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Journal of the Cardioprogress Foundation

Familial form of sick sinus syndrome. New views on polygenic origin and prospects for gene therapy

Echocardiographic changes in patients who experienced COVID-19 after 6 and 12 months of hospital discharge

Prevalence and features of dyslipidemia in different populations depending on race/ethnicity, gender and age

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Contents

Editor's Welcome

Dear colleagues!

We present to your attention the next, thirty-seventh issue of the International Heart and Vascular Disease Journal that includes the leading articles, original and review articles, as well as a clinical case study.

The leading article section opens with a paperwork, which reflects new data on the polygenic origin of familial (congenital) forms of sick sinus syndrome (SSS) and approaches to gene therapy of this pathology. The epidemiology of SSS and the acquired (secondary) causes of its clinical manifestations are also described. It also presents the recent advances in gene therapy of SSS and prospects for its development.

The Original Articles section presents three publications. The first article involving 85 patients studies the dynamics of echocardiographic changes after COVID-19, 6 and 12 months after the hospital discharge. Important findings during the follow-up include an increased incidence of hydropericardium, right ventricular diastolic dysfunction of types 2-3, as well as a significant increase in maximal and mean aortic/mitral valves pressure gradients. In the second article, the comparative assessment of the psycho-cognitive status in 223 elderly patients with atrial fibrillation and comorbid CVDs depending on the presence of post-covid syndrome was carried out. Mixed anxiety–depressive disorder with comorbid pathology was found to occur in 49-61% of cases, with a higher frequency in patients with COVID-19. In the third paper, a three-year prospective study determined the role of complex correction of potentially modifiable risk factors for atrial fibrillation on its primary development in comorbid patients with abdominal obesity and atrial premature complexes. In comorbid patients, a reduction in the actual occurrence of atrial fibrillation, compared to the predicted one, was observed only in patients with comprehensive correction of all potentially modifiable risk factors. The necessary condition was to maintain the target values for 2 or more years.

The Review Articles section presents two works. An article by Siberian scientists showed that chronic stress factors are interlinked with cardiovascular diseases through chronic physiological conditions. Over the past three decades, an evidence base has been formed on the key role of psychosocial factors in the occurrence and development of cardiovascular pathology. The authors have shown that unconventional risk factors can justify more than half of the variability in the detection of CVDs. The second article discusses the age-related influence on the prevalence of dyslipidemia and the mechanisms of cholesterol metabolism disorders with the regard to aging processes. It also presents the data from scientific studies on the prevalence and characteristics of dyslipidemia taking the race, ethnicity, gender and age into account.

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 review

Researchers from Perm University have developed a mathematical model that identifies the least durable places in the coronary stent. This allows to calculate the risk of stent deformation and to prevent an aortic rupture. The researchers look upon the deformation of the wire from which the stents are made on the macro level. On the other hand, their components, i.e. metal grains are considered on the meso level. Thus, the model considers the features of grain boundaries, which, by creating distortions of the crystal lattice, largely determine the deformation of the stent. It is influenced by the size of metal grains, their mutual arrangement and the direction of applied forces. The researchers have identified the most dangerous deformation modes that significantly affect the placement of biomedical stents. In the long term, they will make it possible to perform operations to dilate blocked vessels without risk to the patient.

According to the Materials journal

Cardiovascular diseases at an early age contribute to impaired memory and cognitive function in middle age, according to the US authors. The researchers noted that early onset of CVD is associated with greater hyperintensity in the white matter, temporal and parietal lobes of the brain and with increased mean white matter diffusion, indicating reduced cerebral tissue integrity. 3146 patients aged 18-30 years were included into the study. The mean follow-up time was 30 years. MRI scan of the brain was performed in 656 participants. The researchers stated that people aged 20-30 years should start preventing CVDs to maintain brain health and delay the onset of cognitive decline.

According to the Neurology journal

Long-term therapy with pioglitazone for type 2 diabetes significantly reduced the risk of dementia in elderly patients. According to recent studies, the drug reduces the likelihood of stroke and its recurrence. Researchers analyzed the Korean National Health Insurance System database from 2002 to 2017 to identify the characteristics of patients in whom pioglitazone had the greatest protective effect. The researchers were able to identify 91,000 patients aged 50 and over with type 2 diabetes and without dementia at the start of the study. 3,467 people received pioglitazone.

According to the Neurology journal

The study by scientists from the University of Helsinki and University College London states that patients hospitalized with bacterial or viral infections have an increased risk of subsequent adverse cardiovascular events. The risk associated with infection increased by 7.87 times in the first month after the admission and remained elevated by 1.47 times during the entire follow-up period. Acute myocardial infarction and death from coronary heart disease accounted for more than a half of ACVE. The analysis showed that severe infections can cause 4 to 6% of ACVE, leading to 150 000 deaths each year in high-income countries.

According to the Circulation journal

Scientists believe that genetic diseases can create a predisposition to infertility and other diseases. They sequenced exomes from 197 women between the ages of 18 and 40 with a cause-unidentified infertility. In 6.6% of the participants, they found clinically relevant gene variants that were likely to cause pathologies such as heart disease and breast cancer. In total, the researchers identified 14 clinically significant gene variants, including the well-known BRCA1 and BRCA2, associated with a high risk of developing breast and ovarian cancer. The lifestyle changes or medical interventions could at least reduce their risk. The researchers concluded that infertility could be a 'biomarker' for the development of the other pathologies in the future.

According to the England Journal of Medicine

Researchers from the Finnish hospital found that statin therapy within 90 days of ischemic stroke improved the long-term treatment outcomes. The researchers analyzed data from 59 588 patients admitted to the hospitals in Finland with ischemic stroke. All-cause mortality among participants who did not take statins was 74% higher for up to one year and 37% higher for 12 years compared with patients who started taking statins up to 90 days after the ischemic stroke. The authors of the study believe there is a need to develop interventions aimed at the timely prescription of statins to patients after ischemic stroke to improve long-term treatment outcomes.

According to the Stroke journal

Researchers from China conducted a retrospective study of 190,115 patients from the database of the Chinese Association of Cardiovascular Diseases with acute onset of symptomatic arrhythmia in the period from 2015 to 2021. The analysis included only data collected from 2,025 hospitals with chest pain centers certified by the National Chest Pain Centers Program in 322 cities. The study used a time-stratified cross-case analysis.

Exposure to air pollution is associated with the onset of symptomatic arrhythmia within a few hours, new data indicate.

According to the Canadian Medical Association Journal

Familial form of sick sinus syndrome. New views on polygenic origin and prospects for gene therapy

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Absract

This review article presents the new data on the polygenic origin of the familial (congenital) form of sick sinus syndrome (SSS) and the approaches to gene therapy of this pathology. We also provide information concerning the epidemiology of SSS and the acquired (secondary) causes of SSS. The article presents detailed characteristics of the main genes associated with the development of SSS and the mechanisms of ion channel disorders responsible for arrhythmogenesis. Genetic and phenotypic variants associated with the development and clinical course of familial SSS are also described. We also present the latest achievements in the field of SSS gene therapy and prospects for its development.

Key words: sick sinus syndrome, sudden cardiac death, cardiac arrhythmias, pacemaker, gene therapy.

Conflict of interest: none declared.

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Introduction

Idiopathic or congenital (familial) sick sinus syndrome (SSS) is a primary arrhythmogenic (electrical) disease, genetically heterogeneous and associated with the risk of sudden cardiac death (SCD) [1–3]. In 2003, a familial form of SSS with autosomal recessive type of inheritance was described. It is associated with the mutation in the SCN5A gene that results in impaired sodium channel function[4, 5]. The etiology of SSS remains unspecified, and its clinical manifestations are nonspecific, which complicates its diagnosis and adequate treatment [6, 7]. Given the low survival rate (less than 10 %), the identification of patients with high-risk SSS is essential for the prevention of SCD [8].

It should be noted that modern scientific and medical literature often uses different definitions to describe this condition. According to the current version of ICD-11, the term "sinus node dysfunction" is a broader definition than SSS. Usually, only ECG signs of sinus node (SN) damage without clinical symptoms and/or absence of structural heart lesions are referred to as sinus node dysfunction [6, 9].

SSS Epidemiology

Although SSS is more common in the elderly and in people with structural heart disease, its true prevalence in the general population is unknown. According to the available incomplete information, it is approximately 3:5000 in cardiology patients [2], and according to other data, SSS occurs in 1 of 600 patients with heart disease older than 65 years [10, 11]. There have been reports of SSS signs in 6.3–24 % of the patients with electrocardiostimulators (ECS) [12]. According to some data, this syndrome is an indication for ECS implantation in 30–50 % of cases in Europe and USA [13]. SSS is considered to be equally common in men and women. It has been also shown that in patients who come to the clinic for the first time due to heart rhythm disturbances (HRD), SSS is detected in 3 % of cases, and among those suffering from syncope of unclear etiology, this syndrome occurs in every third person [2].

Jensen P.N. et al. (2014) in the prospective study with average 17-yearfollow-up of 20572 participants identified SSS in 291 patients. Incidence increased with age: over 5 years, the relative risk (RR) was 1.73 [95 % confidence interval (CI) 1.47–2.05]; black patients had 41 % lower risk of SSS than white ones (RR, 0.59; 95 % CI: 0.37 to 0.98). The authors prognose an increase in the annual number of new cases of SSS in the United States from 78,000 in 2012 to 172,000 in 2060. The overall annual incidence of SSS in individuals aged 45 years and older has been shown to be close to 1 per 1000. The age- and race-standardized rate of SSS was 0.8 per 1,000 person-years in women and 0.9 per 1,000 person-years in men [14].

Clinical presentation of SSS

Despite the genetic determinism of familial SSS, the manifestation of symptoms, its severity and prognosis, as well as the choice of therapeutic strategies are determined by acquired diseases [4, 6, 9]. Secondary SSS is caused by external (exogenous) factors (pharmacological, metabolic or autonomic) that have a depressing effect on SN function: hyperkalemia, hypercalcemia, treatment with certain medications that reduce SN automatism, etc. [6, 10]. Moreover, SSS is often a remote complication of cardiac surgery [2].

In most cases SSS is asymptomatic [15]. It is characterized by persistent and inadequate sinus bradycardia, episodes of sinoatrial block and/or chronotropic incompetence [1]. Alternating bradycardia and tachycardia, i.e. tachycardia-bradycardia syndrome, is observed in at least 50 % of patients with SSS [16, 17]. Despite great efforts to study the mechanisms of SSS in terms of abnormal automatism, blockade of SN "output" or intraatrial conduction and excitability disorders, this diagnosis remains mainly electrocardiographic [1, 2, 15].

SSS causes bradyarrhythmia with wide clinical spectrum from no symptoms to SCD [7]. Clinical symptoms result from hypoperfusion of target organs [1]. Two main groups of symptoms form the clinical presentation of SSS: cardiac and cerebral. About 50 % of patients have signs of cerebral hypoperfusion: dizziness, fainting, impaired cerebral circulation. During exercise, many patients experience chest pain, shortness of breath, difficulty breathing or excessive fatigue. This condition increases the risk of life-threatening cardiac events: HRD, atrial fibrillation (AF), heart failure, cardiac arrest and stroke [10].

Fainting may be triggered by coughing and abrupt change in head position, as well as by standing up quickly and being in an unventilated room that is caused byvagotonia. Cardiac syncope is characterized by the absence of aura, seizures (excluding cases of prolonged asystole) and usually has short duration

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and stops on its own, but if prolonged may require resuscitation [4].

Elderly patients may have impaired memory and intellect. Progression of bradycardia may be accompanied by the phenomena of discirculatory encephalopathy (appearance or increase in dizziness, momentary lapses in memory, paresis, irritability, insomnia). Due to hypoperfusion of internal organs, oliguria, acute ulcers of the gastrointestinal tract may develop, the symptoms of intermittent claudication and muscle weakness may increase. Cold and pale skin with a severe drop in BP and cold sweats are possible.

SSS also has stages in its course. Usually starting with one of the initial forms, it gradually progresses to an advanced form of SSS [6, 15]. However, there is often a wave-like course of SSS, when patients with initial manifestations of the syndrome are either detected or disappear. Such fluctuations are caused by different reasons — due to the course of the underlying disease, the dynamics of autonomic effects, medications, etc. Depending on the disease features, clinicians distinguish latent, intermittent and manifesting SSS [1]. Binodal disease is considered a variant of severe SSS, which manifests with a combination of SSS and atrioventricular block (AVB).

Depending on the clinical manifestation, the following forms of SSS and their courses are distinguished [1, 4, 6]:

1) Latent form — absence of clinical and electrocardiographic manifestations. SSS is proved by electrophysiological study.

2) Compensated form: ECG manifestations of SSS are detected, but there are no clinical symptoms of the disease.

3) Decompensated form: SSS is manifested by clinical and ECG signs, thus, there is a clear correlation between the severity of clinical symptoms and the severity of bradycardia. Syncope, decreased tolerance to physical activity, development of heart failure, etc. are possible, which are often indications for ECS implantation.

4) Permanent form of AF with previously diagnosed SSS. It often manifests by tachycardic form of AF, requiring drug-assisted HR control, and later as tachycardic cardiomyopathy (CMP) with the signs of heart failure. The CMP may progress to a persistent bradycardic AF with cardiac pauses and (or) Morgany-Edems-Stokes attacks, requiring ECS implantation.

Genetic etiology of SSS

The literature mentions familial clustering of SSS. Both autosomal recessive and autosomal dominant forms have been described [5, 18, 19]. Currently, 22 genes are associated with the development of hereditary SSS [3]. Molecular genetic studies have confirmed that SSS can be caused by mutations in certain genes (Table 1) [5].

CASQ2 and RYR2 receptors

Cardiac calasequestrin-2 (Casq2), localized in the sarcoplasmic reticulum (SR), is a low-affinity and high capacity Ca^{2+}-binding protein, which regulates the ability of SR to depot and release Ca^{2+} in cardiomyocytes [20]. Potential-dependent L-type calcium channels create an initial influx of Ca^{2+} into the cell, which causes RyR2 receptors to release more calcium from the SR in a process known as calcium-induced calcium release. Calsequestrin, the major Ca^{2+}-binding protein in the SR, attaches to the membrane of the SR via RyR2 (directly or indirectly via triadin and junctin) and regulates Ca^{2+} release via the RyR2 channel. It is important to note that calsequestrin, the ryanodine receptor, junctin, and triadin are essential for the normal calcium cycle in myocytes.

Variants with loss of CASQ2 function can lead to catecholaminergic polymorphic ventricular tachycardia (CPVT), bradycardia, and atrial arrhythmias [21]. It has been shown that CPVT is also induced by RYR2 variants and is closely associated with bradycardia [22]. Thus, the detection of SSS and atrial arrhythmias in patients with CPVT indicates the importance of CASQ2 and RYR2 receptors for normal SC functioning.

G protein-coupled inwardly-rectifying potassium channel 4 (KCNJ5)

G-protein activation via a transmitter is a common type of intercellular communication. Typically, the neurotransmitter binds to the seven-membrane receptor outside the cell, resulting in the exchange of GDP for GTP on the inner side of the receptor, which allows the dissociation of heterotrimeric G-protein subunits, which then act as effectors [23].

To modulate heart rate, the Gbg subunit specifically activates the muscarinic acetylcholine potassium channel (KAch) by binding directly to the N- and C-termini of GIRK1 (G protein-coupled inwardly-rectifying potassium channel) and GIRK4 [5]. The

Table 1. **Genes and proteins involved in the development of SSS in humans**

Protein	Genes	Associated cardiac diseases
Calsequestrin-2	CASQ2	SSS/bradycardia, CPVT, atrial arrhythmias
Ryanodine-2 Receptor	RYR2	SSS/bradycardia, CPVT, atrial arrhythmias
G protein-coupled inwardly-rectifying potassium channel 4 (KCNJ5)	KCNJ5	SSS/bradycardia, atrial arrhythmias, Long QT syndrome type 13, Andersen–Tawil syndrome
Signal-Transducing Guanine Nucleotide-Binding Regulatory Protein Beta Subunit 2/5	GNB2/GNB5	SSS/bradycardia, cognitive impairment, cardiac conduction disorders
Sodium channel protein type 5 subunit alpha	SCN5A	SSS/bradycardia, Long QT syndrome type 3, Brugada syndrome, dilated cardiomyopathy, conduction disorders, sudden infant death syndrome
Sodium/calcium exchanger-1	SLC8A1	Conduction disorders, ventricular arrhythmias, Kawasaki disease
Potassium hyperpolarization-activated cyclic nucleotide-gated channel 4	HCN4	SSS/bradycardia, ventricular arrhythmias, Noncompaction cardiomyopathy of left ventricle
Ankyrin-B	AHK2	SSS/bradycardia, CPVT, atrial arrhythmias, arrhythmogenic CMP
Myosin Heavy Chain	MYH6	SSS/bradycardia, coarctation of the aorta, ventricular arrhythmias
Lamin A	LMNA	SSS/bradycardia, dilated cardiomyopathy, conduction disorders
Voltage-Gated Calcium Channel Subunit Alpha Cav1.3	CACNA1D	Sinus node dysfunction and deafness
Short Stature Homeobox Protein 2	SHOX2	SSS/bradycardia, atrial arrhythmias

KAch channel consists of GIRK1 and GIRK4 subunits (Kir3.4, KCNJ5 gene) in the atria and contributes to heart rhythm regulation. Parasympathetic stimulation activates KAch channels, resulting in slowing heart rate and decreasing cardiac contractility [24]. In mice with Girk4 knockout, not only potassium current through IKAch channel but also Girk1 expression were absent, which confirms the fact that Girk4 plays a leading role in the expression and localization of Girk1 on the cell membrane. The KAch channel is rapidly and reversibly inhibited by membrane stretch, making atrial mechanoelectric regulation possible.

