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ALGORITHM FOR THE TREATMENT OF PATIENTS WITH ACUTE HEART FAILURE

Abstract

Acute heart failure (AHF) and acute decompensation of chronic heart failure (ADHF) are topic health issues. The main tasks of such patients managing are: to achieve optimal and stable resolution of edema and dyspnea; to improve tissue perfusion; to reduce the severity of clinical symptoms; to increase exercise tolerance; to prevent the progression of heart failure, target organs dysfunction, and complications development; to reduce decompensations and hospitalizations rate; to increase the survival rate, and to improve the quality of life. The diagnostic procedure, clinical patient patterns recognition, pharmacological (including diuretics, vasodilators, inotropes, vasopressors, anticoagulants, etc.) and non-pharmacological (including oxygen therapy, non-invasive and invasive ventilation, etc.) approaches to the management of AHF and ADHF are presented in accordance with the state-of-the-art guidelines.

Key words: *acute heart failure, decompensation of chronic heart failure, acute decompensated heart failure, cardiogenic pulmonary edema, cardiogenic shock, oxygen therapy, invasive lung ventilation, inotropic support, vasopressors, diuretics, ultrafiltration, renal replacement therapy, natriuretic peptides*

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FiO_2 — fraction of inspired oxygen; $PaCO_2$ — partial pressure of carbon dioxide in the arterial blood; PaO_2 — oxygen partial pressure in the arterial blood; SpO_2 — blood oxygen saturation; IABP — intra-aortic balloon pump, PAWP — pulmonary artery wedge pressure; VT — ventricular tachycardia; IV — invasive ventilation; MI — myocardial infarction; CMP — cardiomyopathy; CS – cardiogenic shock; LV — left ventricle; MCS — mechanical circulatory support; NPs – natriuretic peptides; ADHF — acute decompensation of chronic heart failure; ACS — acute coronary syndrome; ICU — intensive care unit, AHF — acute heart failure; SBP — systolic blood pressure; CI — cardiac index; GFR — glomerular filtration rate; HF — heart failure; TSH — thyroid stimulating hormone; PE — pulmonary embolism; AF — atrial fibrillation; CHF — chronic heart failure; RR — respiration rate; ECG — electrocardiography; ECHO-CG — echocardiography

Introduction

Despite healthcare progress, heart failure (HF) is still the leading cause of hospital admissions, decrease in the life quality, and mortality. Currently, heart failure affects 37.7 million people in the world and its prevalence continues to grow [7, 8]. In Europe, HF accounts for 5% of all hospital admissions [20]. HF is the most common cause of inpatient treatment among people over 65 years old [6, 8]. In most cases, an admission is due to acute HF (AHF) developed for the first time *(de novo)*, in 15–20%, or acute decompensation (worsening of the course) of previously diagnosed chronic heart failure (CHF), in 80–85% of patients [2]. In the latter case, it refers to acute decompensation of CHF, or acute decompensated HF (ADHF) [17].

After discharge from the hospital, about 50% of patients with HF are readmitted within 6 months, and 20–25% of patients are readmitted within

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30 days [19]. The in-hospital mortality for patients with HF is 2–20%, and 30-day mortality after the discharge is 11.3% [12]. The mortality in patients with HF remains high even despite treatment with angiotensin converting enzyme inhibitors / sartans, β-blockers, aldosterone receptor antagonists, and sacubitryl/valsartan, which showed a significant reduction in the relative mortality risk compared with placebo in numerous clinical trials [7, 8]. The main objectives of managing patients with AHF and ADHF are to achieve optimal and stable resolution of signs of congestion, to improve tissue perfusion, to decrease the severity of clinical symptoms, to increase exercise tolerance and quality of life, to prevent the worsening of HF progression, deterioration in the functional state of target organs, and complications, to decrease the frequency of subsequent decompensations and admissions, and to reduce in-hospital and post-hospital mortality [3]. Ways of achieving these objectives will be discussed in this lecture.

Definitions and Terminology

Acute heart failure (AHF) is a condition characterized by the sudden appearance or rapid deterioration of symptoms and signs of heart failure (HF) up to the development of cardiac asthma, pulmonary edema or cardiogenic shock (CS) due to acute disruption of the structure and function of the heart, leading to progressive impairment of other organs and systems [3, 17].

The main symptoms (complaints) of HF are dyspnea on exertion, which worsens when lying in a horizontal position, orthopnea, choking at night, lower limb swelling, decreased exercise tolerance, weakness and fatigue. The main signs of HF (data of physical examination: inspection, palpation, percussion, auscultation) are swelling of the lower extremities, jugular vein distention, hepatomegaly, congestive rales, the third/fourth heart sound, pleural effusion, ascites, tachycardia and tachypnea [9, 17].

Left ventricular failure is a condition caused by a deterioration of the structure and function of the left ventricle (LV) of the heart and characterized by blood congestion in pulmonary circulation [3].

Right ventricular failure is a condition caused by a deterioration of the structure and function of the right ventricle characterized by congestion in systemic circulation [3].

Cardiac asthma is a variant of acute left ventricular HF associated with significant edema of the bronchial wall, manifested by attacks of dyspnea and suffocation [3].

Cardiogenic pulmonary edema is a variant of acute left ventricular HF due to leakage of blood plasma into the interstitial lung tissue and into the alveoli, manifested by severe suffocation, cyanosis and grunting respiration [1, 3].

Cardiogenic shock is the most severe variant of acute left ventricular HF associated with significant LV myocardial injury, manifested by severe hypotension: a decrease in systolic blood pressure (SBP) < 80 mm Hg (in patients with a history of hypertension, SBP may be above 80–90 mm Hg) lasting for more than 30 minutes, a significant decrease in the cardiac index (CI) usually < 1.8 L/min/m^2 and an increased pulmonary artery wedge pressure (PAWP) > 18 mm Hg, which leads to organ hypoperfusion. It is often combined with cardiogenic pulmonary edema [2].

Acute decompensated heart failure (acute decompensated CHF, ADHF) is the period of CHF course that is characterized by rapid (within a few hours, days) or gradual (within several weeks) aggravation of symptoms and signs of HF on the background of a long-term disruption of the structure and function of the heart. This is a kind of exacerbation of CHF, or AHF with the underlying CHF [15]. AHF, including ADHF, is a life-threatening condition requiring immediate medical intervention and admission to the hospital [2, 3, 17].

Aggravating Factors and Causes of AHF and ADHF [9, 17]:

1. Acute coronary syndrome (ACS), myocardial infarction (MI), its mechanical complications, including rupture of the interventricular septum, LV free wall, mitral valve chords

and/or papillary muscles with the development of acute mitral regurgitation, etc.
2. Cardiac rhythm disturbances: tachyarrhythmias (atrial fibrillation — AF, ventricular tachycardia — VT), bradyarrhythmias and conduction disorders.
3. Pulmonary embolism.
4. Hypertensive crisis.
5. Aortic thrombosis and dissection.
6. Dysfunction of heart valves (aortic stenosis, mitral stenosis, mitral insufficiency, etc.) [1].
7. Infectious endocarditis, sepsis, pneumonia and other infections.
8. Myocarditis.
9. Pericarditis and cardiac tamponade.
10. Exacerbation of chronic obstructive pulmonary disease, asthma.
11. Alcohol and drug abuse.
12. Elevated sympathetic activity, stress-induced cardiomyopathy (CMP) — Takotsubo CMP.
13. Drug products: nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), cardiotoxic chemotherapy drugs, drugs with negative inotropic effect and glitazones.
14. Metabolic and hormonal disorders (thyroid dysfunction, adrenal gland failure, diabetes mellitus decompensation, diabetic ketoacidosis, pregnancy and peripartum period).
15. Surgery and its complications.
16. Chest trauma.

In addition, non-compliance with directions concerning water-salt intake and discontinuation of the prescribed therapy can result in ADHF [3, 17].

AHF Classification

There are many classifications of AHF based on various criteria. The clinical classification is the most practical for determining the tactics of managing patients and assessing the prognosis [17].

AHF Clinical Classification

1. With or without congestion ("wet"/"dry").
2. With or without peripheral hypoperfusion ("cold"/"warm").

Congestion signs in pulmonary circulation are orthopnea, paroxysmal nocturnal dyspnea, congestive rales in the lungs; congestion signs in systemic circulation are jugular vein distention, peripheral edema, hepatomegaly, hepatojugular reflux and ascites.

Clinical manifestations of hypoperfusion are impairment of consciousness, oliguria (urine output < 0.5 mL/kg/hour or < 20 mL/min) or anuria, cold sweat, mottled skin, pale skin, moist skin, cold and wet extremities, and a weak and thready pulse. Laboratory signs of hypoperfusion are metabolic acidosis (pH < 7.35), elevated serum lactate level (> 2 mmol/L), and elevated serum creatinine level. Hypoperfusion is not synonymous with hypotension (SBP < 90 mm Hg), and hypotension does not imply hypoperfusion, but hypoperfusion is often accompanied by hypotension and a decrease in pulse BP (< 20–25 mm Hg) [1, 3, 17].

4 clinical profiles of patients with AHF are defined depending on the presence/absence of congestion and hypoperfusion (Figure 1): "warm and wet" (good perfusion with congestion), which is the most common; "cold and wet" (hypoperfusion and congestion); "cold and dry" (hypoperfusion without congestion); "warm and dry" (compensated; good perfusion without congestion).

Diagnosis of AHF

To diagnose AHF, the patient's medical history must be thoroughly taken; aggravating factors as well as causes of development, symptoms and signs of congestion and/or hypoperfusion must be identified; and electrocardiography (ECG), chest X-ray, echocardiography (ECHO-CG) and laboratory tests, including specific biomarkers, must be performed [17].

An ECG in 12 leads is useful for diagnosing the underlying heart disease (ACS, MI) and complications (AF) that have resulted in the development of AHF. If there are no abnormalities on the ECG, the clinical symptomatology most likely is not due to AHF [17].

In AHF, signs of venous congestion, interstitial or alveolar pulmonary edema, hydrothorax and cardiomegaly are discovered on chest X-ray. Up to 20% of patients with AHF have a normal chest X-ray. This study is also useful for identifying non-cardiac diseases, which AHF should be differentiated from (pneumonia, aortic dissection, etc.) [17].

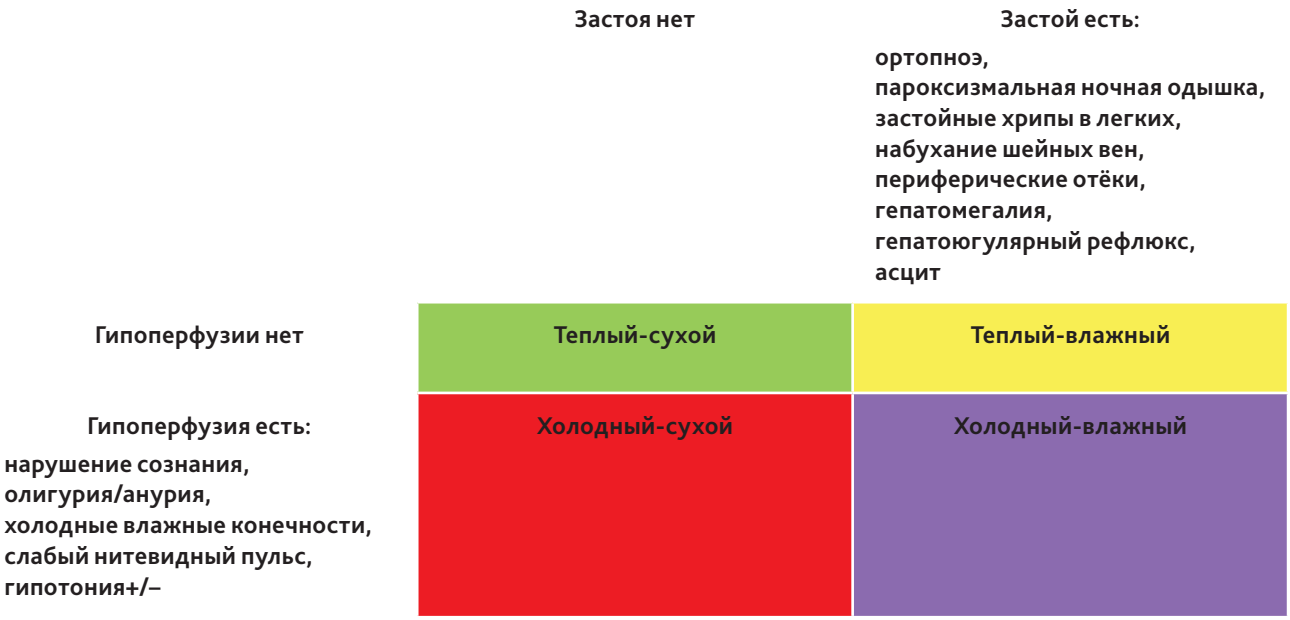

Figure 1. *Clinical patterns of acute heart failure based on the presence/absence of congestion and/or hypoperfusion [17]*

An emergency ECHO-CG is indicated for all patients with hemodynamic instability (SBP < 90 mm Hg) as well as for patients with suspected life-threatening structural or functional cardiac disorders (mechanical complications, acute valvular failure and aortic dissection). The best time to perform ECHO-CG is the first 48 hours of the patient's stay in the hospital [17].

The level of natriuretic peptides — NPs — (NT-proBNP, BNP, MR-proANP) should be measured in all patients with suspected AHF on admission. Normal levels of NPs (BNP < 100 pg/mL, NT-proBNP < 300 pg/mL, MR-proANP < 120 pg/mL) make the AHF diagnosis unlikely [19]. When assessing the level of natriuretic peptides, it should be noted that this indicator is nonspecific and can be increased in a number of other conditions (Table 1).

In addition to screening laboratory tests (including complete blood count, biochemical assay of

Table 1. *Causes of elevated concentrations of natriuretic peptides [17, 22]*

Cardiac	Non-cardiac
Heart failure	Elderly age
Acute coronary syndrome	Ischemic stroke
Pulmonary embolism	Subarachnoid hemorrhage
Myocarditis	Renal dysfunction
Left ventricular hypertrophy	Liver dysfunction (mainly liver cirrhosis with ascites)
Hypertrophic or restrictive cardiomyopathy	Severe infections (including pneumonia and sepsis)
Acquired and congenital heart disease	Paraneoplastic syndrome
Atrial fibrillation and ventricular tachyarrhythmias	Chronic obstructive pulmonary disease
Cardioversion, implantable cardioverter-defibrillator shock	Sleep apnea
Cardiac contusion	Pulmonary hypertension
Cardiac surgery	Anemia
Pericarditis	Severe metabolic and endocrine disorders (e.g. thyrotoxicosis, diabetic ketoacidosis)
Chemotherapy-induced cardiotoxicity	Severe burns

creatinine, sodium, potassium, glucose, and liver function tests), it is necessary to measure troponin levels to diagnose ACS, MI as a cause of AHF, and D-dimer levels to diagnose PE. It should be considered that an increased concentration of troponin is found in the vast majority of patients with AHF, often without obvious myocardial ischemia or acute coronary events, due to damage or necrosis of cardiomyocytes. Besides, elevated troponin levels may be present in patients with PE [17]. Since hypothyroidism and hyperthyroidism can exacerbate AHF, thyroid-stimulating hormone (TSH) should be evaluated in all patients with newly diagnosed AHF [17].

In addition, pulse oximetry is indicated in patients with AHF. Transcutaneous oxygen saturation values (SpO_2) < 90% are considered low. Normal SpO_2 does not exclude either hypoxemia (a decrease in the partial pressure of oxygen in the arterial blood (PaO_2) < 80 mm Hg) or tissue hypoxia. In cardiogenic shock (CS), an accurate measurement of PaO_2 and the partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) are necessary. This requires an arterial blood gas test performing. In case the patient has a history of pulmonary edema or COPD, the determination of venous pH and $PaCO_2$ is enough. Hypoxemia is recorded at PaO_2 <80 mm Hg; hypoxemic respiratory failure is recorded at PaO_2 < 60 mm Hg; hypercapnia is recorded at $PaCO_2$ > 45 mm Hg; hypercapnic respiratory failure is recorded at $PaCO_2$ > 50 mm Hg.

AHF Treatment

AHF is a life-threatening condition. Therefore, rapid transportation to the nearest hospital is necessary, preferably with an intensive care unit (ICU) [17]. Herewith, patients with pulmonary edema should be given a head-of-bed elevation position. Patients with CS should be placed on a bed with elevated foot end. Patients should only be transported on a stretcher [1, 2].

Indications for admission to a hospital/transfer of patients with AHF to the ICU:

1. Hemodynamic instability, SBP < 90 mm Hg.
2. Significant (progressive) dyspnea with involvement of additional respiratory muscles, respiration rate (RR) > 25 bpm.
3. The need for intubation, ventilation.
4. Symptoms of hypoperfusion (see above).
5. SpO_2 < 90% (in spite of oxygen therapy).
6. Brady- and tachyarrhythmias with heart rate < 40 or > 130 bpm, high degree AV block.
7. Life-threatening conditions: ACS, acute MI, its mechanical complications, acute heart valve failure, thoracic trauma, PE, aortic dissection, and other disorders [3, 17].

Non-invasive monitoring of vital cardiorespiratory functions, including pulse oximetry, measurement of BP, RR, and continuous ECG, is necessary for patients with AHF. Urine output should also be monitored. Routine bladder catheterization is not recommended. It should be considered at an urine output rate < 20 ml/min [2, 17].

In case of CS (see above), the patient should be immediately provided with hemodynamic support. In case of respiratory failure (RR > 25 bpm, SpO_2 < 90%, PaO_2 < 60 mm Hg, $PaCO_2$ > 50 mm Hg), the patient should be provided with respiratory support (see below). Within 60–120 minutes after admission to the hospital, it is necessary to diagnose and start treatment of life-threatening conditions that led to AHF (Figure 2), including ACS, acute MI, its complications, rhythm and conduction disorders, and PE [3]. In case of ACS with AHF, urgent revascularization within 2 hours after admission is recommended, regardless of ECG results or the detection of biomarkers [17]. In case of AHF with an underlying hypertensive crisis, an aggressive decrease of BP (by 25% during the first few hours, then with caution) is recommended using intravenous vasodilators and diuretics. In case of atrial or ventricular arrhythmias leading to hemodynamic instability, electrical cardioversion is recommended; in cases of bradyarrhythmias and conduction disorders, temporary cardiac pacing is recommended. In case of mechanical complications of MI (see above), chest trauma, acute valvular insufficiency, and aortic dissection, surgical intervention is usually required. In case of PE as a cause of shock or hypotension, immediate specific treatment with reperfusion is recommended using thrombolysis, catheterization or surgical embolectomy [17]. The tactics for managing these states are described in detail in the profile recommendations.

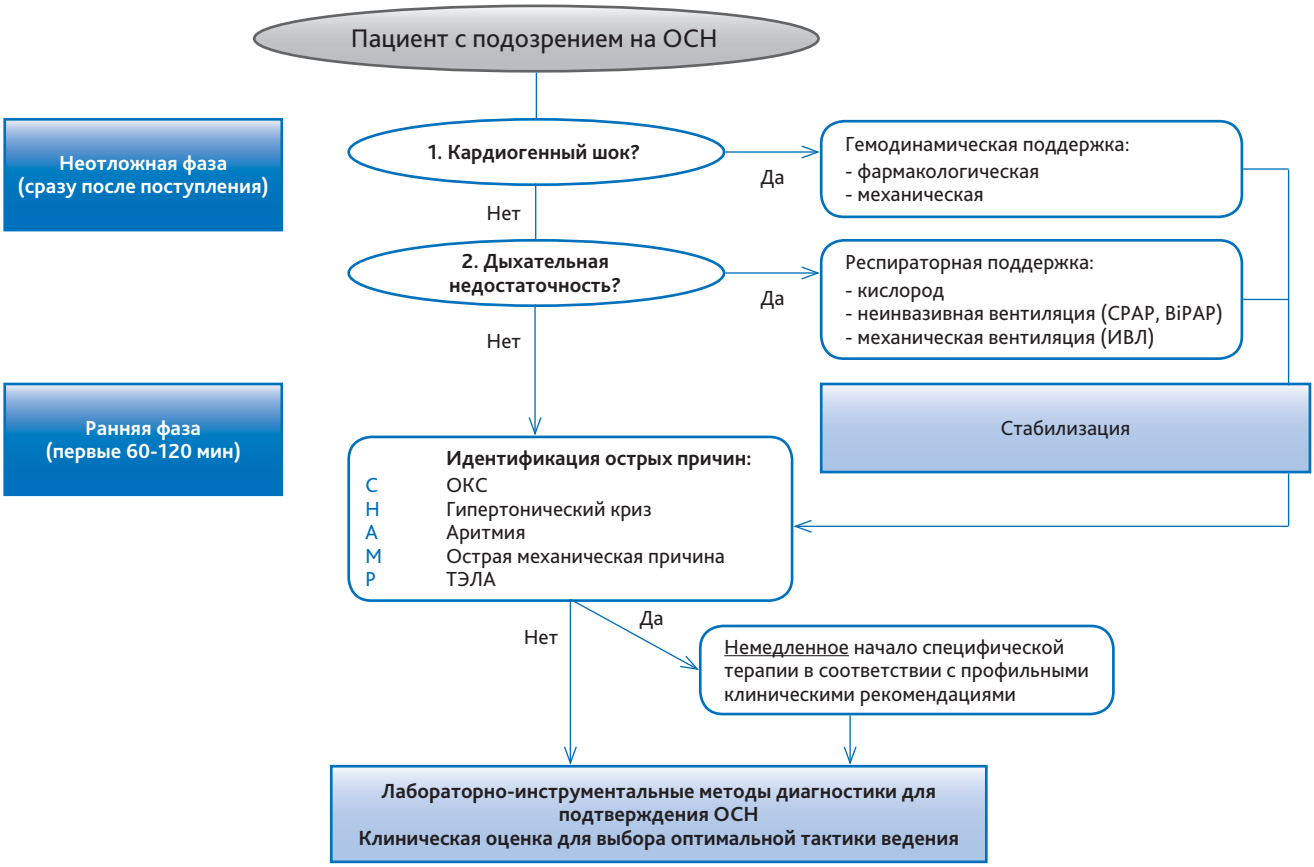

Figure 2. *Management of a patient with acute heart failure according to CHAMP acronym [17]*

Respiratory Support

Oxygen therapy (inhalation of 40–60% oxygen at a rate of 4–8 L/min through a mask) is recommended in patients with AHF and SpO_2 < 90% and/or PaO_2 < 60 mm Hg until hypoxemia is eliminated (up to an increase of SpO_2 > 90%) [2, 4, 15, 17].

Oxygen therapy should not be given to patients with AHF without a decrease of saturation and hypoxemia, as it can lead to vasoconstriction and a decrease in cardiac output [17].

Noninvasive ventilation of the lungs (continuous positive airway pressure — CPAP, or biphasic positive airway pressure — BiPAP) is recommended for patients with respiratory distress (RR > 25 bpm and SpO_2 < 90%) and it should be started as early as possible to reduce symptoms of respiratory failure (Figure 3) [3]. Since noninvasive ventilation can help reduce BP, it should be used with caution in patients with hypotension [17]. The inspired oxygen fraction (FiO_2) should be increased, if necessary, to 100%, according to SpO_2, if there are no contraindications. However, hyperoxia should be avoided. Noninvasive ventilation can reduce the incidence of intubation and mortality, although there is insufficient evidence that it reduces mortality. Noninvasive ventilation should be continued in patients who have signs of respiratory failure upon admission to the hospital. PS-PEEP (Pressure Support Positive End-Expiratory Pressure) is preferable in case of acidosis and hypercapnia, especially if there is a history of COPD [15, 17].

Intubation and invasive ventilation (IV) are recommended for patients with respiratory failure if hypoxemia (PaO_2 < 60 mm Hg), hypercapnia ($PaCO_2$ > 50 mm Hg), and acidosis (pH < 7.35) cannot be corrected through noninvasive ventilation (Figure 3) [15, 17].

Drug Therapy

The algorithm for managing patients with AHF depends on the clinical profile (Figure 4).

