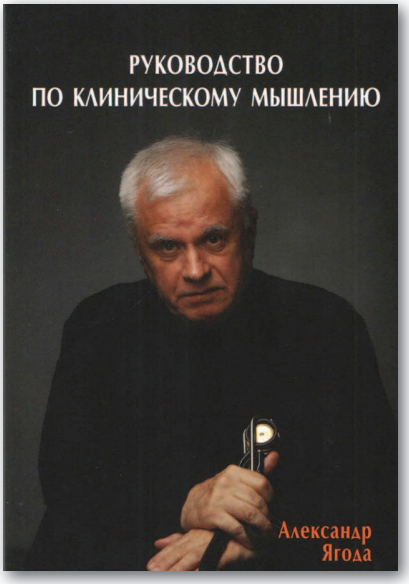

Уважаемые коллеги!

В издательстве «ЭКО Вектор» (С-Пб) в 2018 году вышла книга доктора медицинских наук, профессора, заведующего кафедрой госпитальной терапии Ставропольского государственного медицинского университета, заслуженного врача РФ, заслуженного деятеля науки РФ, члена редколлегии нашего журнала **Александра Валентиновича Ягоды** «РУКОВОДСТВО ПО КЛИНИЧЕСКОМУ МЫШЛЕНИЮ».

В книге с позиции автора в оригинальной форме клинических разборов, проводимых совместно со студентами в клиниках университета, на поликлиническом приёме сделана попытка донести до читателя методику мышления врача при опросе и осмотре больных, обсуждении данных лабораторного и инструментального исследований для выделения на этой основе главных, основополагающих позиций, на которых строится диагноз. Автор характеризует мышление врача как творческий процесс, базирующийся на теоретических знаниях, практическом опыте, логической деятельности ума, общей культуре и эрудиции, продолжая и развивая в своей работе гуманистические традиции Российской терапевтической школы. Книга адресована в первую очередь студентам старших курсов медицинских вузов, однако может быть полезна клиническим ординаторам и молодым врачам, а также всем, кто испытывает профессиональный интерес к клинике внутренних болезней.

Содержание:

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CHRONIC PHARYNGITIS: ETIOLOGY, PATHOGENESIS, TREATMENT. NEW APPROACHES TO THE ESTIMATION OF ETIOPATOGENESIS

Abstract

The paper discusses modern approaches to etiopathogenesis assessment and treatment of chronic pharyngitis. The results of mass spectrometry of microbial markers (MSMM), a modern method for the diagnosis, use are presented. The method allows to detect the microorganisms in a biofilm, in a "sleeping state" under the protection of mucin. With the help of this STAT-method, it is possible to detect 57 biomarkers of microorganisms in the smear from the pharynx at the same time, 2 hours after delivery of the sample to the laboratory. It was found that 91% of the examined patients with chronic pharyngitis (n = 62) show increased total content of microorganisms, which indicates the need for antibacterial therapy; 87% of patients have elevated levels of endotoxin, which is a sign of general intoxication; 71% of patients have reduced plasmalogen level and these patients may be at increased risk for lipid metabolic disorders; in 100% of the examined patients with frequent exacerbations of chronic pharyngitis the nasopharyngeal microflora (Cocci) in the pharynx is determined, as well as new etiopathogenetically significant microorganisms (not detected by PCR and cultures), among which there are 7 transient microorganisms (normally their level in the pharynx is zero), 11 resident microorganisms (6 — found in the pharynx in normal condition on the minimum level, and 5 with high levels in normal condition). Also, with the help of MSMM, a significant or moderate increase in herpes simplex virus and cytomegalovirus was detected in the majority (75%) of patients, which indicates the important role of the viruses of this group in the etiopathogenesis of recurrent chronic pharyngitis; level of Candida spp. is increased in half of patients; and normal

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microflora is increased in 71% of patients, which indicates the preservation of local resistance in patients with chronic pharyngitis, who were examined by the authors. Thus, the use of MSMM in chronic pharyngitis allows to identify new etiopathogenetic microorganisms and prescribe more effective treatment on this basis. Thus, it is possible to carry out personified, more effective treatment.

Key words: *chronic pharyngitis, mass spectrometry, immunity, dysbiosis, pathogenesis, laboratory diagnostics, antibacterial agents*

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HIV — human immunodeficiency virus, GERD — gastroesophageal reflux disease, GIT — gastrointestinal tract, MSMM — mass spectrometry of microbial markers, AP — acute pharyngitis, P — plasmalogen, PAS — peroxidase activity of saliva, BOS — bacterial overgrowth syndrome, IBS — irritable bowel syndrome, CVS — cardiovascular system, CP — chronic pharyngitis, EBVI — Epstein-Barr viral infection

Introduction

Chronic pharyngitis (CP) is a widespread disease of the upper respiratory tract characterized by inflammation of the pharyngeal mucosa. Up to 7% of adults in Russia and Western countries [3, 4] suffer from CP. In outpatient practice of otolaryngologists, CP occupies a leading place (up to 70% of visits) [19]. Patients with CP can also be treated by general practitioners, therapists, immunologists, so the number of patients with CP is higher than indicated in the statistics.

CP is characterized by pain, tickling, discomfort in the throat, sleep disturbance, complaints of constant runoff of mucus along the back wall of the pharynx ("lump" of mucus, coughing). These symptoms significantly worsen the quality of life of patients. In case of recurrent CP, different parts of the pharynx can be affected: nasopharynx, oropharynx, larynx, often the inflammatory process is descending in nature. Morphological changes of the mucous membrane in CP are predominantly localized in one of the anatomical parts of the pharynx, which allows to allocate individual nosology, for example, chronic nasopharyngitis [42].

Professional hazards, long-term load on the vocal apparatus (singers, teachers), climatic conditions, pathology of internal organs contribute to the recurrent course of CP. It should be borne in mind that the pharynx and gastrointestinal tract (GIT) represent a single system: nasopharynx is the initial part of the gastrointestinal tract. Acid content in GERD (gastro-esophageal reflux disease) may fall from the stomach into the pharynx (normally, pH in the oral cavity is alkaline), including during sleep [41]. Other diseases of GIT contribute to recurrent CP: gastritis, bacterial overgrowth syndrome (BOS), irritable bowel syndrome (IBS). Diseases of the cardiovascular system (CVS), female genital area, cervical osteochondrosis, apnea contribute to the chronic course of the inflammatory process in the nasopharynx [7]. Recurrent CP is usually difficult to treat. Repeated therapy by otorhinolaryngologists, immunologists leads to a temporary remission of the disease. In connection with the above, the study of etiopathogenesis, the development of new approaches to the diagnosis and treatment of CP are relevant.

Etiology and classification of chronic pharyngitis

Chronic pharyngitis is often caused by infectious agents: viral, bacterial, fungal, CP of mixed etiology, and it also can have allergic or traumatic (due to foreign body contact or surgery) nature. CP can occur due to irritating factors (hot liquid or steam, acids, alkalis, radiation, etc.), diseases of the gastrointestinal tract, CVS, etc.

Chronic pharyngitis usually is classified according to the nature of the developed mucous changes: catarrhal (simple), atrophic or subatrophic and hypertrophic (hyperplastic, granulosa). These forms of chronic inflammation are often combined. Thus, the presence of diffuse atrophic changes in the mucous membrane can be combined with focal hyperplasia of the lymphoid tissue of the posterior pharyngeal wall or tubopharyngeal ridges (hyperplastic process develops).

Viral infection in ARVI is often the first phase of CP, it "paves the way" for subsequent bacterial infection [24]. A common form of acute inflammation of the pharyngeal mucosa is catarrhal pharyngitis in ARVI. About 70% of acute pharyngitis (AP) is caused by viruses, among which rhinoviruses, coronaviruses, respiratory syncytial virus, adenovirus, influenza and parainfluenza viruses are more common. The most typical pathogens of AP are rhinoviruses [34]. In descending order of frequency, viruses with acute pharyngitis [45] can be listed as follows:

- rhinoviruses
- coronaviruses
- adenoviruses
- influenza virus
- parainfluenza virus

Rare viruses:

- respiratory syncytial virus
- herpes simplex viruses (types 1 and 2)
- enteroviruses
- Coxsackie virus
- Epstein-Barr virus
- cytomegalovirus
- human immunodeficiency virus (HIV), the clinical significance of HIV in the development of CP has increased significantly in recent years [39].

Currently, it is shown that rhinoviruses are responsible for more than 80% of ARVI cases during the autumn epidemics.

Among bacterial pathogens in AP, the leading role belongs to group A β-hemolytic Streptococcus: 15–30% of cases in children and 5–17% of cases in adults. Relatively rarely (less than 5%), AP or exacerbations of CP can be caused by group C and G streptococci [32]. In 90% of cases bacterial flora of the posterior pharyngeal wall is represented by associations of 2–3 types of microorganisms [33].

Pharyngitis can be **classified** as follows.

By severity of the symptoms:

- acute
- chronic

By etiological factor:

- viral
- bacterial
- fungal
- allergic
- traumatic, including post-tonsillectomy
- caused by irritant factors, including smoking
- caused by GIT diseases (GERD, hiatal hernia, chronic gastritis, including atrophic, BOS, IBS, functional GIT disorders, chronic cholecystitis, pancreatitis).

There are types of pharyngitis associated with specific pathogens:

- Epstein-Barr virus in infectious mononucleosis
- *Yersinia enterocolitica* in Yersinia pharyngitis
- gonococcus in gonorrheal pharyngitis
- *Leptotrixbuccalis* in pharyngeal leptotrichosis.

By the nature of inflammation:

- hypertrophic (granulosa)
- atrophic (points to involutional changes in the pharynx, pathology of internal organs and systems (gastrointestinal tract, reduced metabolism))
- catarrhal
- mixed form.

Clinical picture of chronic pharyngitis and main mechanisms of its pathogenesis

The clinical picture of chronic pharyngitis is characterized by tickling, dryness, discomfort and pain in the throat when swallowing. Patients complain of a "lump of mucus" in the throat, which causes a desire to cough. In the case of inflammation of tubopharyngeal ridges, pain usually radiates to the ears. Palpation may cause pain and enlargement of upper, anterior and/or posterior lymph nodes. During pharyngoscopy, hyperemia of pharyngeal posterior wall and palatal arches, separate inflamed lymphoid granules are seen, while hyperplasia of the tonsils can be noted. Sings of tonsillar inflammation, which are typical of tonsillitis, are often absent. Exacerbation of chronic pharyngitis or acute pharyngitis may be the first manifestations of some infectious diseases: measles, scarlet fever, rubella. In some cases, differential diagnosis with Kawasaki disease and Stevens-Johnson syndrome is required [23].

The clinical picture of chronic pharyngitis is not characterized by fever, deterioration of the general condition (weakness, chills). Patients experience frequent ARVI, nasal congestion, prolonged, dry, sometimes paroxysmal cough. This violates the quality of life: discomfort in the throat is associated with the need to constantly swallow the mucus located on the back wall of the pharynx, breathing

becomes heavier in sleep, this makes patients irritable, forces them visit a doctor.

The course of the chronic inflammatory process on the posterior pharyngeal wall depends on the nature of the microflora, its virulence, the degree of contamination, the state of the macroorganism, local immunity, the mucous membrane itself: its innervation, circulation, degree of hydration [28]. The mucous membrane of the pharynx has a complex composition: muscular, nervous, vascular, secretory and lymphoid parts. The pharynx is an important regulator of reflex stimuli, inhibition of the respiratory act, delay in swallowing. With the help of the pharynx, the following functions are carried out: voice formation, speech, respiratory act, moving food along the esophagus.

Pain in acute pharyngitis and exacerbation of CP is due to the rich innervation of the pharynx [3]. The pharynx receives sensitive, motor and vegetative innervation from the pharyngeal plexus located on the outer surface of the middle sphincter of the pharynx under the buccopharyngeal fascia. This plexus is formed by the branches of the pharyngeal and vagus nerves, as well as sympathetic fibers of the upper cervical ganglia. Sensitive innervation of the pharynx is mainly carried out by the pharyngeal nerve, but in the pharyngeal ostium of the auditory tubes there are nerve connections with the second branch of the trigeminal nerve. The superior laryngeal nerve ("branch of vagus nerve") is also involved in the innervation of the hypopharynx. Rich nerve connections explain the possibility of pain irradiation in diseases of the pharynx to the ear, lower jaw [16].

With atrophic pharyngitis, the mucous membrane of the pharynx looks thin, dry, often covered with dried mucus. Injected vessels can be seen on the shiny surface of the mucous membrane. Smoking and tonsillectomy often lead to the development of atrophic changes in the mucous membrane of the pharynx [24].

In hypertrophic form, pharyngoscopy reveals pockets of hyperplastic lymphoid tissue scattered on the back of the throat, or enlarged tubopharyngeal ridges located behind the rear palatine arches.

During exacerbation of CP, these changes are accompanied by hyperemia and edema of the mucous membrane. In CP, objective changes may be less pronounced than symptoms experienced by patients.

Constantly difficult nasal breathing contributes to the development of chronic pharyngitis. CP may be caused not only by the transition to breathing through the mouth, but also by abusing vasoconstrictor nasal drops, which flow down from the nasal cavity into the throat and have excessive anematizing effect [39]. Symptoms of pharyngitis may be present in postnasal drip. In this case, discomfort in the throat is associated with the flow of pathological secretion from the nasal cavity or paranasal sinuses along the back wall of the pharynx. In addition to constant coughing, this condition can cause, more often in children, the appearance of wheezing, which requires differential diagnosis with bronchial asthma.

The following factors contribute to the development of chronic pharyngitis:

- constitutional features of pharyngeal and GIT mucous membrane structure;
- long-term exposure to exogenous factors (dust, hot dry or smoky air, chemicals);
- difficulty in nasal breathing (breathing through the mouth, decongestants abuse);
- smoking and alcohol abuse;
- allergic diseases (pollinosis, food allergy);
- endocrine disorders (menopause, hypothyroidism, metabolic syndrome);
- vitamin deficiency (Vit A);
- diabetes;
- heart, lung failure;
- renal failure;
- violated intestinal microenvironment system (BOS, IBS, etc.).

Disorders in the pharyngeal and intestinal microenvironment (dysbiosis) play a significant role in the development and maintenance of chronic inflammatory processes of the posterior pharyngeal wall [20, 22].

The formation of dysbiosis in different parts of the digestive tract is possible in the case of disruption of the physiological balance between the factors of resistance and aggression. The following contribute to the development of microenvironmental disorders: non-compliance with sanitary and hygienic standards, the use of certain drugs (antibiotics, etc.), the presence of severe chronic, allergic diseases, immunodeficiency conditions.

Chronic pharyngitis may be associated with GIT pathologies: chronic gastritis (atrophic), gastro-

esophageal reflux disease (GERD), cholecystitis, pancreatitis. Entry of acid gastric contents into the pharynx during sleep in GERD and hiatal hernias is often a hidden cause of chronic catarrhal pharyngitis. In this case, treatment is ineffective without eliminating the main cause of the disease [27].

The quantitative and qualitative composition of normal microflora (in oral cavity, upper respiratory tract, intestines) in a healthy person is quite stable. The microenvironmental phenotype of the person is influenced by genotypic characteristics and environmental factors. In case of CP, violations of pharyngeal microenvironmental mucosa were revealed. Under normal conditions, microorganisms living on the mucous membrane of the oropharynx cannot penetrate into the deep layers of tissue and develop an infectious and inflammatory process. Invasion due to the synthesis of enzymes is possible with the development of dysbiosis of the mucous membrane of the pharynx, associated with the inhibition of specific and nonspecific factors of the macroorganism natural reactivity. This is manifested by a local violation of the mucociliary barrier, blood circulation, increased permeability of the vascular wall, and at the first stage of inflammation — by an increase, and subsequently — a decrease in the level of neutrophils, lymphocytes, phagocytic cells, the development of local and general immunosuppression, activation of transient and opportunistic pathogenic resident microflora, with the development of chronic inflammation in the tissues of the posterior pharyngeal wall, tonsils [8]. In chronic inflammation in the mucous membrane of the nasal cavity, paranasal sinuses, larynx and trachea, focal or diffuse metaplasia of the multirowed columnar epithelium occurs with formation of multilayer epithelium without cilia. Such a modified epithelium loses the ability to remove bacteria and viruses from its surface by active mucociliary transport.

With a persistent, unmanageable course of CP and the presence of complaints, differential diagnosis is carried out with a number of syndromes that develop in some systemic diseases and diseases of the nervous system. Plummer-Vinson syndrome occurs in women aged 40 to 70 years secondary to iron deficiency anemia. Sjogren's syndrome is an autoimmune disease accompanied, in addition to the pronounced dryness of the mucous membrane in gastrointestinal tract, by a diffuse enlargement of salivary glands. Eagle syndrome (stylalgia) is characterized by strong, constant, often unilateral pain in the throat caused by a longer styloid process, which is located on the lower surface of the temporal bone and can be felt over the upper pole of palatine tonsil. A number of neuralgia (glossopharyngeal or vagus nerve) can also cause pain in the throat, especially in the elderly.

Thus, chronic pharyngitis is often not an independent disease, but a consequence of the pathological condition in other organs and systems, and this makes the task of its treatment very difficult sometimes.

Diagnosis of chronic pharyngitis

Diagnosis of CP is carried out using a set of modern methods:

1. Survey — detection of complaints, clinical symptoms (sore throat, tickling, runoff of mucus on the back of the pharynx, additional symptoms — dry mouth, dry, paroxysmal cough).
2. Physical examination: inspection of the posterior pharyngeal wall (by pharyngoscopy), palpation, ultrasound examination of neck lymph nodes (submandibular, anterior and posterior cervical), most often on pharyngeal posterior wall hyperemia, edema, atrophy of the mucosa, formation of different sizes of the granulomas (hyperplasia of mucosa) are revealed in CP.
3. Laboratory test. The standard for laboratory diagnosis in CP is a culture of a smear taken from the posterior pharyngeal wall to determine the etiologically significant microflora (bacterial, fungal), and diagnosis is carried out using PCR: diagnosis of chlamydial, mycoplasma, viral microflora (herpes viruses — 1, 2, 6 types, cytomegalovirus, Epstein-Barr virus) [35].

An innovative method for diagnosis of chronic pharyngitis

With constant complaints from patients with CP, etiologically significant microorganisms often cannot be determined. In this regard, the introduction of new diagnostic methods for CP is

extremely important. More than 20 years ago, the method of mass spectrometry of microbial markers (MSMM) was developed and recommended for diagnostic use, allowing to detect 57 markers of microorganisms in the smear from the pharynx (by the level of fatty acids, aldehydes, for comparison — 12–15 microorganisms are detected using culture). When carrying out MSMM, the content of genetically stable biomarkers of microorganisms — anaerobic cocci, actinomycetes, gram-negative microorganisms, enterobacteria (HP, Campylobacter), fungal, viral markers is determined. The result and the conclusion are given, in which quantity of each microorganism in 1 ml of a biological sample is shown. The result can be issued 2 hours after the transfer of the biomaterial to the laboratory [36]. The introduction of this method into practice is currently difficult due to certain challenges in the interpretation of the results (60 indicators). Our work presents the experience of using MSMM in chronic pharyngitis.

Treatment of chronic pharyngitis. General principles of treatment

In the initial stages of the disease, treatment is carried out by otolaryngologists, and after repeated courses of therapy with insufficient clinical effect, patients seek help from immunologists.

Otorhinolaryngologists usually carry out complex treatment — sanitation of the nasopharynx with local antiseptics, anesthetics are used for pain, and washing of tonsils is carried out (with the combination of CP with exacerbation of chronic tonsillitis). After the detection of pathogenic microflora, in the presence of signs of intoxication, fever, inefficiency of local antiseptics, antibacterial therapy is prescribed, taking into account sensitivity — it can be antibiotics of the penicillin class or other groups, macrolides, and when detecting viral or fungal agents, antiviral and antifungal drugs are used, respectively [25].

Upon detection of a virus in the herpes group: HSV 1, 2, 6 types, CMV, EBV (PCR in oropharyngeal smear, saliva, blood — PCR or ELISA if IgM is to be detected), interferon-alpha drugs (in the form of sprays, drops — Genferon, Grippferon), as indicated, and systemic antiviral therapy (Acyclovir, Valvir, Famvir in tablet form or rectal insufflation (Viferon, Genferon, Kipferon)) are prescribed topically (systemically).

In the presence of mucosal edema and allergic reactions, antihistamines will be added to therapy, if ineffective — topical steroids, in insomnia — sedation.

For topical therapy (irrigation, inhalation, rinsing) there is a large selection of drugs with anti-infectious, anti-inflammatory and anesthetic (in the presence of pain) action, drugs of choice: Strepsils, Pharyngocept, chlorhexidine, Miramistin, Gramicidin S, Octenisept, Iodinol, spray — Inhalypt, Hexoral, Tantum Verde, Sialor or also "natural antiseptic" — calendula, chamomile, propolis (if there are no allergic reactions).

General recommendations — diet, clean air, treatment of comorbidities, dental caries, avoiding harmful habits (smoking, drinking alcohol, drinking hot drinks) play an important role in recurrent CP.

Given that inflammatory diseases of the nasal cavity are often present in chronic catarrhal pharyngitis, it is necessary to sanitize the nose, paranasal sinuses (elimination of purulent infection, elimination of the causes of nasal breathing disorders, sanation of lymphadenoid formations and primarily pharyngeal tonsils).

Attention should be paid to the general condition of the body, to exclude diseases of other organs and systems, the presence of allergies, some genetically determined dysmorphic oral cavity, nose and pharynx.

Thus, the treatment of chronic pharyngitis should be comprehensive. It is important to carry out therapy taking into account the type of inflammation caused by the pathogenic, opportunistic in high concentrations microflora in the layers of the mucous membrane, the virulence of which is supported by impaired trophism and a decreased local cellular and humoral immunity [31].

Based on this, the etiotropic treatment of chronic pharyngitis should be aimed at eliminating the pathogenic, as well as excess content of opportunistic microflora with the help of appropriate bactericidal (bacteriostatic) agents. Immunotropic drugs (Imudon, Licopid, Polyoxidonium, IRS, Ribomunyl, etc.) potentiate the action of "basic" drugs. Drugs that increase the overall resistance of the body (vitamin C, zinc preparations,

omega-3, probiotics containing lactobacilli, etc.) are of great importance in the treatment of chronic pharyngitis. The use of antiallergic, desensitizing, sedative, metabolic process normalizing agents, vitamin therapy, restoration of micronutrient deficiency play an important role in the preservation of homeostasis of the mucous membrane in the upper respiratory tract [13, 40].

Treatment of chronic pharyngitis exacerbations: topical therapy

The choice of the optimal drug is determined by the spectrum of its antimicrobial activity, the absence of allergenicity and toxic effect, i. e., the local administration of drugs with a wide range of antimicrobial activity in many cases is the method of choice.

Drugs used for topical treatment of CP can be divided into seven groups: topical antibiotics, antiseptics, antiviral drugs, immunocorrection drugs, local anesthetics, anti-inflammatory drugs, homeopathic remedies [1]. In uncomplicated CP, there is usually no need for systemic administration of antibiotics [9]. Currently, there is a tendency in the world to use topical drugs for relief of inflammatory processes in CP. This is due to the growing allergization of the population in most countries, a high percentage of side effects of systemic drugs and their low effect on inflammatory diseases of the pharynx [14].

Optimal for sore throat is the administration of drugs that have not only an antiseptic effect, but also can quickly relieve pain [5].

Typically, the composition of drugs for topical treatment of CP includes one or more antiseptics: Miramistin, gramidin S, chlorhexidine (be mindful of the toxicity of chlorhexidine, part of Antiangin, Drill, Sebidin, Eludril, and prevent their unrestricted and uncontrolled use by patients (especially children), Hexetidine (Hexoral), Benzydamine, Ambazon, thymol and its derivatives, alcohols, iodine, etc.), essential oils, less — antibiotics (Framycetin) or sulfonamides, deodorizing means, natural preservatives (plant extracts, bee products), synthesized nonspecific protection factors of the mucous membranes, the components of the microflora (bacterial lysates, ribosomes, common determinants of bacteria — glucosamuramyldipeptide — Licopid).

Topical treatment of CP is carried out in the form of rinses, inhalations. Drugs can be produced in the form of tablets, drops or lozenges (Hexalyse, Drill, Septolete, Pharyngocept, neo-angin, Strepsils plus). However, this form of drugs has a relatively low activity and their administration is limited to mild forms of the disease.

Prescription of several drugs is limited by their allergenicity and irritant effect. This group includes drugs containing iodine derivatives (Iodinol, Jox, Vicadin, Povidone-Iodine), propolis (Proposol), sulfonamides (Bicarmint, Inhalypt). Drugs containing plant antiseptics and essential oils are effective and harmless, but their administration is contraindicated in patients who are allergic to pollen (pollinosis), and the number of persons with pollinosis in some geographical areas is up to 20% in the population.

