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HEALTHCARE MANAGEMENT

CLINICAL CASE

Dear colleagues!

The title theme of the ninth issue of the Russian Journal of Cardiology is the socio-psychological aspects of cardiology. This concept requires clarification. We all know that medicine deals not only with the biological characteristics of a person, but also with his social beginning and personality. Cardiovascular pathology is psychosomatic like no other. The life of a human being, a patient, in society, affects his health, leading first to functional and then to morphological changes.

But in addition to psychosomatics, there are many other fields of knowledge in which the doctor worked and has to be oriented. Some of the articles in this issue reveal different aspects of the social and psychological sides of cardiologist's work.

I offer my opinion on the problem of such competences — humanitarian knowledge — for doctors in general and for cardiologists in particular. The problem of development of humanitarian competences is becoming more and more acute. It is quite clear that it is not enough to study philosophy, history and bioethics in being student, as well as the elements of psychology, today, because working with a patient requires not only separate skills, but also a special construction of personality. We can even say that today, in an era of narrow specialization and precision methods, the role of the clinician, as it was a hundred and two hundred years ago, is being rediscovered. But time requires different view and approaches to the conformation of such a doctor.

The issue touches upon the topic of urban space in terms of physical activity as a factor of prophylaxis. This theme is reminiscent of a fairly well-known cultural research trend — urbanism. In the future, doctors, social anthropologists and culturologists, could probably make many interesting discoveries together.

An attempt to talk about the association between psychological "disadaptation" and circulatory disorders is proposed as an opinion. This conversation is always complex, since neuroscience still does not explain how the thought materializes. Nevertheless, it is this phenomenon that a cardiologist deals with when talking about psychological risk factors.

Another important view is disease pattern in the patient's mind. In response to a recently published article by colleagues, we offer an opinion on the reasons for the late help-seeking of patients with clinical picture of acute coronary syndrome, in the qualitative research methodology.

Stress, as the central social and psychological element of cardiology, is certainly in the focus of the current issue of the journal: an article on the results of the ESSE-RF study is devoted to it. And another phenomenon adjoins the concept of stress — masked hypertension, a somatic state closely connected with psychological movements, "soul movements" of the patient.

Finally, ethical and legal aspects should be noted within the scope of the topic. On behalf of the recently opened Ethics Section of the Russian Society of Cardiology, I would like to draw the attention of physicians to the complex intertwining of medical, legal and ethical issues. Two texts written by fellow lawyers and philosophers are devoted to it.

Other articles in the issue, as always, cover many sections of cardiology, including pharmacotherapy, diagnostic methods, risk factors' correction, and fundamental sections of medicine.

I wish you an interesting reading!

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Association of stress with cardiovascular diseases and risk factors in a population (ESSE-RF in Kemerovo region)

Shapovalova E. B., Maksimov S. A., Indukaeva E. V., Artamonova G. V.

Aim. To assess the prevalence of stress and its association with socio-demographic characteristics, cardiovascular risk factors and cardiovascular diseases (CVD) in the Siberian population.

Material and methods. A cross-sectional study was performed in the framework of the Russian multicenter epidemiological study ESSE-RF in the Kemerovo Region in 2013. The presented study included 1628 individuals aged 25 to 64 years. Information was assessed on the presence of stress, some socio-demographic and economic characteristics, a history of CVD, as well as behavioral habits and quality of life. To eliminate the modifying effect of socio-demographic characteristics, a logistic regression analysis was used. The odds ratio (OR) and the 95% confidence interval (CI) were calculated.

Results. The prevalence of stress was 22,6%; stress was statistically significantly more often recorded in women (28,1%) than in men (11,7%). After adjusting for socio-demographic characteristics, stress was statistically significantly more often recorded in people with secondary and primary education compared with those with higher education (24,9% and 19,1%, p=0,006), as well as in people with middle and high financial affluence compared with low affluence (24,5% and 11,3%, p<0,001). This association is observed only at the expense of women. For unemployed participants, the stress rate is higher only among males — 18,8% versus 11,4% among workers (p=0,015). Stress was also statistically significantly more often recorded in groups with arterial hypertension, lack of sleep, quality of life on the EQ-VAS scale and on the EuroQol scale. Smokers are more likely to have stress (23,8% vs 22,0%) and have a history of stroke (35,3% vs 22,2%). Among all CVDs and their risk factors, an inverse association of stress with obesity was revealed only in men.

Conclusion. Study showed that people with stress are under large load of some cardiovascular risk factors. At the same time, ambiguous associations between stress and arterial hypertension and quality of life were obtained. This confirms the need for further study of the association of stress with other factors of cardiovascular risk, taking into account age and gender and socio-economic characteristics of the population.

Key words: stress, risk factors for cardiovascular diseases, epidemiological study.

Conflicts of Interest: nothing to declare.

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It is known that stress can act as a trigger for the development of cardiovascular disease, initiating a systemic inflammation, which may lead to adverse consequences especially for people with low socioeconomic status [1]. However, the contribution of stress to the cause-effect relationships with socio-demographic, behavioral, and psychological risk factors for cardiovascular disease (CVD) is still a subject of discussion. That is because there is no definitive answer to the question of which mechanisms of initiation play the main role in triggering of complex stress-induced pathophysiological processes. The assessment of such a risk factor as stress may include several components and seems to be a laborious and complex process. The reason for this is the lack of a unified assessment of stress, which to some extent may affect the obtained associations [2, 3]. In addition, stress-induced complex body reactions can lead to the development of CVDs in the delayed observation period. INTERHEART study of a representative sample of 24767 people from 52 countries showed that stress doubles the risk of acute myocardial infarction, and this association did not depend on the region of residence, ethnicity, and gender [2]. Another prospective study of the effects of cumulative stress on cardiovascular risk shows association with age, ethnicity, marital status, as well as smoking and obesity, diabetes, depression, and anxiety [4]. As past studies have shown, it is important to take into account the interpretation of the events that have taken place when studying stress, as the same events can have a diametrically opposed meaning for different individuals. Despite differences in research methods (in samples differing in sex, age, and ethnic composition), the negative contribution of stress to the pathogenesis of CVDs has been undisputed for several decades [5]. Difficulties in studying the interaction of stress with cardiovascular risk (CVR) factors and CVDs have led to the accumulation of a vast array of epidemiological, clinical, experimental and pathophysiological studies. However, there are still unresolved issues in the literature regarding the cause-effect relationships between stress and CVDs. It is known that these associations are influenced by external factors (climatic and geographical conditions, legislative and social environment of the region), internal features of the organism (presence of comorbid pathology, certain socio-demographic and behavioral factors, individual susceptibility to stress). Taking into account that the life of any modern person is inseparably associated with stress, its study is given an important place as one of the modifiable CVR factors.

The aim of the study was to assess the prevalence of stress and its associations with socio-demographic characteristics, CVR factors and CVDs in the Siberian population.

Material and methods

The study was carried out as part of the Russian multicenter epidemiological ESSE-RF study in the Kemerovo region in 2013. It included 1628 surveyed persons aged 25 to 64 years.

The questionnaire survey provided information on socio-demographic characteristics (sex, age, education, marital status, employment), stress, behavioral habits (alcohol, smoking, lack of sleep and low physical activity), history of CVD (arterial hypertension, coronary artery disease (CAD), cerebrovascular accident, diabetes mellitus), economic conditions (financial wealth), quality of life.

The criterion of arterial hypertension was considered to be the level of blood pressure ⩾140/90 mm Hg, or lower against the background of hypotensive therapy. CAD presence was assessed on the basis of three epidemiological criteria: coding of electrocardiographic changes according to Minnesota code, Rose questionnaire and history of myocardial infarction.

Obesity was defined as value of body mass index >29 kg/m2. Hypercholesterolemia was diagnosed with total cholesterol levels >5,0 mmol/l, as well as taking of lipid-lowering drugs (mainly statins) in the history. Fasting hyperglycemia was diagnosed with plasma glucose level of venous blood >5,6 mmol/l.

Alcohol consumption was estimated based on the frequency, volume and type of drink consumed. The volume of alcohol consumed per year was calculated and converted to average daily values in grams of ethanol. Those who consumed more than 24 grams of ethanol per day were considered as alcohol abusers.

Smokers were those who smoked at least one cigarette a day or quit smoking less than 1 year ago.

The Perceived Stress Scale was used to determine susceptibility to stress. This scale consists of 10 questions that determined how stressful the previous month was [6]. The order of series obtained was used to calculate the 75th percentile, the values above were considered as a risk factor (5 points and above).

Insufficient sleep was considered to be night's sleep at duration of <7 hours. Insufficient physical activity was taken in case of activity <5 times per week for 30 min (moderate) or physical activity <3 times per week for 20 min (intensive). The level of physical activity was considered to be low if it was below the minimum recommended level

of 150 minutes of moderate or 75 minutes of intensive aerobic exercise per week for adults (medium or high speed walking, or equivalent exercise).

The EUROQOL-EQ-5D international questionnaire and EQ-VAS visual analogue scale were used to assess the quality of life. It was used to score 5 components of the quality of life (mobility, self-care, usual activity, pain/discomfort, anxiety/depression). Each component was assigned 0 points for the absence of disorders, 1 point for moderate disorders and 2 points for severe disorders. The sum of the scores was used as a quantitative assessment of the quality of life. According to the visual analogue scale, interviewers assessed their health status in scores from 0 to 100.

The study was conducted in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Research Institute for Complex Issues of Cardiovascular Diseases. Prior to inclusion in the study, written informed consent was obtained from all participants.

The analysis of stress prevalence depending on socio-demographic characteristics of the sample, presence of cardiovascular diseases and CVR factors was carried out using the Pearson's Chi-square test. Differences in quantitative parameters (age, quality of life according to EQ-VAS and EUROQOL scales) in persons with/without stress were assessed using the Mann-Whitney test and were represented by mean values and standard deviation.

Significant differences in stress prevalence depending on socio-demographic characteristics may affect the association of stress with CVDs and SSR factors. Logistic regression analysis was used to eliminate the modifying effect of socio-demographic characteristics. At the same time, the associations studied were adjusted for the impact of gender, age, employment, level of education, marital status, urban/rural residence, and financial well-being. The odds ratio (OR) and 95% confidence interval (CI) were calculated.

A critical level of statistical significance was 0,05.

Results

Association of stress prevalence with socio-demographic characteristics. The prevalence of stress was 22,6%, and in women (28,1%) it was statistically significantly higher than in men (11,7%), respectively (OR=0,37, 95% CI=0,28-0,49).

Stress prevalence and its association with socio-demographic characteristics are presented in Table 1. Univariate analysis shows differences in stress prevalence depending on gender, employment, level of education, marital status and financial well-being. Thus, stress is statistically significantly more often registered in the unemployed, compared to those who have job (27,2% and 21,0%, p=0,009), persons with secondary and primary education, compared to those with higher education (24,9% and 19,1%, p=0,006), individuals without a family, compared to those with a family (26,5% and 19,8%, p<0,001), participants with medium and high income, compared to those with low income (24,5% and 11,3%, p<0,001).

After adjustment for socio-demographic characteristics, the association with stress became statistically insignificant for such parameters as employment and marital status. In other cases, the regularities remained the same.

Association of CVR factors with stress in different gender groups. An analysis of CVR factors and stress relationships in men and women revealed an association between stress and secondary and primary education, as well as financial well-being (only for women). Thus, stress is more often recorded in women with secondary and primary education (33,4%) compared with higher education (24,2% (p=0,002)), and less often in women with low incomes — 13,5% versus 32,2% (p= 0,001). For unemployed, the stress prevalence is higher only among males — 18,8% versus 11,4% (p=0,015). The adjustment for socio-demographic characteristics did not change the above associations.

Association of stress with CVDs and CVR factors. Univariate analysis showed differences in associations between stress prevalence and arterial hypertension, CAD, as well as factors such as sleep adequacy, alcohol abuse, and average quality of life (both EQ-VAS and EUROQOL) (Table 2). The stress frequency is lower in persons with arterial hypertension than without it (19,7% and 24,8%, p=0,012, respectively), as well as in alcohol abusers, compared to those who do not abuse alcohol (18,9% and 25,6%, p<0,001). In contrast, the stress rate was higher in the group with lack of sleep (29,0% vs. 20,0%, p<0,001) and CAD (30,7% vs. 20,9%, p<0,001). The quality of life of persons with recorded stress, as compared to those without it, was higher on both the EQ-VAS scale (67,9±16,1 vs. 59,6±16,8, p<0,001) and the EUROQOL scale (1,36±1,34 vs. 2,52±1,53, p<0,001).

Adjustment for socio-demographic characteristics has not changed the importance of associations with stress in the groups: with arterial hypertension (OR=0,75, 95% CI 0,57-0,98), lack of sleep (OR=1,72, 95% CI 1,33-2,22), quality of life on the EQ-VAS scale (OR=0,07, 95% CI 0,96-0,98) and on the EUROQOL scale (OR=1,66, 95% CI 1,51-1,82).

Table 1

Associations of stress with socio-demographic characteristics

Characteristics		N	Stress		Logistic regression		
			%, M±SD	P	OR	95% CI	P
Sex	Males	700	11,7	<0,001	0,37	0,28-0,49	<0,001
	Females	928	28,1				
Age	Stress	367	45,6±11,4	0,10	1,00	0,99-1,01	0,86
	No stress	1258	47,6±11,2				
Age groups (years)	25-34	331	21,2	0,20	–	–	–
	35-44	332	19,1				
	45-54	434	25,1				
	55-64	531	23,6				
Employment	Yes	255	21,0	0,009	0,84	0,63-1,11	0,22
	No	112	27,2				
Secondary education	Yes	245	24,9	0,006	1,37	1,05-1,78	0,019
	No	122	19,1				
Lack of family	Yes	172	26,5	<0,001	1,08	0,84-1,39	0,56
	No	191	19,8				
Rural residence	Yes	66	23,9	0,6	0,96	0,69-1,32	0,79
	No	300	22,5				
Low income	Yes	27	11,3	<0,001	0,42	0,27-0,65	<0,001
	No	340	24,5				

Table 2

Associations of stress with CVR and CVD factors

Risk factors		N	Stress		Logistic regression		
			%, M±SD	P	OR	95% CI	P
Lack of sleep	Yes	135	29,0	<0,001	1,72	1,33-2,22	<0,001
	No	232	20,0				
Low physical activity	Yes	92	22,3	0,9	1,16	0,86-1,56	0,91
	No	265	22,4				
Smoking	Yes	118	23,8	0,42	1,61	1,21-2,14	<0,001
	No	249	22,0				
Alcohol	Yes	139	18,9	<0,001	0,99	0,75-1,30	0,92
	No	228	25,6				
Quality of LIfe (EQ-VAS)	Stress	367	67,9±16,1	<0,001	0,97	0,96-0,98	<0,001
	No stress	1258	59,6±16,8				
Quality of life (EUROQOL)	Stress	367	1,36±1,34	<0,001	1,66	1,51-1,82	<0,001
	No stress	1258	2,52±1,53				
Hypercholesterolemia	Yes	194	22,6	0,97	0,91	0,71-1,18	0,48
	No	171	22,7				
Hyperglycemia	Yes	59	21,2	0,53	0,88	0,63-1,24	0,47
	No	306	22,9				
Arterial hypertension	Yes	139	19,7	0,012	0,75	0,57-0,98	0,032
	No	228	24,8				
Coronary artery disease	Yes	83	30,7	<0,001	0,99	0,98-1,01	0,12
	No	280	20,9				
Stroke	Yes	12	35,3	0,074	2,21	1,04-4,73	0,040
	No	351	22,2				
Obesity	Yes	124	21,7	0,53	0,80	0,61-1,04	0,099
	No	242	23,1				
Diabetes mellitus	Yes	13	20,6	0,71	0,92	0,48-1,76	0,80
	No	350	22,6				

Associations of stress with alcohol abuse and CAD were not statistically significant. On the contrary, there were statistically significant associations of stress with smoking and stroke in the history: stress was observed more likely in smokers (OR=1,61, 95% CI 1,21-2,14) and persons with stroke in the history (OR=2,21, 95% CI 1,04-4,73).

Association of stress with CVDs and CVR factors in different sexual groups. Among all CVDs and their CVR factors, only males have an inverse relationship between stress prevalence and obesity. Thus, association of stress prevalence with obesity in men was statistically significantly lower (8,7% vs. 14,7%, respectively, p=0,03), After adjustment for socio-demographic characteristics the significance of the association has not changed (OR=0,54, 95% CI 0,30-0,95). No other associations between stress and CVDs depending of sex were found.

Discussion

Thus, according to the survey results, the prevalence of stress was 22,6%. In women, stress was statistically significantly recorded almost 2 times more often than in men. The high prevalence of stress in women was also observed in the Swedish national study [7], which may indicate a strong association between stress and female sex.

Sleep disorders, like stress, are an important problem in modern society.

A number of studies have found that sleep disorder increases the risk of various diseases, including CVDs. A nationwide Japanese study of the relationship between sleep disorders and stress showed that people who felt high levels of stress were more prone to sleep disorder [8]. In study of Alosaimi FD, et al. (2015) a similar positive association of stress with lack of sleep was observed [9]. Our study obtained a statistically significant direct relationship between insufficient sleep and stress. Behavioural habits such as drinking and smoking were also positively related to sleep disorders. Smoking, as a strategy for correction of sleep disorder, is known to contribute significantly to sleep pathologies. Smokers are more likely to experience sleep disorders such as night apnea, defect sleep quality, insomnia, which, in turn, are risk factors for the development of many chronic diseases of modern civilization (obesity, CVDs, diabetes) [10].

In this study, a statistically significant association of bad habits (smoking and alcohol abuse) with stress has been identified among both smokers and alcohol abusers. However, after adjustment for socio-demographic factors, the significance of the stress relationship remained only for smokers.

Stress has long been recognized as a risk factor for smoking. There is ample evidence, both epidemiological and clinical, of the direct association between stress and substance use behaviour. Stress also relates to both smoking addiction and its successful cessation. For example, past studies have shown that smokers have a higher level of stress than non-smokers and former smokers [11].

It is known that the quality of life directly depends on socio-demographic, anthropometric, anamnestic, psychological factors, as well as the current morbid status. However, there is still no consensus on the factors influencing the quality of life. At the same time, certain nosologies are characterized by their own set of the most studied factors influencing the quality of life. In this study, the reverse association of stress with quality of life is obtained both on the EUROQOL-EQ-5D scale and on the EQ-VAS scale. In this study, people with stress have a higher quality of life than those without it. Thus, stress has been associated with higher quality of life values, which indicates a complex relationship between quality of life and stress.

The study found an association of stress with obesity only in men. Obesity was statistically significantly less common in men with stress than in men without stress. According to the literature, the evidence of the relationship between stress and body mass index is rather contradictory. On the one hand, given the relationship between stress and the addictions underlying many chronic diseases, stress contributes to weight gain, including obesity [10]. On the other hand, a meta-analysis of data from 1,617,46 participants in 13 European studies (49% of men, mean age 43,7 years) showed that stress associated with hard work can be associated with both weight gain and loss, reflecting a U-shaped association of stress and body mass index [12]. In the study by Boyce JA, et al. (2014) examining stress and body mass index in New Zealand freshmen showed that students with high levels of stress gained weight if they had an initial high body mass index, and lost weight in case of initial low body mass index [13].

Previous studies have proven the role of chronic stress in the formation and progression of arterial hypertension in particular and CVDs in general, directly potentiating systemic inflammation, as well as indirectly influencing behavioral changes. In a study by Lu X, et al. (2019) shows that the association of stress with arterial hypertension changed by gender and ethnicity [14]. Asian-American men with high levels of stress were significantly more likely to develop arterial hypertension than men with low stress. There was no association between perceived stress and hypertension for females. In our study of the relationship between stress and arterial hypertension, no association was found for both men and women. On the contrary, persons with normal

blood pressure were more likely to experience stress than persons with hypertension. After adjustment for socio-demographic factors, the statistically significant relationship between hypertension and stress did not change.

Work and stress are inseparably associated in modern society, affecting each other. The results of the research show that people with jobs were less stressed than unemployed people. The unemployed had a higher prevalence of stress only because of their male counterparts, which suggests that stress was more related to unemployment among men than women. This is confirmed by the literature, where a cohort study by Mæhlisen MH, et al. (2018) found that domestic stress almost doubled the risk of unemployment [15].

