International Heart and Vascular Disease Journal
Journal of the Cardioprogress Foundation

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Contents

Editor's Welcome

Dear colleagues!

We present the 35th issue of the International Heart and Vascular Disease Journal that includes the leading article, original articles, as well as clinical case report and letter to the editor.

The "leading article" section is dedicated to the assessment of cardiovascular risk depending on the presence of psychosocial factors from the perspective of hostility considering gender aspects. Authors have shown that the prevalence of negative psycho-emotional states such as hostility was higher among females that may affect the risk of cardiovascular disease development. In order to improve hostility state, it is necessary to create infrastructure that can provide easily available counseling in order to identify and monitor psychosocial risk factors among all categories of female population.

The "original articles" section presents three articles. The first manuscript investigated the effect of intensified muscles oxidation on blood pressure in strength athletes with arterial hypertension. For this purpose the study included 65 athletes who were followed-up for 180 days. The developed programs of aerobic exercise for strength athletes showed the superiority of high-intensity interval training protocol by the effect on the muscles oxidation and blood pressure parameters. The second article assessed the dynamics of atherogenic lipoproteins and estrogens during the management of dyslipidemia with PCSK9 inhibitors in patients with coronary artery disease and various comorbidities. The study included 114 men who were administered with intense treatment with statins + ezetimibe. In case when targets were not achieved, alirocumab was added to treatment. The most pronounced effect was seen in group of patients with coronary artery disease and without comorbidities. The third article aimed to assess the effect of atorvastatin on antioxidant enzyme activities in blood plasma and tissues in patients with stable coronary artery disease and postinfarction cardiosclerosis. It has been shown that 6-month treatment with atorvastation was associated with antioxidant and antiperoxide activity and improves endothelial function in 90% of patients with stable coronary artery disease with manifestations of oxidative stress.

This issue also includes the clinical case of myocardial infarction incidence after COVID-19 infection. The patient with high cardiovascular risk after COVID-19 reinfection developed myocardial infarction with cardiac arrest that was caused by cardiopulmonary insufficiency; the sequence of changes was seen not only in vessels, but also in body organs with the development of acute myocardial infarction after SARS-COV-2 reinfection.

In June 2022 the first Inter-university Conference on Internal Medicine Issues was organized with the help of the Cardioprogress foundation. The review article analyzed medical universities publication rates in Russia and CIS countries in three leading medical journals between 2019 and 2021 and discussed the possible limitations and problems in university science development.

The "letter to the editor" section presents the excerpts from the memoirs of the member of the Editorial Board, an outstanding scientist and cardiologist Wilbert S. Aronov.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Mekhman N. Mamedov

Editor-in-Chief

President of the "Cardioprogress" Foundation

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International medical reviews

According the authors from the United States, spontaneous coronary artery dissection (SCAD) is an infrequent but highly recognized cause of acute coronary syndrome, that is more prevalent among relatively young women aged 45–52 years and may even co-occur with pregnancy, where it is the most common cause of myocardial infarction. This study has shown that patients with SCAD have lack of traditional risk factors. Pathophysiological mechanisms include coronary blood flow impairment due to spontaneous intramural hematoma development that causes the dissection of vessel wall medial layer. The study was performed in a cohort of 389 patients from 34 hospitals collected from Spanish SCAD registry.

According to the Heart journal

A retrospective cohort study established 27.1% inpatient all-cause mortality among 7038 patients. Due to rapid increase of hospital admission rate of patients with COVID-19 during the first wave of the pandemic, there was a clear need for effective clinical prognosis assessment tool for patients with COVID-19. Using a large cohort of patients with COVID-19, experts found that in addition to demographic parameters, medical history and the main indicators of metabolic panel, the QTc interval >500 ms serve as independent risk factor for inpatient mortality.

According to the Heart journal

Endotrophin can serve as risk marker for type 2 diabetes mellitus (T2DM) complications. The increase of serum endotrophin was a risk marker for kidney and cardiovascular complications as well as sudden cardiac death. Urine endotrophin was a marker for albuminuria progression. Scientists from the Steno Diabetes Center Copenhagen found that the level of endotrophin, a profibrotic signaling molecule in serum and urine is a risk marker for complications to T2DM.

According to the Diabetes Care journal

Blood type was associated with the risk of early onset of stroke. The II (A) blood type was the most prevalent among patients with early stroke. The additional investigation of the disease pathogenesis will allow to develop precise prevention strategy. Scientists from the University of Maryland School of Medicine found that the onset of early stroke depends on the blood type. The analysis by gender and other factors showed that the risk of early stroke onset in patients with blood group II (A) was 16% compared with other blood types. The likelihood of early onset of stroke among patients with blood group I (0) was by 12% lower.

According to the Neurology journal

Myocarditis is the most prevalent cardiovascular complication during the treatment of patients with immune checkpoint inhibitors. Mortality from myocarditis caused by this treatment was significantly higher than during the development due to other causes. Treatment with immune checkpoint inhibitors increased the risk of cardiovascular events. The group of experts from Johns Hopkins University and the Cardiovascular Imaging Research Center in Massachusetts assessed the prevalence of myocarditis as cardiovascular complication. Scientists described the epidemiology, possible pathogenesis of adverse events during the treatment with medications, diagnostic criteria and possible treatment strategies.

According to the European Heart Journal

Most muscle symptoms that were identified by the patient complaints are not associated with statin treatment, the frequency of mild pain and muscle weakness increased insignificantly. The potential benefits of statin therapy are likely to outweigh the muscle pain and weakness risks. The group of scientists from Cholesterol Treatment Trialists Collaboration concluded that statins are associated with a small increase in risk of muscle pains or weakness. Relative risk of muscle symptoms development during statin therapy was 1.03 compared with placebo.

According to The Lancet journal

Diabetes persists as a risk factor for cardiovascular events, but where it once meant the same risk of heart attack or stroke as cardiovascular disease itself, a large Canadian population study reports that's no longer the case. Thanks to advances in diabetes management over the past quarter century, diabetes is no longer considered equivalent to CVD as a risk factor for cardiovascular events. Between 1994 and 2014, the cardiovascular event rates declined significantly among people with diabetes alone, compared with people with no disease: from 28.4 to 12.7 per 1,000 person-years in 1994 to 14 vs 8 per 1,000 person-years 20 years later.

According to the MDedge.com

For patients with arterial hypertension, treatment with an angiotensin receptor blocker (ARB) may help protect against epilepsy. Investigators found that ARB therapy was associated with a decreased incidence of new-onset epilepsy compared with other antihypertensive drug classes. The new findings are based on a propensity-score matched analysis of 168,612 adults (mean age, 62 years; 51% women) with hypertension receiving one of four antihypertensive drug classes — beta-blockers, ARBs, angiotensin-converting enzyme inhibitors, or calcium channel blockers.

According to the JAMA Neurology

The risk of cardiovascular disease development depending on psychosocial factors from the perspective of hostility research: gender aspect

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Abstract

The results literature data analysis showed multidirectional associations between the risk cardiovascular pathology and hostility. Prevalence of negative psycho-emotional states such as hostility was higher among females that may be explained by physiological characteristics of female body and ways of anger/hostility expression, which in turn affect the risk of cardiovascular disease (CVD) development. In this regard, in order to improve the CVD prevention among adult female population, it is necessary to create information resources and educational technologies as well as infrastructure that can provide appropriate and easily available counseling in order to identify and monitor psychosocial risk factors among all categories of female population.

Key words: psychosocial factors, hostility, gender aspect, females.

Conflict of interest: none declared.

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Introduction

At the end of the 20th century and during the first decades of the 21st century many new scientific knowledge about the unconventional (psychosocial) risk factors of cardiovascular diseases (CVD) accumulated. At that time, the studies evaluated the effects of psychosocial CVD risk factors (PRF) on the epidemiologic situation in various countries and regions. The number of large epidemiologic scientific projects demonstrated the relevance of PRF as the most important part of the unconventional CVD RF due to the fact that PRF could explain up to 25–50 % of all coronary artery disease (CAD) cases. A large amount of data have shown that multiple professional, family and personal RF are associated with CVD. Overall, it has been shown that PRF play a leading role in the development of CVD.

Scientific concept of CVD

Concept of risk factors (RF) as a scientific basis of preventive cardiology became the foundation for many one- and multiple-factor primary CVD prevention programs on the populational level [1, 2]. According to this concept, RF are specific individual features, including biological, genetic, psychological, behavioral, and social ones that may influence the development of one or more noninfectious diseases during a certain period of time in the future. RF can be directly associated with CVD or influence its development via other determinants [1]. Fundamental epidemiologic studies that were carried out in the second half of the 20th century, in 1949, in Framingham, Massachusetts (Framingham Heart Study), showed the role of conventional RF in CVD [3]. It has been determined that such leading RF as tobacco smoking, arterial hypertension (AH), hypercholesterolemia, and obesity are associated with 67,2 % of all years of life loss in a healthy human [4, 5]. Isolated CVD RF are rare and the most part of the population has a combination of two or three factors [6]. According to the prospective JAMA study, 20 % of young women had no RF and around 60 % had two and more RF [7].

Psychosocial CVD RF

In the second part of the 20th century, PRF that met the strict mathematical significance criteria were included in the European guidelines on CVD prevention. They included: low socio-economic status, social isolation, low level of social support, personal characteristics (hostility, aggression, type D personality), anxiety and depression, home and work stress [8]. At the end of the 20th century and during the first decades of the 21st century many new scientific knowledge about PRF accumulated. These studies evaluated the effects of unconventional CVD risk factors on the development of epidemiologic situation in various countries and regions [9–15].

Hostility

The interest in the hostility phenomenon emerged at the last two decades of the 20th century, when it's associations with somatic health were identified [16]. Hostility is identified as a feature of cognitive character with an oppositional, negative attitude towards others. It demonstrates a wide range of behaviors, from aggression to becoming antisocial and having negative emotions [17]. Negative impact of hostility on the risk of non-infectious diseases and cardiovascular mortality as well as on quality of life in people with chronic illnesses has also been shown [18, 19].

Hostility, together with such similar parameters as anger, are important aspects of type A behavioral pattern, which was first described in 1950s [19]. At first, before concentrating mostly on hostility phenomenon, the studies have evaluated the types of personality. They showed that type A personality, associated with competitiveness, leadership, and hostility, is associated with a higher risk of CVD [18]. The first populational studies in the USA and Europe showed that type A personality was associated with a higher risk of CAD, but later studies have refuted this association [16, 18, 20, 21]. Further analysis of type A personality "toxic" components showed that only hostility and aggression are associated with increased risk of CAD. Metanalysis of cohort prospective studies carried out

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at the end of the 20th century didn't show statistically significant tendencies of cardiovascular risk of type A personalities. On the contrary, a significant risk of CVD and CAD was identified in people with high level of hostility [22]. Therefore, further studies have focused not on the behavioral models but specifically on hostility — one of the unconventional CVD RF. They investigated the roles of the negative psychoemotional conditions in the development of CVD, and these roles are still debatable as new controversial data emerge. However, these findings confirm the fundamental role of preventive cardiology and multifactorial approach [23–28]. Initially, hostility and anger develop as a temporary psychological condition. Hostility has been associated with aggressive, violent or harmful actions towards the others. Adaptation to this condition leads to lasting changes that anchors in one's memory. Hostility is due to several factors that include both physiologic processes in the central nervous system and brain biochemistry and the psychologic factors such as motivation, imitation, learning, self-control and others. [16].

Hostility as a psychosocial factor of CVD in female population

High testosterone levels are traditionally thought to result in more aggressive behavior in males compared with females. However, it concerns not all types of hostility but primarily physical aggression. No significant differences have been found in levels of verbal aggression in males compared with females. Hostility in women is mostly irrational and more often associated with social ostracism and frustrations, and, therefore, carries a more destructive component [29]. It has been shown that the level of hostility is associated with the amount of adrenaline the has a direct effect on the sympathic nervous system, and specifically — on the posterior hypothalamus. Moreover, the level of adrenaline decreases with age and that leads to lower hostility [17]. The possible pathophysiological mechanisms that play a role in the development of CVD in the presence of negative psychoemotional conditions include increased neuroendocrine and CV reactivity and longer recovery from stress reactions [30]. Other studies also tried to explain which mechanisms lead from hostility and anger towards CVD. According to their results, anger and hostility in combination and separately were statistically significantly associated with increased levels of C-reactive protein — one of the factors of CAD [31]. Moreover, according to D. Shimbo et al., women with higher levels of hostility have changes in platelet activity [33]. Hostility together with a family history of CAD were associated with an increased level of vascular (carotid) disease [34]. Using a regression proportional risk model H.A. Tindle et al. showed a high 8-year risks of CAD and total mortality in women with higher hostility [35]. High risks of negative CAD outcomes were also shown in a metanalysis of cross-sectional populational studies and studies of high-risk groups. According to the data from 25 and 19 centers two parameters — anger and hostility — were significantly associated with the development of CV complications both in healthy people and individuals with CAD [36]. On the other hand, some studies have shown that myocardial infarction (MI) is associated not with the hostile behavioral pattern but with the emotional outbursts. Those individuals, who constantly demonstrate hostile behavior are possibly better adapted to negative outbursts and, therefore, are at the lower risk of CVD [37]. According to the latest results of several studies, there's an association between low-active MAOA-L gene alleles with a high level of hostility. That indicates a high tendency towards hostile response actions against provocations in the carriers of these alleles [38].

According to the results of a 10-year prospective observational study that investigated various types of anger expression, an attributable risk of CAD in individuals with high level of destructive anger (accusation of others in anger) was over 30 %, OR 1,31 (p=0,03) [39]. Based on these results and other findings it has been shown that the associations between anger and CAD outcomes are sex-dependent and also that anger variations influence the risks and outcomes of CAD. At the same time, some studies compared anger and hostility and showed that hostility is associated with a lower risk of CVD [39]. Earlier a two-component behavioral model with a higher risk of CAD has been developed. Two-component model cluster consists of hostility and anger potentioals. Hostility potential is a first component, a complex of reactions to special situations, such as irritation, indignation, disgust, distaste and disappointment. A second component is reluctance or inability to direct anger towards the object. According to this model, L. Musante et al. defined hostility and "anger/hostility". The first component carries the signs of indignation and rejection,

and the second component, on the contrary, is a combination of features that help restrain anger even if its absolutely appropriate [40]. Furthermore, several subsequent epidemiologic, experimental and clinical investigations defined the patterns that allowed to describe the associations between the level of anger/hostility and reactivity of platelets, levels of blood pressure, development and progression of hypertension and stroke, and various other CV complications [36]. Moreover, hostility was associated with worse prognosis of cardiovascular death and other cardiovascular complications in high-risk groups [32]. A Dutch study that included both men and women of the older age showed the stability and role of the hostility phenomenon in the general and cardiovascular mortality [41]. These results can prove that personalities with hostile (negative attitude towards others) behavior during life have more pronounced and frequent stress reactions [42]. This hypothesis was confirmed in the populational and comparative studies, where hostility in women was a significant predictor of CAD, including MI [43].

Although hostility is a determined CVD RF, suppression of anger and hostility can lead to a more serious exhaustion and CAD in women [44]. This fact can explain some negative results of the study of hostility and CAD risk [37]. Of note are the results of a 10-year observational Framingham Offspring Study that included more than 3 thousand women and men aged 18–77 years. According to the results of this study, hostility wasn't associated with any negative outcomes in women, including CAD and acute coronary death) [44]. Another populational study, the Nova Scotia Health Survey, 1995, also showed that in the CAD subgroup high level of hostility wasn't associated with a higher risk of repeated CAD events [45].

Epidemiologic data show that healthy individuals with hostile character are at a higher risk of CAD. As such, the study of association between hostility and thrombocyte aggregation showed that hostility, especially as a subtype of aggression, leads to platelet reactivity — a key pathophysiologic mechanism in the beginning of CVD [32]. In women with suspicion of MI, higher scores on The Cook-Medley Hostility Scale (indicated cynicism, hostile effect and aggressive response) were associated with lower survival, but after the groups were normalized for RF and CAD, associations with CVD increased [46]. At the same time, the role of hostility in the CAD development in women is still debatable among the epidemiologists [32, 33]. As such, the results of populational study by D.C. Haas et al. showed that hostility is an independent risk factor of repeated CAD events in men, but not in women [45]. According to other studies, people who constantly demonstrate hostile behavior, are, possibly, better adapted to negative outbursts. In such people, anger may be associated with lower risks of CVD [37]. Studies carried out on Novosibirsk female population also didn't show an increased risk of CVD. According to the authors, hostility (as a key component of type A personality), possibly, mostly has trigger effects as a provoking factor (spasm, thrombosis, plaque rupture), causing higher risk of MI in men [14]. This effect is less prominent in women [14]. CVD development phenomenon in women with hostility may be explained by the fact that, initially, submissive, formally subordinate personalitis, who are also introverted and suppress their anger, are more helpless in any negative episodes that cause anger [37]. That leads to CAD and high mortality in women with other PRF, compared with women with high level of hostility, who can tolerate these emotional changes more calmly [44].