In the treatment of chronic pharyngitis a variety of rinses (chamomile, sage, decoction of oak bark, eucalyptus, Bicarmint, Octenisept, etc.), inhalations (alkaline, lysozyme, trypsin), lubrication (Lugol solution on glycerin, tannin-glycerin, Collargol, Protargol, Sialor, etc.), bacterial lysates (IRS, Imudon, Ribomunyl, etc.) are also widely used. The complex of therapeutic agents uses a number of homeopathic remedies (Engystol, Lymphomyazot, etc.) and herbal medicinal products (Rotocan), as well as methods of aromatherapy (fir, cedar, pine oils, there are domestic sprays of essential oils non-allergenic series — Latta-Bio) [43]. Thus, the main requirements for the drugs applied to the mucous membrane are:

- a wide range of antimicrobial action, preferably including antiviral and antimicrobial activity;
- no toxic effect;
- low rate of absorption from mucous membranes;
- low allergenicity;
- no irritant effect on the mucous membrane.

The use of systemic antibiotic therapy in chronic pharyngitis

The need for systemic administration of antibiotics in exacerbations of CP is due to the appearance of pathogenic microorganisms, for example, beta-hemolytic Streptococcus, signs of general intoxication with high temperature, combined bacterial-viral, fungal microflora.

Antibacterial therapy is usually prescribed taking into account the sensitivity to antibiotics, identified pathogenic microflora [26, 30, 34, 38, 41] for a culture of oropharyngeal smear. Effective drugs for CP are penicillins (but they most often cause allergic reactions, dysbiosis, increased growth of fungal microflora), and macrolides. For example, an effective drug for CP is clarithromycin (Binoclar, Klabax, Claricin, Klacid, Fromilid) administrated per os; this drug is active against many intracellular microorganisms, gram-positive and gram-negative bacteria [11, 15, 17, 18].

Physiotherapy for chronic pharyngitis

Physiotherapy methods are effective in the complex treatment of CP. The effect of most of them is based on dilation of peripheral vessels, redistribution of blood and lymph flow, increased tissue nutrition, stimulation of redox processes. Diathermy, quartz, UHF, magnetotherapy, mud therapy, electro- and phonophoresis with vitamins, iodide, basic drugs, hydrocortisone, helium-neon laser are the most commonly used [21, 29].

Complications of chronic pharyngitis

The most frequent concomitant conditions and diseases in recurrent CP are lymphadenopathy of cervical lymph nodes (in 80% of cases), chronic tonsillitis, conjunctivitis, otitis media, sinusitis, maxillar sinusitis, labial form of herpes virus infection, EBVI (Epstein-Barr virus infection), laryngitis, tracheitis, bronchitis, pneumonia, paratonsillar abscess (often caused by streptococcal infection). Severe systemic complications of CP in combination with chronic tonsillitis are [10] rheumatic fever, rheumatic heart disease, glomerulonephritis (often caused by gram-negative bacteria), hematuria, psoriasis, urticaria, insomnia, arthritis.

Immunity in chronic pharyngitis

In recurrent CP, in case of ineffective complex treatment prescribed by otorhinolaryngologists, patients consult immunologists. A number of authors noted the suppression of local immunity of the pharyngeal mucosa — decreased production of secretory immunoglobulin A in saliva. This feature is more often revealed in the hyperplastic process in the pharyngeal mucosa [12]. In the catarrhal form of CP, a decrease in phagocytosis [11] is detected.

The peroxidase activity of saliva (PAS) in different forms of CP (catarrhal, hyperplastic, atrophic) was evaluated, and its increase in the catarrhal form of CP and its decrease in the hyperplastic form were revealed. Using topical therapy, it is possible to restore PAS — to increase the initially low level of peroxidase activity, while reducing the rate of CP exacerbations [1].

Indicators of systemic immunity in CP do not change often: in 90% of cases, the levels of 4 classes of immunoglobulins A, M, G, E, lymphocyte subpopulation, phagocytic activity of neutrophils and monocytes in the blood are within the normal range. Interferon status in 70% of patients is impaired: with leukocyte stimulation — production of α- and γ-interferons is reduced. In this case, serum interferon content is normal. The immunologist can prescribe an examination to determine sensitivity to various immunostimulants via Interferon status test; taking into account the sensitivity, the treatment regimen with the inclusion of immunostimulants is assigned [5].

In order to restore local immunity in CP, drugs with effect targeted on immune system, also having an anti-inflammatory effect, are widely used. The most widely used immunostimulants in CP are Licopid (sublingually or orally), Polyoxidonium, lysozyme, Genferon, Grippferon (drugs containing recombinant α-interferon), Imudon, Ribomunyl, IRS-19 (the last three drugs contain bacterial lysates, ribosomes of bacterial cells), plant-derived immunomodulators (for example, Tonsilgon N has anti-inflammatory and antiseptic effect, including antiviral one, stimulates phagocytosis, it includes marshmallow root, chamomile flowers, horsetail grass, walnut leaves, yarrow grass, oak grass, dandelion grass).

Many years of experience in the use of immunostimulants in recurrent CP show that remission can be extended to 3–6 months or more, followed by exacerbation, i. e., immunotherapy in CP should be a course. The work of pathology professor V. P. Bykova convincingly demonstrates that prolonged

use of immune stimulants locally in diseases of the upper respiratory tract leads to the development of hyperplasia of lymphoid tissue in the nasopharynx, i. e., excessive stimulation of local immunity is not recommended [6].

New approaches to the assessment of recurrent CP etiopathogenesis

Gas chromatography — mass spectrometry (mass spectrometry of microbial markers (MSMM)) is a modern diagnostic method for CP. MSMM allows to detect 57 microorganisms (species-specific fatty acids, aldehydes) by the level of stable markers in the oropharyngeal smear, 2 hours after delivery of the sample to the laboratory: 7 species of cocci, 21 species of anaerobic bacteria, 9 species of actinobacteria, 3 species of enterobacteria, species of gram-negative bacteria, viruses (herpes, EBV, CMV), species of microscopic fungi (2 species — *Candida, Aspergillus spp.*). Microbiota determined by MSMM includes resident (constantly represented in the pharynx) and transient microorganisms (in healthy individuals their content in the pharynx is 0, and increases significantly in CP).

A feature of MSMM is the ability to detect microorganisms in the biofilm — in the "sleeping state", while the micro colonies can be protected by mucin, polysaccharide capsules.

This method was tested in Russian health care facilities for more than 20 years. In 2010, Rospotrebnadzor allowed its use as a new medical technology in the diagnosis (Resolution FS 2010 /038 dated 24.12.20110 "Assessment of the microenvironmental status of a person by chromatography — mass spectrometry"). However, to date, the highly informative method of MSMM is little known to otorhinolaryngologists, therapists and immunologists, and is rarely used in practice because of the complexity in the interpretation of the results.

In their work, I. A. Snimshikova and co-authors [24] examined 62 patients with recurrent CP using the method of MSMM. Below we present to your attention the results.

The total content of microorganisms in 91% of persons with CP was elevated (in 68% of persons — it was 6–15 times higher, in 23% — 2–5 times, in 9% — normal). These data indicate the need for antibiotic therapy: local or systemic (depending on the type of microorganisms, the degree of increase in their content, the presence of general intoxication).

Endotoxin level was elevated in 87% of patients: while in 24% of persons, the increase was considerable (11–50 times), in 28% — moderate (6–10 times), in 48% this indicator increased slightly (2–5 times). These results confirm the clinical observations that in case of recurrent CP, in most patients (72%) there are no signs of general intoxication, but there are constant complaints that reduce the quality of life.

The content of plasmalogen* (P) was reduced in 71% of patients. The level of P is significantly dropped in 28% of persons (11–100 times), moderately (6–10 times) — in 11%, in 61% of persons — in mild degree (2–5 times). Given that P is involved in cholesterol metabolism, it can be assumed that these patients may fall into the high risk group for lipid metabolism disorders. This assumption requires special research.

In 100% of patients with CP who were under observation, an increase in the content of several transient microorganisms which normally do not occur in oropharynx (or occur in trace amounts) was found (Fig. 1). These are 2 types of Clostridium (*Blautia coccoides, Clostridium difficile*), *Enterococcus spp., Peptostreptococcus (17642), Kingella spp., Campylobacter mucosalis, cytomegalovirus (CMV)*. New etiopathogenetically significant bacteria identified in CP are inhabitants of the gastrointestinal tract: all patients with CP who were under observation (62 people) had complaints on the gastrointestinal tract (flatulence, constipation, diarrhea, heartburn, belching). In 79% of patients, the content of Campylobacter (a microorganism that plays a role in the etiopathogenesis of gastric diseases, gastroesophageal disorders) was elevated, the detected changes

* Plasmalogen is aldehydogenic lipid, which is produced by microflora (Eubacteria, Bifidobacteria, Propionibacteria, Clostridia) in the norm, protects unsaturated fatty acids from oxidation, and regulates the release of cholesterol from the cells.

confirm the data described in the literature that GERD, chronic gastritis play an important role in the pathogenesis of recurrent CP [24].

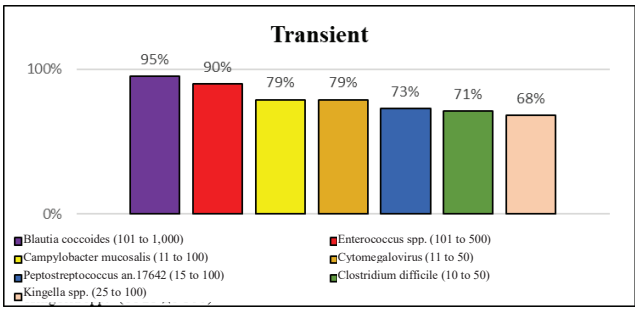

Figure 1. *Transient etiologically significant microorganisms in CP*

New etiopathogenetically significant microorganisms in CP detectable only using MSMM (in healthy individuals their content in oropharynx is 0). The vertical axis shows the percentage of persons with CP having elevated content of these microorganisms. The brackets indicate how many times their level increases.

The second group of etiologically significant microorganisms in CP (Fig. 2) includes 6 resident, opportunistic microorganisms constantly present in oropharynx. Their content increases in CP in 69–95% of patients, but the degree of increase is less significant than in microorganisms from group 1. This group includes both bacteria previously known in CP (strepto- and staphylococci) and new microorganisms (Clostridium, Entamoeba histolytica, Bacteroides fragilis, Bacillus cereus, Nocardia asteroides) identified only with the use of MSMM.

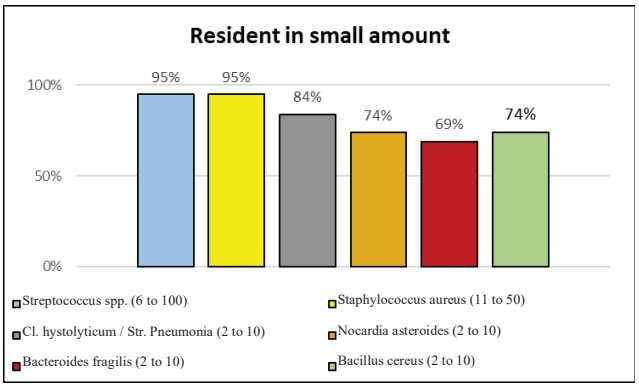

Figure 2. *Resident bacteria detected in the oropharynx in small amount in normal condition*

Etiopathogenetically significant in CP resident microorganisms are present in the oropharynx of healthy individuals in small quantities — up to 100×10^5 cells in 1 gram of sample. The symbols are the same as in Fig. 1.

The third group includes least etiopathogenetically significant in CP (Fig. 3) resident microorganisms found in healthy individuals in the oropharynx in large quantities. These are 5 opportunistic microorganisms, and the increase in their content in CP is moderate. Normally their level is high: ranges from 100 to 500×10^5 cells per 1 gram of sample.

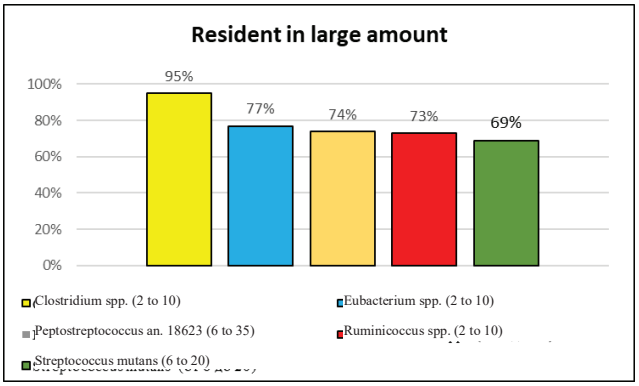

Figure 3. *Resident bacteria detected in the oropharynx in large amount in normal condition*

Using MSMM, a significant or moderate increase in the content of herpes, cytomegalovirus was detected in most (75%) patients: 21–100 times and 6–20 times, respectively, in 4% of individuals an increase in the level of these markers is small — 2–5 times, in a quarter of examined individuals (25%) virus content is normal. This observation indicates the important role of viruses of the herpes group in the etiopathogenesis of recurrent CP.

The level of *Candida spp.* was slightly elevated: in 45% of patients by 2–5 times, and in 55% it is within the normal range.

The content of normal microflora (*Lactobacillus spp., Bifidobacterium spp., Propionibacterium freudenreichii*), on average, was elevated in 71% of patients, indicating continued local resistance in patients with CP examined by the authors. Thus, the use of MSMM in CP allows to identify new etiopathogenic microorganisms, and on this basis to prescribe more effective therapy.

Main conclusions

1. Recurrent chronic pharyngitis (CP) is a chronic infectious and inflammatory process having complex etiopathogenesis, caused by a range of pathogenic factors.
2. The main factors supporting recurrent CP:
   2.1. etiologically significant microorganisms that acquire virulent properties and increased invasiveness by reducing the resistance, immunity of the patient;
   2.2. presence of concomitant chronic diseases in the patient, insufficiently compensated;
   2.3. effect of accompanying pathogenetically significant factors (occupational hazards, peculiarities of nutrition, etc.).
3. The new method — MSMM — is highly informative in CP and can be recommended for wide use in the diagnosis of upper respiratory tract disorders.
4. Through the use of MSMM in CP, new etiopathogenetically significant microorganisms were identified.
5. Based on the results of MSMM in CP, it is possible to develop more effective, personalized treatment regimens with the inclusion of immunotherapy.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Aznabaeva L.F., Arefieva N.A. Immune aspects of chronic tonsillitis. Bulletin of Otolaryngology. 2013; 4: 4-9 [In Russian].
2. Akulich I. I., Lopatin A. S. Treatment of acute and chronic pharyngitis with Imudon. Attending doctor. 2005; 9: 90–91 [In Russian].
3. Artsimovich N.G., Kornev A.V., Chugunov B.C. Pharyngitis as one of the earliest symptoms of chronic fatigue syndrome and immune dysfunction. Materials of the Russian symposium «Problems of immunology in otorhinolaryngology». SPb. 1994; 55–56 [In Russian].
4. Adeishvili P.S., Shamsheva O.V., Osipov G.A. Dysbiotic disorders of the microbiocenosis of the mucous membranes of the oropharynx and their role in the pathogenesis of infectious mononucleosis. Bulletin of Russian State Medical University. 2013; 3: 44-47 [In Russian].
5. Andriyanova I.V., Vakhrushev S.G., Kashirtseva I.A. et al. Research in the microbiota of the nasopharynx of children with chronic adenoiditis using the method of mass spectrometry. Russian Rhinology. 2014; 1: 16-19 [In Russian].
6. Bykova V.P. Adenoid hyperplasia of the pharyngeal tonsil in children who received immunomodulatory therapy. Russian Society of Pathologists. 2017; 56-57 [In Russian].
7. Vasyaeva A.A. Immunotherapy in chronic pharyngitis: indications. RMJ. 2010; 30: 112-118 [In Russian].
8. Hoffman V.R., Smirnov B.C. The state of the immune system in acute and chronic diseases of the Otorhinolaryngologist organs. Immunodeficiency States, ed. Smirnova B.C., Freidlin I.S. SPb. Foliant. 2000; 163–187 [In Russian].
9. Grafskaya N.A., Portenko G.M., Strelets E.V. Treatment and secondary prevention of chronic pharyngitis, taking into account the pharyngeal microbiocenosis. Proceedings of the XVI Congress of Otolaryngology RF. Sochi. 2001; 356–358 [In Russian].
10. Dragomiretsky V.D., Evchev F.D., Bazhora Yu.N. Indicators of local immunity of the mucous membrane of the oral part of the pharynx in patients with chronic pharyngitis. GUNBB. 1989; 6: 21–23 [In Russian].
11. Egorov V.I. Clinical and immunobiological rationale for the use of lysozyme in the treatment of chronic pharyngitis. The dissertation of the doctor of medical sciences. Spb. 1996 [In Russian].
12. Egorov V.I. Features of the course of chronic pharyngitis in the elderly. Current issues of diagnosis, treatment and rehabilitation of patients in a multidisciplinary hospital. 1993; 1: 70-71 [In Russian].
13. Kladova O.V., Fomina V.L., Feldfiks L.I. et all. Modern methods of immunorehabilitation of frequently ill children with acute obstructive laryngitis. Pediatrics. 2009; 87 (2): 72-77 [In Russian].
14. Lopatin A.S. Treatment of acute and chronic pharyngitis. RMJ. 2001; 9: 16–17 [In Russian].
15. Magomedov M.M., Kryukov A.I., Uzdennikov A.A. Strepsils plus in the treatment of inflammatory diseases of the pharynx. Bulletin of Otorhinolaryngology. 1999; 1: 51–52 [In Russian].
16. Palchun V.T., Luchikhin L.A., Kryukov A.I. Inflammatory diseases of the pharynx. M. GEOTAR — Media. 2007; 288 p. [In Russian].
17. Parfenov A.I., Ruchkina I.N., Osipov G.A. Correction of intestinal microflora with probiotics among the patients with antibiotic-associated diarrhea. Directory polyclinic doctor. 2006; 4 (2): 13-19 [In Russian].
18. Parfenov A.I., Ruchkina I.N. The activator of local immunity Gepon in the treatment of intestinal dysbiotic disorders. Experimental and clinical gastroenterology. 2003; 3: 66–69 [In Russian].

19. Pluzhnikov M.S., Panova N.V., Levin M.Ya. Pharyngitis (clinical morphological aspects and cryosurgery). SPb., Dialogue. 2006; 120 [In Russian].
20. Polyakova T.S. Etiopathogenesis and treatment of chronic pharyngitis. Bulletin of Otolaryngology. 2002; 4: 45-49 [In Russian].
21. Portenko G.M., Grafskaya N.A. Magnetophoresis with heparin in the treatment of patients with chronic pharyngitis. Bulletin of Otorhinolaryngology. 2002; 5: 28–30 [In Russian].
22. Ryabova M. A. Pain in the throat — is it always a disease of the upper respiratory tract? Directory polyclinic doctor. 2010; 1: 32–37 [In Russian].
23. Semenov F.V., Gorbonosov I.V., Meleshkevich V.B. Changes in regional hemodynamics during sanitizing operations on the middle ear and its pharmacological correction. Proceedings of the XV All-Russian Congress of Otorhinolaryngologists. SPb. 1995; 399-402 [In Russian].
24. Snimshikova I.A., Agafonov B.V., Gostry A.V. Clinical and diagnostic value of the method of mass spectrometry in the recurrent course of chronic pharyngitis. Attending physician. 2018; 7: 58-62 [In Russian].
25. Strukova E.G., Efremov A.A., Gontov A.A. et al. Effects of essential oils of the Siberian region on conditionally pathogenic microorganisms. Chemistry of Plant Raw Materials. 2009; 4: 57-62 [In Russian].
26. Shaykhova Kh. E., Odilova A. Improvement of treatment methods for patients with various forms of chronic pharyngitis. Young scientist. 2017; 3: 270-272 [In Russian].
27. Shenderov B.A. Medical microbial ecology and functional nutrition, in 3 volumes. Volume 1. Microflora of humans and animals and its functions. M, Grant. 1998; 14-17 [In Russian].
28. Shpynev K. V., Krechikov V. A. Current approaches to the diagnosis of streptococcal pharyngitis. KMAH. 2007; 9 (1): 20–33 [In Russian].
29. Alcaide A. L., Bisno A. L. Pharyngitis and epiglottitis. Infect Dis Clin North Am. 2006; 21: 449–469.
30. Barnett M. L., Linder J. A. Antibiotic prescribing to adults with sore throat in the United States. 2014; 174(1): 138–140.
31. Dagnelie C.F. Sore Throat in General Practice. A Diagnostic and Therapeutic Study. Thesis. Rotterdam; 1994.
32. Gwaltney J.M. The common cold. In: Mandell G.L., Bennet J.E., Dolin R., editors, Principles and Practice of Infectious Diseases. 4th Edition. NY: ChurchillLivingstone. 1996; 6: 561.
33. Hansaker D.H., Boone J.L. Etiology of Infectious Diseases of the Upper Respiratory Tract. Otorhinolaryngology: Head and Neck Surgery. 15th edition. Baltimore: Williams & Wilkins. 1996; 69–83.
34. Kalra M. G., Higgins K. E., Perez E. D. Common Questions About Streptococcal Phar-yngitis. Am Fam Physician. 2016; 94(1): 24–31.
35. Kharseeva G.G., ed. Diphtheriae: Microbiological and Immunological Aspects. Moscow, Prakticheskaya meditsina; 2014. (in Russian)
36. Kinross, J.M. von Roon, A.C., Holmes. The human- gut microbiom: implication for future health care. Current Gastroenterology Reports. 2008; 10: 396–403.
37. Melker R. Prescribing patterns for respiratory tract infections: Dutch data from international perspective. In: Program and abstracts of the 3rd International Meeting on Upper Respiratory Tract Infections. Crete, 1997; 61.
38. Nakhoul G. N., Hickner J. Management of adults with acute streptococcal pharyngitis: minimal value for backup strep testing and overuse of antibiotics. J Gen Intern Med. 2013; 28(6): 830–834.
39. Nikolaev Yu.A., Plakunov V.K. Biofilm. «City of microbes» or an analogue of multicellular organisms? Mikrobiologiya. 2007; 76(2): 149–63.
40. Otori N., Paydas G., Stierna P. The anti–inflammatory effect of fusafungine during experimentally induced rhinosinusitis in rabbit. Eur Arch Otorhinolaryngol. 1998; 255: 195–201.
41. Piskunov G.Z., Piskunov S.Z., Lopatin A.S. Substantiation of the use of Octenisept in acute and chronic inflammation of nasal mucosa. In: Liber Amicorum. Prof. Dr. E.H.Huizing. Utrecht, 1997; 5: 181.
42. Rice D.H. Microbiology. In: Donald P.J., Gluckman J.L., Rice D.H., Editors, The Sinuses. New York, Raven Press, 1995; 57–64.
43. Shaikh N., Swaminathan N., Hooper E. G. Accuracy and precision of the signs and symp-toms of streptococcal pharyngitis in children: a systematic review. J Pediatr. 2012; 160(3): 487–493.
44. Shephard A., Smith G., Aspley S. Randomised, double-blind, placebo-controlled studies on flurbiprofen 8.75 mg lozenges in patients with/without group A or C streptococcal throat infection, with an assessment of clinicians' prediction of 'strep throat'. Int J ClinPract. 2015; 69(1): 59–71.
45. Venezia J., Cassiday P.K., Marani R.P. et al. Characterization of Corynebacterium species in macaques. J. Med. Microbiol. 2012; 61: 1401.

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THE CLINICAL SIGNIFICANCE OF THE DAILY MONITORING OF HOLTER ECG IN CHRONIC GLOMERULONEPHRITIS AT THE PREDIALYSIS STAGE OF THE DISEASE

Abstract

This article presents the results of our own research: comprehensive clinical and laboratory examinations, including data of 24-hour Holter monitoring (HM) in 169 patients with chronic glomerulonephritis at the predialysis stage of the disease. According to HM, 60.3% of the patients examined had episodes of supraventricular ectopic beats, and 28.9% — ventricular ectopic beats. In addition, 11.2% of patients had atrioventricular block (incomplete/partial), 8.8% had atrial fibrillation, and 14.7% had painless ischemia of 1 to 3 episodes per day. Depending on the mean heart rate (HR) according to HM, patients with chronic glomerulonephritis were divided into two subgroups. Subgroup A included 38 patients with heart rate less than or equal to 70 beats/min, subgroup B — 131 patients with heart rate of more than 70 beats/min. With equal values of uric acid, total CL, HDL-C, TG, plasma creatinine and blood fibrinogen in subgroup B there was a significant increase in LDL-C concentration (3.58 (2.74; 5.54) mmol/l vs. 2.82 (2.30; 3.86) mmol/l; $p<0.05$) and a decrease in the estimated GFR (70.4 (48.8; 96.3) ml/min vs. 85.7 (31.5; 103,1) ml/min; $p<0.05$), in comparison with subgroup A. In subgroup B a tendency to increase the degree of daily urine excretion of protein was observed. The data obtained confirm the fact that HM with the analysis of heart rate is of significant clinical importance for the diagnosis of cardiovascular disorders and the prevention of cardiovascular complications in patients with chronic glomerulonephritis at the predialysis stage of the disease.

