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SMOKING CESSATION COUNSELLING

Abstract

Tobacco use is the leading preventable cause of premature morbidity and death in the world and it is responsible for approximately 15 years of healthy life lost. The world average smoking prevalence is 21% (35% for men and 6% for women), with the worst situation in low- and middle-income countries. In the Russian Federation, 31% of adults smoke (51% of men and 14% of women); meanwhile, in the last decade the prevalence of smoking declines by about 1% per year. Clinically, smoking is a behavioral disorder caused by psychophysical dependence from nicotine. Tobacco dependence is associated with the characteristic smoking habits and withdrawal symptoms that prevent successful quitting. The role of physician is to identify smokers on a regular basis, increase their readiness to quit, and support them during a quit attempt. Smoking status should be assessed in any patient who seeks medical care. All tobacco users should be encouraged to quit in a clear and personalized manner. The further content of medical care is determined by the patient's willingness to make a quit attempt. For those who are not ready to discuss smoking cessation, physician should express readiness to help at any time. For the patients who are not ready to quit at this time, physician should initiate brief motivational intervention and discuss possible benefits of smoking cessation and obstacles to successful quitting. For those who are ready to quit, physician provides behavioral counselling and prescribes medications (nicotine replacement therapy or nicotinic receptor partial agonists). At the follow-up visits in a week and a month after the quit date, physician should discuss treatment effectiveness and problems with smoking habits. For continued smokers physician should reassess their readiness to quit at the following visits and repeat motivational interviewing. Screening tests for smoking-related diseases should be recommended when necessary.

Key words: *tobacco use disorder, quitting smoking, motivational interviewing, smoking cessation products*

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NAA — nicotinic agonist-antagonist, NRT — nicotine replacement therapy

Epidemiology of Tobacco Smoking

Tobacco smoking is the leading preventable cause of premature mortality in the world resulting in the deaths of 7 million people annually [1]. The total number of smokers is more than one billion, 80 per cent of whom live in low-and middle-income countries, mainly in China, India and South-East Asia. According to a major epidemiological study — Global Adults Tobacco Survey (GATS) -conducted in 2016 in the Russian Federation (Russia), more than 36 million people or 31% of the adult population smoked [1]. Over the past decade, smoking in the Russian Federation decreased by about 1.2% a year, largely due to the accession to the World Health Organization Framework Convention on Tobacco Control and an active anti-tobacco state policy [2]. Nevertheless, Russia remains among countries with high smoking rates, especially among men (Table 1).

The mean age at which daily smoking begins in Russia is 17 years, 64% of smokers show signs of strong nicotine addition, and 56% plan or think

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Table 1. *Prevalence of tobacco smoking in the Russian Federation compared to world data*

Tobacco smoking prevalence	Overall	Men	Women
Russian Federation[1]	**31%**	51%	14%
High-income countries[2]	**23%**	29%	18%
Global average[2]	**21%**	35%	6%

1. Global Adult Tobacco Survey, Russia, 2016.
2. WHO report on the global tobacco epidemic, 2017.

about quitting [1]. The male sex, smoking family members or peers, poverty, low level of education, as well as a severe psychotraumatic event predispose to the development of tobacco addiction [3]. Mental health disorders, antisocial behavior and criminal behavior are also associated with a higher prevalence of tobacco use [4, 5].

Pathophysiology of Tobacco Dependence

The adverse health effects of tobacco smoke are caused by long-term exposure to nicotine, carbon monoxide and other combustion products. Nicotine has a psychoactive effect, causing a sense of pleasure by stimulating the release of dopamine and endogenous opioids in the brain. Furthermore, nicotine stimulates the release of adrenaline, which leads to increased activity of the central nervous system, the suppression of hunger, as well as elevated blood pressure and heart rate. With regular smoking of tobacco, the natural ability to experience pleasure atrophies, as a result of which, even with temporary deprivation of nicotine, the smoker develops an abstinent syndrome in the form of increased anxiety, irritability, restlessness, concentration disorders, insomnia and increased appetite. As a result, the emotional balance of the daily smoker is largely determined by the presence or absence of nicotine in the blood. The resulting vicious circle leads to the emergence of a strong psychophysical dependence comparable to the dependence on some opiates. Over time, the regular smoker further develops behavioral automatism and smoking rituals, which the smoker thinks help with coping with external stress, fatigue and boredom. In ICD-10, tobacco smoking is naturally attributed to mental and behavioral disorders associated with substance use (code F17.2 — tobacco dependence syndrome). The inhalation of smoke as such is a forced consequence of nicotine dependence, but it is responsible for the main adverse health effects. Tobacco smoking is a strong and often leading risk factor for a large number of cardiovascular, pulmonary and malignant diseases, reproductive disorders, delay in neuropsychiatric development in children, cataracts, osteoporosis, peptic ulcer, thyrotoxicosis etc. [5]. Overall, the effects of systematic smoking can be characterized as premature aging. A daily smoker loses about 15 years of normal life due to the early development of chronic diseases and premature death [3]. A doctor of any specialty can do a lot for the treatment and general improvement of their patients, if they include advice on quitting smoking in the mandatory list of their recommendations.

Counselling a Smoking Patient

Quitting smoking is the most important medical and social task, therefore, in developed health systems, doctors are financially and organizationally encouraged to advise smoking patients. As a rule, quitting smoking is not the main reason for seeking medical help, so the doctor should be ready to give this issue an additional 5-10 minutes of their counselling. It is recommended to carry out a brief consultation following five consecutive rules (originally, 5As: Ask; Advise; Assess; Assist; Arrange [6]):

1. Ask all patients about smoking
2. Advise all smokers to quit
3. Assess readiness to quit smoking
4. Help the patient to quit
5. Support during quitting

1. Ask all patients about smoking

Smoking status must be determined in each outpatient or inpatient older 18 years. A survey

(questionnaire) can be conducted by a doctor, a nurse before seeing a doctor or by an administrator. In addition to the recording of the smoking status, it is desirable to clarify the number of cigarettes smoked per day, smoking experience (in years), and to calculate the index in pack-years (IPY = [average number of cigarettes smoked per day x smoking experience in years] / 20). The smoking status (smokes, never smoked, quit smoking) is recorded in primary medical records, if possible — on the front side of the outpatient card or medical history.

2. Advise all smokers to quit

All smokers should be explicitly encouraged to stop smoking, emphasizing the positive effects of tobacco-free behavior. At the same time, it is desirable to avoid an authoritarian style of communication and accusatory tone. Examples of recommendations: "Quitting smoking is the best thing you can do for your health," "As your doctor, I strongly recommend you to quit smoking". The advice should be clear, unambiguous and personalized. For example, a young woman can be told about the importance of quitting smoking for the birth of a healthy child; parents will appreciate the example they give to children or the harm of passive smoking; in a middle-aged patient the impact of smoking on cardiovascular risk or the course of chronic diseases can be assessed. For example, "continued smoking can significantly worsen the course of your illness, and quitting will lead to rapid relief of symptoms and reduce the need for medication". All smokers should be offered assistance in quitting smoking.

3. Assess readiness to quit smoking

Signs of high readiness or motivation to quit are past attempts to quit smoking, as well as willingness to quit in the near future, including with medical support. Patient motivation and self-confidence can be assessed through two questions "Would you like to quit smoking?" and "How do you assess your chances of quitting successfully?". You can ask a neutral question "What do you think about your smoking?". Depending on the answer to these questions, smoking patients can be divided into three groups: not ready to quit and discuss quitting; not ready to quit at the moment, but not ruling out such a possibility in the future (double-minded); ready to quit in the near future.

Patients who do not want to quit smoking and even refuse to discuss this topic should be given the opportunity to change their mind: "I understand that you are not in the mood to quit now, but if you change your mind, I will always be happy to help you". During further visits, try to return to the topic of quitting smoking in a friendly manner, waiting for a change in the motivation of patients.

With patients who are not ready to quit in the near future, but in the long term do not exclude this possibility, a brief **motivational interview** (the original term — Motivational Interviewing [7]) is conducted. The motivational interview is conducted in a non-confrontational, friendly manner, helping the patient to resolve ambivalence about their own smoking based on long-term positive goals. Ambivalence refers to an internal conflict that is somehow present in most smokers, for example, when the patient is aware of all the unnatural and harmful effects of smoking, but prefers not to think about it or tries to find an excuse for their behavior. The task of the doctor is to show this internal conflict and help the patient to resolve it in a positive direction. The name "motivational interview" or "interview" involves the use of open, unbiased questions that help the patient to express their attitude to smoking. The simplified version of the motivational interview includes five main components (in the original — 5Rs: **R**elevance, **R**isks, **R**ewards, **R**oadblocks, **R**epetition [6]):

1. **Relevance.** Encourage the patient to speak out, why quitting smoking may be important to them personally, for example, "Why would you try to quit smoking?".
2. **Risks.** Ask the patient to voice the problems that he or she associates with smoking. For example, "Do you have health problems that are caused by smoking?", "Do you know anything about the risks to your health or the health of loved ones that may be associated with smoking?".
3. **Rewards.** Ask the patient to list the positive effects of quitting smoking. For example, "What good will happen in your life if you quit smoking?", "Do you know how quitting smoking can improve your health?", or "Will your loved ones be happy if you quit smoking?".

4. **Roadblocks.** Ask the patient about problems that prevent successful quitting and recommend ways to overcome them. This may be a fear of withdrawal or weight gain syndrome, the effect of a smoking environment, or a high level of stress. Patients who are afraid of withdrawal syndrome may be advised to gradually reduce the number of cigarettes smoked during the use of nicotine replacement therapy (see below).
5. **Repetition.** During subsequent visits, it is necessary to return to the topic of quitting smoking and evaluate changes in motivation. If the patient is still not ready to quit, you should end the interview on a positive note, for example, "It's not an easy task, but I'm sure that you can overcome your tobacco dependence, and I'm always ready to help you".

Risks and Rewards are especially important for patients who are doubtful about the need to quit smoking. For patients who want to quit, but are not confident in their ability to cope with smoking, special attention should be paid to the Roadblocks.

4. Help the patient to quit smoking

Patients who are ready to quit smoking in the near future should be given behavioral recommendations, and prescribed a treatment of nicotine addiction according to indications.

Through behavioral counselling, the doctor emotionally supports the patient and teaches the patient self-control skills, helping to overcome behavioral automatism and rituals associated with smoking. As part of the consultation, it is recommended to establish an exact date of quitting, discuss the importance of complete abstinence from smoking especially during the first two weeks; advise to consider protective behavior in typical situations that can provoke a breakdown (excitement, boredom, alcohol consumption, smoking company); recommend ways to overcome the sudden desire to smoke, for example, deep and slow abdominal breathing. It is also recommended to discuss with the patient the main positive expectations and benefits associated with quitting smoking and support the main motive for which an attempt to quit is taken. Patients who are concerned about weight gain should be given recommendations for a balanced diet (e.g., healthy eating pyramid) and increased physical activity. To restore the natural emotional balance as soon as possible, the patient is recommended to avoid conflict situations, to strive for positive emotions, to sleep enough, to avoid alcohol consumption and to acquire relaxation skills.

Drug treatment helps to stop the symptoms of withdrawal syndrome and craving for a cigarette, increasing the chances of successful quitting at least twofold [8]. The stronger the nicotine dependence, the more justified the prescription of drugs is. Signs of strong nicotine dependence are daily smoking of more than 10 cigarettes, smoking the first cigarette within 30 minutes of waking up (morning smoking), as well as typical manifestations of withdrawal syndrome in past attempts to quit or forced abstinence from smoking. Drug treatment is not indicated for those who do not smoke every day or smoke less than 5 cigarettes a day. Nicotine withdrawal syndrome takes place 2 to 4 weeks; drug treatment is prescribed for a period of 8 to 10 weeks. The most studied means of treating tobacco dependence are drugs for **nicotine replacement therapy (NRT)**, and they are most often recommended as first-line drugs. Medical nicotine reduces the symptoms of withdrawal syndrome without development of addiction. For those who smoke 5-10 cigarettes a day, it is recommended to use short-term NRT drugs as needed: Nicorette tablet, chewing gum or spray. A single dose of the drug is usually 2 mg and can replace about 2 cigarettes. Spray is the fastest formulation. When smoking 10-20 cigarettes per day, it is recommended to use Nicorette patch with slow nicotine release having 16-hour action at a dose of 15 or 25 mg; a patch of 25 mg when smoking 20 cigarettes (pack) or more, and one of the short-term agents (chewing gum, tablet, spray) as needed. Niquitin patch with 24-hour action, 21 (14, 7) mg is recommended for severe morning smoking or smoking around the clock (working at night). NRT is prescribed in a full dose two weeks before the date of quitting against the background of a reduction in the number of cigarettes smoked or directly on the day of quitting smoking and lasts for 8 to 10 weeks. During the last weeks of treatment, a Nicorette patch, 10 mg, or short-term agents are used as needed. NRT drugs are usually well tolerated and are sold over-the-counter. In rare cases, there may be side effects associated with the

adrenergic action of nicotine (heartbeat, headache, insomnia, increased BP) or local allergic reactions when using the patch. In these cases, it is recommended to reduce the dose or change the type of drug for NRT. Limitations for NRT drugs are exacerbations of cardiovascular diseases and pregnancy. Another group of drugs for the treatment of tobacco dependence is represented by nicotinic agonist-antagonist (NAA). They competitively bind to the receptors of the pleasure center, blocking the access of nicotine to the brain, and at the same time they alleviate manifestations of withdrawal syndrome due to the stimulating dopaminergic effect. Herbal NAA Tabex (INN — Cytisine) has been successfully used to treat tobacco dependence in Eastern Europe for more than 50 years. In the last decade, in high-quality clinical trials, this drug has proven to be highly effective and safe, comparable to other drugs for the treatment of tobacco dependence [9]. Tabex is prescribed 1-5 days before the date of quitting against the background of a decrease in the number of cigarettes smoked and is taken according to the scheme within one month. The drug is usually well tolerated and sold over-the-counter, contraindications are generally similar to NRT. The advantage of the drug is its low cost, and the disadvantages include a complex regimen.

The only synthetic NAA on the market is Champix (INN — Varenicline). Champix is comparable in effectiveness to combined NRT, increasing the chances of quitting smoking approximately threefold [7]. The drug is prescribed two weeks before the date of quitting in a dose of 0.5–1 mg per day, then taken for 10 weeks in a 1 mg tablet 2 times a day. Champix is generally well tolerated, the most common side effect is nausea (in up to 30% of patients). Previously, there were concerns about increasing the risk of suicidal and cardiovascular events while taking Champix, but in recent major studies, these data are not confirmed [10, 11]. Champix is prescribed by the attending physician, taking into account the contraindications and individual characteristics of the patient; it is available by prescription.

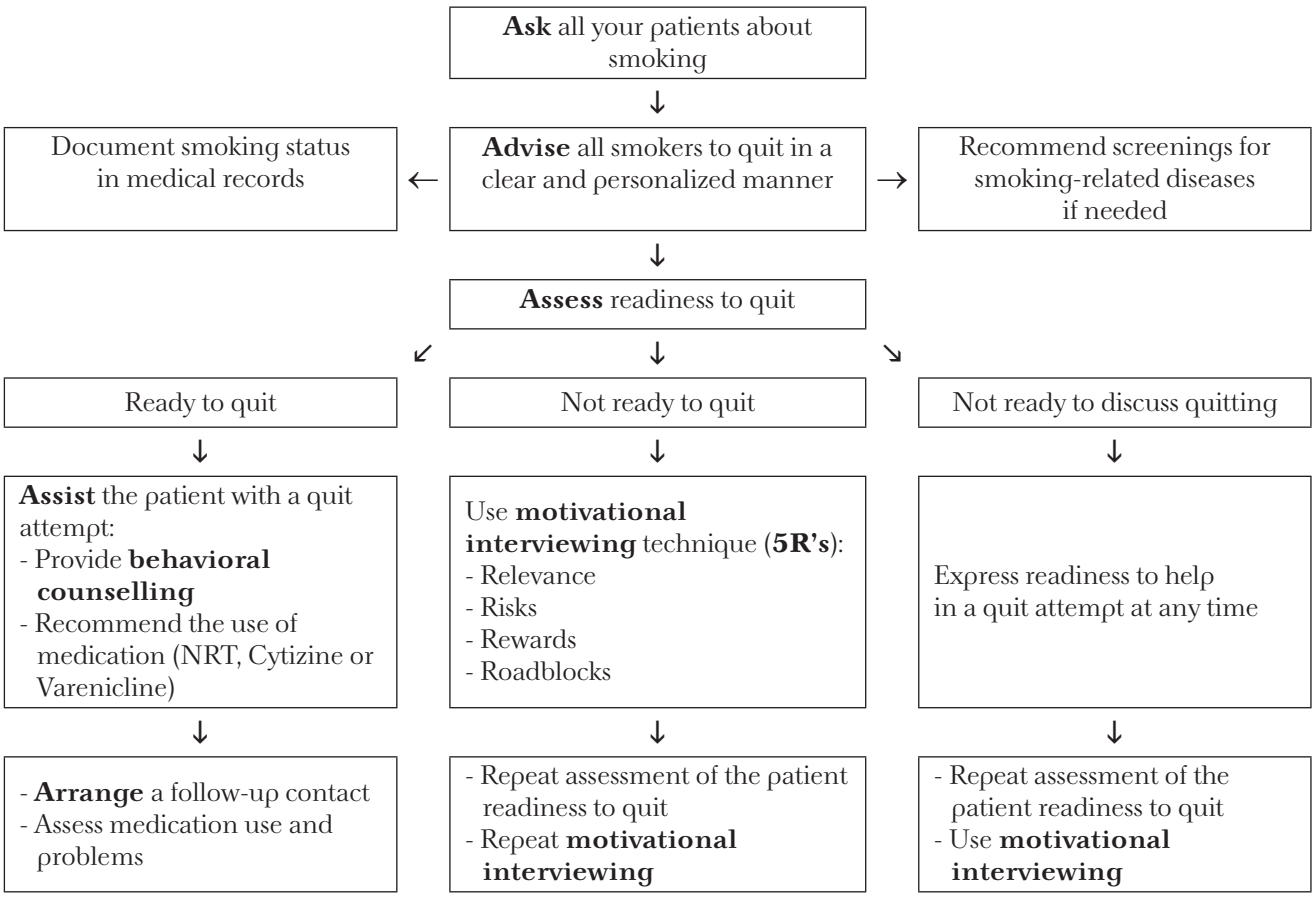

Figure 1. *Smoking cessation counselling approach*

5. Support during quitting

Patients who quit smoking are recommended to repeat consultations a week and a month after the date of quitting. During a re-visit, it is necessary to assess the severity of withdrawal syndrome, to clarify the effectiveness and tolerability of drugs and, if necessary, to adjust the dose or dosage form of drugs for NRT, to assess weight changes. It is also useful to repeat behavioral counselling with an emphasis on positive changes in mental and physical health after quitting and to emotionally support the patient. In case of smoking relapse, it is necessary to analyze the causes of the failure together, recommend a second attempt, and, if necessary, to consider another option of drug treatment.

The patient is considered to be cured of tobacco dependence, if after 6 months from the date of quitting the patient manages to completely refrain from smoking. By this time, in majority of patients, natural self-regulation of mood is restored and smoking rituals die out.

Examination for early diagnosis of smoking-associated chronic diseases (screening).

All smokers at the age of 40 years and older must check their blood pressure and plasma cholesterol and assess 10-year cardiovascular risk using a predictive SCORE scale or analogues (e.g., ASCVD). Patients at the age of 55-85 years with long smoking experience (IPY ≥ 30) are recommended to perform annually low-dose computed tomography for early diagnosis of lung cancer. Smoking men at the age of 65 years and older are recommended a single ultrasound scanning of the abdominal aorta for early diagnosis of an aneurysm [12].

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CLINICAL VALUE OF BLOOD BIOMARKERS IN PATIENTS WITH CHRONIC HEART FAILURE

Abstract

Biomarkers (various laboratory biochemical markers), such as natriuretic peptides (NP), soluble ST2 receptor, copeptin, galectin-3, are widely studied in patients with chronic heart failure (CHF). The European Society of Cardiology recommends the blood NP assay in patients with suspected HF and to use its increase as one of the mandatory criteria for the diagnosis of CHF with preserved and mid-range ejection fraction. Dynamics of NP concentration may reflect the effectiveness of treatment and the necessity of drug titrations. Neprilyzin destroys NP, but does not destroy their precursors, including NT-proBNP. Therefore, it is reasonable to use NT-proBNP as a marker of treatment efficacy and prognosis when using neprilysine inhibitors (sacubitril), which combine the group of ARNI (sacubitril/valsartan). ST2 is a protein receptor for interleukin-33 (IL-33). The transmembrane ST2 (ST2L) binds to IL-33 and forms the IL-33/ST2L complex, which has a cardioprotective effect, prevents the development of myocardial hypertrophy, fibrosis and apoptosis. The soluble ST2 receptor (sST2) is a "trap" for IL-33 and neutralizes the protective effects of the IL-33/ST2L complex, which leads to hypertrophy and fibrosis of the myocardium, dilatation of the chambers and reduction of the myocardial contractility. It can be considered as a marker of unfavorable prognosis in heart failure, but it is not specific. Copeptin is a part of arginine-vasopressin, or antidiuretic hormone, precursor, which plays an important role in the pathogenesis of CHF. Since arginine-vasopressin has a short half-life and is unstable outside the body, copeptin is being actively studied. Its level increases during the CHF decompensation and relates with the functional class of CHF. A combined measurement of the concentration of copeptin and NP may improve the risk stratification in CHF patients. Galectin-3 is a peptide that stimulates the activation of fibroblasts and the development of fibrosis. It increases in CHF patients and is associated with the severity of the condition, systolic and diastolic LV dysfunction and prognosis. Currently, NPs are the best biomarkers that can and should be used in routine clinical practice. To prove the need for widespread use of other biomarkers, additional research is needed.

Key words: *chronic heart failure, biomarkers, biochemical analysis, myocardial infarction, natriuretic peptides, brain natriuretic peptide, NT-proBNP, soluble ST2 receptor, copeptin, galectin-3, prognosis, risk stratification, diagnosis, treatment, management*

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CNP — C-type of natriuretic peptide, DNP — D-type of natriuretic peptide, NT-proANP — N-terminal atrial natriuretic peptide, NT-proBNP — N-terminal brain natriuretic peptide, AVP — arginine vasopressin, ADH — antidiuretic hormone, ADH — antidiuretic hormone, ARB — angiotensin II receptor blocker, SCD — sudden cardiac death, ACEI — angiotensin-converting enzyme inhibitor, CAD — coronary artery disease, IL — interleukin, IL-33 — interleukin-33, BNP — brain Natriuretic Peptide, NP — natriuretic peptide, PC — postinfarction cardiosclerosis, ANP — atrial natriuretic peptide, SBD — systolic blood pressure, GFR — glomerular filtration rate, CVD — cardiovascular disease, CCE — cardiovascular events, LV EF — left ventricular ejection fraction, FC — functional class, CHF — chronic heart failure, ECHO-CG — echocardiographic examination.

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Chronic heart failure (CHF) is a consequence of many cardiovascular diseases (CVD), one of the final stages of the cardiovascular continuum [1,2]. CHF is a condition accompanied by a significant deterioration in the quality and reduction in the patient's life expectancy [1,2]. The prevalence of CHF in the population is quite high. According to epidemiological studies in the Russian Federation, it is 7–10%. In addition, the prevalence of CHF increases with age: from 1% of people in the age group of 50 to 59 years, up to 10% of those who are older than 80 years [3]. According to the Framingham study, five-year survival after the onset of clinical CHF symptoms is only 25% in men and only 38% in women [4].

Since the clinical signs of CHF are not specific enough, and during the echocardiographic study (ECHO-CG) it is not always possible to identify diagnostically significant changes, in the case of suspected CHF it is possible to determine the blood laboratory biochemical markers — biomarkers, among which are currently known natriuretic peptides, soluble ST2 receptor, copeptin, galectin-3 as an alternative diagnostic approach [5]. Said biomarkers are the subject of this review.

Natriuretic peptides

Among the main biomarkers of CHF are natriuretic peptides (NPs) [6]. The value of NP in CHF has been studied in numerous studies, and therefore the European Society of Cardiology recommends to determine the blood NP level in patients with suspected CHF (Figure 1) and to use the increase in its concentration as a diagnostic test for CHF with mid-range and preserved left ventricular ejection fraction (LV EF), Table 1.

NP is a family of related peptides comprising atrial natriuretic peptide (atrial natriuretic peptide, A-type, ANP), brain natriuretic peptide (brain natriuretic peptide, B-type NP, BNP), and later identified C-type NP (CNP) and D-type NP (DNP). The main reason for the increase in NP production is the volume overload of the heart cavities [8, 9].

A similar molecular structure allows combining NPs into one group. They are characterized by the presence of a ring-shaped amino acid nucleus, N-amine and C-carboxyl fragments. The difference between all NP is provided by different amounts of amino acids included in their composition. A- and B-types of NP are synthesized in the body as inactive prohormones [10, 11]. Proteases provide their cleavage into two fragments: active C-terminal and inactive N-terminal. Active C-terminal fragments are actually hormones — ANP and BNP. N-terminal fragments are N-terminal atrial (N-terminal pro-A-type natriuretic peptide, or NT-proANP) and T-terminal brain natriuretic peptides (N-terminal pro-B-type natriuretic peptide, or NT-proBNP), inactive, and they have diagnostic value [10, 11, 12].

Although modern laboratory technologies make it possible to identify all three NPs, the definition of BNP and its precursor NT-proBNP has a number

Table 1. *CHF diagnosis criteria [1, 2, 7]*

Criteria	HFrEF	HFmrEF	HFpEF
1 Clinical pattern	Symptoms and/or signs of heart failure*	Symptoms and/or signs of heart failure*	Symptoms and/or signs of heart failure*
2 LV EF	<40%	40-49%	≥50%
3 NP		↑ NP**	↑ NP**
4 ECHO data		a. Structural cardiac changes (LVH, dilation of LA) and / or b. DD	a. Structural changes in the heart (LVH, dilation of LA) and / or b. DD
Required number of criteria	2	4	4

* — Symptoms and / or signs may not be observed in the early stages of HF and in patients treated with diuretics; ** — BNP> 35 pg / ml and / or NT-proBNP> 125 pg / ml;
LV EF — left ventricular ejection fraction, HFrEF — heart failure (HF) with low (decreased) LV EF, HFmrEF — HF with middle range (intermediate) LV EF, HFpEF — HF with preserved LV EF; NP-natriuretic peptide, BNP-brain NUP, NT-proBNP — N-terminal fragment of BNP, LVH — left ventricular hypertrophy, LA — left atrium, DD — diastolic dysfunction

of advantages. The disadvantage of ANP is that it is more susceptible to factors such as exercise, changes in body position, and has a shorter half-life, which in active ANP is only 3-4 minutes. CNP can be considered as a marker of mainly endothelial dysfunction.