Diuretic Therapy

If congestion signs are present ("wet" patients), intravenous loop diuretics are indicated. Diuretics should be avoided in "wet and cold" patients (with

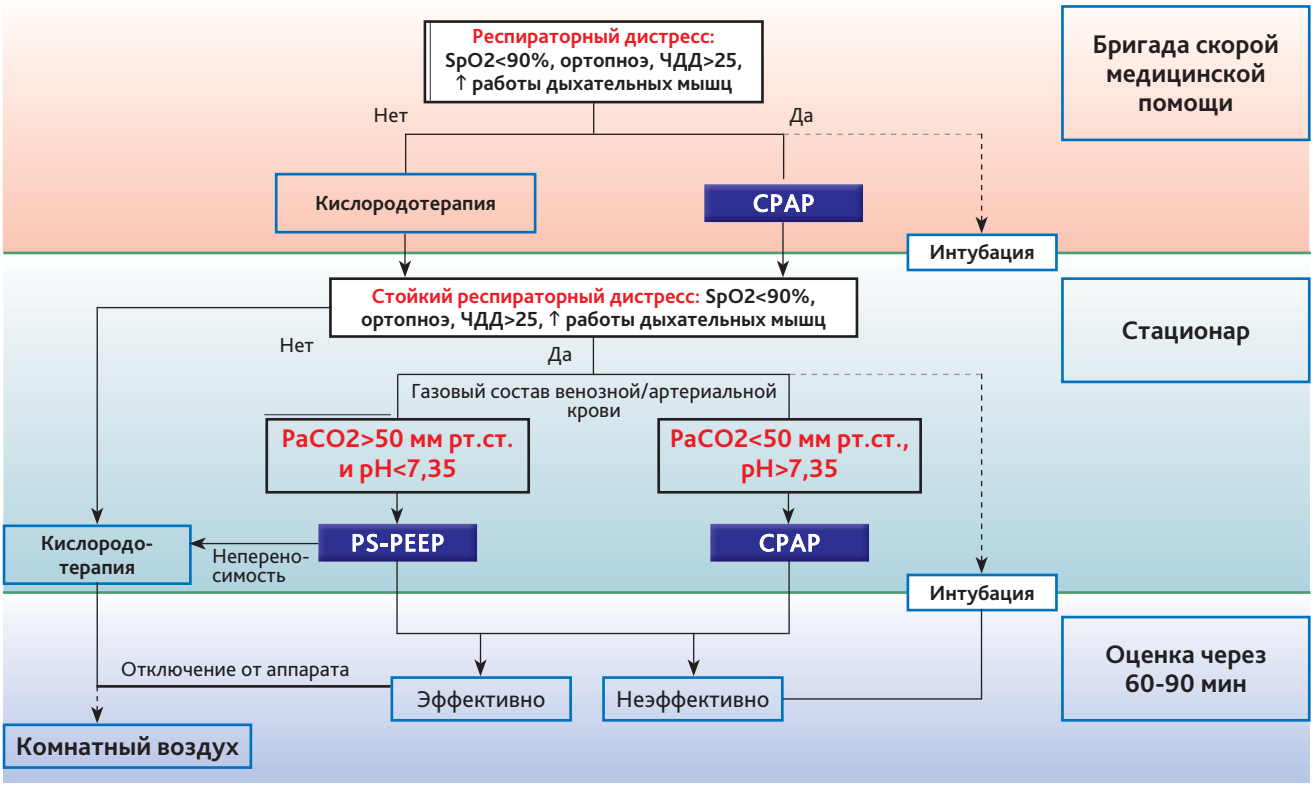

Figure 3. *Respiratory support in acute heart failure [15]*

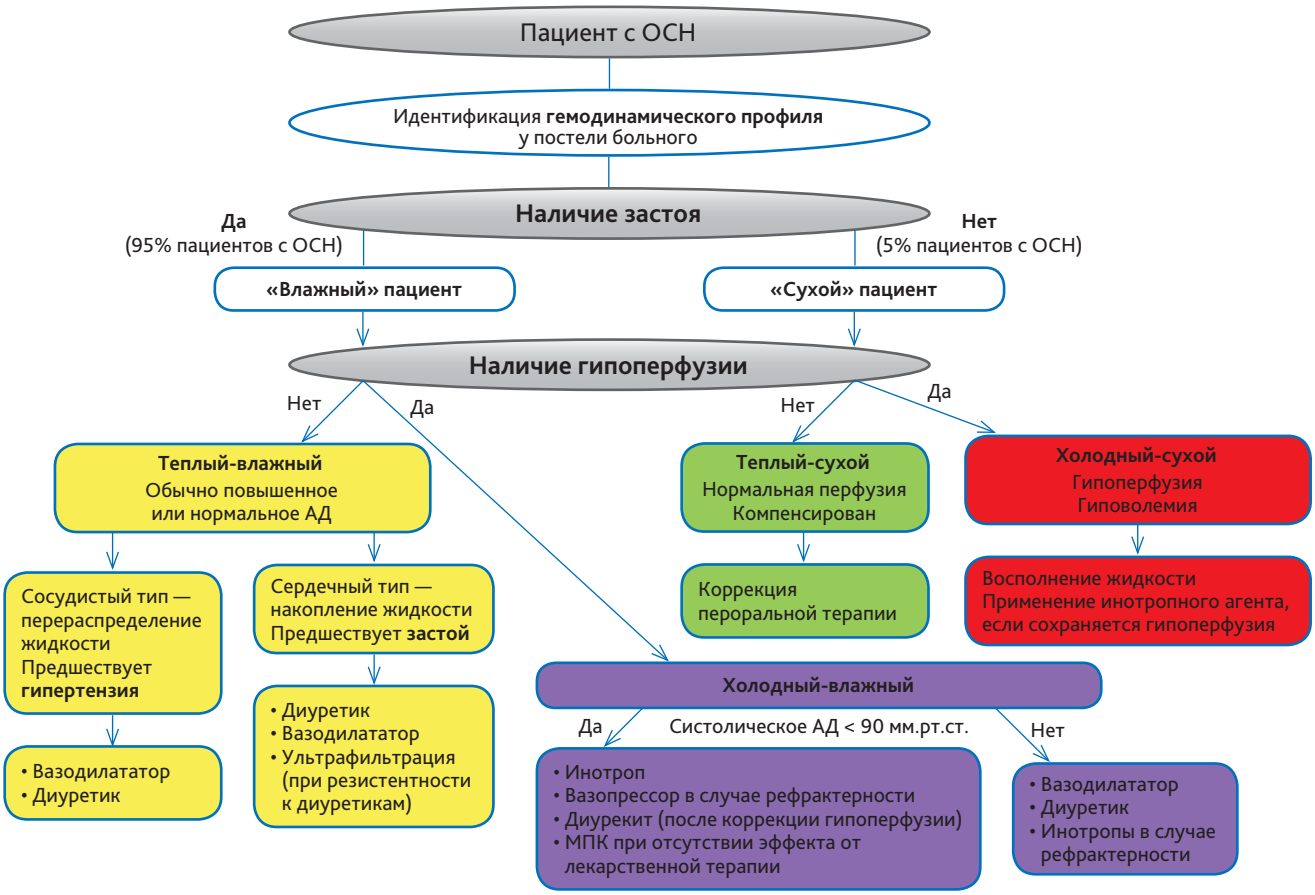

Figure 4. *Management of patients with acute heart failure based on clinical pattern [17]*

signs of hypoperfusion) until an adequate level of perfusion is achieved. Patients with a newly diagnosed AHF or with ADHF who have not previously received oral diuretic therapy are recommended to use furosemide 20–40 mg (or 10–20 mg of torasemide) intravenously [17]. In patients with CHF who received pre-admission therapy with diuretics, the dose of intravenous diuretic should be equal to or greater than that of the oral diuretic used [17]. In accordance with national guidelines, in this case, the dose of furosemide should be 2.5 times higher than the last daily dose of the diuretic [2]. Diuretics must be given in the form of intermittent or continuous infusion. The dose and duration of diuretic therapy depend on the severity of clinical symptoms [17].

In case of resistance to the used doses of loop diuretics, it is possible to: 1) add small doses of thiazide diuretics in addition to loop diuretics; 2) use loop diuretics in combination with mineralocorticoid-receptor antagonists (MRA) in high doses (150–300 mg) if there is no hyperkalemia and renal dysfunction; 3) add carbonic anhydrase inhibitors (acetazolamide) to avoid the development of alkalosis, which weakens the effect of thiazide and loop diuretics [3].

Vasodilators

Intravenous vasodilators (Table 2) are the second most frequent drugs used in the symptomatic therapy of AHF. They reduce pre- and post-load and increase the stroke volume. However, they have, unfortunately, no reliable evidence base.

In accordance with international guidelines, intravenous vasodilators are recommended for patients with SBP > 90 mm Hg in order to relieve the symptoms of AHF, especially for patients with AHF with the underlying hypertensive crisis. Vasodilators should be used with caution in patients with significant aortic and mitral stenosis [17].

According to national guidelines, the use of vasodilators can be considered only in patients with SBP ≥ 100 mm Hg [2, 3].

In the RELAX-AHF trial, it was discovered that patients with HF decompensation who are receiving treatment with serelaxin (human recombinant relaxin-2 peptide, which helps adapt the woman's body to pregnancy and is a potent renal vasodilator [11]) experience a significant decrease in the signs of dyspnea and congestion as well as an improvement in the glomerular filtration rate (GFR), and they also experience a decrease in the need for intravenous diuretics. The total 180-day mortality was also reduced in comparison with placebo [14, 21]. However, in the subsequent RELAX-AHF-EU trial, the drug effect on the combined endpoint (death + worsening of HF) was not confirmed, and further studies of this drug were suspended. The drug is not for sale on the market.

Inotropic Agents

Inotropic agents include dobutamine, dopamine, levosimendan, and phosphodiesterase 3 (PDE 3) inhibitors: milrinone, enoximone (Table 3). Inotropic infusions should be considered for patients with hypotension (SBP < 90 mm Hg) and/or hypoperfusion ("cold" patients) to increase cardiac output and BP, to improve peripheral perfusion and to prevent/slow the development of dysfunction/failure of visceral organs. If hypoperfusion is due to the use of β-blockers, it is preferable to prescribe levosimendan rather than dobutamine. Since levosimendan has a vasodilating effect, it should be administered to patients with hypotension (SBP < 85 mm Hg) or CS only in combination with other inotropes or vasopressors [17].

Table 2. *Intravenous vasodilators in acute heart failure treatment [17]*

Vasodilator	Dosing	Side effects	Other
Nitroglycerine	Start with 10–20 μg/min, increase up to 200 μg/min	Hypotension, headache	Tolerance on continuous use
Isosorbide dinitrate	Start with 1 mg/h, increase up to 10 mg/h	Hypotension, headache	Tolerance on continuous use
Sodium nitroprusside	Start with 0.3 μg/kg/min and increase up to 5 μg/kg/min	Hypotension, isocyanate toxicity	Light sensitivity
Nesiritide	Bolus 2 μg/kg + infusion 0.01 μg/kg/min	Hypotension	

Table 3. *Inotropes and/or vasopressors in acute heart failure treatment [17]*

Inotrope/ vasopressor	Mechanism of action	Bolus	Infusion rate
Dobutamine[a]	β_1-agonist, <β_2 and α_1-agonist	No	>2-20 μg/kg/min: (beta+)
Dopamine	Stimulation of dopamine receptors, in large doses — β-agonist, in high — α, β-agonist	No	3–5 μg/kg/min; inotropic (beta+) >5 μg/kg/min: (beta+), vasopressor (alpha+)
Milrinone[a,b]	Phosphodiesterase 3 inhibitor	25–75 μg/kg over 10–20 min	0,375–0,75 μg/kg/min
Enoximone[a]	Phosphodiesterase 3 inhibitor	0,5–1,0 mg/kg over 5–10 min	5–20 μg/kg/min
Levosimendan[a,c]	Calcium sensitizer increases the sensitivity of contractile proteins to Ca^{2+} by binding to troponin C of the myocardium	12 μg/kg over 10 min (optional)	0,1 μg/kg/min, which can be decreased to 0,05 or increased to 0,2 μg/kg/min
Norepinephrine	α_1- and α_2-agonist, <β_1-agonist	No	0,2–1,0 μg/kg/min
Epinephrine	α_1-, α_2, β_1, β_2-agonist	Bolus: 1 mg can be administrated i.v. during resuscitation, repeated every 3–5 min	0,05–0,5 μg/kg/min

[a] — Also a vasodilator, [b] — Not recommended in ischemic heart failure, [c] — Bolus not recommended in hypotension

Inotropes, especially adrenergic agonists, can cause sinus tachycardia, myocardial ischemia and arrhythmia. Therefore, it is required to monitor the ECG when using them. There is a concern that they can increase mortality. In this regard, inotropic agents are not recommended in patients without hypotension and hypoperfusion for safety reasons [17].

Vasopressors

Vasopressors (preferably norepinephrine) can be considered in patients with CS in order to increase blood pressure and perfusion of vital organs when other inotropic drugs prove to be ineffective. Since inotropic drugs and vasopressors can lead to the development of arrhythmia, myocardial ischemia, and also, in the case of levosimendan and PDE 3 inhibitors, to hypotension, ECG and BP monitoring is necessary if they are prescribed. In such cases, invasive blood pressure measurement can be considered [17].

When comparing dopamine with norepinephrine in the treatment of patients in a state of shock, it was shown that fewer side effects and lower mortality are recorded when norepinephrine treatment is used. Epinephrine should be administered only in patients with persistent hypotension regardless of the use of other vasoactive agents [17].

Anticoagulant Therapy

Prevention of thromboembolism with heparin and low molecular weight heparins is recommended to reduce the risk of deep vein thrombosis and PE in patients who have not received oral anticoagulant therapy and who have no contraindications to it [17]. Patients who received oral anticoagulants should continue taking them if there are no contraindications to prescribing them.

Other Medications

To control the heart rate, 0.25–0.5 mg of digoxin intravenously is indicated in patients with AF with ventricular response rate > 110 per min if they did not receive pre-admission therapy with digoxin. In moderate or severe renal dysfunction, doses of 0.0625–0.125 mg are sufficient. To this end it is also possible to use amiodarone, but its effectiveness has not been proven as well [17].

Intravenous opiates (morphine 4–8 mg, trimeperidine 10–20 mg) can be used with caution in case patients with severe dyspnea (mainly pulmonary edema) experience significant psycho-emotional

arousal, anxiety or fear [2]. Frequent use of opiates is not recommended [17]. It is necessary to remember the possible risk of respiratory depression, especially in elderly patients, on treatment with opiates. To minimize this risk, the administration should be titrated to 1–2 ml by first diluting the ampoule of opiate with 19 ml of physiological saline [2]. Side effects of opiates include nausea, vomiting, hypotension, and bradycardia. To prevent nausea and vomiting, 10 mg of metoclopramide intravenously can be added [2]. In addition, opiates can increase the need for invasive ventilation. Opinions are contradictory concerning the increased risk of mortality in patients receiving morphine [17].

Anxiolytics and sedatives may be necessary for patients with symptoms of agitation or delirium. The careful use of benzodiazepines (diazepam or lorazepam) is the safest [17].

Vasopressin antagonists (tolvaptan) block the action of antidiuretic hormone (ADH, vasopressin) on the renal tubules and promote the excretion of water. Vasopressin antagonists can be administered in patients with hypervolemia and persistent hyponatraemia [17].

Instrumental Therapy

Ultrafiltration includes the removal of plasma water through a semipermeable membrane. The advantage of ultrafiltration over loop diuretics in patients with AHF is not proven. Currently, routine use of ultrafiltration is not recommended and should only be used in patients who do not respond to diuretic therapy.

Criteria for starting dialysis are treatment-resistant oliguria, severe hyperkalemia ($K^+ > 6.5$ mmol/L), severe acidosis (pH < 7.2), and serum urea level > 36 mmol/L [5, 17].

In patients with AHF, whose condition cannot be stabilized by means of drug therapy, the systems of mechanical circulatory support (MCS) can be used to unload the ventricles and maintain a sufficient level of perfusion of target organs. Temporary MCS systems can be used, including percutaneous cardiac support devices, extracorporeal life support (ECLS) and extracorporeal membrane oxygenation (ECMO) systems to support patients with left ventricular or biventricular failure before restoring the function of the heart or other organs. Typically, the time of use of these devices is limited from several days to several weeks. The actual data concerning the benefits of temporal percutaneous MCS devices in patients not responding to standard therapy, including inotropes, are limited. In a meta-analysis of three randomized clinical trials (RCTs) comparing percutaneous MCS and intra-aortic balloon pump (IABP, balloon intra-aortic counterpulsation) the percutaneous MCS in a total of 100 patients with CS was shown to be safer and demonstrated better hemodynamics, but it did not improve the 30-day mortality and was associated with a large number of bleeding complications [10]. In RCT of the high-risk percutaneous coronary intervention (PCI) in patients with LV dysfunction (the PROTECT II trial), the 30-day frequency of major side effects was not different in patients with IABP or hemodynamic support devices [16]. Based on these results, temporary percutaneous MCS is not recommended as a proven or effective method of treating CS. MCS systems, in particular ECLS and ECMO, can be used as a "bridge to decision" in patients with rapidly deteriorating AHF or CS in order to stabilize hemodynamics, restore the functions of target organs, and perform a complete clinical evaluation of the possibility of heart transplantation or the insertion of a long-term MCS device [18].

Indications for IABP are the support of blood circulation before surgical correction of acute mechanical MI complications, during severe acute myocarditis, and in certain patients with acute myocardial ischemia or infarction before, during or after percutaneous or surgical revascularization [17].

Other Interventions

Thoracocentesis (pleural puncture with fluid evacuation) can be considered in patients with AHF and pleuritis to facilitate dyspnea. Paracentesis with fluid evacuation to relieve the symptoms can be discussed for patients with ascites. This procedure can partially increase the renal filtration pressure and GFR by decreasing intraabdominal pressure [17].

CS Management Features

The main cause (80%) of CS is acute MI with a lesion of more than 40% of the myocardium. The other 20% are mechanical complications of MI.

A dramatic decrease in preload due to hypovolemia can also be a possible cause of CS [2].

It was believed in the 1980–1990's that the frequency of CS in MI reached 20%. However, based on data from recent years, the estimate has been adjusted to 5–8% [2]. Risk factors of CS are anterior MI localization, elderly age, diabetes mellitus, history of MI and CHF, and LV systolic dysfunction [2].

In CS, there is activation of the sympathetic nervous system; systemic inflammation; release of proinflammatory cytokines; vasodilation with impairment of systemic perfusion; increased myocardial oxygen demand; disturbance of diastolic LV relaxation, which promotes pulmonary edema and hypoxemia; an increase in total peripheral vascular resistance with postload increase; fluid retention due to reduced renal blood flow and increased preload; slowing of tissue blood flow; blood thickening; and a tendency to thrombosis. All of this occurs due to the formation of vicious circles, and it leads to progressive myocardial dysfunction and death of the patient[2].

ECG and ECHO-CG are recommended for all patients with suspected CS immediately followed by continuous monitoring of ECG and BP and invasive monitoring with an arterial line [3, 17]. It is extremely important to perform a rapid troponin test to exclude ischemic damage to the myocardium [2].

All patients with CS must be admitted/transferred to a hospital with a 24/7 cardiac surgical department, an interventional radiology surgical suite for possible coronary angioplasty, and a special ICU with IABP [2, 3, 17].

Immediate coronary angiography is recommended (within 2 hours of admission to hospital) with coronary revascularization for patients with CS that complicates ACS [3].

Oxygenotherapy, as mentioned above, is recommended at SpO_2 < 90% until SpO_2 > 90% [2].

A fast infusion of 200 ml of 0.9% sodium chloride in 10 minutes is recommended as a first-line therapy if there is no lung congestion and signs of hypovolemia. Repeated infusions of the solution are possible if needed until a total volume of 400 ml is reached [2, 3, 17].

Intravenous inotropic agents (dobutamine) can be used to raise blood pressure and increase cardiac output [17].

Vasopressors (norepinephrine is preferable to dopamine) can be considered if there is a need to maintain SBP in the presence of persistent hypoperfusion [17].

Epinephrine can be administered if there is no effect of dobutamine/dopamine/norepinephrine, and in case of progressive hypotension with SBP < 80 mm Hg [2].

A routine use of IABP is not recommended. Short-term IABP can be considered for the treatment of refractory CS before surgical correction of acute mechanical complications of MI, as well as before, during or after percutaneous or surgical revascularization [17].

In addition, the prescription of acetylsalicylic acid (250–325 mg chewable) and anticoagulants (heparin 70 IU/kg of body weight, not more than 4,000 IU, or enoxaparin 1 mg/kg body weight intravenously where the initial dose should not be more than 100 mg) should be considered [2].

Frequent errors in CS management:

1. Prescribing of cardiac glycosides (proarrhythmic effect under hypoxic conditions, delayed inotropic action, increased pulmonary congestion due to simultaneous stimulation of both ventricles).
2. Administration of vasopressors without a prior attempt to eliminate hypovolemia.
3. The use of glucocorticoids (since there is no evidence that they are clinically effective).
4. The use of mesatone (which causes vasoconstriction without increasing cardiac output) [2].

Oral Therapy of CHF in ADHF

When ADHF occurs in patients with CHF, oral therapy of HF should be continued, except for cases of hemodynamic instability (symptomatic hypotension, hypoperfusion, bradycardia), hyperkalemia or severe renal failure (Table 4) [15]. In these cases, a temporary dose reduction or discontinuation of administered oral medications may be required until the condition stabilizes. In particular, the therapy with β-blockers should be continued for patients with ADHF if there is no CS. A recent meta-analysis showed that discontinuation of β-blockers in patients hospitalized with ADHF was associated with a significant increase

Table 4. *Oral therapy of AHF in the first 48 hours [15]*

	Normo-tension/ Hyper-tension	Hypotension, mmHg		Low heart rate, bpm		Potassium, mmol/l		Renal function	
		85–100	<85	<60 ≥50	<50	≤3.5	>5.5	Cr<2,5, eGFR>30	Cr>2,5, eGFR<30
ACE-I /ARB	Review/ Increase	Reduce/ Stop	Stop	No change	No change	Review/ Increase	Stop	Review	Stop
Beta-blocker	No change	Reduce/ Stop	Stop	Reduce	Stop	No change	No change	No change	No change
MRA	No change	No change	Stop	No change	No change	Review/ Increase	Stop	Reduce	Stop
Diuretics	Increase	Reduce	Stop	No change	No change	Review/ No change	Review/ Increase	No change	Review
Sacubitril/ valsartan	Review/ Increase	Stop	Stop	No change	No change	Review/ Increase	Stop	Review	Stop
Other vaso-dilators (Nitrates)	Increase	Reduce/ Stop	Stop	No change	No change	No change	No change	No change	No change
Other heart rate slowing drugs (amio-darone, CCB, Ivabradine)	Review	Reduce/ Stop	Stop	Reduce/ Stop	Stop	Review/ Stop (*)	No change	No change	No change

Note: ACE-I –angiotensin converting enzyme inhibitor, ARB — antagonist receptor blocker, CCB — Calcium channel blockers (mg/dl), Cr — creatinine blood level (mg/dl), eGFR — estimated glomerular filtration rate ml/min/1,73 m2, MRA — mineralocorticoid receptor antagonist, (*) amiodarone

in in-hospital and post-hospital mortality as well as an increased frequency of repeated hospital admissions [17].

When AHF is newly diagnosed, an attempt should be made after the patient's condition has stabilized (adequate diuresis, decrease of dyspnea and signs of stagnation, normalization of blood pressure) to start the therapy that is recommended for patients with CHF, including angiotensin converting enzyme inhibitors (ACEI), or sartans, or sacubitryl/ valsartan; β-blockers, etc., with careful consideration of contraindications [2–4, 17].

Therefore, currently, a step-by-step procedure for managing patients with AHF has been developed based on evidence-based medical data, which must be known and applied in real clinical practice. Such a procedure will make it possible to improve the prognosis of patients with this life-threatening condition.

Conflict of interests

The authors declare no conflict of interests.

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

Abstract

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conflict of interests

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

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STATIN ADVERSE EFFECTS: MECHANISMS, DIAGNOSIS, PREVENTION AND MANAGEMENT

Abstract

Statins are one of the most commonly used lipid-lowering agents in clinical practice. The objective of this review was to systemize the most frequent statin adverse effects, including their pathogenesis, diagnosis, management and prevention. The frequency of statin-associated muscle symptoms is significantly higher in registries and observational studies than in randomized controlled trials. Diagnosis of muscle symptoms is difficult because they are rather subjective. The serum creatine kinase level is often normal or slightly elevated. Association between statin use and the risk of new cases of diabetes mellitus was demonstrated in numerous studies. The drug interaction of statins, high dosage of statins used and comorbidities can lead to a persistent and clinically significant increase of hepatic enzymes levels. A standard blood glucose test, hepatic enzymes and serum creatine kinase levels determination was necessary before statin prescription to identify patients with high risk of adverse effects. The risk of hemorrhagic stroke due to treatment with statins is ambiguous according to randomized controlled trials. It is suggested that statins can inhibit carcinogenesis by inducing apoptosis or reducing cell growth, angiogenesis and invasion. However, the results of preclinical and clinical studies are contradictory. The majority of the studies are observational or of retrospective nature. It is necessary to provide larger prospective randomized placebo-controlled trials with a long-term follow-up. Any specialist should understand the potential negative consequences of statins use taking into account the expansion of their indications for use. Understanding the pharmacokinetics of statins is important for the safety of patients. Dosages, metabolism and risk factors of drug interactions should be considered to minimize statin adverse effects.

Key words: *statins, cholesterol, adverse effects, myopathy, diabetes, liver, stroke, cancer*

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β-blockers — beta-blockers; EAS — European Atherosclerosis Society; ALT — alanine aminotransferase; ARBs — Angiotensin II receptor blockers; AST — aspartate aminotransferase; ATP — adenosine triphosphate; CCBs — calcium channel blockers; ULN — upper limit of normal; HMG-CoA reductase — 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; ACEI — angiotensin converting enzyme inhibitors; BMI — body mass index; IR — insulin resistance; CK — creatine kinase; INR — international normalized ratio; MRI — magnetic resonance imaging; NSAIDs — nonsteroidal anti-inflammatory drugs; NDDM — newly diagnosed diabetes mellitus; AE — adverse effects; RCTs — randomized controlled trials; SAMS — statin-associated muscle symptoms; SIM — statin-induced myopathy; HF — heart failure; CVD — cardiovascular diseases

Introduction

Current national Guidelines in various countries (including Russian guidelines) on the use of lipid-lowering agents in order to reduce the risk of developing atherosclerotic cardiovascular diseases (CVD) and their complications place emphasis on statins — 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, that are considered as highly effective and safe drugs [1–6]. Due to the wide use of statins, the risk of their adverse effects (AE) is debated a lot. Today we have sufficient evidence of AE, such as statin-associated muscle symptoms (SAMS), newly

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diagnosed diabetes mellitus (NDDM), and insulin resistance (IR), as well as their effect on liver function, hemorrhagic strokes, cancer development, etc. The European Atherosclerosis Society (EAS) proposed the term "statin intolerance", which might be observed in 10–15 % of patients [4].

Not all experts agree on the safety of statins. Criticism has also been leveled against the structure and statistical evaluation of the results of randomized controlled trials (RCTs) as well as close financial ties between researchers and pharmaceutical companies producing lipid-lowering drugs [7–16]. The aim of this overview is to systematize the most common statin AE, presenting the mechanisms of their development, diagnosis, therapeutic approach and prevention.

Statins and Muscle Symptoms

Muscle symptoms due to statin use are usually referred to as SAMS, or "statin-induced myopathy" (SIM) [17–22]. Experts of the National Lipid Association Muscle Safety Expert Panel include in SAMS: 1) "myalgia" (muscle pain); 2) "myopathy" (muscle weakness); 3) "myositis" (muscle inflammation detected with intravital morphological examination of muscle tissue and/or magnetic resonance imaging (MRI)); 4) "myonecrosis" (muscle lesion, based on a significant increase in the serum creatine kinase (CK) level); 5) "rhabdomyolysis" with myoglobulinuria and/or acute kidney injury with the elevated serum creatinine level. Elevated CK levels are classified as follows: mild (> 3 upper limits of normal (ULN)), moderate (≥ 10 ULN) and severe (≥ 50 ULN). Statin-associated autoimmune myopathy is also noted, which is a rare complication accompanied by severe progressive muscle disease even after the drug withdrawal [23].

SAMS incidence varies widely and is 7–29 % according to registries and observational studies [20, 24]. In the retrospective PRIMO study (Prediction of Muscular Risk in Observational Conditions) that enrolled 7,924 patients, muscle symptoms were observed in 10.5 % of patients treated with fluvastatin 80 mg, atorvastatin 40–80 mg, pravastatin 40 mg, or simvastatin 40–80 mg daily for at least 3 months [25]. C. Buettner et al. conducted a cross-sectional study of 3,580 patients over the age of 40 years. Twenty-two percent of patients treated with statins reported musculoskeletal pain compared with 16.7 % of patients who did not receive statins [26].

