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TRAVEL TO COUNTRY IATROGENIC. YATROGENIYA DIAGNOSTIC PROCEDURES (Message 3)

Abstract

A special group of iatrogenic complications are associated with various diagnostic manipulations — from a physical examination of the patient to angiographic studies, diagnostic laparoscopy or thoracoscopy. The article presents data on the frequency and nature of diagnostic iatrogeny in clinical practice. The range of diagnostic iatrogenies in terms of their manifestations, severity and prognosis is wide enough — from skin irritation with ultrasound gel to dissection of the coronary artery during coronary angiography. The article presents examples of diagnostic iatrogenies, starting with the clinical examination process (collection of complaints and medical history, physical examination), and ending with complex invasive examinations. Iatrogeny, which occurs with the use of contrast containing drugs (in particular iodine-containing drugs), which are widely used in clinical practice (enhanced CT, angiography, etc.) with a diagnostic purpose, are discussed in details. The article describes risk factors, understanding of which and awareness of their presence are mandatory before the administration of contrast containing drugs. The review of complications of endoscopic examinations was carried out. The author reminds that iatrogenic events in endoscopic procedures can be manifested not only by complications from the organ under examination (esophagus, stomach, intestines), but also depend on the patient's condition, his preparation for the procedure, and the specialist's skill of endoscopic technique. In conclusion, the author gives a clinical observation in which the risk factor of the iatrogenic event was the presence of an anomaly in the liver and pancreas duct systems in the patient. The author of the article encourages colleagues to pay more attention to the process of making a decision to conduct a diagnostic study, always to evaluate the benefit / risk ratio in terms of the real usefulness of the diagnostic study for the patient and the risk of complication development.

Key words: *iatrogeny, contrast-induced nephropathy, coronarography, endoscopy, esophagogastroduodenoscopy, colonoscopy*

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ICD — iodine-containing drugs, CIN — contrast-induced nephropathy, CCD — contrast containing drugs, ERCP — endoscopic retrograde cholangiopancreatography

The introduction into clinical practice of modern study methods, including invasive ones, carries a potential risk of iatrogenic events associated with various diagnostic manipulations — from physical examination of the patient to angiographic studies, diagnostic laparoscopy or thoracoscopy. There is currently no clear definition and classification of diagnostic iatrogeny.

Meanwhile, iatrogenic events may occur in the course of clinical examination of the patient (collection of complaints and medical history, physical examination). For example, an incorrectly formulated question without taking into account the situation and the psychological state of the patient may seem inappropriate or tactless to the patient and may lead not only to a negative attitude towards

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the doctor, but also serve as a source of psychogenic iatrogeny. Palpation of the abdomen in patients with certain pathology can also cause various complications, regarded as iatrogenic. Here are a few clinical situations observed in clinical practice.

1. Compression fracture of the spine after a test load on the spine axis in a patient with complaints of back pain. Later, according to densitometry of the spine, osteoporosis was diagnosed.

2. Ruptured spleen in a patient with infectious mononucleosis during "thorough" palpation of the left hypochondrium by several doctors (doubts about enlarged spleen). The diagnosis of infectious mononucleosis was assumed in the patient, according to clinical symptoms and peripheral blood parameters, but the risk of ruptured spleen in this category of patients described in 1861 by the Vienna pathologist K. Rokitansky was not taken into account. Spleen rupture can be spontaneous with a frequency of 0.1 to 0.5% [1] or after exposure to mechanical factors (injuries, exercise, etc.).

3. Hypertensive crisis with the development of myocardial infarction in a patient with pheochromocytoma after palpation of the abdomen. It is known that hypertensive crises in pheochromocytoma can be provoked by deep palpation of the abdomen, abrupt movements and other factors.

4. Cutaneous hematoma in the right hypochondrium after palpation of the liver in a patient with idiopathic thrombocytopenic purpura (blood platelets count — 20×10^9/L). This phenomenon is called "palpation symptom" in patients with hemostatic disorders. The appearance of the hematoma caused discontent and complaints from the patient and relatives who regarded this sign as unprofessional treatment of the patient.

Iatrogenic complications in the process of clinical examination of the patient are possible when using simple devices for examination, devices that do not require special skills and assistance from an assistant. For example, when using mercury thermometers, mercury may be spilled and the skin may be injured, and some cases describe wounds in the rectum during rectal thermometry.

As seen, even the traditional clinical examination of the patient, which every doctor begins with, can at this stage become a source of iatrogenic events with all the ensuing consequences. In some cases, these complications can be avoided (careful palpation of the spleen or alternative use of ultrasound in patients with suspected infectious mononucleosis and the risk of ruptured spleen), while in others the complications are unexpected. The development of complications at the stage of clinical examination of the patient, even before the use of additional methods, adds a new problem to the already existing and not yet solved one, which was the reason for patient to consult the doctor. It is obvious that the iatrogenic events acquire not only medical (further studies, consultations, etc.), but also deontological (loss of confidence for the doctor), economic (additional costs on examination and treatment), legal (possible complaints of patients and relatives) aspects.

The range of diagnostic iatrogenies, in their manifestations, severity and prognosis, is quite broad — from skin irritation with gel during ultrasound scanning to dissection of the coronary artery during coronary angiography. With the expansion of indications for diagnostic studies based on the data of physical examination of the patient, the potential risk of diagnostic iatrogenies increases. The patient is at risk of developing skin hematomas after collection of blood from the vein, arrhythmias and angina attacks during ECG recording during exercises, with pneumothorax after diagnostic thoracocentesis, bronchospasm when performing provocative tests with bronchoconstrictors (metacholine, β-blockers), and with severe systemic reactions after skin testing, etc.

According to the analysis of causes and outcomes of iatrogenies among the 38 deaths due to adverse effects of treatment, in 30 cases the deaths were due to diagnostic procedures, with diagnostic iatrogenies proving to be prognostically less favorable in comparison with medical complications [2].

Diagnostic Tests Using Contrast-Containing Drugs

There is a certain risk of iatrogenic complications when using contrast-containing drugs (CCD), in particular, iodine-containing drugs (ICD), which are widely used in clinical practice (contrast-enhanced CT, angiography, etc.) for diagnostic purposes. Usually such complications occur in patients with risk factors, about which the patients should

be informed and aware of before the administration of CCD. These risk factors include:

- Use of NSAIDs, diuretics.
- Creatinine clearance below 60 ml/min.
- Diabetes mellitus with nephropathy.
- Renal hypoperfusion (dehydration, heart failure, hypertension, nephrotic syndrome, liver cirrhosis, etc.).
- Multiple myeloma with the presence of proteinuria.
- Use of ICD for three days before contrast-enhanced examination.
- Age of patients over 65 years (high probability of risk factors).

The frequency of side effects with ICD administration in patients with kidney disease can reach 20%. Special attention should be paid to patients with diabetes, thyroid disease, pregnant women and persons with hypersensitivity to ICD. Among patients with diabetes ICD should be used with caution in young patients prone to hypoglycemia treated with metformin (risk of lactic acidosis with exacerbation of renal failure), patients with renal failure (risk of exacerbation of failure). While ICD may be used in the presence of hypothyroidism, the use of ICD is contraindicated in patients with untreated or poorly controlled thyrotoxicosis. In pregnant women ICD administration is undesirable after 12 weeks of pregnancy (duration of accumulation of contrast in the fetus) due to the risk of thyroidopathy in the fetus. One of the complications of diagnostic studies using CCD is extravascular transfer due to various reasons.

Contrast-Induced Nephropathy (CIN)

CIN is one of the manifestations of diagnostic iatrogeny, the incidence of which has been increasing lately, especially in patients after percutaneous coronary interventions [3]. CIN is defined as an increase in absolute and relative blood creatinine content (above 0.5 mg/dL and more than 25% compared to baseline, respectively) 48 to 72 hours after administration of CCD in the absence of other causes [4]. According to this definition the frequency of CIN in the general population ranges from 1 to 6% [5], and after percutaneous coronary interventions it increases to 3.3% with the need for hemodialysis in 0.3% of cases [6]. In some patients, especially in the presence of cardiovascular disease, the incidence of CIN reaches 20% [4]. There are known cases of acute CIN (2 to 25%, according to various data) after administration of CCD [7, 8]. Risk factors for acute CIN are given in Table 1.

Table 1. *Risk Factors of acute contrast-induced nephropathy [9]*

Patient	Procedure
Elderly age	The large volume of contrast containing drugs
Diabetes mellitus *(diabetic nephropathy)*	High osmolality of contrast containing drugs
Chronic Kidney Disease	Intraarterial administration (in relation to intravenous administration)
Hypertension	
Absolute and relative hypovolemia	
Use of diuretic drugs	
Use of NSAIDs	
Use of ACE inhibitors or angiotensin receptor blockers	

Carotid Angiography

Among 333 patients who underwent 347 diagnostic procedures of carotid angiography, complications were observed in 12 people (3.5%). In one case, a transient ischemic attack was diagnosed, and in two cases, blood transfusions were required due to bleeding. According to literature, the rate of transient neurological complications after carotid angiography ranges from 0 to 2.4%, and other severe complications account for 0.26 to 4.3% [10].

Coronary Angiography

which is the gold standard for the diagnosis and severity of CHD, can cause iatrogenic complications of various severity and prognosis [11]. Table 2 presents the main complications and their frequency in patients after coronary angiography.

In the blood culture performed immediately after and 12 hours after coronary angiography, a positive culture (mainly coagulase-negative

Table 2. *Major complications of coronary angiography*

Nature of complications	Frequency	Reference
Infections	< 1%	[12]
Contrast-induced nephropathy	3,3-16,5%	[13]
Cholesterol embolism	< 2% 25%-30% (according to autopsy data)	[14]
Damage of blood vessels	0,7% — 11,7%	[15, 16, 17]
Bradyarrhythmias	3,5%	[18]
Mortality	3% (left coronary artery dissection)	[19]
Myocardial infarction	0,05%-0,07%	[20, 21]
Cerebrovascular complications		
Dissection of coronary arteries	0,3-0,6%	[22]

Staphylococcus) was isolated in 18% and 12% patients, respectively [23], although clinical signs of infection were not observed. Mortality in coronary angiography increases with percutaneous coronary interventions [24], especially in the presence of risk factors (elderly age, cardiogenic shock, decreased left ventricular ejection fraction, urgent percutaneous coronary interventions, acute myocardial infarction, diabetes, renal failure, multivascular lesions). Mortality rates in these situations range from 0.65% in selective percutaneous coronary interventions to 4.81% in patients with ST elevation myocardial infarction [24].

Complications of Endoscopic Examinations

The development of complications in endoscopic examination depends on many factors and is determined by different situations (age and state of patients, the nature of the underlying and concomitant pathology, use of anticoagulants and antiplatelets, the degree of sedation before the procedure, postoperative period, technique of the procedure, etc.). Depending on the type and purpose of the procedure and specific complications, the following endoscopic iatrogenies may occur:

- Pulmonary and cardiac complications and disorders associated with patient sedation before the procedure.
- Complications of diagnostic endoscopy of the upper gastrointestinal tract.
- Complications of colonoscopy and irrigoscopy.
- Complications of endoscopic retrograde cholangiopancreatography (ERCP).

Iatrogenic events in endoscopic procedures may be manifested not only by complications of the examined organ (esophagus, stomach, intestines), but also depend on the patient's state, the preparation of the patient for the procedure, and the endoscopy technique [25, 26].

Pulmonary and cardiac complications and disorders associated with sedation of patients before the procedure include [27]:

- Excessive drug sedation of patients, making contact difficult during the procedure.
- Paradoxical excitement or sexual fantasies (rarely).
- Drug inhibition of the respiratory center with the development of hypoxia and hypercapnia.
- Aspiration pneumonia.
- Heart rhythm disturbances.
- Hypotension, hypertension, vasovagal reactions.
- Angina and myocardial infarction.
- Stroke.
- Nausea and vomiting.
- Generalized hyperemia and feeling of heat.
- Side effects of cholinergic drugs.

In upper gastrointestinal endoscopy (esophagogastroduodenoscopy) the following complications are possible [28]:

- General discomfort in the throat, abdomen (small complications) — reported by approximately 2% of patients.
- Pulmonary and cardiac disorders (cardiac arrhythmias, myocardial infarction, respiratory arrest, aspiration pneumonia) occur more often in patients with initial pathology.

- Infections (hepatitis B and C, HIV infection).
- Bleedings occur more often in individuals with hemostatic disorders (severe thrombocytopenia — below 20,000 × 10^9/L in mucosa biopsy). Use of antiplatelet agents and anticoagulants does not increase the risk of bleeding [29].
- Perforations (rare complication — 0.03%, mortality — 0.001%). They more often occur in the presence of pathological changes in the esophagus (eosinophilic esophagus) and stomach, or technical errors during endoscopy [30].
- Other rare complications (anaphylactic shock after topical anesthesia, dental injuries, dislocation of the mandibular joint, cases of posterior pharyngeal wall perforation during esophagogastroscopy with the development of neck phlegm).

According to an extensive study, the frequency of complications after esophagogastroscopy, including mucosal biopsy, is 0.13%, and mortality associated with this diagnostic procedure is 0.004% [31].

Colonoscopy complications are difficult to take into account due to the often retrospective diagnosis, non-obvious connection with the procedure, the lack of controlled epidemiological studies [32]. The main complications of diagnostic colonoscopy are:

- Perforation, which rate is 0.13 to 0.19% according to prospective studies [25, 33].
- Bleeding occurs in 0.1 to 0.6% of patients [26], and the risk of bleeding increases with polypectomy. In diagnostic (screening) colonoscopy without polypectomy, the bleeding rate was 3.7/1,000 colonoscopies, and in cases of polypectomy it increased to 8.7/1,000 [34]. Data on the role of antiplatelet agents and NSAIDs in the development of bleeding are contradictory [35].
- More rare complications, including ruptured spleen [36], acute appendicitis, diverticulitis [33], subcutaneous emphysema [37], chemical colitis due to poor removal of disinfectants from the endoscope [38], etc.

One hundred and twenty-eight fatal cases were reported in 371,099 colonoscopies, which determined a case fatality rate of 0.03% [33]. At the same time, 30 days-mortality after colonoscopy was estimated without taking into account specific reasons directly related to the procedure and other factors [39].

Another manifestation of endoscopic iatrogeny is complications associated with endoscopic retrograde cholangiopancreatography (ERCP) [40].
The most frequent and serious complications during ERCP and sphincterotomy are:

- Pancreatitis.
- Bleedings.
- Cholangitis (with septicemia).
- Perforations.

Complications after sphincterotomy occur in 5% of cases, with mild, moderate and severe complications recorded in 60%, 20% and 20%, respectively, and fatal cases in 1%, and, according to recent studies, in 0.2% [41]. The most serious iatrogenic event during ERCP is pancreatitis. High level of blood amylase occurs in 75% of patients after ERCP, but the clinical pattern of acute pancreatitis requiring hospitalization is observed in cases of hyperamylasemia only in 3 to 10% of patients [40]. Acute pancreatitis accounts for more than half of all complications caused by ERCP [42]. According to a study by Freeman M. L. (2002), pancreatitis after ERCP was observed in 5.4% of patients, with severe diseases, including fatal outcome, observed in 0.4% of cases.

Case Report

Patient M., 60 years old, was admitted to the hospital to undergo an examination for jaundice.
Magnetic resonance cholangiopancreatography: MRI-signs of biliary hypertension. Calculous cholecystitis. Common bile duct block cannot be excluded in the intramural part. Ultrasound examination (05/26/2015): multiple concrements of 3.6 mm with a clear acoustic shadow are imaged in the lumen of the gallbladder. The walls of the gallbladder are unevenly thickened and compacted. Diffuse changes present in the pancreas.
Diagnosis on admission: chronic calculous cholecystitis, choledocholithiasis. Mechanical jaundice. An urgent surgery due to the complication of choledocholithiasis is indicated.
There was an unusual situation during ERCP (06/08/2015): the contrast agent constantly

penetrated into the Wirsung duct when attempting to contrast the common bile duct. Under X-ray control the contrast agent is completely aspirated through the catheter. During consilium there were two attempts of cannulation and contrasting with the same effect: bile freely flowed through the catheter and parallel to it, while the contrast agent immediately penetrated into the Wirsung duct. The contrast agent was also completely evacuated. The situation was regarded as an anomaly in the development of liver and pancreas duct systems — single wide opening in combination with common bile duct block caused by the impaction of a concrement in the projection of the common bile duct terminal part. Given the high risk of pancreatitis with underlying choledocholithiasis, it was decided to refrain from full contrast of pancreatic ducts and further attempts of endoscopic treatment of choledocholithiasis. During patient follow-up the situation was initially regarded as acute edematous pancreatitis, but the condition subsequently deteriorated, clinical and laboratory signs of destructive pancreatitis appeared with the development of systemic manifestations of multiple organ failure and fatal outcome.

In this case, the iatrogenic event was due to the presence in the patient of an anomaly in liver and pancreas duct systems, in particular, a single wide opening of Wirsung and the common bile ducts in duodenum. This situation combined with the block of the common bile duct caused by impaction of a concrement inevitably led to the penetration of the contrast agent directly into the Wirsung duct, which subsequently caused the development of pancreatitis. Formally, this case is a typical example of the iatrogenia of diagnostic procedures, which is not always possible to provide. There are many cases of properly performed invasive examination or surgery leading to severe, often fatal complications in medical practice. An example is the case described in 1983 in N. V. Elstein's book titled *Dialogue on medicine.* In one female patient tonsils were removed; a simple, common operation, usually without consequences. But this patient experienced bleeding from the surgical wound, the cause of which was atypical location of the blood vessel, which was damaged during surgery. Fortunately, the bleeding was stopped on time.

When making a decision on the feasibility of any diagnostic examination the following aspects should be kept in mind:

- Will this examination help to verify the diagnosis?
- Will the results radically change the treatment and influence the prognosis?
- Is it possible to conduct a less invasive, but no less informative examination?
- Does this examination pose a potential danger to a particular patient?
- Recommend patients to undergo invasive diagnostic procedures only for strict indications.
- Endoscopic interventions should be carried out with extreme caution under monitoring using video endoscopic equipment.

Conflictum of interest

The authors declare no conflict of interests.

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CARDIOVASCULAR AND METABOLIC IMPAIRMENT IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

Abstract

Since the moment when the obstructive nature of sleep apnea was first revealed, a lot of new in-formation on this disease has been obtained. Now obstructive sleep apnea (OSA) is recognized as an independent predictor of the development of impaired glucose tolerance (insulin resistance, fasting hyperglycemia), type 2 diabetes mellitus (DM2), resistant hypertension, cardiovascular death. The problem of identifying and treating patients with OSA is still actual. In real clinical practice, there is a need for an integrated approach to the diagnosis and therapy of comorbid OSA patients with metabolic disorder and cardiovascular diseases. **The objective** of this review is to assess the clinical and pathogenesis features of metabolic disorders, carbohydrate metabolism, basic metabolism, eating behavior, bodyweight fluctuations in patients with obstructive sleep apnea. **Methods**. In our work, we used a retrospective analysis of published clinical research data of domestic and foreign authors over the past 20 years. The review included studies with adequate design from the standpoint of good clinical practice (GCP) and evidence-based medicine. **The conclusion**. According to modern interpretation, obstructive sleep apnea is considered an independent disease with its pathogenic mechanisms, clinical and functional manifestations. There are several main causes of the effect of OSA on the metabolic component and the work of the cardiovascular system. Among them, intermittent hypoxemia, endothelial dysfunction, fluctuations in intrathoracic pressure, increased activity of the sympathetic nervous system, and the disorder of the structure of sleep are the leading ones. OSA is considered a disease capable of disabling patients of working age, dramatically changing the quality of life, and leading to early mortality due to cardiovascular disasters. Timely detection of clinical symptoms of OSA and the strategy of early administration of CPAP therapy significantly improve the quality of treatment and prognosis of comorbid patients.

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Ra — short leptin receptor, Rb — long leptin receptor, ROS — reactive oxygen species, BP — blood pressure, URT — upper respiratory tract, IL6 — interleukin 6, IR — insulin resistance, LA — pulmonary artery, LV — left ventricle, OSA — obstructive sleep apnea, BM — basal metabolism, RAAS — renin-angiotensin-aldosterone system, RCT — randomized clinical trial, DM — diabetes mellitus, FFA — free fatty acids, CVD — cardiovascular disease, TE — thermogenic effect, PA — physical activity, TNFα — tumor necrosis factor alpha

Introduction

The pathogenetic mechanisms underlying the development of metabolic and hormonal disorders in patients with respiratory disorders during sleep have not been fully studied. An important role is given to the increase in the activation of the sympathetic nervous system against nocturnal intermittent hypoxemia and deprivation of the vital stages of sleep — the main links in OSA pathogenesis [1]. Exposure to these causes disrupts metabolism and contributes to the progression of obesity in patients with OSA. There is a need to search for available clinical and pathogenetic predictors of

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individual predisposition to metabolic disorders in patients with OSA in order to justify the beginning of their primary prevention, the development of comprehensive programs for diagnosis and treatment of pre-existing disorders.

Obstructive sleep apnea (OSA) is a common disease affecting at least 20% of the adult population in urbanized countries [2], in which recurrent episodes of respiratory arrest (apnea) and partial reduction of respiration (hypopnea) occur during sleep lasting from 10 seconds. It has been proven that collapses of the upper respiratory tract repeating every night cause fragmentation of sleep, hypoxemia, hypercapnia, fluctuations in intrathoracic pressure, night-time increase in the activity of the sympathetic nervous system, development of systemic inflammation [3]. Currently, OSA is considered as an independent risk factor for cardiovascular disease (CVD) and metabolic disorders [4, 5].

OSA and Cardiovascular Diseases

The phenomenon of cyclic desaturation with rapid reoxygenation, known as intermittent hypoxia, initiates a cascade of vascular endothelial damage mechanisms [6]. Hypoxia and hypercapnia serve as potential stimulants of vasoactive substances (endothelin and vasopressin) that increase vascular tone leading to increased blood pressure (BP), left ventricular (LV) postload and its hypertrophy [7]. This chronic hypoxemia is accompanied by a reduced production of endogenous relaxing factors including prostacyclin, prostaglandin E2 and nitrogen oxide. These factors are the basis of pulmonary vasoconstriction and increased pressure in the pulmonary artery (PA), which contributes to the development of pulmonary hypertension, hypertrophy and dysfunction of the right ventricle [8]. After respiratory arrest there is always a period of hyperventilation with a typical increase in the amplitude of negative intrathoracic pressure which increases venous blood flow and leads to right atrium distension. Polycythemia, which develops in chronic hypoxemia, contributes to increased blood pressure in PA, increases blood viscosity and is a risk factor for thromboembolism and sudden death in patients with OSA [9].

Disorders of autonomic functions in combination with activation of the renin-angiotensin-aldosterone system (RAAS) and decreased sensitivity of the kidney to the natriuretic hormone can cause persistent drug refractory hypertension and congestive heart failure [10].

OSA and Obesity

OSA can be both an independent disease and a syndrome developing with other pathologies. The prevalence of OSA in patients with overweight exceeds 30%, reaching up to 50–98% in patients with morbid obesity [11]. There is convincing evidence that it is the abdominal type of obesity in patients with OSA, as well as the deposition of visceral fat in the pharynx that contribute to the narrowing of the upper respiratory tract and the development of respiratory arrest during sleep [12].

Normally, the lumen of the respiratory tract is an ellipse with long transverse and short anteroposterior axes. In obesity the shape changes to an oval with long anteroposterior and short transverse axes. According to magnetic resonance imaging of the neck in patients with OSA, such change in the shape of the pharynx with marked luminal narrowing is due to the presence of fat deposits in the soft tissues of the pharynx. With decreased tone of the pharyngeal muscles the probability of the pharynx collapse at the level from palatine uvula to the epiglottis increases. The amount of fat in the lateral walls of the pharynx is a predictor of respiratory disorders and correlates with the severity of OSA. However, visceral fat is not only a mechanical barrier to air passage through the respiratory tract, but also an important structure that triggers metabolic disorders in patients with OSA. For this reason, the measurement of neck circumference is required along with the measurement of waist circumference and body mass index in obese patients [13].

In addition to energy deposition, adipose tissue is a complex hormone-active organ that plays an important role in the regulation of energy balance and homeostasis of the body as a whole [14]. Adipocytes produce about 600 adipokines, which are bioactive substances acting on the basis of paracrine, autocrine, or endocrine effects, and performing communication with the central nervous system, heart, muscle tissue, blood vessels, pancreas, other organs and tissues [15]. Adipokines include classical cytokines, chemokines, proteins of alternative complement system; proteins regulating vascular

homeostasis, angiogenesis, blood pressure, lipid and carbohydrate metabolism [16]. The most studied adipokine of adipose tissue is leptin which means 'thin' or 'spindling' when translated from Greek. Adipocytes secrete leptin in amounts proportional to the mass of adipose tissue. There is evidence of the auto-paracrine leptin effect on the metabolic activity of adipocytes: inhibitory in respect of lipogenesis and stimulatory in relation to lipolysis [17]. In the blood, leptin circulates both in the free and in protein-bound state. Leptin receptors belong to the class of cytokine of type 1. There are 2 isoforms of leptin receptors: long receptor (Rb) localized in the brain and short receptor (Ra) — in peripheral organs and tissues. Rb receptor is localized in satiation center — in ventromedial nucleus of the hypothalamus, as well as in the arcuate, dorsomedial and paraventricular nuclei. Leptin integrated into the feedback system with hypothalamic neuropeptides, especially with neuropeptide Y, is involved in the regulation of energy balance. After penetration into the hypothalamus leptin suppresses appetite through the limbic lobe and brain stem. By stimulating the activity of the sympathetic nervous system, leptin reduces energy consumption and increases its expenditure. The presence of leptin receptors in peripheral organs and tissues (fat, liver, skeletal muscles, pancreas, ovaries, prostate, placenta, kidneys, and lungs) explains its effect on hematopoiesis, angiogenesis, immune responses, blood pressure, and bone metabolism [18].

Most patients with OSA have not only elevated blood leptin levels, but also resistance to leptin. There is no clear concept of mechanisms for sensitivity to leptin in patients with OSA, but there are several hypotheses. According to one of them, there is a slowdown in the penetration of leptin through the blood-brain barrier. According to another hypothesis, decrease in sensitivity to leptin is associated with a breakdown in the work of a specific transport protein, since the hormone circulates in a bound state. The third reason may be a decrease in the sensitivity of hypothalamic receptors to leptin and the disruption of its interaction with said receptors [19]. Excessive amount of leptin and especially resistance to leptin in patients with OSA can cause carbohydrate and lipid metabolism disorders, as well as many potentially atherogenic effects: induction of endothelial dysfunction, impaired platelet aggregation, migration, hypertrophy and proliferation of vascular smooth muscle cells [20].

Tumor necrosis factor alpha (TNFα), insulin, glucocorticoids, estrogens and interleukin-1 stimulate the secretion of leptin. The following substances inhibit the secretion of leptin: catecholamines, androgens, free fatty acids, growth hormone, thyroid hormones, as well as overeating and high fat foods. The second most important adipokine in the pathogenesis of metabolic disorders in patients with OSA is TNFα.

In adipose tissue, ***TNFα*** is suppressed by both adipocytes and preadipocytes. In this case, the cytokine itself affects the differentiation of fat cells and apoptosis of pre- and adipocytes. The increase in TNFα production is associated with the development of insulin resistance, especially in adipose tissue in patients with OSA. Under its influence, the activity of tyrosine kinase of insulin receptor decreases, and phosphorylation of serine substrate of insulin receptor 1 increases; expression of GLUT4 in fat and muscle tissue decreases. Through the activation of hormone-sensitive lipase in adipocytes, TNFα stimulates lipolysis and inhibits the activity of lipoprotein lipase [21].