Signal-Transducing Guanine Nucleotide-Binding Regulatory Protein Beta Subunit 2/5

Notably, subunits 2 and 5 of the guanine nucleotide-binding proteins (GNB2 and GNB5), which create the beta-subunits of G-protein that interact with GIRK1 and GIRK4, also play a role in the development of SSS. GNB5 variants were reported in patients with sinus bradycardia and cognitive impairment. The GNB2 variant has been more closely associated with cardiac conduction abnormalities — SSS and AVB [25].

In 2019, the GIRK4 variant (W1010C) was first identified in a three-generation family with SSS. Interestingly, the W1010C variant in GIRK4 resulted in an increase in IKAch. This variant of enhanced channel function caused increased parasympathetic tone, causing a familial variant of SSS and hyperpolarization of SN cells [23].

Sodium channel protein type 5 subunit alpha

Recent mutation analysis reports have identified more than 200 different mutations in SCN5A, of which at least 20 mutations are associated with SSS [3]. In addition to variable expression, heterozygous SCN5A mutations have shown an incomplete penetrance. Complex heterozygous SCN5A mutations are associated with a recessive form of congenital SSS [26].

Depolarization of atria, ventricles, and Purkinje myocytes, which causes cardiac contraction, is initially regulated by the Nav1.5 sodium channel (pore-forming, ion-conducting **α**-subunit of the heart sodium channel) encoded by SCN5A. Variants of this gene are involved in a wide range of cardiac diseases, such as Brugada syndrome, congenital long QT syndrome (LQTS), AF, SSS, dilated cardiomyopathy (DCM), etc. [27, 28]. SCN5A variants (usually of the autosomal recessive type) have been associated with SSS and conduction abnormalities in humans [15].

Because SCN5A is not expressed in SN and SN action potentials are independent of SCN5A, primary SSS seems unlikely. However, given that the inability of pulses to conduct into the atrium due to the "exit" blockade has been proposed as a cause of SSS [2], this is a likely explanation for the genesis of SCN5A-associated SSS. In addition, certain genetic variants of connexin-40 (Cx40) with concomitant SCN5A mutations have been shown to result in the atrial arrest phenotype [26].

The SSS phenotype identified in SCN5A variants is usually secondary to Brugada syndrome and LQTS3.

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Thus, it has been shown that out of 41 people with the identified E1784K loss-of-function variant, 39 % had SSS, and almost all (93 %) had LQTS3 [28].

Potassium hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4)

Mutations have also been found in the HCN4 gene encoding the α-subunit of a hyperpolarization-activated, ATP-dependent cation channel, predominantly expressed in the SN, responsible for the pacemaker current — If current [28]. This leads to a decrease in pacemaker current, a consequence of which is a severe sinus bradycardia, in some cases combined with prolongation of QT interval and ventricular tachycardia (VT) of pirouette type.

The ability of pacemaker cells of SN to spontaneously initiate an electrical impulse can be explained by the activation of If current, the current of Na+/K+ depolarization [29]. If is the incoming current during diastolic depolarization (phase 4 of Action Potential (AP)), which is then activated by membrane hyperpolarization (hypothesis of "membrane clock" for SN automatism) through binding to intracellular cAMP, which can be modified by sympathetic and parasympathetic pulses, and thereby modulate HR [30]. If-current can also be regulated by cAMP-activated protein kinase A in the SN [29].

Many studies have shown that of the four members of the HCN channel family, HCN2- and HCN4-based channels are expressed in the SN [31]. Moreover, the HCN4 channel has a higher level of expression, which confirms the leading role of HCN4 in controlling the pacing activity of the SN. HCN4 channels and ß2-adrenergic receptors form a complex required for HCN4 channel regulation [30]. Interestingly, the expression of HCN2 and HCN4 channels has been shown to decrease in SN and increase in the atria and pulmonary veins with age, which may explain the disproportionately higher incidence of SSS in the elderly [11].

HCN4 encodes a Potassium hyperpolarization-activated cyclic nucleotide-gated channel 4, which contributes to the native currents of the pacemaker cells of the SN — If current [31]. More than 150 variants of HCN4 have now been reported [30]. Mutations in HCN4 may cause sporadic and familial forms of SSS [18]. In addition to bradycardia, pharmacological blockade of If and genetic knockdown of HCN4 caused long cardiac pauses [32].

The HCN4 variant (573X) causing HCN4 C-terminal shortening was first identified in a patient with SSS manifesting sinus bradycardia and chronotropic incompetence. In addition, familial sinus bradycardia is associated with C-terminal shortening and loss of cAMP-dependent regulation of HCN4 [29]. The G482R HCN4 variant has been reported in a family with bradycardia and noncompact LV [33]. It has also been shown that 573X HCN4 variant causes suppression of If channel sensitivity to cAMP, decreases maximal rate of pacing cell depolarization of SN and HR both at rest and during exercise. This demonstrates that cAMP-mediated regulation of the If current determines baseline and maximal HR, but is not involved in HR adaptation during physical activity [32].

Sodium/calcium exchanger-1 Precursor (SLC8A1)

The sodium-calcium exchanger (NCX) is a cytoplasmic membrane transmembrane protein that transports Ca^{2+} from the cell in exchange for Na^{+}, which enters the cell (via anti-port mechanism). To do this, the exchanger uses the energy stored in the electrochemical sodium gradient, passing three sodium ions into the cell along the concentration gradient and removing one calcium ion from the cell against the concentration gradient.

The cardiac Na^{+}/Ca^{2+} exchanger (NCX1) plays an integral role in diastolic depolarization, which triggers these recurrent APs [34]. After diastolic Ca^{2+} release from the SR via ryanodine receptors, increased cytosolic Ca^{2+} induces an incoming current through NCX, which accelerates late diastolic depolarization to the AP threshold (a "calcium clock" model for pacemaker cell automatism). In addition, inactivation of NCX1 causes complete cessation of SN activation by generating intermittent pulse activation due to intracellular Ca^{2+} overload [35]. NCX1 has 10 transmembrane helices and four ion-binding sites, one for calcium ions and three for sodium ions [36].

NCX1 functions by providing both incoming and outgoing currents depending on the membrane potential. NCX1 is the main way to extrude ("squeeze out") calcium from cardiomyocytes during the resting membrane potential; the high extracellular sodium concentration allows NCX1 to remove calcium from the cell [35]. In general, NCX promotes myocyte relaxation, indicating the role of NCX1 in the contractile process. In addition, spontaneous release of Ca^{2+}

from pacing cells by RyR2 activates NCX1 at the SR membrane, which then pushes the cell to the minimum threshold to trigger PD [36].

Genetic variants in SLC8A1, which encodes NCX1, cause changes in the calcium cycle, leading to ECG signatures of SSS. However, no cases of correlation of SLC8A1 mutation and development of SSS in humans have been reported so far. At the same time, animal models have shown the main SSS phenotypes with loss of NCX1 function [35].

Ankyrin-2 (ANK2)

Ankyrin-B (AnkB, encoded by ANK2) is a membrane adaptor protein critical for recruitment, organization, and stabilization of ion channels and transporters underlying excitation and contraction coupling, particularly in SN. Variants of function loss in ANK2 are associated with a complex cardiac phenotype, including heart rate variability, CPVT, conduction defects, AF, sinus bradycardia, HF, and arrhythmogenic CMP [5].

Two families with severe SSS were found to have variants of the ANK2 allele, making AnkB the first nonionic protein associated with human SSS [37]. Interestingly, people with AF have decreased expression levels of AnkB and increased levels of miR-34a (an amiRNA associated with cardiac fibrosis). The untranslated region 30 of ANK2 also contains a binding site to miR-34a, suggesting a potential role for miR-34a in atrial electrical remodeling and in the regulation of AnkB expression [38].

Although the results of AnkB clinical studies suggest that ANK2 loss-of-function variants are associated with numerous cardiac diseases, the lack of family history in many of these cases and the overall incomplete penetrance of AnkB-associated disease strongly suggest that additional genetic and/or environmental factors must be involved in the development of the severe AnkB syndrome phenotype [18]. Notably, intense endurance exercise or other genetic variants probably play a role in the development of heart disease associated with variants of ANK2 loss of function [37].

Myosin Heavy Chain (MYH6)

MYH6 encodes the α-subunit of myosin heavy chain (TCM-α), a major component of the sarcomere, a necessary component of muscle fiber for proper heart contraction [39]. The MYH6 myosin heavy chain gene is localized in the long arm of chromosome 14, locus 11.2. The missense variant of TCM-α R721W has been identified in Icelandic populations (0.38 % allelic frequency) and is associated with SSS, and 50 % of carriers of this variant diagnosed with SSS. Carriers of the variant who were not diagnosed with SSS still had a decreased HR and prolonged PR interval [38]. Interestingly, another heterozygous variant R654W of TCM-α was identified in an Australian family with severe but diverse cardiac arrhythmias, including SSS and ventricular fibrillation (VF) leading to HF [39].

Lamin A (LMNA)

Lamins A, B1 and B2 are the main components of the nuclear lamina, which plays a vital structural role in the nuclear envelope [5]. LMNA variants are associated with numerous heart diseases, particularly with dilated CMP. A heterozygous c.357–2A >G splice site variant in LMNA was identified in a proband diagnosed with SSS who had a family history of cardiac arrhythmias and SSS [20]. It was hypothesized that this new variant causes haploinsufficiency because the aberrant mRNA from the mutant allele is likely to decay due to nonsense-mediated mRNA decay. Although no LMNA population variant has been identified regarding SSS, the numerous identified familial variants associated with conduction abnormalities provide a basis for further investigation of the lamin A role in the development of SSS.

C Voltage-Gated Calcium Channel Subunit Alpha Cav1.3 (CACNA1D)

Cav1.2 (α-1C) and Cav1.3 (α-1D) subunits make up the potential-activated cardiac L-type calcium channels [3]. Cav1.3 is expressed mainly in SN, AV node and atrial myocytes [35]. In SN, Cav1.3 plays a pivotal role in pacing cell activity, controlling the incoming current during diastolic depolarization and regulating diastolic Ca^{2+} release from the SR [35].

T-type calcium channels consist of three subunits, Cav3.1, Cav3.2, and Cav3.3, which are encoded by three genes: CACNA1G, CACNA1H, and CACNA1I. The three Cav subunits are responsible for the generation of T-type/low-voltage activated calcium currents (T-currents) [1]. Notably, earlier studies reported the expression of calcium current T-type (I_{CaT}) in SN cells and suggested its contribution to pacemaker cell function [7].

A direct contribution of Cav3.1 channels to cardiac SN automatism and conduction functions has been

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demonstrated through genetic ablation of Cav3.1 channels in mice. Genetic inactivation of Cav3.1 channels causes slowing of SN automatism by decreasing the slope of diastolic depolarization in SN pacing cells [35].

The role of other genes involved in the regulation of SN pacing cell function and phenotyping various manifestations of SSS also continues to be investigated: e.g., short stature homeobox protein 2 (SHOX2), transient receptor potential channel 3 (TRPC3), stromal interaction molecule 1 (STIM1), etc. [3–5].

Genotype-phenotypic variants of SSS

Considering the genetic defects and phenotypic manifestations, 4 types of SSS are distinguished [3]. In most cases, SSS is not inherited [10] and is described as sporadic [2]. When SSS results from mutations in the HCN4 gene, it has an autosomal dominant type of inheritance, which means that one copy of the altered gene in each cell is enough to cause the disease [20]. In most cases, one parent of the affected individual has the disease. When SSS syndrome is caused by mutations in the SCN5A gene, it is inherited by autosomal recessive type, which means that both copies of the gene in each cell have mutations [26]. Each parent of a person with autosomal recessive disease carries one copy of the mutated gene, but usually they have no signs and symptoms of the disease.

Type 1 (autosomal recessive type SSS). Congenital SSS type 1 is caused by a compound heterozygous mutation in the SCN5A gene on chromosome 3p22. Mutation in the SCN5A gene associated with SSS type 1 causes association with the following diseases: thyroid dyshormonogenesis, familial AF, ventricular arrhythmias due to calcium release deficiency syndrome from cardiac ryanodine receptors, Brugada syndrome, cardiac conduction abnormalities with or without dilated CMP [1].

SSS type 1 most often occurs in the elderly and is associated with underlying heart disease or prior heart surgery, but can also occur in a fetus, infant, or child without heart disease or other contributing factors. ECG usually shows sinus bradycardia, SN arrest and/or sinoatrial block, prolonged QT interval, and AVB. In addition, a combination of episodes of atrial tachycardia and sinus bradycardia ("tachycardia-bradycardia syndrome") is common. Manifestation of SSS type 1 occurs in fetal state, in infancy or early childhood.

Online Mendelian Inheritance in Man (OMIM) is a medical database that collects information about known diseases with a genetic component and the genes responsible for their development. SSS type 1 is characterized by the following cardiovascular symptoms from the clinical synopsis, according to OMIM: sinus bradycardia, atrial arrest, SN arrest, sinus arrhythmia, absence of P waves, increased QRS duration, sporadic idioventricular rhythm, increased Hys-ventricular conduction time, no structural heart defects, first degree heart block or conduction delay can be observed in heterozygous mutation carriers.

Type 2 (autosomal dominant type SSS or SSS type 2 with "noncompact" LV and/or dilatation of the ascending aorta or familial AF with bradyarrhythmia) [33]. The responsible gene associated with SSS type 2 is HCN4, located in chromosome 15q24 [31]. Electrocardiographic phenotypes are sinus bradycardia, SN and/or sinoatrial arrest, and AVB. Tachycardia-bradycardia syndrome is also common. SSS occurs most often in older adults associated with underlying heart disease or prior heart surgery, but can also occur in a fetus, infant, or child without heart disease or other contributing factors. SSS type 2 begins in a prenatal period or at birth. Affected tissues include the heart, and related phenotypes are mitral valve prolapse and LV hypertrophy.

Cardiovascular symptoms of SSS type 2 that occur in the clinical synopsis (OMIM): sinus bradycardia, in some patients — LV hypertrophy, AF, VF, cardiac arrest (rare). Additionally, dilation of the ascending aorta (in some patients) may present. Concomitant cardiac phenotypes are detected in about 7.5 % of cases: mitral valve prolapse, myxomatous degeneration of the mitral valve, LV hypertrophy, biventricular hypertrabecularity, aortic regurgitation, cardiac arrest and VF.

Type 3 SSS most often occurs in the elderly with the background of underlying heart disease or prior heart surgery. At the same time, SSS type 3 can occur in a fetus, infant, or child without heart disease or other contributing factors. Symptoms are often intermittent and/or nonspecific and include dizziness, fainting, and heart failure. Diseases associated with SSS type 3: CHD, venous insufficiency, hypokalemia, atrial septal defect, scapula-peroneal myopathy, distal myopathy, "noncompact" LV. The only effective treatment for symptomatic and irreversible SSS is ECS implantation [12].

Type 4 (autosomal dominant SSS type 4). SSS type 4 is caused by a heterozygous mutation in the GNB2 gene (G-protein beta-2 subunit) in chromosome 7q22.1. The relationship between phenotype and gene is conditional. The inheritance pattern of SSS type 4 in the family is autosomal dominant [25]. SSS type 4 is characterized by early and progressive manifestation of SSS and AV conduction disorder. The following phenotypes associated with SSS type 4 are very rare (1 % of cases): sinus bradycardia, sinoatrial block, chronotropic failure, AVB, paroxysmal AF, syncope. AVB varies from mild to severe. Many require ECS implantation, but no cases of SCD have been reported [25].