NP receptors are present in the brain, vascular bed, kidneys, adrenal glands and lungs [10, 11, 12]. Under the influence of NP there is dilation of afferent arterioles and constriction of efferent arterioles, an increase in renal blood flow and glomerular filtration rate (GFR). Also, NPs inhibit sodium and

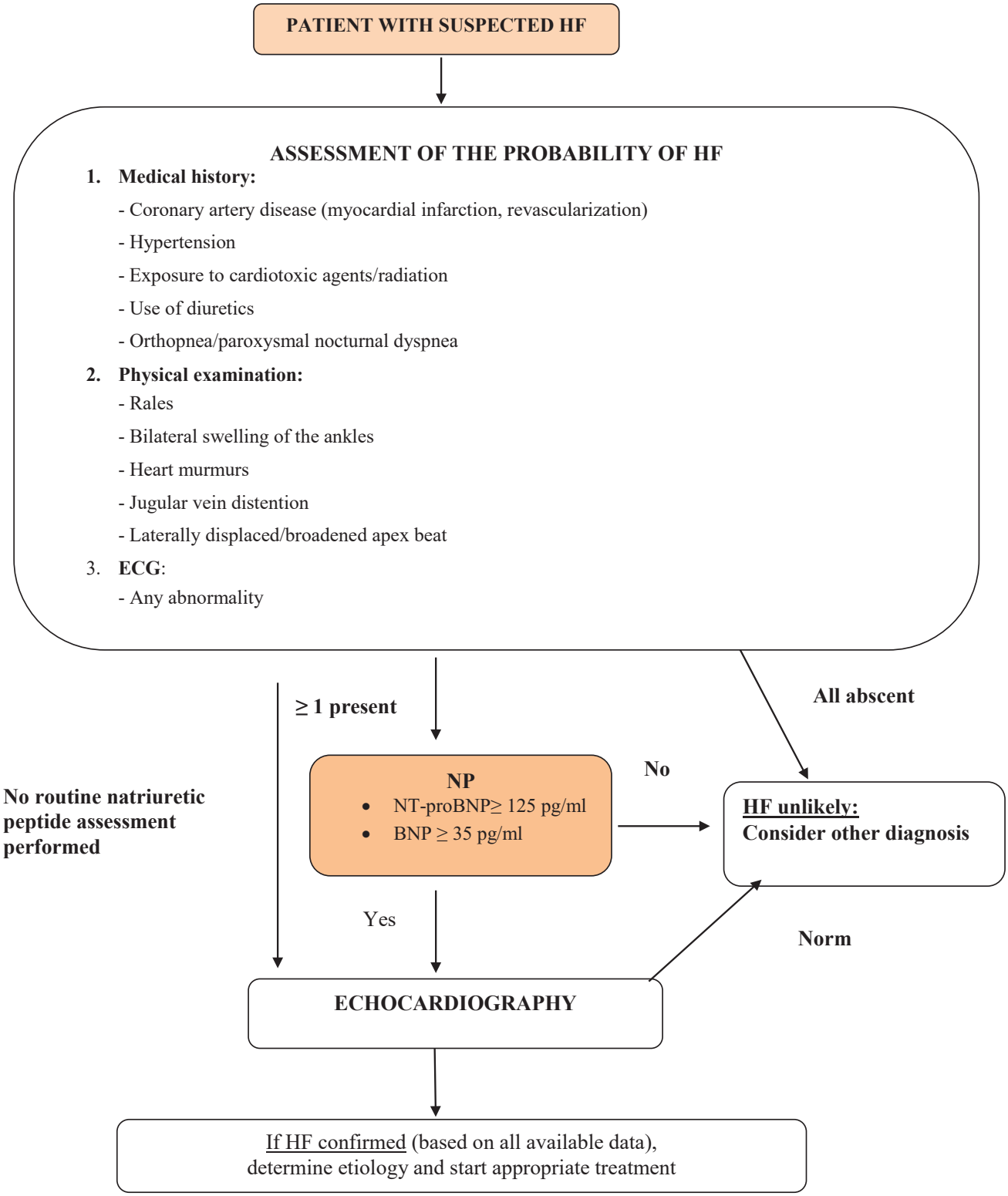

Figure 1. *CHF diagnosis algorithm [2]*

water reabsorption caused by the action of angiotensin II on the proximal tubules, prevent the action of antidiuretic hormone (ADH) on the cortical parts of the collecting tubes and inhibit sodium reabsorption in the medullary parts of the collecting tubes, thereby increasing natriuresis and diuresis, reduce preload. In addition, they inhibit the secretion of renin, aldosterone, inhibit the activity of the sympathetic nervous system, reduce the activity of proliferation and hypertrophy [10, 11, 12].

Normal serum values of NPs have certain variability due to age and gender specificity: their concentration increases with age and is higher in women [13]. In 90% of young healthy subjects BNP level is <25 pg/ml; and NT-proBNP is ≤70 pg/ml. For patients with compensated CHF the upper limit of normal values for BNP is 35 PG/ml and for NT-proBNP it corresponds to 125 PG/ml; for acute decompensation of HF, the maximum acceptable values are 100 pg/ml and 300 pg/ml respectively, and for ANP the optimal value is <120 pmol / l [14, 15]. These diagnostic values are used both in HF with reduced LV EF (CHFrEF) and HF with preserved (CHFpEF) and mid-range (CHFmrEF) LV EF [14, 15].

In 1986, Burnett J. for the first time demonstrated an increase in the blood concentration of ANP with advanced CHF [16]. A little later, Mukoyama M. et al. showed a direct relationship between the level of BNP and the functional class (FC) of CHF [17] during examination of patients with HF of different genesis. At present, the use of BNP and NT-proBNP definitions for diagnosis and assessment of HF severity is widely recommended [18]. Both biomarkers have approximately equal sensitivity and specificity [19, 20].

Determination of NP level in patients with suspected HF in both acute and non-acute onset of the disease is an exclusion test. The normal NP level in an untreated patient practically excludes significant HF, making further research methods unnecessary (Figure 1) [21].

Morwani J. et al. were the first to prove that BNP levels were significantly different in the groups of patients with postinfarction cardiosclerosis (PC) with reduced LV EF and subjects with relatively reduced and normal LV EF in comparison with people without cardiac disease [22]. Similar data were obtained in the study by Davidson N. et al. [23]. Further studies also confirmed the inverse correlation between the level of NT-proBNP and LV EF [18, 21].

Fattah E. et al. found statistically significant positive correlation of the BNP level and severity of mitral insufficiency according to echocardiography (ECHO-CG) [24].

According to McDonagh T. A. et al., it was shown that the prevalence of LV systolic dysfunction according to transthoracic ECHO-CG in the examined group was more than 3% in the study which included 1,252 patients of different age groups by random sampling. The sensitivity and specificity of elevated BNP level of more than 17.9 pg/ml for the detection of systolic LV dysfunction were 77% and 87% respectively, among the examined patients, and the negative predictive value was 97.5%. In the subgroup of patients in the age cohort older than 55 years with coronary artery disease (CAD), in which the rate of LV diastolic dysfunction was 12.1%, test sensitivity was 92%, specificity was 72%, and the negative predictive value was 98.5% [25].

The study conducted by E. V. Alexandrov revealed a strong direct correlation between the deceleration time of early diastolic blood flow at ECHO-CG and blood BNP level, and it was shown that the probability of accurate prognosis is higher than 98% [26].

The data of the diagnostic examination in 1,586 patients with suspected HF (the Breathing Not Properly Multinational Study) provide the following results: for BNP level of 100 pg/ml sensitivity was 90%, specificity was 76%, positive and negative prognostic value was 79 and 89% respectively, and diagnostic accuracy was 83% [27].

According to the results of the British study titled Natriuretic Peptide Study, for NT-proBNP 125 ng/ml the positive and negative prognostic value is 0.44 and 0.97 respectively, and for BNP 100 PG/ml — 0.59 and 0.87 respectively [28].

The study conducted by Aspromonte N. et al. included 357 individuals with and without HF. In the group of patients with CHF, BNP concentration was 469 pg/ml on average, and in the group without signs of LV dysfunction — 43 pg/ml. During the statistical analysis, patients with diagnosed HF were divided into 3 subgroups: with the presence of diastolic dysfunction, systolic dysfunction, as well as combined LV dysfunction. In these three subgroups BNP concentrations were on average 373, 550 and 919 pg/ml respectively. For the

BNP level of 80 pg/ml sensitivity was 84% and specificity — 91% [29].

In the English and American study to determine BNP level in patients with an acute cardiac asthma attack, it was shown that an increase in its concentration with a high degree of probability indicates in favor of dyspnea of cardiac genesis. The researchers noted that for the verification of cardiac dysfunction in such conditions, a sufficiently high rate of BNP is significant (more than 300 pg/ml), while its moderate rise (100-200 pg/ml) occurs in other pathological conditions accompanied by dyspnea [30, 31].

It was also found that the monitoring of the level variation of the peptide and its precursor has a higher informative value for the verification of pressure in the heart cavities than the insertion of the Swan-Ganz catheter [32, 33].

In addition to the primary diagnosis, the use of BNP and NT-proBNP level determination to assess the prognosis and efficacy of therapy is also discussed. Thus, the high concentration of BNP is associated with a poor prognosis, and the decrease in its level correlates with the best prognosis [33]. At the same time, a number of major studies evaluating the efficacy of enhanced therapy aimed at reducing BNP level gave contradictory results, which does not currently allow widely recommending an adjustment of the treatment on the basis of the change in BNP level [32].

SAVE and CONSENSUS II studies have demonstrated that BNP level is a significant prognostic factor indicating the risk of recurrent acute MI, development of HF and death not only in patients with MI, but also in patients with unstable angina [35].

Gong H. et al. revealed in patients with different cardiac pathology that BNP not only significantly correlated with clinical data and transthoracic ECHO-CG parameters, but was also the strongest independent predictor of sudden cardiac death (SCD) [36].

According to Daniels L. et al., it was shown that an increase in NT-proBNP level by more than 300 pg/ml in combination with moderate or severe LV diastolic dysfunction, or an isolated increase in NT-proBNP by more than 600 pg/ml, or an increase in BNP by more than 100 pg/ml significantly worsened the prognosis [37].

The influence of NT-proBNP level on the probability of development of SCD was demonstrated in a large-scale population-based study titled Cardiovascular Health Study. It included 5,447 patients of the older age group with 289 cases of SCD for mean follow-up period of more than 12 years. Elevated levels of NT-proBNP significantly correlated with mortality independently of other risk factors [38].

Data from the Russian clinical study conducted at the Cardiology Research Institute, Tomsk, which convincingly shows a significant association between elevated NT–proBNP levels and post-infarction myocardial remodeling with reduced contractile ability of the left ventricle, and with high myocardial-arterial stiffness, calculated according to the criterion of ventricular-vascular coupling EA/Es, are of some interest. The study included 140 patients at the median age of 60 years with coronary artery disease associated with CHF NYHA II-IV developed secondary to post-infarction and (or) ischemic LV myocardial dysfunction. Increase of EA/Es ratio>1.29 in patients with CHF of III-IV FC along with increase in blood NT-proBNP level by more than 303.4 PG/ml was characterized by prognostically unfavorable course of the disease [39].

Richards M. was the first to suggest that in patients with CHF of II-III FC therapy selection under BNP control is more accurate than based on clinical parameters [40].

The IMPRESS (Inhibition of Metalloproteinase in a Randomized Exercise and Symptoms Study in Heart Failure) study demonstrated a statistically significant decrease in NP with clinically effective doses of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) in one and two years from the beginning of drug therapy [41].

Similar data were obtained in the course of experimental work conducted by Tang S., Peng D. during the study of pharmacological properties of valsartan and benazepril in patients with HF [42].

If the research data on the study of ACEI and ARB are identical, the results of the effect of beta-blockers on NP level are very contradictory. A number of works indicate its reduction with administration of beta-blockers. In particular, Andreev D. A. et al. concluded that the switching of patients with moderate HF from therapy with so-called "non-recommended" beta-blockers to bisoprolol

was accompanied by an improvement in clinical status, quality of life, inotropic heart function and a decrease in NT-proBNP level in patients with initially higher values, regardless of the decrease in heart rate [43].

However, there is evidence of an increase in NP level under the influence of drugs of this pharmacological group. For example, the results of a New Zealand study showed that 6 weeks after the start of treatment with metoprolol in 60 patients with HF, high FC and EF <40% there was a statistically significant increase in BNP, NT-proBNP, ANP and NT-proANP levels [44].

Very similar data are presented in the recently published work by Broch K. dedicated to the study of the metoprolol effect on NT-proBNP level in patients with CHF of I-II FC [45].

The TIME-CHF study is by far one of the largest multi-center (n=499) studies [46]. It included elderly patients with diagnosed CHF of II-IV FC and LV EF ≤45%. Patients had a history of hospitalization for decompensated HF in the last 10-12 months and baseline NT-proBNP of more than 400 pg/ml for patients younger than 75 years or more than 800 pg/ml for patients older than 75 years. The protocol included patients with both reduced and preserved LV EF. The target levels of NT-proBNP are below 400 pg/ml or 800 pg/ml (according to the age). After 1.5 years of standard complex therapy, there were no significant differences in the effect on survival of the groups (HR 0.91, 95% CI 0.72–1.14, p=0.39). Despite significantly more frequent changes of therapy in the group of BNP there were no detected inter-group differences in the change of FC of CHF and the marker level. Further statistical analysis depending on the age of the patients showed that in individuals in the age group younger than 75 years, treatment under NP control leads to a reduction in mortality (HR 0.42, 95% CI 0.24-0.75, p=0.002) and hospitalization due to decompensated HF. At the same time, in patients older than 75 years the efficacy of this therapy approach was not revealed, and in this group there was more common excessive decrease in BP and the phenomenon of renal failure in 10.5% of patients versus 5.5% in patients who were on standard treatment [46].

According to the results of the Russian study conducted by A.A. Skvortsov, the long-term treatment of patients with the use of monitoring of NP level reduces the rate of decompensated CHF and mortality from CVD compared to standard therapy,

Table 2. *High NP level causes [1, 2, 18]*

Cardiac	Non-cardiac
Heart failure	Elderly age
Acute coronary syndrome	Ischemic stroke
Pulmonary embolism	Subarachnoid haemorrhage
Myocarditis	Impaired renal function
Left ventricular hypertrophy	Dysfunction of the liver (mainly cirrhosis with ascites)
Hypertrophic or restrictive cardiomyopathy	Severe infections (including severe pneumonia and sepsis)
Congenital and acquired heart defects	Paraneoplastic syndrome
Atrial and ventricular tachyarrhythmias, including atrial fibrillation	Chronic obstructive pulmonary disease
Cardioversion, discharges of an implantable cardioverter-defibrillator	Obstructive sleep apnea
Heart contusion	Pulmonary hypertension
Cardiac surgery	Anemia
Pericarditis	Severe metabolic and endocrine disorders (e.g., thyrotoxicosis, diabetic ketoacidosis)
Cardiotoxic effect of chemotherapy	Severe burns

and significantly affects the change in quality of life, clinical, functional state and ECHO-CG parameters [47].

It should be noted that neprilysin destroys ANP, BNP and CNP, but does not destroy NT-proBNP. Therefore, with neprilysin inhibitors, which are part of a new group of medicines ARNI (sacubitril/valsartan) levels and effects of ANP, BNP and CNP increase whereas NT-proBNP level does not increase due to neprilysin inhibition and retains its value as a marker of therapeutic efficacy and prognosis [50].

Thus, NP today are generally recognized markers of HF, their high value in determining the prognosis and risk stratification of patients with HF has been repeatedly proven in numerous clinical studies. Their determination should be an integral part of CHF diagnosis, especially with preserved and mid-range LV EF [1,2]. The change of their concentration, mainly NT-proBNP, makes it possible to judge the efficacy of the therapy and the need for dose titration. However, due to the wide variability of NP values, depending on age and gender and concomitant pathology (may increase in acute coronary syndrome, pulmonary embolism, heart contusions, after cardioversion, stroke, renal dysfunction, liver cirrhosis, paraneoplastic syndrome, COPD, anemia, severe infections, burns, thyrotoxicosis, diabetic ketoacidosis, etc., Table 2), they are not ideal markers of HF. In this regard, there is a high interest in the study on new markers of CHF, which are able to reflect the various links in the pathogenesis of the disease, which include the soluble ST2 receptor, copeptin, galectin-3.

Soluble ST2 receptor

ST2 is a receptor of protein nature belonging to the family of interleukins (IL). It is identified in two main forms: transmembrane (ST2L) and soluble (sST2) [49]. The transmembrane form (ST2L) binds to its natural ligand, interleukin — 33 (IL-33), and forms the IL-33/ST2L complex [49]. It is known that this complex has a protective effect on cardiomyocytes experiencing mechanical stress due to hemodynamic load, prevents the development of myocardial hypertrophy and has an antifibrotic effect, and also prevents apoptosis, thereby protecting the cell from death [49, 50].

The soluble form has the opposite effect: sST2 circulating in the blood are a "trap" for IL-33, thereby neutralizing the protective effects of the IL-33/ST2L signaling system, which leads to hypertrophy and fibrosis of the myocardium, dilation of the heart chambers and a decrease in the contractile ability of the LV myocardium [49, 50].

The growing interest in studying the activity of sST2 and ST2L in the pathogenesis of cardiovascular disease (CVD) increasingly pushes the practitioner to evaluate the sST2 receptor as a new marker of cardiovascular events (CVD) and adverse clinical outcomes primarily associated with HF and CAD [51].

The mean normal concentration of sST2 is 18 ng/ml, concentration above 35 ng/ml indicates an elevated risk of CVD [51].

Transient increase in the levels of sST2 was identified for the first time in the development of MI in mice after ligation of the coronary artery [52]. A sufficient number of studies investigating sST2 as a biomarker of CHF was subsequently conducted. In the PRIDE study, which included 600 patients with dyspnea, the concentration of sST2 was correlated with the degree of severity of HF symptoms, FC of CHF, LV EF and creatinine clearance. Patients with preserved LV systolic function had lower sST2 levels compared to patients with systolic dysfunction. In addition, the researchers concluded that the concentration of sST2 is a strict predictor of mortality in HF: in the group of patients with a marker level above the median, the risk of death increased by more than 11 times [53, 54].

According to Shah R., it was shown that high sST2 concentrations are associated with an increase in the size of the myocardium and a decrease in the contractility of the LV [55]. In addition, the association of the sST2 level increase with FC of HF was demonstrated. Mean level of sST2 in patients with I FC was 43.8 (18.4-200.0) ng/ml, II FC — 36.5 (18.4-127.2) ng/ml, III FC — 54.3 (21.5-200.0) ng/ml and IV FC — 72.2 (25.4-200.0) ng/ml, $p<0.05$ [55].

Mueller T. et al., in the study of sST2 levels in 137 patients with decompensation of CHF, showed a significant increase in the median marker concentration in patients who died. The authors concluded that sST2 is a strict predictor of annual mortality independent of other factors [56].

In the Ludwigshafen Risk and Cardiovascular Health Study, the role of ST2 in HF prognosis was examined in 1,345 patients with CAD. During the follow-up period, which lasted 9.8 years, 477 patients died. In the group of patients with the highest content of sST2, the risk of death was 2 times higher than in other groups [57].

The CLARITY-TIMI 28 study proved that regardless of the NT-proBNP precursor level the increase in sST2 concentration is a predictor of mortality from HF [58].

Alan H.B. et al. found that sST2 variability in healthy individuals is lower compared with NP. The authors demonstrated that analytical variability of sST2 within 2 months was 4.2%, and biological individual variability — 11% [59]. The researchers proved that the measurement of this marker can be used for long-term monitoring of the course of CHF. Dieplinger et al. measured biological variability of sST2 for 6 weeks. It was 10.5%, which is consistent with the study of Alan H.B. et al. [60].

Nevertheless, despite the high diagnostic value of sST2, it should be remembered that its increase is also found in a number of other diseases, such as acute and chronic inflammatory, autoimmune diseases and asthma.

Copeptin: Derivative Form of Arginine Vasopressin

Arginine vasopressin (AVP), better known as antidiuretic hormone (ADH), is one of the key hormones involved in many physiological and pathophysiological processes, especially in the maintenance of cardiovascular homeostasis [61]. ProAVP, which is a precursor of AVP, is formed and subsequently released by 2 endocrine mechanisms interacting at the level of neurons [61].

In the first mechanism, proAVP is produced in large-cell neurons of the supraoptic and paraventricular nuclei of the hypothalamus. During axon transport to the posterior lobe of the pituitary gland proAVP is converted into AVP, neurophysin II and copeptin through a cascade of enzymatic reactions [61, 62]. The process is completed at the level of neurohypophysis. These three proteins are subsequently secreted from the neurohypophysis by hemodynamic or osmotic stimulation [62, 63].

In the second mechanism, the AVP precursor is synthesized in the parvocellular neurons of the hypothalamus, and then it enters the pituitary portal system and acts on the cells of the adenohypophysis [64].

In the bloodstream, AVP binds to three receptors: vascular receptor AV1R, renal AV2R and neuroendocrine AV3R. For AVP, AV1R receptors are the most common and predominant. Through the AV1R receptors, AVP induces a vasoconstrictive effect by increasing the level of intracellular calcium. Binding of AVP to the receptor AV2R has an antidiuretic effect. It is associated with an increase in the synthesis of aquaporin-2 in the kidneys, which stimulates an increase in the permeability of collecting tubes for water and strengthening its reverse absorption. In addition, endothelial cells of blood vessels also contain AV2R receptors that play an important role in the mechanisms of blood coagulation. Their activation increases the level of von Willebrand factor, factor VIII, and plasminogen activator in plasma [64]. The third type of AVP receptor — AV3R — is located in the anterior pituitary gland and is involved in the secretion of adrenocorticotropic hormone. In addition to binding to specific receptors, AVP is able to interact with oxytocin and certain purinergic receptors. Oxytocin receptors are localized in the endothelium of the vascular wall, and interaction with them leads to vasodilating action [64].

There are a number of challenges when determining AVP in the blood: short half-life, rapid elimination from the body and instability outside the body. In regard to these aspects, lately there has been active study of the protein copeptin which is related to arginine-vasopressin, synthesized in equimolar quantities of vasopressin and reflecting its nature and activity in the body. It should be noted that copeptin is a fairly stable peptide; its concentrations remain in the blood for several days after blood sampling [64].

Copeptin was first isolated by D. Holwerda in 1972 from the posterior pituitary gland of a pig [64]. Copeptin is a glycosylated protein with a molecular weight of 5000 Da from 39 amino acids with a leucine-enriched segment. This peptide is the C-terminal part of provasopressin (P-proAVP) and is released together with the AVP during the decomposition of the precursor [65]. The blood

copeptin level in healthy people ranges from 1 to 12 pmol/l with a mean value of <5 pmol/l, while males have higher peptide values in comparison with women; the difference in mean hormone value is around 1 pmol/l; there was no significant diagnostic difference between the concentrations in different age groups [64, 65]. Like AVP, copeptin level in blood plasma varies depending on changes in its osmotic pressure. The normal range of copeptin reflects the physiological secretion of AVP essential for maintaining the plasma osmotic pressure. However, in severe conditions, such as shock, sepsis, CVD, the release of AVP is reflected by sharp increase in plasma copeptin level, which has a high diagnostic and prognostic value [66].

In recent years, a number of researchers have demonstrated the clinical significance of this hormone as a biomarker of CHF. Vetrone F. and Santarelli S. found a significant increase in copeptin in patients with decompensated CHF — 42 (0-905) mmol/l, and with compensated CHF, the median biomarker concentration was 20 (0-887) pmol/l [67]. Silva Marques et al., Stephanie Neuhold noted the relationship between copeptin and FC of HF [68.69]. A fairly extensive study which included 577 patients with acute HF proved that patients with hormone levels of more than 57 pmol/l had an unfavorable prognosis for mortality within 3 months [70]. It is very important to note that the combined measurement of copeptin and NP concentration allows improving risk stratification in patients with CHF [71].

Galectin-3

Currently, galectin-3 is considered as a promising biomarker for diagnosis and prognosis of CHF. The American Heart Association has included galectin-3 in the clinical protocol for the prevention and treatment of HF as a marker of stratification for patients at high risk of adverse clinical events [72].

Galectin-3 is a protein with a molecular weight of 26 kDa, belonging to the family of B-galactoside binding proteins [73]. Galectin-3 is widely distributed in the body; the peptide binds to a wide range of extracellular matrix proteins due to the presence in its structure of the collagen-like domain. Galectin-3 is expressed by macrophages, osteoblasts, fibroblasts and neutrophils. Especially important is that this peptide stimulates the activation of fibroblasts and the development of fibrosis in the future by increasing the activity of collagen and the activation of growth factor b. These processes play an important role in HF pathogenesis, as they lead to the development of cardiac remodeling and progression of LV dysfunction [74].

Currently, there is sufficient information on the role of galectin-3 in the development of CHF, progression of atrial fibrosis, and remodeling of heart cavities. Galectin-3 expression was found to be minimal or practically absent in healthy individuals and patients with compensated HF, while it was maximal at the peak of fibrosis and inflammation [73, 74]. Clinical studies have shown that the expression of galectin-3 increases in patients with reduced LV EF regardless of HF etiology, which allowed positioning galectin-3 as a marker of HF [73, 75, 76].

The first report on the role of galectin in the human body was presented by Sharma et al. [73.76]. The study of LV myocardial biopsy material in patients with aortic stenosis and with preserved or reduced LV EF demonstrated increased activity of the peptide in the myocardium in patients with reduced LV inotropic function [73, 76]. A subsequent PRIDE study showed a significant increase in galectin-3 in patients with acute HF compared with the control group (9.2 versus 6.9 ng/ml, p <0.001). The optimal threshold value of galectin-3 for the diagnosis of HF was 6.88 ng/ml, which had a sufficiently high sensitivity — 80%, but lower specificity — 52%. Further multiple factor analysis showed that the precursor of BNP has a more significant diagnostic ability compared to galectin-3. No correlation was found between galectin-3 and FC of CHF [77].

According to the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of exercise training) study, galectin-3 levels were associated with higher FC, elevated serum creatinine levels, low maximum oxygen consumption, and lower systolic blood pressure (SBP) [78, 79].

In the study conducted by Yu.V. Dubolazova, which included patients with HF and preserved and reduced EF, it was shown that serum galectin-3 levels had a statistically significant correlation with LV EF ($p < 0.05$) [80].

The relationship of galectin-3 levels with ECHO-CG parameters was shown by a group of scientists led by Ravi V. Shah: elevated values of the biomarker

were associated with high LV filling pressure (E/E') (r=0.345, p=0.01) and disturbance of its relaxation in diastole — decrease in the peak velocity E' (r=-0.246, p=0.03); a relationship was found between the increase in galectin-3 concentration and the degree of regurgitation on the mitral and/or tricuspid valves (r=0.297 and r=0.258 respectively, p<0.005) [81].

According to the CARE-HF study to assess the effect of galectin-3 on the prognosis of patients with CHF of III-IV FC, the initial level of the marker was directly related to mortality and hospitalization due to HF. The level of plasma galectin-3 >30 ng/ml increased the risk of the end point (death and hospitalization due to CHF) by more than 2 times [82].

In a large cohort of the PREVEND study (Prevention of Real and Vascular END stage) baseline galectin-3 level was an independent predictor of total (but not cancer or cardiovascular) mortality [83].

A number of significant studies have shown the possibility of using galectin-3 as a biomarker of HF. Additional clinical studies are necessary to determine the possibility of its application in everyday clinical practice [84-86].

Conclusion

Thus, today NPs are recognized biomarkers that are included in the guidelines for the management of patients with heart failure. They can and should be used by therapists and cardiologists in real clinical practice. Their determination should be an integral part of the diagnosis of CHF, especially with preserved and mid-range LV EF. The variation of their levels, mainly NT-proBNP, can help in assessing the efficacy of treatment and the need for the drug dose titration. Additional studies are needed to confirm the diagnostic and prognostic value and to identify new highly specific and sensitive biochemical markers in patients with CHF.

Conflict of Interests

The authors declare no conflict of interests.