In the liver, TNFα suppresses the expression of genes involved in glucose uptake and metabolism, fatty acid oxidation; increases the expression of genes involved in de novo synthesis of cholesterol and fatty acids. TNFα has a direct inhibitory effect on the secretion of thyroid hormones and deiodinase activity in the thyroid [22].

Interleukin 6 (IL6) is the third most important cytokine produced by visceral adipocytes, which, in patients with OSA, is associated with disturbed energy homeostasis, thermogenesis, pulsed secretion of luteinizing hormone, growth hormone. By stimulating the formation of C-reactive protein, IL-6 contributes to the development of endothelial dysfunction and the risk of cardiovascular complications in patients with OSA. This cytokine reduces the expression of lipoprotein lipase exerting a local effect on the absorption of free fatty acids (FFA) by adipocytes. IL-6 has a direct effect on metabolic processes in the liver by suppressing the sensitivity of insulin receptors therein. TNFα, glucocorticoids and catecholamines stimulate IL-6 production [23].

Adiponectin is secreted exclusively by mature adipocytes. Normally, adiponectin reduces insulin resistance by stimulating phosphorylation of tyrosine (insulin receptor); reduces FFA intake in the liver and stimulates their oxidation by activating protein kinase contributing to the reduction of glucose production by the liver and synthesis of VLDL triglycerides. In muscle tissue adiponectin stimulates FFA oxidation, reduces intracellular lipid accumulation and improves the sensitivity of muscle tissue to insulin. The experiment also showed that adiponectin had anti-inflammatory and antiatherogenic effects. In the vascular wall, adiponectin inhibits adhesion of monocytes to the endothelium by reducing the expression of adhesion molecules, suppresses the transformation of macrophages into foam cells, reduces proliferation and migration of smooth muscle cells, LDL uptake of the evolving atherosclerotic plaque and production of TNF-α in macrophages. Adiponectin increases nitrogen oxide production in endothelial cells, stimulates angiogenesis. In patients with OSA, reduction of adiponectin synthesis leads to a decrease in its protective properties against the vascular wall due to the progression of atherosclerosis because of lipid metabolism disorders (high levels of LDL, VLDL, triglycerides, significant increase in atherogenic index) [23].

Resistin is produced mainly by preadipocytes and to a lesser extent by mature adipocytes of visceral adipose tissue. The role of this polypeptide in insulin resistance development mechanisms has not been completely elucidated in patients with OSA. With regularly recurring episodes of apnea throughout sleep time, hypertrophy and hyperplasia of adipocytes occur in adipose tissue. As a result the production of cytokines changes, their function is impaired and consequently systemic metabolism fails [23].

Nocturnal Hypoxemia, OSA and Basal Metabolism

Patients with OSA are characterized by the development of energy imbalance (mismatch between energy consumption and expenditure) as a result of disturbance of several major factors affecting energy consumption.

The first one is the level of basal metabolism (BM). It should be proportional to body weight (without fat) and body surface, meet energy expenditure on maintenance of basic physiological functions in standard conditions (in a state of wakefulness and rest, warmth, at least 12 hours after eating).

The second one is thermogenic effect (TE). It represents a specific dynamic action of food which is about 5–15% of the total energy expenditure and is associated with additional energy consumption on digestion with the stimulation of metabolism due to the influx of a new substrate. The third factor is physical activity (PA) [24].

Intermittent hypoxemia is a triggering mechanism of disturbance in basal metabolism in this category of patients. Recent publications report that desaturation index is inversely proportional to energy consumption in sleep and during wakefulness. Postalimentary thermogenesis in obese individuals is significantly lower than in individuals with normal body weight, which may partly be due to disturbance of the sympathetic nervous system activity, as well as to disturbance of sensitivity of β-adrenergic receptors to catecholamines. Disturbance of adaptive thermogenesis function in patients with OSA causes a marked increase in body weight and also creates difficulties with its reduction. A number of scientific papers managed to establish an independent relationship between energy consumption at rest and the severity of respiratory disorders in sleep. As the severity of OSA increases, the respiratory coefficient increases, which leads to the oxidation of carbohydrates instead of fats and to the activation of stress systems. These mechanisms are predisposing for the development of obesity in patients with respiratory disorders at night [25].

Oxidative stress also contributes to the potential mechanisms of metabolic disorders in patients with OSA. The hypoxia/reperfusion cycle in OSA is the basis for increasing the production of reactive oxygen species (ROS). In the human body most metabolic and physiological processes occur with the participation of oxygen, resulting in the formation of aggressive oxygen forms or highly reactive oxygen radicals in cells. The latter include hydrogen peroxide, hydrogen radical, superoxide

anion radical, hypochloric acid and many others. Normally, mitochondria produce intracellular oxygen radicals, which in physiologically low concentrations are involved in the regulation of synthesis of prostaglandins, leukotrienes, thromboxanes, provide cellular immunity, and regulate the growth and differentiation of body cells. In large quantities they can activate free radical oxidation of lipids, damage RNA and DNA, fats and proteins (including enzymes), leading to tissue damage and cell death [26].

To maintain the balance of free radicals, the body employs an antioxidant system which includes urates, glutathione, ubiquinone, thioredoxin, some proteins (ferritin, transferrin, ceruloplasmin, lactoferrin), etc. Oxidative stress occurs when there is an imbalance between reactive oxygen species and the antioxidant system. Intermittent hypoxia accompanying OSA leads to the activation of some NADPH-oxidases, which promotes oxidative damage and increased inflammatory response [27].

In addition to systemic hypoxemia, an increase in fat mass in patients with OSA is accompanied by local hypoxia, which causes the development and maintenance of inflammation of adipose tissue. As a result of the inflammatory reaction, c-Jun-N-terminal kinase (JNK), Kappa bi kinase inhibitor (IKK) and protein kinase are activated. This leads to the release of the nuclear transcription factor of Kappa bi nuclear factor (NF-κB) and hypoxia-induced factor-1 (HIF-1) in cytosol in both adipocytes and macrophages. NF-κB migrates into the cell nucleus and stimulates gene transcription of numerous regulatory substances, including adipokines. Cytokines induce an inflammatory shift in adipocytes which causes an even greater increase in cytokine production. This fact served as the basis for the idea that inflammation of adipose tissue is a self-sustaining process: once initiated, it progresses without the presence of additional factors. At the same time, the more severe night hypoxemia in patients with OSA is, the faster and more significant the inflammation of adipose tissue develops. The typical morphological sign of adipose tissue inflammation is its infiltration by macrophages. In this case, they can be up to 40% of all cells of adipose tissue. With the progression of inflammation secondary to respiratory arrest, fibrosis characterized by the accumulation of connective tissue cells and extracellular matrix in the form of an amorphous zone around hypertrophied and/or dead adipocytes develops [28].

Data on the presence of innate immunity receptors in adipocytes, Toll-like receptors (TLRs), primarily TLR4, are of particular interest for understanding the pathogenesis of metabolic disorders in patients with OSA as a result of inflammation of adipose tissue. A specific ligand of TLR4 is lipopolysaccharide (LPS). Activation of TLR4 involves intracellular kinases. They provide the transfer of the nuclear factor NF-κB into the cell nucleus with the subsequent activation of the formation of proinflammatory genes encoding the synthesis of cytokines, chemokines, adipokines. Stimulation of TLR4 in isolated adipocytes increases the secretion of IL-6, TNFα, resistin and decreases adiponectin level. The combination of these reactions causes the development of insulin resistance (IR) in adipocytes, hepatocytes and muscle cells. Activation of TLRs significantly increases lipolysis. It was found that the presence of TLR4 is a necessary condition for the infiltration of the gastrointestinal tract by macrophages, i.e. a condition for the development of inflammation in adipose tissue [29].

Eating Disorder in Patients with OSA

Eating disorder contributes to excessive weight gain in most patients with OSA. There is a failure of the systems controlling the internal need for food. Programs on excessive storage of nutrients start with blunting satiety and slowing energy consumption.

The energy balance is regulated by two types of neurons in the arcuate nuclei [30]:

1. Proopiomelanocortin neurons (POMC) that produce alpha-melanocyte-stimulating hormone (α-MSH), cocaine and amphetamine-mediated transcripts (CART). They reduce food consumption and increase energy consumption.
2. Neurons producing melanin-mediated protein (AGRP, or agouti-related protein) and neuropeptide Y (NPY, NPN). They increase food consumption and reduce energy consumption.

Alpha-melanocyte-stimulating hormone secreted by POMC-neurons stimulates melanocortin

receptors (MCR3 and MCR4) of paraventricular nuclei, which then activate the neuronal pathway projected onto the nucleus of the solitary tract and increase sympathetic activity and energy consumption. Melanin-mediated protein acts as an antagonist of MCR4 [31].

Insulin, leptin and cholecystokinin (hormones inhibiting AGRP- and NPY-neurons and stimulating adjacent POMC- and CART-neurons) reduce food intake [32].

Ghrelin is produced mainly by P/D1-cells of the mucous membrane in the fundus of the stomach. Ghrelin activates AGRP- and NPY neurons and stimulates food intake. It circulates in the blood mainly in an inactive form and becomes biologically active (acylated ghrelin) in response to fasting. During sleep there is an increase in total ghrelin with a decrease in the total/active ghrelin ratio compared to wakefulness. Distension receptors of the stomach activate sensory afferent pathways within the vagus nerve and together with gastrointestinal hormones (peptide YY (PYY) and cholecystokinin) suppress appetite and further food intake [33].

Hypothalamus and brain stem structures (arcuate nucleus, paraventricular nucleus, single pathway nucleus, dorsal motor nucleus of the vagus nerve, etc.) are involved in the perception of satiety signals mediated by hormones, adipokines, neuropeptides and their metabolites and in the transformation of the information into behavioral reactions. However, the functional organization of the hypothalamus or other nerve centers responsible for eating behavior in people with obesity is different from that in people with no excess body weight. The transformation of the peripheral signal occurs via neurotransmitters which include catecholamines (dopamine, adrenaline and norepinephrine) and indolamines (serotonin). Dopamine, norepinephrine and adrenaline are successive links in sequence of transformations of amino acid tyrosine. The role of dopaminergic neurons in the regulation of eating behavior is extremely important [34].

There are known 5 types of dopamine receptors which are divided into 2 subtypes depending on the effects on adenylate cyclase — D1-like (D1, D5) — activating and D2-like (D2, D3, D4) — inhibitory. The role of D1-like receptors in the regulation of eating behavior has not yet been proven. The role of D2-like receptors is determined not only by their number, but also by the location [35].

Norepinephrine implements its action in the cells of paraventricular and ventromedial nuclei of the hypothalamus. Exposure to α1-, β2- and β3-adrenergic receptors leads to decreased appetite, while stimulation of α2-receptors, on the contrary, stimulates appetite. Serotonin is one of the most important transmitters involved in the regulation of energy homeostasis, which consists in stimulation of some types of neurons and inhibition of others in the hypothalamus by peripheral hormones. It is a compound which, in the human body, has a hormone and neurotransmitter function. Its highest concentration is observed in the pineal gland, where it serves as a precursor for melatonin biosynthesis. Melatonin is the main component of the body's starting system, the function of which is to transmit information on light regime to the body with regulation of the sleep-wake cycle [36].

Serotonin is synthesized from tryptophan. The effects of serotonin are realized through its receptors. In the pathogenesis of obesity, only part of them is involved: 5-HT2C, 5-HT1A and 5-HT2B as well as the still underexplored 5-HT6 [37].

The target of serotonin action is the melanocortin system. In the arcuate nuclei of the hypothalamus, serotonin activates POMC/CART-neurons, which leads to increased production of α-MSH and, consequently, decreased food intake, and interaction with ATP-neurons prevents the suppression of α-MSH secretion. The serotonin produced in the digestive tract also contributes to energy regulation by stimulating the motility of the gastrointestinal tract and the secretion of hydrochloric acid in the stomach and bicarbonates in the duodenum and carries vasoactive properties in the mucous and submucous membranes and determines the sense of taste. The following is necessary for the production of serotonin in the body: 1) dietary intake of tryptophan — essential amino acid needed for the direct synthesis of serotonin in the synapses; 2) glucose intake, stimulation of insulin release into the blood, stimulation of catabolism in the tissues and, consequently, increased tryptophan level in the blood [38].

Bulimia and addiction to carbohydrate-rich food may be directly related with these facts. Serotonin can cause a subjective feeling of satiety, and when the body takes in food, including tryptophan,

production of serotonin increases, which lifts the mood. The brain quickly establishes the connection between these phenomena — and in the case of depression (serotonin fasting) it immediately requires additional tryptophan or glucose intake with food. The most tryptophan-rich foods that are almost entirely composed of carbohydrates, such as bread, bananas, chocolate, or pure carbohydrates: sugar or fructose [39].

The reason for the failure of the normal functioning of hypothalamus and pineal body centers responsible for the energy balance in patients with OSA is hyperactivation of the sympathetic nervous system, which is repeated every night, as a result of intermittent hypoxemia and sleep structure disorders. This leads to an imbalance of hunger and satiety, disruption of the daily eating rhythm.

Night eating syndrome often develops when patients have a strong feeling of hunger in the evening and at night. They cannot sleep without eating too much food. However, in some cases it does not bring satisfaction. Mental disorders can often develop. A sharp increase in food consumption, an increase in calorie intake due to easily digestible carbohydrates and fats in patients with OSA is a kind of protective mechanism against anxiety and emotional discomfort. Reduced physical activity due to excessive daytime sleepiness further exacerbates weight gain and contributes to the progression of night respiratory disorder. A vicious circle is formed. A large proportion of the consumed nutrients unbalanced by the processes of liposynthesis is transformed into metabolically inert fat mass. The growing metabolic needs are compensated with excess food. This leads to inadequate use of the energy resource or cell starvation which in sleep apnea phenomena is supplemented by oxygen starvation with even greater accumulation of visceral fat [40].

OSA and Carbohydrate Metabolism Disorders

Currently, OSA is considered as an independent risk factor for glucose intolerance (insulin resistance (IR), fasting hyperglycemia) and diabetes mellitus (DM). According to randomized clinical trials (RCTs), the development of carbohydrate metabolism disorders occurs in 29.6% of patients with mild OSA, in 50% of patients with moderate OSA and in 61.8% of patients with severe apnea. Epidemiological studies conducted in different countries and populations revealed a significant relationship between the apnea-hypopnea index and the risk of IR, DM2 development [41].

One of the objectives of the multi-center population-based cohort study, Sleep Heart Health Study (2004), was to identify the relationship between OSA, glucose intolerance and insulin resistance in the general population. Polysomnography, detection of insulin, fasting glucose, HOMA-index and OGTT were performed in 2,656 patients. Compared with the reference group (IAG < 5/h), in patients with moderate to severe OSA the odds ratio for glucose intolerance was 1.27 and 1.46, respectively, after adjustment for age, sex, BMI and waist circumference. HOMA index increased in the studied subjects as the average saturation decreased during sleep. It is known that the increase in body weight, especially due to visceral fat, is a risk factor for the development of IR. The results of the Sleep Heart Health Study showed that OSA is associated with abnormal fasting glucose level and glucose intolerance regardless of gender, age, race, BMI and waist size. The authors concluded that OSA leads to impaired glucose metabolism regardless of obesity. Sleep apnea increases the risk of developing diabetes through pathophysiological mechanisms different from those in obesity [42].

A number of studies have found that each additional sleep apnea increases fasting insulin levels and HOMA-index by 0.5% in one hour of sleep. In addition, the level of HbA1c and fasting glucose are higher in patients with OSA compared to those who did not have respiratory arrest at night regardless of body mass index [43, 44].

A number of population studies have demonstrated disorders of carbohydrate metabolism not only in OSA, but also in the presence of snoring. Follow-up study of 2,668 men aged 30–69 years for over 10 years showed that snoring men with obesity are 7 times more likely to be at risk of developing diabetes than non-snoring men with obesity regardless of age, weight gain, smoking, alcohol and physical activity [45].

Data from another study titled Nurses' Health Study involving 69,852 nurses aged 40–65 years without diabetes, cardiovascular diseases and tumors at the time of the study showed that for 10 years constant snoring leads to a 2-fold increase in the risk of developing DM2 regardless of age and BMI. It was found that when severity of OSA increased regardless of age and BMI, fasting and post-exercise glucose levels increased, and insulin sensitivity decreased [46].

The pathogenesis of carbohydrate metabolism disorders in patients with OSA includes several interrelated links. Intermittent hypoxia and fragmentation of sleep cause an increase in the activity of the sympathetic nervous system and in the level of catecholamines; there is an increase in cortisol levels associated with impaired regulation of the hypothalamic-pituitary-adrenal axis. Catecholamines stimulate glycogenolysis, gluconeogenesis and glucagon secretion. In addition, the activation of SNS stimulates lipolysis, thereby increasing the circulation of free fatty acids and glycerol in the portal bloodstream. By entering the liver, FFAs become a substrate for the formation of atherogenic lipoproteins, and also prevent the binding of insulin to hepatocyte. Insulin resistance of hepatocytes leads to a decrease in glycogen synthesis, activation of glycogenolysis and gluconeogenesis. With the depletion of pancreatic B cell function, decompensation of carbohydrate metabolism occurs, first in the form of impaired fasting glycemia, glucose intolerance, and then as type 2 diabetes [47].

Oxidative stress initiates systemic inflammation which affects the metabolism and secretion of adipose tissue, increases levels of circulating interleukins and TNFα. The anti-steatogenic effect of leptin is impaired. Normally, by affecting the activity of AMP kinase, it increases fatty acid oxidation in muscles, reduces the content of intramyocellular lipids, increases tissue sensitivity to insulin, thereby protecting the body against the development of lipotoxicity. In the treatment of patients with OSA in combination with metabolic and hormonal disorders it is important to prevent the development of pharyngeal collapse, to decrease of the sympathetic activity secondary to nocturnal hypoxemia, and to eliminate coarse fragmentation of sleep. It is necessary to break the vicious circle of vascular endothelial damage, to reduce cardiovascular risks, to normalize carbohydrate and lipid metabolism, and to restore adequate processes of energy metabolism and eating behavior of patients [48].

According to the results of several studies, respiratory support using different variants of masks in constant positive airway pressure (CPAP) mode is able to solve set tasks. Respiratory support is aimed at creating an air stent that counteracts the development of upper respiratory tract collapses (URT) and sleep apnea [49].

Unfortunately, the effect of CPAP therapy on metabolic syndrome remains little-understood. In most studies, there was a significant stabilization of blood pressure using CPAP [50]. In studies on the effects of CPAP therapy on insulin resistance and lipid profile conflicting results were reported. The choice of ventilation support modes, duration thereof and development of algorithms for complex treatment of patients with OSA and metabolic syndrome require further studies [51].

Conflict of interests

The authors declare no conflict of interests.

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CHRONIC HEPATITIS B AND C IN WOMEN: COURSE OF PREGNANCY, DELIVERY AND MORPHOLOGICAL CHARACTERISTICS OF THE PLACENTA

Abstract

Despite the widespread global prevalence of chronic hepatitis, the impact of these diseases on the pregnancy course and on delivery is still insufficiently studied. Recently, some studies have been published, discussing the relationship between the state of the placenta and the risk of the mother-to-child transmission of hepatitis. The objective of this work was to make a comparative analysis of the features of pregnancy in women with chronic hepatitis B and C (CHB and CHC, respectively), to evaluate the relationship between inflammatory changes in the placenta and the frequency of hepatitis markers detection in umbilical cord blood. In this work we present a retrospective analysis of randomly selected birth histories of women with chronic hepatitis, from the Maternity Hospital No. 16 in St. Petersburg. In total, 35 pregnant women with CHB and 36 pregnant women with CHC were included in this study. Exclusion criteria were co-infections, cirrhosis and severe concomitant diseases. The studied groups had no significant differences in age, weight and height, as well as in the number of pregnancies and deliveries in their medical history. According to the results of our study, there were no significant differences in the state of newborns of mothers with CHB and CHC. According to our data, anemia during pregnancy occurred significantly more frequently in women with CHB, than with CHC. It has been shown that in both groups, the choriodeciduitis was observed in almost a half of women. Remarkably, the frequency of premature rupture of membrane in both groups was significantly higher than the average in the population. In addition, a reliable relationship between inflammatory changes in the placenta and the detection of HBsAg in umbilical cord blood was revealed. This relationship suggests that in women with inflammatory changes in the placenta, the risk of hepatitis B vertical transmission may be higher.

Key words: *chronic hepatitis B and C, placenta, inflammatory changes*

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HBV — hepatitis B virus, HCV — hepatitis C virus, PRM — premature rupture of membranes, ERM — early rupture of membranes, CHB — chronic hepatitis B, CHC — chronic hepatitis C

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Introduction

Despite the progress made in recent years, chronic hepatitis B (CHB) and hepatitis C (CHC) remain a serious health problem. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection differs significantly between regions. The infection rate in pregnant women generally corresponds to the average infection rate in the population of this region.

In Europe the prevalence of HBsAg in pregnant women can range from 0.1 % in the Northwest to 1–4 % in the South. In the Russian Federation (RF) frequency of HBsAg in pregnant women was 0.5 % in 2015 [1].

The prevalence of HCV infection in pregnant women in Europe ranges from 1 to 2.5 % [2]. In Russia the detection rate of anti-HCV antibodies in pregnant women was 2.8 % in 2002 [3]. According to official statistics, in some regions of the Russian Federation the number of pregnant women with anti-HCV antibodies in the blood is now 3–5 times higher compared to 2000-2001. Currently, the examination for HBsAg and anti-HCV antibodies in the first and third trimesters of pregnancy is regulated by the order of the Ministry of Health of the Russian Federation No. 572n dated 1.11.2012 [4].

To date, the effect of pregnancy and childbirth on the course of CHB has not been sufficiently studied. It is believed that women usually tolerate pregnancy well with underlying CHB in the absence of cirrhotic remodeling of the liver. During pregnancy there are generally no exacerbations of CHB, cytolytic activity parameters are often normalized. In Russia, the course of CHB during pregnancy was studied only in some regions. A fairly detailed study was conducted in the Republic of Sakha (Yakutia) [5, 6]. It was shown that clinical manifestations of CHB in pregnant women were characterized by a predominance of asthenic-vegetative and dyspeptic syndromes (63 %). Hemorrhagic syndrome in the form of bleeding gums was observed in 15 % of women and hepatomegaly occurred in 10 % [7]. It is well known that when there is no specific immunologic prophylaxis, the risk of vertical HBV transmission from HBsAg-positive mothers can reach 90 % [8]. It has been shown that HBsAg easily overcomes the utero-placental barrier [9] and is often found in umbilical cord blood in children born to HBsAg-positive mothers. At the same time, HBsAg is not always found in the umbilical cord blood. The reasons why in some cases the placenta becomes permeable to HBsAg are not well understood. Recent studies have actively studied the relationship between HBV and HBsAg detection in the placenta and vertical HBV transmission rate [10, 11]. It has been shown that there is a statistically significant association between HBsAg detection in newborns and the presence of HBsAg in the placenta. There were significantly higher risks of infection transmission in the case of infection in cells of villous endothelium [11].

CHC infection in a woman usually does not have a significant impact on the course of pregnancy. There are studies indicating a higher incidence of gestational diabetes in HCV-infected women compared with HCV-negative women, but this trend is significantly more pronounced in women with excessive weight gain during pregnancy, while increased incidence of gestational diabetes was not observed in women with insufficient or adequate weight gain. Some authors note the relationship between the presence of CHC and premature rupture of membranes [12]. In addition, it was found that the presence of CHC in the mother is more often associated with the birth of low-weight children [12]. It has also been shown that children born to mothers with CHC are more likely to require mechanical ventilation [12]. However, there are certain difficulties in evaluation of the effect of CHC in the mother in particular, since in order to obtain reliable results the impact of other factors such as drug use has to be excluded. Recent studies in large groups of patients have shown that CHC increases the risk of premature birth, low birth weight, premature rupture of membranes, as well as the risk of gestational diabetes in the mother and birth defects in babies [12–16]. In addition, there are studies indicating that HCV infection in the mother may be associated with more frequent development of cholestasis in pregnant women [13, 15].

Large population studies have shown that there is a relationship between CHC in the mother and premature birth [13, 16]. However, it should be borne in mind that premature birth can be induced by other factors. In the study conducted by L. E. Connell et al. [13] a multivariate statistical analysis that included factors such as drug use, tobacco use, and

alcohol use was performed. In this study, it was shown that patients with CHC had a greater risk of premature birth [13]. In addition, the same study showed that children born to mothers with CHC are more likely to have lower birth weight and malformations. In a study conducted in New Mexico [15] premature birth (up to 37 weeks of gestation) was significantly more common in HCV-positive women (24.5 % vs. 14.9 %), but multivariate analysis showed that differences cease to be significant when excluding methadone use, smoking and previous premature birth in history.

In 2011, the results of a large population-based study conducted in the United States from 1998 to 2007 were published, and in this study the incidence of perinatal complications in women with and without CHB and CHC was analyzed [13]. Significant differences were demonstrated in the frequency of premature rupture of membranes with and without CHB. It was shown that gestational diabetes was significantly more likely to develop in women with CHB and CHC than without these infections. In addition, anemia during pregnancy is also more common in women with CHB and CHC. The incidence of anemia in pregnant women differs significantly in different countries. In Europe, according to WHO, anemia in pregnant women occurs in 18.6–31.6 % of cases, while in Africa this figure is 52.8–61.3 % [17]. At the same time, anemia in pregnant women in developed countries occurs on average in 14 %, while in developing countries this figure may be 59 % [18].

In full-term pregnancy premature rupture of membranes occurs in 2.7–17 % of cases [19]. At the same time, this figure is significantly higher in premature birth. Prenatal rupture of membranes accompanies preterm birth in up to 30–56 % of cases [19–21]. Premature rupture of membranes (PRM) is considered to be the rupture of membranes before birth regardless of the pregnancy period. Early rupture of membranes (ERM) is indicated in the case of rupture of the membranes after the beginning of delivery, but before the cervix is completely opened [22]. English-language literature has adopted the term premature rupture of membranes which combines both these concepts. In Russian-language literature, there are very little data on the incidence of this complication of pregnancy in women with chronic hepatitis.

Placental insufficiency is a syndrome that occurs in various diseases of the mother and fetus with manifestations in the form of molecular, cellular, tissue and organ disorders in the mother-placenta-fetus system. Placental insufficiency can be compensated, subcompensated and decompensated. The incidence of placental insufficiency in pregnant women with chronic hepatitis is insufficiently studied.

Inflammatory changes in the placenta are common in various diseases, but can also occur in apparently healthy women [23]. These changes may cause septic complications in the postnatal period in the mother, and they may also cause various pathological conditions in the newborn. Data on the frequency of histologically confirmed inflammatory processes in the placenta are contradictory: according to different authors, they are found in 5 % to 40 % of all full-term pregnancies.

Chronic deciduitis occurs in 15 to 41 % of cases [24], and is much more common in premature birth. According to Russian authors, choriodeciduitis is found in 21.7±2.4 % of timely birth cases [25]. The relationship between the presence of inflammatory changes in the placenta and vertical transmission rate is insufficiently studied. The objective of this work was to conduct a comparative analysis of pregnancy features in women with CHB and CHC, and to assess the relationship between inflammatory changes in the placenta and the frequency of detection of hepatitis markers in the umbilical cord blood.

Materials and methods

This study employed a retrospective analysis of randomly selected labor and delivery medical records of women who gave birth in the maternity hospital No. 16 in St. Petersburg (Chief Medical Officer — MD, prof. Shapkayts V. A.) in 2014–2015.