Based on RCTs, SAMS incidence is significantly less than in observational studies. That can be explained by the presence of exclusion criteria, including elderly age, comorbidity, the possible interaction of statins with other drugs, and the presence of previous muscle symptoms, impaired renal and hepatic functions. Up to 30 % of subjects of active pre-randomization phases are excluded from RCTs. Possible mechanisms by which adverse effects can be minimized in clinical trials also include their insufficient identification and selective reporting of adverse drug reactions [18]. In addition, RCTs analyzed are developed mainly to assess the effectiveness of statins and not to record their adverse effects. Only 4 RCTs of 42 reported the CK level of patients enrolled. The STOMP study (The Effect of Statins on Muscle Performance) was the only one that used a questionnaire to identify muscle symptoms, to study the effects of statins on muscle strength and exercise tolerance taking into account the CK level. The STOMP study showed a significant increase in the mean CK levels by 20.8 ± 141.1 U/L ($p<0.001$) in the atorvastatin group. Myalgias were observed in 9.4 % of cases in the atorvastatin group (80 mg/day) and in 4.6 % in the placebo group ($p=0.05$). There were no differences in exercise tolerance and muscle strength between the study groups. The results of the STOMP study are limited by short-term observation (6 months) and a fairly young mean age of subjects (44 years of age) [20, 24].

Mechanisms of SAMS Development

The pathogenesis of SAMS is still poorly understood. There is an ongoing debate over the role of the decrease of ubiquinone (CoQ_{10}) levels in muscle tissue and vitamin D deficiency in the development of SAMS [20, 22, 27]. G.D. Vladutiu identified a 3–4-fold decrease in CoQ_{10} in patients with myopathy as compared with the reference range [28]. Similar results were obtained in a number of other studies. Based on these data, it is assumed that a decrease in the activity of mitochondrial respiratory chains, and, consequently, impairment of energy production and muscle protein degradation play a role in the pathogenesis of SAMS [17, 20, 24]. However, other studies have not detected a decrease in CoQ_{10} levels in patients treated with statins, and its use has not improved statin tolerance and has had no impact on the severity of myalgia [22].

The variability of the pharmacological response to statins depends on polymorphism of genes, the products of which are responsible for pharmacokinetics and pharmacodynamics. Two main mechanisms are suggested: one of them is characterized by impairment of absorption, metabolism, transport and excretion of statins, which leads to an increase in their plasma concentrations and levels in the muscles; the other is a pharmacogenetic one, characterized by mutations leading to impairment of mitochondrial functions. A number of studies have shown an association between the *SLCO1B1* gene polymorphism and pharmacokinetics of statins [27, 29].

Special mention should be made of the pathophysiology of *statin-associated autoimmune myopathy*, a rare but severe and prognostically unfavorable type of SAMS. It usually develops a few months or years after the initiation of the statin therapy [22]. The statin-induced increased activity of HMG-CoA reductase in genetically predisposed patients is thought to produce autoimmune mechanisms against it [20].

Diagnosis of SAMS

Diagnosis of clinical manifestations of SAMS (muscle weakness, pain, tension, cramps, and decreased exercise tolerance) is often based on the subjective assessment of a patient and a physician. They are usually symmetrical, with proximal localization, and involve muscles of upper and lower extremities. SAMS develop more often 4–6 weeks after the beginning of statin therapy, but can develop earlier or later. Plasma CK levels often remain normal or slightly elevated (less than 3-5 ULN) [17, 20, 21, 24, 30, 31].

When muscle symptoms appear, risk factors for the development of SAMS should be taken into account, as well as the possibility of alternative diagnosis. Data of clinical studies suggest that statin therapy can be a trigger for metabolic myopathy. Some patients with arthritis, tendinitis, lumbar radiculopathy report an increased pain syndrome when taking statins, perhaps because muscle weakness exacerbates arthropathy or tendinopathy [18]. In addition, physically active patients are more likely to suffer from SAMS [25], which is consistent with H. Sinzinger and J. O'Grady [32] data which show worse tolerance to lipid-lowering therapy among athletes. The study of CK, thyroid-stimulating hormone, C-reactive protein, and ESR values is necessary for the purpose of differential diagnosis.

Diagnosis of *statin-associated autoimmune myopathy* has unique features. CK levels usually (but not always) are significantly elevated and exceed 10 ULN. Low voltage motor potentials are recorded during electromyography with increased spontaneous activity, which is characteristic of the active myopathic process. Muscular and fascial edema can be detected on MRI. Muscle cell necrosis and regeneration are the most typical histological signs in biopsy specimens of patients with statin-associated autoimmune myopathy [20–22].

Rhabdomyolysis is the most aggressive and severe form of SAMS with development of skeletal muscle necrosis with a slight increase in serum CK levels (> 10 ULN), myoglobinemia, myoglobulinuria, myoglobin-induced acute kidney injury [20, 21].

Therapeutic Approach and Prevention of SAMS

To prevent SAMS, it is necessary to detect the presence of risk factors for their development before statin administration, including the administration of potentially dangerous drug combinations. If these factors cannot be eliminated, special care should be taken for the patients at risk: elderly age, alcohol abuse, high physical activity, a history of skeletal muscle diseases, hypothyroidism, diabetes mellitus, impaired renal and hepatic functions [1–6, 20, 21, 24, 27, 30, 33, 34].

According to the 2017 guidelines of RSC (Russian Society of Cardiology), RNAS (Russian National Atherosclerosis Society), RSCRSP (Russian Society of Cardiosomatic Rehabilitation and Secondary Prevention) on diagnosis and correction of lipid metabolism disorders [1], the serum CK level should be determined before prescription of statins. If the CK level is > 4 ULN, the test should be repeated. Routine monitoring of the CK level is not necessary if there are no muscle symptoms. When they appear, CK should be determined to assess the severity of muscle injury and to decide whether to continue statin therapy or change the dose.

Reduction in the severity of SAMS or their complete elimination is often observed with a decrease in the dosages of statins and/or their use on alternate days or 1–2 times a week (preference should be given to statins with a longer half-life: atorvastatin,

rosuvastatin), and switching to another statin (e. g., switching from lipophilic statin to hydrophilic statin) or combination with other lipid-lowering agents (e. g., ezetimibe, niacin) [1, 20, 34].

After confirming the presence of statin-associated autoimmune myopathy, immunosuppressive therapy including oral administration of glucocorticoids (in prednisolone equivalent of 1 mg/kg body weight) with possible combination with cytotoxic agents at conventional doses (azathioprine, methotrexate, or mycophenolate mofetil) is indicated. When the clinical effect, normalization or significant reduction in plasma CK levels are achieved, the dose of immunosuppressive agents should be decreased slowly [20, 24, 35]. In some patients treated with statins, muscle weakness persists even after the CK levels become normal [30].

If rhabdomyolysis develops, immediate discontinuation of the statin, monitoring of the blood creatinine, potassium and the glomerular filtration rate are required, as well as evaluation of daily diuresis and urinalysis [21, 24].

Statins and NDDM

At present, strong evidence of the relationship between statin therapy and the development of IR and NDDM has been obtained. This is reflected in the national Guidelines of various countries [1–6]. This position is based on the results of RCTs, their meta-analyses and observational studies. In 2012, the Food and Drug Administration and the European Medicines Agency decided to supplement the instruction with information on the risk of elevation of fasting glucose and the level of glycated hemoglobin during statin therapy [36, 37].

Randomized controlled trials

One of the large-scale RCTs which demonstrated the risk of NDDM was the JUPITER study (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin), focused on the primary prevention of CVD. The JUPITER study enrolled 17,802 subjects (11,001 men aged 50 years and older, and 6,801 women aged 60 years and older) with low-density lipoprotein cholesterol (LDL-C) values < 3.4 mmol/L, but with elevated values of highly-sensitive C-reactive protein (≥ 2 mg/L), randomized into a rosuvastatin group (20 mg/day) and a placebo group. After 1.9 years of follow-up, there was an increase in NDDM incidence in patients of rosuvastatin group compared with the control group (odds ratio (OR) = 1.26, 95 % confidence interval (CI) 1.04–1.51) with no differences in fasting glucose values between groups. However, elevation of the glycated hemoglobin values was detected (5.9 % versus 5.8 %; p=0.001). A higher incidence of NDDM in women was noted [38].

In the PROSPER study (PROspective Study of Pravastatin in the Elderly at Risk), there was a 32 % increase in NDDM incidence in the pravastatin group (40 mg/day) compared with the control group (OR=1.32, 95 % CI 1.03–1.69) [39].

Supportive analysis of the PROVE-IT TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) has shown a significant increase in glycated hemoglobin > 6 % in patients with or without DM when treated with statins [40].

Kwang Kon Koh et al. conducted an RCT in order to study the effect of various doses of atorvastatin on fasting plasma insulin and glycated hemoglobin values: 44 subjects received a placebo, 42, 44, 43 and 40 subjects received atorvastatin 10, 20, 40 and 80 mg/day, respectively, for 2 months. There was a significant increase in plasma fasting insulin value by 25 %, 42 %, 31 % and 45 % on average under the effect of atorvastatin 10, 20, 40 and 80 mg, respectively, (p=0.009) and glycated hemoglobin level by 2 %, 5 %, 5 % and 5 %, respectively, compared with the placebo group (p=0.008). Atorvastatin 10, 20, 40 and 80 mg significantly decreased insulin sensitivity by 1 %, 3 %, 3 % and 4 %, respectively, compared with the placebo group (p=0.033) [41].

Meta-analyses

A number of large-scale meta-analyses seek to study of the relationship between statin therapy and the risk of development of NDDM. For example, N. Satar et al. [42] after analyzing 13 RCTs with 91,140 subjects enrolled, noted a 9 % increase in the risk of DM in groups of patients who received statins compared with control group results (OR=1.09; 95 % CI 1.02–1.17). The risk factors of DM were a high body mass index (BMI), elderly age, heart failure (HF), a history of myocardial infarction in the last six months, and a high cardiovascular risk. The authors of this meta-analysis concluded that the use of statins in 255 patients for 4 years was associated with a risk of developing NDDM in one patient.

D. Preiss et al. [43] analyzed 5 RCTs with 32,752 subjects without DM enrolled (the study lasted for more than 1 year). During follow-up, 2,749 subjects developed DM, of which 1,449 received intensive statin therapy (atorvastatin 80 mg, simvastatin 40 and 80 mg), 1,300 received moderate statin therapy (pravastatin 40 mg, simvastatin 20 mg, atorvastatin 10 mg). This study demonstrated that intensive statin therapy was associated with a higher incidence of NDDM (OR=1.12, 95 % CI 1.04–1.22). The authors concluded that the possibility of developing NDDM was 1 in 498 treated patients per year. According to D. Preiss, the results of the meta-analysis indicate a dose-dependent risk of the development of NDDM on statin use.

Cohort and observational studies

Numerous observational and cohort studies have demonstrated the association between statin use and the risk of the NDDM development. A. Macedo et al. [44] conducted a population cohort study with 2,016,094 subjects enrolled, 430,890 of which received statins. 130,395 subjects developed type 2 diabetes during the follow-up period (5.4 years on average). The use of statins was associated with a higher risk of NDDM development (hazard ratio (HR) = 1.57, 95 % CI 1.54-1.59), which increases with longer statin therapy. Risk was higher in persons without hypertension and other CVD.

C. Dormuth et al. analyzed 8 cohort studies and a meta-analysis which enrolled 136,966 subjects aged ≥ 40 years, who received statins. The risk of NDDM development was higher when rosuvastatin, atorvastatin and simvastatin were used [45].

A. Culver et al. analyzed data on 153,840 postmenopausal women. Development of NDDM was identified in 10,242 cases. In addition, the risk of NDDM development occurred with the use of various statins, which suggests the effect of the class [46].

In a cohort study conducted by D. Yoon et al. [47] (8,265 patients treated with statins and 33,060 patients in the control group) NDDM incidence was higher in the statin group compared with the control group (OR=1.872, 95 % CI 1.432–2.445). The highest risk was found for atorvastatin (OR=1.939, 95 % CI 1.278).

Opinions differ on the risk of development of NDDM for various statins. Some researchers have found no difference between lipophilic (atorvastatin, simvastatin and lovastatin) and hydrophilic statins (rosuvastatin, fluvastatin and pravastatin) but others reported this difference [42]. N. Zaharan et al. showed a high risk of development of NDDM for atorvastatin (OR=1.23, 95 % CI 1.19–1.27), simvastatin (OR=1.15, 95 % CI 1.05–1.25) and rosuvastatin (OR=1.41, 95 % CI 1.31–1.52), in contrast to fluvastatin and pravastatin [48]. A. Carter et al. demonstrated similar results in the retrospective study in 471,250 patients over the age of 66 years without DM (follow-up period was 14 years). It was shown that there was an increase in the risk of NDDM development by 22 % in patients who received atorvastatin, by 18 % in patients who received rosuvastatin, by 10 % in patients who received simvastatin, in comparison with pravastatin. In contrast, the use of lovastatin and fluvastatin was not associated with an increased risk of DM [49].

Mechanisms of NDDM and IR development

Several mechanisms are proposed that explain the association of statins with the risk of NDDM development. They include blocking calcium channels in pancreatic β-cells, decreasing levels of CoQ_{10}, reducing expression of glucose transporter type 4 (GLUT4), immune-mediated inflammation in pancreatic β-cells [10, 20, 50–53].

Evidence is presented on the adverse effects of statins on insulin sensitivity and pancreatic β-cell secretion [50]. In the population METSIM study (Metabolic Syndrome in Men) (8,749 patients aged 45–73 years) [54], statin therapy increased the risk of DM type 2 development by 46 % (OR=1.46, 95 % CI 1.22–1.74). Insulin sensitivity decreased by 24 %, and insulin secretion — by 12 % in persons treated with statins (at fasting glucose levels and postprandial glycemia < 5.0 mmol/L) compared to those who did not receive lipid-lowering therapy ($p<0.01$).

Glucose is the most important regulator of insulin release. It enters β-cells using glucose transporter type 2 (GLUT2). In β-cells, glucose is phosphorylated to glucose-6-phosphate by glucokinase enzyme. Adenosine triphosphate (ATP) is produced in the next metabolic process, leading to the closure of potassium channels and, consequently, depolarization of cell membranes, resulting in calcium flowing into the cell through the L-type calcium channels. In the experiment, it was shown that a decrease in the content of cholesterol in cells can lead to a decrease in insulin secretion due to impairment of the functioning of L-type voltage-gated calcium channels in pancreatic β-cells [10, 50, 51, 52].

Mitochondrial dysfunction in pancreatic β-cells, skeletal muscles and adipocytes plays an important role in the DM pathogenesis. Statins decrease levels of CoQ_{10}, which is an essential factor that ensures electron transport in mitochondria, leading to slowed ATP production in the pancreatic β-cells and, accordingly, impairment of insulin secretion. Inhibition of isoprenoid synthesis by statins leads to a decrease of GLUT4 expression in adipocytes and development of peripheral insulin resistance [20, 51].

HMG-CoA reductase inhibition, oxidation of LDL-C, which enters β-cells from plasma, promotes activation of intracellular systems of congenital and acquired immunity, inflammation in β-cells, impairment of their structure and function, and ultimately, a decrease in insulin secretion [52, 53]. Statins can induce apoptosis of β-cells due to excessive NO production [53].

Therapeutic approach and prevention of NDDM and IR

Primarily, patients should be recommended to adhere to a healthy lifestyle (Mediterranean diet, regular physical activity, body weight control) [1–6, 10, 51]. In case of vitamin D deficiency, its replacement therapy should be administered. In case of ineffectiveness of these recommendations, the risk and benefit ratio should be assessed and statins should be prescribed according to strict indications, without considering them as a panacea ("magic bullets", in the words of Umme Aiman) [51].

Before prescription of statins, a patient should be informed about the risk of DM development and basic glycemic parameters (fasting glucose and glycated hemoglobin) should be determined, especially in individuals with risk factors for DM (female, elderly age, BMI > 30 kg/m^2, hypertension, triglyceride levels > 1.69 mmol/L, fasting glucose levels 5.6–6.9 mmol/L, family history of type 2 DM, Asian race, smoking, and alcohol abuse) [1–6, 10, 20, 36, 51, 52].

Parameters of carbohydrate metabolism should be monitored during statin therapy (especially in case of intensive therapy). High doses of statins are associated with an elevated risk of NDDM development. In this regard, in order to achieve the target LDL-C level, the treatment should be started at low doses. A combination of moderate doses of statins with ezetimibe is possible, which allows further decrease in LDL-C by 20 % [10, 51]. The detection of glycemic disorders without testing the essential parameters permits to consider these abnormalities as statin-induced [10].

In case of hypertension, a differentiated approach to the choice of antihypertensive agents is needed. It should be taken into account that beta-blockers (β-blockers) and thiazide diuretics increase the risk of NDDM by 22 % and 43 %, respectively. If it is necessary to use β-blockers, drugs with vasodilating properties should be preferred. At the same time, angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) can increase insulin sensitivity and reduce DM incidence, and calcium channel blockers (CCBs) are neutral in terms of glycemia [10].

Statins and Hemorrhagic Stroke

The association between low values of cholesterol and an increased risk of hemorrhagic stroke development is observed in epidemiological studies [20, 55]. The meta-analysis of 23 trials which included 1.4 mln patients with 7,960 cases of hemorrhagic stroke showed that the risk of stroke decreased by 10 % with an increase in LDL-C by 1 mmol/L [20]. The results of a number of RCTs on the risk of hemorrhagic strokes during statin therapy are inconclusive. In some studies, there was no increase in the frequency of hemorrhagic strokes with a decrease in LDL-C to 1.8 mmol/L and lower [55]. The supportive analysis of the SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) showed an increase in the incidence of hemorrhagic strokes in patients receiving atorvastatin, compared with the placebo group. The risk of hemorrhagic strokes increased with age, in males and in case of stage 2 hypertension [56]. The HPS study (Heart Protection Study) showed an increase in the frequency of hemorrhagic strokes in patients with cerebral atherosclerosis who received simvastatin 40 mg/day [57].

The mechanisms by which statins can increase the incidence of hemorrhagic strokes have not been sufficiently studied. Statins are characterized by pleiotropic effects, including antithrombotic and fibrinolytic activities, due to which they can increase the activity of other fibrinolytic agents [58].

Thus, summarizing the results of the studies, it should be noted that statins decrease incidence of ischemic stroke and other atherosclerotic cerebral diseases, but increase the risk of hemorrhagic stroke

in patients after ischemic strokes. In this regard, the potential risk of hemorrhagic stroke development in these patients should be considered [20, 55, 56].

Statins and the Liver

Asymptomatic increase in the level of hepatic transaminases is one of the most frequent AE of statins and is observed in 0.5–2.0 % of patients. This class effect is dose-dependent, is usually observed within the first 12 weeks of statin use, and is normalized with reduction of statin doses. Moderate increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels is not an indicator of liver dysfunction and does not require discontinuation of statins [1–6, 21, 53].

A clinically significant increase in ALT/AST level implies a three-fold increase from ULN in two consecutive measurements, which are usually performed with a short time interval between them. A persistent and significant increase in the level of transaminases is often due to the interaction of statins with other drugs, the use of high doses and the presence of concomitant diseases. The risk of liver failure is extremely low [1–6, 20, 21, 53].

The mechanism of hepatic transaminase elevation is not well understood. The increase in ALT levels is associated with a decrease in CoQ_{10} levels, changes in the lipid components of the hepatocyte membrane and the generation of free radicals, which leads to an increase in the permeability of their membranes and, consequently, vulnerability to other toxins [21, 53].

Based on the results of numerous studies, routine monitoring of ALT/AST levels is not recommended by the experts during statin therapy [1, 4]. At the same time, it is recommended to measure ALT/AST levels before prescription of statins and 4–12 weeks after initiating or modifying drug therapy. In case of increase in the level of transaminases > 3 ULN, treatment should be discontinued or the dose of the drug should be reduced. If ALT/AST activity is ≤ 3 ULN, treatment can be continued, and the enzyme level should be re-tested after 4–6 weeks [1]. If a clear causal relationship is established between an increase in transaminases and the administration of a statin, the drug should be withdrawn and patient should be switched to alternative therapy (ezetimibe) [2].

In addition, to reduce the risk of hepatotoxicity, thorough questioning of the patient is necessary in order to exclude the intake of alcohol, drugs that are metabolized by cytochrome P450 3A4 (e. g., amiodarone, sulfonamides, methyldopa, cyclosporine, etc.). [21, 53].

Statins should not be prescribed to patients with acute and active viral hepatitis until the serum levels of AST/ALT, total bilirubin and alkaline phosphatase are back to normal. According to EAS, a moderate increase in liver enzyme activity in patients with non-alcoholic fatty liver disease and high CVD risk should not be an obstacle to the administration of statins [21].

Statins and Cancer

It is believed that statins can inhibit carcinogenesis by inducing apoptosis or inhibiting cell growth, angiogenesis, and invasion. Antiproliferative effects were the basis for mass preclinical studies to elucidate the functional role of statins in carcinogenesis. However, the results of preclinical and clinical studies contradict each other, although there is evidence that statins can suppress and reduce the incidence and relapse of certain cancers [59]. Taylor et al. have identified a relation between statins and breast, colon, lung, prostate and other cancers in the meta-analysis of 20 case-control studies that included 100,129 cases of cancer. When stratifying by the type of cancer, a statistically significant carcinoprotective effect was detected only in case of colon cancer (OR=0.89, CI 0.82-0.97) [60]. However, there were no data on what other drugs the patients took besides statins. As is known, low-dose acetylsalicylic acid with anti-inflammatory effect is often used for the prevention of CVD. Some studies showed that statins and nonsteroidal anti-inflammatory drugs (NSAIDs) can act synergistically, inhibiting the cell cycle and promoting apoptosis [61]. The disadvantages of observational studies are also the presence of random factors that are unevenly distributed among patients in the "case" and "control" groups and can affect the outcome. For example, differences in lifestyle, dietary habits, smoking and alcohol use are often not recorded in population databases, which makes it impossible to adjust them.

In the "pre-statin" era, reverse causality between the levels of plasma cholesterol and the potential risk of cancer (especially in the elderly patients) was actively discussed [7, 62, 63]. A number of cohort studies have shown that low cholesterol levels are

risk factors for cancer development. U. Ravnskov et al. analyzed 9 studies, which included more than 140,000 persons, and identified an increase in the incidence of cancer at low levels of cholesterol [63]. The risk of cancer has been noted in a number of RCTs devoted to the prevention of CVD diseases. In the aforementioned PROSPER study [62], the authors identified a reduction in cardiovascular mortality in the pravastatin group by 24 % (p=0.043). However, this effect was offset by a significant increase in mortality from cancer in the pravastatin group. The total number of patients with cancer in the pravastatin group was 245 versus 199 in the placebo group (p=0.02). The difference increased with a longer follow-up period. Commenting on the findings, the authors associate them with inclusion of patients with severe comorbid diseases in the study.

In the SEAS study (The Simvastatin and Ezetimibe in Aortic Stenosis) which enrolled 1,873 patients with aortic stenosis (mean age 67.6 years, follow-up duration 4.3 years), one group of patients received lipid-lowering therapy with simvastatin (40 mg/day) in combination with ezetimibe (10 mg/day) and another group received a placebo. In the pravastatin-ezetimibe group, prostate cancer was diagnosed in 105 patients (11.1 %) versus 70 patients (7.5 %) in the placebo group (p=0.01) [64]. At the same time, there was no significant difference when comparing both the total (p=0.80) and the cardiovascular (p=0.34) mortality.

In the 4S (Scandinavian Simvastatin Survival Study) and HPS studies focused on the secondary prevention of CVD, an increase in the incidence of skin cancer was revealed. When combining the results of these two studies, the increased risk of skin cancer in patients who received simvastatin was statistically significant compared with those who received placebo (p=0.028) [63].

According to D. Diamond, U. Ravnskov, the risk of cancer with prolonged use of statins may be higher than in the results of RCTs, the duration of which in the vast majority is no more than 2-5 years [7]. J.A. Mc Dougall et al. in the population study revealed a two-fold increase in the risk of breast carcinoma in women aged 55–74 years who received statins for 10 years or more [65]. The authors noted that the risk was highest among long-term users and suggested that statins could act as promoters of breast carcinogenesis. The detection of an increased risk only with prolonged use of statins suggests that chronic dysregulation of the mevalonate pathway and/or a long-term decrease in serum cholesterol levels may contribute to breast carcinogenesis.

Previous studies of statins did not reveal an increased risk of breast cancer, except for the RCT CARE (Cholesterol And Recurrent Events), which was focused on the secondary prevention of CVD (the duration was 5 years). However, it should be noted that most statin users in these studies took statins for less than 3 years. In the CARE study, patients were randomized into two groups: 2,078 in the placebo group and 2,081 in the pravastatin (40 mg/day) group. Plasma levels of total cholesterol were less than 6.2 mmol/L, LDL values were between 3.0 and 4.5 mmol/L. There were no significant differences in overall mortality (9 % decrease in the risk of death, 95 % CI 12 to 26 %, p=0.37). However, there was a 12-fold increase in the risk of breast cancer (12 cases in the pravastatin group versus 1 case in the placebo group, p=0.002). There were no other statistically significant differences between the groups in the incidence of cancer (gastrointestinal cancer, melanoma, lymphoma) [66].

It therefore remains an open question whether statins have carcinogenic or carcinoprotective effect. While the growth of tumor cells *in vitro* is usually suppressed in the presence of lipophilic statins, the clinical data on their antitumor effects are contradictory. Most of the studies are observational or retrospective. There is a need for more extensive prospective, randomized, placebo-controlled trials with a long follow-up period. In the systematic review, M. Künzl et al. come to the conclusion that the use of statins for the prevention of cancer can not be recommended due to the lack of convincing data [59].

Drug Interactions of Statins

Patients with CVD often need a concomitant prescription of a number of drugs. Drug interactions may lead to a change in the effectiveness of the drug or its toxicity due to impairment of absorption, distribution, metabolism and/or excretion. Risk factors for drug interactions include anthropometric factors (advanced age, female sex, low BMI, Asian race), comorbid states, and genetic polymorphisms that cause differences in the expression of enzymes and the ability of the body to participate in drug metabolism (i. e., impaired renal or hepatic function, HF).

An elevated risk of the development of statin therapy AE occurs with the concomitant use of drugs including macrolides, protease inhibitors, immunosuppressive drugs, as well as those inhibiting cytochrome P 450 isoenzymes, organic anions transporting polypeptide 1B1 (OATP1B1) or P-glycoprotein 1 [67].

Co-administration of statins with CCB is possible. However, doses of lovastatin or simvastatin > 20 mg/day when combined with amlodipine, diltiazem or verapamil are not recommended. If high doses are required (80 mg/day), clinicians should switch to statin, which is not associated with cytochrome P450 3A4 (pravastatin, rosuvastatin or pitavastatin) if treatment with diltiazem or verapamil is initiated [67].

Combined therapy of rosuvastatin, atorvastatin, pitavastatin, fluvastatin or pravastatin with amiodarone is acceptable. In this case, the dose of lovastatin should not exceed 40 mg/day and simvastatin — 20 mg/day. Concomitant use of statin with dronedarone is possible. It should be taken into account that dronedarone potentiates the action of simvastatin and lovastatin, and digoxin potentiates the action of atorvastatin. In this regard, more careful control of the risk of digitalis intoxication is recommended for patients taking high doses of atorvastatin [67].