Perspectives of SSS gene therapy

ECS implantation is the most effective method for the treatment of symptomatic forms of SSS [13]. Currently, patients with SSS account for the vast majority of cases of ACS implantation [13]. This method improves the quality of life and increases its duration, which is determined by the nature and severity of concomitant organic heart disease, mainly myocardial dysfunction [12]. Currently there are no therapies for the treatment of the primary genetic cause in patients diagnosed with primary or chronic SSS [2, 5]. Despite the successes achieved in the development of implantable ECSs, it is still not possible to solve the problem of a biological pacemaker prototype completely, and the implantable ECSs produced to date are physiological only to a certain degree [12].

In the post-genomic era, an interest in the alternative molecular therapies for patients with SSS has emerged. In recent years, several groups of researchers have explored the possibility of creating a biological pacemaker that would eventually allow the replacement of implantable ECS [40]. Proposed strategies include gene therapy, transplantation of donor excitable myocardium, and delivery of modified embryonic stem cells to the heart.

Fetal and neonatal cardiac cells have been shown to functionally integrate and act as ectopic pacing cells when transplanted into the myocardium of dogs and pigs [41]. Gene therapy approaches include overexpression of beta-adrenergic receptors, inhibition of intrinsic potassium current rectification (IK1), insertion of HCN2 pacing gene into atrium using adenoviral or naked plasma vectors [5]. Another approach to the biological treatment of SSS is the engraftment of embryonic stem cells, which have differentiated, into atrial tissue [34].

A promising direction in the treatment of SSS is considered to be the stimulation of native pacemaker function or the creation of an ectopic pacemaker focus by gene transfer into existing cardiomyocytes or transplantation of pacemaker (including genetically modified) cells into the heart [41]. However, a complete solution to the challenges of creating a biological pacemaker should include a set of interventions to create a complex cellular and molecular structure similar to that of a biological SN.

Calcium-activated potassium channel 4 (HCN4) is known to be involved in cardiomyocyte automatism [28]. TRAM-34 (a selective blocker of HCN4 channels) has been shown to successfully reduce late postdepolarization and inhibit calcium turnover in induced human cardiomyocytes derived from pluripotent stem cells (hiPSC–CM) of patients with CPVT type 2 [42]. It has been shown that injection of TRAM-34 into CASQ2-D307H knockout mice results in a reduction of arrhythmias at rest and during exercise. Thus, TRAM-34, as a selective HCN4 channel blocker, has great therapeutic potential for humans with CASQ2 variants with loss-of-function [42].

Dysfunctional If-current causes an unusual exchange of calcium ions, disrupting the activity of pacemaker cells. If-current-deficient in mice have shown to have defects in pulse generation and conduction, which can be eliminated by a genetic deletion of cardiac muscarinic channels inactivated by G-protein (GIRK4) [23]. Although HCN4 and GIRK4 loss-of-function variants have been seen in SSS, the combination of silencing of both of these genes causes the phenotype of severe SSS associated with an AV blockade and ventricular arrhythmias [31].

The ability of the pharmacological inhibition of the IKACh channel to improve SN function has been demonstrated in a patient with a history of SSS [31]. Suppression of GIRK4 expression in human atrial myocytes effectively reduced IKACh density and, therefore, is a potential tool for the treatment of SSS. Thus, a gene therapy or pharmacological strategy targeting GIRK4 channels could be an important focus for SSS treatment in clinical practice.

HCN4 lentiviral gene transfer has demonstrated the bioengineering potential to allow the use of pacemaker cells. HCN4 transduction restored autonomic rhythm and increased sensitivity to autonomic regu-

lation in HCN4 transduced myocytes [5]. In addition, Myocyte enhancer factor-2 and activator protein-1 with binding sequences located on conserved non-coding sequence 13 (CNS13) are involved in HCN4 amplification through the HCN4 promoter [30] and can be used to activate HCN4 and thereby stimulate pacing activity of SN.

Thus, the problem of creating a biological pacemaker for SSS treatment is partly related to the complexity of genetic abnormalities and partly to the pleiotropy of genes. Many gene variants associated with SSS can exhibit several unrelated phenotypic traits. Currently, the clinical management of patients with SSS is limited to the relief of arrhythmia symptoms. Understanding the complexity of the genetics that contribute to the progression of SSS is for the development of new therapeutic strategies for this complex, life-threatening disorder.

Conclusion

The familial form of SSS is a fairly common disease characterized by a wide range of cardiac manifestations from asymptomatic cases to the development of life-threatening arrhythmias. Given the polygenic origin of SSS, timely genetic testing is necessary, including family members of the proband. In this regard, identification of various gene mutations involved in the genesis of SSS is difficult, especially in when genetic overlap syndrome is present. In recent years, due to advances in genetic research on inherited cardiac arrhythmia syndromes, progress has been made in identifying gene therapy targets and in the development of genotype-specific therapy strategies for SSS. This creates prerequisites for the introduction into clinical practice of effective, safe methods of gene-modifying therap. The development of genotype-targeted pharmacotherapy, as well as functional capabilities of implantable pacemakers improvement as a prototype of biological pacemaker are also of high priority.

Conflict of Interest. None declared.

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Echocardiographic changes in patients who experienced COVID-19 after 6 and 12 months of hospital discharge

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Abstract

Objective. To determine the dynamics of echocardiographic changes in patients who experienced COVID-19 at 6 and 12 months after hospital discharge.

Materials and methods. The study included 85 patients (40 men and 45 women, mean age 50.1 ± 8.7 years) who received inpatient treatment in 2020–2021 for COVID-19 of moderate (n = 49; 58 %) or severe (n = 36; 42 %) course. All patients underwent: general clinical examination with collection of complaints and medical history, physical examination, standard electrocardiography and transthoracic echocardiography.

Results. The dynamics of echocardiographic parameters in the examined patients was not with clinical manifestations after 6 and 12 months. The important findings during 12-month follow-up were the increased frequency of hydropericardium (relative risk (RR) 3.727 at 95 % confidence interval (CI) 2.058–6.749), types 2 and 3 of right ventricular diastolic dysfunction (RR — 9.5 at 95 % CI — 4.33–20.842), significant increases of maximal and mean aortic valve pressure gradients, and mean mitral valve pressure gradient.

Conclusion. It is reasonable to monitor patients with persisting cardiovascular symptoms to prevent severe and

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long-term complications using transthoracic echocardiography after COVID-19.
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Introduction

Currently, along with studies regarding the management of patients with acute phase of coronavirus infection (COVID-19), clinicians are paying attention to the investigation of its long-term concequences. This interest is confirmed by the rapid increase in the number of publications on the problem of post-covid syndrome [1]. Russian experts agree with the definition of post-covid syndrome that is given in the guidelines of the United Kingdom National Institute for Health and Care Excellence. It is defined as the signs and symptoms that develop during or after COVID-19 and last for over 12 weeks andcannot be explained by another cause [2]. Between 10 % and 30 % of patients experience long-term symptoms after SARS-CoV-2 infection, some of which may be related to cardiovascular system [3]. Since cardiovascular diseases are the main cause of death after discharge from hospital [4], there is the need to conduct studies to assess the state of the cardiovascular system after COVID-19 infection. It is important that the techniques used in them are not only informative, but are also available in routine clinical practice.

We investigated the clinical status and changes in echocardiography parameters in patients 6 months after moderate and severe COVID-19 [5]. We followed-up the examined patients to determine the dynamics of symptoms and detect echocardiographic changes 6 and 12 months after hospital discharge.

Methods

The research was conducted in the Specialized Clinical.

Infectious Diseases Hospital located in Krasnodar 6 and 12 months after discharge of patients from the hospital. The study enrolled 85 patients (40 men and 45 women; mean age — 50.1 ± 8.7 years) who received inpatient treatment between 2020–2021 for moderate (n = 49; 58 %) or severe (n = 36; 42 %) COVID-19.

We did not include in the study patients younger than 18 years old or older than 60 years old. We also excluded those with a history of cardiovascular and/or other diseases that could significantly affect study results (coronary heart disease, chronic heart failure, heart defects, atrial fibrillation/ atrial flutter, hypertension, chronic kidney disease ⩾ 3a stage, cancer, alcohol abuse and mental disorders).

All patients underwent: general clinical examination with the collection of complaints, medical history, physical examination, standard 12-lead electrocardiography. Additionally we performed a transthoracic echocardiography by standard technique [6] using "Samsung HS70A" ultrasonic device (Malaysia) with 2.0–4.0 MHz sensor in sectoral scanning mode with color Doppler mapping, pulse, continuous wave and tissue Doppler sonography. Visualization of the heart, measuring the sizes of its structures and cavities were performed in the supine and left lateral position in B-mode and M-mode. Local contractile dysfunction of left ventricular myocardium was assessed in 16 segments, and at least 2 segments were considered diagnostically significant.

A chest computed tomography and the measurement of SARS-CoV-2 IgG and IgM titers were performed in each case.

The study was performed in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki. The local Independent Ethics Committee approved the study protocol. Written informed consent was obtained from all participants before inclusion into the study.

Statistical analysis

We performed the statistical processing of the study results using StatTech v. 2.8.5 (developer — Stattech LLC, Russia). Quantitative indices were assessed for their correspondence to normal distribution using the Kolmogorov-Smirnov criterion. Quantitative indices with normal distribution are described as arithmetic

mean (M) with standard deviations (SD), 95% CI limits. Since data deviated from normal distribution, quantitative data are described as median (Me) with lower and upper quartiles (Q1-Q3). Categorical data are presented as absolute values with percentages. The comparison of two groups quantitative parameters that had a normal distribution was performed using Student's t-test. The Mann-Whitney U-test was used to compare quantitative indicator between two groups that deviated from normal distribution. Qualitative characteristics were compared using the Yates-adjusted x-square test and Fisher's exact test (two-sided). Hypothesis testing for associations between variables was conducted using Pearson correlation coefficient. Statistical significance was set as $p < 0.05$.

Results

All study participants were followed up for 6 and 12 months after the disease. A positive level of SARS-CoV-2 IgM was detected in 47 patients at the 6-month visit and in another 28 patients at the 12-month visit, indicating a recurrent coronavirus infection that did not lead to hospital admission. After the first examination, patients received treatment for chronic heart failure and myocarditis, according to current clinical guidelines.

A general clinical examination of COVID-19 patients revealed the following main signs and symptoms during hospitalization 6 and 12 months after the disease onset (Table 1).

There was a significant regression of a number of clinical manifestations 12 months after the COVID-19 — BP, dyspnea and palpitations rate decreased. Frequency of cardiac arrest, cardialgia, and the lower extremities swelling tended to decrease, but differences in the dynamics did not reach statistical significance.

According to the results of statistical processing none of the presented clinical manifestations correlated with echocardiographic changes in the examined patients.

The main echocardiography data of patients who underwent COVID-19 are presented in Table 2.

The frequency of cardiac complications according to echocardiography in patients who underwent COVID-19 is presented in Table 3.

According to the results, at 12 months after the COVID-19 the relative risk of patients having per-

Table 1. **Number of patients with major clinical signs and symptoms 6 and 12 months after inpatient COVID-19 treatment**

Parameter	During the hospitalization	After 6 months	After 12 months	P2–4	P3–4
Rise of blood pressure > 140/90 mm Hg	68	11	9	0,0001*	0,86
Heart palpitations	64	27	15	0,0007*	0,69
Arrhythmias	21	3	7	0,16	0,47
Chest pain	26	12	5	0,22	0,57
Dyspnea	85	46	21	0,0001*	0,067
Swelling of the lower extremities	46	37	34	0,32	0,95

**Comment. ***$p < 0.05$ using Yates-adjusted x2 test and Fisher's exact test (two-sided).

Table 2. **The results of the echocardiography of the patients after inpatient COVID-19 treatment**

Parameter	During the hospitalization	After 6 months	After 12 months	P2–4	P3–4
LVPWd, mm	42,8 ± 0,8	44,5 ± 1,2	44,4 ± 1,1	0,19	0,91
LV EF, % (by Simpson)	52,9 ± 2,9	60,9 ± 2,7	59,5 ± 2,2	0,06	0,85
IVSd, mm	13,4 ± 0,4	10,9 ± 0,4	10,9 ± 0,4	0,001*	0,30
LV PW, mm	11,4 ± 0,4	10,6 ± 1,7	11,4 ± 1,5	0,17	0,94
STIS, %	34,1 ± 5,1	49,2 ± 4,1	58,7 ± 6,8	0,013*	0,29
STPW LV, %	27,8 ± 5,1	55,7 ± 6,6	62,7 ± 6,0	0,0001*	0,45
AVOA, mm	18,6 ± 0,4	18,5 ± 0,5	17,4 ± 0,5	0,12	0,15
AV MPG, mm Hg	12,1 ± 0,8	16,8 ± 1,2	20,7 ± 1,3	0,0004*	0,04*
AV APG, mm Hg	3,4 ± 0,3	4,4 ± 0,2	4,8 ± 0,5	0,04*	0,81
LV SVI, ml/m^2	23,2 ± 1,6	24,3 ± 2,0	22,8 ± 1,6	0,73	0,76
LV MMI, g/m^2	106,2 ± 6,7	109,5 ± 8,3	97,6 ± 6,2	0,39	0,31
LA VI, ml/m^2	26,4 ± 1,7	26,9 ± 1,6	24,7 ± 1,4	0,39	0,26
RV SVI, ml/m^2	14,2 ± 0,8	11,1 ± 1,3	12,1 ± 1,4	0,19	0,84
RV WT, mm	4,8 ± 0,2	5,5 ± 0,3	5,0 ± 0,2	0,60	0,16
RV EF, % (by Simpson)	51,6 ± 3,9	51,2 ± 3,2	60,1 ± 3,7	0,17	0,03*
RV FAC, %	42,2 ± 2,0	39,1 ± 3,4	42,7 ± 3,1	0,71	0,41
RAVI, ml/m^2	27,3 ± 1,7	31,9 ± 2,3	29,8 ± 2,0	0,17	0,50
RA ESV, cm^2	12,0 ± 0,7	12,9 ± 1,0	13,1 ± 1,0	0,17	0,57
MV fibrous ring velocity (lateral), cm/s	10,1 ± 0,7	12,2 ± 0,6	11,4 ± 0,5	0,21	0,32
MV APG, mm Hg	1,1 ± 0,1	1,6 ± 0,2	2,0 ± 0,2	0,002*	0,10
MV regurgitation, %	17,1 ± 2,1	13,5 ± 1,6	10,1 ± 1,4	0,009*	0,076
TV fibrous ring velocity (septal), cm/s	11,4 ± 0,6	10,7 ± 0,6	10,0 ± 0,3	0,10	0,44
TV regurgitation, %	14,3 ± 2,5	15,6 ± 1,9	14,0 ± 2,0	0,34	0,52
PA diameter, mm	24,8 ± 0,8	28,5 ± 0,9	27,9 ± 0,7	0,003*	0,53
PA right branch diameter, mm	18,8 ± 0,6	20,3 ± 0,6	19,2 ± 0,5	0,50	0,21
MPGPA, mm Hg	19,8 ± 1,9	23,9 ± 1,7	22,2 ± 1,2	0,09	0,46

Comment. n — number of patients,
*$p < 0.05$ using Kruskal-Wallis test.

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Table 3. **Frequency of cardiac complications according to echocardiography in patients who underwent COVID-19**

Parameter	During the hospitalization	After 6 months	After 12 months	P2–4	P3–4
Hypokinesis, n	48	39	31	0,16	0,73
Hydropericardium, n	11	62	41	0,05*	0,63
LVDD types 2–3, n	11	48	9	0,06	0,31
RVDD types 2–3, n	6	68	57	0,0004*	0,25

**Comment. ***p < 0.05 using Yates-adjusted x2 test and Fisher's exact test (two-sided).

sistent hypokinesis was 0,646 (95% CI 0.461–0.905), hydropericardium was 3,727 (95% CI 2.058–6.749), left ventricular type 2–3 diastolic dysfunction — 1.222 (95% CI 0.534–2.798), right ventricular type 2–3 diastolic dysfunction — 9.5 (95% CI 4.33–20.842). Thus, in a year after the COVID-19 the frequency of detection of hydropericardium and diastolic dysfunction of the right ventricle did not decrease, but, on the contrary, increased.

Comparison of echocardiographic parameters in dynamics showed statistically significant increase of maximal and mean pressure gradients on aortic valve from its level during hospitalization to 6 month and further — to 12 month after discharge. Simultaneously, there was a tendency to an increase in the mean pressure gradient on the aortic valve, which reached statistical significance when comparing the index after 12 months with the initial one. There was a tendency to decrease in the amplitude of aortic valve opening.