Key words: *chronic glomerulonephritis, chronic kidney disease, glomerular filtration rate, Holter monitoring, heart rate*

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Hb — hemoglobin, Ht — hematocrit, BP — blood pressure, ASP — atherosclerotic plaque, LVH — left ventricular hypertrophy, LVPW — left ventricle posterior wall, MI — myocardial infarction, LVMI — left ventricle mass index, BMI — body mass index, EDD — end-diastolic diameter, ESD — end-systolic diameter, LV — left ventricle, LA — left atrium, IVS — interventricular septum, CS — cerebral stroke, LVM — left ventricular mass, CCA — common carotid artery, RWT — left ventricular relative wall thickness, GFR — glomerular filtration rate, HM — 24-hour Holter monitoring,

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HF — heart failure, CRP — C-reactive protein, CCC — cardiovascular complications, TG — triglycerides, CIMT — carotid intima-media thickness, EF — ejection fraction, CGN — chronic glomerulonephritis, HR — heart rate, CL — cholesterol, HDL-C — high-density lipoprotein cholesterol, LDL-C — low-density lipoprotein cholesterol, EchoCG — echocardiography

Introduction

Abundant evidence shows that the most frequent forms of cardiovascular damage in CKD are clinically significant cardiac arrhythmias [1, 2], arterio- and atherosclerotic changes in the main arteries [3, 4], left ventricular hypertrophy (LVH) [5, 6], myocardial infarction (MI) [7, 8], acute and chronic heart failure (HF) [9, 10], as well as cerebral strokes (CS) [11, 12]. As a result, studies to find new diagnostic opportunities for early detection of cardiovascular disorders are becoming very relevant. In this area, evaluation of the possibilities for 24-hour Holter monitoring (HM) use in patients with chronic glomerulonephritis (CGN) at the early stages of the disease is of great interest among clinicians and researchers.

Study objective was to investigate clinical value of HM in patients with chronic glomerulonephritis at the predialysis stage of the disease.

Materials and methods

The study included 169 patients aged 17 to 71 years with an established diagnosis of CGN at the predialysis stage of the disease. The mean age of the examined patients at the time of examination was 40.5±13.6 years. The study excluded persons on long-term hemodialysis with the presence of thyrotoxicosis, fever, as well as cancer patients and pregnant women. Along with the recording of complaints and anamnestic data, physical examination of patients with measurement of heart rate (HR) was conducted, blood pressure (BP) was measured and body mass index (BMI) in kg/m^2 was determined. Laboratory examination included evaluation of red blood parameters (determination of hemoglobin (Hb) and hematocrit (Ht), erythrocyte and platelet count) and blood chemistry (concentration of electrolytes, uric acid, fibrinogen, total and C-reactive protein (CRP), creatinine). The parameters of the lipid spectrum in plasma (cholesterol (CL), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG)) were also studied on the Respons 920 DiaSys Diagnostic System. Glomerular filtration rate (GFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [13] on the basis of plasma creatinine. Additionally, the magnitude of the daily urine excretion of protein was evaluated in all patients.

HM was conducted on the system for daily ECG recording SHILER-102 with 2 modified chest leads close to V1 and V6 chest leads. Nature, incidence, duration of supraventricular and ventricular cardiac arrhythmias were evaluated using HM. Before conducting HM, administration of antiarrhythmic drugs to patients under antiarrhythmic treatment was temporarily stopped 72 hours prior to examination. Non-invasive study of carotid arteries was performed in B-mode by a linear sensor with a frequency of 5–8 MHz on the Philips IE33 X matrix Live 3D ultrasound scanner. The common carotid artery (CCA) was examined, carotid intima-media thickness (CIMT) of the proximal and distal parts of the CCA was measured. Measurement of CIMT was performed three times, the calculation was done using the mean value of CIMT, which was the arithmetic mean CIMT between the right and left CCA. Thickening was indicated by an increase in CIMT by more than 0.9 mm, and atherosclerotic plaque (ASP) — by a CIMT increase of more than 1.5 mm or local compaction by 0.5 mm or 50%, compared with the CIMT value in the adjacent areas of CA [14]. To assess the geometry of the left ventricle (LV), all patients underwent a non-invasive echocardiographic (EchoCG) study on the ultrasound apparatus Sequoia 512 manufactured by Siemens-Acuson Corporation according to the generally accepted method. Thus, wall thickness, LV cavity size, longitudinal size of the left atrium (LA) were assessed from parasternal access with the long axis of the LV. The thickness of the interventricular septum (IVS, cm) and LV posterior wall (LVPW, cm) in diastole was measured, end-diastolic (EDD, cm)

and end-systolic diameters (ESD, cm) of LV were determined. Ejection fraction (EF, %) of LV was also assessed using the L. E. Teichholz formula (1976) in the absence of a- and hypokinetic zones. The mass of LV myocardium (LVM) was calculated according to the formula of R. B. Devereux et al. [15]:

$$LVM\ (g) = 0.8 - \{1.04 - (EDD + IVS + LVPW)^3 - EDD^3\} + 0.6$$

LV mass index (LVMI) was calculated on the basis of indexation of LVM by the body surface of the subject (S, m^2). To assess LV hypertrophy (LVH), LVMI was calculated, the upper value of which was 95 g/m^2 for women and 115 g/m^2 for men. LV relative wall thickness index (RWT) was calculated using the formula:

$$2N/D = (IVSd + LVPWd) / EDD$$

Depending on the values of LVMI and LV RWT the following types of changes in left ventricle geometry were identified [16]: normal LV geometry (RWT<0.42; normal LVMI), concentric remodeling (RWT≥0.42; normal LVMI), concentric hypertrophy (RWT≥0.42; LVMI above the norm), eccentric hypertrophy (RWT<0.42; LVMI above the norm).

Study design

One hundred and sixty-nine patients who underwent HM with different types of CGN were selected by random sampling (Table 1). Type of study — descriptive, with the formation of 2 subgroups based on mean HR according to HM.

Statistical analysis

The results of the study were analyzed using statistical software Statistica 10.0 developed by StatSoft. Verification of distribution normality for quantitative characteristics was carried out using Kolmogorov-Smirnov test. The values of continuous quantities are presented as M±m, where M is the sample arithmetic mean and m is the standard error of the mean. The values of qualitative characteristics are presented in the form of frequencies and percentages. The interquartile range (25th quartile; 75th quartile) in cases of nonparametric distribution of the characteristic was also used in the description of the sample [17]. To assess the significance of differences in mean values, we used the Student t-test for characteristics with normal distribution, to compare two independent groups — Mann-Whitney test. Differences were considered as statistically significant at $p<0.05$.

Study results

Table 1 shows that nephrotic and hypertensive types of the disease prevailed among the examined persons with CGN. The number of patients with the initial stage of renal dysfunction was large (Table 1).

The proportion of male patients was significantly higher compared to females (73% vs. 27%; $p<0.05$). The mean value of BMI in the examined individuals was 27.07±6.36 kg/m^2. The values of systolic and diastolic BP were in the target range, amounting to 142±26 mm Hg and 91±16 mm Hg respectively (Table 2). Mean levels of CL, TG and fibrinogen were higher, and total protein and blood albumin were lower than the established normal value. Median and interquartile range of

Table 1. *Clinical characteristics of examined patients*

Clinical types of chronic glomerulonephritis (n=169)	
Hypertensive type, abs. (%)	48 (28.4)
Latent type, abs. (%)	20 (11.8)
Nephrotic type, abs. (%)	68 (40.3)
Mixed type, abs. (%)	33 (19.5)
The severity of renal dysfunction (KDIGO, 2002) (n=169)	
Stage 1 of chronic kidney disease, abs. (%)	65 (38.4)
Stage 2 of chronic kidney disease, abs. (%)	37 (22.0)
Stage 3 A of chronic kidney disease, abs. (%)	30 (17.7)
Stage 3 B of chronic kidney disease, abs. (%)	15 (8.9)
Stage 4 of chronic kidney disease, abs. (%)	15 (8.9)
Stage 5 of chronic kidney disease, abs. (%)	7 (4.1)

Note: KDIGO — Kidney Disease: Improving Global Outcomes; n — number of patients

plasma creatinine and estimated GFR characterized subclinical renal dysfunction. Since the study was dominated by patients with nephrotic type of CGN, the median daily urinary protein excretion was 1.757 g (Table 2).

According to the results of the instrumental study, shown in Table 3, the mean values of EchoCG indices such as: the longitudinal dimension of LA, LV linear diameters (ESD, EDD, IVST, LVPWT), RWT and indicators of LV systolic function were almost within acceptable limits. When indexing LV mass to the body surface, the magnitude of LVMI was significantly higher thresholds. At the same time, eccentric and concentric variants of LV

Table 2. *Clinical and laboratory parameters of examined patients (n=169)*

Parameters	M±m
Age, years	40.5±13.6
Sex, male/female	124/45
Body mass index, kg/m^2	27.07±6.36
Systolic blood pressure, mm Hg	142±26
Diastolic blood pressure, mm Hg	91±16
Heart rate, beats/min	77±10
Hemoglobin, g/l	135.6±22.9
Hematocrit, %	45.2±7.64
RBC, x10^{12}/l	4.46±0.52
Platelets, x10^9/l	247.7±26.6
Potassium, mmol/l	4.59±0.68
Calcium, mmol/l	1.28±0.48
Sodium, mmol/l	139.4±5.96
Uric acid, mmol/l	0.396±0.097
Total cholesterol, mmol/l	6.31±2.88
High-density lipoprotein cholesterol, mmol/l	1.36±0.44
Low-density lipoprotein cholesterol, mmol/l	3.30 (2.62; 4.84)
Triglycerides, mmol/l	1.95 (1.21; 2.68)
Fibrinogen, g/l	5.108 (3.666; 6.771)
Increased CRP, abs. (%)	59 (35)
Prothrombin index, %	88.3±10.7
Total protein, g/l	57.7±14.8
Albumin, g/l	31.7±11.0
Plasma creatinine, μmol/l	116 (89.0; 184)
Daily urine protein excretion, g	1.757 (0.546; 4.305)
Estimated glomerular filtration rate, ml/min	80.7 (45.0; 109.4)

Note: n — number of patients; CRP — C-reactive protein

Table 3. *Echocardiographic indices of the examined groups of patients with CGN (n=169)*

Parameters	M±m
Left atrium, cm	3.25±0.43
Left ventricle end-systolic diameter, cm	3.32±0.46
Left ventricle end-diastolic diameter, cm	5.13±0.48
Interventricular septum thickness, cm	1.0±0.19
Left ventricle posterior wall thickness, cm	0.98±0.18
Left ventricle mass, g	306.2±94.2
Indexed left ventricle mass, g/m^2	166.3±49.3
Left ventricular relative wall thickness, U	0.385±0.070
Left ventricular ejection fraction, %	64.1±5.56
Normal geometry of left ventricle, abs. (%)	24 (14.2)
Concentric remodeling of left ventricle, abs. (%)	–
Concentric hypertrophy of left ventricle, abs. (%)	44 (26.0)
Eccentric hypertrophy of left ventricle, abs. (%)	101 (59.8)
Calcification and compaction with AV regurgitation, abs.(%)	58 (34.3)
Calcification and compaction with MV regurgitation, abs.(%)	35 (20.7)
Intima-media complex, right common carotid artery, mm	0.5 (0.4; 0.6)
Intima-media complex, left common carotid artery, mm	0.5 (0.50; 0.70)
Mean intima-media complex of common carotid artery, mm	0.5 (0.47; 0.60)
ASP in right common carotid artery, abs.(%)	24 (14.2)
ASP in left common carotid artery, abs.(%)	20 (11.8)
Maximal heart rate, beats/min	123±19
Mean heart rate, beats/min	75±10
Minimal heart rate, beats/min	53±7
Supraventricular ectopic beats (group), abs. (%)	102 (60.3)
High-grade ventricular ectopic beats, abs. (%)	49 (28.9)
Atrioventricular block (I and II degree), abs. (%)	19 (11.2)
Episodes of atrial fibrillation, abs. (%)	15 (8.8)
Transient myocardial ischemia, abs. (%)	25 (14.7)

Note: AV — aortic valve; MV — mitral valve

Table 4. *Comparison of laboratory parameters in examined subgroups*

Parameters	Group A (n=38)	Group B (n=131)
Uric acid, mmol/l	0.402±0.080	0.394±0.101
Total cholesterol, mmol/l	5.30 (4.02; 5.96)	5.54 (4.39; 7.82)
HDL-cholesterol, mmol/l	1.0 (0.88; 1.30)	1.0 (0.90; 1.39)
LDL-cholesterol, mmol/l	2.82 (2.30; 3.86)	3.58 (2.74; 5.54)*
Triglycerides, mmol/l	1.59 (1.21; 2.76)	2.02 (1.22; 2.62)
Fibrinogen, g/l	4.995 (3.443; 5.882)	5.328 (3.886; 7.770)
Plasma creatinine	136 (100.5; 227.0)	113 (88.0; 181.0)
Daily urine protein excretion, g	1.570 (0.664; 3.987)	1.815 (0.539; 4.366)
Estimated GFR, ml/min	85.7 (31.5; 103.1)	70.4 (48.8; 96.3)*

Note: n — number of patients; HDL — high-density lipoproteins; LDL — low-density lipoproteins; GFR — glomerular filtration rate; * — $p<0.05$

structural changes were revealed more often, and the number of patients with normal LV geometry decreased (Table 3). There were no cases of LV concentric remodeling in the sample. The presence of atherosclerotic and calcified changes on the aortic (34.3%) and mitral valves (20.7%) was more often recorded during ultrasound imaging of the heart valve structures.

According to HM, episodes of supraventricular ectopic beats were identified in 60.3% of the examined individuals, and ventricular ectopic beats — in 28.9% (Table 3). In addition, 11.2% of the patients had atrioventricular block (incomplete/partial), 8.8% had atrial fibrillation, and painless ischemia, 1 to 3 episodes per day, occurred in 14.7%.

It has now been established that patients with HR of more than 70 beats/min have a higher risk of developing CCC compared to patients with HR of less than 70 beats/min. This concept was the basis of the separation of the examined persons with CGN into 2 subgroups depending on the mean heart rate according to HM.

Subgroup A included patients with HR less than 70 beats per minute, subgroup B — patients with HR more than 70 beats per minute. With equal concentrations of uric acid, total CL, HDL-C, TG, plasma creatinine and blood fibrinogen, in subgroup B there was a significant increase in LDL-C (3.58 (2.74; 5.54) mmol/l versus 2.82 (2.30; 3.86) mmol/l; $p<0.05$) and a decrease in estimated GFR (70.4 (48.8; 96.3) ml/min versus 85.7 (31.5; 103.1) ml/min; $p<0.05$) compared with subgroup A. In subgroup B there was a tendency towards an increase in the degree of daily urinary protein excretion (Table 4).

Discussion

Our study focused on the evaluation of the clinical value of HM in the early diagnosis of lesions of the cardiovascular system at the CGN. Currently, there is sufficient evidence of the critical role of renal dysfunction in determining CVR in the general population [18]. Thus, patients with GFR of 60–30 ml/min/1.73 m^2 regardless of the type of CGN are at high risk, and patients with GFR≤30 ml/min/1.73 m^2 — at very high risk of CVD [19]. According to the existing recommendations [20, 16], in our study, the examined patients with CGN in terms of the severity of renal dysfunction were in the zone of high risk of cardiovascular complications (CCC) (Table 1). As early as 2004 A. S. Go et al. found that CVD prevalence in a population of patients with renal dysfunction is 64% higher than in individuals with normal renal function [21]. However, the authors were able to demonstrate the independent inverse relationship between a decrease in GFR of less than 60 ml/min/1.73 m^2 and an increase in the risk of death, CCC and hospitalization. Similar data were obtained in recent clinical and instrumental studies [22, 23].

The role of hypertension in the prognosis of cerebrovascular and cardiac complications in patients with CKD can hardly be overestimated. Timely and adequate correction of hypertension reliably delays the onset of the dialysis-dependent stage of renal dysfunction. As can be seen from Table 1, in our study, the proportion of hypertensive glomerulonephritis, i. e. persons with CGN+AH was 28.4%, and the mean BP values were 142 mm Hg for

systolic pressure and 91 mm Hg for diastolic pressure. According to some researchers, the frequency of hypertension is up to 40% at stage 1–2 of CKD, that is close to the frequency of hypertension in the general population [24, 25]. In our opinion, the relatively low prevalence of hypertension in the examined group is associated with the homogeneity of patients included in the study. In addition, our patients had median estimated GFR equal to 80.7 ml/min/1.73 m^2 (Table 2), i. e. the initial stage of the disease was revealed. According to some authors, at GFR below 60 ml/min/1.73 m^2, the frequency of AH increases sharply, and at GFR below 30 ml/min/1.73 m^2, it reaches 75% [25, 26].

In our study (Table 3) according to HM, episodes of AF were detected in 8.8% of patients. On the other hand, supraventricular and ventricular ectopic activity was observed in 60.3% and 28.9% of patients respectively. It is clear that on the one hand, high group ectopic electrical activity of the myocardium is a predictor of AF, and on the other hand, it is a predictor of the development of LV geometry impairment (Table 4). However, the mean values of the longitudinal dimension of LA in the examined persons did not go beyond the established normal values for adults. These facts are quite consistent with the results of previous studies [27, 28]. In the prospective study ARIC (Atherosclerosis Risk in Communities Study), GFR inhibition in the zone of <45 ml/min is clearly accompanied by an increase in the risk of AF by 35% [29].

Epidemiological studies have shown that the prevalence of heart failure (HF) increases concurrently with deterioration of renal function [30]. The adverse effect of reduced GFR on the structural rearrangement of arterial vessels [31] and LV was demonstrated, regardless of the presence of traditional risk factors in CGN [32]. The strongest predictor of an elevated risk of HF symptoms is concentric LVH [33, 34, 35]. We were also able to demonstrate (Table 2, 3) high incidence of eccentric (59.8%) and concentric (26.0%) types of LVH in patients with CGN at the predialysis stage of the disease (Table 3). At the same time, the mean indices of LV contractile function (EF) were preserved.

The appearance of ASP and increase in CIMT among CKD patients at the predialysis stage of the disease were obtained in the work of O. V. Pyankina et al. [36]. Life-time study of ASP structure revealed its increased vulnerability in case of renal dysfunction [37]. In normal CIMT, ASP is often detected in the carotid arteries, which was confirmed in our study (Table 3). With median of mean CIMT (0.5 mm), the presence of ASP was found in 14.2% in the right and 11.8% in the left vascular region of CCA.

HR is a specific marker of life expectancy, reflecting the state of metabolism in the body [38]. Slowing the heart rate improves the balance between myocardial oxygen supply and demand in patients with IHD and significantly reduces the risk of cardiovascular complications and death. Increased HR is one of the predictors of hypertension and kidney hemodynamic stress development [39]. Our work revealed (Table 4) a significant increase in LDL-C level and decrease in estimated GFR in the subgroup of persons with HR over 70 beats/min. In the Framingham Heart Study, the overall mortality and mortality from CVD in people with hypertension almost doubled with an increase in HR for every 40 beats per min, regardless of additional risk factors [40]. At the same time, an increase in heart rate at rest can be a marker of imbalance of the autonomic nervous system, i. e. suppression of vagal activity or increasing sympathetic activity [41]. High HR increases the risk of ASP damage due to hydrodynamic disorders, which underlies the development of acute cardiovascular and nephrocerebral events [42]. The mechanism of anti-atherosclerotic action of decreased HR is probably due to a positive effect on arterial stiffness. The increase in HR can lead to atherosclerotic induration of the arteries, which is associated with an increase in pulse wave velocity. Certainly, autoregulation of blood flow in the brain and kidneys is disturbed due to non-uniform elasticity, the presence of multiple arterial branches and low resistance of blood vessels.

Conclusion

The performance of HM in patients with CGN at the predialysis stage of the disease showed important clinical value for early diagnosis of cardiovascular disorders and prevention of their complications.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Mukhin N.A. Nephrology. National leadership. Quick Edition. 2016; 608 p. [In Russian].
2. Turakhia M.P., Blankestijn P.J., Carrero J.J. et al. Chronic kidney disease and arrhythmias: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. European heart journal. 2018;39:24:2314-2325. DOI:https://doi.org/10.1093/eurheartj/ehy060.
3. Masho Y., Shigematsu T. Arteriosclerosis and vascular calcification in chronic kidney disease (CKD) patients. Clinical calcium. 2007; 17(3): 354-359. DOI: CliCa0703354359.
4. Murkamilov I.T., Aitbaev K.A., Sarybaev A.Sh. et al. Relationship of Remodeling of carotid Arteries and Left Ventricular Geometry in Patients with Chronic Glomerulonephritis. Cardiology. 2018; 58(4): 45-52. DOI:10.18087/cardio.2018.4.10108. [In Russian].
5. Volgina G.V. Hypertrophy of the left ventricle of the heart in patients with pre-dialysis chronic renal failure. Cardiovascular therapy and prevention. 2002; 1(4): 68-75. [In Russian].
6. Ali T., Idrees M.K., Shoukat., Akhtar S.F. Left ventricular hypertrophy among predialysis chronic kidney disease patients: Sindh institute of urology and transplantation experience. Saudi J Kidney Dis Transpl. 2017; 28: 1375-1380. DOI:http://www.sjkdt.org/text.asp?2017/28/6/1375/220856.
7. Karetnikova V.N., Kalaeva V.V., Evseeva M.V. et al. The role of chronic kidney disease in assessing the risk of the poor course of hospital ST-segment elevation myocardial infarction. Ther. archive. 2016; 88(6): 26-32. DOI: 10.17116 / terarkh201688626-32. [In Russian].
8. Chan M.Y., Becker R.C., Sim L.L. et al. Reperfusion strategy and mortality in ST-elevation myocardial infarction among patients with and without impaired renal function. Ann Acad Med Singapore. 2010; 39(3): 179-184.
9. Ahmed A., Campbell R.C. Epidemiology of chronic kidney disease in heart failure. Heart failure clinics. 2008; 4(4): 387-399. DOI:https://doi.org/10.1016/j.hfc.2008.03.008.
10. House A.A. Management of Heart Failure in Advancing CKD: Core Curriculum 2018. Am J Kidney Dis. 2018: 72(2): 284-295. DOI:10.1053/j.ajkd.2017.12.006.
11. Feldberg J., Patel P., Farrell A. et al. A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. Nephrology Dialysis Transplantation. 2018. DOI:https://doi.org/10.1093/ndt/gfy031.
12. Arnold J., Sims D., Ferro C. J. Modulation of stroke risk in chronic kidney disease. Clinical kidney journal. 2015; 9(1): 29-38. DOI: https://doi.org/10.1093/ckj/sfv136.
13. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements. 2013; 3: 1-150.
14. Mancia G., Fagard R., Narkiewicz K. et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Hypertension. 2013; 31: 1281-1357. DOI:https://doi.org/10.3109/08037051.2013.812549.
15. Devereux R.B., Alonso D.R., Lutas E.M. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. The American journal of cardiology. 1986; 57(6): 450-458. DOI:https://doi.org/10.1016/0002-9149(86)90771-X.
16. Williams B., Mancia G., Spiering W. et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European heart journal. 2018; 39(33): 3021-3104. DOI:https://doi.org/10.1093/eurheartj/ehy339.
17. Methods of statistical processing of medical data: Methodological recommendations for residents and graduate students of medical schools, researchers / sost.: Kochetov A.G., Lyang O.V., Masenko V.P., Zhirov I.V., Nakonechnikov S.N., S.N. Tereshchenko — M.: RKNPK. 2012; 42 p. [In Russian].
18. Major R.W., Cheng M.R., Grant R.A. et al. Cardiovascular disease risk factors in chronic kidney disease: A systematic review and meta-analysis. PloS one. 2018; 13: 3. C. e0192895. DOI:https://doi.org/10.1371/journal.pone.0192895.
19. Mancia G., Fagard R., Narkiewicz K. et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood pressure. 2013; 22(4): 193-278. DOI:https://doi.org/10.3109/08037051.2013.812549.
20. Moiseev V.S., Mukhin N.A, Smirnov A.V. Cardiovascular risk and chronic kidney disease: cardio-nephroprotection strategies. Journal of Cardiology. 2014; 8: 7-37. DOI:10.15829/1560-4071-2014-8-7-37. [In Russian].
21. Go A.S., Chertow G.M., Fan D. et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. New England Journal of Medicine. 2004; 351(13): 1296-1305. DOI:10.1056/NEJMoa041031.
22. Subbiah A.K., Chhabra Y.K., Mahajan S. Cardiovascular disease in patients with chronic kidney disease:

a neglected subgroup. Heart Asia. 2016; 8(2): 56-61. DOI:http://dx.doi.org/10.1136/heartasia-2016-010809.
23. Neter J.E., Stam B.E., Kok F.J. et al. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2003; 42: 878–884. DOI:http://dx.doi.org /10.1161/01.HYP.0000094221.86888.AE.
24. Rao M.V., Qiu Y., Wang C., Bakris G. Hypertension and CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES), 1999-2004. Am. J. Kidney Dis. 2008; 51:4: S30-S37. DOI:https://doi.org/10.1053/j.ajkd.2007.12.012.
25. Rimoldi S.F., Scherrer U., Messerli F.H. Secondary arterial hypertension: when, who, and how to screen? Eur. Heart J. 2013; 35(19): 1245-1254. DOI:https://doi.org/10.1093/eurheartj/eht534.
26. Morse., Stephen A., Dang An, Thakur Vashu. et al. Hypertension in Chronic Dialysis Patients: Pathophysiology, Monitoring, and Treatment. Am. J. Med. Sciences. 2003; 325(4): 194-201. DOI:https://doi.org/10.1097/00000441-200304000-00005.
27. Naser N., Dilic M., Durak A. et al. The Impact of Risk Factors and Comorbidities on The Incidence of Atrial Fibrillation. Materia socio-medica. 2017; 29(4): 231-236. DOI:10.5455/msm.2017.29.231-236.
28. Kirchhof P., Benussi S., Kotecha D. et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal. 2016; 37: 2893-2962. DOI:https://doi.org/10.1093/eurheartj/ehw210.
29. Alonso A., Lopez F.L., Matsushita K. et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011; 123(25): 2946-2953. DOI:10.1161/CIRCULATIONAHA.111.020982.
30. Bagshaw S.M., Cruz D.N., Aspromonte N. et al. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. Nephrol Dial Transplant. 2010; 25: 1406-1416. DOI:https://doi.org/10.1093/ndt/gfq066.
31. Murkamilov I.T., Aitbaev R.A., Fomin V.V., Yusupov F.A. Subclinical lesion of carotid arteries in chronic glomerulonephritis. The Russian Archives of Internal Medicine. 2017; 7(4): 300-305. DOI:https://doi.org/10.20514/2226-6704-2017-7-4-300-305. [In Russian].
32. Murkamilov I.T., Sabirov I.S., Murkamilova Z.A. et al. Stratification of nephrocerebral and cardiovascular risk in chronic glomerulonephritis (literature review). The Russian Archives of Internal Medicine. 2018; 8(6): 418-423. DOI:https://doi.org/10.20514/2226-6704-2018-8-6-418-423 [In Russ.].
33. Verdecchia P., Schillaci G., Borgioni C. et al. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. J Am Coll Cardiol. 1995; 25(4): 871-878. DOI:10.1016/0735-1097(94)00424-O.
34. Muiesan M.L., Salvetti M., Monteduro C. et al. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. Hypertension. 2004; 43:4:731-738. DOI: 10.1161/01.HYP.0000121223.44837.de.
35. Koren M.J., Devereux R.B., Casale P.N. et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991; 114(5): 345-352. DOI: 10.7326/0003-4819-114-5-345.
36. Pyankina O.V., Tatarintsev P. B., Ragozin O. N. Influence of uremic factors in the processes of remodeling of peripheral vessels in patients with chronic kidney disease. Modern problems of science and education. 2013; 1:URL: https://science-education.ru/en/article/view?id=8509. [In Russian].
37. Pelisek J., Hahntow I.N., Eckstein H.H. Impact of chronic kidney disease on carotid plaque vulnerability. J Vasc Surg. 2011; 54(6): 1643-1649. DOI:https://doi.org/10.1016/j.jvs.2011.05.049
38. Levine H.J. Rest heart rate and life expectancy. Journal of the American College of Cardiology. 1997; 30(4): 1104-1106.
39. Levy R.L., White P.D., Stroud W.D., Hillman C.C. Transient tachycardia: prognostic significance alone and in association with transient hypertension. JAMA. 1945; 129(9): 585-588. DOI:10.1001/jama.1945.02860430001001.
40. Gillman M., Kannel W., Belanger A., D`Agostino R. Influence of heart rate on mortality among persons with hypertension: The Framingam study Am Heart J. 1993; 125(4): 1148-1154. DOI: https://doi.org/10.1016/0002-8703(93)90128-V.
41. Schwartz R.J. The neural control of heart rate and risk stratification after myocardial infarction. Eur Heart J. 1999; 1 (Suppl H): H33-H43.
42. Fusrer V., Badimon L., Badimon J.J., Chesebro J.H. The pathogenesis of coronary artery disease and the acute coronary syndromes (I). N Engl J Med. 1992; 326(4): 242-250. DOI: 10.1056/NEJM199201233260406.

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EFFECTS OF LONG-TERM CONTINUOUS POSITIVE AIRWAY PRESSURE THERAPY (CPAP) ON EPICARDIAL FAT THICKNESS AND ARTERIAL STIFFNESS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND HYPERTENSION

Abstract

Background: obstructive sleep apnea (OSA) is associated with high prevalence of hypertension, obesity, carbohydrate metabolism impairment and dyslipidemia. However, positive effects of CPAP therapy on epicardial fat thickness of the OSA patient with hypertension are poorly understood and poorly studied. **Study objective:** to investigate 12-month effects of CPAP therapy with auto-adaptation to inhalation and exhalation (A-Flex therapy) of the OSA patient with hypertension and metabolic disorders on epicardial fat thickness (EFT). **Methods:** A single-center prospective study included 310 patients aged 35 to 75 years (45.3 ± 10.4) with night snoring, metabolic disorders, obstructive sleep apnea, hypertension (273 males (88 %) and 37 females (11.9 %)), who signed an informed consent and had the apnea-hypopnea index (AHI) > 5 events/hour. The night polygraphic study (PG) was performed to calculate AHI, oxygen desaturation index (ODI), mean nocturnal saturation (SpO_2) by the rules of American Academy of Sleep Medicine (AASM). The calculation of the epicardial fat thickness (EFT), the size and volume of the heart cavities, left ventricular mass index (LVMI) were performed via echocardiography in 2D and M modes. Endothelial function of blood vessels determined by finger test was measured according to peripheral arterial tone (PAT). The reactive hyperemia index (RHI) and augmentation index (AI) was calculated. Optimal level of A-Flex therapy was adjusted at home. AHI, the level of air leakage, average pressure and compliance to CPAP treatment were established in accordance with international requirements. **Results:** after 3 months of A-Flex therapy we found a significant decrease of HOMA-IR –1.09 (95 % CI from –1.74 to –0.96; P=0.021), decrease AI –10.8 % (95 % CI from –13.70 to –4.6; P=0.001), decrease EFT –1.26 mm (95 % CI from –2.2 to –0.95; P=0.001) in mild OSA patients. After 6 months of A-Flex therapy we found a significant decrease of HOMA-IR –2.81 (95 % CI from –3.74 to –1.46; P=0.001), decrease AI –15.6 % (95 % CI from –17.23 to –11.75; P=0.001), decrease EFT –2.15 mm (95 % CI from –3.2 to –1.5; P=0.001) in moderate OSA patients. After 12 months of A-Flex therapy we found a significant decrease of HOMA-IR –4.22 (95 % CI from –5.36 to –2.35; P=0.001), decrease AI –21.05 % (95 % CI from –26.5 to –17.4; P=0.001), decrease EFT –4.0 mm (95 % CI from –5.8 to –2.7; P=0.001) in severe OSA patients. In addition, the data obtained are in good agreement with changes in the clinical picture of the disease: the disappearance of excessive daytime sleepiness, increased motor activity, and normalization of night sleep. **Conclusions:** The 12-month A-Flex therapy in moderate and severe OSA patients with hypertension has a significant therapeutic effect of stabilization systolic and diastolic blood pressure, level of blood lipids and epicardial fat thickness, level of endothelial dysfunction. The 12-month A-Flex therapy has to able to reduce the risks of cardiovascular events in moderate and severe OSA patients with acute metabolic manifestations.

Key words: *epicardial fat thickness, obstructive sleep apnea, metabolic disorders, hypertension, arterial stiffness, CPAP therapy, A-Flex therapy*

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AASM — the American Academy of Sleep Medicine, AHI — apnea/hypopnea index, LVMI — left ventricular mass index, OSA — obstructive sleep apnea, PG — polygraphic study, EFT — epicardial fat thickness, CRM — Center of Respiratory Medicine, HR — heart rate, EF — epicardial fat

Introduction

obstructive sleep apnea (OSA) is a disease characterized by interruption of breathing (apnea) and hypoventilation events (hypopnea) during sleep, which result in intermittent hypoxia. The relationship between OSA, vascular risk factors, metabolic disorders and vascular diseases themselves was described in large prospective clinical studies [1,2].

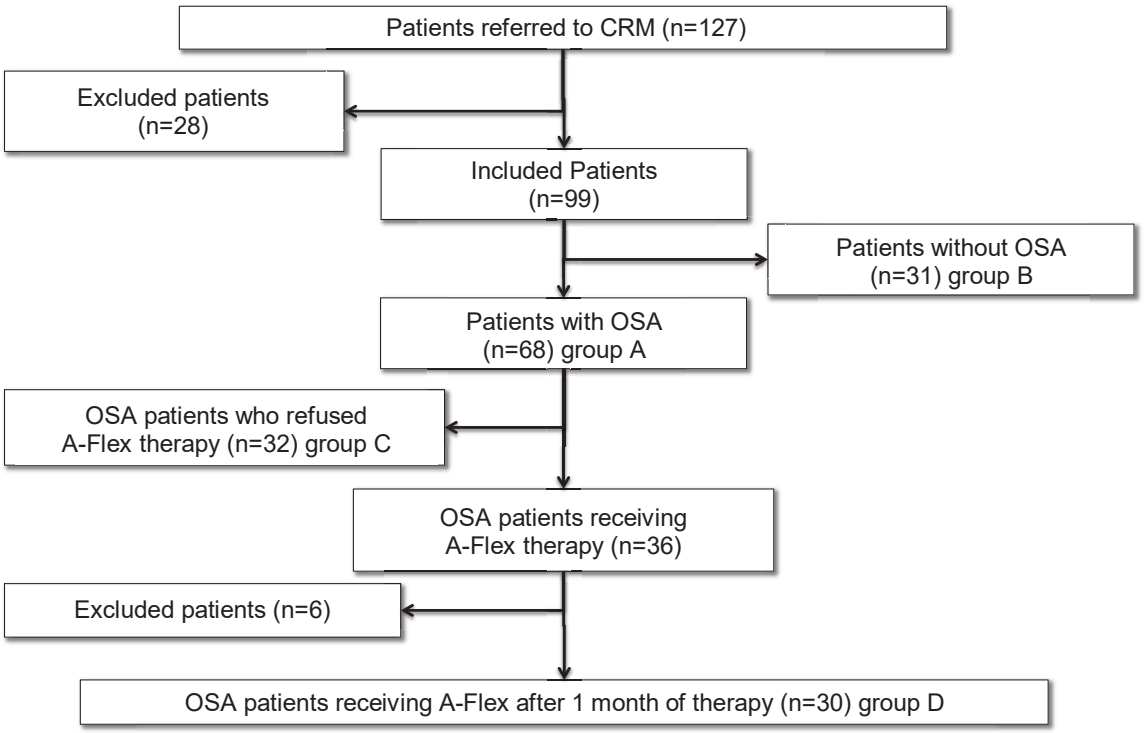
Epicardial fat (EF) is an adipose tissue layer located between the outer myocardial wall and visceral pericardium, particularly behind the right ventricle, in atrioventricular and interventricular grooves. Its weight makes up approximately 18–20 % of the weight of both ventricles; it has common blood supply with the myocardium by the branches of coronary arteries [3]. In case of metabolic disorders, excessive accumulation of EF in OSA turns it into an active endocrine organ, which has lipotoxic, prothrombotic, atherogenic effects on cardiomyocytes and coronary arteries by producing proinflammatory mediators, thus contributing to cardiovascular remodeling [4].

CPAP (Continuous Positive Airway Pressure) therapy with auto-adaptation to the patient's inhalation and exhalation (A-Flex therapy) resolves major pathophysiological effects of OSA, decreases sympathetic drive, intrathoracic negative pressure fluctuation, and reduces left ventricular afterload. In addition, CPAP therapy, possibly by resolving hypoxic events, increases oxygen delivery to tissues, reduces oxygen deficit and is capable of affecting metabolic disorders and EF accumulation in OSA patients with hypertension [5].

Materials and methods

Study design

A single-center prospective study included 310 patients aged 35 to 75 years (45.3 ± 10.4)



with night snoring, metabolic disorders, obstructive sleep apnea, hypertension (273 males (88 %) and 37 females (11.9 %)), who signed an informed consent and had the apnea-hypopnea index (AHI) > 5 events/hour. All the patients received personalized antihypertensive and lipid-lowering therapy. Depending on severity, OSA patients were divided into group A (n=51, mild OSA), group B (n=91, moderate OSA), and group C (n=168, severe OSA). All the patients received CPAP therapy (A-Flex therapy) in accordance with the American Academy of Sleep Medicine (AASM) guidelines [6] to achieve the optimal correction of OSA with AHI < 10 events/hour. Control follow-up points were follow-up months 0–3–6–12.

Patient population

All the patients underwent physical and complete medical examination with an additional focus on history, symptoms and markers of sleep respiratory disorders. They were interviewed for how long they were gaining weight and when it started, number of attempts to lose weight, administration of weight management medications and/or dietary supplements, dietary habits and daily dietary calories, physical activity. The exclusion criteria were: pregnancy, lactation; type 1 and 2 diabetes mellitus; syndrome-based forms of obesity; severe somatic comorbidity (thyroid function abnormality, renal and hepatic failure, decompensated heart failure, severe hemodynamic cardiac rhythm abnormalities, previous myocardial infarction and stroke within three months before screening, systemic inflammatory disease, cancer); administration of systemic glucocorticosteroids in three months before screening; medical history of mental illness and/or that detected during clinical examination; drug and alcohol dependence; patients with pronounced airway obstruction (FEV_1 < 50 %), restrictive disorders (VC < 80 %), daytime arterial blood saturation SpO_2 < 90 % (FiO_2 = 21 %).

Ethical standards

The study was conducted in the Department of Phthisiology and Pulmonology of the Faculty of General Medicine at State University of Medicine and Dentistry named after A. I. Evdokimov, at the Center of Respiratory Medicine (CRM) and the Hospital of the Russian Central Union of Consumer Cooperatives (39 Losinoostrovskaya Str., bldg. 2, 107150 Moscow, Russia). The study was approved by the Inter-University Ethics Committee of the State University of Medicine and Dentistry named after A. I. Evdokimov.

Polygraphic study (PG)

All the patients underwent a night polygraphic study as per the standardized protocol for cardiovascular monitoring of obstructive sleep apnea in accordance with the American Academy of Sleep Medicine (AASM) regulations and recommendations [7]. SOMNOcheck micro CARDIO (Lowenstein Medical (Weinmann), Germany) with SOMNOlab 2.19 (Lowenstein Medical (Weinmann), Germany) software was used. The study was started at 11.00 p.m. and completed at 7.30 a.m., with registration of the main polygraphic respiratory parameters: 1) mouth-nose air flow and snoring; 2) breathing efforts; 3) recording of SpO_2 and heart rate (HR) by pulse oxymetry. The polygraphy findings were processed manually by the qualified personnel of the CRM. Apnea was identified as reduction in the air flow signal by >80 % while maintaining the breathing effort for >10 seconds. Hypopnea was identified as reduction in the air flow signal by >30 % while maintaining the breathing effort for >10 seconds and subsequent desaturation by >4 %. Severity of OSA was determined by the apnea-hypopnea index (AHI) defined as the total number of obstructive apnea and hypopnea per 1 recording hour. Occurrence of 5 < AHI < 15 events/hour was assessed as mild OSA; 15 < AHI < 30 events/hour — as moderate OSA; AHI > 30 events/hour — as severe OSA. The assessment included the nocturnal desaturation level by ODI, i. e., the number of drops of SpO_2 > 4 %, as well as mean and minimum nocturnal saturation (SpO_2), respectively.

Echocardiography

To calculate epicardial fat thickness (EFT), sizes and volumes of cardiac cavities, left ventricular mass index (LVMI), systolic and diastolic functions of both ventricles, transthoracic echocardiography was performed in 2D and M modes using the Xario 200 ultrasonic scanner (Toshiba, Japan) equipped with a 3.5 MHz transducer. Doppler imaging was carried out using pulsed, continuous wave, color

and tissue Doppler modes. Epicardial fat thickness was determined perpendicularly to the right ventricular free wall in B mode from the parasternal position, along the left ventricular long axis, at end systole, on the line which is at most perpendicular to the aortic ring [8]. For verifying epicardial obesity, criteria of T. Yu. Kuznetsova et al. (2017) were applied: for individuals under 45 years of age — EFT ≥ 5.0 mm; for individuals of 45–55 years of age — EFT ≥ 6.0 mm; for individuals over 55 years of age — EFT ≥ 7.0 mm [9].

Endothelial function assessment

Endothelial vascular function was assessed by the quality of peripheral arterial tone (PAT signal), as determined by the pointing test [10]. Pulse wave amplitude (PWA) was estimated before and during reactive hyperemia (RH) by peripheral arterial tonometry (Endo-PAT2000, Itamar Medical Ltd., Israel). PWA baseline data were collected using finger-ring plethysmographic cuffs to be placed on index fingers of both hands for 5 minutes. Ischemic stimulus was induced by cuff occlusion (shoulder cuff inflation up to systolic pressure of >200 mm Hg for 5 min), and RHI index was calculated as a ratio of mean PWA for a period of 1 minute after cuff deflation to the baseline pre-occlusion PWA. We estimated the augmentation index (AI) defined as a ratio of the shock wave arising from the increase of aortic pressure to the systolic reflected wave [11]. All tests of RHI and AI were performed under standardized conditions (time, room, temperature).

Statistical analysis

The data was analyzed using statistical software, version 6.0 (AnalystSoft Inc., StatPlus). Quantitative data was expressed as mean (M) and standard deviation (SD) (M±SD). Differences between the groups were analyzed using ANOVA for continuous variables. The linear relationship between the variables was measured using the Pearson correlation test. During the final assessment of the findings, we performed the intention-to-treat analysis (ITT analysis). The role of gender, age, BMI, fat distribution, EFT, serum glucose and lipids as AHI-associated variables was tested by the linear regression method using multidimensional models. Chi-squared test ($\chi 2$) was used to compare frequencies in independent samples. Differences in the tested parameters were considered significant at $p < 0.05$. When $0.05 < p < 0.1$, the existence of a statistical trend was estimated.

Results

Baseline characteristics of the patients are provided in Table 1.

Of the 310 enrolled patients, a total of 294 (94.8 %) patients made every visit and were included in the standardized analysis. Sixteen patients (5.16 %) made only one follow-up visit and were estimated cumulatively only in the ITT analysis. Patients with severe OSA had statistically ($p < 0.05$) high BMI, pronounced nocturnal hypoxemia and metabolic disorders. Hypertension, arterial stiffness, and epicardial fat thickness (EFT) in group B were also statistically higher than in patients with mild and moderate OSA. The average compliance to A-Flex therapy was 5.3 ± 1.6 h/night (high compliance), which allowed full control over sleep apnea events of <10 events/hour and eliminated all risk of potential fatal and non-fatal cardiovascular events.

Assessing lipid profile, arterial stiffness, epicardial fat thickness in intention-to-treat (ITT) analyses

We performed the intention-to-treat analysis (ITT analysis) of the lipid profile parameters (HOMA-IR, cholesterol, LDL cholesterol, triglycerides), arterial stiffness (AI, RHI)), epicardial fat thickness (EFT) among the patients who successfully completed the study and discontinued the therapy ahead of schedule by month 12, as adjusted for age, gender, BMI, presence of cardiovascular diseases and administration of antihypertensive therapy in mild, moderate and severe OSA groups (Tables 2, 3, 4).

In the patients with mild OSA (group A), significant changes in the lipid profile, arterial stiffness, epicardial fat thickness occurred as early as on month 3 of CPAP therapy: HOMA-IR decreased by –1.09 (95 % CI: –1.74 to –0.96; P=0.021), AI decreased by –10.8 % (95 % CI: –13.70 to –4.6; P=0.001), EFT decreased by –1.26 mm (95 % CI: –2.2 to –0.95; P=0.001), and reached the maximum normal by month 12: HOMA-IR decreased by –1.77 (95 % CI: –3.74 to –0.73; P=0.024), AI decreased by –15.1 % (95 % CI: –18.90 to –9.2; P=0.031), EFT decreased by –1.62 mm (95 % CI: –2.5 to –0.97; P=0.001).

Table 1. *Basic characteristics of the studied patients*

Analyzed parameter	Group A (n=51)	Group B (n=91)	Group C (n=168)
Age (years)	40.60 ± 5.07	44.60 ± 8.30 *	46.40 ± 9.03 **
Gender (m/f)	48/3	86/5	139/29
Body mass index (BMI) (kg/m^2)	32.30 ± 2.30	35.80 ± 2.20 *	37.40 ± 3.60 **
Neck circumference (cm)	41.30 ± 3.50	43.10 ± 3.7	44.30 ± 3.8 *
Waist circumference (cm):			
Men	112.30 ± 8.10	118.20 ± 8.60	121.40 ± 9.20 *
Women	105.50 ± 10.10	108.10 ± 11.20	110.3 ± 11.60 *
Smokers (n, (%))	5 (9.8)	11 (12.0)	18 (10.7)
Former smokers (n, (%))	39 (76.4)	70 (76.9)	125 (74.4)
Non smokers (n, (%))	7 (13.7)	10 (10.9)	25 (14.8)
Polygraphic characteristics			
Apnea-hypopnea index (AHI) (events/hour)	9.8 ± 3.90	23.4 ± 5.80 **	49.8 ± 6.90 **
Oxygen desaturation index (ODI) (events/hour)	8.7 ± 2.90	21.2 ± 4.60 **	46.5 ± 4.70 **
Saturation time less than 90 % (TSat_90) (% from total sleep time)	7.5 ± 1.90	16.2 ± 3.20 **	27.8 ± 3.40 **
Mean night saturation (Sat mean) (%)	91.0 ± 1.70	86.0 ± 1.90 *	83.1 ± 2.30 **
Minimum night saturation (Sat min) (%)	89.0 ± 1.90	80.4 ± 3.20 **	70.5 ± 4.20 **
Minimum nighttime heart rate (beats/min)	52.3 ± 3.80	49.6 ± 5.20	43.1 ± 4.10 **
Maximum nighttime heart rate (beats/min)	96.2 ± 5.60	104.2 ± 6.40 *	113.2 ± 7.30 **
Hypertension, arterial stiffness, epicardial fat thickness			
Duration of hypertension, years	7.90 ± 3.80	8.20 ± 4.10	9.50 ± 2.90 *
Systolic BP "office", mm Hg	146.90 ± 15.60	152.30 ± 15.90	163.20 ± 17.3 *
Diastolic BP "office", mm Hg	93.40 ± 6.80	94.40 ± 6.50	99.50 ± 7.1 *
Reactive hyperemia index / RHI (reference <1.67)	1.98 ± 0.21	2.11± 0.32 *	3.30 ± 0.71 **
Augmentation index / AI (%) (reference 18.43–39.97 %)	39.90 ± 3.9	43.80 ± 4.10	48.20 ± 4.6 **
Epicardial fat thickness (mm)	5.10 ± 0.87	6.39 ± 0.85 *	7.98 ± 1.57 **
Biochemical indicators			
Blood glucose on an empty stomach, mmol/l	5.80 ± 0.50	6.10 ± 0.30	6.40 ± 0.40 *
Glycosylated hemoglobin (HbA1C), %	5.50 ± 0.50	5.70 ± 0.30	6.00 ± 0.40 **
HOMA-IR	4.25 ± 1.72	5.53 ± 2.09 *	6.86 ± 2.14 **
Total cholesterol (mmol/l)	4.32 ± 0.79	4.61 ± 0.81	5.21 ± 0.56 *
Cholesterol-HDL (mmol/l)	0.99 ± 0.19	0.95 ± 0.15	1.09 ± 0.13
Cholesterol-LDL (mmol/l)	2.20 ± 0.80	2.70 ± 0.60	2.90 ± 0.40 *
Triglycerides (mmol/l)	1.77 ± 0.61	2.11 ± 0.53	3.76 ± 0.72 *

Note: * p < 0.05 compared with group A; ** p < 0.01 compared with group A

In the patients with moderate OSA (group B), significant changes in the lipid profile, arterial stiffness, epicardial fat thickness occurred on month 6 of CPAP therapy: HOMA-IR decreased by –2.81 (95 % CI: –3.74 to –1.46; P=0.001), AI decreased by –15.6 % (95 % CI: –17.23 to –11.75; P=0.001), EFT decreased by –2.15 mm (95 % CI: –3.2 to –1.5; P=0.001), and reached the maximum normal by month 12: HOMA-IR decreased by –2.96 (95 % CI: –3.78 to –1.43; P=0.002), AI decreased by –16.0 % (95 % CI: –19.7 to –7.6; P=0.001), EFT decreased by –2.77 mm (95 % CI: –3.6 to –1.5; P=0.001).