It is known that chronic stress increases the risk of CAD [1, 2]. INTERHEART's study in a representative sample of 52 countries showed that stress doubles the risk of myocardial infarction, regardless of gender, race, or region of residence. In this study, people with CAD were more likely to have stress than people without CAD, but this association was not strong in case of elimination the modifying effects of socio-demographic characteristics. Thus, we did not get a significant association of stress with CAD. The REGARDS's study showed that groups of people with high levels of stress were at increased risk of CAD, but only for those with below average income [16].

Poverty is known to be a source of chronic stress and can have a negative impact on both physical and mental health. At the same time, it can be ambiguously perceived by the population, as indicated by study of Hjelm L, et al. (2018) examining the impact of state poverty alleviation programmes on stress among poor households in Zambia, South Africa. The study found that financial programmes did not change the frequency of stress, but that this improved food security associated with improved food quality, resulting in an indirect reduction in the prevalence of stress [17]. Absence of associations of financial income with stress was also noted in another study [9]. However, persons over 60 years old have an association between low income and higher levels of stress [7], which indicates a modifying effect of age. In the present study, stress was almost twice as rare in low-income individuals as in middle- and high-income individuals. Adjustment for socio-demographic factors did not change the importance of association. However, this association was observed only at the expense of women.

A statistically significant association of secondary education and stress is obtained. Thus, among individuals with secondary education stress prevalence is higher than with higher education. Moreover, this association is observed among women. Thus, women with secondary education were statistically significantly more likely have stress. For men, the association of the level of education with stress was not found in our study. In the study by Hjelm L, et al. (2018) among poor households in Zambia, the level of education also did not show a strong association with stress among both men and women [17].

However, in a population study examining the prevalence of stress after 65 years of age, higher average levels of d stress were associated with low levels of education [7].

Stress was less common among married people than among single people, but the adjustment for socio-demographic factors led to a leveling of this relationship. The absence of a relationship between marital status and stress was also noted in the study by Alosaimi FD, et al. (2015) [9]. At the same time, in a population study, singlehood was statistically significantly associated with stress in older persons [7].

Conclusion

Thus, when studying the relationship of stress with CVD risk factors, it was revealed that stress is more often recorded in women and in people with lack of sleep. Socio-demographic factors such as secondary education and financial well-being are also closely related to stress.

It has been shown that people with stress have a large load of some CVR factors. At the same time, ambiguous associations of stress with arterial hypertension and quality of life were obtained.

It is noteworthy that these associations remained after the adjustment for the socio-demographic factors. This confirms the need for further study of the association of stress with other CVR factors, taking into account the sex, age and socio-economic characteristics of the population, to identify the effects of stress on the cardiovascular system.

Limitations. An important limitation due to the cross-sectional design of the study is the inability to draw conclusions about the cause-effect associations. We have also not studied the contribution of depression, which in itself can cause stress and, conversely, lead to additive effect. We have not studied the modifying effects of age and socioeconomic status, although there is evidence that age may influence the associations obtained, and low socioeconomic status is an aggravating factor for stress. In addition, stress levels were not graded, which could lead to ambiguous interpretation of the results.

Conflicts of Interest: nothing to declare.

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Modern fixed combinations of antihypertensive drugs in the treatment of arterial hypertension and obesity: can this comorbid pathology be effectively controlled?

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Aim. To assess the effect of azilsartan/chlortalidone and irbesartan/hydrochlorothiazide fixed combinations on office, daily peripheral and central blood pressure (BP), daily parameters of aortic stiffness and structural and functional state of the left ventricle in patients with arterial hypertension (AH) and obesity.

Material and methods. The study included 46 patients with hypertension and obesity aged 35 to 55 years. In the beginning of the study and after 6 months of treatment with azilsartan/chlortalidone (AZL/C) or irbesartan/hydrochlorothiazide (IRB/H) all patients underwent a comprehensive clinical and instrumental and laboratory examination, including a general examination with anthropometric measurements, office measurement of BP, electrocardiography, echocardiography, 24-hour BP monitoring with analysis of central BP and the main parameters of aortic stiffness, biochemical blood tests.

Results. Long-term use of two fixed combinations of sartan and diuretic was accompanied by a significant decrease of office and daily BP. However, in the AZL/C use, this change was more pronounced than in the IRB/H. Also, in the AZL/H group, a significantly larger number of patients reach a normalization of 24-hour BP profile. Both studied drugs significantly reduced central BP, which indicates their positive effect on aortic stiffness. However, a significant change in the daily pulse wave velocity determined by the Vasotens system was not detected. During therapy, in both groups, a decrease in left ventricular myocardial mass indexed by body surface area was revealed. It was more noticeable in the AZL/H group and when height indexed^{2,7}. In both groups, an insignificant decrease in creatinine level and an increase in glomerular filtration rate, more noticeable with the administration of AZL/H, were noted. There were no significant fluctuations in the level of uric acid and potassium, which confirms the safety of the use of the studied combinations in patients with AH and obesity.

Conclusion. According to studies, AH in obese patients is less well controlled than in patients with normal body weight. AZL/H and IRB/H are effective and safe drugs for the treatment of AH in obese patients. However, long-term treatment of AZL/H allows reaching a more pronounced decrease in peripheral and central BP, improving the structural and functional state of the left ventricular myocardium in comparison with IRB/H.

Key words: arterial hypertension, metabolically active obesity, azilsartan/chlortalidone, left ventricular geometry, central blood pressure, daily pulse wave velocity.

Conflicts of Interest: the study was carried out with the financial support of OOO Takeda Pharmaceutical, the study was sponsored by Society of Heart Failure Specialists.

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Obesity and associated cardiovascular diseases (CVDs) pose a serious public health threat. CVDs are the leading cause of death among obese patients. Arterial hypertension (AH) is one of the most closely related to obesity disease. According to the ESSE-RF study, in the group of patients with normal body weight the AH prevalence is 32,9% and 26,0% among men and women, in the group with overweight — 45,8% and 38,5%, in the group with class 3 obesity AH is revealed in 71,9ц% and 67,8% of cases [1]. Blood pressure (BP) control is an important requirement for successful AH treatment. Research shows that people with obesity have less controlled AH. Thus, in the study by Booth HP, et al. researchers analyzed data from 153,000 patients aged 30 to 100 in the UK [2]. As the body mass index (BMI) increased, the number of patients receiving combined antihypertensive therapy was found to be increasing. At the same time, the number of patients who reached the target BP levels decreased, becoming the lowest in class 3obesity (69% in normal weight, 51% in morbid obesity).

According to ESC/ESH Arterial Hypertension (Management of) Guidelines, most patients, with the exception of patients with stage 1 AH of low cardiovascular risk, are shown to be treated with two drugs using a fixed combination of angiotensin converting enzyme inhibitors (ACEI) or an angiotensin receptor antagonist (ARA) with calcium channel blocker (CCB) or diuretic [3]. According to recent studies, azilsartan/chlorthalidone (AZL/C) is an effective and currently the only fixed combination of ARA and thiazid-like diuretic. A multicenter study by Neutel J, et al. compared the efficacy and safety of fixed combinations of AZL/C and olmesartan/hydrochlorothiazide (OLM/H) in 837 patients with stage 2 AH over 18 years of age.

The follow-up period was 52 weeks. Both drugs were effective and safe in reducing blood pressure, but lower doses of the drug were used in the AZL/C group than in the OLM/H group to achieve target levels [4]. Similar data with the same drugs were obtained in study by Bakris G, et al. involving 153 patients with stage 3 chronic kidney disease (CKD) [5]. The effect of AZL/C on renal function was evaluated in rat with metabolic syndrome or diabetes mellitus (DM). The studied combination had more pronounced nephroprotective and anti-inflammatory properties than AZL or chlortalidone monotherapy [6, 7]. In most studies with AZL/C using, the effect of the drug on office and daily peripheral BP was studied. The purpose of our study was a comparative assessment of the influence of AZL/C (Edarbi Klo, Takeda, Japan) and a fixed combination of irbesartan/hypothiazide (IRB/H, Coaprovel, Sanofi, France) on the office, daily peripheral and central BP, daily parameters of aortic stiffness and structural and functional of the left ventricle (LV) in patients with AH and obesity with long-term treatment.

Material and methods

The study included 46 patients with AH and obesity at the age of 35 to 55 years. AH was diagnosed by office BP measurements (⩾140/90 mmHg), obesity was diagnosed with an increase in BMI >30 kg/m². The exclusion criterion was the presence of acute myocardial infarction (AMI), acute cerebrovascular accident (ACA), diabetes mellitus (DM), severe renal and hepatic failure in the history. The majority of patients (43%) receive combined antihypertensive therapy before inclusion in the study, 25% — monotherapy, 31% did not take any drugs. All patients signed informed consent for voluntary participation in the study.

The combination therapies were prescribed according to the instructions for use. For comparability of the study groups, the medications were prescribed in a strict sequence: the first patient included in the study was prescribed the original AZL/C, the second — the original IRB/H. Such a sequence of prescribing two fixed combinations was maintained in the following.

The general characteristics of patients are presented in Table 1. All patients at inclusion in the study and after 6 months of therapy were carried out a comprehensive clinical, instrumental and laboratory examination, including general examination with anthropometric measurements, office BP measurement, echocardiography, 24-hour monitoring with the analysis of central BP and the main parameters of aortic stiffness.

BP measurement. The office BP measurement was carried out upon inclusion in the study, after 1, 3 and 6 months of therapy following a 10-minute sitting period using an Omron 5 automatic BP monitor. The first measurement was excluded from the analysis and the mean value between the 2nd and 3rd measurement was determined. Between visits, patients performed a BP self-monitoring using an automatic BP monitor 2 times a day (in the morning and evening), followed by a mean value between the 2nd and 3rd measurements (the first of which was excluded), which was recorded in a diary.

24-hour BP monitoring was carried out when included in the study and after 6 months of therapy using the BPLab system. The following indicators were analyzed: average daily, day and night values of systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), type of daily curve, day and night variability of SBP and DBP.

Table 1

General characteristics of the patients included in the study

Parameter	AZL/C (n=23) group	IRB/H (n=23) group
Age (years)	46,4±7,0	48,8±5,5
Sex	males. 13 (56%) females 10 (44%)	males 12 (52%) females 11 (48%)
Waist (sm)	males 113,1±12,9 females 110,6±10,9	males 113,1±12,3 females 104,8±10,3
Waist/hip width	males 0,98±0,07 females 0,95±0,09	males 0,98±0,06 females 0,89±0,06
Waist/height	0,64±0,06	0,64±0,07
AH stage, n (%)	1 — 11 (48%) 2 — 12 (52%)	1 — 13 (57%) 2 — 10 (43%)
SBP (mm Hg)	152,4±12,5	152,5±10,6
DBP (mm Hg)	100,2±9,7	100,2±8,0
Dyslipidemia, n (%)	15 (75%)	14 (70%)
Total cholesterol (mmol/L)	5,7±0,9	5,6±1,0
LDL (mmol/L)	3,6±0,8	3,4±0,7
Triglycerides (mmol/L)	2,1±0,9	1,8±0,9
Microalbuminuria, n, (%)	10 (43%)	8 (35%)
Creatinine (μmol/L)	86,1±16,4	84,9±12,3
GFR (ml/min/1,73 m2)	94,8±13,0	95,5±9,9

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure, LDL — low density lipoproteins, HDL — high density lipoproteins, GFR — glomerular filtration rate.

Aortic stiffness analysis. All patients were analyzed for aortic stiffness and central pulse wave within 24 hours using BPLab Vasotens system when including in the study and after 6 months of antihypertensive therapy. The following parameters were estimated: average values of central SBP, DBP and PP, aortic augmentation index (AIxao), pulse wave velocity (PWV).

Echocardiography. Echocardiography was performed on a VIVID 7 apparatus of General Electric (USA) in accordance with the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI). The basic linear and volume indicators of the LV, LV mass (LVM), followed by indexing onto the body surface area or height, the relative thickness (RT) were determined and calculated. Violation of LV geometry was determined by LVM and RT. The linear and volume dimensions of the atria and the function of the right ventricle were also evaluated.

Laboratory tests. When included in the study, all patients underwent a biochemical blood test with an assessment of the lipid profile, glucose, creatinine, uric acid, electrolytes. To assess the safety of the studied combined drugs, the level of creatinine, uric acid and blood electrolytes was determined again after 3 and 6 months of antihypertensive therapy.

Statistical analysis. Statistical processing of the material was carried out with the help of the "Stastica 10.0" (Statsoft, USA) software package. When choosing the method of data comparison, the normality of distribution of a characteristic in subgroups was taken into account, considering the Shapiro-Wilk test. Under normal distribution, the mean value and standard deviation were calculated. The null hypothesis when comparing groups deviated at a significance level of $<0,05$. The comparability of the formed groups was assessed by quantitative indicators using the Student's t-test, by qualitative indicators using the Pearson's chi-squared test or the Fisher's exact test. In multiple comparisons, one-way ANOVA test was used.

The study was conducted in accordance with Good Clinical Practice standards and the principles

Table 2

Динамика офисного АД на фоне терапии исследуемыми препаратами

Visit	AZL/C (n=23) group		IRB/H (n=23) group	
	SBP (mm Hg)	DBP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)
Inclusion	152,4±12,5	100,2±9,7	152,5±10,6	100,2±8,0
Visit 2 (1 month)	129,9±15,0*	87,0±9,5*	131,3±15,2*	88,5±9,7*
Visit 3 (3 months)	129,7±14,6*	86,8±9,5*	134,9±13,9*	91,9±9,6*
Visit 4 (6 months)	122,9±8,8*	84,2±6,9*	133,4±12,3*#	91,9±7,8*#

Note: * — p<0,05 in comparison with the inclusion visit, # — p <0,05 in comparison with the AZL-X group.

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure.

of the Declaration of Helsinki. The study protocol was approved by the Inter-university Ethical Committee. Prior to inclusion in the study, written informed consent was obtained from all participants.

This article is a fragment of the Prospective observational stUdy of aZilsartan/chlortalidone compared with irbesartan/hydrochlorothiaZide combination therapy in patients with arteriaL hypertension and obEsity in routine clinical practice (PUZZLE), organized by its authors. This prospective study, including the publication of its preliminary results with the above aim, objectives and design, has been approved by international experts and registered on the clinicaltrials.gov website under the number: NCT03006796.

Results

The study included patients of middle age (47,6±6,25 years) with 1-2 stage AH and metabolically active form of obesity, which was confirmed by anthropometric data, the presence of metabolic disorders in patients, in particular, dyslipidemia, which was found in most (75%) patients. Microalbuminuria (MAU) from 30 to 100 mg/dL was observed in 18 (39%) patients. No renal dysfunction was detected. When comparing the data of the patients included in the study, there were no significant differences between the group of AZL/C and IRB/H.

Over the entire follow-up period 4 visits were made, during which the office BP measurement was carried out: an inclusion visit, after 1, 3 and 6 months of therapy (Table 2). Against the background of AZL/C and IRB/H intake, a reliable decrease in the office SBP and DBP was found during the month, by an average of 22,4 and 12,3 mm Hg, respectively. After 3 months, BP in the AZL/C group was stabilized, while the IRB/H group showed an increase in BP in some patients, which required an increase of the drug dose. By the end of the observation (after 6 months of therapy), a significantly lower BP was observed against the background of AZL/C intake than in the IRB/H group (122,9 and 84,2 mm Hg vs. 133,4 and 91.9 mm Hg, respectively).

Table 3

The number of patients reached the target BP level during treatment

Visit	AZL/C (n=23) group	IRB/H (n=23) group
Visit 2 (1 month)	18 (78%)	15 (65%)
Visit 3 (3 months)	21 (91%)	18 (78%)
Visit 4 (6 months)	21 (91%)	19 (83%)

During the observation period, 21 (91%) patients reached the target values of office BP (<140/90 mm Hg) in the group of AZL/C, and 19 (83%) patients in the IRB/H group (Table 3). In the majority of patients, BP normalization occurred during the 1st month of therapy. In the IRB/H group after 3 months of therapy, 7 patients (30%) needed a dose correction to achieve the target BP levels.

For comparison, in the AZL/C group dose correction was nor requires on the 3st visit.

When analyzing the data of 24-hour BP monitoring (Table 4), in both groups, a significant decrease in the average daily, day and night values of SBP and DBP was observed, on average, by 13,5 and 11,2 mm Hg. for SBP and DBP during the day. In the analysis of daily BP variations on the background of 6-month antihypertensive therapy in both groups the increase in the number of patients with normalized daily BP profile (dipper) was revealed. However, in the AZL/C group such patients were much more than in the IRB/H group (26% of patients with dipper type before treatment, 61% — after treatment). In both groups there was a tendency to decrease the variability of SBP and DBP during day and night time, but no

Table 4

Changes in 24-hour BP monitoring in patients taking studied drugs

Parameters		AZL/C (n=23) group		IRB/H (n=23) group	
		Before treatment	After treatment	Before treatment	After treatment
av. dly SBP		140,5±12,0	126,1±6,7*	139,4±11,5	128,7±7,4*
av. dly DBP		98,1±10,8	78,7±6,5*	89,1±5,2	82,1±4,2*
av. SBP day		143,1±11,3	128,7±7,7*	143,6±10,2	134,6±8,4*
av. DBP night		93,7±10,2	82,6±9,1*	93,5±5,7	87,5±5,3*
av. SBP day		134,3±13,6	119,8±11,0*	123,8±12,9	114,2±7,9
av. DBP night		85,3±12,5	74,5±10,2*	76,7±6,8	70,1±5,7*
Type	dipper non-dipper over-dipper n.peaker	6 (26%) 13 (57%) 1 (4%) 3 (13%)	14 (61%)* 8 (35%) 1 (4%) 0	10 (43%) 11 (48%) 2 (9%) 0	15 (66%) 7 (30%) 1 (4%) 0
Variability SBP (day)		14,1±3,8	13,2±3,1	13,6±3,1	11,7±3,4
Variability SBP (night)		12,1±4,3	11,6±3,6	11,8±4,3	10,8±2,4
Variability BBP (day)		10,8±3,5	10,2±3,0	11,2±2,5	10,8±2,3
Variability BBP (night)		9,9±3,5	8,7±3,3	10,8±4,2	9,0±2,6

Note: * — p<0,05 in comparison with the data before treatment.

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure.

Table 5

Changes of central blood pressure and aortic stiffness parameters in patients taking studied drugs

Parameters	AZL/C (n=23) group		IRB/H (n=23) group	
	Before treatment	After treatment	Before treatment	After treatment
av. dly SBP (mm Hg)	131,1±10,9	116,6±7,3*	129,9±11,3	118,0±6,4*
av. dly DBP (mm Hg)	94,3±10,5	82,5±7,9*	92,9±5,1	84,4±4,3*
av. SBP day (mm Hg)	132,4±10,6	119,0±8,5*	134,2±10,7	123,1±7,2*
av. DBP day (mm Hg)	96,6±10,3	84,9±8,8*	97,7±5,7	89,8±5,5*
av. SBP night (mm Hg)	126,5±13,2	111,7±10,9*	118,6±12,6	106,6±8,2
av. DBP night (mm Hg)	87,9±12,8	76,7±10,2*	81,5±5,6	72,3±5,2*
av. dly Aix (%)	26 (18-30)	16 (12-33)	28 (19-34)	14 (9-23)
av. dly PWV (m/s)	10,4±1,0	10,3±1,1	9,9±1,1	9,8±1,4

Note: * — p <0.05 in comparison with the visit before treatment.

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure, AIx — augmentation index, PWV — pulse wave velocity.

significant differences between the groups were revealed.