There was a significant increase in mean pressure gradient in the mitral valve 12 months after discharge.

By the 12 months after hospital discharge there was a significant decrease in interventricular septal thickness with an increase in the percentage of its systolic thickening, a decrease in regurgitation of the mitral valve, as well as decrease in the number of those examined with left ventricular wall hypokinesis. This could indirectly indicate the incidence of myocarditis as COVID-19 complication.

During the observation period the right ventricular ejection fraction and pulmonary artery diameter increased statistically significantly in the examined patients.

Discussion

Only about ¼ of patients who were hospitalized for COVID-19 felt completely cured one year after the SARS-CoV-2 infection [7]. A large study, accounting the presence of symptoms even before COVID-19 developed, showed that the frequency of post-covid syndrome symptoms decreased over time, but persisted in about 1 in 8 of the patients even 2 years after the infection [8].

In our study, patients 12 months after COVID-19 had improved office BP, and the complaints regarding dyspnea and heart palpitations were reported significantly less frequently. Echocardiography parameters changed differently in dynamics. The increased frequency of hydropericardium, diastolic dysfunction of the right ventricle, significant increase of maximal and mean pressure gradients on aortic valve, as well as mean pressure gradient on mitral valve have raised our concerns.

COVID-19 survivors have increased risk of cardiovascular diseases. During the following year, it is several times higher in hospitalized patients, especially in ICU, but complications can occur more frequently even in people who seemed to have fully recovered from a mild infection [9, 10]. Among COVID-19 survivors, within 4 months after infection, the risk of congestive heart failure was about 2.5 times higher compared with those who were not infected [11].

There are still few articles in the current literature presenting echocardiography findings over time in patients who underwent COVID-19 a year ago, and they are not always consistent with each other. According to Ovrebotten T. et al. (2022) dyspnea, fatigue, dizziness and tachycardia in long-term COVID-19 survivors cannot be conclusively confirmed by progressive changes in heart structure and function [12]. One year later, in COVID-19 patients with pneumonia, Yaroslavskaya E.I. et al. (2022) noted increasing changes in ventricular geometry accompanied by worsening of diastolic and systolic left ventricular function, which these authors associated mainly with the development of arterial hypertension and chronic heart failure [13].

In our study, echocardiographic changes were observed in people with no previous significant cardiovascular diseases, which may be associated with decreased elastic properties of the aorta, major arteries, and myocardial damage. These assumptions are consistent with the current understanding of the

mechanisms of cardiovascular lesions in SARS-CoV-2 infection. Possible mechanisms of long-term cardiovascular complications of COVID-19 are believed to include direct and indirect cellular damage mediated by the virus, procoagulant state, immunological response affecting structural integrity of myocardium, pericardium and conduction system, suppression of angiotensin converting enzyme 2 [14]. According to most experts, initially the virus penetrates endothelial cells, causing their inflammation, dysfunction and accelerated apoptosis with the development of thrombosis and rapid progression of atherosclerosis. Further, autoantibodies and immune cells damage many organs, including the heart. Vaccination reduces but does not eliminate the risk of delayed cardiovascular complications [15]. In addition, the researchers cannot exclude the potential risk of antibody-dependent enhancement induced by SARS-CoV-2 in humans.

Conclusions

Given that many millions and presumably even billions of people have been infected with SARS-CoV-2, clinicians are wondering whether the infectious pandemic will be followed by a wave of cardiovascular pathology. Researchers are trying to establish the profiles of people at most risk for cardiovascular disease and complications after COVID-19, the duration of the period of increased risk, and the pathogenesis of the observed pathological changes. Despite the insufficient study of the cardiovascular consequences of SARS-CoV-2 infection, a dynamic follow-up of patients with persisting cardiovascular symptoms and signs to prevent severe and long-term complications, including the use of widely available transthoracic echocardiography, might be beneficial.

Conflict of interest. None declared.

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Comparative analysis of psycho-cognitive status in elderly patients with comorbidities depending on the presence of post-COVID syndrome

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Abstract

Objective. To compare psycho-cognitive status of elderly patients with various comorbidities depending on the presence of post-covid syndrome.

Materials and methods. This observational analytical cohort study included 133 patients with atrial fibrillation and various comorbidities (coronary artery disease, arterial hypertension, obesity, type 2 diabetes mellitus (T2DM)) aged 60–72 years with and without history of SARS-CoV-2 infection and post-covid syndrome (PCS). Patients were divided into 2 groups: group 1 included 123 patients without the history of COVID-19, group 2 — 110 patients with the history of SARS-CoV-2 infection. All study participants underwent general clinical examination; assessment of psycho-cognitive status using the "SPMSQ" and "HADS" scales. Statistical analysis has been performed using RStudio software.

Results. Anxiety and depression have been established in 49–61% of patients with comorbid diseases and were more prevalent among patients after COVID-19. Subclinical anxiety was seen in 29% of patients without COVID-19 and in 27% of patients with PCS; clinically significant anxiety — in 13% of patients from both groups. The analysis of patients' cognitive functions showed that cognitive dysfunction was more prevalent among patients with PCS (p = 0,007); while the prevalence of mild cognitive impairment was comparable between groups, but was higher among patients with PCS – 22% vs. 8% (p = 0,005). Severe cognitive impairment was seen only in patients with PCS – 2%. The analysis of separate groups with various comorbidities showed significant differences in patients with T2DM, 51% in those without PCS compared with 28% among patients with PCS (p = 0,012).

Conclusion. The effects of COVID-19 remain uncertain. Therefore, the assessment of long-term consequences after the infection in patients with various comorbidities is required and can be achieved by reprofiling and initiation of large cohort studies aimed not only to assess long-term outcomes of SARS-CoV-2 infection, but also to investigate psycho-cognitive dysfunction.

Keywords: anxiety, depression, cognition, comorbid diseases, SARS-CoV-2, post-covid syndrome.

Conflict of interest: none declared.

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Introduction

Nowadays the prevalence of psycho-cognitive disorders grows in general medical practice and especially among patients with various comorbid diseases. Neuropsychiatric disorders that manifest not only with anxiety or depression but also with cognitive impairment are of special importance since they can significantly aggravate life quality [1, 2]. It is known that viral infections can affect cognitive functions and lead to the development of dementia, and the current coronavirus infection affect both cognitive and psychological functions [3–5]. Exposure to powerful stressor in most cases is associated with higher depression and anxiety levels, both in the short and long term, that can not only impair life quality, but can also affect the prognosis. The increased stress may affect immune system and increase the risk of infectious diseases development, including the new coronavirus infection [6, 7]. According to current literature approximately 1/5 of patients experience cognitive impairment within 12 weeks after COVID-19, that is associated with gender (women), age, the severity of illness and the presence of comorbidities [8]. The study by Premraj L. et al., that included 15530 patients 3 months after COVID-19, have established cognitive impairment, decreased attention, "brain fog" in 1/3 of patients, anxiety and depression in 23% and 17%, respectively. Cognitive impairment did not depend on the course of post-COVID syndrome (cognitive deficit slightly increased rather than disappeared over time), while anxiety and depression were significantly more prevalent among those who recovered from infection more than 6 months ago [9, 10]. Several mechanisms of cognitive impairment are discussed in the literature [11]. MRI usually shows no signs of structural changes; however, positron emission tomography

(PET) reveals zones of decreased metabolism [12]. Neuropsychological changes manifest by impaired memory and ability to memorize [13, 14]. Several studies attempted to search for the evidence of direct effect of the SARS-CoV-2 virus on brain cells. The results of such studies [10, 11], which included patients with various disease severity, did not establish the presence of the virus in the brain tissue or cerebrospinal fluid (CSF) or indirect signs of viral infection. The revealed increase in the level of neurospecific proteins in the CSF of patients with COVID-19 may indicate brain cells damage, although it gives no clue as to the nature of the pathological process. At the same time, the data obtained may indicate that the COVID-19 may initiate mechanisms of delayed brain damage and cause neurodegenerative diseases [15, 16]. It is also considered that SARS-CoV-2 RNA remains in the brain tissue for a long time and, therefore, aggravates the loss of neurons over time [17, 18]. The relationship between inflammation markers and cognitive impairment in patients with post-COVID has been established [19]. Several studies established increased permeability of the blood-brain barrier that can prolong neuroinflammation and cause memory and attention impairment, as well as direct viral invasion into the central nervous system through the olfactory bulb [20–22]. It is also noteworthy that hypoxia caused by insufficient oxygen supply to the brain due to impaired lung function and endothelial dysfunction that occurred during COVID-19 may manifest as cognitive dysfunction in the long-term period [23–25]. The increase in the frequency and severity of psycho-cognitive disorders together with the limitation of its diagnosis highlights the importance of psycho-cognitive status assessment at early stages of the disease, including the assessment of anxiety and depression. This study aimed to assess mentioned above psychopathological symptoms.

Objective. To compare psycho-cognitive status in elderly patients with various comorbidities, depending on the presence of post-COVID syndrome.

Materials and methods

This observational analytical cohort study included 223 patients with atrial fibrillation and various comorbidities (coronary heart disease (CHD), arterial hypertension (AH), abdominal obesity (AO), type 2 diabetes mellitus (T2DM)) aged 60–74 years, with and without the history of documented SARS-CoV2 infection with post-COVID syndrome. Patients were divided into two groups: group 1 included 123 patients (64 [62; 69.5] years) without the history of COVID-19 and group 2–110 patients (65 [62; 68] years) with the history of COVID-19. Group 2 included 55.5 % of men and 44.5 % of women, group 2–52.8 % and 47.2 % men and women, respectively. Each group has been divided into two subgroups depending on the presence of various comorbidities: T2DM and obesity. The subgroup with obesity included patients under 64 [61; 67] years old, and had more women (53.8 %). The inclusion criteria were: signed voluntary informed consent to participate in research; age from 60 to 74 years old; stage 3 arterial hypertension; CHD, I–II functional class of angina pectoris; atrial fibrillation (all types, without cardiac embolism); T2DM with HbA1c level under 8.5 %; obesity stages I and II; the presence or absence of COVID-19 with SARS-CoV-2 RNA identification. In those who had documented history of COVID-19 caused by SARS-CoV-2, the duration of the disease over 12 weeks (for the group of patients with post-COVID syndrome). Exclusion criteria: symptomatic hypertension; CHD, III–IV FC of angina pectoris, microvascular, vasospastic, unstable angina; stages 4–5 of chronic kidney disease; T2DM with HbA1c level over 8.5 %; type 1 and other specific types of diabetes; chronic obstructive pulmonary disease; anemia (hemoglobin level below 130 g/l in men and below 120 g/l in women); malignant neoplasms; acute stages of other chronic diseases; mental disorders; alcohol consumption over 21 standard drinks per week for men and over 14 standard drinks for women.

All study participants underwent general clinical examination, biochemical blood test, lipid panel, glucose, glaciated hemoglobin, potassium, estimation of glomerular filtration rate, C-reactive protein, NT-proBNP level; Echo-CG according to the standard protocol; assessment of systolic and diastolic blood pressure (SBP and DBP) (office and self-measurement monitoring with the calculation of average level); assessment of cognitive status using the SPMSQ (Short Portable Mental Status Questionnaire) — a portable mental status questionnaire for cognitive deficits; HADS (Hospital Anxiety and Depression Scale) to identify and assess the severity of depression and anxiety among study participants.

The study was conducted in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki, the protocol was

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approved by the ethics committee of the Novosibirsk State Medical University of the Ministry of Healthcare of Russian Federation (protocol No. 148). All included patients signed voluntary informed consent to participate in research.

Statistical analysis

Statistical data analysis was performed using the RStudio software (version 2021.09.2 Build 382 — © 2009–2022 RStudio, Inc., USA, URL https://www.rstudio.com/) and the R language (version 4.0.2, URL https://www.R-project.org/). Descriptive characteristics are presented as median [first quartile; third quartile] for numerical data, percentages with confidence interval (CI) [lower bound of 95 % CI; upper bound of 95 % CI] for categorical data. The Mann-Whitney U-test with the calculation of 95 % CI was used to assess the statistical difference between the numerical characteristics of compared groups. The level of statistical significance was set as $p < 0.05$.

Results

The average age of study participants was 64 [62; 68] years. Since blood pressure instability is one of the main causes of cognitive deficit, especially in patients with post-COVID syndrome, all the patients underwent the assessment of hemodynamic parameters. Patients with the history of COVID-19 infection had lower DBP (66 [60; 72.75] mmHg) compared with patients from group 1 (80 [70; 88] mmHg ($p < 0.001$)). At the same time median SBP did not differ between groups — 156 [143.25; 165] mmHg ($p = 0.668$). Target SBP values were exceeded in 80 % [70 %; 87 %] of the elderly (⩾ 140 mm Hg) patients from group 1 versus 79 % [68 %; 86 %] from group 2 ($p = 0.862$). Elevation of DBT ⩾ 80 mm Hg was noted in 42 % [32 %; 53 %] of patients without the history of COVID-19 and in 12 % [6 %; 21 %] of patients from group 2 ($p < 0.001$), and decreased DBP < 70 mm Hg was found in 30 % [21 %; 41 %] and 57 % [46 %; 68 %] of patients from groups 1 and 2, respectively ($p = 0.001$). Pulse blood pressure ⩾ 60 mmHg was registered in 78 % [68 %; 86 %] of patients from the group 1 vs. 89 % [80 %; 94 %] — from group 2 ($p = 0.082$). In group 2 the median heart rate was 77 [74; 80] beats per minute versus 76 [67; 78] beats per minute in group 1 ($p < 0.001$). The comparative analysis of the coronary heart disease (CHD)/ arterial hypertension (AH)/atrial fibrillation (AF)+ T2DM subgroups depending on the history of COVID-19 revealed high SBP, heart rate and low DBP in patients after viral infection, DBP ($p < 0.001$) and heart rate ($p = 0.002$) differences were statistically significant. SBP in the group without and with PCS was 152 [143; 165] mmHg and 154 [141.5; 164.25] mm Hg, DBP was 78 [69; 82] mmHg and 68 [60; 76] mmHg, heart rate was 75 [67; 77] and 77 [73.75; 80] beats per minute, respectively. Similar data were obtained in the subgroups with CHD/AH/AF + AO depending on the presence of post-COVID syndrome.

Thus, average SBP values were increased in all study participants, and the subgroups with CHD/AH/AF + AO + PCS had the highest values — 162 [145.25; 168] mm Hg, as well as the lowest DBP values — 60 [60; 70] mm Hg, while patients with abdominal obesity without PCS had the highest DBP values — 82.5 [78; 88] mmHg. In general, SBP target values in elderly was ⩾ 140 mmHg, and DBP ⩾ 80 mmHg, as well as DBP decrease < 70 mmHg was also detected (Table 1).

It is known that psychological state change in the elderly, people of senile age and centenarians predominantly with the development of anxiety and depression. In this study we assessed psychological state using the HADS (Hospital Anxiety and Depression Scale) that is widely used in clinical practice by general practitioners, cardiologists, geriatricians, and rehabilitation specialists. In current study the median anxiety score in both patients without and with the history of coronavirus infection and PCS was 7 [6; 8] and 8 [6; 9] ($p = 0.031$), respectively, which can be interpreted as slight anxiety increase in patients with PCS without statistical significance, but with the development of subclinical anxiety in patients after COVID-19. It was found that 0–7 points or the absence

Table 1. **Hemodynamic parameters in groups with various comorbidities**

Group	SBP, mmHg	DBP, mmHg	HR, beats per minute
CHD/AH/AF + T2DM	156 [143,25; 165]	80 [70; 88]*	76 [67; 78]*
CHD/AH/AF + T2DM + PCS	156 [143,25; 165]	66 [60; 72,75]*	77 [74; 80]*
CHD/AH/AF + AO	161.5[145,25; 68]*	82.5 [78; 88]*	76[68; 80]
CHD/AH/AF + AO + PCS	162 [145,25; 168]*	60 [60; 70]*	78 [74; 80]

Comment. * — difference is statistically significant.