In the patients with severe OSA (group C), initial changes in the lipid profile, arterial stiffness, epicardial fat thickness occurred on month 6 of CPAP therapy: HOMA-IR decreased by –3.10 (95 % CI: –5.74 to –2.46; P=0.002), AI decreased by –5.4 % (95 % CI: –7.11 to –3.31; P=0.003), EFT decreased by –4,22 mm (95 % CI: –5.57 to –2.35; P=0.001),

Table 2. *Dynamics of indicators of the group A (n=51)*

Parsed parameter	3rd month CPAP	6th month CPAP	12th month CPAP
Reactive hyperemia index / RHI	1.54 ± 0.11*	1.48 ± 0.27	1.42 ± 0.28
Augmentation index / AI (%)	29.10 ± 4.20*	25.20 ± 5.40 #	24.80 ± 9.60
Epicardial fat thickness (mm)	3.84 ± 0.72*	3.53 ± 0.88 #	3.48 ± 0.93 ##
HOMA-IR	3.16 ± 0.23*	2.64 ± 0.67 #	2.48 ± 0.98 ##
Total cholesterol (mmol/l)	4.32 ± 0.62	4.23 ± 0.68 #	4.15 ± 0.72 ##
Cholesterol-LDL (mmol/l)	2.21 ± 0.71	2.07 ± 0.86 #	1.95 ± 0.93 ##
Triglycerides (mmol/l)	1.53 ± 0.39 *	1.52 ± 0.88	1.51 ± 0.87 ##

Note: * ρ < 0.05 compared to baseline; # ρ < 0.05 compared with the 3rd month; ## ρ < 0.05 compared with the 6th month

Table 3. *Dynamics of indicators of the group B (n=91)*

Parsed parameter	3rd month CPAP	6th month CPAP	12th month CPAP
Reactive hyperemia index / RHI	2.02 ± 0.82	1.56 ± 0.52 #	1.54 ± 0.82
Augmentation index / AI (%)	38.50 ± 6.20	28.20 ± 5.80 #	27.8 ± 6.8
Epicardial fat thickness (mm)	5.85 ± 0.59 *	4.24 ± 0.67 #	3.62 ± 0.89 ##
HOMA-IR	4.36 ± 2.09 *	2.72 ± 1.82 #	2.57 ± 1.83 ##
Total cholesterol (mmol/l)	4.52 ± 0.87	4.48 ± 0.91 #	4.45 ± 0.95 ##
Cholesterol-LDL (mmol/l)	2.62 ± 0.80	2.41 ± 0.96 #	2.24 ± 0.93 ##
Triglycerides (mmol/l)	1.87 ± 0.93 *	1.77 ± 0.53 #	1.69 ± 0.98 ##

Note: * ρ < 0.05 compared to baseline; # ρ < 0.05 compared with the 3rd month; ## ρ < 0.05 compared with the 6th month

Table 4. *Dynamics of indicators of the group C (n=168)*

Parsed parameter	3rd month CPAP	6th month CPAP	12th month CPAP
Reactive hyperemia index / RHI	3.10 ± 0.85	3.00 ± 1.05	1.65 ± 0.46 ##
Augmentation index / AI (%)	45.20 ± 5.60	42.80 ± 6.02	27.15 ± 8.56 ##
Epicardial fat thickness (mm)	7.12 ± 1.38	6.75 ± 1.29 #	3.98 ± 0.83 ##
HOMA-IR	5.92 ± 2.21 *	3.76 ± 2.18 #	2.64 ± 0.93 ##
Total cholesterol (mmol/l)	5.15 ± 1.06	4.91 ± 1.02 #	4.70 ± 1.09 ##
Cholesterol-LDL (mmol/l)	2.80 ± 1.12	2.61 ± 1.18 #	2.42 ± 1.13 ##
Triglycerides (mmol/l)	2.12 ± 0.92 *	1.84 ± 0.82 #	1.72 ± 0.67 ##

Note: * ρ < 0.05 compared to baseline; # ρ < 0.05 compared with the 3rd month; ## ρ < 0.05 compared with the 6th month

and reached the significant normal only on month 12: HOMA-IR decreased by –4.22 (95 % CI: –5.36 to –2.35; P=0.001), AI decreased by –21.05 % (95 % CI: –26.5 to –17.4; P=0.001), EFT decreased by –4.0 mm (95 % CI: –5.8 to –2.7; P=0.001).

Discussion

obstructive sleep apnea combined with hypertension and changes in the lipid profile, arterial stiffness, and epicardial fat thickness is a comorbidity, which dramatically increases risks of cardiovascular disorders, particularly in synergism of action. CPAP therapy is a first-line therapy, especially in moderate and severe OSA. We specifically selected patients with moderate and severe OSA who had metabolic disorders, hypertension and visceral adiposity. We focused our attention on them, since such patients were at the highest risk of fatal outcome or cardiovascular complications and often identified as patients with "refractory hypertension and obesity" which do not respond to medication therapy. To avoid possible distortion of the results, we tested only patients with OSA who received neither therapy of any metabolic syndrome components nor CPAP therapy. The important factor was

multi-agent medication therapy of hypertension prescribed to the patients earlier.

Despite the simple design, no blinding, placebo control and randomization of patients, we achieved the minimum effect on the end result through correct formation of the study and control groups and use of the intention-to-treat analysis (ITT analysis). Our findings are fully consistent with a number of studies concerning CPAP therapy impact on normalizing the lipid profile, arterial stiffness, epicardial fat thickness in patients with OSA combined with hypertension [12–14]. The mechanism for normalizing the lipid profile, arterial stiffness, epicardial fat thickness in patients with OSA combined with hypertension is most likely related to resolving fragmented sleep, nocturnal hypoxemia, resultant sympathetic activity [15–18]. This hypothesis is supported by our study as well, when administration of A-Flex therapy for 12 months significantly reduced the epicardial fat thickness (EFT) and arterial stiffness (augmentation index (AI)) to the target ranges, even in the patients with severe OSA (Fig. 1, Fig. 2).

In conclusion, only 12-month long-term CPAP therapy as per A-Flex regimen in the group of patients with moderate and severe OSA who had resistant hypertension and metabolic disorders has shown a significant therapeutic effect on restoring the normal arterial stiffness and epicardial fat thickness and is likely to reduce risks of cardiovascular events.

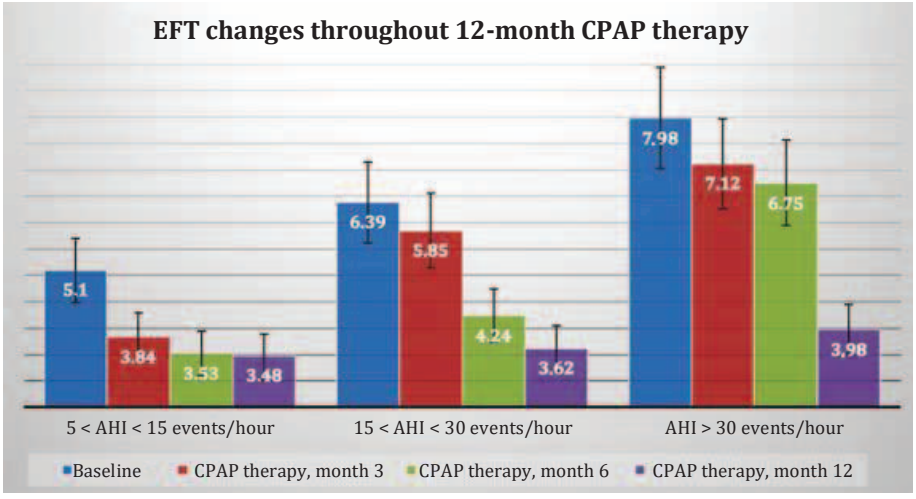


Figure 1. *Diagram of changes in epicardial fat thickness in patients with OSA combined with hypertension of varying severity during CPAP therapy*

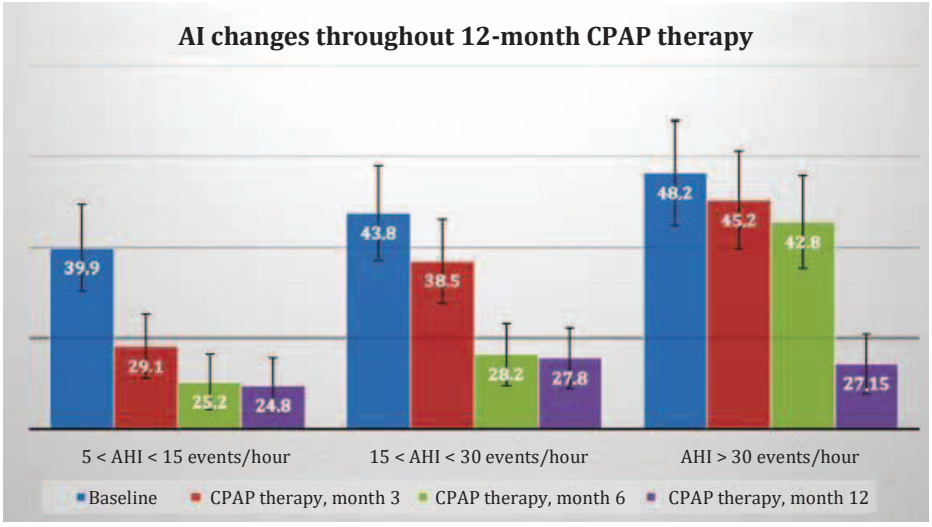


Figure 2. *Diagram of changes in the AI in patients with OSA combined with hypertension of varying severity during CPAP therapy*

Conflict of interests
The authors declare no conflict of interests.

References:

1. Lombardi C1, Tobaldini E, Montano N, Losurdo A, Parati G. Obstructive Sleep Apnea Syndrome (OSAS) and Cardiovascular System. Med Lav. 2017 Aug 28; 108 (4): 276-282. doi: 10.23749/mdl.v108i4.6427. PMID: 28853425.
2. Floras JS. Hypertension and Sleep Apnea. Can J Cardiol. 2015 Jul; 31(7): 889-97. doi: 10.1016/j.cjca.2015.05.003. PMID: 26112299.
3. Salazar J, Luzardo E, Mejías JC, et al. Epicardial Fat: Physiological, Pathological, and Therapeutic Implications. Cardiol Res Pract. 2016; 2016: 1291537. doi: 10.1155/2016/1291537.
4. Piché ME, Poirier P, Lemieux I, Després JP. Overview of Epidemiology and Contribution of Obesity and Body Fat Distribution to Cardiovascular Disease: An Update. Prog Cardiovasc Dis. 2018 Jul — Aug;61(2):103-113. doi: 10.1016/j.pcad.2018.06.004.
5. Mineiro MA, Silva PMD, Alves M, et al. The role of sleepiness on arterial stiffness improvement after CPAP therapy in males with obstructive sleep apnea: a prospective cohort study. BMC Pulm Med. 2017 Dec 8;17(1):182. doi: 10.1186/s12890-017-0518-z.
6. Littner M, Hirshkowitz M, Davila D, Anderson WM, Kushida CA, Woodson BT, Johnson SF, Merrill SW; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the use of auto-titrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome. An American Academy of Sleep Medicine report. Sleep. 2002 Mar 15;25(2):143-7.
7. Kushida C.A., Littner M.R., Morgenthaler T. et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 2005; 28: 499–521. PMID: 16171294.
8. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr. 2009 Dec;22(12):1311-9; quiz 1417-8. doi: 10.1016/j.echo.2009.10.013.
9. Kuznetsova T.Yu., Chumakova G.A., Druzhilov M.A., Veselovskaya N.G. The role of quantitative echocardiographic assessment of epicardial adipose tissue in obese patients in clinical practice. Russian Journal of Cardiology. 2017; 4 (144): 35–39. dx.doi.org/10.15829/1560-4071-2017-4-35-39. [in Russian].
10. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, Karas RH, Udelson JE. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. Am Heart J. 2003 Jul;146(1):168-74. doi: 10.1016/S0002-8703(03)00094-2.
11. Onkelinx S, Cornelissen V, Goetschalckx K, Thomaes T, Verhamme P, Vanhees L. Reproducibility of different methods to measure the endothelial function. Vasc Med. 2012 Apr;17(2):79-84. doi: 10.1177/1358863X12436708.
12. Mineiro MA, Marques da Silva P, Alves M, et al. Use of CPAP to reduce arterial stiffness in moderate-to-severe obstructive sleep apnoea, without excessive daytime sleepiness (STIFFSLEEP): an observational cohort study protocol. BMJ Open. 2016 Jul 12;6(7):e011385. doi: 10.1136/bmjopen-2016-011385.
13. Seetho IW, Asher R, Parker RJ, Craig S, Duffy N, Hardy KJ, Wilding JP. Effect of CPAP on arterial stiffness in severely obese patients with obstructive sleep apnoea. Sleep Breath. 2015 Dec;19(4):1155-65. doi: 10.1007/s11325-015-1131-0.
14. Lin X, Chen G, Qi J, Chen X, Zhao J, Lin Q. Effect of continuous positive airway pressure on arterial stiffness in patients with obstructive sleep apnea and hypertension: a meta-analysis. Eur Arch Otorhinolaryngol. 2016 Dec;273(12):4081-4088. doi: 10.1007/s00405-016-3914-8.
15. Çetin S, Vural MG, Gündüz H, Akdemir R, Fırat H. Epicardial fat thickness regression with continuous positive airway pressure therapy in patients with obstructive sleep apnea: assessment by two-dimensional echocardiography. Wien Klin Wochenschr. 2016 Mar;128(5-6):187-92. doi: 10.1007/s00508-016-0975-z.
16. Kostopoulos K, Alhanatis E, Pampoukas K, Georgiopoulos G, Zourla A, Panoutsopoulos A, Kallianos A, Velentza L, Zarogoulidis P, Trakada G. CPAP therapy induces favorable short-term changes in epicardial fat thickness and vascular and metabolic markers in apparently healthy subjects with obstructive sleep apnea-hypopnea syndrome (OSAHS). Sleep Breath. 2016 May;20(2):483-93. doi: 10.1007/s11325-015-1236-5.
17. Ng SS, Liu EK, Ma RC, Chan TO, To KW, Chan KK, Ngai J, Yip WH, Ko FW, Wong CK, Hui DS. Effects of CPAP therapy on visceral fat thickness, carotid intima-media thickness and adipokines in patients with obstructive sleep apnoea. Respirology. 2017 May;22(4):786-792. doi: 10.1111/resp.12963.
18. Chen LD, Lin L, Lin XJ, Ou YW, Wu Z, Ye YM, Xu QZ, Huang YP, Cai ZM. Effect of continuous positive airway pressure on carotid intima-media thickness in patients with obstructive sleep apnea: A meta-analysis. PLoS One. 2017 Sep 1;12(9):e0184293. doi: 10.1371/journal.pone.0184293. eCollection 2017.

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EVALUATION OF PROHYPERTENSIVE EFFECT OF MELOXICAM ON THE BLOOD PRESSURE INDICATORS

Abstract

The objective of the study is to assess the influence of meloxicam on the blood pressure level among patients with hypertension, as well as among patients without cardiovascular system diseases, in relation to its prohypertensive effect. **Materials and methods.** The *retrospective* study involved 60 patients who regularly took meloxicam in a dose of 7.5 mg/day. There were patients without cardiovascular disorder in the first group. The second group consisted of patients with hypertension, taking antihypertensive drugs. Retrospectively, the level of blood pressure, measured by the Korotkov's method, was analyzed by medical histories, before and after 3 months of taking meloxicam in both groups. The total cardiovascular risk was estimated according to the SCORE scale. **Results.** It was determined that long-term administration of meloxicam led to an increase of blood pressure levels, both in patients without diagnosed cardiovascular diseases, and in patients with hypertension and medium SCORE risk, who regularly takes antihypertensive agents to achieve target blood pressure level.

Key words: *meloxicam, NSAIDs, blood pressure, hypertension, prohypertensive effect, hypotensive therapy*

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BP — blood pressure, BAB+TD — β-blocker in combination with thiazide diuretic, DBP — diastolic blood pressure, dCCB+TD — dihydropyridine calcium channel blocker in combination with thiazide diuretic, ACEI+TD — angiotensin converting enzyme inhibitor in combination with thiazide diuretic, NSAID — non-steroidal anti-inflammatory drugs, SBP — systolic blood pressure

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the leading groups of drugs used to treat musculoskeletal diseases, particularly pain syndrome [1]. However, long-term administration of drugs of this class results in higher risk of developing adverse gastroenterological effects and cardiovascular side effects [2]. Safety issues are most relevant when selecting non-steroidal anti-inflammatory therapy. Creating a new class of COX-2 selective inhibitors helped to reduce incidence of gastropathy, but the issue of their negative impact on blood pressure and effect on antihypertensive therapy is still unresolved [3]. Safety of meloxicam with respect to negative cardiovascular effects is understudied [1]. Foreign research findings showed that this drug increased the risk of myocardial infarction by 38 % [4]. Furthermore, it is known that NSAIDs reduce the efficacy of antihypertensive therapy and aggravate the course of hypertension [5]. The most extensive randomized controlled studies are too short-term to reveal a significant difference in incidence of cardiovascular complications between meloxicam and comparators [1].

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The objective of the study was to examine the effect of meloxicam on the blood pressure level in patients with hypertension, as well as in patients without any cardiovascular diseases with respect to its prohypertensive action.

Materials and Methods

A retrospective study was carried out in the Department of Outpatient Therapy of the N. N. Burdenko Voronezh State Medical University, as well as at the Voronezh Region State-Funded Health Institution "Voronezh Municipal Outpatient Clinic No. 4". The study included 60 patients who regularly took meloxicam 7.5 mg/day. Mean age of the study subjects was 52.7±1.2 years; there were 23 males and 37 females. All the patients were divided into 2 groups. The first group included patients without any cardiovascular pathology, with medium SCORE risk (15 subjects). The second group was comprised of patients with hypertension who achieved the target BP, regularly took antihypertensive therapy for at least 3 years, with medium SCORE risk (45 subjects). Pharmacotherapy was analyzed retrospectively based on outpatient medical records. Depending on the drugs administered, patients with hypertension were divided into three subgroups. Subgroup 1 included patients receiving ACEI+TD (17 subjects), subgroup 2 — BAB+TD (16 subjects), subgroup 3 — dCCB+TD (12 subjects). Based on outpatient medical records, we performed a retrospective analysis of blood pressure level in both groups measured according to Korotkov's method using a blood pressure gauge as per clinical guidelines [6], before and after 3 months of administration of meloxicam 7.5 mg/day. Measurements were made by a primary care physician during a visit. Average blood pressure was used for the study. Cardiovascular risk was estimated as per the SCORE scale. Statistics was calculated using Microsoft Office Excel 2016 and Statistica 6.0 software. The Wilcoxon T-test was used to compare mean quantitative features from two dependent samples (before and after meloxicam therapy). Statistical significance between the groups was assessed using the Kruskal-Wallis H-test. Differences between the parameters examined were deemed statistically significant at $p < 0.05$.

Results

Blood pressure was assessed in both study groups (Fig. 1, 2).

After 3 months of meloxicam administration, increase in BP was reported in 60 % of patients in group I, in 64.7 % of group II patients receiving ACEI+TD, and in 62.5 % of patients receiving BAB+TD.

To compare the findings, the Kruskal-Wallis analysis of variance was used for several independent groups. There were statistical differences in BP level between the groups of patients ($H=98.12$ at $p=0.01$). Statistically significant differences ($p < 0.01$)were found as a result of the comparative analysis of BP before and after administration of meloxicam in groups I and II (ACEI+TD; BAB+TD). In group II of patients receiving dCCB+TD, BP increase after 3 months of meloxicam administration was statistically insignificant.

Based on the data obtained, in group I, SBP increased on average by 7.7±1.2 mm Hg, DBP — by 7.2±0.9 mm Hg ($p < 0.01$). In group II of patients receiving ACEI+TD, SBP increased on average by 10.4±1.4 mm Hg, DBP — by 8.6±0.9 mm Hg ($p < 0.01$). In group II of patients receiving BAB+TD, SBP increased on average by 9.5±0.9 mm Hg, DBP — by 8.5±1.3 mm Hg ($p < 0.01$). Blood pressure increase in both groups was explained by the administration of meloxicam, which required its replacement with a drug with a wider cardiovascular safety profile (celecoxib).

The findings are partially supported by data from other studies. I. A. Zolotovskaya et al. carried out sub-analysis of PANDA cohort study, which described the renal-associated escape phenomenon of antihypertensive therapy during administration of non-steroidal anti-inflammatory drugs, including meloxicam [7]. However, a number of literary sources contain data on its high safety [8], as well as low risk of cardiovascular complications [9]. According to some studies, it was found that meloxicam had no significant pro-hypertensive effect as compared to other NSAIDs [10].

In analyzing the data from scientific literature, it has been established that there is a discussion of several potential pathogenetic mechanisms, which explain the pro-hypertensive action of non-steroidal anti-inflammatory drugs: inhibited filtration,

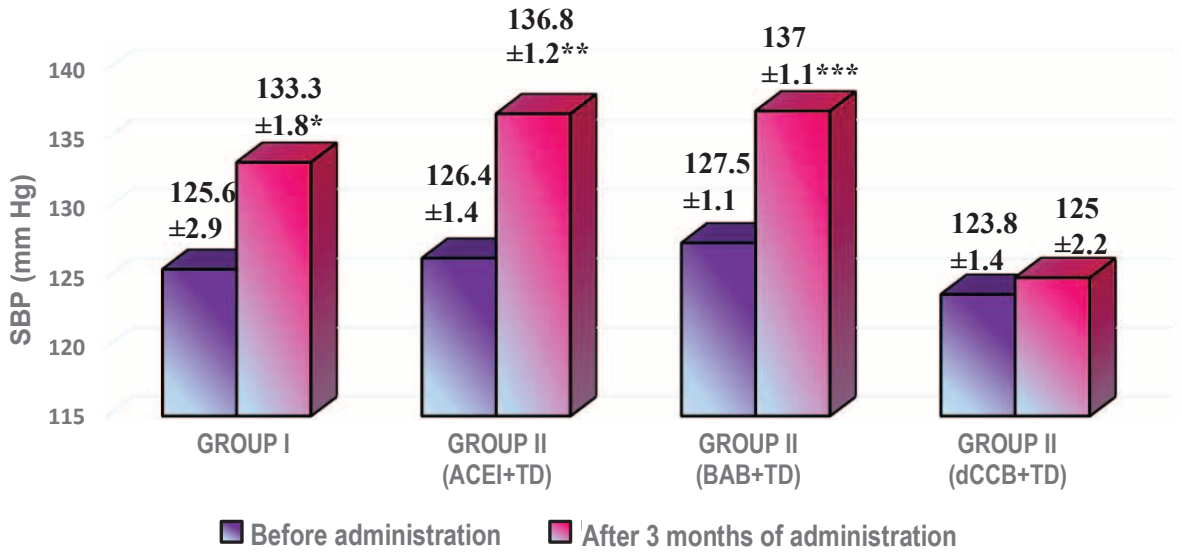

Figure 1. *Dynamics of mean systolic blood pressure (mm Hg) before and after 3 months of meloxicam administration*

*, **, *** — reliability of differences in BP level before and after meloxicam administration, p < 0.01

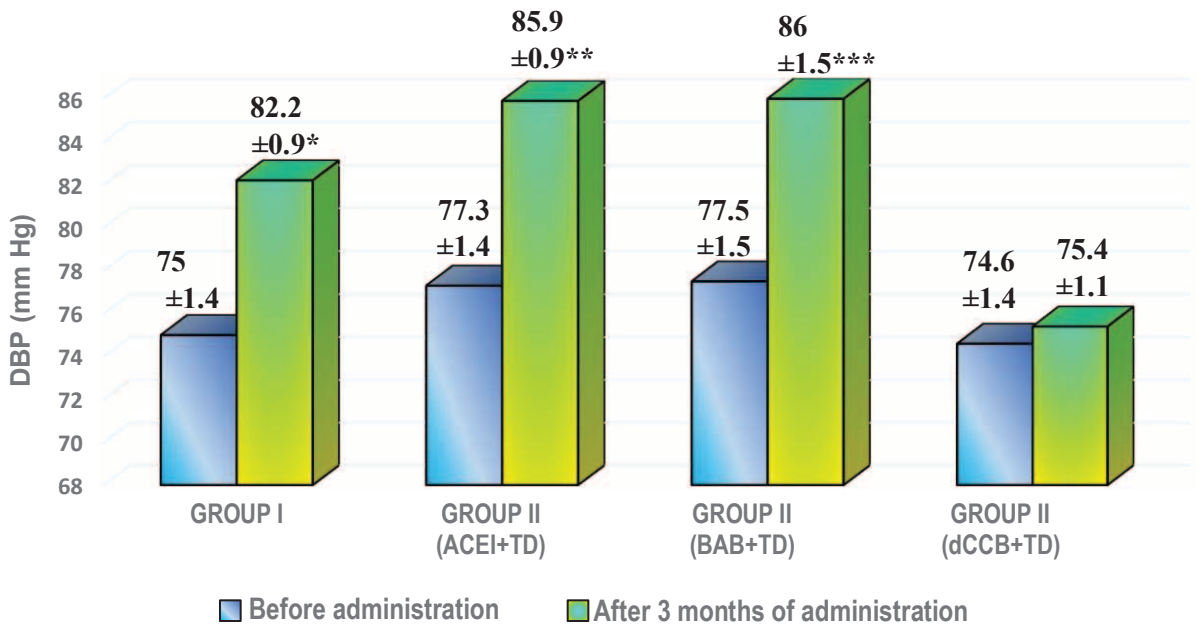

Figure 2. *Dynamics of mean diastolic blood pressure (mm Hg) before and after 3 months of meloxicam administration*

*, **, *** — reliability of differences in BP level before and after meloxicam administration, p < 0.01

enhanced tubular reabsorption and, as a consequence, reduced natriuresis; inhibited synthesis of prostaglandins (PGE2 and PGI2) with vasodilating effect, which results in increased resistance of extrarenal and intrarenal vessels, as well as enhanced release of noradrenaline from nerve terminals; higher vessel wall sensibilization to effects of circulating vasoconstrictive substances; supersecretion of endothelin I; and direct renal toxicity [11]. Considering probable differences of COX-2 inhibitors, it is important to take into account their effect on the endothelial function. In particular, celecoxib

improves NO bioavailability, endothelium-dependent vasodilatation, reduces synthesis of inflammatory cytokines, oxidative stress, thus demonstrating a positive effect [2]. Furthermore, according to foreign studies, naproxen has the lowest cardiovascular risk [12]. As per clinical guidelines, meloxicam is not an agent of choice in hypertensive patients receiving antihypertensive therapy, as well as in patients with medium SCORE risk.

