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CLINICAL CASES

Dear colleagues!

The current issue of the Russian Journal of Cardiology is dedicated to urgent and multidisciplinary questions of cardiology and cardiac surgery.

In particular, fundamental and/or personalized cardiology includes the following publications: "New variant of *PRDM16* gene nucleotide sequence in a family with various phenotypic manifestations of the non-compacted myocardium" and "Polymorphism of *ACE*, *AGT*, *AGTR1* genes as genetic predictors of hypertension". The article "Genetic and epigenetic factors regulating the expression and function of the vitamin D receptor in patients with coronary artery disease" addresses the urgent issue of vitamin D importance in such category of patients, which has been the subject of a large number of publications and discussions in recent years.

Although the relevance of COVID-19 is gradually descending, the research and practical issues of this disease remain urgent. In particular, the article "Coronary artery bypass grafting in patients with coronary artery disease and COVID-19: search for an optimal strategy" discusses cardiac surgery during a pandemic, while the paper "Osborn wave in a patient with COVID-19: a case report" presents the patient with such electrocardiographic abnormalities and SARS-CoV-2 infection.

Due to the constant increase in life expectancy and aging-associated cardiovascular changes, the publication "Cardiovascular system status of long-livers in Moscow: the prevalence of cardiovascular diseases and their risk factors" will be not without interest.

The issues of secondary and tertiary prevention in atrial fibrillation and hypertension are discussed in the following papers: "Effectiveness of a comprehensive ambulatory monitoring system for patients with atrial fibrillation after cardioembolic stroke" and "Orthostatic hypertension in cardiovascular risk stratification in hypertensive patients".

The article "Laboratory medicine in modern teaching clinical physicians" discusses the main educational goal of the RJC. Education journal and the growing role of laboratory medicine in training of medical specialists.

Recent successful randomized clinical trials on gliflozins' use are reflected in the publication "Sodium-glucose co-transporter-2 inhibitors in heart failure and chronic kidney disease: the role of empagliflozin".

Two interesting and unusual cases of Takayasu's arteritis and a rare cause of pulmonary hypertension are presented in the following papers: "Takayasu's arteritis in a patient with suspected acute coronary syndrome — a literature review and a case report" and "Difficult diagnostics of a rare cause of pulmonary hypertension: a case report".

We hope that the presented publications will be of interest to a wide range of readers, cardiologists, and scientists.

Respectfully,
Head of the Department of Propaedeutics of Internal Diseases,
Bashkir State Medical University
FESC, IACC, Doctor of Medical Sciences,
Professor Naufal Sh. Zagidullin

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New variant of *PRDM16* gene nucleotide sequence in a family with various phenotypic manifestations of the non-compacted myocardium

Myasnikov R. P.[1], Bukaeva A. A.[2], Kulikova O. V.[1], Ershova A. I.[1], Petukhova A. V.[2], Zotova E. D.[2], Meshkov A. N.[1], Mershina E. A.[3], Kiseleva A. V.[1], Divashuk M. G.[1,4], Pilyus P. S.[3], Kharlap M. S.[1], Mikova V. M.[2], Koretsky S. N.[1], Gandaeva L. A.[5], Sinitsyn V. E.[3], Basargina E. N.[5,6], Boytsov S. A.[7], Snigir E. A.[2], Akinshina A. I.[2], Kashtanova D. A.[2], Makarov V. V.[2], Yudin V. S.[2], Drapkina O. M.[1]

The article presents the examination of three generations of a family with diagnosed left ventricular noncompaction (LVNC) and various phenotypic manifestations of the disease (isolated, hypertrophic and dilated type of LVNC). As a result of a molecular genetics tests, a previously undescribed single nucleotide deletion in the *PRDM16* gene was revealed in all family members with the LVNC phenotype, leading to a frameshift mutation in exon 9 and the formation of a premature termination codon. This gene encodes a transcription factor responsible for after-birth suppressing the expression of genes involved in prenatal development. Despite the presence of previous studies showing the relationship of the *PRDM16* gene with LVNC development, currently there are insufficient data to prove the pathogenicity of the identified variant. However, the segregation of the symptomatic variant in three generations supports the association of the identified variant with LVNC. With the accumulation of information about changes in *PRDM16* in patients with cardiomyopathies, it is possible to change the status of this gene and clarify its contribution to primary heart diseases.

Keywords: non-compacted myocardium, sequencing, phenotype, *PRDM16*.

Relationships and Activities: none.

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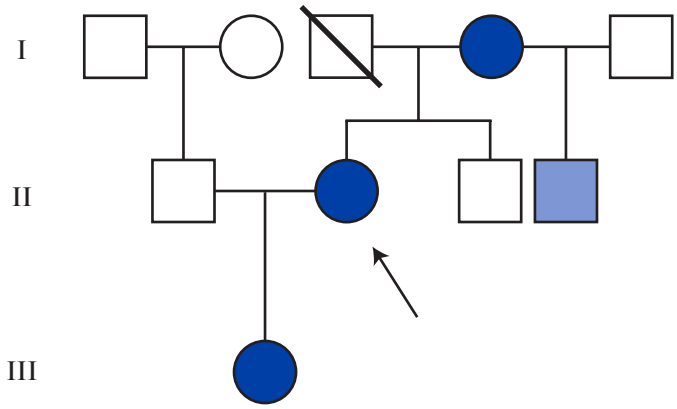
Left ventricular noncompaction (LVN) is a rare disorder characterized by an abnormal myocardial structure with a pronounced noncompact layer and increased trabecularity [1]. In recent years, the incidence of LVN has increased significantly due to improvement of imaging methods. However, along with this, the complexity of correct clinical interpretation of this phenomenon is also growing. There are different conditions with LVN, which varies from primary cardiomyopathies (CMP) and other congenital diseases leading to severe heart failure (HF) and requiring radical treatment, to incidental finding in people without complaints (for example, athletes and pregnant women) [2]. In this regard, the assessment of LVN morbidity, the determination of its contribution in decompensated HF and the prognosis in each case are possible only after a comprehensive analysis of the clinical performance, family and genetic history [3, 4].

According to current estimates, at least half of LVN cases are hereditary; in about 30% of cases, it is possible to detect a pathogenic or potentially pathogenic genetic variant by DNA diagnostics [1]. Genetic determinism, i.e. the presence of genetic variants mediating the LVN is classified as an independent risk factor for fatal cardiovascular events and an unfavorable prognosis of CMP [2]. In this regard, genetic testing is recommended for patients with an established diagnosis of LVN [5]. To date, at least 80 genes are associated with LVN, and this list is expanding with the accumulation of next-generation sequencing (NGS) data. Although a significant proportion of the variants detected in patients with LVN is attributed to cardiac sarcomere protein genes, which are also associated with various types of primary CMP (in particular, *MYH7*, *MYBPC3*, *TTN*). The variety of genetic findings in LVN is much wider and includes a large number of variants in genes encoding many factors of cell development and differentiation, including factors of myocardial embryogenesis, etc. These data support the hypothesis of LVN embryonic origin, however, to clarify the role of such genes and increase the evidence of their relationship with LVN, more data on genotype-phenotype correlations are needed.

This article presents a family with different phenotypic manifestations of LVN with the same polymorphism encoding the transcription factor responsible for after-birth suppressing the expression of genes involved in prenatal development (Figure 1).



I-1	No data available
I-2	No data available
I-3	Died suddenly at 35 (alcohol abuse)
I-4	58 years old, hypertension, cardiomyopathy, hypertrophic type
I-5	58 years old, not examined
II-1	33 years old, no data available
II-2	33-year-old proband, cardiomyopathy, heart failure, cardiac arrhythmias
II-3	38 years old, healthy
II-4	25 years old, increased left ventricular trabecularity
III-1	4 years old, cardiomyopathy, heart failure

Figure 1. Pedigree.

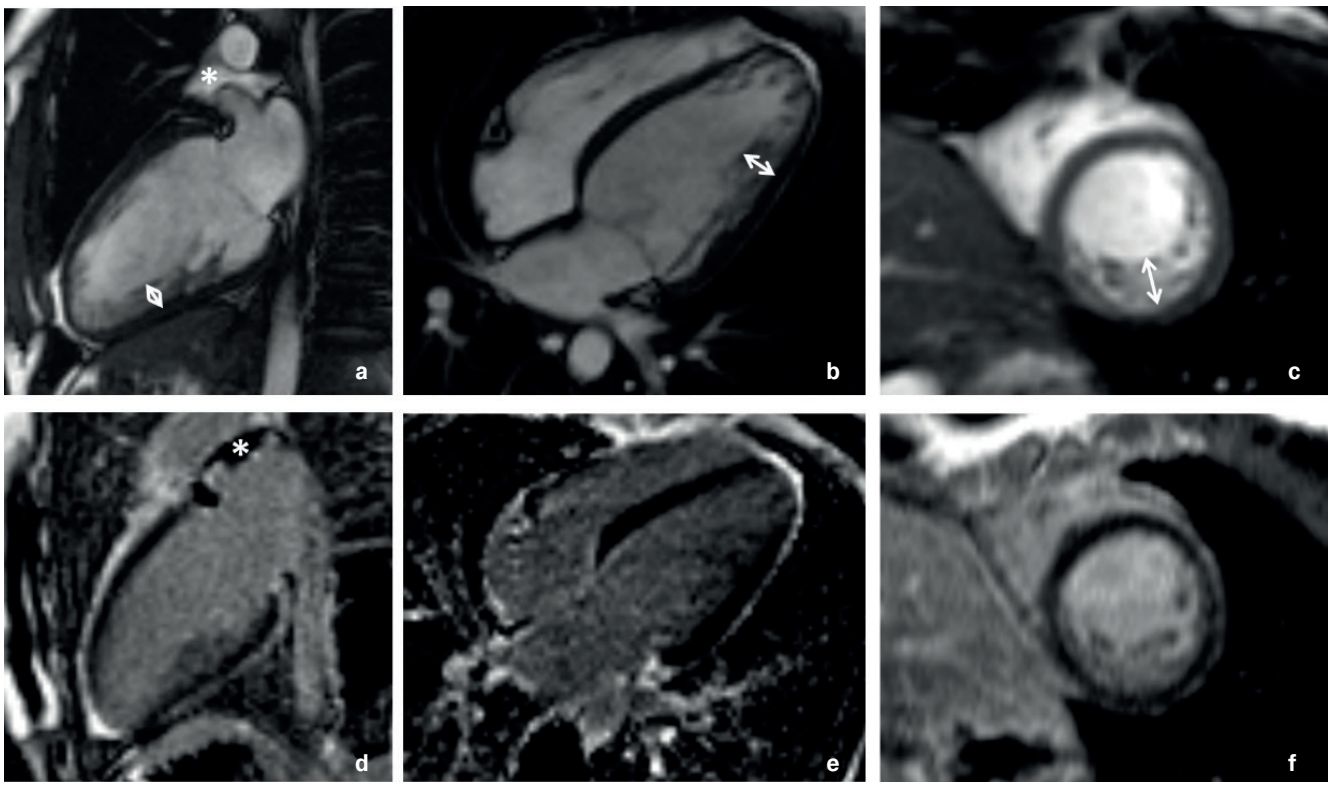


Figure 2. Cardiac MRI of the proband (II-2). (**a**-**c**) cine-mode, SSFP sequence: **a** — long axis 2 chamber view, **b** — long axis 4-chamber projection, **c** — short axis, (**d**-**f**) — delayed contrast enhancement, IR sequence with suppression of myocardial signal. There are no areas of intramyocardial fibrosis, scarring and post-inflammatory lesions.
Notes: arrows indicate an increase in LV trabecularity in the medial lateral and lower segments; the non-compact and compact layer thickness is 12-15 and 5 mm, respectively; * — a small amount of free fluid in the superior pericardial recess.

Table 1

Clinical data

Patients/Symptoms	I-4	II-2	II-4	III-1
Age, years	59	33	25	2
Sex	F	F	M	F
Height, cm	162	167	160	
Weight, kg	74	67	60	
Echocardiography (LVN)	+	+	+	+
MRI (LVN criteria)	+	+	-	Not conducted
Arrhythmias	+	+	-	+
HF	-	+	-	+
Implantable devices	-	-	-	-
EF	54%	46%	56%	36%
TEE	-	-	-	-
Sudden death	-	-	-	-
Neuromuscular diseases	-	-	-	-
CHD	-	-	-	+

Abbreviations: CHD — congenital heart disease, MRI — magnetic resonance imaging, left ventricular LVN — non-compaction, TEE — thromboembolic events, EF — ejection fraction, HF — heart failure.

Case report

The proband is a 33-year-old normosthenic woman who is being followed up by a cardiologist at the National Medical Research Center for Therapy and Preventive Medicine.

At the age of 27, she began to feel palpitations during the first pregnancy. Then, there was a short of breath, dizziness. In October 2015, she underwent examination at the National Medical Research Center for Therapy and Preventive Medicine. In blood tests, all the standard parameters were within the normal range. Twenty-four hour Holter monitoring (24HM) revealed rare premature ventricular contractions (PVCs). Echocardiography revealed end diastolic dimension (EDD) of 5,2 cm, interventricular septum thickness (IVST) of 0,8 cm, left ventricle (LV) ejection fraction (LVEF) of 47%, as well as the signs of LVN in the apex and lateral wall (Chin, Stollberger, Jenni criteria). Contrast-enhanced cardiac magnetic resonance imaging (MRI) (Figure 2) showed data suggestive of a myocardial noncompaction without cavity dilatation (LVEF 45%). Beta-blockers, angiotensin-converting enzyme inhibitors,

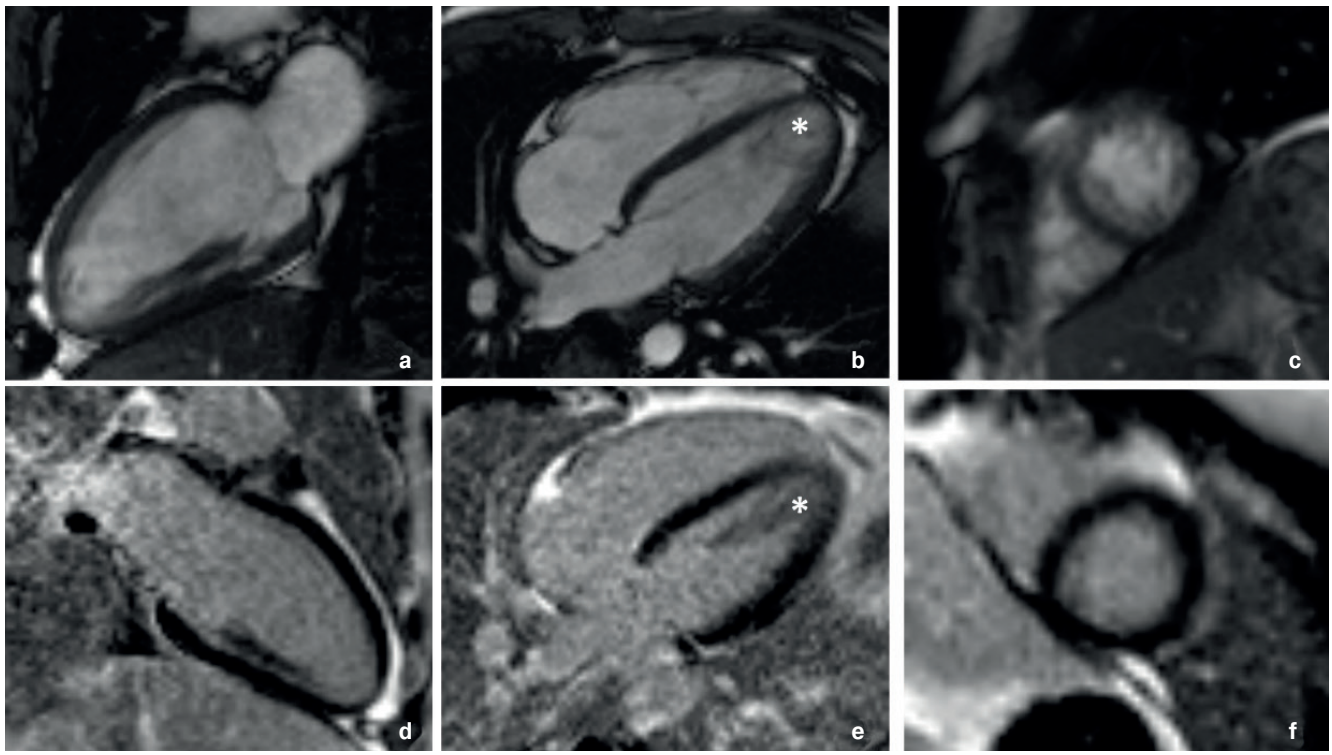


Figure 3. Cardiac MRI of the proband's half-brother (II-4). (**a**-**c**) cine-mode, SSFP sequence: **a** — long axis 2 chamber view, **b** — long axis 4-chamber projection, **c** — short axis, (**d**-**f**) — delayed contrast enhancement, IR sequence with suppression of myocardial signal. There are no areas of intramyocardial fibrosis, scarring and post-inflammatory lesions.
Note: * — increased LV apex trabecularity due to the "loose" papillary muscle structure.

and mineralocorticoid receptor antagonists were prescribed. After hospitalization, the patient felt satisfactory and did not take medications all the time. There was deterioration since the spring of 2017, when the palpitations and weakness appeared. According to 24HM with bisoprolol therapy (2,5 mg a day), a sinus rhythm with a heart rate (HR) of 46-78-144 bpm, 6640 isolated PVCs, 10638 bigeminy episodes, 40 coupled PVCs were detected, no pauses were recorded. Echocardiography revealed EDD of 5,3 cm, IVST of 0,8 cm, LVEF of 38%, type 2 diastolic dysfunction, signs of LVN in the apex and lateral wall (Chin, Stollberger, Jenni criteria) (Chin, Jenni, Stollberger criteria [6-8]). The therapy was altered as follows: increasing bisoprolol dose, adding spironolactone and perindopril. The patient's condition stabilized. With annual dynamic follow-up, according to echocardiography, the normal cardiac dimensions and LVEF of 45% are preserved.

The diagnosis of LVN in the proband was established by echocardiography criteria for myocardial noncompaction [9] and was confirmed by MRI criteria (Jacquier and Petersen) [10, 11].

Phenotypic cascade screening

Pedigree and clinical data on the proband's relatives are presented in Figure 1 and Table 1.

The 38-year-old biological brother of the proband underwent cardiac screening, which did not reveal LVN.

The proband's maternal normosthenic (height 160 cm, weight 60 kg) half-brother, 25 years old, underwent a comprehensive cardiac examination. All standard blood indicators were within the normal range. Echocardiography revealed EDD of 4,9 cm, IVST of 1,0 cm, LVEF of 53%, as well as signs of myocardial noncompaction in the apex, lateral and posterior walls (Stollberger criterion). According to cardiac MRI (Figure 3), the cardiac cavities were not dilated, the LV contractility was not reduced; there were no fibrosis, scarring and post-inflammatory lesion areas; the myocardial structure was normal, the trabecularity of middle and apical segments of the lateral and posterior LV walls was slightly increased.

The 58-year-old proband's mother. During the third birth, an increase in blood pressure (BP) up to 160/100 mm Hg was noted. She was not further examined and BP was not measured. From the age of 50 years, there was BP increase up to 160-180/100-110 mm Hg. She did not take antihypertensive drugs. For the first time, she was examined at the National Medical Research Center for Therapy and Preven-

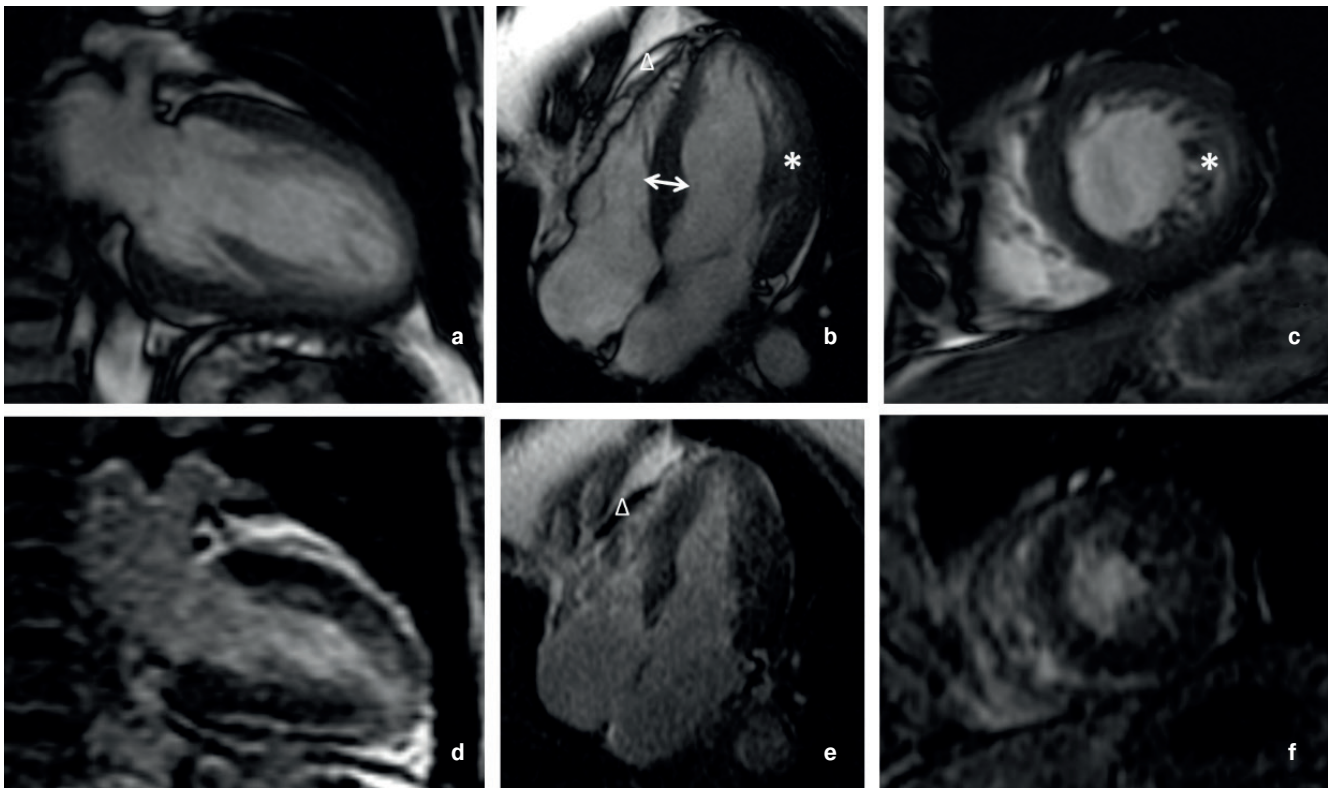


Figure 4. Cardiac MRI of the proband's mother (I-4). (**a**-**c**) cine-mode, SSFP sequence: **a** — long axis 2 chamber view, **b** — long axis 4-chamber projection, **c** — short axis, (**d**-**f**) — delayed contrast enhancement, IR sequence with suppression of myocardial signal. There are no areas of intramyocardial fibrosis, scarring and post-inflammatory lesions.
Notes: arrows indicate a hypertrophied anterior septal segment (14 mm thick); * — arrows indicate an increase in LV trabecularity in the medial lateral segments; the non-compact and compact layer thickness is 15 and 6 mm, respectively; Δ — a small amount of fluid in the pericardial cavity from the right side.

tive Medicine at the age of 55. Echocardiography revealed signs of myocardial noncompaction, IVST of 1,2 cm, outflow tract 1,4 cm, LV posterior wall of 1,5 cm, EDD of 5,4 cm, inceased LV trabecularity, especially in the posterolateral LV wall area. The LV myocardium had sponge-like network structure with intertrabecular lacunae stained by Doppler color flow mapping. The ratio of compact (6 mm) and non-compact (18) myocardial layers in the posterior wall area was 3,0 (pronounced myocardial noncompaction according to the Chin, Stollberger, Jenni criteria). Electrocardiography revealed sinus rhythm with a heart rate of 65 bpm, left axis deviation, complete left bundle branch block. Contrast-enhanced cardiac MRI (Figure 4) revealed asymmetric LV hypertrophy (thickness of the basal anterior and anterior septal segments — 13-14 mm; thickness of other basal and middle segments — ⩽7-9 mm; apical — 4-6 mm), papillary muscle hypertrophy (9-12 mm) with increased trabecularity in the apex and along the anterolateral LV wall with a non-compact and compact layer of 10-20 mm and 4-7 mm thick, respectively. The non-compacted myocardial mass was 16% of compacted one. After the examination, angiotensin-converting enzyme inhibitors and beta-blockers were prescribed, which the patient takes irregularly. Currently, the BP is 160-170/90 mm Hg.