Against the background of 6-month combination therapy, in both groups there was a significant decrease in the central daily, day and night SBP and DBP, on average, by 13,2 and 10,2 mm Hg for SBP and DBP per day (Table. 5). One of the parameters of aortic stiffness (AIxao) also decreased in both groups; however, there was no significant difference between the groups. In addition, in both groups, there was no

Table 6

Changes of EchoCG parameters in patients taking studied drugs

Parameters		AZL/C (n=23) group		IRB/H (n=23) group	
		Before treatment	After treatment	Before treatment	After treatment
LVMI m		96,7±11,2	95,6±9,4	97,8±9,3	96,0±9,1
LVMI f		87,6±9,1	86,7±8,8	86,1±8,9	85,7±9,0
LVMH m		47,5±5,1	43,2±4,8	41,9±5,4	46,1±4,3
LVMH f		43,7±5,3	40,7±5,4	38,2±4,9	39,4±5,3
LV geometry	normal CR CH EH	6 (26%) 11 (49%) 4 (17%) 2 (8%)	12 (53%)* 7 (30%) 4 (17%) 0	8 (35%) 10 (43%) 3 (14%) 2 (8%)	11 (49%) 7 (30%) 4 (17%) 1 (4%)
LVEDVI (ml/m^2)		59,2±8,4	56,9±8,2	59,8±8,9	60,5±9,2
LVEF, %		63,7±5,7	64,4±4,4	62,7±4,2	61,3±4,9
LAVI (ml/m^2)		28,6±5,9	28,3±4,6	26,3±5,8	25,8±5,9
RAVI (ml/m^2)		22,4±5,9	20,7±3,9	20,7±5,2	22,1±3,9
LV basal diameter (sm)		3,5±0,3	3,6±0,4	3,4±0,4	3,6±0,5
TAPSE		2,2±0,2	2,3±0,3	2,3±0,4	2,4±0,3

Note: * — p<0,05 in comparison with the visit before treatment.

Abbreviations: LVMI — left ventricular mass index (f — female, m — male), CR — concentric remodeling, CG — concentric hypertrophy, EG — eccentric hypertrophy, LVEDVI — left ventricular end-diastolic volume index, LVEF — LV ejection fraction, LAVI — left atrium volume index, RAVI — right atrium volume index, TAPSE — tricuspid annular plane systolic excursion.

Table 7

Changes of creatinine levels and GFR in patients taking studied drugs

Visit	AZL/C (n=23) group		IRB/H (n=23) group	
	Creatinine (μmol/L)	GFR (ml/min/1.73 m^2)	Creatinine (μmol/L)	GFR (ml/min/1.73 m^2)
Inclusion	85,5±15,2	95,6±17,1	84,9±12,3	95,5±9,9
Visit 3 (3 months)	73,5±10,9	102,4±15,8	85,3±11,2	94,6±8,1
Visit 4 (6 months)	78,1±10,9	102,4±13,2	82,1±11,3	101,1±4,5

Abbreviation: GFR — glomerular filtration rate.

Table 8

Changes of laboratory parameters in patients taking studied drugs

Visit	AZL/C (n=23) group		IRB/H (n=23) group	
	Uric acid (μmol/L)	Potassium (mmol/L)	Uric acid (μmol/L)	Potassium (mmol/L)
Inclusion	383,8±41,1	4,4±0,5	340,8±45,3	4,7±0,4
Visit 3 (3 months)	367,2±43,1	4,6±0,4	365,4±31,6	4,3±0,6
Visit 4 (6 months)	352,9±43,0	4,5±0,3	374,5±44,2	4,4±0,3

significant change in the daily PWV during therapy, which may be related to the peculiarities of determining this indicator by Vasotens system.

When included in the study, all patients were given recommendations to reduce body weight: a diet with a calorie restriction of food to 1,500 kcal/day in women and 1800 kcal/day in men, regular exercise up to 30 minutes a day, changes in eating behavior (reduction of the portion size, restriction of food intake in the evening and night, regular frequent meals in small amounts.

In both groups there was a decrease in body weight by 7,2±2,8 kg on average. At the analysis of the structural and functional state of myocardium according to EchoCG data in dynamics (Table 6) LVM was indexed not only on the body surface area (BSA), but also on growth2,7. On the background of antihypertensive therapy in both groups there was a slight LVMi decrease.

In the analysis of LVMi dynamics, a more pronounced decrease was found in the AZL/C group, but there were no significant differences between the groups. Also, in the group of AZL/C, more patients had normalization of LV geometry: 2 patients from the subtype "eccentric hypertrophy" and 4 patients from the subtype "concentric remodeling" went to the "norm". The number of patients with LV concentric hypertrophy before and after treatment did not change in the group of AZL/C. Number of patients with LV concentric hypertrophy in the group of IRB/H increased by 1 patient, which may be related to insufficiently long period of observation and progression of AH.

In both groups, no significant dynamics of the LV, RV and atria volume were revealed.

To assess the safety of combined drugs, as well as their nephroprotective effect, we analyzed the laboratory data of patients when included in the study, after 3 and 6 months of therapy. During the whole period of observation in both groups there was a tendency to decrease the creatinine level and increase glomerular filtration rate (GFR), calculated by CKD-EPI formula (Table 7). It was more noticeable against the background of AZL/C intake. No significant variations of urine acid and potassium levels were found in both groups during therapy (Table 8), which confirms the safety of the studied combinations in patients with AH and obesity.

Discussion

An important requirement for successful AH treatment is the control of BP levels. Most patients require at least two antihypertensive drugs to achieve the target BP level. In our study, a comparative assessment of the efficacy and safety of AZL/C and IRB/H in patients with AH and obesity was carried out against a background of 6-month therapy. In the analysis of office measurements and 24-hour BP monitoring it was found that both combinations effectively reduce peripheral and central BP, but in the group of AZL/C this reduction was stronger and was achieved by taking lower doses of the drug. Possibly, the efficacy of AZL/C in patients with obesity is explained by nephroprotective and anti-inflammatory effects of azilsartan, as well as the ability to increase the sensitivity of tissues to insulin. The study by Kumar K, et al. involved 305 patients with AH and DM 2 with excess body weight (BMI 26,6±3,8 kg/m²) [8].

One hundred fifty two patients received AZL, the rest ones received telmisartan for 6 months. In the AZL group a more significant decrease in BP, as well as in the level of glucose and glycated hemoglobin (HbA1C), was observed than in the telmisartan group, which, according to the authors, is associated with the pleiotropic effect of the drug [9]. In our study, a stable BP decrease on the background of AZL/C intake resulted in a more significant decrease in LV myocardium mass and improvement of its structural and functional state than in the IRB/H group. However, no significant change in aortic stiffness parameters was revealed. This may be due to the fact that our study analyzed 24-hour PWV, and its significant variations during the day did not allow to reveal the dynamics on the background of treatment. In our study, prolonged use of AZL/C and IRB/H was not accompanied by hyperuricemia and electrolyte disorders. A more significant decrease in creatinine and an increase in GFK levels was found in the AZL/C group. Also in this group, 6 (26%) patients showed a decrease or complete absence of MAU, which may indicate the nephroprotective effect of the drug. In the IRB/H group, there were only 2 (8%) such patients.

Conclusion

According to research data, AH patients with obesity are less controlled than patients with normal weight. Combination therapy, particularly with ARA and diuretics, can help achieve targeted BP levels. AZL/C and IRB/H are effective and safe drugs for the treatment of AH in obese patients. Prolonged treatment of AZL/C allows to achieve more stable reduction of peripheral and central BP, improvement of structural and functional state of LV myocardium, than treatment of IRB/H.

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Rapid test for the qualitative simultaneous determination of cardiac fatty acid-binding protein and cardiac troponin I in the diagnosis of acute coronary syndrome

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Aim. To study the diagnostic characteristics of the rapid test for qualitative simultaneous determination of cardiac fatty acid-binding protein (FABPs) and cardiac troponin I (cTnI) CARD-INFO 1+1 in patients with acute coronary syndrome (ACS).

Material and methods. The study included 168 patients undergoing inpatient treatment after ACS, with typical anginal pain lasting at least 20 minutes occurred in the previous 1-24 hours. In addition to routine diagnostic procedures, on admission, we determined FABPs and cTnI concentrations using the high-quality immunochromatographic rapid test CARD-INFO 1 1 (OOO CARDIO-Plus, Russia).

Results. The sensitivity of the CARD-INFO 1+1 rapid test was 88,1%, specificity — 89,8%, diagnostic accuracy — 88,7%. The indicators of the diagnostic effectiveness of CARD-INFO 1+1 test in patients with STE-ACS and NSTE-ACS did not significantly differ (p>0,05). The sensitivity of the rapid test reached a maximum in the period from 3 to 6 hours from the onset of pain. Compared with the determination of cTnI performed on admission to the hospital, a higher sensitivity of the CARD-INFO 1+1 test was revealed in patients with STE-ACS (87,7% vs 75,3%; p=0,044), in the first 1-3 hours after the beginning of clinical manifestations (86,8% vs 60,5%; p=0,041) and in the entire sample as a whole (88,1% vs 77,1%; p=0,033), with comparable specificity (89,8% and 93,2%, respectively; p=0,741).

Conclusion. Qualitative immunochromatographic CARD-INFO 1+1 rapid test for the simultaneous determination of the content of FABPs and cTnI I is highly effective in the diagnosis of various forms of ACS. The highest diagnostic characteristics of the test were observed in patients in the early stages of the disease (the first 1-6 hours after the onset of pain). Carrying out the CARD-INFO 1+1 test revealed 12 MI cases more (11%) than the first determination of cTnI. Further studies will clarify the place of this technique in the modern algorithm for the management of patients with ACS and evaluate the possibility of using the rapid test in predicting the course of the disease.

Key words: acute coronary syndrome, cardiac fatty acid-binding protein, cardiac troponins, rapid test, multi-marker approach.

Conflicts of Interest: nothing to declare.

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Despite significant progress in treatment of diseases and the reduction of statistical parameters of deaths, mortality from myocardial infarction (MI) in the Russian Federation remains higher than in most of the world's economically developed countries. According to Rosstat, in 2018, MI caused the death of 54427 Russians [1, 2]. Early diagnostics and timely start of treatment are key factors to reduce hospital and long-term mortality, as well as the incidence of disabling complications.

In accordance with modern recommendations, cardiac troponins (cTn) are considered to be the leading biomarkers for the diagnosis of myocardial damage, and it is preferable to use highly sensitive methods (hs-cTn) for their determination [3]. Despite the numerous advantages, hs-cTn is not free of disadvantages. In particular, their determination is not sufficiently informative in the first hours after myocardial damage. Hs-cTn tests of different manufacturers have different values of 99th percentile and diagnostic levels, as well as algorithms for evaluating the results, which makes it difficult to compare and standardize the data obtained. The need for serial determination of hs-cTn, the economic aspect and the absence of "bedstand" express tests limit the possibility of their widespread use. A number of major studies have shown that the hs-cTn use in clinical practice instead of "normal" sensitivity tests has increased the frequency of MI detection and the number of percutaneous coronary interventions (PCI) performed, but has not led to a decrease in the mortality and MI prevalence [4, 5].

One of the most promising early markers of myocardial damage is Heart-type fatty acid binding protein (hFABP). Its main advantage is its rapid entry into the systemic circulation in case of cardiomyocyte damage, which allows detecting an increase in diagnostic concentrations within 30-60 minutes after the appearance of clinical symptoms [6]. Experts' opinions on the role and place of hFABP detection in IM diagnostic algorithms are contradictory.

In recent years, the possibilities of a "multi-marker approach" with simultaneous identification of several myocardial damage markers have been actively studied. Its potential advantages include faster and more reliable diagnosis verification and no need for routine determination of cTn, which may reduce the frequency and duration of hospitalizations and, consequently, economic costs [7, 8].

Studies have shown that the combined determination of hFABP and cTn makes it possible to confirm and exclude MI more correctly compared with the single determination of cTn, as well as combinations of cTn with myoglobin and/or creatine phosphokinase MB (CPK-MB), especially in the early (up to 6 hours) periods of the disease. The combination of hFABP and cTn I with copeptin has also been studied [9, 10]. Less single-valued results were obtained in the studies of the combined determination of FSLBC with hs-cTn [11-13].

It should be noted that in most of these studies the determination of the hFABP was carried out by a quantitative method, conducting of which has a number of limitations in real clinical practice. In 2017, the first report on the development of a rapid test for the combined qualitative immunochromatographic determination of hFABP and cTn I appeared, and in 2018 a similar test was created in our country. The CARD-INFO 1+1 diagnostic test (OOO Cardio-Plus, Obninsk) provides one-step express analysis for the detection of hFABP and cTn I in capillary or venous blood, as well as its serum. The results of the pilot study of this test showed good diagnostic parameters [14].

The aim of present research was to study the diagnostic characteristics of the CARD-INFO 1+1 rapid test for simultaneous qualitative determination of hFABP and cTn levels in ACS patients.

Material and methods

One hundred eighty-four patients were screened and admitted to the Department of Anesthesiology and Intensive Care with ACS, characterized by typical anginal pain lasting at least 20 minutes and the time from their onset was 1-24 hours. The study did not include patients who had stroke, acute ischemia of limbs or other organs, severe injuries, burns and cardiac surgery during the previous 30 days.

In 16 (8,7%) patients, the diagnosis of ACS was not confirmed, and therefore they were excluded from the study. Thus, the final analysis included 168 patients with verified ACS, including 54 women (32,1%) and 114 men (67,9%). The average age of the patients was 63 [54-72] years.

Anamnestic characteristics of the studied patients are presented in Table 1.

The diagnosis of IM was established according to the Third Universal Definition of Myocardial Infarction (2012) [15]. The diagnosis of unstable angina was established in the presence of clinical signs of myocardial ischemia and absence of hypertensemia.

Hs-cTn I was used as marker which was determined serially (on admission to hospital and after 3-6 h), by quantitative method using Pathfast analyzer (Mitsubishi Chemical, Japan). The reference value of 99% percentile corresponded to a concentration of 0,02 ng/ml. Echocardiographic examination (EchoCG) was performed in 157 (93,5%) patients, coronary angiography — 122

(72,6%). In 10 (6,0%) patients who died during hospitalization, the diagnosis of IM was confirmed on autopsy.

In addition to routine diagnostic procedures, on admission, all patients were assessed for the hFABP and cTn I levels using the high-quality immunochromatographic rapid test "CARD-INFO 1 + 1" (OOO CARDIO-Plus, Russia), which has an analytical threshold for hFABP — 7 ng/ml, cTn I — 1,2 ng/ml. The test strip located in the plastic cassette contains monoclonal mouse antibodies to hFABP and ctn I. One antibody clone is conjugated with dye (colloidal gold), the other is plotted as lines in the test zone of the test strip. When a blood sample with a buffer solution is introduced, the liquid spreads along the test strip according to the thin layer chromatography principle. In the presence of antigens, they bind to monoclonal antibodies and form a specific immune complex with the appearance of stained lines in the test zone corresponding to each biomarker. The test was considered positive when two or three pink lines appeared — one or two in the test zones showing the presence of hFABP and/or cTn I, as well as the control zone. When a pink line appeared only in the control zone, the test was regarded as negative. The test was performed immediately after taking the blood. The result was evaluated visually 20 minutes after the introduction of the blood sample by an independent researcher who did not have information on anamnestic, ECG and laboratory data of patients.

The diagnostic effectiveness of the CARD-INFO 1 + 1 test and hs-cTn I test were evaluated by sensitivity parameters (the proportion of positive test results in patients with MI), specificity (the proportion of negative test results in patients without MI) and accuracy (the proportion of right positive and right negative results among the total number of test results). The indicated parameters were evaluated in the entire sample, as well as depending on the type of ECG changes and the time from the onset of clinical manifestations to the test. The diagnostic characteristics of the rapid test were also compared with the results of the first determination of hs-cTn performed at admission to the hospital. For this, a quantitative parameter of the hs-cTn I concentration was converted to binary, depending on whether it reached the level of 99% percentile or not.

The monitoring of patients continued until they were discharged from hospital.

Table 1

History characteristics of studied patients

Characteristics	N	%
Stable angina	54	32,1
Postinfarction cardiosclerosis	49	29,2
Arterial hypertension	144	85,7
Chronic heart failure	25	14,9
Prior percutaneous coronary interventions or coronary artery bypass grafting	36	21,4
Hypercholesterolemia	39	23,2
Atrial fibrillation	29	17,3
Smoking	61	36,3
Obesity Class I Class II Class III	58 9 1	34,5 5,4 0,6
Type 2 diabetes mellitus	35	20,8
Lower extremity arterial disease	4	2,4
Stroke or transient ischemic attack	21	12,5
Chronic bronchopulmonary diseases	12	7,1
Gastrointestinal diseases	32	19,0
Chronic kidney diseases	21	12,5
Anemia	7	4,2

Table 2

Diagnostic efficiency of «CARD-INFO 1+1» and markers singly depending on ACS form

Diagnostic characteristic	Test interpretation	STEACS	NSTEACS	p
Sensitivity	hFABP test zone	86,4 (77,1-92,4)	85,7 (67,9-94,9)	0,823
	cTn I test zone	49,4 (38,8-60,1)	60,7 (42,4-76,5)	0,301
	Common test interpretation	87,7 (78,6-93,3)	89,3 (72,0-97,1)	0,914
Specificity	hFABP test zone	88,9 (54,3-99,9)	90,0 (78,2-96,1)	0,619
	cTn I test zone	88,9 (54,3-99,9)	94,0 (83,2-98,6)	0,874
	Common test interpretation	88,9 (54,3-99,9)	90,0 (78,2-96,1)	0,619
Accuracy	hFABP test zone	86,7 (78,0-92,4)	88,5 (79,3-94,0)	0,907
	cTn I test zone	53,3 (43,1-63,3)	82,1 (72,0-89,1)	<0,001
	Common test interpretation	87,8 (79,3-93,2)	89,7 (80,8-95,0)	0,876

Note: data is presented in % format (95% CI).

Table 3

Diagnostic efficiency of «CARD-INFO 1+1» and markers singly depending on the time from onset of pain

Diagnostic characteristic	Test interpretation	1-3 h	3,1-6 h	> 6 h
Sensitivity	hFABP test zone	84,2 (69,2-92,9)	92,3 (79,0-98,1)	81,3 (64,3-91,5)
	cTn I test zone	44,7 (30,1-60,3)	46,2 (31,6-61,4)	68,8 (51,3-82,2)
	Common test interpretation	86,8 (72,2-94,7)	92,3 (79,0-98,1)	84,4 (67,2-94,7)
Specificity	hFABP test zone	100,0 (81,0-100,0)	90,0 (68,7-98,4)	79,0 (56,1-92,1)
	cTn I test zone	100,0 (81,0-100,0)	100,0 (81,0-100,0)	79,0 (56,1-92,1)
	Common test interpretation	100,0 (81,0-100,0)	90,0 (68,7-98,4)	79,0 (56,1-92,1)
Accuracy	hFABP test zone	89,7 (78,9-95,5)	91,5 (81,3-96,7)	80,4 (67,4-89,2)
	cTn I test zone	63,8 (50,9-75,0)	64,4 (51,6-75,4)	72,6 (59,0-83,0)
	Common test interpretation	91,4 (81,0-96,7)	91,5 (81,3-96,7)	82,4 (69,5-90,7)

Note: data is presented in % format (95% CI).

Abbreviations: hFABP — heart-type fatty acid binding protein, cTn I — cardiac troponin I.

Statistical analysis of the data was carried out using Microsoft Excel (2013) and SPSS Statistics 22.0. The number and percentage of observations are given in the description of parameters presented as alternative variables. The distribution of parameters was assessed using the Kolmogorov-Smirnov test. In the case of normal distribution, the data are presented in the form of M±m, with a different from normal — in the form of median and interquartile range (Me [Q1-Q3]). Calculation of 95% confidence interval (CI) by means of the modified Wald method was carried out. Pearson's chi-squared test was used to compare diagnostic characteristics. For small samples, Yates' correction or Fisher's exact test was applied. Differences were considered valid at $p<0,05$.

The study was carried out in accordance with the principles of the Helsinki Declaration and Good Clinical Practice (GCP) standards. All patients signed an informed consent to participate in the study. The study was approved by the independent ethics committee of N. I. Pirogov Russian National Research University.

Results

The average duration of clinical manifestations at the time of the test was 4,0 [2,7–7,2] hours (including from 1 to 3 hours in 58 (34,5%) patients, from 3 to 6 hours — 59 (35,1%) and >6 hours — 51 (30,4%)). According to the results of the survey, MI diagnosis was established in 109 (64,9%) cases, unstable angina — in 59 (35,1%).