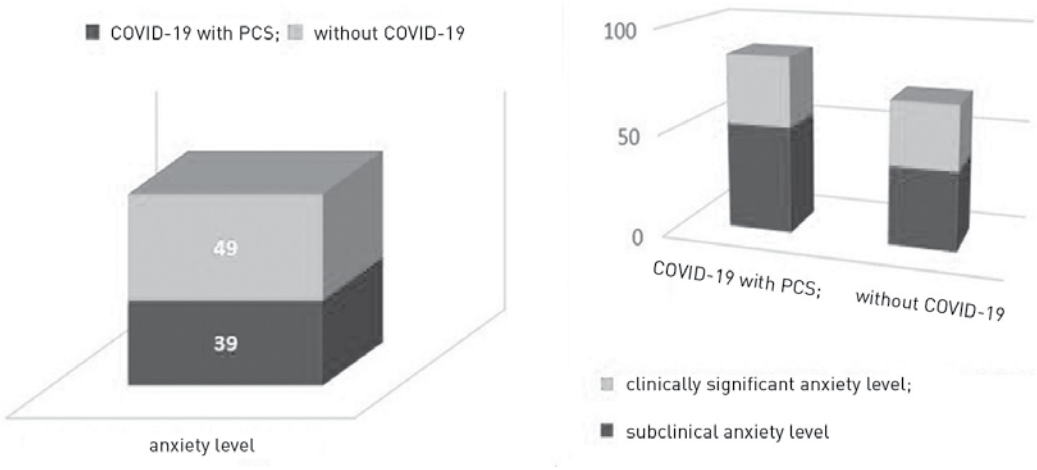

Figure 1. Anxiety level depending on the presence of COVID-19 with post-COVID syndrome

of anxiety, was noted in 61 % [52 %; 69 %] of patients without the history of coronavirus infection and in 49 % [40 %; 58 %] of patients with PCS (p = 0.086), 8–10 points or subclinical anxiety — in 26 % [19 %; 34 %] and 27 % [20 %; 36 %] of patients (p = 0.882), 11 points and above or clinically significant anxiety in 13 % [8 %; 20 %] and 13 % [8 %; 20 %] of patients (p = 0.041), respectively. In the subgroup of patients with comorbid pathology and type 2 diabetes, similar results were obtained — 7 [6; 9] points against 8 [7; 11] points (p = 0.037). The comparative analysis of anxiety level showed greater number of patients with subclinical and clinically significant anxiety after coronavirus infection — 8–10 points scored 25 % [16 %; 37 %] of patients after viral infection and 22 % [13 %; 33 %] without the history of COVID-19 (p = 0.681), 11 or more points — 30 % [20 %; 42 %] and 17 % [10 %; 28 %] (p = 0.099), respectively (Fig. 1). The level of anxiety did not differ depending the presence of obesity, the median HADS anxiety scores were similar and within the normal range.

The presence and the severity of cognitive impairment were assessed depending on the presence of PCS in patients with cardiovascular diseases (CVD) with metabolic syndrome. The median error rate in patients without the history of COVID-19 was 3 [1; 3] errors, and in those with PCS — 3 [2; 4] errors (p < 0.001) that can be interpreted as the absence of cognitive impairment in patients with PCS.

The assessment of cognitive state and the comparison of the degrees of cognitive impairment established that normal cognitive functioning was preserved in less patients after coronavirus infection (27 % [20 %; 36 %] compared with those without the history of infection 45 % [36 %; 54 %] (p = 0.007)) (Figure 2).

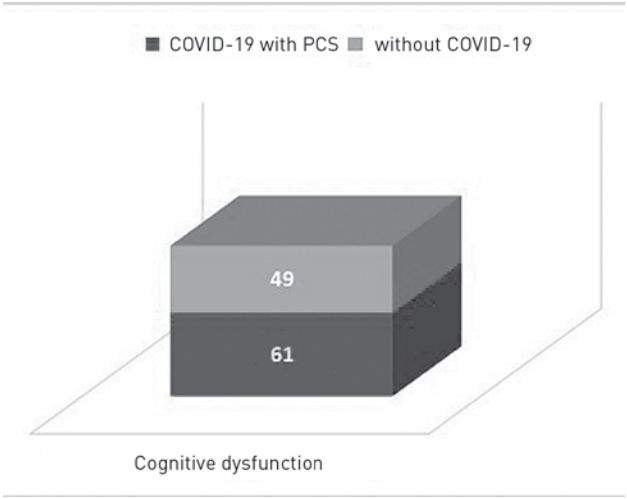

Figure 2. Cognitive impairment depending on the presence of COVID-19 and post-COVID syndrome

The levels of mild cognitive impairment did not differ significantly between compared groups, however patients from the group with PCS showed more pronounced cognitive impairment, moderate cognitive impairment was higher in patients with PCS — 22 % [15 %; 30 %] vs. 8 % [4 %; 14 %] (p = 0.005), severe cognitive impairment was found only in those with PCD — 2 % [1 %; 6 %] (p = 0.001) (Figure 3). The subgroups with obesity had the same number of errors — 3 [1; 4] errors in patients without PCS and 3 [2.25; 5] errors in those with PCS (p = 0.020).

After dividing study participants by the severity of cognitive impairment, statistical significance was achieved only in those who made 5–7 errors, which corresponds to moderate cognitive impairment, thus,

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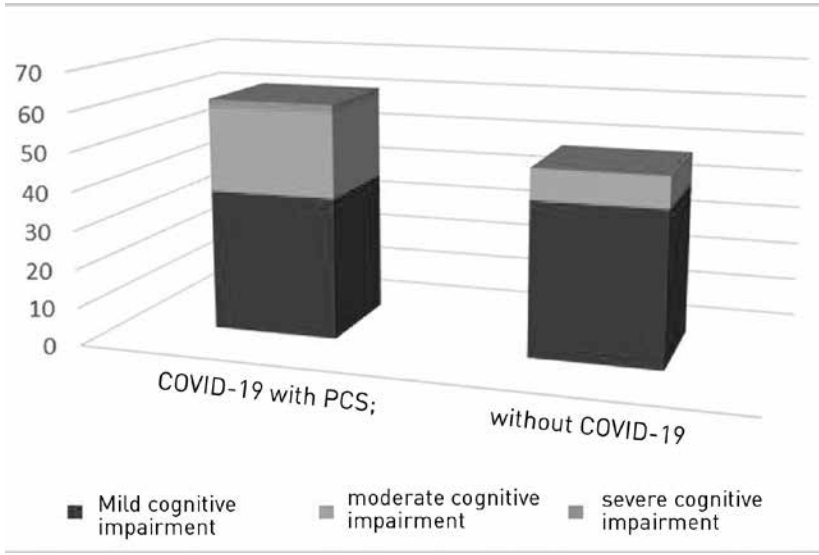

Figure 3. The severity of cognitive impairment depending on the presence of COVID-19 and post-COVID syndrome

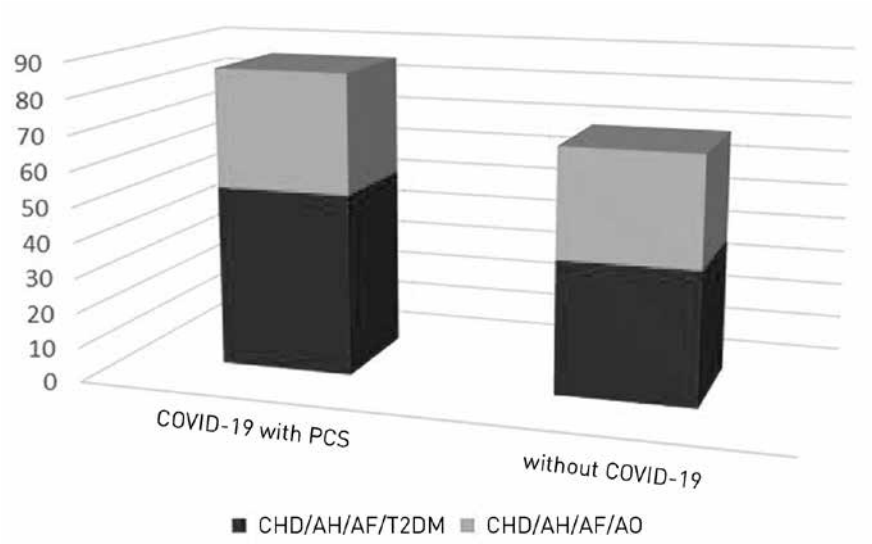

Figure 4. Cognitive impairment in clinical subgroups depending on the presence of COVID-19 and post-COVID syndrome

35 % [23 %; 49 %] of patients with PCS compared with 9 % [4 %; 19 %] of patients without PCS (p = 0.001) made from 5 to 7 errors by the SPMSQ. Cognitive impairment positively correlated with and anxiety and depression groups (r = 0.345, p = 0.033).

When comparing the subgroups of patients with CVD and T2DM depending on the of COVID-19 infection, patients with PCS showed statistically significantly more errors — 3 [2; 4] errors vs. 2 [1; 3] errors (p = 0.006). In addition, statistically significantly less patients did not score more than 2 errors and more patients without PCD showed normal cognitive functions — 51 % [39 %; 63 %] compared with 28 % [19 %; 40 %] in those with PCS (p = 0.012) (Figure 4).

Thus, despite almost equal median of errors made by patients by short portable mental status questionnaire (SPMSQ) that was used to assess the presence and severity of cognitive deficit through the number of errors, patients after new coronavirus infection more often had mild, moderate and severe cognitive impairment and less often showed normal cognitive status.

Discussion

To this day there are data indicating the relationship between arterial hypertension (AH) and cognitive impairment [26]. At the same time, it is known that endothelial dysfunction leads to renin-angiotensin-al-

dosterone system imbalance and causes not only transformation of the vascular bed, but also contributes to the blood-brain barrier dysfunction that eventually cause cognitive impairment [27, 28]. The data of cognitive state assessment can be used as marker for the progression of cerebral damage, especially in the elderly, which was highlighted in our study.

According to the World Health Organization, in 2019 every eight person on the planet suffered from mental disorder, with anxiety and depression being the most prevalent. In 2020 during the pandemic of COVID-19 infection, the number of patients with anxiety and depression has increased significantly. Within one year, the prevalence of these disorders increased up to 28% [29]. Long-term psychological consequences after COVID-19 are still being investigated [30]. Several researchers noted the increase in the number of patients with mental disorders in the post-COVID period [31]. In our work, we have found that anxiety and depression were more prevalent among patients with the history of COVID-19, cognitive impairment with the predominance of moderate and severe levels was also more often observed in patients after COVID-19, which confirms the data of previous studies.

Conclusion

The effects of COVID-19 remain uncertain, and if COVID-19 will continue to circulate for many years, its long-term outcomes could grow exponentially. In this regard, it is necessary to follow up patients after COVID-19 to assess the long-term consequences, especially those with comorbid pathologies that serves as poor prognostic factor. This could be achieved by reprofiling and initiation of large cohort studies aimed not only to assess long-term outcomes of SARS-CoV-2 infection, but also to investigate psycho-cognitive dysfunction.

Conflict of interest: None declared.

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Primary prevention of atrial fibrillation with the correction of its potentially modifiable risk factors in comorbid patients with abdominal obesity. Prospective study

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Abstract

Objective. To assess the role of the improvement of potentially modifiable risk factors (RF) for the primary development of atrial fibrillation (AF) in comorbid patients with abdominal obesity (AO) and atrial premature complexes (APCs) with high risk of the development of this arrythmia.

Materials and methods. The study included 489 patients with AO and APCs aged from 58 to 72 years (67,9 ± 0,7 years on average). After the examination, a 3-year prog-

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nostic time range for the development of AF was established for all patients. All study participants underwent the correction of potentially modifiable risk factors of AF (body mass, blood pressure, glucose and blood lipid levels, etc.) until target values have been reached, as well as smoking cessation, physical activity, etc. The study endpoint was the sinus rhythm preservation or AF manifestation.

Results. All study participants were divided into two groups. Group 1 included 278 (56,85 %) patients with insufficient RF correction, group 2 included 95 (19,43 %) patients who achieved target values of all potentially modifiable RFs of AF. Patients without RF correction were included into the control group. Studied groups did not differ significantly by sex, age, comorbid diseases, risk factors for the development of AF.

Patients from all groups did not differ significantly by the incidence of AF (paroxysmal and persistent forms) during the first year of follow-up, and had AF in 92.68 %, 85.29 % and 93.54 % of cases, respectively. Patients from group 2, who maintained the achieved target values of potentially modifiable RFs for 2 years or more, had 57.58 % and 14.29 % actual and predicted AF development ratio during the 2nd and 3rd year of observation, respectively.

Conclusion. The decrease of actual AF compared to predicted AF was observed only in patients with AO and APCs with complex correction of all potentially modifiable AF RFs who reached RF's target values and maintained them for over 2 years.

Keywords: atrial fibrillation, primary prevention, correction of potentially modifiable risk factors.

Conflict of interests: None declared.

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Introduction

The combination of abdominal obesity (AO), arterial hypertension (AH), diabetes mellitus (DM), dyslipidemia, hypodynamia increase "cardiometabolic" risk of various cardiovascular diseases, including atrial fibrillation (AF) [1, 2]. The main causes of AF development in comorbid patients with AO are the intracardiac hemodynamic disorders, in particular, left ventricular dysfunction, atrial dilatation, etc. Moreover, profibrogenic inflammatory mediators (galectin-3, transforming growth factor β1, etc.) due to the increase in epicardial fatty tissue may also affect myocardium [3–5]. In recent years, using the model of dynamic observation of comorbid patients with AO, including the analysis of signal-averaged ECG parameters, dispersion of P(Pd) wave, the number and the type of atrial premature complexes (APCs), researchers identified patients with high 3-year risk of development of primary AF as well as assessed probable time range of its manifestation [5].

Risk change of primary AF development after the correction of separate potentially modifiable factors is well studied by using the various risk-stratification models in comorbid patients with AO without APC registration [6]. However, data on the effect of complex correction of potentially modifiable risk factors (RF) of AF on its primary development in comorbid patients with AO and CHD with the assessment of potential prognostic time interval of this arrhythmia development in the literature is scarce.

The aim of the study was to determine the role of complex correction of potentially modifiable RF of AF formation on its manifestation in comorbid patients with AO and APC with high risk of this arrhythmia development.

Methods

The study included 489 patients with AO and APCs aged between 58 and 72 years (mean 67.9 ± 0.7 years). The number of males and females was 198 (40.49 %) and 291 (59.51 %), respectively ($p > 0.05$). AH was detected in 415 (84.87 %) patients, DM in 328 (67.08 %), chronic obstructive pulmonary disease in 109 (22.29 %), hyperlipidemia in 427 (87.32 %), tobacco smoking in 334 (68.30 %), hypodynamia in 409 (83.64 %).

All patients after clinical-laboratory examination, echocardiographic examination, daily ECG monitoring, registration of signal-averaged ECG, etc. were

subjected to inclusion criteria. Methods and hardware for determination of left ventricular contractility and dysfunction, cardiac chamber volumes, as well as filtered P-wave duration of signal-averaged ECG (FiP-P), Pd, prognostic index of AF (PI) were described earlier [5]. The diagnosis of AO, body mass index (BMI), hypodynamia, functional class of heart failure (6-minute test), mean BP was performed according to generally accepted criteria [1, 2].

Based on atrial ectopy analysis, PI was calculated according to the formula:

$$PI = (A \div B) \times (C \div N),$$

where PI is the prognostic index of AF development, A and B are the duration of FiP-P and Pd determined by signal-averaged atrial ECG and daily ECG monitoring data, respectively (in m/s). C is the linear deviation of the corrected coupling interval in more than 20 APCs, N is the number APCs used for the study, expressed as number/hour [5].

The three-year risk of primary AF was determined at PI ⩽ 8 points. The PI was subsequently assessed at follow-up intervals of 1–3 months. If the PI decreased from baseline and at follow-up, the x prognostic time range for AF (PPTRAF) was calculated (in months) according to the formula:

$$PPTRAF = [PI_1 - 0.01] \div [PI_1 - (PI_2, PI_3, \text{etc.})] \times I,$$

where, PPTRAF is the potential prognostic time range of AF development. PI_1 — PI values after the first examination, PI_2, PI_3, etc. — PI_2, PI_3 values in 2–3 and subsequent studies respectively, 0.01 — PI values at which spontaneous episodes occur, I — interval in months between first and subsequent (2–3 etc.) studies [5]. Then the calculated PPTRAF was compared with the actual development of AF.

The inclusion criteria were: presence of sinus rhythm, detection of ⩾ 100 APCs per day of the follow-up [2, 7], chronic heart failure of I–II functional class according to NYHA, absence of AF registration with at least 4–5 procedures of 24–72 hour ECG monitoring at least once in 1–2 weeks for 2–3 months, with preserved left ventricular ejection fraction (LVEF) (⩾ 54 %) [2, 7], 3-year risk of development of AF with determination of PPTRAF [5], informed consent from the patient to participate into the study. The study was approved by a local ethics committee.