The proband's father died suddenly at the age of 35 (prior alcohol abuse).

The 4-year-old proband's daughter. The girl did not gain weight from 3 months old, then shortness of breath, tachypnea appeared. During a routine examination, a congenital heart defect was suspected. Echocardiography revealed LVEF of 35%, increased LV trabecularity, left to right shunt in the central part of interatrial septum measuring 3 mm. Renal ultrasound showed an increase in both kidneys. Therapy was prescribed with prednisolone 5 mg a day, spironolactone 12,5 mg a day, and digoxin 0,05 mg a day. There was no positive response to treatment. To verify the diagnosis, she was referred to the National Medical Research Center for Children's Health. Echocardiography demonstrated pronounced left heart dilatation (EDD, 3,8; ESD, 3,0 cm), LVEF of 36%, LVN, patent foramen ovale of 1,5 mm. The 24HM revealed sinus rhythm with

Table 2

The severity of myocardial non-compaction in the proband and his relatives, according to cardiac MRI

№	Non-compacted/compacted ratio																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
I-4	0,0	0,0	0,0	1,8	1,3	2,8	0,8	0,7	0,0	1,6	2,4	2,6	1,6	0,4	1,2	1,4	3,5
II-2	0,0	0,0	0,0	3,9	4,6	2,5	2,3	0,0	0,0	3,1	3,4	3,7	2,1	2,1	3,1	4,1	7,9
II-4	2,2	1,1	0,0	2,3	0,6	3,0	2,6	0,9	0,0	1,4	2,3	2,1	1,1	1,8	1,6	1,8	5,2

Table 3

Cardiac MRI parameters in the proband and his relatives

№	EDD, ml/m^2	LVEF, %	Grothoff				Jacquier %	Petersen
			NM mass index g/m^2	NM/myocardial mass, %	Non-compacted/ compacted ratio ⩾3:1 in 1 segment 1-3, 7-16	Non-compacted/ compacted ratio ⩾2:1 in 4-6 segments		
I-4	67	54	16	17	-	+	17,00%	+
II-2	68	45	18	18	+	+	18,00%	+
II-4	87	67	11	16	-	+	16,50%	+

Abbreviations: EDV — end diastolic volume, NM — noncompacted myocardium, LVEF — left ventricular ejection fraction.

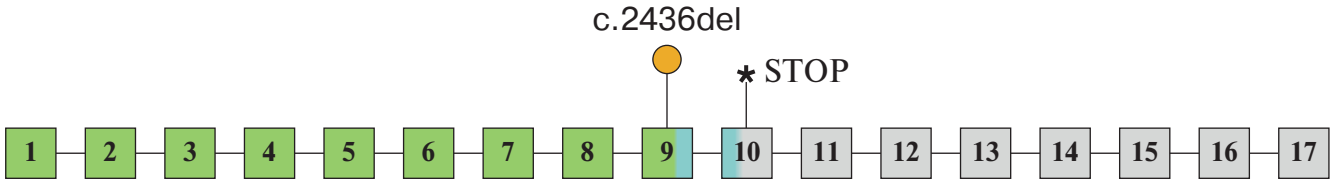


Figure 5. Exon structure of the *PRDM16* gene. The correct reading sequence is marked in green, the reading area in the wrong reading frame is marked in blue, and the unreadable area is marked in gray. A yellow marker indicates a mutation, an asterisk indicates a premature stop codon.

a heart rate of 80-122-172 bpm, preexcitation phenomeno, an isolated PVC. With selected therapy, the condition improved. She constantly takes amiodarone 50 mg a day, conventional diacarb therapy, digoxin 0,02 mg a day, captopril 2,5 mg 3 times a day, furosemide 3 mg a day, carvedilol 0,78 mg 2 times a day. At present, the myocardial noncompaction manifistations are practically arrested. The child develops normally.

Tables 2 and 3 combine the imaging results of the proband and her relatives.

Genetic cascade screening

Proband and all first-degree relatives underwent molecular genetic analysis.

Whole genome sequencing and bioinformatics analysis

DNA was isolated from whole blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Germany). The whole genome sequencing (WGS) library was prepared using the Nextera DNA Flex kit (Illumina, USA) according to the manufacturer's instructions. The average sequencing depth (150 bp) was 30X or more. The reads were aligned to the reference genome (GRCh38), and small variants were found using the Dragen Bio-IT platform (Illumina, USA) and refined using GLnexus [12]. The annotation was carried out using Ensembl VEP [13]. For clinical interpretation, nucleotide sequence variants in LVN-related genes according to the available literature, with frequencies <0,5% in the gnomAD database, were selected. The assessment of the pathogenicity of the variants was carried out in accordance with the current national guidelines for NGS interpretation [14]. Findings were verified by bidirectional Sanger sequencing.

Results of molecular genetic analysis

A molecular genetic analysis revealed a previously undescribed single nucleotide deletion in the *PRDM16* gene, leading to a reading frame shift in exon 9 and the formation of a premature stop codon (NM_022114.4: c.2436delT; NP_071397.3: p.Ala813ProfsTer58) (Figure 5). The variant was

confirmed in the proband, her daughter, mother and maternal half-brother. Based on the actual pathogenicity criteria, the find was classified as a pathogenic variant (class V). This variant was not found in the proband's biological brother.

Discussion

This paper presents a family with different phenotypes of LVN. The most severe course of the disease is observed in the proband's daughter, who was diagnosed with dilated LVN with severe heart failure. The proband had an isolated LVN with a slight decrease in LV systolic function to 46%. The clinical picture is dominated by symptomatic cardiac arrhythmias in the form of frequent PVCs, without ventricular tachycardia runs. In the proband's mother, attention is drawn to myocardial hypertrophy against the background of LVN, which, in turn, may be due to an increases BP. Given the asymptomatic course, the actual onset of hypertension remains unknown, and therefore it is not possible to rule out hypertension as a cause of myocardial hypertrophy against the background of an initially compromised myocardium.

All family members with the LVN phenotype (the proband, her daughter, mother, and maternal half-brother) were found to have the *PRDM16* pathogenic variant, leading to the loss of a gene copy. *PRDM16* encodes a transcription factor protein containing zinc finger domains. *PRDM16* forms complexes with various transcriptional cofactors and chromatin modulators. Depending on the biological task, it can stimulate or suppress tissue-specific gene expression. The role of PRDM16 has been extensively studied in adipose tissue [15]. Simultaneously, the expression of *PRDM16* in mouse and human cardiomyocytes was shown [16, 17].

The association of the *PRDM16* gene with LVN was first suggested in the study by Arndt A-K, et al. in 2013 [16] based on high prevalence of dilated CMP and LVN in carriers of 1p36 deletion of on chromosome 1, which includes this gene. Subsequent studies have confirmed the role of variants leading to the loss of *PRDM16* copy in the development of LVN and dilated CMP in children [18]. In experiments on *PRDM16* knockout mice, the role of *PRDM16* in the development of hypertrophic CMP was shown [17, 19]. Normally, *PRDM16* plays a protective role, but the absence of *PRDM16*, according to Cibi et al. (2020), leads to myocardial hypertrophy, excessive ventricular fibrosis, mitochondrial dysfunction and metabolic disorders in the cell, which contributed to heart failure in adulthood [17]. The effect is mediated by the reactivation of the genetic program of embryogenesis in adult mice, i.e. preservation of high activity of genes involved in embryonic development, but in a deactivated state after birth. In *PRDM16* knockout mice, activation of hypertrophic genes *NPPA*, *NPPB*, *MYH7*, *MYL14*, increased expression of genes involved in fibrosis development (*TGFb2, CTGF, TIMP4, LTBP2*), genes involved in carbohydrate metabolism (*BDH1, PDK4, GLUT1, HMGCS2, PPARG*), decreased expression of genes involved in fatty acid oxidation (*FASN, CD36, SCD1, SCD2, ADIPOQ*), genes responsible for mitochondrial function (*mt-ND4, GPAM, UCP3, DLAT, MTHFD2*), iron metabolism (*TFRC, HAMP, ALAS1, ALAS2, LCN2*) and others [17]. Cibi DM, et al. (2020) also showed that hypertrophic CMP could develop in young mice, but in response to metabolic stress [17].

However, there are still too few clinically significant findings for variants in the *PRDM16* gene to confidently assess its contribution to disease etiology. In the Clinical Genome Resource database (www.clinicalgenome.org), the level of evidence for a gene-disease relationship for *PRDM16* is currently designated as limited. The importance of the *PRDM16* gene product for the normal development of cardiomyocytes has been shown in animal models [16]. However, the available data are insufficient for an unambiguous conclusion about the association of this gene with LVN and primary CMP.

Cosegregation of a variant with symptoms within the family is one of the key arguments in favor of the association of this variant with disease and the basis for increasing the pathogenicity class. We believe that our finding confirms the available data on *PRDM16* role in the pathogenesis of LVN and indicates the rationale of including this gene in genetic panels for CMP diagnosis. However, the question of the diversity of clinical manifestations within the same family remains open. First, according to the literature, the *PRDM16* variants themselves can be associated with both diastolic and hypertrophic CMP (in an animal experiment). There are no explanations for this fact in the literature. Secondly, the severe phenotype in the proband's daughter allows to expect the presence of a second pathogenic variant, which aggravates the CMP course, but no other potentially significant variants were identified in the child. Thirdly, the early and more severe course of LVN in a proband's daughter may be the result of metabolic disorders in the neonatal period. There are no clear anamnestic data in favor of this assumption, however, the clinical stabilization and the normal child development over the past three years speak in favor of prior stress factor, which led to metabolic disorders and triggered an episode of significant activation of genes responsible for embryonic development, which was not prevented due to absence of *PRDM16* expression.

Conclusion

This paper presents a family with different phenotypic manifestations of LVN in the presence of the same previously undescribed *PRDM16* gene variant encoding a transcription factor responsible for afterbirth suppressing the expression of genes involved in prenatal development. The segregation of the symptomatic variant in three family generations testifies in favor of the association of the identified variant with LVN. At the moment, due to the low awareness of *PRDM16* gene contribution in the disease development, the influence of its variants on the clinical course and, moreover, about the therapy personalization for carriers of such variants, we cannot in any way change the tactics of patient management based on our findings. However, in the context of the increasingly widespread introduction of high-throughput molecular genetics methods into the patient monitoring strategies with primary heart diseases, the information of such findings, which do not carry any obvious practical benefit at this stage, seems necessary to draw attention to insufficiently studied candidate genes for LVN. The current scheme of DNA diagnostics of CMP often involves focusing attention on well-studied genes. The variant discovered by us and its cosegregation with LVN signs in three generations, together with the previous literature data on *PRDM16* findings, indicate that this gene also deserves the attention of clinicians and inclusion in diagnostic panels. The accumulation of information on *PRDM16* changes in patients with CMP will make it possible to clarify the contribution of this gene to primary heart diseases and will develop knowledge about their etiology in general.

Relationships and Activities: none.

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Coronary artery bypass grafting in patients with coronary artery disease and COVID-19: search for an optimal strategy

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Extent of cardiac surgery aid has dropped significantly globally due to reallocation of health care resources due to COVID-19 pandemic.

Aim. To evaluate the results of chosen management strategy for patients with coronary artery disease (CAD) and COVID-19 manifested in the early postoperative period after coronary artery bypass grafting.

Material and methods. We present our experience of treating 19 patients with CAD and COVID-19 manifested in the early postoperative period after coronary artery bypass grafting. The main symptoms of COVID-19 in these patients were high-grade fever, severe general weakness, shortness of breath, and decreased blood oxygen saturation. Laboratory data showed significant increases in fibrinogen, C-reactive protein, ferritin, procalcitonin, and D-dimer levels. In all patients, according to the chest computed tomography, a picture of unilateral or bilateral multisegmental pneumonia in the form of ground-glass opacity areas was determined. The damaged lung area varied from 10% to 55%.

Results. Patients were treated in accordance with the Russian guidelines, followed by transfer to continue therapy in specialized infectious diseases hospitals. Sixteen patients transferred to infectious diseases hospitals were subsequently discharged from in a satisfactory condition. Three patients died from various complications of COVID-19 (mortality rate, 16%).

Conclusion. The development of new screening strategies, standard guidelines and protocols for the management of cardiac surgery patients in a pandemic will contribute to an earlier detection of COVID-19 and, accordingly, a timely change in treatment strategy.

Keywords: COVID-19, coronary artery disease, coronary artery bypass grafting.

Relationships and Activities: none.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first described in early December 2019 and has rapidly spread globally, significantly disrupting healthcare delivery in many countries. The extent of cardiac surgical care also significantly changed due to the redistribution of bedspace resources, which decreased number of cardiac surgery operations around the world. While the measures applied have been beneficial for patients with coronavirus disease 2019 (COVID-19), the implications of postponing elective cardiac surgery for cardiovascular patients need to be considered. It can be assumed that these patients will have progression of the underlying disease, which will increase the number of patients in need of emergency cardiac surgery.

Currently, there are papers where the authors report successful cases of cardiac surgery in COVID-19 patients [1, 2]. This is a very rewarding experience to understand how cardiac surgery can be adapted to work in a pandemic.

In this article, we want to present our experience in cardiac surgery of patients with coronary artery disease (CAD) and COVID-19 manifested in the early postoperative period after coronary artery bypass grafting (CABG). Given that the incubation period is up to 14 days, it is highly likely that most of these patients had COVID-19 during surgery.

Material and methods

In 2020, 315 patients with CAD underwent elective or emergency CABG (isolated or in combination with treatment of valvular heart disease) in the cardiac surgery department № 11 of V. P. Polyakov Samara Regional Clinical Cardiology Dispensary. In 19 patients, the early postoperative period was complicated by COVID-19 pneumonia. The preoperative characteristics of these patients are presented in Table 1 and some laboratory parameters in Table 2.

All patients participating in our study signed written informed consent. This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee of V. P. Polyakov Samara Regional Clinical Cardiology Dispensary approved this study.

Statistical analysis. Quantitative variables are presented as mean with standard deviation; categorical variables — as value and its percentage. Descriptive statistics were used to analyse the results.

Results

In the preoperative period, 3-5 days before the procedure, all patients underwent an analysis for identification of SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swabs by real-time polymerase chain reaction (RT-PCR). All patients were negative for SARS-CoV-2 RNA.

All patients (n=19) with positive SARS-CoV-2 tests in early postoperative period after CABG, operations were performed through a median sternotomy, under cardiopulmonary bypass and blood cardioplegia. In addition to CABG, three patients (16%) underwent treatment of mitral insufficiency. The mean duration of cardiopulmonary bypass was 58,3±11,2 minutes, while the artificial ventilation after surgery lasted 8,3±2,2 hours. No patient had resternotomy for bleeding in the first 24 hours after surgery.

In the early postoperative period (3-5 days), these patients manifested with COVID-19. The following symptoms were common to all patients:

- high-grade fever, poorly treated with standard antipyretics;
- general weakness, more pronounced than in patients after CABG without COVID-19;
- severe shortness of breath;
- moderate (92-95%) to severe (<90%) decrease in blood oxygen.

According to chest X-ray, only one patient (on the 4th day after surgery) was diagnosed with double pneumonia, while other patients (on the 3-5th day after surgery) had normal chest X-ray performance.

Table 1

Preoperative characteristics of patients

Parameter	
Age, years	67±6
Sex, male, n (%)	13 (68%)
Preoperative echocardiography, CA	
Triple-vessel coronary artery disease, n (%)	19 (100%)
Valvular heart disease requiring surgical treatment, n (%)	3 (16%)
LVEF, %	57±16
Comorbidity, n (%)	
Diabetes	5 (26%)
Obesity, BMI >30 kg/m^2	7 (37%)
Hyperlipidaemia	16 (84%)
Hypertension	19 (100%)
Chronic kidney disease	8 (42%)
Cerebrovascular disease	5 (26%)
Prior stroke	2 (11%)
Type of surgery, n (%)	
Elective	11 (58%)
Emergency	8 (42%)

Abbreviations: BMI — body mass index, CA — coronary angiography, LVEF — left ventricular ejection fraction.

Table 2

Changes in laboratory parameters

Parameter	Before surgery	After surgery	Normal values
WBC ($\times 10^9$/L)	8,3±2,8	18,5±4,5	4-9
Lymphocytes (%)	21±6	15±9	19-37
Haematocrit (%)	0,41±0,09	0,32±0,04	0,36-0,48
Platelet count ($\times 10^9$/L)	230±95	210±55	180-320
Creatinine (mmol/L)	110,0±38,0	125,0±14,0	44,0-115,0
Fibrinogen (g/L)	2,3±0,8	8,2±2,3	2-4
C-reactive protein (mg/L)	0,5±0,2	10,5±3,2	0,00-1,00
Ferritin (mg/L)	45,0±18,0	230±3850	10,0-300,0
D-dimer (ng/ml)	0,2±0,1	2,3±0,5	0-0,5
Procalcitonin (mg/ml)	0	1,5±0,3	0-0,046

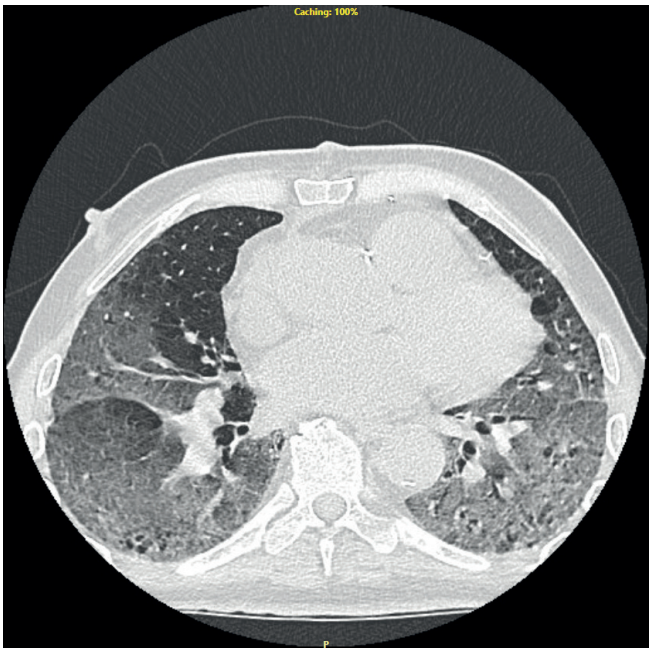

Figure 1. Chest CT scan of the patient 4 days after CABG with signs of pneumonia.

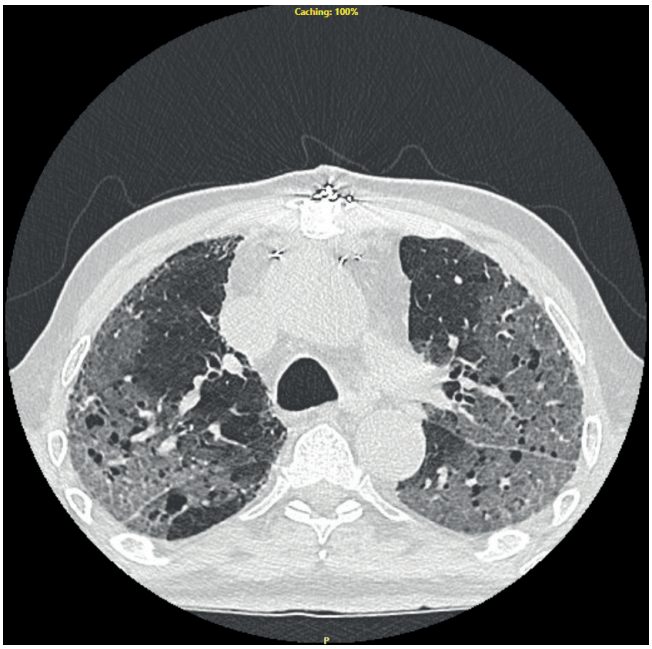

Figure 2. Chest CT scan of the patient 5 days after CABG with signs of pneumonia.

According to chest computed tomography (CT), all patients had a picture of single or double multisegmental pneumonia in the form of ground-glass opacity areas. The lesion area of lungs varied from 10% to 55% (Figures 1, 2).

In all patients, according to laboratory tests, an increase in the level of fibrinogen, ferritin, procalcitonin, C-reactive protein and D-dimer was noted (Table 2).

After suspicions of COVID-19, the patients were re-analysed for SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swabs using real-time RT-PCR and 11 (57,8%) patients were positive.

Patients with suspected COVID-19 were sequestered in an isolation ward. Conservative treatment was carried out in accordance with Russian Ministry of Health guidelines [3]. All patients were transferred to infectious diseases hospitals within 24 hours after detection of pneumonia using CT.

Sixteen patients transferred to infectious diseases hospitals were subsequently discharged from hospitals in a satisfactory condition on days 14-17 after transfer. Three patients died from various COVID-19 complications in the next 7-10 days (mortality rate, 16%). Two of them, 65- and 72-year-old men, who underwent elective isolated CABG, did not have severe comorbidities. The third deceased patient, a 76-year-old woman, underwent a combined operation — CABG and mitral valve repair. Among the comorbidities, the woman had class I obesity, stage IIIB chronic kidney disease, type II diabetes.

Discussion

The COVID-19 pandemic has led to a significant decrease in extent of elective cardiac surgery worldwide. In addition, cardiologists and cardiac surgeons faced the need to solve a serious problem: the risks arising from postponing surgery in cardiovascular patients should be correlated with the risks of performing surgery during the incubation period or the hospital-acquired COVID-19.

Currently, there are few data on surgical treatment outcomes in patients with COVID-19. Lei S, et al. reported the treatment outcomes of 34 patients who underwent various operations during the COVID-19 incubation period. The authors suggested that surgery may worsen the progression of disease, since the mortality rate among these patients was 20,6% (higher than in surgical patients without COVID-19) [4]. The international multicenter cohort COVIDSurg Collaborative study with 1128 patients with confirmed COVID-19 who underwent a wide range of operations, the 30-day mortality rate was 23,8%, which is also higher compared to patients without COVID-19 [5].

Rescigno G, et al. [6] presented the outcome of emergency CABG surgery in an asymptomatic patient who died in the early postoperative period due to COVID-19 related pulmonary complications. The authors acknowledge that an undiagnosed infection may have caused a refractory pathological response after cardiac surgery. Indeed, recent studies have suggested that COVID-19 patients are at a higher risk of thromboembolism. In addition, there is a consensus that SARS-CoV-2 has a direct adverse effect on the myocardium due to the high expression of angiotensin-converting enzyme 2 [7].