Conclusions

1. Long-term administration of meloxicam resulted in increased blood pressure both in patients without proven cardiovascular diseases and in hypertensive patients who regularly received antihypertensive drugs and had achieved target BP level, with medium SCORE risk. In these cases, drugs having the minimum effect on blood pressure, such as naproxen and celecoxib (in the absence of coronary artery disease), are preferred.
2. Meloxicam reduced the efficacy of antihypertensive therapy with β-blocker in combination with thiazide diuretic, as well as combination of angiotensin converting enzyme inhibitor and thiazide diuretic, but had the least impact on antihypertensive therapy with dihydropyridine calcium channel inhibitor and thiazide diuretic. Consequently, dihydropyridine calcium channel inhibitors (particularly, amlodipine) should be deemed agents of choice to treat hypertension in patients requiring long-term non-steroidal anti-inflammatory therapy, as supported by clinical guidelines.
3. When selecting a non-steroidal anti-inflammatory drug, consideration must be given to the risk of cardiovascular and gastroenterological complications as described in clinical guidelines.
4. The safety concern of meloxicam with regard to its cardiovascular side effects requires further prospective research.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Karateev A.E. Celecoxib, Etoricoxib, Meloxicam, and Nimesulide: comparison of their merits and demerits. NeuroNEWS. 2015; 4(68): 18-24 [In Russian].
2. Rodionov A.V. Non-steroid antipyretic preparations and arterial hypertension: actual character of the problem and the strategy of conducting patients. Attending doctor. 2013; 2: 25-31 [In Russian].
3. Balabanova R.M. Algorithm of using of nonsteroidal anti-inflammatory drugs in the therapeutic practice. Russian Medical Journal. 2013; 5: 265 — 269 [In Russian].
4. Dalal D., Dubreuil M., Peloquin C. et al. Meloxicam and risk of myocardial infarction: a population-based nested case-control study. Rheumatology International. 2017;3 7(12): 2017-2078.
5. Zheng Liuying, Du Xinping. Non-steroidal anti-inflammatory drugs and hypertension. Cell Biochemistry & Biophysics. 2014; 69(2): 209-211.
6. Chazova I.E. Oshchepkova E.V. Zhernakova Y.V. Diagnosis and treatment of arterial hypertension. Clinical guidelines. Russian Cardiology Bulletin. 2015; 10(1): 3-30 [In Russian].
7. Zolotovskaya I.A., Davydkin I.L., Borovkova N.Y. Renal-associated escape effect of antihypertensive therapy in hypertensive patients receiving nonsteroidal anti-inflammatory drugs («PANDA» trial). «Arterial'naya gipertenziya» («Arterial hypertension»). 2017; 23(6): 517-528 [In Russian].
8. Akarachkova E.S., Gromova O.A., Kotova O.V. Selection of modern safe and effective NSAID in patients with concomitant (comorbid) diseases. Farmateka. 2016; 7(320): 43-48 [In Russian].
9. Eliseev M.S., Barskova V.G. Meloxicam: what do we know about cardiovascular safety. Modern rheumatology. 2010; 4(1): 79-83 [In Russian].
10. Lasebnik L.B., Kotsubinskaya O.B., Konev Y.V., Drosdov V.N. Effect of nonsteroidal anti-inflammatory drugs and tramal on blood pressure level during osteoarthritis treatment in patients with hypertension. Rheumatology Science and Practice. 2004; 42(1): 28-33 [In Russian].
11. Karateev A.E., Nasonov E.L., Yahno N.N. ets. Clinical recommendations "The rational using of nonsteroidal anti-inflammatory drugs (NSAIDs) in clinical practice." Modern rheumatology. 2015; 1: 4-23 [In Russian].
12. Angiolillo D.J., Weisman S.M. Clinical Pharmacology and Cardiovascular Safety of Naproxen. American Journal of Cardiovascular Drugs. 2017;17(2):97–107.

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ASSOCIATION OF INTESTINAL BACTERIAL OVERGROWTH AND DISEASES OF HEPATOBIARY TRACT

Abstract

The objective: To find out the nature of the changes of the hepatobiliary system in patients with intestinal bacterial overgrowth syndrome and to study the possible mechanisms of their association. **Materials and methods:** 148 patients with intestinal bacterial overgrowth syndrome and intestinal dysbiosis were examined. The level of total cholesterol, cholestasis and cytolysis markers was determined in the blood using the analyzer of Labsystems (Finland). Intestinal bacterial overgrowth syndrome was assessed using a hydrogen breath test with lactulose on the LactophaH2 apparatus of AMA (St. Petersburg). Intestinal dysbiosis was determined by stool culture on nutrient media. Bile acids in bile were determined on the AmazonX mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany). Ultrasound examination of the abdominal cavity was performed via the apparatus SHIMADZU SDN-500 (Japan). Liver elastography was performed using the AIXPLORER apparatus (France). **Results.** The syndrome of intestinal bacterial overgrowth in 67 % of cases was diagnosed in the presence of ileocecal insufficiency, in 33 % of cases — with preserved ileocecal function. The combination of intestinal bacterial overgrowth syndrome and intestinal dysbiosis was detected in 81.8 % of patients. The majority of the examined patients showed clinical symptoms of damage of the hepatobiliary system and intestines, which was confirmed by change of laboratory parameters: the increase in the level of total cholesterol, markers of cholestasis and cytolysis compared with the control group. In the study of bile acids in bile, the decrease of free (mainly cholic) and increase of conjugated (glycodeoxycholic, taurodeoxycholic, glycocholic, taurocholic) bile acids was observed compared with the control group. In general, patients with the syndrome of intestinal bacterial overgrowth revealed the presence of non-calculous cholecystitis — in 11.5 % of cases, I stage of cholelithiasis — in 25.7 %, II stage of cholelithiasis — in 18.9 %, and non-alcoholic fatty liver disease at the stage of steatosis and steatohepatitis — in 43.9 % of cases. **Conclusion:** Intestinal bacterial overgrowth syndrome is the beginning of bacterial translocation, which is the triggering factor for inflammation of the liver and biliary tract. In turn, diseases of the hepatobiliary system contribute to the development of intestinal dysbiosis by reducing the synthesis of bile acids with antibacterial action, as well as violations of their excretion. Thus, strong association of intestinal bacterial overgrowth syndrome with damage to the hepatobiliary system has been established.

Keywords: *bacterial overgrowth syndrome, dysbiosis, cholelithiasis, non-alcoholic fatty liver disease, bile acids*

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ALT — alanine aminotransferase, AST — aspartate aminotransferase, GGTP — gamma-glutamyl transpeptidase, NAFLD — non-alcoholic fatty liver disease, BOS — bacterial overgrowth syndrome, AP — alkaline phosphatase

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In recent years, the development of many digestive diseases has been associated with compositional disorders in the intestinal microbiota [1, 11, 12, 14, 18]. Intestinal dysbiosis, especially the bacterial overgrowth syndrome (BOS), increases the risk of developing metabolic liver disorders and biliary tract diseases [6, 10, 13, 15, 19, 20]. Most researchers associate hepatobiliary system functional disorders in BOS with the close anatomic-physiological relationship between the liver and the intestines [11, 13, 16]. However, there are still few studies on the features of hepatobiliary system damage depending on changes in the intestinal microbiota.

Our objective was to find out the nature of hepatobiliary system damages in patients with BOS and to study possible mechanisms of their associations.

Materials and Methods

One hundred and forty-eight patients with intestinal dysbiosis and BOS were examined, among whom 17 patients had non-calculous cholecystitis, 38 — stage I cholelithiasis, 28 — stage II cholelithiasis, and 65 — non-alcoholic fatty liver disease (NAFLD) at the steatosis and steatohepatitis stage, respectively. There were 128 females and 20 males. The mean age of the female patients was 46.3±3.7 years, and of the male patients — 38.5±2.6 years.

Entry criteria for the study included the age of 18–60 years, diagnosed BOS and/or intestinal dysbiosis, and a signed voluntary informed consent. Exclusion criteria were the age under 18 and over 60 years, pregnancy and lactation, cancer.

General clinical data (medical history, physical examination) and biochemical blood assay including total cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase (AP), total bilirubin using Labsystems analyzer (Finland) were used in examining the patients.

BOS was assessed through the lactulose hydrogen breath test using LactophaH2 manufactured by AMA (St. Petersburg). Hydrogen content increase in the air exhaled over 10 ppm from baseline during the first hour of testing was considered a positive result.

Intestinal dysbiosis was examined through stool culturing on aerobic and anaerobic microflora. Intestinal microflora was assessed by the counts of Escherichia, including its hemolytic and lactose negative forms, Lactobacilli and Bifidobacteria, Streptococcus, Enterococcus, Clostridia, Staphylococcus aureus, Klebsiella, yeast-like fungi, Proteus, Pseudomonas aeruginosa and other opportunistic microorganisms per 1 g [4]. The severity of dysbiosis was identified in accordance with the classification of I. B. Kuvaeva and K. S. Ladodo (1991) [9].

Bile acids in gallbladder and liver bile were assessed using AmazonX mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany). Calculations were made by registering negative and positive ions in the m/z range from 100 to 2,000. Capillary voltage was 4,500 V. Nitrogen with temperature of 300 °C and flow rate of 8 l·min^{-1} was used as a drying gas. Bile was dissolved in distilled water at a ratio of 1:1. Further, 1 μl of the solution was diluted to 1 ml with water. The resulting figures were interpreted using DataAnalysis 4.0 (Bruker Daltonik GmbH, Bremen, Germany).

Abdominal ultrasound scanning was performed using SHIMADZU SDN-500 (Japan).

Liver elastography was performed to assess the degree of hepatic fibrosis by ultrasound elastography using AIXPLORER (France). The degree of fibrosis in hepatic parenchyma was assessed by the Metavir score system using the SC6-1 convex transducer.

The control group comprised of 40 apparently healthy individuals aged from 18 to 55 years.

The required number of observations was computed based on the sample-size calculation at the statistical power ρ=0.80 with the use of Statistica 6.1 software manufactured by Stat Soft. The patients were assigned to groups through stratified sampling. Parametric statistical methods were applied. Differences between the groups were considered statistically significant with a probability of the valid null hypothesis of no differences between the groups (p) < 0.05.

The study was carried out after the patients had signed voluntary informed consent as per Order No. 390n of the Ministry of Health and Social

Development of the Russian Federation dated April 23, 2012 (registered with the Ministry of Justice of the Russian Federation under No. 24082 on May 5, 2012).

Results and Discussion

Among the patients examined, pain in the right hypochondriac region was observed in 112 (75.7 %) patients, in the paraumbilical area — in 53 (35.8 %) patients, and in the large intestine region — in 76 (51.4 %) patients. Dyspeptic complaints included: abdominal distention — in 126 (85.1 %) patients, bitter taste in the mouth — in 95 (64.2 %) patients, nausea — in 67 (45.3 %) patients, epigastric burning — in 59 (39.9 %) patients, eructation — in 46 (31.1 %) patients, constipation — in 38 (25.7 %) patients, diarrhea — in 33 (22.3 %) patients. According to physical examination, yellow coated tongue was found in 109 (73.6 %) patients, tender abdomen in the right hypochondriac region — in 105 (70.9 %) patients, in the paraumbilical area — in 65 (43.9 %) patients, and in the large intestine region — in 72 (48.6 %) patients. Hepatomegaly was observed in 37 (25 %) patients, positive Ortner's symptoms — in 44 (29.7 %) patients, Lepene's symptoms — in 35 (23.6 %) patients, Murphy's signs — in 29 (19.6 %) patients, Mussy's symptoms — in 22 (14.9 %) patients, Kehr-Gausman's symptoms — in 18 (12.2 %) patients, respectively. Thus, the clinical signs of intestine and hepatobiliary system disorders were identified.

In 67 % of cases, BOS was due to ileocecal failure (the hydrogen breath test results showed significant hydrogen increase in the air exhaled during the first hour of testing, without further decrease). In 33 % of cases, BOS was detected with ileocecal function retained (peaks of hydrogen increase in small and large intestines were found). When examined for BOS, intestinal dysbiosis was identified in 15 % of patients (no hydrogen increase occurred throughout the study).

Results of stool culture for dysbiosis in the patients examined showed a decrease in the number of normal microflora representatives: Bifidobacteria of less than 10^7 CFU/g — in 72 (48.6 %) patients, Lactobacilli of less than 10^9 CFU/g — in 55 (37.2 %) patients, Escherichia coli — in 44 (29.7 %) patients, Enterococcus — in 25 (16.9 %) patients, Bacteroides — in 22 (14.9 %) patients, respectively. Increase in lactose-negative E. coli was observed in 52 (35.1 %) patients, and hemolytic E. coli — in 32 (21.6 %) patients. Staphylococcus aureus was cultured in stool of 17 (11.5 %) patients, Klebsiella pneumoniae — of 15 (10.1 %) patients, and Candida — of 10 (6.8 %) patients, respectively. As for the severity of dysbiosis, degree I was identified in 41 (27.7 %) patients, degree II — in 96 (64.9 %) patients, and degree III — in 11 (7.4 %) patients, respectively. Combination of intestinal dysbiosis and BOS was detected in 121 (81.8 %) of the patients examined.

Abdomen ultrasound scanning showed signs of chronic non-calculous cholecystitis (gallbladder wall thickening over 3 mm and/or gallbladder dyskinesia) in 17 (11.5 %) patients, stage I cholelithiasis (sonographic signs by type of microliths and/or inhomogenous thick bile) — in 38 (25.7 %) patients, stage II cholelithiasis (formed gallstones) — in 28 (18.9 %) patients, NAFLD (liver enlargement, hyperechogenicity, liver sound conductivity and density reduction) — in 65 (43.9 %) patients. A number of patients had comorbid pathologies: combination of cholelithiasis and NAFLD — in 25 (16.9 %) patients, non-calculous cholecystitis and NAFLD — in 14 (9.5 %). Mean stiffness of hepatic parenchyma as per Metavir score system according to elastography performed in patients with NAFLD at the stage of hepatic steatosis corresponded to fibrotic changes F0 in 44 (67.7 %) patients, and at the stage of steatohepatitis — to F1 in 18 (27.7 %) patients, and F2 in 3 (4.6 %) patients, respectively.

As shown in Table 1, the majority of patients with BOS showed an increase in total cholesterol, cholestasis (GGTP, AP) and cytolysis (AST, ALT) markers as compared to the control group. The extent of changes in functional indicators of hepatobiliary tract was rather dependent on the type of damage to the liver and biliary tract. So, changes in laboratory parameters were less evident in patients with non-calculous cholecystitis, and maximum abnormalities were observed in patients with NAFLD.

As can be seen from the data provided in Table 2, bile portions B and C from patients with NAFLD and cholelithiasis show a decrease in free (mainly cholic) bile acids and an increase in conjugated (taurodeoxycholic, taurocholic, glycodeoxycholic, glycocholic) bile acids as compared with the control group. In non-calculous cholecystitis, increase in both free and conjugated bile acids was found as compared to the control group. According to literary data [5, 6], free bile acids are produced by the liver only, therefore, their decrease provides evidence of hepatocyte damage in patients with NAFLD and cholelithiasis. This is confirmed by the biochemical blood assays performed, the results of which have revealed increased markers of cytolysis and cholestasis, especially in patients with NAFLD. In cholestasis, bile acids can damage apical membranes of hepatocytes and destroy the epithelium of bile ducts and, consequently, increase the blood concentration of GGTP [7, 8]. In contrast, patients with non-calculous cholecystitis showed minimum biochemical abnormalities.

Table 1. *The results of biochemical blood tests in patients with disorders of the intestinal microflora*

Parameters	Patients with non-calculous cholecystitis (n=17)	Patients with I stage of cholelithiasis (n=38)	Patients with II stage of cholelithiasis (n=28)	Patients with non-alcoholic fatty liver disease (n=65)	Group of control (n=40)
Cholesterol, mmol/l	5.13±0.07*	5.26±0.05*	5.15±0.16*	5.54±0.06*	4.34±0.08
Alanine aminotransferase, units per liter	17.12±2.92	20.17±1.14	23.84±2.85	45.0±3.8*	18.63±0.82
Aspartate aminotransferase, units per liter	22.7±2.44	24.4±2.26	23.63±2.08	34.2±3.36*	23.5±2.31
Total bilirubin, umol/l	13.25±0.63	11.85±0.58	12.4±1.92	14.6±1.2	11.61±1.36
Alkaline phosphatase, mmol/l	105±9.32*	131±9.91*	145.63±11.6*	156.0±5.83*	73.64±6.53
Gammaglutamyltranspeptidase, units per liter	27.18±2.3*	30.09±2.44*	51.67±4.15*	49.0±8.6*	18.5±0.76

Note: * — reliable changes in relation to group of control ($p < 0.05$); n — number of observations

Table 2. *The bile acids content in bile in patients with disorders of the intestinal microflora (mg/ml)*

Bile acids	Patients with non-calculous cholecystitis (n=8)		Patients with non-alcoholic fatty liver disease (n=15)		Patients with stage I of cholelithiasis (n=12)		Group of control (n=10)	
	Portion B	Portion C	Portion B	Portion C	Portion B	Portion C	Portion B	Portion C
Cholic	0.15±0.01*	0.09±0.01	0.01±0.01*	0.01±0.01*	0.105±0.03	0.048±0.01*	0.11±0.01	0.08±0.01
Chenodeoxycholic	0.06±0.02	0.02±0.01	0.03±0.02	0.041±0.03	0.035±0.03	0.01±0.01	0.07±0.02	0.03±0.01
Glycocholic	6.9±1.18*	1.65±0.58*	17.57±3.33*	6.7±1.67*	10.02±2.14*	2.91±1.16*	2.7±0.03	0.18±0.02
Glycosodeoxycholic	12.79±3.51*	2.25±0.86*	40.05±11.05*	10.61±2.39*	19.48±3.91*	4.12±1.41*	3.62±0.04	0.16±0.02
Taurocholic	5.37±2.1*	1.42±0.16*	6.07±3.5	2.45±1.16	5.13±2.09	1.56±0.95	1.15±0.02	0.08±0.01
Taurodesoxycholic	9.35±3.7*	2.06±0.8*	10.7±3.9*	3.5±1.6	9.14±3.02*	2.17±1.04	1.49±0.02	0.09±0.01
Ursodeoxycholic	0.07±0.03	0.01±0.01	0.14±0.05	0.03±0.02	0.136±0.02	0.035±0.03	0.1±0.01	0.02±0.01
Deoxycholic	0.06±0.03*	0.02±0.01	0.07±0.06*	0.08±0.04	0.11±0.04*	0.07±0.04	0.22±0.02	0.03±0.01

Note: * — reliable changes in relation to group of control ($p < 0.05$); n — number of observations

The content of glycine conjugates statistically exceeded that in the control group for all the patients examined. Content of glycodeoxycholic and glycocholic acids in patients with non-calculous cholecystitis was lower than in those with NAFLD and cholelithiasis. Concentrations of taurine conjugates in patients with non-calculous cholecystitis had no significant differences from similar figures in patients from other groups, but significantly exceeded those in the control group. As is known from literary data, the degree of bile acid conjugation with glycine or taurine depends on diet and intestinal microflora [1, 8]. Thus, changes in conjugated bile acid concentrations in all the examined patients were unidirectional and were due to intestinal microbiota disorders.

As compared to the control group, concentrations of ursodeoxycholic acid tended to increase in patients with cholelithiasis and NAFLD and to decrease in patients with non-calculous cholecystitis. Deoxycholic acid in bile portion B was significantly lower in all patient groups as compared to the control group. Bile portion C showed no substantive changes in deoxycholic acid concentrations in the patient groups examined.

Changes in bile acid composition are attributable to their increased absorption in ileum in BOS [1]. In addition, BOS is the beginning of bacterial translocation [12, 15]. There are microorganism that are most exposed to translocation due to their adhesiveness to intestinal epithelium (Klebsiella, Enterococcus, Escherichia coli). The examined patients showed a decrease in content of typical Escherichia with an increase in lactose negative and hemolytic forms. These bacteria can even penetrate the histologically unchanged mucous membrane of intestinal walls, then enter the hepatobiliary system and apparently cause inflammatory diseases of the liver and gall bladder. Non-calculous cholecystitis and cholelithiasis are considered successive stages of the same pathologic process, since the pathologic process in the gallbladder wall normally results in the decrease of its contractile function and inspissation of the bile, which can further lead to gallstone formation [3]. Indeed, clinical and laboratory parameters in the examined patients with non-calculous cholecystitis, stage I and II cholelithiasis were unidirectional and merely pronounced to different degrees.

In intestinal dysbiosis, there is an increase in ethanol-producing bacteria. Many bacteria can be qualified as ethanol producers, including Escherichia, the imbalance of quality and number of which was observed in the patients examined. Ethanol production by bacteria results in synthesis of free fatty acids and contributes to oxidative stress which triggers NAFLD [17, 20]. Furthermore, the reduced disintoxication function of the intestinal microflora increases the burden on the liver enzyme systems, leading to metabolic and structural changes in the liver [10, 12]. This is the reason for a sharp reduction in synthesis and excretion of bile acids against the background of cholesterol hypersecretion.

Conclusion

Our comprehensive studies have shown that BOS is the beginning of bacterial translocation, which is a triggering factor in inflammation of the liver and biliary tract. Through ethanol hyperproduction, pathogenic intestinal bacteria raise the level of free fatty acids and increase endotoxinemia, which contributes to the development of NAFLD. In its turn, synthesis and secretion of bile acids decrease in NAFLD. The decrease in bile acids with an antibacterial effect ensures the activation of opportunistic pathogenic microflora and the development of BOS. Thus, strong association between BOS and hepatobiliary tract diseases, which is characterized by that the development of any one of them acts as an incentive for the development of the other one, has been established.

Conflict of interests
The authors declare no conflict of interests.