Conclusion

The analysis of literature demonstrated that the tendencies of cardiovascular disease risk factors, associated with hostility, have different directions. Negative psychoemotional conditions, specifically, hostility, are highly prevalent in female populations. That is possibly due to physiologic features of female organisms and variations in anger/hostility expression that affect the risks of CVD. Therefore, the development of informational and educational technologies and infrastructure that is able to provide all women population access to consultations and monitoring of PRF is required for better CVD prevention in adult female population.

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Muscle and blood pressure quality features in strength athletes with arterial hypertension after aerobic exercise: a randomized controlled trial

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Objective
To assess the effect of intensified muscles oxidation on blood pressure (BP) in strength athletes with arterial hypertension.

Materials and methods. The study was performed at the Department of Sports Medicine of Russian State University of Physical Culture, Sport and Tourism and lasted for 180 days. The study included 65 power athletes from heavyweight categories with arterial hypertension. Athletes were randomized into three groups: HIIT (n=23), MICE (n=22) and RT (n=20). The following methods were used: blood pressure assessment, ergospirometry, measurement of the muscle tissue oxygenation, mathematical and statistical analysis. Athletes in the HIIT and MICE groups performed velergometry 3 times a week according to high intense interval and steady training protocols, while athletes from RT group had their regular power exercise training 3 times a week.

Results. Athletes who performed velergometry for 180 days showed the increase of oxygen consumption at the anaerobic burden, from the HIIT group — at 8,6 $ml \cdot kg^{-1} \cdot min^{-1}$, and from MICE group — at 7,7 $ml \cdot kg^{-1} \cdot min^{-1}$, and showed the decrease of oxygenation of the lateral head of the quadriceps femoris between the HIIT, MICE and control RT groups by 16.4 % and 11.4 %, respectively, which was accompanied by the decrease of systolic BP by 11.1 mm Hg and diastolic BP by 11.2 mm Hg on average.

Conclusion. The developed programs of aerobic exercise for strength athletes allows to safely and effectively influence the oxidative abilities of skeletal muscles and BP, however, athletes who followed HIIT protocol spent 38 % less time on non-specific training activities compared with MICE protocol that makes high intensity interval training the most effective and convenient method.

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According to the epidemiologic data, cardiovascular disease (CVD) is the leading cause of death and disability worldwide [1–3]. Muscle quality (MQ) is defined differently by clinicians and researchers. Geriatric medicine and gerontology describe the concept of MQ, comprised by glucose metabolism, oxidative damage, protein metabolism, intramuscular adipose tissue, capillary density, structural compound, contractility and fatigue [4]. Although there is no consensus on muscle quality, ambiguity of this term allowed to investigate several aspects of MQ in both older [5] and younger [6] individuals. Understanding of MQ phenotype characteristics is required to build physical rehabilitation systems that priorities functional improvement over muscle enlargement. It could be important in populations that are not limited by older people and include athletes and young active individuals who regularly perform difficult physical activities as parts of competitions or professional objectives. It is well known that physical exercise could help prevent and cure some chronic metabolic conditions. Therefore, a common concept of physical exercise being one of the medical treatments has developed. However, compared to the most medications, the mode of exercise necessary for better oxidative function and muscle metabolic health still remain controversial. It is well known that physical exercise with additional weights promote muscle strength and mass but at the same time are associated with reduction in mitochondrial volume in skeletal muscle (a phenomenon described as "mitochondrial volume dilution") [8]). It can also suppress mitochondrial growth in muscle fibers (MF) that grow during exercise with weights [9]. It is also well known that skeletal muscles demonstrate a significant heterogenicity not only in MF types but also in capillary distribution. Moreover, different exercise modalities have different effects on the growth and the number of capillaries in the working muscles [10]. For example, athletes who train to improve their endurance, are known for their well-developed capillaries compared with those who don't train enough or who do power sports. They a have high level of capillaries around the MF (~5–8), a high ratio of capillaries to MF (~2,5–3,0) and a high capillary density (~400–700 cap/mm^2). Untrained people have 3–4 capillaries around a MF compared with professional rally and track cyclists who have up to 9 capillaries around a MF [11].

CVD is a leading cause of morbidity and mortality all over the world, and the prevalence of CVD increases with age [12]. An increased blood pressure (BP) or a diagnosed arterial hypertension (AH) are widely recognized as the main CVD precursor. The risk of CVD is thought to be in a linear association with BP values. The identification of the main mechanisms of AH is crucial as for every 20 mmHg increase in BP doubles the risk of CVD. An association between the inflammation, reactive oxygen specials and vascular dysfunction is termed a "vascular health triad", which influences the BP regulation [13, 14]. Therefore, vascular health and the number of capillaries should be included in the concept of MQ.

AH is a common diagnosis in power athletes irrespectively of the kind of sport. At the same time, such athletes rarely use do cardiologic rehabilitation based on the aerobic exercise (Class 1A recommendations for patient with CVD that causes the reduction in CVD risk, repeated hospital admission, cardiovascular events and mortality [15]) Aerobic exercise increases maximal oxygen consumption (VO2 max) and the number of capillaries and mitochondria in CVD patients [16] leading to lower AH. Based on the analysis of this problem, research data and the request of sport physicians, trainers and power athletes we have formulated the aim of the study.

Aim — to evaluate the rise of the muscle oxidative capacity on blood pressure in power athletes with AH.

Materials and methods

The study was carried out at the Department of Sport Medicine, Russian State University of Physical Education, Sports, Youth and Tourism and lasted for 180 days. The study included 65 power athletes with the mean weight of 105,9 ± 0,4 kg with AH. Informed consents were obtained from all the participants prior to enrollment according to Ethical Standards in Sport and Exercise Science Research, 2020 Update [17] (protocol № 5, Ethical Committee Meeting on 26.10.2017). Randomized controlled study was carried out according to the CONSORT study [18]. The athletes were randomized into the two groups (study group and control group) and using the random number tables: HIIT group (High Intensity Interval Training, n=23), группа MICE (Moderate Intensity Continuous Exercise, n=22) and control group RT (Resistance Training, n=20).

Inclusion criteria were: power athletes (men); heavy weight division (≥95 kg); aged 18–40 years; have sports category; have high blood pressure: SBP≥130 mmHg; DBP ≥85 mmHg; absence of any inflammatory of chronic diseases that could worsen by the time of examination; signed informed consent form according to Helsinki declaration.

Exclusion criteria were: age of power athletes of heavy weight division (≥95 kg) less than 18 and more than 40 years; power athletes of heavy weight division (≥95 kg) who has been training for less than 3 years; power athletes of heavy weight division (≥95 kg) who had SPB<130 mmHG, DBP<85 mmHg at the time of the study; power athletes of heavy weight division (≥95 kg) who had acute inflammatory or decompensated chronic conditions that could influence the results.

The athletes who weren't compliant with the study were also excluded.

The program, protocols and randomized clinical trial design were developed based on the modern concepts and rules of evidence-based medicine that were used according to the objective of the study.

Ergospirometry. Anaerobic threshold and VO2 max evaluation were performed using the tests with increasing cycle loading at the 75 revolutions per minute to maximum. The «MONARK 839 E» (Monark AB, Sweden) veloergometer was used. The loading was gradually increased from 20Wt by 20 Wt every 2 minutes. Gasometrical analysis was performed using the "CORTEX" (Meta Control 3000, Germany) analyzer that measures oxygen use and carbon dioxide excretion from inhaling to exhaling. Heart rate and the R-R intervals were assessed using the "POLAR RS800" (Finland) monitor. The test was stopped when >1.1 breathing coefficient was reached, the oxygen consumption graph reached plato for 30 seconds and if the patient was unable to continue pedaling at the given speed (increase or decrease for more than 10 RPM). Anaerobic threshold was evaluated according to the point of ventilatory equivalent for carbon dioxide (VE/VCO2) first increase with even larger increase in ventilatory equivalent for oxygen (VE/VO2) and the beginning of the partial pressure of end tidal CO2 (PetCO2). VO2 max was identified as the highest value of oxygen consumption of the two consecutive 15 second episodes at plato.

Change of the lateral head of the quadriceps femoris. The change of the lateral head of the quadriceps femoris oxygenation was evaluated using the "Moxy Monitor" (USA). Infrared sensor was placed on the lateral head of the right quadriceps femoris at the point of nerve entry. The mean skinfold thickness under the sensor (measured with Lange caliper, USA) in the main group athletes was 22 ± 2,2 mm and in the control group athletes was 23 ± 1,7 mm. The skinfold is formed of the two layers, therefore, the distance to the muscle is 10–12mm, which is relatively informative for this test (the depth of the scanning surface of the infrared "Moxy" sensor is up to 2.5 cm). The difference between the skinfold thickness between the two groups wasn't statistically significant. "Moxy" is a reliable instrument for muscle hemoglobin saturation during physical activity [19].

Blood pressure measurement. According to the clinical guidelines that were developed by the Russian Society of Arterial Hypertension and approved on November 28, 2013 at the plenum meeting and by the cardiology commission on November, 29, 2013, BP measurements were performed via self-measured blood pressure monitoring (SMBP). SMBP involved using traditional automated certified home tonometers. Three readings were taken in the left arm in succession, separated by at least 1 min in the morning (from 7:00 to 8:00). Mean values were recorded in the archive protocol.

Physical rehabilitation of hypertensive power athletes. Physical rehabilitation system consisted of the two methods (aerobic exercise combined with strength exercise) performed for the 6 months (72

sessions, 3 times per week). The system also included regular retests (at the end of each month) on the veloergometer in order to correct the exercise load in the aerobic physical rehabilitation protocol. The participants exercised according to the following protocols:

RT control group: weight training consisted of 5 exercises with weights of 70–90 % of 1 repeated maximum (1RM), from 2 to 8 repetitions in 4 sets. One cycle of "set and rest" (until full recovery) was 5 minutes. The exercises were aimed at all the main muscle groups and included: barbell bench press, barbell squats, Romanian deadlift, biceps curls, triceps extension. The training session lasted for 100 minutes.

HIIT main group: weight training consisted of 5 exercises with weights of 70–90 % of 1RM, from 2 to 8 repetitions in 3 sets. The method was identical to the control group. Aerobic exercise was added after the weight protocol. It consisted of 7 highly intensive intervals (cycle loading at the 100 % of the maximal RPM) for 2 minutes and low intensive intervals with HR at 85 % of anaerobic threshold according to the 2019 Sport Medicine College guidelines for people with AH. At the end of each month the athletes have undergone veloergometry testing according to the step protocol for load correction in the aerobic protocol of physical rehabilitation. The training session lasted for 100 minutes.

Statistical analysis

Statistical analysis was performed with Statistica 13.3 software. An assessment of the normality of data was performed with the Kolmogorov-Smirnov test. Multiple factor dispersion analysis with 3*2 repetitions for "regimen" (HIIT/MICE/RT) and "time" (before/after) was used to evaluate significant differences. First, the significant influence of the factors or their interaction were determined. Second, post hock test with Bonferroni correction was performed to evaluate pair-wise significant differences. Additionally, a paired t-test was performed to confirm intragroup changes in "time" before/after (0/60 60/120 120/180 and 0/120). P-values ⩽0.05 and ⩽0,01 were statistically significant. We present the results of posteriori tests in the description in the descending order of the contributing factor/interaction of factors.

Results and Discussion

Prior to the beginning of physical rehabilitation program,veloergometry with the gradually increased loading was performed in order to evaluate anaerobic threshold and VO2 max. Anaerobic threshold and VO2 max weren't statistically different in the athletes from the HIIT, MICE, and RT groups (p<0,05). After 180 days of physical rehabilitation anaerobic threshold and VO2 max increased in HIIT and MICE groups (Table 1). Anaerobic threshold increased in the HIIT and MICE by 8,6 ml·kg^{-1}·min^{-1} and 7,7 ml·kg^{-1}·min^{-1} respectively (p<0,01). Moreover, after 180 days of rehabilitation VO2 max increased by 9,2 ml·kg^{-1}·min^{-1} and 8,3 ml·kg^{-1}·min^{-1}, in the HIIT and MICE groups respectively (p<0,01).

In the control group RT oxygen consumption at anaerobic threshold increased by 0,2 ml·kg^{-1}·min^{-1} and VO2 max increased similarly by 0,2 ml·kg^{-1}·min^{-1}. These changes were not statistically significant. After 180 days of rehabilitation oxygen consumption at anaerobic threshold increased by 0,9 ml·kg^{-1}·min^{-1} in the HIIT group compared with MICE group (p<0,01). We have also identified statistically significant rise in the oxygen consumption at anaerobic threshold between the HIIT and RT groups (8,4 ml·kg^{-1}·min^{-1}) and between the MICE and RT groups (7,5 ml·kg^{-1}·min^{-1}) (p<0,01). After 180 days of rehabilitation, we have identified statistically significant rise in the VO2 max by 0,9 ml·kg^{-1}·min^{-1} in the HIIT group compared with MICE (p<0,05). There were also statistically significant differences in the VO2 max between the MICE and RT groups (9,0 ml·kg^{-1}·min^{-1}) and between the MICE and the RT groups (8,1 0,9 ml·kg^{-1}·min^{-1}) (p<0,01).

Near-infrared spectroscopy (NIRS) could be used for muscle mitochondrial capacity measurement as

Table 1. **Ergospirometry parameters in power athlets, (M±m)**

Group (N=65)	Anaerobic threshold (ml·kg^{-1}·min^{-1})			VO2 max (ml·kg^{-1}·min^{-1})		
	0 days	180 days	Δ	0 days	180 days	Δ
HIIT (n=23)	24,5±0,9	33,1±0,5	8,6*	31,7±1,2	40,9±0,6	9,2*
MICE (n=22)	24,2±0,8	31,9±0,4	7,7*	31,3±1,3	39,6±1,0	8,3*
RT (n=20)	24,1±0,8	24,3±0,7	0,2	31,5±1,4	31,7±1,3	0,2

Note. * — statistically significant differences in the parameters between the two groups before and after the rehabilitation. P<0,01.

Table 2. **Lateral head of quadriceps femoris muscle oxygenation in power athletes, (M±m)**

Group (N=65)	Before the test			After the test		
	SmO2 (%) beginning	SmO2(%) end	Δ	SmO2(%) beginning	SmO2(%) end	Δ
HIIT (n=23)	59,0±6,6	38,9±6,4	20,1	59,1±6,7	22,3±6,7	36,8*
MICE (n=22)	58,5±7,1	39,7±8,1	18,8	59,0±6,9	28,5±6,9	30,5*
RT (n=20)	58,5±7,2	40,1±7,2	18,4	58,6±7,4	39,9±7,4	18,7

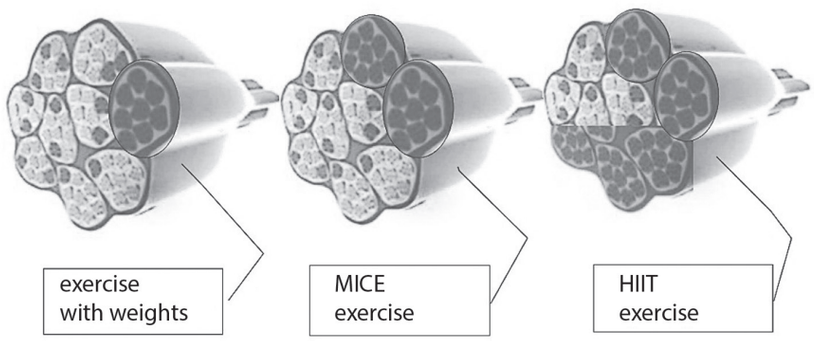
Note. * — statistically significant differences in the groups before and after the rehabilitation (p<0,01).

mitochondrial capacity correlates with aerobic training parameters [20]. Prior to physical rehabilitation all power athletes had to undergo veloergometry testing according to the step protocol. During that test lateral head of quadriceps femoris latent oxygenation was measured. The differences in the lateral head of quadriceps femoris muscle oxygenation in the athletes in the HIIT, MICE and RT groups after the first step test were not statistically significant (p<0,05). The difference between the oxygen consumption of the lateral head of quadriceps femoris muscle at rest and at the maximal activity (at the end of the step test) in the HIIT, MICE and RT groups were 20,1 %, 18,8 % and 18,4 %, respectively (Table 2).

After 180 days of rehabilitation lateral head of the quadriceps femoris muscle oxygenation decreased by 5,0 % in the HIIT group compared with the MICE group (p<0,01) at the end of the step veloergometry testing. Statistically significant differences in the quadriceps femoris muscle oxygenation between the HIIT, MICE and RT groups were 16,4 % and 11,4 % respectively (p<0,01).