Table 4

Comparison of the diagnostic characteristics of the "CARD-INFO 1 + 1" test and the first estimation of hs-cTn I

Characteristic	Sensitivity (n=109)		Specificity (n=59)		Accuracy (n=168)	
	CARD-INFO 1+1	hs-cTn I	CARD-INFO 1+1	hs-cTn I	CARD-INFO 1+1	hs-cTn I
STEACS	87,7* (78,6-93,3)	75,3 (64,9-83,5)	88,9 (54,3-99,9)	88,9 (54,3-99,9)	87,8* (79,3-93,2)	76,7 (66,9-84,3)
NSTEACS	89,3 (72,0-97,1)	82,1 (63,9-92,6)	90,0 (78,2-96,1)	94,0 (83,2-98,6)	89,7 (80,8-95,0)	89,7 (80,8-95,0)
1-3 h	86,8* (72,2-94,7)	60,5 (44,7-74,4)	100,0 (81,0-100)	95,0 (74,6-99,9)	89,7* (78,9-95,5)	72,4 (59,7-82,3)
3,1-6 h	92,3 (79,0-98,1)	79,5 (64,2-89,5)	90,0 (68,7-98,4)	100,0 (81,0-100)	91,5 (81,3-96,7)	86,4 (75,2–93,2)
Over 6 h	84,4 (67,2-94,7)	93,8 (78,8-99,3)	79,0 (56,1-92,1)	84,2 (61,6-95,3)	80,4 (67,4-89,2)	90,2 (78,6-96,2)
Whole sample	88,1* (80,5-93,0)	77,1 (68,3-84,0)	89,8 (79,2-95,6)	93,2 (83,4-97,8)	88,7 (82,9-92,7)	82,7 (76,3-87,8)

Note: data is presented in % format (95% CI). * — p <0,05.

ECG shows diagnostically significant elevation of the ST segment in 84 (50,0%) cases, in 41 (24,4%) — depression of the ST segment, in 35 (20,8%) — there were no changes or were non-specific, in 5 (3,0%) — a total block of the left bundle branch (LBB) or, and in 3 (1,8%) cases a pathological Q wave was detected for the first time without deviations of the ST segment. The result of the CARD-INFO 1 + 1 test was regarded as positive in 102 (60,7%) cases (including a positive test reaction for hFABP in 100 (59,5%) patients, and in cTn I — 61 (36,3%), both markers characterized by a positive reaction in 59 (35,1%) cases), as negative — in 66 (39,3%) patients. In 1 case (0,6%), the reaction was absent, which required repeated testing.

According to established diagnoses, 96 (57,1%) of the test results are interpreted as true positive, 6 (3,6%) as false positive, 53 (31,5%) true negative and 13 (7,7%) false negative. Thus, the sensitivity of the test with the determination of both markers was 88,1% (95% CI: 80,5-93,0), specificity 89,8% (95% CI: 79,2-95,6), diagnostic accuracy — 88,7% (95% CI: 82,9-92,7).

Parameters of the diagnostic effectiveness of each of the biomarkers, as well as their combined determination using the CARD-INFO 1+1 test, depending on the ACS variant and the time elapsed since the onset of the pain syndrome, are presented in Tables 2 and 3.

No significant differences in the sensitivity, specificity and diagnostic accuracy parameters of the CARD-INFO 1+1 test were found in patients with STE-ACS and NSTE-ACS (p>0,05). When comparing the parameters obtained for each of the biomarkers used in the rapid test, there was a higher sensitivity of hFABP to cTn I in STE-ACS (p<0,001) and a similar tendency with NSTE-ACS (p=0,071), with comparable specificity (p>0,05). The sensitivity of the CARD-INFO 1+1 test reached a maximum in the time interval of 3-6 hours from the onset of pain. The specificity parameter tended to decrease, which, apparently, is associated with small samples of patients without MI. There were significantly higher sensitivity and diagnostic accuracy of hFABP compared with cTn I in the intervals of 1-3 hours and 3-6 hours (p <0,001 for both parameters) from the onset of clinical manifestations to testing, in the absence of specificity differences (p>0,05).

Of the 6 cases considered as false positives, a positive response to hFABP was noted in all cases, and to cTn I — in 4 (66,7%).

The level of hs-cTn I determined on admission to the hospital simultaneously with the CARD-INFO 1+1 test exceeded the reference value in 88 cases (52,4%). The sensitivity of hs-cTn I test was 77,1%. The results of efficacy comparing of rapid test with hs-cTn I test are presented in Table 4. The higher sensitivity of the CARD-INFO 1+1 test was revealed in comparison with hs-cTn I in patients with STE-ACS (87,7% vs. 75,3%, p=0,044), in the first 3 hours since the development of clinical manifestations (86,8% vs. 60,5%, p=0,041) and in the whole sample (88,1% vs. 77,1%, p=0,033). A higher diagnostic accuracy of the rapid test was noted than in the case of hs-cTn I in STE-ACS (p=0,05) and in the terms of 1-3 hours from the moment of the disease development (p=0,034). Specificity parameters of hs-cTn I and CARD-INFO 1+1 tests did not differ significantly (93,2% vs. 89,8%, p=0,741).

Conclusion

Thus, immunochromatographic rapid test CARD-INFO 1+1 for the simultaneous determination of hFABP and cTn I levels is highly effective in the diagnosis of various forms of ACS. The highest diagnostic characteristics of the test

were observed in patients in the early stages of the disease (the first 1-6 hours after the onset of pain). Carrying out the CARD-INFO 1+1 test made it possible to identify 12 cases (11% in absolute value) of MI more than the first hs-cTn I determination (8 of them — in the first 6 hours of the disease).

Further studies will define the place of this technique in the modern algorithm for the management of patients with ACS and assess the possibility of rapid test using in predicting of the disease course.

Conflicts of Interest: nothing to declare.

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Humanitarian competencies of a doctor (cardiologist)

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The article reveals the features of working with the patient as a social and psychological subject, who, in addition to somatic pathology, has an experience of the disease situation. Psychosocial risk factors for cardiovascular (and more generally non-infectious) pathology, as well as social well-being as a component of positive health, are considered as elements of a doctor-patient relationship. Work with a person requires from a doctor competency that differs from working with pathology at a biological level. Perhaps, the time has come to single out "biomedical doctors" and "medical doctors" in clinical medicine, of which the first ones are not required humanitarian competencies. Since non-infectious pathology largely includes psychosomatic features, and mental processes are filled with an experience of social reality, the clinician must have skills of human sciences to work with them. This is especially important in view of the physician's power as an ambassador of medicine and health. The following competencies are discussed: internal work skills, situational search and interpretation, communicative and ethical competence, development of positive health.

Key words: psychosocial risk factors, health, psychosomatics, non-communicable diseases, patient orientation, psychocardiology, medical ethics, continuing education.

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Higher education standards include the concept of general professional and universal competencies. This level of competence combines the knowledge and skills typical of a person with higher education in general and a doctor as a specialist in particular.

Among the universal competences (in the project of Federal State Educational Standard of Higher Education with account of professional standards in the specialty 31.05.01 — Medical Doctor [1]), as well as among general cultural, general professional and professional (in the current FSES HE 31.05.01 — Doctor — medical care [2]) should be highlighted a number of related to humanitarian knowledge (Table 1).

In addition, in the case of primary specialized accreditation in cardiology, the "Communication" station of the objective structured clinical examination includes situations of "difficult" patient" and "bad news" [3].

The doctor is a representative of medicine. Medicine — teaching, private science, practice, cultural phenomenon that has formed in the millennia of confrontation with nature. Its task is to prolong life with maximum quality, to preserve and achieve full health — well-being on the physical, mental and social levels of human being [4].

Man is biosocial in nature. Bioelectricity creates conditions for thinking and communication, which are realized in the form of symbols expressed, perceived and interpreted by people. This is how culture is created — the second nature or everything that is not nature.

Work in medicine requires taking into account 1) the biological side of man, his physiology and pathology, 2) the social and cultural side (worldview, personality, contacts), 3) close two-way relationship between biological and cultural.

The biopsychosocial nature of human beings, as defined in the World Health Organization's definition of health, can be reduced to a biosocial nature without losing meaning. The psychological level in this case (without diminishing the importance of psychology) is the transition level, the door between the biological material processes of the body and the semantic, symbolic reality of society, i.e. communication [4]. The soul, psyche or anima, is processes of body animation, mental functions: thinking, intelligence, memory, emotions, mood, etc. Their filling is somehow symbolic, communicative, and they are realized due to biochemical mechanisms of muscle contraction, isolation of neurotransmitters, bioelectricity.

Medicine of the turn of the XX-XXI centuries was purely biologic [5]. This is easy to understand, because the rapid development of natural sciences has overshadowed the slow and contradictory

Table 1

Doctor's competencies according to Federal standards (adapted from [1, 2])

Competency level	Formulation
HE FSES project "3 ++" with occupational standards	
Universal	Ability to analyze and take into account the diversity of cultures during intercultural interaction
	Identify and implement the priorities of their own activities and ways to improve it on the basis of self-assessment and lifelong learning
	Maintain an adequate level of physical fitness
Current HE FSES	
General cultural	Ability to use philosophical knowledge to form a worldview
	Ability to take social and ethical responsibility for decisions made
	Willingness to self-development, self-actualization, self-education, use of creative potential
	Willingness to work in a team, to tolerate social, ethnic, religious and cultural differences
General occupational	Ability and willingness to implement ethical and deontological principles
	Ability and willingness to analyze the results of own activities to prevent mistakes
Occupational	Willingness to engage in educational activities to address risk factors and develop healthy lifestyle skills

Note: HE FSES — Higher Education Federal State Educational Standard.

growth of human understanding of oneself through philosophy, culturology, sociology, psychology and art. Nevertheless,

medicine as an aid to a human being requires work with both biological and cultural parts of it. Within clinical specialties, there is probably a moment of dichotomy: either we persist in developing the humanitarian competence of the physician, or we divide medical practice into two types — one that implies such competencies and the other that does not.

The conservative way in which the scientific and pedagogical community is following now will require a renewal of approaches to the formation of humanitarian competencies among doctors (and among the first — cardiologists taking care of patients with psychosomatic pathology [6]). Another way is to realize that it is impossible to embrace the entire complexity of biosocial interrelationships, and to identify clinicians who are able and unable to work with a person. This recognition of defeat is possible, but maybe it is a requirement of evolution, a new, modern view of medical care. “Medical doctor” and “biomedical doctor”, for example, the names of two types of clinicians that differ by way of working with a patient. The first one suggests a high level of communicative and social skills, the second one — only actions in the field of pharmacology, surgery, diagnostic methods, physiotherapy with minimal and formal communication.

The conservative way is more comfortable. If you follow it, what are the competences of a clinician capable of working with the social self of a patient no less effectively than with the biological processes of his body, taking into account the close relationship between the social and biological aspects?

When interacting with a sick person or a patient as part of primary prevention, the doctor deals with both the "pure" biology and the symbolic reality of this individual. The administration of the drug, not to mention surgical intervention, is nothing but the effect on the biology of the patient. But the psychological processes of experience (negative and positive emotions, mood) are biochemical states. It is associated with a reflection on social life. Cognitive science explores "embodied cognition" [7]. There is plenty of evidence that emotions influence the development of chronic diseases and their exacerbation. Stress is a typical example of a body's biochemical response to understanding social reality: stress factors such as changes in currency exchange rates and job losses.

The biological response is well studied, and it is quite simple in nature. The processes of experience are much more complex — semantic and symbolic processes. They are complicated simply because, unlike biological (natural science) processes, it is impossible to generalize, make a sample and calculate reliability. They are purely individual and require skills of interpretation according to the laws of humanitarian knowledge. Although some natural scientists do not consider humanitarian knowledge to be scientific in principle, it is not so much a matter of designating it as of its essence and practical significance. As such, science itself is only one way to know and change the world [8]. Medicine, on the other hand, is a broader science that has the reality of life with its subject matter, including notions that are imperceptible (fate, god, soul, etc.), but that are important for the patient and, as a result, through experience, affect his or her coping with the disease. Working with a person (alive, in the mind), one cannot help but understand him, decode the factors influencing his adherence to the disease, his attitude to the situation of the disease, his ability to change his lifestyle due to the medical situation.

Psychology is partly responsible for the study of the human being's social. This science has both strict biological fields (neuroscience) and social fields (consultative psychology). Doctor's humanitarian competences are at least psychological competences. But they are not enough for effective work. Moreover, the work with the individual is done with the help of another person, and the clinician cannot abstract his or her personality from the patient's personality, in which case he or she becomes a "biomedical doctor" (see above). Therefore, the key humanitarian competence is the skill and ability to work internally, build awareness, reflexivity, constructive self-criticism, and the ability to change yourself.

Self-identification is a person's experience of the self in relation to social categories. For example, fitness as a muscle building represents the realization of a certain image of body, which is perceived as a standard. And for one man the aim will be the hypertrophy of the muscles as such, for the other — the achievement of "Greek" proportions and relief. In both cases, the processes take place at the somatic level and a person may eventually become a cardiologist's patient due to, for example, arterial hypertension or cardiomyopathy. An even simpler example is alcohol consumption as a social practice. If a person's self-identification requires recognition in a certain social group, he or she will be forced to consume an excessive amount of alcohol in a feast; the classic situation — “do you respect me? — then drink”. When working with such a patient, it is not enough to simply forbid the

harmful action, not even to scare with consequences (the reaction may be the opposite, for example, depression, negativism), you need to be able to understand his motivation. Motivation comes from values, value is conditioned by the correlation of the image of the self with the wishful one in the society, and the wishful one is a construct based on the whole human experience.

The above is enough for a somatic doctor to draw a conclusion about the complexity and potential infinity of working with an individual as a person, the social self. But the matter is not in the complexity of this knowledge. The main feature is a qualitative difference of such knowledge. It is non-generatable, unrepeatable, irreplaceable. It is interpretive, and therefore requires tools for analysis: knowledge of history and philosophy of culture, knowledge of psychology, skills to communicate in order to understand the person, not only to collect data. For a "biomedical doctor", pain as a symptom is only a "talking biology," which has a process that manifests itself in complaints of pain. For a clinician, pain is also the patient's experience, his or her perceptions and fears, projection on life, the question "for what?" or "will it always be so now? In doing so, the doctor does not have to suffer pain together with the patient; the ability of a conscious attitude allows one to be involved in person's problem without crossing the boundaries of oneself.

The importance of quality methodology in cardiology was discussed in the article [6]. In fact, this is how the old clinical school returns to a new phase of medical development. Simple references to the full collection of anamnesis, to the correct conversation with the patient, to the consideration of personal traits will sound conservative and sentimental today, if they are not supported by modern ideas about the biosocial relationships, ways to understand the cultural part of the patient, and the doctor himself — to construct his own social identity.

Traditionally, the "non-biological part" of the patient is devoted to the specialty and field of medicine with the word root of "psych-" in its name: psychiatry, psychosomatics, psychocardiology. Although they nominally deal with processes of psychological level, any manifestation of such processes consists in felt, perceived and interpreted symbols. Bio-psychological processes are not available until they are expressed and become psychosocial phenomena. Already V.A. Gilyarovsky said "every epoch has its own psychiatry" [9]. Extrapolating this idea into psychocardiology, stress, harmful habits, and unhealthy lifestyles as cardiovascular risk factors lies in the information environment. It means that the etiopathogenetic tangle has to be unraveled from above. Psychosomatics, psychocardiology, if not redefined, acquire a different level of work. This can be looked at even more widely, because all noninfectious pathology somehow begins with psychosocial risk factors.

Patient-centered care is attached to such doctor's work, with elements of quality methodology. Its simplest attitudes always require positive mood, empathy, respect, constructive communication, joint decision making and tolerant information sharing.

Finally, decision making in ethically complex situations requires the physician to be an ethical subject, i.e. a person capable of understanding and solving each unique situation. Especially if the legal framework is not sufficiently detailed.

Where to find the resource to do this — both formally and substantively? Obviously, it's about humanitarian competencies. Humanitarian — according to the vocabulary definition, refers to society, human beings and their culture (as opposed to the sciences of nature). The following competences can be defined as:

Internal work — the ability to reflect on one's feelings, one's attitude towards another person (colleagues, patients, relatives of patients), to the situation; find the reasons for their attitude to the situation, their feelings, analyze and rationalize them; the tendency to fulfill the postulate "doctor, heal thyself."

Situational search and interpretation — the ability to ask questions about hidden meanings and sources of what is happening — both locally, in the situation of assistance, and globally; to find codes with which the information is presented, its possible distortion and substitution.

Communicative competences — the ability to conduct a dialogue with patients, their relatives, colleagues, in a constructive manner, without creating situations of misunderstanding, conflict; to be aware of their own experiences and meanings generated by communication; to express themselves in the manner necessary for effective communication, taking into account the phenomenon of power of the doctor as a representative of medicine and health care [10].

Ethical competences — the ability to highlight the ethical element of a situation, to distinguish between good and bad, right and wrong; to obtain additional information necessary to make ethically loaded decisions.

Positive health development — understanding of the structure of health (wellbeing) at the socio-cultural level; ability to interpret socio-cultural determinants of disadvantage and find ways to

resolve them (it should be added that the considered standards and draft standards of education of the levels of specialization and residency considered do not reveal competencies related to health as an interdisciplinary concept according to WHO).

The development of humanitarian competencies among students and physicians in postgraduate and continuing education is possible with the proper "tuning" of humanitarian and psychological disciplines. The most important is the essential component — the formation of a way to think analytically, to use different points of view to understand the same phenomenon. In today's era of information abundance, the key skill is to preserve one's self-identification as autonomous and independent of external information influences as possible. For a doctor as one of the most important actors in the lives of other people, this is especially important.

Conflicts of Interest: nothing to declare.

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Maladaptive neuropathological syndrome of blood vessel aging

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This article discusses the relationship between maladaptation and blood vessel aging. The work shows that upright posture created an additional load on the circulatory system, and the lifestyle of a modern human is an additional risk factor of cardiovascular diseases. It has been suggested that a disorder of the nervous regulation of vascular tone is the main etiopathogenetic mechanism of morphofunctional changes in blood vessels and their aging. We discussed the statute that vascular reactions in humans is based on the formation of a maladaptive circuit in the cerebral cortex, consisting of a matrix of motor, sensory and associative cortical neurons involved in the maladaptive process. This hypothesis is based on the fact that any irritations entering the cerebral cortex from the periphery (thermal, pain, and others) cause cortical-vascular reflex reactions that change their tonic activity. Based on this principle, a model of vascular aging is further constructed, which is based on the maladaptive damage to all layers of the vascular wall (intima, media and adventitia). The opinion is expressed about the need for early diagnosis and prevention of vascular disorders to maintain human health. In conclusion, it is concluded that if the age of a person is really determined by the age of his blood vessels, then in order to achieve active longevity it is necessary to normalize the relationship in the adaptation-maladaptation-environment. Detailed study of hypertrophy and calcification of blood vessels is needed, since aging always reveals vascular wall thickening and stiffness increase.

Key words: cardiovascular diseases, maladaptation, vascular tone, vascular aging, morphofunctional changes, prevention of vascular aging.

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There is a perception that one of the main reasons for the increase in the prevalence of cardiovascular diseases (CVDs) is the steady ageing of the population. Blood vessels (BV) of the human body are also vulnerable to aging. It is the age-related changes in blood vessels that are an important risk factor for CVDs. Morphofunctional changes in the vascular wall developing with age contribute to the beginning and progression of CVDs.

The nature of CVDs is complex and still not clear enough, because the mechanisms of BV aging are quite complex and diverse. But every year vascular biology and medicine reveals new facts that allow a deeper understanding of the molecular mechanisms of vascular wall damage and on this basis to prevent or minimize the early BV aging.

Cardiology attaches great importance to the development of new concepts and pathophysiological models for a better understanding of cardiovascular risks, early diagnosis, treatment, reduction of morbidity and mortality from cardiovascular pathology. Many studies are now aimed at finding etiological factors that accelerate the aging process of BV. Important role in the disturbance of systemic and peripheral blood circulation is played by mechanisms of vascular tone regulation, which can be easily disturbed in everyday life of people. It is not a secret that every year the number of different kinds of environmental factors that disrupt the neurohumoral regulation of vascular tone and thus trigger the molecular mechanisms of BV aging increases [1]. The neuropathological syndrome of BV aging developing in a human being is, on the one hand, caused by the disturbance of vascular tone regulation, and, on the other hand, by the damage of all layers of the vascular wall (adventitia, media, and intima) due to morphological changes.

The aim of this review is to acquaint the reader with the main mechanisms of the occurrence and development of a maladaptive neuropathological syndrome of BV aging in humans.