The study included 35 pregnant women with CHB (mean age of 30.46±1.53 years) and 36 pregnant women with CHC (mean age of 33.47±1.17 years). All women included in the study had a full-term pregnancy. All women underwent standard clinical and biochemical studies regulated by documents for pregnancy management. In addition, umbilical cord blood was tested for HBsAg in patients with CHB, and umbilical cord blood was

tested for anti-HCV antibodies in women with CHC. Blood sampling was carried out from the umbilical vein immediately after birth. The studies were conducted at the City Virology Diagnostic Center (Chief Medical Officer — Vashukova S. S., Can.Med.Sci.). For HBsAg detection, the HBsAg-confirming-ELISA-BEST reagent kit manufactured by Vector Best (sensitivity of 0.01 IU/ml) was used for immunoassay to confirm the presence of HBsAg. Anti-HCV antibodies in umbilical cord blood were determined using the reagent kit for immunoassay detection of anti-HCV immunoglobulins from G and M classes for automatic immunoassay analyzers Best anti-HCV-auto (manufacturer — Vector Best).

Assessment of fibrosis degree during pregnancy was not carried out (transient elastography is contraindicated, liver biopsy is undesirable, FibroTest is uninformative due to altered hormonal background). However, the women included in the study had no clinical signs of advanced stages of liver fibrosis.

Histological examination of the placenta was carried out in hospital No. 16.

The exclusion criteria were: co-infection with HIV, mixed hepatitis caused by CHB and CHC, co-infection with hepatitis Delta, premature birth, cirrhotic stage of chronic hepatitis, syphilis, clinically expressed diseases of the urogenital tract.

For assessment of the statistical significance of differences between groups for qualitative features, χ-square test was used, including Fisher's correction for small samples, and Mann-Whitney test was used for quantitative parameters. Differences were considered statistically significant with $p<0.05$.

Results

The clinical features of the examined women are presented in Table 1.

As shown in Table 1, examined patients with CHB and CHC had no significant differences in age, weight and height, the number of pregnancies and births in their history. Cesarean delivery was performed in 7 (20 %) women with CHB and in 1 (2.8 %) woman with CHC. The reasons for the operation in the group of pregnant women with CHB were: fetal hypoxia in 4 cases, myopia in the mother and/or large fetus in 3 cases. In the group of patients with CHC cesarean section was performed due to the presence of a scar on the uterus after previous cesarean section.

In the group of pregnant women with CHB only 4 (11.4 %) patients were HBsAg-positive. Data on viral load in pregnant women in the third trimester are presented in Table 2.

Pregnancy complications which were observed in examined women are presented in Table 3. The most common events were anemia, swelling in pregnant women and premature rupture of membranes.

Anemia during pregnancy was significantly more common in the group of women with CHB.

There were no statistically significant differences between the groups in the incidence of edema in pregnant women. In both groups, there was

Table 1. *Clinical characteristics of women with CHB and CHC in the studied groups*

Parameters	CHB n=35	CHC n=36	p
Height	164.97±1.69	163.89±1.62	0.33
Weight	77.63±5.92	73.09±4.15	0.83
Number of pregnancies	2.54±0.46	4.19±1.19	0.15
Number of births	1.74±0.28	1.97±0.28	0.25

Table 2. *Viral load in women with CHB and CHC in the third trimester of pregnancy*

	Median	1 quartile	3 quartile
CHB (IU/ml) n=18*	4,200	1,300	177,000
CHC (IU/ml) n=36	317,000	140,000	1,410,000

***** For 17 patients with CHB the data were not available.

Table 3. *Frequencies of the appearance of specific pregnancy complications*

Complication	CHB n=35	CHC n=36	p-value
Anemia	54.3% (19)	19.4% (7)	0.002*
Swelling during pregnancy	17.1% (6)	5.6% (2)	0.12
Premature rupture of membranes	42.9% (15)	55.6% (20)	0.29

***** Significant difference between the groups ($p<0.005$).

Table 4. *Main characteristics of newborns of mothers with CHB and CHC*

Parameters	CHB	CHC	p-value
Height	51.77±1.08	51.11±0.84	0.16
Weight	3,482±213.17	3,311.94±179.97	0.23
Apgar score (1 min)	7.57±0.2	7.58±0.2	0.94
Apgar score (5 min)	8.6±0.18	8.58±0.2	0.99

Table 5. *Relationship between inflammation in placenta and the HBsAg presence in umbilical cord blood*

	HBsAg+	HBsAg-	Total
Inflammation	14	6	20
No inflammation	3	12	15
Total	17	18	35

a significant incidence of premature and early rupture of membranes: 42.9 % — in the group with CHB and 55.6 % — in the group with CHC. There were no statistically significant differences between the groups in relation to this complication.

The duration of membrane rupture to delivery interval in the group with CHB was on average 411±242 min. In the group with CHC this parameter was 242±76 min. There were no significant differences in this parameter between groups.

The analysis of the state of newborns was carried out in the studied groups. There were no statistically significant differences in such parameters as height, weight, Apgar score (Table 4).

We studied the incidence of various inflammatory changes in the placenta of women with CHB and CHC. The examined women had the following inflammatory changes: choriodeciduitis, villitis, intervillositis, membranitis. Choriodeciduitis was the most common inflammatory process in placenta which was found in almost half of the women examined (48.6 % of women with CHB and 50 % of women with CHC). Other inflammatory changes in the placenta were significantly less common. There were no inflammatory changes in the placenta in 42.85 % of women with CHB and only in 33.3 % of women with CHC. There were no statistically significant differences between the groups in relation to any of these parameters.

The relationship between the presence of inflammatory changes in the placenta and HBsAg detection in umbilical cord blood was evaluated. The results are shown in Table 5.

For the data in Table 5 the value of $\chi 2$-test is 8.578, while the critical value of $\chi 2$ is 6.635 at the significance level of $p<0.01$. Thus, the relationship between the presence of inflammation in the placenta and the presence of HBsAg in umbilical cord blood is statistically significant at the significance level of $p<0.01$.

At the same time, anti-HCV antibodies were present in all umbilical cord blood samples taken from mothers with CHC regardless of the presence or absence of inflammatory changes in the placenta.

Results and discussion

Patients with CHB and CHC included in the study were comparable in terms of main clinical parameters (age, height, weight, number of pregnancies and births in history).

The results obtained in our study showed that anemia was significantly more common during pregnancy in women with CHB than in women

with CHC. It should be noted that no women included in the study had advanced stages of fibrosis, and therefore anemia could not be due to the severity of hepatitis. Thus, the mechanisms of anemia during pregnancy in women with CHB require further study.

Our data on the incidence of anemia during pregnancy in women with CHC are comparable with data on the incidence of anemia in pregnant women in European countries. At the same time, our study showed that anemia during pregnancy was significantly more common in women with CHB. This result is consistent with the data obtained by L. E. Connell et al., which also showed statistically significant differences ($p<0.0001$) in the frequency of anemia during pregnancy in women with and without CHB [13].

In this study, there were no significant differences in the incidence of swelling in pregnant women in the study groups.

The results obtained in this study indicate that the frequency of premature rupture of membranes in women with CHB and CHC did not differ significantly. It should be noted that the frequency of this pregnancy complication is significantly higher in the study groups than in the general population. This is consistent with the claims of other authors who noted the relationship between the presence of CHC in the mother and premature rupture of membranes [12]. In CHB, a higher rate of premature rupture of membranes was also recorded compared to patients without CHB ($p=0.01$) [13].

There were no significant differences in the status of newborns from mothers with CHB and CHC in the study groups. Newborns in the study groups did not differ in terms of such parameters as height and weight. Some studies have shown that the presence of CHB in the mother leads to the birth of children with lower Apgar scores [26, 27]. In this study, Apgar score at the first and fifth minutes did not have significant differences in the groups, and it was quite high. In addition, some studies [12, 13] indicate that the presence of CHB or CHC in the mother may lead to the birth of children with lower body weight, but the present study did not confirm this.

In a recent study, it was shown that the incidence of placental insufficiency in women with CHB and CHC is significantly higher than in women without hepatitis [28]. In the present study, it is shown that chronic compensated placental insufficiency was the most common in both groups. Conspicuous is the fact that a fully compensated placenta was identified only in 4 women with CHB and in none of the women with CHC.

This study also showed that there was a statistically significant relationship between the presence of inflammation in the placenta and the presence of HBsAg in the umbilical cord blood ($p<0.01$). The presence of any inflammatory process in the placenta leads to altered permeability, which in turn can increase the risk of vertical infection transmission.

Conclusions

1. Anemia during pregnancy was significantly more frequent in women with CHB than in women with CHC.
2. There were no significant differences in the rate of premature rupture of membranes between the study groups, but in both groups it was significantly higher than the average in the population.
3. There was a significant relationship between the presence of inflammatory changes in the placenta and HBsAg detection in umbilical cord blood. This relationship suggests that women with inflammatory changes in the placenta may have a higher risk of vertical HBV transmission.

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Conflict of interests

The authors declare no conflict of interests.

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THE EFFECTIVENESS OF PRECONDITIONING AND POSTCONDITIONING WITH ADENOSINE IN PREVENTION OF REPERFUSION DAMAGE IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Abstract

The study aimed to evaluate the effectiveness of pharmacological pre-conditioning and post-conditioning with sublingual adenosine in prevention of reperfusion damage in patients with acute myocardial infarction with ST-segment elevation (STEMI). **Material and methods.** In our prospective trial 166 patients with STEMI were randomized to the group of sublingual adenosine administration prior and after percutaneous coronary intervention (n=82) or to the group of standard therapy (n=84). Reperfusion arrhythmia, blood level of troponin T and effectiveness of reperfusion was assessed. **Results.** According to PCI results, angiographic success was achieved in 88.1 % patients of adenosine group and in 92.7 % patients of standard therapy group ($p > 0.05$). The reperfusion arrhythmias rate was significantly low in adenosine group (78 %) compared to the control (92.9 %, $p = 0.013$). The use of adenosine was associated with 25.4 % reduction of life-threatening reperfusion arrhythmias risk ($p < 0.01$). In 24 h after PCI, troponin T level decreased in both groups, more significantly in the group of adenosine administration ($p < 0.05$). The use of adenosine was associated with 8.3 % reduction of myocardial reperfusion damage risk ($p < 0.05$). **Conclusions.** The pharmacological pre-conditioning and post-conditioning with sublingual adenosine in the perioperative period of PCI in patients with STEMI is useful to prevent myocardial reperfusion damage but does not affect the efficiency of reperfusion.

Key words: *acute myocardial infarction, pharmacological pre-conditioning, adenosine, reperfusion damage*

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STEMI — acute myocardial infarction with ST-segment elevation, PCI — percutaneous coronary intervention

Early reperfusion strategy is currently, the cornerstone in the management of patients with acute myocardial infarction with ST-segment elevation (STEMI) [1]. Timely and successful revascularization of the infarct-related artery is the key to limiting the size of cardiac muscle necrosis, slowing down the processes of its remodeling and improving further prognosis [2]. At the same time, the sudden resumption of perfusion in the ischemic area of the myocardium can lead to further damage of the cardiac muscle, decreased contractile function and the onset of life-threatening arrhythmias [3]. In recent years, such adverse effects of intracoronary interventions have been referred to as small myocardial lesions [3, 4]. These lesions generally do not have any specific clinical signs and are

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diagnosed with an increased level of cardiospecific enzymes or the occurrence of severe reperfusion rhythm disturbances.

Effective methods of prevention of myocardial reperfusion injuries have not yet been developed, and clinical studies in this area are isolated. One of the most promising directions in the prevention of the above complications is considered to be the pharmacological protection of the myocardium using adenosine, which is based on the phenomena of pre- and post-conditioning [5]. In some studies, intravenous adenosine administration along with thrombolytic therapy or percutaneous coronary intervention (PCI) led to reduced volume of necrotic myocardium and decreased size of the perfusion defect in patients with acute myocardial infarction [6]. However, intravenous use of adenosine is limited by the complexity of dosing and the need for careful monitoring of hemodynamic parameters, and its efficacy is limited by the rapid degradation of the drug in the bloodstream. Therefore, it is important to search for substances similar to adenosine, but with a more favorable pharmacokinetic profile.

The objective of this study was to evaluate the efficacy of pharmacological pre- and post-conditioning with adenosine-containing drug Advocard in the prevention of reperfusion myocardial damage in patients with STEMI subject to primary PCI.

Materials and methods

A prospective open-label study was conducted involving 166 patients admitted to the Department of Emergency Cardiology, Institute of Emergency and Reconstructive Surgery n.a. V. K. Husak with a diagnosis of STEMI. The inclusion criteria were:

1) age over 18 years;
2) STEMI of the 1st type with duration of less than 12 hours;
3) planned urgent myocardial revascularization by means of PCI;
4) signed informed consent.

STEMI was diagnosed if the patient had an episode of angina in combination with persistent (lasting at least 20 min) ST-segment elevation or new left bundle branch block on the electrocardiogram (ECG) and elevated levels of myocardial injury biomarkers. ST-segment elevation was considered to be significant in terms of ischemia at least in two consecutive leads, if its value at J-point level was ≥ 0.2 mV in men or ≥ 0.15 mV in women in V2–V3 leads and/or ≥ 0.1 mV in other leads.

The exclusion criteria were:

1) use of thrombolytic therapy for myocardial revascularization;
2) conducting PCI procedures before the beginning of the study;
3) myocardial infarction of type 2, 3, 4A, 4B, 5 according to the Third universal definition of myocardial infarction;
4) cardiogenic shock;
5) uncontrolled hypertension (systolic blood pressure ≥ 160 mm Hg);
6) hemodynamically significant bradyarrhythmia (sinus bradycardia with < 55 beats/min > 10 min; atrioventricular block of the 2nd or 3rd degree);
7) permanent atrial fibrillation;
8) implanted pacemaker;
9) history of coronary artery bypass grafting;
10) use of adenosine-containing drugs for the last 30 days;
11) severe asthma;
12) use of sildenafil citrate;
13) severe decompensated comorbidities;
14) pregnancy;
15) alcohol and drug abuse;
16) participation in another clinical trial within the previous 30 days.

The patients were divided into 2 groups by envelope method: the first group included 84 patients in whom PCI was performed with standard therapy without pharmacological protection of the myocardium by triggers of ischemic pre- and post-conditioning; the second group consisted of 82 patients who, for initiation of pharmacological pre- and post-conditioning before performing PCI, were administered sublingually adenosine-containing drug Advocard using the following regimen: 1 tablet, after 30 minutes — 2 tablets, followed by 1 tablet 3 times a day with an interval of 8 hours for 4 weeks. Patients in both groups were administered

a standard drug therapy of STEMI (angiotensin converting enzyme inhibitors, β-blockers, statins, antithrombotic agents, if necessary, nitrates, narcotic analgesics) in accordance with current recommendations.

The efficacy of reperfusion, presence and severity of reperfusion arrhythmias, changes in blood troponin T levels were evaluated in all patients.

Immediate angiographic success was defined as complete (TIMI 3) restoration of blood flow in infarct-related artery in the absence of dissections and thrombosis. The phenomenon of "no-reflow" was defined as the lack of adequate myocardial perfusion after recanalization (TIMI < 3). In addition to TIMI blood flow, a marker of successful reperfusion was also considered to be positive dynamics of the ST-segment on the ECG, which was defined as a decrease in ST-segment height by ≥ 70 % from the baseline in 60 min after intervention. ECG reflection of "no-reflow" phenomenon was considered to be the absence of reduction of ST-segment elevation corresponding to the criteria of successful reperfusion with satisfactory (TIMI 2–3) blood flow through the main infarct-related artery.

The presence and type of reperfusion arrhythmias were assessed using continuous ECG monitoring for 24 hours after PCI using Horizon XVU hemodynamic monitoring device (Mennen Medical, Israel). Analysis of rhythm and conductivity changes was performed according to the classification of Goldberg and Vita, wherein life-threatening disorders included complete atrioventricular block, paroxysmal ventricular tachycardia, fibrillation, flutter and ventricular pause.

Blood troponin T level was determined twice: at baseline, before PCI and in 24 h after intervention by electrochemiluminescence method with immunochemical analyzer Cobas 6000 (e 601 module) using test-system TNT-HS Roche Diagnostics (Germany).

Processing was performed on a personal computer using Microsoft Excel and statistical analysis software packages MedStat and Statistica 6.0. χ^2 and Shapiro-Wilk W tests were used to check the distribution for normality. At normal distribution the quantitative characteristics were presented as mean ± standard deviation (m ± σ), in a case other than normal distribution — as median and 1st, 3rd quartiles (Me (Q1; Q3)). For comparison of two samples of continuous variables subject to the normal distribution law, paired and unpaired Student's t-tests were used while the Wilcoxon test was used for other distribution than normal one. We used the standard method of analysis of contingency tables using the χ^2 criterion to study the distribution of discrete features in different groups and to compare relative values. The reduction of the absolute risk of events was determined with a 95 % confidence interval (CI). Fisher's angular transformation was used for its calculation. In all cases of hypothesis testing, the differences were considered significant at $p < 0.05$.

The study was conducted in accordance with international GCP standards. The study protocol and informed consent form for patients were approved by the local Ethics Committee, Institute of Emergency and Reconstructive Surgery n.a. V. K. Husak (minutes of meeting No. 14 dated 23.09.2013).

Results and discussion

Initially, both groups of patients were comparable in relation to the main clinical and demographic characteristics: gender, age, severity of cardiac pathology and comorbidities (Table 1).

The time from the onset of the episode of angina to hospitalization was on average 4.5 (2; 6) hours in group 1 and 5 (2; 7) hours in group 2 ($p > 0.05$). Time from the moment of hospitalization to revascularization (door-to-balloon) did not exceed 60 minutes in both groups. There were no significant differences in the initial angiographic characteristics of patients between the groups (Table 2).

According to the results of PCI, direct angiographic success was achieved in 88.1 % of patients in group 1 and 92.7 % of patients in group 2 ($p > 0.05$). "No-reflow" phenomenon in PCI outcome was found in 11.9 % of patients in group 1 and 7.3 % in group 2, but the differences in frequency did not reach statistical significance (Table 3).

Table 1. *Patients' initial clinical characteristics*

Characteristic	Group 1 (n=84)	Group 2 (n=82)
Age, years, m±σ	54.0±7.2	52.6±6.9
Males, number of patients (%)	71 (84.5)	68 (82.9)
BMI, kg/m^2, m±σ	29.4±2.8	28.8±2.4
Smoking, number of patients (%)	52 (61.9)	48 (58.5)
Hypertension, number of patients (%)	74 (88.1)	70 (85.4)
Diabetes mellitus, number of patients (%)	16 (19.0)	13 (15.9)
Renal dysfunction, the number of patients (%)	32 (38.1)	40 (48.8)
Dyslipidemia, the number of patients (%)	70 (83.3)	69 (84.1)
Previous cerebral circulation disorders, number of patients (%)	8 (9.5)	6 (7.3)
Previous MI, the number of patients (%)	15 (17.9)	15 (18.3)
Previous PCI, the number of patients (%)	7 (8.3)	8 (9.8)
Preinfarction angina, number of patients (%)	51 (60.7)	43 (52.4)
LV EF, %, Me (Q1; Q3)	42 (40; 46)	43 (40; 46.5)
Time from symptoms onset to admission, h, Me (Q1; Q3)	4.5 (2; 6)	5 (2; 7)
Time from admission to revascularization (door-to-balloon), min, Me (Q1; Q3)	45 (30; 45)	45 (30; 45)
MI localization, number of patients (%):		
Anterior	44 (52.4)	46 (56.1)
Posterior	38 (45.2)	35 (42.7)
Apical	2 (2.4)	1 (1.2)
Killip class, number of patients (%):		
I	62 (73.8)	57 (69.5)
II	18 (21.4)	20 (24.4)
III	4 (4.8)	5 (6.1)

Note: BMI — body mass index, EF — ejection fraction, LV — left ventricular, MI — myocardial infarction, PCI — percutaneous coronary intervention. All differences are not statistically significant (*Ps* > 0.05).

Table 2. *Patients' initial angiographic characteristics*

Characteristic	Group 1 (n=84)	Group 2 (n=82)
Infarct-related artery, number of patients (%):		
Left main coronary artery	1 (1.2)	0
Left anterior descending artery	40 (47.7)	43 (52.4)
Circumflex artery	5 (5.9)	4 (4.8)
Right coronary artery	35 (41.8)	32 (39.0)
Diagonal arteries	1 (1.2)	0
Left marginal artery	2 (2.4)	2 (2.4)
Intermediate artery	0	1 (1.2)
Type of coronary system damage, number of patients (%):		
Single-vessel	35 (41.7)	38 (46.3)
Two-vessel	21 (25)	24 (29.3)
Multivessel	28 (33.3)	20 (24.4)

Note: all differences are not statistically significant (Ps > 0.05).

Table 3. *PCI results*

Characteristic	Group 1 (n=84)	Group 2 (n=82)	Differences between groups
PCI duration, min, Me (Q1; Q3)	60 (50; 70)	60 (50; 75)	p=0.978
Drug-eluting stents, number of patients (%):	12 (14.3)	9 (11)	χ^2=0.17, p=0.684
Nondrug-eluting stents, number of patients (%):	72 (85.7)	73 (89)	χ^2=0.17, p=0.684
Immediate angiographic success, number of patients (%):	74 (88.1)	76 (92.7)	χ^2=0.55, p=0.461
Phenomenon "no-reflow", number of patients (%):	10 (11.9)	6 (7.3)	χ^2=0.55, p=0.461

Note: PCI — percutaneous coronary intervention.

Analysis of changes in ECG also showed no significant differences in the incidence of rapid positive dynamics in ST-segment between the two groups (89.3 % in group 1 vs. 92.7 % in group 2, χ^2=0.24, p=0.623). Thus, the use of adenosine did not have a significant impact on the efficacy of reperfusion in patients with STEMI subject to primary PCI.

One of the myocardial reperfusion injury markers is various arrhythmias that occur in the first hours after the restoration of blood flow in the infarct-related artery. Reperfusion cardiac arrhythmias are often classified as life-threatening, and can be fatal sometimes. In this regard, one of the objectives of our study was to assess the effect of adenosine on reperfusion arrhythmogenesis in the study cohort of patients.

Initially, there were no significant differences in heart rate (HR) between the groups. The median heart rate before PCI in group 1 was 80 [62; 106] min^{-1}, in group 2 it was 78 [68; 110] min^{-1}; after the procedure — 66 [58; 76] min^{-1} and 64 [56; 80] min^{-1}, respectively (p > 0.05). Differences were found in maximum heart rate after PCI: this figure was significantly higher in group 1 (110 [98; 118] min^{-1}) compared to group 2 (101 [90; 106] min^{-1}, p=0.02).

In general, various disorders of rhythm and conduction before PCI were reported in 33 (39.3 %) patients of group 1 and in 28 (34.1 %) in group 2 (χ^2=0.28, p=0.6). During 24 h after PCI their frequency was significantly higher in group 1 (92.9 %) compared to group 2 (78 %) (χ^2=6.21, p=0.013).

In the analysis of the frequency of prognostically unfavorable arrhythmias it was found that in the adenosine group sinus tachycardia with a heart rate > 110 min^{-1} (51.2 % vs. 71.4 %), frequent group and polytopic ventricular extrasystoles (39 % vs. 70.2 %) and idioventricular rhythm (19.5 % vs. 34.5 %, all p < 0.05) developed significantly less frequently.

The prevalence of life-threatening arrhythmias was almost twice lower in group 2 (31.7 %) compared to group 1 (57.1 %) (χ^2=9.86, p=0.002). When analyzing certain types of arrhythmia it was found that patients receiving adenosine rarely experienced paroxysmal ventricular tachycardia (34.1 % of patients, p < 0.05), while in all cases it was monomorphic and unstable. In the comparison group, episodes of ventricular tachycardia were reported in 51 (60.7 %) patients, two of them (2.4 %) experienced torsade de pointes which transformed into ventricular fibrillation. Ventricular fibrillation in the first day after PCI was not reported in the adenosine group, in contrast to the control group, in which it developed in two patients. However, these differences did not reach statistical significance. There were no asystolic episodes in any of groups.

Thus, the use of adenosine was associated with decrease of the frequency of life-threatening reperfusion arrhythmia by 25.4 % (95 % CI 10.3 to 39.0 %, p < 0.05), while in the case of ventricular tachycardia episodes it had the type of monomorphic arrhythmia and was unstable.

We carried out a comparative assessment of the levels of myocardial necrosis biomarker troponin T before and after PCI in two groups. Initially, the concentration of troponin T in the blood did not differ significantly between the groups. One day after PCI its level significantly decreased in both groups, and more significantly — in the 2nd group (Table 4).

Table 4. *Troponin T level before and after PCI, pg/ml, Me (Q1; Q3)*

Characteristic	Group 1 (n=84)	Group 2 (n=82)	Differences between groups
Before PCI	684 (528; 896)	698 (516; 921)	p=0.96
After PCI	264 (128; 356)	168 (105; 286)	p<0.001

Note: PCI — percutaneous coronary intervention.

Four (4.8 %) patients in the 1st group and 1 (1.2 %) patient in the 2nd (χ^2=0.78, p=0.379) reported an increase in troponin T titer by more than 20 % from baseline, which met the criteria for the diagnosis of myocardial infarction of type 4A (PCI-related) in combination with the phenomenon of delayed contrast enhancement of the infarct-related artery and the absence of positive ECG dynamics in these patients. There was no significant decrease in the troponin T level compared to the baseline in 8 (9.5 %) patients in group 1 and 1 (1.2 %) patient in group 2 (χ^2=4.08, p=0.043) 24 h after PCI. However, due to the absence of other clinical, electrocardiographic and angiographic signs of persistent or increasing myocardial ischemia, this finding was regarded as a marker of minor myocardial damage caused by reperfusion.

Thus, the results of the study indicate the presence of infarct-limiting properties in adenosine-containing drug Advocard: its use as an inducer of pre-and post-conditioning is associated with a more pronounced positive dynamics of troponin T levels after PCI and decrease in the risk of reperfusion myocardial damage by 8.3 % (95 % CI 1.2 to 16.5 %, p < 0.05).

The results may be due to increased myocardial resistance to acute anoxia as a result of the beginning of pharmacological pre- and post-conditioning processes initiated by adenosine. It is known that endogenous adenosine production is triggered in conditions of acute ischemia and reperfusion [7]. Currently, four types of adenosine receptors are found on the surface of cardiomyocytes: A1, A2A, A2B and A3. Experimental studies have shown that activation of all four types of receptors is accompanied by the restriction of the necrotic zone and improvement of myocardial function recovery after acute ischemia [8].

The positive effect of adenosine on reperfusion arrhythmogenesis seems to be due to increased electrical stability of the myocardium due to the initiation of endogenous cardioprotection processes. Stimulation of specific adenosine receptors on the surface of cardiomyocytes by the drug leads to the activation of numerous links of the enzymatic cascade focused on implementation of protective mechanisms. The most well-known end points of adenosine-mediated cardioprotection are the opening of ATP-dependent mitochondrial potassium channels and the closure of specific ion channels of the inner mitochondrial membrane. The consequence of these processes is the maintenance of ATP reserves, prevention of cardiomyocyte membrane damage by reactive oxygen intermediates, reduction of intracellular calcium overload, stimulation of nitrogen oxide synthesis and decrease of endothelial dysfunction, which ultimately contributes to the improvement of electrophysiological properties of cardiomyocytes and the prevention of reperfusion arrhythmias [9].

Conclusions

1. The use of adenosine-containing drug Advocard as a trigger of ischemic pre- and post-conditioning in the perioperative period of PCI in patients with STEMI is associated with a significant (p < 0.05) reduction in the risk of myocardial reperfusion damage by 8.3 % (95 % CI 1.2 to 16.5 %) and a decrease in the incidence of life-threatening reperfusion arrhythmias by 25.4 % (95 % CI 10.3 to 39.0 %).

2. The use of pharmacological pre-conditioning with Advocard in the perioperative period of primary PCI does not significantly affect the efficacy of reperfusion and the frequency of the “no-reflow” phenomenon.