Thus, the available data assume that cardiac surgery patients are the most vulnerable cohort of patients who have worse outcomes in the presence of concurrent COVID-19. This is also confirmed by our results of cardiac surgery treatment of patients in the incubation period of COVID-19. Mortality after CABG among these patients was 16%, while the average mortality worldwide in this category of patients is ~1%.

At the same time, a number of authors reported relatively satisfactory outcomes of CABG in patients during the incubation period of COVID-19, as well as in height of disease [1, 2]. The analysis of these works is necessary to develop a certain strategy for the management of cardiac patients in the context of COVID-19 pandemic.

The outcomes of CABG obtained by us and foreign authors in patients with CAD and COVID-19 allow to single out following recommendations:

1. All patients indicated for cardiac surgery should undergo a full preoperative examination, after which, a multidisciplinary team of specialists (Heart Team) should assess the urgency of surgery;
2. To reduce the risk of hospital-acquired COVID-19, patients should be in the hospital for as little time as possible before the operation, and after procedure, it is necessary to minimize the number of patient contacts with others;
3. Routine testing for SARS-CoV-2 should undergo all patients preparing for surgery to identify asymptomatic and subclinical disease;
4. Considering that the sensitivity of RT-PCR for SARS-CoV-2 RNA in nasopharyngeal swab is <70% (according to some data, 30-40%), it is necessary to analyse the level of laboratory infection markers (C-reactive protein, ferritin, procalcitonin, fibrinogen, D-dimer), as well as data from additional diagnostic tests, such as measuring the blood oxygen saturation, and in doubtful situations — chest CT;
5. Any clinical change suspecting COVID-19 in the perioperative period is an indication for additional RT-PCR and chest CT (chest CT has a higher sensitivity (98%) than RT-PCR to determine the COVID-19);
6. When COVID-19 is confirmed, it is necessary to start treatment as soon as possible in accordance with current guidelines.

Conclusion

Despite the COVID-19 pandemic, it is necessary to continue to provide cardiac surgery for cardiovascular patients. The development of new screening strategies, standard guidelines and protocols for the management of cardiac surgery patients in a pandemic will contribute to an earlier detection of COVID-19 and, accordingly, a timely change in treatment strategy.

Relationships and Activities: none.

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Effectiveness of a comprehensive ambulatory monitoring system for patients with atrial fibrillation after cardioembolic stroke

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Aim. To improve the long-term outcomes of patients with atrial fibrillation (AF) after cardioembolic stroke by creating and testing a comprehensive ambulatory monitoring system.
Material and methods. The present study included 139 AF patients after cardioembolic stroke for the period 2016-2019, of which 80 (57,55%) were women and 59 (42,45%) were men. The mean age of the patients was 72,25±6,33 years. Before the hospital discharge, all patients signed an informed consent and were randomized into two groups. Patients of the group I (n=72) were followed up during the year in accordance with a specially developed comprehensive ambulatory monitoring system. This system included a rehabilitation program created individually for each patient, monthly visits to a physician-researcher, during which a complex of diagnostic tests was carried out. Also, the changes of complaints, symptoms, and medical adherence were assessed. The latter was corrected. A physician talked with the patient's relatives about the need to comply with the recommended medication regimen, supporting the motivation for treatment. Patients of group II (n=67) were followed up at the primary care level in accordance with the current program, and a control visit to was performed for them once — after 12 months.
Results. After one-year follow-up, a significant decrease in all-cause mortality was obtained in the first group in comparison with the second one: 3 (4,17%) and 18 (26,87%) deaths, respectively (p=0,021).
In addition, in group II, a relationship was found between the death and absence of anticoagulant therapy (odds ratio, 7,68; 95% confidence interval, 1,59-37,03; p=0,01). The ROC analysis confirmed the relationship between the absence of anticoagulant therapy and death, while the regression quality was good (area under the curve, 0,77, sensitivity — 94,74%, specificity — 59,17%)
Conclusion. Comprehensive ambulatory monitoring program for AF patients after cardioembolic stroke has proven high effectiveness, and its widespread practice is an urgent task of modern healthcare.

Keywords: atrial fibrillation, cardioembolic stroke, ambulatory monitoring, secondary prevention.

Relationships and Activities: none.

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Atrial fibrillation (AF) is a type of arrhythmia that occurs in 2-4% of the adult population. In the coming years, a further increase in AF prevalence is expected, both due to an increase in the life expectancy of population, and due to the improvement of diagnostic methods [1]. This arrhythmia is associated with a high risk of stroke and other thromboembolic events (TEE) [2, 3]. Stroke is the leading cause of disability worldwide, and is also the second leading cause of death due to cardiovascular disease (CVD) [4]. According to modern statistics, the proportion of cardio-embolic stroke (CES) reaches 38% of all stroke ischemic events [5]. The pathogenesis of CES is based on occlusion of cerebral arteries by thrombi formed in the heart chambers, as a result of which, to reduce the risk of TEE, patients with AF should take oral anticoagulants for a long time [1, 6].

After discharge from specialized neurological departments, patients with stroke are admitted to the outpatient stage of treatment. The tasks of this stage are to continue rehabilitation measures and carry out a set of preventive measures in order to prevent the repeated TEE and secondary complications of stroke. The success of stroke prevention in patients with AF depends on the appointment of optimal drug therapy by a physician and high medical adherence of a patient. However, despite the number of clinical guidelines regulating long-term therapy of patients with AF, there are currently no clearly developed programs for their outpatient management after a CES [7].

The aim of this study was to improve the long-term results of treatment of AF patients CES by creating and testing a comprehensive ambulatory monitoring system.

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical

Practice standards. The medical ethics committees of the Samara State Medical University approved this study. We included 139 patients with AF after CES for the period of 2016-2019 (women, 80 (57,55%); men, 59 (42,45%)). The mean age of the patients was 72,25±6,33 years.

The CES was confirmed in all patients by brain computed tomography (CT) or magnetic resonance imaging (MRI). AF has been documented by electrocardiography (ECG) or 24-hour ECG monitoring. Patients were treated in accordance with the current international guidelines for the management of patients with stroke and AF.

All patients underwent the following examination at the time of hospitalization:

- physical examination;
- laboratory diagnostics (complete blood count, biochemical blood test: albumin, urea, creatinine, lipid profile, glucose, alanine aminotransferase, aspartate aminotransferase, total bilirubin, potassium, sodium, coagulation testing, clinical urine test);
- instrumental tests (ECG, chest x-ray, echocardiography, brain CT or MRI, Doppler ultrasound of brachiocephalic arteries; if necessary, 24-hour ECG monitoring and esophagogastroduodenoscopy).

During hospitalization, all patients underwent training at the "Rehabilitation school", the program of which included classes devoted to raising the awareness of patients and their relatives about AF and CES, the formation of recovery motivation, the implementation of physician's recommendations, the acquisition of skills for self-monitoring, proper nutrition, adequate exercise, cessation of bad habits. At the time of discharge, all patients were selected for the optimal individualized drug therapy.

Before discharge from the hospital, all patients signed an informed consent, after which they were randomized into two groups using a random number method. Patients of the group I (experimental) (n=72) were followed up for one year in accordance with a specially developed comprehensive ambulatory monitoring system. This system included not only a rehabilitation program created individually for each patient in accordance with his clinical characteristics, but also regular monthly visits to physician, during which a complex of diagnostic investigations was carried out. At each visit, complaints, symptoms and medical adherence were assessed, and, if necessary, were adjusted. Also, the doctor talked with the patient and his relatives about the need to comply with the recommended regimen and taking medications, supporting the motivation for treatment. Patients of group II (control) (n=67) were followed up at the primary care level in accordance with the current program, and a control visit to was performed for them once — after 12 months.

The primary efficacy endpoint was the combination of myocardial infarction (MI), ischemic stroke, and cardiovascular death; the secondary efficacy endpoints were all-cause mortality and hospitalization for decompensated HF. The primary safety endpoint was an episode of major or clinically relevant non-major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) classification.

Statistical analysis was carried out using IBM SPSS Statistic 22.0 (IBM, USA), Statistica 10.0.228.8, Excel-2013, Access-2010, Word-2010 (Microsoft Corp., USA). Differences were considered significant at $p<0,05$; at $p\leqslant0,01$ — very significant; at $p\leqslant0,001$ — highly significant.

Table 1

Patterns of the compared groups by age and main anthropometric parameters*

Parameter	Group I (n=72)	Group II (n=67)	$p^{I}p^{II}$
Age	72,50 (67,00; 76,00)	73,00 (69,00; 77,00)	0,158
Height, cm	168,00 (161,50; 173,00)	168,00 (160,00; 175,00)	0,808
Weight, kg	81,00 (74,50; 90,00)	80,00 (72,00; 90,00)	0,742
BMI, kg/m^2	28,00 (26,00; 31,00)	29,00 (25,00; 31,00)	0,958

Note: * — parameters are presented as median (Me) and interquartile range (Q_1-Q_2).
Abbreviation: BMI — body mass index.

Table 2

Patterns of the compared groups by sex, comorbidity profile, CVD risk factors, AF type, history of bleeding

Parameter, n (%)	Group I (n=72)		Group II (n=67)		$p^{I}p^{II}$
Sex	Women	Men	Women	Men	0,647
	43 (59,72%)	29 (40,28%)	37 (55,22%)	30 (44,78%)	
Hypertension	72 (100,00%)		66 (98,51%)		0,879
Prior myocardial infarction	16 (22,22%)		18 (26,8%)		0,637
Prior stenting	4 (5,56%)		1 (1,49%)		0,680
Prior CABG	3 (4,17%)		1 (1,49%)		0,786
HF	72 (100,00%)		66 (98,51%)		0,879
Permanent AF	39 (54,17%)		48 (71,64%)		0,076
Persistent AF	23 (31,94%)		16 (23,88%)		0,412
Paroxysmal AF	10 (13,89%)		3 (4,48%)		0,339
Implanted pacemaker	5 (6,94%)		3 (4,48%)		0,802
Prior RFA	3 (4,17%)		2 (2,99%)		0,904
Gastrointestinal diseases	7 (9,72%)		2 (2,99%)		0,493
Diabetes	14 (19,44%)		13 (19,40%)		0,997
Smoking	7 (9,72%)		6 (8,96%)		0,938
Prior bleeding	3 (4,17%)		6 (8,96%)		0,626

Abbreviations: MI — myocardial infarction, CABG — coronary artery bypass grafting, RFA — radiofrequency ablation, CVD — cardiovascular diseases, AF — atrial fibrillation, HF — heart failure.

The study used the receiver operator characteristic analysis (ROC-analysis), which allows to classify positive and negative examples. Its graphical interpretation was the ROC curve, which reflects the results of binary classification and shows the dependence of correctly classified positive examples on the number of incorrectly classified negative examples. A quantitative interpretation was provided by the area under ROC curve (AUC). It is generally accepted that the AUC coefficient, which is in the range of 0,9-1,0, reflects the excellent quality of model; 0,8-0,9 — very good; 0,7-0,8 — good; 0,6-0,7 — sufficient; 0,5-0,6 — poor quality. The chi-square test was used to test the independence of categorical variables in crosstable. The strength of the relationship between exposure and disease was assessed by odds ratio (OR) of event incidence in the comparison groups. With OR >1, the probability of an outcome in the experimental group is higher than in the control group. Moreover, the higher the OR value, the higher the probability of event development. With OR <1, the probability of an outcome in the study group is lower than in the control group.

Results

At the first statistical analysis stage, the groups of randomized patients were assessed for normal distribution. Due to the fact that traits in these groups were non-normally distributed, for their comparison we used the Kolmogorov-Smirnov test. Data on the age patterns, main anthropometric parameters, sex, comorbidity prevalence, main risk factors for CVD, AF type, presence of prior bleeding events, with intergroup comparison, are presented in Tables 1 and 2.

Table 3

Patterns of the compared groups by risk of thromboembolic and bleeding events*

Score	Group I (n=72)	Group II (n=67)	$p^{I}p^{II}$
CHA_2DS_2-VASc	6,00 (5,00; 7,00)	6,00 (6,00; 7,00)	0,054
HAS-BLED	2,00 (2,00; 2,00)	2,00 (2,00; 2,00)	0,354

Note: * — parameters are presented as median (Me) and interquartile range (Q_1-Q_2).

Table 4

Incidence of endpoints (cardiovascular death, MI, stroke) in the compared groups

Event, n (%)	Group I (n=72)	Group II (n=67)	$p^{I}p^{II}$
Primary efficacy endpoint	2 (2,78%)	23 (34,33%)	0,001
All-cause mortality	3 (4,17%)	18 (26,87%)	0,021
HF-related hospitalization	0 (0,00%)	13 (19,40%)	0,049
ISTH major or clinically relevant non-major bleeding	0 (0,00%)	1 (1,49%)	0,879

Abbreviations: HF — heart failure, ISTH — International Society on Thrombosis and Haemostasis.

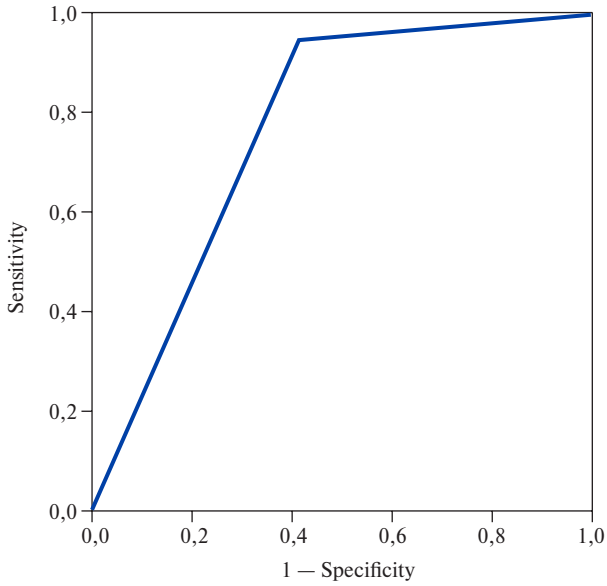

Figure 1. Analysis of the relationship between no anticoagulant therapy and death.

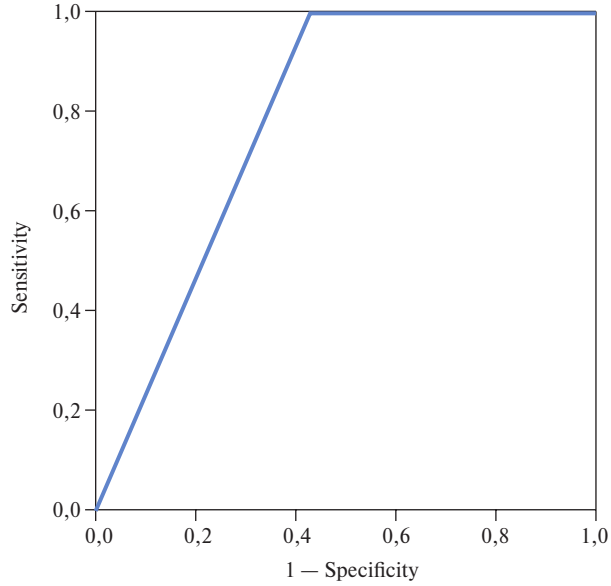

Figure 2. Analysis of the relationship between no diuretic therapy and HF decompensation within 12 months.

Thus, the experimental and control groups at the time of randomization were comparable in age, main anthropometric parameters, sex, comorbidity prevalence, AF type, and a history of bleeding events.

At baseline, the groups were compared in terms of the risk of thromboembolic and bleeding events using the CHA_2DS_2-VASc and HAS-BLED scores, respectively, which did not reveal significant differences (Table 3).

At the time of discharge, the groups were comparable in all main statistical characteristics, which rule out the possible influence of the latter on the study outcomes.

Based on 1-year follow-up, an incidence of endpoints was compared between groups I and II (Table 4).

After 12 months of outpatient rehabilitation, the compared groups significantly differed in the incidence of the following events: the primary composite efficacy endpoint (cardiovascular death, MI, and ischemic stroke) and two secondary efficacy endpoints (all-cause mortality and HF-related hospitalization), which in group I patients were observed less frequently. At the same time, there were no differences in the incidence of the primary safety endpoint between the groups.

In addition, in group II, a relationship was found between the death and no anticoagulant therapy (OR 7,68; 95% confidence interval, 1,59-37,03; p=0,01). The ROC analysis confirmed the relationship between no anticoagulant therapy and death,

while the regression quality corresponded to good (AUC 0,77; sensitivity 94,74%; specificity 59,17%) (Figure 1).

We also found a relationship in group II between decompensated HF and no diuretic intake (χ^2 — 7,38, p=0,007). According to logistic regression analysis of decompensated HF, the prognostic significance of diuretic therapy was shown, while the regression quality corresponded to good (AUC 0,783; sensitivity 100%; specificity 57,14%) (Figure 2).

In group I, during 12-month outpatient follow-up, a significant proportion of patients required changes in the drug therapy prescribed at hospital discharge. This could be a drug replacement, a decrease or increase in dose, the addition of another drug with a different mechanism of action to enhance the effect. For example, alteration of antihypertensive therapy was required in 34 patients (47,22%), anticoagulant therapy — in 13 patients (18,06%). Most often, a dose change was required in warfarin therapy — out of 12 people taking it, 8 had an instability in international normalized ratio level. However, in the end of 1-year follow-up, adherence to anticoagulant and antihypertensive therapy in group I was 100%. Correction of HF therapy was required in 24 patients (33,33%), while not a single patient of group I during our study was hospitalized due to decompensated HF.

In group II, antihypertensive drugs were taken by 53 (79,10%), anticoagulants — 26 (38,81%), and adequate HF therapy — 13 (19,40%) patients, which, of course, influenced the incidence of endpoints.

Discussion

The importance of secondary stroke prevention is currently not in doubt. Over the years, the approach to long-term management of stroke patients has undergone dramatic changes. Currently, stroke patients, including those after CES, receive a list of recommendations for further treatment upon discharge, which consists of non-drug and drug measures for the secondary prevention of recurrent stroke and other cardiovascular events.

Drug therapy in such patients, as a rule, consists of several classes of drugs. Life-long anticoagulant prophylaxis of TEE is of paramount importance in patients with AF after CES [1, 6]. In addition, it is necessary to assess the rationale of antiarrhythmic drug therapy, depending on the chosen strategy for controlling the rhythm or heart rate. The need to take other medicines is specified by comorbidity profile. For example, the vast majority of patients with AF require antihypertensive therapy. Thus, in the population of patients included in our study, the prevalence of hypertension reached 100% in group I and 98,51% in group II. The choice of an antihypertensive drug largely depends on the comorbidity status of a particular patient, and often a combination of antihypertensive drugs is required. The presence of coronary artery disease in a patient, depending on its course, may require intensifying antithrombotic therapy, which increases the risk of bleeding events. In addition, within the secondary prevention, treatment of HF and diabetes should be carried out. Hepatic and renal dysfunction must also be taken into account when choosing specific drugs, due to a possible change in their pharmacokinetic parameters.

All these factors are assessed and taken into account when planning an inpatient treatment and formulating recommendations at discharge. Further, at the outpatient stage of management, a periodic reassessment of clinical symptoms and some investigational parameters is required. For example, taking warfarin requires mandatory monthly determination of the international normalized ratio, and taking antiarrhythmic drugs requires regular assessment of the QT interval on the ECG. All patients with AF require renal function monitoring, the regularity of which depends on the initial value of the glomerular filtration rate of a particular patient and is calculated using a special equation. In addition, it is necessary to regularly reevaluate the risks of thrombotic and bleeding events, as well as the balance of benefits and risks from the treatment. All these features of the management of AF patients are reflected in modern guidelines [1, 6], and the prognosis of patients' life directly depends on its optimal implementation.

The implementation of this program of secondary prevention of CES in full is possible only with regular follow-up by a specially trained specialist. The rationale of widespread implementation of this approach to the outpatient rehabilitation is also evidenced by our study — patients followed up in accordance with comprehensive ambulatory monitoring system within a year after discharge had a significant decrease in the primary composite endpoint (cardiovascular death, MI, ischemic stroke), as well as such secondary efficacy points as all-cause mortality and HF-related hospitalization.

Regular monthly visits to a specialist made it possible to timely adjust the treatment, as well as maintain a high level of medical adherence, which in group I reached 100%. A number of studies have been published confirming that it is the high medical adherence that can influence the prognosis of patient life [8-11]. However, to date, the quality of outpatient management of stroke patients remains insufficient [10, 12, 13]. According to our own data published earlier, adequate prevention of TEE in

actual clinical practice is extremely rare — only in 16,2% of AF patients, outpatient physicians recommended taking anticoagulants [14]. Non-compliance with modern guidelines for outpatient management can be explained by significant workload of doctors, as well as, possibly, insufficient awareness of modern approaches to treatment.

Conclusion

Based on the above, we believe that comprehensive ambulatory monitoring program for AF patients after CES has proven high effectiveness, and its widespread practice is an urgent task of modern healthcare. The approaches to the outpatient management of AF patients after CES should be globally reviewed. It seems relevant to create ambulatory offices for the secondary prevention of stroke, which will deal with the adjustment of risk factors, the selection of optimal drug therapy and monitoring of medical adherence.

Relationships and Activities: none.

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Cardiovascular system status of long-livers in Moscow: the prevalence of cardiovascular diseases and their risk factors

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Over the past century, an increase in life expectancy has been observed in Russia and in the world. According to the United Nations, by 2100, the number of centenarians worldwide will reach 25 million. Despite the annual increase in the number of super-centenarians, this age group remains poorly understood.

Aim. To estimate the prevalence of cardiovascular diseases (CVD) and the main risk factors among super-centenarians in Moscow.

Material and methods. According to the register of long-livers in Moscow, 82 people aged 95 to 105 were included. Participants were examined at home. The history of life and the presence of chronic diseases was collected by participant words. To assess the state of cardiovascular system, an ultrasound of the heart and main arteries was performed.

Results. Conventional CVD risk factors were the exception rather than the rule among study participants (smoking — 8 patients (9,8%), alcohol abuse — 4 (4,9%), obesity — 6 (7,3%)). Dyslipidemia was relatively widespread (n=37; 45,1%), however, there were no pronounced abnormalities in the lipid profile: the maximum increase in low-density lipoproteins was 5,6 mmol/L. The most common CVDs among the participants were hypertension (n=64; 78%), coronary artery disease (n=42; 51,2%), and heart failure (n=26; 31,7%); other diseases were much less common. The most common echocardiographic changes were left atrial dilatation (n=38; 74,5%), increased left ventricular mass, thickening of left ventricular posterior wall (n=24; 48%) and interventricular septum (n=51; 100%). Diastolic and systolic heart failure were not widespread among long-livers: 16 (32%) and 2 (3,9%), respectively. Despite a rather large number of atherosclerotic plaques in the common carotid and femoral arteries, the number of hemodynamically significant plaques was low (n=3; 4,6%). An intima-media thickening up to 1,0-1,1 mm was found.

Conclusion. Long-livers in Moscow are characterized by a low prevalence of traditional CVD risk factors (with the exception of hypertension) and a fairly high prevalence of atherosclerotic CVDs, which are characterized by a subclinical course.

Keywords: long-livers, risk factors, smoking, intima-media thickness, hypertension, dyslipidemia.

Relationships and Activities: none.