Maladaptive disorders of vascular tone during aging

Maladaptation, being a general pre-pathological (interjacent) state of an organism, triggers numerous mechanisms leading to the degradation of biological systems and the development of morphofunctional changes in organs and systems, including BV [2]. Currently, it is believed that the main mechanisms of vascular aging associated with the adaptation process are oxidative stress, endothelial dysfunction, chronic inflammation, apoptosis of endothelial cells, impaired function of endothelial progenitor cells, age-related dysregulation of vascular system [3].

An occlusion test can be used to detect dysregulation disorders of microcirculation and vascular tone, which reveals a decrease in the reserve of capillary blood flow, a change in the reactivity of microcirculatory vessel, and an increase in stagnation in the microvasculature [4]. The biochemical component of vascular tone assessing can be the detection of Rho-associated protein kinase activity in smooth muscles and vascular endothelium, which is involved in the regulation of vascular tone both in normal state and in vascular disorders [5]. At the same time, it is known that the arginase enzyme promotes microvascular endothelial dysfunction in obesity in humans.

However, its effect significantly decreases with age due to a higher level of vascular oxidative stress. Thus, it is possible that obesity is accompanied by accelerated microcirculatory vessels' remodeling, which is associated with the arginase content in the vessel wall [6]. But one cannot ignore the fact that in the group of young patients with stiff vessels, compared with people with elastic vessels, a higher level of total cholesterol and low-density lipoprotein cholesterol was detected [7].

It is worth noting one more interesting fact related to vascular tone maintaining, namely, the effect of endothelial zinc (Zn) homeostasis on this process. The pathways of the influence of Zn as a biogenic element and nitric oxide (NO) in the human body are closely related. The labile chemical element Zn can mediate important functions of NO, including vascular cytoprotection and vasodilation [8].

The situation is somewhat different with the regulation of vascular tone during aging in patients with cardiovascular pathologies than without it. An analysis of the literature shows that in patients with arterial hypertension, pronounced microcirculatory disorders associated with changes in vascular tone and blood rheological properties are noted. This, in turn, determines the value of the total peripheral vascular resistance [9]. It was also found that increasing stiffness of elastic-type vessels in young patients is associated with an increase in systolic blood pressure, and in muscle-type vessels, with an increase in diastolic blood pressure [10]. Arterial stiffness increases with age and increases the risk of CVDs. However, functional disorders of the elastic properties of the carotid artery walls can occur even before the formation of structural changes and can be detected by ultrasound imaging even before the onset of CVD symptoms [11].

Vascular stiffness, determined by pulse wave velocity in the carotid and femoral arteries, is now used to predict cardiovascular risk and assess vascular tone disorders [12].

However, it has been found that the severity of autonomic cardiovascular dysfunction during orthostatic stress among patients does not depend on tolerance to hypoxia [13]. Violation of vascular signaling processes (for example, decreased bioavailability of nitric oxide) is usually called endothelial dysfunction, which is a recognized risk factor for CVD [14].

In older people, endothelial dysfunction occurs as an altered endothelial ability to regulate hemostasis, vascular tone and cell permeability. These changes enhance the procoagulant status that develops with aging and emphasize the key role of endothelium in the development of thrombosis during aging [15]. Gender differences in hemodynamic values such as vascular stiffness, elastic modulus, and pulse wave velocity are not excluded. This can give general ideas about the treatment strategy regarding developing drug therapy for different sexes [16].

There is an opinion that the hemodynamic response of the cardiovascular system varies significantly with healthy aging and depends on the level of arterial oxygen tension [17]. Thus, it should be recognized that aging worsens endothelial function both in the cerebral arteries and in parenchymal arterioles, mainly by affecting the endothelial regulation of vascular tone, which depends on nitric oxide [18]. Endothelial aging is associated with impaired renal artery function, which is partially characterized by arterial stiffness and reduced vasodilating ability due to excessive formation of reactive oxygen species, resulting in the so-called endothelial dysfunction [19, 20].

Neurophysiological associations

To explain the processes of altered regulation of the cardiovascular system, it is proposed to introduce the following concept. A peculiar matrix of nerve networks in the cerebral cortex and subcortex forms a "maladaptive contour". Such a pathodynamic complex includes neurons of the motor, sensory, and associative zones of the cortex, since they have a strong (constrictive and dilative) effect on the vascular lumen. Supporting role in this process is played by neurons of the frontal and parietal lobes. The maladaptive pathodynamic contour along the descending paths directly affects the pressor and depressor parts of the hypothalamus and the same parts of the underlying vasomotor center of the medulla oblongata, causing a change in the functions of neurons of the spinal vasomotor center and BV.

Nevertheless, it can be concluded that a neuropathological complex of maladaptive disorders of vascular tone is formed in the structures of the central nervous system, which manifests itself in humans in certain life situations and with aging. The disintegration of the maladaptive contour, which consists of hyperactive neurons and nerve centers involved in the maladaptive process, under the influence of treatment, rehabilitation measures and pharmacotherapy leads to normalization of the hemostasis, disappearance of pathological cortical-vascular reactions, normalization of arterial pressure, and the subsidence of psychological, physical and functional manifestations of maladaptation.

Maladaptive damage to the vascular wall during aging

Long-term maladaptive disorders of vascular tone over time lead to morphological changes in the vessels and impaired function. It was shown [21] that BV aging is accompanied by a violation of the state and function of its three main layers: intima, media, and adventitia. With age, each of these cell layers undergoes complex changes, leading to a total of two consequences — a thickening of the vascular wall and an increase in its stiffness. These two components of pathogenesis create an unfavorable basis for vascular aging and clinical manifestations of CVD [22].

The scientific data discusses the fact that accelerated aging of BV is associated with their calcification, which directly affects the higher mental functions of a person. For example, calcification of the carotid artery has a significant correlation with cognitive impairment, and intracranial calcification of BV is associated with extensive changes in the white matter and causes pronounced neuropsychiatric symptoms [23-25]. Nevertheless, there is evidence that the biological age of the arteries (stiffness and elasticity) is interrelated with risk factors for atherothrombosis. Premature aging of BV is associated not only with disruption of glucose utilization by cells, but also with initial manifestations of chronic inflammation of the arterial wall and a tendency to thrombosis [26].

It should be noted that an increase in arterial stiffness is currently considered to be a link between diabetes and a high risk of CVD. Insulin resistance is an important factor in the formation of vascular aging processes [27, 28]. BV aging occurs intensively in the menopausal period, which is often characterized by endothelial dysfunction and arterial stiffness, which is the main risk factor for CVD. In this case, the endothelial function of the vessels progressively decreases, and the acceleration of vascular aging can be associated with the loss of the vasodilating, antioxidant, anti-inflammatory and antiproliferative effects of estradiol on the vessel wall [29]. It has been shown that in obese individuals respiratory disturbances in sleep can be a risk factor for early vascular aging [30].

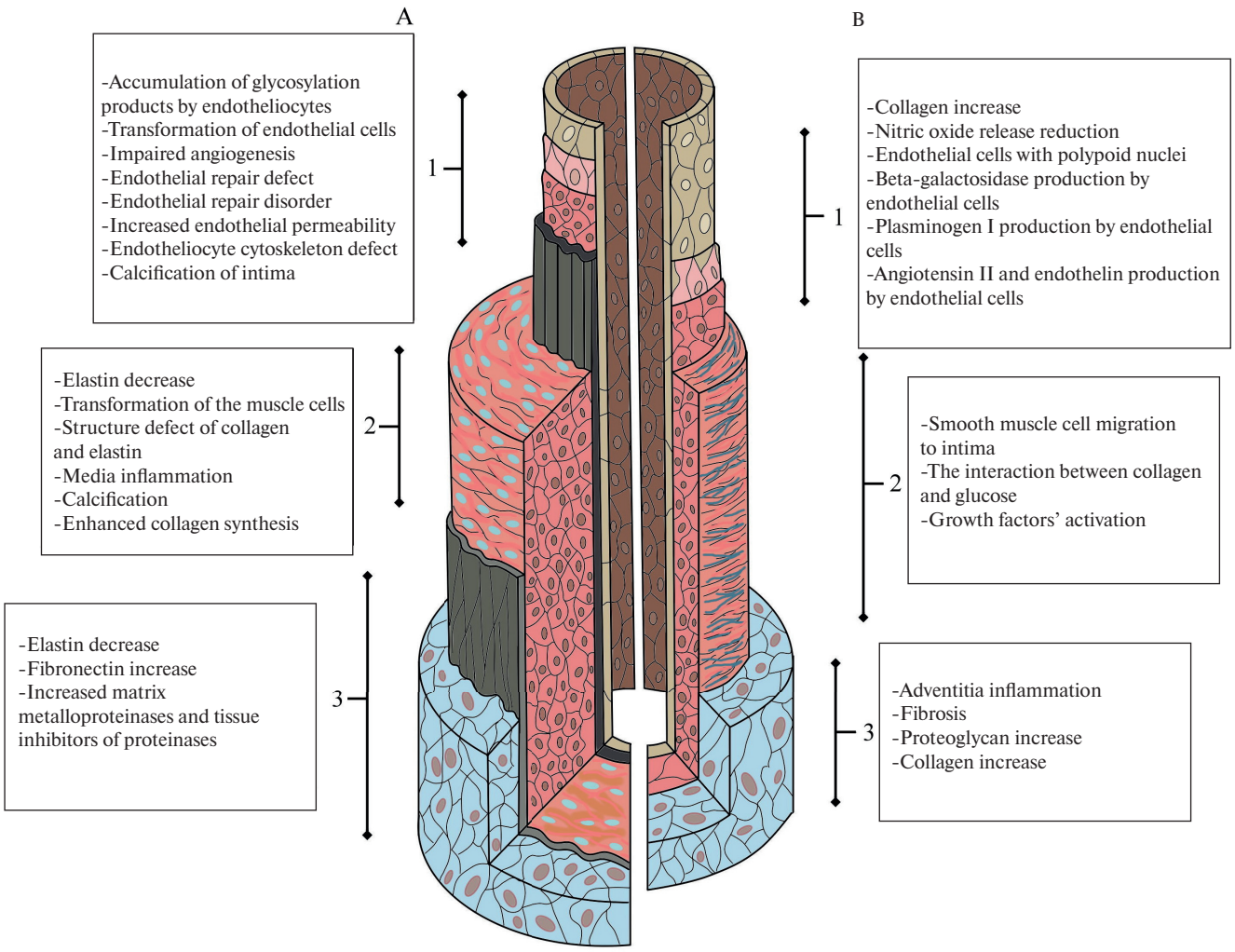

Fig. 1. The main pathogenetic mechanisms of vascular aging: A — artery. B — vein. 1 — innermost layer (tunica intima); 2 — middle layer (tunica media); 3 — outermost layer (tunica adventitia).

It is possible that in patients with arterial hypertension, in combination with overweight and obesity, an increase in cerebral and hemodynamic pathologies is accompanied by anxiety-depressive disorders [31]. At the same time, the presence of such an additional risk factor as smoking leads to the occurrence and progression of changes in the artery wall even in apparently healthy humans [32]. Smoking can also have a negative effect on vascular aging in a group of patients after cancer-related radiation therapy [33].

Thus, vascular remodeling during aging is an adaptation process, including structural and functional transformations of the vascular wall that occur in diseases, injuries, and ultimately lead to damage of target organs [34]. Arterial hypertension causes remodeling of vessels of all types already in the adult period of life, while increasing the integral biological age of the patient [35].

With the aging and development of hypertension, endothelium, vascular wall and adventitia undergo functional and structural changes. The endothelial function of BV in this case is impaired, and the vascular wall is thickened. The extracellular adventitia matrix undergoes remodeling with increased collagen deposition, a decrease in the elastin content and an increase in the number of inflammatory cells. These processes contribute to vascular fibrosis and increase vascular stiffness [36].

Study of the volume of arterial and venous vessels of the renal cortex and medulla revealed the morphological changes during aging, which are characterized as nephrosclerosis [37]. It should be noted that among the signs of vascular aging, activation of the renin-angiotensin-aldosterone system as the main source of chronic inflammation and oxidative stress is being

considered [38]. Not without reason we can say that the precursor of the miR-34a family of microRNA effector molecules is associated with vascular calcification and its stimulation. This, in turn, includes the transdifferentiation of vascular smooth muscle cells caused by aging, inhibiting cell proliferation and, thus, leading to mineralization of the arterial wall [39]. Therefore, vascular smooth muscle cells play a crucial role in vascular aging and the formation of aneurysm of the ascending thoracic aorta. The occurrence of aneurysm is characterized by an increase in the permeability of the vascular wall, leading to transmural migration of plasma proteins, which can interact with vascular smooth muscle cells and extracellular matrix components [40].

The result of pathological processes in the vessels is an increase of pulse wave velocity [41]. Summarizing the available data on the BV aging issue, we note that maladaptation of the body plays an important role in the damage to all layers of the vascular wall. Being a general biological systemic process [42], it inevitably leads to malregulation disorders of vascular tone, persistent distention or constriction of BV, and numerous metabolic disturbances in endothelial, smooth muscle and adventitia cells already appear. (Fig. 1).

Thus, with BV aging, malregulation disorders are primary, and then changes in the vascular wall already occur. That is because vegetovascular disorders can be observed in the early stages of postnatal ontogenesis (children, adolescents and young people). At the later stages of ontogenetic development (in adult, senile and elderly age), irreversible structural changes in the vascular wall already occur and lead to its dysfunction.

Diagnostics, prevention and correction of vascular disorders

Based on the sphygmography method with the of vascular age determination, a screening examination of the population can be carried out for early detection of changes in the vascular wall [43].

The concept of "vascular age" analyzes the possibility of using the pulse wave velocity and central aortic pressure as the stiffness markers of main elastic-type arteries of the depending on the chronological age is analyzed [44]. Depending on age and gender, if necessary, longitudinal movements of the intima-media complex of the common carotid artery can be detected [45].

The use of transspinal micropolarization for the treatment of impaired brain systems associated with the regulation of vascular tone is also justified [46]. The possibility of aging markers using such as myocardial hypertrophy and left ventricular diastolic dysfunction as cardiovascular markers of aging has been proven. In this regard, the necessity of assessing the rate of vascular aging was substantiated in order to identify young patients with a high risk of myocardial infarction [47].

Experimental studies indicate that millimeter-wave electromagnetic radiation exhibits properties. By regulating the exposure of a culture of vascular endothelial cells, we can activate the expression of signaling molecules, the synthesis of which underlies endothelial dysfunction during aging [48]. Other studies have shown that multipotent mesenchymal stromal adipose tissue cells can stimulate angiogenesis [49]. There is also an opinion that mediators of the sympathetic nervous system (adrenaline and noradrenaline) protect vascular cells from the damaging effects of nitrogen dioxide formed during hypoxia, ischemia, inflammatory and other pathological processes [50].

In addition, it was found that in the late stages of postnatal ontogenesis, pharmacotherapy of vascular diseases plays an important role. Data on the positive effect of angiotensin-converting enzyme inhibitors as geroprotectors on the vascular wall are given [51]. The vasoprotective activity of indapamide has been shown [52]. Meantime, determination of the features of microcirculatory disorders in patients in the recovery period after ischemic stroke allows us to recommend drugs that improve the flow of arterial blood to tissues, reduce vascular spasm, as well as massage, physiotherapy, reflexology, physiotherapy exercises [53]. Adding melatonin to the traditional therapy of metabolic syndrome in patients with sleep disorders improves the function of endothelial cells, reduces vascular stiffness and normalizes blood pressure [54]. It was also shown that combinative antihypertensive therapy with a calcium antagonist and an angiotensin-converting enzyme inhibitor increases the estimated vascular age of patients by an average of nine years [55, 56]. To protect the endothelium, herbal products rich in polyphenols are studied [57, 58].

In this study, it was shown that the inclusion of aerobic training, strength gymnastics and darsonvalization in the rehabilitation complex provides the normalization of heart rate and blood pressure. It is known that at the same time stress of adaptation mechanisms decreases, sympathetic effects on the heart and blood vessels weaken, and vascular tone normalizes [59]. These data are confirmed by studies that indicate improvement in cerebral circulation and cognitive functions under the influence of aerobic exercise [60].

Thus, it can be established that “vascular age” is a new parameter of health and, ultimately, an integral parameter of damage to internal organs (heart, brain

and kidneys). And arterial stiffness is the most commonly used measure of BV aging. It is known that over time there is a steady increase in arterial stiffness with an average blood speed of 0,2 to 0,7 m/s. Therefore, arterial stiffness is very important for vascular aging assessing [61].

Conclusion

Human health is determined by the age of his blood vessels — that is the conclusion that can be drawn by summarizing the presented data. Such an opinion is currently coming to specialists dealing with the problem of aging and longevity. Today, preventive measures aimed at preventing premature BV aging are at the forefront. Healthy vessels are needed to maintain a person's active longevity.

However, we are becoming increasingly convinced that the biosocial nature of human being, civilization, the nutrition and lifestyle of modern man have a negative impact on BV. Preserving healthy vessels and prolonging human life is the task of gerontology and preventive medicine in the future.

One of the directions of such work is the normalization of relationships in the system of adaptation-maladaptation-environment. Indeed, in the modern world the number of stressful situations and borderline states of mental maladaptation is growing, and as we know, any neuropsychiatric disorder will certainly affect the BV tone. It is maladaptive disorders of neurohumoral regulation of vascular tone that are the root cause of morphological changes in the vascular wall. It should be emphasized that a clear sign of vascular aging is a thickening of the vascular wall and an increase in its rigidity. True BV hypertrophy and their calcification develop as a result of impaired neurohumoral regulation of functions. And then, with the loss of regulatory effects on the vessels, metabolic disturbance, their calcification, atherosclerosis and progressive dysfunction occur. In any case, it seems that the phenomenon of compensatory BV hypertrophy associated with calcification should be carefully studied.

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Delayed help-seeking in acute coronary syndrome — view of a problem in terms of narrative medicine

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The article suggests the reasons for the delayed help-seeking in patients with acute coronary syndrome in terms of individualization of work. For analysis, the approach of narrative medicine was used, that is, a way to conceptualize medical situations using the methods of the humanities, or rather, to understand the disease as an event in the patient's life — his biographical narrative. These categories are important both from the standpoint of ethics and patient orientation, and from the standpoint of health improving through education of the population. A number of attitudes are shown that lead to delay in help-seeking: rigidity of thinking, unwillingness to cause discomfort, atypical manifestations, distrust of medicine and the unknown medical process. In general, the inclusion of a disease in the biographical process occurs through denial of the disease, distrust of medicine and/or healthcare, procrastination. As a solution of these problems, an assessment of the general informational background of patients as society participants and education depending on the social category, is proposed.

Key words: compliance, patient orientation, clinical performance, psychosomatics, sociocultural factors, myocardial infarction, healthcare organization.

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In a recently published article by Kontsevaya A.V. et al. (2019) considered the problem delayed help-seeking in acute coronary syndrome [1]. The average time from the onset of symptoms to an ambulance call is about 2 hours, with little or no change in the past decades.

Much work is being done to analyze the reasons for this delay, as the potential for reducing the time of arrival of the ambulance team to improve outcomes has already been exhausted. One of the main strategies that can be used is to educate the population about knowledge and suspicion about the symptoms of a severe cardiovascular event. Of course, this is an important part of the work.

It can be carried out on two levels: simple informing and creating a conscious attitude and understanding. The second option requires a better understanding of the processes of personality, the experience of the disease, its picture to formulate more effective ways of informing.

Narrative medicine is a kind of inclusion of ideas and methods of analysis accepted in the humanities (culturology, sociology, anthropology, psychology, etc.) to understand the problems of non-biological (non-biomedical) nature [2]. Narrative is a sequential recital. Taking into account that a person is a biosocial being, it is important to learn to take into account the "social" part of the person, i.e. the world of his personality, symbolic interaction, communication. This is done with the help of psychological quantitative and qualitative methods, such as in-depth and/or semi-structured interviews. In addition, the social sciences view allows decoding the processes taking place in the social environment to offer an explanation of the problems that eventually become part of medical practice and health care parameters.

In our previous study [3] in patients with myocardial infarction, in the form of an in-depth semi-structured interview, a number of paradigms were found that interfered with the time to seek help. In particular, the delay before calling an ambulance ranged from 2 hours to 2 weeks, including the detection of changes in the electrocardiogram when contacting the clinic for another reason. The reasons were as follows: “impossibility to imagine” the development of a myocardial infarction in oneself due to young age and general well-being, playing sports; an idea of health problems due to older age, and not disease; "Distrust of health care", fear of queues in clinics. These and other similar ideas can be detected during a conversation with the patient — during the study or in practice, i.e. when history taking, discussing treatment. But only awareness gives quite a bit in terms of influence on it. Further, we offer the results of a deeper, narrative analysis of attitudes related to procrastination in case of symptoms of the disease, according to the literature and our own data.