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THE ROLE OF INTERVENTIONAL METHODS IN TREATMENT OF PULMONARY EMBOLISM

Abstract

This review concerns current interventional methods of acute pulmonary embolism treatment. The article provides a rationale for catheter approaches, detailed description of patient selection and risk stratification including an estimation of thromboembolic event massiveness, risk of acute pulmonary embolism, bleeding risk assessment, and individual patient characteristics. The review contains the up-to-date classification of pulmonary embolism on the basis of 30-day mortality assessment and estimation of disease outcome according to the original and simplified Pulmonary Embolism Severity Index. A special attention is paid to interventional methods, in particular, to catheter directed thrombolysis, rheolytic thrombectomy, thrombus fragmentation and aspiration. The results of studies of efficiency and safety of endovascular approaches to pulmonary embolism management are reported. The article emphasizes the importance of further study of various clinical aspects of these methods in order to obtain comprehensive information about the treatment of this severe disease, which is associated with significant disability and mortality.

Key words: *pulmonary embolism, treatment, risk stratification, patient selection, interventional approaches, catheter methods, catheter directed thrombolysis, ultrasound, endovascular treatment*

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tPA — tissue plasminogen activator; ACT — anticoagulant therapy; VTE — venous thromboembolism; CT — computed tomography; CDT — catheter-directed thrombolysis; PA — pulmonary artery; PE — pulmonary embolism; RV — right ventricle; RCT — randomized clinical trials; CO — cardiac output; DVT — deep-vein thrombosis; ECHO-CG — echocardiography

Introduction

Venous thromboembolism (VTE) is a severe and common clinical condition and includes deep-vein thrombosis (DVT), pulmonary embolism (PE), or their combination [1, 2]. The annual incidence of VTE is 100-200 per 100 thousand people [3]. VTE worldwide is estimated at about 10 million cases per year and is associated with significant disability and mortality [4].

The real number of deaths as a result of PE is difficult to determine, as the patient's sudden death is more often attributed to the outcome of a cardiac disease than a thromboembolic event. In USA, up to 600 thousand cases of VTE and approximately 100 thousand deaths due to these conditions are reported annually [5]. In Europe, life-time diagnosis was made only in 7% of cases out of 317 thousand deaths due to PE registered in 2004 [3]. Moreover, in 34% of the total number of tragedies, the disease developed as a sudden PE, and in 59% of cases, death occurred as a result of PE that was not diagnosed during life-time.

Over the past three decades, the general understanding of VTE has improved significantly, but the therapeutic paradigm has undergone only minor changes compared to other common diseases that are associated with high mortality (e.g., cancer

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and cardiovascular diseases, including myocardial infarction and stroke) [6]. The efforts of scientists and practitioners involved in the treatment of PE which has already occurred are aimed at using highly accurate methods to remove a thrombus from the pulmonary circulation system with minimal risk of periprocedural complications, which is usually accompanied by a dramatic improvement in the patient's condition and a decrease in the risk of adverse outcomes [7]. The objective of this review is to discuss interventional approaches in the management of patients with PE, including the use of catheter-directed thrombolysis (CDT), as well as modern methods of fragmentation, aspiration and removal of blood clots from the pulmonary arterial bed using specialized catheter systems.

Interventional Approaches Justification

The adverse effects of systemic thrombolysis, as well as its ineffectiveness, were the basis for studying the possibilities of removing a thrombus with a catheter as an alternative therapeutic option [8, 9]. The use of catheter technology is designed to reduce some of the risk of hemorrhagic complications associated with systemic delivery of thrombolytic agents in various ways [10]. On one hand, the necessary medication that goes directly into the thrombus or even beyond it, may allow to reduce both the fibrinolytic drug dosage and the systemic hemorrhagic effect mediated by it [6]. On the other hand, the use of supplementary methods of thrombectomy reduces the overall duration of treatment, as well as the total dosage of drugs. Among the advantages of invasive methods, the capacity of catheters to directly determine the pressure in the pulmonary artery (PA), cardiac output (CO), and other hemodynamic parameters should be highlighted, which allows the monitoring of the hemodynamic response to the therapy. Finally, thrombectomy based on catheter techniques may sometimes be the only available choice for patients with life-threatening PE who cannot resort to either surgical embolectomy or systemic thrombolysis [11]. The rapidly evolving evidence base forces us to seek a better understanding of when and under what conditions various invasive approaches will prove their benefit in the treatment of serious patients [6].

Treatment based on catheter techniques is aimed at rapidly reducing obstruction and restoring pulmonary blood flow, which leads to an improvement in CO and the change of the patient's hemodynamic status from unstable to stable [2, 7, 11 to 13]. At the same time, the administration of fibrinolytic drugs can be stopped or their dosage can be reduced. There are several approaches based on catheter technology (Table 1) [1, 12]:

- Catheter-directed thrombolysis, including ultrasound exposure;
- Thrombus fragmentation using a pigtail catheter or balloon catheter;
- Rheolytic thrombectomy with a hydrodynamic catheter;
- Aspiration thrombectomy;
- Rotation thrombectomy.

Table 1. *Catheter approaches to acute pulmonary embolism management*

Device	Size, mm (French scale)	Mechanism of action
Pigtail catheter	2-2,67 (F6-8)	Fragmentation
Peripheral balloon	5-10	Fragmentation
Catheter-directed fibrinolysis	1.33-2 (F4-6)	Direct infusion of fibrinolytic agent
Ultrasound-accelerated thrombolysis	2 (F6)	Direct infusion of fibrinolytic agent plus, ultrasound for clot separation#
Guide catheter	2-3.33 (F6-10)	Manual aspiration
Pronto Xl catheter	2-4.67 (F6-14)	Manual aspiration
Penumbra Indigo system	2-2.67 (F6-8)	Suction pump aspiration
Inari FlowTriever	7.33(F22) guidewire	Disruption, retraction, and aspiration of clot
AngioVac	F-26 guidewire and F-18 catheter	Large-volume aspiration with return of filtered blood using a centrifugal pump

Notes: US — ultrasound; # — is currently the only method approved by the Food and Drug Administration (USA)

Over the past two decades, promising endovascular treatment methods have been developed to reduce acute and chronic disability due to VTE [14, 15]. However, careful selection of patients is necessary for the effective use of endovascular therapy, which includes an assessment of the condition severity, the risk of bleeding, the features of the technique used, and the patient's individual characteristics.

Patient Selection and Risk Stratification

Careful selection of patients is a fundamental step in the use of individually tailored endovascular techniques in clinical practice. When addressing the endovascular approach, three key points have to be considered: 1) severity and acuteness of the disease; 2) probability of serious bleeding; and 3) individual patient's characteristics.

Clinical Classification of Pulmonary Embolism Severity

Assessment of the massiveness of PE or the severity of the mortality risk in this event is a crucial step in determining the principles and stages of the treatment strategy [16]. The clinical classification of the severity of a PE episode is based on the calculated risk of early (up to 30 days) mortality due to a thromboembolic event [1]. This distribution (or stratification), which is important in both the diagnostic and therapeutic approaches, is based on an assessment of the patient's clinical status at the time of presentation of the event [17]. High-risk PE is assumed or confirmed in the presence of shock or persistent hypotension, and non-high-risk PE (intermediate or low) — in their absence (Table 2) [1].

Similar to the above classification based on an assessment of the mortality risk, dividing PE into massive, submassive and nonmassive is also used [8, 13]. At the same time, massive PE occurs with hemodynamic disorders (hypotension or the need for inotropic support); submassive — with the right ventricle (RV) dysfunction determined by echocardiography, computed tomography (CT) or elevated cardiac biomarker levels, and non-massive or low-risk PE occurs without evidence of RV dysfunction or hemodynamic insufficiency [12]. Many studies have shown that PE accompanied by hemodynamic disorders is associated with a worse outcome of the disease. The International Cooperative Pulmonary Embolism Registry (ICOPER), which studied the outcomes of 2110 patients with established PE, demonstrated a 90-day mortality rate of 58.3% in patients with massive PE, compared with 15.1% in submassive PE [18].

Comparable findings were obtained in Germany from a study of the MAPPET registry (Management Strategy and Prognosis of the Pulmonary Embolism Registry), consisting of 1,001 patients with acute PE [19]. The intrahospital mortality rate was 8.1% for hemodynamically stable patients compared with 25% for those in whom the disease manifested with cardiogenic shock, and 65% for those requiring cardiopulmonary resuscitation measures.

Terms such as "massive", "submassive" and "nonmassive" embolism, despite their widespread use in specialized literature, are rather vague and variable in interpretation, according to many scientists, resulting in ambiguity (entanglement) in the assessment of the concept itself [8]. On the other hand, although it seems tempting to stratify PE variants based on the absolute frequency of complications, in particular mortality, this approach is difficult due

Table 2. *Classification of patients with acute pulmonary embolism based on early mortality risk*

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V sPESI >I	Imaging Signs of RV dysfunction	Cardiac biomarkers
High		+	(+)	+	(+)
Intermediate-	**high**	–	+	Both positive	
	low	–	+	Either one (or none) positive	
Low		–	–	Assessment optional; if assessed, both negative	

Note: PESI — Pulmonary embolism severity index; sPESI — ≥ 1 point(s) indicate high 30-day mortality risk; RV — right ventricle

to frequent comorbidities [20]. For example, a non-massive PE can be associated with a high risk of complications in a patient with numerous comorbidities [21], such as obstructive pulmonary disease or congestive heart failure. Massive PE is traditionally defined on the basis of the angiographic extent of an embolic lesion using the Miller score [22], but this definition is limited in routine clinical practice due to insufficient equipment of medical institutions with angiography equipment firstly [8]. From a radiological point of view, massive PE is understood as the reduction of pulmonary perfusion in one lung (>90%) or the total occlusion of the main pulmonary artery, as established by CT pulmonary angiography [13].

In addition to assessing the risk or determining the massiveness of PE after diagnosis, it is extremely important to calculate the prognosis of the disease, in which the PESI (Pulmonary Embolism Severity Index) considers hypotension (systolic blood pressure <100 mmHg) as a predictor of poor prognosis [1].

The PESI score became widely popular in both the original [21] and the simplified version (Table 3) [1, 23].

This method helps to determine the severity of the disease by predicting 30-day mortality and long-term mortality. Patients with a higher index need more aggressive treatment. Traditionally, intravenously administered recombinant tissue plasminogen activator (tPA), alteplase at a dose of 100 mg for 2 hours, is used to treat massive PE [24]. There are opinions in literature that CDT in capable hands can be used as a first line, as an alternative to intravenously administered alteplase, although this approach seems ambiguous so far [25].

According to the guidelines of the American College of Cardiology/American Heart Association, the use of catheter embolectomy is considered for clear cardiopulmonary failure or for submassive PE, when patients have clinical signs of poor prognosis. The European Society of Cardiology recommends a two-stage risk stratification, first using the approved clinical and prognostic assessment of

Table 3. *Original and simplified PESI*

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age >80 years)
Male	+10	–
History of cancer	+30	1 point
History of chronic heart failure	+10	1 point
History of chronic pulmonary disease	+10	1 point
Heart rate ≥ 110 bpm.	+20	1 point
Systolic blood pressure <100 mm Hg	+30	1 point
Respiratory rate >30 breaths per minute	+20	–
Temperature <36° C	+20	–
Altered mental status	+60	–
Arterial oxygen saturation <90%	+20	1 point
	Risk class*	
	Class I: ≤65 points, very low 30-day mortality risk (0-1.6%) Class II: 66-85 points, low mortality risk (1.7-3.5%)	0 points = 30-day mortality risk 1.0% (95% CI 0.0%-2.1%)
	Class III: 86-105 points, moderate mortality risk (3.2-7.1%) Class IV: 106-125 points, high mortality risk (4.0-11.4%) Class V: >125 points, very high mortality risk (10.0-24.5%)	≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5%-13.2%)

Note: * — based on the sum of points; bpm. = beats per minute; PESI = Pulmonary embolism severity index; CI = confidence interval

PESI (original or simplified), and then using the visualization methods and determination of biomarkers [21, 23].

In case of a positive clinical and objective risk assessment, catheter-directed therapy may be considered if there are signs of an inevitable deterioration of the functions of the cardiopulmonary system. The lack of large randomized clinical trials (RCTs) in this area leads to discrepancies in recommendations.

Endovascular interventions are not recommended for patients with low risk of PE due to low levels of disability and mortality. The only exceptions are those who have a large saddle embolus without any adverse hemodynamic consequences or RV disorders.

Bleeding Risk Assessment

All patients being considered for endovascular intervention should be evaluated for the risk of bleeding. Active bleeding, recent cerebrovascular or intracranial pathology (stroke, transient ischemic attack, traumatic brain injury, recent neurosurgery) or absolute contraindications to anticoagulant therapy (ACT) are also absolute contraindications to the endovascular treatment including thrombolytics (Table 4). Relative contraindications, especially if not correctable on time, should be carefully reviewed on a case-by-case basis.

Determining Individual Patient Characteristics

Patient preference should be the main criterion in determining which endovascular treatment approach is appropriate for a particular case. It is the responsibility of the physician to determine the risks and benefits and discuss them in the context of each individual patient's life expectancy and functional status. This is especially important when choosing an endovascular method of treating PE/DVT, as it is not performed to prevent death, but with the goal of improving the quality of life in the long run [26]. Careful consideration must be given

Table 4. *Absolute and relative contraindications to catheter-directed thrombolysis*

Absolute	Active bleedingr
	History of recent* CVA or TIA
	History of recent neurosurgery
	History of recent intracranial trauma
	Absolute contraindications to anticoagulation
Relative	History of recent cardiopulmonary resuscitation
	History of recent gastrointestinal bleeding
	History of recent abdominal, ophthalmic or obstetric surgery
	Known severe allergy or adverse reaction to thrombolyic agent or contrast media (with no effect of steroids/antihistamines)
	History of recent trauma (other than intracranial)
	Severe thrombocytopenia
	Known intracranial tumor or vascular abnormality
	Known right-to-left cardiac or pulmonary shunt
	Uncontrolled hypertension: systolic BP >180 mm Hg, diastolic BP >110 mm Hg
	Severe dyspnea or other condition that would preclude ability to tolerate procedure
	Suspected intracardiac thrombus
	Suspected infected venous thrombus
	History of chronic kidney disease
	Severe liver disease
	Pregnancy
	Active infection

Note: *Recent = <3 months; CVA = cerebrovascular accident TIA = transient ischemic attack; BP = blood pressure

to the effect of chronic co-morbidities to the functional status of patients, as well as their ability to tolerate the procedure itself.

Catheter-Directed Thrombolysis

After the publication of the results of some studies that demonstrated low 90-day mortality in patients with submassive PE, who underwent anticoagulant monotherapy (2-3%), and a clearly elevated risk of bleeding was detected when using systemic thrombolytic drugs, many clinicians reluctantly agreed with the use of aggressive treatment methods for this disease [27-29]. CDT remains a rather controversial method, as an alternative to the systemic use of a fibrinolytic drug [7]. Some physicians are concerned that the risks associated with the procedure can be summarized with the appropriate hemorrhagic potential of thrombolytic agents [30]. Others consider CDT as an effective, minimally invasive and safe treatment method to prevent the patient's clinical deterioration and to improve RV function [27, 31].

The primary goal of treatment with CDT is to reduce the RV afterload due to the formation of channels of unobstructed blood flow through the pulmonary arteries, which reduces the pressure in the PA itself, the severity of RV dysfunction and improves the total CO (Figure 1). In patients with massive PE, the goal is to prevent death and at least to transfer patients from the "massive" category to a less threatening condition [25]. In patients with submassive PE, the goal is to prevent long-term disability and mortality due to this event. For successful CDT, the thrombolytic agent must be injected directly into the thrombus that occludes the vessel lumen. Numerous studies have shown that the injection of thrombolytic agent proximal to a blood clot does not provide additional benefits, because the drug will mainly pass in the free, rather than obturated arterial branches [25].

Back in 1988, one small study randomized 34 patients with major (according to angiography data) PE in two groups: patients who received intravenous tPA and those who received infusions of the drug through a catheter at a dose of 50 mg for 2 hours. [32]. The study showed comparable efficacy according to angiographic and hemodynamic results when using both techniques. However, the locally injected dose of fibrinolytic agent in this 30-year-old work was much greater than the dosages used today.

In a later prospective study of 101 patients with massive and submassive PE, in which the catheter technique was used (mainly local fibrinolysis), there was a significant decrease in PA pressure and improvement of RV function without serious complications, major bleeding or strokes [33]. Considering the low risk of major complications, it is reasonable to consider CDT in patients with already stabilized massive PE, having contraindications to

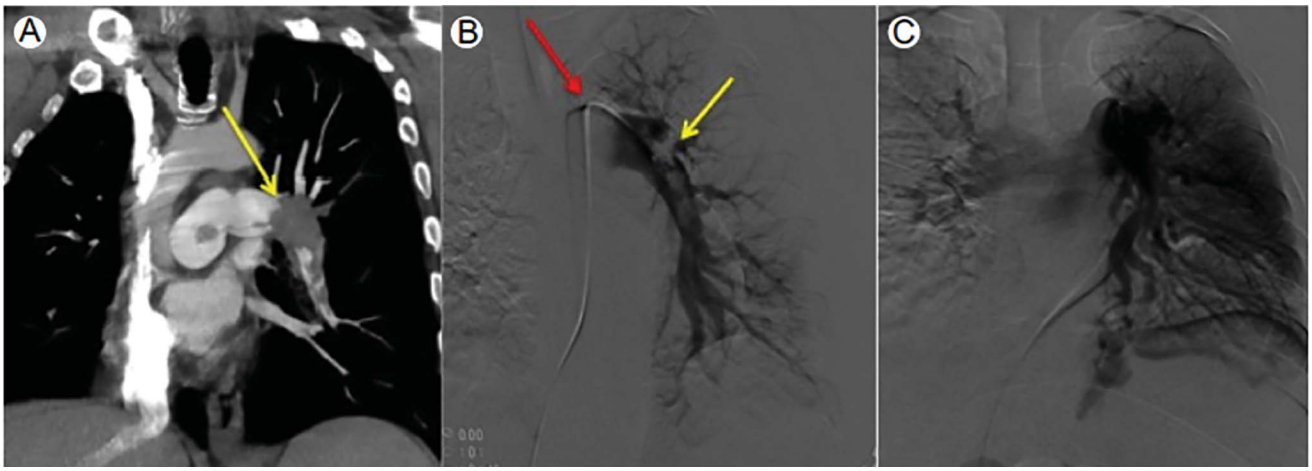


Figure 1. *Catheter-directed thrombolysis in pulmonary embolism treatment*

Notes: A 39-year-old woman with massive pulmonary embolism treated with catheter-directed thrombolysis. Computer tomography and initial pulmonary angiography demonstrate acute thrombus (yellow arrows) within pulmonary arteries (A and B). A standard angled pigtail catheter was used for catheter-directed thrombolysis (red arrow), with the catheter and its side holes embedded within the thrombus. After 14 hours (C), there is a significantly decreased clot burden in the left pulmonary artery. Adopted from A.Bhatt et al. (2017) [25].

systemic thrombolysis, and in patients with intermediate-high risk (presence of RV dysfunction and elevated levels of biomarkers), especially in individuals with an estimated high risk of hemorrhagic complications with use of full doses of systemic fibrinolytic agents [12]. When 52 patients with PE were treated with CDT, a more pronounced favorable hemodynamic effect was observed with duration of symptoms of <14 days compared to the group with longer duration of symptoms [34].

The results of the study (OPTALYSE PE) on the assessment of the dosage and duration of tPA administration in patients with intermediate risk of PE documented by CT angiography were published just recently [35]. One hundred and one patients were divided into 4 groups depending on the treatment regimen: treated with tPA at a dose of 4 mg/one lung for 2 hours; 4 mg/one lung for 4 hours; 6 mg/one lung for 6 hours; and 12 mg/one lung for 6 hours. During administration of a fibrinolytic agent, the dose of heparin was reduced to 300-500 U/hour. In addition, an ultrasonic signal for treatment of the thrombus and a cooling agent were provided through a triple-lumen catheter. Parameters for evaluating the effectiveness of treatment were considered the change in the ratio of the right ventricle to the left ventricle diameters (RV/LV) and the modified Miller score.

According to OPTALYSE PE results, the treatment was accompanied by a statistically significant improvement in the RV/LV diameter ratio (main evaluation criterion) in all groups of patients compared with baseline values. The RV/LV diameter ratio improved in 4 groups by about 25%. The modified Miller score also statistically improved in all groups, although the improvement in this parameter was more pronounced with an increase in the tPA dosage and infusion duration. The following version is considered by the authors as being among the reasons explaining such a difference (almost equal improvement in the RV/LV diameter ratio in all groups regardless of the dosage of the drug, and dose-dependent and time-dependent improvement of the Miller score). Low doses of thrombolytic agents can improve the functional vessel radius enough to improve pulmonary perfusion (Poiseuille's Law) and, therefore, the RV/LV diameter ratio. However, higher doses or longer infusions of thrombolytic drug are required to produce a similar reduction in overall clot burden assessed by the Miller score [35]. The level of major bleeding was 4%, and two cases (2%) occurred in the fourth group, which was the reason for stopping the randomization of patients in the last one.

Percutaneous Thrombectomy

Several percutaneous approaches are used in patients with absolute contraindications to thrombolysis, both separately and in combination. These include thrombus fragmentation with a rotating pigtail catheter, aspiration and rheolytic thrombectomy [13]. Unfortunately removal of a thrombus is not always achieved with simple insertion of a catheter into the PA and aspiration. The aspirated material obtained by catheter extraction or surgical removal usually consists of acute thrombi and older, more organized parts. Removal of the latter through a thin catheter or using aspiration presents considerable challenges. Thus, mechanical catheter-directed thrombectomy is primarily aimed at displacing and changing proximal thrombi, first of all their size, in order to quickly achieve narrowed lobar and segmental arterial branches, increasing the cross-sectional area of arterial tree vessels, and, consequently, reducing the pressure in PA and RV dilatation [6, 13].

Thrombus Fragmentation

Thrombus fragmentation techniques that use balloon angioplasty or pigtail catheter rotation (Fig. 2A and Fig. B) are probably the earliest examples of intervention in the treatment of acute PE [7, 10, 36, 37]. The idea is to use the side holes of the catheter, fully immersed in the thrombus. This allows the thrombolytic agent to contact the maximum surface of the clot [25]. This method is rarely used on its own due to the risk of distal and proximal embolization. New catheters for fragmentation, e. g., the Amplatzer-Helix catheter (EV3, Endovascular, USA), improve clot fragmentation by using microturbines to crush a thrombus, but they do not have the ability to aspirate the fragments formed and cannot move them through the catheter guide.

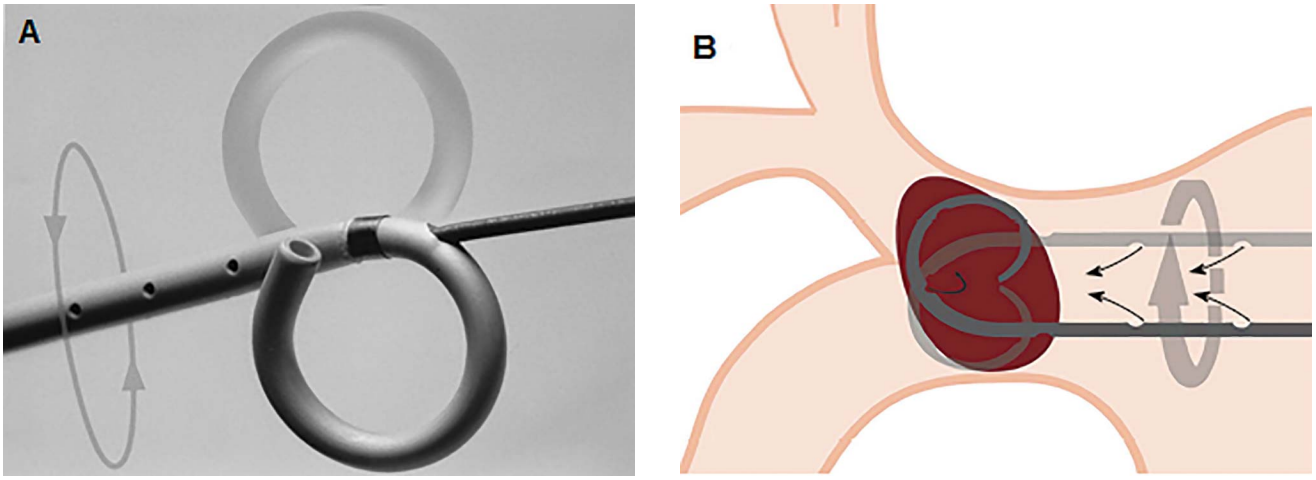


Figure 2. *Pigtail catheters for thrombus fragmentation.*

Notes: Distal ends of pigtail catheters. A — appearance of the catheter with side holes and curved end resembling a tail of a pig; B — schematic representation of mechanical thrombolysis of the thrombus (dark red color) in a pulmonary artery and the infusion of fibrinolytic agents through side holes (marked by little arrows) of the pigtail catheter. Modified from T.Schmitz-Rode et al. (2000) [37] and M.A.DeGregorio et al. (2017) [13].

Ultrasound-Accelerated Catheter-Directed Thrombolysis

CDT efficiency can be increased by using the energy of ultrasonic waves (US-CDT) [6, 27]. The mechanism of action to speed up the fibrinolytic process is associated with the use of ultrasonic energy, which breaks fibrin strands, increasing the surface area of the thrombus and, thus, providing more plasminogen activator receptors for the fibrinolytic action. Thus, low-energy ultrasound disaggregates fibrin fibers in an acutely occurring thrombus, which is used in the EKOS device (EkoSonic, Bothell, USA), combining the radiation of low-energy ultrasound waves and the infusion of a thrombolytic agent through a catheter with several side holes (Fig. 3 and Fig. 4).

Given the available data on US-CDT in the treatment of acute PE, the use of this technique should be applied on a strictly case-by-case basis. N.Kucher et al. (2014) [9] have conducted a multicenter RCT and recommend the following approach to the use of US-CDT based on the results obtained.

Figure 3. *EKOS-catheter with ultrasound transducers embedded within the catheter (marked by blue arrows)*

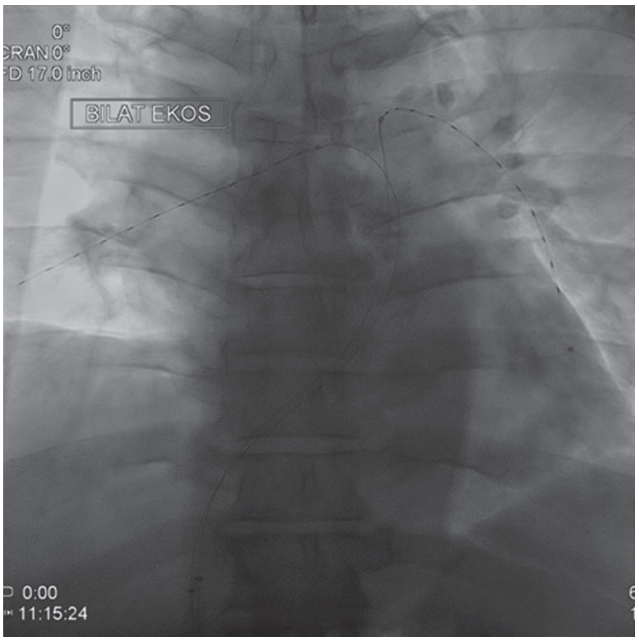


Figure 4. *Bilateral EKOS-catheters placed in the pulmonary arteries via the right common femoral vein approach*

Patients with proven acute PE should be immediately administered an intravenous ACT using first a bolus of 80 units/kg of unfractionated heparin, and then subsequent infusion of the drug. Then an assessment of the function and size of the PV, RV/LV ratio, troponin and brain natriuretic peptide levels is necessary. In addition to the clinical and hemodynamic assessment of the patient's condition, the consent of the patient should be taken into account.