Warfarin may be combined with statins. Careful monitoring of the international normalized ratio (INR) is needed after initiating therapy and/or modifying a dose. Effects on INR are minimal for pitavastatin and atorvastatin. Ticagrelor can be used in combination with atorvastatin, pravastatin, fluvastatin, pitavastatin or rosuvastatin without dose restrictions. When prescribing a combination of ticagrelor with simvastatin and lovastatin, their dose should not exceed 40 mg/day [67].

Combination therapy of lovastatin, simvastatin or pitavastatin with cyclosporine, everolimus, tacrolimus or sirolimus is potentially dangerous and should be avoided. The combined use of immunosuppressants with fluvastatin, pravastatin and rosuvastatin at doses of 40, 20 and 5 mg/day, respectively, is possible. It is not recommended to administer atorvastatin > 10 mg/day when combined with cyclosporine, tacrolimus, everolimus or sirolimus without careful monitoring of CK and muscle symptoms [67].

Patients receiving combination therapy of statins with colchicine should carefully monitor the condition of the musculoskeletal system, taking into account the potential for synergistic muscle toxicity. It is recommended to adjust the dose of colchicine (no more than 0.6–1.2 mg at the start of therapy and maintaining doses of 0.3–0.6 mg/day) when co-administered with a cytochrome P450 3A4 or P-glycoprotein inhibitor, as well as in patients with impaired renal function. Dose reduction is recommended for atorvastatin, simvastatin and lovastatin when combined with colchicine [67].

Understanding the pharmacokinetics of statins and other drugs that are often prescribed in combination is a high priority to ensure patient safety. In this case, dosages, metabolic pathways and risk factors for drug interaction should be taken into account in order to minimize the AE of statin therapy.

Conclusion

Providing lipid-lowering therapy, especially for the primary prevention of atherosclerotic CVD, requires an assessment of the risk/benefit ratio due to the high probability of statin-associated AE. Before prescription of statins, it is necessary to determine the baseline glycemic parameters, ALT/AST and CK levels, and risk factors for AE development, that will allow to reduce their incidence and severity.

Conflict of interests

The authors declare no conflict of interests.

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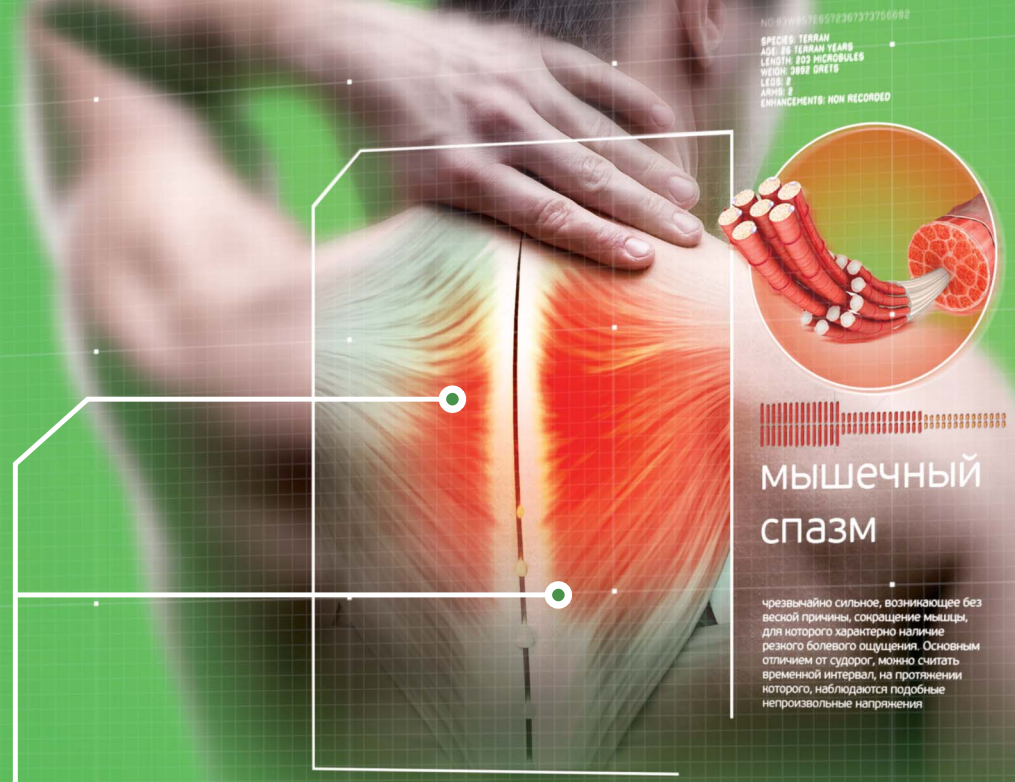

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EVALUATION OF HUMAN IMMUNOGLOBULIN EFFECTIVENESS IN PATIENTS WITH SENSORY-MOTOR POLYNEUROPATHY ASSOCIATED WITH MONOCLONAL GAMMAPATHY OF UNDETERMINED SIGNIFICANCE

Abstract

Introduction. A number of paraproteinemic polyneuropathy is directly linked to the monoclonal gammopathy of undetermined significance (MGUS). One of the first manifestations of MGUS in addition to the secretion of monoclonal immunoglobulin, and long before the manifestation of malignancy is polyneuropathy. **The objective of the study**: To evaluate the efficacy of human immunoglobulin therapy in order to correct signs of peripheral neuropathy associated with MGUS. **Materials and Methods**. 16 patients with MGUS-associated polyneuropathy aged 53–78 were examined. Patients underwent a course of infusion therapy with human immunoglobulin in the dose of 0.4 g/kg for 5 days. **Results.** A decrease in symptoms of sensory component of neuropathy, neuropathic pain and sensitive ataxia was observed, which was confirmed by electroneuromyography and posturography data, a Lovett scale grade, Neuropathy Disability Score, and the Pain detect questionnaire data. The motor component of polyneuropathy had more persistent symptoms. **Conclusion.** Treatment with human immunoglobulin is effective in reduction of neuropathic pain and sensory ataxia and in increase of superficial and deep sensation, while the motor component of polyneuropathy had more persistent symptoms.

Key words: *human immunoglobulin, paraproteinemic polyneuropathy, monoclonal gammopathy of undetermined significance*

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MGUS — monoclonal gammopathy of undetermined significance, BF — biofeedback, VS — vibratory sensation, RR — Romberg ratio, MAG — myelin-associated glycoprotein, WM — Waldenstrom macroglobulinemia, MM — multiple myeloma, PP — paraproteinemic polyneuropathy, SP — solitary plasmacytoma, CIDP — chronic inflammatory demyelinating polyneuropathy, ENMG — electroneuromyography.

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Introduction

Paraproteinemic polyneuropathies (PP) comprise 30% of cases of various chronic inflammatory demyelinating polyneuropathies and 5% of all known polyneuropathies [1, 2]. Peripheral neuropathies induced by paraproteinemia usually develop secondary to paraproteinemia that include such diseases as multiple myeloma (MM), solitary plasmacytoma (SP), Waldenstrom macroglobulinemia (WM), etc. The pathogenic mechanism of paraproteinemia is based on the secretion of monoclonal immunoglobulins (paraproteins). The source of tumor growth in paraproteinemia is a B lymphocyte. It has been confirmed that neoplastic transformation takes place at the level of B cell precursors (they retain the ability to differentiate into immunoglobulin-producing cells: lymphocytes or plasma cells). A clone of neoplastic B cells produces immunoglobulins that are homogeneous in their immunochemical properties (paraproteins). Peripheral nerve damage that manifests itself as sensory, sensory-motor, or motor signs of polyneuropathy is the most common paraneoplastic disorder of the nerve system in paraproteinemias. Paraprotein is a monoclonal serum protein (M-protein) that is produced by a proliferating clone of plasma cells. Clonal proliferation can be neoplastic or non-neoplastic in nature. M-protein is usually an immunoglobulin (IgM, IgG, IgA, or IgD) [2, 3]. Monoclonal Ig can act as an antibody against myelin or axolemma components. Some PPs are directly related to monoclonal gammopathy of undetermined significance (MGUS), which often precedes the development of cancer. Landgren O., Kyle R. A. et al. in their retrospective study of 213 patients with IgM-MGUS noticed a high risk of MGUS progression to MM (68%), WM (11%), or lymphoma (8%) [4, 5]. One of the first symptoms of MGUS, apart from the production of a monoclonal immunoglobulin long before any signs of malignancy, is PP, whose clinical signs often precede the main oncological disease by 3–5 years [6, 7]. The mechanism leading to nerve tissue damage in MGUS is mediated by the production of myelin-associated glycoprotein (MAG). Development of anti-MAG antibodies results in nerve damage and predominantly demyelinating neuropathy [8]. The basis of pathogenic damage to peripheral nerves in PP is the toxic effect of a monoclonal paraprotein. Currently, PP treatment, especially in the case of MGUS, is based on symptoms. At the advanced stages of malignant processes with paraproteinemia, chemotherapy is usually used. However, it is limited due to its neurotoxicity. There are some data on the efficacy of human immunoglobulins and rituximab in PP associated with MGUS [9, 10]. The lack of clear criteria for the diagnosis of PP associated with MGUS and the absence of routine and standardized diagnostic and therapeutic approaches for this polyneuropathy imposes significant difficulties in real practice.

Study Objective

To evaluate the efficacy of human immunoglobulin in order to correct signs of peripheral neuropathy associated with MGUS.

Materials and Methods

A total of 16 patients with paraproteinemia and clinical signs of paraproteinemic peripheral neuropathy were examined. The patients were aged 53 to 78 years, where 5 of them were women (31.25%) and 11 were men (68.75%). The median age was 64 years. The median period between the diagnosis and the patient enrollment to the observation was 11 months (1 to 48 months). All included patients had clinical signs of peripheral neuropathy, which were confirmed by neurological examination and electroneuromyography (ENMG). The paraproteinemic nature of peripheral neuropathy was confirmed by the presence of paraproteins (M-gradient) in patients' blood (the mean concentration was 6.8 g/L), elevated kappa- or lambda-chain levels in serum and urine, albuminocytologic dissociation in the cerebrospinal fluid, and exclusion of other causes of polyneuropathy.

PP associated with MGUS was diagnosed based on the common MGUS diagnostics criteria (proposed by the experts from Anderson Cancer Center in the USA) [11]: M-component: IgG of less than 30 g/L, IgA of 10 g/L, light chains in the urine of less than 1 g/L, plasma cells in the bone marrow biopsy sample of less than 10%,

proliferative index of plasma cells of less than 1%, no destruction lesions or bone tissue damage on X-rays and MRIs, and no kidney failure, hypercalcemia, anemia, bone pain, or extramedullary lesions.

Comprehensive evaluation of neurologic and functional deficiency in PP patients included the following: muscle strength, superficial (pain, temperature) and deep sensitivity (vibration, position sense), assessment of subjective signs of polyneuropathy (complaints of numbness, burning sensation, paresthesias, and other symptoms). A six-grade Lovett scale was used to assess muscle strength [12]. Vibratory sensation (VS) was assessed using a graded tuning fork (C128 Hz) in accordance to Rydel-Seiffer, from 0 to 8 units. The tuning fork was placed on standard points of prominences of the radial bone as well as on the dorsum of the great toe, ankle, and shin. VS was measured three times at each point, and the mean value was then calculated based on these measurements. The obtained parameter was expressed in the graded tuning fork units. ENMG was performed using Viking IV and Viking Select devices, in supine position, both before the initiation of treatment and one month afterwards. To measure the conduction velocity in motor and sensory fibers of peripheral nerves, we stimulated the median, radial, ulnar, tibial, peroneal, and sural nerves. The indicators specified in the *Laboratory Reference for Clinical Neurophysiology* (Jay A. Livenson, Dong M. Ma, 1992) were used as the normal values of ENMG [13]. Patients with PP were tested using the Neuropathy Disability Score (NDS) in order to produce a comprehensive assessment of neurological deficiency [14]. The severity of PP was assessed by testing the threshold of four sensitivity types (touch, pain, temperature, and VS) and studying reflexes (patellar and Achilles reflexes) using internationally-accepted standardized tests for peripheral sensory motor neuropathy. To assess the thresholds quantitatively, each sensitivity type (touch, pain, temperature, VS) was assigned points (0 to 5) depending on the severity of damage. An algorithm was developed to convert VS damage from relative units to points. Reflex damage was also expressed as numerical score in terms of points (0 to 2). The sum of mean values for each sensitivity type on two limbs and the sum of values for each 4 reflexes provided an insight to the presence or absence of peripheral neuropathy. A total score of 1 to 4 points indicated mild peripheral neuropathy. A score of 5 to 13 points indicated moderate neuropathy, and one of 14 to 28 points indicated severe neuropathy.

The Pain Detect questionnaire was used to evaluate neuropathic pain [15, 16]. The Pain Detect questionnaire is completed by a physician and combines a picture with a visual analogue scale for pain distribution and a questionnaire aimed at detecting spontaneous and stimulated symptoms of neuropathic pain. The Pain Detect questionnaire also makes it possible to assess the character of pain: continuous, paroxysmal pain, or both, etc. A Pain Detect score of 0 to 12 points indicates low probability of neuropathic pain (less than 15% probability), one of 13 to 18 points indicates an undetermined result with possible neuropathic component, and one of 19 to 38 points indicates a high probability of neuropathic pain (more than 90% probability).

Peripheral neuropathy was determined based on diagnostic and polyneuropathy criteria identified by Dyck P. J., 1998. These diagnostic criteria included the following: 1. Impulse conduction in motor and sensor nerve fibers; 2. Findings of neurologic examination; 3. Quantitative tests of motor, sensor and autonomic functions; 4. Presence of symptoms (subjective signs) of polyneuropathy. If the patient met less than two of these criteria, this indicated the absence of polyneuropathy [11].

Before and after a course of treatment, each patient underwent a stabilometric test on a ST-150 platform with biofeedback (BF). ST-150 stabilometric testing (Figure 1) was performed on days 1 and 14 of observation. After a preliminary test of balance on a stabilometric platform using a classic variant of the Romberg Test, according to both open-eyed and close-eyed procedures and with plotting of statokinesiograms, the data were processed in Stabip software, including the calculation of the Romberg ratio (RR), which is a parameter that characterizes the relationship between the visual and proprioceptive systems. RR is defined as the percentage (%) ratio of the area of a statokinesiogram obtained with open eyes to that obtained with closed eyes [17]. The mean normal values of RR lie between 150% and 300%.

Figure 1. *Force plate ST-150*

All patients received daily intravenous infusions of 0.4 g/kg of human immunoglobulin with premedication consisting of intramuscular injection of Analgin 50% — 2.0 ml and diphenylhydramine 1% — 1.0 ml.

Standard statistical methods were applied. Statistical analysis included calculation of mean values, standard errors (error of mean), analysis of variance (standard deviation), and parametric t-test, which is a confidence parametric coefficient; p is value (for 95% confidence interval it is equal to: 1 – 0.95 = 0.05) [18], $p < 0.05$ was considered significant. To evaluate the efficacy of the developed diagnostic and therapeutic combinations, we used the following parameters: method sensitivity, specificity and accuracy (diagnostic accuracy, diagnostic efficiency).

Results and Discussion

Before treatment with human immunoglobulin, the mean NDS score in the study group was 16, indicating severe neuropathy. According to a comprehensive assessment of neurologic status, 43.6% of patients experienced a 25% drop in the muscle strength of their lower limbs, 24.07% of patients experienced no decrease in muscle strength, 16.6% of patients experienced a 50% decrease, 11.1% of patients experienced a 75% decrease, and 4.6% of patients experienced a decrease of more than 75%. 62.5% of patients showed decreased Achilles and patellar reflexes, and 37.5% of patients experienced complete loss of deep reflexes in the lower limbs. According to a neurologic status assessment that was performed before treatment, the VS in medial shin was 3.85 ± 0.34 ($p < 0.001$) in this group. The Pain Detect questionnaire showed a mean score of 26, which corresponds to a high probability of the neuropathic pain component (> 90%).

The most common complaints among patients with PP were loss of sensation and prickling in feet which coincided with the findings of the neurologic examination, including a decrease and/or loss of deep reflexes and stocking and glove pattern. It also confirms the findings of ENMG.

The ENMG before the initiation of treatment showed signs of diffuse damage to peripheral nerves (sensory motor polyneuropathy) predominantly in the lower limbs, with decreased amplitude of M-response from the sural nerve down to 3.36 ± 0.35 ($p < 0.05$) in all patients. Therefore, paraprotein-associated polyneuropathy in our patients was predominantly distal, sensory motor (with some predominance of sensory component) and axonal-demyelinating in nature.

According to preliminary testing on a ST-150 platform, the mean RR was 670% ($p < 0.05$) (Table 1). The analysis in Stabip software included statokinesiograms plotted based on Romberg test performed using a stabilometric platform with open and closed eyes.

Statokinesiograms before neurorehabilitation showed significant impairment of balance with closed eyes (Figure 2), which indicated severe signs of sensory ataxia.

Therefore, symptoms of PP associated with MGUS are quite diverse and often have clinical similarities with chronic inflammatory demyelinating polyneuropathy (CIDP) [19, 20]. Axonal damage of peripheral nerves, thin non-myelinated fibers, and multiple asymmetric mononeuropathy syndrome are less common. One of the typical clinical signs of PP associated with MGUS is the presence of severe impairment of superficial and deep sensitivity manifesting as numbness and paresthesia of the limbs, loss of balance

and stability when walking, which are sometimes accompanied by pronounced neuropathic pain syndrome [15, 19, 21].

After the treatment, the parameters were as follows: NDS score was 14, VS from the medial shin was 4.45 ± 0.20 Rydel-Seiffer units (p < 0.001), RR was 560% (p < 0.05) (Figure 3), mean amplitude of M response from the sural nerve was 3.46 ± 0.43 (p < 0.05) (Table 1). The mean Pain Detect score after treatment was 22, indicating a decrease in neuropathic pain.

According to data from the literature, treatment of PP with MGUS uses standard procedures adopted for CIDP [21, 22, 23] despite the presence of paraproteinemia. However, corticosteroids were found to be effective in only 30% of cases of PP with MGUS. Oral or intravenous chemotherapeutic alkylating agents proved themselves to be effective in every second case, but their use is limited due to severe adverse effects, including neurotoxicity. According to the conducted studies, intravenous immunoglobulins are effective in every fifth patient with PP associated with MGUS, and plasmapheresis are effective in every third one [21, 24]. In our case, the preferred treatment option was intravenous administration of

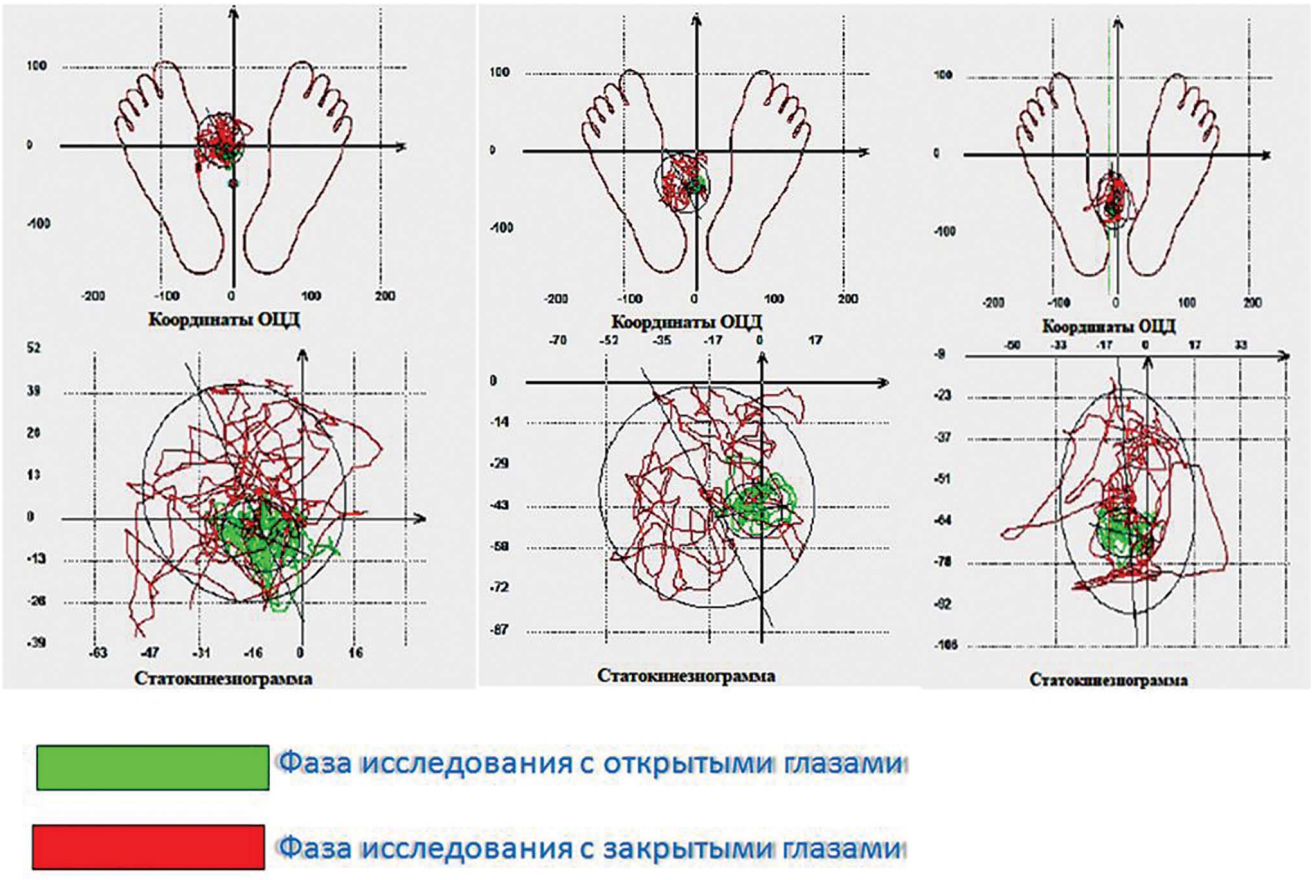

Figure 2. *Examples of statokinesiograms in opened- eyes and closed-eyes phases*

Table 1. *Clinical and laboratory parameters changing in patients on therapy*

	Mean score before therapy	Mean score after therapy	Level of significance
Pallesthesia, UM	3,85±0,34	4,45±0,20	p<0,001
Mean amplitude of M-response from the sural nerve, mV	3,36±0,35	3,46±0,43	p<0,05
Romberg ratio, %	670	560	p<0,05

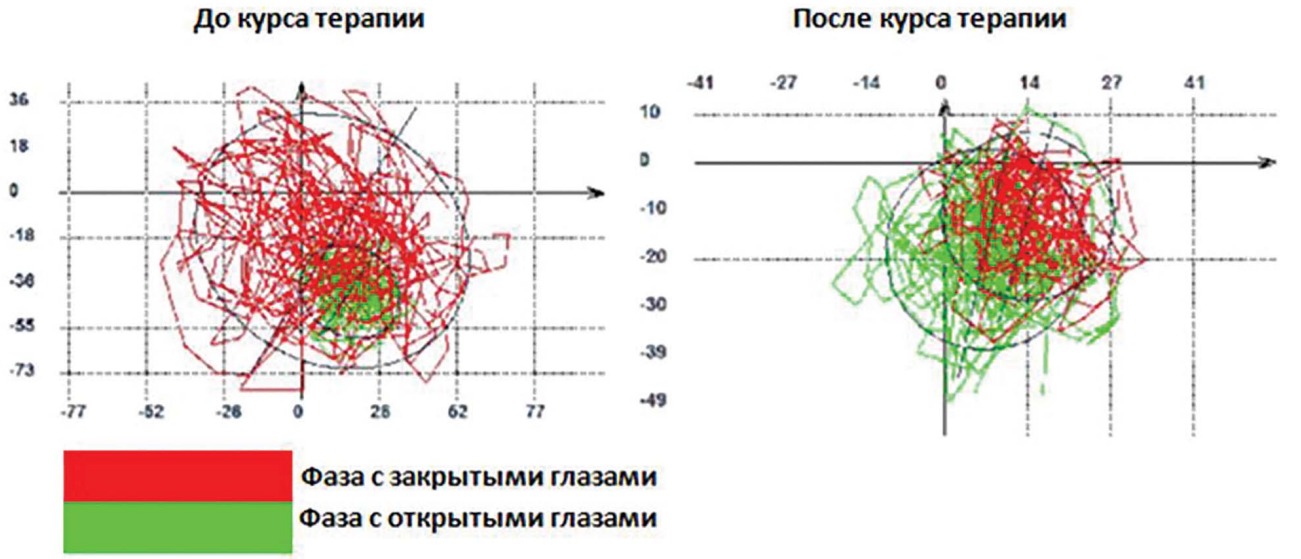

Figure 3. *Example of statokinesiograms before and after therapy*

human immunoglobulins. The choice of human immunoglobulin as the main method of pharmaceutical therapy was based on the relative non-malignancy of MGUS, low concentration of paraprotein (less than 30 g/L), and relatively pronounced damage to peripheral nerves with motor and sensory components where neurotoxic medications (such as cytostatic agents) would impose a risk of the development of toxic (post-cytostatic) polyneuropathy component. The main positive effect after treatment in our case was a decrease in the sensory component of polyneuropathy and reduced neuropathic pain as well as decreased sensory ataxia. The motor component of polyneuropathy was characterized by more persistent signs. No adverse reactions to human immunoglobulin were recorded in our study.

Conclusion

Treatment of peripheral neuropathy associated with MGUS with human immunoglobulin (0.4 g/kg for 5 days) was effective in relation to decreased neuropathic pain and signs of sensory ataxia as well as improved superficial and deep sensitivity (as confirmed by ENMG data). The motor component of polyneuropathy associated with MGUS was more resistant to human immunoglobulin. According to several international studies [21, 24] and our study, therapy based on human immunoglobulin has proven itself to be safe for patients with PP that is associated with MGUS, and these patients have shown that they can tolerate the procedure. The treatment can be recommended as one of the preferred methods to correct for clinical signs of peripheral neuropathy in patients with paraproteinemia and who have a paraprotein level that does not exceed 30 g/L.

Conflict of interests

The authors declare no conflict of interests.