The material and methods are described in the previous article [3]. Selected variants of paradigms, semantic intentional constructs, which eventually led to a late help seeking, are shown below.

Rigidity of thought. Difficulty of switching from "healthy" to "sick". In contrast to diseases that usually develop subtly, acute coronary syndrome is a sudden event. In one of the patients, a departure was planned for the next morning, when he felt pain behind the sternum at night. He didn't want to spread panic and was afraid of cancelling the trip. The importance of symbolic filling of cultural practices can be greater than painful symptomatology. For example, a patient who eventually developed myocardial rupture was not called for an ambulance until after midnight. That was because the family was celebrating the New Year's Eve, although the pain syndrome developed one and a half hours before midnight.

"What if it would disappear by itself" is an attitude that takes place if the symptoms do not intensify, and even more so if it decreases. Relation of values: for example, the value of a lost vacation is compared to another value — and if it turns out that life and health are on the scales, the decision will be made in favor of seeking help (“If only I knew...”). But before the diagnosis is made, these data are not available, and therefore the decisions are based on well-being and on known information. The disease may be perceived as invading life, and the rigidity of thinking does not allow us to switch to a new event as being of higher value than current activities. Providing a clear picture of the options for acute coronary syndrome development and the importance of time will allow patients to make more adequate decisions.

Reluctance to make a disturbance. Delicacy, reluctance to attract attention, make a disturbance to relatives, as well as once again call an ambulance, for some patients are a cause of delay. In this case, the patient’s position in the family is taken into account: if he is the “head of the family”, the earner, his health may appear more important than the dependent (and especially elderly) family member, in his own submission.

Atypical manifestations. Acute coronary syndrome does not always take on forms that indicate heart disease. A stereotype of myocardial infarction as a "heart attack" can reduce attention to symptomatology if the disease is manifested, for example, by general weakness. If your heart hurts, the situation is perceived to be more important.

Distrust in medicine. This setting is related to the feeling of danger in relation to the events that occur to the patient when he gets to the clinic. For example, a 70 year old patient refused to be hospitalized if

diagnosed with non-ST segment elevation myocardial infarction, and had to take an ambulance to visit her three times, and then visit her every day for a week by district therapist. She explained her refusal to go to the hospital by trusting only "doctors she knows". If it is not possible to “agree” on the place of hospitalization, she prefers to stay at home with satisfactory health. This attitude, of course, causes condemnation, but in the analysis it is clear that the reason is the picture of healthcare formed by the patient as a result of life and social interactions. The formation of a favorable attitude towards doctors and the healthcare system is a serious task that can be solved both in the system itself and at the level of creating its information image.

Unknown medical process. Apart from distrust in medicine, there is a misunderstanding (and fear) of those events that will occur in the case of seeking help. Surgical intervention, painful procedures, risks and side effects are the components of the picture of the disease in case of contact with doctors and the medical institution.

You can find other options for attitudes, for example, regarding gender stereotypes: “a man must endure pain” turns out to be a delay factor in the presence of pain. But on the whole, it seems that the principal options for including the disease narrative in the patient’s narrative are the denial of the disease, distrust of medicine, and procrastination as such, due to the rigidity of the thoughts’ change. A disease event disrupts the patient’s life, i.e. his biographical narrative.

If the patient denies the disease for various reasons, he does not accept the fact or suspicion; both simple ignorance and transcendental categories of fate, god, can play a role in this process. In case of distrust in medicine, idea of medicine as a social institution, one's own experience of interaction, the experience of acquaintances and information from different sources play an important role. Procrastination associated with the psychological phenomenon of intention behavior gap [4] is a more complex motivational and intentional phenomenon in which there are the need for a "critical mass" of motifs that can finally inspire action: to call health workers.

The severer the symptomatology, the more understandable or (eerily) incomprehensible it is, the easier it is to close the gap. In addition, the value of abandoning the planned course of life (going to work, going on vacation, celebrating, etc.) is compared with the perceived risks, which are calculated on the basis of the interpretation of feelings (symptoms) and "medical" knowledge. Even a well-defined diagnosis of myocardial infarction may not be a strong enough reason to abandon plans in favour of hospitalization unless there are clear symptoms and knowledge of the risks of the disease.

Assuming that the patient is an active participant in society, involved in information exchange, it is quite easy to explain the presence of these attitudes. It is accepted, experienced and assimilated material that is offered to the patient from the Internet, media, friends, family, books, movies and other sources. The final picture of medicine and health care is unique for everyone, although it contains some common features for the territory, age group (generation), gender, class, occupation, income, marital status. Accordingly, when planning sociological research to clarify the targeting of health education, it is important to consider the target group with its properties: what is the information agenda of the selected group. Moreover, when providing information within the framework of primary prevention, screening, and medical examinations, it would be desirable for the doctor to differentiate the methods of information. Pre-tested and published materials can help to do this, both in a popular form that reveals the problem of acute coronary syndrome itself and anticipating the attitudes that will make it difficult for the patient to seek help when the event occurs.

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Correction of hypertriglyceridemia in order to reduce the residual risk in atherosclerosis-related diseases. Expert Council Opinion

Russian Society of Cardiology, Russian Scientific Medical Society of Therapists, Eurasian Association of Therapists, Russian National Atherosclerosis Society, Russian Association of Endocrinologists, National League of Cardiologic Genetics

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In opinion the Expert council provides management tactics for patients with hypertriglyceridemia (HTG). It is demonstrated that HTG is a common condition in overweight patients and is an important component of residual risk. HTG creates additional conditions for the progression of atherosclerosis, so the level of triglycerides (TG) is recommended to be measured in patients with a high, very high and extremely high risk level. An indication for the appointment of drugs that reduce the concentration of TG is its level of more than 2,3 mmol/L. Statins are the agents of choice to reduce the risk of cardiovascular disease in high-risk patients with hypercholesterolemia and HTG. Fenofibrate is used to correct HTG, and in case of intolerance to it or when the target level of TG is not reached, omega-3 ethers of polyunsaturated fatty acids in a dose of 2-4 g/day are recommended. In patients with HTG with a TG level >5,6 mmol/L, fenofibrate is the agent of choice.

Key words: hypertriglyceridemia, fenofibrate, omega-3 PUFAs, cardiovascular disease, residual risk of cardiovascular complications.

Conflicts of Interest: nothing to declare.

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An expert meeting was held on February 15, 2019 in St. Petersburg on the topic "The use of fibrates and omega-3 polyunsaturated fatty acids (PUFAs) in the treatment of atherogenic mixed dyslipidemia". Its purpose was to discuss and develop a joint expert position on dyslipidemia problems, residual risk and treatment approaches.

Urgency of the issue

Coronary artery disease (CAD) remains the leading cause of death in all developed countries. Cardiovascular mortality is far ahead of mortality from infectious and oncological diseases. According to WHO estimates, by 2030 about 23,6 million people will die from cardiovascular diseases (CVDs) every year [1].

According to various sources, the annual total frequency of deaths is 1,2-2,4%, while the frequency of deaths from CVDs is 0,6-1,4%, and the frequency of non-fatal myocardial infarction (MI) is from 0,6% (according to the RITA-2 study) to 2,7% (according to COURAGE) [2-8]. In very high-risk patients, the annual death rate increases to 3,8%, while in patients with hemodynamically insignificant coronary artery atherosclerosis, it is 0,63% (according to REACH register) [9].

According to the SWEDEHEART study, after the use of new therapeutic methods, such as percutaneous coronary intervention (PCI), dual antiplatelet therapy, statins and angiotensin converting enzyme inhibitors (ACEs), from 1995 to 2009 there was a significant decrease in annual mortality due to MI from 25% to 15%.

However, over the past 6-8 years, the mortality rate has leveled off and remains unchanged [10]. In this regard, the search for additional opportunities to reduce the risk of cardiovascular complications (CVC) and the progression of atherosclerosis is relevant.

Residual risk and its association with triglycerides

Recently, it has become apparent that even when the target level of low-density lipoprotein cholesterol (LDL-C) is reached, patients still have a residual risk of CVC. Important reasons for the residual risk are high levels of triglycerides (TG) and low levels of high density lipoprotein cholesterol (HDL-C) in the blood plasma.

Thus, according to the Framingham Study, a TG level of >1,7 mmol/L is associated with significantly higher risk of CVC [11]. For example, even when the target level (TL) of LDL-C is reached (<1,8 mmol/L), CVC risk in patients with HDL-C <1,0 mmol/L is 64% higher than in patients with HDL-C ⩾1,4 mmol/L [12]. Elevated levels of TG and low levels of HDL-C synergistically increase the risk of cardiovascular events in patients with already reached of LDL-C TL (<2,1 mmol/L) [13]. It has been shown that in patients with a TG >2,3 mmol/L and, at the same time, HDL-C <0,8 mmol/L, the risk of CVC increases by 10 times compared with patients with normal values of TG and HDL-C [13, 14].

The scientific communities differently define hypertriglyceridemia (HTG) and severe HTG. Despite the epidemiological data on an increase in cardiovascular risk with an increase in TG levels >1,7 mmol/L, nevertheless, clinical studies of drug therapy confirm its effectiveness in patients with TG levels >2,3 mmol/L. According to NCEP ATP III, the normal TG value is determined by a level of less than 1,7 mmol/L, the borderline high — from 1,7 to 2,3 mmol/L, and the HTG is from 2,3 to 5,6 mmol/L, severe HTG >5,6 mmol/L [15]. Russian and European guidelines 2016 recommend starting drug therapy at a TG level >2,3 mmol/L in high-risk patients [16, 17]. In view of this, we consider it appropriate to start drug treatment of patients at a level of >2,3 mmol/L with a TL of TG <1,7 mmol/L. TG level in the range of 1,7-2,3 mmol/L requires non-drug correction.

Among the primary reasons of TG increase are hereditary mechanisms (increase of very low-density lipoproteins (VLDL) production, TG hydrolysis defect, defect in clearance of TG remnants in the liver). In this case, acute pancreatitis is the leading clinical manifestation of familial HTG [18].

A modern clinician should have an idea that secondary HTG is much more common than primary and can be caused, first of all, by insulin resistance and related conditions: type 2 diabetes mellitus (DM), metabolic syndrome and obesity. In this case, a characteristic manifestation of dyslipidemia, along with a high LDL level, is high level of TG and VLDL, as well as a low level of HDL. This condition is called combined dyslipidemia [14]. Combined dyslipidemia is an extremely common condition, and its significance is usually underestimated by clinicians. According to the NHAMES study, it is observed in 62% of CVD patients [19].

Among 22,063 patients receiving statin monotherapy in Europe and Canada, increased levels of TG and decreased levels of HDL-C were observed in 38,8% and 26%, respectively [20]. Other reasons for increasing of TG levels may include chronic kidney disease, hypothyroidism, alcohol abuse, systemic lupus erythematosus, and the use of antiretroviral drugs and corticosteroids [21].

The predominant mechanism underlying the atherosclerotic process in HTG is the overproduction of VLDL in the liver. It was noted that in atherogenic combined dyslipidemia, the transfer of TG from VLDL to LDL and, at the same time, the transfer of

cholesterol esters from LDL to VLDL occur. An additional pathway for atherogenesis appears: VLDL, which lost part of the TG in exchange for cholesterol, become smaller, which significantly increases their atherogenicity (the ability to penetrate the vessel wall) [22]. In addition, in patients with atherogenic combined dyslipidemia, the level of small dense low-density lipoproteins (sdLDL) is increased. It penetrate the vascular wall even more easily due to their small size, are more susceptible to peroxidation, more often retained in the vascular wall, and contribute to the development of endothelial dysfunctions. Due to increase of thromboxane synthesis, it increase platelet activity, do not bind to liver receptors and, therefore, are more slowly excreted from the bloodstream, leading to an acceleration of atherogenesis [22, 23].

In this regard, in patients with obesity and type 2 DM, non-HDL cholesterol (non-HDL cholesterol=TC-HDL) gives much more information for cardiovascular risk assessing [24]. According to some studies, non-HDL cholesterol has a higher level of prognostic significance compared with LDL in patients with metabolic syndrome and DM [25]. International guidelines propose considering non-HDL cholesterol as a secondary aim after reaching the LDL TL [15, 26].

For quite a long time, despite the availability of a large amount of epidemiological data on the contribution of a high TG level to the atherosclerotic process, there was no convincing evidence that with TG decrease there is a decrease in cardiovascular events rate. The line was drawn under the role of TG in atherogenesis by the ACCORD-LIPID (subanalysis of the data of patients with elevated TG levels) and the REDUCE-IT studies, the results of which will be discussed below [27, 28].

Approaches to the HTG treatment and atherogenic combined dyslipidemia

LDL is the most atherogenic plasma particles, and as a result, treatment of a patient with dyslipidemia should begin with drugs aimed to reducing this particular parameter — HMG-CoA reductase inhibitors (statins). Second-line drugs designed to achieve LDL target level are cholesterol absorption inhibitors (ezetimibe) and PCSK9 inhibitors (evolocumab, alirocoumab).

If an elevated TG level is detected (>5,6 mmol/L), it is recommended to start fenofibrate therapy. At a TG level of 2,3-5,6 mmol/L, drugs aimed at TG lowering should be combined with statin therapy: fibrates (fibroic acid derivatives) and omega-3 PUFA ethyl esters.

The mechanism of action of fibrates is the activation of peroxisome proliferator-activated receptor alpha (PPARα). These receptors are located in the liver, muscles, adipose tissue, heart, kidneys, macrophages and platelets.

The main role of PPARα receptors is to regulate the metabolism of lipids and lipoproteins, inflammation and endothelial function. Activated PPARα receptors bind to specific DNA sites, stimulating or inhibiting the main genes encoding metabolic processes. It should be noted that from the class of fibrates, only fenofibrate can be used in combination with statins [17, 29].

Fenofibrate increases the synthesis of ApoA1, ApoA2, the activity of lipoprotein lipases, and reduces the synthesis of ApoC III, ApoB100 and the concentration of sdLDL. Correspondingly, this leads to an increase in HDL-C by 10-30%, accelerated conversion of chylomicrons into their remnants, a decrease in LDL-C by 25%, sdLDL — by 50%, and TG and VLDL synthesis reducing. TG levels can decrease on average up to 50% [30-32].

Table 1 shows the mechanisms of action and the comparative effectiveness of fenofibrate, statins and ezetimibe in terms of their effect on the lipid profile [15, 30, 33-35].

In addition to the effect on lipid metabolism, fenofibrate reduces the level of uric acid by an average of 25%, fibrinogen — by 21% and C-reactive protein — by 34% [30-32].

Clinical studies are important, proving the effects of fenofibrate therapy on surrogate and hard endpoints. One of the first studies in this category was the DAIS study, which showed the positive effects of micronized fenofibrate therapy at a dose of 200 mg/day on the size of the atherosclerotic plaque [36]. The results of the ACCORD and FIELD studies turned out to be even more significant [27, 37].

The first major study in patients with type 2 DM was the FIELD study [37, 38]. The aim of this randomized clinical trial was to evaluate the effect of fenofibrate intake on cardiovascular mortality in patients with type 2 DM (n=9,795). Inclusion criteria were: history of type 2 DM, age of 50-75 years, total cholesterol (TC) level from 3,0 to 6,5 mmol/L, ratio of TC/HDL-C levels ⩾4 or TG level from 1,0 to 5,0 mmol/L.

The primary endpoint was myocardial infarction (MI) or death due to CVC. Patients were randomized to 200 mg fenofibrate or placebo treatment groups, and the follow-up was 5 years on average. In the fenofibrate group compared with placebo, the number of cases of MI and cardiovascular death was reduced by 11%, although this difference was not statistically significant (P=0,16). However, in the fenofibrate group, the incidence of nonfatal MI significantly decreased by 24% (p=0,01), the number of cases of revascularization by 21% (p=0,035), there were also significantly lower number of CVC cases

Table 1

Comparison of the effectiveness of fenofibrate, statins and ezetimibe [adapted from 15, 30, 31, 33-35]

Mechanism of action	Fenofibrate	Statins	Ezetimibe
	PPARa activation leading to normalization of lipid metabolism	Inhibit HMG-CoA reductase, which is involved in the synthesis of cholesterol	Selectively inhibits the absorption of cholesterol and certain plant sterols in the intestine
LDL-C decrease [15]	5-20%	18-55%	15-30%
Triglycerides' decrease [15]	20-50%	7-30%	do not change
HDL increase [15]	10-20%	5-15%	3-5%
LDL particle size increase [28, 29]	50%	no	no

(p=0,003). However, the incidence of all-cause mortality, non-cardiovascular mortality and strokes did not significantly change. It should be noted that the study patients were allowed to use statins, and by the end of the study there was a disproportion in the number of patients who received it (17% in the placebo group and 8% in the fenofibrate group, p<0,0001). According to the authors, this fact could "blur" the result in the main group of the study [37, 38].

A further ACCORD Lipid study included 5518 patients with type 2 DM. Unlike the previous study, in this research all patients took simvastatin at a dose of 20-40 mg/day and were randomized to a 160 mg/day fenofibrate therapy group or placebo.

The follow-up was an average of 4,7 years. The primary endpoint is the first CVC (non-fatal MI, non-fatal stroke, cardiovascular death). The secondary endpoint is the difference in outcomes against the background of various treatment regimens, overall mortality, microvascular complications, quality of life, and efficiency-cost ratio. The primary endpoint reached: 2,4% of patients/year in the placebo group and 2,2% of patients/year in the fenofibrate group (risk ratio (RR) 0,92 (95% confidence interval (CI) 0,79-1,08), p=0,32). Cardiovascular mortality was 0,72% per year in the fenofibrate group and 0,83% per year in the placebo group (p=0,26). All-cause mortality was 1,47% per year in the fenofibrate group and 1,61% per year in the placebo group (p=0,33) [27]. The main result of the study was that fenofibrate therapy reduced macrovascular events (CVD risk) in the group of patients with atherogenic combined dyslipidemia (TG ⩾2,3 mmol/L and HDL cholesterol ⩽0,9 mmol/L) by 31% Moreover, the combination therapy with fenofibrate and simvastatin was well tolerated. Consequently, in the ACCORD study, cardiovascular risk remained elevated despite statin therapy, and was associated with HTG and decreased HDL-C level.

ACCORD Lipid results supported current guidelines for the treatment of lipid disorders: additionally prescribe drugs from the fibrate group to a patient taking statin monotherapy with a TG level >2,3 mmol/L.

The guidelines of ESC/EAS 2016 and the Russian National Society of Atherosclerosis 2017 for the management of dyslipidemias include the following non-drug methods for reducing TG: reduce overweight (body mass index (BMI) 20-25 kg/m2, waist circumference <94 cm (men) and <80 cm (women)), decrease alcohol consumption (patients with HTG should completely refuse alcohol), increase regular physical activity (exercise for at least 30 minutes every day), reduce the carbohydrates and salt intake (up to 5 g/day), increase the intake of omega-3 PUFAs, decrease the consumption of mono- and disaccharides, trans fats (<1% of total consumption) and saturated fats (<10% of total consumption), replace saturated fats with mono- and polyunsaturated [16, 17]. The management strategy for patients with combined dyslipidemia is presented below (Fig. 1).

Based on the developed common attitude, the Council of Experts proposes to clarify the medical methods for lowering of TG levels presented in the guidelines of ESC/EAS 2016 and the Russian National Society of Atherosclerosis 2017, namely: the possibility of prescribing omega-3 acid ethyl esters at a dose of 2-4 g/day in non-drug therapy futility at a TG level of 1,7-2,3 mmol/L, as well as in fenofibrate intolerance or in failure to achieve target TG level <1,7 mmol/L. It is also need to clarify practicability to add fenofibrate to statin therapy in patients of high, very high and extremely high risk, to determine whether fenofibrate as a first-line drug at a TG level of ⩾5,6 mmol/L (Table 2).