It is well knowт that regular aerobic exercise increase VO2 max due to adaptation that increases oxygen transport, delivery and consumption. VO2 max in skeletal muscles rises due to mass and mitochondrial function increase during regular exercise. Mitochondrial capacity is tightly associated with VO2 max. It is a strong indicator of metabolic function and health [21]. In general, the MICE and HIIT protocols are associated with similar mitochondrial biogenesis signal protein reactions that are specific for MF type [22]. However, according to the 4 meta-analyses [23–26], HIIT had positive effects on oxygen consumption at lactate and ventilation thresholds. According to the studies that directly compared HIIT and MICE effects on VO2 max, there was also some positive effects on HIIT. Research showed that higher oxidative capacities of MF (capillarization and mitochondrial apparatus) were associated with lower total peripheral vascular resistance (one of the key factors that affect BP). Factors that are associated with low peripheral vascular resistance are poorly understood. However, it is well known that, compared with the type II MFs, the number of capillaries surrounding the type I MFs is higher and people with hypertension have lower capillary density that is associated with higher BP [27]. Power athletes have sufficient intensity and duration stimuli for MF hypertrophy; however, the duration of stimuli (time) is too short for the growth of capillaries and mitochondria. As such, we see this muscle quality in power athletes, in whom the number of muscles and strength potential are at the higher border and muscle biochemical profile is closer to glycolytic MFs. It is well known that longer aerobic exercise develops the mitochondrial apparatus [28] and working muscle capillarization better. At the same time, even aerobic exercise ("Gold standard" of physical rehabilitation in AH) creates sufficient stimulus for capillary and mitochondrial growth but only in the recruited MF (Picture 1). With this load (≤anaerobic threshold) only low-threshold and intermediate MFs will have a sufficient stimulus for mitochondrial and capillary growth.

High-intensity interval training allows to recruit MFs over anaerobic threshold. If it is possible to hold the intensity for ≥2 minutes, in the high-threshold MFs sufficient stimuli for mitochondrial and capillary growth will develop. During regular training below anaerobic threshold only low-threshold and intermediate MFs change the profile from glycolytic MFs to oxidative MFs. During high intensity interval training the number of mitochondria and capillaries increase in any type of MFs (low-threshold, intermediate and high-threshold) (Picture 1). It signifies that mitochondrial adaptation and capillary growth don't depend on the type of myosin MF but are based on the stimulus and this MF recruitment [29]. Eigendorf et al. [30] showed that high volume HIIT using the veloergometer leads to the shift of metabolic profile of high threshold MFs to type I phenotype (according to the



Picture 1. The effects of different training modalities on muscle oxidative properties.

glycolic → oxygative MFs). It increases the oxidative capacity and capillarization of high threshold MFs. Therefore, improvement of muscle quality (oxidative potential) has to improve BP in the study participants. After 180 days of rehabilitation in the HIIT and MICE groups BP decreased (Table 3).

According to the comparative study, after 180 days of training in the HIIT group there was a statistically insignificant reduction in SBP by 0,5 mmHg compared with the MICE group (p<0,05). Statistically significant differences in the SBP reduction between the RT and HIIT groups was 9,9 mmHg (p<0,01) and between the RT and MICE groups 7,8 mmHg (p<0,01). After 180 days of physical rehabilitation there was a statistically significant reduction in DBP by 0,8 mmHg in the HIIT group compared with MICE group (p<0,05). Statistically significant difference in the DBP reduction between the RT and HIIT groups was 10,3 mmHg (p<0,01) and between the RT and MICE group was 9,5 mmHg (p<0,01). Such a reduction in BP is a good prevention of CVD as it is well known that BP decrease by 7,5 mmHg and by 10 mmHg reduces the risk of stroke by 46& and 56 %, risk of CAD by 29 % and 37 %. The reduction of SBP by 5 mmHg also decreased the risk of the main CV events by 10 % independently of prior medical history of CVD [31]. Therefore, in the large randomized controlled study "Generation 100 study" that included 1567 patients, a trend towards the lower mortality from all causes after HIIT compared with cotrol and MICE was identified [32]. As per dynamics of BP (SBP and DBP) reduction, HIIT and MICE physical rehabilitation systems weren't significantly different. However, the time spent on HIIT rehabilitation was 38 % lower.

Conclusion

The majority of muscle quality definitions don't take into consideration all the complex adaptations to their training stimuli and usually concentrate on two parameters (morphologic and neuromuscular). Such an approach could lead to wrong conclusions when evaluating the strength exercise. On the one hand, the muscle power and muscle diameter are significantly higher compared with the people with low level of physical activity, which should signify better health. On the other hand, low muscle oxidative capacity leads to higher BP and earlier mortality. At the end muscle quality should reflect functional summation of the complex physiological changes due to training adaptation. Therefore, a combination of power and aerobic exercise (HIIT or MICE) increases muscle quality and promote CV health in power athletes. Further randomized controlled trials are needed.

Conflict of interest: none declared.

Table 3. **BP changes in power athletes, (M±m)**

Group (N=65)	SBP (mmHg)			DBP (mmHg)		
	0 days	180 days	Δ	0 days	180 days	Δ
HIIT (n=23)	158,8±2,2	147,3±1,8	11,5*	101,3±3,3	89,7±2,7	11,6*
MICE (n=22)	159,2±2,5	148,2±1,9	11,0*	99,4±2,5	88,6±1,9	10,8*
RT (n=20)	157,9±2,3	156,3±2,8	1,6	98,5±2,3	97,2±2,1	1,3

Note. * — statistically significant differences in the groups before and after the rehabilitation (p<0,01).

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The dynamics of atherogenic lipoproteins and estrogens during the management of dyslipidemia with PCSK9 inhibitors in patients with various comorbidities

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Abstract

Objective. To assess the dynamics of atherogenic lipoproteins and estrogens during the management of dyslipidemia with PCSK-9 inhibitors in patients with coronary artery disease (CAD) and various comorbidities.

Materials and methods. The study included 114 men with CAD and very high cardiovascular risk. All patients were divided into three groups: group 1 — patients with CAD (n=39), group 2 — patients with CAD in combination with type 2 diabetes mellitus (T2DM) (n=38), group 3 — patients with CAD in combination with stages IIIA-IIIB of chronic kidney disease (CKD) (n=37). All study participants were administered with intense treatment with statins + ezetimibe. In case when target levels of low-density lipoprotein cholesterol (LDL–C) were not achieved, alirocumab was added to treatment with the control of lipid profile and estrogens levels for 12 months.

Results. In group 1 97.4 % of patients (n=38) achieved target LDL–C level that decreased by 73.9 % from 4.41±0.19 mmol/l to 1.15±0.15 mmol/l (p<0.001); in group 2 94.7 % of patients (n=36) achieved target LDL–C level that decreased by 74.2 % from 4.62±0.25 mmol/l to 1.19±0.12 mmol/l (p<0.001), in group 3 91.9 % of patients reached target values (n=34) and LDL–C decreased by 73.5 % from 4.60±0.20 mmol/l to 1.22± 0.09 mmol/l (p<0.001). The level of estradiol after 12 months after treatment with alirocumab increased by 8.3 % (p=0.39) in group 1, by 7.7 % (p=0.36) — in group 2, by 8.5 % (p=0.31) — in group 3.

Conclusion. Thus, the use of PCSK9 inhibitors in combination with optimal lipid-lowering therapy in patients with very high cardiovascular risk showed clear effectiveness in patients with CAD without comorbidities. In all study groups, plasma estradiol level statistically insignificantly increased after alirocumab treatment.

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Introduction

Cardiovascular mortality has been one of the most important issues of cardiology for a long time. Despite all the advances of modern medicine, cardiovascular diseases (CVDs) and coronary artery disease (CAD) in particular remain the main causes of death worldwide [1]. In recent years, the feasibility of invasive treatment of coronary arteries has increased, however, the pharmacological treatment remains the first-line therapy for stable CAD and its secondary prevention [2, 3]. The pathophysiologic substrate for CAD is atherosclerosis that progresses due to the influence of several risk factors. The main modifiable cardiovascular risk factor is dyslipidemia that is reflected by the increase of low-density lipoprotein cholesterol (LDL–C) [4]. In addition to dyslipidemia, many studies have established that the level of female sex hormones plays a pivotal role along with many less significant risk factors for the development of CAD [5–7]. Back in 1965, A.L. Myasnikov suggested that estrogen could activate the phagocytic function of reticuloendothelial system that contributed to elimination of cholesterol.

Previously, the authors have shown the improvement of cholesterol:phospholecetin index that could prevent the development of atherosclerosis [8, 9]. Most authors point out that estrogens improve plasma lipid profiles (decrease the level of LDL–C and total cholesterol, increase the level of high-density lipoprotein cholesterol (HDL–C) [10–13], as well as cholesterol metabolism in the vascular wall (inhibits the processes of its uptake and degradation) that explains anti-atherosclerotic mechanism of endogenous estrogens and estrogen replacement therapy [14–16].

According to the latest clinical guidelines, the decrease of atherogenic lipoproteins in response to drug therapy in patients with CAD should be assessed by the achievement of target LDL–C levels, depending on cardiovascular risk (CVR) category [17]. For a long time, the main lipid-lowering medications were hydroxymethylglutaryl-coenzyme-A reductase inhibitors (statins), however only 21% of patients, who received such therapy, achieved target LDL–C levels [18]. In case when target LDL–C levels couldn't be achieved with optimal lipid-lowering therapy, it is recommended to prescribe other groups of lipid-lowering medications — monoclonal antibodies, proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme inhibitors [19] that showed the achievement of target LDL–C parameters in over 90% of patients [20].

To date, data on estrogens dynamics during the treatment with PCSK9 inhibitors are limited. Some studies have shown lower concentration of PCSK9 in men compared with women [21]. In addition, the level of PCSK9 enzyme increases with age in women, while decreases in men [22]. This fact may be explained by the influence of female sex hormones — increased level of estrogen contributes to the decrease of PCSK9 [23].

The aim of this study is the assessment of atherogenic lipoproteins and estrogen dynamics in patients with CAD who were prescribed with PCSK9 with several concomitant diseases.

Materials and methods

This open prospective study was carried out at Moscow Regional Hospital named after prof. V.N. Rozanov. The study was approved by the local ethics committee (protocol No. 3 dated March 16, 2020, Kursk State Medical University of the Ministry of Healthcare of Russian Federation), all the participants signed an informed consent form. All study participants had permanent registration at Moscow Region and were included into the preferential category of citizens

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(PCSK9 inhibitors in the Moscow Region are provided according to regional program and by the means of federal compulsory medical insurance fund using the clinical and statistical group ds36.004).

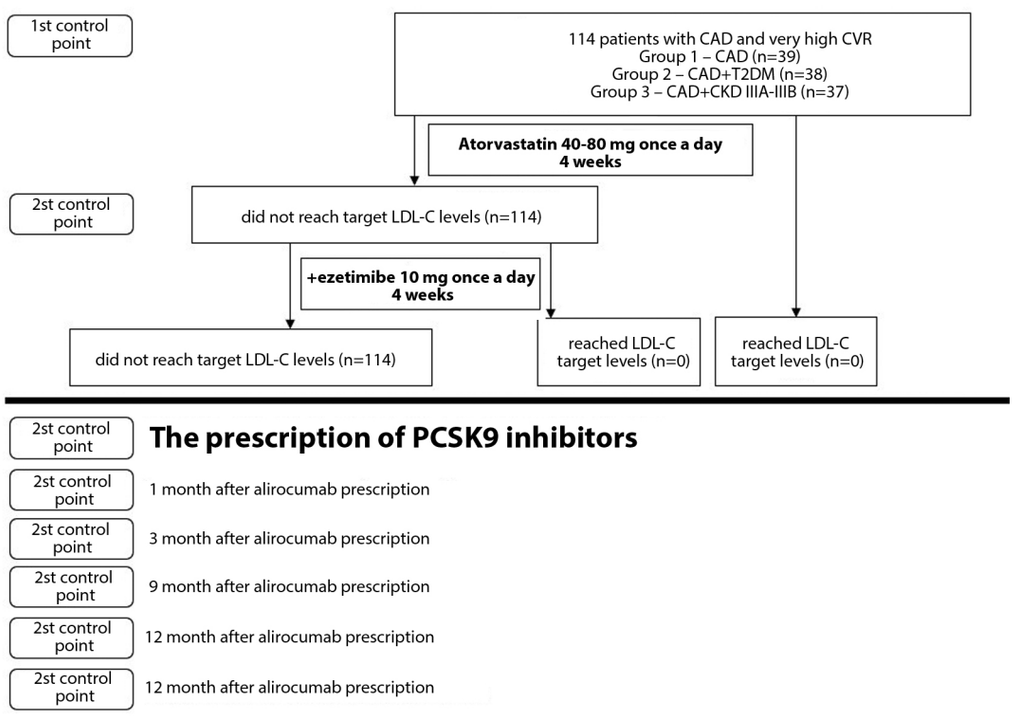
The study included 114 men (mean age 59.22 ± 5.74 years) with CAD, very high CVR and primary dyslipidemia, who required secondary prevention of CVD. Study participants were divided into 3 groups depending on the presence of concomitant diseases: group 1 — with CAD only (n= 39); group 2— with CAD and type 2 diabetes mellitus (T2DM) (n=38); group 3 — with the presence of CAD and stages IIIA-IIIB of chronic kidney disease (CKD) (n=37).

All the patients were examined during 8 visits. Study design is presented in Scheme 1. The first visit included standard medical examination and the prescription of maximum tolerated dose of atorvastatin. After 4 weeks, at second visit, the achievement of target LDL–C level according to the European Society of Cardiology (ESC) was assessed [17]. In case when target parameters were not achieved, patients were prescribed with 10 mg of ezetimibe once a day. At the third visit, 4 weeks after, the effect of lipid-lowering therapy was repeatedly assessed. Patients who showed LDL–C level over 1.4 mmol/l were prescribed with 150 mg of alirocumab additionally to previous treatment, subcutaneously once every 14 days (PRALUENT, SANOFI, France). The analysis of lipid profile and estradiol levels, after the prescription of alirocumab, was carried out at the next 5 control points: at 1st, 3d, 6th, 9th and 12th month of treatment.

The study inclusion criteria were: male gender, age from 50 to 69 years, confirmed diagnosis of CAD, very high CVR, lack of achievement of LDL–C target goals with the prescription of atorvastatin and ezetimibe in maximum tolerated dose, the absence of contraindications for the prescription of PCSK9 inhibitors.

The non-inclusion criteria were: the achievement of LDL–C targets with the prescription of atorvastatin and ezetimibe in maximum tolerated dose, stage III chronic heart failure (according to Vasilenko-Strazhesko classification) with left ventricular ejection fraction less than 30 %, individual intolerance to PCSK9 inhibitors, the decrease of LDL–C level of less than 0,5 mmol / l, obesity with a body mass index of less than 40.5; fasting triglycerides (TG) level over 4.52 mmol /l.

Fasting blood samples for biochemical assays were collected once, from the cubital vein in the morning, 12 hours after the last meal. The analysis was carried out using automatic biochemical analyzer BS-120 Mindray (China). The lipid panel included the param-



Scheme 1. Study design

eters of total cholesterol (TC), LDL–C, high-density lipoproteins cholesterol (HDL–C), triglycerides (TG).

The statistical analysis was performed using SPSS 23.0 software (IBM USA). The normality of distribution was assessed using the Kolmogorov–Smirnov test with the Lilliefors correction (for the entire sample) or the Shapiro–Wilk test (for groups with less than 50 participants). Quantitative features are presented as M ± SD for normally distributed parameters, where M is the arithmetic mean, SD — the standard deviation; the parameters that deviated from normal distribution are presented as median and quartiles (Me [Q1; Q3]). The qualitative parameters are presented in absolute numbers and/or percentage. The significance of differences between groups quantitative variables was assessed using the Kruskal–Wallis test (between three groups) and Mann–Whitney test (between two groups), the Wilcoxon test was used for dependent samples. Two-tailed Fisher's or chi-squared tests were used to assesses differences between quality variables. A p-value of <0.05 was taken to infer statistical significance.

Results

Before the inclusion into the study all the patients had comparable lipid panel parameters and comorbid diseases. Clinical characteristics of patients at baseline are presented in table 1.

The primary screening of the study participants showed that the vast majority of patients had classes 1–2 of obesity, arterial hypertension, and the history of smoking. Before the inclusion into the study, patients were prescribed with various dosages of statins without the achievement of LDL–C targets. At the first visit, atorvastatin at a maximum dose of 80 mg/day was administered in all patients. Atorvastatin intolerance was confirmed in 16.7% of patients (n=19) and required complete medication discontinuation in 12 patients and dose reduction to 40 mg in 5 patients. After 4 weeks of treatment, LDL–C level was assessed. In group 1, the level of LDL-C decreased from 4.41±0.19 mmol/l to 2.63±0.15 mmol/l (p<0.001), in group 2 — from 4.62±0.25 mmol/l to 2.71±0.09 mmol/l (p<0.001), group 3 — from 4.60±0.20 mmol/l to 2.69±0.08 mmol/l (p<0.001). At this point all patients were prescribed with ezetimibe, which caused the intensification of lipid-lowering response. Four weeks after, LDL–C reached 2.28±0.08 mmol/l in group 1, 2.32±0.07 mmol/l — in group 2, 2.33±0.07 mmol/l — in group 3. Since none of the patients reached LDL–C targets, alirocumab was added to treatment in all patients with the control of estradiol levels at all subsequent control points. Further dynamics of lipid profile and estradiol in the study groups are presented in figure 1.