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Over the past century, there has been an increase in life expectancy: from 1950 to 2017, the mean life expectancy increased from 48,1 to 70,5 years for men and from 52,9 to 75,6 years for women [1]. At the same time, the number of long-livers and centenarians is increasing: people who have reached the age of 85 and 100 years, respectively. According to calculations of the United Nations (UN) by 2100, the number of centenarians worldwide will reach 25 million people [2].

In Russia, the same trends are observed: the annual growth of long-livers since 2014 is 600-900 people per year, and by 2019, 20582 centenarians (5895 men and 14687 women) live in the country [3].

Cardiovascular diseases (CVDs) have been the leading cause of death for people 65 years of age and older in Russia and in the world for at least the last 20 years. Despite the increase in the number of centenarians, to date, the state of cardiovascular system and the main cardiovascular risk factors (RF) have been little studied in this age group.

The aim was to assess the state of cardiovascular system, the prevalence of CVDs and related main risk factors (RFs) among centenarians.

Material and methods

The study protocol was approved by the independent ethics committee of the Pirogov Russian National Research Medical University, Russian Clinical and Research Center of Gerontology (meeting № 02/15 dated February 12, 2015). This study is registered with ClinicalTrials.gov № NCT02876809. The study recruitment was initiated in 2015: 82 residents of Moscow aged 95 and older were included, who personally (if impossible, with the help of relatives or guardians) agreed to undergo the examination. Fifty-one participants underwent echocardiography, while 64 — laboratory examination, including biochemical analysis and complete blood count.

The inclusion criterion was age 95 and older. There were no exclusion criteria, with the exception of refusal to participate in the study.

Patients were seen at home in the presence of a social worker and/or the patient's relatives.

History was collected by patient's and/or his relatives' account. To identify chronic diseases and analyze the therapy taken, when possible, data from available medical records were used.

We collected data on weight and height and then calculated the body mass index (BMI). BMI <18,5 kg/m^2 was considered as underweight, from 18,5 to 24,9 kg/m^2 — normal body weight, from 25 to 29,9 kg/m^2 — overweight, and 30 or more kg/m^2 — obesity [4].

The study of the lipid profile and glycated hemoglobin levels was carried out using an AU 680 (Beckman Coulter) clinical chemistry system.

There were following reference values for lipid profile parameters: <5,0 mmol/L for total cholesterol (TC), 3,5 mmol/L for low density lipoproteins (LDL) and <1,7 mmol/L for triglycerides (TG). For men, the level of high-density lipoproteins (HDL) was considered low at <1,2 mmol/L, and for women — 1,0 mmol/L [5].

Ultrasound of the heart and main arteries was performed using a Samsung Medison U6 portable ultrasound machine. Cardiac structure and function was assessed using the normal ranges from 2012 Russian Society of Cardiology guidelines [6]. Vascular stiffness was determined using SphygmaCor technology (AtCor, Sydney, Australia).

Statistical data processing was performed using the SPSS 23.0 program (SPSS Inc., USA). Due to the small number of observations, the analysis of quantitative traits' distribution was not carried out. Quantitative variables are presented as Me (25%; 75%), where Me is the median, 25% — 25th percentile, 75% — 75th percentile, since the data is not normally distributed.

Results

The mean age was 98,3 (95-105) years, of which 72 (87,8%) were women. At the same time, the age of 66 participants in the study was from 95 to 99 years old and 16 was 100 years old or more.

Risk factors. The majority of long-livers never smoked (n=73; 89%), while 8 (9,8%) participants were former smokers, and one (1,2%) continued to smoke (up to 5 cigarettes a day). The median duration of smoking among smokers was 5 years (range 1 to 65 years).

Alcohol consumption was not widespread among long-livers: 78 people (95,1%) drank alcohol-containing products 2-3 times a year (up to 2 glasses per meal), and 4 (4,9%) drank alcohol regularly.

For the most part, centenarians led a sedentary lifestyle (56 (68,3%)). The minority regularly went for walks (18 (22%)) or did morning exercises (7 (8,5%)). Of these 25 people (30,5%), 16 (19,5%) spent up to 30 minutes a day on sports, 4 (4,9%) — up to 1 hour, and the remaining 5 (6,1%) — more than an hour.

Obesity and overweight were in 6 (7,3%) and 28 (34,1%) study participants, respectively.

Thus, the classic RFs for CVD were the exception rather than the rule among participants (Figure 1).

CVD. The most common diseases among the study participants were hypertension (64 (78%)), coronary artery disease (CAD) (42 (51,2%)) and heart failure (HF) (26 (31,7%)). Acute myocardial infarction (MI) or stroke were significantly less common — in 16 (19,5%) and 17 (20,7%) participants. Occlusive peripheral arterial disease and atrial fibrillation were

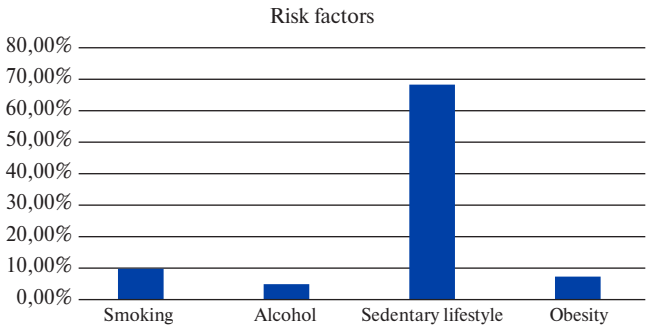

Figure 1. Prevalence of conventional RFs (n=82).

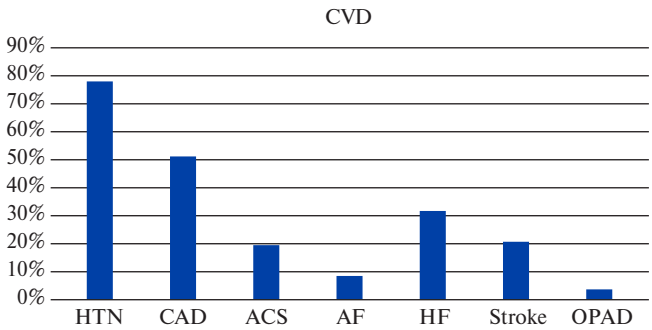

Figure 2. CVD prevalence among participants (n=82).
Abbreviations: HTN — hypertension, CAD — coronary artery disease, ACS — acute coronary syndrome, AF — atrial fibrillation, HF — heart failure, OPAD — occlusive peripheral arterial disease.

extremely rare: (3 (3,7%)) and (7 (8,5%)), respectively (Figure 2).

Therapy. One of the most widespread drugs among long-livers was acetylsalicylic acid as primary (20 (24,4%) and secondary prevention of CVD (14 (17,1%)).

The most frequently prescribed antihypertensive therapy were angiotensin-converting enzyme inhibitors (25 (30,5%)) and beta-blockers (22 (26,8%)). Significantly less frequently, patients took angiotensin II receptor blockers (13 (15,9%)) and calcium channel blockers (16 (19,5%)).

Slightly less than a quarter (17 (20,7%)) received diuretic therapy (thiazide and loop diuretics). Five (5,6%) subjects took long-acting nitrates. None of the patients with atrial fibrillation took anticoagulants (Table 1).

Cardiac ultrasound. Echocardiography was performed in 51 study participants. There were following echocardiographic findings: left atrium (LA) dilation (74,5%), interventricular septum thickening >1,1 cm (100%), increased pulmonary artery pressure >30 mm Hg (48%) and left ventricular (LV) diastolic dysfunction (32%). Systolic dysfunction was observed in 2 (3,9%) subjects (Tables 2, 3).

Ultrasound of carotid and femoral arteries. All long-livers had atherosclerotic plaques in the common carotid (CCA) and femoral arteries (mean, 5). However, hemodynamically significant stenoses (70% or more) were extremely rare: 3 and none in the CCA and femoral artery systems, respectively. The median intima-media thickness in the CCA system was approximately 1 mm, while in the femoral one — 1,5 mm (Table 4).

Vascular stiffness. The vascular stiffness was determined in 67 centenarians, of which the median pulse wave velocity was 10 m/s, and the augmentation index was 31,3 (Table 5).

Lipid profile. The lipid profile was analyzed in 65 study participants. According to formal criteria, dyslipidemia was found in 55%. Three patients continued to take statins (atorvastatin at a dose of 10-20 mg a day). An increase in TC >5,0 mmol/L was in 55% (3,0-7,5 mmol/L), TG >1,7 mmol/L — in 5,3% (0,6-1,8 mmol/L), LDL >3,0 mmol/L — in 44% (1,7-5,5 mmol/L), and a decrease in HDL <1,0 mmol/L — in 43% (0,7-2,8 mmol/L) (Figure 3).

Discussion

A healthy lifestyle, regular physical activity, healthy balanced diet, freedom from nicotine and alcohol products reduces the risk of CVD and cancer and, as a result, increases the duration of an active life in general.

Smoking (1,2%) and alcohol consumption (4,9%) are not very common among long-livers in Moscow. International data on this issue vary: in the Italian GEHA register, 3,2% of participants smoked [7]; in the Chinese Dijiangyan Study — 43% [8]. The same variability can be traced with regard to alcohol consumption: just over 50% of centenarians in Italy consumed 1 glass of wine per day throughout their lives, among Chinese centenarians — 27% (however, the volume and frequency of alcohol consumption is not indicated). It was typical for Moscow centenarians to drink alcoholic beverages on holidays and in a little amount (Social drinking).

Most of the patients led a sedentary lifestyle (68,3%) at the time of inclusion in the study, and 7,8% did exercise and 22% went for a walk regularly, but the majority of centenarians during the survey reported that they had an active lifestyle in youth and maturity. These results are inferior to the Italian GEHA data, where 37% did daily walking [7], and the Chinese, where up to 40% did daily exercise [8].

Overweight among young and middle-aged people is a well-known RF for CVD. Among older age people, BMI ceases to be such an unambiguous unfavorable factor. Recent studies have shown that among older patients, a low and normal BMI (<23) is associated with higher mortality than those who

Table 1
Medicines taken by study participants (n=82)

Drug group	Result, n (%)
ACE inhibitors	25 (30,5%)
Angiotensin II receptor antagonists	13 (15,9%)
Calcium channel blockers	16 (19,5%)
Beta blockers	22 (26,8%)
Diuretics	17 (20,7%)
Lipid-lowering therapy (3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors)	4 (4,9%)
Vasodilators (nitrates)	5 (6,1%)
Antiplatelet agents (acetylsalicylic acid)	34 (41,5%)

Abbreviation: ACE — angiotensin converting enzyme.

Table 2
Results of echocardiography (n=51)

Parameter	Result (median (25; 75 percentile))
Aorta (cm)	3,5 (3,2; 3,7)
LA size (cm)	4,3 (4,0; 4,7)
LA volume (cm^3)	63 (50,0; 80,0)
LV index	37 (32,0; 57,0)
LV EDD (cm)	4,8 (4,4; 5,0)
LV EDV (ml)	72 (58,0; 86,5)
LV ESV (ml)	27 (21,0; 32,0)
Interventricular septum thickness (cm)	1,4 (1,3; 1,6)
LV posterior wall thickness (cm)	1,0 (1,0; 1,0)
LV relative thickness (cm)	0,43 (0,39; 0,46)
RA volume (cm^3) Women Men	 46,0 (38,0; 56,5) 64 (48,0; 92,0)
RV EDD (cm)	2,9 (2,5; 3,0)
Pulmonary artery pressure (mm Hg)	39,6 (30,0; 48,8)
LV mass (g) Women Men	 163 (131; 199) 160 (157; 252,3)
LVMI Women Men	 103 (87,0; 120,7) 108 (89,7; 149,5)
EF (%)	62 (60; 66)
E/A	0,7 (0,6; 0,9)
e’	7,0 (6,0; 9,0)
e’/’	0,7 (0,5; 0,8)
E/e’	9 (7,0; 11,0)

Abbreviations: LVMI — left ventricular mass index, EDV — end diastolic volume, EDD — end diastolic dimension, ESV — end systolic volume, LV — left ventricle, LA — left atrium, RA — right atrium, RV — right ventricle, EF — ejection fraction.

Table 3
Prevalence of echocardiographic abnormalities among centenarians (n=51)

Parameter	Number	Proportion	Total number
Aortic root expansion	8	15,7%	51
LA dilation	38	74,5%	51
Increased LA volume	30	58,8%	51
Interventricular septum thickening	51	100%	51
LV posterior wall thickening	42	82,4%	51
Pulmonary hypertension	23	57,5%	42
LV mass	24	48%	51
Diastolic dysfunction (E/e >9)	16	32%	50
Ejection fraction <40%	2	3,9%	51

Abbreviations: LV — left ventricle, LA — left atrium.

Table 4
Results of duplex ultrasound of main arteries (n=65)

Parameter	Result (median (25; 75 percentile))
Maximum carotid artery stenosis	45 (35; 50)
Number of atherosclerotic plaques in carotid system	5 (4; 6)
Average IMT of the right CCA, mm	1,0 (0,93; 1,16)
Average IMT of the left CCA, mm	1,1 (0,94; 1,22)
Maximum stenosis in femoral artery system	40 (30; 45)
Average IMT of the right CFA, mm	1,53 (1,23; 1,9)
Average IMT of the left CFA, mm	1,54 (1,2; 2,0)

Abbreviations: CFA — common femoral artery, CCA — common carotid artery, IMT — intima-media thickness.

Table 5
Results of vascular stiffness examination (n=64)

Parameter	Result (median (25; 75 percentile))
Pulse wave velocity (m/s)	10 (8,8; 11,3)
Augmentation index	31,3 (15,3; 46,0)

had it in the range from 23 to 32 (which corresponds to overweight and even partially class 1 obesity) [9]. Among the study participants, underweight and obesity were quite rare — 13,4% and 7,3%, respectively. There was no significant difference in BMI between survivors and deaths.

Severe dyslipidemia was not widespread among centenarians of Moscow and generally corresponded

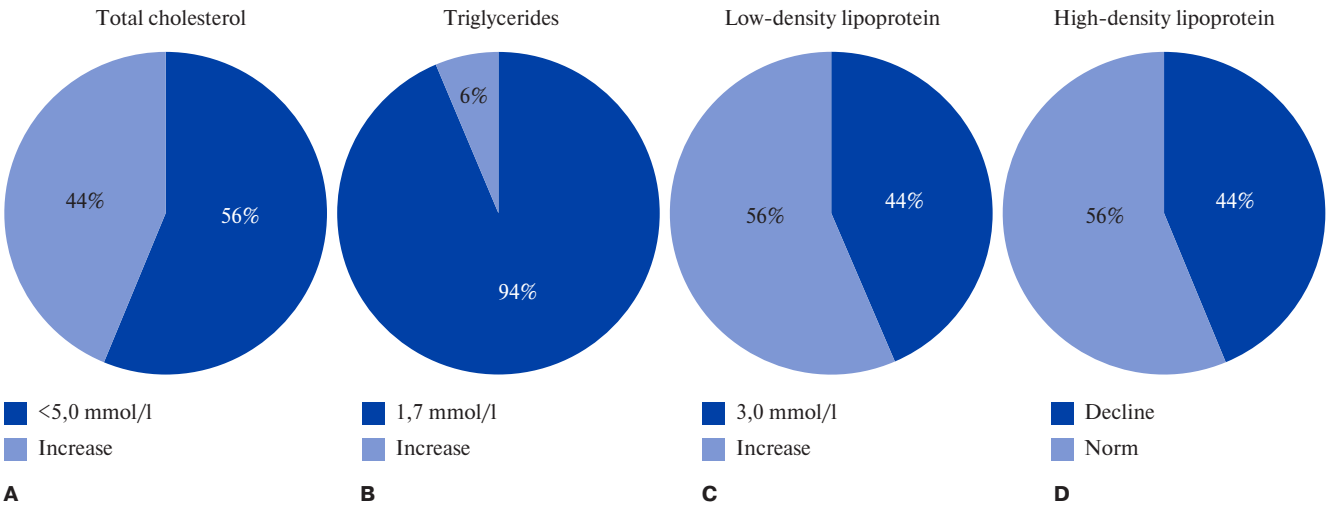

Figure 3. The pie chart shows the distribution of TC levels among centenarians (n=64) (**A**). The pie chart shows the distribution of TG levels among centenarians (n=64) (**B**). The pie chart shows the distribution of LDL levels among centenarians (n=64) (**C**). The pie chart shows the distribution of HDL levels among centenarians (n=64) (**D**).
Abbreviations: LDL — low-density lipoprotein, HDL — high-density lipoprotein.

to the international data from Italy (TC, 5,2±1,2 mmol/L; LDL, 3,1±0,9 mmol /L) and China (TC, 4,2±0,8 mmol/L; LDL, 2,3±0,7 mmol/L) [7, 8].

A feature of centenarians is the late development of aging-associated diseases, including CVD [10]. Among centenary veterans of the United States, the prevalence of hypertension was 45%, CAD — 20%, MI — 15% and HF — 32%) [10]. The prevalence of hypertension and CAD was higher among Moscow centenarians, while the incidence of MI and HF was comparable.

In the literature there is little data on instrumental diagnostic tests of centenarians. Doppler ultrasound of the pulse wave of Okinawa long-livers demonstrated that, in general, the pulse wave velocity was <10 m/s, which is typical for younger patients [11] and correlates with the results of the Moscow study.

We have demonstrated the following patterns: LA dilation, increased LV mass, interventricular septal thickening, widespread pulmonary hypertension and diastolic dysfunction among the study participants.

All the data obtained correspond to the structural and functional cardiac abnormalities that occur with age. Thus, the Framingham study demonstrated that the prevalence of LA dilation increases with age and correlates with RFs for CVD [12]. Another aging-associated change is LV diastolic dysfunction; its incidence doubles every decade starting at age 65 in men, and triples in women. In 2008, discrete upper septal thickening (DUST) was described for the first time [13]. The prevalence of this phenomenon is directly proportional to age and, according to the Framingham study, reaches 18% among people over 85 years old. The question remains about the good quality of these changes and their impact on the human condition. There is evidence that hypertrophy of the interatrial septal basal part does not affect the normal rest function of a person, but can limit his physical activity, causing limitation of blood flow through the aortic valve [13]. It has also been shown that the prevalence of diastolic dysfunction in different age groups varies and can reach 50% among healthy volunteers aged 65 and over [14].

Despite the rather large number of atherosclerotic plaques in the common carotid and femoral arteries, the number of hemodynamically significant plaques was minimal. An intima-media thickening up to 1,0-1,1 mm was found, which corresponds to the estimated age norm for centenarians [15].

A study limitation is the design, which does not allow for clarification of causal relationships.

Conclusion

Over the past century, there has been a steady trend towards an increase in life expectancy. Long-livers in Moscow are characterized by a low prevalence of conventional RFs for CVD (with the exception of hypertension) and a fairly high prevalence of structural and functional cardiac and vascular abnormalities.

Relationships and Activities: none.

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Polymorphism of *ACE*, *AGT*, *AGTR1* genes as genetic predictors of hypertension

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The genetic architecture of blood pressure (BP) includes more than 30 genes, the polymorphic variants of which cause phenotypic heterogeneity of BP. Given that a human genetic information is largely stable from birth, it can act as an early predictor of hypertension (HTN). Identification of polymorphic variants of genes associated with a high HTN risk may be one of the promising areas of early diagnosis and prevention of this disease. In addition, the availability of this data will make it possible to clarify the prognosis of patients already with HTN, as well as to personalize the treatment approach. The review analyzes the papers devoted to the molecular genetic basis of hypertension and identifies the possible role of gene polymorphism of the renin-angiotensin-aldosterone system in hypertension development. A large number of studies have revealed an association between HTN and polymorphic variants of the *ACE*, *AGT*, *AGTR1* genes. In addition, polymorphism of these genes is involved in the development of atherosclerosis and related diseases, kidney and central nervous system disorders, and justifies the effectiveness of angiotensin-converting enzyme inhibitors in the treatment of HTN.

Keywords: gene polymorphism, hypertension.

Relationships and Activities: none.

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The genetic architecture of blood pressure (BP) currently includes >30 genes, including genes with rare mutations leading to hereditary forms of hypertension or hypotension, and 1477 polymorphic variants. This determines the phenotypic heterogeneity of BP and corresponds to Page's mosaic theory, according to which the development of essential hypertension (HTN) is associated with a complex of interrelated disorders in various systems: hemodynamic, metabolic, neurohumoral. This theory considers essential HTN not as a single disease, but as a combination of diseases (subtypes of essential HTN) differing to one degree or another with different origins, development and consequences. The mosaic of HTN causes, if it exists for essential hypertension, needs clarification, since it potentially opens up new opportunities for stratification, the development of new drugs, and personalized medicine [1, 2].

General view of single nucleotide polymorphism. The most common cause of differences in gene structure is point mutations — single-nucleotide polymorphism (SNP), which is the replacement of one nitrogenous base with another in a DNA or RNA region, leading to the appearance of a particular phenotypic trait. A large number of studies confirm that SNPs can contribute to the predisposition to some diseases, in particular to HTN [3]. However, a certain polymorphism is not always associated with the certain phenotypic trait. Currently, the phenomenon of pleiotropy is known, which means that the same polymorphism can have several phenotypic manifestations. For example, a genetic predisposition to smoking is associated with 361 polymorphic variants in 14 genes involved in the development of cardiovascular pathology [4]. These phenotypic differences can be due to various reasons, including interaction of different SNPs [5, 6].

In clinical practice, genetic analysis is more often carried out using molecular testing of candidate genes for disease susceptibility. These are genes, hereditary (polymorphic) variants of which, to a relatively small extent affecting the encoded proteins (enzymes), in combination with unfavourable external factors, can cause various diseases [7].

Given that a human's genetic information is largely stable from birth, it can act as an early predictor of HTN. Identification of polymorphic variants of genes associated with a high risk of HTN can be one of the promising areas of early diagnosis and prevention of this disease. In addition, the availability of this information will clarify the prognosis of people already suffering from this disease, as well as personalize the approach to patient treatment [1, 3, 7-10]. Such a personalized approach to treatment, based on data on various effects of drugs, depending on the genome of a particular individual, is the most important task of pharmacogenomics. It should be noted that, despite the progress achieved in this field in recent years, there are still no official guidelines on a personalized approach that takes into account the pharmacogenomics of antihypertensive drugs. However, for example, regarding oral anticoagulants and some anticancer drugs, such guidelines were developed.

Twin studies have shown that the heritability of hypertension is 40%. To assess the heritability of BP, American scientists used genomic polymorphism data from the Atherosclerosis Risk in Communities (ARIC) study. According to this paper, heritability was 20%/50% and 27%/39% for systolic/diastolic BP in individuals of European and African descent, respectively [11].

The profile of candidate genes involved in HTN is quite wide and includes groups of genes that control various metabolic and homeostatic systems. In particular, there are genes of the renin-angiotensin-aldosterone system (RAAS) (angiotensinogen (*AGT*) gene, renin gene, angiotensin-converting enzyme (*ACE*) gene, angiotensin-II receptor type 1 gene (*AGTR1*), etc.), genes for lipid metabolism (apolipoprotein A1 gene, apolipoprotein B gene, apolipoprotein C gene, apolipoprotein E gene, lipoprotein lipase gene, etc.), and genes determining the vascular endothelium status (endothelial nitric oxide synthase gene, endothelin gene, paraoxonase gene, etc.) [3, 12].

The review analyses the works devoted to the molecular genetic basis of HTN and identifies the possible role of RAAS genes' polymorphism. The literature review included following works: reports of randomized and cohort studies on large populations; meta-analyses and systematic reviews; papers in English and Russian.