The procedure starts with access through the common femoral vein using a 2 mm single lumen guidewire (F6) for unilateral therapy, two guidewires (2 mm, F6) or one mm dual lumen guidewire with a diameter of 3.33 mm (F10) for bilateral therapy. When performing the procedure, a standard catheterization of the right heart is needed, with simultaneous monitoring of oxygen saturation levels in both systemic circulation and mixed venous blood. To reach the pathological segment, a guidewire with a diameter of 0.89 mm should be used along with a standard diagnostic angiographic catheter. Then the angiographic catheter should be replaced with the selected catheter system. When using an ultrasound system, the guidewire can be removed and the ultrasound transducer system can be attached to the catheter. While the patient is in an intensive care unit, continuous administration of tPA can be initiated at a rate of 1 mg/h into each pulmonary artery. The dose of tPA is divided in half by 5 hours with 0.5 mg/h over the next 10 hours.

The recommended maximum dose of tPA is 20 mg for bilateral catheter placement and 10 mg for unilateral use. tPA infusion and ultrasound exposure should be discontinued after 15 hours. During the active phase of infusion, patients are in the intensive care unit on strict bed rest with continuous monitoring of vital signs, hemoglobin, platelets, fibrinogen levels and activated partial thromboplastin time. After completion of therapy, hemodynamic parameters are re-evaluated. The catheter system and guiding catheter should be removed, followed by manual pressing of the access site until the bleeding stops and stable hemostasis is achieved. In the follow-up period, echocardiography is performed to determine the RV size and function.

According to the data available, US-CDT was superior to the use of heparin alone in reversing RV dilatation at 24 hours without serious hemorrhagic complications or recurrent VTE [9]. In 150 patients in a multi-center study in the USA, US-CDT reduced the mean PA systolic pressure by 30% and the mean RV/LV diameter ratio by 25% [38]. After 90 days, there was a statistically significant difference in the improvement of the RV systolic function due to US-CDT. At the same time there was a tendency to improve the RV/LV diameter ratio, which did not reach statistical significance ($p = 0.07$). No patient experienced intracranial hemorrhage, while one patient had a major bleeding complication. Such an approach offers great promise and is probably preferable for this category of patients, although questions remain as to the safety of the outcome and medium-term and long-term mortality data.

Analysis of subgroups in the PERFECT registry, which compared thrombolysis using ultrasound with a standard CDT, showed an insignificant difference in pressure levels in PA before and after the intervention, despite similar doses of thrombolytic and duration of infusion [33].

In a meta-analysis performed in 2018, which summarized 20 studies with a total of 1,168 patients with high- and intermediate-risk PEs, the pooled estimate for clinical success, 30-day mortality and major bleeding after CDT and US-CDT were analyzed [31]. In the group of patients at high risk, the pooled estimate for clinical success was 81.3% (95% confidence interval (CI), 72.5-89.1), 30-day mortality rate was 8% (95% CI, 3.2-14.0%) and major bleeding was 6.7% (95% CI, 1.0-15.3%). Among patients with intermediate-risk PE, the following results were obtained: 97.5% (95% CI, 95.3-99.1%), 0% (95% CI, 0-0.5%) and 1.4% (95% CI, 0.3-2.8%), respectively. Clinical success in the group of high-risk PE patients who underwent CDT and US-CDT was noted in 70.8% (95% CI, 53.4-85.8%) and 83.1% (95% CI, 68.5-94.5%), respectively. In the group of patients at intermediate risk, the efficacy parameters for both methods differed not so significantly (95% for CDT and 97.5% for US-CDT) [31]. The authors emphasize the clinical success of KDT among high-risk and intermediate-risk PE patients, warning of higher mortality and major hemorrhages in high-risk patients. In addition, the ultrasound assisted CDT showed better values, especially in the group of patients at high risk.

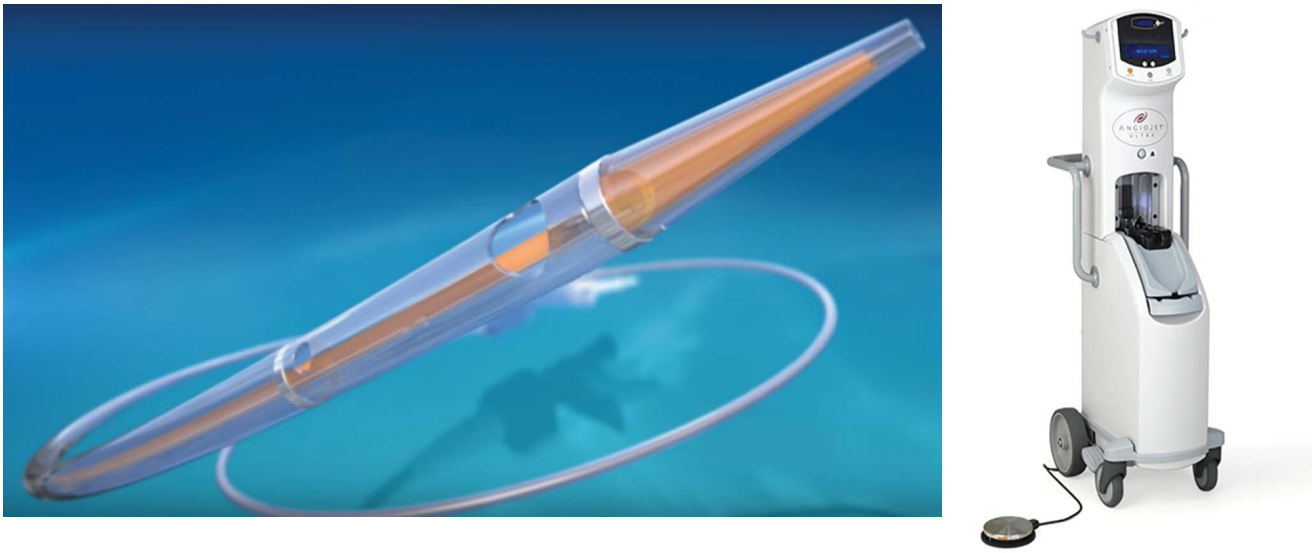


Figure 5. *AngioJet system for rheolytic thrombectomy*

Rheolytic Thrombectomy

Rheolytic thrombectomy is performed using the **AngioJet** device (Boston Scientific, USA), the size of which is selected depending on the target vessel (Fig. 5) [7, 13]. Catheters with a diameter of 2 mm or 2.67 mm (F6-8) are usually advanced in the pulmonary arteries directly to the thrombus using a 0.89 mm guidewire. Fibrinolytic agent (tPA) is delivered through the side holes, and then a high-speed jet is blown through the inner tube to the end of the catheter and back through the wide outer tube. According to the Bernoulli principle, jets that rush under pressure inside the catheter back from the end of the catheter to the pump are used to create zones with relatively low pressure in the region of the large side holes of the catheter. Through these holes, the thrombus or its fragments are captured, destroyed and removed from the body. In addition, these devices can be used for power infusion of a thrombolytic agent, e. g., tPA instead of saline, which is likely to increase the effectiveness of thrombolysis. In the pulmonary vascular system, rheolytic thrombectomy should be used with caution. Caution in the use of AngioJet is associated with relatively frequent complications due to the use of a catheter in the right heart and pulmonary arteries, and includes bradycardia, conduction disorders, hemoglobinuria, renal failure, hemoptysis, and even death [13, 39]. Ensuring proper positioning of the catheter is vital to prevent the risk of catastrophic vascular damage, as well as distal thrombus embolization when using high-pressure injection systems. Therefore, the use of computed tomography is recommended for monitoring when placing any drug delivery system. Despite the precautions, AngioJet (when it is available to use) remains an acceptable choice in the treatment of patients with PE [6, 40].

Aspiration Thrombectomy

A simple vacuum assisted aspiration thrombectomy is a rather easy mechanical option involving the use of an end-hole catheter [25]. An end hole is directed to the thrombus and manual suction is provided by a catheter and a large-volume syringe. Devices for aspiration embolectomy, such as a Greenfield catheter, have advantages over large diameter catheters, as they can remove the thrombus without the adverse effects observed in fragmentation and rheolytic techniques [41]. New devices, such as the Indigo System (Penumbra Inc., USA) and the FlowTriever System (Inari Medical, USA), specially designed for patients with absolute contraindications to thrombolytic therapy, are still at the research stage.

The **Penumbra Indigo** system is a relatively new device that actually automates this process. This mechanical aspiration thrombectomy system is designed to perform continuous drainage [36].

Penumbra Indigo aspiration device consists of 2-2.7 mm (F6-8) straight or curved catheters and a separator pump (Fig. 6AB). The device is approved

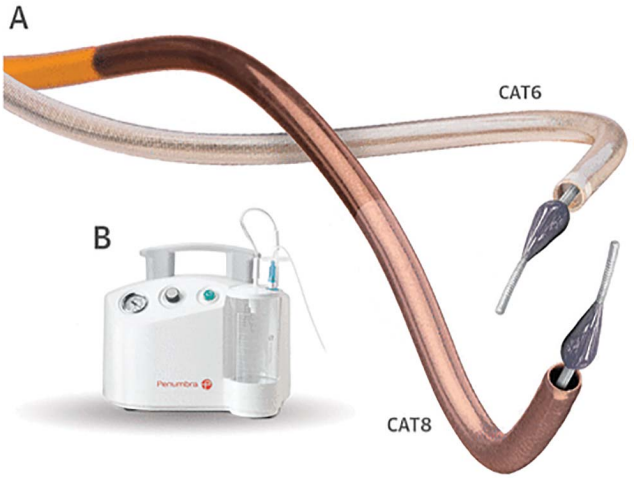
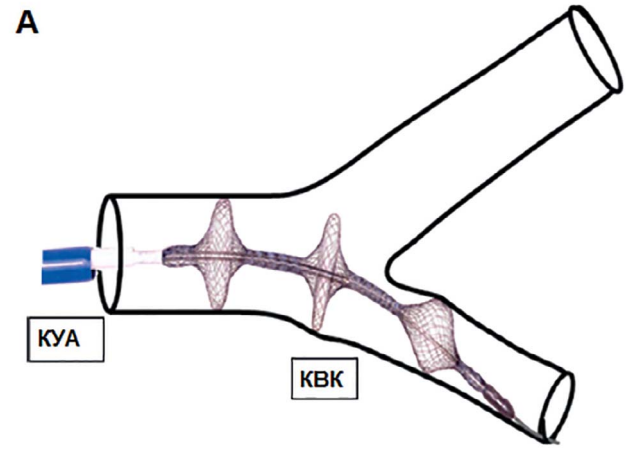


Figure 6. *Penumbra Indigo system with the catheters (A) and the pump-separator (B)*



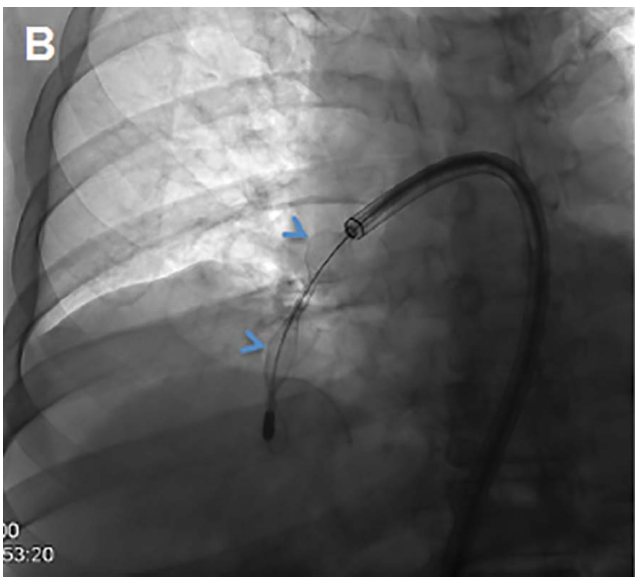


Figure 7. *Schematic illustration of catheter system FlowTriever (A) and radiologic appearance of catheter position in the pulmonary artery being occluded with the thrombus (B)*

Notes: AGC — aspiration guide catheter; FRC — flow restoration catheter. Modified from W.A.Jaber et al. [12].

for removal of thrombi from both the arterial and venous systems [12]. The advantage of the method is that the device requires 2.7 mm (F8) guidewire, which can be placed in the PA system quickly via the catheter delivery system with a guidewire. Once it reaches the thrombus, the thrombectomy catheter moves to the end and the suction mode is activated with a pump. A probe connected to the separator is used to clean the system from thrombotic masses, because the catheter is inside the artery during operation [12].

The **FlowTriever** infusion aspiration system (Inari Medical, USA) consists of three components. First, there is a catheter with a self-expanding nitinol mesh, presented in the form of three closely spaced nitinol discs (Fig. 7A). The discs are equipped with a guiding catheter (the second component) with a diameter of not more than 6.67 mm (F20), inserted immediately to the thrombus over a guidewire [36]. Approaching a thrombus, destroying FlowTriever is advanced straight into the thrombus through the catheter guide into the delivery catheter so that the protected nitinol disks can expand inside the thrombus (Fig. 7B). Then the discs are released using a suction extraction device, which coordinates the mechanical removal of the clot through the FlowTriever and aspiration of the thrombus through the guiding catheter into the device (the third component) [25].

The **AngioVac** system (Angiodynamics, USA) is a circuit with two large diameter catheters connected with a centrifugal pump. A catheter with a diameter of 7.33 mm (F22) with a funnel tip is advanced to the thrombus, and after that, the thrombus is aspirated to the cardiopulmonary pump (Fig. 8). The thrombus is retained inside the pump, and the aspirated blood is returned to the patient through

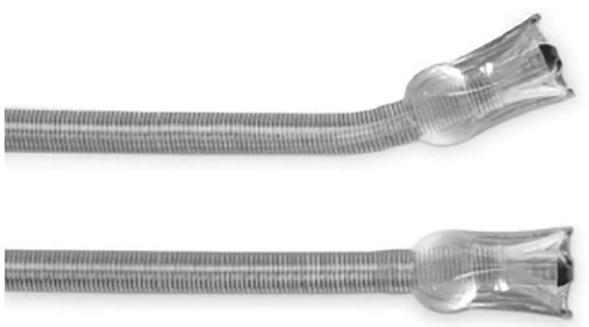


Figure 8. *Aspiration suction cannula AngioVac*

the second venous catheter with a diameter of 5.67 mm (F17) [25, 36]. Due to the scheme presented, a unique requirement for the effective use of the AngioVac system is the presence of a perfusiologist, who should keep the pump working during the thrombus aspiration.

Aspirex S (Straub Medical, Switzerland), a thrombectomy catheter, is also used for aspiration thrombectomy. This device has a single lumen catheter with a diameter of 3.33 mm, which can be advanced through a 0.89 mm hydrophilic guidewire. Aspirex has an L-shaped aspiration port that is advanced to the thrombus. Once inside the thrombus, the internal spiral turbine begins to rotate at high speed, aspirating the thrombus through the port and removing it in a spiral, like a screw. The catheter is connected to an external accumulation system where thrombotic masses are deposited. Although this system is widely used in acute DVT or dialysis access thrombosis, however, there is limited experience in its use in the treatment of high-risk PE patients [42]. The Aspirex catheter system is currently not approved for PE treatment in USA [6, 25].

Provision of Access and Perioperative Management in Endovascular Treatment

The approach suggested in the guidelines of the American Heart Association is recommended to access the vascular bed [8]. An access is made using a 2 mm femoral venous guidewire (F6) and a pigtail-type angular catheter of the same diameter, is advanced into each main PA. The extent of the lesion can be visualized at this stage by the injection of low-osmolar or iso-osmolar contrast agents (30 ml > 2 s). Unfractionated heparin should be used to maintain clotting time > 250 s. A direct thrombin inhibitor, e. g., bivalirudin (0.75 mg/kg IV bolus, then 1.75 mg/kg/h) can be used as an alternative to heparin if there are contraindications to the heparin administration which are not related to bleeding. A 2 mm guiding catheter (F6) is used to reach a thrombus, which after that may be approached by a hydrophilic guidewire, through which, in turn, devices for percutaneous mechanical thrombectomy are advanced. This approach is limited to main and lobar PA branches.

Postprocedural Patient Management

Currently, there are no comparative studies and guidelines regarding the type, dose and duration of use of anticoagulant or antiplatelet drugs after endovascular catheter therapy. Some authors employ an empirical approach to antiplatelet therapy and ACT in these patients. After completion of CDT in acute PE or DVT, ACT is resumed with unfractionated heparin shortly after stopping the bleeding at the puncture point. Then, if necessary, patients are switched to therapy with new oral anticoagulants or vitamin K antagonists. And, finally, in patients with PE/DVT, it is necessary to use compression bandages until acute edema is resolved, and then switch to kneesocks with a pressure of 30-40 mm Hg. After discharge, patients should be followed-up regularly, and during repeated visits, it is necessary to evaluate clinically the possibility of disease recurrence, changes in life quality, as well as to perform continuous analysis of the bleeding risk in those who continue to be on the ACT.

Predictors of Adverse Events

Since endovascular strategies continue to be updated and improved, and specialized catheter systems are widely introduced into modern practice, it is essential to predict the adverse events associated with catheter therapy in both acute DVT and PE. Early studies [9, 43], including the recently completed ATTRACT study [26], did not reveal significant differences in the safety of CDT and anticoagulant therapy alone. In turn, the results of extensive observations in the USA demonstrated that the presence of factors such as age > 75 years, Latin American ethnicity, the presence of shock, cancer, paralysis, renal or congestive heart failure are significant predictors of mortality or intracranial hemorrhage in patients who underwent CDT due to PE [44]. In addition, in patients with cancer and chronic kidney disease, who underwent CDT for PE, there was a higher incidence of acute renal failure and hemorrhagic complications, including intracranial hemorrhages [45, 46]. Before the start of endovascular therapy in acute PE, comorbidities and other risk factors should be considered until

the results of new prospective comparative studies are obtained regarding the safety and efficacy of a particular CDT method.

Special attention should be paid to considering the relationship between the high volume of interventions performed in a medical institution and the level of favorable outcomes of endovascular therapy [2]. The results of a recent national study in the USA showed that institutions with a higher annual volume of procedures (> 5 procedures per year) had rates of mortality and intracranial hemorrhages in the CDT group comparable to the group of patients who received ACT only [47]. In turn, in the centers with a smaller volume of medical procedures (<5 per year), significantly higher levels of mortality and intracranial bleeding were observed in comparison with the group of anticoagulants alone. These data probably reflect heterogeneity in modern practice in the USA and are due to differences in patient selection and monitoring before and after the procedure. It is extremely necessary to standardize endovascular VTE therapy protocols, as this can improve the results of the technique, especially at institutions that perform a low number of interventions [48].

Conclusion

Along with the conventional methods of acute PE treatment (surgical embolectomy, ACT and systemic thrombolysis), in recent times more attention has been paid to the use of catheter treatment approaches that have a number of advantages. The use of the catheter method allows targeted delivery of a fibrinolytic drug, treatment of a PA thrombus with ultrasound and mechanical devices, and also removing thrombus fragments using various rheolytic and aspiration devices. However, at this stage there is no convincing evidence in favor of the routine use of the described techniques in the treatment of submassive or massive PE. In addition, no device is significantly superior to another, based on available literature data. The lack of a strong evidence base regarding the safety of the interventional approach and its effectiveness in comparison with monotherapy with anticoagulant drugs most likely suggests that the endovascular treatment of PE is still in its infancy. Most patients continue to be treated conservatively, and more aggressive methods are reserved only for cases of high-risk or intermediate-high-risk PE in the absence of contraindications. Obviously, it is necessary to conduct larger studies on the comparative analysis of the use of interventional methods of acute PE treatment in regard to their efficacy and safety. In addition, data are needed on the safety and efficacy of indirect oral anticoagulants and vitamin K antagonists after the thrombus is removed by the catheter method in PE, both in terms of therapeutic advantage and in terms of patient preference. It is necessary to use an extremely individualized approach, including patient selection, the type of therapy, the level of experience of both the operating team and the medical institution, in order to maximize the benefits of the intervention strategy and minimize the risk of harm to the patient.

Conflict of interests

The authors declare no conflict of interests.

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INFLAMMATION ROLE IN FORMATION OF EARLY DISTURBANCES OF A FUNCTIONAL CONDITION OF A LIVER AT COMMUNITY — ACQUIRED PNEUMONIA (LITERATURE REVIEW)

Abstract

Community-acquired pneumonia (CAP) is a topic issue of medicine nowadays due to its high incidence, the severity of its course, the increasing antibiotic resistance, a large number of complications and high mortality rate. Now in the pneumonia pathogenesis the leading role belongs to various changes of metabolism, including the induction of lipid peroxidation and oxidative stress. The importance is attached to the liver function impairment in patients with pneumonia. The pathogenetic mechanisms of this impairment are diverse and include vascular endothelium dysfunction. At the same time, among the therapeutic approaches to normalize the metabolism of body cells, the priority role is given to peroxidation substrates. It is shown that the succinate-containing drugs have various pharmacological effects, generally providing the cytoprotective action that allows considering them the perspective compounds with hepatoprotective activity, which are essential in complex treatment of community-acquired pneumonia (CAP).

Key words: *Community-Acquired Pneumonia (CAP), endothelium dysfunction, liver dysfunction, succinate-containing drugs*

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ATP — adenosine triphosphate; ROS — reactive oxygen species; CAP — community-acquired pneumonia

Today, community-acquired pneumonia (CAP) ranks fourth among causes of death after cardiovascular, cerebrovascular diseases and cancer [3, 25].

Despite the great progress made in understanding the etiology, pathogenesis and treatment of this pathology, there is an increase in the number of patients worldwide, and, consequently, mortality [4, 6]. Specifically, the average annual incidence of community-acquired pneumonia among adults in recent years in Europe was 1.07–1.2 per 1,000 inhabitants per year, and in older age groups it was 14 per 1,000 person-years [9]. Primary morbidity rates in the CIS generally indicate a significant increase in the incidence of respiratory diseases [8]. In the Russian Federation, the primary morbidity of respiratory diseases increased by 1.3% in 2015, accounting for 338 cases per

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1,000 people [7]. It is believed that one of the reasons for the increase in mortality from CAP is the lack of treatment efficacy at early stages of the development of the disease [8].

During the past decades, the so-called "metabolic" trend has been rapidly developing in medicine. Ideas about the role of cellular energy metabolism disorders in a variety of pathological processes are emerging very rapidly [10].

Being the physiological component of the body's response to infectious inflammation, changes in metabolism are pathological in nature, leading to irreversible damage to cellular structures and failure of individual organs and systems. At the same time, biochemical markers of inflammation are often ahead of morphological changes in tissues and therefore can be considered as early criteria for the development and resolution of the pathological process in various diseases [6, 2].

Inflammation that occurs in community-acquired pneumonia, along with hypoxia, is among the most common typical pathological processes [14]. It should be noted that the protective role of inflammation is indisputable. However, this reaction is also of a pathological nature, since the mechanisms of inflammation lead to secondary self-injury of tissues. The severity of inflammation along with other factors determines the severity and prognosis of the disease in CAP [22]. Therefore, CAP is accompanied by a systemic body response to inflammation in the lung tissue, and its components determine the pathogenetic mechanisms of disease development and play an important role in the course of pneumonia [5, 23]. Thus, in particular, under the influence of an infectious agent, free radical oxidation of lipids is activated through a cascade of reactions, which contributes to the development of oxidative stress, accompanied, among other things, by endothelial dysfunction with damage to biological macromolecules and cell membrane structures [1, 16].

A number of authors note that the endothelium is involved not only in the formation of a barrier between the blood and vascular smooth muscle cells, but also provides a dynamic equilibrium of vasoconstrictor and vasodilator factors regulating the processes of hemostasis, affecting vascular permeability and participating in the immune response of the body [30, 33].

To date, there is evidence that the endothelium is a neuroendocrine system that performs secretory, hemostatic, and vasotonic functions, and also participates in the processes of inflammation and remodelling of the vascular wall [23].

Consequently, the endothelium becomes a direct target for damage in inflammatory processes in the body, and endothelial dysfunction can affect damage to the membranes of the cells of internal organs under conditions of oxidative stress [28]. In view of this, in recent years, more attention has been paid to the role of the vascular endothelium in the pathogenesis of community-acquired pneumonia [1].

It has been shown that in patients with CAP, endothelial dysfunction is expressed in an imbalance of opposite vasodilating, vasoconstrictive, anticoagulant and procoagulatory factors [1, 17]. It should be noted that the activation of systemic inflammation and the reaction of the hemostatic system in the pulmonary vessels and tissues are considered important for maintaining activity at the site of an infectious damage, making this relationship necessary in regards to the formation of a pathological barrier between healthy and damaged tissue [27].

At the same time, chronic inflammation leads to structural changes in the vascular endothelium, specifically to enrichment of the basement membrane with sulfated glycosaminoglycans, which makes them similar to the endothelium of lymph node venules, which contribute to a faster release of lymphocytes, and further development of angiogenesis [30]. An increase in inflammatory infiltrate in the lung tissue enhances mechanical compression of arterioles, which ultimately increases the pressure in the pulmonary artery.

Thus, a vicious circle, based on endothelial dysfunction, arises in CAP, the end result of which is oxidative stress, which further leads to the development of respiratory failure, impaired ventilation-perfusion relationships, aggravation of hypoxia and worsening of the disease course [20].

The liver occupies a special place in the development of inflammatory response, as it is the organ that maintains homeostasis of the whole organism, while affecting the development of any given disease [30]. The liver is directly involved in the processes of detoxification and elimination of waste products of infectious agents, is central to

the regulation of the acute phase inflammatory reaction, the metabolism of biologically active and antibacterial substances [7, 35].

Liver tissue damage is based on both tissue hypoxia resulting from impaired oxygen utilization in hepatocytes and the action of toxic substances (drug products), as well as circulatory hypoxia, resulting from local or central hemodynamic disorders (shock, traumatic injuries, liver cirrhosis) [15].

A similar scenario of the development of the pathological process with different initiating agents forms liver diseases that can occur, at a more or less extent, with an acute inflammatory reaction [7].

In addition, the liver takes part in the synthesis of immunity factors that are directly involved in the inactivation of foreign cells and antigens [1]. Thus, Kupffer cells along with hepatocytes produce group E prostaglandins and acute-phase proteins (neutralizing proteases), which are intensively produced during inflammation. The hypothalamic-pituitary-adrenal axis is activated by interacting with a complex cascade of reactions through the secretion of corticotropin-releasing factor, and thereby an inflammatory response is further activated [29].

Intrahepatic hemodynamics disorder in the presence of vascular system remodelling is important in the pathogenesis of liver damage in inflammatory processes in the lungs, which may be associated with damage to the endothelial lining of the hepatic sinusoids and the early development of endothelial dysfunction [32].

According to a number of authors, the interaction of the immune system components with protein and lipid metabolism in the liver plays a certain role in the development of liver dysfunction [7, 23, 29, 31]. Thus, the hepatocytes themselves are damaged with the excessive production of both cytokines and acute-phase proteins, which ultimately leads to changes similar to different forms of hepatitis [20]. The pathogenetic mechanisms of liver damage in CAP (especially chlamydial, legionella and viral etiology) are diverse. They are characterized by hepatomegaly with the development of cytolysis and an inflammatory reaction, with subsequent progression of fibrosis [19].

Liver damage as organ dysfunction in the systemic inflammatory reaction syndrome is observed in 21%, and the incidence of its development in the general population of patients with CAP is 2.7% [4].

As noted above, tissue hypoxia also plays a significant role in the pathogenesis of hepatocyte damage, leading to dysfunction of mitochondria, depletion of adenosine triphosphate (ATP) reserves with activation of free radical processes [15]. Among cell metabolites with oxidative properties, the central role belongs to the reactive oxygen species (ROS). It should be emphasized that ROS perform the most important regulatory and metabolic functions in the body under physiological conditions [25]. However, the uncontrolled generation of ROS with the failure of the protective antioxidant system causes oxidative modification of proteins, nucleic acids, initiates free radical oxidation of lipids in membranes, which leads to membrane-destroying processes [4, 12].