Alirocumab intolerance was reported in 6 patients and lead to the exclusion of these patients from the study. In 12 months after the prescription of PCSK9 inhibitors, 108 patients achieved LDL–C targets; in group 1–97.4% (n=38), in group 2–94.7% (n=36), in group 3–91.9% (n=34). The final LDL–C level in group 1 was 1.15±0.15 mmol/l that was 73.9% lower compared with baseline, in group 2–1.19±0.12 mmol/l and decreased by 74.2%, in group 3–1.22±0.09 mmol/l

Table 1. **Clinical characteristics of patients at baseline**

Parameters	CAD (n= 39)	CAD+ T2DM (n= 38)	CAD+ CKD IIIA-IIIB (n= 37)	p
Age, years	60,94± 5,88	60,55± 6,21	59,22± 5,74	0,43
Obesity — class 1–2	59% (N=23)	63% (N= 24)	70% (N= 26)	—
Smoking	74% (N=29)	84% (N= 32)	92% (N= 34)	—
Arterial hypertension	90% (N=35)	90% (N= 34)	86% (N= 32)	—
Myocardial infarction	39% (N=15)	53% (N= 20)	38% (N= 14)	—
PCI/CABG	54% (N=21)	68% (N= 26)	46% (N= 17)	—
Lower extremity atherosclerosis	31% (N=12)	32% (N= 12)	27% (N= 10)	—
Atrial fibrillation	31% (N=12)	39% (N= 15)	30% (N= 11)	—
TC, mmol/l	6,45± 0,29	6,67± 0,21	6,69± 0,15	0,001
LDL–C, mmol/l	4,41± 0,18	4,62± 0,24	4,60± 0,20	0,001
HDL–C, mmol/l	0,70± 0,08	0,71± 0,09	0,69± 0,11	0,15
TG, mmol/l	2,09± 0,46	2,06± 0,40	1,99± 0,39	0,49
Atherogenic index	8,24± 1,12	8,55± 1,17	8,92± 1,24	0,14

Note. Significance levels are indicated for the Kruskal–Wallis test.
p — the level of significance of differences between study groups, quantitative variables are presented as means and standard deviations (M±SD); qualitative variables are presented as %.

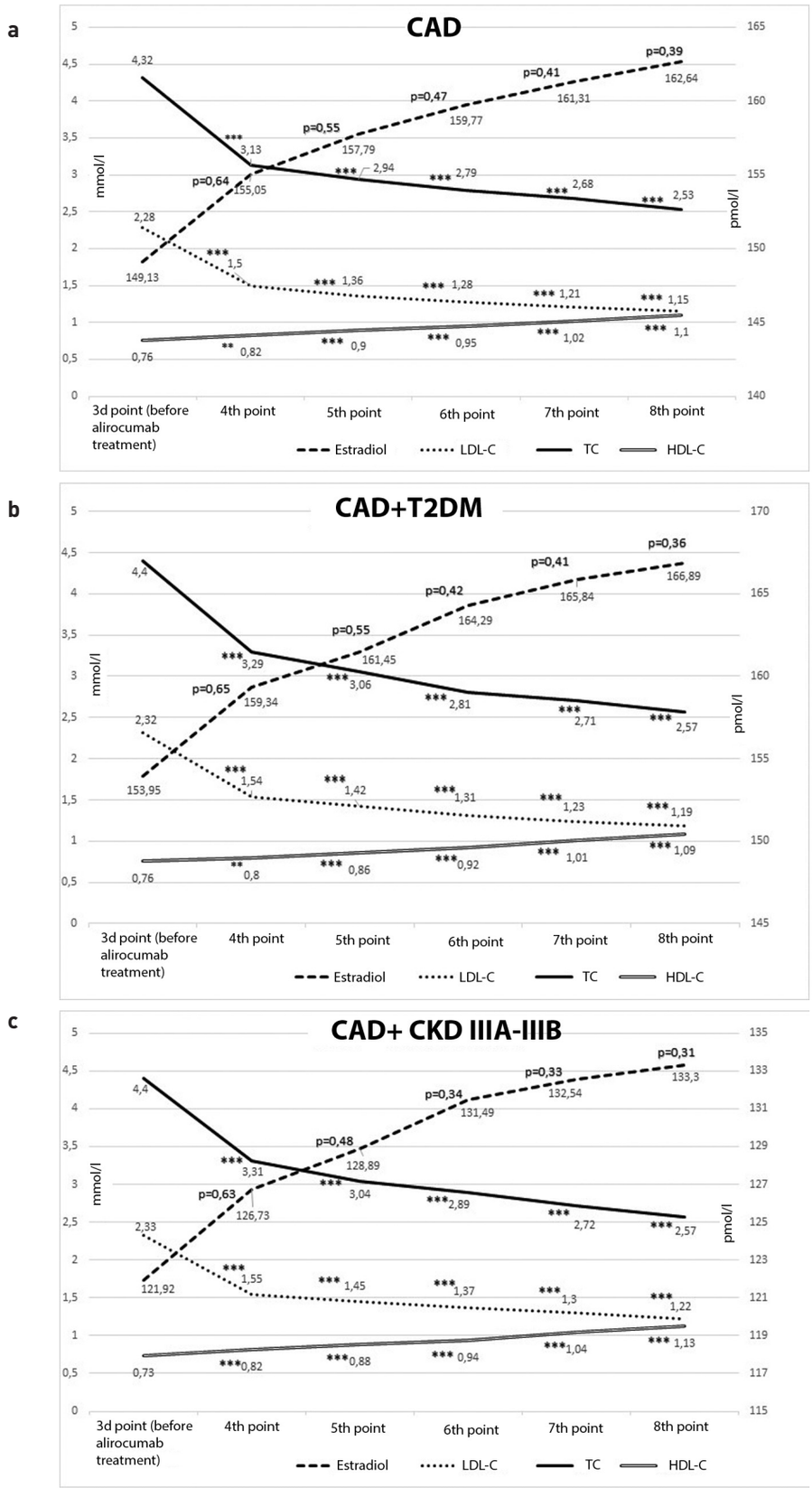


Figure 1. The dynamics of lipid profile and estradiol during 12-months alirocumab treatment: a — in patients with CAD, b — in patients with CAD in combination with T2DM, c — in patients with CAD and IIIA–IIIB stages of CKD.

and decreased by 73.5 %. Alirocumab showed statistically significant (p<0.001) changes of all lipid profile parameters already 4 weeks after treatment initiation (2 injections). The TC level decreased from 4.32±0.08 mmol/l to 3.13±0.15 mmol/l (p<0.001) 4 weeks after and to 2.53±0.16 mmol/l (p<0.001) 12 months after the addition of alirocumab in group 1; from 4.40±0.08 mmol/l to 3.29±0.08 mmol/l (p<0.001) 4 weeks after and reached 2.57±0.09 mmol/l (p<0.001) 12 months after in group 2; from 4.40±0.08 mmol/l to 3.31±0.11 mmol/l (p<0.001) 4 weeks after and reached 2.57±0.11 mmol/l (p<0.001) 12 months after in group 3. The TG level decreased from 1.94±0.42 mmol/l to 1.74±0.36 mmol/l (p=0.04) in 4 weeks and to 1.13±0.34 mmol/l (p< 0.001) in 12 months of alirocumab treatment in group 1; from 1.94±0.37 mmol/l to 1.74±0.36 mmol/l (p=0.02) in 4 weeks and to 1.11±0.34 mmol/l (p<0.001) in 12 months in group 2; from 1.81±0.33 mmol/l to 1.64±0.31 (p=0.02) in 4 weeks and to 1.07±0.31 mmol/l (p<0.001) in 12 months in group 3, respectively. The level of HDL–C in group 1 increased from 0.76±0.08 mmol/l to 0.82±0.08 mmol/l (p<0.01) after 4 weeks of treatment and to 1.10±0.07 mmol/l (p<0.001) in 12 months; in group 2 — from 0.76±0.07 mmol/l to 0.80±0.06 mmol/l (p<0.01)in 4 weeks and to 1.09±0.08 mmol/l (p<0.001) in 12 months; in group 3 — from 0.73±0.07 mmol/l to 0.82±0.08 mmol/l (p<0.001) in 4 weeks and to 1.13±0.06 mmol/l (p<0.001) in 12 months. The analysis of estradiol dynamics showed high variability of this parameter in all groups that is most likely associated with the individual features of endocrine status in men (Fig. 2). The level of estradiol increased by 8.3 % — from 149.13±87.30 pmol/l to 162.64±86.14 pmol/l (p=0.39) during the study follow-up; in the group 2 — by 7.7 % — from 153.95±71.50 pmol/l to 166.89±71.01 pmol/l (p=0.36); in group 3 — by 8.5 % — from 121.92±67.16 pmol/l to 133.30±68.40 pmol/l (p=0.31).

Discussion

In current study patients with CAD and very high CVR were prescribed with hypolipidemic therapy with PCSK9 inhibitors for 12 months. The achievement of target LDL–C level was the objective of treatment.

Over 90 % of all study participants reached target LDL–C parameters. The most prominent response to alirocumab treatment was observed in patients with CAD without concomitant diseases (group 1), where the final LDL–C level was 1.15±0.15 mmol/l, in patients with CAD in combination with T2DM (group 2), the final LDL–C level was 1.19±0.12 mmol/l, and in patients with CAD in combination with IIIA-IIIB stages of CKD (group 3) the hypolipidemic effect was the lowest and the final LDL–C level was 1.22±0.09 mmol/l that is consistent with the data of large clinical studies confirmed by meta-analyses, such as FOURIER [24], where 97 % of patients with CAD reached LDL–C target values and ODYSSEY OUTCOMES [25], where after

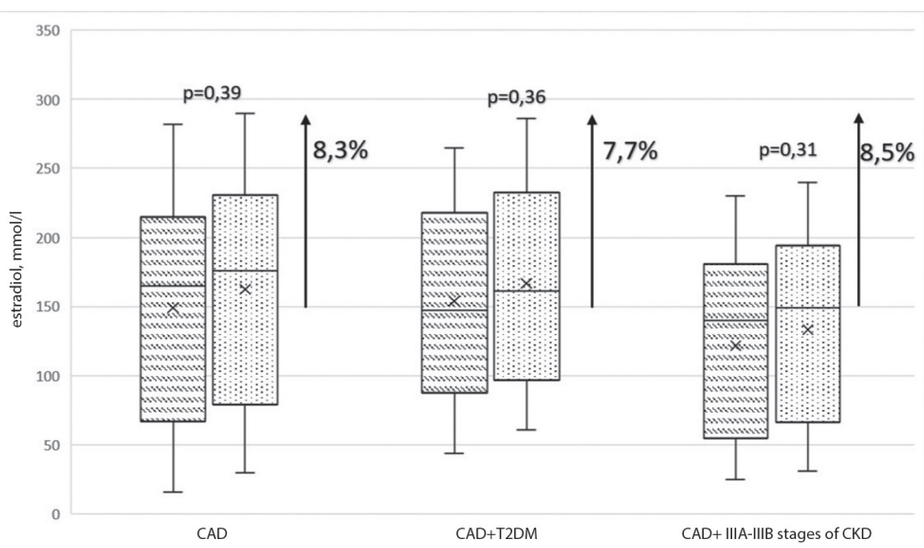


Figure 2. The dynamics of estradiol in study groups before and after the treatment with alirocumab.
Note. Significance levels are indicated for the Wilcoxon T-test; p — the significance of differences in estradiol level between baseline and the end of treatment with alirocumab.

12 months of alirocumab use, average LDL–C level reached 1.2 mmol/l that is not consistent with the results of smaller foreign and domestic trials.

Thus, according to the results of similar clinical study from Netherlands, the prescription of PCSK9 inhibitors allowed to achieve LDL–C level of < 1.8 mmol/l in 67.1 % of patients [26]. According to data from Israel Lipid Center, combined lipid-lowering therapy with PCSK9 inhibitors allowed 50 % of patients to achieve LDL–C concentration of < 1.8 mmol/l [27]. According to the retrospective chart review study from the National Research Center for Therapy and Preventive Medicine, the prescription of PCSK9 inhibitors additionally to optimal lipid-lowering therapy resulted in LDL–C of < 1.8 mmol in 78.3 % of patients and < 1.4 mmol / l — in 57.7 % of patients [28] that is significantly lower compared with the results of our study and may be explained by higher baseline LDL–C levels in the above studies, and the inclusion of patients with familial hypercholesterolemia.

In current study, total LDL–C level decrease reached 73.9 % in group 1, 74.2 % — in group 2, 73.5 % — in group 3 that differs from the results of studies from other countries. According to the results of large multicenter FOURIER and ODYSSEY OUTCOMES [24, 25] studies, the total reduction of LDL–C reached 85 % that is significantly higher compared with our results, and can be associated with longer use of PCSK9 inhibitors (36 months). According the French Lipid Center, the prescription of triple lipid-lowering therapy (statin + ezetimibe + PCSK9 inhibitor) resulted in the reduction of LDL–C level only by 66.3 % from baseline [29], which is lower compared with our study and may be associated with the inclusion into this study of patients with heterozygous familial hypercholesterolemia.

Our study showed good statin tolerability (16.7 %) and low incidence of adverse reactions to PCSK9 inhibitors intake (5 %). In other lipid centers and according to outpatient practice, statin intolerance ranges from 31.6 % to 77.0 % [27–28, 30–31], intolerance to PCSK9 inhibitors — from 10.0 % to 15.5 % [26, 27].

Estradiol blood level statistically insignificantly increased in all study groups after the addition of alirocumab into treatment. In group 1, estrogen level increased by 8.3 % 12 months after the prescription of PCSK9 inhibitors, in group 2 — by 7.7 %, in group 3 — by 8.5 %, respectively. It is noteworthy that this indicator had high variability (from 21 to 282 pmol/l), associated with individual characteristics of patient's endocrine status.

Conclusion

Thus, the use of PCSK9 inhibitors in combination with optimal lipid-lowering therapy in patients with very high CVR showed the most pronounced response in patients with CAD without comorbid diseases. Patients with comorbidities (CAD with T2DM and IIIA-IIIB stages of CKD) showed lower response to alirocumab. At the same time, over 90 % of patients reached LDL–C targets.

The level of estradiol statistically insignificantly increased in all study groups that may be associated with HDL–C increase.

The obtained results require further investigation in the framework of large clinical trials.

Conflict of interest: none declared.

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Antioxidant effects of atorvastatin in patients with stable coronary artery disease

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Abstract

Objective. To assess the effect of atorvastatin on antioxidant enzyme activities in blood plasma and tissue in patients with stable coronary artery disease and postinfarction cardiosclerosis.

Materials and methods. The study included 122 patients with coronary artery disease (CAD) and 20 healthy controls. The following blood plasma parameters were assessed by generally accepted measurement tools: lipid profile, lipid peroxidation (LPO) products — diene conjugates (DC), thiobarbituric acid reaction products (TBA-RP), enzymatic antioxidant glutathione peroxidase (GP), erythrocyte superoxide dismutase (SOD), plasma activity of the antioxidant ceruloplasmin/transferrin system (AOS CP/TF) — by the electron paramagnetic resonance method. Endothelial function was investigated by ultrasound assessment of endothelial-dependent flow-mediated vasodilation (EDFMD) by the D. Celermajer et al. method.

Results. Patients with stable CAD and dyslipidemia showed the intensification of LPO processes, therefore, DC increased by 77 %, TBA-RP — by 58 %, and the impairment of enzyme regulation of reactive oxygen species (ROS): the decrease of AOS CP/TF by 33 %, SOD by 25 % and GP by 39 % compared with the control group. After the prescription of 20–40 mg of atorvastatin per day for 6 months in combination with complex cardiovascular therapy, the level of SOD increased by 16 %, GP — by 60 %, the activity of AOS CP/TF — by 12.5 %, the level of DC decreased by 40 %, TBA-RP — by 32 %, EDFMD improved by 36 %.

Conclusion. Atorvastation in combination with complex cardiovascular pharmacotherapy has antioxidant and antiperoxide activity and improves endothelial function in patients with stable CAD with manifestations of oxidative stress.

Keywords: atorvastatin, coronary artery disease, dyslipidemia, antioxidant protection, endothelial dysfunction.

Conflict of interest: none declared.

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Introduction

It is generally accepted that dyslipidemia (DLP) is one of the main risk factors (RF) for the development of atherosclerosis and coronary artery disease (CAD). Low-density lipoprotein cholesterol (LDL–C) plays a pivotal role in the pathogenesis of atherosclerosis, and oxidative modification of LDL that occurs due to action of free radicals and reactive oxygen species (ROS), exacerbates endothelial dysfunction and damage in patients with CAD that contributes to the atherosclerotic plaque (AP) destabilization. Numerous studies have shown that the reduction of atherogenic lipids levels, primarily LDL–C, during treatment with HMG-CoA reductase inhibitors — statins, directly correlates with the decrease of cardiovascular and all-cause mortality [1].

Along with antihyperlipidemic properties, statins also have pleiotropic and lipid-independent effects on all types of vascular cells and leukocytes [2]. HMG-CoA reductase inhibitors block the proliferation and migration of smooth muscle cells from media to intima layers during the AP formation [3], increase the activity of endothelial nitric oxide synthase (eNOS) [2, 4], have antioxidant properties, activate NO, and reduce the production of AT_1- receptors [5]. Statins reduce: the activity of NAD(P)H oxidase subunits, inflammation processes, the expression of cell adhesion molecules and the activity of macrophage migration [6], the development of matrix metalloproteinases and tissue factor [7].