Conflict of interests
The authors declare no conflict of interests.

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FORECASTING CORONARY EVENTS BASED ON THE ANALYSIS OF THE DYNAMICS OF MORPHOFUNCTIONAL PARAMETERS OF THE CARDIOVASCULAR SYSTEM IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN THE NORTH

Abstract

Modern science has relatively recently identified chronic obstructive pulmonary disease (COPD) as an independent nosologic unit. COPD along with cardiovascular diseases (CVD) makes up the major group of the socially significant chronic diseases and is one of the most urgent medical and social issues in pulmonology.

The **objective of the study** was to determine the possibility of predicting and early diagnosis of ischemic heart disease in patients with chronic obstructive pulmonary disease living in the North on the basis of evaluation of morphofunctional parameters of the cardiovascular system.

Materials and methods. During the prospective five-year observation, an extended instrumental examination of 182 patients with chronic obstructive pulmonary disease was performed to identify the five-year dynamics of the morphofunctional parameters of the cardiorespiratory system at various levels of coronary risk taking into account gender differences. In 66 patients (mean age 64.0 ± 1.1 years) (comparison group), nonfatal coronary events were registered during the observation.

The conclusion. 1. In the North, cardiac remodeling in patients with chronic obstructive pulmonary disease includes changes in the right chambers due to persistent obstructive disorders and a decrease in pulmonary volumes, as well as an enlargement of left chambers, a decrease in myocardial contractility, and progressive left ventricular hypertrophy. 2. In the course of prophylaxis in case of outpatient examination of patients with chronic obstructive pulmonary disease, it is necessary to determine the criteria for predicting high and very high coronary risks according to the formula d = 0.000108 (Systematic Coronary Risk Evaluation × "Northern Experience" × frequency of exacerbations of chronic obstructive pulmonary disease × end-diastolic dimension of the left ventricle (mm) × systolic blood pressure in the pulmonary artery (mm)) for women and d = 0.000078 (Systematic Coronary Risk Evaluation × frequency of exacerbations of chronic obstructive pulmonary disease × end-diastolic dimension (mm) × expiratory reserve volume (%)) for men. A high and very high risk can be determined at d≥ 27.5 for women; and at d≥ 16.2 for men.

Key words: *chronic obstructive pulmonary disease, coronary risk, ischemic heart disease, comorbidity.*

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SCORE — Systematic Coronary Risk Evaluation, BP — blood pressure, Ao — aortic diameter, IC — inspiratory capacity, VC — vital capacity of lungs, PW_{LV} — posterior wall of the left ventricle, IHD — ischemic heart disease, PA — pulmonary artery, LV — left ventricle, IVS — interventricular septum, MEF — maximum expiratory flow, FEV_1 — forced expiratory volume in 1 second, PEF — peak expiratory flow, ERV — expiratory reserve volume, SPAP — systolic pulmonary arterial pressure, CVD — cardiovascular diseases, SV — stroke volume, EF_{LV} — ejection fraction of the left ventricle, FVC — forced vital capacity of lungs, COPD — chronic obstructive pulmonary disease, ECG — electrocardiogram

Introduction

Modern science has relatively recently identified chronic obstructive pulmonary disease (COPD) as an independent nosologic unit. COPD along with cardiovascular diseases (CVD) makes up the major group of the socially significant chronic diseases and is one of the most urgent medical and social issues in pulmonology [1, 2].

Currently, the problem of COPD and CVD comorbidity is becoming extremely relevant. It has been established that the main cause of lethality in patients with COPD is not only respiratory failure, but also CVD [3, 4, 5]. Patients suffering COPD are at 2 to 3 fold higher risk of cardiovascular mortality [6]. And this risk is 5 to 6-fold higher in the northern regions [7] and contributes approximately 50% of the total number of deaths [6]. Chronic obstructive pulmonary disease and ischemic heart disease (IHD) are considered to be mutually aggravating and often concomitant diseases: 62% of elder patients with COPD suffer IHD [8]. Based on the Systematic Coronary Risk Evaluation score (SCORE), every second patient (47.6%) is at very high coronary risk, a high coronary risk is observed in every eighth patient (12.7%) and a moderate risk is observed in 33.6% of patients among patients with COPD [9, 10]. Therefore, early diagnosis of IHD in COPD patients remains relevant. However, it is complicated due to similarity of the symptoms, low diagnostic value of routine electrocardiogram (ECG) examination, peculiarities of clinical signs when one disease leaves another in "the shadow" [11, 12]. It is considered relevant to search for more distinct CVD risk markers in patients with COPD. The detection of such risk at the early stage of CVD before the cardiovascular accident occurs shall be considered one of the issues of predictive diagnostics [13].

Current literature data are contradictory concerning myocardial remodeling in isolated COPD and insufficient concerning peculiarities of cardiovascular dysfunction development in case of cardiorespiratory impairment. They do not reflect issues of cardiorespiratory impairment relation with systemic inflammation and endothelial dysfunction; insufficiently cover data on clinical outcomes and early markers of cardiovascular accident development in patients suffering COPD. Thus, further studies are required.

The objective of the study was to identify the possibility of prediction and early diagnosis of IHD in patients with COPD in the North based on the evaluation of morphofunctional parameters of the cardiovascular system.

Materials and Methods

In the course of a prospective five-year observation, an extended instrumental examination of 182 patients with COPD was performed in order to identify a five-year trend of morphofunctional parameters of the cardiorespiratory system at different levels of coronary risk while taking into consideration gender differences. During the period of observation, non-fatal coronary events (IHD) were registered in 66 patients (mean age (64.0 ± 1.1) years) (Table 1). Among 116 patients making up the main study group, we examined 20 females (mean age (55.4 ± 2.8) years) and 96 males (mean age (61.8 ± 1.0) years) ($p = 0.140$). In the control group of 66 patients the male to female ratio was 10:1: 60 males (mean age (64.0 ± 1.2) years) and 6 females (mean age (75.0 ± 0.9) years) ($p = 0.005$). Based on the five-year trend results of the cardiac remodeling in patients suffering isolated COPD and COPD registered at the time of IHD observation, we detected predictors of coronary events. Echocardliography and spirometry were performed at the beginning of the study and five years later.

An inclusion criterion was the presence of confirmed COPD (Global Initiative for Chronic Obstructive Lung Disease ((GOLD) 2014). Exclusion criteria

Table 1. *Clinical characteristics of patients*

Parameter	COPD n=116	IHD + COPD n=66	ρ-value	χ^2
Men	96	60	ρ=0,761	χ^2=0,092
Women	20	6	ρ=0,271	χ^2=1,214
Mean age, years	60,7±1,00	64,0±1,18	**ρ=0,040**	
Duration of COPD, years	8,83±0,61	8,59±1,40	ρ=0,857	
«North» experience, years	30,9±1,47	33,81±3,86	ρ=0,407	

Note: the reliability of the differences by criterion χ^2

were: IHD at the time of the beginning of the study, concomitant diseases of the respiratory system, cancer and hematologic diseases, end-stage kidney or liver failure, congestive heart failure of functional classes 3 and 4, and diabetes mellitus types 1 and 2. The study used data of patients' medical history. In all patients with COPD, complaints were assessed using the survey method, which makes it possible to identify the leading clinical syndromes, as well as the age, duration of COPD and smoking status. This information was obtained during history taking. The history of smoking was evaluated for each patient as a present or absent factor. Presence of this risk factor implied smoking at least one cigarette a day. The clinical examination included blood pressure (BP) assay as well as the evaluation of the degree of manifestation of major clinical syndromes of COPD and IHD by means of physical examination. General (complete blood count) and biochemical (total cholesterol, lipid profile) tests were performed. Instrumental examination methods included ECG, spirometry, echoCG, and plain X-ray of the chest. EchoCG parameters were obtained using Vivid 7 Pro ultrasound system (USA) in M- B- and Doppler modes using 3.5 mHz transducers following the standard procedure and taking into consideration the guidelines of the American Society of Echocardiography [14]. The standardized study included patients with satisfactory visualization of cardiac structures. We determined linear dimensions of the right atrium (RA, mm), right ventricle (RV, mm), left atrium (LA, mm), end diastolic dimension of the left ventricle ($EDD_{LV,}$ mm), end systolic dimension of the left ventricle ($ESD_{LV,}$ mm), end diastolic volume of the left ventricle ($EDV_{LV,}$ mm) and end systolic volume of the left ventricle ($ESV_{LV,}$ mm). Systolic and diastolic volumes were calculated using Simpson's method of discs.

The following systolic function parameters of the left ventricle were determined: stroke volume (SV, ml) and ejection fraction of the left ventricle (EF_{LV}, %). SV was calculated by blood flow velocity integral in the LV outflow tract. EF_{LV} was calculated as a percentage ratio of SV_{LV} to $EDV_{LV.}$ We determined the diameter of ascending aorta (Ao, mm) and diameter of the pulmonary artery (PA, mm), area of the aortic valve ($S_{AV,}$ cm^2), blood flow velocity at the aortic valve ($V_{AV,}$ $m•s^{-1}$), peak pressure gradient at the aortic valve ($P_{AV,}$ mm Hg), area of the mitral valve ($S_{MV,}$ cm^2), blood flow velocity at the mitral valve ($V_{MV,}$ $m•s^{-1}$), peak pressure gradient at the mitral valve ($P_{MV,}$ mm Hg), area of the tricuspid valve ($S_{TV,}$ cm^2), blood flow velocity at the tricuspid valve ($V_{TV,}$ $m•s^{-1}$), peak pressure gradient at the tricuspid valve ($P_{TV,}$ mm Hg), blood flow velocity at PA valve ($V_{PA,}$ $m•s^{-1}$), peak pressure gradient at PA valve ($P_{LA,}$ mm Hg), and systolic pressure in PA (SPAP, mm Hg). We measured thickness of the interventricular septum (IVS, mm), thickness of the left ventricle posterior wall ($PV_{LV,}$ mm).

We evaluated parameters of the respiratory function using spirometry and bronchial challenge test software of the Jager Master Lab diagnostic complex (Germany). The following parameters were measured: vital capacity of lungs (VC, l; %); forced VC (FVC, l; %); forced expiratory volume per 1st second ($FEV_{1,}$ l; %); Tiffeneau index (FEV_1/VC, %); maximum expiratory flow rate at level of 25%, 50% and 75% from the forced vital capacity of the lungs — MEF_{25}, MEF_{50} and MEF_{75} (l/s; %); inspiratory capacity (IC, l; %); expiratory reserve volume (ERV, l; %); peak expiratory flow rate (PEF, l/s; %) i.e. maximum air flow rate achieved in the process of expiration. Based on the guidelines of the European Respiratory Society, the obstruction degree and dynamics were evaluated based on FEV_1. During general clinical examination, all

the patients underwent X-ray of the chest in frontal view performed via Siemens Multix Pro system (Germany).

The obtained data were systematized using the Microsoft Excel 2007 spreadsheet package, and statistical calculations were made using the IBM SPSS Statistics 22 software package. Student's t-test was used to evaluate differences between the groups. The sampling was tested for normal data distribution using Kolmogorov-Smirnov's test. We used c^2 Pearson's *z*-test to analyze contingency tables. The differences were considered significant at $p < 0.05$. The contribution of the factors to the risk of coronary accident development was determined using multifactor analysis: a cluster analysis based on classification tree construction and K-means as well as a factor analysis of the principal components. We used a stepwise discriminant analysis to predict cardiovascular events. The grouping factor was $EDD_{LV.}$ In 82% of cases the grouped initial observations were classified correctly when predicting coronary risk for males. The same was true in 76% of cases for females.

Results and Discussion

It is known that cardiovascular diseases are observed more frequently as the bronchial obstruction progresses. The cohort of the studied patients included patients with moderate bronchial obstruction (54%, n = 62, 95% CI 51.3 to 56.6% (study main group); 50%, n = 33, 95% CI 48.3 to 56.7% (control group) ($p > 0.05$)), whose number was 6-fold higher than the number of patients experiencing the extremely severe disease (8.6%, n = 10, 95% CI 6.9 to 10.5% (study main group); 7.3%, n = 5, 95% CI 4.2 to 9.4% (control group) ($p > 0.05$)) ($p < 0.001$). The smallest percentage of the patients had mild course of the disease (4.2%, n = 5, 95% CI 2.9 to 5.5%) (main group); 3.8%, n = 3, 95% CI 1.8 to 4.4%) (control group) ($p > 0.05$). Every third of the studied patient had severe disease (33.2%, n = 39, 95% CI 30.2 to 36.2% (study main group); 38.9%, n = 25, 95% CI 34.2 to 39.3% (control group)) ($p > 0.05$). Thus, the bronchial obstruction degree was comparable in the study groups (Table 2).

The rate of the systemic hypertension occurrence in the chronic pulmonary patients varies from 4.0 to 38.8% [4] and even increases two-fold in combination with IHD. Based on the results of the in-office measurements, every second COPD patient from the main group had an increase in BP correspondent to hypertension (n = 59, 51.2%). This parameter was comparable with the control group (n = 40, 60%) ($p > 0.05$), which is correspondent to general population level. Mean BP value was (128.7 ± 1.51) mm Hg in the main group and (132.72 ± 1.63) mm Hg in the control group ($p > 0.05$). Thus, the hypertension occurrence rate was the same in the main group and the control group.

Table 3 presents EchoCG parameters in groups of COPD patients and in groups of COPD patients with confirmed IHD at the study onset.

Differences are found in the values of the pressure gradient at AV ($p = 0.005$), blood flow rate and pressure gradient at MV ($p = 0.001$). These differences were significant in patients with confirmed

Table 2. *Respiratory function parameters in patients with COPD and COPD + IHD diagnosed during the study (M±m)*

Parameters	Patients with COPD n=116	Patients with IHD and COPD n=66
VC, l	3.09 ± 0.11	2.89 ± 0.09
VC, %	81.82 ± 2.53	78.14 ± 2.86
FVC, l	2.83 ± 0.10	2.60 ± 0.09
FVC, %	76.09 ± 2.35	73.02 ± 2.93
FEV_1, l	2.21 ± 0.48	1.33 ± 0.08
FEV_1, %	50.79 ± 2.13	47.72 ± 2.76
Tiffeneau index, %	61.43 ± 1.73	58.60 ± 2.24
MEF_{25}, l/s	1.67 ± 0.66	0.31 ± 0.03
MEF_{25}, %	21.58 ± 1.78	22.90 ± 2.85
MEF_{50}, l/s	2.15 ± 0.76	0.75 ± 0.08
MEF_{50}, %	20.23 ± 1.66	18.08 ± 1.76
MEF_{75}, l/s	1.94 ± 0.18	1.62 ± 0.18
MEF_{75}, %	26.66 ± 1.97	23.43 ± 2.45
IC, l	4.76 ± 1.80	2.15 ± 0.09
IC, %	81.89 ± 3.63	80.15 ± 3.92
ERV, l	1.14 ± 0.16*	0.73 ± 0.05
ERV, %	90.83 ± 4.98*	74.08 ± 5.08
PEF, l/s	3.55 ± 0.21	3.44 ± 0.22
PEF, %	47.14 ± 2.46	44.86 ± 2.64

Note: * $p < 0.05$ — the reliability of differences between COPD and COPD and CHD

Table 3. *EchoCG parameters in patients with COPD and COPD + IHD diagnosed during the study (the beginning of the study) (M ± m)*

Parameters	Patients with COPD (the beginning of the study) n=116	Patients with IHD and COPD (the beginning of the study) n=66
Aorta, mm	31.31 ± 1.13	30.66 ± 0.61
$S_{AV,}$ cm^2	18.48 ± 0.98	18.13 ± 0.45
$V_{AV,}$ $m•s^{-1}$	1.89 ± 0.39	1.46 ± 0.12
ΔP, AV	5.47 ± 0.46*	10.28 ± 2.08
RA, mm	30.30 ± 1.17**	36.00 ± 0.60
RV, mm	27.94 ± 0.75***	30.69 ± 0.98
LA, mm	29.81 ± 0.69**	35.30 ± 0.70
EDD_{LV}, mm	43.54 ± 1.43**	47.84 ± 0.83
ESD_{LV}, mm	28.92 ± 0.90	31.30 ± 0.80
EDV, ml	95.77 ± 5.56	99.16 ± 3.47
ESV, ml	34.55 ± 2.61	37.00 ± 1.97
SV, ml	58.12 ± 3.45	59.50 ± 3.24
PW_{LV}, mm	9.00± 0.37**	10.69 ± 0.18
IVS, mm	9.36 ± 0.30*	10.61 ± 0.20
$EF_{LV,}$ %	63.72 ± 1.05	61.50 ± 0.99
$S_{MV,}$ cm^2	24.89 ± 0.97	27.40 ± 0.26
ΔP, MV	2.22 ± 0.24**	3.46 ± 0.27
V_{Av} $m•s^{-1}$	0.74 ± 0.02**	1.15 ± 0.12
ΔP, TV	1.36 ± 0.12	1.50 ± 0.12
V_{TV} $m•s^{-1}$	0.92 ± 0.12	0.85 ± 0.07
$ρ_{PA,}$ mm Hg	22.86 ± 1.77**	38.75 ± 2.34
V_{PA} $m•s^{-1}$	0.94 ± 0.03	1.01 ± 0.03
PA, mm	21.90 ± 0.67	20.90 ± 0.42
ΔP, PA	3.81 ± 0.36	4.32 ± 0.31

Note: : * ρ<0,01; **ρ<0,001; ***ρ<0,05 — The reliability of the differences between COPD and COPD and IHD at the beginning of the study.

Table 4. *EchoCG parameters in patients with COPD and COPD + IHD diagnosed during the study (the end of the study) (M ± m)*

	Patients with COPD (the end of the study) n=116	Patients with IHD and COPD (the end of the study) n=66
Aorta, mm	32.12 ± 1.17	32.27 ± 0.79
$S_{AV,}$ cm^2	17.75 ± 0.85	17.40 ± 0.53
$V_{AV,}$ $m•s^{-1}$	1.76 ± 0.33	1.55 ± 0.10
ΔP, AV	5.99 ± 0.67	9.90 ± 1.62
RA, mm	34.36 ± 0.78**	36.92 ± 1.10
RV, mm	31.01 ± 0.78	32.61 ± 1.09
LA, mm	31.66 ± 0.60***	37.35 ± 0.78
EDD_{LV}, mm	47.74 ± 0.81	50.23 ± 1.47
ESD_{LV}, mm	32.21 ± 0.76**	34.97 ± 1.08
EDV, ml	107.40 ± 4.47	118.41 ± 10.50
ESV, ml	42.36 ± 2.27	50.66 ± 5.19
SV, ml	65.61 ± 2.87	67.00 ± 7.56
PW_{LV}, mm	10.64 ± 0.29	10.78 ± 0.22
IVS, mm	11.02 ± 0.28	10.76 ± 0.26
$EF_{LV,}$ %	60.15 ± 0.91*	56.61 ± 0.80
$S_{MV,}$ cm^2	21.66 ± 1.50	24.38 ± 1.32
ΔP, MV	2.91 ± 0.29	3.13 ± 0.33
V_{Av} $m•s^{-1}$	0.78 ± 0.03*	1.14 ± 0.15
ΔP, TV	1.52 ± 0.21	1.33 ± 0.08
V_{TV} $m•s^{-1}$	0.73 ± 0.04	0.81 ± 0.07
$ρ_{PA,}$ mm Hg	28.09 ± 2.14**	35.12 ± 3.02
V_{PA} $m•s^{-1}$	0.96 ± 0.03	0.96 ± 0.02
PA, mm	23.44 ± 0.69	25.27 ± 1.08
ΔP, PA	4.14 ± 0.29	4.07 ± 0.27

Note: * ρ <0,01; ** ρ <0,05; *** ρ <0,001 — the reliability of differences between COPD and COPD and IHD at the end of the study.

IHD. They also showed significant differences in the linear dimensions of RA (ρ < 0.001) and RV (ρ = 0.028). Pulmonary hypertension was observed in patients with confirmed IHD (ρ < 0.001). Beside the increased linear dimensions of right chambers, the left heart was also remodeled, namely LA, which remodeling degree was significant in the control group (ρ < 0.001) as well as the thickness of PW_{LV} and IVS (ρ = 0.001 and ρ = 0.004, respectively). After the five-year period of the observation, the pressure gradient at the aortic valve (ρ = 0.01), blood flow velocity at the mitral valve (ρ = 0.003), and RA (ρ = 0.050) and LA (ρ < 0.001) dimension values were higher in patients of the control group. The LV systolic function impairment progressed in all patients. EF_{LV} value was lower in the group of patients with confirmed IHD (ρ = 0.009), and conversely SPAP values were higher (ρ = 0.050) (Table. 4).

Therefore, during the five-year period of observation, remodeling of right chambers was observed in COPD patients. These changes were conditioned by a natural increase of SPAP value as the result of persistent obstructive impairments and reduced lung volumes (ρ < 0.05), as well of cardiac dysfunction progress.

The process of cardiac remodeling in COPD also has an effect on the left heart, particularly on LV, and the literature has indicated this fact more frequently in recent years. At a particular stage of chronic cor pulmonale (CP) development in COPD patients, the process of cardiac remodeling naturally involves its left chambers, where changes imply diastolic dysfunction of LV, which is often restrictive, a confident increase in the LV sphericity index and systolic myocardial strain (MS) as well as a trend to increase in LV mass, index of LV EDV, index of LV ESV and sizes of LA. Patients with decompensated CP show not only more pronounced signs of LV remodeling as compared to the patients with the compensated CP, but also a decrease of its systolic function leading to additional loss of life quality and an increase in the risk of death. The major cause of structural and functional changes in the left chambers of the heart in CP patients is the restricted diastolic function of LV conditioned by interventricular interaction disorder, increased asynchronism in RV and LV interaction, and paradoxic motion of IVS [15].

An important feature of this study was also the detection of left chamber remodeling, and mainly LV hypertrophy development. We also noted a decrease of LV contractility, which did not reach the values of the systolic dysfunction in most cases ($p < 0.05$). In addition, the values of EDD did not increase during the period of observation. Thus, we can suppose presence of diastolic dysfunction (Figure 1), which, along with the progressing bronchial obstruction, causes the left chamber remodeling in examined patients.

Analysis of EchoCG parameters in the group of COPD patients according to the coronary risk degree showed more apparent changes of the main parameters when there was higher risk. Most of mean values of EchoCG were comparable in males and females (n = 116) among the COPD patients if no coronary event was observed. Nevertheless, it should be noted that we found the highest values of SPAP levels as well as LV eccentric hypertrophy in the group of COPD males at high coronary risk. Most of the females demonstrated normal LV model and concentric hypertrophy. The most apparent changes in EchoCG parameters were detected among the females with a moderate coronary risk. A rate of IHD occurrence determined on the basis of prospective observation of this group was comparable to high risk in males.

An analysis of EchoCG data in patients of control group demonstrated, along with right chambers remodeling, a significant increase of left chambers dimensions, decreased myocardial contractility, and more pronounced LV hypertrophy as compared to the cases of isolated COPD ($p < 0.05$). It should be noted that the dynamics of respiratory function parameters in these patients were less pronounced as compared to the patients with isolated COPD (Figure 2).

When predicting the risk of coronary accident development in COPD patients taking into consideration the results of the expanded instrumental

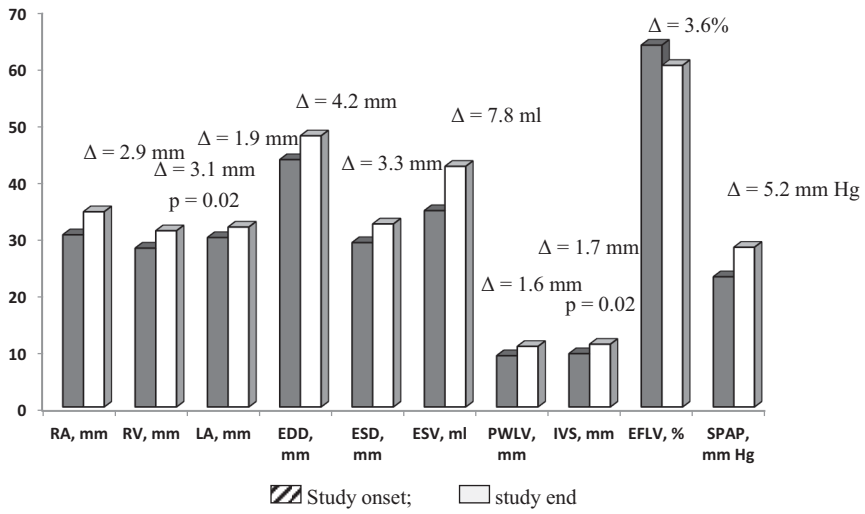

Figure 1. *Dynamics of echocardiographic parameters in patients with COPD over a five-year period (n = 116)*

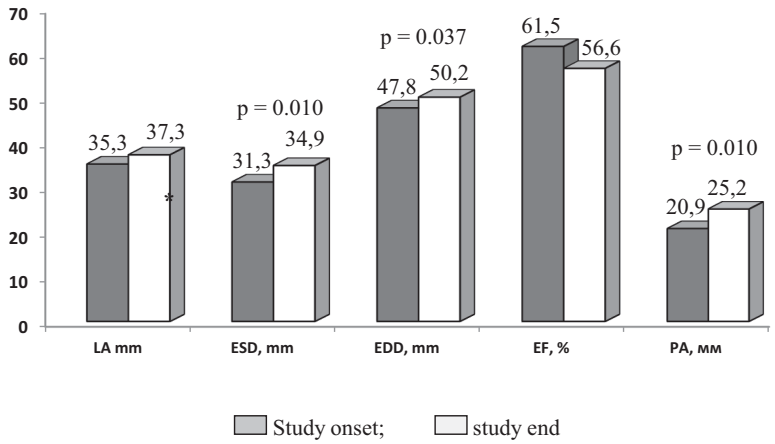

Figure 2. *Dynamics of echocardiographic parameters in patients with COPD and IHD, over a five-year follow-up period (n = 66)*

examination (spirometry, echoCG), we can identify high and very high risk groups to provide primary prevention of cardiovascular disease.

The stepwise discriminant analysis used for predicting cardiovascular events in COPD patients shall consider medical history data (annual number of aggravation episodes requiring hospitalization, period of employment in northern regions), age, total cholesterol, systolic blood pressure and EchoCG data (EDD_{LV}, SPAP) and spirometry data (expiratory reserve volume, ERV). High and very high risk of a cardiovascular event requiring preventive care can be calculated for females using the formula:

D = 0.000108 (SCORE × period of employment in the northern regions × × occurrence of COPD aggravation episodes × EDD_{LV} (mm) × SPAP (mm)

The high and very high risk may be determined at *D ≥ 27.5*.

It should be noted, that in case of males, the length of stay in the North is less critical then the annual rate of COPD aggravation episodes. A high or very high risk of cardiovascular event requiring preventive care can be calculated for males using the formula:

D = 0.000078 (SCORE × occurrence of COPD aggravation episodes × × EDD_{LV} (mm) × ERV (%)

A high or very high risk may be determined at *D ≥ 16.2*.

Thus, predicting coronary risk while taking into consideration EchoCG data allows us to identify high and very high risk groups which require prevention of cardiovascular diseases with a set of medications affecting the myocardial remodeling process.

Conclusion

The issue of the cardiorespiratory system remodeling in patients with COPD remains relevant. There are different points of view on cardiac remodeling in cases of isolated COPD. According to the classical understanding, in case of CP development, the right ventricle is remodeled following generally the same pattern as it happens with the left ventricle in case of IHD. Initially, in pulmonary hypertension, hypertrophy of the right ventricle develops, and then its cavity dilates. Some authors do not rule out that right ventricle dilatation develops long before the onset of RV heart failure [16], and RV hypertrophy is a very late and non-compulsory stage of its development [17]. Discussions of CP have not covered the state of left heart chambers over a long period of time. No clear understanding of these stages of CP development has been presented. However, the data from the latest studies do not exclude involvement of the left ventricle in the cardiac remodeling process in COPD patients [18]. Our study confirms CP development in COPD patients in the course of the disease progression: dimensions of the right ventricle increased somewhat earlier. The pulmonary artery remodeling

process and pulmonary hypertension development process reached the acceptance thresholds at the end of the five-year observation period. Beside the right chambers, the left ventricle was also involved in the remodeling process in our patients. LV hypertrophy development was observed [19].