Role of some polymorphic variants of *ACE, AGT, AGTR1* genes in HTN development. Dysfunction of the RAAS plays a leading role in HTN pathogenesis. The activity of this system is to a certain extent determined genetically and depends on polymorphism of *ACE, AGT, AGTR1* genes [3]. Characteristics of polymorphic variants of these genes are presented in Table 1. It should be noted that in recent years there is information about a relatively small number of studies devoted to relationship between the polymorphism of these genes and a predisposition to HTN. The most studied is the *ACE* gene rs4340 (Alu I/D) polymorphism.

Clinical value of Alu I/D (rs4340) polymorphism of *ACE* gene. The *ACE* gene is located on chromosome 17 (17q23.3) and is responsible for ACE synthesis, which plays an important role in the regulation of BP and electrolyte balance. ACE is secreted from the lung and renal endothelial cells and promotes the conver-

Table 1

Characteristics of the studied polymorphic variants

Locus	Substance	Polymorphism	rs	Genotype variants
ACE	Angiotensin converting enzyme	Alu I/D	rs4340	II; ID; DD
AGT	Angiotensinogen	T207M C>T	rs4762	CC; CT; TT
AGT	Angiotensinogen	M268T T>C	rs699	TT; TC; CC
AGTR1	Angiotensin II receptor type 1	A1666C A>C	rs5186	AA; AC; CC

sion of angiotensin I to angiotensin II (AT-II), which is a powerful vasopressor and aldosterone stimulating substance. In addition, the enzyme is capable of inactivating bradykinin, which acts as a vasodilator [4]. The influence of the *ACE* gene has been well studied, and most of the published data refer to the rs4340 (Alu I/D) polymorphism leading to the insertion (I) or deletion (D) of the 289 bp Alu repeat sequence, affecting serum and tissue ACE levels. In individuals with a carrier of allele II, it is minimal, and in individuals with the DD allele — maximal [8]. A large number of studies have revealed the relationship of the DD variant with HTN [12-15].

A Chinese study found that *ACE* Alu I/D polymorphism was associated with in-stent restenosis in patients with coronary artery disease (CAD) after percutaneous coronary intervention and intracoronary drug-eluting stent implantation [16].

In addition, one of the studies conducted among children and adolescents reported a higher risk of high BP in individuals with genotype ID, especially among boys [15]. There is also information about the association of this polymorphic variant with atherosclerosis, CAD, myocardial infarction [13, 17, 18]. Thus, the Polish study found that in patients with CAD, the *ACE* gene D allele was significantly more frequent, which was also associated with increased levels of total cholesterol, low-density lipoprotein cholesterol [19]. In addition, there is evidence of an increased risk of diabetic nephropathy in individuals with ID/DD allele [20].

There is a genetic hypothesis about the participation of this gene polymorphism in the pathogenesis of coronavirus disease 2019 (COVID-19), determining the severity of the clinical course. It was found that the *ACE* gene D/D polymorphism in the genotype is associated with a more severe course and increased mortality among the Caucasian race. Most likely, this is due to the RAAS hyperactivation after SARS-CoV-2 infection, mainly due to virus and ACE-2 interaction and thus penetrating the target cells [21].

Clinical value of T207M C>T (rs4762) and M268T T>C (rs699) polymorphism of *AGT* gene. The *AGT* gene is located on chromosome 1 (1q42). This gene encodes the angiotensinogen, serum globulin produced by liver cells, from which, under the action of renin, AT-II precursor angiotensin I is formed, which is a strong vasopressor. To date, >15 polymorphic variants of the *AGT* gene are known, most of which lead to amino acid substitutions [22].

The following polymorphic variants of the *AGT* gene are associated with blood angiotensinogen level: T207M C>T (rs4762) — replacement of the cytosine nucleotide with thymine, leading to the replacement of the amino acid threonine with methionine at position 207 of the protein; M268T T>C (rs699) — replacement of the thymine nucleotide with cytosine, leading to the replacement of the amino acid methionine with threonine at position 268 of the protein. Among population, the prevalence of these polymorphic variants of the *AGT* gene is 34-43%. The presence of risk alleles 207M and 268T of this gene is associated with an increased level of angiotensinogen expression and HTN development [23]. In addition, there are data on the relationship of the 207M and 268T alleles with other cardiovascular diseases. In particular, the M268T (rs699) polymorphism of the *AGT* gene is significantly associated with increase in CAD risk [24-26].

The presence of risk alleles 207M and 268T was also associated with the atrial fibrillation according to the Xinjiang (China) study [27].

Moreover, the M268T T>C polymorphism of the *AGT* gene was associated with an increased cardiovascular risk in patients with acromegaly [28].

Also, the 268T polymorphism of the *AGT* gene determines the effectiveness of ACE inhibitors in the treatment of HTN and congestive heart failure [29]. There is evidence of the association of this polymorphism with renal tubular dysgenesis, portal hypertension in patients with hepatitis C, and diabetic nephropathy in Asians [30-32].

These polymorphic variants of the *AGT* gene were also associated with vascular complications during pregnancy and hormone replacement therapy (since the *AGT* gene expression increases in response to ethinylestradiol action) [33-37].

Clinical value of A1166C A>C (rs5186) polymorphism of *AGTR1* gene. The *AGTR1* gene is localized

Table 2

Clinical value of the studied polymorphic variants

Gene	Polymorphism	Allele	Increased risk of development and/or severity of clinical course
ACE	Alu I/D	ID/DD	— hypertension, — atherosclerosis, CAD, — myocardial infarction, — diabetic nephropathy
AGT	T207M C>T	TT	— hypertension, — atrial fibrillation — vascular complications during pregnancy and hormone replacement therapy
AGT	M268T T>C	CC	— hypertension, — CAD, — renal tubular dysgenesis, — vascular complications during pregnancy and hormone replacement therapy, — effectiveness of ACE inhibitor therapy, — diabetic nephropathy in Asians
AGTR1	A1666C A>C	CC	— hypertension, — atherosclerosis

Abbreviations: ACE — angiotensin-converting enzyme, CAD — coronary artery disease.

on chromosome 3 (3q24) and encodes type I receptors for AT-II, located in the vascular endothelium and mediating all the main cardiovascular effects of angiotensin. Like other RAAS components, this gene is involved in BP regulation [4]. More than 50 of its polymorphic variants are known. The greatest clinical significance is the A1166C A>C (rs5186) polymorphism. In this case, the adenine nucleotide is replaced by cytosine at position 1166 of the DNA.

The presence of the C risk allele in the A1666C A>C polymorphism leads to an increased sensitivity of type 1 receptors to the normal AT-II level and, consequently, to higher BP. The prevalence of this polymorphism among the Caucasian race is quite wide and amounts to 27%. Studies have shown that hypertensive people were significantly more likely to have the A/C or C/C genotype of the *AGTR1* gene compared with healthy people [38-40].

This polymorphism is associated with a change in *AGTR1* gene expression regulation through interaction with miR155, which is a noncoding RNA molecule capable of complementary binding to untranslated regions of the target mRNA. MiR155 negatively regulates the expression of the *AGTR1* gene, which increases protein synthesis and is associated with HTN [41]. In addition, there are 3 more aspects of AGTR1 regulation. First, activation of AGTR1 decreases the amount of the receptor in the cell. Secondly, long-term stimulation of AT-II decreased the production of AT-II through protein kinases. Third, there is modulation of *AGTR1* gene expression [42].

It has also been shown that the *AGTR1* gene plays an important role in atherogenesis. In the study with patients with occlusive peripheral arterial disease, it was found that carriers of *AGTR1* gene CC genotype have significantly higher levels of low-density lipoprotein cholesterol (p=0,034) and triglycerides (p=0,007) [34]. The Chinese study showed that the *AGTR1* gene AC genotype may be an additional independent risk factor for drug-eluting stent restenosis in patients with CAD over 60 years of age [16].

One of the most important factors contributing to the implementation of this or that genetic information is epigenetic influence. One of the epigenetic mechanisms of gene expression regulation is DNA methylation, which is the methylation of cytosine to 5-methylcytosine, primarily at CpG dinucleotides [43]. The recent study showed that AGTR1 methylation levels were significantly associated with CAD risk in men, suggesting sex-dependent effects in CAD pathogenesis. It has been shown that AGTR1 hypermethylation is associated with CAD risk in men, but not in women [44].

The study was also carried out on the relationship between the characteristics of intrarenal blood flow and the *AGTR1* gene A1166C polymorphism in patients with grade 1-2 essential HTN and stage I-III chronic kidney disease (CKD). A decrease in systolic, diastolic, and averaged maximum blood flow velocities and an increase in blood flow acceleration time were found in patients with a higher stage of CKD, which may indicate an increased risk of early CKD development in patients with grade 1-2 essential HTN and *AGTR1* gene 1166C risk allele [45].

Conclusion

The presented data suggests an important and undoubted role of RAAS genes' polymorphism in HTN development. In addition, it was shown that the studied polymorphic variants of the RAAS genes are involved in the development of atherosclerosis

and related diseases, disorders of the kidneys and central nervous system, the vascular complications during pregnancy and hormone replacement therapy, and justifies the effectiveness of ACE inhibitors in HTN therapy (Table 2). Most of the studies are devoted to the influence of any one gene polymorphism on BP level. Considering that the contribution of each of them individually is relatively small, it is obvious that accurate prediction of HTN risk will be possible by studying the cumulative impact of these multiple variants. This is done by means of a polygenic risk score (PRS), which is a mathematical disease risks' combination associated with all SNPs involved in the regulation of BP [1]. In this regard, further study of the joint effect of several polymorphic variants of the RAAS genes and other systems involved in BP regulation on HTN seems to be very promising.

Relationships and Activities: none.

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Orthostatic hypertension in cardiovascular risk stratification in hypertensive patients

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Hypertension (HTN) is an important modifiable risk factor for cardiovascular disease associated with poor outcomes and high health care costs. The assessment of cardiovascular risk (CVR) according to the current ESC/ESH guidelines for the treatment of hypertensive patients presents a number of difficulties and initiates the search for new diagnostic methods that contribute to understanding the patient's phenotype, personalizing diagnostic and treatment tactics, and improving the outcomes of hypertensive patients.

Regulatory mechanisms involved in the body's orthostatic response, such as activation of the sympathetic nervous system, catecholamine production, endothelial function, significantly contributes to maintaining blood pressure levels. Their violation plays an active role in hypertension development, which allows considering orthostatic HTN in a hypertensive patient as a marker of CVR stratification. The article discusses the diagnostic criteria for orthostatic HTN, its pathophysiological mechanisms and possible use as a marker of CVR stratification.

Key words: orthostatic hypertension, hypertension, essential hypertension, cardiovascular risk.

Relationships and Activities: none.

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Hypertension (HTN) is the most important modifiable risk factor (RF) for cardiovascular diseases and remains one of the most significant medical and social problems in the world [1-3]. Annual mortality and disability, associated with increased blood pressure (BP), confirm a direct relationship between BP and cardiovascular risk (CVR) [1, 4]. In addition, the incidence of HTN among young people increases, but this group often escapes the attention of physicians, which leads to a long absence of therapy, asymptomatic target organ damage and an increased risk of cardiovascular events (haemorrhagic and ischemic stroke, myocardial infarction, sudden death, heart failure and peripheral arterial disease), as well as end-stage renal failure [1, 3].

Orthostatic test (OT) is an easy-to-perform and available method for assessing the cardiovascular system and its autonomic regulation, performed on an outpatient basis by an any physician and does not require additional equipment [3].

The change by the patient of body position from horizontal to the vertical one causes multidirectional changes in the hydrostatic pressure of cardiovascular system relative to some hydrostatic indifference point located several centimetres below the diaphragm level. The action of gravity shifts the intravascular volume from the chest (~400-1000 ml) into the splanchnic circulation and limb veins, complicating venous return and reducing the volume of circulating blood: most of the changes occur ~ in the first 10 seconds of orthostasis. The change in blood flow leads to a decrease in right ventricular filling and a decrease in cardiac output (CO), as a result of which there is a transient BP decrease and heart rate increase, which stimulates the baroreceptor areas and the central part of the autonomic nervous system (ANS), resulting in a decrease in vagal tone and increase in sympathetic tone. This reflex causes compensatory vasoconstriction of resistance and capacitance vessels in the visceral, musculocutaneous and renal vascular systems, an increase in peripheral vascular resistance and stroke volume, providing venous return, BP maintenance and organ perfusion [5-7]. Systemic vasoconstriction is a key factor in maintaining upright BP, more than an increase in heart rate. In a healthy person, orthostatic stabilization is achieved within 60 seconds and less.

The inability of regulatory mechanisms to adequately compensate for stress causes orthostatic intolerance, a type of which is orthostatic hypertension (OH). Since the regulatory mechanisms of the orthostatic response make a significant contribution to maintaining the blood pressure level, and their violation plays an active role in HTN development, this allows us to consider the presence of OH as a marker of CVR stratification [3].

Definition and diagnostic criteria for OH

The term 'OH', described as elevated blood pressure in an upright position and used by the medical community since 1940, is a condition rarely assessed by physical examination or regarded as an unexpected and illogical outcome of OT [5, 6].

The diagnostic criteria for OH are not defined [5, 6], and the number of related studies is rather low: the term 'OH' is not included and is not defined by the current guidelines for HTN [1, 8]. The proposed diagnostic criteria for OH were structured in the paper by Jordan J, et al. (2020) in a table (Table 1) [5]. Table 1 [5] includes studies [9-24], which are the first in the literature to suggest or apply specific definitions of OH, but none of them were based on normative data or CVR assessment. Most of them [10-16, 20-24] used the absolute difference in systolic BP (SBP) and/or diastolic (DBP) in the horizontal position and orthostasis as a diagnostic criterion. The other studies [9, 17, 22, 24] defined OH as the transition of normal BP in a horizontal position to increased BP in orthostasis, which depended on HTN definition [5].

The use of increased DBP in orthostasis as a diagnostic criterion is less reliable, since in an upright position due to peripheral vasoconstriction and decreased stroke volume, an increase in DBP by 5-10 mm Hg is physiological [5, 25]. Jordan J, et al. (2020) [5] consider an important and rarely discussed aspect of a patient's BP change during OT: when should BP rise in orthostasis and how long should it remain elevated to confirm OH. In 2019, Finucane C, et al. proposed 2 diagnostic criteria for OH: a stable increase (>1 min) in SBP ⩾20 mm Hg or >140 and 90 mm Hg, if the patient has normal BP in the horizontal position [5, 24].

Pathogenetic mechanisms of OH

The pathogenetic mechanisms of OH are not fully understood [5, 6, 25]. The conventional explanation is the initial increased sympathetic activity and excessive sympathetic response caused by a decrease in CO as a result of orthostasis [6, 9, 13, 20, 25, 26]. In addition, the pathogenetic mechanism of OH (Figure 1, first published in the paper by Magkas N, et al., 2019) may be caused by ANS dysfunction (impaired sensitivity of baroreceptors and/or baroreflex inability to adapt to "normal" BP), α-adrenergic vascular hyperactivity, increased norepinephrine concentration, renin-angiotensin-aldosterone system (RAAS) activation and increased secretion of vasopressin [6, 13, 20, 25, 27-29]. Factors associated with OH development include arterial stiffness and remodelling of small arteries, excessive venous pooling [5, 6, 9, 20, 30, 31].

Hypertension, along with aging, diabetes and neurological disorders, conditions associated with

Table 1

Diagnostic criteria for OH first published by Jordan J, et al. (2020) [5]

Study	OH criteria (BP change with standing)	Comments
Streeten DH, et al. (1985) [9]	DBP supine <90 mm Hg and DBP standing >90 mm Hg	The study was carried out in a population of hypertensive patients who did not receive antihypertensive therapy (n=1800), 10% were diagnosed with OH. This definition does not include orthostatic change in SBP. There is a risk of OH overestimation due to normal increase in DBP on standing
Hypertension and Ambulatory Recording Venetia Study (HARVEST) Vriz O, et al. (1997) [10]	DBP increase ⩾11 mm Hg (post hoc analysis)	The study was performed on a younger population of stage I hypertensive patients (n=1029; age, 18-45 years). This criterion identified 6,4% (n=66) of patients as having hyperreactive orthostatic response. The term orthostatic hypertension was not applied
Matsubayashi K, et al. (1997) [11] Kohara K, et al. (2000) [12] Kario K, et al. (2002) [13]	SBP increase ⩾20 mm Hg	The authors do not report the rationale for this specific cut-off limit. Kohara et al refers to ARIC study [14]
Kario K, et al. (1998) [15]	SBP increase ⩾10 mm Hg	The study was performed in a population of elderly patients with hypertension (n=110, age ⩾60 years). The authors performed head up tilt testing instead of active standing test. The rationale for such a sensitive SBP change criterion was not provided
Honolulu Heart Program (HHP) Alagiakrishnan K, et al. (2000) [16]	SBP increase ⩾10 mm Hg or DBP increase ⩾10 mm Hg	The study was performed on an elderly population (n=3741, age — 71-93 years). There is a risk of OH overestimation due to sensitive diagnostic criteria in relation to SBP and DBP change. The rationale for such sensitive criteria was not provided
Yoshinari M, et al. (2001) [17]	SBP increase from <140 mm Hg to ⩾140 mm Hg or DBP increase from <90 mm Hg to ⩾90 mm Hg	This definition was applied in a population of patients with diabetes mellitus. The authors refer to studies by Kario et al where different definitions were proposed [6, 13, 15]
Coronary Artery Risk Development in Young Adults (CARDIA) Study Thomas RJ, et al. (2003) [18]	SBP increase ⩾5 mm Hg	The study was carried out in a population of young people (n=2781, age — 18-30 years). There is a risk of OH overestimation due to a very sensitive diagnostic criterion in relation to SBP change. The rationale for such sensitive criterion was not provided. In the ARIC Study [14], this criterion would classify 30% of all participants as having orthostatic hypertension
Japan Morning Surge-1 (JMS-1) Study Hoshide S, et al. (2008) [19]	SBP increase ⩾11,5 mm Hg (=the top decile)	The study was performed on a population of older hypertensive patients (n=605). The orthostatic change in SBP was measured from sitting to standing position. This criterion is dependent on the investigated population
Kario K. (2013) [20]	Verified OH — increase in SBP ⩾20 mm Hg, if OT is performed at home — increase in SBP ⩾10 mm Hg; probable — an increase in SBP ⩾10 mm Hg.	Applicable to both OT and tilt testing; the choice of OH criteria is justified by the analysis of previously published studies
Systolic Blood Pressure Intervention (SPRINT) Study Townsend RR, et al. (2016) [21]	SBP increase ⩾20 mm Hg or DBP increase ⩾10 mm Hg	The study was performed on a large population of hypertensive patients (n=8662, age ⩾50 years). The authors performed one standing measurement only (after 1 minute). There is a risk of OHTN overestimation due to normal increase in DBP on standing
Weiss A, et al. (2016) [22]	Any increase in SBP or DBP	The study was performed on older patients (n=474, mean age, 81,5±6,8 years) admitted to emergency department. The rationale for this approach to orthostatic hypertension definition was not provided. The authors identified 86% of all patients as having orthostatic hypertension
Systolic Hypertension in the Elderly Program (SHEP) Study Kostis, et al. (2019) [23]	SBP increase ⩾15 mm Hg	The study was performed on a large population of hypertensive patients (n=4736, age >60 years). The orthostatic change in SBP was measured from sitting to standing position. The rationale for this criterion was not provided
Finucane, et al. (2019) [24]	A sustained increase (>1 min) in SBP ⩾20 mm Hg or above 140/90 mm Hg, if patient is normotensive supine	A practical guide to active standing test with beat-to-beat BP monitoring. The absolute DBP criterion is not included due to normal increase in DBP on standing

Abbreviations: HTN — hypertension, BP — blood pressure, DBP — diastolic blood pressure, SBP — systolic blood pressure, OH — orthostatic hypertension, OT — orthostatic test.

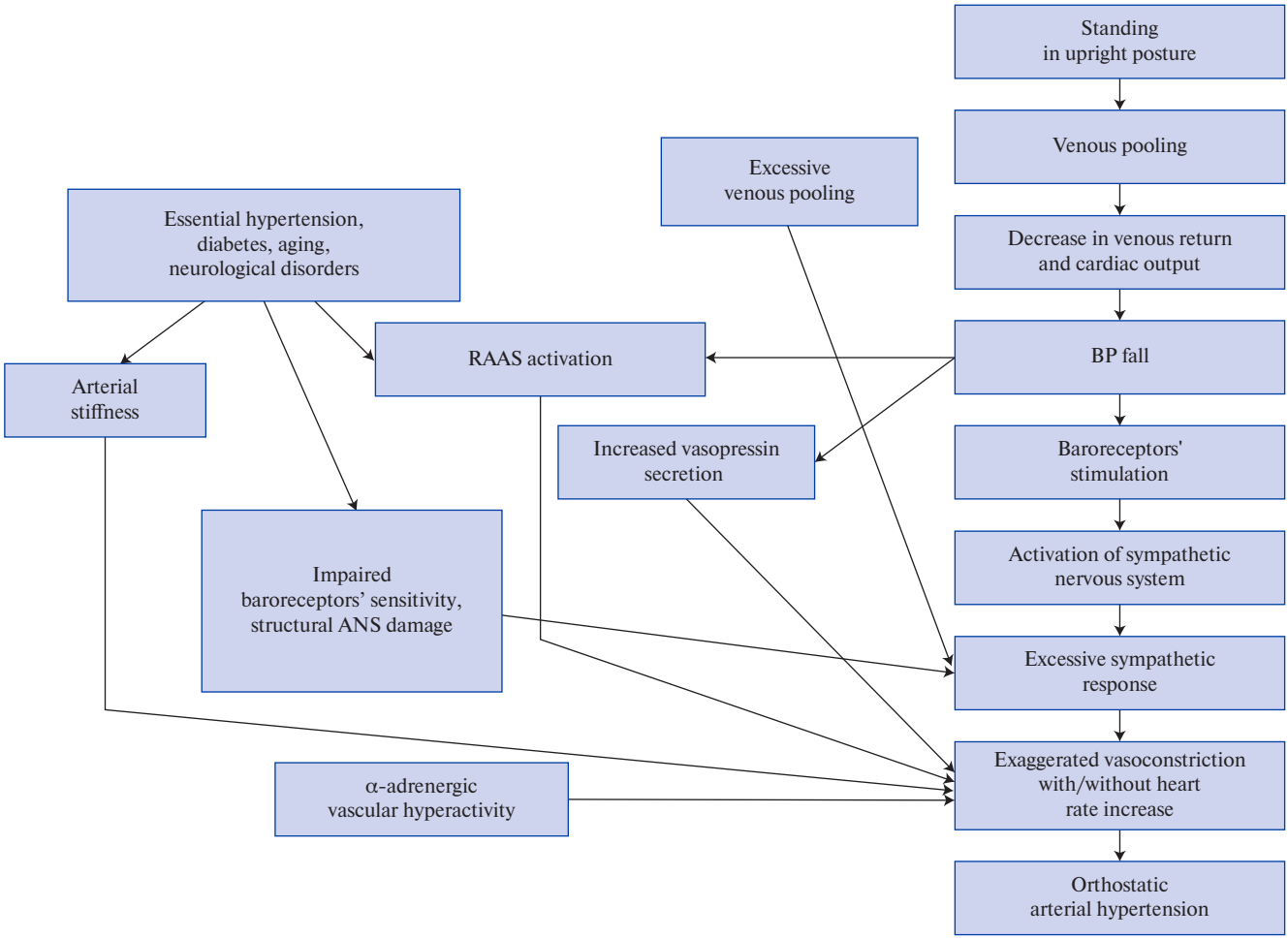

Figure 1. Mechanisms proposed to underlie pathogenesis of orthostatic hypertension; the figure first published in the paper by Magkas N., et al. (2019) [6].