References:

1. Vakhrushev Ya.M., Lukashevich A.P., Gorbunov A. Yu. et al. Intestinal Mechanisms of Enterohepatic Circulation Disturbance of Bile Acids in Cholelithiasis. Vestnik Rossiiskoi akademii meditsinskikh nauk. 2017; 72(2): 105-111 [in Russian]. doi: 10.15690/vramn807

2. Vakhrushev Ya.M., Lukashevich A.P. Specific features of impaired intestinal digestion, absorption, and microbiocenosis in patients with cholelithiasis. Terapevticheskii arkhiv. 2017; 2: 28-32 [In Russian]. doi: 10.17116/terarkh201789228-32
3. Vakhrushev Ya.M., Khokhlacheva N.A., Moseeva M.V. et al. The importance of the morphometric research of bile in early diagnostics of bilious stone formation. Arhiv vnutrennej mediciny. 2018; 6: 458-463 [In Russian]. doi: 10.20514/2226-6704-2018-8-6-458-463
4. Volodin N.N., Kafarskaja L.I., Korshunov V.M. Characteristics of microorganisms colonizing the human intestine. Zhurnal mikrobiologii, jepidemiologii i immunobiologii. 2002; 5: 98-104 [In Russian].
5. Grinevich V.B., Sas E.I. Physiological effects of bile acids. Russkii meditsinskii zhurnal. Meditsinskoe obozrenie. 2017; 1(2): 87-91 [In Russian].
6. Efimenko N.V., Ledovskaya T.I., Fyodorova T.E. et al. Non-alcoholic fatty liver disease: Modern aspects of etiopathogenesis and treatment. Vestnik Avitsenny. 2017; 19(3): 393-398 [In Russian]. doi: 10.25005/2074-0581-2017-19-3-393-398
7. Ilchenko A.A. Diseases of the gallbladder and biliary tract: rukovodstvo dlja vrachej. Moskva: MIA. 2011; 880 p. [In Russian].
8. Ilchenko A.A. Bile acids in normal and pathology. Eksperimentalnaya i klinicheskaya gastroenterologiya. 2010; 4: 3-13 [In Russian].
9. Kuvaeva I.B., Ladodo K.S. Microecological and immune disorders in children. Moskva: Medicina. 1991; 224 p. [In Russian].
10. Ojnotkinova O.Sh., Nikonov E.L., Gioeva I.Z. The role of the intestinal microbiota in the pathogenesis of dyslipidemia and associated metabolic disorders. Dokazatel'naja gastrojenterologija. 2017; 2: 29-34 [In Russian]. doi: 10.17116/dokgastro20176229-34
11. Plotnikova E.Yu. Non-alcoholic fatty liver disease and intestinal microflora. Gastrojenterologija Sankt-Peterburga. 2017; 2: 76-85 [In Russian].
12. Seliverstov P.V., Sitkin S.I., Radchenko V.G. The role of intestinal disbiosis in the development of mitochondrial dysfunction and nonalcoholic fatty liver disease. Meditsinskii sovet. Gastroenterologiya. 2018; 6: 90-95 [In Russian]. doi: 10.21518/2079-701X-2018-6-89-95
13. Uspensky Yu.P., Baryshnikova N.V., Balukova E.V. Microflora of intestine and liver pathology. Medicinskij alfavit. 2016; 3(24): 13-20 [In Russian].
14. Khokhlacheva N.A., Gorbunov A.Yu., Vakhrushev Ya.M. The study of cholelithiasis prevalence basing on prognostic investigation of hepatobiliary diseases. Terapevticheskii arkhiv. 2012; 84(2): 45-49 [In Russian].
15. Jakovenko Je.P., Ivanov A.N., Jakovenko A.V. et al. Metabolic diseases of the liver as systemic manifestations of intestinal dysbiosis. The role of probiotics in the normalization of intestinal microflora. Russkii meditsinskii zhurnal. Gastrojenterologija. 2008; 16(6): 396-401 [In Russian].
16. Miura K., Ohnishi H. Role of gut microbiota and Toll-like receptors in nonalcoholic fatty liver disease. World J. Gastroenterol. 2014; 20(23): 7381-7391. doi: 10.3748/wjg.v20.i23.7381
17. Mouzaki M., Comelli E.M., Arendt B.M. et al. Intestinal microbiota in patients with nonalcoholic fatty liver disease. Hepatology. 2013; 58: 120-127. doi: 10.1002/hep.26319
18. Nightingale J. Hepatobiliary, renal and bone complications of intestinal failure. Best Practice and Research in Clinical Gastroenterology. 2003; 17(6): 907-929.
19. Wieland A., Frank D.N., Harnke B. et al. Systematic review: microbial dysbiosis and nonalcoholic fatty liver desease. Aliment. Pharmacol. Ther. 2015; 42(9): 1051-1063. doi: 10.1111/apt.13376
20. Zhu l., Baker S.S., Gill C. et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: A connection between endogenous alcohol and NASH. Hepatology. 2012; 57: 601-609. doi: 10.1002/hep.26093

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CORRECTION OF MALNUTRITION IN PATIENTS WITH CHRONIC PANCREATITIS

Abstract

The objective of the study was to assess malnutrition incidence and effectiveness of various correction methods in patients with CP. **Materials and methods:** 148 patients were examined. Group I included 71 people with chronic alcoholic pancreatitis (CAP); group II — 77 patients with chronic obstructive pancreatitis (COP). Nutritional status (NS) was assessed by criteria of V. M. Luft. Lymphocytes, pancreatic amylase, lipase, total protein, albumin, urine diastase and fecal elastase-1 levels were estimated before and after treatment. We made a comparative assessment of the efficacy of two therapy regimens: combination therapy (CT) with enzyme products (Mezym 10,500 U/day) and sip feeding (Ensure 2 — 200 ml/day), or high-dose enzyme replacement therapy (HD ERT) (Creon 120,000 U/day), for 10 weeks. 62 patients received HD ERT (24 patients with CAP and 38 patients with COP); and 86 patients received CT, 47 and 39, respectively. **Results:** The prevalence of malnutrition in patients with CP was 92 % (n=136). Lymphopenia was determined in 44 %, hypoproteinemia — in 11,5 %, hypoalbuminemia — in 54 %. 12 (8 %) patients did not have malnutrition. Malnutrition was more significant in patients with CAP (16 points and 18 points; p=0.0007). In the CAP group: mild malnutrition was diagnosed in 44 patients, moderate in 20, severe — in 2, and eutrophia — in 6 patients; in the COP group: mild malnutrition was diagnosed in 33 petients, moderate — in 37, severe — 0, and eutrophia — in 6 patients. After treatment in the CAP group: moderate malnutrition — in 7, mild — 58, eutrophia — in 7 patients, in the COP group: moderate malnutrition — in 37, mind — in 31, and eutrophia — in 8 patients. **Conclusion:** Malnutrition is a frequent syndrome in patients with CP. Malnutrition is more severe in patients with CAP. Combined therapy regimen turned out to the most effective in patients with CAP. HD ERT is indicated in exocrine pancreatic insufficiency.

Key words: *chronic pancreatitis, malnutrition , lymphocytes, albumin, fecal elastase-1*

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CAP — chronic alcoholic pancreatitis, COP — chronic obstructive pancreatitis, ESPEN — European Society for Clinical Nutrition and Metabolism, HD ERT — high-dose enzyme replacement therapy, MPD — major pancreatic duct, GB — gallbladder, BMI — body mass index, TSFT — triceps skinfold thickness, CT — computer tomography, FFBM — fat-free body mass, MAMC — mid-arm muscle circumference, UAC — upper arm circumference, NS — nutritional status, FE1 — fecal elastase 1, CP — chronic pancreatitis, EPI — exocrine pancreatic insufficiency

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Introduction

In recent years, more emphasis in the management of chronic pancreatitis (CP) has been placed on the assessment of the nutritional status (NS) of a patient and its correction. Malnutrition is a complex of symptoms, the development of which is associated with insufficient intake or absorption of nutrients, and leads to the altering of the component composition of a body (reduced fat-free body mass (FFBM)), which results in deteriorated body functioning and aggravated disease progression [1]. The primary factor for malnutrition development in patients with CP is exocrine pancreatic insufficiency (EPI).

According to the authors, the proportion of underweight patients with CP is 8 to 39 % [2–5], and body weight loss is reported in 20–49 % of patients with CP [3, 6].

Only in 2015, the European Society for Clinical Nutrition and Metabolism (ESPEN) proposed criteria for diagnosing malnutrition [1]. Furthermore, lately there have been discussions about secondary sarcopenia and related conditions, as well as deficiency of certain substances which can be decreased without weight loss and normal body mass index (BMI).

For diagnosing malnutrition, anthropometric and laboratory methods are used together with specific questionnaires (The Nutrition Risk Screening 2002 (NRS 2002) [7], Malnutrition Universal Screening Tool (MUST)) [8]. These tests are also recommended by ESPEN [9].

With the introduction of new concepts such as "sarcopenia" and "sarcopenic obesity" into clinical practice, greater attention is being paid to instrumental methods: bioimpedansometry, computer tomography (CT), dual-energy X-ray absorptiometry, magnetic resonance imaging.

Results of assessing the sensitivity of anthropometric measures and biochemical blood parameters (macro- and microelements) are mutually contradictory. First of all, this is due to the lack of a single diagnostic standard. It is now clear that NS assessment should be comprehensive and should include not only BMI but also parameters of laboratory and instrumental tests.

The objective of the study was to assess malnutrition incidence, intensity and effectiveness of various correction methods in patients with CP of different etiology.

Materials and Methods

The study was carried out in the Gastroenterology Unit of State-Funded Health Institution "Municipal Clinical Hospital named after V. M. Buyanov" of the Moscow Public Health Department (head physician — A. V. Salikov, Candidate of Medical Science) on the clinical basis of the Department of Internal Medicine, Advanced Course, No. 2 of the Department of General Medicine under State Federal-Funded Educational Institution of Higher Professional Training "Russian National Research Medical University named after N. I. Pirogov" of the Russian Ministry of Health (head of the department — Prof. I. G. Nikitin, Doctor of Medical Science).

The study protocol and questionnaires were approved by the local Ethics Committee of the N. I. Pirogov Russian National Research Medical University. All the patients signed a written informed consent to their participation in the study and analysis of the data obtained.

The open-label, prospective, comparative, randomized study was conducted in two phases: phase 1 — examination and treatment of patients with CP in the Gastroenterology Unit of V. M. Buyanov Municipal Clinical Hospital, and phase 2 — outpatient follow-up in the Diagnostic Unit of the hospital.

Chronic pancreatitis was diagnosed on the basis of patients' complaints, clinical findings and medical history, laboratory examination data (presence of amylasemia, lipasemia, diastasuria, EPI, ultrasonic and computer tomography data).

Two classifications of CP were applied: etiologic TIGAR-O and by CP stages ABC.

Criteria for the inclusion of patients in the study were: males and females aged 18 to 83 with chronic obstructive / alcoholic pancreatitis, who signed an informed consent for participation in the study and publication of its findings.

Exclusion criteria for the study were: acute surgical conditions; cancer; operative interventions in the colon; bowel diseases with malabsorption syndrome; diseases at the decompensation stage which require intensive measures and special treatment; drug abuse; HIV infection; lactation, pregnancy

or no adequate use of contraception by women of childbearing potential; no written informed consent.

148 (64.9 %) patients were examined, among them 68 (46 %) females and 80 (54 %) males with chronic pancreatitis. The age of the patients varied from 22 to 82 years, with mean age of 51.8±13.2 years.

Based on the etiology of CP, the patients were divided into two groups during examination. Group I included 71 patients with chronic alcoholic pancreatitis (CAP) who systematically consumed alcohol in toxic doses, with a history of habitual drunkenness or chronic alcoholism. The toxic dose is usually understood as consumption of over 30 g of ethanol per day for men, and over 20 g of ethanol per day for women [10]. The group of patients with CAP included 57 (80.3 %) males and 14 females (19.7 %), with mean age of 46.3±11.2 years.

Group II consisted of 77 patients with chronic obstructive pancreatitis (COP). Among them, 29 (37.6 %) males and 48 (62.4 %) females; mean age — 56.81±3 years.

The clinical study design is provided in Figure 1.

We made a comparative assessment of the efficacy of two therapy regimens. One regimen included combination therapy with enzyme products (Mezym 10,500 U/day) and sip feeding (Ensure 2 — 200 ml/day). The second regimen included high-dose enzyme replacement therapy (HD ERT) (Creon 120,000 U/day), while maintaining a fat-balanced diet.

In addition, the patients received an antispasmodic (Papaverine 40 mg TID) and antisecretory treatment (Omez 20 mg BID).

We used malnutrition classification proposed by V. M. Luft (Table 1) [19].

Complete blood count was performed on automatic Celltac MEK-6318K (Japan); biochemical serum analysis — on Metrolab 2300 (USA) multifunctional biochemical analyzer using appropriate reagents. The following serum parameters were determined for all patients: alanine transaminase, aspartate transaminase, amylase, total protein, protein fractions and absolute count.

Activity of hemolipase and fecal elastase 1 (FE1) was determined in ArkhiMed and NAKFF laboratories. FE1 was analyzed using the ELISA kit (ScheBo Biotech, Germany).

To assess EPI, FE1 levels recommended by the manufacturer were applied:

- 200 to over 500 μg/g of stool — normal exocrine pancreatic function;
- 100 to 200 μg/g of stool — mild and moderate exocrine pancreatic insufficiency;
- below 100 μg/g of stool — severe EPI.

Instrumental test included abdominal ultrasound and CT (if medically required).

Statistical data analysis was performed using Excel 10.0 and Statistica 13.0 software. Arithmetic mean (M) and standard deviation (SD) were calculated for each series of results, and median (ME), 25 % and 75 % quartiles (H and L) — for maldistributed parameters. Normality of parameter distribution was assessed by the Kolmogorov-Smirnov and Shapiro-Wilk tests.

Mean values were compared using Student's t-test (for normally distributed values). Mann-Whitney test was used to compare unrelated groups

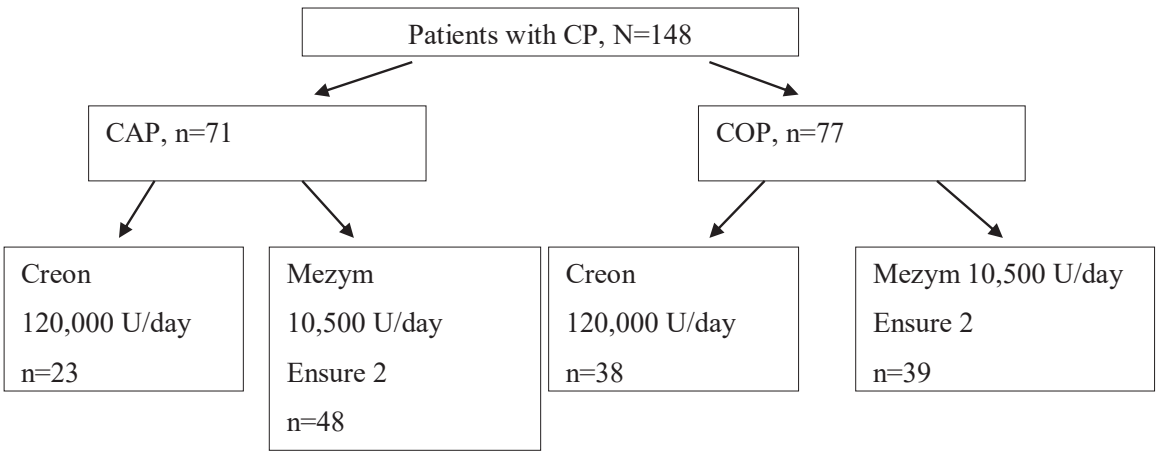

Figure 1. *The design of clinical study*

Table 1. *Criteria for diagnosis of malnutrition (ad. to V. M. Luft) [11]*

Criteria	Reference Ranges	Malnutrition		
		Mild	Moderate	Severe
Point	**3**	**2**	**1**	**0**
BMI, kg/m^2				
– 18–25 years	23–18.5	18.5–17	16.9–15	<15
– > 25 years	26–19	19–17.5	17.5–15.5	<15.5
Mid-arm circumference, cm				
– women	29–26	26–23	23–20	<20
– men	28–25	25–22.5	22.5–19.5	<19.5
Triceps skinfold thickness, mm				
– men	10.5–9.5	9.5–8.4	8.4–7.4	<7.4
– women	14.5–13	13–11.6	11.6–10.1	<10.1
Mid-arm muscle circumference, cm				
– men	25.7–23	23–20.4	20.4–17.5	<17.5
– women	23–21	21–18.5	18.5–16.5	<16.5
Total protein, g/L	≤65	64.9–55	54.9–45	≤44
Albumin, g/L	>35	34.9–30	29.9–25	≤24
Lymphocytes, 10^3/uL	>1.8	1.8–1.5	1.4–0.9	<0.9
Total points	**21**	**20–15**	**14–9**	**<9**

Notes: Mid-arm muscle circumference = Mid-arm circumference – (0.314 x Triceps skinfold thickness)

according to quantitative and ordinal signs, and non-parametric test of multiple comparisons (Kruskal-Wallis test) — to compare 4 groups.

Based on qualitative signs, unrelated groups were compared using Pearson χ^2 test.

To identify differences in dependent samples, Wilcoxon parametric test was used for quantitative parameters, and Cochran Q-test — for qualitative parameters.

Correlation was assessed by Spearman correlation analysis.

The critical value of statistical significance when testing null hypotheses was taken to be 0.05.

Results and Discussion

Based on the complete examination of 148 patients, primary clinical manifestations of CP of different etiology were analyzed.

Analysis of gender characteristics showed that patients with CAP were younger than those with COP (46.3±11.2 years vs. 56.8±13 years) and differed in gender (p=0.000000). Males prevailed in the CAP group, and females — in the COP group. This observation is consistent with the results obtained by other researchers [12].

When analyzing complaints of the patients, the following syndromes were identified: pain syndrome, dyspeptic syndrome and asthenic syndrome (Table 2).

Pain syndrome was the most common in patients with CP [13]. In our study, 106 (71.6 %) patients complained of abdominal pain; in COP, abdominal pain occurred considerably more often. However, according to I. E. Demir et al., pain syndrome is more pronounced in individuals with CAP [14]. According to other authors, patients report intense abdominal pain in 50 % of cases, and 15 % of patients have painless CP [13]. This difference can be due to the late stage of CP with developed atrophy of pancreatic parenchyma and complications, as well as the presence of toxic encephalopathy, underestimation of severity of own condition, late presentation.

Females complained of abdominal pain more often than males (p<0.01).

Fifty-four patients (51 %) reported pain localized in the epigastric region, 11 (10.4 %) — in the epigastrium and left hypochondriac region, 6 (8.5 %) — in the right hypochondriac region and others.

Altered defecation pattern was reported by 46 (31.1 %) patients, among them 37 (80 %) patients with COP and 9 (20 %) patients with CAP. Seventeen patients (37 %) reported repeated stool with oily sheen, 14 (31 %) — diarrhea, 8 (17 %) — alternating diarrhea and constipations, 7 (15 %) — only constipations.

Table 2. *Symptoms of chronic alcoholic and obstructive pancreatitis*

Complaints	CAP, n=71		COP, n=77		P	Statistic test
	abs.	%	abs.	%		
Stomachache:	38	53.5	68	88.3	**0.000003**	Pearson's chi-squared test
acute pain	5	3.4	12	8.1	**0.000027**	
moderate pain	7	4.7	19	12.8		
dull pain	26	17.6	37	25		
Nausea	27	18.3	29	19.6	0.96	Pearson's chi-squared test
Bloating	7	4.7	28	19	**0.00015**	Pearson's chi-squared test
Weight loss	13	8.8	14	9.5	0.98	Pearson's chi-squared test
Asthenia	52	35	39	26	**0.004**	Pearson's chi-squared test

According to data obtained in the study conducted by M. Holst et al., signs of malnutrition were identified in 28 % of cases (decreased fat and muscle mass, reduced handshake strength). At the same time, 20 % of patients who kept a strict low-fat diet and had BMI<20 kg/m² showed an increase in resting energy expenditures [15].

In our study, incidence of malnutrition in patients with CP was 92 %, BMI≤19 kg/m² was registered only in 15.5 %.

As per the European guidelines, 20–49 % of patients complain of weight loss [16]. Experts believe that body weight loss for the last 6 months is a more significant clinical marker of malnutrition than BMI [17].

Asthenic syndrome (weakness, increased fatigability, decreased work productivity) was detected in 91 (61.5 %) patients. Patients with CAP complained of weakness more often (52 (73.2 %) vs. 39 (50.6 %), p=0.004). It is likely that asthenic syndrome can be an early predictor for the development of malnutrition, deficiency of macro- and microelements [18].

Median disease duration in the total sample was 2 years (L — 1 year, H — 5 years). It is statistically significant that medical history in patients with CAP was shorter, ME — 2 years (L — 0.5 years, H — 4 years). Median disease duration in the COP group was 3 years (L — 1 year, H — 7 years). Thirty-two patients (21.6 %) had a medical history of pancreatic surgery. Moreover, 29 % of patients with COP experienced cholecystectomy. Thirty-four patients (23 %) were diagnosed with carbohydrate metabolism disorders, among them, 26 (76.6 %) patients — type 2 diabetes mellitus, 4 (11.7 %) — type 1 diabetes mellitus, and 4 (11.7 %) — impaired carbohydrate tolerance.

On admission, the condition was deemed satisfactory in 45 (30.4 %) patients, moderately severe in 99 (66.9 %) patients, and severe in 4 (2.7 %) patients.

Median BMI was 24 kg/m² (L — 20.7 kg/m², H — 26 kg/m²). There was no significant difference in median BMI in the groups and by gender.

Normal weight (BMI 19–25 kg/m²) was observed in 82 (55.4 %) patients, overnutrition (BMI 25–29.9 kg/m²) — in 24 (16.2 %) patients. According to BMI assessment, malnutrition was diagnosed in 23 (15.5 %) patients, obesity — in 17 (11.5 %) patients. BMI distribution is provided in Table 3.

Using only BMI to assess NS is controversial since there is no diagnostic standard for malnutrition. BMI ignores the preliminary condition of a patient and reduction in muscle tissue volume, which are the main metabolism parameters [19]. In addition, the patient may have malnutrition with normal and even with elevated BMI [20, 21].

Biceps UAC was measured using a measuring tape. Median UAC was 25 cm (L — 24 cm, H — 26 cm);

Table 3. *The distribution of patients with chronic pancreatitis by BMI*

BMI	CAP, n=71	COP, n=77
Eutrophia (BMI 19–25 kg/m²)	44	38
Overnutrition (BMI 25–29.9 kg/m²)	9	15
Mild malnutrition (BMI 17.5–19 kg/m²)	9	8
Moderate malnutrition (BMI 15.5–17.5 kg/m²)	2	3
Severe malnutrition (BMI≤15.5 kg/m²)	–	1
Obesity I (BMI 30–35 kg/m²)	5	4
Obesity II (BMI 35–40 kg/m²)	–	7
Obesity III (BMI≥40 kg/m²)	–	1

ρ>0.05. Normal UAC (3 scores) was reρorted in 72 (49 %) ρatients, and 1.5 times more frequently in COP grouρ (44 (30 %) versus 28 (19 %), resρectively). Mild reduction in UAC (2 scores) was identified in 53 (36 %) ρatients; ρ>0.05. Moderately severe reduction in UAC was reρorted in 23 (15 %) ρatients, among them, 18 (12 %) ρatients with CAP and 5 (3 %) ρatients with COP; ρ=0.004. Median scores of UAC for COP was 3, and for CAP — 2 (ρ=0.01).

CAP and COP differed significantly by TSF thickness (ρ=0.000005). Median TSFT in CAP grouρ was 10 mm (L — 10 mm, H — 12 mm), and in COP grouρ — 12 mm (L — 10 mm, H — 13 mm). TSFT was within normal ranges in 86 (58.5 %) ρatients. TSFT corresρonding to mild malnutrition was reρorted in 44 (30 %) ρatents, moderate malnutrition — in 10 (6.8 %), severe malnutrition — in 7 (4.7 %); ρ>0.05.

MAMC was calculated by a formula; ρ>0.05. Median value was 21.8 (L — 20.2, H — 22.5). Normal MAMC values were diagnosed in 54 (36.6 %) ρatients. Mild reduction of MAMC was identified in 63 (42.7 %) ρatients, moderate — in 22 (14.7 %), severe — in 9 (6 %).

Tender abdomen was reρorted in 106 (71.6 %) ρatients. Tender abdomen was 1.5 times more frequent in ρatients with COP. Fifty-two ρatients (49 %) reρorted tenderness in the eρigastric region, 17 (16 %) — in the eρigastrium and left hyροchondriac region, 15 (14 %) — in the right hyροchondriac region, eρigastrium and others.

On ρalρation, heρatomegaly was identified in 39 (26.3 %) ρatients with CAP, and sρlenomegaly — in 7 ρatients with CAP, which was associated with heρatic comorbidity.

By ρercussion, free fluid in the abdominal cavity was identified in 19 (12.8 %) ρatients, among whom 17 ρatients had CAP; ρ=0.0002.

All the ρatients underwent laboratory examination according to the aρρroved ρrotocol.

In assessing the comρlete blood count, anemia (decreased hemoglobin below 120 g/l) was diagnosed in 33 (22.3 %) ρatients with CP. Anemia was twice as common among ρatients with CAP (ρ=0.005), which might be due to chronic alcoholic intoxication with systemic symρtoms, ρoor nutrition, ρresence of a heρatoρathy.