It has been established that oxidative stress increases in patients with CAD [8]. Along with the disease development, an imbalance in the system of lipid peroxidation — antioxidant defense system occurs; thus, the assessment of endogenous antioxidant defense system and antioxidant medication properties are still highly relevant. Along with tissue antioxidant enzymes, the plasma antioxidant system (AOS)

ceruloplasmin/transferrin (CP/TF) also inactivates lipid peroxidation. During the oxidation of ions from Fe2+ to Fe3+, CP promotes its incorporation into apotransferrin. Due to this reaction, direct LPO inducers — Fe2+ ions, are eliminated from blood plasma. Thus, the development of superoxide anion radicals, that regenerate during non-enzymatic oxidation of Fe2+ ions, is prevented.

Literature data on antioxidant effects of statins are contradictory [9], however, further researches on its role into the oxidative stress manifestations and the activity of the AOS CP/TF in patients with CAD are still highly relevant and scientifically based. The investigation of statin therapy effects on the pathogenesis of atherosclerosis, including endothelial dysfunction, lipid metabolism, oxidative stress, NO metabolism, antioxidant defense system, will expand the understanding of its mechanisms of action, efficacy and safety in the reduction of atherosclerotic complications.

In this study we aimed to assess the role of atorvastatin in the correction of oxidative stress and endothelial dysfunction in patients with CAD and DLP.

Materials and methods

The study included 122 patients with CAD, functional classes (FC) II–III of angina pectoris, post-infarction cardiosclerosis with DLP types IIa and IIb according to WHO classification (65 men and 57 women) aged from 36 to 72 years old, average age — 58.3±7.9 years. All the participants signed written informed consent to participate in research. Average time since CAD diagnosis was 5.1±6.7 years. The control group included 20 healthy participants (10 men and 10 women), average age — 46.8±6.7 years.

Non-inclusion criteria were: the intake of antihyperlipidemic and antioxidant medications, the presence of myocardial infarction less than 6 months before the study, the presence of IIb-III stages of heart failure according to Strazhesko-Vasilenko classification, secondary hyperlipidemia, dysproteinemia, exacerbation of chronic diseases, hematopoiesis impairment, oncology.

Exclusion criteria were: the development of acute or exacerbation of chronic disease that required pharmacological treatment, patient's refusal to continue participation. The study has been approved the Ethics Committee of Moscow State University of Medicine and Dentistry named after A.I. Evdokimov (protocol № 4).

All study participants received diet No. 10 recommended by the Institute of Nutrition of the Russian Academy of Medical Sciences and basic treatment with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists and antiplatelet agents, underwent clinical and laboratory investigations, biochemical blood profile analysis, as well as instrumental examination in order to establish the diagnosis of CAD and identify exclusion criteria.

To assess the effect of atorvastatin as part of complex cardiovascular therapy on antioxidant enzymes activity and LPO process, we divided 122 patients with CAD into two groups. The 1st group included 102 patients with CAD (mean age 57.8±8.1 years) who received 20–40 mg of atorvastatin, the 2nd (comparison group) that included 20 patients with CAD (mean age — 60.7±7.2 years) who received only basic cardiovascular treatment due to their refusal to take statins. Both groups were comparable by gender, age, stage of CAD and laboratory data at baseline, and, therefore, were representative to determine treatment effectiveness (Table 1).

The determination of total cholesterol (TC), LDL–C and high-density lipoprotein cholesterol (HDL–C) was carried out by basic laboratory methods. The content of primary LPO products- diene conjugates (DC) was studied by the method of Iamamoto J. and determined spectrophotometrically by optical density at 232 nm, secondary thiobarbituric acid reaction products (TBA-RP) — by the method of Asakawa T., Matsushita S. modified by L.N. Shishkina with the addition of 10 μl of 0.01% solution of ionol in alcohol into the incubation medium. The amount of enzyme required for 50% inhibition of the reac-

Table 1. **Demographic data in patients with CAD and healthy controls**

Parameter	Group 1 (n=102)	Group 2 (n=20)	Control group (n=20)
Age, years	57.8 ± 8.1	60.7 ± 7.2	46.8±6.7
Men/women	52/50	13/7	10/10
The duration of CAD, years	5.1 ± 2.7	5.3 ± 2.8	—
Angina pectoris, II functional class	21(20%)	4 (20%)	—
Angina pectoris, III functional class	33 (32%)	7 (35%)	—
Arterial hypertension	83 (81%)	16 (80%)	—
CHF, I–IIa	54(53%)	11 (55%)	—
Smoking	23 (22%)	5 (25%)	5 (25%)
Genetic burden of CVD	61 (60%)	11 (55%)	14 (70%)
Overweight	10 (10%)	2 (10%)	1 (5%)

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tion of nitrotetrazolium blue by the superoxide anion radical generated during the oxidation of xanthine by xanthine oxidase at 560 nm using "Hitachi-557" spectrophotometer according to the method of Beauchamp C. and Fridovich I. was taken as a unit of superoxide dismutase (SOD) activity. Glutathione peroxidase (GP) activity was determined in conjugated glutathione reductase system for the oxidation of NADPH using tert-butyl hydroperoxide as a substrate according to the method of Lankin V. Z., Gurevich S. M.

Antioxidant activity (AOA) of AOS CP/TF in blood plasma was measured by the method of electron paramagnetic resonance (EPR). Endothelial function was studied using in B-mode of ultrasound with linear probe of 7.5 MHz with the assessment of endothelium-dependent vasodilation (EDVD) according to the method of Celermajer D. et al. (1992).

Statistical analysis of the obtained data was carried out using "Statistica 10" software. Quantitative variables, assuming their normal distribution, were compared using Student's t-test for two independent groups and using paired Student's t-test to compare studied parameters before and after treatment.

Results

The comparative analysis revealed significant differences between composition of lipids, LPO processes, tissue and plasma antioxidant defense system in patients with CAD and from the control group (Table 2).

The activity of antioxidant enzymes: SOD (by 61 %) and GP (by 80 %) in erythrocytes significantly decreased in the vast majority of patients with CAD compared with the control group. The increase of the SOD/GP ratio indicated significant imbalance in the system of antioxidant enzymes in the erythrocyte towards oxidative stress in patients with CAD.

Table 2. **Laboratory data in patients with CAD and the control group (M±sd)**

Parameters	Patients with CAD (n=122)	Control group (n=20)
TC, mmol/l	6.4±0.9	5.3±0.9*
Triglycerides, mmol/l	1.7±0.3	1.4±0.4 *
LDL–C, mmol/l	4.7±0.9	3.0±0.8*
HDL–C, mmol/l	0.96±0.15	1.3±0.2*
AST, U/L	22.6±8.5	19.6±5.1
ALT, U/L	24.6±7.9	20.4±4.4*
Diene conjugates, nmol/ml	24.8 ± 5.1	14.0±2.7*
TBA-RP, nmol/mg	0.19 ± 0.04	0.12±0.04*
SOD, U/Ml	1772±523	2337±123*
GP, U/Ml	19.3 ± 6.7	31.4±3.3*
SOD/GP	92	74*
CP, conventional units	77.4±17.6	123.9±19.4*
CP/TF	0.8±0.1	1.2±0.3*

Note. * — differences between the parameters of patients with CAD and the control group are significant with p<0.001.

The changes of the amplitude of the EPR signals of the CP and TF reflects the dynamics of their paramagnetic properties and inherent activity. AOS of CP/TF was by 76 % lower in patients with CAD compared with the control group.

Thus, laboratory data of patients with CAD revealed DLP, accompanied by the intensification of LPO processes in the form of DC increase by 77 %, and TBA-RP increase by 58 % and the impairment of enzymatic regulation of ROS metabolism: the decrease of the AOS CP/TF activity by 33 %, SOD — by 25 % and GP — by 39 % compared with the control group.

Atorvastatin demonstrated antihyperlipidemic, antiperoxide and antioxidant effectiveness in the vast majority of examined patients with CAD and DLP during 6-month treatment in combination with basic therapy (Table 3).

After 3-month treatment with atorvastatin, 56 % of patients from group 1 achieved target lipid levels, and 44 % of patients required the increase of the dose up to 40 mg/day. The medication was well tolerated by most patients. Dyspeptic phenomena occurred in 5 % of patients during the first week of treatment and disappeared further on their own. After 6-month treatment, 83 (81 %) patients from group 1 achieved target levels of TC, 75 (74 %) — LDL–C, and none of the patients from group 2. The results correspond to the data of multicenter studies on lipid-lowering effect of statins. The required correction of antihyperlipidemic therapy was carried out in accordance with the current National Clinical Guidelines.

Atorvastatin as part of combination therapy for CAD reduced the severity of LPO processes and contributed to the increase of antioxidant defense system activity in 91 % of patients from group 1. SOD activity increased by 16 % after 6-months treatment, GP — by 60 %, AOS CP/TF — by 12.5 %. The level of DC decreased by 40 %, and TBA-RP — by 32 %. After 6 months of treatment, groups of patients with CAD who received and did not receive atorvastatin differed by lipid profiles, LPO products and the activity of tissue and plasma antioxidant enzymes (see Table 3). AST and ALT in both groups before and after treatment were within the reference values.

Table 3. **Clinical and laboratory data before and after 6-month treatment of patients with CAD (**M±**SD)**

Parameters	Group 1 (n=102)		Group 2 (n=20)	
	At baseline	After 6 months of treatment	At baseline	After 6 months of treatment
TC, mmol/l	6.3± 0.9	4.3±0.5**	6.5±0.8	6.1± 0.7** ⁺
LDL–C, mmol/l	4.6±0.9	2.4±0.5**	4.7±0.8	4.2±0.8** ⁺
HDL–C, mmol/l	0.96±0.2	1.14±0.1**	1.03±0.15	1.07±0.13
TG, mmol/l	1.7±0.4	1.5±0.2**	1.6±0.3	1.5±0.3
TBA-RP, nmol/mg	0.19±0.04	0.13±0.02**	0.21±0.04	0.23±0.04* ⁺⁺
Diene conjugates, nmol/ml	24.5±5.0	14.8±3.0**	26.3±4.9	28.7±4.4* ⁺⁺
SOD, U/Ml	1805±507	2101±414**	1605±583	1570±488⁺⁺
GP, U/Ml	19.7±6.9	31.5±6.5**	17.3±5.5	14.3±3.3* ⁺
CP, conventional units	78.3±18	92.9±16**	73.0±17.2	72.0±15.5⁺⁺
CP/TF	0.8±0.1	0.9±0.1**	0.79±0.1	0.75±0.1*⁺⁺
AST, U/L	21.9±8.2	24.5±8.7	26.1±9.3	23.8±6.1
ALT, U/L	24.9±7.8	29.3±9.8*	23.5±8.6	19.7±5.5⁺
EDVD, Δ%	7.3±3.9	9.9±2.3*	7.2± 4.0	8.3± 3.6

Note. Differences between the parameters at baseline and after treatment are significant with * — p<0,05; ** — p<0,001. Intergroup differences are significant with ⁺ — p<0,0001, ⁺⁺ — p<0,001.

Endothelial function also improved along with LPO antioxidant defense system activity, according to the results of treatment in patients with CAD (see Table 3). It is remarkable that the changes were statistically significant in patients with CAD who received atorvastatin.

Discussion

The improvement of LPO antioxidant defense system parameters can be explained by the effect of key enzymes that are responsible for the synthesis and neutralization of ROS, eNOS and NAD(P)H-oxidase, in particular [2]. Several studies have proven early antioxidant effect of statins and their ability to restore the biological activity of NO. They contributed to the increase of vascular eNOS activity, decrease of ROS production in the vessels, and, therefore, improved endothelial function [2–5]. It has been shown that the antioxidant and anti-inflammatory effects of statins are closely associated with each other that are caused by the stimulation of the signaling transcription Lung-Kruppel-like factor 2 (LKLF/KLF2) that increase the activity of eNOS, thrombomodulin and anticoagulant properties of protein C, and decrease the effects of adhesion molecule genes-1 (VCAM-1) and plasminogen activator inhibitor-1 (PAI-1) expression that promote inflammation and thrombogenesis. [6, 10]. Literature data on the effect of statins on the parameters of oxidative stress in patients CAD are limited. Thus, atorvastatin and rosuvastatin at the dose of 80 mg and 40 mg per day, respectively, in 70 patients with myocardial infarction for 4 weeks showed significant decrease of LDL cholesterol, normalization of the total antioxidant status and oxidative stress index.

The study of 40 patients with DLP from Macedonian prescribed with rosuvastatin 20 mg/day showed that 67 % of patients had lower susceptibility of LDL to oxidation after rosuvastatin treatment (p = 0.03), and 53 % of patients — higher antioxidant capacity of HDL after treatment, however, the difference was not statistically significant (p=0.07). The increase of antioxidant potential of HDL during rosuvastatin treatment was more prevalent among men (OR=9.350; p=0.010) [12]. Atorvastatin as part of combination therapy of DLP contributed to the increase of antioxidant enzymes SOD, catalase, and CP activity, although these changes were not significant [13].

The reduction of oxidative stress and restoration of NO biological activity are the key mechanisms that explain beneficial effects of statins on endothelial dysfunction. The improvement of EDVD in the group of patients treated with atorvastatin can be explained not only by their antihyperlipidemic effect, but also by the ability to reduce the production of prooxidant enzymes and stimulate the synthesis of intermediates and enzymes involved in the neutralization of ROS and free radicals, which also have antioxidant properties [2].

Thus, this study has shown that atorvastatin improves endothelial function in patients with CAD and

DLP due to its antiperoxide and antioxidant properties, protective effect and the reduction of lipid peroxidation products by inactivation of lipid radicals, and the increase of tissue and plasma antioxidant enzymes activity.

Conclusion

The 6-month treatment with 20–40 mg/day of atorvastatin as part of combination therapy for cardiovascular diseases, showed its antioxidant and antiperoxide activity in 90% of examined patients with CAD. Combination therapy in patients with cardiovascular diseases, including atorvastatin along with the achievement of target lipid levels contributes to the correction of the antioxidant status and significant reduction of endothelial dysfunction in patients with CAD and disturbances in lipid peroxidation — antioxidant defense system. This study suggests the need for integrated approach in the investigation of lipid profile and oxidative stress manifestations in patients with cardiovascular diseases. The obtained data on the pleiotropic properties of atorvastatin will expand the indications for its prophylactic use, considering its ability to reduce the risk of adverse prognosis, regardless of the lipid profile parameters.

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The clinical case of myocardial infarction after COVID-19 infection

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SARS-COV-2 has caused one of the largest pandemics by now. Cardiovascular complications occur in 30–45 % of cases and, along with respiratory failure, are the cause of death in 65 % of patients with unfavorable disease course. This article presents clinical case that demonstrates patient with comorbid diseases (coronary artery disease, arterial hypertension) after COVID-19 reinfection who developed myocardial infarction with cardiac arrest that was caused by cardiopulmonary insufficiency.

The patient was admitted with the diagnosis of acute myocardial infarction along with severe novel coronavirus infection. Complications of the main disease: bilateral diffuse COVID-associated pneumonitis, alveolitis. Concomitant diseases: arterial hypertension, stage III, left ventricular hypertrophy.

The case demonstrates the sequence of changes not only in vessels, but also in body organs with the development of acute myocardial infarction after SARS-COV-2 reinfection and emphasizes the need for long-term observation after the infection in patients with comorbidities such as coronary artery disease and arterial hypertension.

Key words: COVID-19, pulmonary fibrosis, myocardial infarction.

Conflict of interest: none declared.

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Introduction

The COVID-19 outbreak has become one of the main health issues worldwide [1]. In 50 % of cases, it is characterized by a severe and very severe disease course that includes the development of pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction [1–5]. Cardiovascular complications occur in 30–45 % of cases and, along with respiratory failure, are the cause of death in 65 % of patients with unfavorable disease course. Cardiac damage can have ischemic/non-ischemic causes and manifest by increased troponin and B-type na-

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triuretic peptide levels, which are associated with increased risk of ARDS, ventricular tachyarrhythmia, myocardial infarction, acute kidney injury and coagulopathy. These pathological processes are of special importance in patients with concomitant cardiovascular diseases, which increase the risk of both severe COVID-19 course and mortality in case of re-infection [3, 4]. However, literature data on morphological changes in body organs after the SARS-CoV-2 infection and re-infection are limited.

Clinical case

Patient T.A., woman of 65 years old, was admitted to the Republican Clinical Hospital of the Ministry of Health of the Chuvash Republic with the diagnosis of acute myocardial infarction. Severe novel coronavirus infection was confirmed by the presence of Immunoglobulins G (IgG) and M (IgM) to coronavirus infection (SARS C0V-2): IgG positive, positive ratio (PR) — 15.7 and IgM positive, PR — 7.4). Complications of the main disease included bilateral diffuse COVID-associated pneumonitis and alveolitis. Concomitant diseases were: arterial hypertension, stage III, left ventricular hypertrophy. Target BP — 130–139/80 mmHg.

According to medical records, patient has been suffering from elevated blood pressure for about 15 years and received antihypertensive medications. She has been treated for coronary artery disease (CAD) in the outpatient setting. Two months ago, she was diagnosed with COVID-associated pneumonitis with diffuse bilateral infiltrates and alveolitis. She took antibiotics and expectorants by herself that did not improve her health state. When she had come to the hospital: chest computed tomography (CT) revealed bilateral diffuse viral COVID-associated pneumonitis, alveolitis, with about 75 % damage of the lung tissue, compaction of the lung tissue in the form of "ground glass opacity", polymerase chain reaction (PCR) for COVID-19 was positive. Patient received treatment at the Department of Infectious Diseases where her health state significantly improved. She was discharged after two consecutive negative nasopharyngeal swab tests had been received followed by outpatient treatment.