At the same time, one of the typical cardiovascular complication in cases of COPD is increased pressure in the pulmonary artery system contributing CP development. There are data evidencing an increase in the percentage of patients with pulmonary hypertension and increased pulmonary vascular resistance among patients with COPD and IHD. In fact, pulmonary hypertension was observed in patients who developed comorbid IHD on the background of COPD, and this hypertension led to remodeling and an increase in pulmonary artery diameter ($p = 0.010$). Probably, the signs of cardiac remodeling that were not detected in time and the presence of pulmonary hypertension gave rise to IHD onset in these patients. Taking into consideration the progressing restrictive respiratory dysfunction, which is probably conditioned by a postcapillary pulmonary hypertension, and taking into consideration the remodeling of LV myocardium in COPD patients, the presence of "silent" LV dysfunction in COPD patients cannot be excluded.

In cases of concomitant IHD and COPD, cardiac remodeling is more complex and is manifested in hypertrophy and dilatation. Changes to the heart diastolic function are more pronounced, and pressure in the pulmonary artery system increases. These facts were confirmed by our study. It should be noted that diastolic function of the heart is impaired while the global diastolic function remains within the normal range. It has been established that when two diseases occur together, the rate of myocardial remodeling processes is higher. It is one more piece of evidence of the negative influence of COPD on the course of IHD in general, and particularly on myocardium [20].

However, there is an opinion that LV dysfunction in patients with CP can be explained by concomitant cardiovascular diseases (IHD, essential hypertension, etc.). In our study, we had observed comparable groups of COPD patients suffering from essential hypertension and of COPD patients developed IHD during the observation period. The available data obtained by a retrospective analysis of COPD patient post-mortem examination data demonstrate an aggravating comorbid background of COPD: in 85% of cases we observe essential hypertension with target organ lesions, in 64% of cases we observe significant coronary atherosclerosis, and in 19% of cases there was an ischemic stroke in the medical history. As the study results show, sclerotic changes of aorta and aortic valve were noted in patients who developed IHD during the observation period. These changes are manifestations of coronary atherosclerosis not detected at the outpatient stage of the examination. Based on the current literature, myocardial injury often remains undetected and, thus, we observe an underdiagnosis of IHD in COPD patients [21].

Furthermore, arterial hypoxemia has a particular influence on LV functional status, and this may be the one of the major causes of the vascular remodeling onset and the basis of cardiovascular changes. Our opinion is confirmed by the observation of some authors that LV remodeling in patients with COPD influences the development of restrictive LV diastolic dysfunction.

Therefore, cardiac remodeling in COPD patients in the North includes changes in right chambers of the heart as the result of persistent obstructive impairments and decreased lung volumes as well as a decrease of the myocardial contractility and progressing LV hypertrophy. During the preventive medical examination of COPD patients it is required to evaluate criteria predicting the high and very high risk of the coronary event using the formulas: $d = 0.000108$ *(SCORE × period of employment in the northern regions × occurrence of COPD aggravation episodes ×* EDD_{LV} *(mm) × SPAP (mm) for females and* $d = 0.000078$ *(SCORE × occurrence of COPD aggravation episodes ×* EDD_{LV} *(mm) × ERV (%)) for males*. A high and a very high risk may be determined at $d \geq 27.5$ for females, and at $d \geq 16.2$ for males.

Conflict of interests

The authors declare no conflict of interests.

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PHARMACOGENETIC FEATURES OF THERAPY OF PATIENTS WITH ATHEROSCLEROSIS

Abstract

The complexity of therapy of lipid metabolism disorders is not only in comorbidity and polypragmasy, but also in predicting a genetically determined response to treatment. Our objective was to study the pharmacogenetics features of pharmacotherapy of patients with non-alcoholic fatty liver disease, with various forms of IHD, and patients taking statins.

We examined four study groups: I — 60 patients with 2 type diabetes and non-alcoholic fatty liver disease (*APOE* polymorphism); II — 187 patients with IHD (*eNOS, AGTR2, CYP2D6* polymorphisms); III — 111 people with essential hypertension and CHF (polymorphisms: *AGT*: 704 (Met235Thr), *AGT*:521 (Thr174Met), *AGTR1*: 1166, *AGTR2*: 1675, *CYP11B2*: -344, *GNB3*: 825, *ADD1*: 1378 (Gly460Trp), *NOS3*: -786); IV — 62 patients taking atorvastatin (*SLCO1B1*5* polymorphism).

Patients with E2, E4 alleles of the *APOE* gene, taking essential phospholipids, significantly improved parameters of total cholesterol, HDL, LDL, CA, AP; patients with E3 alleles had a positive dynamics of cholesterol, HDL, TG, LDL, VLDL, CA, and urea levels. Patients having "slow" variants of gene *CYP2D6*10*, *CYP2D6*4* had received metoprolol, had greater decrease in heart rate: 1.6 times for *CYP2D6*10*, and 1.7 — for *CYP2D6*4*. Earlier onset of IHD was noted in patients with TT variants of the eNOS gene comparing with the patients with GG and GT variants. Dosages of perindopril depend on *AGTR2* gene polymorphisms.

The prevalence of polymorphisms *AGTR2*: 1675, *CYP11B2*: -344, *NOS3*: -786, *AGT*: 704, *GNB3*: 825 increases with the increase of CHF stage. The parameters of intracardiac hemodynamics in patients with CHF are associated with *AGT*: 704, *NOS3*:-786, *GNB3*: 825, *ADD1*: 1378, *AGT*: 521 polymorphisms. Allele C of the *SLCO1B1*5* gene is associated with an additional risk of statin-induced myopathy. Thus, an individualized approach to the treatment of patients with diseases associated with lipid metabolism disorders is required to provide its safety and effectiveness.

Key words: *pharmacogenetics, IHD, CHF, polymorphism, APOE, eNOS, AGTR2, CYP2D6, AGT: 704 (Met235Thr), AGT: 521 (Thr174Met), AGTR1: 1166, AGTR2: 1675, CYP11B2: -344, GNB3: 825, ADD1: 1378 (Gly460Trp), NOS3: -786, SLCO1B1*5, metoprolol, atorvastatin*

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Introduction

Cardiovascular diseases have remained the main cause of deaths for the majority of European populations over the past 40–50 years [1]. Cardiovascular diseases (CVD) remain the leading cause of deaths in the Russian Federation. According to Rosstat data, in 2016 mortality from CVD was 615 per 100,000 of population, and absolute losses were about 900,000 people [2].

The etiological factor of this pathology is atherosclerosis, which is a systemic disease that generally affects several vascular territories and manifests as a dysfunctions of many vital organs [3]. Atherosclerosis is based on disorders of lipid metabolism, which play an important role in the development of various diseases such as non-alcoholic fatty liver disease, ischemic heart disease, strokes, atherosclerosis of the lower extremities, etc. [4, 5, 6, 7]. Difficulties in therapy of such diseases lie not only in comorbidity and polypharmacy [8, 9, 10], but also in predicting a genetically determined response to treatment [11].

Thus, the objective of our work was to study the pharmacokinetic features of pharmacotherapy in patients with nonalcoholic fatty liver disease and with various forms of ischemic heart disease, as well as in individuals taking statins.

Materials and Methods

This study involved 4 groups of patients comprising a total of 420 people with various forms of atherosclerosis and lipid metabolism disorders. All patients signed an informed consent to participate in the study.

The first study group consisted of 60 patients aged 18 years and older (8 (13.3%) males, 52 (86.7%) females with mean age of (58.2 ± 6.8) years), with an established diagnosis of type 2 diabetes and non-alcoholic fatty liver disease. The study group, in addition to a previous standard treatment of this pathology (Table 1), additionally received essential phospholipids — Glycyrrhizic acid + Phospholipides.

The *APOE* gene was studied. Patients with alleles of the *APOE* gene predisposed to lipid metabolism disorder (E2, E4) were combined into APOE 1 treatment subgroup consisting of 21 (35.0%) individuals. Patients with an isoform of the *APOE* gene not predisposed to lipid metabolism disorder (E3/E3) were combined into APOE 2 subgroup consisting of 39 (65.0%) individuals. The following patients were not included in the study: with type 1 diabetes mellitus or gestational diabetes; without ultrasonic liver changes typical for diffuse increased fat content; without liver dysfunction and hypercholesterolemia or dyslipidemia; with alcohol abuse; with the history of hepatitis regardless of its etiology; with any severe concomitant pathology; with the development of an adverse drug reaction; those taking drugs that can have a hepatotoxic effect.

The second group included 187 patients with various forms of IHD: myocardial infarction (n = 98), stable (n = 43) and unstable forms of angina (n = 46) (total of 108 males and 79 females with mean age of (62.9 ± 1.3) years). The following genetic associations were studied: *eNOS, AGTR2, CYP2D6* with the onset of IHD and peculiarities of pharmacotherapy. This study did not include patients: with diabetes, permanent forms of cardiac arrhythmias, thyroid diseases, cancers, mental illnesses, heart diseases.

The third group consisted of 111 individuals with hypertension and CHF (mean age of (63.5 ± 11.6) years). The following polymorphisms in their effects on the success of CHF

Table 1. *Characteristics of treatment in the group of essential phospholipids effectiveness study*

Treatment	Study group, n=60 (%)	Control group, n=67 (%)
I. Insulin therapy	20 (33,4)	21 (31,3)
II. Oral hypoglycemic drugs	34 (56,6)	39 (58,2)
III. Lifestyle change	6 (10,0)	7 (10,5)
IV. Hypotensive therapy	56 (93,3)	52 (77,6)
V. Hypocholesterolemic therapy	6 (10,0)	7 (10,4)

therapy and intracardiac hemodynamic parameters were studied: *AGT*: 704 (Met235Thr), *AGT*: 521 (Thr174Met), *AGTR1*: 1,166, *AGTR2*: 1675, *CYP11B2*: –344, *GNB3*: 825, *ADD1*: 1,378 (Gly460Trp), *NOS3*: –786. The study did not include patients with cancer and heart disease.

The fourth group included 62 patients (a total of 24 (38.7%) males and 38 females (62.3 %, mean age of (65.6 ± 1.7) years)) taking atorvastatin. The relationship between *SLCO1B1*5* gene polymorphisms and the severity of atorvastatin pleiotropic effects was determined. This study did not include patients: taking *CYP3A4* inhibitors or inducers with the exception of atorvastatin and amiodarone; with current exacerbation of rheumatological diseases or exacerbation in history over the past 6 months; with severe decompensated somatic diseases; with mental illness, disability, alcoholism or drug abuse in history; pregnant or lactating women; not willing to participate.

Statistical processing of the results was performed using Microsoft Excel and STATISTICA 10 software packages. To assess quantitative characteristics with normal distribution, Student's t-test was used, and to assess characteristics not related to normal distribution, the Mann-Whitney test was used. Differences were considered significant at $p < 0.05$ (p — achieved significance level). The Kruskall-Wallis test was used when analyzing the values for 3 groups. Regression analysis was used to determine the dependence of one characteristic on another; Spearman's correlation analysis was used to calculate the correlation between characteristics.

Results

APOE 1 and APOE 2 subgroups maintained differences in triglyceride levels between themselves ($p < 0.05$, Mann-Whitney test): before treatment (0.7 mmol/l) and at the end of treatment with essential phospholipids (0.6 mmol/l). The results are shown in table (Table 2).

It was found that EPL treatment leads to positive changes in lipid and carbohydrate metabolism: in comparison with the control group, HDL levels increased, and cholesterol, TG, LDL, CA, HbA1c, total and direct bilirubin, AST, and ALT levels decreased.

Table 2. *Mean values of biochemical parameters in patients with type 2 diabetes and non-alcoholic fatty liver disease: disposed (APOE 1) and undisposed (APOE 2) to atherosclerosis according to APOE alleles*

Parameter	APOE 1, n=21 (M ± m)		APOE 2, n=39 (M ± m)	
	Before treatment	After treatment	Before treatment	After treatment
Total cholesterol	6,1±0,2	5,0±0,2	5,9±0,2	5,1±0,2
Triglycerides	2,8±0,3	2,5±0,3	2,1±0,2	1,9±0,2
High density lipoprotein	0,9±0,04	1,2±0,03*	1,0±0,03	1,2±0,03*
Low density lipoprotein	3,5±0,2	2,8±0,2*	3,5±0,2	3,1±0,1*
Very low density lipoproteins	1,4 ±0,1	1,4±1,3	1,0±0,07	1,1±0,1
Coefficient of atherogenicity	5,2±0,5	3,8±0,2*	4,6±0,2	3,4±0,2*
HbA1c	8,0±0,4	6,9±0,3*	8,2±0,3	7,2±0,2*
Total bilirubin	17,6 ±1,8	14,8±1,2	18,7±12	16,5±0,9*
Direct bilirubin	4,8±0,6	3,4±0,3*	5,0±0,4	3,7±0,2*
AST	30,0±3,2	22,2±1,1*	36,0±4,1	28,2±1,9*
ALT	32,7±3,6	21,1±1,4	40,5±5,6	29,9±2,9*
AP (Alkaline phosphatase)	205,1±14,48	192±10,5	219,9±11,0	228,8±8,8
Urea	5,7±0,4	4,6±0,7	5,5±0,2	4,6±0,2*

Note: * — $p<0.05$ when comparing results before and after treatment (Wilcoxon test)

All target values of lipid metabolism parameters in each individual patient with diabetes could not be reached.

Differences in the efficacy of EPL therapy in patients with the studied diseases associated with *APOE* gene polymorphism were revealed:

- Patients with alleles of the *APOE* gene, predisposed to atherosclerosis (E2, E4), during EPL treatment have significantly improved overall cholesterol, HDL and LDL, CA, and ALP levels.
- Patients with only protective alleles (E3) in relation to the development of atherosclerosis had an improvement in cholesterol, HDL, TG, LDL, VLDL, CA, and urea levels.

In the second study group, association of the TT allele of the *eNOS* gene with early onset of IHD compared with GG and GT alleles (Table 3) was detected. Regression analysis revealed that the presence of polymorphic T allele was associated with earlier development of coronary artery disease ($b = -2.54$, $p < 0.05$).

Analysis of mean perindopril doses needed for sufficient hypotensive effect in patients with different alleles of the *AGTR2* gene revealed that in patients with homozygous GG allele, perindopril doses were 1.3 times lower than in homozygotes with polymorphic AA variant (GG — (4.6 ± 1.9) mg, AA — (6.2±2.0) mg, $p < 0.05$).

Pharmacogenetic study of CYP2D6*10 and CYP2D6*4 in patients taking metoprolol showed that in carriers of slow variants of the *CYP2D6*10* gene, *CYP2D6*4*, unlike carriers of normal alleles, greater decrease in HR was detected when taking comparable doses of metoprolol: 1.6 times for *CYP2D6*10*, 1.7 times for *CYP2D6*4* (Table 4).

Thus, the presence of slow GA and CT variants of the *CYP2D6*4* and *CYP2D6*10* genes, respectively, requires the administration of lower doses of metoprolol than for GG and CC carriers.

In the third study group it was found that the rate of gene polymorphisms varies depending on the CHF stage (Table 5). In particular, it can be traced for *AGTR2*: 1675, *CYP11B2*: –344 and *NOS3*: –786 gene polymorphisms. The incidence of *AGTR2*: 1,675 gene polymorphism is most significant at stage 2A (21.3%) compared to stage 1 of CHF (the Russian Classification System of CHF). The detected changes were associated with changes in the frequency of heterozygotes. When comparing the incidence of gene polymorphisms at stage 1 and 2B, the results showed a high frequency of *AGTR2*: 1,675 (37.5%) and *CYP11B2*: –344 (62.5%) gene polymorphisms at the severe stage of CHF. It can be assumed that these gene polymorphisms are responsible for a more

Table 3. *Age of IHD onset: stable and unstable angina, myocardial infarction depending on the polymorphism of the eNOS gene*

Polymorphic variant of the *eNOS* gene	Age of IHD onset	t value	p-value
GG	56,4±0,7*	2,25	0,03
GT	55,8±0,7**	2,46	0,02
TT	47,0±0,8*, **	-	-

Note: — * — when comparing GG with TT; ** — when comparing GT with TT. Statistical processing was carried out by Student's t-test

Table 4. *The difference in heart rate before and after administration of metoprolol depending on CYP2D6 * 10 and CYP2D6 * 4 variants*

Gen	Alleles	Difference in heart rate, n=113	Heart rate before metoprolol administration
*CYP2D6*10*	Homozygote — norm (CC)	10,7±0,5*	76,0±1,9
	Heterozygote (CT)	16,8±0,7*	78,1±0,9
*CYP2D6*4*	Homozygote — norm (GG)	10,6±0,5**	76,1±1,5
	Heterozygote (GA)	17,9±0,7**	78,4±0,9

Note: — *, ** $p<0.05$. Student's t-test

Table 5. *Frequency of occurrence of gene polymorphisms depending on the stage of CHF*

Gene polymorphisms	stage 1, n=40 (36,03%)	stage 2A, n=47 (42,3%)	stage 2B, n=24 (21,6%)
ADD1: 1378	8 (20%)	11 (23,4%)	7 (29,2%)
- mutation-homozygote	-	-	1 (4,2%)
- heterozygote	8 (20%)	11 (23,4%)	6 (25%)
AGT: 704	30 (75%)	39 (82,9%)	20 (83,3%)
- mutation-homozygote	11 (27,5%)	16 (34,5%)	6 (25%)
- heterozygote	19 (47,5%)	23 (48,9%)	14 (58,3%)
AGT: 521	11 (27,5%)	12 (25,5%)	9 (37,5%)
- mutation-homozygote	1 (2,5%)	2 (4,2%)	2 (8,3%)
- heterozygote	10 (25%)	10 (21,3%)	7 (29,2%)
AGTR1: 1166	13 (32,5%)	15 (31,9%)	8 (33,3%)
- mutation-homozygote	1 (2,5%)	1 (2,1%)	1 (4,2%)
- heterozygote	12 (30%)	14 (29,8%)	7 (29,2%)
AGTR2: 1675	15 (37,5%)	24 (51,1%)	11 (45,8%)
- mutation-homozygote	13 (32,5%)	14 (29,8%)	7 (29,2%)
- heterozygote	2 (5%)	10 (21,3%)*	9 (37,5%)**
CYP11B2: -344	27 (67,5%)	37 (78,7%)	19 (79,2%)
- mutation-homozygote	13 (32,5%)	12 (25,5%)	4 (16,7%)
- heterozygote	14 (35%)	25 (53,2%)	15 (62,5%)**
GNB3: 825	19 (47,5%)	23 (48,9%)	12 (50%)
- mutation-homozygote	4 (10%)	4 (8,5%)	-
- heterozygote	15 (37,5%)	19 (40,4%)	12 (50%)
NOS3: -786	33 (82,5%)	39 (82,9%)	23 (95,8%)
- mutation-homozygote	13 (32,5%)	23 (48,9%)	8 (33,3%)
- heterozygote	20 (50%)	16 (34%)	15 (62,5%)#
NOS3: 894	18 (45%)	19 (40,4%)	9 (37,5%)
- mutation-homozygote	4 (10%)	4 (8,5%)	1 (4,2%)
- heterozygote	14 (35%)	15 (31,9%)	8 (33,3%)

Note: * — ρ<0.05 when comparing CHF 1 and 2A, ** — ρ <0.05 when comparing CHF 1 and 2B, # — ρ <0.05 when comparing 2A and 2B of CHF stage

unfavorable course of CHF. In addition, the frequency of *AGTR2*: 1,675 and NOS3: –786 gene polymorphisms increases by 16.2% and 28.5%, respectively, at stage 2B compared to stage 2A of CHF ($\rho < 0.05$).

Thus, with the increase in CHF severity, the incidence of gene polymorphisms increases and reaches maximum values at stage 2B. This primarily pertains to *NOS3*: –786 gene polymorphism which was significantly more common in more severe manifestations of CHF.

Association of polymorphisms with a favorable course of CHF was also studied: no worsening of symptoms and signs of CHF within 1 year, no hospitalization within 1 year; and with unfavorable course: CHF progression, an increase in CHF stage or functional class (FC) within 1 year, hospitalization within 1 year.

Hospitalization was associated with an increase in the incidence of *AGTR2*: 1,675 gene polymorphism in the form of combined mutations: homozygotes and heterozygotes by 32.2%, and separately for heterozygotes by 31.1% ($\rho < 0.05$). A similar trend was observed on the part of *GNB3*: 825 gene polymorphism heterozygote by 26.9%.

The relationships between the parameters of intracardiac hemodynamics and gene polymorphisms were identified. With unfavorable echocardiographic parameters, *AGT*: 704, *NOS3*: –786 and

GNB3: 825 gene polymorphisms were the most frequently reported. These polymorphisms were associated with reduced LVEF (< 50%), increased EDD (> 57 mm) and ESD (ESD > 44 mm), LV PWD (> 12 mm) and IVST (> 12 mm). Statistically significant data were obtained in relation to LVEF and IVST. Reduced LVEF was associated with *AGT*: 704 and *GNB3*: 825 gene polymorphisms, increase in IVST with *ADD1*: 1,378 and *AGT*: 521 gene polymorphisms ($p < 0.05$). With increased LA sizes (> 40 mm) there was a tendency to an increase in the frequency of *AGT*: 521 gene polymorphism by 16%.

In the fourth study group: all patients were divided into two subgroups: carriers of the wild (T) variant of the genotype in allelic gene *SLCO1B1*5* — TT group, and carriers of C allele associated with the risk of statin-induced myopathy in the genotype — TC group. Analysis of safety parameters for the use of atorvastatin in groups separated by genetic feature, which included biochemical parameters (CPK, ALT, AST), values of hand dynamometry, did not reveal significant differences.

According to the assessment of statin pleiotropic effects in TT and TS groups, the mean value of the inflammatory reaction marker interleukin 6 was significantly higher in the TT group, the differences in this parameter were significant between the groups ((4.85 ± 1.45) pg/ml and (1.67 ± 0.26) pg/ml, respectively, $p < 0.05$).

Lower levels of interleukin 6 indicate a more pronounced anti-inflammatory (pleiotropic) effect of atorvastatin. The correlation was evaluated using the Spearman test, a statistically significant direct relationship between the level of interleukin 6 and the presence of C allele in the allele gene genotype *SLCO1B1*5* ($rs = 0.25$; $p < 0.05$) was found. Thus, C allele is associated with an additional risk of statin-induced myopathy, due to an increased plasma statin concentration compared to the carrier of the TT genotype.

Results and Discussion

In the course of our work it was possible to identify associations of genes involved in vascular wall tone: *eNOS, AGT, AGTR2* with more severe course of CHF, with early development of IHD, with the presence of adverse hemodynamic parameters. Endothelial NO-synthase produces nitric oxide, which provides vasodilation, inhibition of adhesion molecule expression and platelet aggregation, has antiproliferative, antiapoptic and antithrombotic effects. Genes involved in RAAS regulation also have a great influence on the regulation of vascular wall tone, including the mechanisms of increasing nitric oxide production [12, 13], cell proliferation and apoptosis [14, 15].

Thus, the expression of these genes has interdependent effects provided through the synthesis of nitric oxide that in the presence of their polymorphisms can significantly change both the course and rate of cardiovascular disease progression, and the dynamic response to pharmacotherapy [16].

The safety and efficacy of the drugs was also related to the presence of polymorphisms of genes involved in drug metabolism, and responsible for drug binding with the receptor. There was a link between carriership of *CYP2D6* slow alleles and more pronounced decrease in HR when taking metoprolol — greater decrease in HR was detected in carriers of slow alleles of the gene (*CYP2D6*10*, *CYP2D6*4*) in contrast to carriers of normal alleles when taking comparable doses of metoprolol: by 1.6 times for *CYP2D6*10*, by 1.7 times for *CYP2D6*4*. This is an important factor in predicting pharmacodynamic response in titration of lipophilic beta-blocker doses. Thus, an individualized approach to metoprolol administration in IHD should be carried out taking into account the results of genetic testing on the *CYP2D6* gene. The presence of slow allelic GA and CT variants of the *CYP2D6*4* and *CYP2D6*10* gene, respectively, requires the administration of lower doses of metoprolol than for GG and CC carriers

Polymorphism of *AGTR2* involved in vasodilation can also be associated with a different effect on therapy [17], with more pronounced pharmacodynamic response in patients with the homozygous GG allele of the *AGTR2* gene receiving perindopril, and ACE inhibitor doses required for a sufficient antihypertensive effect in patients with homozygous GG allele are 1.3 times lower than those for homozygous individuals with polymorphic AA variant.

Differences in the efficacy of EPL therapy in patients with the studied diseases associated with *APOE* gene polymorphism were revealed:

- Patients with alleles of the *APOE* gene predisposed to atherosclerosis (E2, E4), during EPL treatment, have significantly improved overall cholesterol, HDL and LDL, CA, and ALP levels.
- Patients with only protective alleles (E3), in relation to the development of atherosclerosis, had an improvement in cholesterol, HDL, TG, LDL, VLDL, CA and urea levels.

The development of statin-induced adverse reactions is increasingly associated with the peculiarities of organic anion carriers encoded by the *SLCO1B1* gene and carrying out statin uptake by hepatocytes [18, 19].

The indication for the use of the pharmacogenetic test is the prediction of the development of myopathies (including rhabdomyolysis) in patients who are indicated to the statins use and to the individualized selection of the maximum statin dose. *SLCO1B1*5* (c.521 T>C, rs4149056) is a variant (polymorphic marker) of the *SLCO1B1* gene (encodes polypeptide transporting organic anions involved in statin bile excretion by the liver) [20, 21].

The distribution of genotypes by *SLCO1B1*5* in the Russian population according to many authors is approximately presented as follows: TT genotype — 61%, TC — 32.5%, CC — 6.5% of patients [22, 23]. This suggests a common occurrence of C-allele of the *SLCO1B1* gene in the Russian population, and therefore patients should be expected to have a high risk of myopathy when taking statins.

As a result of our work, it was found that the carriership of genotypes for *SLCO1B1*5* variant does not affect atorvastatin markers of myopathy (CPK, pain syndrome, dynamometry data) administered in an average daily dose of (20.5 ± 5.03) mg. In general the detection of the TC and CC genotype variant of the *SLCO1B1*5* allelic gene in pharmacogenetic testing can be used to predict a more pronounced pleiotropic anti-inflammatory effect of atorvastatin. This effect is preserved by the co-administration of atorvastatin and amiodarone.

Thus, an individualized approach to the treatment of patients with diseases associated with lipid metabolism disorders based on genetic analysis can allow the prescription of more effective and safer pharmacotherapy.

Conflict of interests

The authors declare no conflict of interests.