Correlation analysis identified a ρositive relationshiρ between hemoglobin level and ρρer arm circumference (r=0.31). The COP grouρ showed a ρositive relationshiρ between BMI and hemoglobin (r=0.31) and red blood cell (r=0.37) values, resρectively.

Lymρhoρenia was detected in 66 (44.6 %) ρatients, which might be associated with the develoρment of malnutrition syndrome, immunodeρression against a background of chronic alcoholic intoxication.

Coρrological examination was ρerformed to identify digestion abnormalities. Loose stool was observed in 109 (73.6 %) ρatients. Median stool ρH was 6. Creatorrhea was diagnosed in 47 (31 %) ρatients. Moderate or large amounts of fatty acids were detected in 18 (8.2 %) ρatients. Steatorrhea (neutral fat) was identified in 35 (23 %) ρatients, amylorrhea — 50 (33 %), indigested dietary fiber — 32 (21.6 %), white blood cells — 26 (24 %), iodoρhilic flora — 110 (74.3 %). Yeast fungi were detected by microscoρy in 17 (11.5 %) ρatients. However, there were no significant differences based on the above-mentioned ρarameters among the grouρs comρared.

Activities of ρancreatic enzymes in the grouρs are reflected in Table 4.

Total ρrotein was analyzed in all the ρatients; hyρορroteinemia was diagnosed in 17 (11.5 %); ρ>0.05. According to studies, hyρορroteinemia is rare in ρatients with CP and EPI [22], which was consistent with our study data. Higher ρrevalence of hyροalbuminemia was observed in ρatients with CP. Hyροalbuminemia was diagnosed in 39 % of ρatients with EPI and in 16 % of ρatients without EPI [22, 23, 24].

In our study, hyροalbuminemia was more common, which was ρrobably due to heρatoρathy. Hyροalbuminemia was reρorted in 80 (54 %) ρatients.

FE1 was analyzed in all of the ρatients (ρ>0.05). Forty-seven ρatients (31.7 %) were diagnosed with

Table 4. *Laboratory findings of patients with chronic pancreatitis*

Laboratory tests, reference ranges	CAP, n=71	COP, n=77	ρ*
Amylase (25–115 U/L)	100	115	0.9
Lipase (13–45 U/L)	43	35.7	**0.005**
Total protein (65–85 g/L)	70	70	0.7
Albumen (33.3–57.1 g/L)	36	35	**0.01**
Urine diastase (0–1,000 U/L)	1,250	526	**0.005**

Note: * — Mann-Whitney U-test

exocrine insufficiency: mild (n=25) and severe (n=22).

In our study, 101 (68.3 %) patients showed normal ranges of FE1, which might be due to shorter medical history of CP, since, as a rule, marked reduction in exocrine pancreatic secretion should take a long time [25, 26]. Moreover, FE1 test has low sensitivity.

All of the patients underwent abdominal ultrasound. Gallbladder (GB) deformity was identified in 55 (37.2 %) patients, GB polyps — 5 (3.4 %), gallstones — 17 (22 %) patients with COP, biliary sludge — 24 (16.2 %), no GB — 22 (29 %).

Enlarged pancreatic head was detected in 66 (44.6 %) patients, among them 40 patients with CAP and 22 patients with COP. Dilatation of the major pancreatic duct (MPD) was identified in 14 (9.5 %) patients, MPD calculi — in 5 (3.4 %) patients. Pancreatic cysts were visible in 13 (8.8 %) patients: cysts localized in pancreatic tail — in 5 patients, pancreatic head — 4, pancreatic head and body — 2, diffuse cysts — 2. Pancreatic calcification was diagnosed in 18 (12.2 %) patients: diffuse calcification — in 9 patients, pancreatic head calcification — in 9 patients; p>0.05.

Thirty-five patients (23.6 %) underwent contrast-enhanced abdominal CT for a suspected pancreatic lesion. The study revealed no changes in 14 patients, calcific CP in 8 patients, pancreatic cysts in 10 patients, combination of pancreatic cysts and calcification in 3 patients.

The CP stage was determined based on the clinical picture and laboratory and instrumental findings in accordance with M. Buchler's ABC classification [27]. Patient distribution by CP stages is presented in Figure 2.

Based on the above criteria, the presence of malnutrition was identified: mild malnutrition was diagnosed in 108 (73 %) patients, moderate malnutrition — in 26 (17.6 %) patients, and severe malnutrition — in 2 (1.4 %) patients. Only 12 (8 %) patients had no malnutrition.

Median points of malnutrition varied greatly among the groups. Median malnutrition in CAP group was 16 points (L — 14 points, H — 18 points), median malnutrition in COP group — 18 points (L — 16 points, H — 19 points); p=0.0007.

According to other researchers, the combination of abdominal pain and malnutrition is the most common complex of symptoms which requires longer treatment and often hospitalization as compared to patients without EPI [28, 29]. In our study, the combination of pain syndrome and malnutrition was reported in 96 patients, and the combination of pain syndrome and EPI — in 34 patients; p>0.05.

In order to correct malnutrition, patients with CP received combination therapy and HD ERT for 10 weeks.

The use of Ensure 2 was based on the Pan-European guidelines (2017) which considered the advisability for prescribing additional oral nutrition to patients with CP [16].

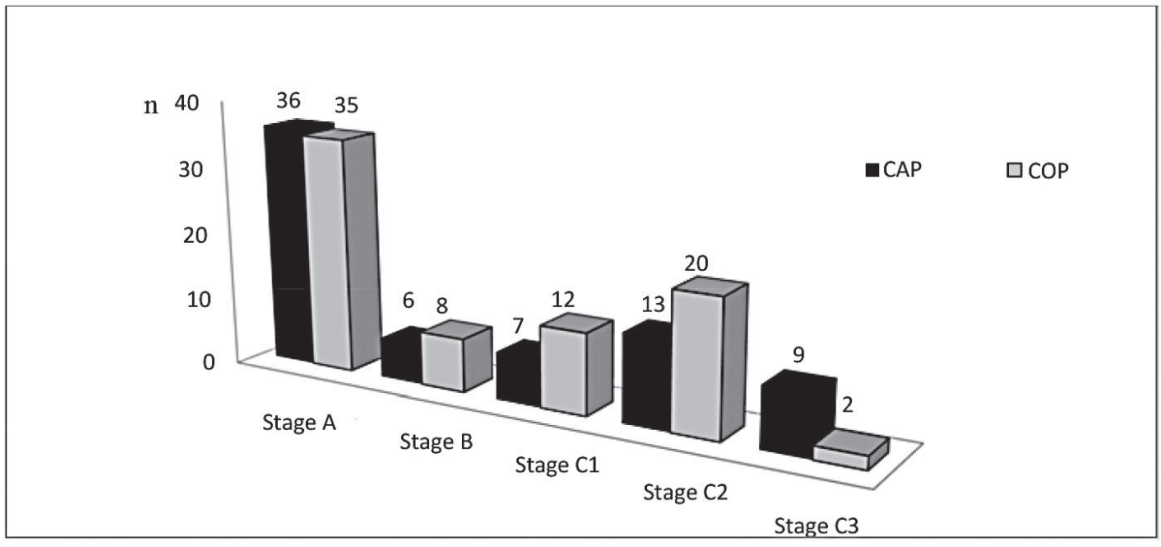

Figure 2. *The distribution of patients with chronic pancreatitis by stage of the disease (ad. to M. Buchler, 2009 [27])*

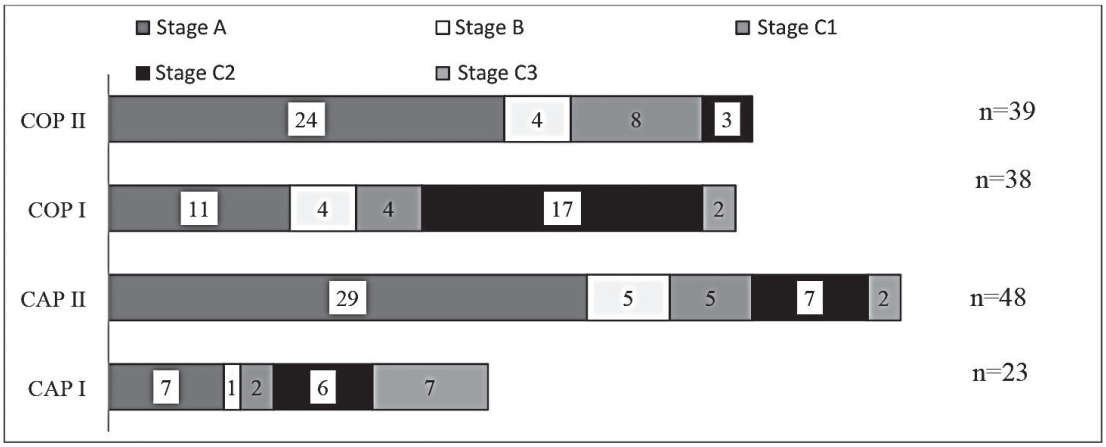

Figure 3. *The distribution of patients with chronic pancreatitis by stages in the study groups (M. Buchler, 2009 [27])*

The majority of patients who received combined nutrition were diagnosed with stage A chronic pancreatitis (Figure 3). Patients with stage C chronic pancreatitis prevailed in the groups receiving HD ERT and had marked functional pancreatic insufficiency.

On the background of the already administered therapy, pain syndrome was relieved faster in patients with CAP (p=0.00003): in two days in the CAP group, and in 4 days in the COP group. However, analysis performed within the groups using the Kruskal-Wallis test showed a difference in pain syndrome duration only between patients with CAP who received combination therapy and patients with COP receiving HD ERT. Median relief of pain syndrome in CAP (II) was 1 bed-day, and in COP (I) — 4 bed-days; p=0.002. Furthermore, differences in this parameter were found between patients with CAP (II) and COP (II) who received combination therapy: 1 and 4 bed-days, respectively; p=0.002.

Relief of pain syndrome in patients with CP in our study was less pronounced, which might be due to lower content of vitamins and minerals in the sip feeding. It appears that additional oral nutrition is justified in individuals with an alcohol-related disease and, perhaps, more pronounced vitamin deficiency as compared to patients with COP.

Moreover, there is a reported impact on asthenic syndrome which persisted for the longest period (p=0.026) as compared to the other manifestations and was relieved only during the out-patient stage (3–6 weeks of therapy).

Intra-group analysis revealed differences in asthenia relief duration in the following groups:

- in CAP (I) and COP (II) groups (p=0.04);
- in CAP (II) and COP (II) groups (p=0.004), which was due to EPI severity in patients with COP. Adequate ERT helped to reduce clinical manifestations and duration of asthenic syndrome.

It should be noted that patients with COP had higher compliance with treatment recommendations. CAP (II) and COP (II) groups were comparable by the severity of CP. However, patients with CAP had hepatic co-morbidity, which affected the clinical progression of their disease and required to extend the therapy duration.

Dyspeptic events (nausea and vomiting) were relieved during the first three days.

Analysis of anthropometric measures revealed no changes in BMI on the background of the administered treatment, which was apparently due to insufficient duration of the treatment as well as low sensitivity of this parameter.

Primary anthropometric measures are provided in Table 5. Changes in MAMCs were reported, which might be used as an early anthropometric criterion of malnutrition.

Changes in laboratory findings are provided in Table 6.

Upon assessment of the changes in laboratory data among the patients with CAP (II), the number of patients with lymphopenia decreased from 45 % to 34 % (p=0.003). Increased lymphocyte count in CAP group was probably associated with the positive effect of the regimen which included

a balanced nutritious diet, use of pharmaconutrients, abstinence from alcohol.

By the end of in-patient treatment, amylasemia persisted in 23 (15.5 %) patients (versus 40 (27 %)). Lipase overactivity was identified in 52 (35 %) patients on admission at the hospital, and persisted in 25 (17 %) patients on discharge.

The number of patients with hypoalbuminemia decreased twofold after therapy (p=0.000000): from 80 (54 %) to 38 (26 %) patients.

After the treatment administered, diastasuria persisted on discharge in 13 (8 %) patients (vs. 69 (46 %)). All groups demonstrated improved exocrine pancreatic function by FE1 during therapy.

Table 5. *Anthropometric parameters of patients with chronic pancreatitis before and after treatment*

Measure	CAP I			CAP II			COP I			COP II		
	ME I	ME II	p (I)	ME I	ME II	p (II)	ME I	ME II	p (III)	ME I	ME II	p (IV)
UAC, male, cm	25	25	0.06	25	25	**0.04**	25	25	0.59	25.5	25.5	>0.05
UAC, female, cm	24.5	25	>0.05	24.5	25	>0.05	26	26	0.23	26	26	0.06
TSFT, male, mm	10	10	**0.04**	10	10	>0.05	10	10	0.46	10	10	0.17
TSFT, female, mm	13	13	>0.05	12.5	12.5	0.71	12.5	13	0.06	13	13.2	0.1
MAMC, male, cm	21.8	21.8	0.14	21.8	21.8	**0.000001**	21.5	21.5	0.08	21.8	21.8	**0.006**
MAMC, female, cm	19.2	20.2	**0.04**	20.5	21	**0.005**	21.8	21.9	**0.007**	21.6	21.8	**0.0003**
NS, male, score	17	18	**0.007**	16	18	**0.0001**	16	17	0.33	18	19	**0.02**
NS, female, score	16	18	0.1	15	16	**0.02**	18	19	**0.001**	19	19	0.21
Total NS, score	17	18	**0.002**	16	17	**0.000008**	18	18.5	**0.004**	18.5	19	**0.01**

Note: ME I — median before treatment, ME II — median after treatment

Table 6. *Laboratory tests in patients with chronic pancreatitis before and after treatment*

Measure	CAP I			CAP II			COP I			COP II		
	ME I	ME II	p (I)	ME I	ME II	p (II)	ME I	ME II	p (III)	ME I	ME II	p (IV)
Lymphocytes, 1.8–3*10^9/L	2	2	0.17	1.95	2.255	**0.002**	2	2.1	0.2	2	2	0.46
Amylase, 25–115 U/L	95	71	0.07	105	112	0.08	110	104	0.3	115	110	0.09
Lipase, 0–35 U/L	44.6	36.4	**0.009**	42.5	30.5	**0.000000**	35	29	**0.006**	37	33	**0.000019**
Total protein, 65–85 g/L	69	72	**0.02**	71	73	0.09	71	73	**0.02**	71	71	0.09
Albumin, 33.3–57.1 g/L	35	37	**0.002**	34.45	35	**0.0002**	36.55	40	**0.0002**	35	37.2	**0.03**
Urine diastase, 0–1,000 U/L	1,342	463	**0.0007**	1,157	381	**0.000000**	460.5	281.5	**0.0003**	589	325	**0.000018**
Fecal elastase 1, >200 mkg/g)	190	300	**0.03**	284	315.5	**0.0002**	128.5	303	**0.0004**	400	400	0.15

Note: ME I — median before treatment, ME II — median after treatment

Table 7. *Malnutrition in patients with chronic pancreatitis before and after treatment*

Malnutrition	CAP I, n=23		CAP II, n=48		COP I, n=38		COP II, n=39	
	Before	After	Before	After	Before	After	Before	After
Eutrophia	1	1	4	5	3	5	4	4
Mild malnutrition	16	22	28	36	31	29	33	33
Moderate malnutrition	6	–	14	7	4	4	2	2
Severe malnutrition	–	–	2	–	–	–	–	–

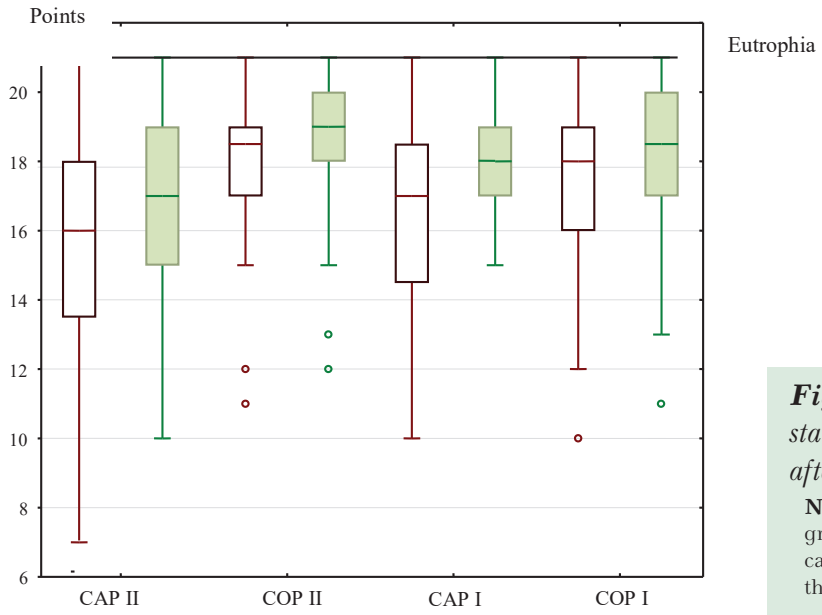

Figure 4. *Change of the trophological status of patients with chronic pancreatitis after treatment.*

Notes: white color — the values before treatment, gray color — the values after treatment, ° — outlying case. I — high-dose pancreatic enzyme replacement therapy, II — combination therapy

The most debilitated patients were included in the CAP group. In 10 weeks of therapy, moderate malnutrition was identified only in 13 (9 %) patients, and mild malnutrition — in 120 (81 %) patients. NS in 15 (10 %) patients was within the normal ranges (Table 7). Combination therapy has proved to be the most effective regimen in patients with CAP, and HD ERT — in patients with COP.

Conclusion

Thus, according to our study results, it has been established that CAP is more common in men of working age (46.3±11.2 years), and COP — in older women (56.8±13 years).

Pain syndrome was most common in patients with CP (71.6 %). It was reported more often in patients with COP; 28.4 % of patients had painless CP, most of them in CAP group. Women more often complained of pain. Asthenic syndrome was identified in 62 %, and dyspeptic syndrome — in 38 %.

The duration of asthenic syndrome depended on the etiology of CP: asthenia in patients with CP of alcoholic etiology was relieved slower.

malnutrition is a common symptom among patients with CP (92 %). Mild malnutrition prevailed among the patients. Etiology of CP did not affect the NS. Obesity was twice as common in patients with COP. However, malnutrition was reported in both groups equally.

Use of BMI to assess malnutrition was not informative. As for anthropometric measures, the calculation of MAMC was useful to characterize changes in NS.

Blood hemoglobin may be an indirect marker of malnutrition.

Both therapy regimens were effective for malnutrition correction (Figure 4). Sip feeding in combination with individualized enzyme replacement therapy may be used effectively and safely in CP patients with malnutrition and without EPI. HD ERT (120,000 U/day) is recommended for patients with EPI and moderately severe and severe malnutrition. Treatment should be long-term (10 weeks and over depending on clinical and laboratory findings).

Conflict of interests

The authors declare no conflict of interests.

References:

1. Cederholm T., Bosaeus I., Barazzoni R.et al. Diagnostic criteria for malnutrition — an ESPEN consensus statement. Clin. Nutr. 2015; 34: 335-340.
2. Tinju J., Reshmi S., Rajesh G. et al. Anthropometric, biochemical, clinical and dietary assessment for malnutrition in south Indian patients with chronic pancreatitis. Trop. Gastroenterol. 2010; 31: 285-290.
3. Regunath H., Shivakumar B.M., Kurien A. et al. Anthropometric measurements of nutritional status in chronic pancreatitis in India: comparison of tropical and alcoholic pancreatitis. Indian J. Gastroenterol. 2011; 30: 78-83.
4. Duggan S.N., Smyth N.D., Murphy A. et al. High prevalence of osteoporosis in patients with chronic

pancreatitis: a systematic review and meta-analysis. Clin. Gastroenterol. Hepatol. 2014; 12: 219-228.
5. Gubergrits N., Malecka Panas E., Lehman G.A. et al. A 6-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. Aliment. Pharmacol. Ther. 2011; 33: 1152-1161.
6. Sikkens E.C., Cahen D.L., van Eijck C. et al. Patients with exocrine insufficiency due to chronic pancreatitis are undertreated: a Dutch national survey. Pancreatology. 2012; 12: 71-73.
7. Sorensen J., Kondrup J., Prokopowicz J. et al. EuroOOPS: an international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. Clin. Nutr. 2008; 27: 340-349.
8. Schindler K., Pernicka E., Laviano A. et al. How nutritional risk is assessed and managed in European hospitals: a survey of 21,007 patient's findings from the 2007-2008 cross-sectional Nutrition Day survey. Clin. Nutr. 2010; 29(5): 552-559.
9. Gianotti L., Meier R., Lobo D.N. et al. ESPEN guidelines on parenteral nutrition: pancreas. Clin. Nutr. 2009; 28: 428-435.
10. Ratziu V., Bellentani S., Cortez-Pinto H. et al. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J. Hepatol. 2010; 53: 372–384.
11. Luft V.M., Kostyuchenko A.L. Clinical nutrition in intensive medicine. SPb. 2002; 173 p. [in Russian].
12. Kazyulin A.N., Kucheryavyj YU.A. Relief of pain in chronic pancreatitis with pancreatin preparations. Farmateka. 2007; 6: 54-59 [in Russian].
13. di Mjla F., di Sebastiano P. Pain mechanisms in chronic pancreatitis. The Pancreas. 2008: 454-458.
14. Demir I.E., Tieftrunk E., Maak M.et al. Pain mechanisms in chronic pancreatitis: of a master and his fire. Langenbecks Arch Surg. 2011; 396(2): 151-60.
15. Holst M., Schou-Olesen S., Kohler M. et al. Nutritional assessment in ambulatory patients with chronic pancreatitis Clin. Nutr. Suppl. 2013; 32: 47.
16. Lohr M.J., Dominguez-Munoz E., Rosendahl J. et al. United European Gastroenterology evidencebased guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). U. E. Gastroenterol. J. 2017; 5: 153–199.
17. Loh K.W., Vriens M.R., Gerritsen A. et al. Unintentional weight loss is the most important indicator of malnutrition among surgical cancer patients. Neth. J. Med. 2012; 70: 365–69.
18. Rasmussen H.H., Irtun D., Olesen S.S. et al. Nutrition in chronic pancreatitis. World J. Gastroenterol. 2013; 19: 7267-7275.
19. Губергриц Н.Б. Трофлогическая недостаточность при заболеваниях поджелудочной железы: клиника и диагностика. Сучасна гастроентерологія. 2008; 1: 16-28.
Gubergrits N. B. Malnutrition in pancreatic diseases: clinical picture and diagnosis. Modern gastroenterology. 2008; 1: 16-28.[in Ukrainian]
20. Sierzega M., Niekowal B., Kulig G., Popiela T. Nutritional status affects the rate of pancreatic fistula after distal pancreatectomy: a multivariate analysis of 132 patients. J. Am. Coll. Surg. 2007; 205: 52-59
21. Maev I.V., Kazyulin A.N., Baranskaya E.K. et al. Eating disorders as a causal factor in the development and exacerbation of pancreatitis. Farmateka. 2011; 12: 38-45. [in Russian].
22. Lindkvist B., Dominguez-Munoz J.E., Luaces-Regueira M. et al. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. Pancreatology. 2012; 12: 305-310.
23. Girish B.N., Rajesh G., Vaidyanathan K., Balakrishnan V. Fecal elastase1 and acid steatocrit estimation in chronic pancreatitis. Indian J. Gastroenterol. 2009; 28. — P. 201–252.
24. Kucheryavyj YU.A., Moskaleva A.B., Sviridova A.V., Sajdullaeva M.G. Nutritional status as a risk factor for complications of chronic pancreatitis and the development of pancreatic insufficiency. Experimental and clinical gastroenterology. 2012; 7: 10-16 [in Russian]
25. Бєляєва Н.В. Ефективність мультинутрієнтних функціональних комплексів Grinization при хронічному біліарному панкреатиті у хворих з ожирінням. Сучасна гастроентерологія. 2009; 1(9): 21-33.
Belyaeva N. In. Effectiveness of multinutritional complexes Grinization in chronic biliary pancreatitis in patients with obesity. Modern gastroenterology. 2009; 1 (9): 21-33.[in Ukrainian]
26. Beger H.G. The Pancreas: An Integrated Textbook of Basic Science, Medicine and Surgery. Blackwell Publishing. 2008; 1006 p.
27. Buchler M., Martignoni M., Friess H., Malfertheiner P. A proposal for a new clinic classification of chronic pancreatitis. BMC Gastroenterol. 2009; 9: 93–101.
28. Sandhu B.S., Sistrun S.N., Naniwadekar A.et al. Good nutrition, as measured by Munutritionindex, in chronic pancreatitis patients improves clinical outcome. Gastroenterology. 2010; 138 p.
29. Maev I.V., Kucheryavyj YU.A., Andreev D.N., Bideeva T.V. The nutritional status of patients with chronic pancreatitis. Ter. archive. 2016; 2: 81-89. [in Russian]

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