The tissue of both the lungs and the liver has a high metabolic activity and, accordingly, significant energy needs, which determines its high sensitivity to hypoxia [20, 35].

At the same time, the need for correction of the resulting disorders of its functional state is obvious and requires the development of new pathogenetic approaches in complex therapy of CAP. Today the priority role in the implementation of therapeutic approaches to the normalization of the body cell metabolism is given to oxidation substrates, the use of which in a number of diseases marked the beginning of the so-called "metabolic correction" [27].

This circumstance determines the urgency of finding new ways to optimize pathogenetic therapy, including, in particular, the support of not only adequate tissue perfusion and oxygenation, but also cellular metabolism [13]. Thus, it is possible to use drugs that include succinate-containing compounds to correct hypoxia and to normalize the metabolic processes in cells and tissues in critical conditions [9]. The most rapid way of correcting tissue hypoxia is succinate oxidase oxidation, which is achieved by increasing the activity of succinate dehydrogenase and improving the penetration of exogenous succinate into the cell's mitochondria.

The presented drugs have the ability to enhance the therapeutic effect of some medications

(including antibiotics), have antiplatelet effect due to membrane stabilizing effect on blood cells, including platelets, improve blood rheology and hemodynamics, weaken the effect of osmotic shock on the cell, which is associated with the formation of stable complexes with blood albumin and membrane proteins due to strong hydrogen bonds [18, 24].

Experimental models of liver damage have shown that succinate-containing drugs implement antioxidant, membrane stabilizing, antihypoxic and detoxifying pharmacological effects, providing a generally cytoprotective effect, which enables to consider them as promising compositions with hepatoprotective activity, which are obviously necessary in complex therapy of CAP [9].

Thus, early hepatic functional impairment as well as the resulting endothelial dysfunction is currently an important but poorly understood area in the pathogenesis of CAP. We would like to note in the review, that such changes can have a significant impact on the course of CAP. We also tried to substantiate the relevance of new approaches to the correction of systemic disorders arising in CAP.

Conflict of Interests

The authors declare no conflict of interests.

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STUDYING OF COMORBID PATHOLOGY AT THE 2 TYPES DIABETES AS THE COMPLICATION OF THE METABOLIC SYNDROME

Abstract

The objective was to define features of comorbidity in patients with type 2 diabetes, to estimate a possibility of use of comorbidity indices in the management of these patients.

Materials and methods. Patients with type 2 diabetes participated in the study. The retrospective analysis of medical records with calculation of comorbidity indices using CIRS, Kaplan-Feinstein and Charlson systems was made. Taking into account the received indices, prognostic indicators of mortality risk (%) within the next year and 10-year survival were defined. Correlation between laboratory metabolic syndrome parameters and values of comorbidity indices were defined.

Results. It was defined that in structure of comorbidity in studied patients cardiovascular, nervous and genitourinary disorders prevailed. Besides the specified systems, in women the proportion of endocrine pathology was high. With age, there is a tendency to the prevalence of comorbid pathology of these systems, as well as an increase in the average score of the comorbidity indices for all systems and deterioration in prognostic indicators are revealed. Statistically significant direct link between comorbidity indices and certain components of metabolic syndrome, and with the disease duration was also detected.

Key words: *type 2 diabetes, comorbidity, comorbidity indices, metabolic syndrome*

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CI — comorbidity index, MS — metabolic syndrome, DM — diabetes mellitus.

Introduction

The phenomenon of comorbidity is the simultaneous existence of two or more diseases in the patient that are linked by the mechanisms of pathogenesis occurring at the same time or are a complication of an underlying disease or its treatment. The problem of comorbid pathology prevalence among patients is becoming increasingly important. This is due to the fact that in conditions of comorbidity, many diseases acquire an atypical course, and the risk of complications increases; the problem of polypragmasia is aggravated, and the patients' adherence to treatment decreases. This ultimately leads to difficulties in the diagnosis and management of these patients. This problem is of particular importance in the primary health care sector due to the predominance of elderly patients. Geriatric patients usually have a particularly high level of comorbidity [1, 2].

Within comorbidity, type 2 diabetes mellitus (T2DM) is one of the most important non-infectious

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diseases due to the large variety of comorbid pathology in such patients, very high incidence, and steady increase in the number of patients [3]. According to forecasts by the International Diabetes Federation, the number of patients with diabetes mellitus will exceed 642 million people by 2040, while maintaining the current rate of increase in morbidity [4]. This is due to the increasing age of the population, increasing urbanization, increasing prevalence of inactivity, unhealthy diet and other risk factors. Thus, the prevalence of metabolic syndrome (MS) according to modern data is 2 times higher than the prevalence of DM, and in the next 25 years it is expected to increase its growth rate by 50% [5]. The presence of metabolic syndrome in patients leads to pronounced changes in metabolism, which subsequently may affect the development of type 2 diabetes, hypertension, atherosclerosis of blood vessels and other diseases [6]. All this determines the prerequisites for the emergence of a high level of comorbid pathology in these patients. The study of comorbidity structure in patients with type 2 diabetes is of great importance. Awareness of prevalence of certain system pathology and individual nosological forms in patients of different gender and age can contribute to the improvement of diagnosis and rational choice of therapy. The use of comorbidity index (CI) calculation systems in patients with type 2 diabetes mellitus makes it easier to assess the level of comorbidity among gender and age groups, to assess prognostic indicators of the risk of death and ten-year survival of patients and, if necessary, to change the treatment strategy [7, 8].

The aim was to study the features of comorbid pathology in patients with type 2 diabetes mellitus. The objectives of the study included the determination of comorbidity structure in patients with type 2 diabetes mellitus; calculation of comorbidity indices in patients with type 2 diabetes mellitus using CIRS, Kaplan-Feinstein, Charlson systems, and their comparison; identification of prognostic indicators of mortality in the next year, and the value of the 10-year survival in selected patients; detection of the individual components of the metabolic syndrome and the duration of the disease effect on the level of comorbidity in patients with type 2 diabetes mellitus.

Materials and methods

The study was conducted at the Federal State Budgetary Institution of Higher Education Voronezh State Medical University named after N.N. Burdenko, Department of Outpatient Treatment and General Practice; the 6th building of Budgetary Healthcare Institution of Voronezh Oblast Voronezh City Emergency Clinical Hospital No. 10. A retrospective analysis was performed with 70 medical records of outpatients with type 2 diabetes mellitus (mean age of 65.82 ± 9.24 years), including 38 women (mean age of 66.34±8.53 years) and 32 men (mean age of 65.24±9.3 years). Four groups were formed on the onset of old age (60 years) to study the gender and age aspects.

For the calculation of the comorbidity index CIRS, Kaplan-Feinstein, Charlson systems were used. Prognostic indicators of mortality risk during the year and 10-year survival were determined by the Charlson calculation system.

Statistical data processing was performed using Microsoft Excel 2010 and Statistica 20.0 software and using the Kruskal–Wallis H–test. The Kruskal–Wallis H–test is a generalization of the Mann–Whitney test in the case for more than two independent samples. The test does not require the hypothesis of a normal distribution. The null hypothesis H_0 means that only random differences exist between the samples. The alternative hypothesis H_1 means that the differences in the studied parameter that exist between the samples are not random. The differences were considered significant at $p \leq 0.05$. The evaluation of the close relationship between the signs was made using the Spearman's rank correlation coefficient: the coefficient <0.3 was considered to be an indicator of a very weak relationship; 0.3–0.5 — weak; 0.5–0.7 — medium and ≥0.7 — strong.

Results

At the first stage of the study, the overall comorbidity structure among the selected patients was determined (Figure 1).

It was found that in the overall structure of comorbidity pathology of the central and peripheral nervous system (95%) is in the first place, cardiovascular

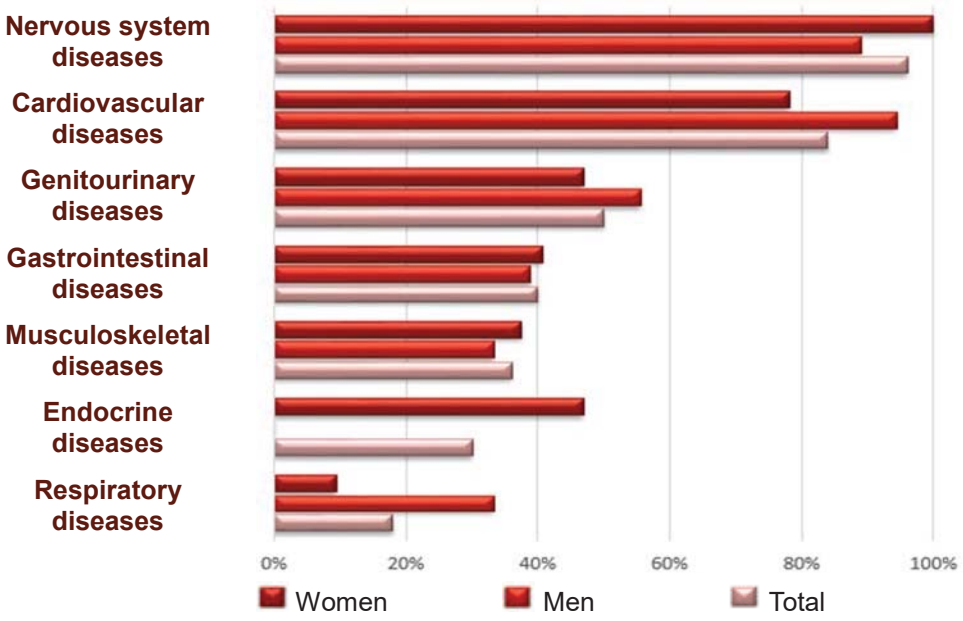

Figure 1. *Structure of comorbid pathology: gender-based and in total*

diseases (86%) — in the second, genitourinary diseases (54%) — in the third place.

In determining comorbidity structure depending on gender, the following data were obtained: In men, the most common pathology are cardiovascular diseases (97%), in the second place — pathology of the nervous system (88%), and in the third one — pathology of the genitourinary system (56%). In women, the pathology of the nervous system prevails (100%), diseases of the cardiovascular system are in second place (80%), and diseases of the genitourinary system and endocrine system are in third place (48%). A greater proportion of endocrine pathology in women may be associated with hormonal imbalance that occurs in the menopausal and postmenopausal period.

The structure of comorbidity in the studied age groups is shown in Figures 2, 3.

In the study of age groups, it was found that in the group of men at the age of 60 years (56-60 years) cardiovascular diseases (89%), pathology of nervous system (81%) and genitourinary diseases (45%) also prevail. In men aged over 60 (60–75 years), cardiovascular diseases (100%) and diseases of the nervous system (100%) come to the fore. In the age groups among women (57-60 years and 60–74 years) pathology of the nervous system (100% in both groups), cardiovascular diseases (63% and 85% respectively, in groups), urogenital and endocrine system pathology (50% and 46%) also prevail.

Among the pathology of the cardiovascular system in the studied patients the following nosological forms were identified: hypertensive heart disease (I11.0, I11.9) — in 95% of patients, ischemic heart disease (I20.8, I25.1) — in 57%, cardiac arrhythmias (I48.0, I48.1, I48.2) — in 21.4%, varicose veins of lower extremities (I83.9) — in 16.7%, which in men were with more severe course compared to women, with a history of myocardial infarction (I25.2) and cerebrovascular accident (I61.2, I63). Among the diseases of the nervous system, diabetic polyneuropathy (G63.2, in 89.6% of patients), cerebrovascular disease (I67.9, in 64.6%) and degenerative spine disease (M42.1, in 39.6%) occupy leading positions in men and women. The pathology of the genitourinary system in the studied patients includes: chronic pyelonephritis (N10) — in 40% of patients, chronic prostatitis (N41.1) and BPH (N40) — in 36% and 32%, respectively, urolithiasis (N20, N21) — in 20%, and chronic cystitis (N30.1) — in 12%. Comorbid pathology of the endocrine system was detected only in women, and it is represented by mastopathy (N60.1) — in 80% of the subjects, thyroid diseases (E04.1, E04.2, E06.3) — in 53.3%.

At the next stage in the selected patients, mean CI values using CIRS, Kaplan-Feinstein, Charlson systems were calculated and prognostic indicators of the death risk were determined in the next year and 10-year survival (Table 1, 2).

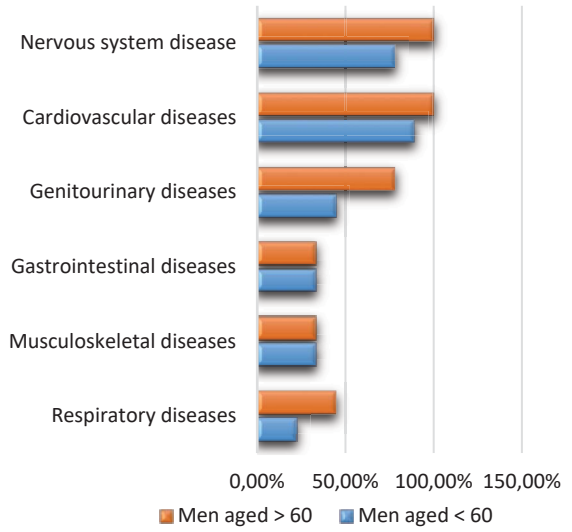

Figure 2. *Structure of comorbid pathology in age group, men*

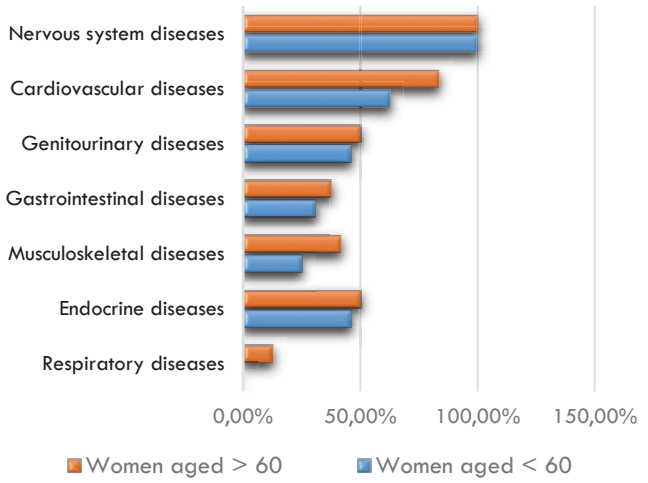

Figure 3. *Structure of comorbid pathology in age groups, women*

Table 1. *Mean comorbidity indices in subjects of different gender and age groups*

Index / Study group	CIRS, mean score	Kaplan-Feinstein, mean score	Charlson, mean score
All studied	13.14+3.54	9.77+2.67	6.54+2.32
Men	11+3.64	8.23+2.56	6.45+2.08
including:			
Men up to 60 years (inclusive)	8.48+2.54	7.56+2.54	4.6+1.75
Men older than 60 years	14.0+2.53	10.1+0.5	8.1+1.23
Women	12.6+3.21	10.5+3.2	6.7+2.45
including:			
women up to 60 years (inclusive)	9.2+1.34	7.5+1.3	4.5+1.2
Women older than 60 years	14.4+3.7	11.9+2.56	7.7+1.9

Table 2. *Prognostic indicators in subjects of different gender and age groups*

Group / Parameter	All studied	Men including:	Men up to 60 years (inclusive)	Men older than 60 years	Women including:	women up to 60 years (inclusive)	Women older than 60 years
Mortality risk:							
85%	76%	66.7%	33.3%	100%	81.25%	25%	100%
52%	24%	33.3%	66.7%	0%	18.75%	75%	0%
10-year survival:							
21% and below	76%	66.7%	33.3%	100%	81.25%	25%	100%
53%	18%	27.7%	55.6%	0%	12.5%	50%	0%
77%	6%	5.5%	11.1%	0%	6.25%	25%	0%

Table 3. *Frequency of metabolic syndrome components occurrence in studied patients*

MS component	Incidence, absolute	Incidence, relative
Carbohydrate metabolism disorder	70	100%
Lipid metabolism disorder	65	93%
Obesity	70	100%
Hypertension	68	97%

Table 4. *Mean values of metabolic syndrome components in patients*

Component of metabolic syndrome	Glucose at the time of the first visit	Glucose at the time of the last visit	Total cholesterol at the time of the last visit	Waist size at the time of the first visit	Body mass index at the time of the first visit	Systolic BP
Mean value	9.51+1.34 mmol/l	7.93+0.88 mmol/l	6.43+0.96 mmol/l	103.16+8.41 cm	34.04+4.89 kg/m²	165±5.28 mm Hg

It was found that the mean CI values across all systems tend to increase with age, both in men and women. The highest mean values of CI were observed in the group of women aged over 60 years. A large percentage (76%) of the studied patients have a very high risk of mortality during the year (85%) and low (21% and below) 10-year survival rate. In patients aged over 60 years, these prognostic parameters were observed in 100% of cases.

Further, the influence of individual components of the metabolic syndrome on comorbidity rate was analyzed.

Incidence and mean values of these components in patients are presented in Tables 3 and 4.

The following data were obtained during Spearman correlation analysis: significant strong positive correlation (r=0.83, p≤0.05) was found between blood glucose recorded at the time of the first visit and CI by Charlson. The same relationship was found between blood glucose at the time of the last visit and CI using CIRS system (r=0.74, p≤0.05) and using Kaplan-Feinstein and Charlson systems — a significant positive correlation of moderate strength (r=0.71 and r=0.68 respectively, p≤0.05). When studying the effect of total blood cholesterol at the time of the last visit on the comorbidity rate of patients, a significant strong positive relationship was revealed (r=0.82, r=0.75, r=0.70 respectively, by systems; p≤0.05). The analysis also established a strong significant positive relationship between the body mass indices determined during the first visit and mean CI values using Charlson system (r=0.78; p≤0.05). The same strong significant positive correlation was found between the waist size in the patient at the time of the first visit and mean CI values using Charlson system (r=0.74, p≤0.05). The data obtained allow us to conclude that the studied components of the metabolic syndrome directly affect the prevalence of comorbid pathology in patients with type 2 DM.

At the next stage the influence of the duration of type 2 diabetes on the comorbidity level was analyzed. Mean duration of the disease in the studied patients was 9.8+5.6 years. There was a significant strong positive relationship between the duration of the disease and CI using all systems (r=0.91, r=0.79, r=0.78 respectively, by systems; p≤0.05), a significant positive relationship of moderate strength between the duration of the disease and the risk of mortality within the next year (r=0.65; p≤0.05); a significant negative relationship of moderate strength between the duration of the disease and the 10-year survival of patients(r=-0.61; p≤, 05). The data obtained allow us to conclude that the duration of the disease directly affects the comorbidity rate and prognosis of patients with type 2 diabetes.

Conclusions

1. In the general structure of comorbidity in patients with type 2 diabetes mellitus, diseases of the central and peripheral nervous system, cardiovascular and genitourinary systems prevail; in the structure of comorbid pathology in men, pathology of the cardiovascular system prevails; in women, pathology of the nervous system prevails, and the proportion of endocrine pathology not detected in men is also high; with aging in men and women, the overall structure of comorbid pathology remains the same, and in men over 60 years, the pathology of the nervous system also comes to the fore.
2. With aging, patients with type 2 diabetes mellitus have an increase in the mean CI score determined by CIRS, Kaplan-Feinstein, Charlson systems and accordingly an increase in comorbidity rate.
3. In 76% of the studied patients there are unfavorable prognostic indicators of death risk within the next year and 10-year survival which were detected in 100% of cases in age groups older than 60 years.
4. Components of the metabolic syndrome have a direct impact on the rate of comorbid pathology in patients with type 2 diabetes.
5. With an increase in disease duration there is an increase in mean CI values using CIRS, Kaplan-Feinstein, Charlson systems; and the percentage of death risk increases and 10-year survival decreases.

Conflict of interests

The authors declare no conflict of interests.

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CLINICAL AND PROGNOSTIC VALUE OF HYPONATREMIA IN PATIENTS WITH CHRONIC HEART FAILURE

Abstract

The objective was to assess the short-term prognostic value of different types of hyponatremia in patients hospitalized due to acute decompensated chronic heart failure. **Material and Methods:** A prospective study included 396 patients hospitalized due to acute decompensated chronic heart failure. Hyponatremia was diagnosed in cases of serum sodium level of less than 135 mmol/l. The pre-hospital hyponatremia was defined as a decreased serum sodium level on admission, whereas the hospital hyponatremia was referred to cases occurred during hospitalization. In patients with pre-hospital hyponatremia the reduction of sodium levels by ≥ 3 mmol/l during hospitalization was defined as a progressive hyponatraemia. The influence of different types of hyponatremia on the hospital prognosis was determined, while the combined primary endpoint was all-cause mortality and/or transfer to the intensive care unit. **Results:** Patients with hyponatremia were older and had more severe clinical signs of chronic heart failure, lower left ventricle ejection fraction and more pronounced diastolic dysfunction than normonatremic patients. After adjustment for age, comorbidity and severity of chronic heart failure, the Cox regression showed that hyponatremia was an independent predictor of all-cause mortality and transfer to the intensive care unit (odds ratio 3.1; $p < 0.05$). Pre-hospital hyponatremia had a higher prognostic value for outcome compared with hospital hyponatremia (odds ratio 3.9 versus 2.9, respectively; $p < 0.05$). Progressive hyponatremia was associated with a marked increase of mortality and transfer to the intensive care unit (odds ratio 6.8; $p < 0.05$). **Conclusion:** Pre-hospital and hospital hyponatremia are independent predictors for short-term outcomes in patients hospitalized due to acute decompensated chronic heart failure. Progression of the pre-hospital hyponatremia is associated with significant increase of all-cause mortality and risk of transfer to the intensive care unit.

Key words: *hyponatremia, chronic heart failure, decompensation, severity of the disease, prognosis, mortality*

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CI — confidence interval, OR — odds ratio, FC — functional class, CHF — chronic heart failure

The attention of various clinical specialists is currently focused on the problem of electrolyte metabolism disorders in hospitalized patients. The most common electrolyte abnormality among patients hospitalized for any reason is hyponatremia [1]. It accompanies the course of a number of diseases and is associated with prolonged hospitalization, high costs of treatment and worsening of prognosis [2-4].

Among patients hospitalized with decompensated chronic heart failure (CHF) hyponatremia on admission to hospital is detected in 5-35% of cases [5-8], while its prevalence depends on the patient population and the timing of determining sodium

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level in the blood. In most studies devoted to this issue, the prevalence and prognostic significance of reduced blood sodium levels recorded on admission to hospital [9-13] were studied. At the same time, the incidence and clinical significance of hyponatremia developing during hospitalization have not been studied. However, the normal sodium level in a single measurement in the first days of hospitalization does not exclude the possibility of its further reduction against the background of the natural course of the disease and active diuretic therapy. In addition, the rate of prehospital hyponatremia progression during hospitalization also remains unexplored.

In this regard, the aim of our study was to assess the clinical and prognostic significance of different types of hyponatremia in patients hospitalized due to decompensation of CHF.

Materials and Methods

The authors performed a prospective study involving 396 patients hospitalized in the V.K. Gusak Institute of Urgent and Reconstructive Surgery due to decompensation of CHF for the period 2013-2016. Inclusion criteria in the study were as follows: age over 18 years, hospitalization due to decompensation of CHF and signed informed consent.

The exclusion criteria were as follows: acute coronary syndrome, valvular and septal heart defects, myocarditis, hypertrophic and dilated cardiomyopathy, other conditions associated with hyponatremia (burn disease; acute gastrointestinal disorders; liver cirrhosis; nephrotic syndrome, glomerular filtration rate of <15 ml/min, adrenal insufficiency, acute hypovolemia), decompensation of concomitant disease, pregnancy, cancer, alcohol and drug abuse, participation in another clinical study during the previous 30 days.

The serum sodium level was determined in all patients on admission to hospital and during the hospital treatment period. The study was performed using ion-selective electrodes on an automatic biochemical analyzer Cobas C 311 (Roche Diagnostics, Germany). The electrolyte concentration was expressed in mmol/L. Hyponatremia was diagnosed with a decrease in serum sodium level of <135 mmol/l. The severity of hyponatremia was assessed in accordance with generally accepted recommendations: with sodium levels of 130-134 mmol/l hyponatremia was regarded as mild, with 125-129 mmol/l as moderate, and with <125 mmol/l as severe [14-16]. Hyponatremia was considered as prehospital when detected on admission, as hospital when it developed during inpatient treatment. In order to assess the period of development of hospital hyponatremia, the examination of electrolyte levels was carried out every 3 days. The change of the sodium level during hospitalization was also analyzed in patients with prehospital hyponatremia, while in the case of reduction of sodium levels by ≥ 3 mmol/l from baseline, progressive hyponatremia was diagnosed.

The effect of different types of hyponatremia on the course and hospital prognosis of CHF was determined, with the primary end point of the study being the combined indicator of death and/or transfer to the intensive care unit.

The clinical status of patients was assessed using the clinical assessment scale of CHF in the modification by V.Yu. Mareyev. To objectify the clinical and functional state of the patient and determine their tolerance to physical activity, a 6-minute walk test was performed.

The patients included in the study received medical therapy in accordance with modern standards of treatment [17-19] and followed a diet with restricted water and salt consumption [20, 21]. During the period of active diuretic therapy patients were recommended moderate restriction of sodium consumption with food (<3 g/day) after compensation of the condition — according to the functional class (FC) of CHF. In case of CHF of I FC, patients were advised not to eat salty food (sodium consumption restriction to 3 g/day), in case of II FC, patients were recommended not to add salt to food (sodium consumption restriction to 1.5–2 g/day), in case of III–IV FC, patients were asked to use products with low salt content and prepare meals without salt (sodium consumption restriction to 1 g/day). During active diuretic treatment, patients were prescribed to limit fluid intake to 1.5 L/day, and less than 2 L/day after complete compensation of CHF.

The results were processed on a personal computer using biomedical data statistical analysis packages MedStat and Microsoft Office Excel 2007.

The χ^2 and Shapiro-Wilk W tests were used to check the distribution for normality. For normal distribution, the data were given as mean ± standard deviation (m ± σ) for continuous variables and as a particle (percentage) for categorical variables. In a distribution other than normal one, the data were given as median and interquartile ranges (Me (Q1; Q3)). To compare two samples of continuous variables, which are subject to the normal distribution rule, we used paired and unpaired Student's t-test, and Wilcoxon test in the case of distribution other than normal distribution rule. To compare more than two samples subject to the normal distribution rule, a one-way analysis of variance was used, and in the presence of a statistically significant difference between the groups, a pairwise comparison using the Scheffe test was used, and the Dunnett's test with the control group. If the distribution rule differed from the normal distribution rule, one-way Kruskal-Wallis analysis of variance by ranks was performed, and a comparison was made using Dunn's test if there was a statistically significant difference between the groups. We used a standard method of analysis of contingency tables using the χ^2 test to study the distribution of discrete features in different groups and to compare relative values. Multivariate logistic regression analysis with odds ratio (OR) and 95% confidence interval (CI) was used to study the relationship between the features. The critical level of significance for statistical hypothesis testing was assumed to be 0.05.

Results

Patients with hyponatremia were significantly ($p < 0.05$) older than those with normal sodium levels, among them patients were more likely to have anemia, concomitant chronic obstructive pulmonary disease, type 2 diabetes and renal dysfunction. There were no significant differences in body mass index, prevalence of concomitant hypertension, atrial fibrillation, and myocardial infarction between the groups (Table 1).