ANS degeneration and sympathetic activation, is considered as a precipitating factor of OH [12, 18, 20, 32]. Structural and/or functional disorders of the renal vascular system, as in HTN, can also determine the pathogenetic mechanisms of OH. A decrease in renal blood flow activates the RAAS, further causing vasoconstriction, water and salt retention, and BP increase (renovascular hypertension, nephroptosis) [5, 6, 30, 33, 34]. Thus, it is obvious that OH and HTN have common pathogenetic mechanisms, but it remains unclear whether OH is a cause, effect or phenotype of HTN [6]?

Other rare causes of OH include vascular myelopathy, norepinephrine transporter deficiency, baroreflex failure, mutation of the gene encoding phosphodiesterase 3A, pheochromocytoma, mast cell activation syndrome, and posture disorders (Table 2) [5, 6, 25, 35]. In children, endothelial damage and the related decrease in plasma levels of nitric oxide and nitric oxide synthase, vitamin D deficiency, as well as its participation in ANS and RAAS regulation

Table 2

Conditions determining the pathogenetic mechanisms of OH

Primary chronic diseases
Hypertension in the elderly
Hypertension (extreme-dipper profile)
Hypertension with orthostatic deposition
Type 2 diabetes
Peripheral neuropathy
Mutation of the gene encoding phosphodiesterase 3A
Autonomic dysfunction conditions
Postural orthostatic tachycardia syndrome
Mast cell activation syndrome
Norepinephrine transporter deficiency
Baroreflex failure
Central autonomic dysfunction
Conditions potentially resolved by surgery
Pheochromocytoma
Renovascular hypertension
Nephroptosis
Vascular myelopathy
Postural disorders

are also considered pathogenetic mechanisms of OH [25, 29, 36].

Epidemiology of OH and its potential use in CVR stratification for hypertensive patients

The absence of generally accepted diagnostic criteria for OH complicates the comparison of research results: in studies defining OH as an increase in SBP ⩾20 mm Hg, the prevalence of OH varied from 1,1% in young patient population to 28% in elderly one [6, 25, 37, 38]. In studies using lower SBP elevation levels as diagnostic criteria, the prevalence of OH was expected to be higher.

OH is a pathological body response to orthostasis, but the consequences of its diagnosis in terms of CVR stratification are far from clear [3, 5-7, 13, 15-19, 21, 32, 38, 46].

OH is interconnected with all components of the cardiovascular continuum in HTN: RFs, Asymptomatic HTN-mediated organ damage, and associated conditions (Table 3).

The relationship between OH and HTN [6, 10, 13, 16, 18, 21, 36, 37], hypertriglyceridemia [6, 17, 32], diabetes [6, 17, 42], body mass index, obesity and metabolic syndrome has been demonstrated [16, 21, 25, 32, 46], however, age, apparently, is decisive

Table 3

Clinical studies studying OH and hypertension

Study and total number of participants	Design	Description	OH criteria	Results
Frohlich ED, et al. (1967) [39]; n=69	Observational cross-sectional prospective study	Hypertensive patients who did not receive antihypertensive therapy, without HF signs (n=52) Control group (n=17)	Increase in mean BP ⩾10 mm Hg	Patients with HTN and OH had a higher TPVR after the tilt testing in comparison with the control group, patients with hypertension and normal OT, HTN and orthostatic hypotension, in a horizontal position — compared with patients with hypertension and orthostatic hypotension. HF, cancer and resistant HTN were less common among patients with hypertension and OH compared with patients with hypertension and normal OT, HTN and orthostatic hypotension.
Streeten DH, et al. (1985) [9]; n=1800	Observational cross-sectional prospective study	Hypertensive patients who did not received antihypertensive therapy	DBP supine <90 mm Hg and DBP on standing >90 mm Hg	Greater decrease in CO and LV EDV, increase in venous pooling and increase in plasma norepinephrine after 5-60 min of comparison in patients with OH
Hypertension and Ambulatory Recording Venetia Study (HARVEST) Vriz O, et al. (1997) [10]; n=1029	Observational cross-sectional prospective study	Patients with stage 1 hypertension; mean age, 33 years	Increase inDBP ⩾11 mm Hg	In patients with hyperreactive OR, higher BP values during the daytime and 24 hours, lower BP values in the horizontal position, hyperkinetic hemodynamic pattern with a large urinary norepinephrine release, higher CO and lower TPVR were recorded
Matsubayashi K, et al. (1997) [11]; n=334	Observational cross-sectional prospective study	Hypertensive patients; mean age, 80 years; 50% did not receive antihypertensive therapy	Increase in SBP ⩾20 mm Hg	OH may be associated with stroke and neurocognitive deficits regardless of HTN presence
Kario K, et al. (1998) [15]; n=110	Observational cross-sectional prospective study	Patients did not receive antihypertensive therapy for at least 14 days prior to enrolment, age ⩾60 years White coat HTN (n=29) Extreme dippers (n=14) Dippers (n=56) Non-dippers (n=11)	Increase in SBP ⩾10 mm Hg	Pathological 24-hour BP variability is interrelated with pathological postural BP variability in elderly patients with hypertension: in elderly extreme-dippers, OH was diagnosed during a tilt test; vertical position during wakefulness can cause pathological diurnal BP variability
Atherosclerosis Risk in Communities (ARIC) Study Nardo CJ, et al. (1999) [14]; n=13340	Observational multicenter longitudinal prospective cohort study	Age of 45-64 years old	Increase in SBP ⩾20 mm Hg	Patients in the upper 3 decile groups of orthostatic SBP had higher SBP values in the sitting position and a greater 8-year risk of CAD compared with patients with the middle 4 deciles of orthostatic SBP changes.

Table 3. Continuation

Study and total number of participants	Design	Description	OH criteria	Results
Kohara K, et al. (2000) [12]; n=154	Observational cross-sectional prospective study	Age >65 years	Increase in SBP ⩾20 mm Hg	Patients with the highest orthostatic SBP tertile had the highest IMT values.
Honolulu Heart Program (HHP) Alagiakrishnan K, et al. (2000) [16]; n=3741	Observational longitudinal prospective cohort study	Males, American-Japanese population, age 71-93	Increase in SBP ⩾10 mm Hg and DBP ⩾10 mm Hg	OH was associated with hypertension in sitting, lower BMI. No associations with all-cause mortality were found after a six-year follow-up period
Yoshinari M, et al. (2001) [17]; n=405	Observational cross-sectional prospective study	Patients with type 2 diabetes without hypertension (n=187) Hypertensive patients with type 2 diabetes (n=90) Patients without diabetes (n=128)	SBP increase from <140 mm Hg to ⩾140 mm Hg or DBP from <90 mm Hg to ⩾90 mm Hg	Triglyceride concentrations and cardiothoracic ratio in diabetic patients with OH were significantly higher than in diabetic patients with normal BP. OH may be associated with the development early-stage neuropathy and hypertension
Kario K, et al. (2002) [13]; n=241	Observational cross-sectional prospective cohort study	Age ⩾60 years Patients with hypertension and OH (n=26) Patients with hypertension and orthostatic hypotension (n=23) Patients with hypertension and normal blood pressure during a tilt test (n=192)	Increase in SBP ⩾20 mm Hg	Silent strokes prevailed in the group of patients with hypertension and OH (3,4/patient; p<0,0001), hypertension and orthostatic hypotension (2,7/patient; p=0,04) in comparison with patients with hypertension and normal blood pressure during tilt test (1,4/patient). Patients with OH (p<0,0001) and orthostatic hypotension (p=0,01) had greater variability in blood pressure compared with patients with normal blood pressure during the tilt test. In the group of patients with OH, relationships were obtained with ECG signs of LVH, increased BP variability, and an extreme-dipper BP profile.
Coronary Artery Risk Development in Young Adults (CARDIA) Study Thomas RJ, et al. (2003) [18]; n=2781	Observational longitudinal prospective cohort study	Age — 18-30 years old Decreased SBP in orthostasis ⩾5 mm Hg (n=741) Change in SBP in orthostasis ±5 mm Hg (n=1590) Increased SBP in orthostasis ⩾5 mm Hg (n=450)	Increase in SBP ⩾5 mm Hg	The eight-year incidence of HTN was highest in the group with an elevated systolic BP in orthostasis (12,4%, p<0,001)
Eguchi K, et al. (2004) [40]; n=86	Observational cross-sectional prospective study	Patients did not receive antihypertensive therapy within 14 days prior to enrolment; mean age, 67,6 years Patients with hypertension and OH (n=16) Patients with hypertension and orthostatic hypotension (n=18) Patients with hypertension and normal BP during a tilt test (n=25) Control group (n=27)	Increase in SBP ⩾10 mm Hg	The number of silent strokes and their prevalence prevailed in the group of patients with HTN and OH in comparison with all other groups; patients with hypertension and OH have an increased risk of silent stroke and CVE
Japan Morning Surge-1 (JMS-1) Study Hoshide S, et al. (2008) [19]; n=605	Experimental randomized controlled trial	Patients with hypertension without heart failure (n=434) Control group (n=171)	Increase in SBP ⩾11,5 mm Hg	In patients with HTN and an increased BNP levels and albumin to creatinine ratio, regardless of the BP levels at home, OH detection can be a factor of high CVR
Fan XH, et al. (2010) [41]; n=5537	Observational cross-sectional prospective study	Age of 40-75 years Patients with hypertension (n=4711) Patients with normal blood pressure (n=826)	Increase in SBP ⩾20 mm Hg	HTN is independently associated with OH risk; OH is associated with peripheral arterial disease (OR, 1,36; 95% CI, 1,05-1,81; p<0,05) and stroke (OR, 1,76; 95% CI, 1,27-2,26; p<0,01)

Table 3. Continuation

Study and total number of participants	Design	Description	OH criteria	Results
ARIC Study Yatsuya H, et al. (2011) [42]; n=12817	Observational longitudinal prospective cohort study	Patients without stroke at the time of inclusion, median follow-up of 18,7 years: ischemic stroke (n=680): lacunar — 153, non-lacunar thrombotic — 383, cardioembolic — 144	Increase in SBP ⩾20 mm Hg	U-shaped relationship between changes in SBP in orthostasis and incidence of lacunar strokes (p=0,004). Patients with OH were older and had higher prevalence of hypertension and diabetes
Barochiner J, et al. (2013) [38]; n=304	Observational cross-sectional prospective study	Patients with hypertension receiving antihypertensive therapy; age, 66,7±13,8 years	Increase in SBP ⩾5 mm Hg	OH was a factor independently associated with masked HTN (OR, 3,65; 95% CI, 1,27-10,51)
Xu J, et al. (2014) [43]; n=2849	Observational cross-sectional prospective study	Age >40 years	Increase in SBP ⩾10 mm Hg	OH was associated with age and history of hypertension. After orthostasis, in patients with OH, pulse pressure increased; in patients with OH and normal BP in orthostasis, on the contrary, it decreased.
Shimanami Health Promoting Program (J-SHIPP) Study Tabara Y, et al. (2016) [44]; n=884	Observational cross-sectional prospective study	Age, 66,3±8,9 years	Increase in SBP ⩾10 mm Hg; SBP changes were recorded as the difference between SBP in orthostasis and SBP in the sitting position	Ortostatic change in SBP and differences in office BP were interrelated (r=-0,422; p<0,001); the relationship remained at the second visit (n=101, r=-0,326; p=0,001). Multivariate analysis showed an independent inverse relationship (β=-0,23; p<0,001) on possible covariances, including baseline office BP and antihypertensive therapy. OH was associated with large differences between office and outpatient SBP (p=0,001). The prevalence of detected masked hypertension (52,1%) was higher in patients with OH than in the group of patients with normal BP (27,5%) (OR, 3,01; p=0,001)
Systolic Blood Pressure Intervention (SPRINT) Study Townsend RR, et al. (2016) [21]; n=8662	Experimental randomized controlled trial	Patients with hypertension, age ⩾50 years	Increase in SBP ⩾20 mm Hg and DBP ⩾10 mm Hg	OH at the time of study enrolment was more common in women and African Americans and was associated with higher BMI and lower BP (sitting)
Nibouche-Hattab WN, et al. (2017) [32]; n=108	Observational cross-sectional prospective study	Patients with normal BP and recently diagnosed type 2 diabetes (n=108), age 40-70 years, follow-up period — 1 year Normal blood pressure in orthostasis (n=74) Orthostatic hypotension (n=12) OH (n = 22)	Increase in SBP ⩾20 mm Hg and/or DBP ⩾10 mm Hg	Patients with OH had higher SBP in horizontal position (p=0,029), waist circumference (p=0,022), LDL cholesterol (p=0,041). They were more likely to have obesity (p=0,036), LVH (p=0,024), MS (p=0,042), cerebrovascular events (p=0,050) in comparison with patients with normal BP in orthostasis. One year later, the prevalence of HTN was higher in the group of patients with OH (p=0,0008)
Barochiner J, et al. (2018) [45]; n=186	Observational cross-sectional prospective study	Hypertensive patients receiving antihypertensive therapy	Increase in SBP ⩾20 mm Hg and DBP ⩾10 mm Hg	OH was associated with a higher variability of the systemic vascular resistance, heart rate in orthostasis, and a lower level of DBP supine. Patients with OH had a lower TPVR in the horizontal position compared to patients with orthostatic hypotension
Systolic Hypertension in the Elderly Program (SHEP) Study Kostis, et al. (2019) [23]; n=4736	Experimental randomized controlled trial	Patients with isolated systolic hypertension, age >60 years	Increase in SBP ⩾15 mm Hg	OH was associated with higher cardiovascular and all-cause mortality after adjusting for age, sex, and baseline SBP, but after adjusting for RF for CVDs and other comorbidities, the relationship lost significance

Table 3. Continuation

Study and total number of participants	Design	Description	OH criteria	Results
SPRINT Rahman M, et al. (2021) [48]; n=9329	Secondary retrospective analysis	Mean age, 67,86±9,4 years, 35,6% — blacks, 31,6% — women	Increase in SBP ⩾20 mm Hg and DBP ⩾10 mm Hg	The proportion of patients with OH was 21,2%; female sex, Negroid race and higher BMI predisposed to OH (p<0,001). OH was associated with a higher CVE risk in the intensive antihypertensive therapy group, but not in the standard antihypertensive therapy group. An intensive regimen of antihypertensive therapy compared with the standard regimen does not decrease the CVE risk in patients with OH

Abbreviations: HTN — hypertension, BP — blood pressure, LVH — left ventricular hypertrophy, DBP — diastolic blood pressure, CI — confidence interval, CAD — coronary artery disease, BMI — body mass index, LV EDV — left ventricular end diastolic volume, MS — metabolic syndrome, TPVR — total peripheral vascular resistance, OR — orthostatic reaction, OR — odds ratio, SBP — systolic blood pressure, CO — cardiac output, CVD — cardiovascular diseases, CVE — cardiovascular events, CVR — cardiovascular risk, IMT — intima–media thickness, RF — risk factors, LDL– low–density lipoprotein, HF — heart failure, BNP — brain natriuretic peptide.

in OH pathogenesis [6, 17, 20, 25, 32, 36, 42, 47]. The pathophysiological prerequisites and clinical characteristics of OH may differ depending on age and have different meanings: for a young patient, there is increased risk of HTN in the future [3, 5, 6, 18, 20, 25, 32], and in an elderly patient — independent CVR factor [13, 20]. The relationship between OH and masked HTN was revealed [37, 38].

OAS is interrelated not only with HTN, but also with BP changes during the day: the level of morning BP increase, BP variability and an excessive nocturnal BP decrease (Extrime-dipper profile), which are known markers of stroke [3, 13, 15, 20]. Patients with extreme-dipper HTN have a higher prevalence of silent stroke diagnosed by magnetic resonance imaging compared with patients with dipper hypertension. In addition, patients with extreme-dipper hypertension have a greater risk of manifested stroke, and in case of the latter, have a worse prognosis. OH can be RF in hypertensive patients, because two-thirds of strokes in such extreme-dipper patients occur in the morning, when patients have a morning BP rise [15]. In 1997, Matsubayashi K, et al. [11] found a relationship of OH with stroke and neurocognitive deficits, independent of OH presence. The relationship between OH and the incidence of lacunar strokes was later confirmed by the ARIC study [42] and Nibouche-Hattab WN, et al. (2017) [32], while papers by Kario K, et al. (2002) [13], Eguchi K, et al. (2004) [40], Fan XH, et al. (2010) [41] revealed an increased risk of stroke in a cohort of patients with HTN and OH.

Cross-sectional studies have demonstrated the relationship between OH and HTN-mediated organ damage: an increase in natriuretic peptides and albumin-to-creatinine ratio [19], left ventricular hypertrophy [13, 32], the intima-media thickness [12]; as well as associated clinical conditions: peripheral arterial disease [41] and coronary artery disease [14], which allows to consider the diagnosed OH as a factor of CVR stratification in HTN patients.

In 2019, Kostis, et al. [19], based on the Systolic Hypertension in the Elderly Program (SHEP) study, revealed an association of OH with higher cardiovascular and all-cause mortality after adjusting for age, sex, and baseline SBP. However, after adjusting for RFs of cardiovascular and other concomitant diseases, the relationship lost significance. In 2021, Rahman M, et al. published data from a retrospective analysis of the Systolic Blood Pressure Intervention Trial (SPRINT): in the intensive antihypertensive therapy group, OH was associated with a higher risk of cardiovascular outcomes [48].

Thus, although it is obvious that OH and HTN are interrelated conditions, the evidence base is small and there are no studies on the prognosis in patients with HTN and OH, and not in the general population of patients with OH. There are no criteria for the diagnosis of OH, approved by the medical community. Based on the foregoing, large-scale studies are needed to clarify the possibility of using diagnosed OH in hypertensive patients as a marker of CVR.

Relationships and Activities: none.

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Genetic and epigenetic factors regulating the expression and function of the vitamin D receptor in patients with coronary artery disease

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Coronary artery disease (CAD) remains the leading cause of death and disability in developed countries. Using traditional risk factors for CAD, it is possible to predict the likelihood of acute coronary events in no more than 50% of cases. Therefore, the study of influence of genetic and epigenetic factors on the development of CAD is extremely important. Research in recent years has shown that vitamin D deficiency is a new risk factor for atherosclerosis and immune inflammation. Vitamin D implements protective effects against immune inflammation through receptors in the vascular wall. A single nucleotide polymorphism of the vitamin D receptor (*VDR*) gene is a potential risk factor for CAD associated with low vitamin D levels. VDR expression correlates with the expression of pro-inflammatory cytokines and is regulated by microRNAs — microRNA-125a-5p, microRNA-125b-5p, microRNA-214-3p and microRNA-21 These microRNAs regulate the action, synthesis and metabolism of vitamin D and can themselves be influenced by VDR signals through dynamic feedback, which can lead to destabilization of mRNA and inhibition of translation. This literature review highlights the effect of a single nucleotide polymorphism of the *VDR* gene and microRNA on the pathogenetic mechanisms of CAD.

Keywords: coronary artery disease, myocardial infarction, vitamin D receptor, vitamin D, gene polymorphism, cytokines, microRNA.

Relationships and Activities: none.

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Coronary artery disease (CAD) is the most common cardiovascular disease (CVD) and is the leading cause of disability and mortality worldwide, including working-age people [1, 2]. It is a complex, multifactorial and polygenic disease, the pathogenesis of which is based on the interaction between genetic predisposition and environmental factors [2].

Recent studies have shown that traditional risk factors (RF), including dietary errors, obesity, diabetes, hypertension, dyslipidemia, smoking and alcohol abuse, can predict the risk of cardiovascular events and complications only in 50% of cases. [3]. Therefore, it is extremely important to study new RFs of CAD, especially genetic and epigenetic ones [4].

A number of authors have found that genetic screening will allow 12% of patients to requalify the CVD risk from moderate to high, therefore, a multilocus genetic risk score for diseases and its complecations has been developed [5].

To analyze the hereditary predisposition to CVD, characteristic of polygenic diseases, in addition to genetic factors affecting the CAD risk, an important role is played by the assessment of atherogenesis-related epigenetic factors, primarily the microRNAs, which are small noncoding RNAs that regulate transcriptional or posttranscriptional expression [6].

Recent studies have shown that vitamin D is not only the most important regulator of calcium and phosphorus metabolism, but also plays an important role in vascular immune inflammation, pathogenesis of atherosclerosis [7], and carcinogenesis [8].

Both epidemiological and laboratory studies have shown a positive effect of vitamin D on cardiovascular function [7, 9].

Vitamin D receptor

The vitamin D receptor (VDR) is a member of the steroid hormone receptor. It is necessary to implement the functions of related ligand, vitamin D, being an important regulator of the pathogenetic pathway of vitamin D, since VDR is involved in the conversion of serum 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D [10].

The VDR consists of 427 amino acids and has 2 main functionally significant domains: the N-terminal domain, through which the nuclear receptor is attached to DNA, and the C-terminal domain, which is required for ligand binding. It is known that VDR belongs to nuclear receptor superfamily — transcription factors that regulate the expression of many genes. After binding to ligands, nuclear receptors are activated and bind in the cell nucleus with DNA regions localized in the promoter of target genes [11].

VDR in the human body is found in many organs and tissues: vascular smooth muscle cells, endothelial cells, cells of the immune system, kidneys, intestines, bones, parathyroid glands. The ubiquitous distribution of VDR reflects its pleiotropic biological activity [10].

VDR regulates the expression of some genes involved in atherogenesis. The presence of VDR in vascular smooth muscle and endothelial cells, combined with the ability of vascular tissues to activate vitamin D, indicates the role that vitamin D may play in normal vascular physiology and its importance in CAD prevention. This is supported by the Valcheva P, et al. Study with laboratory mice: vascular smooth muscle cells of *VDR* knockout mice more actively produced cathepsin D (enzyme with renin-like activity) and angiotensin II [12].

In a laboratory study by Yao T, et al., the protective role of vitamin D in modeled myocardial infarction (MI) was shown: VDR stimulation with related ligands improved the cardiac contractile function and decreased the MI area due to the improvement of mitochondrial function, reduction of endoplasmic reticulum damage and inhibition of cardiomyocyte apoptosis [13].

It was found that VDR affects the plaque stabilization by suppressing the neoangiogenesis, which predisposes to rupture of unstable atherosclerotic plaques. VDR, binding to the ligand, suppresses angiogenesis by inhibiting the vascular endothelial growth factor production. In addition, vitamin D through the VDR in endothelial cell cultures reduces the P-selectin (CD62P) expression [14].

Vitamin D has been shown to reduce the expression of endothelin, tissue factor, and epidermal growth factor by smooth muscle cells with VDR on their surface. This prevents the migration of smooth muscle cells and slows down the atherosclerotic plaque growth [15].

***VDR* gene polymorphism**

The recent studies established that a single nucleotide polymorphism of the *VDR* gene is a potential RF for CAD associated with low vitamin D levels, but the exact mechanisms underlying the effect of polymorphic *VDR* gene variants on CAD pathogenesis are not fully understood [16, 17].

The *VDR* gene was discovered by Baker AR, et al. in 1988 [18]. This gene is located on chromosome 12 (12q12-14) and includes at least 5 promoter regions generating several tissue-specific transcriptions, 8 exons encoding a protein, and 6 untranslated exons with alternative splicing [19]. The *VDR* gene is 100 kb in size.