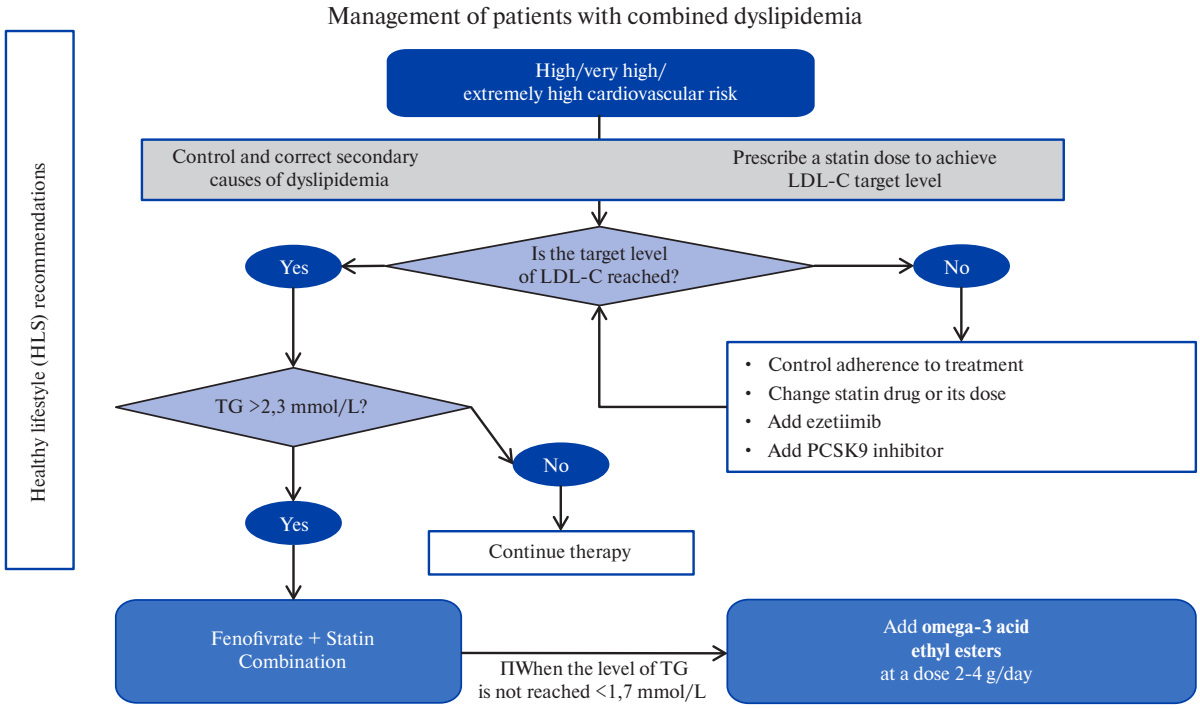

Fig. 1. Management of patients with combined dyslipidemia.

Omega-3 acid ethyl esters (Omacor) are second-line drugs using to reduce the TG level. Recently, a REDUCE-IT study involving 8 thousand patients was completed, which proved the effect of omega-3 PUFAs on hard endpoints [31]. Inclusion criteria were: a history of CVDs (~ 70% of patients) or type 2 DM+>1 RF, TG level ⩾2,3 mmol/L and <5,6 mmol/l, achieved LDL TL >1,03 mmol/L and ⩽2,6 mmol/L.

The primary endpoint was the time from randomization to the first event: cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, revascularization, unstable angina pectoris. A 25% reduction in the relative risk of major adverse cardiovascular events was demonstrated ($p<0,001$) in the group of patients taking omega-3 PUFAs (eicosapentaenoic acid 4 g/day) compared with placebo.

Thus, the treatment regimen for HTG can be represented as follows (Fig. 2).

Combination therapy of combined dyslipidemia with statins and fenofibrate has long been included in clinical practice and is recommended by international and Russian associations [16, 17]. In clinical studies, the effectiveness of fenofibrate was evaluated in combination with simvastatin [27], rosuvastatin [40, 41], atorvastatin [40] and pravastatin [42, 43]. The use of fenofibrate and statins combination made it possible to achieve the TL of LDL-C, non-HDL-C and TG 5 times more often compared with medium-dose statin monotherapy [44].

Due to the advisability of combination therapy using, safety data on the combined use of statins and fenofibrate deserve special attention. Fenofibrate is the only drug in this group that can be combined with statins. Fenofibrate, unlike statins, is metabolized by the action of uridining glucuronyl transferase (UGT), without the participation of cytochromes and their metabolic pathways do not cross. In view of this, the combined use of fenofibrate with various statins does not increase their plasma concentration and the area under the concentration-time curve (Cmax and AUC) [29]. It is known that combination therapy does not lead to a risk of myositis or rhabdomyolysis in comparison with statin monotherapy [27, 29]. In the ACCORD-Lipid study, the use of the combination of simvastatin and fenofibrate for 4,7 years did not increase the risk of myositis or rhabdomyolysis compared to simvastatin [27]. According to the FDA, the incidence of rhabdomyolysis when using the combination of statin-fibrate is 0,58 per 1 million patients. In clinical studies, in 3-4% of patients there may be increase of liver enzymes level 3 times higher than normal [29].

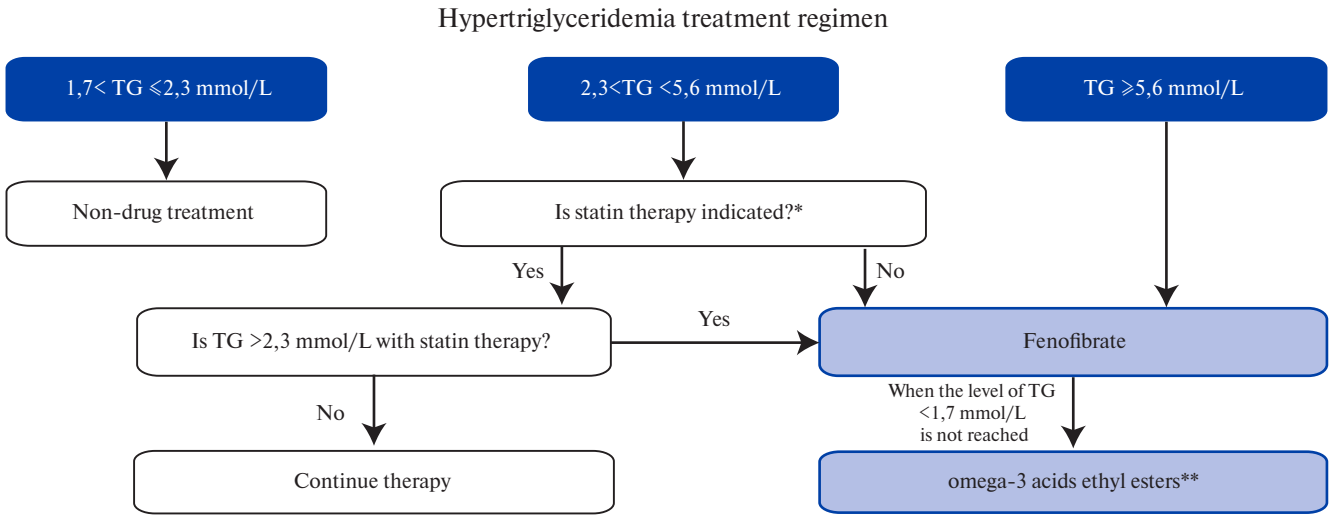

Fig. 2. Hypertriglyceridemia treatment regimen [adapted from 36-39].
Note: * — taking into account the clinical phenotype of the patient (hypercholesteremia), ** — omega-3 acids ethyl esters at a dose of 2-4 g/day. In severe hypertriglyceridemia, consider the use of plasmapheresis.

Table 2

Recommendations of the Council of Experts on the HTG treatment

At a TG level of 1,7-2,3 mmol/L, non-drug therapy should be performed. If there is no effect, consider omega-3 acids ethyl esters in a dose of 2-4 g/day.
Drug therapy should be started in patients with triglycerides >2,3 mmol/L
Statins are first-line drugs to reduce CVD risk in high-risk patients with hypercholesterolemia and hypertriglyceridemia
In patients of high, very high and extremely high risk with triglycerides level >2,3 mmol/L, despite the treatment with statins, fenofibrate should be added to therapy
In TG level of ⩾5,6 mmol/L, the priority is to prevent pancreatitis with the use of fenofibrate
In case of fenofibrate intolerance or if the target TG level (<1,7 mmol/L) is not reached, it is advisable to use omega-3 acids ethyl esters at a dose of 2-4 g/day.

It should be noted that combination of fenofibrate and various statins (simvastatin, atorvastatin, rosuvastatin) has been used for a sufficiently long period of time, and the risk-benefit ratio of this combination is certainly positive for patients with HTG [14, 29].

Conclusion

At a TG level above 2,3 mmol/L, phenofibrate or omega-3 acid ethyl esters should be added to strategy. HTG is most common in patients with obesity, insulin resistance, type 2 DM, metabolic syndrome, and chronic disease kidneys, as well as in alcohol abusers. HTG significantly complements the mechanisms that affect atherogenesis, which cannot be completely eliminated with the help of statins and ezetimibe. The Council of Experts considers it appropriate to increase the awareness of clinicians about the role of HTG in the pathogenesis of atherosclerosis, the importance of assessing the level of TG in patients with high, very high and extremely high cardiovascular risk in routine practice of general practitioners, cardiologists, therapists, endocrinologists and about possible treatment options. Recent data on the TG level as an independent risk factor for CVDs, along with LDL and TC, can contribute to the further study of methods for HTG correcting. Fenofibrate is the main drug in the strategy for lowering of TG levels in addition to statin therapy in patients with TG levels >2,3 mmol/L. The second-line drugs for TG level lowering are omega-3 acid ethyl esters in a dose of 2-4 g.

Conclusion. Management of patients with HTG

— In patients with a high, very high and extremely high risk of atherosclerosis-related CVDs and their

complications, it is necessary to measure the level of fasting TG;

— It is necessary to consider the possible causes of HTG and assess the total cardiovascular risk;

— To achieve target levels of LDL in accordance with the risk category; statins, ezetimibe, and PSCK9 inhibitors are designed to lower LDL;

— To reach the TG target level of <1,7 mmol/L; a decrease in TG is an important component in cardiovascular risk reducing;

— At a TG level of 1,7-2,3 mmol/L, non-drug therapy should be given;

— At a level of TG >2,3 mmol/L, fenofibrate must be prescribed for its correction;

— At a TG level of ⩾5,6 mmol/L, fenofibrate is first-line drug to prevent the development of pancreatitis;

— In case of fenofibrate intolerance or failure to reach the target level of TG <1,7 mmol/L, it is advisable to use omega-3 acids ethyl esters in a dose of 2-4 g/day.

Conflict of Interest: nothing to declare.

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Constitutional guarantee of the right to health and the practice of medical care: legal positions of the judicial authorities in cases related to cardiovascular pathology

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The article discusses a number of situations related medical and constitutional aspects of cardiovascular medical care. The ability to prevent the negative consequences caused by diseases is not only a task of medicine as a scientific and practical field, but also a task of the Constitution of the Russian Federation. Article 41 of the Constitution of the Russian Federation establishes the protection of human life and health as one of the main tasks of the state. Medical and civil aspects of the methods for preventing diseases and its consequences are shown. An integrated approach to the analysis of this problem contributes not only to the systematization of knowledge and experience in this field, but also helps to implement the definition of health of the World Health Organization.

Key words: pulmonary embolism, stroke, medical ethics, patient orientation, judicial practice, Constitution of the Russian Federation, Supreme Court of the Russian Federation.

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The doctor is a representative of medicine and a healthcare. These two categories should be separated. Medicine is an ancient cultural practice and a private science that learns about the world in a certain way, and then influences it for a certain purpose. The purpose of medicine is to prolong a person's life with maximum quality. This is the ethical side of medicine, its essence. Unlike medicine as such, healthcare is a legal institution.

Healthcare fulfils medical tasks, as well as those of the state in the field of medical categories. The importance of the institution of healthcare is confirmed, in particular, by the provisions of Article 41 of the Constitution of the Russian Federation, which guarantees the right of everyone to health and medical care, as well as Article 25 of the Universal Declaration of Human Rights, which establishes the right of everyone to medical care and the necessary social services needed to maintain the health and well-being of himself and his family [1].

Thus, the Russian Federation, as the main subject of legal relations, sets one of its priority goals to fulfill the objectives of medicine: to preserve and extend life with the highest quality for all citizens.

Legal regulation of health issues

The implementation of healthcare tasks puts medicine in a position of regulation and tight control, that is, makes medicine a part of the legal system. This is confirmed both by the relevant regulation on the part of federal legislation, and adopted by industry regulatory legal acts of the Government of the Russian Federation, the Ministry of Health of the Russian Federation and other acts of departments. The fundamental legal act in this area is Federal Law of November 21, 2011 № 323-ФЗ "On fundamental healthcare principles in the Russian Federation", which establishes that the state recognizes the protection of public health as one of the most important conditions for physical and mental development. Medical organizations are required to recognize and respect the rights of citizens in the field of health care. Correspondingly, the branches of law — constitutional, civil, administrative, criminal, as well as the adopted acts of rule-making, become part of the medical process, which in its essence is the process of legal relations between the doctor (wider — the health worker) and the patient (wider — and his representatives). The correlation of responsibility for the quality of the implementation of goals and the specifics of the subject of medicine, including many a priori disregarded factors, leads to the fact that state guarantees face difficulties in their implementation. They are also complicated by the resource-intensiveness of modern healthcare: the inclusion of relevant scientific tools and knowledge in the process. In fact, medicine balances between predictability and unpredictability, and such a balance should be controlled and regulated by the state.

All of the above suggests that the legal basis of the specialist's activities in the analyzed area acts both as a measure to protect the doctor's reputation and as a legal instrument. This instrument provides ability for doctor to feel as his own freedom and independence, significance the decision taken, and responsibility for their work [2].

Attitude of the judiciary on health issues

The importance of human life is demonstrated by both domestic and international authorities.

In its judgment № 27-P of 6 November 2014, the Constitutional Court of the Russian Federation noted that when it comes to the death of a person, the reality of the suffering of family members is not questioned. In addition, "It is all the more significant in case when a spouse or close relative has a suspicion that the death of a loved one was caused by untimely or poor quality medical care provided by a health care institution"*. The European Court of Human Rights, in its judgment of 27 June 2006 in the case of "Byrzykowski vs. Poland", stressed that possible mistakes made in the course of providing medical assistance and acquired as a result of the consideration of such cases should be immediately generalized and brought to the attention of medical workers in order to prevent the repetition of such mistakes and improve the safety of patients [3].

The Plenum of the Supreme Court of the Russian Federation, as one of the main courts, also plays an essential role in the qualification of an act. In particular, in Resolution № 10 of the Plenum of the Supreme Court of the Russian Federation of December 20, 1994, "Certain Questions of Applying of Legislation on Compensation for Moral Damage", the degree of moral or physical suffering is assessed by the court taking into account the actual circumstances of damage, the individual characteristics of the victim and other specific

* Judgement of the Constitutional Court of the Russian Federation of 30.11.2016 № 27-P "in the case of the constitutionality verification of paragraph 1 of Part 8 of Article 14 of the Federal Law "On Insurance Contributions to the Pension Fund of the Russian Federation, the Social Insurance Fund of the Russian Federation, the Federal Compulsory Medical Insurance Fund" and Article 227 of the Tax Code of the Russian Federation in connection with the request of the Kirov Regional Court". Computer-assisted legal research system "ConsultantPlus", local version (date of request 22.07.2019).

circumstances indicating the severity of the suffering. The most important role in this issue is played by Resolution № 522 of the Government of the Russian Federation of August 17, 2007 "On Approval of Regulations for Determining the Degree of Severity of Damage to Health on the Basis of Danger to Human Life". It establishes the criteria for determining the causal link between injuries that have caused harm to the health/death of a patient and the actions of physicians.

Clinical-legal example

As a special case, illustration of ethical legal relations in the process of implementation of human rights guarantees provided by Article 41 of the Constitution of the Russian Federation, with a doctor as a subject of medicine and a subject of the legal system — the main active element and the main responsible person (and later — a possible defendant), we cite an example from the practice of cardiovascular care, namely — acute cerebrovascular event.

The example is based on the verdict of the Moscow District Court, the appeal judgment of the regional court. The peculiarity of this case is that as a result of poor quality of medical services, expressed in the improper performance of official duties, the patient died. The man N. was hospitalized in a cardiac clinic of the regional center due to acute coronary syndrome. He was given a thrombolytic treatment, followed by coronary angiography and then a minimally invasive intervention, after which his condition was stabilized. By evening, however, the patient had symptoms of acute cerebrovascular accident. Since the hospital did not have a neurological service and the necessary diagnostic equipment, the patient was transferred to the regional hospital. But when the patient was brought in and examined by a neurologist, a neurosurgeon, he was given a CT scan and hospitalization was denied. At the time of his research, his neurological status was stable and there was no indication of neurosurgical intervention. Due to the patient's registration in one of the districts of the regional center, it was recommended that he be transported to the city hospital for further treatment. In particular, the decision was justified by the lack of beds in the regional hospital. In the course of transportation, the neurological status of the patient worsened and, despite treatment at the city hospital, he died.

In this case, legal, organizational, biomedical and ethical aspects are intertwined.

From a legal and organizational point of view, questions such as the causal link between the physician's actions and the patient's death are at top of mind. For the legal qualification of the act, both the actions of the doctor (objectively unjustified transportation of the patient) and inaction (failure to provide the necessary medical, intensive care help) are significant. In other words, it is important to understand whether medical assistance has been provided in accordance with the norms of the law: right, timely and in full.

From a biomedical point of view, it is important to take into account the physician's qualifications and experience in the field of intensive care for people with vital organs' disorders until their activities are stabilized.

In addition, relevant medical organizations must be provided with the necessary number of doctors, equipment and drugs. In doing so, the physician must take such measures as not to result in the severity of the disease, as well as the development of its complications in one form or another. The objective difficulties of clinical diagnostics and tactics are clear. They are caused by the complexity of the pathological processes underlying the cardiovascular complication. For example, the development of thrombotic and thromboembolic episodes in the arterial system depends on the balance of the pro- and anticoagulant systems [4], and the further course of ischemic events in a particular territory may be exacerbated both in the case of physician action and in case of inaction. The actions are based on diagnostic information that may be insufficient for a variety of reasons, whether purely medical, organizational or professional.

From an ethical point of view, the fundamental issue is whether to decide whether to provide medical care in strict compliance with existing regulations or not. In such a situation, the physician is asked whether he has the right to treat a patient if there are no available beds in the hospital; whether he is entitled to hospitalize a patient if there is a lack of legal documentation or if there is a likelihood (even low) of such a patient dying. Is it the right of the doctor to decide to transport the patient if this in any way extends the period from the beginning of the complication to the provision of specialized medical care? All these rather controversial, but at the same time important questions in law and medicine are not unambiguously answered, and the ethical actions to be taken in the event of an unfavourable course of disease may raise the issue of harm to health. In the case of certain doubts, the physician has to make a decision in accordance with his ideas of professional duty. But in the event of doubts about the outcome, the parties to legal relations in each case have the right to appeal to the court.

It is also important to note the aspects of communication between doctors and relatives of patients, doctors and other healthcare professionals. According to the case file, there are statements like

"complain to the President", "have you made an agreement with me?", "too many documents have to be processed" heard by the patient's relatives.

Comments by some healthcare providers on the actions of others also matter. In the process of patient routing, when difficulties arise, communication is often the factor that forms a picture of care in the minds of the patient's relatives (especially in the case of complications or fatal outcomes) [5]. As a result, it is non-constructive communication that can be the starting point for a lawsuit.

In the present case, the intensive care physician refused to provide medical assistance to the patient because he had registration in another constituent entity of the federation, there was no free bed in the medical center, and the required specialist (neurosurgeon) was in another medical organization. The decision was made to transport the patient, which led to worsening in his condition, resulting in his death after a period of time. During the session of the court, it was established that the attending physician had the opportunity to provide medical care in a particular medical center (without transferring the patient), but the intensivist treated the patient carelessly, which resulted in the death of the patient. The court found the physician guilty of causing the death by negligence and imposed a criminal penalty.

All of this, of course, does not mean that the legal position on a particular case is universal, ultimatum and cannot be corrected. Referring to the above example, it is worth noting that the respondent party used its right to appeal against the court decision in order to make an acquittal (however, ineffective: the appeal courts left the verdict of the court of first instance unchanged, the stated requirements — without satisfaction).