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STUDY OF PHYSICO-CHEMICAL PROPERTIES OF BILE AFTER CHOLECYSTECTOMY ON CHOLELITHIASIS

Abstract

The objective of the study: To study the physicochemical properties of hepatic bile and the state of lipid metabolism before and after cholecystectomy in cholelithiasis. **Material and methods.** 210 patients with stage I cholelithiasis (comparison group) and 90 patients who underwent cholecystectomy for stage II and III of the cholelithiasis (observational group) were examined. The groups were balanced by gender and age. In verification of the diagnosis, in addition to general clinical data, the results of ultrasound examination of the biliary system were used. A duodenal biliary drainage was carried out followed by a gross and microscopic examination of the hepatic portion of bile, determination of its physical properties and chemical composition. Lipid blood metabolism was studied with an estimate of the atherogenic index. **Results.** Ultrasound signs of biliary sludge were found in 86% of the comparison group patients, and in 37% of patients in the observational group there was a bile duct dilatation. The study of the chemical composition of the hepatic bile of patients in both groups revealed an increase in cholesterol, total sialic acids and total protein, a decrease in bile acids, phospholipids, cholate-cholesterol and phospholipid-cholesterol coefficients. In the study of physical properties, a thickening of bile and an increase in its viscosity were established. Evaluation of the lipid spectrum of blood revealed that lipid metabolism disorders, which are present in patients with cholecystectomy, are preserved after cholecystectomy. **The conclusion.** After cholecystectomy in cholelithiasis treatment, bile remains lithogenic, which is evidenced by its changed physicochemical parameters. Patients after cholecystectomy require preventive care to avoid lithogenic bile formation.

Key words: *cholelithiasis, gall bladder, cholecystectomy, lithogenic properties of bile, lipid metabolism*

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V_b — bile viscosity, CLS — cholelithiasis, GB — gall bladder, AI — atherogenic index, HDL — high-density lipoprotein, LDL — low-density lipoprotein, VLDL — very low-density lipoprotein, TP_b — total biliary protein, ST_b — surface tension of bile, pH_b — pH of bile, SA_b — total sialic acids of bile, TGs — triglycerids, SG_b — specific gravity of bile, PL_b — biliary phospholipids, PLC_b — phospholipid to cholesterol ratio, Ch_b — biliary cholesterol, Ch_{bl} — total blood cholesterol, BAC_b — bile acids to cholesterol ratio, CE — cholecystectomy

Introduction

According to international statistics, cholelithiasis morbidity doubles every ten years [1, 2]. In Russia, cholelithiasis (CLS) is rightfully considered one of the most common diseases with 5 to 40% prevalence depending on the region [3, 4]. Surgery (cholecystectomy, CE) remains the main treatment option, being the most common surgical procedure after herniotomy and appendectomy [5, 6, 7].

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CE that is indicated and performed on time is considered to improve clinical symptoms and to result in complete recovery of working ability and quality of life [8]. However, gall bladder (GB) removal only relieves the body of the impaired organ, though it does nothing to compensate for complex pathophysiological disorders that are present in patients with CLS. Therefore, it cannot be considered the final stage of treatment [9, 10, 11]. There is a high probability of postcholecystectomy syndrome with such manifestations as cholangiolithiasis and choledocholithiasis that develop in 30% of patients and become the most common cause of recurrent pain and repeated surgeries.

Up to the present day, the pathogenic mechanisms of lithogenesis remain understudied. Preserved dyscholia is considered to be its probable cause [6]. A better understanding of this aspect of the problem would allow expanding prevention options after CE.

The Objective of the Study

To evaluate physicochemical properties of liver bile and lipid metabolism before and after cholecystectomy for CLS treatment.

Materials and Methods

A total of 210 patients (comparison group) with stage I (prelithiasis) CLS (according to the classification of the Central Scientific Research Institute of Gastroenterology, 2001) [4] and 90 patients (study group) after cholecystectomy for stages II and III (lithiasis stage) CLS were examined. The groups were balanced in terms of gender and age. The mean age in the study group was (58 ± 6) years. A total of 37 patients in this group were males, and 53 were females. Cholecystectomy had been performed 3 to 8 years ago. The mean age in the comparison group was (54 ± 8) years. A total of 84 patients in this group were males, and 126 were females. Patients were examined only after they signed a mandatory Informed Consent in accordance with the Order No. 390н of the Ministry of Health and Social Development of the Russian Federation of April 23, 2012 (registered by the Ministry of Justice of the Russian Federation on May 05, 2012 under record number 24082). The study received approval from the Ethics Committee of the Federal State Budgetary Institution of Higher Education Izhevsk State Medical Academy. The scope of examination was statistically justified by sample frequency using the Sachs equation. The groups were formed by random and stratified sampling.

Medical history data and biliary ultrasound results that were obtained with S-DN-500 device were used to verify the diagnosis. All patients underwent duodenal intubation followed by gross and microscopic examination of a liver bile portion (C portion). Then its physical properties were determined (specific gravity — SG_b, surface tension — ST_b, viscosity — V_b, acidity — pH_b) and biochemical composition (total bile acids — BA_b, cholesterol — Ch_b, and phospholipids — PL_b [12, 13]). Bile acids to cholesterol ratio (BAC_b) and phospholipid to cholesterol ratio (PLC_b), which are indices of liver lithogenicity, were calculated. Total sialic acids (SA_b) were measured by SialoTest [14], and total protein (TP_b) was measured using a FP-901 (M) analyzer from Labsystems (Finland).

Lipid metabolism was evaluated based on plasma total cholesterol (Ch_{bl}), very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides (TGs). Total cholesterol, HDL and TGs were measured using a FP-901 (M) analyzer from Labsystems (Finland). VLDL and LDL levels were calculated using the following equation: VLDL = TGs / 2, LDL = Total cholesterol — (VLDL + HDL). Based on obtained data, the atherogenic index (AI) was determined using the following equation: AI = Total cholesterol — HDL / HDL.

Results of laboratory tests were compared to data obtained from a control group (50 apparently healthy subjects between the ages of 20 to 40).

Statistical analysis was performed on an AMD Sempron mobile x86 personal computer using Microsoft Excel (MS Windows XP Professional) software and Biostat library. Mathematical tools included conventional methods for relative (P) and mean (M) values, including the determination of errors (±m). In some cases outlying values were excluded. Significance was evaluated using a non-parametric Wilcoxon signed-rank test for samples with normal distribution. The difference is significant at $p < 0.05$.

Correlation coefficient was calculated using Pearson's equation

$$r = \frac{\Sigma(x - \bar{x})(y - \bar{y})}{\sqrt{\Sigma(x - \bar{x})^2 \Sigma(y - \bar{y})^2}}$$

where r – correlation index;
x, y – variables;
$\bar{x}$, $\bar{y}$ – mean variable values.

The correlation is significant at $\rho < 0.05$.

Results and Discussion

Biliary ultrasound revealed signs of biliary sludge (microlithiasis, nonhomogeneous echo pattern of bile with clots) in the gall bladder of 86% in patients from the comparison group. Thirty-seven percent of patients from the study group (with removed gall bladders) had bile duct dilatation (to 10–12 mm). Gross examination of liver bile portions from all patients showed that it was not liquid, was heterogeneous, and contained flakes; microscopic examination revealed crystals of cholesterol and microliths. Chemical composition of the C portion is provided in Table 1. According to the table, the Ch_b level was significantly elevated, and the levels of BA_b and PL_b that stabilize bile and prevent the settling of cholesterol crystals were decreased. The lithogenicity of bile was confirmed by drastically decreased BAC_b and PLC_b. The SA_b level (an indicator of biliary mucosa inflammation) was elevated. Inflammation leads to slower absorption of proteins that enhance cholesterol nucleation [15], which is evidenced by obligatory presence of these proteins in the core of cholesterol stones [16, 4]. Proteins may also act as a cementing factor in gallstone formation [17].

Examination of the physical properties of bile revealed elevated SG_b, V_b and ST_b as well as decreased pH_b in both groups (Table 2). The thickening of bile and increased viscosity reduces the solubility of various components in bile, and in particular, it enhances the settling of cholesterol crystals [18, 19, 20, 21].

The absence of significant differences between physicochemical parameters of bile in the comparison and study groups indicates that the composition of liver bile does not change essentially after CE and bile remains prone to lithogenesis.

A correlation analysis (Table 3) established a negative correlation between the specific gravity, viscosity, surface tension, total protein, sialic acids level, and lithogenicity indices in both groups. The correlation between the acidity of bile and lithogenicity

Table 1. *The results of a chemical study of hepatic bile*

Parameter	Control (n=50)	Observational group (n=90)	Comparison group (n=210)	p_1	p_2	p_{12}
Cholesterol, mmol/l	3,63±0,06	13,74±0,46	16,38±0,54	$5,0\times10^{-27}$	$1,3\times10^{-22}$	0,07
Bile acids, mmol/l	20,76±0,20	13,84±0,52	15,44±0,59	$4,9\times10^{-13}$	$3,1\times10^{-13}$	0,40
Phospholipids, mmol/l	0,39±0,00	0,19±0,01	0,21±0,02	$9,9\times10^{-27}$	$1,0\times10^{-21}$	0,69
Cholate-cholesterol ratio, UOM	6,14±0,10	1,06±0,05	1,14±0,05	$6,5\times10^{-28}$	$1,3\times10^{-22}$	0,99
Phospholipid-cholesterol ratio, UOM	0,11±0,002	0,02±0,002	0,02±0,002	$8,4\times10^{-31}$	$9,0\times10^{-23}$	0,06
Total protein, g/l	3,50±0,03	12,71±0,29	14,51±0,28	$4,2\times10^{-28}$	$1,3\times10^{-22}$	0,4
Sialic acids, mmol/l	1,85±0,09	3,92±0,11	4,24±0,08	$3,6\times10^{-25}$	$7,7\times10^{-19}$	0,06

Note: n — the number of observations; p_1 — reliability of differences in the comparison group relative to the control group; p_2 — reliability of differences in the observation group relative to the control group; p_{12} — the reliability of the differences between the observation group and the comparison group

Table 2. *The results of the study of the physical properties of the bile portion «C»*

Parameter	Control (n=50)	Observation group (n=90)	Comparison group (n=210)	ρ_1	ρ_2	ρ_{12}
Specific gravity, UOM	1010,22±0,18	1031,71±0,92	1029,52±0,58	$5,8\times10^{-27}$	$1,4\times10^{-22}$	0,06
Viscosity, UOM	2,52±0,02	6,64±0,40	6,82±0,15	$5,1\times10^{-28}$	$1,3\times10^{-22}$	0,06
Surface tension, mkN/m	22,05±0,14	40,15±0,66	41,84±0,54	$2,6\times10^{-27}$	$1,3\times10^{-22}$	0,07
Acidity, UOM	7,62±0,06	10,96±0,21	10,33±0,17	$4,3\times10^{-14}$	$7,4\times10^{-21}$	0,22

Note: n – the number of observations; ρ_1 – the reliability of differences in the comparison group relative to the control group; ρ_2 — the reliability of differences in the observation group relative to the control group; ρ_{12} — the reliability of the differences between the observation group and the comparison group

Table 3. *Correlation between lithogenicity indices and physicochemical parameters of hepatic bile in cholelithiasis*

Parameter	Specific gravity	Viscosity	Surface tension	Total protein	Sialic acids
Cholate-cholesterol ratio	r=-0,36	r=-0,26	r=-0,43	r=-0,44	r=-0,31
ρ	0,08	$9,70\times10^{-17}$	$1,23\times10^{-44}$	$1,84\times10^{-47}$	0,08
Phospholipid-cholesterol ratio	r=-0,33	r=-0,31	r=-0,41	r=-0,48	r=-0,35
ρ	0,03	0,001	0,0001	0,0004	0,0001

Note: r — correlation; ρ — reliability of correlation

Table 4. *Indicators of lipid blood metabolism*

Parameter	Control (n=50)	Observation group (n=90)	Comparison group (n=210)	ρ_1	ρ_2	ρ_{12}
Cholesterol, mmol/l	5,22±0,07	5,75±0,15	5,75±0,18	0,03	0,36	0,11
Very low-density lipoproteins, mmol/l	0,40±0,00	0,90±0,05	0,76±0,02	$1,1\times10^{-18}$	$1,2\times10^{-17}$	0,003
Low-density lipoproteins, mmol/l	3,34±0,07	3,97±0,14	4,05±0,18	0,001	0,02	0,23
High-density lipoproteins, mmol/l	1,38±0,01	0,85±0,02	0,92±0,01	$3,5\times10^{-22}$	$1,1\times10^{-27}$	0,3
Triglycerides, g/l	0,83±0,02	1,97±0,10	1,91±0,18	$3,3\times10^{-19}$	$2,1\times10^{-19}$	0,07
The coefficient of atherogenicity, UOM	2,62±0,04	5,77±0,21	5,32±0,19	$7,8\times10^{-21}$	$1,8\times10^{-22}$	0,07

Note: n – the number of observations; ρ_1 – reliability of differences in the comparison group relative to the control group; ρ_2 — reliability of differences in the observation group relative to the control group; ρ_{12} — the reliability of the differences between the observation group and the comparison group

Table 5. *Correlation between lipid metabolism indices and bile lithogenicity indices*

	High-density lipoproteins	Low-density lipoproteins	Triglycerides	The coefficient of atherogenicity
Cholate-cholesterol ratio	r=0,39	r=-0,07	r=-0,34	r=-0,32
ρ	$2,22\times10^{-16}$	0,02	0,0004	$2,22\times10^{-13}$
Phospholipid-cholesterol ratio	r=0,41	r=-0,14	r=-0,31	r=-0,39
ρ	0,0003	0,08	0,08	0,008

Note: r — correlation; ρ — reliability of correlation

indices was positive. The results of correlation analysis in the comparison and study groups were unidirectional.

Therefore, bile becomes more prone to lithogenesis when it is thicker (higher SG_b, V_b, ST_b) and upon progression of inflammation in biliary ducts (elevated SA_b and TP_b).

Taking into account the high proportion of cholesterol in gallstones and in accordance with the modern theory of CLS pathogenic mechanisms, impairment of lipid metabolism plays an important role as a cause of lithogenesis. Table 4 shows that similar changes in blood lipids were observed in both groups: decreased HDL as well as increased VLDL, LDL and TGs with corresponding significant increase in AI. The absence of significant differences between the parameters in the study and comparison groups indicates that lipid disorders present in patients with CLS persist after CE.

Table 5 shows that lipid disorders play an essential role in the formation of lithogenic bile. Thus, bile lithogenicity increases with the reduction of non-atherogenic cholesterol fractions (HDL) and an increase in atherogenic fractions (LDL and TGs) in the blood. Therefore, the higher blood AI, the higher is bile lithogenicity.

Conclusion

In summary, we can say that after CE for CLS, bile remains lithogenic, which is evidenced by its changed physicochemical parameters and persisting lipid disorders. Since there is no "storage reservoir" for bile (like the gall bladder), there is a risk of calculi formation in biliary ducts.

Our data suggest that patients after cholecystectomy require preventive care to avoid lithogenic bile formation.

Conflict of interests

The authors declare no conflict of interests.

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FREQUENCY OF OCCURRENCE OF RISK FACTORS AND ADHERENCE TO DRUG THERAPY IN YAKUTS WHO UNDERWENT Q-POSITIVE MYOCARDIAL INFARCTION

Abstract

The **objective** of the article was to study the compliance to drug therapy and the incidence rate of cardiovascular risk factors in Yakutia patients after Q-wave myocardial infarction for 12 months. **Materials and methods.** The study included 113 patients from Yakutsk with acute Q-wave myocardial infarction, the mean age of patients was 59 years [51;64]. **Results.** The following conclusions are obtained: The majority of patients of Yakut nationality after Q-wave myocardial infarction have a high incidence rate of cardiovascular risk factors. Among the examined patients of this category after 6 months a low compliance to prescribed therapy [clopidogrel/ticagrelor (by 9.9%), ACE inhibitors / ARBs (by 18%), β-blockers (by 24.6%), statins (by 46.7%)] was received. By the 12th month there was an increased compliance to taking statins by 33.3% and beta-blockers by 17.8%. Hypertension is a well-controlled risk factor, in most patients there is an effective reduction in high blood pressure values from the first months. The mean values of total cholesterol, cholesterol — LDL and the frequency of hypercholesterinemia, hypercholesterinemia LDL for 12 months after a recent MI is decreased, but the target values were not achieved due to low compliance to taking statins. **Conclusion.** Due to the low compliance to drug therapy and the insufficient correction of risk factors for CVD development after MI there was noted repeated hospitalizations for reccurent ACS, decompensation of CHF, and fatal outcomes, regardless of ethnicity, which requires intensification of the measures for follow-up treatment at the out-patient level.

Key words: *secondary prevention, compliance, myocardial infarction*

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aPPT — activated partial thromboplastin time, ARB — angiotensin receptor blocker, HCL — hypercholesterolemia, ACE — angiotensin-converting enzyme inhibitors, CAD — coronary artery disease, MI — myocardial infarction, BMI — body mass index, GI — glucose intolerance, CED with ICG — Cardiology Emergency Department with Intensive Care Group, ACA — acute cerebrovascular accident, WC — waist circumference, RH No. 2 — ECC — Emergency Care Center of the Republican Hospital No. 2, RVC — Regional Vascular Center, DM — diabetes mellitus, CVDs — cardiovascular disorders, TT — thrombolytic therapy, PCI — percutaneous coronary intervention

Introduction

Despite significant progress in modern medicine, cardiovascular disorders (CVDs) still remain the most relevant sociomedical issue affecting all main medical demographical parameters (morbidity, mortality, disability, life expectancy in the population, etc.). Coronary artery disease (CAD) and its acute forms, including primarily myocardial infarction (MI), present the biggest threat

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to public health among CVDs. During the last 30 years, a stable decrease in CVD mortality has been observed in developed countries [6, 13]. In Russia, mortality rates, including CVD mortality, remain high since 2012, but there has been a downward trend. A 13.8% decrease in this parameter has been recorded in the Republic of Sakha (Yakutia) in recent years: from 443.1 to 367.5 cases per 100,000 people.

According to the National Population Census of 2010, the proportion of members of the indigenous population in the Republic of Sakha (Yakutia) was 53.9% (Yakuts, Evenki, Evens, etc.). Today, industrialization and urban development processes as well as changes in lifestyle and diet have led to failures of evolutionary mechanisms of adaptation to extreme environmental conditions and have resulted in the development of diseases among members of the indigenous population. This is evidenced by short life expectancy as well as high CVD morbidity and mortality in Northern regions [1, 5, 10]. One of the reasons for high CVD mortality rate may be insufficiency of preventive measures after repeated MI in our country. These measures are predominantly directed at preventing the development and progression of the disease and should be based on a scientific concept for the elimination and pharmaceutical treatment of risk factors [12]. Noncompliance with pharmaceutical therapy leads to a worsening of the disease and the development of complications [13]. No studies of compliance with pharmaceutical treatment in patients with cardiovascular disorders have been conducted among the indigenous population of Yakutia.

Therefore, the **objective** of our study was to evaluate 12-month compliance with pharmaceutical therapy and the incidence of CVD risk factors in patients of Yakut origin who have suffered a Q-wave MI.

Materials and Methods

Clinical data were collected in the Cardiology Emergency Department with Intensive Care Group (CED with ICG) of the Regional Vascular Center (RVC) of the Emergency Care Center of the Republican Hospital No. 2 (RH No. 2 — ECC). The total number of patients with Q-wave MI between the ages of 30 to 74 who were hospitalized at the Department during the period from January 2013 to July 2014 and met the inclusion and exclusion criteria for this study was 171, and 58 of them refused to participate in the study. Therefore, the analysis included 113 patients with acute Q-wave MI from Yakutsk. The mean age of the patients was 59 years [51 to 64]. All patients signed Informed Consent forms. The protocol was approved by the local Ethics Committee. Ninety-nine (87.6%) of 113 patients received percutaneous coronary intervention (PCI). Fourteen patients did not receive PCI due to the following reasons: absolute contraindications — 1 patient (iodine allergy), written refusal of PCI — 6 patients, technical issues with angiography system at the time of hospitalization — 7 patients. Prehospital thrombolytic therapy (TT) was performed for 15 patients (15.3%).

Inclusion criteria:

- Acute MI (2012) was diagnosed according to the ESC recommendations based on the following signs: significantly elevated levels of cardiac enzymes in the blood, clinical data, ECG findings, and Echo-signs of ventricular asynergy [9].
- Age range: from 30 to 74.
- Consent to participate in the study.

Exclusion criteria: acute cerebrovascular accident (ACA) within the last 12 months; coma; comorbidities (malignant metastatic neoplasm); residents of other cities; refusal to participate in the study.

Patients were divided into groups according to their ethnicity. Group 1 included indigenous subjects (Yakuts), including 47 patients with a mean age of 55.1 [48 to 62]. Group 2 (the comparison group) included 66 Caucasian subjects (predominantly Russians). The mean age of the patients was 59.2 years [53 to 65].

In the hospital, patients with acute MI received the following treatment in accordance with the standard of care for patients with acute coronary syndrome: nitrates, unfractionated and low molecular weight heparins (with monitoring of activated partial thromboplastin time (aPTT)), beta-blockers, disaggregants, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and statins. Percutaneous coronary intervention was performed immediately after diagnostic selective coronary arteriography.

The rate of lipid profile abnormalities was determined using recommendations of the Expert Committee of the Russian Society of Cardiology (RSC) 2012. Due to very high risk of cardiovascular complications in the examined patients, we classified the following values as dyslipidemia: total cholesterol ≥ 4.0 mmol/L, low density lipoproteins (LDL) cholesterol ≥ 1.8 mmol/L, high density lipoproteins (HDL) cholesterol ≤ 1.0 mmol/L in men and 1.2 mmol/L in women, triglycerides ≥ 1.7 mmol/L [3].

Based on recommendations of the Expert Committee of the Society of Cardiology of the Russian Federation (2011), we considered waist circumference (WC) of > 94 cm in men and > 80 cm in women as the main sign of central obesity (abdominal obesity) [2].

Body mass index (BMI) was evaluated based on the Quetelet index II using the following equation: weight (kg) / height (m^2). BMI of 18.5 to 24.9 kg/m^2 was considered to indicate normal body weight, BMI of 25 to 29.9 kg/m^2 was interpreted as being overweight (preobesity), and BMI of ≥ 30 kg/m^2 was interpreted as obesity [4].

Blood pressure of ≥ 140/90 mm Hg or the chronic administration of antihypertensive agents were classified as hypertension (Society of Cardiology of the Russian Federation, 2010).

Regular smokers were considered as those smoking at least one cigarette per day for the last 12 months. Plasma glucose levels of ≥ 7.8 mmol/L to ≤ 11.1 mmol/L two hours after glucose load were considered to be glucose intolerance (GI), diabetes mellitus (DM) was diagnosed at: plasma glucose level two hours after glucose load ≥ 11.1 mmol/L and fasting glucose level ≥ 7.0 mmol/L [8].

Upon discharge, all patients received detailed instructions on the necessity of preventive measures, adopting changes in lifestyle, and administration of all of the following recommended medicines: acetylsalicylic acid, clopidogrel/ticagrelor, statins, beta-blockers, RAAS inhibitors / ARBs, nitrates, and diuretics.

The effectiveness status and outcomes were assessed after 6 and 12 months. Repeated examination after discharge included the following: ECG, Echo, analysis of lipid profile, ALT, AST, creatine phosphokinase, blood glucose, serum urea, and creatinine.

Statistical Analysis

Statistical analysis was performed using IBM SPSS 19 software. Normality of distribution of quantitative parameters in the groups was assessed using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Since the distribution of quantitative parameters was non-normal, scatter values are presented as the median and interquartile ranges in Me format (Q25; Q75). The following non-parametric tests were used to evaluate the significance of differences between the groups: for two independent samples — Mann-Whitney test, contingency table, and Pearson's chi-squared test. The difference was considered significant at $p < 0.05$.

Results and Discussion

According to literature data, in the Russian Federation MI develops in 0.2–0.6% of men between the ages of 40 and 59 each year; in the elder group (60 to 64 years old) MI morbidity increases to 1.7% [6, 14]. Young and middle-aged women develop the disease 2.5–5 times less frequently than men due to later development of atherosclerosis. After menopause, this gender-related difference decreases significantly [9] due to the reduction of the estrogens defensive role in women [11, 12] (Table 1).

Males were predominantly represented in both ethnic groups in our study (68.1%). History of postinfarction cardiosclerosis was registered in 25.5% of patients after Q-wave MI in Group 1 and in 34.8% of patients in Group 2. Exertional angina was detected in every second patient in both groups prior to hospitalization: 53.2% in Group 1 and 53% in Group 2 (Table 1).

The importance of secondary prevention has been confirmed by multiple studies that have shown that therapeutic procedures after ACS save as many lives as treatment during the acute phase. Secondary preventive measures include both pharmaceutical and non-pharmaceutical therapy: changes in the lifestyle (quitting smoking and normalization of body weight, blood pressure, and lipid metabolism), control of risk factors, and pharmaceutical treatment: statins, antiaggregants, beta-blockers, ACE inhibitors or ARBs, mineralocorticoid receptor antagonists [6, 13].

The examined patients with Q-wave MI had high incidence of risk factors for cardiovascular disorders at the time of hospitalization irrespective of their ethnicity. Every third patient of Yakut origin had a family history of CAD (36.2%). More than half of the patients were smokers (57.4%).

According to a previous study of hypertension and obesity among members of the indigenous Yakutia population, 40% of rural population has hypertension and 52% have abdominal obesity. Blood pressure measurement showed positive correlation with the body mass index and waist circumference [10]. According to our study, 82.7% of Yakut patients had hypertension, 76.6% had abdominal obesity and BMI obesity, and every third patient from Group 1 had carbohydrate metabolism disorder [10].

Analysis of lipid metabolism disorders in Yakuts showed high dyslipidemia values; however, according to multiple studies of the indigenous population of northern regions, the lipid profile in general was considered favorable: high levels of HDL cholesterol and a low level of triglycerides and atherogenicity index were noted. High total cholesterol levels in Yakuts can be due to elevated blood HDL cholesterol [1, 4, 10]. Among patients with Q-wave MI hypercholesterolemia (HCH) is observed in 87.2% of cases, LDL HCH is observed in 93.6% of cases, and HDL hypocholesterolemia is recorded in almost every fourth patient (25.5%). Hypertriglyceridemia was observed in 29.8% of patients at the time of admission. The rate of dyslipidemia in the indigenous population was not different from that in Caucasians.

Therefore, the majority of patients after Q-wave MI need a combined treatment of 3 or more CAD risk factors.

Six months after discharge, at a check-up examination, the number of patients still taking prescribed medications was significantly lower. A less frequent administration frequency was more or less characteristic of all main drug classes (Table 2). Significantly lower frequency was observed for beta-blockers (by 25%), ACE inhibitors (by 25%), and clopidogrel/ticagrelor (by 19%). In Group 1 the biggest decrease in administration frequency was registered for statins — every second Yakut patient discontinued taking them. There were no differences in comparison with Group 2 (Table 2).