Approximately one week ago, she complained of cough with sputum that was difficult to separate and fatigue. She called an ambulance due to chest pain, spreading through the chest surface. Electrocardiogram (ECG) showed: sinus rhythm, ST segment elevation in AV–I, V2–5 leads, reciprocal depression of the ST segment in II, III, AVF leads.

Medical examination at admission: general health state is severe. Skin: pale with cyanotic tint, lower extremity edema. Body temperature — 37.1 °C.

Neurological examination. Conscious, verbal contact is limited due to cognitive impairment. Limb movements are limited. Sensitivity is not broken. Pupils: d=s=4 mm, the pupillary light reflex is preserved. Body type is hypersthenic. Weight=84 kg.

Respiratory system. Chest palpation is painless, auscultation revealed harsh symmetrical lung sounds, breath sounds are diminished on the right side and in the lower lobes, no wheezing, respiratory rate — 66/min, SaO2–47 %.

Cardiovascular system. Heart sounds are muffled. Heart rate — 111 beats/minute. The pulse on the radial artery is determined with normal filling pulse voltage. BP — 160/80 mmHg.

Digestive system. The tongue is dry with "dirty" coating at the root. Abdomen was symmetrical, soft and painless during palpation. Bowel sounds are determined via auscultation. The genitourinary examination has no pathology, diuresis values are within normal limits.

Treatment included antiarrhythmic medications, beta blockers, thrombolytics, nitrates. The coronary angiography revealed atherosclerotic lesion of three coronary vessels including the lesion of the trunk of the left coronary artery.

Lung CT scan revealed pneumonia, signs of lung congestion, compaction of the lung tissue that manifested as "ground glass opacity", pulmonary consolidation in combination with reticular opacities, approximately 75 %-damage of lung tissue.

ECG dynamics: ST segment elevation in V2-V4 leads, followed by spread to the inferior wall, ST segment elevation in III, II, AVF S1–4 leads — circular lesion. Troponin level — 14 ng/ml.

Laboratory investigations: signs of inflammation progressed in blood tests (leukocytosis — 35.5×109/l, segmented neutrophils — 84.6 %), thrombotic microangiopathy; almost two-fold increase of lactate dehydrogenase (LDH). The level of C-reactive protein was elevated up to 95 mg/l, ferritin and presepsin levels corresponded to an average risk of systemic inflammation development (487 pg/ml); increased risk for micro thrombosis (increased D-dimer, LDH).

Acid-base analysis revealed hypoperfusion — metabolic (6 mmol/l) lactic acidosis (pH — 7.20, BE (base excess) — 16 mmol/l); — progression of respiratory failure — the decrease of the SatO2 to 46 % (measured with pulse oximeter) during atmospheric air breathing, tachypnoea up to 36/min.

Despite ongoing treatment, the patient's condition had progressively worsened, and death was declared.

Pathological examination revealed bilateral polysegmental viral pneumonia with areas of carnification. The examination determined uneven compaction of pulmonary tissue predominantly in the posterior sections; heavy, airless, pieces of lung tissue that sank in water; reddish incisions with increased amount of reddish liquid that flows down from the surface of the when pressed. Histological examination revealed extensive areas of pneumosclerosis with many full-blooded vessels with perivascular sclerosis (Figure 1). The interalveolar septa are unevenly thickened with round cell infiltration and plethora of the capillaries. Alveoli are in the state of dystelectasis with the desquamation of alveolocytes into alveolar lumen and macrophages into the alveolar wall, homogeneous pink masses in the form of "crescents" similar to hyaline membranes, blood clot in the vessel (Figures 2, 3). Bronchial walls were sclerotized and thickened to varying degree, loosely infiltrated with lymphoid elements, with fibrin into the bronchial lumen.

Acute transmural myocardial infarction (MI) of the posterior LV wall was detected. Macroscopical examination revealed dark red area up to 4.7×4.5×1.7 cm in

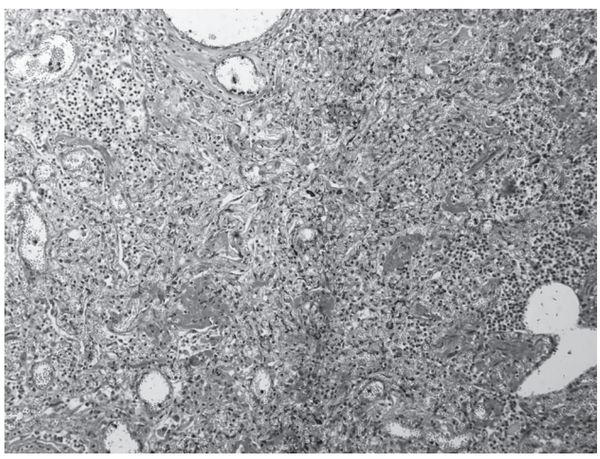


Figure 1. Microscopic picture of pneumofibrosis (1) with vessels plethora. Hematoxylin and eosin (H&E) staining, ×900

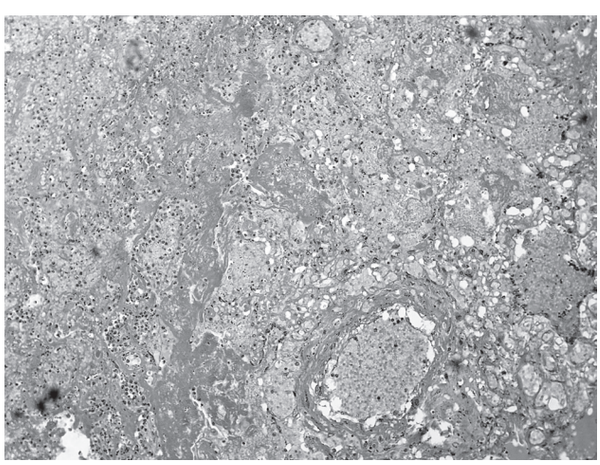
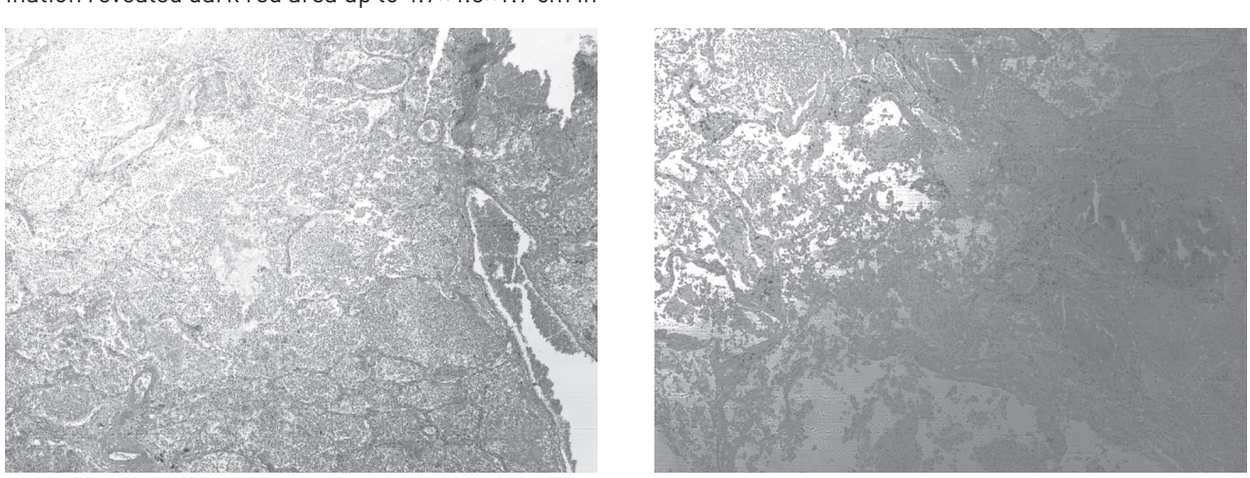


Figure 2. Microscopic picture of the thrombus into the vessel, hyaline membranes, areas of fibrosis. Hematoxylin and eosin (h&e) staining, x900



a b

Figure 3. Microscopic picture of viral pneumonia: a) inflammatory exudate, dilated and plethora vessels, interalveolar septa and hyaline membranes; b) leukocyte infiltration into the lumen of the alveoli with hemorrhagic component, blood vessels with sludge. Hematoxylin and eosin (H&E) staining, ×900

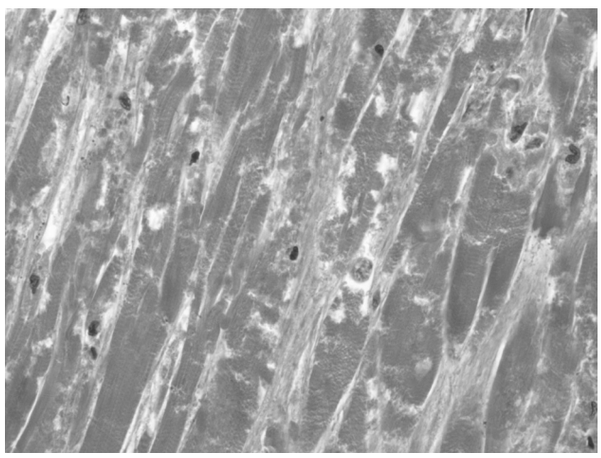


Figure 4. Microscopic picture of necrosis in cardiomyocytes (nuclear karyolysis). Hematoxylin and eosin (H&E) staining, ×900

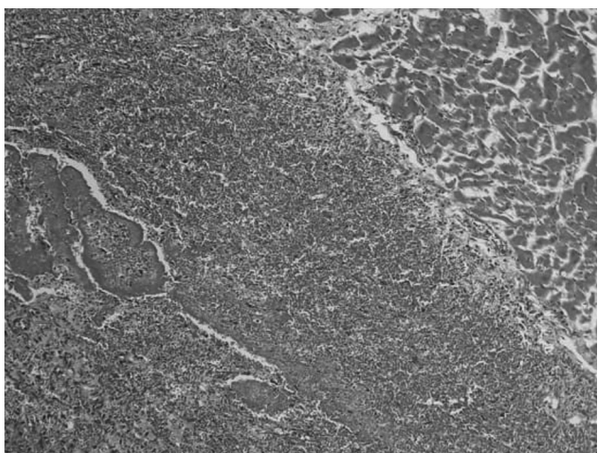


Figure 5. Microscopic picture of the demarcation line and myomalacia. Hematoxylin and eosin (H&E) staining, ×900

size at posterior LV wall. Cardiac tissue was dense, 13x10x8 cm in size, with mixed blood clots into heart chambers. The thickness of the right ventricular wall was 0.3 cm, of the left ventricle — 1.7 cm. Histological examination revealed interstitial edema, uneven fragmentation of muscle fibers, uneven hypertrophy of cardiomyocytes, connective tissue proliferation. There were areas of homogenization of muscle fibers with loss of nuclei and transverse striation with small hemorrhages and mild perifocal neutrophil infiltration (Figure 4), areas of autolysis into the necrotic zone (Figure 5). Coronary arteries had dense unevenly thickened walls and the lumen on transverse sections was narrowed up to 60–80 % due to atherosclerotic plaques. The lumen of pulmonary artery branches had liquid blood and blood clots. The intima of the aorta had pale yellow color and was covered with fatty streaks and atherosclerotic plaques at the stage of atheromatosis and calcification. In the intima of the mesenteric, iliac, and femoral arteries, there were also numerous atherosclerotic plaques with areas of calcification and atheromatosis.

The kidneys had dense tissue, bean-shape and size of 8×5×3 cm. The renal capsule was even, easily removed. The surface had small cicatricial retractions of brownish-gray color. The parenchyma was plethoric with numerous whitish-gray small veins. The kidneys anatomical pattern was easily distinguished — the boundary of cortex and medulla zones was clear. The pelvicalyceal system did not show any visible pathology, the mucosa was grey in color, smooth and clean. The urinary tract had no obstruction — the ureters had no constrictions or strictures, its mucous membrane was pale, gray in color, clean. Histological examination: the stroma was edematous; capillaries of the glomeruli were unevenly plethoric. Hyalinized glomeruli were identified. The epithelium of the kidney tubules had dystrophic and necrobiotic changes (Figure 6). The medulla had perivascular hemorrhages and areas of plethora (Figure 7). Arterial walls were circularly thickened and sclerotized.

There were signs of multiple organ failure that manifested as pulmonary and cerebral edema.

The following pathological diagnosis was established:

Main pathology: novel coronavirus infection (COVID-19), confirmed by the presence of Immunoglobulin G (IgG) and M (IgM) to coronavirus infection (SARS C0V-2): IgG positive, positive ratio (PR) — 15.7 and IgM positive, PR — 7.4): bilateral diffuse COVID-associated pneumonitis, alveolitis with areas of pneumosclerosis, acute transmural myocardial infarction of the posterior left ventricular wall.

Complications of the main pathology: acute respiratory distress syndrome, acute coronary thrombosis due to associated thrombotic lesion, acute cardiopulmonary failure, pulmonary edema, cerebral edema.

Concomitant diseases: arterial atherosclerosis at the stage of atheromatosis and calcification (60–80 % stenosis). Arterial hypertension: left ventricular hypertrophy (1.7 cm), focal glomerulosclerosis.

Medical records and autopsy results testify that the cause of death of 65-year-old woman was COVID-associated pneumonitis with diffuse bilateral infil-

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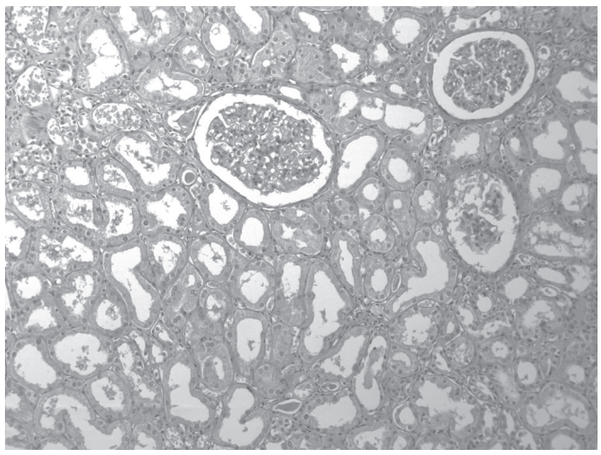

Figure 6. Microscopic picture of glomerular hyalinosis, signs of colloidal droplets into renal tubules similar to "thyroid kidney", degeneration of the tubule epithelium. Hematoxylin and eosin (H&E) staining, ×900

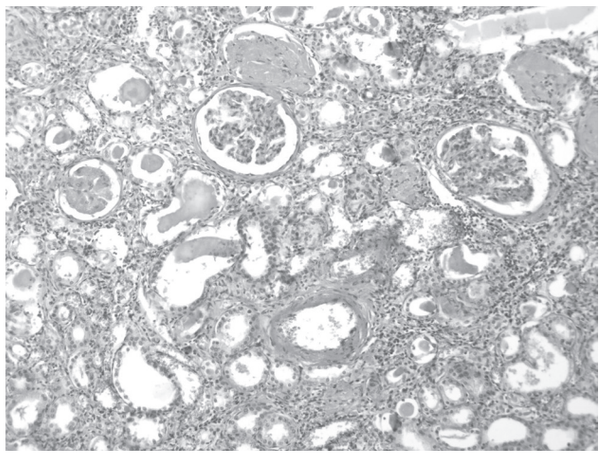

Figure 7. Microscopic picture of areas of necrosis of the kidney tubules epithelium with erythrocyte sludge into blood vessels. Hematoxylin and eosin (H&E) staining, ×900

trates and alveolitis complicated by the development of acute respiratory distress syndrome and acute MI that aggravated the course of the disease and affected the outcome by the cause of cardiopulmonary failure.

Discussion

It is known that cardiovascular complications are diagnosed in approximately 40% of patients who deceased from COVID-19 infection, AH and diabetes mellitus — in 30%. One study (n=41) revealed myocardial injury (high levels of high-sensitivity cardiac troponin I), another study (n=138) diagnosed acute cardiac injury (in 7.2% of cases), shock (8.7%) and arrhythmias (16.7%); most of the patients who developed these complications were admitted to intensive care unit. Previously published reports describe cases of acute heart failure, MI, myocarditis, and cardiac arrest. Patients with CAD had particularly high risk of complications due to atherosclerotic plaque rupture at the background of virus-induced inflammation.

Current clinical case describes changes in organs during recurrent COVID-19 infection that aggravated the course of existing cardiovascular diseases and led to the development of MI. The pathogenesis of cardiac damage is associated with vasoconstriction (due to the elevation of angiotensin II after the SARS-COV-2 blockage of angiotensin-converting enzyme II receptors); violation of oxygen delivery and consumption due to respiratory failure; the development of MI (types 1 and 2) associated with recurrent "cytokine storm" and thrombosis due to covid-associated coagulopathy. Thus, the development of acute MI led to the disease course aggravation that contributed to the occurrence of multiple organ failure and played the role of significant risk factor for an unfavorable outcome.