Currently, more than 470 types of *VDR* gene single nucleotide polymorphism have been found, while among them 4 polymorphisms (FokI (rs10735810), BsmI (rs1544410), ApaI (rs7975232) and TaqI

(rs731236)) have been thoroughly studied for their effect on various physiological and pathological phenotypes, such as cancer, diabetes, Parkinson's disease, myocardial infarction and CAD [19-21].

VDR gene polymorphic variants can potentially affect *VDR* expression and VDR mRNA stability [7].

VDR FokI polymorphism is localized in the second exon of the fifth codon [22] and is characterized by cytosine-to-thymine substitution in the start-codon ATG→ ACG. Among the many different types of *VDR* gene polymorphism, this polymorphism is the only one not associated with other *VDR* gene polymorphisms, as well as the only polymorphism that leads to two different VDR protein products [23].

The minor f (T) allele of this gene encodes a full-length protein of 427 amino acids, with translation initiation occurring at the first ATG site, while in carriers of the F (C) allele, translation begins at the second ATG start codon in exon 2. Thus, the F (C) allele encodes a protein shortened by 3 amino acids, which is 1,7 times more efficient than the long one for transactivation of target genes due to more active transcription [7]. Consequently, the *VDR* gene FF genotype play a significant role in CAD development indirectly through vitamin D deficiency [7].

These data were also confirmed by the analysis of 20 fibroblast cell lines, where it was revealed that the shortened protein encoded by the F allele interacts more actively with the transcription factor due to special genetic effects in the promoter region of targeted genes. Thus, some promoter regions of targeted genes for VDR are sensitive to these genotype-dependent differences in activity [8].

The results of studies on relationship between *VDR* FokI polymorphism and CAD are contradictory. He l, Wang M [16] showed an association between *VDR* FokI polymorphism and CAD in the Chinese population, but Pan XM, et al. [22] do not reveal such association. This can be explained by the small sample size of subjects. The study by Shanker J, et al. with the Indian population also did not reveal an association between *VDR* FokI polymorphism and CAD [23]. Perhaps this is due to the peculiarities of *VDR* gene polymorphism distribution in different populations.

Results from studies by Hossein-Nezhad A, et al. showed that vitamin D deficiency is less common in patients with *VDR* gene FF genotype, which implies a protective role of the F allele in CAD development [9].

These findings are supported by a 2016 meta-analysis by Lu S, et al. The authors showed that carriers of *VDR* gene FF genotype had 19% reduced risk of CAD [7].

TaqI, ApaI and BsmI polymorphisms of the *VDR* gene are interrelated and localized between the eighth and ninth exons in the 3' terminal region of the *VDR* gene, containing microsatellite sequences of different lengths — short (S) and long (L), which can affect the translational activity and stability of VDR mRNA [16].

There are 3 main haplotypes of the *VDR* gene with different activities [16]:

1) baT haplotype — 48% of the population;
2) BAt haplotype — 40% of the population;
3) bAt haplotype — occurs much less often.

There were no differences between haplotypes with regard to regulation of messenger RNA stability. Only a tendency for the BAt haplotype to express higher levels of messenger RNA in monocytes was revealed as compared to baT haplotype carriers [16].

The prospective DIABHYCAR study found that the bAt haplotype of the *VDR* gene (AAC) was associated with an increased CAD risk in type 2 diabetes patients. This effect was independent of the influence of other known CVD RFs [24].

BsmI and ApaI polymorphisms of the *VDR* gene control protein expression by regulating the messenger RNA stability and are localized in the 8th intron of the 3' regulatory region. This is most common for steroid hormone receptors, which contain large regulatory regions. Patients carrying the BB and Bb genotypes of the *VDR* gene had a higher hypertension prevalence. An association of the bb/Aa genotype with ischemic stroke was noted [25].

In the Arab population, El-Barbary AM, et al. found a relationship between the bb genotype of the *VDR* gene and atherosclerotic vascular lesions [26], while Al-Ghamdi AS, et al. [27] reported no association of this genotype with CAD in Saudi Arabia. The small number of patients examined may partly explain the conflicting results.

A stratified analysis of *VDR* BsmI polymorphism by ethnicity revealed an increased risk of CAD in the European population among b (A) allele carriers by 23% compared with B (G) allele carriers. Moreover, bb (AA) and Bb (AG) carriers had 56% and 20% higher risk of CAD than BB (GG) carriers [28].

In the Asian population, there was no association between the *VDR* BsmI polymorphism and CAD risk. This may be due to the fact that the alleles of this polymorphism are located between the 8th intron and the 9th exon of the VDR gene, which has an unbalanced linkage in different ethnic groups [28].

VDR ApaI polymorphism affects the stability of messenger RNA [29]. Since VDR plays an important role in vitamin D signaling, it can be assumed that the *VDR* ApaI polymorphism may also influence the CAD risk, either by altering the sensitivity of the receptor to ligands, or by gene-gene interactions or environmental effects on genes.

Carriage of *VDR* gene Aa (CA) genotype was associated with a decrease in CAD risk in type 2

diabetes patients, and it is likely that this genotype may be associated with a low risk of CAD, but larger studies are required to confirm this [24].

VDR TaqI polymorphism was described in 1994 [28]. It is due to cytosine-to-thymine replacement at codon 352. This leads to the replacement of the AUU (isoleucine) codon with AUG (methionine) [10]. According to the meta-analysis, the tt genotype is associated with an increased risk of CAD in the range from 14% to 27% in various studies [30].

The results of studies on relationship between the *VDR* gene polymorphism and CAD are contradictory. For example, the meta-analysis conducted by Alizadeh S, et al. did not show a relationship between FokI, BsmI, ApaI and TaqI polymorphisms of the *VDR* gene with CAD risk [30], which may be associated with the different prevalence of the above genotypes in different ethnic and racial groups. For example, the prevalence of *VDR* gene f allele (FokI polymorphism) was less common among Africans than among Asians, while the B allele BsmI polymorphism) was less common in Asians than in Europeans and Africans [16]. In the literature, there are practically no studies devoted to the occurrence of FokI, BsmI, ApaI and TaqI polymorphisms of the *VDR* gene and their relationship with CAD risk and its clinical course features in the Northwestern region of Russia.

Prabhakar P, et al. did not establish a relationship between the carriage of different ApaI and TaqI genotypes of the *VDR* gene polymorphism and ischemic stroke. In examined carriers of *VDR* gene ff genotype, the risk of ischemic stroke increased by 2,97 times, while in carriers of the Ff genotype — by 1,52 times. Homozygous carriage of *VDR* gene f allele was associated with increased total cholesterol levels. Carriage of *VDR* gene bb genotype increased the risk of ischemic stroke by 1,76 times. In addition, the authors found that persons with vitamin D deficiency (<20 mg/ml) also have an increased risk of ischemic stroke [31].

TaqI, ApaI and BsmI polymorphisms of the *VDR* gene can affect the expression of VDR mRNA and contribute to a decrease in vitamin D levels in CAD patients. Although genetic factors contribute significantly to the variability of circulating vitamin D levels, heritability is estimated to be 30-40% [28]. An imbalance was observed only in these three polymorphisms, and they were in the same haploid domain with a 3' regulatory domain. The haploid domain includes 4-9 exons and a 3' regulatory domain, which is associated with gene expression regulation, especially with the regulation of mRNA stability.

Apparently, carriers of unfavorable prognostic genotypes of the *VDR* gene also have a reduced ability to inhibit the NF-kB signaling pathway. NF-kB, in turn, prolongs the activation of macrophages and increases the expression of adhesive molecules on endothelial cells, thereby supporting the development and progression of atherosclerotic vascular lesions [32].

Epigenetic mechanisms of vitamin D receptor regulation

The recent studies have shown that 80% of genome function consists in the epigenetic regulation of the expression of genes encoding proteins. MicroRNAs are small noncoding RNAs that are the most important regulators of transcriptional and posttranscriptional gene expression. MicroRNAs are single-stranded regulatory molecules for 30% of all genes. They have a specific hairpin-like structure, ranging in length from 19 to 24 nucleotides, which are formed from longer RNA precursors [6]. MicroRNAs suppress the posttranscription expression of genes encoding proteins due to incomplete hybridization with the 3' regulatory untranslated region of mRNA, which has complementary sites.

MicroRNAs are effective posttranscriptional regulators of gene expression [6]. They drive complex posttranscriptional regular networks required to regulate gene expression. Thus, microRNAs are required for the fine-grained transcriptional regulation of gene expression, but they can also play different roles in the proliferation, differentiation, and function of certain cell types.

Currently, 1000 microRNAs have been identified in the human body, 50 of which are probably associated CVD risk [29].

MicroRNAs, like cytokines, form an interconnected regulatory system that controls apoptosis, proliferation, and tissue differentiation. MicroRNAs play an important role in the normal physiology, facilitating the expression of genes in complex tissue systems, but also contribute in pathology develoment, including endothelial dysfunction, the formation and subsequent rupture of an atherosclerotic plaque [33, 34]. Some microRNAs are considered as possible diagnostic markers of CAD [6, 34].

The expression activity of *VDR* gene can be modulated both by vitamin D itself and by other factors that play an important role in epigenetic modifications, such as microRNA [35].

Regulatory networks of microRNAs are especially important for signaling molecules, which include vitamin D, which have pleiotropic effects on various organs and tissues. Recent studies have shown a role for 1,25(OH)D in epigenetic regulation of genes, especially as a modulator of microRNA function [36].

It has been shown that VDR expression correlates with the expression of such proinflammatory cytokines as interleukin-1, 6, and 8, and can be regulated

by microRNA [36]. The authors explain this correlation by the fact that microRNAs may play a decisive role in obesity-related changes in VDR expression through the local effect of vitamin D in adipose tissue inflammation, however, further studies are needed to confirm this [37].

As already mentioned, vitamin D suppresses the expression of proangiogenic microRNA-155, which is a negative regulator of cytokine signaling suppressor expression, by inhibiting the pathogenetic NF-ϰB pathway[35].

A potential binding site for microRNA-125b was identified in *VDR* gene 3' untranslated region [38], where the BsmI, ApaI, and TaqI polymorphisms of the *VDR* gene are localized, which can potentially affect the interaction of microRNA-125b and the *VDR* gene. The study of MCF-7 cell line (an epithelium-like cell line obtained from breast cancer) revealed that increased expression of microRNA-125b was accompanied by a 40% decrease in the level of endogenous VDR protein [38].

VDR expression in visceral adipose tissue in obese patients negatively correlated with microRNA-125a-5p, microRNA-125b-5p, and microRNA-214-3p levels [36].

The binding site of microRNA-21 is also located in the 3' regulatory domain of the *VDR* gene [38] and, as in the case of microRNA-125b, can potentially be influenced by single nucleotide polymorphisms localized in this region. MicroRNA-21 is expressed in endotheliocytes and regulates their functions. Lisse TS, et al. in 2013 found that with an increase in the expression of microRNA-21 in endotheliocytes, their migration and proliferation decrease, which may indicate its antiangiogenic function. The expression of microRNA-21 is significantly increased in atherosclerotic plaques and macrophages [30]. Therefore, increased expression of microRNA-21 may indicate progressive growth of atherosclerotic plaques.

MicroRNAs interact with the 3' untranslated region of the target mRNA through complementarity with its sequences, and primarily suppress gene expression, causing degradation or inhibition of translation of transcripts through partial complementary binding of base pairs to three primary untranslated or exon regions. The microRNA function can also be influenced by other factors, primarily changes in gene structure — genetic polymorphisms, amplification, gene deletion, impaired processing and methylation [37].

VDR can either suppress or induce microRNAs through two mechanisms:

1) direct transcription regulation through promoter sequences of *VDR* gene or microRNA;

2) indirect regulation involving other transcription factors.

MicroRNAs, in turn, can regulate the action, synthesis, and metabolism of vitamin D or be themselves influenced by VDR signals due to dynamic feedback mechanisms, which can lead to destabilization of mRNA and/or inhibition of translation [30].

Conclusion

In recent years, the role of genetic polymorphism of the *VDR* gene and microRNA in the development of CAD and its complications has been actively studied. The results of studies on relationship between the *VDR* gene polymorphism and CAD are contradictory, which may be due to the different prevalence of above genotypes in various ethnic and racial groups. In the literature, there are practically no studies devoted to the prevalence of FokI, BsmI, ApaI and TaqI polymorphisms of the *VDR* gene and their relationship with CAD risk and its clinical course in the Northwestern region of Russia.

VDR expression can be regulated by microRNA-125a-5p, microRNA-125b-5p, microRNA-214-3p, and microRNA-21 and have a negative correlation with proinflammatory cytokines. However, larger-scale studies are required to confirm these data. In the literature, there are isolated papers showing that the above microRNAs themselves can be influenced by polymorphic *VDR* gene variants due to dynamic feedback, which can lead to mRNA destabilization and inhibition of translation. Therefore, the study of genetic and epigenetic factors regulating the expression and VDR function is extremely important.

Relationships and Activities: none.

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Sodium-glucose co-transporter-2 inhibitors in heart failure and chronic kidney disease: the role of empagliflozin

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The development of chronic kidney disease (CKD) is a risk factor not only for cardiovascular diseases, but also for heart failure (HF). This article is a literary review on the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with CKD and HF. The paper describes in detail the action of SGLT2 inhibitors in the light of nephro- and cardioprotection. In addition to the glucosuric effect of SGLT2 inhibitors, they have a natriuretic and diuretic effect. One of the effects of SGLT2 inhibitors is the ability to lower blood pressure. One of the key effects of SGLT2 inhibitors, explaining nephroprotection, is the influence on glomerular filtration. The ability of SGLT2 inhibitors to suppress the peroxidation in mitochondria of proximal tubular epithelium was shown. Another putative mechanism of the organ protection action of SGLT2 inhibitors is their ability to inhibit the activation of the sympathetic nervous system.

The results of studies using empagliflozin in HF and CKD are presented. In particular, the EMPA-REG OUTCOME study showed that in patients with type 2 diabetes and concomitant cardiovascular diseases, empagliflozin led to a 35% decrease in hospitalization risk due to decompensated HF and decrease of cardiovascular death risk by 38% regardless of baseline renal function. According to the EMPEROR-Reduced study, empagliflozin showed a favourable safety profile.

Keywords: kidney disease, sodium-glucose co-transporter-2 inhibitors.

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In the case of chronic kidney disease (CKD) development in patients with cardiovascular diseases (CVD), heart failure (HF) is more frequent and more severe [1]. Conversely, the development of CKD is a risk factor not only for CVD, but also for HF [2]. The search for new drug approaches to the management of patients with HF, including in the case of CKD, is a relevant issue. More than 30 years have passed since studies using the natural glucoside phlorizin in diabetes that demonstrated glucosuric effect and later the ability to block sodium glucose cotransporters 1 and 2 (SGLT1, 2) [3]. Currently, a large number of SGLT2 inhibitors have received approval for use in clinical practice, including those approved in the United States and Europe: canagliflozin, dapagliflozin, empagliflozin and ertugliflozin, as well as ipragliflozin, luseogliflozin and tofogliflozin approved in Japan. In India, there are remogliflozin and dual SGLT1/SGLT2 inhibitor sotagliflozin, approved for use in patients with type 1 diabetes in Europe, but not yet launched for clinical use. It should be noted that for SGLT2-inhibitors, HF has recently been considered and registered as an additional indication for prescription.

Mechanisms of SGLT2-inhibitor action in the light of nephro- and cardioprotection

In a healthy person, ~180 g of glucose is filtered daily in the kidneys, while its almost complete reabsorption is observed (~99,9%). In the proximal tubule, in its initial section, where most of the SGLT2 is concentrated, up to 97% of glucose is reabsorbed, the rest is reabsorbed in the distal part of proximal tubule by SGLT1 transporters [4]. In patients with diabetes, the glomerular filtration of glucose is significantly increased, but this is accompanied by an increase in its reabsorption up to 600 g/day [5].

In addition to the glucosuric effect of SGLT2 inhibitors, they have a natriuretic and diuretic effect, which is manifested by an increase in urine volume by about 300 ml/day during the first 2-3 days and return to the initial diuresis within several weeks due to the restoration of sodium and water balance. Urine output with the use of SGLT2-inhibitors increases both with euglycemia and, to a greater extent, with hyperglycemia, and also remains elevated in stage 3-4 CKD, HF and acute HF [6].

A decrease in plasma volume during SGLT2-inhibitor therapy occurs by about 7% (5-12%) by the third month of treatment [7]. Normally, SGLT2 is responsible for the reabsorption of ~5% of sodium in tubular urine, while in diabetes the reabsorption volume increases to 15%, which is explained by an increase in SGLT2 and SGLT1 expression in proximal tubules [8]. Thus, the SGLT2 inhibition is accompanied by natriuresis. Moreover, SGLT2 inhibitors can also affect the Na^+/H^+ exchanger 3 (NHE3) in the proximal tubules, also reducing sodium reabsorption [9]. The effect of SGLT2 inhibitors on NHE3 can be explained by the close functional and organic relationships between SGLT2 and NHE3 [10]. In experimental models, it was shown that the use of SGLT1/SGLT2 inhibitor phlorizin markedly increases the excretion of Na^+ and HCO^{3-} in the urine. These data are consistent with *in vivo* stationary microperfusion of the proximal tubule, in which the addition of phlorizin to the luminal fluid sharply decreases the NHE3 activity even without glucose. This suggests that the effect of SGLT inhibition cannot be simply mediated by osmotic diuretic mechanism induced by luminal glucose. Moreover, using immunofluorescence experiments, it was shown that SGLT2, but not SGLT1, are expressed together with NHE3 on the apical membrane of proximal tubule epithelium [10]. In addition, literature data indicate the multimeric protein complexes in renal proximal tubular cells, which includes two scaffolding protein PDZK1 and MAP17 [11-13]. It has been shown that the MAP17 protein directly interacts with SGLT2, which is necessary for the implementation of its transport function. The MAP17 protein also interacts with PDZK1, which directly interacts with NHE3 [12].

One of SGLT2 inhibitor effects is blood pressure (BP) decrease. Systolic blood pressure in patients with type 2 diabetes and hypertension decreases by an average of 3-5 mm Hg, diastolic — by 1-2 mm Hg [14]. Moreover, this effect remains in full in patients, despite a decrease in renal function [15].

One of the key effects of SGLT2 inhibitors, explaining their nephroprotective effect, is the effect on glomerular filtration. Through SGLT2, not only glucose is reabsorbed, but also sodium. In the case of SGLT2 inhibition, the sodium concentration in the primary urine increases, which effect the juxtaglomerular apparatus (macula densa) in distal tubule. This, in turn, leads to the release of adenosine triphosphate from juxtaglomerular apparatus cells, which is degraded to adenosine. Adenosine effects the adenosine A1 receptors in afferent arteriole wall, which is accompanied by its contraction and pressure decrease, as well as suppression of hyperfiltration in the renal glomerulus. To a lesser extent, the effect of adenosine on A2 receptors in the efferent arteriole, the activation of which is accompanied by vascular dilatation, has been shown [16, 17].

The use of SGLT2 inhibitors is accompanied by a decrease in albuminuria. The meta-analysis of 48 randomized clinical trials on SGLT2 inhibitors' use for >12 weeks, including 50 thousand patients, showed a decrease in albumin-to-creatinine ratio

(weighted average difference, -14,6 mg/g, p=0,006), with more pronounced effect in subjects with a higher baseline albumin-to-creatinine ratio [18]. In particular, a decrease in the risk of microalbuminuria (relative risk (RR), 0,69, p=0,032), macroalbuminuria (RR, 0,49, p<0,001), nephropathy progression (RR, 0,73, p=0,012) and end-stage renal failure (RR, 0,70, p=0,001).

In recent years, the focus from hyperfiltration as an independent factor in renal parenchyma damage is gradually shifting to the proximal tubules. Hyperfiltration is considered as a factor in increasing the functional load on the proximal tubular epithelium, which leads to its damage. And damage to the proximal tubular epithelium can be considered as a key universal mechanism of kidney damage not only in diabetes, but also in a number of other pathological processes that occur with hyperfiltration phenomena. With the use of SGLT2 inhibitors, due to the relief of hyperfiltration, the transport load on the proximal tubules decreases. However, a direct nephroprotective effect of these rugs on the tubular epithelium has also been shown.

The ability of SGLT2 inhibitors to suppress the peroxidation in mitochondria of the proximal tubular epithelium has been shown [19, 20]. Hyperglycemia in diabetes and renin-angiotensin-aldostenorone system activation can cause inflammatory reactions, as well as hyperproduction of reactive oxygen species in proximal tubular cells, and these effects are suppressed by SGLT2 inhibitors [21]. During therapy, there is a decrease in the expression of inflammation genes in the renal tissue, as well as the reduction of oxidative stress [22]. The anti-inflammatory effects of SGLT2 inhibitors are manifested in a decrease in interleukin-6 level and tumour necrosis factor in the blood, as well as nuclear factor-kB and interleukin-6 in the renal tissue of rats with diabetes [16, 23].

SGLT2 inhibitor action increases the reabsorption load in the lower tubular areas, which consume a smaller oxygen volume. This leads to the activation of hypoxia inducible factor (HIF)-dependent processes with a subsequent increase in the production of erythropoietins and improved oxygen delivery to the renal tissue [24]. This mechanism is also considered as a possible tubular protective effect of SGLT2 inhibitors.

SGLT2 inhibitor therapy is accompanied by decreased leptin production, as well as a decrease in fat deposition in the perivisceral, pericardial, and perivascular spaces, which may contribute in improving the course of metabolic processes [25, 26].

SGLT2 inhibitors also lead to a decrease in blood uric acid level due to a decrease in urate reabsorption by proximal tubular epithelium through GLUT9b [27]. Large meta-analysis of 62 clinical studies on SGLT2 inhibitors showed that blood uric acid level decreased by about 35-45 μmol/L, while the effect developed quickly and persisted throughout the treatment period [28].

The cardioprotective effect of SGLT2 inhibitors is explained by different ways. Despite the fact that cardiomyocytes do not express SGLT2, SGLT2 inhibitors are able to directly effect cardiomyocytes by affecting NHE1. An increase in its activity is shown in HF, which leads to an sodium and calcium increase in cardiomyocyte cytoplasm and may be associated with the activation of oxidative stress in arrhythmias [29]. Accordingly, *in vitro* use of SGLT2 inhibitor empagliflozin has demonstrated the ability to inhibit NHE1 in cardiomyocytes, reducing intracellular sodium and calcium levels [30]. Most of the cardioprotective effects of SGLT2 inhibitors are mediated. Among them are the sodium diuretic effect, a decrease in the number of glycation products with pro-inflammatory and endotheliotoxic properties, the normalization of carbohydrate metabolism, a decrease in blood pressure and body weight, etc [31]. The use of SGLT2 inhibitors is accompanied by a decrease in intrarenal renin-angiotensin-aldostenorone system activity, as well as a decrease in plasma renin secretion [32-34].

Another putative organ protective action of SGLT2 inhibitors is their ability to inhibit the sympathetic nervous system. Sympathetic hyperactivity in the proximal tubule area is associated with impaired renal regulation of glucose, sodium, and water [35]. The argument in favor of this mechanism is that renal sympathetic denervation in OLETF rats with diabetes improved glucose metabolism, which was explained by an increase in its urine excretion due to SGLT2 suppression [36]. Stimulation of the renal sympathetic innervation resulted in NHE3 hyperactivity in the apical membrane of the proximal tubule, which was accompanied by antinatriuretic and antidiuretic effects [37]. In turn, in experimental models, SGLT2 inhibitors reduce sympathetic activity in the kidneys and heart [38].