Patients with hyponatremia had more pronounced clinical signs of CHF (Table 2). According to echocardiography, they had a smaller ejection fraction and more pronounced diastolic dysfunction of the left ventricle compared to normonatremic patients.

Analysis of drug therapy (Table 3) showed that patients with hyponatremia were more likely to receive thiazide and thiazide-like diuretics compared to patients with normonatremia. In the group with hospital hyponatremia, in addition, the rate of administration of mineralocorticoid receptor antagonists was higher than in other groups of patients.

A detailed analysis of diuretic therapy during the active phase revealed differences in drug doses: patients with hyponatremia were prescribed higher doses of hydrochlorothiazide, indapamide and spironolactone compared with patients with normal sodium levels. The highest doses of spironolactone were taken by patients with hyponatremia which developed during hospitalization (Table 4).

The rate of development for combined primary end-point of death and/or transfer to the intensive care unit and its individual components was analyzed (Table 5) to assess the impact of different types of hyponatremia on the course and hospital prognosis of the disease. Adverse outcomes more often developed in patients with hyponatremia, and the period of their stay in hospital was longer compared with persons with normal blood sodium level.

The reasons for the transfer to the intensive care unit were analyzed, while the main reason was selected as the analysed one in the presence of several indications for transfer (Table 6). It was found that patients with hyponatremia compared with patients with normal sodium levels during hospitalization more often experienced hypotension or hypoperfusion of organs requiring treatment in the intensive care unit. Among individuals with pre-hospital hyponatremia, the emergence of resistance to diuretics was more often observed.

According to the results of pathoanatomical studies, cardiovascular diseases dominated in the structure of hospital mortality in both groups of patients, and cardiovascular mortality was higher among patients with hyponatremia. Persons with reduced sodium levels died more often than patients with normal electrolyte levels due to progression of heart failure, and statistical significance of differences was achieved due to a subgroup of patients with prehospital progressive hyponatremia. It is noteworthy that mortality against the backdrop of worsening symptoms of CHF decompensation

Table 1. *Initial clinical characteristics of patients*

Parameter	Prehospital hyponatremia (n=64)	Hospital hyponatremia (n=68)	Normo-natremia (n=264)
Age, years, Me (Q1; Q3)	69 (65; 73.5)*	70 (66; 74.5)*	64 (61; 66.5)
Male, number of patients (%)	38 (59.4%)	49 (72.1%)	157 (59.5%)
BMI, kg/m^2, m±σ	31.4±2.9	30.8±3.1	29.6±2.8
SBP, mmHg, m±σ	119.3±3.6*	118.2±2.9*	132.3±3.7
DBP, mmHg, m±σ	74.2±3.1	70.6±1.9*	76.2±3.9
HR at rest, bpm, Me (Q1; Q3)	88 (80; 94)	85 (79; 93)	86 (78; 96)
Hypertension, number of patients (%)	56 (87.5%)	62 (91.2%)	236 (89.4%)
Myocardial infarction, number of patients (%)	48 (75.0%)	49 (72.1%)	164 (62.1%)
Atrial fibrillation, number of patients (%)	19 (29.7%)	21 (30.9%)	49 (18.6%)
Stroke, number of patients (%)	8 (12.5%)	9 (13.2%)	31 (11.7%)
Chronic obstructive pulmonary disease, number of patients (%)	21 (32.8%)*	28 (41.2%)*	41 (15.5%)
Diabetes mellitus, number of patients (%)	24 (37.5%)*	24 (35.3%)*	49 (18.6%)
Anemia, number of patients (%)	17 (26.6%)*	19 (27.9%)*	40 (15.2%)
Glomerular filtration rate, ml/min, m±σ	42.3±7.4*	44.8±6.4*	58.3±6.5
Serum sodium level on admission, mmol/l, m±σ	132.5 (132; 133.5)*	136.5 (136; 137.5)*	139.5 (138; 142.5)

Note: BMI — body mass index, DBP — diastolic blood pressure, HR — heart rate, SBP — systolic blood pressure; * — differences are significant (p<0.05) compared to patients with normonatremia

Table 2. *The severity of CHF (m ± σ, Me (Q1; Q3))*

Parameter	Prehospital hyponatremia (n=64)	Hospital hyponatremia (n=68)	Normo-natremia (n=264)
NYHA class	IV (III; IV)*	IV (III; IV)*	III (III; IV)*
Signs of fluid retention in two circles of blood circulation, number of patients (%)	56 (87.5%)*	61 (89.7%)*	183 (69.3%)
Anasarca, number of patients (%)	13 (20.3%)	17 (25.0%)	29 (11.0%)
6-minute walk test distance, m, m±σ (n=286)	154.5±9.1*	168.4±11.3*	205.6±13.2
Clinical Assessment Scale of CHF (V. Yu. Mareyev), points, Me (Q1; Q3)	9 (8; 10)*	10 (8; 11)*	7 (6; 8)
Left ventricular ejection fraction, %, m±σ	41.6±6.9*	43.8±7.1*	49.6±7.8
E/e, m±σ	17.8±6.8*	18.4±7.9*	15.6±5.3

Note: * — differences are significant (p<0.05) compared to patients with normonatremia

Table 3. *Hospital medical therapy (number of patients, %)*

Group of drugs	Prehospital hyponatremia (n=64)	Hospital hyponatremia (n=68)	Normo-natremia (n=264)
ACE inhibitors	54 (84.4%)	53 (77.9%)	221 (83.7%)
ARBs	10 (15.6%)	15 (22.1%)	38 (14.4%)
β-blockers	56 (87.5%)	59 (86.8%)	238 (90.2%)
Loop diuretics	64 (100.0%)	68 (100.0%)	264 (100.0%)
MCR antagonists	54 (84.4%)	66 (97.1%)#*	202 (76.5%)
Thiazide and thiazide-like diuretics	19 (29.7%)*	28 (41.2%)*	42 (15.9%)

Note: ACE — angiotensin converting enzyme, ARBs — angiotensin-2 receptor ablockers, MCR — mineralocorticoid receptors; * — differences are significant (p<0.05) compared to patients with normonatremia; # — differences are significant (p<0.05) compared to patients with prehospital hyponatremia

Table 4. *Types and daily average doses of diuretics in the period of active diuretic therapy*

Group of drugs	Prehospital hyponatremia (n=64)	Hospital hyponatremia (n=68)	Normo-natremia (n=264)
Loop diuretics:			
Furosemide, number of patients (%)	52 (81.3%)	46 (67.7%)	194 (73.5%)
Torasemide, number of patients (%)	12 (18.8%)	22 (32.4%)	70 (26.5%)
Average daily dose (in terms of furosemide), mg, (Me (Q1; Q3))	80 (60; 120)	80 (80; 120)	80 (60; 120)
Thiazide diuretics (hydrochlorothiazide):			
Number of patients (%)	11 (17.2%)	27 (39.7%)*	29 (11.0%)
average daily dose, mg, (Me (Q1; Q3))	25 (12.5; 25)*	25 (12.5; 25)*	12.5 (12.5; 25)
Thiazide-like diuretics (indapamide):			
Number of patients (%)	8 (12.5%)	11 (16.2%)*	13 (4.9%)
average daily dose, mg (Me (Q1; Q3))	1.25 (1.25; 1.5)*	1.25 (1.25; 1.5)*	0.625 (0.625; 1.25)
Mineralocorticoid receptor antagonists:			
Spironolactone, number of patients (%)	51 (79.7%)	62 (93.9%)*#	188 (71.2%)
Spironolactone, average daily dose, mg (Me (Q1; Q3))	100 (75; 100)*	150 (100; 150)*#	75 (50; 100)
Eplerenone, number of patients (%)	3 (4.7%)	4 (5.9%)	14 (5.3%)
Eplerenone, average daily dose, mg (Me (Q1; Q3))	25 (25; 25)	25 (25; 25)	25 (25; 25)

Note: * — differences are significant (p<0.05) compared to patients with normonatremia; # — differences are significant (p<0.05) compared to patients with prehospital hyponatremia

Table 5. *Primary endpoint and duration of hospitalization*

Group of patients	Parameter			
	The combined primary endpoint, number of patients (%)	Hospital mortality, number of patients (%)	Transfer to intensive care unit, number of patients (%)	Duration of hospitalization, days, m±σ
Hyponatremia, all types (n=132)	38 (28.8%)*	16 (12.1%)*	22 (16.7%)*	19.6±3.8*
Prehospital hyponatremia, all types (n=64)	20 (31.3%)*	9 (14.1%)*	11 (17.2%)*	18.2±3.7*
Prehospital non-progressive hyponatremia (n=48)	12 (25%)*	3 (6.3%)	6 (12.5%)	17.9 ± 2.9
Prehospital progressive hyponatremia (n=16)	8 (50%)*	6 (37.5%)*	5 (31.3%)*	19.8±4.0*
Hospital hyponatremia (n=68)	18 (26.5%)*	7 (10.3%)	11 (16.2%)*	19.2±3.5*
Normonatremia (n=264)	27 (10.2%)	14 (5.3%)	13 (4.9)	16.2±3.2

Note: * — differences are significant (p<0.05) compared to patients with normonatremia

Table 6. *Reasons for the transfer of patients to the intensive care unit, number of patients (%)*

Group of patients	Reasons				
	Hypotension / hypoperfusion of organs	Pulmonary edema	Diuretic resistance	Arrhythmias	Other reasons
Hyponatremia, all types (n=132)	7 (5.3%)*	5 (3.8%)	6 (4.5%)	2 (1.5%)	2 (1.5%)
Prehospital hyponatremia, all types (n=64)	3 (4.7%)	3 (4.7%)	4 (6.3%)*	-	1 (1.6%)
Prehospital non-progressive hyponatremia (n=48)	2 (4.2%)	1 (2.1%)	2 (4.2%)	-	1 (2.1%)
Prehospital progressive hyponatremia (n=16)	1 (6.3%)	1 (6.3%)	3 (18.8%)*	-	-
Hospital hyponatremia (n=68)	1 (1.5%)	3 (4.4%)	4 (5.9%)	1 (1.5%)	2 (2.9%)
Normonatremia (n=264)	2 (0.8%)	2 (0.8%)	3 (1.1%)	2 (0.8%)	4 (1.5%)

Note: * — differences are significant (p<0.05) compared to patients with normonatremia

Table 7. *Structure of hospital mortality, number of patients (%)*

Group of patients	Reasons of death								
	Cardiovascular death	Heart failure	Thrombosis and thromboembolism	Myocardial infarction	Stroke	Other cardiovascular causes	Not cardiovascular death	Pneumonia	Other reasons
Hyponatremia, all types (n=132)	12 (9.1%)*	8 (6.1%)*	3 (2.3%)	1 (0.8%)	-		4 (3.0%)	3 (2.3%)	1 (0.8%)
Prehospital hyponatremia, all types (n=64)	7 (10.9%)*	5 (7.8%)*	1 (1.6%)	-	1 (1.6%)		2 (3.1%)	1 (1.6%)	1 (1.6%)
Prehospital non-progressive hyponatremia (n=48)	3 (6.3%)	2 (4.2%)			1 (2.1%)				
Prehospital progressive hyponatremia (n=16)	5 (31.3%)*	5 (31.3%)*#	-	-	-		1 (6.3%)	1 (6.3%)	
Hospital hyponatremia (n=68)	5 (7.4%)	2 (2.9%)	1 (1.5%)	1 (1.5%)	-	1 (1.5%)	2 (2.9%)	1 (1.5%)	1 (1.5%)
Normonatremia (n=264)	9 (3.4%)	4 (1.5%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	5 (1.9%)	3 (1.1%)	2 (0.8%)

Note: * — differences are significant (p <0.05) compared to patients with normonatremia, # — differences are significant (p <0.05) compared to patients with hospital hyponatremia

Table 8. *Relation of different types of hyponatremia with the outcomes*

Group of patients	Endpoints					
	Combined primary endpoint		Hospital mortality		Transfer to the intensive care unit	
	OR	95% CI	OR	95% CI	OR	95% /CI
Hyponatremia, all types (n=132)	3.1*	2.0-6.6	2.2*	1.2-4.9	2.6*	1.7-6.4
Prehospital hyponatremia, all types (n=64)	3.9*	2.1-8.2	2.6*	1.1-6.1	3.6*	1.3-8.1
Prehospital non-progressive hyponatremia (n=48)	2.6*	1.2-6.1	1.1	0.3-3.9	1.8	0.9-8.2
Prehospital progressive hyponatremia (n=16)	6.8*	2.8-23.1	8.7*	5.4-31.2	6.3*	2.3-25.0
Hospital hyponatremia (n=68)	2.9*	1.2-5.2	1.9	0.9-4.3	2.6*	1.4-6.5

Note: OR — odds ratio, CI — confidence interval, * — p < 0.05

among this cohort of patients was several times higher than in the subgroups of patients with hospital and prehospital non-progressive hyponatremia and reached 31.3% (Table 7).

Age-, comorbidity- and CHF severity-adjusted regression analysis showed that the presence of hyponatremia was associated with a significant increase in the risk of death and transfer to the intensive care unit (Table 8). In this case, prehospital hyponatremia had a greater prognostic value in relation to unfavorable outcome compared to the hospital one. It is noteworthy that the progression of hyponatremia which existed at admission significantly increased the risk of the end point achievement. At the same time, in-hospital non-progressive hyponatremia retained its influence in the multivariate model only on the risk of developing a combined end point, while its prognostic value for individual components of the latter did not reach statistical significance.

Discussion

The results of the study confirm the literature data that hyponatremia is a common disorder of the water-electrolyte balance in patients hospitalized for decompensated CHF. According to our data, in general, its rate reached 33.3%, while 48.5% of patients had it at the prehospital stage and 51.5% during treatment in the Department. Hospital hyponatremia developed on average by the end of the first week of hospital stay. Interestingly, at the time of discharge, spontaneous normalization of sodium levels occurred only in 7.8% of patients, and on the contrary, there was a progression of hyponatremia in 25% of patients. In the vast majority of cases, patients with decompensated CHF experienced mild hyponatremia, while the incidence of moderate and severe hyponatremia was low (84.8% and 4.6%, respectively).

It is believed that a decrease in blood sodium level in CHF is a variant of hypervolemic hypernatremia and is caused mainly by a violation of water excretion by the body [22, 23]. In this case, the pathophysiological basis for the development of hyponatremias is excessive neurohumoral activation in conditions of reduction of cardiac output. Despite the absolute excess of water in the extracellular space of the body in decompensated CHF, the effective volume of circulating blood remains low, which promotes non-osmotic stimulation of antidiuretic hormone secretion and the effectors of the renin-angiotensin-aldosterone system through the system of baroreceptors. Such neurohumoral activation is compensatory in nature and is aimed at normalization of perfusion pressure by limiting the excretion of sodium and water. The release of antidiuretic hormone directly increases the reabsorption of water in the collecting tubules of the kidneys, while angiotensin-2 and noradrenaline limit the delivery of water to the kidneys by reducing their perfusion and therefore contribute to the reduction of its excretion [24]. In addition, the decrease in cardiac output and a high level of angiotensin-2 are potent stimuli of thirst, which leads to an increase in water consumption.

The degree of neurohumoral activation in CHF, and therefore the risk of hyponatremia usually correlate with the severity of cardiac dysfunction, as confirmed in our study. Indeed, patients with hyponatremia had more severe clinical (FC by NYHA, the severity of congestion, distance in 6-minute walk test) and echocardiographic (the degree of systolic and diastolic dysfunction) signs of CHF compared with patients with normal blood sodium level.

It can not be excluded that active diuretic therapy has a certain contribution to the development of hospital hyponatremia. Thus, according to the results of our study, patients with hyponatremia significantly more often and in higher doses received thiazide, thiazide-like diuretics and spironolactone. It is noteworthy that the highest doses of spironolactone were taken by patients with hyponatremia which developed during hospitalization. Of course, providing adequate sodium consumption and diuresis is an important factor in the prevention of symptoms of decompensated CHF, and a necessary condition for their elimination in the development of hypervolemia signs. However, it is worth remembering that the use of diuretic therapy may be accompanied by the development of adverse side effects, among which the leading position is occupied by various electrolyte disorders including hyponatremia. According to literature, hyponatremia is most often observed with the use of thiazide and thiazide-like diuretics, and more rarely with loop and potassium-sparing diuretics [22].

Thiazide diuretics have a mixed mechanism of hyponatremic action: they enhance the effect of antidiuretic hormone at the level of collecting tubules and at the same time stimulate natriuresis. The development of hyponatremia when using spironolactone, in addition to the natriuretic effect of the drug, is associated with its ability to block the release of sodium from the cell, which leads to an increase in the intracellular electrolyte content and a decrease in its blood concentration.

Thus, active diuretic therapy in patients with decompensated CHF, especially with the use of thiazide, thiazide-like diuretics and high doses of spironolactone, should be carried out with caution, under the control of blood electrolytes, which is regulated by modern guidelines [21].

It remains unclear whether hyponatremia per se is a factor determining the deterioration of the prognosis for CHF, or whether it only acts as a laboratory marker of disease severity. Further extensive studies are needed to answer this question. However, in any case, reducing the level of blood sodium can serve as a simple and reliable tool for risk stratification in patients with decompensated CHF, as it is associated with deterioration of the hospital prognosis and prolongation of hospitalization.

Conclusion

Hyponatremia is a frequent disorder of the water-electrolyte balance in patients hospitalized due to decompensated CHF. In general, its rate reaches 33.3%, while 48.5% of patients experience it at the prehospital stage and 51.5% during treatment in the Department. By the time of discharge, spontaneous normalization of sodium levels occurs only in 7.8% of patients, and on the contrary, there is a progression of hyponatremia in 25% of patients.

Presence of both pre-hospital and in-hospital hyponatremia is associated with more severe CHF, poor in-hospital prognosis and prolonged period of stay in the hospital. The progression of existing hyponatremia significantly increases the risk of death and transfer to the intensive care unit.

Conflict of interests

The authors declare no conflict of interests.

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UDC 61 (47+57) (092) The Botkins

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EVGENY SERGEEVICH BOTKIN AND SERGEY SERGEEVICH BOTKIN AS REPRESENTATIVES OF THE SCIENTIFIC CLINICAL SCHOOL SERGEI PETROVICH BOTKIN

Abstract

The article is devoted to activity of the sons of the outstanding Russian clinician and scientist Sergey Petrovich Botkin (1832-1889), Eugene Sergeyevich Botkin (1865-1918) and Sergey Sergeyevich Botkin (1859-1910), in the field of medicine. Sergey Petrovich Botkin is the founder of the first in Russia and one of the largest scientific therapeutic schools. His sons were among the doctors who were trained in the clinic of the Military Medical Academy while Sergey Petrovich Botkin worked there; however, their names are not traditionally mentioned among his students in the publications on the scientific clinical school of Sergey Petrovich Botkin. The authors made an attempt to trace the life stages of the sons of Sergey Petrovich Botkin, in particular, study and work in the Military Medical Academy, scientific training abroad, medical activities in healthcare institutions of St. Petersburg and organization of medical care as part of the Red Cross during the Russo-Japanese War (1904-1905). The work of Eugene Botkin as the family physician of the last Russian Emperor Nicholas II is considered separately. The article reveals the influence of S.P. Botkin and his closest disciples on E.S. Botkin and S.S. Botkin, as well as the continuity of clinical views and research of S.P. Botkin and his sons. The authors emphasize the similarity of ethical principles of medical activity applied by Sergey Petrovich Botkin and his sons. The materials presented in the article confirm that the sons of Sergey Petrovich Botkin, Eugene Sergeyevich Botkin and Sergey Sergeyevich Botkin, belong to his scientific clinical school.

Key words: *Sergey Petrovich Botkin, Eugene Sergeyevich Botkin, Sergey Sergeyevich Botkin, history of internal medicine, clinical medicine*

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Introduction

Distinguished Russian clinician Sergey Petrovich Botkin (1832–1889) is the founder of the first Russian and one of the largest scientific therapeutic schools [1]. Under his leadership, 107 residents were trained and 87 of them successfully defended their PhD theses in Medicine. More than 40 of his students were awarded the title of professor, and 27 of them specialized in internal medicine [2].

His sons were among doctors who took a training course in the hospital of the Military Medical Academy during his active years [3]. Eugene Sergeyevich Botkin (1865–1918) and Sergey Sergeyevich Botkin (1859–1910) left a noticeable mark in the history of medicine. Works devoted to the scientific clinical school of S.P. Botkin do not usually mention his sons among his students [4, 5]. It appears that the personalities of E.S. Botkin and S.S. Botkin are not only worthy of an in-depth

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study, but should also be considered when analyzing the influence of their father's personality and ideas on their work.

Sergey and Eugene Botkin Parenting and Primary Education

The atmosphere in the home of the Botkins significantly influenced the formation of the personalities of Sergey Sergeyevich and Eugene Sergeyevich.

According to the memoirs of N.A. Belogolovy, who was Sergey Petrovich's friend and biographer, S.P. Botkin "... was of a mild and easygoing nature, completely immersed in his work. He didn't care about little things of life, avoided quarrels and didn't like unnecessary disputes. All these peaceful personal qualities were particularly vivid in the home environment; here he was open-hearted and loving, possessing an inexhaustible good nature and mild humor. Being surrounded by his twelve children aged 1 to 30 (he had five sons and one daughter from the first marriage, and six daughters from the second one), he looked like a true biblical patriarch; his children adored him despite the fact that he knew how to keep home discipline and blind obedience to himself..." [6].

The mother of Sergey Sergeyevich and Eugene Sergeyevich — Anastasia Alexandrovna nee Krylova (1835–1875), the first wife of S.P. Botkin, had an excellent education, was proficient in foreign languages, played music [2]. According to comments by contemporaries, Anastasia Alexandrovna "passionately loved her children but still knew how to keep the necessary pedagogical self-control, carefully and intelligently attended to their education, and timely eradicated their weaknesses..." [6].

The house of Sergey Petrovich Botkin was open to prominent men of science and art. Among Botkin's friends and patients were famous figures of Russian culture, such as M.E. Saltykov-Shchedrin, N.A. Nekrasov, I.S. Turgenev, N.N. Kramskoy, A.P. Borodin, M.A. Balakirev [7]. According to N.A Belogolovy, "Botkin's Saturdays" are famous for the fact that "...during their 30-year existence, almost all Petersburgers from scholarly, literary, artistic and, of course, medical circles visited them" [6].

It is interesting to note that A.A. Botkina's brother, Victor Alexandrovich Krylov, was a famous Russian playwright and critic. According to his contemporary, "V.A. Krylov undoubtedly occupies one of the prominent places in the history of Russian literature of the nineteenth century. Apart from Ostrovsky, it's hardly possible to mention any other playwright similar to V.A. Krylov, who so generously supported the repertoire of the Russian drama theater and, moreover, practically did so much for the development of theatrical art" [8].

Vasily Petrovich Botkin, S.P.Botkin's brother, was an outstanding Russian writer and critic. According to Maxim Gorky, his "Letters from Spain are not comparable to any other literary work. It is the only book about a foreign country written by a Russian" [9].

Subsequently, the brothers' wide area of thought and cultural knowledge contributed to the fact

Figure 1. *Monument to Sergey Petrovich Botkin (1832-1889) near the therapeutic clinic of the Military Medical Academy in St. Petersburg*

that Eugene Botkin worked as a doctor in the Court Chapel for a short period of time [10], while Sergey Sergeyevich Botkin became a famous art collector, a full member of the Imperial Academy of Arts [11]. Alexandre Benois wrote: "No, Sergey Sergeyevich had nothing in common with a pedant collector, a dry, aloof moneymaker. Rather, he was a passionate hunter. Sergey Sergeyevich spent a lot of time trying to find and then get art works worthy of being included into his collection. And if you happen to meet him riding in his open carriage along St. Petersburg's streets, you know that he has either just left a patient and is going to an antique dealer, or, vice versa, from an antique dealer to one of his patients" [12]. Similar to his father's home, the mansion of S.S. Botkin and his wife (a daughter of P.M. Tretyakov, the founder of the Moscow Art Gallery) was situated at the corner of Potemkinskaya and Furshtadtskaya streets became one of the centers of St. Petersburg cultural life [13].

Sergey Petrovich Botkin raised his children on the ideals of public service, and the Botkin brothers grew up with a firm foundation of adherence to their profession and love for the motherland.

After an excellent primary home education, both brothers successfully continued their studies at the 2nd St. Petersburg Gymnasium, after which they wanted to choose the profession of a doctor following their father's example. However, they initially had to enroll in the Faculty of Mathematics and Physics at St. Petersburg University instead of entering the Military Medical Academy because the undergraduate admission to the Academy was canceled as a part of reforms implemented there in those years. The Academy only accepted third-year students from different Russian universities [10].

Medical Education and Medical Practice of E.S. Botkin and S.S. Botkin

The Botkin brothers took their first step towards their medical profession when they entered the Military Medical Academy after a short period of a successful study at the university. Upon graduating from the academy, Sergey Sergeyevich Botkin was awarded the I.F. Bush Prize for academic excellence, and his name was included in the Academy Wall of Honor [14]; Eugene Sergeyevich Botkin was awarded the title of a doctor with distinction and a personalized Paltsevskaya Prize which was awarded to "the student who got the third highest score in his course" [10].

It should be particularly noted that the study at the Military Medical Academy, where a whole series of famous scientists worked, including S.P. Botkin and his students (A.G. Polotebnov, V.A. Manassein, N.P. Simanovskiy, D.I. Koshlakov, I.P. Pavlov, etc.), made the invaluable contribution to the formation of the brothers' medical skills. [2]. Recalling his father's personality in a letter to his brother, E.S. Botkin admired his work: "What an outstanding interest and passion he had during his work!" [15].

Ivan Petrovich Pavlov — the first Russian Nobel laureate, an outstanding physiologist, a student and a colleague of S.P. Botkin — greatly appreciated his teacher throughout his life. I.P. Pavlov said the following about S.P. Botkin: "I was privileged to work close to the deceased clinician in the laboratory industry for 10 years... Not being enticed by immediate success, his deep mind was looking for a solution to the great puzzle: what a sick person is and how to help him/her — both in the laboratory and in a live experiment. For decades I saw his students going to the laboratory, and such a high experiment appreciation by the clinician, in my opinion, contributes to Sergey Petrovich's glory no less than his clinical work known throughout Russia" [16].

I.P. Pavlov was the research advisor of Sergey Sergeyevich Botkin's PhD thesis entitled "The Influence of Rubidium and Cesium Salts on the Heart and Blood Circulation Resulting from the Legality of the Alkali Metals Physiological Effect" (1888) and the opponent during Eugene Sergeyevich Botkin's defense of his PhD thesis entitled "The Albumoses and Peptones Influence on Certain Animal Functions" (1893).

Like their father, both brothers completed their scientific internship in leading European medical institutions: Sergey Sergeyevich Botkin — in 1889–1892 [7], Eugene Sergeyevich Botkin — in 1890–1892 and in 1895–1896 [10].