Patients with myocarditis, cardiomyopathies, Wolff-Parkinson-White syndrome, malformations, various clinical forms of coronary heart disease and alcohol abuse were excluded from the study.

All patients were offered the correction of AF potentially modifiable RF. The targeted correction values of modifiable factors were: reduction of BMI < 25 kg/m^2 and/or waist circumference ⩽ 80 cm and ⩽ 94 cm in women and men, respectively, BP ⩽ 139/89 mm Hg, but not below 130/80 mm Hg. [1], plasma total cholesterol and triglycerides ⩽ 5.2 mmol/L and ⩽ 1.7 mmol/L, respectively; plasma low-density lipoprotein cholesterol ⩽ 1.4 mmol/L; fasting blood glucose ⩽ 5.8 mmol/l, increased high-density plasma lipoprotein cholesterol ⩾ 1.0 mmol/l in men and ⩾ 1.2 mmol/l in women [1]. All patients were advised to eat a healthy diet, regular aerobic physical activity (150 minutes or more per week), to quit smoking. Hypotensive drugs (indapamide, telmisartan, valsartan, etc.) were used to normalize BP. Hypoglycemic and hypolipidemic drugs (metformin, empagliflozin, liraglutide, statins, as well as diet, etc.) were used to normalize blood glucose and lipids levels [1]. No antiarrhythmic drugs were used to reduce APCs. When the subjective sensation of atrial ectopy appeared, sedatives, potassium drugs (combination of potassium asparaginate and magnesium asparaginate, etc.) were recommended.

Assessment of the effectiveness of potentially modifiable RFs correction on AF development was determined (in points) according to the formula: K ×D, where K is equal to "0" and "1" in absence and incomplete correction (not achieving the target values) respectively, "2" in case achieving the target values of predictors of this arrhythmia (in units). D is the duration of corrected RFs retention after their modification (in months).

Patients were followed up for up to 3 years. A registration of AF or the maintenance of the sinus rhythm was the end point of the study. All investigations, including daily ECG monitoring, PI determination, PPTRAF calculation were performed on sinus rhythm at least once in 2–3 months, ECG registration — once a month. Nursing staff monitored BMI, waist circumference, BP, fasting blood glucose. The patients themselves performed regular monitoring of heart rate and blood pressure at least twice a day, using household tonometers. If an irregular heart rate was detected, an ECG was recorded on a smartphone or by contacting the family doctor's office, polyclinic, etc.

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[2]. The episode of AF was the reason for prescribing anticoagulants (dabigatran, rivaroxaban, etc.) [2]. When this arrhythmia occurred, all studies were performed after the resolution of the first episode, and in the case of pharmacological cardioversion, after 5–7 half-lives of the antiarrhythmic drugs used for its elimination.

The study was conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki.

Statistical analysis

Mean values as well as the error of the mean values (M ± m), standard deviation (σ), 95% CI of the mean values, Student's t test, X^2 test were used for statistical processing of the obtained data, $p < 0,05$ values were taken as statistically significant difference of the values. The normality of the distribution of the quantitative variables was assessed using the Kolmogorov-Smirnov test and the ±3σ rule (Gaussian distribution). Pearson and Spearman linear and rank correlation (r) were used (for nonparametric variables) respectively, and the comparison between two binary variables was assessed by using logistic regression with odds ratio (OR) in version 11.0 of «Statistica» computer software.

Results

After the inclusion in the study, all patients had a decrease in PI from baseline and at follow-up, due to a decrease in the duration of the APCs coupling interval and its variability (OR = 8.2), an increase in Pd (OR = 6.9) and the number of extrasystoles (OR = 0.91).

All patients, depending on the correction degree of the potentially modifiable RFs of AF development, were divided into two groups. The first group consisted of 278 (56,85%) patients with incomplete correction, the second group included 95 (19,43%) patients with the achievement of the target values of all potentially modifiable RFs, including those due to dietary compliance, regular aerobic physical activity, tobacco cessation. The control group included the remaining patients without correction of modifiable AF predictors.

At baseline, a statistically significantly shorter duration of AF registration before the correction was detected in the second group patients compared to the first and control groups, while the other studied parameters did not differ significantly (Tables 1, 2).

Table 1. **Status of clinical and instrumental parameters, PPTRAF in patients from groups I and II at baseline[1]**

Parameters	Control group n = 116	I group n = 278	II group n = 95
Age, years	66,8 ± 0,63 (58,6–74,5)	65,9 ± 0,36 (59,7–73,6)	65,9 ± 0,8 (57,7–69,8)
BMI, kg/m^2	36,5 ± 0,48 (30,8–43,7)	36,8 ± 0,32 (30,4–42,8)	35,8 ± 0,42 (31,5–39,4)
Waist circumference, cm	128,2 ± 1,5 (106–149)	129,8 ± 1,1 (109–151)	130,2 ± 1,9 (105–148)
Blood glucose, mmol/l	9,3 ± 0,4 (6,4–14,4)	9,3 ± 0,26 (6,6–13,8)	8,8 ± 0,8 (6,8–14,9)
Total cholesterol, mmol/l	7,8 ± 0,1 (6,1–9,8)	8,0 ± 0,1 (6,5–10,9)	8,2 ± 0,2 (6,4–9,9)
Low density lipoprotein cholesterol, mmol/l	4,7 ± 0,2 (3,6–5,9)	4,9 ± 0,1 (3,6–6,1)	4,5 ± 0,2 (3,2–5,6)
High density lipoprotein cholesterol, mmol/l	1,1 ± 0,1 (0,8–1,5)	0,9 ± 0,1 (0,7–1,6)	1,1 ± 0,5 (0,8–1,4)
Triglyceides, mmol/l	2,5 ± 0,1 (1,6–3,5)	2,3 ± 0,1 (1,3–3,6)	2,6 ± 0,2 (1,7–4,4)
AO duration before correction, years	39,3 ± 0,8 (29–52)	38,7 ± 0,8 (27–54)	14,1 ± 1,1*◊ (8–20)
PPTRAF, months	34,6 ± 2,1 (4–59)	35,2 ± 1,3 (6–58)	22,9 ± 1,2 (5–36)

Comment. 1 – up M ± m, down – 95% CI mean values,
* – statistically significant difference in parameters when comparing with the control group,
◊ – II group in comparison to the I group (at $p < 0,05$).

There was no significant difference in gender, age, frequency of hypertension, DM, chronic obstructive pulmonary disease, tobacco smoking, and hypodynamia between patients from the first and second groups, either among themselves or in comparison with controls.

In 164 (58,99%), 34 (35,79%), 62 (53,45%) patients from the first, second and control groups respectively, PPTRAF was 6–12 months ($p > 0,05$), in 56 (20,14%), 33 (34,74%), 36 (31,03%) 13–24 months ($p > 0,05$), and in the remaining patients of these groups — 25 to 36 months ($p > 0,05$).

In 94 (33.81%) and 28 (29.47%) patients of the first and second groups the maintenance of the achieved indices was kept for 12 months, in 88 (31.65%) and 29 (30.53%) — for 12–23 months, and in the remaining patients of these groups — for more than 24 months. The achievement of the target values of potentially modifiable RF and their maintenance for more than 2 years from the start of correction correlated with the duration of AF registration before the correction for less than 15 years (OR = 12, 8), performing regular aerobic physical activity (OR = 10.9), dietary compliance (OR = 8.5), use of a glucagon-like peptide-1 receptor agonist (liraglutide) (OR = 5.4), empagliflozin (OR = 2.4).

Table 2. **Status of clinical and instrumental parameters in patients from groups I and II at baseline (A) and at the end of the predicted period of AF development or at its onset (B)[1]**

Group	Control group n = 116		I group n = 278		II group n = 95	
Parameter	A	B	A	B	A	B
LV EF, %	61,84 ± 0,67 (54–69)	54,01 ± 0,68* (46–62)	61,54 ± 0,32 (55–68)	60,38 ± 0,35 (52–70)	61,47 ± 0,89 (54–68)	68,35 ± 0,91* (59–77)
E/A, units	0,95 ± 0,02 (0,71–1,23)	0,78 ± 0,01* (0,61–0,95)	0,94 ± 0,01 (0,75–1,15)	0,96 ± 0,01 (0,84–1,08)	0,94 ± 0,01 (0,74–1,15)	1,07 ± 0,01* (0,92–1,21)
LAEDD index, ml/m^2	31,78 ± 0,25 (28–33)	37,93 ± 0,57* (31–41)	31,54 ± 0,24 (29–35)	35,84 ± 0,23* (30–39)	31,43 ± 0,25 (28–34)	25,32 ± 0,43* (22–29)
Amount of APC per hour	374 ± 6 (301–446)	597 ± 22* (324–876)	384 ± 3 (311–467)	376 ± 8 (188–559)	384 ± 11 (297–462)	234 ± 16* (132–307)
Mean BP, mmHg	117,1 ± 1,2 (103–131)	108,7 ± 0,9* (97–121)	118,1 ± 0,7 (102–132)	107,8 ± 0,5* (96–119)	118,9 ± 1,4 (104–131)	105,2 ± 1,3* (95–116)
6-minute walking test, meters	436,5 ± 6,7 (365–510)	375,7 ± 5,1* (315–436)	447,9 ± 6,3 (372–516)	442,7 ± 6,7 (368–518)	422,9 ± 7,3 (358–489)	546,5 ± 9,8* (445–648)

Comment. 1 — up M ± m, down – 95 % CI mean values
* — II group in comparison to the I group (at p < 0,05).

In patients from the control and first groups, the ratio (in %) of actual to predicted development of first AF episodes was 87.93% and 88.13%, respectively (p > 0.05), whereas in second group it was 54.74% (p < 0.05) (Table 3). In all patients from the first, second and control groups, the incidence of AF did not differ significantly during the first two years of follow-up after inclusion in the study (see Table 3). In patients from the second group, at maintenance of the reached target values of potentially modifiable RFs for more than 1 year, the ratio of actual AF development to the predicted one in the 2nd and 3rd years of follow-up was 57.58% and 14.29% respectively (see Table 3). No lethal outcome, myocardial infarction, stroke or other complications were observed in the above-mentioned patients.

For the patients in the control group, a significant decrease in LV EF, E/A ratio, mean BP, 6-minute test performance and a statistically significant increase in the number of APCs and Left atrium end-diastolic dimension (LAEDD) index were observed by the end of the predicted period of AF development or at its onset. On the other hand, only a significant decrease in mean BP was found in the first group of patients, while other parameters in these groups compared with baseline data did not change significantly (see Table 2). A statistically significant decrease in mean BP, LAEDD index, the number of APCs, as well as significant increase in LV EF, E/A, and the 6-minute test were observed in patients from the second group, compared with the baseline (Table 2).

Discussion

Currently, there are various predictors of AF development, such as: left atrial dilatation, decreased LV EF, deterioration of transmitral flow, detection of APC, abnormal values of signal-averaged ECG, Pd, etc. [8]. For the early diagnosis of AF in all patients, especially over 65 years old when identifying predictors of its development or thromboembolic complications, it is recommended to assess pulse regularity by the principle of "pulse-screening-test", determining both palpation and by using household tonometers, followed, if necessary, by ECG registration on a smartphone

Table 3. **Effect of the potentially modifiable AF RFs correction on the development of the first attacks of this arrhythmia in groups I and II[1]**

Duration of the follow-up after the inclusion into the study	Control group n = 116	I group n = 278	II group n = 95
From 6 to 12 months	58/62 (93,54 %)	150/164 (92,68 %)	29/34 (85,29 %)
From 13 to 24 months	29/36 (80,56 %)	47/56 (83,93 %)	19/33(57,58 %)*◊
From 25 to 36 months	15/18 (83,33 %)	48/58 (82,76 %)	4/28 (14,29 %)*◊
Total	102/116 (87,93 %)	245/278 (88,13 %)	52/95(54,74 %)*◊

Comment. 1 – numerator — actual AF development rate, denominator — projected PPTRAF, % — ratio of actual to projected AF development rate over the observation period;
* – statistically significant difference in parameters when comparing with the control group,
◊ – II group in comparison to the I group (at p < 0,05).

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or when contacting medical institutions [2]. At least 25 risk-stratifications have been proposed to assess the risk of primary AF development in comorbid patients, with a five-year predictive accuracy averaging between 20 % and 50 % [6]. However, risk-stratifications and predictors of AF development determine the presence of potential risk without definition of concrete terms of its realization. In recent years, sporadic work on specific timing of PPTRAF registration, based on a model of dynamic patient follow-up, has appeared [5].

A total of 489 comorbid patients with AO and APC aged between 58 and 72 years (mean, 67.9 ± 0.7 years) were followed up.

The "obesity paradox" is observed in patients with excessive BMI: patients with AO have a minimum probability of mortality due to various cardiovascular diseases and their complications [2]. Similar data were obtained in the present study.

It is now known that atrial ectopy due to the trigger mechanisms, such as delayed postdepolarization, is usually associated with the hyperpolarization of cell membranes of cardiomyocytes within 60–70 mV, which indirectly reflects potentially reversible nature of their dysfunction. Its induction may be the result of stress, vegetative or electrolyte imbalance, etc., and after the cause elimination, APCs usually stop [8]. In most cases, APCs due to the development of these mechanisms are regarded as supraventricular ectopias with a favorable prognosis, usually not requiring the use of the antiarrhythmic therapy, except for the presence of a subjective sense of extrasystole [2, 8]. Meanwhile, further hyperpolarisation of myocardiocyte membranes, e.g. between 50–60 mV, is associated with a local delay in the spread of excitation with Wenckebach phenomena and the formation of unidirectional conduction block in this area, leading to a persistent re-entry loop and/or an ectopic focus. The occurrence of this mechanism is associated with deeper metabolic abnormalities and/or as a result of organic myocardial damage such as inflammation [8]. Persistent and/or recurrent supraventricular extrasystole caused by these mechanisms can independently or indirectly induce the development of myocardial areas with irregular refractoriness, causing the formation of atrial substrate, predisposing to the appearance of primary AF as well as "atrial arrhythmogenic cardiomyopathy" [2, 8–11].

In our study, after determining the 3-year risk of AF development in comorbid patients with AO and APC, PPTRAF was calculated at least once every 2–3 months at decreasing PI over the course of follow-up. The decrease in PI values from baseline and at follow-up was due to decreased variability of the APC clutch interval, increased Pd and, to a lesser extent, the number of extrasystoles, which probably reflects the formation of AF substrate [10, 11]. It should be noted that the low variability of the APC coupling interval is indirectly confirmed by "re-entry" mechanisms and/or the formation of a pathological ectopic focus, while high values of this index show the presence of trigger mechanisms [8, 10, 11].

According to the obtained data, in 89.31 % of comorbid patients with AO and APC, despite the recommendations to implement a "healthy lifestyle", there was virtually no or incomplete correction of all potentially modifiable RFs of AF development, while in the rest — correctable predictors reached the target values. The maintenance of the target values of potentially modifiable RFs for 2 or more years correlated mainly with the duration of AF registration before the correction for less than 15 years and, to a lesser extent, with regular aerobic physical activity, dietary compliance and the use of the hypoglycemic agents (glucagon-like peptide-1 receptor agonist and empagliflozin).

The results of the study showed that the ratio (in %) of actual to predicted development of the first AF episodes in patients with and without incomplete correction of RFs did not differ significantly and was 87.93 % and 88.13 %, respectively.

During the first year of follow-up, the incidence of this arrhythmia was not significantly different in comorbid patients with AO with maintained target values of potentially modifiable RFs and in patients without or with incomplete correction of RFs: 85.29 %, 93.54 % and 92.68 %, respectively.

In comorbid patients with AO and APC, the ratio of actual to predicted occurrence of AF during the second and third year of follow-up was 57.58 % and 14.29 %, respectively, when target values of potentially modifiable RFs were maintained for 2 years and longer.

In comorbid patients with AO and APC, the "delayed effect" of correction of potentially modifiable RFs, manifesting in the 2nd and 3rd year of follow-up after reaching their target values, is probably be-

cause APCs may have been registered indefinitely before study inclusion. That may induced the appearance of atrial myocardial zones with conduction and refractoriness variability and/or the formation of multiple ectopic foci [7, 9]. Other contributing factors include the fact that patients with AO have a rather slow regression of excess epicardial adipose tissue, and a prolonged effect of the glucagon-like peptide-1 receptor agonist (liraglutide), empagliflozin, lead to a reduction in the release of profibrogenic inflammatory mediators from epicardial adipose tissue products in comorbid patients with DM and AO [4, 12].