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THE MECHANISMS OF THE DISORDERS OF MOTOR-EVACUATION FUNCTION OF GALL BLADDER AND THEIR IMPORTANCE IN THE DEVELOPMENT OF CHOLELITHIASIS

Abstract

The objective was to study the role of gastrin in the gallbladder motor-evacuation function damage and the biochemical properties of bile in cholelithiasis. **Material and methods.** 230 patients with pathology of the biliary system were examined. In verification of the diagnosis, in addition to general clinical data, the results of ultrasound examination of hepatobiliary system were used. Cholecystometry and dynamic hepatobiliary scintigraphy were used to examine the functional state of the gallbladder. In different variants of the gallbladder motor-evacuation function disorder, biochemical properties of bile (cholesterol, bile acids, cholate-cholesterol coefficient) obtained as a result of multifractional duodenal drainage were studied. The level of the gastrointestinal hormone gastrin in the peripheral blood was determined by the enzyme-linked immunoassay. **Results.** According to US results, 78 % of the patients are diagnosed with signs of biliary sludge. In 75.4 % of cases crystals of cholesterol and calcium bilirubin were detected via microscopic examination of bile. The study of the biochemical composition revealed an increase in cholesterol, a decrease in bile acids and cholate-cholesterol ratio in B bile and C bile. Gallbladder motor-evacuation function disorders, which are one of the pathogenetic factors of cholelithiasis, were detected in 72 % of patients. In patients with the disorder, gastrin level was reduced, and to a greater extent — in patients with hypokinetic gallbladder dysfunction. The significant role of gastrin in the functional state of the gallbladder and, therefore, in the formation of lithogenic bile, is established by the method of correlation analysis. **The conclusion.** Studies of the parameters of the gallbladder motor function and the biochemical properties of bile on the one hand and the level of the gastrointestinal hormone gastrin on the other have shown the important role of hypogastrinemia in the formation of lithogenic bile by suppressing the emptying of the gallbladder.

Key words: *gallbladder, motor-evacuation function, lithogenic properties of bile, cholelithiasis, gastrin*

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CLT — cholelithiasis, GB — gallbladder, BAB — bile acids of bile B, BAC — bile acids of bile C, CBB — cholesterol of bile B, CCB — cholesterol of bile C, CCRB — cholate-cholesterol ratio of bile B, CCRC — cholate-cholesterol ratio of bile C

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Introduction

One of the most urgent problems faced by clinical medicine is cholelithiasis (CLT) [1, 2, 3, 5, 6], whose prevalence is high and increasing from year to year, and which has a pronounced negative impact on social activity and quality of life. According to statistics, in recent decades, the increase in the incidence of CLT is a steady trend; and if today it is registered in more than 10 % of the population [2, 3, 6, 7], and if the current rate of morbidity growth remains, 20 % of the world's population will be suffering from CLT by 2050 [8].

The formation of calculi in the gallbladder (GB) is a long multistage process. Debate is still going on over the pathogenetic factors of cholelithiasis. In addition to the formation of lithogenic bile [9, 10], a necessary condition for gallstone formation is a GB motor function disorder [11, 12]. Animal experiments have shown the involvement of gastrointestinal hormones in the processes of bile formation and bile secretion [13]. However, the mechanisms of changes in bile metabolism and GB contractile capacity have not been studied enough.

Study Objective

To study the role of gastrin in GB motor-evacuation function disorders and biochemical properties of bile in CLT.

Materials and methods

Two hundred and thirty patients with stage I CLT (classification of Central Research Institute of Gastroenterology (CRIG), 2001) [4], secondary to hepatobiliary diseases (functional disorders of the biliary system, chronic non-calculous cholecystitis, steatohepatitis and steatohepatitis of alimentary etiology) were examined. Mean age of the patients was 47±6 years, including 113 men and 117 women. Examination of patients was carried out with the compulsory signing of a voluntary informed consent in accordance with order No. 390n of the Ministry of Health and Social Development of the Russian Federation dated April 23, 2012 (registered by the Ministry of Justice of the RF on May 5, 2012 under No. 24082). This study was approved by the Ethical Committee of Izhevsk State Medical Academy. The scope of examination was justified statistically by the sampling frequency using the L. Zaks formula.

For verification of the diagnosis, along with the anamnestic and general clinical data, the results of ultrasound examination (ultrasound) of the hepatobiliary system using S-DN-500 (with two standard transducers (linear and convex) with a frequency of 3.5 MHz) were taken into account. For assessment of GB functional state, data on cholecystometry and dynamic hepatobiliary scintigraphy (HBS) were used. Cholecystometry was performed according to the standard technique, which consists of measurement of GB volume before and after choleretic breakfast with intervals of 10 minutes (for 1.5 hours) by ultrasound scanning. The choleretic breakfast consisted of 2 raw egg yolks. GB volume was calculated with the formula V=3.14 dH, where d is the diameter of GB; H is the longitudinal axis of the GB. The following parameters were evaluated: baseline GB volume; duration of GB contraction phase; degree of maximal contraction from baseline; rate of GB emptying (ratio of the maximum contraction to duration of contraction phase). HBS was performed using the MB-9200 gamma camera with a Super Segams processor after intravenous administration of the hepatotropic radiopharmaceutical agent (RPA) Bromesida-Tc99 with a total activity of 185–370 MBq using choleretic stimulation consisting of 2 raw egg yolks. In the analysis of hepatograms, GB deposit function based on the time of maximum accumulation of RPA in GB (GB Tmax), motor-evacuation function of the gallbladder according to RPA half-life from GB (GB T½) and according to the latent time with choleretic breakfast were evaluated.

Microscopic and biochemical examination of bile obtained by multifractional duodenal drainage was carried out. In B and C portions the total concentration of bile acids (BAB, BAC), and cholesterol (CBB, CCB) [14] was determined, and cholate-cholesterol ratio (CCRB, CCRC), which is a bile lithogenetic index, was calculated. In peripheral blood the level of the gastrointestinal hormone gastrin was studied by a two-step sandwich enzyme-linked immunoassay.

The control group comprised of 30 apparently healthy individuals aged from 20 to 25 years.

Statistical processing of the results was performed using a standard package in Microsoft Office Excel editor, version 2010. The data presented as mean values (M) with the definition of their errors (±m) were compared by correlation analysis with the calculation of the correlation coefficient (*r*) according to Pearson's formula. The reliability was evaluated by Student's test with normal distribution of the sample.

Results and discussion

All patients suffered from abdominal pain; in 84 % of cases the pain was localized in the right hypochondrium, and in 16 % — in the epigastrium. Constant, dull pain intensifying after eating (mainly after fatty foods) accompanied by sense of pressure, bursting, with irradiation in the back, under the right scapula, in the right shoulder was observed in 68 % of patients, and 32 % of patients noted a short-term, colic-like pain arising from deviations in the diet. In addition, symptoms of biliary dyspepsia, which were dominated by eructation, nausea and bitter taste in the mouth, were found in 76 % of the patients during history-taking. In physical examination 78 % of patients had excessive nutrition, 56 % of patients had yellow or gray-yellow tongue coating, teeth prints at tongue edges, 83 % had pain during palpation with localization in the right hypochondrium and positive gallbladder symptoms. During ultrasound scanning, induration and thickening of GB wall were observed in 62 % of patients, GB deformation — in 30 % of patients, the presence of biliary sludge (microlites, putty-like bile) — in 78 % of patients.

Based on the results of cholecystometry, patients were divided into three subgroups: 1 — with GB dysfunction of hypokinetic type, 2 — with normal contractile activity of GB, 3 — with GB dysfunction of hyperkinetic type. Subgroups were balanced in terms of age and sex. The 1st subgroup included 49 women and 40 men with mean age of 51±2 years; the 2nd subgroup included 36 women and 39 men with mean age of 44±4 years, and the 3rd subgroup included 32 women and 34 men with mean age of 49±4 years. According to *Table 1*, there are no significant differences between baseline GB volume at different motor options.

As shown in Figure 1, in patients with GB dysfunction of hyperkinetic type the rate of GB emptying increases after test breakfast, not only due to a higher degree of maximum contraction but also due to a shorter duration of the contraction phase. In case of GB dysfunction by hypokinetic type the decrease in the emptying rate was associated with a decrease in the degree of maximum contraction and a longer duration the of contraction phase.

Unidirectional changes in GB motor activity parameters according to cholecystometry and HBS (Table 2) suggest of their information value and equivalence in the early diagnosis of CLT.

Basal gastrin level in the examined patients was reduced (Table 3), with a greater extent in GB dysfunction of hypokinetic type. At present there are conflicting data about the involvement of gastrin in the process of choleresis and cholekinesis. It has been proven that GB muscle wall contains gastrin receptors. Gastrin has a stimulating effect on GB contraction and a relaxing effect on the sphincter of Oddi, causing decreased pressure in the biliary tract [15]. Some authors prove the increase of cholecystokinin secretion in the duodenum by gastrin [16] which has a stimulating effect on GB contractility. Others note the improvement of hepatic blood flow under the influence of gastrin, resulting in positive changes in hepatic metabolic processes and in increased choleresis [17].

Table 1. *Gallbladder motility data in different functional disorders*

Parameter	Control (n=30)	Subgroup 1 (n=89)	Subgroup 2 (n=66)	Subgroup 3 (n=75)
Contraction phase duration, min.	45.64±4.2	52.41±4.4 *	46.62±3.4 *	39.25±2.5 *
The degree of maximum contraction, %	46.43±3.8	29.24±2.7 *	47.01±5.8 *	63.63±6.2 *
The rate of the gallbladder emptying, %/min	1.02±0.4	0.85±0.04 *	1.03±0.09 *	1.87±0.2 *
The initial volume of the gallbladder, cm^3	16.75±1.8	17.1±2.0*	16.85±2.4*	16.23±2.1*

Note: * — P < 0.05 compared with the control.

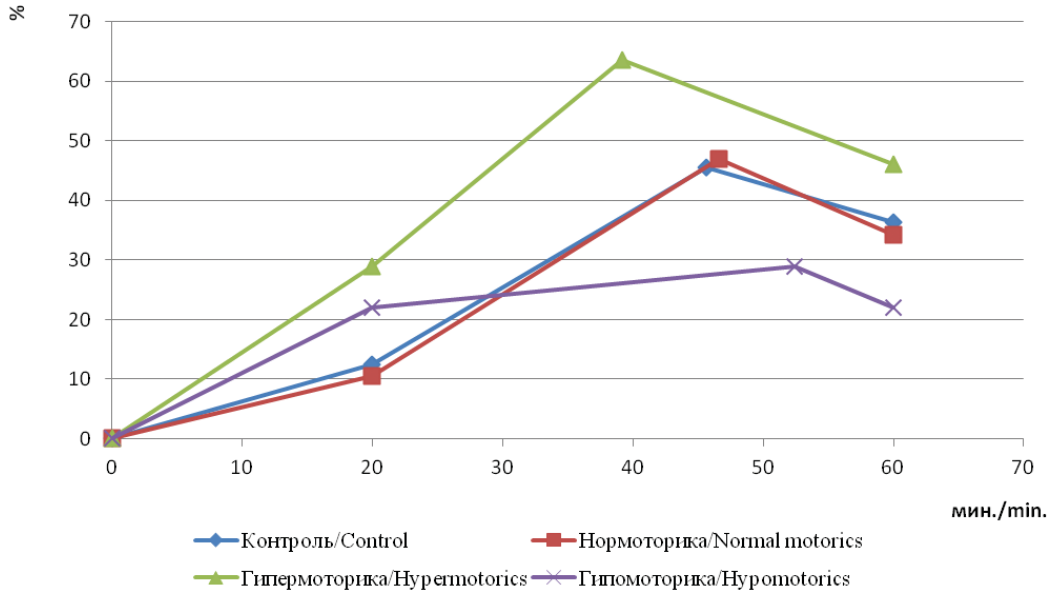

Figure 1. *Contractile function parameters of the GB after the test breakfast*

Table 2. *Correlation analysis of GB motor-evacuation function parameters in different examination methods*

Parameter	Half-life of RPA from GB according to HBS	Latent time of choleretic breakfast according to HBS
Duration of the contraction phase according to cholecystometry	r=0.49	r=0.36
The rate of emptying of the GB according to cholecystometry	r=–0.70	r=–0.60

Table 3. *Basal gastrin level in different GB functional disorder*

Parameter	Control (n=30)	Subgroup 1 (n=89)	Subgroup 2 (n=66)	Subgroup 3 (n=75)
Gastrin (pg/ml)	66.14±3.32	24.45±2.91*	27.06±3.02*	28.44±2.13*

Note: * — P < 0.05 compared with the control.

The results of the correlation analysis (Figure 2) indicating the existence of a relationship between gastrin level and GB functional state are evidence that hypogastrinemia leads to decreased GB emptying rate, maximum GB contraction degree by cholecystometry, as well as to increased RPA half-life and the latent time of choleretic breakfast during HBS.

In 75.4 % of patients crystals of cholesterol and calcium bilirubinate, which are typical for the first (pre-calculus) stage of CLT, were found by bile microscopy. Assessment of the biochemical composition of bile was carried out depending on the type of motor-evacuation function of the gallbladder. As shown in the *Table 4*, in the examined patients, the bile content of CL was elevated in both bile B and bile C compared to the control. In contrast, BA level was decreased in both bile B and bile C in comparison with the control. There was a significant decrease in CCR in both portions of bile in comparison with the control group. The highest degree of bile lithogenicity was observed in GB dysfunction of hypokinetic type.

According to Table 5, changes in the biochemical composition of bile are directly dependent on gastrin level. With decreased gastrin level, an increase in CL content and a decrease in BA levels in bile B and bile C are observed. A positive correlation between gastrin level and CCR was revealed, that is, CCR decreases with decrease in gastrin content.

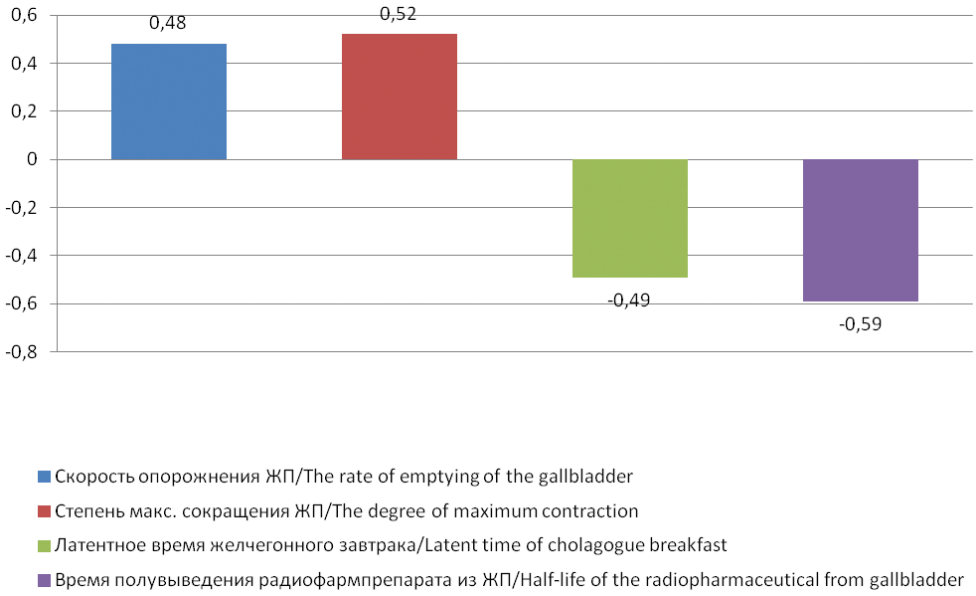

Figure 2. *The data of correlation analysis between the gastrin level and GB functional state parameters*

Table 4. *Biochemical parameters of bile in different GB motility disorders*

Parameter	Control (n=30)	Subgroup 1 (n=89)	Subgroup 2 (n=66)	Subgroup 3 (n=75)
CL (mmol/l)				
B bile	7.53±2.14	30.14±4.9*	19.91±4.6*	26.73±3.8*
C bile	3.45±0.9	21.28±3.6*	10.78±2.1	15.84±3.4*
BA (mmol/l)				
B bile	53.52±5.4	24.25±4.4	49.14±4.8*	37.24±3.1*
C bile	19.14±2.7	14.76±2.5*	17.37±1.4*	18.44±2.7*
CCR (U)				
B bile	9.53±1.1	0.84±0.04*	2.46±0.6	1.33±0.09
C bile	6.37±1.7	0.69±0.01*	1.61±0.4*	1.16±0.09*

Note: * — P < 0.05 compared with the control.

Table 5. *The data of correlation analysis between the gastrin level and biochemical properties of bile*

Parameter	CLв	CLc	BAв	BAc	CCRв	CCRc
Gastrin	r=–0.31	r=–0.31	r=0.47	r=0.35	r=0.38	r=0.31

Thus, hypogastrinemia, which correlates with the GB functional state disorder and altered biochemical composition of bile, indicates the significant role of gastrin in gallstone formation.

Conclusion

Disorders of GB motor-evacuation function were found in 72 % of patients with hepatobiliary system diseases. GB dysfunction of hypokinetic type has a more unfavorable prognosis in relation to possible gallstone formation. Studies of GB motor function parameters and biochemical properties of bile, on the one hand, and studies of gastrointestinal hormone gastrin levels on the other helped to show the important role of hypogastrinemia in the formation of lithogenic bile by inhibiting GB emptying.

Conflict of interests
The authors declare no conflict of interests.

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THE INFLUENCE OF ADHERENCE TO TREATMENT ON MYOCARDIAL DYSFUNCTION IN ELDERLY AND SENILE PATIENTS WITH ISCHEMIC HEART DISEASE AND HEART FAILURE

Abstract

The objective was to study the influence of adherence to treatment on myocardial dysfunction in elderly and senile patients with ischemic heart disease (IHD) and chronic heart failure (CHF). **Material and methods.** The study included 86 patients with ischemic heart disease (IHD) of older age groups admitted to the hospital due to the progression of CHF: 21 patients aged 65 to 74 years, and 65 patients aged 75 to 89 years. A standard clinical examination, echocardiography with global longitudinal strain assessment (GLS), and the Morisco-Green test were performed. **Results.** It was determined that in the group of senile aged patients there was a lower adherence to treatment and more pronounced structural and functional changes in the myocardium. The following correlations were revealed: total score of the Morisco-Green test with the left ventricular end-diastolic volume ($r = -0.33$, $p < 0.05$), with E/e' ($r = -0.37$, $p < 0.05$), and with GLS ($r = 0.53$). **The conclusion.** The findings indicate a lower adherence of the senile patients to treatment of IHD and CHF in comparison with the group of elder patients. Low adherence to therapy, as well as postinfarction cardiosclerosis, can apparently be considered as one of the factors contributing to the progression of myocardial dysfunction.

Key words: *ischemic heart disease, heart failure, adherence to treatment, elderly and senile age, left ventricular dysfunction, echocardiography, global longitudinal strain of the myocardium*

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IHD — ischemic heart disease, WMSI — regional wall motion score index, GLS — global longitudinal strain, LV — left ventricle, PICS — postinfarction cardiosclerosis, LVEF — ejection fraction of the left ventricle, CHF — congestive heart failure, EchoCG — echocardiography

Introduction

Congestive heart failure (CHF) is one of the most common diseases and the leading cause of mortality in elderly and senile patients [3, 4]. In the recent years, emphasis has been placed on patient compliance with doctor's prescriptions which is essential for the successful treatment of chronic diseases [1, 10]. Compliance with a prescribed course of therapy is the degree to which a patient adheres (in terms of drug administration, changes in lifestyle and/or dieting) to the medical advice given by a healthcare professional [12]. The criterion of compliance is considered to be the administration of at least 80% of the prescribed doses [8]. In clinical practice, questionnaires are the most practicable

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method of assessing patient compliance [7, 11, 13]. A number of studies demonstrated reduced compliance in patients in the elderly age groups [2, 7, 8, 9]. Therefore, it is considered important to evaluate how the compliance of CHF patients influences the structural and functional changes in myocardium.

The objective of this study is evaluation of the influence of the adherence to medical advice on myocardial dysfunction in elderly and senile patients suffering from ischemic heart disease and congestive heart failure.

Materials and Methods

The study enrolled 86 elderly and senile patients with ischemic heart disease (IHD) who were admitted to a hospital due to the IHD progression. Mean age of the studied group was (83.2 ± 10.6) years (65 to 89 years), 53 females (61.7%) and 33 males (38.3%) were enrolled.

Only patients who signed the informed consent form according to the Order No. 390n of the Ministry of Healthcare and Social Development of the Russian Federation dated April 23, 2012 (registered by the Ministry of Justice of the Russian Federation on May 5, 2012, No. 24082) were examined. This study was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education North-East State Medical University n. a. I. I. Mechnikov of Ministry of Healthcare of Russia.

According to the WHO definition, age of 65 to 74 years is considered elderly, age of 75 to 89 is considered senile. According to this classification, the patients were divided into two age groups: the first group included patients of 65 to 74 years (24.4%); the second group included those of 75 to 89 years (75.6%). Table 1 presents clinical features of the examined groups.

As the presented data show, 84.8% of the examined patients suffered from angina of 3 functional class, 62.7% had postinfarction cardiosclerosis (PICS) in medical history, 75 patients (87.2%) suffered from congestive heart failure of NYHA class 3. The most common concomitant disorders were hypertension (95.3%), type 2 diabetes mellitus (44.1%), renal disorders (26.7%), and chronic obstructive pulmonary diseases (45.3%). Multifocal atherosclerosis was detected in 52.3% of patients, and CVA was observed in the medical history of 31 patient (36%). Total duration of IHD history was (16.8 ± 14.69) years. Smoking as a risk factor was observed in the first group of patients (65 to 74 years). In the second age group, a large number of patients had myocardial infarction in the medical history. The percent of patients having a concomitant disorder and lesions of other vascular territories was higher.

The main exclusion criteria were: episode of acute coronary syndrome within the previous month, severe global impairment of contractility (EF below

Table 1. *Clinical and anamnestic data of patients in age groups*

Parameters	Group 1 (65-74 y. o.), n= 21 (24.4 %)		Group 2 (75-89 y. o.), n= 65 (75.6 %)		Total (65-89 y. o.), n = 86	
Mean age	69,5±1,8		82,04±2,6		83,2±10,6	
Duration of IHD	11,4±1,6		17,6±2,8		16,8 ±14,69	
Angina pectoris III FC	14	66,7%	59	86%	73	84,8%
History of MI	7	33,3%	47	72,3%	54	62,7%
CHF III FC	14	66,7%	61	93,8%	75	87,2%
Hypertension	19	90,5%	63	96,9%	82	95,3%
Diabetes mellitus type 2	6	28,6%	32	49,2%	38	44,1%
COPD	10	47,6%	29	44,6%	39	45,3%
Kidney disorders	8	38,1%	15	23,1%	23	26,7%
History of acute cerebrovascular event	7	33,3%	24	36,9%	31	36,0%
Atherosclerosis, multiple localization	10	47,6%	35	53,8%	45	52,3%
Smoking	12	57,1%	10	15,4%	22	25,6%

35%), several episodes of myocardial infarction and coronary bypass surgery, complete left bundle branch block, and persistent atrial fibrillation.

According to the medical records, treatment for every patient was prescribed in compliance with the National Guidelines [3].

The patient examination included standard clinical workup (physical, laboratory, and electrocardiography examinations), echocardiography (EchoCG) including evaluation of tissue velocity imaging parameters, and the global longitudinal strain (GLS) of myocardium as well as validated Morisco-Green test.

The EchoCG examination was carried out following the current guidelines using Toshiba Artida ultrasonic system (Japan) and a 3.5 MHz transducer. The evaluation was focused on the LV myocardium wall thickness and local systolic function of the left ventricle (LV), and structural and functional status of the valvular apparatus. The ejection fraction of the left ventricle (LV EF) was calculated using the Simpson's method of discs. The local contractility was evaluated according to 16-segment model of LV recommended by ASE. In addition, the wall motion score index (WMSI) of LV myocardium was calculated. The LV diastolic function was evaluated based on the mitral flow propagation velocity determined in an apical four-chamber view obtained in pulsed wave Doppler mode as well as based on the tissue velocity imaging parameters such as early diastolic mitral annular velocity (*e*') and ratio of transmitral early filling velocity (E) to *e*' (E/*e*'). The global longitudinal strain (GLS) was evaluated using three apical views (2-chamber, 3-chamber and 4-chamber views) obtained by 2D-speckle-tracking method and calculation of mean value.

A validated Morisco-Green test [11] was used to evaluate adherence to the current treatment. The test consisted of four questions concerning the attitude of the patient to the drug administration. The test can be filled by the patients themselves. However, a doctor/relative can also read out the questions and tick the received answers. Answers to each question were "Yes" or "No", 0 points were assigned to "Yes" and 1 point was assigned to "No". Patients having greater adherence to treatment gained 3 or 4 points. Poorly adhering and non-adhering patients gained 2 points or less.

Statistical processing of the data was carried out using Statistica 8.0 for Windows software. Qualitative characteristics are expressed in absolute values and percents. Quantitative variables were presented as median, 25th and 75th percentiles, i.e. Me [25;75]. The Mann-Whitney U-test was used to evaluate statistical significance of differences among the groups of patients. The differences were considered significant at $p < 0.05$. The relation of the variables was studied on the basis of a correlation analysis and determining Spearman's rank correlation coefficient.

Results and Discussion

Eleven patients (12.8%) filled in the questionnaires themselves, and 70 patients (81.4%) filled in the questionnaires with the help of a doctor or a relative, whereas 5 patients from the second group did not answer the questions. There were no statistically significant differences in terms of anamnestic and clinical parameters observed between patients who filled in the questionnaires themselves and those who were helped. ($p > 0.05$). Table 2 presents the results of the tests in both groups.

Table 2. *Morisco-Green test results*

Parameter	Group 1 (65-74 y. o.), (n = 21)		Group 2 (75-89 y. o.), (n = 60)		p-value
	Total	%	Total	%	
Patients forgot to take the drug	5	23,8	39	65,0	< 0,05
Patients were neglectful to the time of the drug administration	2	9,5	27	45,0	< 0,05
Skipping administration if feeling well	1	4,8	31	51,7	< 0,05
Skipping administration if feeling unwell	4	19,0	20	33,3	< 0,05
Median (Me [25;75])	3,0 [2,5;3,5]		2,5 [2,0;3,0]		< 0,05

Table 3. *Comparative evaluation of structural and hemodynamic parameters, obtained via two-dimensional echocardiography, in examined groups.*

Parameter	Group 1 (65-74 y. o.), (n = 21)	Group 2 (75-89 y. o.), (n = 65)	p<
IVSd, mm	1.1 [0.9;1.6]	1.1 [0.8;4.3]	blank
PWd, mm	1.1 [0.9;1.3]	1.1 [1.0;1.3]	blank
LV EDD, mm	41.5 [40.1;45.9]	44.5 [42.3;49.4]	0.05
LV ESD, mm	28.0 [27;34]	29.0 [28;35]	blank
LV EDV, mm	88.5 [84.5;105.5]	111.0 [98;123]	0.05
LV ESV, mm	38.0 [36.4;45.2]	45.0 [42;56.2]	0.05
LAind, mm/m2	30.0 [29;32]	30.0 [29;34.5]	blank
LAVind, ml/m2	32.1 [31.0;33.2]	34.0 [32.4;35.3]	0.05
RWT	0.52 [0.51;0.54]	0.53 [0.52;0.54]	blank
LV MMI, g/m2	99.0 [96.3;116.4]	102.0 [110.4;118.1]	blank
EF, %	54.0 [51;63]	53.5 [50;62]	blank
WMSI	1.2 [1;1.3]	1.26 [1.2;1.8]	blank
GLS, %	-13.6 [-12.3;-15.1]	-11.6 [-9.4;-14]	0.05
E/A, RU	0.7 [0.6;0.8]	0.8 [0.7;1.02]	blank
e' lat. MVFR, cm/s	8.47 [7.5;9.3]	9.91 [8.3;10.4]	blank
E/e', per-unit value	7.0 [6.5;9.5]	8.3 [7.6;10.1]	blank
DT, mc	0.21 [0.20;0.24]	0.23 [0.21;0.24]	blank

Note: The data are presented in the form of Me [25; 75]. **IVSd** — The thickness of the interventricular septum in diastole; **PWd** — Thickness of the posterior wall in diastole; **LV EDD** — End-systolic size of the left ventricle; **LV EDV** — End-diastolic volume of the left ventricle; **LV ESV** — End-systolic volume of the left ventricle; **LAind** — The index of the left atrium, **LAVind** — The index of the volume of the left atrium; **RWT** — Relative wall thickness; **LV MMI** — Left ventricular myocardial mass index; **EF** — LV ejection fraction by Simpson method; **WMSI** — regional wall motion score index; **GLS** — global longitudinal strain; **E/A** — Ratio of peak diastolic velocities of mitral valve blood flow; **e' lat. MVFR** — Tissue early diastolic velocity of the lateral part of the MV fibrous ring; **E/e'** — The ratio of the early diastolic velocities of the MV blood flow and the motion of the lateral part of the MV fibrous ring; **DT** — Is the delay time of the early diastolic flow

Lower adherence to treatment was observed in the senile age group (75 to 89 years) ($p < 0.05$). Patients of this group were more likely to forget to take the drug, were more neglectful to the time of the drug administration, and were more likely not to take the dose when they felt well.