Sergey Sergeyevich Botkin's establishment as a clinician was directly guided by his father during their work in an academic therapeutic hospital. S.S. Botkin gained important practical experience

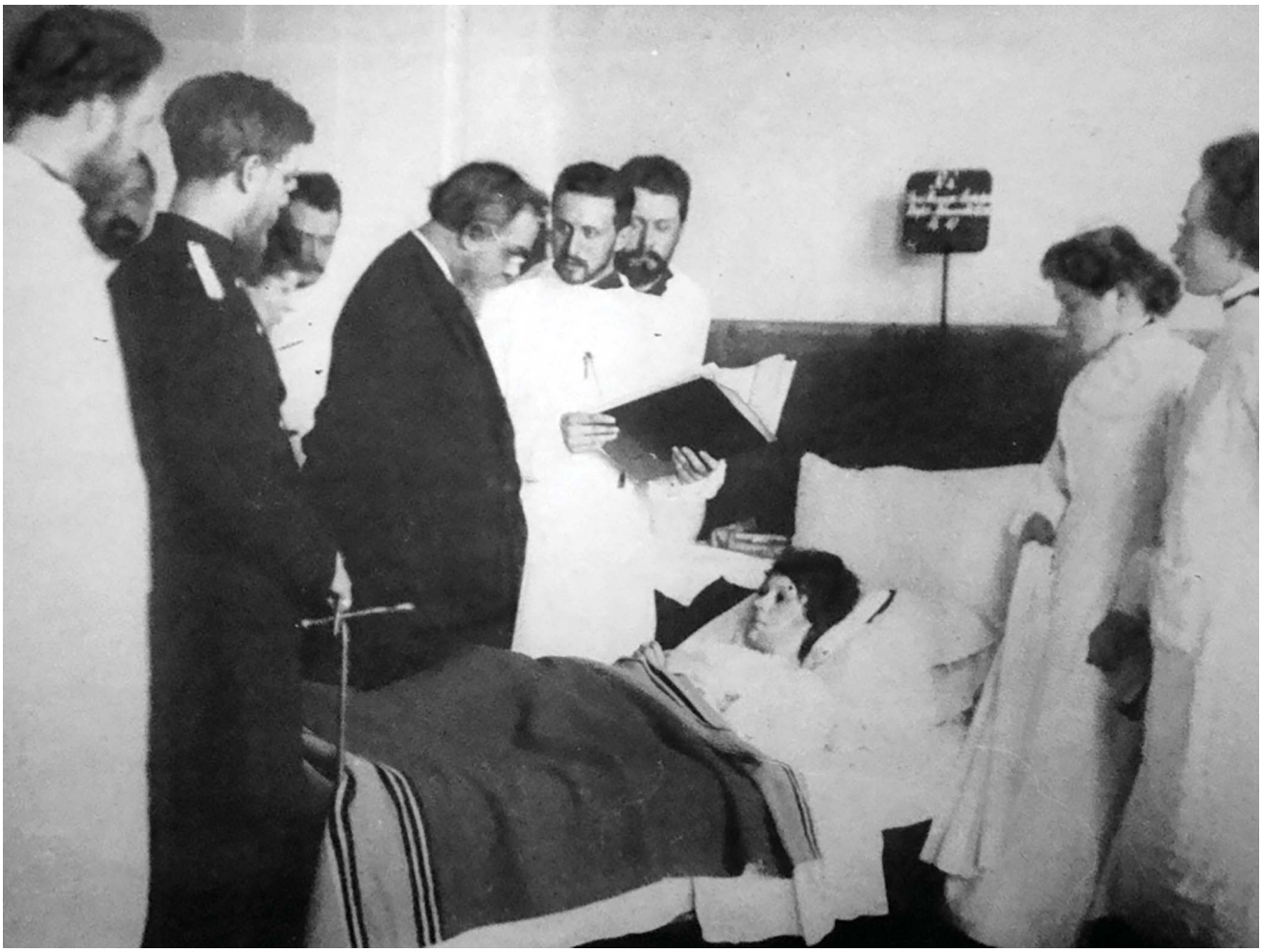

Figure 2. *Examination of the patient by professor Sergey Petrovich Botkin in the clinic*

in the City Camp Hospital where he worked as a department head for several years [11]. In 1896, Sergey Sergeyevich Botkin was elected the head of the first Russian department of bacteriology and contagious diseases at the Military Medical Academy, and in 1898 he became the head of the academic therapeutic hospital which had been previously headed by his father [3].

S.S. Botkin's key scientific works are devoted to the research of gastric acid during fever, the study of anaerobic bacteria (he designed a device for growing anaerobic bacteria), and the study of leukolysis. He was the first to point out the possibility of examining the leukolysis phenomenon under a microscope based on the tracking of lymphocytes, destroyed during the smear preparation process, which were later called Botkin and Gumprecht bodies [11].

Eugene Sergeyevich Botkin began his medical career as an assistant doctor at the St. Petersburg Mariinskii Low-Income Hospital in January 1890, after his father's death [17]. V.I. Alyshevskiy, one of S.P. Botkin's students, was the chief physician at that time. He created a system to allow doctors to improve their qualifications, which was similar to the academic one [10].

After his father's death, E.S. Botkin wrote the following about the therapeutic specialty, S.P. Botkin wished for his sons: "... this will is sacred to me as it belongs not only to my father, but also to my indispensable teacher. I'm doing my best to follow my father's will and pray for help in fulfilling at least a small part of what my father wanted me to achieve" [15].

Over the years, in the Mariinskiy Hospital E.S. Botkin published a number of original scientific papers on the description of interesting clinical observations and the study of the leukocyte functions [10]. E.S. Botkin's experience and his special attention to patients' needs contributed to his recommendation for the position of a doctor of the Sisters of Mercy Communities [10], and his high

Figure 4. *Sergey Sergeyevich Botkin (1859-1910)*

Figure 3. *Eugene Sergeyevich Botkin (1865-1918)*

scientific influence saw him elected as a privat-docent at the Military Medical Academy [17, 18].

Like their father who twice served as a doctor in military operations — in the Crimean (1853–1856) and the Russo-Turkish (1877–1878) Wars, the brothers participated in the Russo-Japanese War (1904–1905) providing medical care. Sergey Sergeyevich Botkin worked as a chief representative of the Red Cross in the Northeast Region (in Vladivostok, Khabarovsk, and then in Harbin) [3]. Eugene Sergeyevich Botkin worked as a medical assistant chief representative of the Red Cross in the field forces and directly participated in the battles of Wafangou, Liaoyang and the Battle of Shaho, whereupon he was awarded Orders of Saint Vladimir, 3rd and 4th classes, for Personal Courage [10].

Eugene Botkin's literary diary "Light and Shadows of the Russo-Japanese War of 1904–1905. (From Letters to His Wife)", published in 1908 in the form of letters to his wife from the front line, became vivid evidence of the epoch [19]. Here he partly repeated the experience of his great father, who had published "Letters from Bulgaria" — the diary of his medical observations from the front line of the Russo-Turkish War [20]. E.S. Botkin's book is also perfectly written and full of impartial descriptions of reality and accurate doctor's observations.

The Botkin brothers summarized the experience gained in providing health care during military operations and shared the results at meetings of scientific communities. In 1906, Eugene Sergeyevich Botkin presented a report "The Red Cross Activity in the Field Forces Area During the Russo-Japanese War of 1904–1905" at the meeting of the Society of Russian Doctors dedicated to the memory of S.P. Botkin, and in 1909 Sergey Sergeyevich Botkin presented a report "On Manchurian Typhoid" at the first congress of therapists in Moscow.

It should be noted that the medical practice of S.S. Botkin and E.S. Botkin was guided by principles of attitude towards patients similar to those demonstrated by their father throughout his life. "Thousands of his (S.P. Botkin's) patients and students can witness his gentle and remarkably cordial treatment of patients, rejection of self-profit, devotion not only to science, but also to every suffering person" [6].

It is no coincidence that comments by contemporaries on the brothers' medical practice are so similar to comments on S.P. Botkin.

Renowned Russian philosopher Vasily Rozanov told about Sergey Sergeyevich Botkin that "being a military doctor and a professor, he certainly served like any other decent Russian person, but he was a man who didn't care about his uniform or fixed working hours. The feeling of privacy and exclusive home atmosphere surrounded him. There was no other person less official than he was..." [21]. Sergey Dyagilev, another well-known Russian artist, who was acquainted with Sergey Sergeyevich Botkin, recalled that his "healing power" was based not on science but on his cheerfulness, and this helped him establish close relations with people and experience their most diverse sensations" [22].

The St. George Sisters of Mercy Community, which put E.S. Botkin forward for a decoration, emphasized that "possessing extensive knowledge, experience and passion for his work, Eugene Sergeyevich cordially, carefully and kindly treated not only his patients, but all people who interacted with him" [23]. And the letter of appreciation presented to E.S. Botkin by nurses he had worked with during the Russo-Japanese War, read: "Dear Eugene Sergeyevich, for the short period of time spent with us, you've done so many good and kind things that now, when we have to part with you, we want to express our deep, sincere feelings. Instead of a stern, unemotional leader, we've seen a deeply dedicated, sincere, sympathetic, empathetic person who is like a father ready to help in difficult times, and it's so important here, far from our relatives, especially for women who are oftentimes inexperienced, impractical and young. Dear Eugene Sergeyevich, accept our deep and sincere gratitude..." [15].

Working as a teacher, E.S. Botkin sought to promote a careful, humane treatment of patients among the academy students. In the opening lecture given to students of the Military Academy of Sciences on October 18, 1897, E.S. Botkin emphasized: "Patients' confidence you've gained becomes a sincere devotion to you, when people get convinced of your cordial attitude towards them. When you enter the ward, you find patients in a cheerful and cordial mood — that is a precious and powerful medication that can be more efficient than any mixtures and powders... But your heart should be constantly open, and you need to sincerely and cordially care about every sick person. So accustom yourself to provide help and care to those who need them. Let's go with love to patients in order to learn how to be useful to them" [24].

Unfortunately, S.S. Botkin's scientific and social activities were interrupted on January 29, 1910, when he suddenly died of stroke [14].

Eugene Sergeyevich Botkin was also not destined to have a long-lasting medical career. On April 13, 1908, like his father, he was appointed as the Tsar's family physician [10]. In this position, Eugene Sergeyevich accomplished a moral medical feat — after the abdication of Nicholas II in 1917, he continued to perform his duties as a physician, provided moral support to the Tsar's family members and voluntarily went into exile with them, where he conducted free private practice [15, 25]. In the night of July 16th to 17th (N.S.), 1918, Eugene Botkin, members of the royal family and three servants were shot in Yekaterinburg [17]. On February 3, 2016 the Bishops' Council of the Russian Orthodox Church canonized Botkin as Righteous Passion-Bearer Eugene the Physician [15].

Conclusion

Eugene Sergeyevich Botkin and Sergey Sergeyevich Botkin became worthy successors of Sergey Petrovich Botkin's work. The medical activities of the Botkins brothers were in harmony with their father's words [26]: "The moral development of a practicing physician will help him maintain the mental balance that will enable to fulfill the sacred duty to his fellowmen and motherland, and this will determine the true happiness of his life."

The analysis of the life and medical practice of the Botkin brothers shows that they passed through the key stages of medical education and clinical training (at the Military Medical Academy and hospitals in St Petersburg) under the leadership of S.P. Botkin and his closest students. The Botkin brothers' scientific researches continued the laboratory work actively developed by their father and teacher, and their practical work (following S.P. Botkin's ideas) in the field of both civil and military medicine delivered benefits to the motherland.

Conflict of interests

The authors declare no conflict of interests.

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CLINICAL AND STATISTICAL EVALUATION OF THE CALLS OF PATIENTS WITH ATRIAL FIBRILLATION

Abstract

This article presents the results of the clinical and statistical evaluation of calls made by patients with atrial fibrillation to the emergency medical service in Moscow.

Emergency teams performed a voluntary survey of 5,003 patients with AF. The proportion of calls regarding heart rhythm disorders was 17 % of the total number of calls regarding cardiovascular diseases, of which 88 % pertained to atrial fibrillation. A clear trend was observed in the prevalence of AF in men of working age and in women in the older age group. Among the respondents paroxysmal form of AF prevails in 70.1 % of cases. The average score of the risk of thromboembolic complications in patients with atrial fibrillation/flutter according to CHA_2DS_2-VASc was 3.56 ± 1.71. The average score of risk assessment of ischemic stroke in patients with nonrheumatic atrial fibrillation/flutter according to $CHADS_2$ was 1.85 ± 1.13. The number of patients with a score of two or more on both scales was 87.7 % and 59.3 % respectively. 28 % of patients with AF asked for medical help at least 48 hours after the onset of the paroxysm. Regular follow-up by a cardiologist is carried out in 50.5 % of cases, by a physician in 62.8 %, jointly by a physician and a cardiologist in 45 % respectively. Continuous oral anticoagulant therapy is performed in 29.8 % of patients with AF. The percentage of medical evacuations of patients with AF increased from 23.8 % in 2015 to 27.1 % in 2016. The study shows that regular clinical and statistical analysis of the effectiveness of medical care at all stages for patients with AF is necessary.

Key words: *emergency medicine, cardiac arrhythmias, atrial fibrillation*

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BP — blood pressure, CAD — coronary artery disease, INR — international normalized ratio, TIA — transient ischemic attack, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, HR — heart rate, ECG — electrocardiogram

Russia has seen an increase in the number of patients with circulatory system diseases in recent years [1]. Heart rhythm disorders are a significant fraction in this pathology's structure [2, 3]. In turn, atrial fibrillation (AF) is the most frequent rhythm disorder, which is the cause for emergency calls. Almost half of the patients with cardiovascular diseases are diagnosed with this arrhythmia [2, 3]

The AF prevalence correlates with age, hypertension presence, the development of other comorbidities — coronary artery disease (CAD), diabetes mellitus, chronic obstructive pulmonary disease

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(COPD), etc., as well as atherosclerosis progression, which in turn increases the number of hospital admissions and the mortality rate among patients [2, 4, 5].

According to the World Health Organization, up to 50 % of all cardioembolic strokes are associated with AF, which leads to more severe disability and mortality among patients compared with stroke caused by another etiology [6, 7]. AF also contributes to the incidence of chronic heart failure.

Hypertension and coronary artery disease dominate in the etiological structure of atrial fibrillation, less common arrhythmia causes are diabetes mellitus, COPD, cardiomyopathy, thyroid disorders, etc. [8].

Patients with AF need long-term, almost lifelong, anticoagulation therapy to reduce the risk of thromboembolic complications. For many years the main indirect anticoagulant drug was warfarin, an antagonist of vitamin K [9], which requires regular monitoring of the international normalized ratio (INR), which in reality cannot always be accomplished by patients due to different reasons. A new generation of oral anticoagulants — rivaroxaban, dabigatran etexilate, apixaban — are an alternative to warfarin for prevention of thromboembolic complications in patients with AF. They directly inhibit coagulation factor Xa (Stuart–Prower factor, the active protein gamma-globulin form) or thrombin. The drugs have fixed dose schedule and do not require INR monitoring [10, 11, 12].

The medical and social significance of AF is determined by the high frequency of emergency calls and the need for hospital admissions for optimal treatment strategies. Each year from 10 to 40 % of patients with AF are admitted for various reasons.

According to statistics from the First aid station named after A. S. Puchkov, Moscow, in 2015, the proportion of calls regarding heart rhythm disorders was 17 % of the total number of calls regarding cardiovascular diseases, of which 88 % pertained to atrial fibrillation. In 2016, these indicators were 17.6 % and 89.6 %, respectively. The percentage of medical evacuation of patients with AF in 2015 amounted to 23.8 %, and to 27.1 % in 2016.

The objective of the study was to conduct clinical and statistical evaluation of the frequency of calls made by patients with atrial fibrillation to the emergency medical service in Moscow, to evaluate the effectiveness of paroxysmal form management at the pre-hospital stage, which could be used later in the assessment of treatment effectiveness in organizations providing primary medical care.

Materials and methods

The study conducted at the First aid station named after A. S. Puchkov, Moscow, contains data about emergency calls and medical evacuation of patients with AF to hospitals. In 2016, 5,003 patients with AF took part in a voluntary survey, the information received was put in the original individual survey

Table 1. *Characteristics of patients with AF who applied for emergency medical care*

Indicators	Quantity of patients	
	Absolute number	%
All patients	5,003	100
Men	1,660	33.2
Women	3,343	66.8
Mean age, years	72.9 ± 9.8	
Duration of the health condition, years	6.0 ± 4.6	
Form of AF		
permanent	902	18.03
paroxysmal	3,508	70.12
newly diagnosed	593	11.85
Duration of current AF:		
≤48 hrs	3,548	70.92
≥48 hrs	1,394	27.86
Duration of AF is not defined	61	1.22
Hypertensive disease	4,276	85.47
History of myocardial infarction	1,340	26.78
Cardiomyopathy, myocarditis, valvular heart disease	230	4.60
History of stroke/TIA	577	11.53
NYHA 3-4 CHF	690	13.79
History of pulmonary embolism	60	1.74
Diabetes mellitus	641	12.81
COPD/ asthma	290	5.80

form, which was filled in by a doctor (medical assistant) only after the patient had received medical care. The emergency teams during calls conducted a survey by questioning the patients and obtained information about the duration of the main health condition, regularity of self-monitoring blood pressure (BP) and heart rate (HR), presence of other chronic diseases, drug therapy, medical evacuation to hospitals due to atrial fibrillation.

Atrial fibrillation was diagnosed taking into account medical history, analysis of complaints and examination results. For diagnostics and verification of diagnosis, emergency teams recorded and interpreted electrocardiograms (ECG) in 12 standard leads. Medical assistant teams were provided with means of sending the ECG to cardiological medical advisory panel at the First Aid Station working around the clock.

Clinical and gender characteristics of the AF patients are presented in Table 1.

Statistical processing of the obtained data was carried out using Microsoft Office Excel and the IBM SPSS Statistics 21 software package.

Results and discussion

As part of this study, 5,003 questionnaires of patients with atrial fibrillation were analyzed, 66.8 % of whom were female. The mean age of the patients was 72.9 ± 9.8 years, the duration of the health condition was 6.0 ± 4.6 years. The gender differences in the development of AF among our patients should be noted: if among working age people from 20 to 59 years men were predominant, from the age of 60 the percentage of females was predominant (Fig. 1).

Analysis of the data showed that the main reasons for emergency calls in these patients were as follows: heart rhythm disorders (66.3 %), palpitation (46.7 %), deterioration of health state (35.2 %), dyspnea/choking (9.3 %), and cardiac pain (2.4 %).

According to the study, paroxysmal AF accounts for 70.1 % (n = 3,508) of the total number of calls, which confirms the literature data [13]. It is the predominant form of rhythm disorders that occurs outside of medical organizations. The permanent AF form was 18.0 % (n = 902). In 11.8 % (n = 593) of cases, the new cases of atrial fibrillation were diagnosed by the emergency teams.

According to the literature, approximately one-third of patients with AF have no clinical symptoms, and the patients are unaware of the existence of arrhythmia [14]. Arrhythmia diagnosis made by the emergency teams allows timely commencement of treatment, thus preventing the development of complications in this group of patients [15].

A detailed analysis of the obtained data showed that in 70.9 % (n = 3,548) of cases the duration of arrhythmia did not exceed 48 hours, while in 1,394 (27.9 %) patients the attack lasted more than 48 hours, and in 1.2 % (n = 61) the duration of AF was not established. Such delay by patients in seeking medical attention worsens the prognosis of the disease and is fraught with the development of serious cardiovascular complications.

A significant factor affecting the risk of development of ischemic events in patients with AF is the presence of other diseases. Our analysis showed that among patients with AF, the most common are hypertension in 4,276 (85.5 %) patients and CAD in 1,340 (26.8 %) patients, respectively. These health conditions themselves are very serious risk factors for the development of cardiovascular complications (stroke and systemic embolisms), and this risk significantly increases in combination with AF [16].

According to the questionnaire, 577 (11.5 %) patients had a history of stroke or transient ischemic attack. Among other pathologies, congestive

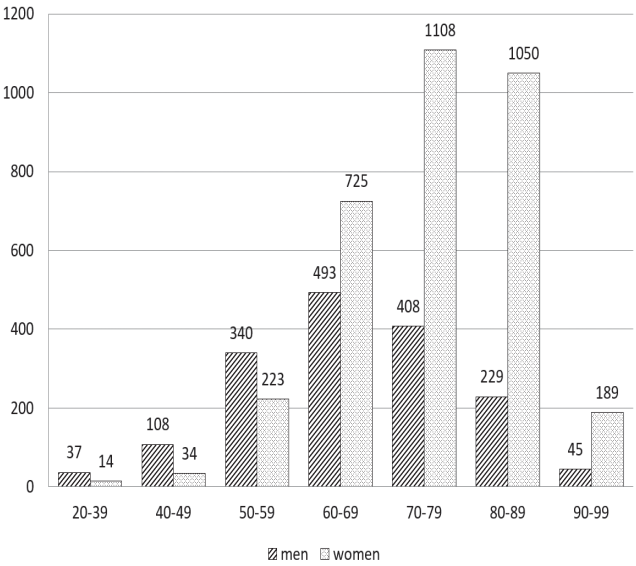

Figure 1. *Gender differences in patients with atrial fibrillation*

heart failure (690 cases, 13.8 %), diabetes mellitus (641, 12.8 %), and COPD / bronchial asthma (290, 5.8 %) were observed in patients with AF.

Thus, patients with atrial fibrillation are characterized by comorbidity that significantly aggravates the course of the pathological process.

Patients with AF, taking into account the high risk of cardiovascular complications, need regular medical check-up. Regular follow-up by a physician was carried out in 958 (57.7 %) men and in 2,184 (65.3 %) women. Such follow-up by a cardiologist was conducted in 827 (49.8 %) men and in 1,704 (50.9 %) women. 2,253 patients (45.0 %) were consulted by a physician and a cardiologist at the same time.

According to international and Russian guidelines for the management of AF there are 3 strategic steps: constant anticoagulant therapy, heart rate control with the retention of the optimal rate and additional therapy of concomitant diseases.

In our study, the average score on the scale of thromboembolic complications risk assessment in patients with atrial fibrillation / atrial flutter CHA_2DS_2-VASc (**C**ongestive heart failure, 1 point; **H**ypertension, 1 point; **A**ge — over 75 years, 2 points; **D**iabetes mellitus, 1 point; **S**troke — stroke / TIA / systemic embolism in anamnesis, **2** points; **V**ascular disease — vascular damage (history of myocardial infarction, atherosclerosis of peripheral arteries, atherosclerosis of the aorta), 1 point; **A**ge — 65–74 years, 1 point; **S**ex **c**ategory — gender (female), 1 point) was 3.56 ± 1.71. The average score on the scale of ischemic stroke risk assessment in patients with non-rheumatic atrial fibrillation / atrial flutter $CHADS_2$ (**C**ongestive heart failure, **H**ypertension, **A**ge — > 75 years, **D**iabetes mellitus, **S**troke — ischemic stroke or transient ischemic attack (TIA) in the medical history) amounted 1.85 ± 1.13.

The number of patients who scored 2 or more points on both scales (that is, those patients requiring continuous anticoagulation therapy) was 4,385 (87.7 %) and 2,967 (59.3 %), respectively, of all 5,003 patients.

However, according to our study, only 568 (11.3 %) patients received indirect anticoagulant warfarin under the INR level control, and 928 (18.5 %) patients received new oral anticoagulant drugs (rivaroxaban, dabigatran etexilate, apixaban). Patients with a score of two or more on the scales CHA2DS2-VASc and CHADS2, were taking indirect and direct anticoagulants in a similar percentage of patients — 11.5–11.8 % and 19.4–19.7 %, respectively.

34.1 % (n = 1,705) of patients were taking antiarrhythmic drugs regularly. Surgical intervention because of AF (ablation) was performed in 4.7 % of cases (n = 236).

Analysis of the obtained survey materials revealed a fairly high level of AF patients who self-monitor their blood pressure (78.8 %) and heart rate (74.1 %).

Rational tactics of AF therapeutic and preventive measures suggests effective treatment of other clinically significant diseases in such patients. The vast majority of patients (85.5 %) had hypertension, due to which antihypertensive drugs were recommended to achieve the target blood pressure level, these patients took: ACE inhibitor / angiotensin receptor blocker — 51.3 % of patients, -blockers — 46.7 %, calcium antagonists — 16.5 %.

In patients with paroxysmal AF, at the pre-hospital stage, paroxysm was stopped in 962 patients (30.3 %), including 778 (24.5 %) patients on the primary call.

Cardioversion performance analysis was not carried out in the research group.

According to data of this questionnaire, after emergency teams provided medical care to AF patients, 1,342 (26.8 %) patients were evacuated to specialized medical institutions. The main indications for medical evacuation of patients with atrial fibrillation were: new cases of AF paroxysm; unmanaged AF paroxysm lasting less than 48 hours; AF paroxysmal form lasting more than 48 hours; AF permanent form, complicated by angina or acute heart failure; and lack of effect from treatment.

Of the 5,003 patients participating in the survey, in 2015, 1,773 patients (35.4 %) called the emergency case service for the first time regarding AF, 2,124 (42.5 %) patients called the emergency case service up to 5 times during the year, 730 (14,6 %) patients — from 6 to 10 times, 376 (7,5 %) patients — more than 10 times, and in 2016, respectively, for the first time — 670 (13.4 %), up to 5 times — 3,641 (72.8 %), 6–10 times — 488 (9.8 %) and more than 10 times — 204 (4.1 %) patients.

Conclusions

1. The provision of emergency medical care is of great importance to patients with atrial fibrillation, especially in new cases (11.8 %).
2. Gender analysis among AF patients revealed a clear domination of working age in men — 9.8 % (women — 5.4 %), and older age in women — 61.4 % (men — 23.9 %).
3. Among the polled patients, paroxysmal atrial fibrillation was diagnosed in 70.1 % of cases.
4. Twenty-eight percent of patients sought medical care 48 hours after the beginning of the atrial fibrillation attack.
5. According to the survey results, 62.8 % of AF patients were provided with active follow-up by a physician in an outpatient clinic, 50.5 % by a cardiologist, and 45.0 % by a physician and a cardiologist at the same time.
6. Constant anticoagulant therapy was used in 29.8 % of AF patients.
7. Clinical and statistical analysis should be carried out regularly to assess the effectiveness and quality of medical care for AF patients at the emergency health care stage.

Conflict of interests

The authors declare no conflict of interests.

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SEARCH OF THE STRESS INDUSED VENTRICULAR TACHICARDIA REASONS — THE METABOLIC THERAPY OPPORTUNITIES

Abstract

A clinical case of a 56-year-old man is presented. In this case ventricular tachycardia alone (no clinical and ECG criteria of myocardial ischemia) was recorded during the exercise test. Ventricular tachycardia was the only reason for stopping the test. The case demonstrates all the difficulties in determining causes of ventricular arrhythmias induced by physical activity. The objective of the study was to show all the difficulties in determining the cause of exercise-induced ventricular arrhythmia. The literature data on exercise-induced arrhythmia differentiation is rather poor. It is only known that if a patient develops and progresses ventricular arrhythmia, a treadmill test is considered questionable. Exercise-induced ventricular arrhythmias, especially ventricular tachycardia, are the most unfavorable types of arrhytmias. Therefore, additional diagnostic methods were used to reveal the main health condition as the background of ventricular tachycardia. Results of pharmacological test with nitroglycerine were the indication of the ischemic origin of ventricular tachycardia. Coronary angiography did not reveal coronary artery stenosis. Positron emission tomography revealed coronary microcirculation disturbances and a decision about metabolic therapy with Mexicor was made. The correct choice of the drug (Mexicor) was confirmed by the results of control tests: the improvement of metabolism and antiarrhythmic effect were revealed. The choice of the exercise-induced ventricular arrhythmia treatment in patients with stable coronary artery disease should be individual and based on the pathogenesis.