All patients with AO have indications for the complex correction of potentially modifiable RFs of AF development, reaching target values, as well as lifestyle modification, including dietary compliance, regular aerobic physical activity, tobacco cessation, etc. According to the data obtained, in 12.47% of comorbid patients with AO and APC, a positive effect of potentially modifiable RFs correction was observed in case of the maintenance of target values for 2 years and more. The choice of therapy used for the primary prevention of AF in this category of patients, especially with no or incomplete correction of potentially modifiable RFs, is a subject for further study. When a 3-year PPTRAF is detected, the antiarrhythmic pharmacotherapy may be the method of choice as the primary prevention of this arrhythmia in comorbid patients with AO and APC without or with the incomplete correction of potentially modifiable RF [7, 13, 14]. However, in these patients, with long-term antiarrhythmic drugs, the potential risk of adverse events may exceed the predicted benefit of treatment [7, 14]. On the other hand, if the 3-year PPTRAF is detected, the use of pharmacological antiarrhythmic therapy, represented by beta-adrenoblockers or by another kind of treatment, is most likely indicated for the primary AF prevention in comorbid patients with AO and APC, who managed to maintain the target values of potentially modifiable RF, during the first year of follow-up [7, 13].

Subsequently, one year later, continuation of antiarrhythmic therapy, while maintaining the target corrected values, in these patients seems to depend on the assessment of PPTRAF.

Conclusion

In comorbid patients with AO, APC and 3-year PPTRAF, a decrease in the primary AF development was observed only in patients with comprehensive correction of all potentially modifiable RFs and only if the target values were maintained for 2 or more years. The achievement of the target values of potentially modifiable RFs mainly correlated with the duration of AO before correction for less than 15 years and to a lesser extent — with regular aerobic physical activity and dietary compliance.

Conflict of interest. None declared.

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Some factors of chronic social stress accompanying the development of cardiovascular diseases

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Abstract

Chronic stress factors include family stress, work stress, dissatisfaction with social status, social isolation, and domestic factors. The literature analysis has shown that chronic stress factors are associated with cardiovascular diseases (CVDs) through chronic physiological events. Chronic stress refers to a nonspecific systemic response that occurs when the body is stimulated by various internal and external negative factors over a long period. The physiological response to chronic stress serves as a powerful modulator of atherosclerosis onset. Thus, the scientific studies carried out over the last three decades have formed the evidence base about the key role of psychosocial factors in the development of cardiovascular pathology. Moreover, more than half of the cardiovascular disease cases could be affected by non-conventional risk factors

Keywords: risk factors, chronic stress, psychosocial stress, cardiovascular disease, cardiovascular events

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Introduction

According to modern concepts, stress reactivity may underline mechanism of psychological stress influence on cardiovascular diseases (CVD). A number of studies have investigated physiological parameters associated with the psychological stress – the predictors of the cardiovascular outcomes [1]. A meta-analysis by Chida Y. et al. demonstrated the relationship of increased reactivity and decreased recovery time after stress with negative cardiovascular outcomes. Researchers have found its strong correlation with the development of arterial hypertension (AH) and the increase of intima-media thickness [2]. Gabbay F.H. et al. showed that the stress is a predictor of myocardial ischemia in circulatory insufficiency. In addition, Gullette E.C. et al. found the twofold increase of ischemia relative risk (RR) among patients with CVD, during the periods of psycho-emotional stress. Moreover, researchers proved the increase of irregular heart rate in connection with stressful events in patients after myocardial infarction (MI) [3].

The risk of cardiovascular diseases development depending on the chronic social stress factors

Association between psychosocial stress and cardiovascular risk was studied in two clusters due to their different influence on cardiovascular events (CVE): chronic stressors and triggers (acute stressors) [4]. Triggers include: disasters, large-scale sport events, as well as excessive sexual activity [5]. Acute psychological stress influence on the development of cardiovascular diseases and contribute to the growth of MI rate, myocardial ischemia, stroke and arrhythmias [6-8]. Chronic stress factors include: family and work stresses, dissatisfaction with social status, social isolation, household factors [9-15]. Social integration can be particularly important as a predictor of CVD risk in women: on the one hand, it can be disruptive and, at the same time, be protective to the extent that it enhances both biological and behavioral pathways of stress resistance [16]. Chronic stress factors interconnect with CVD through chronic physiological states [8]. Chronic stress refers to a nonspecific systemic response that occurs when the body is stimulated by various internal and external negative factors over a long period of time. The physiological response to chronic stress has long been recognized as a powerful modulator of the atherosclerosis development.

Several clinical and epidemiological studies have shown that chronic stress is an independent risk factor (RF) of CVD and increased morbidity and mortality in patients with existing coronary heart disease (CHD) [17-21]. One of the possible mechanisms of this process is that chronic stress causes endothelial damage by directly activating macrophages, promoting the formation of foam cells and causing the formation of atherosclerotic plaques. This mechanism involves many variables, including inflammation, signaling pathways, lipid metabolism, and endothelial function [22]. Thus, the scientific studies carried out over the last three decades have formed the evidence base about the key role of psychosocial factors in the occurrence and development of cardiovascular pathology and have shown the possibility that non-conventional RFs can contribute to more than half of the CVD cases.

Stress in the family and at work according to the epidemiological studies. The gender aspect

Epidemiological studies review two kinds of families. These are the nuclear family, which is a married couple or a couple with children, and the extended family, which includes other relatives. Research has shown that the extended family can serve as protective factor for IM. The family provides a sense of security and safety, as well as economic, emotional, social, and other forms of support [12]. Social support can play a protective role, being the barrier in difficult life situations. The scientific literature shows different forms of social support, including, among others, an index

of close contacts. There are accumulated data on the dependence of CVDs and their complications on the levels of social support. Among a number of investigated physiological mechanisms, the neuroendocrine and immunological models are the most demanded [23-25]. Lett H.S. et al. in one of the most extensive reviews, considering social support in relation to cardiovascular pathology, showed that the risk of CVD development at low levels of social support was 1.5-2 times higher both in patients with CVD and in the general population. Moreover, of all forms of social support, the most significant predictor of CVDs and their complications was material (functional) support. The Finnish study, on the contrary, demonstrated a high demand for emotional support for women. In elderly and middle-aged patients with CHD, it was shown that in the cluster with low resilience, introversion, and high neuroticism, women were more often lonely, had fewer personalized connections, and spent more time at work. At the same time, despite attempts to cope with stress in different ways, high levels of depression and anxiety were found in the high-distress group after six months [26]. The Stockholm Prospective Study of Women's Coronary Risk showed that stress in interpersonal relationships increases the risk of CHD among married women. Women with CHD have an almost threefold increased risk of recurrent CHD with high levels of family stress. Since women in general are more susceptible to stress, it allows them to use and develop necessary compensatory mechanisms when faced with prolonged stress and seek social and emotional support. Women are better adapted to severe and prolonged stresses, which has been shown to correlate with a less significant deterioration in their health status, including the incidence of CVDs.

Considering the role of the family, it should be noted that the death of a spouse can be the most serious stressful event that one has to face in family life. At the same time, scientific research has shown that widowhood is less traumatic for women than for men in the gender aspect. Other things being equal, widowers had a 10% higher mortality rate, while no such correlation among widows - the overall mortality rate among widows was insignificantly higher compared to married women. The primary source of stress in response to the loss of a spouse is closely related to the fact that the roles of men and women in the family are different. Marital life is less favorable for women, which also makes women less vulnerable to the loss of a spouse. In addition, widowed women spent less time on household chores. Another study analyzed the quality of social roles in both sexes as a predictor of morbidity and overall mortality. The women who were well off in the family and at work had lower morbidity and mortality. For married women, companionship with a partner and equality in decision-making were the predictors of overall mortality. No significant effect of the parental role in women was found in this study [27]. The Luecken L.J. et al. study examined the effects of family and parental status on daily urinary catecholamine and cortisol excretion in a sample of 109 working women to assess the biological and psychological effects of role overload. Other parameters included work and home stress and social support. Results showed that working women with children at home, regardless of marital status or social support, excreted more cortisol and experienced higher levels of home stress [28]. The Russian study showed that women's stress related to childcare and other family responsibilities affects mental and physical well-being significantly more than stress at work [29].

There is an evidence that in women, chronic family stress associated with caring for a seriously ill spouse also increases the risk of CHD [30]. There is a proven hypothesis that one of the main sources of distress in working women with family is a role conflict [31]. It has been shown that women negate the stress received at work by acting both as mothers and as sexual partners. At the same time, women become mentally and physically healthier, when performing more social roles compared to those who have a smaller role set. When both spouses work full-time in the family, no sex differences emerge in the structure of their psychological distress from the roles of parent, employee, and sexual partner, and then the distress of one spouse induces the distress of the other. Therefore, it is assumed that for the married women, the husband's job may be a stressor, inducing stress in women in the family [32]. In Lebanon, a weak association between cardiovascular mortality and social status was found in never-married women. In contrast to the male cohort, widowhood in women was not associated with overall mortality. The authors attributed the resulting patterns to women frequently living with children and grandchildren. At the same time, the risk of cardiovascular events significantly increased in both sex groups when there was an adult married/married child in the family [33]. In a five-

year prospective observational study in the MONICA trial, the relative cardiovascular risk in single women was statistically insignificant [34]. In a Japanese study, single women aged 40-79 years had a higher overall mortality rate compared to the control group of married women [35]. At the same time, unmarried women did not show a tendency to an increased cardiovascular risk compared with married women. To date, there is a viewpoint, according to which family stress in women is considered to be a more unfavorable prognostic factor of CVD development compared to men [36].

A considerable amount of data have been accumulated on cardiovascular risks and negative prognosis in women because of workplace stress [27, 37–39]. Several significant stressors at work are discussed in the scientific literature as possible triggers. These are the feeling of deprivation, unfairness due to relatively low social status, personnel changes, and impossibility to influence administrative decisions. In addition, it is high competition in the work team, as well as the excess of costs over the income of working people. Workplace hypertension has been described, which appears to be a variant of stress-induced AH. Women were found to be less prone to such hyperreactivity than men were. These differences were exacerbated when estrogen levels increased in women (e.g., when they were in the menstrual phase) because of the specific stress-protective effects of estrogen [39-41]. Regarding women, associations of work stress with low health self-esteem and mental disorders have been established [42, 43]. A Finnish study of working women in Helsinki showed an association between psychosocial working conditions and angina symptoms in women - work fatigue was strongly associated with angina symptoms. A meta-analysis by Eller N.H. et al. found a quantitative interdependence between the development of CHD and work-associated psychosocial factors. The authors concluded that the risk of developing CHD increased with high psychological demands at work and low social support. Other studies related to workplace stress also predicted high cardiovascular risk [11, 44].

The wide variety of methods for measuring stress and workload in the scientific literature has made it objectively difficult to compare the impact of work stress on cardiovascular risks. Therefore, regarding studies of work stress and its influence on the risk of cardiovascular death, researchers focused on two specific models, for which there is no doubt about the relationship with the development of CVD. In the 1980s, the Karasek/Theorell "Job strain model" was demonstrated, which represented a cluster of high psycho-emotional stress at work with an inability of independent decision-making opportunities. According to the model, the workers who were most at risk were those who were subjected to high demands without decision-making power. As a result, the "risky" groups were predominantly consisting of women. Nurses, waiters, and middle managers belonged to this vulnerable group, which experienced the influence of control from both subordinates and managers [22]. Later it has been proven that job strain model predicts recurrent cardiovascular events in persons who suffered acute MI and returned to work. Marmot M.G. et al. showed that first-onset CHD is more often found in persons with minimal control capacity at work, and female low-level employees had 1.5 times higher risk of CHD than female supervisors. The analysis of cross-sectional studies showed that those examined in the Job strain model more often revealed conventional CVD RFs [45].

A prospective cohort study examined the association between working during pregnancy and pregnancy-induced hypertension. The connection was not explained by other RFs such as physical activity, work hours, housework, and child care. Gestational hypertension was associated with low decision-making ability and low job complexity among women in low-status positions. The urge to move from low to higher social status also tends to cause chronic social stress [46]. According to Dressler W.W., the risk of developing AH was higher when there was high psycho-emotional stress associated with ambition for promotion. According to another study, career success in working women was a predictor for lower risks of overall mortality [27]. Significantly less research on female populations has been conducted in Siegrist J. "effort-mismatch – reward" theoretical model but it is the one that has identified higher risks of CHD in women. The model demonstrates an increase in cardiovascular risk when combining high workload with low wages [47]. In the following decades, the model has been repeatedly tested through analysis of both single and cohort cross-sectional studies. Siegrist J. suggests testing the model by external and internal cluster measurements. The external cluster is measured by the growth in work-

place demands and material compensation. On the other hand, a workplace stress coping is measured in the internal cluster as it consists of the ways to adapt to stress, including a component of job satisfaction opportunities. For women, the situational (external) cluster, determined by hierarchical advancement and power, plays a much smaller role. At the same time, it turned out that psychological adaptation (internal cluster) for women plays a significant role in determining the cardiovascular risks [48]. In a study conducted in Finland, employees (including more than 200 women) without a history of CVD were examined. They studied the influence of imbalance between labor input and payment, which predicted a high risk of cardiovascular death at duration of follow-up more than 25 years. The researchers found a connection between unidirectional increases in workload and total plasma cholesterol over a five-year follow-up period [49]. There are also studies that combine the independent effects on cardiovascular risks of both models [50]. These include prospective studies on a population of British employees, concerning a four-fold excess of the risk of cardiovascular death at low levels of social support and job rank. Meanwhile, the patterns were found only for the male cohort.

A large cluster of studies investigated the work stress related to the impact of night and shift work on the development of cardiovascular pathology in women. A Danish study established the correlation of the shift work with the 7% higher CVD development. Researchers also connect the development of AH and dyslipoproteinemia with the night and shift work, which in a combination with behavioral CVD RFs increases cardiovascular morbidity and mortality. Thus, there is strong evidence showing that psycho-emotional stress at work adversely affects cardiovascular health in women.

Conclusion

Overall, the research in recent years has been focused on the study of the CVDs psychosocial risk factors not only from the perspective of possible reduction of the cardiovascular risks but in the aspect of searching for the new technologies of preventive intervention as well. At the same time, the demand for such studies due to consistently high levels of cardiovascular morbidity and mortality in the world and in Russia is obvious and is supported by leading cardiologists and epidemiologists.

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Prevalence and features of dyslipidemia in different populations depending on race/ethnicity, gender and age

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Abstract
The increasing number of cardiovascular diseases (CVDs) in both developed and in the majority of developing countries emphasizes the importance of epidemiological research on cardiovascular disease risk factors (RFs) and their relationship, including dyslipidemia. Evidence from international randomized clinical trials suggests that elevated cholesterol levels are associated not only with atherosclerosis, but also with other chronic non-infectious diseases. These relationships are based on changes in lipid metabolism, increased concentration of free fatty acids, insulin resistance, and other mechanisms. Hypertriglyceridemia and decreased high-density lipoprotein cholesterol, being significant independent RFs of cardiovascular diseases, nevertheless show a weaker association compared to hypercholesterolemia, and the possibilities of their pharmacological correction are less bright. Many factors influence the prevalence of dyslipidemia, including certain racial-ethnic group with certain lifestyle, genetic and cultural differences. The same CVD risk factors may differ in males and females. The article discusses the age-related aspects of dyslipidemia prevalence and mechanisms of cholesterol metabolism disorders with a regard to aging processes. We present the data of scientific research on the prevalence and characteristics of dyslipidemia considering race/ethnicity, gender and age.

Keywords: dyslipidemia, cardiovascular disease; racial/ethnic, age and gender differences.