In both groups, males took drugs less regularly: 25% vs. 47.3% for females ($p < 0.05$).

The EchoCG examination showed signs of the cardiac diastolic dysfunction at normal mean values of the LV ejection fraction (Table 3).

At the same time, the values of the global longitudinal strain (GLS) describing the global longitudinal systolic function of LV were obviously lowered in the both groups.

A comparison of the EchoCG results of the two groups demonstrated significant differences of the LV EDD, LV EDV, LV ESV, LAVind, and GLS values. Generally, more apparent structural and functional changes of the myocardium were observed in patients from the second age group.

The analysis of correlation between the adherence to treatment and the parameters describing the myocardial dysfunction helped to reveal an inverse correlation between the total Morisco-Green score and LV EDV ($r = -0.33$; $p < 0.05$), between the total Morisco-Green score and E/*e'* parameter describing the diastolic function ($r = -0.37$; $p < 0.05$), as well as direct correlation between the total Morisco-Green score and the LV global longitudinal strain ($r = 0.53$).

Discussion

The results of the quantitative assessment of the adherence among the elderly age group patients suffering IHD and CHF based on the validated Morisco-Green test showed that the adherence to treatment in the elder group patients (65 to 74 years) is higher than in the group of senile patients. The obtained results evidencing the lower adherence to treatment of the senile patients are consistent with the literature [7].

Females followed the medical advice better in both age groups. According to the literature, females are more likely to adhere to treatment and to the medical advice than males [7].

Possible causes of the lower adherence can be conventionally divided into the main five groups [14]:

- Factors related to the patient (sex, age, education level, personal features).
- Factors related to the doctor (awareness on the disease and the treatment benefits, establishing or failure to establish confidential relations with the doctor, inadequate supervision and/or advice upon discharge).
- Social and economic factors (medication cost).
- Factors related to the medication features (efficiency, complexity of the dosage regimen, adverse events).
- Factors related to the disease (asymptomatic disease course, psycho-emotional state, presence of depression, cognitive impairment).

The results obtained in the study can evidence that one of the causes of the poor adherence to treatment in patients of the elderly age groups suffering IHD and CHF are memory impairment [4, 9]. Furthermore, the literature indicates that reasons of neglectful attitude to the time of the drug administration and the failure to take the dose when feeling well may include the poor awareness of the patient of the disease and the treatment methods, the importance of the current treatment, the cost of the prescribed medications if they are to be administered over a long period time, the complexity of the dosage regimen, and fear of the adverse events induced by the administered drugs [1, 2, 8].

On the one hand, more apparent impairment of the LV myocardium structure and function in patients of the senile age group (75 to 89 years) can be attributed to the higher occurrence of postinfarction cardiosclerosis [6]. On the other hand, lower adherence to treatment observed in this group can also have negative influence on the myocardial dysfunction. This can be proved by the correlation between the adherence level score (total Morisco-Green score) and EchoCG parameters. It should be noted that the correlation is demonstrated not only with the diastolic dysfunction parameter (E/*e'*), but with the LV global longitudinal strain, which is currently considered indicative of the LV systolic function [5].

Conclusion

The obtained data indicate the lower adherence of senile patients to a prescribed course of treatment for IHD and CHF when compared with elderly age patients. The poor adherence to treatment along with postinfarction cardiosclerosis apparently can be considered one of the factors promoting the progression of myocardial dysfunction.

Conflict of interest

The authors declare no conflict of interests.

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ИНФОРМАЦИОННОЕ ПИСЬМО

Главное военно-медицинское управление МО РФ;
Военно-медицинская академия имени С.М. Кирова
Научно-практическое общество баротерапевтов
Санкт-Петербурга и Ленинградской области

17 — 18 мая 2018 года проводят

Юбилейную X Всеармейскую научно-практическую конференцию «БАРОТЕРАПИЯ В КОМПЛЕКСНОМ ЛЕЧЕНИИ И РЕАБИЛИТАЦИИ РАНЕНЫХ, БОЛЬНЫХ И ПОРАЖЁННЫХ»

Конференция состоится в Военно-медицинской академии имени С.М. Кирова по адресу: 194044, Санкт-Петербург, Военно-медицинская академия имени С.М. Кирова, ул. Академика Лебедева, д. 6. Проезд до станции метро «Площадь Ленина».

На конференции предполагается рассмотреть теоретические и прикладные вопросы лечения раненых, больных и пораженных; проблемы реабилитации человека со сниженной работоспособностью различными видами и методами баротерапии; теоретические и практические положения гипербарической физиологии и водолазной медицины.

ТРЕБОВАНИЯ К ОФОРМЛЕНИЮ ТЕЗИСОВ

Тезисы, объемом не более одной машинописной страницы (формат RTF, шрифт 12, Times New Roman, количество знаков в строке не более 70, поля 2,0 см, через 1,5 интервала, с отступом в начале абзаца), принимаются отпечатанные на бумаге (1 экземпляр с подписями авторов), плюс — в электронном виде на USB-флеш-накопителе или компакт-диске и по электронной почте. *Убедительная просьба к авторам проверять электронные носители на наличие «вирусов».*

Верхняя строка — инициалы и фамилии авторов жирным шрифтом (ФИО докладчика подчеркивается шариковой ручкой в экземпляре, отпечатанном на бумаге); ниже — заглавными буквами — название работы; ниже — учреждение, город; ниже текст.

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1. Фамилия, имя, отчество (полностью);
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4. Адрес и телефон (рабочие и, желательно, домашний);
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Иванов И.И.

ИНДИВИДУАЛЬНАЯ ОПТИМАЛЬНАЯ ДОЗА КИСЛОРОДА ПРИ ОДНОМ СЕАНСЕ ГБО (ОДНОРАЗОВАЯ ДОЗА)

Военно-медицинская академия имени С.М. Кирова, Санкт-Петербург
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В исследовании по проблеме оптимальной дозы кислорода при гипербарической оксигенации принимали участие 88 практически здоровых мужчин в возрасте 24-34 лет...

Рассматриваться будут тезисы, отправленные в оргкомитет до **1 марта 2018 года** по адресу: **194044, Санкт-Петербург, Военно-медицинская академия имени С.М. Кирова, ул. Академика Лебедева, д. 6, кафедра физиологии подводного плавания** с пометкой: **Конференция-2018** и по электронной почте an.a.an@mail.ru, arseniyshitov@mail.ru

При ***необходимости*** в марте-апреле 2018 г. в адрес участников конференции будут направлены **Приглашения.**

Для участников конференции 18 мая планируется культурная программа.

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CASE OF CHRONIC CALCULOSIS PANCREATITIS IN PATIENT WITH ALCOHOLIC CIRRHOSIS

Abstract

The article describes clinical features, differential diagnosis and treatment of the patient with chronic calcific pancreatitis (HCP) and alcoholic liver cirrhosis (LC). The etiologic role of chronic alcohol intoxication in the development of these diseases is discussed. The patient has a history of long-term use of alcoholic beverages at hepatotoxic doses and smoking. Patient was examined before admission to our clinic. Chronic heart failure, nephrotic syndrome, paraneoplastic syndrome were excluded as the cause of generalized edema.

Patient R. was admitted to the Gastroenterology Department with ascites of unknown etiology. The severity of the patient's condition was caused by malabsorption syndrome and hepatocellular insufficiency leading to the development of edema-ascitic syndrome and trophological insufficiency. The decrease of protein levels (total protein — 38 g / l), low of albumins (14 g \ l) was observed. EGDS showed signs of portal hypertension: 1 degree esophageal varices, portal gastropathy; In addition, an increase in the size of the papilla of Vater. To clarify the nature of the pancreas damage endoscopic ultrasound was performed, which revealed multiple calcifications in the pancreas tissue. To resolve biliary hypertension stenting of the common bile duct was performed. Pancreatic duct drainage failed due to the presence of calculus at the level of the isthmus. The preferred method of treatment for the patient is Roux-En-Y hepaticojejunostomy. This case demonstrates social importance of HCP and LC combination, which leads to reduced quality of life, early disability, reduced life expectancy, as well as to an increase in treatment costs.

Key words: *calcific pancreatitis, alcoholic chirrosis*

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EV — esophageal varices, DD — duodenum, PH — portal hypertension, PG — pancreatic gland, HE — hepatic encephalopathy, CNT — connect-the-numbers test, FCS — fibrocolonoscopy, CP — chronic pancreatitis, LC — liver cirrhosis

Introduction

We know that excessive alcohol consumption is the cause of a large number of diseases (more than 60) and traumas leading to significant social and economic consequences [1]. This is an independent risk factor leading to the development of such diseases as chronic pancreatitis (CP) and liver cirrhosis (LC). According to J. Rehm et al., 2009 [2] alcohol contributes 3.8% of all cases of death. Occurrence of CP varies from 1.6 to 23.0 cases per 100,000 people; an increase of the occurrence is observed [3].

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Both of these chronic diseases more often develop in case of prolonged alcohol intoxication (80 g/day) over the course of at least six years [4], while the risk growth is exponential and the type of the alcoholic drink makes no difference [5].

The severity of these diseases is determined based on the maintained pancreas and liver functions. In case of apparent morphological changes, the patients show aggravating impairment of protein synthesis, exocrine and endocrine insufficiency, which result in loss of quality of life and disability. Combination of CP and LC, particularly in males, leads to early disablement, reduced life span, and an increase in the costs of treatment. So this is a topical medical and social issue.

We present a case of combined pancreas and liver injury in a patient who has consumed toxic doses of alcohol for a long time.

Clinical Case

Patient R., 45 years old, was admitted to the Gastroenterology Department with Hepatological Facilities of the State Clinical Hospital n. a. V. M. Buyanov (clinical practice base of the Department of Internal Medicine (advanced course) No. 2 of the Federal State Budgetary Institution of the Higher Education Russian National Research Medical University n. a. I. I. Pirogov of Ministry of Healthcare of the Russian Federation) as part of the "Heath Capital" program.

On admission the patient complained of weakness, increased size of the abdomen, apparent leg swelling, episodes of unstable bowel movements of up to 4 to 5 times a day (where there was a tendency to constipation over the last 2 months), and loss of 12 kg weight over the 6 months prior to the hospitalization.

The medical history includes information on prolonged consumption of drinks with high alcohol content at a dose of about 60 g/day and smoking (pack-year index of 25). The patient suffered from hepatitis A in childhood.

In 2005, he underwent pancreatic drainage indicated due to pancreonecrosis. In 2007, the patient had an episode of a significant jaundice; during the following years increased cytolytic enzymes activity (up to 4 norms from the upper threshold) was periodically observed.

The current aggravation started in 2016 and included leg swelling and development of ascites and anasarca in spring, 2017. Examinations performed at the local hospital demonstrated changes in the following biochemical blood parameters: hypoproteinemia (56 to 37 g/l), hypoalbuminemia (15 g/l); no other deviations were detected. Esophagogastroduodenoscopy (EGD) showed small bulging in the area of major duodenal papilla without exophytic growth, and FCS showed small polyps in the various sections of the colon. The additional examination including EchoCG, abdominal cavity MRI, diagnostic laparocentesis, sternal biopsy, determination of 24-hour proteinuria , etc., made it possible to rule out congestive heart failure as well as nephrotic and paraneoplastic syndromes as the cause of swelling and ascites syndromes.

The local hospital diagnosed chronic biliary pancreatitis and ascites of unclear etiology. A conservative therapy (pancreatine, torsemide, spironolactone) had no effect. The decision was made to perform laparocentesis to treat the refractory ascites. The procedure was complicated with perforation of the jejunum wall and subsequent plication thereof.

When the patient was admitted to our department (November 2017), his condition was assessed as moderate. Examination results: normosthenic constitution, decreased nutrition (BMI 18 kg/m^2); muscle hypotrophy of the upper pectoral arch; edema of lower limbs up to the hips and scrotum, ascites, and anasarca. Skin and scleras are of normal color, watch-glass nails. A postoperative scar, 20 cm in length, along the white line, and venous collaterals on the lateral walls of the abdomen were observed. Auscultation shows reduced breath sounds in the lower parts of the lungs as well as no rales in the lungs. Respiratory rate was 22 breaths per minute. The peripheral blood was saturated with oxygen for 96%. No abnormalities were found in the cardiovascular system. The abdomen was distended, and free fluid was determined by percussion. Palpation of the liver and spleen was impossible due to ascites and flatulence. The liver size determined by Kurlov method was 13 × 9 × 10 cm. Urination was free, and CVA tenderness was negative at both sides.

Examination Results

The patient underwent complex clinical, laboratory and instrumental examination.

There were no significant abnormalities found in the total blood count and urinalysis. Only relative lymphopenia was noted.

The biochemical blood analysis showed such pathological changes as significant hypoproteinemia (total protein was 38 g/l), hypoalbuminemia (14 g/l) and hypocholesterolemia (2.0 μmol/l). HbA1c level was 5.2%. A coagulogram showed reduced Quick value of 58.50%, INR 1.390, content of D-dimers of 1,150 ng/ml.

A stool test showed a significant amount of fatty acids, extracellular amylum, and bacteria (bacilli and cocci).

Taking into consideration clinical and biochemical data, the patient was diagnosed with stage II trophological insufficiency according to V. M. Luft [6].

Blood tests for cancer-specific markers demonstrated increased CA 125–285.5 U/ml (normal level is up to 35 U/ml), and CA 19-9, PSA, CA 72-4, and AFP were within the reference range.

A count-the-numbers test (CNT) showed a mild hepatic encephalopathy (HE) (CNT 62 s).

X-ray of the lungs demonstrated a hemidiaphragm elevated up to the 5th to 6th ribs as well as bilateral pleural effusion. US of the abdominal cavity showed free fluid; heterogenous liver structure with fibrosis areas; a suspension in the gallbladder; the pancreas was not satisfactory visible; an interintestinal formation containing fluid (176 × 102 × 128 mm) in the right mesogastrium.

To clarify the parameters of the pancreas changes we performed an abdominal cavity enhanced-CT (100 ml of Scanlux-370). The CT confirmed the presence of free fluid in the abdominal cavity, encapsulated liquid formations, diffuse changes in liver as well as apparent degenerative changes in pancreas such as multiple "lumpy" calcifications of the structure.

EGD showed signs of portal hypertension (PH) such as esophageal varices of the stage I and portal gastropathy. In addition, an increase of the major duodenal papilla dimensions (up to 12 mm) was noted. Visually, its orifice is swollen and includes section of hyperplasia with lobulation.

Endoscopic US was performed to complete the examination. At the level of the intrapancreatic section, the bile duct has a relatively compressed narrowed structure (3 mm), upper bile duct has width of up to 8 mm; common hepatic duct is 8.5 mm; the duct wall is not thickened along the entire length; it has three layers and non-echogenic lumen. Contours of the pancreas are clear and uneven, and the echostructure is changed due to presence of multiple hyper-echogenic inclusions of uneven rounded form of 5 to 8 mm with or without acoustic shadows; visible parenchyma has apparently low echogenicity and heterogenous structure. In the area of the pancreas head at the outlet third part of the duct of Wirsung, an oval concrement of 8 mm diameter is detected. One more concrement of up to 8 mm in size is located more distally, and both concrements have an acoustic shadow. The duct of Wirsung is in the head of the pancreas, has a form of a moderately curved tubular structure of up to 8 mm. Distally from the isthmus it is up to 9 mm in width, and its lumen is heterogenous. The parenchyma in the body of the gland is atrophic, the body width is up to 12 mm; there are multiple concrements along the duct wall, in its lumen and lateral branches (up to 3 to 5 mm); the lateral branches are dilated and curved. The duct wall is hyperechogenic, uneven, with calcification inclusions in walls (Figure 1).

In paraduodenum, slightly below the papilla, in the duodenum wall there are two adjacent cystic inclusions of up to 2 cm in size (Figure 2).

An ERCP examination was performed with regard to the pancreatic and biliary hypertension and followed with a stenting of the bile duct with a polymer stent of 8 cm in length, 10 F diameter. When the conducting system was removed, the bile containing air bubbles vigorously flew via the stent. It was not possible to drain the pancreatic duct since it was obstructed with a concrement at the isthmus level.

Based on the performed examination, chronic metabolic pancreatitis caused by intoxication, stage C3 as per Buchler [7], alcoholic LC, class B as per Chaild-Pugh (score 7) was diagnosed.

The course of the disease was complicated by the calcification in the pancreas stroma, lithiasis of the duct of Wirsung, stenosis of the bile duct distal section, pancreatic and biliary hypertension, formation of the biliary sludge (gallstone disease, stage I), and papillary cysts of the duodenum walls. In addition, the classical complications of LC were detected: stage I esophageal varices, portal gastropathy,

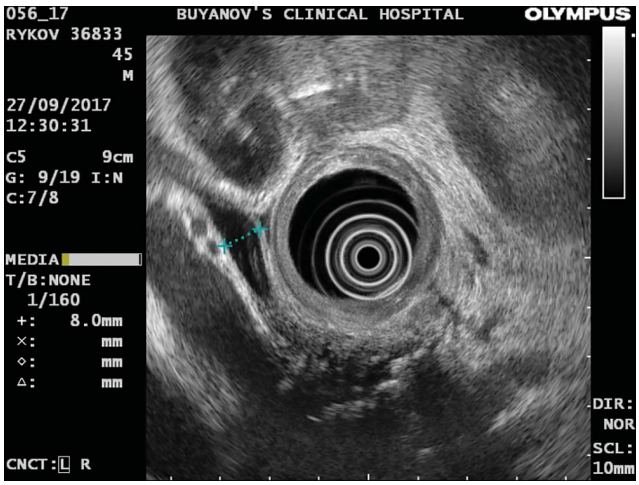

Figure 1.

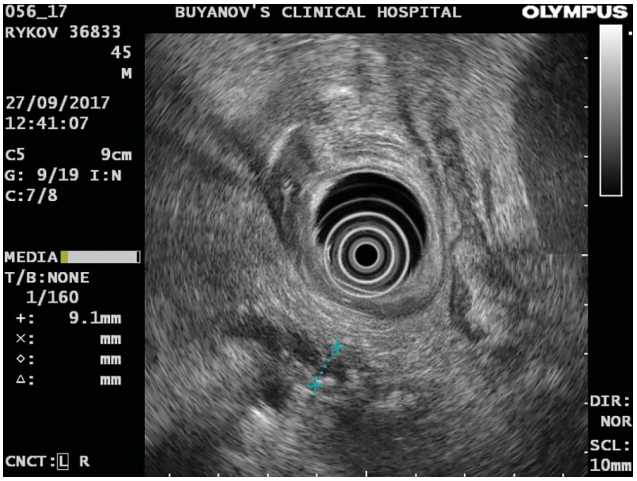

Figure 2.

swelling and ascites syndromes, bilateral pleural effusion, and significant liver dysfunction (hypoalbuminemia, hypocoagulation, stage 1 HE). Furthermore, multiple surgeries (2005 and 2017) resulted in onset of abdomen cavity peritoneal adhesions.

The patient R. was treated with diuretics, aldosterone antagonists, non-selective β-blockers, enzymes, spasmolytics, vitamins, and parenteral nutrition, including repeated albumin transfusions. In the course of the prescribed treatment, the patient reported a decrease in weakness, and swelling and ascites syndrome regressed. The patient's weight increased by 3 kg.

The following advice was given at discharge: changes in the lifestyle (completely stop smoking and drinking alcohol), bland diet (half portions with a sufficient amount of proteins), high-dosage enzyme replacement therapy and diuretics, non-selective β-blockers, hepatoprotectors, and food supplements. Follow-up is continuing.

Discussion

The patient R. was diagnosed with a combined injury of the pancreas and liver as the result of complications.

The disease severity was conditioned by malabsorption syndrome and significant impairment of the protein synthesis liver function, which resulted in the trophological insufficiency and development of swelling and anasarca. It is known that trophological insufficiency in CP patients aggravates impairment of the pancreas exocrine function and promotes a "vicious circle" formation [8]. In addition, hypoproteinemia was a major manifestation of the above mentioned pathological processes.

The differential diagnosis included a range of diseases, some of which had been already excluded at the pre-hospitalization stage. Thus, EchoCG demonstrated an unchanged ejection fraction and normal volume of the heart cavities, absence of valve regurgitation.

Peritoneal adhesions that developed after surgeries and that were confirmed by the results of the visualization methods (encapsulated liquid formations in the abdominal cavity showed by US and CT) were manifested as constipation and obscured CP and LC clinical patterns.

During the course of examinations, no evidence of neoplastic process was found, and the increased level of CA 125, apparently, was caused by the chronic inflammation process in the abdominal cavity [9].

CP was diagnosed based on the medical history and the results of laboratory and instrumental examinations.

According to M. W. Buchler et al., 1992 [10]; J. Izbicki et al., 1995 [11], an episode of acute pancreatitis leads to significant structural changes in the pancreas. A chronic inflammation of the pancreas head results in narrowing of the major pancreatic duct, cysts formation and, finally, in calcification of tissues along with the exocrine insufficiency onset. These changes were noted in patient R. based on the results of endoscopic US and CT. Calcifications in the various pancreas sections are a pathognomonic sign of the complicated CP course [5]. As we observed, the morphological changes in the pancreas led to significant exocrine insufficiency and biliary hypertension, which aggravated the course of the disease, and, moreover, represented a risk

of both jaundice onset and recurrent episodes of pancreonecrosis.
In the course of the examination, patient R. demonstrated symptoms, which are not typical for CP such as hypoalbuminemia, coagulopathy, esophageal varices, portal gastropathy, i.e. signs of LC.
One of the signs of the complicated LC course is hepatocellular insufficiency. As we observed, the significant manifestation of hypoalbuminemia was conditioned by the LC and CP combination.

As the result of pancreatic duct obstruction, the applied methods of the conservative treatment had no effect. In such cases, endoscopic stenting helps to solve the problem effectively [12].
However, presence of a concrement at the place of the desired stent location in our case made it impossible to ensure complete relief of pancreatic hypertension. Roux-En-Y hepaticojejunostomy should be considered as a method of treatment. It is currently preferred if the patient has no pain syndrome [13].

Conclusion

The cause of LC and CP in patient R. was chronic alcoholic intoxication. According to the international and Russian guidelines, alcohol has an equally negative impact on the pancreas and liver tissues. Currently discussions are being held about what is the ethanol dosage that will result in irreversible changes in the pancreas. Thus, according to the pan-European guidelines, it is 80 g/day [5]. However, according to meta-analysis performed by N. M. Irving, 2009, this dose may only be 40 g/day [14].
Taking into account the episode of pancreonecrosis in 2005, it is considered that alcohol in high doses triggered not only morphological changes but also hepatobiliary system changes in patient R.
Combined injury of the pancreas and the liver had mutually negative influence on the course of the disease. Development of such pronounced hypoalbuminemia (14 g/l) in absence of adequate drug and surgical treatment determines prognosis letalis in a patient with calculous pancreatitis and LC.

Conflict of interests
The authors declare no conflict of interests.

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APPLICATION OF INTENSIVE LIGHT RADIATION IN THE PATIENT WITH ERYTHEMATOTELANGIECTATIC ROSACEA

Abstract

We present a case report of a patient with erythematotelangiectatic form of rosacea. Rosacea is a chronic recurrent dermatosis, characterized by skin lesions of the face in the form of erythema and papulopustular elements, which has polyethiological origin. The disease occurs more frequently in women aged 30-50 years who have a certain genetic predisposition to transient face hyperemia, less often — hyperemia of the neck and décolleté zone. It is believed that individuals with I and II phototypes are more prone to dermatosis, but the disease can occur in any skin phototype. The patient was admitted with complaints on rashes in the chin area and nasolabial triangle, flushing of the face, accompanied by tingling and burning. She never consulted a dermatologist before. The patient was diagnosed with: erythematotelangiectatic form of rosacea (according to the classification proposed by National Rosacea Society in USA, stage I — persistent erythema and telangiectasia). The score according to Rosacea Diagnostic Evaluation Score (RDES, the Russian Score) was 12 points. There are many approaches to rosacea treatment. Drug therapy is divided into systemic, topical and complex schemes. Systemic therapy has a number of side effects, so for mild and moderate-to-severe rosacea, just topical therapy is often prescribed. Because of the presence of pathologically altered vessels and low efficacy of metronidazole, a course of phototherapy with intense incoherent pulsating light at standard parameters was prescribed. There was a significant improvement after two procedures, but vessels smaller than 0.4 mm remained intact, so the duration of the first pulse was increased in order to influence small-caliber vessels. Individual selection of parameters (duration of the first impulse and energy density) was performed based on the dermatoscopic pattern and patient's phototype, which resulted in a significant clinical effect and persistent remission. RDES score was 1 point after treatment. This clinical case demonstrates the effectiveness of phototherapy with intense incoherent pulsating light with individual selection of the duration of the first pulse and energy density in patients with erythematotelangiectatic rosacea. In IPL-treatment schemes, it is desirable to select individual parameters for the duration of the first pulse and energy density, based on the features of the dermatoscopic pattern and skin phototype of each patient.

Key words: *rosacea, erythematotelangiectatic subtype, Intense Pulsed Light Therapy, pulse duration, Demodex*

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IPL — Intense Pulsed Light

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Introduction

Rosacea (ICD-10 L71) is chronic recurrent dermatosis characterized by skin lesions in the form of erythema and papulopustular elements having a polyethiological origin. The disease is more common in women aged 30 to 50 years with a certain genetic predisposition to transient face hyperemia, less often — hyperemia of the neck and décolleté zone [1]. It is believed that individuals with I and II phototypes are more prone to dermatosis, but the disease can occur with any skin phototype [1].

In Europe, the incidence of rosacea ranges from 1.5 to 10%. According to Russian authors, rosacea accounts for about 5% of all dermatological diagnoses [2]. In the USA the percentage of rosacea among dermatoses ranges from 8 to 9%, and in Scandinavian countries and Germany — from 7 to 10% [3].

There are 4 main subtypes of rosacea (corresponding to erythematous, papulopustular, hypertrophic stages and ophthalmic rosacea in previous classifications) and one type — granulomatous rosacea.

Rosacea subtypes:

- Subtype I — erythematotelangiectatic.
- Subtype II — papulo-pustular.
- Subtype III — phymatous.
- Subtype IV — ocular [1].

The disease may be accompanied by severe psychological discomfort in patients. There is a high degree of anxiety, vulnerability, stress associated with the outward appearance of patients [4].

There are many approaches to the treatment of rosacea. Drug therapy is divided into systemic, topical or complex therapy. Antibiotics from the group of tetracyclines, macrolides, and systemic retinoids are most often used for systemic therapy [1]. The drug of choice is doxycycline [1]. However, systemic therapy has a number of side effects, therefore, in mild and moderate rosacea only topical therapy is more often prescribed [5].

A number of studies have proven the efficacy of IPL-systems (Intense Pulsed Light) in the treatment of the erythematotelangiectatic subtype of rosacea [6]. IPL-therapy is characterized by minimal side effects and prolonged remission after treatment, and therefore topical drugs lose their relevance [5, 7].