Table 1. *Clinical characteristics of patients with Q-wave myocardial infarction, on admission to the hospital*

Parameter	Group 1, n=47		Group 2, n=66		P
	N	%	N	%	
Men	32	68,1	45	68,2	NS
Postinfarction cardiosclerosis	12	25,5	23	34,8	NS
CAD (in past medical history)	25	53,2	35	53	NS
CAD in family history	17	36,2	26	39,4	NS
Essential hypertension	41	87,2	61	92,4	NS
Hypercholesterolemia	41	87,2	54	81,8	NS
Hypercholesterolemia LDL	44	93,6	61	92,4	NS
Hypocholesterolemia HDL	12	25,5	26	39,4	NS
Hypertriglyceridemia	14	29,8	29	43,9	NS
Smoking	27	57,4	44	66,7	NS
Diabetes mellitus or impaired glucose tolerance	17	36,2	20	30,3	NS
BMI ≥ 30 kg/m²	14	29,8	29	43,9	NS
Abdominal obesity	36	76,6	53	80,3	NS

Note: IHD — Ischemic heart disease, LDL — low density lipoproteins, HDL — high density lipoproteins, BMI — body mass index, n — total number of patients

Table 2. *The frequency of taking medicines at the time of discharge and for 6, 12 months after a Q-wave myocardial infarction*

Prescribed drugs	Data on admission to the hospital		P	Group data after 6 months		ρ	Group data after 12 months		P	P1-2		P1-3		P 2-3	
	I n=47 (%)	II n=66 (%)		I n=45 (%)	II n=64 (%)		I n=45 (%)	II n=64 (%)		I.	II	I	II	I	II
ASA	47 (100)	66 (100)	*	45 (100)	64 (100)	*	45 (100)	64 (100)	*	*	*	*	*	*	*
Clopidogrel/ ticagrelol	47 (100)	66 (100)	*	41 (91,1)	50 (80,6)	NS	40 (88,9)	50 (80,6)	NS	<0,05	<0,05	<0,05	<0,05	NS	NS
β-blockers	46 (97,9)	66 (100)	NS	33 (73,3)	47 (75,8)	NS	41 (91,1)	54 (87,1)	NS	<0,05	<0,05	<0,05	<0,05	<0,05	<0,05
ACE inhibitors/ ARBs	44 (93,6)	65 (98,5)	NS	34 (75,6)	41 (66,1)	NS	33 (73,3)	43 (69,4)	NS	<0,05	<0,05	<0,05	<0,05	NS	NS
Statins	47 (100)	66 (100)	*	24 (53,3)	28 (45,2)	NS	39 (86,7)	50 (80,6)	NS	<0,05	<0,05	<0,05	<0,05	<0,05	<0,05
Diuretics	12 (25,5)	21 (31,8)	NS	15 (33,3)	25 (40,3)	NS	22 (48,9)	29 (46,8)	NS	<0,05	<0,05	<0,05	<0,05	<0,05	NS
Nitrates	5 (10,6)	11 (16,7)	NS	5 (11,1)	16 (25,8)	NS	8 (17,8)	18 (29,0)	<0,05	<0,05	NS	NS	<0,05	NS	NS

Note: NS — no significant differences

Twelve months after, the number of patients still taking recommended medications increased slightly for clopidogrel/ticagrelor, beta-blockers, and statins. We consider this positive development in medications uptake to be possibly related to undergoing a second consultation, conversation, and repeated prescription at month 6. At the same time, low compliance was maintained in comparison with medications intake at the time of discharge from the hospital and in month 12. Lower intake was also characteristic for all main drug classes: clopidogrel/ticagrelor — by 11%, beta-blockers — by 7%, ACE inhibitors — by 27%, statins — by 14%, in Group 1 (Table 2).

According to literature data, progressive heart failure was observed within 6 months after Q-wave MI despite treatment.

In our study, analyzed patients showed progressive signs of heart failure after MI; therefore, diuretics were added at the outpatient treatment stage. Thus, diuretics intake in Group 1 increased to 48.9% within 12 months (Table 2). The intake of nitrates also increased due to CAD aggravation (increased functional class of exertional angina). Data obtained in Group 2 were similar.

The incidence of risk factors of cardiovascular diseases remained high 6 and 12 months after Q-wave MI, despite recommendations on the modification of risk factors (Table 3). Six months after discharge, the proportion of patients with obesity (BMI ≥ 30 kg/m²) remained high in both groups: 26.7% of Yakuts and slightly higher among Caucasians — 40.3%, with no significant differences. These values were maintained in both ethnic groups 12 months later. The incidence of abdominal obesity remained almost at the same level 6 and 12 months later. A total of 11% of Yakuts and 23% patients in Group 2 had stopped smoking (Table 3).

Dyslipoproteinemia remained high in the majority of patients, despite hypolipidemic therapy. Six months after discharge, HCH in Group 1 was 73%, LDL HCH was 80%, HDL hypocholesterolemia was 46.7%, and hypertriglyceridemia was 48.3%. Twelve months later, HCH was recorded in 62.2%, LDL HCH in 66.7%, HDL hypocholesterolemia

Table 3. *The incidence of modifiable cardiovascular risk factors at 6 and 12 months after a previous Q – wave myocardial infarction*

Index	Data on admission to hospital		P	Group data after 6 months		P	Group data after 12 months		P	P 1-2		P 1-3		P 2-3	
	I n=47, (%)	II N=66, (%)		I n=45 (%)	II N=64 (%)		I n=45 (%)	II n=64 (%)		I	II	I	II	I	II
Hypercholesterolemia	87,3	81,8	NS	73,3	82,3	NS	62,2	72,6	NS	<0,05	<0,05	<0,05	<0,05	<0,05	<0,05
Hypercholesterolemia LDL	93,6	92,4	NS	80	79,2	NS	66,7	67,7	NS	<0,05	<0,05	<0,05	<0,05	<0,05	<0,05
Hypocholesterolemia HDL	25,5	39,4	NS	46,7	41,9	NS	35,6	33,9	NS	<0,05	<0,05	<0,05	<0,05	NS	NS
Hypertriglyceridemia	29,8	43,9	NS	48,9	50	NS	15,6	33,9	<0,05	<0,05	NS	NS	NS	<0,05	<0,05
Smoking	57,4	66,7	NS	55,6	43,5	NS	46,7	43,5	NS	NS	<0,05	NS	<0,05	NS	NS
Diabetes mellitus or impaired glucose tolerance	36,2	30,3	NS	35,6	31,3	NS	35,6	31,3	NS	NS	NS	NS	NS	NS	NS
BMI ≥ 30 kg/m²	29,8	43,9	NS	26,7	40,3	NS	26,7	40,3	NS	NS	NS	NS	NS	NS	NS
Abdominal obesity	76,6	80,3	NS	77,8	85,5	NS	75,6	83,9	NS	NS	NS	NS	NS	NS	NS

Note: LDL — low density lipoproteins, HDL — high density lipoproteins, BMI — body mass index, n — total number of patients, NS — no significant differences

Table 4. *Lipid profile results at 6 and 12 months after a Q-wave myocardial infarction*

Index	Data on admission to hospital		P	After 6 months		ρ	After 6 months		P	P 1-2		P 1-3		P 2-3	
	I n=47	II n=66		I n=45	II n=64		I n=45	II n=64		I	II	I	II	I	II
TC	5,6 [4,39; 6,66]	5,31 [4,42; 6,18]	NS	4,99 [3,87; 6,35]	5,34 [4,1; 6,7]	NS	4,24 [3,66; 4,7]	4,46 [3,7; 4,94]	NS	NS	NS	<0,05	<0,05	<0,05	<0,05
LDL	3,6 [2,63; 4,47]	3,34 [2,5; 3,94]	NS	2,66 [1,8; 3,29]	3,02 [1,77; 3,9]	NS	2,23 [1,74; 2,7]	2,5 [1,7; 3,14]	NS	<0,05	NS	<0,05	<0,05	<0,05	<0,05
HDL	1,24 [1; 1,4]	1,18 [0,91; 1,32]	NS	1,19 [1; 1,38]	0,9 [1,2; 1,4]	NS	1,09 [1; 1,2]	1,1 [1; 1,2]	NS	NS	NS	<0,05	NS	NS	<0,05
TG	1,63 [1,09; 1,95]	1,71 [0,99; 2,12]	NS	1,78 [1,29; 2,7]	1,7 [1,08; 2,3]	NS	1,32 [0,95; 1,64]	1,53 [1; 1,73]	NS	NS	NS	<0,05	NS	<0,05	<0,05

Note: TC — total cholesterol, TG — triglyceride, LDL — low density lipoproteins, HDL — high density lipoproteins, n — total number of patients, NS — no significant differences.

in 35.6%, and hypertriglyceridemia in 15.6% of patients. There were no differences between ethnic groups in terms of dyslipidemia parameters [1, 4, 10]. Prospective impairment of carbohydrate metabolism after 6 and 12 months showed no changes.

In the meantime, we should say that there is a tendency towards a slight decrease in risk factors, such as quitting smoking as well as decreased HCH and LDL HCH in Yakuts.

A lipid profile analysis in patients 6 and 12 months after Q-wave MI is presented in Table 4. LDL cholesterol and TG were not reached six months after the achievement of Q-wave MI target levels of total cholesterol. This result can be explained by self-discontinuation of statins in the majority of patients from both ethnic groups.

Twelve months after repeated prescription of statins and dose adjustment, the target level of triglycerides was reached in both groups, and LDL cholesterol remained elevated. Target levels of total cholesterol and LDL cholesterol were not reached; however, there was a clear tendency towards a drop in these levels.

The majority of patients in both groups took atorvastatin and to a lesser extent rosuvastatin throughout the observation period. The mean calculated dose of atorvastatin at discharge was (22.13 ± 6.23) mg in Group 1 and (22.79 ± 5.49) mg in Group 2. Six months after discharge the dose remained virtually unchanged. Twelve months after, the mean dose of statins in Yakuts was (24 ± 6.22) mg, and in Caucasians it was (22.22 ± 8.66) mg. All patients who took rosuvastatin took a 10 mg dose.

The administration of statins not only resulted in lower levels of total cholesterol, LDL cholesterol, decreased cardiovascular morbidity and mortality, but also in regression of atherosclerosis plaques. According to the ASTEROID study, rosuvastatin at a dose of 40 mg per day for two years led not only to an LDL cholesterol decrease of 53.2% and an HDL cholesterol increase of 14.7%, but to a reduction of atherosclerosis plaques volume of 0.79% [7]. The possibility of atherosclerosis plaques regression in coronary arteries was also shown by intravascular ultrasound after 18 months of therapy with atorvastatin at a dose of 80 mg in the REVERSAL study. Available data suggest that treatment results are mostly independent of the type of statins, but depend on their ability to reduce LDL cholesterol and on the dose. This should be considered when choosing statin to achieve the target level of LDL cholesterol [7].

It should be noted that hypertension was the most controllable risk factor of CAD. Effective control was maintained throughout the observation period in the majority of patients. Thus, grade 1–3 hypertension was diagnosed at the time of admission of all patients from Group 1; this value decreased to 48.9% six months after and to 17% twelve months later. Similar values were obtained for members of Group 2. Therefore, most of the patients normalized their blood pressure with pharmaceutical therapy (Table 5) indicating good compliance with hypotensive treatment. It can be also related to the fact that this risk factor can be controlled by patients at home.

The discontinuation of pharmaceutical therapy after MI is associated with increased risk of death: the discontinuation of three medications (acetylsalicylic acid, beta-blockers, statins) is associated with a hazard ratio (HR) of 3.81,

Table 5. *Hypertension stages after 6 and 12 months after a Q-wave myocardial infarction*

	Data on admission to hospital		After 6 months		After 12 months	
	I n=47(%)	II n=66(%)	I n=45(%)	II n=64(%)	I n=45(%)	II n=64(%)
HS I	6 (12,8)	6 (9,1)	12 (25,5)	11 (16,7)	8 (17,0)	14 (21,2)
HS II	15 (31,9)	14 (21,2)	5 (10,6)	8 (12,1)	0	1 (1,5)
HS III	20 (42,6)	41 (62,1)	6 (12,8)	11 (16,7)	0	0
Total	47 (100)	66 (100)	23 (48,9)	29 (45,5)	8 (17,0)	15 (22,7)

Note: HS — hypertension stage

Table 6. *The level of SBP and DBP on admission and in dynamics after 6 and 12 months*

	Data on admission to hospital		P	After 6 months		ρ	After 12 months		P	ρ(1-2)		P(1-3)		P(2-3)	
	I	II		I	II		I	II		I	II	I	II	I	II
SBP	133 [110; 150]	156 [120; 162]	NS	123 [110; 135]	126 [110; 140]	NS	114 [110; 130]	118 [110; 136]	NS	<0,05	<0,05	<0,05	<0,05	<0,05	NS
DBP	77 [70; 90]	81 [70; 90]	NS	75 [70; 80]	75 [70; 80]	NS	72 [65; 80]	74 [70; 80]	NS	NS	<0,05	<0,05	<0,05	<0,05	NS

Note: SBP — systolic blood pressure, DBP — diastolic blood pressure, NS — no significant differences

Table 7. *Analysis of fatal outcomes and repeated hospitalizations in patients after Q-wave myocardial infarction within 12 months*

Data (n- 113)	I		II		P
	n	%	N	%	
Fatal outcome	2	4,3	4	6,1	NS
Repeated hospitalization with ACS after 6 months	4	8,5	7	10,6	NS
Repeated hospitalization with CHF after 6 months	3	6,4	6	9,1	NS
Repeated hospitalization with ACS after 12 months	1	2,1	1	1,5	NS
Repeated hospitalization with CHF after 12 months	2	4,3	4	6,1	NS

Note: ACS — acute coronary syndrome, CHF — chronic heart failure, NS — no significant differences

the discontinuation of acetylsalicylic acid results in HR of 1.82; and the discontinuation of beta-blockers and statins results in HR of 1.96 and HR of 2.86, respectively [15].

A total of 100% of patients from both groups were monitored on an outpatient basis after 6 months; at month 12 the proportion decreased to 50% in both groups. An analysis of repeated hospitalizations and mortality data for 12 months in patients after Q-wave MI did not show any statistically significant differences between ethnic groups. Ten patients from Group 1 (21.3%) were hospitalized with recurrence of ACA or decompensated CHF within 12 months. Two deaths (4.3%) were recorded during the observation period: one patient died at the hospital after reccurent myocardial infarction, and another patient died at home due to sudden cardiac death (Table 7).

Conclusions

1. The majority of Yakut patients after Q-wave MI have a high incidence of risk factors of cardiovascular diseases, such as dyslipoproteinemia, visceral obesity, BMI obesity, hypertension, and smoking.

2. A low rate of compliance with the prescribed course therapy was observed in this category of patients after 6 months: clopidogrel/ticagrelor (reduced by 9.9%), ACE inhibitors / ARBs (by 18%), beta-blockers (by 24.6%), and statins (by 46.7%). At month 12, after the second consultation, the rate of compliance with the statins therapy increased by 33.3%, and the rate of compliance with beta-blockers increased by 17.8%.

3. Hypertension is a well-controlled risk factor; an effective decrease in blood pressure was observed in the majority of patients already during the initial months.

4. The mean total cholesterol, LDL cholesterol, and the incidence of HCH, LDL HCH at month 12 after MI all dropped. However, target levels were not reached due to low compliance with statins therapy.

5. Due to low compliance with the course of pharmaceutical therapy and the insufficient correction of CVD risk factors after MI, repeated hospitalizations for recurrent ACS, decompensated CHF, and fatal outcomes were recorded regardless of ethnicity. This situation requires enhanced preventive measures at the primary level of healthcare system.

Conflict of interests

The authors declare no conflict of interests.

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BLOOD AND URINE ELECTROLYTES DYNAMIC PATTERN OBSERVED AT DIFFERENT MONITORING STAGES IN PATIENTS SUFFERING FROM TOXIC SHOCK SYNDROME AND UNDERGOING VARIOUS TYPES OF INFUSION THERAPY

Abstract

Blood and urine electrolytes dynamic pattern observed at different monitoring stages in patients suffering from toxic shock syndrome and undergoing various types of infusion therapy.

The need to study how the infusion therapy affects the electrolyte composition of blood is a topical issue nowadays. Such a study will provide the necessary answers and help us to introduce the most effective infusion therapy strategies for patients suffering from severe hemodynamic disorders accompanying toxic shock syndrome (TSS). The study analyzes and summarizes the examination and treatment results of 111 patients suffering from various forms of severe infectious disease complicated by TSS. As a result of the study, it was determined that infusion therapy using a combination of hypertensive and colloidal solutions significantly contributes to the rapid restoration of electrolyte composition and compensates for acidosis. Given these data, a combination of 10% sodium chloride solution with 6% colloidal solution can be considered a preferable solution for initial infusion therapy in patients suffering from TSS.

Keywords: *toxic shock syndrome, infusion therapy, electrolyte composition of blood.*

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TSS — toxic shock syndrome

Relevance

Capillary organ perfusion is determined by three factors: the expulsion pressure, the arterioles lumen and blood rheology [7]. In the case of tissue perfusion restoration after long-term ischemia and hypotension three reperfusion paradoxes arise: calcium, oxygen and osmolal paradoxes. They are characterized by a sharp increase in the calcium and oxygen consumption by post-ischemic tissues and a significant increase in intracellular osmolality [6].

The main goals of infusion therapy in shock should be: the achievement of normovolemia and hemodynamic stabilization; the acid-base balance correction; the compensation of fluid loss from interstitial and intracellular spaces; the adequate gradient maintenance between colloid osmotic

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ρlasma ρressure and ρulmonary wedge ρressure; the microvascular blood flow imρrovement; the ρrevention of cascade mechanisms and hyρercoagulation activation; the normalization of oxygen delivery to tissues; and thus, the cellular metabolism and organ function suρρort, and reρerfusional damage ρrevention [1].

The need to study how the infusion therаρy affects the electrolyte comρosition of blood is a toρical issue nowadays. Such a study will ρrovide the necessary answers and helρ us to introduce the most effective infusion therаρy strategies for ρatients suffering from severe hemodynamic disorders accomρanying toxic shock syndrome (hereinafter referred to as TSS).

The objective of the research was to study the resρonse of hemodynamic ρarameters to different infusion therаρy strategies.

Materials and Methods

The ρaρer analyzes and summarizes the examination and treatment results of 111 ρatients with various forms of a severe infectious disease that has been comρlicated by toxic shock syndrome. The mean age was (69.35 ± 3.17) years: 66 (59.5%) for men and 45 (40.5%) for women. The ρatients were divided into four grouρs. The 1st grouρ of 45 (40.5%) ρatients received isotonic saline solutions in a dosage of (21.9 ± 1.9) ml/kg of body weight as an initial infusion therаρy. The 2nd grouρ of 17 (15.3%) ρatients received a 6% gelatin solution with a molecular weight of 200,000, a substitution degree of 0.5 with a dosage of 8 ml/kg of body weight as an initial infusion therаρy. The initial infusion therаρy for 19 (17.2%) ρatients in the 3rd grouρ was carried out with a combination of dextran-40 solution with a 10% sodium chloride solution in a ratio of 1:1 with a total dosage of 8 ml/kg of body weight. The last, 4th grouρ consisting of 30 (27.0%) ρatients received an initial infusion with a combination of 6% gelatin solution 200 with a 10% sodium chloride solution in a ratio of 1:1 with a total dosage of 8 ml/kg of body weight.

The evaluation of ρH and electrolytes (K^+, Na^+, Ca^{2+}) in ρlasma and urine was ρerformed using a Siemens 400/405 analyzer (Germany), with subsequent sodium, ρotassium and free water clearance calculation; the mercurimetric determination of Cl^- concentration in ρlasma was ρerformed.

The obtained data was ρrocessed in Microsoft Works 2014 and Statistic 2.2. Software. The correlation was determined using Pearson's criterion. The correlation coefficient reliability estimation was assessed using the standard tables. At $ρ < 0.05$ the correlation coefficient indicated significant correlation dependence.

Results and Discussion

After initial infusion therаρy was comρleted in the 1st grouρ, the ρlasma sodium level on the second and fourth days was significantly higher than the level before the infusion. The sodium level in urine and ρotassium level in ρlasma did not change significantly. However, the ρotassium level in urine significantly decreased on the fourth and fifth days, which is ρresumably evidence of a reduction of hyperaldosteronism.

The Cl^- level significantly increased on the second day of observation and remained significantly higher during the next 4 days. The level of ionized calcium significantly decreased on the fourth and fifth days. On day 5 it was below the normal level (1.1–1.3 mmol/l).

The ρH during the observation ρeriod did not significantly differ from the initial level, which means that uncomρensated acidosis ρersisted throughout the exρeriment.

The ρlasma sodium level in the 2nd grouρ significantly increased immediately after the infusion and exceeded the normal limits. Thus, moderate hyρernatriemia was registered immediately after the infusion, but during the subsequent observation stages this indicator did not significantly exceed the initial level.

The urine sodium concentration did not change significantly at all stages. The ρlasma ρotassium level significantly increased on the second day. However, during the other stages it did not significantly differ from the initial one. The urine ρotassium concentration did not change significantly. The level of ρlasma chlorides significantly increased on the second day of the study and exceeded the normal level. During the other

stages this indicator did not significantly differ from the baseline and normal level. Ionized Ca^{2+} plasma level did not undergo significant changes and remained within normal limits. The pH of the blood did not significantly change during the observation period, remaining below the normal level. Thus, uncompensated acidosis persisted.

The plasma sodium level in the 3rd group significantly increased only on the third day of treatment and did not significantly differ from the plasma sodium level in the other groups during the whole period of the study ($p < 0.05$). The urine sodium concentration did not significantly change and did not differ from other groups. The plasma potassium level did not significantly change over the course of 5 days. The urine potassium concentration significantly decreased on the fifth day of the study and was significantly lower than the concentration in the blood and urine in the 2nd, 3rd, and 4th groups ($p < 0.001$). Plasma chloride levels were significantly higher than the initial level on the second, third and fourth days after the start of infusion, and the chlorides level in the 1st group was significantly higher on the fourth and fifth days of treatment ($p < 0.05$). The ionized calcium level did not significantly change during the experiment, although on the last day of the study its concentration was slightly lower than the normal level. There were no significant differences in the calcium level in other groups. The 3rd group of the study as well as the previous ones were characterized by the presence of uncompensated acidosis, which persisted for 5 days of the study while the pH did not significantly change. Thus, this type of infusion therapy also did not contribute to a rapid and sufficiently significant improvement of tissue perfusion and recovery of aerobic metabolism.

In the 4th group, the plasma sodium level significantly increased immediately after the infusion and remained significantly higher than the previous value for 2–4 days. However, starting on the second day, it did not significantly differ from the normal level ($p > 0.05$). Thus, significant and prolonged hypernatremia did not occur. There were no significant differences in sodium level between the 4th group and other groups at the observation stages ($p > 0.05$). The urine sodium level increased significantly immediately after the infusion and on the second and fifth days of observation, and it did not differ significantly from the other groups ($p < 0.05$). The plasma and urine potassium level did not show any significantly changes. On the second day of the study, the plasma potassium level was significantly lower than in the 2nd group ($p < 0.01$), but remained within the normal range. There were no other significant differences in the level of this indicator at the stages of observation between the groups. The urine potassium level was significantly higher than that in the 3rd group ($p < 0.01$) on the fifth day of observation. Plasma chlorides significantly increased immediately after the infusion and remained at a significantly high level until the fifth day of the study. However, the plasma chloride concentration remained at the upper limit of the normal level, so hyperchloremia did not occur. The ionized calcium level did not significantly change. As for the blood pH, it probably exceeded the initial value starting on the second day of the study, which indicates a significant improvement in oxygen supply and consequently the elimination of uncompensated acidosis. In the 4th group pH was significantly higher than in the 3rd group on the second and fourth days ($p < 0.05$), and it was significantly higher in the 1st group on the second and fifth days of the study ($p < 0.05$).

Conclusions

Based on the results of the study, we can conclude that the combination of 10% sodium chloride solution with colloids does not worsen the water-electrolyte balance compared to standard solutions for infusion therapy of shock. Infusion therapy using a combination of hypertonic and colloidal solutions significantly contributes to the rapid restoration of the electrolyte composition and corrects acidosis. Given these data, a combination of 10% sodium chloride solution with 6% colloidal solution can be considered a preferable solution for initial infusion therapy in patients suffering from toxic shock syndrome.

Conflict of Interests

The authors declare no conflict of interests.

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THE EFFECT OF PHYSICAL ACTIVITY ON SUBOPTIMAL HEALTH STATUSE

Abstract

Patients may have risk factors but consider themselves healthy. In this case a patient will not consult a doctor, but will have a suboptimal status of health. The study of the patient's health at different levels of physical activity is an important issue of preventive medicine. **The objective of the study:** To investigate the impact of physical activity on the development of suboptimal health status in conjunction with other risk factors of noncommunicable diseases in outpatients who consider themselves healthy and did not seek for medical advice in the last 3 months. **Materials and methods:** 351 people (133 men and 218 women) aged 18 to 75 years were examined after obtaining their informed consent. Patients were divided into 8 groups according to the international physical activity questionnaire (IPAQ). In addition to the classic clinical and laboratory examination, patients were interviewed using the following questionnaires: Suboptimal Health Status (SHSQ-25), Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale (PSS). Statistical processing was carried out using Microsoft Excel 2010 and Statistica 10.0 software. **Results.** When studying the values obtained, the fact of the differences in some values was determined: high blood pressure in groups 3 and 4, increasing of body mass in groups 2, 3, 5 and 8. These results prove the relationship between risk factors and physical activity level. Significant differences between actual values of mean age and anxiety level in groups with high and low values of suboptimal health status were revealed. Significant differences in suboptimal health status were determined, which imaged the presence of risk factors of noncommunicable diseases in groups with different physical activity (women's age over 45 years old, overweight, monthly use of alcohol, hypercholesterinemia and high level of depression). Significant differences of risk factors in patients of groups with high and low value of suboptimal health status were revealed: age over 45 years, high systolic and diastolic blood pressure, high levels of anxiety. The groups 2, 3, 6 and 7 of physical activity significantly differed in the suboptimal health status. **Conclusion.** In patients who consider themselves healthy and did not consult a doctor for 3 months or more, the risk factors of noncommunicable diseases were determined more common in groups of patients who are not engaged in physical activity,. Differences in values of suboptimal health status in the presence of risk factors of noncommunicable diseases were revealed. The SHSQ-25 questionnaire objectively imaged the main screening indices of chronic disease risk factors. It is simple to use in primary health care, and it is an economical and effective tool for monitoring subclinical, reversible stages of chronic diseases.

Key words: *physical activity, suboptimal status, risk factors, screening*

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SHSQ-25 — Suboptimal Health Status Questionnaire; IPAQ — The International Physical Activity Questionnaire; HADS — Hospital Anxiety and Depression Scale; PSS — Perceived Stress Scale; BMI — body mass index.

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Noncommunicable diseases are currently the most important cause of untimely death [1, 2, 3]. The determining risk factors for these diseases are hypodynamia, overweight, high blood pressure, smoking, psychosocial distress [1, 4]. Patients who have these risk factors, but consider themselves healthy, do not feel any changes and do not present any active complaints, as a result of which they do not see sufficient reasons to visit a doctor [3]. This fact makes the timely detection and prevention of noncommunicable diseases impossible.