Ethical analysis

Ethical analysis can be a useful tool in resolving such contentious issues. A number of ethical algorithms can be used to support medical intuition, not just theoretical but applied ones. The combination of actions in this and any such situation can be imagined as an equation where the replacement of variables can be obtained from a conditional "1" (100%), in the case when the patient is fully recovered, to a "0", representing the lethal outcome. Intermediate results can be a kind of assessment of the patient's well-being and health. The physician is required to maximize the result of the equation under the available conditions.

One of the main variables of the equation will be the conditions of certainty/uncertainty and risk. Obviously, the uncertainty conditions increase the risk assessment and exclude the possibility of the physician orientation an unequivocally optimistic outcome as the starting point for choosing the best solution. Maximal risk minimization in uncertainty is a priority for the physician.

In the above situation of the patient's non-hospitalization with the subsequent statement of claim we have a number of mistakes in the decision making by the doctor. Firstly, the situation seems to have been mistakenly perceived as clear and defined. Secondly, there is a lack of risk assessment: cardiovascular pathology a priori has an increased risk to the patient's life. This requires the doctor to double-check own beliefs that the patient is safe, rather than hoping for a well outcome.

In this context, we can see that the deontological imperative of caring for the patient's life is a medical duty, which is combined with an analytical approach to assessing the situation. A child's understanding of simple moral functions arises before rational thinking, which speaks in favor of the possibility of a preset understanding of moral concepts, and thus of their quicker reproducibility and coordination, than in rational reasoning. In other words, ethical decisions are made intuitively, but can also be the result of analysis.

It is not necessary to translate difficult ethical decisions into the language of mathematics in case of acute pathology. But if the key points are fixed, properly formulated, and complemented by qualitative rationalization in advance, it is possible to significantly reduce the number ethical decisions and strategies of interaction with the patient that leads to the death. This assumption is reinforced by the fact that lethal outcomes and complications are not the result of malice, but of behavioral patterns of the mentally healthy and most likely rational physicians who, for various reasons, have made the wrong emphasis on assessing the situation.

Thus, despite the absolute need to understand the legal aspects of medicine, a well-structured sense of rapid analysis of the situation in emergency situations can be an effective and even independent protection against dangerous decisions.

Conclusion

"Infliction of death by negligence" is the worst case scenario for medical, legal and ethical reasons. For this reason, it is necessary not only to take into account the existing legal norms of health care regulation, but also personal perceptions of duty, honor, conscience, right and wrong [6]. It can be characterized by complex contradiction.

The importance of providing medical care and the value of human life is highlighted not only in federal

and regional legislation, but also directly in the Constitution of the Russian Federation. This only confirms the key value for society of the decisions that a doctor makes every day.

Conflicts of interest: nothing to declare.

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Constitutional and ethical medical points of view on the importance of hospitalization of a patient with emergency cardiovascular pathology

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The article discusses the constitutional, ethical and medical aspects of hospitalization of patients with a life-threatening cardiovascular event. In itself, a medical condition is a complex biological event with many unpredictable aspects of its own course and adverse events and reactions in case of medical intervention. A doctor, as the central subject of medical care, faces four categories of difficulties: law, organizational, biomedical and ethical. Medical care is regulated by both article 41 of the Constitution of the Russian Federation and departmental acts of the health care system. Actually, doctor as a part of the healthcare system implement this right. The article provides an example of delivered judgment regarding complicated course of acute coronary syndrome. It shows the complexity of the medical situation, that regards the issues of doctor's legal liability.

Key words: medical ethics, patient orientation, emergency care, legal aspects of healthcare, legal liability' psychosocial risk factors, judicial practice, Constitution of the Russian Federation, Constitutional Court of the Russian Federation.

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Cardiovascular diseases, being the main cause of death in the world, usually develop without a pronounced clinical picture, slowly. Often its debut is an acute cerebral accident, acute myocardial infarction or pulmonary thromboembolism, not to mention a sudden cardiac death. The health care system is required to be able to influence this type of pathologies (so-called non-communicable diseases) or at least its severe complications. However, primary prevention, treatment and secondary prevention may not be effective enough.

In order to prevent adverse scenario on the part of the legislator, a number of health regulations have been adopted and are subject to immediate implementation. This state of affairs is mainly due to the fact that the Constitution of the Russian Federation (RF), namely Article 41, directly fixes the protection of human life, health and improvement of the quality of its existence as one of its priorities [1]. At the same time, there are still a lot of questions in terms of legal regulation that arise from specific legal facts in this field.

Answers to such questions are often formed in court practice during the consideration of specific cases. One of the peculiarities of cases' consideration involving cardiovascular disease is the lack of medical knowledge in the judicial community (which also leads to a lack of experience in consideration of such cases). Such a state of affairs often leads to the fact that interested parties are forced to appeal to higher judicial instances, up to the Supreme Court of the Russian Federation, and if there is a doubt as to whether provision of the law is in compliance with Article 41 of the Constitution of the Russian Federation (or other constitutional and legal prescriptions), the party concerned has the right to appeal to the Constitutional Court of the Russian Federation (having passed all the stages of the national judicial protection: the court of first instance, appeal, cassation, review, and, if there is new or newly discovered circumstances). It is important to understand that courts of different instances may come to the opposite conclusions on the same problem, and then the Supreme Court of the Russian Federation will have to resolve the arising legal conflict [2].

Court practice

The Supreme Court of the Russian Federation, in its decision № 69-KG18-22 of 25 February 2019, focused on the fact that the victim in this case was misdiagnosed, and as a result the courts of different instances made conflicting decisions (the data were taken from open sources).

In 2017, the victim went to Megion Regional Hospital № 1 of the Khanty-Mansiysk Autonomous Okrug — Ugra, where he was diagnosed with acute bronchitis with moderate bronchial obstruction. A few hours later, he died the same day. The cause of death on the medical death certificate was a pulmonary embolism with a reference to an acute pulmonary heart. According to the case report of the hospital's specialist department, the patient died as a result of a massive thromboembolism, and defects in medical care to the patient (unintentional examination, inadequate treatment) were also identified, concluding that the lack of examination was due to the young doctor's insufficiency of clinical experience. In the course of the expert committee's work on the case, it was established that the patient had not undergone a chest X-ray examination, the history was poorly collected; signs of thrombophlebitis were not detected, chest X-ray, echocardiography were not performed [3].

As a result of the work of the expert commission on the profiles of "cardiology", "cardiovascular surgery", "therapy", "anesthesiology-resuscitation", it was concluded that the patient's death was conditionally preventable.

In the course of examination of the materials of the forensic medical examination, the Court of First Instance e concluded that the patient had been provided with medical assistance in an untimely and low-quality manner. It also concluded that there were shortcomings in the maintenance of medical records, and there was no information in the medical record about the medical preparations he had been given. The cause of death was deep vein thrombophlebitis of the left lower limb with a separation of the thrombus from the vein wall and the development of pulmonary embolism, the development of respiratory and cardiovascular failure. In addition, the Court of First Instance found that the victim was lying on the floor at the time of his clinical death, which caused his wife moral suffering. As a result, the Court of First Instance ruled in favour of the patient's spouse and ordered the medical institution to pay a fine.

This decision was appealed. The Court of Appeal overturned the decision of the Court of First Instance on the grounds that there was no causal link between the actions of the medical staff of the medical institution and the consequences of the patient's death caused by pulmonary edema, massive thromboembolism. The Court of Appeal also considered that the Court of First Instance had exceeded its jurisdiction, i.e. it had allowed a claim that had not been made by the plaintiff (the patient's wife). The case was then transferred to the Judicial Collegium for Civil Cases of the Supreme Court of the Russian Federation. The Supreme Court considered that the Court of Appeal's findings were based on misinterpretation and application of the

law, and were made with a significant breach of procedural norms. In its ruling, the Supreme Court directly referred to a violation of Article 41 of the Constitution of the Russian Federation by a medical institution, and the decision to refuse plaintiff's relief for compensation for moral damage was made without taking into account the normative provisions of Federal Law № 323-FL "On Fundamental Healthcare Principles in the Russian Federation" of 21 November 2011.

Since the representatives of the medical institution did not appear before the Supreme Court, the conclusions of the Court of First Instance and the forensic medical examination were not refuted, and it was also noted that these conclusions were not refuted by the Court of Appeal.

The Supreme Court upheld the decision of the Court of First Instance and overturned the decision of the Court of Appeal in this case*. Thus, when combining medical and legal aspects, including procedural aspects, the courts of different instances made opposite decisions.

It is important to bear in mind that in its definitions, rulings and decisions, the court has the right to specify certain issues (concepts) arising from the proceedings (it should be noted that the only body empowered to take a position on cases of interpretation is the Constitutional Court). Thus, in particular, the case considered by the Supreme Court of the Russian Federation on March 21, 2017 in case № 18-KG17-27 is curious**. During the consideration of this case it was established that the plaintiff and the insurance company concluded an accident insurance contract in 2015. Three months later, the plaintiff had an ischemic stroke and was eventually diagnosed with Group I disability. The insurance company refused to pay the payments on the grounds that the disability was established as a result of a general illness and that such an event was not an insured one. As a result of the review of the case file, the Supreme Court concluded that a stroke was a disease caused by external factors, occurring suddenly, unexpectedly and against the will of the patient, and therefore constituted an insurance case. In addition, the court noted that, by virtue of paragraph 44 of the Resolution of the Plenum of the Supreme Court of the Russian Federation of June 28, 2012, № 17 "On the consideration by the courts of civil cases on disputes over consumer protection", the court proceeds from the assumption that the consumer (patient) has no special knowledge of the properties and characteristics of the service provided (otherwise, "improper medical manipulations" may occur).

It is necessary to take into account that certain variants of cerebrovascular disorders can have serious consequences not only for a person's physical condition, but also influence his legal status. For example, in 2017, the plaintiff N. applied to the Zavodskoy District Court of Orel to invalidate the civil transactions of her sister M. and to declare M. incapacitated.

The stated requirements were motivated by the fact that between 24.06.2014 and 04.08.2014 M. was seriously ill and underwent treatment for hemorrhagic stroke, intracerebral hemorrhage in the left brain hemisphere, with a blood rupture into the ventricles. Immediately after the medical procedures and discharge from the medical institution, M. concluded several civil law transactions. As a result of the examination, M.'s diaphragm was established: "hemorrhagic stroke; recurrent cerebral hemorrhage in the left brain hemisphere with a burst to ventricles; subdural hemorrhage in the left brain hemisphere; coronary artery disease; atherosclerotic cardiosclerosis". Medical experts found that the disease had caused M. to develop an organic personality disorder, a decline in intelligence, behavioural disorders, and untidiness in clothing and everyday life. All these factors together led to the conclusion that at the time of the civil law transactions M. had such a significant mental disorder that she was unable to understand the meaning of her actions and to direct them. In addition, representatives of the forensic medical expertise noted that M. had made a civil law deal as early as 2 weeks after discharge from hospital, while the psychological consequences of such a disease persisted during the acute period of stroke for at least six months, with full rehabilitation. Thus, the court satisfied the stated requirements.***

This situation illustrates the crucial medical position reflected in the World Health Organization's definition of health, the biopsychosocial model. Biological events — body diseases have consequences for the social individual. The development of this fact is also expressed in the legal field: changes in the legal status of a person due to the emergence of a particular pathology. And it is important to understand that the key factor for making legal decisions is the formulation of physicians — experts

* Official website of the Supreme Court of the Russian Federation. URL: http:// www.vsrf.ru/stor_pdf.php?id=1748488

** Determination of the Supreme Court of the Russian Federation of 21 March 2017 in case No. 18-KG17-27. Computer-assisted legal research system "ConsultantPlus", local version (date of request

*** The decision of the The decision of the Zavodskoy District Court of Orel, 8 June 2017, in Case No. 2-321/2017. Computer-assisted legal research system "ConsultantPlus", local version (date of request 21.07.2019)

in the medical (medical and biological) part of the situation. Interdisciplinarity of work with the patient already well understood in the light of patient-centeredness and psychosocial risk factors, and also extends into the legal field [4]. The first example, at the beginning of the article, also points to this ratio: the "moral suffering" of patients' relatives, which was caused by the process of care in the medical and biological field (resuscitation), becomes an element of the court decision.

Conclusion

As a result, we can conclude that the issue of regulating the quality of life and health of citizens is one of the most important not only for the legislator, but also for the judiciary. This is particularly true for cardiovascular diseases, which is confirmed by the number of cases examined on this issue as well as by regular situations in each court.

The significant workload of the courts in this category of cases indicates disagreements between the parties (usually the patient and the medical institution), which are not regulated by the general rule, and also the ambiguity in the interpretation of the care provided in a particular field of medicine. The ambiguity of medical and biological processes, clinical situations, on the one hand, and the fundamental unambiguity necessary in the legal system, enter into complex relations that require the attention of both doctors and lawyers.

Conflicts of Interest: nothing to declare.

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Pheochromocytoma associated with neurofibromatosis type 1: a clinical case

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A clinical case of pheochromocytoma in combination with neurofibromatosis type 1 is presented in a man admitted to the cardiology department with acute coronary syndrome on the background of hypertensive crisis. The crisis was complicated by myocardial ischemia, myeloid leukemoid reaction, hyperglycemia and acute renal damage. Pheochromocytoma was verified by blood metabolites of catecholamines test and histological method. Surgical adrenalectomy was performed.

Key words: pheochromocytoma, neurofibromatosis type 1, hypertensive crisis.

Conflicts of Interest: nothing to declare.

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Fig. 1. Multiple neurofibromas of the skin in patient P.

Fig. 2. 12 lead electrocardiogram of the patient P.

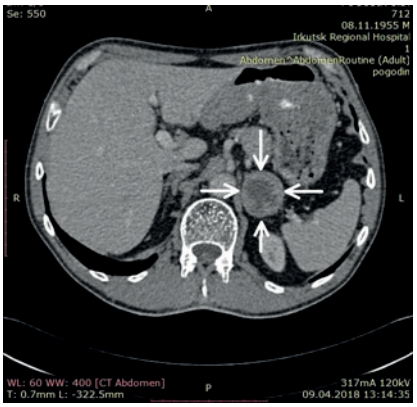

Fig. 3. Multispiral computed tomography of the abdominal cavity of patient P.
Note: axial section. Arrows indicate a tumor of the left adrenal gland.

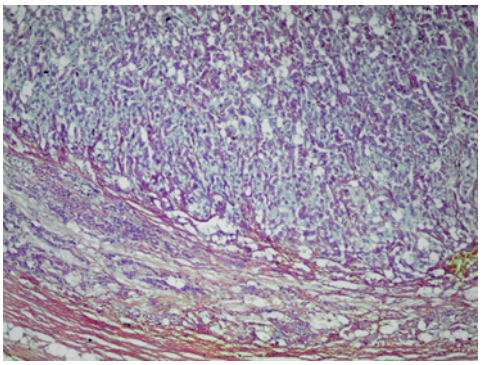

Fig. 4. Micrograph of a fragment of an adrenal tumor.
Note: hematoxylin-eosin stain, x40.

Pheochromocytoma is a tumor of the adrenal medulla that produces catecholamines. Every year, 3-6 new cases of the disease are detected per 1 million people. The prevalence among patients with arterial hypertension (AH) is 0,5-2%. Up to 30-40% of pheochromocytoma cases may have a genetic nature. Pheochromocytoma associated with neurofibromatosis type 1 (NF1) belongs to the hereditary one [1]. NF1 is an autosomal dominant disease, the skin manifestations of which are multiple pigmented cafe-au-lait macules and neurofibromas. A genetic defect in NF1 is localized on the 17th chromosome (17q11.2). This gene encodes a neurofibromin protein, which is a tumor suppressor. The incidence is 1 in 3 thousand children. Pheochromocytoma is diagnosed in 0,1-5,5% of patients with NF1, however, when NF1 is combined with hypertension, the frequency increases to 20-56% [2, 3].

We present a case of pheochromocytoma and NF1 in a patient with hypertensive crises and suspected acute coronary syndrome (ACS).

Patient P., 62 years old, in March 2018 was admitted to the cardiology department of the Irkutsk Regional Clinical Hospital with complaints of intense pain behind the sternum, trembling in the body, sweating, headache, increased blood pressure (BP) with a diagnosis of ACS. For 6 years, hypertensive crises with a BP rise to 220/120 mm Hg were observed 1 time in 1-2 months. Patient did not underwent examination and not taking antihypertensive drugs. The patient noted spots on the skin since childhood, tumor growths on the skin from a young age, but the NF1diagnosis was not previously made.

Condition on admission was severe. The heart rate was 92 per minute, BP — 164/100 mm Hg. The skin is moist. On the skin were neurofibromas (Fig. 1). On the ECG, low atrial rhythm, ST segment elevation in leads III, avF, ST depression in V2-V4 (Fig. 2).

An emergency coronary angiography was performed. Pathology of the coronary bed is not revealed. Troponin T at admission was 0,12 mg/L, after a day — 0,024 mg/L (0,01-0,17). According to echocardiography, the valves are not changed. Estimated pressure in the right ventricle was 30 mm Hg. The size of the cavities of the heart was not increased. Left ventricular ejection fraction was 64%,

interventricular septum, posterior wall of the left ventricle are not thickened. Zones of hypo- and akinesis were not identified. The filling pattern of the left ventricle is rigid.

In the clinical blood analysis on the second day from the onset, leukocytosis of 29,2x109, neutrophils of 90% was detected. After two days, the number of leukocytes decreased to 7,9x109. Upon receipt, fasting glycemia was 18,8 mmol/L, after a day — 3,8 mmol/L without treatment. On the day of admission, blood creatinine level was 320 μmol/L, on the 6th day it decreased to 100 μmol/L. Diuresis did not decrease.

The combination of cutaneous signs of NF1 and complicated hypertensive crisis with transient neutrophilic leukocytosis and hyperglycemia suggested pheochro-mocytoma.

Multispiral computed tomography of the abdominal organs was performed (Fig. 3). In the left adrenal gland, a heterogeneous round formation (hypo-intensive in the central sections (8 HU) and hyper-intensive on the periphery (31 HU), 37x38 mm sized, intensively accumulating contrast around the periphery (up to 72 HU) with the preservation of avascular central sections. Conclusion: space-occupying lesion of the left adrenal gland (pheochromocytoma?).

Parameters of secretion of catecholamine metabolites: methanephrine >900,00 pg/ml (⩽120 pg/ml), normetanephrine — 370,6 pg/ml (⩽200 pg/ml). Levels of alstosterone, cortisol, adrenocorticotropic hormone in the blood, plasma renin activity are normal.

In May 2018, the patient underwent a left-sided adrenalectomy with laparotomy access. Protocol of pathological and anatomical examination of the surgical material: adrenal gland 32 g 8,0x4,5x4,0 cm with a clearly delimited tumor 4,0 cm in diameter. Histologically, adrenal tissue with nodular hyperplasia of the cortical substance, the tumor is constructed of round, elongated and polygonal cells with granular cytoplasm, with the formation of solid, trabecular and alveolar structures, with an abundant network of sinusoidal vessels, with hemorrhage focuses, areas of sclerosis, surrounded by a capsule. Conclusion: Pheochromocytoma (Fig. 4).

The clinical picture of pheochromocytoma is diverse. The presence of crises in a patient with skin manifestations of NF1 maximizes the disease risk [1-3]. With pheochromocytoma, various variants of myocardial damage are possible: direct damage with catecholamines, ischemia and type 2 infarction due to spasm of the coronary arteries and increased oxygen demand against tachycardia and hypertension, takotsubo cardiomyopathy [2, 4, 5].

The absence of coronary artery pathology in coronary angiography made it possible to exclude coronary artery disease. The absence of violations of local contractility on echocardiography contradicts takotsubo cardiomyopathy. Type 2 myocardial infarction is excluded according to the results of troponin test. Severe neutrophilic leukocytosis on admission required considering of the infectious process, however, a rapid decrease in leukocytes in dynamics made it possible to associate it with pheochromocytoma [5]. Acute renal damage was probably due to severe vasoconstriction and ischemia of the renal parenchyma against the background of hypercatecholaminemia. Our data are confirmed by the description of isolated cases of acute renal failure associated with pheochromocytoma [6].

Thus, this case demonstrates a late diagnosis of pheochromocytoma, despite the presence of skin manifestations of NF1 and hypertensive crises.

Conflicts of Interest: nothing to declare.

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