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Introduction

Dyslipidemia is an established risk factor (RF) for cardiovascular diseases (CVD) and can be defined as: elevated serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) or reduced serum high-density lipoprotein cholesterol (HDL-C) concentration [1, 2]. These plasma lipid disorders can be primary, due to the interaction of genetic predisposition and environmental RF, or secondary, from other diseases (e.g., diabetes, hypothyroidism and nephrotic syndrome) [3, 4]. LDL cholesterol is a major modifiable risk factor for the incidence of revascularization, ischemic strokes, atherothrombotic process and CVD mortality [5-7]. The importance of the LDL cholesterol role is confirmed by numerous studies, including clinical trials of proprotein convertase inhibitors subtilisin/kexin 9 (PCSK9), which increase LDL cholesterol receptor expression in hepatocytes, as well as liver clearance of LDL cholesterol [8, 9]. It is known that elevated cholesterol (CH) levels (hypercholesterolemia), especially LDL cholesterol, contribute to the process of atherosclerosis, leading to the deposition of CH and fatty acids in the arterial wall, while HDL cholesterol is usually considered a protective factor [1]. However, while De Freitas E. et al. reported that low HDL cholesterol is a RF of CVD in the elderly [10], a systematic review and meta-analysis by Briel M. et al. showed that elevated HDL cholesterol was not associated with reduced CVD risk or mortality [11]. A National Health and Nutrition Examination Survey (NHANES) report from 2003 to 2006 indicated that 53% (105.3 million) of US adults had at least one lipid metabolism disorder: 27% (53.5 million) had high LDL-CH, 23% (46.4 million) had low HDL-CH, and 30% (58.9 million) had high TG levels. In addition, 21% (42.0 million) of adults in the United States have mixed dyslipidemia, defined as the presence of high LDL-CH in combination with at least one other lipid metabolism disorder [12]. The results of the relationship between the risk of CVD and its complications with dyslipidemia should consider various factors that may determine the intensity of the atherosclerotic process, which may determine the possibility of using medications with cardioprotective and angiorotective effect. Cromwell W. et al. adjusted their data regarding age, sex, BP, smoking and intake of hypolipidemic drugs [13], and Van den Berg M. et al. adjusted their data taking age, sex, BMI, smoking, alcohol intake, diabetes mellitus and intake of hypolipidemic drugs into account [14]. A number of studies have found that elevated TG levels increase CVD risk in men to a greater extent than in women, although the role of TG in the pathogenesis of cardiovascular pathology and atherosclerosis is still unclear. Nevertheless, it may be related to the concentration of CH in TG-rich lipoproteins rather than to the role of TG particles themselves [15].

Racial-ethnic, gender, and age factors effect on dyslipidemia prevalence

One of the most important factors determining the prevalence of dyslipidemia is belonging to certain racial-ethnic groups. According to Pu J. et al. there are significant racial-ethnic differences in the prevalence of dyslipidemia, the mortality rate associated with dyslipidemia, and the response to hypolipidemic drugs [16]. Frank A. et al. found a significant heterogeneity in the pattern of dyslipidemia prevalence, its association with coronary heart disease (CHD) and stroke mortality, and response to hypolipidemic agents in racial-ethnic groups [17]. These differences in dyslipidemia provide important information that may partially explain the differences in the burden of CVD observed in different racial-ethnic subgroups, which is very important and necessary for the prevention, screening and treatment of cardiovascular pathology [7, 8]. Thus, according to Frank A. et al. among all racial-ethnic groups, Indians of Asian origin, Filipinos and Hispanics are at the highest risk of dyslipidemia development and progression, which is consistent with higher rates of mortality from CHD in these cohorts. According to the authors, these are risk groups that should receive more attention for timely detection and treatment of dyslipidemia [17].

U.S. scientists found differences in CHD mortality rates between different racial and ethnic groups. According to Enas E. et al. in the United States, mortality rates from CHD were the highest among African Americans, moderate among Caucasians and Hispanics, and the lowest in some Asian subgroups [18]. Although Asian subgroups traditionally have been referred to as a "model minority", Ye J et al. demonstrated a disproportionately high burden of CHD and stroke mortality in these cohorts of examinees, such as Asian Indians, Filipinos, and Japanese [19]. There are also racial-ethnic differences regarding lifestyle RFs such as unhealthy diet, obesity, and physical inactivity. According to the 2008-2010

National Health Interview Survey (NHIS), Asian adults are less likely to smoke or be obese [20]. Interestingly, both vegetarians and non-vegetarians in India have a higher prevalence of coronary artery disease, considered as "Indian paradox" [18, 21]. Black adults in the United States were more likely to be physically inactive, obese, and sleep-deprived. Hispanics were less likely than non-Hispanic adults to smoke cigarettes, to be sleep-deprived, but more likely to be inactive in terms of aerobic exercise and muscle-building activities [22]. Immigration and acculturation have a profound effect on the lifestyles of both Latinos and Asians in the United States [23]. For example, the Ni-Hon-San study showed an increased rate of CHD mortality and a decreased incidence of stroke among Japanese American men compared with those in Japan, indicating a differential effect of acculturation on Western lifestyles [24].

In 2013, NHANES data showed that the prevalence of high LDL cholesterol was the highest among Mexican men (40%) and women (30%), followed by non-Hispanic black men (33%) and women (31%). Non-Hispanic white men (30%) and women (29%) had the lowest prevalence of high LDL-C levels among these 3 racial/ethnic groups [25].

A study (SHARE) assessing health and health risk in ethnic groups was conducted in three Canadian cities. This study examined the prevalence of CHD in a multinational cohort. The researchers found that South Asians, mostly Asian Indians, had higher levels of CHD and LDL cholesterol compared with Europeans and Chinese [26].

There were mixed data regarding HDL cholesterol levels. According to the NHANES, 20% of black men and 10% of black women were found to have low HDL-CH (less than 40 mg/dL for both men and women), which was lower than in non-Hispanic white men (33%) and women (12%). It has also been demonstrated that Mexican-American men and women had higher prevalence of low HDL cholesterol (34% and 15%, respectively) compared with non-Hispanic whites [23]. According to NHANES data from 2011 to 2012, 25% of Asian American men and 5% of Asian American women had low HDL cholesterol levels. Asian Indian men (53%) and women (55%) had the highest prevalence of low HDL cholesterol among subgroups of Asian Americans; it was also higher than that of the Mexican American men (48%) and women (51%), non-Hispanic black men (34%) and women (40%), and non-Hispanic white men (36%) and women (31%) [17]. Similarly, data from the SHARE study showed that South Asians, including Asian Indians, had an increased prevalence of low HDL cholesterol compared to Europeans and Chinese [26]. Indians not only have low levels of HDL cholesterol but are also characterized by pro-inflammatory small dense dysfunctional HDL cholesterol particles. According to Radhika G. et al., the predisposition of South Asians to lower HDL cholesterol levels is due to a higher prevalence of insulin resistance and associated metabolic abnormalities, which may result from a combination of genetic predisposition, lack of physical activity and high carbohydrate content in the daily diet [27].

The results of studies examining the prevalence of hypertriglyceridemia have been very peculiar. NHANES data from 1999 to 2008 showed that 35% of Mexican Americans had high levels of TG, followed by 33% of non-Hispanic whites and 16% of non-Hispanic blacks [28]. Data from a Northern California clinical cohort from 2008 to 2011 showed that Filipino men (60%) and Mexican women (45%) had the highest prevalence of high TG compared to Mexican men (56%) and Filipino women (42%), Asian Indian men (55%) and women (37%), non-Hispanic white men (43%) and women (28%), and non-Hispanic black men (30%) and women (18%) [17]. Data from the SHARE study showed that South Asians had the highest prevalence of high TG [26]. In the Multi-Ethnic Study of Atherosclerosis (MESA), Goff D. et al. found that ethnic differences were significantly mitigated by providing an equal access to medical care [29].

Considering gender differences in the prevalence of dyslipidemia, according to Heidari S. et al. the risk of CVD in men increases after 40 years. In comparison, this risk in women group develops 7–10 years later [30]. Before the second half of the twentieth century, women were not included in experimental studies, so most of the current knowledge about the main diseases affecting public health comes from studies conducted exclusively in men, and their results were also applied to women [31]. Evidence from the current state of preventive cardiology indicates that health care delivery and outcomes continue to differ between women and men. Particularly alarming are the findings that women with the same CVD risk as men are less likely to receive treatment or preventive recommendations [32].

Despite the fact that CVDs are the main cause of death in women, they are still perceived as a male pathology [33]. Male gender can be a RF of dyslipidemia, which can be caused by excessive fat accumulation, significant increase in blood pressure (BP) and lack of exercise, although men constitute the main workforce in society. In addition, male lifestyle choices with the presence of smoking and alcohol consumption are associated with dyslipidemia, whereas female estrogen has some protective effect on lipid levels [34]. Although women and men tend to have the same CVD risk factors, they show different effects depending on gender. For example, in women, metabolic syndrome is the most important RF for the development of CHD at a young age; smoking more often causes CHD in women than in men; and arterial hypertension (AH) and dyslipidemia in women develop later, but are also worse controlled [35]. Poor control of dyslipidemia in both sexes may be related, on the one hand, to the limitations of the prognostic ability of the SCORE scale to detect CVD, and, on the other hand, to clinical inertia, defined by Phillips L. et al. as "the failure of physicians to start or increase treatment when it was indicated" [36]. This term was later reformulated as therapeutic inertia. Some studies have reported low control of LDL cholesterol in all patients, but especially in women, indicating less intensive treatment of dyslipidemia in women, thus, a greater therapeutic inertia in this group. The ESCARVAL-GENERO study examined 58,970 patients, including 27,311 (46.3%) men and 31,659 (53.7%) women with CVD RF but no CVD (CHD or cerebrovascular disease), who attended routine primary care between 2008 and 2012. The majority of those examined (81.9%, n = 48,300) had been diagnosed with dyslipidemia or had been treated for this pathology, and 18.1% (n = 10,670) had altered lipid levels and were neither diagnosed nor treated, indicating diagnostic inertia. This result was higher in women (20.1%, n = 6358) than in men (15.8%, n = 4312, $p < 0.001$). These differences may be related to gender stereotypes, which refer to a set of imposed and largely assumed perceptions about the characteristics, attitudes, and abilities of women and men [23].

Moreover, women are less likely to receive intensified treatment or achieve optimal treatment effects. When these differences systematically lead to gender inequalities associated with established roles and stereotypes, this can be a determinant of differences in health outcomes. In 2018, Aggarwal et al. concluded that the RFs of CHD should be stratified by gender [7]. Although recent studies show the deleteriousness of gender bias in terms of diagnostic delay and error in women, with no studies evaluating differences in the use of diagnostic criteria for dyslipidemia between men and women. The incidence of CHD in premenopausal women is 3 to 4 times lower than in men [37]. After menopause, due to the loss of vasodilatory properties of estrogen and increased sympathetic activity, the risk of CHD increases and is similar to that in men [38]. The RFs unique to women are the use of oral contraceptives, menopause, hormone replacement therapy, gestational AH and diabetes. Obesity and metabolic syndrome are also more common in women [39].

Age-related factors affecting the prevalence of dyslipidemia, CHD and its complications have been studied profoundly [1]. Plasma cholesterol levels and LDL cholesterol levels are similar in both sexes during infancy and adolescence. LDL cholesterol levels increase progressively in both men and women after the age of 20 years, but more rapidly in men. LDL cholesterol particle size decreases with age in men, whereas in women it remains stable until menopause, after which it becomes smaller [40]. Historically, it has been established that older age is the most contributing factor of dyslipidemia. Both cross-sectional and longitudinal studies have shown that concentrations of TC, LDL cholesterol, and TG rose with age, while the HDL cholesterol concentrations fell [41]. Thus, Chinese researchers studied age-related aspects of dyslipidemia in urban residents of southwestern regions of China. According to Huang C. et al. the prevalence of dyslipidemia decreases with age in men and increases in women. High TG concentrations were detected in men, where they reached their highest values in participants aged 45-54 years old compared with those aged 35–44 years old. Then they decreased in those 55–64 and 65–79 years old. In women, the prevalence of hypertriglyceridemia increased with age. High levels of TC in men did not change significantly with age, while in women hypercholesterolemia increased with age. The prevalence of high LDL cholesterol levels in men increased with age, reaching its highest level in participants aged 55-64 years, and then decreasing thereafter. In women, the prevalence of high LDL cholesterol levels fluctuated with age. The prevalence

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of low HDL cholesterol in men was the highest among participants aged 35-44 years, and then decreased. Among women, there were no significant changes in HDL cholesterol with age [42]. This result was consistent with other studies, which may be related to changes in estrogen levels in women before and after menopause [43, 44].

The aging process is associated with an increase in both TC and LDL cholesterol. Ericsson S. et al. reported an increase of TC from 4.8 mmol/l in young (20-39 years), to 5.14 mmol/l in middle-aged (40–59 years) and to 5.44 mmol/l in elderly (60–80 years) healthy Scandinavian participants [45]. In addition, according to Abbott R. et al., LDL cholesterol levels increased with age from 3.37 mmol/L in the young to 3.76 mmol/L in the middle-aged and to 4.05 mmol/L in the elderly. In addition, the level of very low-density lipoprotein cholesterol either remains stable or increases with age, whereas the level of HDL cholesterol seems to be independent of the aging process [2].

Cho S. et al obtained interesting data regarding the association of age-related dyslipidemia prevalence with education level. In individuals with higher education in all age groups the prevalence of dyslipidemia was relatively lower than in the cohort with lower education level. The prevalence of hypercholesterolemia reached its peak in the 50–59 years old age group regardless of education level, and then declined in the elderly. Up to the fifth decade, the increase in cholesterol was more frequent in the group with low education, and its prevalence was higher in those with high education after 50 years of age. The prevalence of hypertriglyceridemia and hypoalphaliproteinemia was consistently higher in the low-educated group in all age groups. Interestingly, the prevalence of hypercholesterolemia was lower in women in the fourth decade than in the third decade in both the low (11.8% versus 15.8%) and high (14.9% versus 18.6%) education groups. An important fact is that while the level of LDL cholesterol increased with age in the group of persons with high education, this indicator of dyslipidemia in persons with low education showed a decrease in prevalence from 10.4 % at the age of 50–59 years to 5.7 % in the group of examinees 60-64 years (5.7 %) [50].

Based on the laboratory studies of 63,606 different patients conducted in Slovenia between 2008 and 2019, Markovič R. et al. found an increase in the proportion of patients with high levels of TC in the age groups 55-59 years, which then decreased. The proportion of patients with glucose levels above the norm increased until the age group of 75–79 years, and then began to decrease [41]. This decrease, according to the authors, does not mean that patients became healthier, but it indicates that patient survival depends on glucose and lipid levels. The proportion of male patients with elevated levels of TC and LDL cholesterol began to decline between 45 and 49 years of age. In women, this decrease was observed a decade later (age group 55–59 years). The proportion of male patients with normal serum HDL cholesterol levels was significantly lower than the proportion of female patients with normal serum HDL cholesterol levels in all age groups. Importantly, the mean level of TC increased more rapidly than glucose levels and peaked in the age group of 50–59 years. In this age group, mean serum cholesterol levels began to decline, while mean serum glucose levels continued to rise until the age group of 70–79 years. After that, both mean serum cholesterol and glucose levels began to decline. With age, women were characterized by lower glucose levels but higher levels of TC than men. Thus, women reached their highest serum cholesterol levels ten years later than men, with mean serum TC levels never returning to normal in women but remaining elevated. Laboratory results show that the peak proportion of patients with elevated serum cholesterol levels preceded the peak proportion of patients with elevated glucose levels by about 20 years.

According to Gobal F. and Mehta J. at the age of 50 to 60 years (men) and 60 to 70 years (women), serum LDL cholesterol levels remain at a plateau. Women have lower levels of LDL cholesterol than men throughout life, but levels increase sharply after menopause and are higher than in men over age 60 [47]. In addition, Mari A. et al. note higher LDL cholesterol levels in women and higher TG levels in men [48]. As for sex and age differences of serum HDL cholesterol levels, higher serum HDL cholesterol levels were found in female patients compared to male patients regardless of age [32]. According to Markovič R. et al. the decrease in the proportion of the population with abnormal lipid and/or glucose levels may be influenced by medication administration, and in older age by mortality [41].

Considering the pathogenetic mechanisms of age-related changes in the prevalence of dyslipid-

emia, it should be noted that with age there may be disorders of cholesterol metabolism. These include: decrease of LDL cholesterol clearance; potential increase of cholesterol absorption; decrease of bile acid synthesis; decrease of bacterial bile acids modification. According to Morgan A. et al., age-related dysregulation of cholesterol metabolism and accumulation of LDL cholesterol is associated with changes in several key mechanisms, including cholesterol absorption, LDL cholesterol clearance, bile acids synthesis, and subsequent bacterial modification. Several changes occur in the gut microflora with age, including a decrease in the number and species diversity of Lactobacillus and Bifidobacterium. Consequently, it is possible that the age-related decrease in the number of these bacterial species reduces bile acid deconjugation and, in turn, reduces the conversion of CH to bile acids. This may play a role in the accumulation of cholesterol with age [49].

Conclusion

Studies devoted to the role of certain dyslipidemia subtypes and other RFs should be continued, as this will help to explain the higher risk of CVDs in certain groups of subjects with a regard to racial-ethnic groups, sex and age, as well as allow clinicians to make personalized recommendations for the prevention and treatment of dyslipidemia.

Conflict of Interest. None declared.

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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).

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Example of design:

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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.

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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.

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2. Summary with key words
3. List of abbreviations
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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.

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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.

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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.

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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)

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XIV. Journal subscription

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

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