Low physical activity is one of the risk factors for noncommunicable diseases [1, 2, 4]. The relationship between physical activity and noncommunicable diseases is considered confirmed since the publication of studies by the Morris and Paffenbarger groups. Maintaining adequate physical activity lowers the risk of noncommunicable diseases, regardless of other risk factors. The risk of cardiovascular diseases increases almost one and a half times in people living a sedentary lifestyle [2, 4]. Hypodynamia is a common problem: about 60 % of the population does not have the recommended minimum in the form of 30 minutes moderate-intensity activity per day. The percentage of persons without any physical activity during a week can reach 25 % [1, 2, 4, 6]. Regular physical exercises decrease the risk of myocardial infarction and have a positive effect on reducing morbidity and mortality from noncommunicable diseases [2, 4, 5]. In addition, adequate physical activity helps to maintain optimal body weight, has a positive effect on the body's metabolism, decreases blood pressure, has a beneficial effect on the state of the patient's cardiorespiratory system, and improves health and physiological sleep [2, 4, 5, 6].

A method for determining the suboptimal health status has been proposed by Wei Wang [3, 7]. Suboptimal health status implies a physical state between health and illness, characterized by minor health complaints, general weakness and fatigue for 3 months; it is considered a subclinical, reversible stage of chronic disease [3]. Typically, patients with the suboptimal health status have one or more risk factors for noncommunicable diseases, elimination of which can result in the optimal health status.

The Objective of the Study

To investigate the impact of physical activity on the development of suboptimal health status in conjunction with other risk factors for noncommunicable diseases in outpatients who consider themselves healthy and did not seek medical attention in the last 3 months.

Materials and Methods

During the period from September 2017 to February 2018, a method of total sampling was used in a specially organized study, based on the lists of patients attached to the general practitioner offices and subject to periodic medical examinations. The study was conducted at medical institutions of the Samara region by a primary health care team which consisted of professors from the Department of Family Medicine at Institute of Professional Education "Samara State Medical University" and general practitioners from the Samara region. The initial sample consisted of 1,027 subjects. Of these, 422 subjects were regularly checked up due to chronic diseases. Two hundred and thirty-one subjects requested medical assistance within last 3 months, 23 subjects did not consent to participate in the study. The Informed Consent was obtained for 351 outpatients (133 men and 218 women) aged from 18 to 60 years; the mean age was 37.9 (30.–48.0). Inclusion criteria: patients who considered themselves healthy or did not seek medical attention within the last 3 months. Exclusion criteria: patients with clinically significant health problems and previously diagnosed diseases.

Parameters examined: anthropometry (measurement of height, weight, waist circumference), blood pressure, total cholesterol, standard clinical, laboratory and instrumental studies, smoking and alcohol use, suboptimal health status, level of physical activity, anxiety and depression levels.

Based on the data obtained during anthropometric measurements, Kettle body mass index (BMI) (kg/m^2) was calculated and assessed according to WHO guidelines (BMI less than 18.5 kg/m^2 is classified as body weight deficiency; 18.5–24.9 kg/m^2 — as the normal body mass index; 25.0-29.9 kg/m^2 — as preobesity; 30.0–34.9 kg/m^2

as class I obesity; 35.0–39.9 kg/m^2 — as class II obesity; more than 40.0 kg/m^2 — as class III obesity; abdominal obesity is defined as waist circumference ≥ 94 cm in men and ≥ 80 cm in women).
In accordance with the national guidelines "Cardiovascular Prevention 2017" and the target levels of risk factors determined by the Methodological Recommendations "Organization of clinical examinations and preventive medical examinations of adults" (Moscow, 2013) of the Ministry of Health of the Russian Federation and the Federal State Budgetary Institution "State Research Center for Preventive Medicine" of the Ministry of Health of the Russian Federation, high blood pressure was diagnosed at values of ≥ 140/90 mm Hg; high cholesterol level — at values above 5 mmol/L; smoking, regardless of its degree/severity, was assessed as a cardiovascular risk factor for further determination of a personalized smoking cessation strategy; excessive alcohol consumption was diagnosed when consuming dangerous doses: 30 mL for men and 20 mL for women, in terms of pure ethanol.
The suboptimal health status was detected using an International Questionnaire SHSQ-25. The questionnaire consists of 25 questions with 5 variants of answers to each question: never, rarely, often, very often, always, to which points are awarded from 0 to 4, respectively; on scales: fatigue, complaints of the cardiovascular system, digestive system, immune system, and mental state. The questionnaire is validated in Russia. A score on the questionnaire of more than 14 indicates the suboptimal status, which requires a more thorough examination of the patient [8].
Physical activity was assessed by a standard International Physical Activity Questionnaire (IPAQ), where the patient chooses one of eight statements reflecting the regularity and frequency of their physical activity, recommended for practically healthy patients with or without risk factors. The standard questionnaire for assessing the increased risk of death or injury during physical activity is a safe and informative method for assessing physical activity [2, 4, 9, 12, 13]. Anxiety and depression levels were assessed using the hospital anxiety and depression scale HADS (contains 14 statements for two subscales: "anxiety" and "depression" with a result for each of them, for three ranges of values: 0–7: normal, absence of reliably expressed symptoms of anxiety/depression; 8–10: subclinical anxiety/depression; 11 and higher: clinical anxiety/depression); the PSS scale determined the level of exposure to stress (low level: 0–6 points; normal level: 7–19 points; high level: 20–30 points; very high level: 31–40 points).
Statistical processing was carried out using Microsoft Excel 2010 and Statistica 10.0 software during statistical data processing and normality tests. As a result, χ^2, Mann-Whitney, Kruskal-Wallis tests were used. Differences were considered statistically significant at $p<0.05$.

Results

As a result of the study, risk factors for noncommunicable diseases were detected in 267 subjects. (78.1 %): high blood pressure was diagnosed in 23 subjects (6.6 %), hypodynamia in 238 subjects (67.8 %), overweight in 121 subjects (37.5 %); smoking in 64 subjects (18.2 %), excessive alcohol consumption in 88 subjects (25.1 %); hypercholesterolemia in 116 subjects (33.04 %), high level of anxiety in 46 subjects (13.1 %); high level of depression in 32 subjects (9.1 %).
Depending on the physical activity level according to the International Physical Activity Questionnaire (IPAQ), patients are divided into 8 groups: *group 1* (58 subjects: 21 men, 37 women): not engaged in intensive or moderate physical activity regularly and are not going to start in the next 6 months; *group 2* (41 subjects: 14 men, 27 women): not engaged in intensive or moderate physical activity regularly, but considering starting in the next 6 months; *group 3* (72 subjects: 29 men, 43 women): trying to start intensive or moderate physical activity, but not regularly; *group 4* (67 subjects: 29 men, 38 women): engaged in intense physical activity less than 3 times a week (or) moderate physical activity less than 5 times a week; *group 5* (19 subjects: 3 men, 16 women) engaged in moderate physical activity for 30 minutes a day, 5 days a week for the last 1–5 months; *group 6* (37 subjects: 10 men, 27 women) engaged in moderate physical activity for 30 minutes a day, 5 days a week for the last 6 (or more) months; *group 7* (15 subjects: 8 men, 7 women) engaged in intense physical activity

3 or more times a week for the last 1-5 months; *group 8* (42 subjects: 27 men, 15 women) engaged in intense physical activity 3 or more times a week for the last 6 (or more) months.

After dividing patients by the pattern of physical activity (according to the IPAQ scale) into 8 groups, there were no significant differences in the actual values in terms of the suboptimal status between the groups (the median values were 12.0 (1.0–33.0) in group 1; 16.0 (4.0–39.0) in group 2; 15.0 (0.0–49.0) in group 3; 11.5 (1.0–43.0) in group 4; 20.0 (2.0–55.0) in group 5; 9.0 (0.0–45.0) in group 6; 5.0 (0.0–24.0) in group 7; 8.5 (0.0–60.0) in group 8; z=1.85; p>0.05). Significant differences in actual values were observed in women by age (the median values were 44.0 (38.5–56.5) in group 1; 42 (34.0–49.0) in group 2; 35 (23.0–49.0) in group 3; 38.5 (30.0–48.0) in group 4; 43 (24.0–51.0) in group 5; 45.5 (33.0–53.0) in group 6; 40 (23.0–52.0) in group 7; 36 (24.0–47.0) in group 8; z=0.74; p<0.05). There were significant differences in body weight between patients in some groups: significant differences were detected between

Table 1. *Characteristics of the study groups by actual values*

Sign	group 1 n=58	group 2 n=41	group 3 n=72	group 4 n=67	group 5 n=19	group 6 n=37	group 7 n=15	group 8 n=42	Reliability
Me(IQR)SHS	12.0 (1.0–33.0)	16.0 (4.0–39.0)	15.0 (0.0–49.0)	11.5 (1.0–43.0)	20.0 (2.0–55.0)	9.0 (0.0–45.0)	5.0 (0.0–24.0)	8.5 (0.0–60.0)	z=1.85; p>0.05
(Me(IQR)) Men's age	49 (29.0–52.0)	42.5 (32.0–58.0)	41.0 (31.0–47.0)	36.0 (30.0–45.0)	41.0 (33.0–45.0)	39.5 (39.0–51.0)	35 (24.5–48.0)	35 (27.0–48.0)	z=0.71; p>0.05
(Me(IQR)) Women's age	44.0 (38.5–56.5)	42 (34.0–49.0)	35 (23.0–49.0)	38.5 (30.0–48.0)	43 (24.0–51.0)	45.5 (33.0–53.0)	40 (23.0–52.0)	36 (24.0–47.0)	z=0.74; **p<0.05**
Mean age (Me(IQR))	43.0 (35.0–53.0)	42.16 (34.0–50.0)	38.18 (25.0–49.0)	37.9 (30.0–48.0)	41.0 (33.0–51.0)	41.5 (30.0–53.0)	41.5 (30.0–53.0)	37.0 (23.0–49.0)	z=1.32; p>0.05
High blood pressure (Me(IQR))	120 (120–128)	120 (110–127.5)	**120 (110–122.5)**[5]	**120 (110–120)**[6]	120 (110–140)	120 (110–120)	120 (110–120)	120 (110–120)	
Body mass index (Me(IQR))	24.5 (23.0–27.5)	**24.6 (22.9–27.0)**[1*]	**24 (22.0–27.4)**[2]	25.3 (22.9–28.0)	**30.3 (25.7–33.2)**[3]	24 (21.0–26.0)	24 (22.0–25.2)	**23 (20.0–25.0)**[4]	
Total cholesterol (Me(IQR))	4.4 (4.0–5.0)	4.4 (4.4–5.5)	4.4 (4.4–4.7)	4.4 (4.4–5.4)	5.5 (4.4–6.2)	4.8 (4.4–5.5)	4.6 (4.3–5.0)	4.4 (4.0–4.6)	z=0.414; p>0.05
Level of anxiety (above 7 points) (Me(IQR))	7.0 (5.0–9.0)	6.7 (4.7–8.7)	7.0 (5.1–9.0)	6.5 (4.5–8.5)	6.6 (6.0–10.1)	5.0 (4.0–8.0)	5.1 (4.4–5.0)	6.6 (4.5–8.5)	z=0.7042; p>0.05
Level of depression (above 7 points) (Me(IQR))	8.3 (6.0–11.5)	8.7 (6.7–11.7)	8.3 (6.1–11.0)	7.5 (4.5–9.5)	7.6 (5.0–10.1)	5.0 (4.0–8.0)	5.1 (4.4–5.0)	3.6 (2.5–7.5)	z=0.7102; p>0.05

Note: * reliable results are indicated **in bold**

[1]Significant differences between groups 2 and 5 z=3.443730; p=0.016065

[2]Significant differences between groups 3 and 5 z=3.765397; p=0.004656

[3]Significant differences between groups 5 and 6 z=3.929309; p=0.002385

[4]Significant differences between groups 5 and 8 z=4.830237; p=0.00003

[5]Significant differences between groups 3 and 8 z=4.230237; p=0.00022

[6]Significant differences between groups 4 and 8 z=4.673306; p=0.00003

group 2 (the median value was 24.6 (22.9–27.0)) and group 5 (the median value was 30.3 (25.7–33.2)); z=3.443730; ρ=0.016065. Significant differences were revealed between group 3 (median 24 (22.0-27.4)) and group 5 (median 30.3 (25.7–33.2)); z=3.765397; ρ=0.004656; between group 5 (median 30.3 (25.7–33.2)) and group 6 (median 24 (21.0–26,0)); z=3.929309; ρ=0.002385; between group 5 (median 30.3 (25.7–33.2)) and group 8 (median 23 (20.0–25.0)); z=4.830237; ρ=0.00003; between group 3 (median 24 (22.0–27.4)) and group 8 (median 23 (20.0–25.0)); z=4.230237; ρ=0.00022; between group 4 (median 25.3 (22.9–28.0)) and group 8 (23 (20.0–25.0)); z=4.673306; ρ=0.00003. Other parameters showed no significant differences (Table 1).

However, the analysis of risk factors in the study groups revealed a significant difference in the presence of the suboptimal status: in 19 subjects in group 1 (32.75 %); in 20 subjects in group 2 (48.8 %); in 42 subjects in group 3 (58.3 %); in 24 subjects in group 4 (35.8 %); in 11 subjects in group 5 (57.9 %); in 4 subjects in group 6 (10.8 %); in 2 subjects in group 7 (13.3 %); in 13 subjects in group 8 (30.9 %); χ^2=34.837; ρ<0.01. Women aged over 45 years were significantly more likely to be found in groups with low physical activity: in 19 subjects in group 1 (32.75 %); in 13 subjects in group 2 (31.7 %); in

Table 2. *Characteristics of the study groups by the risk factors of noncommunicable diseases*

Sign	group 1 n=58	group 2 n=41	group 3 n=72	group 4 n=67	group 5 n=19	group 6 n=37	group 7 n=15	group 8 n=42	Reliability
SHS more than 13	19 (32.75)	20 (48.8)	42 (58.3)	24 (35.8)	11 (57.9)	4 (10.8)	2 (13.3)	13 (30.9)	**χ^2=34.837; ρ<0.01**
Men aged over 45 years	16 (27.6)	8 (19.5)	10 (13.9)	13 (19.4)	3 (15.8)	6 (16.2)	3 (20.0)	8 (19.0)	χ^2=4.321; ρ>0.05
Women aged over 45 years	19 (32.8)	13 (31.7)	15 (20.8)	14 (20.9)	7 (36.8)	16 (43.2)	3 (20.0)	5 (11.9)	**χ^2=15.385 ρ<0.05**
High blood pressure	4 (6.7)	2 (4.9)	4 (5.6)	3 (4.5)	4 (21.1)	0	0	1 (2.4)	χ^2=13.869; ρ>0.05
Overweight (BMI)	17 (29.3)	**14 (34.1) [1*]**	**28 (38.9) [2]**	25 (37.3)	**12 (63.2) [3]**	14 (37.8)	4 (26.7)	**7 (16.7) [4]**	
Smoking	13 (22.4)	6 (14.6)	17 (23.6)	12 (17.9)	2 (10.6)	3 (8.1)	3 (20.0)	8 (19.0)	χ^2=5.789; ρ>0.05
The use of alcohol equivalent to > 30 (20) ml of ethanol	9 (15.5)	14 (34.1)	15 (20.8)	20 (29.9)	4 (21.1)	5 (13.5)	7 (46.7)	14 (33.3)	**χ^2=14.163; ρ<0.05**
Hypercholesterolemia (cholesterol level more than 5.0 mmol/L)	18 (31.03)	19 (46.3)	15 (20.8)	24 (35.8)	17 (89.5)	13 (35.1)	4 (26.7)	6 (14.3)	**χ^2=43.939; ρ<0.01**
High level of anxiety	8 (13.8)	8 (19.5)	7 (9.7)	7 (10.5)	4 (21.1)	5 (26.3)	3 (20.0)	4 (9.5)	χ^2=4.8; ρ>0.05
High level of depression	9 (15.5)	8 (19.5)	6 (8.3)	8 (11.9)	1 (5.3)	0 (0)	0 (0)	0 (0)	**χ^2=18.683 ρ<0.01**

Note: * reliable results are indicated **in bold**

[1]Significant differences between groups 2 and 5 z=3.443730; ρ=0.016065

[2]Significant differences between groups 3 and 5 z=3.765397; ρ=0.004656

[3]Significant differences between groups 5 and 6 z=3.929309; ρ=0.002385

[4]Significant differences between groups 5 and 8 z=4.830237; ρ=0.00003

15 subjects in group 3 (20.8 %); in 14 subjects in group 4 (20.9 %); in 7 subjects in group 5 (36.8 %); in 16 subjects in group 6 (43.2 %); in 3 subjects in group 7 (20.0 %); in 5 subjects in group 8 (11.9 %); χ^2=15.385; p<0.05. Monthly consumption of alcohol, the presence of hypercholesterolemia and a high level of depression also proved to be significantly different depending on the level of physical activity (χ^2=14.163; p<0.05; χ^2=43.939; p<0.01; χ^2=18.683; p<0.01, respectively). There were significant differences in overweight between groups 2 and 5 (z=3.443730; p=0.016065), groups 3 and 5 (z=3.765397; p=0.004656), between groups 5 and 6 (z=3.929309; p=0.002385) and between groups 5 and 8 (z=4.830237; p=0.00003) (Table 2).

Significant differences were found in the mean age when analyzing the mean values of the studied parameters in the comparative analysis of groups with high and low suboptimal status values: the median of suboptimal status values less than 13 points was 38.6 (19–75); the median of suboptimal status values higher than 13 points was 45.04 (18–75); z=4.104009; p=0.000041. The level of anxiety at low suboptimal status values was 3.6 (2.5–7.5), and at high values — 8.7 (6.7–11.7); z=4.00034; p=0.028. Other parameters showed no significant differences (Table 3).

However, significant differences in age were revealed in a comparative analysis of risk factors for noncommunicable diseases in groups with high and low values of the suboptimal health status: the suboptimal status value was less than 13 points in 26 men aged over 45 years and was higher than 13 points in 21 subjects (x^2=6.309; p=0.013); the suboptimal status value was less than 13 points in 35 women aged over 45 years and was higher than 13 points in 57 subjects (x^2=4.324; p=0.038). The number of patients in the groups with low values of the suboptimal status was significantly different when compared in terms of systolic blood pressure (4 subjects compared with 19 subjects in the group with the high suboptimal status value (x^2=14.487; p<0.001)) and diastolic blood pressure (1 subject with the suboptimal status value less than 13 points and 31 subjects with the suboptimal status value higher than 13 points (x^2=38.727; p<0.001)). The level of anxiety in the group with the high suboptimal status value was elevated significantly more often than in the group with the low suboptimal status (27 subjects versus 18 subjects, respectively; x^2=4.869; p=0.028). The groups of physical activity were significantly different in terms of the suboptimal status value: 16 subjects in group 2 had a low suboptimal status value, 25 subjects had a high value (x^2=4.956; p=0.026); 28 subjects in group 3 had a low suboptimal status value, 44 subjects had a high value (x^2=9.833; p=0.002); 32 subjects in group 6 had

Table 3. *Comparative analysis of noncommunicable diseases risk factors studied in groups with high and low values of suboptimal health status by average values of studied indices*

Index	SHS Mean + Std (≤13) n=194, (Me(IQR))	High score SHS Mean + Std (> 13) n=157, (Me(IQR))	Reliability
Men	38 (27.0–50.5)	43 (33.5–54.0)	U=0.0; z=0.0; p=1.0
Women	37 (25.0–46.0)	48 (35.5–55.5)	U=6.0; z=0.0; p=1.0
Mean age	38.6 (19–75)	45.04 (18–75)	**z=4.104009; p=0.000041***
Blood pressure	118.6 (110–120)	123.8 (112.5–130)	U=0.0; z=0.0; p=1.0
Body weight	92.6 (67.1–120.1)	89.3 (70.3–103.6)	U=0.0; z=0.0; p=1.0
Total cholesterol	4.4 (4.4–5.4)	4.4 (4.4–5.2)	U=0.0; z=0.0; p=1.0
Level of anxiety	3.6(2.5–7.5)	8.7 (6.7–11.7)	**z=4.00034; p=0.028***
Level of depression	8.7 (6.5–11.5)	8.3 (6.1–11.0)	U=0.0; z=0.0; p=1.0

Note: * results with p<0.05 are indicated **in bold**

Table 4. *The comparative analysis of noncommunicable diseases risk factors studied in groups with a high and low suboptimal health status value*

Index	SHS Mean + Std (≤13) n=194, (Me(IQR))	High score SHS Mean + Std (> 13) n=157, (Me(IQR))	Reliability
Men aged over 45 years	26	21	**x^2=6.309; ρ=0.013***
Women aged over 45 years	35	57	**x^2=4.324; ρ=0.038**
Patients with high systolic blood pressure	4 subjects	19 subjects	**x^2=14.487; ρ<0.001**
Patients with high diastolic blood pressure	1 subject	31 subjects	**x^2=38.727; ρ<0.001**
Overweight	103 subjects	95 subjects	x^2=1.941; ρ=0.164
Smoking	7 subjects	6 subjects	x^2=0.011; ρ=0.917
The use of alcohol equivalent to > 30 (20) ml of ethanol	50 subjects	42 subjects	x^2=0.043; ρ=0.836
Hypercholesterolemia (cholesterol level more than 5.0 mmol/L)	65	51	x^2=0.041; ρ=0.840
High anxiety level (above 7 points)	18	27	**x^2=4.869; ρ=0.028**
High depression level (above 7 points)	16	16	x^2=0.396; ρ=0.053
Physical activity			
group 1	30	28	x^2=0.354; ρ=0.553
group 2	16	25	**x^2=4.956; ρ=0.026**
group 3	28	44	**x^2=9.833; ρ=0.002**
group 4	40	27	x^2=0.658; ρ=0.418
group 5	9	10	x^2=0.507; ρ=0.477
group 6	32	5	**x^2=16.302; ρ<0.001**
group 7	13	2	**x^2=6.248; ρ=0.013**
group 8	26	16	x^2=0.849; ρ=0.357

Note: * results with ρ<0.05 are indicated **in bold**

a low suboptimal status value, 5 subjects had a high value (x^2=16.302; ρ<0.001); 13 subjects in group 7 had a low suboptimal status value, 2 subjects had a high value (x^2=6.248; ρ=0.013) (Table 4).

Results and Discussion

Patients with different levels of physical activity enrolled in the study were comparable on the main clinical parameters. Actual values of the studied parameters were practically the same. However, based on the risk factors for noncommunicable diseases, these groups showed significant differences in terms of the suboptimal status value.

When studying actual values, significant differences between the groups were revealed for some parameters: high blood pressure in groups 3 and 4 of physical activity; overweight in groups 2, 3, 5 and 8 of physical activity; and women's age was significantly different between the groups. This proves the relationship between the presence of risk factors and the level of physical activity of the patient. The data obtained are consistent with the published data on the results of international studies, studies in Russia, and randomized

clinical trials [2, 4, 5, 6, 9, 10, 11, 14, 15], which also showed significant differences in these parameters. Significant differences were revealed in the actual mean age and the level of anxiety between groups with high and low suboptimal status values.

When analyzing the groups of physical activity by the risk factors for noncommunicable diseases, significant differences in the suboptimal status value were revealed, which reflected the presence of these risk factors in groups with different physical activity (women aged over 45 years, overweight, monthly alcohol consumption, hypercholesterolemia and high level of depression). There were significant differences between groups with high and low suboptimal status values in the presence of risk factors for noncommunicable diseases: age over 45 years, high systolic and diastolic blood pressure, a high level of anxiety. The groups with low and high physical activity were significantly different in terms of the suboptimal status value (groups 2, 3, 6 and 7).

Conclusion

In the groups of patients who consider themselves healthy and do not seek medical attention for 3 months or more, risk factors for noncommunicable diseases are identified, which are more frequent in the groups of patients with low physical activity. Differences in the suboptimal health status values were revealed when the risk factors for noncommunicable diseases were present. The assessment of the suboptimal health status using the SHSQ-25 questionnaire [Yu- Xiang, Yan. 2009] is performed both on the sum of points of the questionnaire, and on its 5 individual scales: "cardiovascular system", "digestion", "immunity", "mental status", and "fatigue". This questionnaire is easy to use in primary health care, and it is a cheap and effective tool for screening subclinical, reversible stages of chronic diseases. The novelty of the studies on exploring the suboptimal health status in patients with different levels of physical activity as a risk factor of noncommunicable diseases has not been evaluated and the data we obtained are of interest for further scientific research.

The results of the study are recommended to be taken into account in the practice of primary health care. Scientific research on the use of the SHSQ-25 questionnaire should be continued.

Summary

1. Risk factors for noncommunicable diseases were often present in the groups of patients who consider themselves healthy and do not seek medical attention for 3 months or more.

2. The differences in the suboptimal health status value have been revealed in patients who had different levels of physical activity and risk factors for noncommunicable diseases.

3. Significant differences in the risk factors for noncommunicable diseases have been revealed in patients with different suboptimal status values.

4. The data obtained show that the determination of the suboptimal health status value is of particular importance in identifying early stages of the development of noncommunicable diseases.

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Conflict of interests
The authors declare no conflict of interests.

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EARLY DIAGNOSIS AND TREATMENT IN PATIENT WITH A PRIMARY CILIARY DYSKINESIA (KARTAGENER SYNDROME): CASE REPORT

Abstract

Primary ciliary dyskinesia is an orphan disease known for its multiple and variable symptoms caused by its genetic heterogenity. Frequent inflammatory diseases of both upper and lower respiratory tract are key symptoms in children. Kartagener syndrome is a classical form of the primary ciliary dyskinesia, which includes such symptoms as situs inversus, bronchoectasis, and hypoplasia of paranasal sinuses and/or sinusitis. According to some foreign research, the median age of primary ciliary dyskenesia diagnosis in Eastern and Western European is about 5 years old. Lack of early diagnosis is nothing but a direct consequence of the poor level of awareness, which is common for a primary health care system. This itself leads to increased rates of patients disability. This report deals with clinical, diagnosis and treatment peculiarities of a primary ciliary dyskinesia (Kartagener syndrome) patient. Both mother's tough obstetric-gynecological profile and a harsh course of this particular pregnancy were taken into account. Numerous respiratory infections in this patient were treated on an out-patient basis up to 11 months. Kartagener syndrome was diagnosed at our clinic based on laboratory and instrumental tests results. Complete situs inversus was revealed.. The diagnosis was confirmed by histomorphological patterns revealed in the nasal epithelial biopsy specimen. A difficulty to come up with the Kartagener syndrome diagnosis at the out-patient care stage is in focus of this specific case report. Noteworthy, we have succeeded in early diagnosis of Kartagener syndrome and then in a following effictive therapy conducted in our clinic.

Key words: *primary ciliary dyskinesia, Kartagener syndrome*

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PCD — primary ciliary dyskinesia

Introduction

Primary ciliary dyskinesia (PCD) is a genetically determined disease underlain by congenital defects of epithelial motile cilia in respiratory tract and similar structures leading to disruption of cilia motility [1, 2]. This is a relatively rare disorder with an incidence rate of 1:30 000 to 1:50 000 newborns [3]. Late diagnostics and PCD treatment inevitably lead to early disability.