We present a clinical case of treatment with intense light radiation in a patient with the erythematotelangiectatic subtype of rosacea.

Case Report

Female patient N, 40 years old, came to the clinic with complaints of periodic rashes on the chin and in nasolabial triangle, as well as facial hyperemia periodically accompanied by tingling and burning in this area. Transient facial hyperemia has occurred during the last ten years with intake of spicy food, red wine, psycho-emotional stress. Over the past year, the frequency of the above complaints has increased considerably — up to several times a day. Erythema of the nasolabial triangle region has become persistent (**Figure 1**).

The female patient experienced severe psychological discomfort, and she attributed the loss of her job to her appearance. She started avoiding friends. She had never consulted a dermatologist before.

Status localis: during the first consultation with the dermatologist, there were symmetrically dilated vessels, telangiectasia and isolated exacerbated

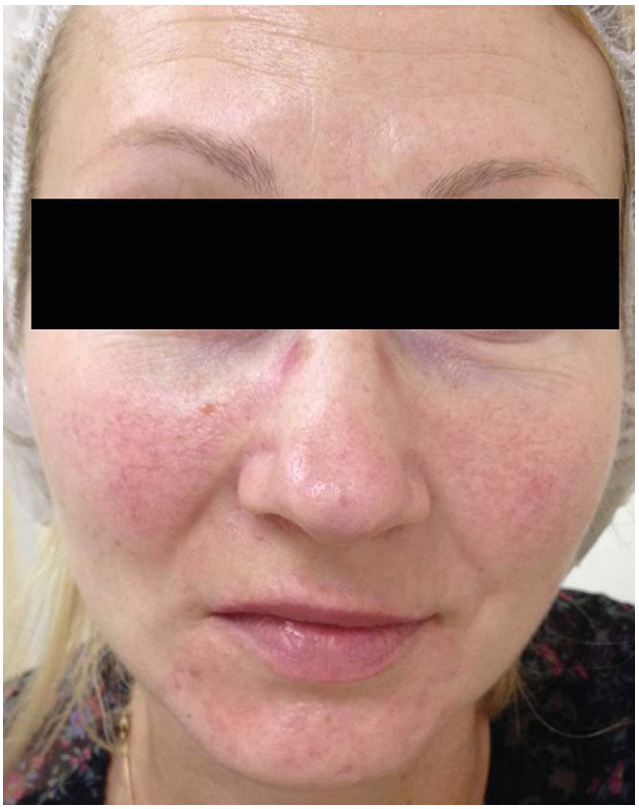

Figure 1. *Erythema of the nasolabial triangle*

papules in the chin area. Fitzpatrick skin phototype II. The skin of the trunk, upper and lower extremities was of normal color and free from rashes.

Dermatoscopy revealed dilation and branching of blood vessels of different caliber, follicular plugs and scales.

The patient was diagnosed with: erythematotelangiectatic form of rosacea (according to the classification proposed by National Rosacea Society in USA, stage I — persistent erythema and telangiectasia). The score according to Rosacea Diagnostic Evaluation Score (RDES, the Russian Score) was 12 points [8].

Counseling by psychotherapist: the state of consciousness was normal. All kinds of orientation are preserved. Delirium and perceptual deception are not revealed. She has contact willingly, but has difficulties in articulating complaints. She reports paroxysmal itching in the face comparable with insect bites. At the same time there is an irresistible desire to strongly scratch the itchy area of the skin. When she tries to hold back the state becomes painfully unbearable: internal stress rises dramatically, she may lash out and shout at those around. She can restrain herself for a few minutes at most. She notes that itching is exacerbated by stressful situations. She knows in advance when the exacerbation will occur. The urge to scratch the skin increases on with conflicts and troubles. Borderline affective disorders with obsessive and phobic symptoms present in the mental status. Personality traits with anxiety suspiciousness, adhesiveness, pedantry and compulsion. Criticism to own status is preserved. She expresses a desire to undergo psychotherapy.

Conclusion: obsessive-compulsive disorder F42. A course of cognitive behavioral therapy is recommended.

Consultation with a gastroenterologist: biliary dyskinesia of hypokinetic type. Recommendations: diet No. 5, 10% solution of magnesium sulphate in amount of 1 tablespoon 2–4 times per day 10–15 minutes before meals, tincture of ginseng.

Consultation with a gynecologist-endocrinologist: no pathology was revealed.

Test for Demodex folliculorum: positive.

Prescribed treatment: metronidazole gel 0.75% in the morning, metronidazole cream 1% at bedtime, applied in a thin layer under occlusive dressing on pre-cleansed skin. The patient was recommended skin care using mild cleansing, moisturizing and photoprotective agents designed for sensitive skin, and to avoid aggressive cosmetic procedures.

At the dermatologist's appointment in 8 weeks: the patient notes improvement, burning in erythema area disappeared. Symmetrically dilated vessels and telangiectasia were on the facial skin. Erythema is persistent (**Figure 2**). Papules are observed, no excoriation. RDES score was 10.

Dermatoscopy: without changes.

Taking into account the pronounced vascular changes on the face and the slight effect of metronidazole, the patient was prescribed a course of phototherapy with intense incoherent pulsed light. The treatment was carried out using a device that transmits a wavelength of 560 nm and can change the number and duration of pulses, energy density and delay time between pulses. The procedures were carried out with frequency of once a month. The facial skin was treated with two passes in staggered order with a time interval of 2 seconds between pulses. The spot size of

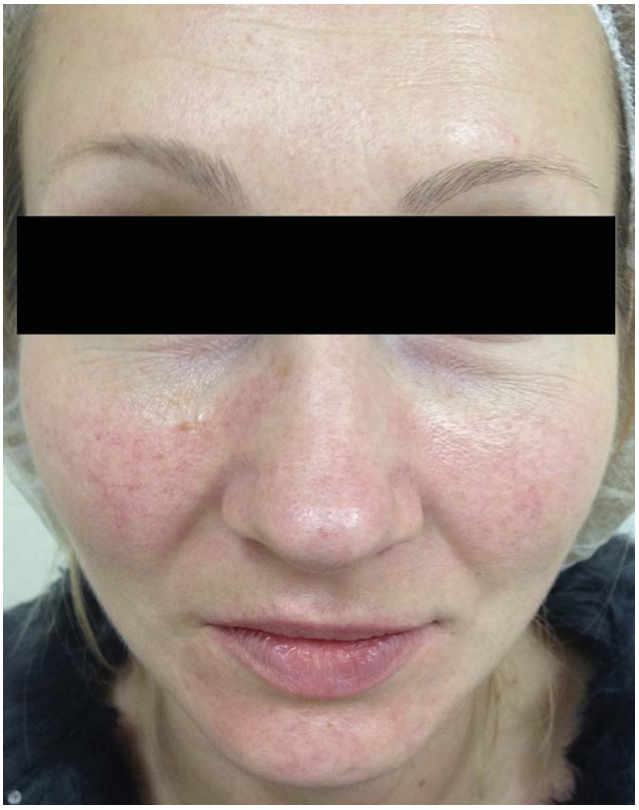

Figure 2. *Erythema of the nasolabial triangle (after 8 weeks)*

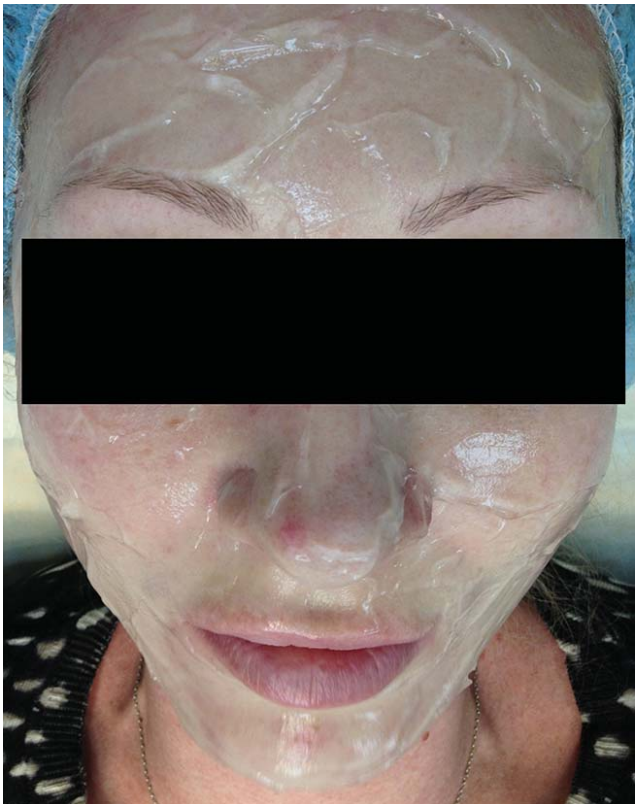

Figure 3. *The course of phototherapy*

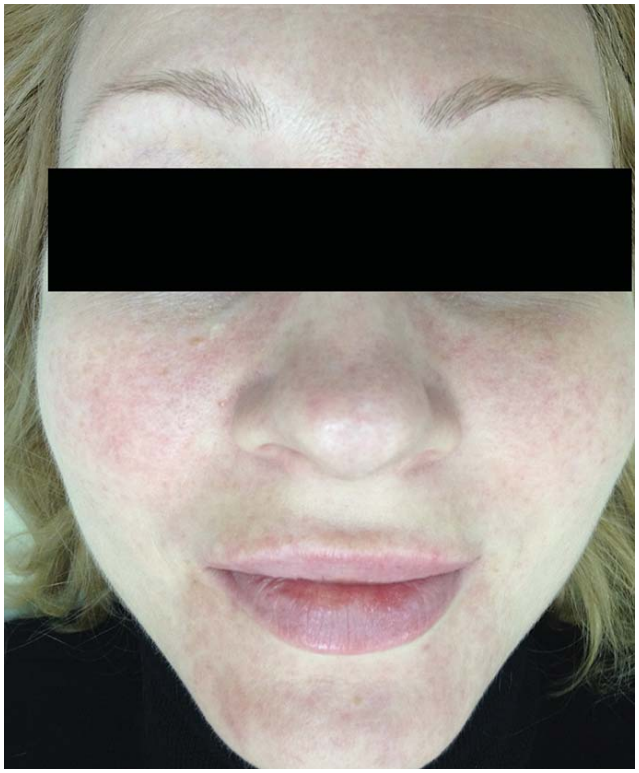

Figure 4. *Type of erythema of the nasolabial triangle after 2 procedures of phototherapy*

Table 1. *Scheme of treatment of patient N*

№ procedure	Program	Pulse Type	Pulse width 1 (ms)	Pulse width 2 (ms)	Delay (ms)	Energy density (J / cm²)
1	Program 1	Double	2,0	4	15	24
2	Program 1	Double	2,0	4	15	26
3	Program1 (User defined pulse type parameter)	Double	2,2	4	15	28
4	Program1 (User defined pulse type parameter)	Double	2,2	4	15	28
5	Program1 (User defined pulse type parameter)	Double	2,4	4	15	28
6	Program1 (User defined pulse type parameter)	Double	2,4	4	15	30

the handpiece was 8 × 34 mm². Cooled gel was applied on the treated surface beforehand. Application anesthesia was used (**Figure 3**).

The first two procedures were carried out using standard parameters laid down by the manufacturer (duration of the first pulse of 2.0 ms, duration of the second pulse of 4.0 ms and delay time of 15 ms). Clinical improvement was achieved in the patient: erythema became less pronounced, the area of telangiectasia decreased, RDES — 5 points (**Figure 4**).

The dermatoscopic picture has improved significantly, and most of the dilated vessels were small-caliber vessels, which remained intact, while vessels with a diameter of more than 0.4 mm were coagulated. Given the situation it was decided to increase the duration of the first pulse to affect small-caliber vessels.

Therefore, from the third to the sixth procedure we consecutively increased the duration of the first pulse from 2.0 ms (1 and 2 procedures) to 2.2 ms (3 and 4 procedures) and to 2.4 ms (5 and

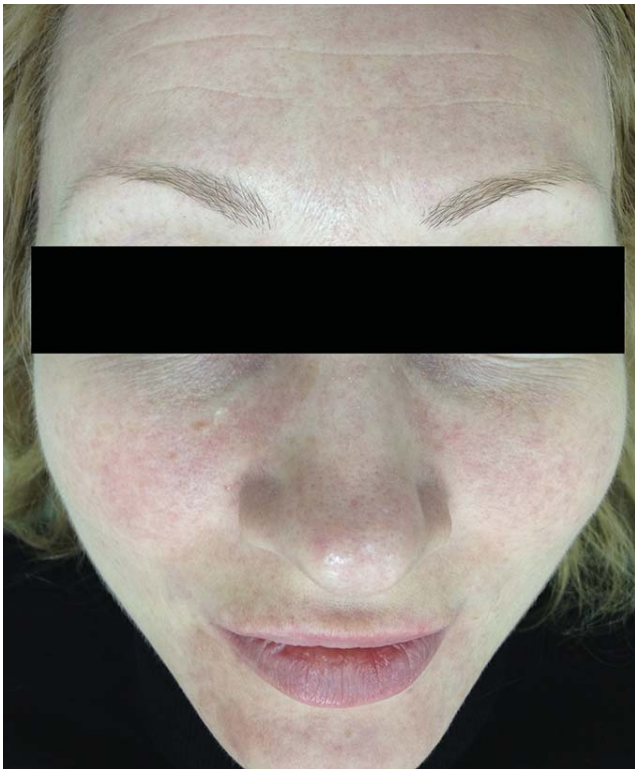

Figure 5. *Type of erythema of the nasolabial triangle after 6 procedures of phototherapy*

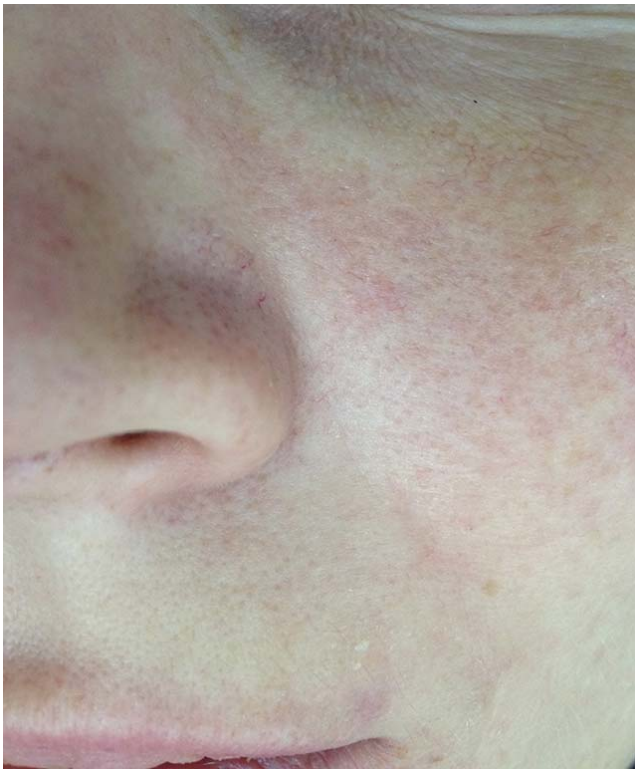

Figure 5A. *Type of erythema of the nasolabial triangle after 6 procedures of phototherapy*

6 procedures). The energy density varied from 24 to 30 J/cm^2. After a course of six procedures, a significant clinical improvement was achieved: erythema became insignificant, telangiectasia regressed, RDES — 1 point (**Figures 5 and 5A**). Dermatoscopy revealed a decrease in the number of vessels of different caliber, including vessels with a diameter of less than 0.4 mm, a decrease in the sizes of the stoma of the hair follicles.

Test results for *Demodex folliculorum*: negative.

After the therapy, the patient was followed-up, during the first month — every other week, and then every six months. After 24 months, there was a positive permanent clinical effect.

Discussion

We presented a clinical case of IPL-therapy in a female patient with erythematotelangiectatic form of rosacea with individual selection of the duration of the first pulse and energy density resulting in long-term clinical remission.

In 1997, the IPL-system was for the first time used to treat benign vascular skin lesions [9]. Many clinical studies confirm the efficacy, safety and long-term outcomes of this method [9, 10].

Kubanova A. A. and Makhackova Yu. B. describe the results of IPL-treatment efficacy with change of energy density depending on the subtype of the disease and the skin phototype of the patients [11]. In this clinical case, not only the energy density was changed during treatment, but the duration of the first pulse was also consistently increased to 2.4 ms, which made it possible to achieve photothermolysis of pathologically altered vessels with a diameter of less than 0.4 mm. The parameters of the duration of first radiation pulse should be selected individually for each patient taking into account the level at which the epidermis absorbs the energy of photons (phototype of the particular patient), as well as the target on which we want to act. In the erythematotelangiectatic form of rosacea, oxyhemoglobin, which is contained in the vessels, is used as a target. For implementation of selective photothermolysis of pathologically altered vessels it is necessary for the target vessel to have a higher radiation absorption coefficient than chromophores in the surrounding tissues, and for the duration of light exposure to be short enough to prevent irreversible thermal damage to the tissues adjacent to the target vessel [12].

Course treatment with IPL-systems is usually carried out using standard or empirically verified parameters [7, 10]. Photothermolysis of vessels with a diameter of less than 0.4 mm was achieved, and thus the results of IPL-therapy were improved due to longer duration of the first pulse.

Conclusion

We presented a clinical case of treatment in a female patient diagnosed with erythematotelangiectatic form of rosacea, who reported significant clinical improvement after a course of phototherapy with intense pulsed light. In IPL-treatment regimens it is desirable to choose the individual parameters for the duration of the first pulse and the energy density based on the characteristics of the dermatoscopic pattern and the skin phototype of each patient.

Conflict of interests

The authors declare no conflict of interests.

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TRANSIENT GLOBAL AMNESIA IN A PATIENT WITH HYPERTENSIVE CRISIS

Abstract

Transient global amnesia was introduced into clinical practice by Fisher and Adams in 1964 to denote a sudden onset of transient disorders in all the types of memory along with loss of memory abilities, retrograde amnesia and inability to recall recent events while still retaining consciousness. The incidence of TGA is 5 to 10 people per 100,000 members of the population per year, but the real incidence is unknown because the episodes of memory loss are temporary and many patients do not consult a doctor at the time when amnesia develops. The triggers of TGA are physical activity, sexual intercourse, pain, Valsalva maneuver, etc. TGA is of interest not only for the neurological practice but therapeutic practice as well since cases of its development are reported in patients with hypertension, patent foramen ovale, cardiac conduction disorders, and mitral valve prolapse. We present a case of a 57-year-old female patient with TGA. She was admitted to the hospital due to hypertensive crisis and an impaired ability to retain new information that started after physical activity. The diagnosis of TGA was based on information from the attack witnesses, the sudden onset of anterograde amnesia, normal consciousness of the patient and short duration of the attack. Also, the patient had no features of stroke, acute hypertensive encephalopathy, epilepsy or alcohol-related blackout. TGA is more typical for females over 50 years with symptoms that start after physical activity and resolve within 24 hours. It is characterized by reversibility of all symptoms and benign outcome according to 2-year follow-up results. This clinical case is considered interesting since it expands the therapeutic concept of cerebral manifestations of hypertensive crisis.

Key words: *transient global amnesia, hypertensive crisis*

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BP — blood pressure, HR — heart rate, ECG — electrocardiogram

A hypertensive crisis can be accompanied by the onset of such cerebrovascular disorders as hypertensive encephalopathy, transient ischemic attack, stroke and subarachnoid hemorrhage. The literature contains data on possible onset of transient global amnesia (TGA) in patients with hypertension [1, 3, 12]. TGA term was introduced into clinical practice by Fisher and Adams in 1964 to denote a sudden onset of transient disorders in all the types of memory along with loss of memory abilities, retrograde amnesia and inability to recall recent events while still retaining consciousness [2]. The incidence of TGA is 5 to 10 people per 100,000 members of the population per year [8]. But the real incidence is unknown because the episodes of memory loss are temporary and many patients do not consult a doctor at the time when amnesia develops. TGA more often develops in women of middle and elderly age; the ratio of female to male patients is 4:1 [2, 8]. Amnesia development can be preceded by physical strain, emotional stress, exposure to extremely intense temperature factor, pain, sexual

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intercourse and Valsalva maneuver [1, 3, 11, 15]. An amnesia episode can last from several hours to several days [1, 4, 8]. The subject of the present discussion is the relation of TGA physiopathological mechanism to local angiospasm, possible microembolism of intracranial vessels and hypoperfusion of brain regions responsible for mnestic functions, and constricted venous outflow from the cranial cavity [3, 4, 9, 16]. The TGA development may be conditioned by a special selective vulnerability to metabolic and oxidative stress of a hippocampus Ca1 region, which is critical for the memory consolidation process [2]. A TGA outcome is favorable in most cases. Repeated amnesia episodes or cerebral strokes are rare [1, 10, 14]. Despite its benign progression, TGA remains one of the most intriguing syndromes in the field of clinical neurology due to its sudden onset and not completely clear pathogenesis [7]. TGA is of interest not only for the neurological practice but therapeutic practice as well since cases of its development are reported in patients with hypertension, patent foramen ovale, cardiac conduction disorders, and mitral valve prolapse [5, 6, 15].

We will discuss a clinical case of TGA in a patient suffering from hypertensive crisis. Patient M., female, 57 years old was admitted to a neurological department with complaints on moderate headache of diffuse pattern. The taken medical history revealed that during the last 3 years the patient has had episodic (no more often than 3 times a year) rises in BP up to 140/90 mm Hg, provoked by stress and overstrain. The patient took antihypertensive drugs (enalapril 10 mg) only in the periods of aggravation. She didn't take the drugs regularly. Being a healthcare professional, the patient sought to keep a healthy lifestyle. She attended callanetics trainings twice a week for three years and did not indulge in any harmful habits. The patient and her relatives indicated that they had no epilepsy in the medical history. On the day of admission, the patient completed callanetics training and decided to stay for aerobics and strength training. At that time she noted hot flashes that went away when she rested. When the patient was back home, her relatives noticed her unusual behavior: she was confused, could not answer the question about the reason for coming 3 hours later than usual, did not remember about the events that occurred at the end of sports classes and after them (how she changed after the training, how she came home). When the same person phoned repeatedly, she did not recall the previous talk they had had few minutes ago and asked the same questions; asked relatives the same questions, while was unable to remember the answers to them. The relatives phoned the trainer and ascertained that she really had completed several trainings at the fitness club. At the recommendation of a healthcare professional who was familiar with the patient's case, they measured BP, which had increased up to 200/140 mm Hg. Therefore, they called the ambulance. A doctor of the emergency team administered enalaprilat at the pre-hospital stage. The patient was admitted to the Neurological Department of the City Hospital, since it was suspected that she had suffered from an acute cerebrovascular accident (CVA). Examination results: patient of normal body build, BMI is 22 kg/m^2; skin (including the head) is of normal color and hydration, and free of damage; heart sounds are rhythmic; heart rate is 68 bpm; BP is 170/100 mm Hg. The patient stated her name, age, and occupation correctly, recognized her relatives but could not describe events after the end of the training; she was disoriented concerning the time and could not state the year, month and date. The retrograde amnesia manifested itself as partial impairment of autobiographical episodic memory with regard to some events of private life. Impairment of verbal and visual memory was notable. The patient repeatedly asked what happened to her, repeatedly asked questions about her health status, and she failed to remember the answers that she received. She failed to recognize doctor on duty during reexaminations. At the same time she correctly carried out habitual actions and the commands of doctor during the examination. She was able to find her way around the room. The patient was critically concerned about her condition, and she clearly understood that she was experiencing problems with her memory. This understanding was accompanied by perplexity and anxiety. An examination for local neurological disorders showed no speech disturbance. TBI was ruled out. Computed tomography scanning of brain was performed to rule out CVA. It showed moderate subatrophy of brain

tissue as well as signs of constricted drainage via superficial veins of the brain. At the extracranial level, triplex scanning of the head major arteries showed signs of diffuse atherosclerotic changes in brachiocephalic artery walls while blood flow values were within the age norm. There were found signs of extravasal influences on the vertebral arteries with impaired venous outflow and ectasia of the right jugular vein. Results of electroencephalography showed disorganization of cerebral bioelectrical activity. Meanwhile, no epileptiform activity or abnormal activity areas were observed. X-ray of the cervical spine showed signs of intervertebral osteochondrosis at C4–C5. The ECG that was taken at admission showed sinus rhythm with heart rate of 75 bpm, and normal electrical axis. Twenty-four hour Holter monitoring that was performed on the third day of the hospital stay registered rare supraventricular polytopic extrasystoles. No conduction disorder was observed. Twenty-four hour monitoring of the blood pressure was performed on the fifth day during the course of antihypertensive therapy. Based on the results of the examination, average values of systolic and diastolic pressure, changes in BP from day to night, and 24-hour index of the systolic pressure were normal (dipper); the 24-hour index of diastolic pressure was classified as over-dipper. Echocardiography showed left ventricular diastolic dysfunction (abnormal relaxation), which can be explained by hypertension. Ophthalmoscopy showed pale pink optic disc, moderately narrowed arteries; moderate myopia of both eyes was detected. Renal ultrasound detected no abnormalities. Laboratory tests carried out in full compliance with current standards showed no abnormalities. Improvement of the patient's condition was observed on treatment with 10 ml 25% magnesium sulphate solution intravenously, 10 ml Cerebrolysin intravenously, 6 ml 5% Mexidol intravenously, 10 mg enalapril, 2.5 mg Arifon per day, 75 mg Curantyl and 75 mg Cardiomagnyl. After 24 hours target BP values were achieved and subsequently remained normal. At the same time, regression of the retrograde amnesia was observed. The patient fully regained the ability to keep recent events in mind, and her aural, visual and gustative memory was completely restored. The memory of the events that occurred during the period of disorder was not restored.

The performed examination helped to exclude CVA, transient epileptic amnesia and TBI. There were no reasons to draw a conclusion of acute hypertensive encephalopathy since there were no distinct clinical signs (intense headache, nausea and vomiting). There were no signs of cerebral edema. Diagnosis of TGA was based on generally accepted criteria [13]: availability of information from episode witnesses, sudden onset of anterograde amnesia (impaired ability to keep new information in mind and no recall of events that took place after the cerebral dysfunction onset), retrograde amnesia (impaired ability to recall information gained before the disease), absence of other cognitive dysfunctions, intact consciousness and personal identity, absence of local neurological symptoms, ruled-out other reasons of amnesia and short duration of the amnesia episode. The hypertensive crisis was classified as a complicated one based on the revised TGA classification as transient cerebral ischemic attack and related syndromes (G45) according to the International Classification of Diseases 10.

After the discharge, the patient has received outpatient follow-up by cardiologist and neurologist for 2 years. Anxiety due to the fear that amnesia would reoccur was observed for the first 2 months. After 2 months the patient overcame the fear and returned to callanetics training. However, she avoids intensive physical exertion. On regular administration of 50 mg losartan on a daily basis, the targeted BP was achieved. The patient feels well. During the follow-up period, no TGA episodes were observed.

It is possible to identify distinct features of TGA development in the presented clinical case: a middle-aged woman who exerted herself excessively, relief of the mnestic function disorder within twenty-four hours without restoration of the memories from the period of amnesia and favorable outcome. The ectasia of the right internal jugular vein is also quite typical for TGA since valve insufficiency of the right internal jugular vein is distinctly related to TGA [5, 6]. Taking into consideration the fact that TGA can develop both after excessive physical exertion and BP rise following a period of no previous physical exertion, it is not absolutely clear whether TGA onset is related to hypertensive

crisis only or whether both TGA and the crisis were provoked by the excessive physical strain and happened at the same time. Nevertheless, this clinical case is considered interesting since it expands the therapeutic concept of cerebral manifestations of hypertensive crisis.

Conflict of interests

The authors declare no conflict of interests.

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