Key words: *stable coronary artery disease, ventricular arrhythmias, ventricular tachycardia, Holter monitoring, exercise test*

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Ng — nitroglycerin, NO — nitric oxide, AA — antiarrhythmic, BP — blood pressure, SCD — sudden cardiac death, CE — cycle ergometry, VA — ventricular arrhythmia, FA — fatty acids, VT — ventricular tachycardia, VPC — ventricular premature complexes, CAD — coronary artery disease, CA — coronary arteries, CAG — coronary angiography, LV — left ventricle, PET — positron emission tomography, RP — radiopharmaceutical, SA — sinoatrial blockade, FFA — free fatty acids, EF — ejection fraction, PA — physical activity, HM — Holter monitoring, HR — heart rate, EMI — electric myocardial instability

The era of studying risk stratification and the factor combination influence on a given clinical outcome began in the second half of the 20th century. In the early 21st century, publications appeared, that took into account not only the clinical forms of coronary artery disease (CAD), but also other conditions that worsen the prognosis. Among them there are: postinfarction cardiosclerosis, left ventricle (LV) systolic dysfunction, permanent ventricular tachycardia (VT) with hemodynamic disorders, cardiac arrest episode or a documented sudden cardiac death (SCD) episode in the medical history [1]. However, despite the publication of study results proving the cause-effect relationship of ventricular arrhythmias (VA) with myocardial ischemia (ischemia can cause electrical myocardial

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instability (EMI) and act as an arrhythmia trigger) in patients with CAD, the necessary emphasis has not yet been made on circumstances against which arrhythmic events develop [2–4].

Based on our clinical experience and ESC guidelines, in 2017 we proposed an algorithm for managing patients with stable CAD with an intact/moderately reduced LV ejection fraction (EF) (≥ 40 % by Simpson's method) and VA taking into account their nature [5]. According to this algorithm, even based on complaints of typical anginal pains and/or equivalents of angina with the pretest probability level, the physician can presume that the patient has CAD and determine the range of necessary examinations [6]. If rhythm disorders are suspected, the examination always starts with ECG and Holter monitoring (HM). This is the class I of indications [1, 6, 7]. However, experience shows that CAD patients do not always subjectively feel arrhythmia, especially if it occurs during physical activity (PA). Therefore, in our algorithm, at the stage following HM, we recommend conducting a test with PA to identify transient myocardial ischemia, assessing tolerance to PA, and determining the angina functional class. Exercise stress ECG (cycle ergometry (CE) and treadmill), and also imaging stress-techniques (stress Echo, myocardial perfusion scintigraphy, positron emission tomography (PET), magnetic resonance imaging) were recommended. Imaging techniques, considering their higher sensitivity and specificity in comparison with ECG, are preferable in myocardial ischemia diagnosis. However, patients with VA and CAD have additional tasks for PA tests: VA "behavior" analysis during exercises (recommendations class IB) and evaluation of its temporary connection with clinical and/or ECG ischemia signs [1, 6, 7]. It should be noted that when evaluating the HM and exercise test results, the arrhythmic events reproducibility is important. It should be set forth in a medical conclusion along with other indicators (the VA number and complexity, heart rate (HR), blood pressure (BP), the appearance time of significant ST depression and/or anginal pain, tolerance to PA, etc.). Moreover, in our studies we showed that the physician's opinion on VA in a patient with stable CAD largely depends on the exercise test results [5, 8, 9]. VA "behavior" evaluation during PA is very important, since its results can be different even with a positive exercise test. A positive PA test is assessed based on clinical and ECG data, i. e. if there is an anginal attack, confirmed by a horizontal/skewed depression of the ST segment ≥ 1 mm in at least 2 ECG leads, or by the steep-rising depression of ST ≥ 2 mm.

So, **with a positive PA test** in a patient with CAD, the VA "behavior" during PA may not show any connection with myocardial ischemia signs* **(variant A):**

1) In the presence of ventricular premature complexes (VPC) at rest during PA, they can significantly decrease in number/complexity.
2) They can completely disappear at the PA peak.
3) They can remain unchanged throughout the test.

The appearance and/or buildup of VA **against the background of a positive exercise test (variant B)** allows it to be regarded as ischemic, especially if it arises and/or progresses simultaneously with anginal pain and/or with significant depression in the ST segment [2]. The increase in the number of VPCs and/or their complexity indicates the progression of VA during PA. Increased complexity is the appearance of paired (if there were only single) VPCs and an increase in their number during the VT episodes [2, 10]. During HM, it is also possible to suspect the ischemic nature of arrhythmia, additionally assessing its distribution over the day (e. g. daytime), the connection of VA to PA, the ischemia / ST segment depression episodes [11].

There is another VA "behavior" type during PA (**variant C**), which unambiguous interpretation is not very easy. The appearance and/or progression of VA at the PA peak and up to the 3rd minute of the recovery period without clinical and/or ECG myocardial ischemia signs is considered to be an

* This VA "behavior", which has no connection with myocardial ischemia, allows to conclude that it is not ischemic. Among the main causes of non-ischemic VA in patients with stable CAD are autonomic nervous system dysfunction and psychological status disorders. In addition, VA can occur long before the CAD development and can be associated with other conditions and diseases, for example, with hypertension or thyroid gland dysfunction.

arrhythmic variant of a questionable PA test [12]. Indeed, it is difficult to understand the origin of VT when it is the only criterion for stopping the test. In such cases it is very important to establish or exclude VA ischemic genesis, since it can be the first and only myocardial ischemia manifestation, and in some cases, even long before other CAD signs appear [2, 10, 13]. To explain this questionable PA test result in 2004 we patented the "Method for predicting ischemic ventricular rhythm disorders in patients with ischemic cardiac disease" [14]. The essence of the method is that with a repeated reproducible exercise test having previously taken 0.5 mg nitroglycerin (Ng) sublingually in case of a significant VPC reduction (single — by 75 %, paired — by 90 % and VT paroxysms — by 100 %), along with increasing PA tolerance, the pharmacological test is considered positive, and VA is considered ischemic [14]. In addition to the paired pharmacological stress test with Ng, an imaging stress test is recommended in case of questionable results.

In the clinical case, we want to demonstrate the complexity of differentiating the VT nature induced by PA.

In 2004, a 56-year-old patient was admitted, complaining of intermittent palpitations episodes accompanied by shortness of breath, which he associated with PA. He had previously considered himself relatively healthy, he skied, had been swimming regularly up to 1,000 m in the pool. When speaking of the concomitant diseases, he mentioned periodically high level of BP for more than 20 years with a maximum of 160/90 mm Hg (no permanent antihypertensive treatment was received). ECG showed sinus rhythm with heart rate of 62 beats per min, slightly (–) T wave in leads V1–V4; slightly (+) T wave in V5, V6. Changes in repolarization without significant dynamics in comparison to ECG of previous years were observed. Echo revealed: initial signs of LV hypertrophy, interventricular septum fibrosis signs, local contractility zones were not seen, global contractility was preserved (LV EF = 60 % by Simpson's method). Blood tests showed dyslipidemia. The results of HM showed: single VPC (with signs of parasystole) of 2 types, with one type predominance — 16,453 per day; paired mono- and polymorphic parasystoles — 172 per day; episodes of unstable VT with a ventricular contraction frequency (VCR) to 130 per minute — 295 per day (17 of them — more than 3 QRS complexes) (Fig. 1 A, B).

So, VA was observed during day-time, and physical activity was significant for the patient on the day of HM. Episodes of unstable VT were recorded only during PA (Fig. 1, A). The unstable VT of the greatest complexity coincided with the time of vigorous walking (Fig. 1, B). There were no changes in the ST segment on the ECG.

Initially (at rest) the heart rate was 60 per min without rhythm disorders (Fig. 2A). During the CE at a heart rate of 100 per minute, a reproducible unstable VT appeared, which served as the only criterion for stopping the test (Fig. 2B). Subjectively the patient complained of minor dyspnea (respiratory rate of 23 per min). At the same time, there was no typical anginal syndrome and ischemic ECG changes, BP was 170/80 mm Hg. The test was considered questionable. The next CE (Fig. 2B) was performed after taking 500 μg (1 tb) of Ng. Taking into account the increase in PA tolerance, the achievement of submaximal heart rate (136 bpm) and the absence of VA, the pharmacological test was interpreted as positive. This seemed to suggest the ischemic nature of VT.

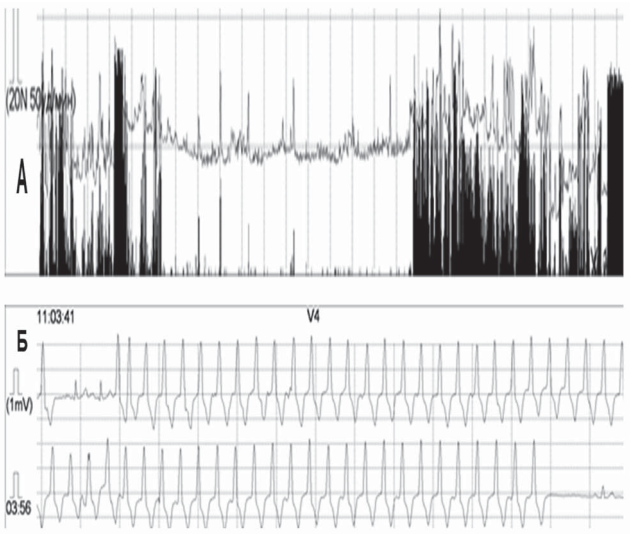

Figure 1. *A – The distribution of ventricular arrhythmias (VA) per day. B – Fragment of Holter monitoring (HM) during exercise test: unstable ventricular tachycardia. Explanation in the text*

The patient's examination was continued considering the PA-induced VT, a positive pharmacological test with Ng, and risk factors (male, 56-year-old, dyslipidemia). Stress echocardiography showed no signs of transient myocardial ischemia, and coronaroangiography (CAG) revealed no hemodynamically significant coronary arteries (CA) stenoses. Nevertheless, the stressful nature of VA was a cause for concern, since it is known that VT, arising against the background of sympathicotonia, increases the risk of developing SCD [2, 14, 15]. Therapy with β-blockers is prescribed as the first-line treatment for exercise-induced arrhythmias. Taking into account the patient's active lifestyle, it was decided to prescribe him a β-blocker. The pharmacological paired exercise test with anaprilin (60 mg) was performed to predict the effectiveness of β-blockers, and it was positive. However, during constant intake of 5 mg Betaxolol with a good antiarrhythmic (AA) effect, there was a pronounced bradycardia (40 bpm) and a transient sinoauric blockade of 2 degree (type 2) with pauses of up to 4 s (accompanied by presincope). The revealed side effect forced to discontinue betaxolol and pushed to further search for the true genesis of exercise-associated VA and the possibilities of its treatment.

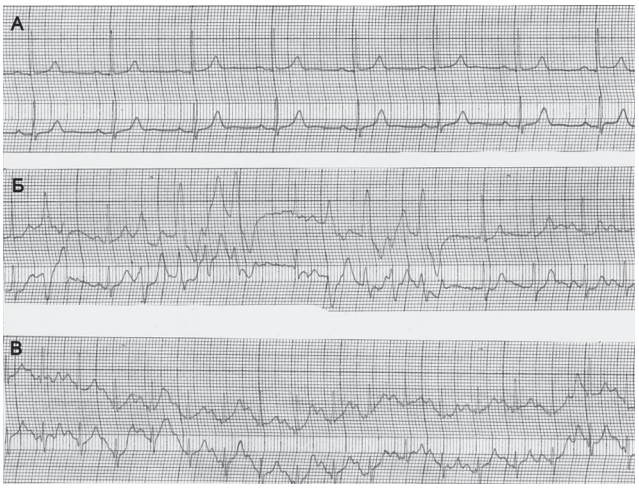

Figure 2 (A, B, C). *Fragments of the cycle ergometry (CE) (2, A – at rest, 2, B – unstable ventricular tachycardia at the peak of the test (stop test criterion); 2, C – at the peak of repeated CE after taking nitroglycerine). ECG leads: Dorsalis and Anterior. Recording speed 25 mm/sec. Explanation in the text*

The absence of hemodynamically significant CA stenoses according to CAG did not exclude the ischemic nature of arrhythmia and for visualizing the possible ischemic substrate for exercise-induced VT. In addition, PET with CE was performed to assess myocardial perfusion, which revealed transient local disorders in the anterior interventricular branch of the left CA. At the PA peak during the PET, VT was recorded with complexes of the same shape as in other exercise tests. While studying fatty acid (FA) metabolism in the myocardium with sodium ^{11}C-butyrate, there was a decrease in FA extraction mainly in the anterior LV wall. The radiopharmaceutical (RP) clearance rate was more than 40 % in all LV parts (Fig. 4). Thus, the PET results in combination with the pharmacological Ng test confirmed the ischemic nature of the exercise-induced VT. The assumed arrhythmogenic substrate could be myocardial ischemia and metabolic disorders that develop against its background, which can be described through a brief insight into the features of biochemical processes in cardiomyocytes [2]. In conditions of cardiomyocyte hypoxia, oxygen is distributed between the oxidation of free fatty acids (FFA) and glucose, while the productivity of both energy paths is reduced. With ischemia, glucose breakdown is mainly performed through anaerobic glycolysis, resulting in the formation of pyruvate. With an oxygen deficit, pyruvate turns into lactate, since it can not pass through all the oxidative decarboxylation stages in the mitochondria. Lactate, accumulating in the cytosol, leads to intracellular environment acidosis, overloading of cells with sodium, calcium and disrupts the ability of cardiomyocytes to relax and contract. In addition, an excess of calcium ions in the cell cytosol activates the phospholipase, resulting in cardiomyocyte membrane damage. In the conditions of oxygen deficit, the main part of aerobic synthesis of ATP is due to beta oxidation of FFA. Such a pathway for the formation of ATP in ischemic conditions is metabolically disadvantageous, since it requires large oxygen expenditure. In this regard, hypoxia leads to excess formation of FFA and acetyl-CoA, which inhibit the pyruvate-dehydrogenase complex, and leads to further glycolysis and oxidative decarboxylation dissociation, as well as free radical oxidation activation. Accumulation of free radical oxidation products in the cell cytoplasm also has

a damaging effect on the cardiomyocyte membrane and disrupts cardiomyocyte function [16, 17]. Thus, during hypoxia, the processes underlying the cardiac muscle dysfunction development are activated: local inflammation and peroxidation, cellular acidosis, a decrease in ATP synthesis, and ionic equilibrium disorder. All this, in turn, causes the development of EMI and arrhythmogenesis foci formation.

In a number of experimental and clinical studies, it was demonstrated that with the proven ischemic nature of VA, the treatment of stable CAD can be supplemented by metabolic drugs, as a "substrate" treatment direction [18–20]. Unlike traditional treatment methods aimed at immediately improving coronary circulation, the effect of modern cytoprotectors is based on their property to increase the myocardium ability to withstand ischemia without losing or quickly restoring its functional activity. The hypothesis that ischemic tissue protection from oxidative stress consequences and the energy balance restoration of cardiomyocytes which form arrhythmogenesis foci can lead to the normalization of its electrophysiological functions, served as the basis for prescribing ethylmethyl hydroxypyridine succinate for the patient (Mexicor) at an average daily dosage of 300 mg. The emoxipin included in its composition exhibits a powerful antioxidant and cytoprotective effect on myocardial cells. Succinate, in turn, gives the drug a pronounced antihypoxic activity. Also, Mexicor has a vasodilating effect preventing NO degeneration (due to emoxipin) [21].

After 2 months of taking the cytoprotector, according to HM there was a significant decrease in the number and complexity of VPC, namely, a 91 % reduction in the number of single polymorphic ventricular parasystoles (from 16,453 to 1,528 per day); paired polymorphic — by 90 % (from 172 to 17 per day); VTs were not registered (Fig. 3). The optimal AA effect was also confirmed by the control reproducible CE results: absence of high-complexity VA at the submaximal heart rate (123 bpm) was seen.

There was no exercise-induced VT, but a more even distribution of RP, and an increase in the rate of RP clearance from all LV parts were observed during repeated FA metabolism evaluation on the Mexicor therapy (Fig. 4 and Tab. 1).

The patient's state stabilized, dyspnea and palpitations disappeared during continued Mexicor treatment. The patient was given recommendations on antihypertensive therapy and long-term Mexicor therapy, dosing 300 mg/day. He returned to normal active lifestyle.

After 7 years, the patient complained of typical anginal pain when walking for 200 meters or walking uphill. The clinical situation was regarded as unstable angina. The patient was urgently admitted to the hospital.

Very frequent single VPC were registered during HM, mainly of one morphology — 17,308/day; paired monomorphic VPC — 1,411/day; episodes of unstable VT — 73/day maximum up to 9 QRS with VCR up to 207 per min. The VPC morphology was identical to that observed during HM during the first examination of the patient. Repeated CAG (7 years after the first) revealed hemodynamically significant anterior interventricular branch stenosis of the LCA: 70–75 % in the middle third, local stenosis at the border of the middle and distal third up to 70 %, stenosis of the mouth of the diagonal branch up to 65 %. Angioplasty and stenting of the anterior interventricular artery (2 stents) were performed with achievement of the optimal angiographic result. Mexicor (300 mg/day) was resumed. For 4 years after myocardial revascularization, anginal pain did not recur. Control HM and follow-up exercise tests demonstrated a good AA effect.

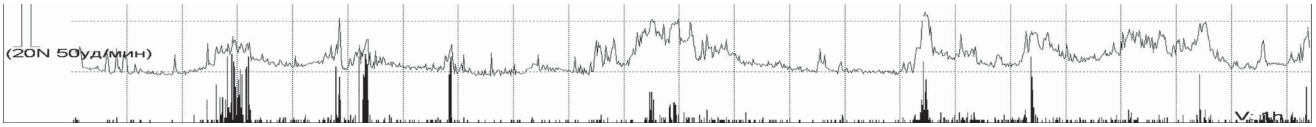

Figure 3. *The distribution of VA in a patient taking Mexicor per day according to HM. Explanation in the text*

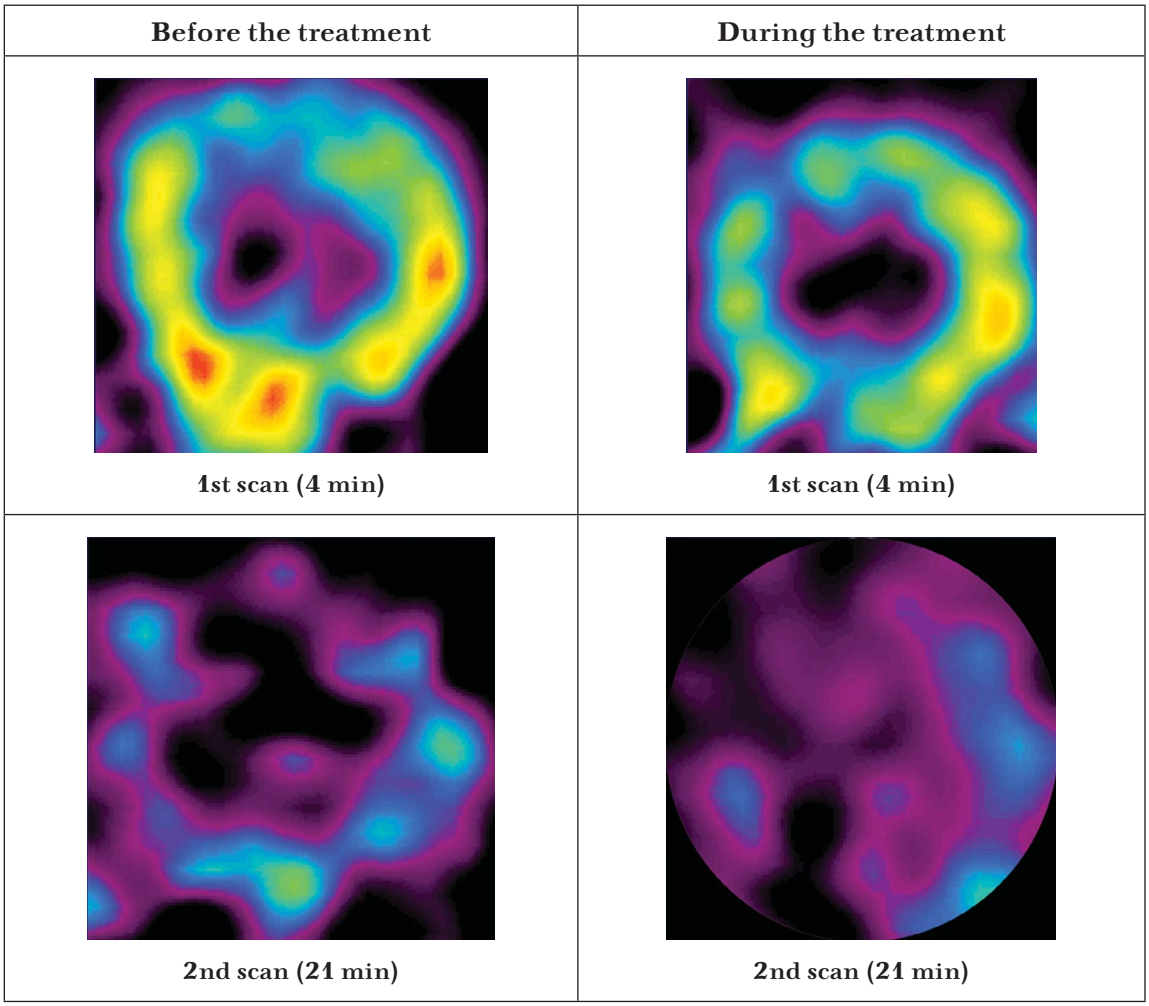

Figure 4. *Estimation of fatty acid metabolism by positron emission tomography with sodium ^{11}C-butyrate. Explanation in the text*

Table 1. *Estimation of fatty acid metabolism by positron emission tomography with sodium ^{11}C-butyrate. The excretion of the radiopharmaceutical before and during the treatment with Mexicor (explanation in the text)*

Left ventricular segments	Before Mexicor treatment (%)	During Mexicor treatment (%)
	Apical segments	
Apical anterior	59	82
Apical lateral	54	80
Apical inferior	56	70
IVS, Apical	57	76
	Mid-cavity segments	
Mid anterior	62	76
Mid lateral	58	71
Mid inferior	60	80
IVS, Mid	65	64
	Basal segments	
Basal anterior	60	70
Basal lateral	57	71
Basal inferior	56	65
IVS, Basal	61	78

Discussion

Summarizing the literature data based on the multi-centre study results and our own experience, it should be admitted that there are many unresolved issues in the VA problem in patients with CAD and choosing AA therapy. In cases where the arrhythmia locus coincides with the ischemia zone, successful myocardial revascularization has a full AA effect, contributes to the patients' survival and a decrease in SCD over a long period of follow-up [1, 22]. According to our data, ischemic VA, especially VT, is arrhythmia with the most unfavorable prognosis, and the myocardial revascularization AA effect ranges from 84 % in the early postoperative period to 65 % in 12 months [2, 9].

With the help of HM, the test with PA, the paired pharmacological exercise tests with Ng, it is possible to evaluate the VA behavior, to confirm its ischemic origin [1, 2, 5, 12]. These seemingly routine and quite accessible methods in many ways help shed light on the VA genesis and choose the correct tactics for managing patients with CAD with concomitant arrhythmia. They are especially useful in those doubtful cases, when the only criterion for stopping an exercise test is the exercise-induced VA/VT. An error in interpreting this test can have very serious consequences, SCD.

It was this type of clinical case that was presented to the readers. Its complexity was associated with both the analysis of PA-induced arrhythmia and the choice of the subsequent therapeutic tactic. There were difficulties in such VT interpretation because it was not accompanied by either clinical or electrographic myocardial ischemia signs and was not explained by the CAG results. However, we can never be convinced of the "benign" nature of exercise-induced VT. Literature contains numerous descriptions of cases of early VA detection and only after a sufficiently long time serious heart diseases were diagnosed [23, 24].

In this particular case, it could not be ruled out that the PA-induced reproducible VT was stopped by Ng, and this forced us to search for evidence of the ischemic nature of arrhythmia. As is known, sympathetic-dependent nature of VT is often associated with myocardial ischemia due to the peculiarities of myocardium innervation — ischemic changes in the anterior wall of the LV lead to an increase in the activity of sympathetic afferent nerves [25]. The assumption of the ischemic nature of VA, based on a positive pharmacological test with Ng, can be explained by the fact that the Ng action mechanism is associated with the release of nitric oxide active substance (NO) in the smooth muscles of the vessels. Subsequently, it was established that in normal physiological conditions, NO serves not only as a powerful vasodilator, but also inhibits vascular wall remodeling processes, prevents platelet adhesion and aggregation, monocyte adhesion, thus protecting the vascular wall from pathological restructuring, followed by atherosclerosis and atherothrombosis development [26]. In addition, based on the literature data, the disappearance of stress-induced myocardial hypoperfusion in intact CA when taking Ng supports vasomotor CA dysfunction as a cause of microcirculation disorder (dynamic obstruction) [27–28].

Continuing the examination of the patient, it was possible to come closer to clarifying the nature of VT. As is known, the PET method with sodium ^{11}C-butyrate determines the myocardial ischemia areas with high accuracy (before the appearance of ECG and Echo ischemia signs) [29]. The PET results in our patient were the evidence of the ischemic origin of VT and could have been caused by vasomotor CA dysfunction, which creates conditions for PA-induced ischemia, and as a result, leads to local metabolic myocardium disorders, and the development of electrical myocardium instability (EMI) manifesting by exercise-induced VT.

It is not only diagnostic difficulties that forced us to continue the examination in search for the true cause of VA. The situation with treatment was complicated by the fact that β-blockers, which are necessary in exercise-induced VT cases, were contraindicated because of the arisen symptomatic sinoatrial (SA) blockade. There was a need to look for ways to treat the patient with ischemic VT, and to prevent possible serious complications. At that time the patient categorically refused pacemaker implantation, which would allow prescribing the indicated β-blockers. We were inspired by

the current hypothesis that ischemic VA is caused by a cascade of metabolic disorders in ischemic myocardium. It made us think that restoring the cardiomyocytes metabolism can lead to the "normalization" of electrophysiological functions of the arrhythmogenesis focus. We started treating our patient with Mexicor after receiving confirmation of microcirculation impairment according to PET with sodium butyrate. That this was the right choice of tactic was proven by the positive results of the Mexicor AA efficacy, confirmed by HM, exercise test and control PET during the treatment.

In our opinion, the further course of clinical events followed this scenario. Vasomotor dysfunction of coronary arteries as a cause of myocardial ischemia at the microcirculatory level accompanied with metabolic disorders in cardiomyocytes was a pathogenetic factor in the mechanism of occurrence of ischemic VT during primary admission of the patient. Over time, developed dysfunction and endothelium microdamage, coupled with dyslipidemia, led to the gradual development and progression of CA atherosclerosis and not dynamic, but organic CA obstruction. Confirmation of this was the match of the ischemia zone detected on the PET and further CA stenosis areas.

Conclusion

So, taking into account the VA etiological and trigger factors, the background clinical situation, we emphasize the importance of determining the nature of arrhythmia in a patient with CAD: whether it is caused by myocardial ischemia or not. It is not always that arrhythmia in a patient with CAD is associated with the disease itself, as it is not always life-threatening and does not force undertake emergency measures. Such ischemic VA characteristics as reproducibility and AA response to nitrates can constitute an important link in diagnosis, choosing the treatment method and predicting its effectiveness. In addition to ischemia, there are other reasons for VA in a patient with stable CAD, which is why the search for the etiology of arrhythmia is the key to success in its elimination. The combination of standard antianginal therapy with metabolic drugs (in particular, Mexicor) in a patient with CAD with ischemic VA is not pointless and can be an important addition, especially in those patients for whom myocardial revascularization is not indicated.

Obviously, the choice of the VA treatment method in a patient with stable CAD should be individual and pathogenetically justified, since the nature of development of arrhythmia in these patients is so diverse, and the approaches to their treatment should differ.

In addition, with this report (a description of a complex clinical case), we want to draw the attention of cardiologists and physicians performing exercise tests to PA-induced ventricular rhythm disorders, even if they are not accompanied by clinical and ECG myocardial ischemia signs. PA-induced VT in patients with CAD risk factors may be its onset.

Conflict of interests

The authors declare no conflict of interests.

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