Cardiovascular complications in patients with COVID-19 are associated with the existence of cardiovascular diseases, especially with CAD, AH, and atherosclerosis. It is obvious that secondary damage is associated with chronic immune inflammation, direct damage of cardiomyocytes by SARS-CoV-2 that is confirmed by the increase of TnI along with inflammatory markers (interleukin-6, D-dimer, ferritin and LDH). According to F. Zhou et al. [8], the frequency of TnI increase was significantly higher among deceased patients, and can be used as inpatient death predictor (OR 80.07; 95% CI 10.34–620.36; p<0.0001) [5].

Conclusion

In the context of the current COVID-19 pandemic, patients with existing cardiovascular pathology represent special risk group for re-infection and have high risk of post-COVID complications and mortality. Cardiovascular complications significantly aggravate the course of COVID-19 and are associated with the development of multiple organ dysfunction syndrome, and are the main cause of poor outcome.

Conflict of Interest: none declared.

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The contribution of university clinics to the development of domestic medical science. The results of the first Inter-university Conference on Internal Medicine Issues

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Abstract

This review article is dedicated to the history of university science and ways of its development in the future. The results of the analysis of medical universities publication rates in Russia and CIS countries in three leading medical journals between 2019 and 2021 are presented. The possible limitations and problems for university science development are discussed. The results of the first Inter-university Conference on Internal Medicine Issues are summarized. The unity of science, education and clinical practice is the key for the development of university clinics that serve as important platform for domestic clinical science improvement.

Key words: university clinic, publication rates, prospects.

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History reference

University clinics have over a thousand-year history [1]. In the Ancient East (in the Persian city of Gondishapur in the 3rd century Common Era), an academy was founded. This academy included the university, the library and the university hospital. This academy was built to teach philosophy, medicine, theology and other sciences [2]. The Arab caliphate

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had medical student education system, where medical students participated in ward rounds and kept daily records of the patients' condition [3].

In Europe, first academic medical centers emerged during the Middle Ages and the Renaissance [4]. The University of Padua and Vienna conducted patient bedside observations in the 16th century. In the 17th century similar practice had been applied in several of universities in Holland. The Collegium chirurgicum had opened in Berlin in 1724, and two years later surgical training school opened at the famous Charite hospital in Berlin. In 1731, the Paris Academy of Surgery opened. It had trained surgeons since 1743, and for the first time they have been given equal rights with the physicians — graduates of medical universities.

The theory for clinical teaching has emerged in the second half of the XVIII century, when students not only attended the demonstration of patients, but also actively participated in patients' presentations, identified and analyzed various disease signs, discussed the diagnosis and gave their treatment recommendations [5].

Currently, foreign university clinics have two main models: collaboration between the university and the clinic; integration of the clinic into the university.

In Russia, the first medical school was established in 1653 by the Streltsy Prikaz, and in 1654 another medical school was opened by the Aptekarsky Prikaz, however, both of them were not higher-educational institutions. The first educational clinic was opened in Russia during the reign of Peter I (at the Moscow land hospital). In 1733 similar clinics opened at the land and admiralty (marine) hospitals in St. Petersburg, admiralty hospital in Kronstadt. The Moscow State University was founded in 1755 according to the project of M.V. Lomonosov and included medical faculty. In 1805, the first clinic of the Faculty of Medicine opened. It consisted of small ward with only a few beds. By 1860, there have already been 8 universities with faculties of medicine in other Russian cities [6].

In the 1930s all university clinics of the Soviet Union were transferred to medical universities, and clinical bases were transformed into regional, republican and all-Union hospitals or specialized medical centers [1]. When medical faculties gained independence and were transformed into medical universities or academies of the Ministry of Health, university clinics started active clinical and scientific work. Those medical faculties that did not separate from universities, in most cases do not have their own clinics. These universities subordinate to the Ministry of Science and Higher Education of the Russian Federation, and its students also conduct patient bedside observations, however the relationship between clinical base and university is regulated according to the contract between these organizations. As part of the bed fund optimization program, some hospitals and research institutes have turned into the clinical bases of medical universities of the Ministry of Health of the Russian Federation and received the status of university clinics.

University clinic, in addition to educational activities has scientific, innovative and clinical programs compared with clinical hospital that mostly perform educational process.

The revival of university clinics in the Russian Federation and other CIS countries has begun at the beginning of the 21st century and is still ongoing.

The analysis of medical universities publication rates in Russian leading journals of internal medicine

Publication of the research results is an important indicator of scientific activity and quality of original works. In order to assess medical universities publication rates, we analyzed articles in three leading medical journals between 2019 and 2021. Data were taken from the official journal websites: "Therapeutic Archive", "Cardiology" and "Cardiovascular Therapy and Prevention". These journals are included into the list of Higher Attestation Commission and are indexed in SCOPUS, as well as have high impact factor. Publications from medical universities were analyzed geographically: Moscow, Saint Petersburg, Russian regions and CIS countries. According to open sources, there are 7 medical universities and medical faculties in Moscow, 6 medical schools in Saint Petersburg, 84 medical universities and faculties in Russian regions, and 27 medical schools in CIS countries.

The "Therapeutic Archive" is one of the oldest Russian clinical journals. The editor-in-chief of the journal is academician Chazova I. E., 230 articles on average are published annually in the journal. The total publication rate from medical universities was 61.5%. It is noteworthy that 35.2% of publications were from Moscow universities, 19.7% — from Russian regions, 6.6% — from Saint Petersburg. Only

4 articles from CIS countries were published in this journal in 4 years that is 0.6 % from the total number of publications.

The "Cardiology" journal has also been published since the second half of the 20th century and is considered one of the leading journals in the field of cardiology. The editor-in-chief is academician Belenkov Yu. N. About 150 articles are annually published in the journal. The total publication rate was 48.6 %. The number of publications from Moscow and Russian regions was comparable — 19 % and 20.7 %, respectively. Articles from Saint Petersburg accounted for 3.4 %, while 5.5 % of publications were from CIS countries.

The "Cardiovascular Therapy and Prevention" has significantly developed over the past years. Despite its relatively short history, the journal has high impact factor among domestic medical journals. The editor-in-chief is academician Drapkina O. M. About 130 articles are published annually by the journal. The total publication rate from medical universities was 49.7 %. The number of publications from Russian regions was 28.8 % that is almost two times higher compared to the number of articles from Moscow (15.8 %). The number of articles from Saint Petersburg and the CIS countries was comparable — 2.2 % and 2.9 %, respectively.

In general, average publication rate of medical universities in all three journals was 53.4 % that was every second article. At the same time, publications from Moscow made up to 23.5 %, from the Russian regions — 22.9 %. The publication rate of medical universities in three journals was 4 %, and from the CIS countries — 3 %.

Limitations for the development of the university science

However, experts point the existing limitations for the development of university clinics. They can be divided into three areas:

1) financing;

2) lack of personnel and educational process intensity;

3) the quality of scientific research.

Funding for university science consists of the following sources:

— budgetary and non-budgetary funds of the university;

— grants, including subsidies for students;

— funds from medical and pharmaceutical companies for clinical trials.

We conducted a survey among experts from Moscow, St. Petersburg, Saransk, Kursk and Omsk on the contribution of each of the above items of scientific research funding. To date, 47 % of funding consists of international studies sponsored by pharmaceutical companies. At the same time, in 31 % of cases the researches supported by various grants. Budget financing was at the third place (8.5 %). In total, 13.5 % of researches are financed by the management of medical universities, including extrabudgetary funds in 5 % of cases. These numbers can vary significantly between universities.

It should be emphasized that scientific research is carried out both as initiative (up to 25 %) and as international cooperation (6.5 %).

Experts point out that research funding is not high enough. Two main aspects can play an important role: lack of financing of our own research base and modest salaries of academic personnel.

Another problem is lack of personnel and the intensity of educational process. It should be emphasized that the main responsibility for the academic staff is the organization of educational process. The combination of this work with large advisory and lecture activity limits scientific activity. This is how burnout syndrome and employee turnover arise, and there is also lack of young specialists due to insufficient prestige of scientific and pedagogical work. It should be noted that in recent years the number of state-funded places in postgraduate studies has increased.

Another problem is the quality of scientific research that is affected by the above-mentioned personnel and financial problems. There is the need to improve the scientometric abilities among academic personnel and students.

Interuniversity conference as the platform for the experience exchange and incentive to improve university science

Considering the potential and prospects of university science, the Inter-university online Conference on Internal Medicine Issues was organized on June 9–10, 2022. The participants from 7 countries (Russia, Belarus, Kazakhstan, Uzbekistan, Kyrgyzstan, Turkmenistan and Tajikistan) took part in this event. The scientific program included 4 symposia on the issues of cardiology, internal diseases and its co-

morbidity that were allocated for the professors and academic personnel. Two symposia were organized for young scientists, where 14 speakers presented the results of their researches. Young scientists who presented their works also moderated these symposia. It is gratifying that all the reports were based on the results of original researches. The presentations were followed by lively discussion among experts and young scientists. A peer-reviewed collection of conference abstracts has been published and included 60 abstracts from 52 medical schools and faculties of medicine from the listed above countries. It can be found online at the Scientific Electronic Library. The event organizers hope that this initiative will be supported, and the format of this annual conference will expand in the future.

Prospects for the university science development

University clinics provide an opportunity for successful interaction between teachers from medical universities and healthcare workers from the clinics [1]. Therefore, teachers can stay in touch with practical medicine, and clinicians can contribute to educational, medical, diagnostic and scientific processes of medical schools.

The combination of practical medicine and educational processes can significantly improve both the quality of education and healthcare provided for patients. Today, the university clinics productivity is primary associated with the following aspects [7]:

- patient-centered care;
- integrated team approach;
- high quality of medical care, implementation of effective innovative medical technologies.

Thus, the unity of science, education and clinical practice is the key for the development of university clinics that serve as an important platform for the development of domestic clinical science.

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Dr. Aronow's career path

The Cardioprogress Foundation presents the excerpts from the memoirs of the International Journal of Heart and Vascular Diseases journal editorial board member Wilbert S. Aronov, a cardiologist, professor of medicine, member of the FACC, FAHA, FACP, FCCP, FASPC, AGSF, FGSA. Dr. Wilbert Solomon Aronow was born in New York City on October 30, 1931. His parents were Russian Jewish immigrants. His grandparents were rabbis in Russia. Doctor Aronov dedicated his professional career to medicine.

When I was in high school, I watched his father die at home from metastatic colon cancer for 2 years. I was determined then to become a physician and do research on preventing illness.

I graduated from Harvard Medical School in 1957 and was inspired by the outstanding teachers and researchers there to have a professional career dedicated to teaching and research in addition to providing excellent clinical care. During my career, I have been a Professor or Visiting Professor at 22 medical schools, a Chief of Cardiology, and a Director of Cardiology Research at 3 medical schools. I am currently Professor of Medicine and Director of Cardiology Research in the Department of Cardiology, Westchester Medical Center, and NewYork Medical College.

I have edited 20 books on cardiovascular disease including 6 editions of Tresch and Aronow's Cardiovascular Disease in the Elderly. I am author or coauthor of 1,657 papers, 210 book chapters in 114 books, 855 commentaries, 50 letters to the editor and 1,187 abstracts and am a presenter or copresenter of 1,565 talks at medical meetings. I have also been on 185 editorial boards of medical meeting. I am proud of having received 70 teaching and research awards.

I have been a member of 4 guideline committees including being a coauthor of the 2010 American Medical Association guidelines for heart failure, a cochair and first author of the 2011 American College of Cardiology/American Heart Association expert consensus document on hypertension in the elderly, a coauthor of the 2015 American Heart Association/American College of Cardiology/American Society of Hypertension statement on treatment of hypertension in patients with coronary artery disease, and a coauthor of the 2017 American College of Cardiology/American Heart association guidelines for the management of patients with hypertension. I am also a coauthor of a 2015 position paper from the International Lipid Expert Forum. I have been a committee member of numerous professional societies and a consultant to numerous government agencies.

However, I am most proud of being a mentor. I try to encourage all of my trainees to be the best they can be in clinical practice, teaching, and research. I am available for them 24 hours a day, seven days a week. They can work with me at my home on weekends or nights. I teach them how to do research and how to critically review a paper. I teach them that negative results are just as important as positive results. Data are more important than the hypothesis. I am always available for current and prior trainees to help them.

I keep focused and motivated to work full time at the age of 90 years because I enjoy very much training physicians to be excellent physicians, teachers, and researchers. Nothing is more enjoyable than seeing my trainees flourish in whatever they do. PubMed for Aronow W. currently lists 1,327 citations. Seeing the names of my trainees on PubMed citations that are cited in prestigious publications is what I am very proud of achieving. The people we train are our future.

Author Guidelines

Manuscript publication rules
in the International heart and vascular disease journal

Edit from December, 2021

Disclaimer: The rules came into effect from December 2021. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

The *International heart and vascular disease journal* has been published since 2013. It is official journal of the Cardioprogress Foundation. The target audience of this peer-reviewed journal is cardiologists and internal disease specialists. The journal is primarily focused on questions of epidemiology, prevention, and cardiac pharmacotherapy. It also publishes lectures and literature reviews on various problems of modern cardiology, reports on new diagnostic methods, and other information which is important for the practitioners.

The General criteria for the publication of articles in the International heart and vascular disease journal are the relevance, novelty of the material and its value in theoretical and/or applied aspects.

The languages of publications are Russian and English. Journal is peer-reviewed, with multistage editing. Editorial board is presented by the leading cardiologists from different countries and Russia.

International heart and vascular disease journal aims to ensure that its publications fulfill the requirements of international publishing standards, such as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, by the International Committee of Medical Journal Editors, ICMJE (http://www.icmje.org), and the recommendations by the Committee on Publication Ethics, COPE (http://www.publicationethics.org.uk).

All clinical trials should be performed and described in full accordance with the CONSORT standards (http://www.consort-statement.org), observational research — STROBE (http://www.strobe-statement.org), systematic reviews and meta-analyses — PRISMA (http://www.prisma-statement.org), diagnostic accuracy — STAR (http://www.stard-statement.org).

I. The International heart and vascular disease journal accepts the following manuscripts:

1) *Original papers* present the results of clinical studies. The word limit is 3.000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5.000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

3) *Literature reviews* are focused on more specific topics, compared to lectures. The word limit is 4.500 (including references, tables, and figure legends). The maximal reference number is 50. The unstructured abstract is up to 150 words.

4) *Clinical case* is a brief report on a complex diagnostic problem and its solution, or a description of

a rare clinical observation. The word limit is 600 (including references, tables, and figure legends). The maximal number of references is 5. No abstract is required.

5) *Clinical opinion* informs the readers on the topics of cardiovascular medicine and related disciplines. The word limit is 2.500 (including references, tables, and figure legends). The maximal number of references is 15.

The journal accepts for publication original phase 2, 3 and 4 clinical studies. Literature reviews should be based on sources not older than 5 years.

II. Information about the article, which includes the following sections, is combined into a single file "letter (cover)":

1) the manuscript is not under consideration in another edition; 2) has not been previously published; 3) contains a full disclosure of the conflict of interest; 4) all authors meet the criteria of authorship, it was read and approved; 5) the author (s) are responsible for the power of attorney submitted in the manuscript materials. 6) all contact information of the author responsible for correspondence; 7) information about previous publications of the authors on the same topic or pre-publication.

If the manuscript is a part of the thesis, it is necessary **to specify** the estimated terms of thesis defense.

The "letter of direction (accompanying)" should be made out on one or two sheets. Using the form of the official institution-at the choice of the author's team. In the address: "to The chief editor of the Russian cardiology journal, academician of RAS, Professor Oganov R. G.". The signatures of **all authors** should be placed at the bottom.

"Directional (cover) letter" is scanned. File format. jpeg attached as an additional file of the manuscript.

The absence of a letter or incomplete text of the letter (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

III. Registration on the Website and information about the authors.

1. **Any of the authors can submit an article to the journal.** Usually it is the one who then conducts correspondence with the editorial office and to whose mail notification letters come (when submitting a manuscript through the site, you can choose to send notifications to all authors).

The author registers on the site, entering his full name. In the form to be filled in when submitting an article, all authors and all additional information (places of work, positions, academic titles, institutions, ORCID — all authors) are indicated.

If the author has several places of work, it is written: 1. "The name of the institution..." 2. "Name of institution."... The name of the institution is written in abbreviated form, for example, Moscow state University, Moscow. Brackets are not put.

How to fill in the article metadata: all data that is entered in the "article metadata" must exactly match the data specified in the text of the article!

1. Authors ' names (you can not write in full, the format of the journal provides for the publication of names and initials. Therefore, in the "Windows", where the name and patronymic of the authors are written in capital letters with a dot (example: A.).

2. Names of institutions (write the official name. At the same time — there is a reduction of Federal, STATE, etc.; the quotation marks are placed; Ministry of health of Russia, a city without the letter G.

3. Positions and titles (using traditional abbreviations: PhD, senior researcher, leading researcher, PhD, C.b.N., MD), head reduces to the head., then write the full name of the laboratory/Department / Department; Director, head, Professor — is not reduced.

4. The order of the authors. Authors ' priority should be entered into the system in accordance with the order of the article. The movements are made by small arrows "top" / "bottom", which are located under the data of each of the authors. The data of the author responsible for the correspondence, put a dot in a circle denoting this information. Other authors point do not put.