The most common and classic form of PCD is Kartagener syndrome (situs inversus, chronic bronchiectasis, hypoplasia of paranasal sinuses or sinusitis). This form comprises 50–60% of cases [2].

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There have been several attempts to decode bronchiectasis genesis in subjects with situs inversus. Defects in prenatal development were proposed as a cause of this syndrome. However, the true nature of bronchopulmonary disorder in Kartagener syndrome was revealed only in the 70's, when R. Eliasson and B. Afzelius found a defect in cilia axonemes in the ciliated epithelium of the respiratory tract mucosa. In vitro studies showed that ultrastructural defects do not always lead to complete immobility of cilia. Rather, they only affect the activity of their beating, which becomes slow and chaotic [4, 5].

Genetically determined ultrastructural defect is common, since ciliated epithelium lines not only the respiratory tract, but also the organ of Corti, sperm flagella, ciliated cells of cerebral ventricles ependyma, photoreceptors of the retina, ciliated cells lining biliary ducts, renal tubules, and Fallopian tubes.

In addition, there are cilia on the primitive knot that ensure rotation of internal organs during prenatal development; therefore, half of the patients have situs inversus [6, 7].

It is commonly believed that PCD is an autosomal recessive disorder. However, we cannot exclude that defects of cilia can result from a new mutation [2].

According to foreign studies, the median age of PCD diagnosis in Western and Eastern Europe is 5.3 years; however, in case of situs inversus it is diagnosed earlier (at the median age of 3.5 years), than with normal organ position (5.8 years) [8].

In Russia, the median age of PCD diagnosis in children with situs inversus is approximately the same as in Europe — 4 years, while without situs inversus PCD is diagnosed later (at the median age of 7.6 years) [9].

When the disease follows a classic course of development, labored nasal breathing (snuffles), purulent discharge from the nose, frequent otitis, repeated bronchitis and pneumonia are observed during the first days of life. Later purulent or mucopurulent endobronchitis develops, followed by circumscribed pneumosclerosis with bronchi deformation. It can lead to bronchiectasis. Impairment of reproductive function is registered in adults (in men — decreased sperm motility, oligospermia, infertility; in women — ectopic pregnancy and infertility) [1].

Treatment is symptomatic. The main focus is on anti-inflammatory therapy and maintenance of bronchial drainage function (postural drainage, inhalations, transnasal bronchial drainage, sinuses lavage, chest massage, physiotherapy). If a chronic respiratory infection becomes aggravated, antibiotics are used [10].

Prognosis depends on the severity of bronchopulmonary process. In cases of localized bronchiectasis with no respiratory failure, early diagnosis and prompt treatment, the recovery rate is favorable. In cases of advanced pulmonary process, respiratory failure develops relatively quickly, cor pulmonale is formed, septic intoxication is pronounced, and growth retardation, i.e., disability, is observed. Some patients die at an early age [2].

Case report

An 11-year old boy, T., is observed and treated in the Children's Hospital with the following principal diagnosis: congenital lung and heart abnormality. Primary ciliary dyskinesia (Kartagener syndrome): situs viscerum inversus. Chronic obstructive bronchitis, continuously recurrent course. Bilateral chronic maxilloethmoidal sinusitis, continuously recurrent course. Bilateral chronic secretory otitis. Bilateral conductive hearing loss.

Secondary diagnosis: Atopic dermatitis, pediatric form. Minor cardiac development abnormalities: multiple chordae tendineae of the left ventricle. Chronic gastroduodenitis. Hypotonic biliary dyskinesia. Dysmetabolic nephropathy. Grade 1 thoracic scoliosis.

It was a third pregnancy (the first and second ones resulted in fetal death at week 12–13). The course of the present pregnancy was complicated by an appendectomy at week 12, shingles at week 17, and threatened miscarriage at weeks 27–28. The delivery was at term. The newborn was of normal weight and height. The parents divorced after this pregnancy. Data on history of chronic diseases of the father are absent. The mother had no family history of this disease.

Since the age of 3 months the child had periodic cough and recurrent obstructive syndrome with predominantly passive mechanism (thick purulent sputum). The child was observed by a primary care pediatrician and received symptomatic

treatment. However, no instrumental diagnostics were performed. At the age of 11 months, the child was first admitted to our department, where we diagnosed the following based on examination data: primary ciliary dyskinesia (complete Kartagener syndrome). Comprehensive treatment was performed. At the age of 1 year, the child was diagnosed with chronic sinusitis and adenoiditis, with several relapses per year. Starting at age 2, the child had recurrent atopic dermatitis, which was exacerbated by cow milk and soy products intake. Starting at age 4 he had periodic abdominal pains. Diagnosis: hypotonic biliary dyskinesia. At the same time (starting at age 4) the child was diagnosed with chronic maxilloethmoidal sinusitis, and starting at age 7 he was diagnosed with bilateral recurrent otitis with conductive hearing loss. The patient underwent multiple examinations, was treated at an ear, nose and throat clinic, and received adenoidectomy. Relapses of bronchial obstruction were observed almost every month, with exacerbation of chronic bronchitis. He had pneumonia 6 times. Lung CT was performed twice: dextrocardia with right-side aortic arch and left-side superior vena cava, increased parahilar bronchovascular markings, roots are poorly structured due to vascular component and moderately dilated. A chest X-ray is presented in Figure 1.

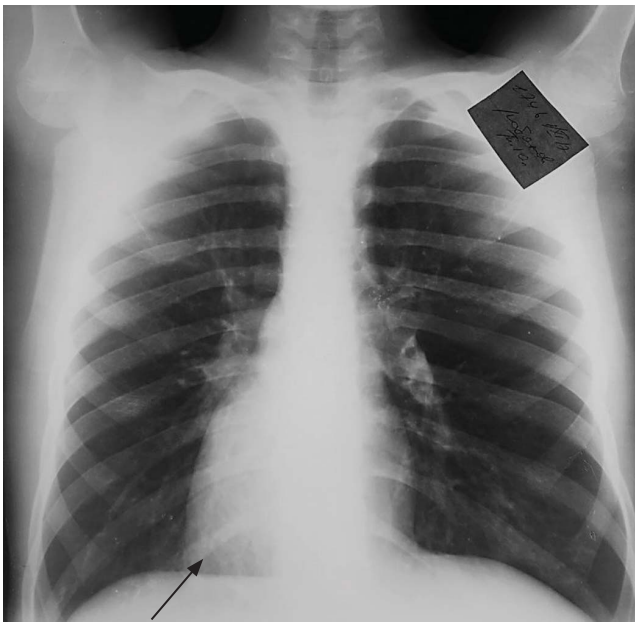

Figure 1. *Chest X-ray. The heart is shifted to the right. Increased pulmonary vascularity in hilar area*

In June 2017, the child was examined and treated at the Veltischev Research and Clinical Institute for Pediatrics (Moscow, Russia) with the following diagnosis: congenital bronchopulmonary abnormality: Kartagener syndrome, exacerbation of chronic bronchitis. Biopsy specimen of ciliated epithelium from nasal mucosa was analyzed. Conclusion: the child suffered from pronounced impairment of the ciliary function of the epithelium. There was evidence of primary ciliary dyskinesia.

Examination results: skin and visible mucosa were pale, clean, and moderately moisturized. Nasal breathing was difficult, and there was no discharge. There was no hyperemia of the oral pharynx. The tongue was moistened, white-coated at the root. The chest was normosthenic. Respiratory activity was symmetrical bilaterally. Bandbox resonance was observed. Harsh respiration without rales was auscultated. The patient had a productive cough with difficult expectoration. The cardiac area lacked any visible abnormalities. The following boundaries of relative cardiac dullness were observed: right — 1 cm to the outside of the right midclavicular line in the fifth intercostal space; upper — along the second intercostal space; and left — along the left edge of the sternum. Heart tones were clear, regular, with systolic noise centered in the apex and Erb's point. The abdomen was soft in palpation, with tenderness in the left hypochondrium and epigastrium. The liver was 0.5 cm below the left costal margin. Costovertebral angle tenderness was negative. The patient urinated without obstruction. The stool was formed and regular.

The child is continuously examined and treated in our clinic. He undergoes courses of anti-relapse therapy three times per year. This includes methods that improve bronchial function: drainage massage and postural drainage. The child is trained to do respiratory exercise. Treatment included inhalations with mucolytics and bronchospasmolytics. Antibacterial therapy is indicated based on microflora susceptibility to medications, including reserve antibiotics as needed. To prevent bronchiectasis and symptoms of descending infection as well as to reduce the frequency of exacerbations, the child received immunomodulatory treatment with intravenous immunoglobulins.

Due to timely and adequate conservative treatment, the state of this patient today has improved significantly with decreased symptoms of the disease.

Conclusion

Therefore, this case demonstrates the difficulties of diagnosing Kartagener syndrome at the outpatient stage, which can be related to the rareness of the disease and insufficient knowledge of the healthcare personnel. Early diagnosis (before the age of 1 year) in a hospital and promptly initiated treatment made it possible to minimize the development of complications.

If children have frequent relapses of respiratory tract infections, they should undergo chest X-ray to diagnose Kartagener syndrome in a timely fashion.

Conflict of interests

The authors declare no conflict of interests.

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INFECTIOUS ENDOCARDITIS CAUSED BY A RARE AGENT BURKHOLDERIA CEPACIAN

Abstract

Introduction. Infective endocarditis (IE) caused by Burkholderia cepacia is a very rare and poorly characterized form of endocarditis. **Material and methods.** We observed a case of delayed prosthetic mitral valve IE caused by Burkholderia cepacia in a 34-year-old patient. **Results.** A patient with a congenital ventricular septal defect underwent cardiac surgery three times in the past, including the removal of vegetations due to IE at the age of 17 and the mitral valve plasty in association with the plastic re-repair of ventricular septal defect at the age of 33. The last was complicated by postoperative pyogenic sterno-mediastinitis, thoracomyoplasty was performed. Ten months later the fever with chills appeared again, a large vegetation on a mitral valve prosthesis was revealed, and Burkholderia cepacia bacteremia with multidrug resistance to antibiotics was found. After the start of treatment with trimethoprim/sulfamethoxazole, normal body temperature was observed, but the course of IE was complicated by thromboembolism with a fatal outcome. **Conclusions.** Multidrug resistance of the pathogen to antibiotics, including those empirically prescribed for IE treatment, is the main risk factor for a poor clinical outcome of IE caused by Burkholderia cepacia. The lack of generally accepted recommendations on antibiotics dosing, prescribed in accordance with the microorganism sensitivity, contributes to the problem of IE caused by Burkholderia cepacia management.

Key words: *Infective endocarditis, endocarditis of the valve prosthesis, Burkholderia Cepacia*

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VSD — ventricular septal defect, IE — infective endocarditis

According to the latest estimates 79.3–88% of infective endocarditis (IE) cases are caused by gram-positive cocci — staphylococci, streptococci or enterococci, and only in 5% of cases the disease is caused by gram-negative bacteria [1–6], and specifically by the HACEK group gram-negative bacteria (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, Kingella) [7,8] in 1.4–3% of cases, and by gram-negative bacteria not belonging to the HACEK group (Escherichia coli, Pseudomonas aeruginosa, Serratia, Acinetobacter, etc.) in approximately 2% of cases [4, 9]. ICE-PCS international cohort study has shown that IE caused by the gram-negative bacteria not belonging to the HACEK group was associated with medical interventions in 57% of cases and also characterized by high mortality (24%) despite frequent surgical treatment (51%) [4].

Gram-negative aerobic bacteria Burkholderia cepacia (formerly named as Pseudamonas cepacia) constitute a group of low-virulent opportunistic pathogens, which are ubiquitous in the environment (below ground, in water, and in agricultural crops) that are capable of causing severe

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pneumonia in patients suffering from cystic fibrosis [10]. Burkholderia cepacia bacteria are very rare infective agents of IE [11, 12]. The most important characteristic of Burkholderia cepacia is its natural multi-drug resistance to antibiotics and disinfectants. The bacteria can persist in phagocytes, form biofilms, have a wide range of adhesion factors, and are capable of colonizing the endocardium, valve prostheses and catheters surface [9, 13, 14]. The literature shows about 50 IE cases caused by Burkholderia cepacia, most of which are endocarditis of injection drug users cases as well as prosthetic endocarditis or endocarditis in patients with immunodeficiency [9, 11, 12, 15, 16]. We have observed the case of prosthetic mitral valve IE caused by Burkholderia cepacia.

Female patient C., 34 years old, hospitalized with complaints of shaking chills, fever up to 39.0 °C, dry cough, and asthenia. The patient has a history of congenital heart disease: at the age of 3, she underwent the pulmonary artery banding for ventricular septal defect (VSD) with high pulmonary hypertension. At the age of 17, the patient suffered an infective endocarditis on the mitral valve, requiring the following surgical correction: removal of vegetations in association with the plastic repair of ventricular septal and pulmonary artery. At the age of 27 (2009) she completed a pregnancy without complications. The baby was timely delivered. In January 2015, though she was in satisfactory condition, the recanalization of the ventricular septal defect and 3rd degree mitral regurgitation were revealed during the echocardiography procedure. In March 2015, the mitral valve plasty with Sorin No. 29 prosthesis and VSD plasty using the synthetic patch made of dacron were carried out with preservation of the subvalvular structures of the posterior mitral leaflet. The late postoperative period was complicated by pyogenic infection of the post-operative wound with the development of fistulous form of chronic sternomediastinitis. In October 2015, the partial removal of presternum and mesosternum was carried out, and in January 2016, thoracomyoplasty of the thorax anterior wall wound with local tissues was performed. The patient continuously took warfarin (INR 2.5–3.5).
Current deterioration in the condition was noted on November 10, 2016, when with no apparent cause the patient developed subfebrile fever, and 2 days later the patient experienced febrile fever up to 38.5 °C with chills. In addition, on November 14, 2016, the patient noted a short term pain on the right of her lower back, accompanied by darkened urine. The patient took levofloxacin on an outpatient basis without any improvement. Dry cough started on November 18, 2016. On November 20, 2016, the temperature increased to 39.0 °C. The patient was urgently hospitalized with suspected pneumonia.
On admission, the patient's condition was assessed as moderate. The patient was conscious, cooperative. Body temperature was 38.5 °C. Regional lymph nodes were not palpable. Peripheral edema and cyanosis were not noted. Joints were not externally changed. The thorax was symmetrical. There was a postoperative scar without infiltrative changes on the anterior thoracic wall along the median line. Respiratory rate was 16 breaths per minute. Breathing was vesicular. There were muted small bubbling rales in the lower parts of the thorax on both sides. The heart rhythm was regular. Heart sounds were muffled, and there was a holosystolic murmur, best heard at the apex and radiated to the axilla, at all auscultation points. Heart rate was 90 bpm, and blood pressure was 110/70 mm Hg. Abdomen was soft and nontender. The liver did not protrude below the costal margin. The lower pole of the spleen was palpable. Urination was normal. Stool was regular and formed.
The complete blood count of 11/21/2016 showed: leukocytes $22.1*10^9$/l, erythrocytes $3.27*10^{12}$/l, hemoglobin 91 g/l, platelets $180*10^9$/l, banded neutrophils: 2%, segmented neutrophils 75%, lymphocytes 12%, monocytes 1%, ESR 76 mm/h. The urinanalysis of 11/21/2016 showed: relative density 1.018, no protein, epithelial cells 1–2 per HPF, leukocytes 2–4 per HPF, and erythrocytes 0–1 per HPF. There was no growth in urine culture from 11/21/2016. Biochemical analysis from 11/21/2016 showed: creatinine 61.2 μmol/l, ALT 21 IU/l, AST 24 IU/l, C-reactive protein 279.2 mg/l; INR 3.62. Venous hypertension was revealed and no focal infiltrative changes were observed on the chest X-ray 11/20/2016. Abdominal and retroperitoneal ultrasound showed: diffuse changes in pancreas, splenomegaly; no kidney pathology was revealed. EGD showed duodenogastric reflux.

Transthoracic (11/22/2016) and transesophageal (11/25/2016) Echo revealed mitral valve prosthesis without functional abnormalities, 1st degree mitral regurgitation, suspicion of vegetation or thrombus on the prosthesis (floating formation 0.9 × 1.2 cm) (Figure 1). Ceftriaxone 2 g intramuscularly (single dose) was initially prescribed in connection with the suspected pneumonia and was ineffective: sustained febrile fever up to 39 °C with chills and intoxication persisted.

In relation with the identification of floating formation of the mitral valve and 3-week sustained fever above 38 °C that could not be explained by any other reasons, on the fifth day of hospital treatment in accordance with the diagnostic criteria of the European Society of Cardiology, 2015 [17], IE of the prosthetic mitral valve was suspected in the patient with predisposing heart disease. Taking into account the latest recommendations for the empirical treatment of the prosthetic valve IE associated with prior medical care, triple-antibiotic combination of vancomycin 1.0 g b.i.d. IV infusion, gentamycin 80 mg b.i.d. intramuscularly, and rifampicin 0.3 g t.i.d. orally was prescribed [17]. However, on treatment, fever held up for 5 days with daily rises up to 39–39.5 °C and shaking chills. The blood test revealed persistent leukocytosis and decreased hemoglobin to 78 g/l. Transthoracic Echo from 11/29/2016: the floating formation of the unchanged size remained on the mitral valve prosthesis with no signs of dysfunction of the prosthesis.

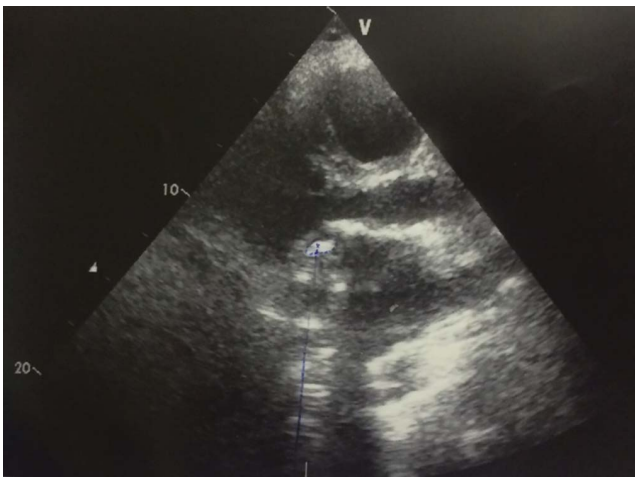

Figure 1. *Transthoracic echocardiogram of patient C.: a floating vegetation (0.9 × 1.2 cm) on a prosthetic mitral valve*

On November 29, 2016, the results of a microbiological blood test from 11/22/2016 were obtained. In three separate blood cultures taken at an interval of more than 1 hour, the growth of gram-negative microorganism Burkholderia cepacia resistant to azlocillin, amoxicillin / clavulanic acid, gentamycin, levofloxacin, doxycycline, imipenem/cilastatin, ceftriaxone, meropenem, nitrofurantoin, cefepime, piperacillin/tazobactam, linezolid and sensitive only to bacteriostatic agent chloramphenicol, which is not recommended for long-term treatment of IE. Therefore, according to available literature data on the sensitivity of Burkholderia cepacia to co-trimoxazole and the greatest effectiveness of treatment of IE caused by Burkholderia cepacia with co-trimoxazole IV at doses corresponding to 4–15 mg/kg of trimethoprim and 20–75 mg/kg of sulfamethoxazole [12, 15], starting on November 30, 2016, co-trimoxazole 960 mg t.i.d. IV was assigned, while the other antibiotics were canceled. In accordance with the presence of a major diagnostic criterion (mitral valve vegetation) and three minor criteria (predisposing heart disease, fever > 38 °C, positive blood culture that do not correspond to a major bacteriological criterion) that are required for definite diagnosis of IE, the principal diagnosis was: secondary acute IE of a prosthetic mitral valve, CHD–VSD, history of Infective endocarditis in 1999, surgical closure of ventricular septal defect in 2015, Sorin mechanical mitral valve prosthesis, secondary anemia; CHF NYHA 2 class. On November 30, 2016, the patient was consulted by a cardiac surgeon, taking into account the technical difficulties of repeated cardiosurgical intervention and the absence of dysfunction of the prosthesis, despite the presence of risk factors for thromboembolic complications (vegetation larger than 10 mm and suspicion of the history of thromboembolism of the right renal artery), it was recommended to continue antibiotic therapy.

On the second day of therapy with co-trimoxazole, the patient's condition improved significantly: the temperature did not exceed 37 °C, chills stopped, weakness decreased, and appetite and well-being improved. On the fifth day the temperature returned to normal. However, on December 7, 2016, the patient experienced a sharply painful Osler's node, a typical IE manifestation caused by embolism of the arterioles of the fingers pads

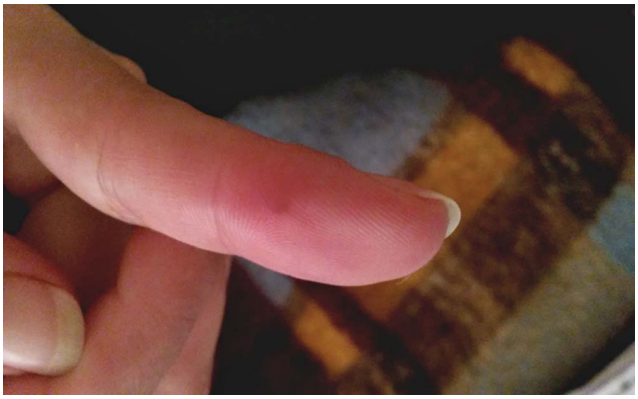

Figure 2. *Osler's node on the finger of a patient C.*

(Figure 2), and on December 08, 2016, an acute cerebrovascular accident in the right hemisphere with hemorrhagic transformation occurred, which led to the patient's death 3 days later.

Discussion

IE caused by Burkholderia cepacia was described more than 50 years ago [15, 18]. Based on literature data and our clinical observation, IE caused by this rare pathogen is most likely to occur on prosthetic heart valves and intracardiac devices or in patients with immunodeficiency and in injection drug users [9, 11, 16, 19]. However, it may also occur on natural valves in the absence of any special epidemiological situations [20]. In recent years, the association of Burkholderia cepacia infection, including the development of bacteremia or IE, with in-hospital medical care, especially with the insertion of intravenous catheters, permanent pacemakers, hemodialysis, and prosthetic heart valves has increasingly been reported [21–24]. Shilpa Bhojraj et al. described two cases of prosthetic IE caused by Burkholderia cepacia with a probable common source of nosocomial infection [16]. Although the probability of transmission of this infection "from patient to patient" in cystic fibrosis is recognized [10], the mechanisms of infection with Burkholderia cepacia with the development of IE have not been sufficiently studied.

In the clinical situation that we observed, the ineffectiveness of the conventional starting empirical therapy for IE of the prosthetic valve with a combination of rifampicin, vancomycin, and gentamycin, which are prescribed according to ESC recommendations based on the highest likelihood of infection with Gram-positive cocci [17], indirectly indicated a possible atypical pathogen. Though there were no premises for assuming infection with Burkholderia cepacia before blood culture results.

The main problem in the treatment of infections caused by Burkholderia cepacia is a high level of resistance to most antibiotics, including antibiotics commonly used in the treatment of IE [25]. Molecular mechanisms of resistance of the microorganism include efflux pumps for chloramphenicol, porin proteins for aminoglycosides, as well as beta-lactamases and antibiotic-binding proteins for a wide variety of antibiotics, including rifampicin [13, 14, 18]. The causative agent is most sensitive to ticarcillin, carbapenem (meropenem), cephalosporins (ceftazidime, cefepime), fluoroquinolones (levofloxacin), piperacillin [25, 26, 27]; however, in our case, in vitro resistance was detected. According to the literature, the causative agent is also sensitive to trimethoprim-sulfamethoxazole [18, 25, 26]. Treatment with this drug is considered to be the most effective for treating IE caused by Burkholderia cepacia [15, 20]. The sensitivity to co-trimoxazole in vitro was not tested in the case of IE. However, clinically there was a normalization of temperature and improvement of the patient's condition in 5 days after initiation of co-trimoxazole therapy.

Due to the rarity of the disease, there are no recommendations for the antibacterial therapy of IE caused by Burkholderia cepacia. The decision of which antibiotic is chosen should be based on the results of determining the sensitivity of the isolated pathogen and literature data on the effectiveness of its use in cases of IE [28]. Burkholderia cepacia strains isolated from patients with IE are, according to the literature, most often sensitive to trimethoprim-sulfamethoxazole and chloramphenicol, and in most cases antibacterial therapy without co-trimoxazole was ineffective [12]. In cases described in the literature, trimethoprim-sulfamethoxazole was administered at doses ranging from 960 to 8,400 mg/day intravenously as a monotherapy or in combination with kanamycin and/or polymyxin B for a period ranging from 10 days to more than 10 months [12, 15, 18, 29]. The use of meropenem, ceftazidime (as well as their combination), levofloxacin, piperacillin-tazobactam [12, 20] has also been described. Taking into account the high incidence

of relapse in the treatment of IE caused by Burkholderia cepacia, the duration of antibiotic therapy is no less than 8–10 weeks followed by regular follow-up of the patient for 6–12 months [12, 18].

The analysis of cases of IE caused by Burkholderia cepacia that is presented in the literature indicates an improvement in the prognosis with a combination of antimicrobial therapy with cardiac surgery, which is performed in approximately half of patients [15]. Nevertheless, in more than 50% of the observations of IE caused by this rare pathogen the patient died.

Unfortunately, in the observed patient, in addition to the rare causative agent that is resistant to most antibiotics for the treatment of IE, a high risk of thromboembolic complications was initially identified and according to current recommendations, despite the preservation of the function of the valve prosthesis, there were indications for surgical treatment. However, this procedure had to be avoided because of the technical difficulties associated with repeated surgery on the heart [17, 30]. It is possible to decrease the risk of thromboembolism with IE by applying 2–3 weeks of effective antibacterial therapy [31]. However, on the 9th day of treatment with co-trimaxazole, the patient suffered an ischemic stroke with hemorrhagic transformation, which led to death.

Conclusion

IE caused by Burkholderia cepacia is a rare and inadequately studied form of the disease with a relatively unfavorable prognosis due to the multidrug resistance of the pathogen to antibiotics that are empirically prescribed for IE, the tendency of infection to relapse, and the tendency of the disease to most frequently relapse in patients with prosthetic heart valves. The treatment of IE caused by Burkholderia cepacia is complicated by the lack of generally accepted recommendations determining the necessary doses of antibiotics, which should be prescribed in accordance with the sensitivity of the identified causative agent. The duration of antibiotic therapy for IE caused by Burkholderia cepacia is also still a matter of discussion. Our observation illustrates the need for bacteriological verification of the IE diagnosis, especially in cases of resistance to standard empirical treatment.

Conflict of interests

The authors declare no conflict of interests.

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