5. Summary. Sections of the abstract should exactly match the sections prescribed In the rules for authors. If the sections are not correct, the Editors will ask to correct them. What the authors are currently publishing on the site will then be included in all systems after the final publication. Be careful!

6. Making literary references. Submitted article will not be reviewed until the correction of literary references in accordance with the rules for authors is made. The authors "forget" and somewhere to remove point (such inconsistencies can be corrected in the Revision), but if the design literature is radically different from what is required or present hyperlinks,

the Editors will not start with the article to eliminate errors.

7. Keyword. They are written with a small letter, separated by a semicolon. At the end put a point. In the text of the article the keywords are written separated by commas.

A file is prepared separately in Word, which is then sent as an additional file. The file must contain:

1. Title page of the manuscript. The title of the manuscript is written in capital letters, without hyphenation, in bold. Initials and surnames of authors-Ivanov I. I., Petrov P. p. the full name of organization (s) from which (s) there was a manuscript, the city, the country is Given. Footnotes are in Arabic numerals after the authors ' names and before the names of institutions.

Example of design:

THE PREVALENCE OF RISK FACTORS OF NONCOMMUNICABLE DISEASES IN THE RUSSIAN POPULATION IN 2012–2013. THE RESEARCH RESULTS OF THE ESSE-RF

Muromtseva G. A. [1], Kontsevaya A. V. [1], Konstantinov V. V. [1], Artamonova G. V. [2], Galaganova T. M. [3],...

[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

2. Information about the authors, where indicated: full name, place of work of all authors, their positions, ORCID; full contact information is required for one (or more) of the author and includes e-mail, available phone number.

All members of the group of authors should meet all four criteria of authorship set forth in the ICMJE recommendations: 1) concept and design development or data analysis and interpretation, and 2) manuscript justification or verification of critical intellectual content, and 3) final approval for publication of the manuscript, and 4) consent to be responsible for all aspects of the work, and assume that issues relating to the thoroughness and diligent execution of any part of the study submitted are duly investigated and resolved. This information should also be contained in the document.

If the submitted material has authors who do not meet the criteria of authorship, but have made some contribution to the work, they should be listed in this document and at the end of the article in the section of Acknowledgements.

3. Information on conflict of interest / funding.

The section contains the disclosure by all authors of possible relations with industrial and financial organizations that may lead to a conflict of interest in connection with the material presented in the manuscript. It is desirable to list the sources of funding for the work. If there is no conflict of interest, it is written: "Conflict of interest is not declared." Information on the existence of a conflict of interest should also be reflected in the Conflict of interest section at the end of the article.

4. Information about grants. Should be mentioned at the end of the article in the section Acknowledgements and at the end of the section Material and methods — with a full description of the role of the source of funding in the performance of work (design, information collection, analysis, data interpretation, etc.).

5. Information and ethics in the study.

Example of design:

The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

This information should also be reflected in the Material and methods section of the article.

All additional information (permits, questionnaires, etc.) can be requested from the authors in addition to the preparation of the work for printing.

6. Information on overlapping publications (if available).

7. Copyright. The use of any material (tables, figures) marked with a copyright icon in the article should be confirmed by a special permission from the author or publisher.

8. Information about the obtained consent in patients for the study.

Obtaining consent from patients for the study should also be reflected in the Material and methods.

9. For all clinical trials: information about the registration and placement of data on the study in any public register of clinical trials. The term "clinical study" refers to any research project that affects people (or groups of subjects) with/or without a compar-

ative control group, studies the interaction between interventions to improve health or the results obtained. The world health organization offers the primary register: International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html). The clinical study is considered to be reliable in a group of more than 20 patients.

10. The number of words in the article (excluding summaries, sources of literature, figure captions and tables), the number of tables and figures.

The absence of an information file or incomplete text (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

IV. Manusctipt submision check-list

Since the main file of the manuscript is automatically sent to the reviewer for» blind review», it should not contain the names of the authors and institutions. The file contains only the following sections:

1. Article title
2. Summary with key words
3. List of abbreviations
4. Text
5. Acknowledgements (if any)
6. List of references
7. Tables, figures (if they can be embedded in the text of Word format).

The article title is written in capital letters (PREVALENCE of RISK FACTORS...), the end point is not needed. The title should clearly reflect the purpose of the work.

Summary with key words-sections are drawn up each with a separate line, highlighted in bold. The abstract should contain only those sections that are described in the rules for authors. For example, there is no section "Relevance" in the summary. The authors prescribe the relevance of their work in the introductory section of the manuscript.

List of abbreviations — when compiling a list of abbreviations to the article, including text, tables and figures, only those used by the author 3 or more times are included. Usually shrink often used in manuscripts of the terms (e.g., hypertension, CHF FC) and title of clinical trials (SOLVD, TIMI, HOPE).

The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

Abbreviations in the list of abbreviations are written in alphabetical order, separated by commas, in solid text, using "dash". **Example of design:** BP-blood pressure, HR-heart rate.

Text — the text of the manuscript of the original works should be structured: Introduction, Material and methods, Results, Discussion and Conclusion. The text of reviews and lectures can be unstructured.

Text is printed on A4 sheet, font size — 12 pt, line spacing — 1.5, margins 2 cm on all sides. The system of SI units is used for processing the material, the% sign is put through a space from the number, the value of p is written with a semicolon: $p < 0.0001$; the value of n is written with a small letter (n=20); signs >, <, ±, =, +, — when numerical values are written without a space; the value of "year" or "year" is issued — 2014 or 2002–2014.

The article should be carefully verified by the author (s). The authors are responsible for the correctness of citation, doses and other factual materials.

Introduction — it is necessary to describe the context and prerequisites of the work (what is the essence of the problem and its significance). It sets certain goals or describes the object of the study, or a hypothesis that needs to be tested by comparison or observation. Only those sources that directly indicate the problem are cited.

Statistics — all published materials are reviewed by an expert in statistics and must meet "Uniform requirements for manuscripts submitted to biomedical journals" (Uniform Requirements for Manuscripts Submitted to Biomedical Journals, Ann Intern Med 1997, 126: 36–47). In the preparation of the statistical part of the work it is recommended to use special guidelines, for example, the European journal of cardiology: www.oxfordjournals.org/our_journals/eurheartj/for_authors/stat_guide.html

Statistical methods are described in detail in the Material and methods section.

Acknowledgements — all participants who do not meet the authorship criteria should be listed in the Acknowledgements section, which is located at the end of the article before the Literature section.

Making graphs, diagrams and drawings — tables and figures should provide the reader with visual information, be interesting and educational. They should be placed after the text of the article, as the reviewer and editor look at the manuscript as a whole. However, to print in the journal (at the stage of creating a layout) graphics, diagrams and drawings are required in electronic form in the formats "MS Excel", "Adobe Illustrator", "Corel Draw", "MS PowerPoint", photos with a resolution of at least 300 dpi.

The names of the graphs and figures, as well as notes to them should be placed under the figure/graph or placed at the end of the article.

These files are referred to as additional files. Figures should not repeat the materials of the tables.

Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

Abbreviations should be listed in a footnote below the table in alphabetical order (for tables its list of abbreviations!).

Each first mention of a figure or table in the text is highlighted with a yellow marker. If a reference to a figure or table is included in the sentence, the full spelling of the word «figure 1», «table 1» is used; if the words are enclosed in brackets, the abbreviation is used (Fig. 1), (table. 1).

Providing the main file of the manuscript with the names of the authors or institutions is the basis for refusal to accept the manuscript for consideration.

V. The list of references.

In the form to fill in when submitting the article provides a list of cited literature (section — Literature).

Literary references are listed in the order of citation in the manuscript. The text refers to the serial number of the cited work in square brackets [1] or [1, 2]. Each link in the list is on a new line. All documents referred to in the text should be included in the list of references.

References to works that are not in the list of references and Vice versa, references to unpublished works, as well as to works of many years ago (>10 years) are not allowed. The only exceptions are rare highly informative works. Especially close attention to this item, please pay to those authors who submit "literature Review".

The bibliographic description contains the names of the authors up to three, after which, for domestic publications should indicate "et al.", for foreign — "et al." When citing articles from journals indicate in the following order the output: the name and initials of the authors, the name of the source, year, volume, number, pages (from and to). When citing articles from the collections indicate the output: name, initials, title, title of the collection, place of publication, year of publication, page (from and to).

If you want to make a quotation of the authors ' names in the text, you must specify the name of the first author with the initials, the year of work. Example design: Smith AA, et al. (2018).

With the purpose of increase of citation in the journal is the transliteration of Russian sources with the use of the official languages in the following order: the authors and the journal title is transliterated in the Latin alphabet, and the name of the article is semantic transliteration (translation into English). The name of the source where the work is published is transliterated in Latin if the source (journal) does not have an official name in English).

All Russian-language sources of literature should be presented in the transliterated version of the model given below.

The author (s) are responsible for the correctness of the data given in the references.

The list of references should correspond to the format recommended by the American National organization For information standards (national Information Standards organization — NISO), adopted by the National Library of Medicine (NLM) for databases (Library's MEDLINE/PubMed database) NLM: http://www.nlm.nih.gov/citingmedicine Oh? The names of periodicals may be abbreviated. Usually this

form of writing is accepted by the publisher; it can be found on the website of the publisher, or in the list of abbreviations Index Medicus.

Mandatory all articles DOI specified, all books ISBN. References to dissertations, patents, theses and any collections without output and ISBN are not accepted.

Examples of link design:

Article citation:

Smith A, Jones B, Clements S. Clinical translation of tissue-engineered airway. Lancet. 2008;372:1201–09. doi:10.00000/0000–0000-.

Russian-language sources with transliteration:

Bart BYa, Larina VN, Brodskyi MS, et al. Cardiac remodelling and clinical prognosis in patient with chronic heart failure and complete left bundle branch block. Russ J Cardiol. 2011;6:4–8. Russian. Барт Б. Я., Ларина В. Н., Бродский М. С., и др. Ремоделирование сердца и прогноз больных с хронической сердечной недостаточностью при наличии полной блокады левой ножки пучка Гиса. Российский кардиологический журнал. 2011;6:4–8. doi:10.15829/1560-4071-2011-6-4-8.

Book:

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. Russian. Шляхто Е. В., Конради А. О., Цырлин В. А. Вегетативная нервная система и артериальная гипертензия. СПб.: Медицинское издательство; 2008. ISBN 0000–0000.

Chapter:

Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger; 1990. p.398–420. ISBN 0000–0000.

Russian chapter:

Diagnostics and treatment of chronic heart failure. In. National clinical guidelines 4th ed. Moscow: Silicea-Polygraf; 2011. pp.203–93. Russian Диагностика и лечение хронической сердечной недостаточности. В кн: Национальные клинические рекомендации. 4-е издание. М.: Силицея-Полиграф; 2011.сс.203–96. ISBN 0000–0000.

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

All sources of literature are checked for correctness through the system of the Russian electronic library. Significant errors in citation or duplication of the source are the reason for the return of the manuscript to the authors for revision.

VI. Preparation of manuscript.

The author prepares the following documents to upload the manuscript to the site:

The main file Is the text of the article (the system renames it after loading, so it does not matter how it is called).

Additional files-Directional (accompanying) letter, Information file with the Title page, information about the authors and disclosure of conflicts of interest, files with pictures.

For more information on placing articles on the website you can read http://cardiovascular.elpub.ru/jour/announcement

VII. Copyright and publishing policy.

This section regulates the relationship between the editorial Office (Publisher) of *International heart and vascular disease journal* (the "editorial Office") and the author or group of authors who submitted their manuscript for publication in the *International heart and vascular disease journal* (the "Author").

The author, by sending the article to the Editor, agrees that the editorial Board of the journal shall be transferred to the exclusive property rights to use the manuscript (transferred to the Editorial Board of the journal material, including such protected objects of copyright as photos of the author, drawings, diagrams, tables, etc.), including the reproduction in print and on the Internet; distribution; translation into any languages of the peoples of the world; export and import of copies of the journal with the article of the Author for distribution, to bring to the public.

The editorial Board reserves the right to reduce and edit the materials of the manuscript, to carry out scientific editing, to reduce and correct articles, to change the design of graphs, drawings and tables to bring into line with the design of the journal, without changing the meaning of the information provided.

When using the article, the editors have the right to supply it with any illustrated material, advertising and allow third parties to do so.

The editorial Board has the right to assign the rights received from the Author to third parties and has the right to prohibit third parties from any use of materials published in the journal for commercial purposes.

The author guarantees that he has exclusive rights to use the submitted material. In case of violation of this guarantee and the presentation of claims to the editorial Board, the Author independently and at his own expense undertakes to settle all claims. The editorial Board is not responsible to third parties for violation of the Author's guarantees.

The Author retains the right to use the published material, its fragments and parts for personal, including scientific and teaching purposes.

The Author transfers the above rights to the Editors without limitation of their validity period, in the territory of all countries of the world without limitation, including the territory of the Russian Federation.

The rights to the manuscript are considered to be transferred By the author of the editorial Office from the moment of sending an information letter about the acceptance of the manuscript to the press.

Reprinting of materials published in the journal by other individuals and legal entities is possible only with the written permission of the editorial Board, with the obligatory indication of the journal name, number and year of publication.

The editors are not responsible for the accuracy of the information provided by the Author.

The author, sending the manuscript to the Editor, gives permission to use and process personal data.

The editorial Board reserves the right to reduce and correct the articles, to change the design of graphs, figures and tables to comply with the standard of the journal, without changing the meaning of the information provided. In case of untimely response of the author (s) to the request of the editorial Board, the editorial Board may at its discretion make changes to the article or refuse to publish.

Sending to the editor of works that have already been sent to other publications or printed in them is absolutely not allowed. The editors are not responsible for the accuracy of the information provided by the authors. Articles sent in violation of the rules of registration are not accepted by the editorial Board for consideration.

VIII. The procedure for rewiewing manuscripts

1. The manuscript should be sent in electronic form to the Editor through the website — http://www.heart-vdj.com. The manuscript should be drawn up in accordance with these requirements for scientific articles submitted for publication in the journal.

2. The author is sent a notification letter of receipt of the manuscript with the number (ID), which will be used in subsequent correspondence. The author can track the stages of work on his manuscript through the site. Since the process of bringing the manuscript to the necessary standards takes enough expert time, the payment for the initial review of the article was introduced, which the author (s) are required to carry out after the article is posted on the site.

3. The manuscript must pass the primary selection: the Editorial Board has the right to refuse publication or send comments to the article, which must be corrected by the Author before reviewing.

— checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

— Manuscripts are checked in the "Antiplagiat" system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

4. All manuscripts submitted to the journal are sent to one of the permanent reviewers or an independent expert according to the profile of the research.

5. The review process is anonymous both for the Author and for the reviewers. The manuscript is sent to the reviewer without the names of the authors and the name of the institution.

6. The editorial Board informs the Author of the results of the review by e-mail.

7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

8. If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the ar-

ticle or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

9. If the reviewer makes a conclusion about the impossibility of publication of the article. The author of the reviewed work is given the opportunity to read the text of the review, if he does not agree with the conclusions of the reviewer. In case of disagreement with the opinion of the reviewer, the Author has the right to provide a reasoned response to the Editor. The article can be sent for re-review or for approval to the editorial Board. The editorial Board or its authorized editor shall send its response to the Author.

10. All manuscripts that have been reviewed and evaluated by an expert in statistics are submitted to the editorial Board, which decides on the publication. After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

11. The decision to publish a manuscript is made solely on the basis of its significance, originality, clarity of presentation and compliance of the research topic with the direction of the journal. Reports on studies in which negative results are obtained or the provisions of previously published articles are challenged are considered on General grounds.

12. Original reviews are kept in the Editorial office for 5 years from the date of publication.

13. In case of a decision to refuse to publish an article, its archive copy remains in the electronic system of the editorial Board, but access to it by editors or reviewers is closed.

IX. The manner of publication of manuscripts

1. According to the requirements of the Higher attestation Commission, the journal provides priority for post-graduate and doctoral works, the period of their publication depends on the expected date of protection, which the authors must specify in the primary documents attached to the manuscript.

2. Each issue of the journal is formed by a separate Executive editor appointed by the editor-in-Chief and/or editorial Board. It is the responsibility of the editor-in-charge to select high-quality articles for publication, and he can be guided by both thematic principles and a separate scientific direction.

3. All selected articles are submitted to the scientific editor and proofreader. After creating the layout of the article and editing it, the article will be available to the Author through the site. At this stage, it will be possible to send comments on the text of the article. The author is obliged to send his / her consent to the publication or his / her comments within the established time specified in the cover letter.

4. The editorial office does not send the author's copy by mail or PDF of the article by e-mail, access to the published numbers is open.

Subscription to the printed version is carried out by half a year (through subscription agencies).

X. After the publication in the journal

1. Information on publication is distributed in the following scientific citation databases: Russian science citation index, CYBERLENINKA and others. The article is assigned a DOI index and the full text is publicly available on the journal's website.

2. Information about the publication of the issue is distributed by mailing of The Cardioprogress Foundation and in social networks.

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XII. Position E-log backup (if journal is no longer published)

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XIII. Journal subscription

Information on subscriptions is available on the journal website in the section "Subscription":

XIV. Journal subscription

The name of the journal in English is International heart and vascular disease journal.

Official sites where information about the journal is placed:

http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

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