Thus, the cardioprotective effect of SGLT2 inhibitors in HF is realized both through a direct effect on cardiomyocytes and an indirect effect (diuretic, hypotensive effects, sympathetic nervous system suppression, effective treatment of type 2 diabetes). Renoprotective effect of SGLT2 inhibitors in HF is a guarantee of a beneficial effect on the cardiorenal continuum.

Results of studies on empagliflozin use in HF and CKD

The randomized, double-blind, placebo-controlled study EMPA-REG OUTCOME evaluated the effects of empagliflozin at a dose of 10 mg or 25 mg once a day compared with placebo on car-

diovascular events in adults with type 2 diabetes, high cardiovascular risk and a glomerular filtration rate >30 ml/min/1,73 m^2 [39]. It was shown that in patients with type 2 diabetes and concomitant CVD, the use of empagliflozin led to a 35% decrease in hospitalization risk due to decompensated HF, as well as (in subgroup analyses) to an improvement in HF outcomes, such as the risk of loop diuretics' introduction and HF-related rehospitalization [40]. There was also an early and sustained 38% relative reduction in the cardiovascular death risk, regardless of baseline renal function. In patients with type 2 diabetes and CVD, empagliflozin therapy led to a rapid 59% reduction in the relative risk of development or progression of nephropathy, a 44% relative risk of doubling serum creatinine, and a 55% risk of initiating renal replacement therapy compared with placebo [41]. Also, the incidence of adverse events associated with acute kidney injury was lower in the empagliflozin group than in the placebo one.

It should be noted that the positive effect of empagliflozin on cardiovascular mortality and HF-related hospitalizations persisted regardless of CVDs such as heart failure [40], atrial fibrillation [42] (Böhm M, et al., 2020), kidney disease [41], as well as ongoing antihyperglycemic therapy [40].

Empagliflozin continues to be studied in the EMPOWER program, which includes patients with HF, CKD, and myocardial infarction. Thus, the double-blind placebo-controlled study EMPEROR-Reduced on empagliflozin therapy at a dose of 10 mg in patients with reduced ejection fraction (EF) compared with placebo was conducted. The study included 3730 patients with an mean age of 67 years (female, 24%): 75% of patients had NYHA class II HF, 24% — class III and <1% — class IV. Half of the patients had a history of type 2 diabetes, 73% had a left ventricular ejection fraction of 30% or less, 79% had an N-terminal pro-brain natriuretic peptide (NT-proBNP) of at least 1000 pg/ml, 48% had an estimated glomerular filtration rate (eGFR) <60 ml/min/1,73 m^2, and almost 20% of patients received sacubitril/valsartan [43]. It is important to note that the researchers planned in advance to include severe patients with LVEF <30%, and those hospitalized due to decompensated HF within prior 12 months or having high NT-proBNP levels, as well as eGFR >20 ml/min/1,73 m^2.

The primary endpoint (cardiovascular mortality or HF-related hospitalization) was less common by 25% in the empagliflozin group compared with placebo, and primary or repeated hospitalizations due to HF — 30% less frequently [43]. It should be noted that the positive effect of empagliflozin on the primary endpoint was observed regardless of presence/absence of diabetes, baseline renal function, and initial therapy with mineralocorticoid receptor antagonists or angiotensin receptor blocker neprilysin.

One of the secondary endpoints was eGFR decline over the study. The difference in eGFR decrease in the empagliflozin group compared with placebo was 1,73 ml/min per year (p<0,001) in favour of the SGLT2 inhibitor. Empagliflozin therapy in patients with HF reduced the risk of composite renal endpoint by 50% (initiation of renal replacement therapy, kidney transplantation, or stable decrease in eGFR >40% of the baseline) — RR, 0,50 (95% confidence interval, 0,32-0,77).

According to the EMPEROR-Reduced study results, empagliflozin showed a favorable safety profile without cases of ketoacidosis, and the incidence of hypoglycemia was comparable to placebo. In addition, there were no significant differences with the placebo group in adverse events, including hypovolemia, hypotension, renal impairment, hyperkalemia.

The results of this study open up additional prospects for empagliflozin use in patients with HF without diabetes, including with reduced renal function and regardless of a number of drugs used for HF therapy.

The results of the ongoing EMPA-KIDNEY study in adult patients with documented CKD should be expected within a year. This study investigates the nephroprotective and cardioprotective efficacy of empagliflozin in patients with GFR >20 ml/min [44]. Obtaining information on the effect of empagliflozin in this study will provide additional information about its effectiveness in patients with CKD and HF.

Conclusion

SGLT2-inhibitors have a number of direct and indirect cardio- and nephroprotective effects, ensuring the effectiveness of their use in HF, including in patients with CKD. Research results show that empagliflozin is effective in reducing the risk of cardiovascular death and HF-related hospitalizations in patients with type 2 diabetes and CVD, and these effects persist in different patient subgroups. In patients with HF with reduced EF, empagliflozin has also been shown to be effective in reducing the risk of HF-related hospitalizations and cardiovascular death, as well as in slowing the renal function decline compared with placebo. Thus, empagliflozin prevents the CVD progression in patients with type 2 diabetes and those with heart failure with reduced ejection fraction, regardless of diabetes.

The EMPOWER program will expand the variety of empagliflozin effects in patients where modern therapy has serious limitations.

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Osborn wave in a patient with COVID-19: a case report

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The classic Osborn wave in the form of characteristic changes at the depolarization end or ventricular repolarization beginning is more often associated with hypothermia (body temperature below 35,6° C). Some researchers have noticed Osborn wave at normal body temperature, various pathological conditions and diseases: hypercalcemia, myocardial ischemia, postoperative pericarditis, with central nervous system, etc. We presented a case report of a 72-year-old female inpatient with moderate COVID-19, confirmed by polymerase chain reaction, and 48% lung damage. Before admission to the hospital, electrocardiogram had no Osborn wave, which first appeared at admission. There was a significant increase in serum C-reactive protein and a moderate increase in serum biomarkers and no changes in intervals and segments on the electrocardiogram. The appearance of Osborn wave may be associated with intramyocardial electrolyte imbalance, a consequence of antiviral and antibacterial therapy that violate intraventricular conduction.

Keywords: Osborn wave, COVID-19 pneumonia, COVID-19.

Relationships and Activities: none.

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Osborn wave is reflected as a late positive wave following the QRS complex. It can also be interpreted as a serrated descending R-wave in the form of an additional r-wave. This electrocardiographic (ECG) change is associated not with abnormal depolarization of the myocardium, but with repolarization, which is confirmed by J point deflection, which is the initial part of the ST segment. In 1920-1922, a similar ECG performance was described by Kraus F in hypercalcemia [1], and in 1938 by Tomaszewcki W in patients with hypothermia [2]. In 1953, in experiments on dogs under conditions of hypothermia, Osborn JJ demonstrated the J-point elevation in the ventricular ECG complex [3]. Since 1955, hypothermic waves have been named after him. Currently, the critical factor in Osborn wave is considered to be the transmural voltage gradient due to the heterogeneity of the outgoing potassium current in the ventricle [4], arising from various disorders.

The clinical significance of the Osborn wave is specified by its predictive value as a predictor of ventricular fibrillation and sudden cardiac death. The appearance of this wave is a very unfavorable prognostic factor, which increases the risk of ventricular fibrillation. In patients with hypothermia, the association of characteristic ECG abnormalities with ventricular fibrillation in 1957 was confirmed by Fleming PR and Muir FH [5]. As shown earlier, in patients with nervous system diseases, Osborne wave was accompanied by a clinical deterioration [6]. Cases of Osborn wave detection have been described in patients with coronary artery disease, both with previous myocardial infarction (MI) [7] and in patients with vasospastic angina, complicated by ventricular fibrillation [8].

We present a case of Osborn wave detection in a patient with coronavirus disease 2019 (COVID-19) and lung damage.

Case report

Complaints and anamnesis. Seventy-two-year-old female patient was admitted with complaints of dyspnoea at rest, weakness, fever up to 38,5° C, loss of taste, and bitter taste. She considered herself ill for 2 weeks, when the above symptoms first appeared. She took a combination of analgin and diphenhydramine on her own, and did not notice any improvement in the next 10 days. After the appearance of severe shortness of breath during normal physical activity, she applied to the clinic. Despite taking prescribed antiviral therapy (oseltamivir 75 mg/day), shortness of breath increased over the next 3 days. Computed tomography (CT) revealed bilateral ground-glass opacities (48%), after which she was admitted to the COVID-19 Bashkir State Medical University Clinic.

She had history of hypertension (HTN) for 6 years. She regularly took antihypertensive drugs (amlodipine 5 mg/day, telmisartan 40 mg/day), antiplatelet agents (acetylsalicylic acid 50 mg/day) and statins (atorvastatin 20 mg/day).

Objective status on admission was moderate, conscious, body temperature of 37,7° C, heart rate of 92 bpm, blood pressure of 126/82 mm Hg. Respiratory rate was 22 breaths per minute. Blood oxygen saturation (SpO_2) was 94%.

Diagnostic tests. Blood tests revealed nonspecific signs of inflammation. In the complete blood count, leucocytosis up to $10*10^9$/L and elevated erythrocyte sedimentation rate of 50 mm/h was detected (Table 1). In a biochemical blood tests, C-reactive protein (CRP) was significantly increased to 88,4 mg/L, creatine phosphokinase (CPK) — 261 U/L, lactate dehydrogenase (LDH) — 447 U/L, and aspartate aminotransferase (AST) — 49,5 U/L (Table 2). No SARS-CoV-2 RNA was detected in nasopharyngeal swabs by the polymerase chain reaction, but it was detected 3 days before the patient was admitted to the hospital. Also, upon admission, an increase in anti-SARS-CoV-2 IgM to 7,6 U was revealed. Only low concentration of IgG was determined.

There were no potassium and sodium levels' abnormalities in the blood serum (Table 2). Blood albumin concentration corresponded to the lower reference value. Carbohydrate metabolism parameters were within normal range. The serum procalcitonin level used as a marker of bacterial superinfection was also within the acceptable range. A moder-

Table 1

Complete blood count dynamics

	RBC, 10^{12}	Hb, g/L	WBC, 10^9	Segs, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, 10^9/L	TPC, 10^9/L	ESR, mm/h
Admission	4,43	123	5,26	61	30	9	0,167	–	252	50
2nd day	4,37	122	5,01	46	45	9	0,07	0,005	321	28
7th day	4,3	127	10,2	63	34	3	–	–	364	18

Abbreviations: RBC — red blood cells, Hb — haemoglobin, WBC — white blood cells, Segs — segmental neutrophils, ESR — erythrocyte sedimentation rate.

Table 2

Biochemical blood test dynamics

	CRP, mg / l	CPK, U/L	LDH, U/L	AST, U/L	ALT, U/L	Creatinine, μmol/L	Urea, mmol/L	Albumin, g/L	K^+, mmol/L	Na^+, mmol/L	Glu, mmol/L	Procal-citonin, ng/ml	D-dimer, ng/ml
Admission	82,6	261	447	46,8	49,4	98,5	6,17	38,8	4,1	141	5,5	0,24	820
2nd day	88,4	202	407	49,5	58,3	97,2	6,62	38,3	3,5	145	–	–	760
7th day	-	–	–	44	106,3	–		–	–	–	3,7	–	570

Abbreviations: ALT — alanine aminotransferase, AST — aspartate aminotransferase, CPK — creatine phosphokinase, LDH — lactate dehydrogenase, CRP — C-reactive protein.

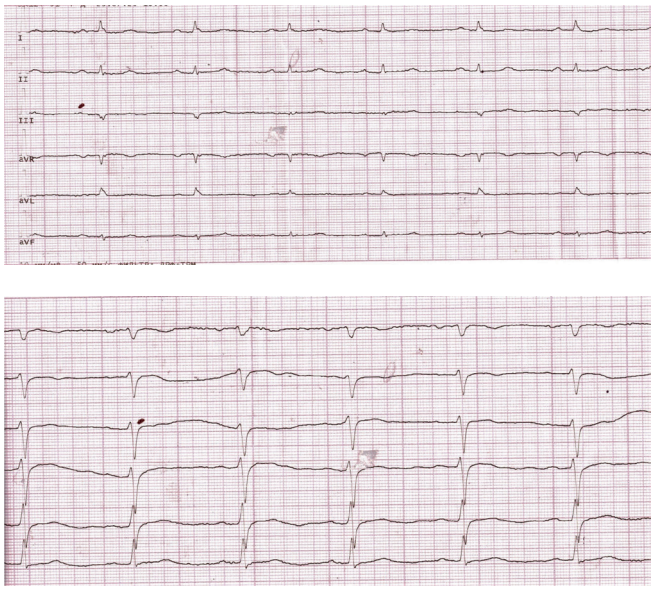


Figure 1. Initial ECG of the 72-year-old female patient: limb and precordial leads.

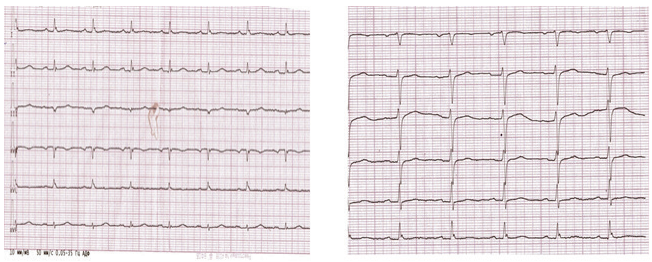
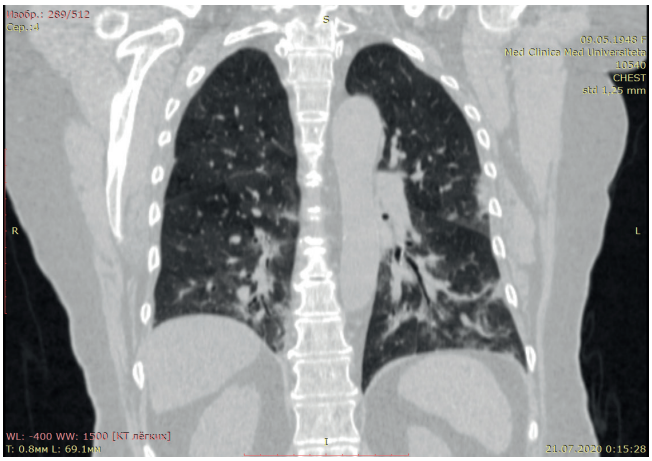


Figure 2. Initial ECG of the 72-year-old female patient after 6 days.



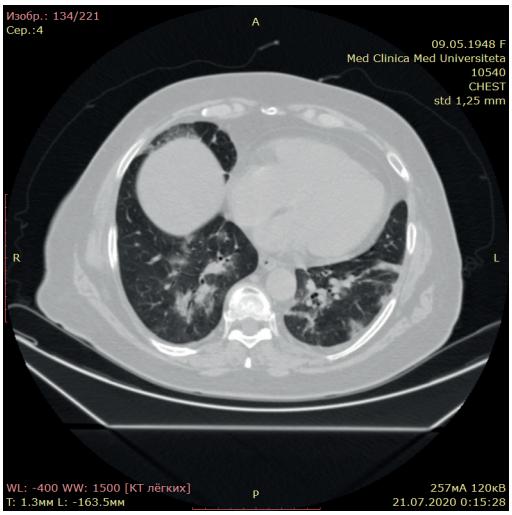


Figure 3. Chest CT scan of the 72-year-old female patient with COVID-19 pneumonia. The lung involvement of 48%.

ate increase in D-dimer with a gradual decrease in its activity was revealed.

On admission, ECG (Figure 1) was characterized by sinus rhythm, heart rate of 85 bpm, left axis deviation. PQ =0,18 sec, QRS =0,08 sec, QT =0,30 sec, QT_{cor} =0,36 sec. Osborn wave was recorded in I, II, aVL leads. Moderate repolarization impairment in the left ventricular (LV) anterior apical area (ST segment elevation by 1,0 mm in V_{3-4} with a biphasic T wave in V_{1-4}). The control ECG (Figure 2) showed an increase in Osborn wave amplitude in I, II, aVL leads, its appearance in V_6, an improved repolarization in V_{3-4}. There was no Osborn wave on the available ECGs before the patient was admitted to the hospital. The last ECG was performed 1 year before admission to the hospital.

According to chest CT upon admission, there was uneven pneumatization of the pulmonary fields,

with alternating areas of moderately low and high airiness (Figure 3). In both lungs, there were multilobar, multisegmental bilateral ground-glass opacities. The upper right lobe is damaged up to 5%, the middle right lobe — 50%, and the lower right lobe — 50%. The upper left lobe is damaged up to 25%, the lower left lobe — 50% (Figure 3). Conclusion: CT showed bilateral multisegmental pneumonia (interstitial infiltration). The lung involvement was 48%. After 5 days, additional CT revealed decrease in the size of ground-glass opacities in both lungs. Conclusion: CT showed bilateral multisegmental pneumonia (interstitial infiltration) with a positive trend in comparison with previous CT scan. The lung involvement was 48%.

The patient received anti-inflammatory and immunosuppressive therapy in accordance with the Ministry of Health of the Russian guidelines: hydroxychloroquine at a dose of 200 mg (400 mg 2 times a day for 2 days, then 200 mg 2 times a day); methylprednisolone at a dose of 1 mg/kg every 12 hours for 4 days, with a transition to a maintenance dose of 8 mg a day for 3 days, then 6 mg a day for 3 days; anticoagulant therapy — enoxaparin sodium 0,4 ml 1 time a day for 10 days, paracetamol 500 mg (with fever >38° C); ambroxol 30 mg 3 times a day. Antihypertensive therapy was continued with calcium channel blockers and sartans in previously selected individual doses. Statin therapy at maintenance doses providing targeted low-density lipoprotein levels was also continued.

The patient was discharged with improved condition 10 days after admission: there were no shortness of breath, cough and fever. SpO_2 rose to 98-99% 3 days before discharge from the COVID-19 hospital.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committees of all participating centers approved this study. All patients signed informed consent.

Discussion

The guidelines for the prevention, diagnosis and treatment of COVID-19 indicate that, despite the many clinical and morphological masks of COVID-19, cardiac damage is in the first place after lungs among other organs and systems. Possible development of myocarditis or myocardial infarction against the background of coronary artery thrombosis due to viral endothelial injury [9].

The literature describes the classic Osborn wave not only in hypothermia, but also in such various pathological conditions and diseases with normal body temperature as hypercalcemia, postoperative pericarditis, after clinical death, cocaine use, haloperidol overdose, various types of coronary artery disease (after MI and vasospastic angina), nervous system diseases [5-8, 10-12].

In the current case report, the Osborn wave was determined on the ECG upon admission to the hospital with COVID-19 and specific pneumonia. This wave was identified in I, II, aVL, V_6 leads. An increase in nonspecific myocardial damage markers (LDH by 2,1 times, CPK by 1,6 times), liver transaminase (AST by 1,6 times), inflammatory biomarker (CRP by 14,6 times) had a more pronounced dynamics compared to patients with COVID-19-related myocarditis described in the literature. Due to the retrospective design, specific cardiac enzymes were not detected in this patient.

Although the available literature does not describe these ECG changes in COVID-19, previously shown arrhythmias may be the result of an abnormal electric wave course during the switch from depolarization into repolarization due to intra- and extracellular calcium pool imbalance. Thus, experimental studies have shown that the initial transmural electrical heterogeneity (in the presence of Osborn wave) can be significantly aggravated under certain conditions (use of drugs and electrolytes, autonomic tone changes), which can lead to fatal arrhythmias [13]. On the other hand, cardiac arrhythmias are of great predictive value for the survival of patients with COVID-19. For the first time, ectopic activity, as well as an increase in pre-existing paroxysmal tachycardia episodes, may reflect myocardial damage during a viral infection. For example, in 7,3% of patients with COVID-19, palpitations were one of the first symptoms of the disease [14]. In general, the prevalence of detected cardiac arrhythmias in patients with COVID-19 was 15,7%. In the intensive care unit, arrhythmias were detected in almost every second patient with COVID-19 [15]. With an increase in the troponin damage marker, life-threatening arrhythmias (ventricular tachycardia/ventricular fibrillation) were recorded in 11,5% of cases, which also did not rule out the viral myocarditis against the background of COVID-19 [16].

Sala S, et al. [17] described a 43-year-old female patient with acute viral myocarditis in COVID-19 (SpO_2, 89%) and ECG abnormalities in the form of ST segment elevation in V_1-V_2 leads and reciprocal changes in V_4-V_6. The corrected QT interval was 452 ms; a U-wave was observed in most ECG leads. However, according to ECG records presented by the authors, the QRS complexes in II, III, aVF leads, in our opinion, had change that resembled an Osborn wave [17]. Biomarkers of myocardial damage were increased (high-sensitivity troponin, N-terminal pro-brain natriuretic peptide and CRP). Echocardiography revealed a moderate decrease in LV myocardial contractility (LV ejection fraction (LVEF) — 43%)

and inferolateral hypokinesia. Contrast-enhanced cardiac magnetic resonance (7th day of admission) revealed myocardial oedema as pseudohypertrophy without myocardial scarring, with an increase in contractility (LVEF increased to 65% with persisting moderate hypokinesia). The diagnosis of acute COVID-19-related virus-negative myocarditis was finally confirmed by endomyocardial biopsy [17].

Thus, ECG abnormalities similar to Osborn wave, in addition to typical cases of hypothermia described in the literature, can be a sign of COVID-19, as a reflection of disturbed electrolyte current in cardiomyocytes against the background of oxidative stress, and can become a predictor of future fatal cardiac arrhythmias, which will require long-term ECG monitoring in discharged patients. The appearance of the Osborn wave may be associated with violated intraventricular conduction. In particular, in the patient described by Sala S, et al. [17], QRS complex width and corrected QT interval were at the upper normal limit — 452 ms, which may be associated with the ongoing antiviral therapy (hydroxychloroquine at a dose of 200 mg). In our case, normal values of QRS complex width (80 ms) and corrected QT interval (360 ms) were noted, although the patient also took hydroxychloroquine. In general, taking into account such variability of ECG parameters, according to current Russian guidelines for the diagnosis and treatment of COVID-19 [9], it is necessary to monitor corrected QT interval in all patients receiving specific therapy (hydroxychloroquine, antibiotics).

Study limitations. ECG abnormalities were found retrospectively, which did not allow timely echocardiography and analysis of specific serum cardiac enzymes.

Conclusion

The Osborn wave in patients with COVID-19 pneumonia may be associated with intraventricular conduction impairment, myocardial electrolyte disturbances and the effect of causal treatment. Unfortunately, viral myocarditis cannot be established due to absence of a specific diagnosis of the disease (specific cardiac markers, magnetic resonance imaging, myocardial biopsy). In a similar fashion, given the risk of fatal arrhythmias in patients with the classic Osborn wave in hypothermia, patients with COVID-19 and Osborn wave require long-term ECG monitoring after discharge from the hospital. In the future, it will be possible to assess the reproducibility of the Osborn wave in COVID-19, as well as its significance in terms of cardiovascular events' development.

Relationships and Activities: none.

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Takayasu's arteritis in a patient with suspected acute coronary syndrome — a literature review and a case report

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Takayasu's arteritis is a chronic granulomatous vasculitis of large vessels of unclear aetiology, predominantly affecting the aorta and its main branches, with possible involvement of the coronary and pulmonary arteries. The true prevalence of this disease is unknown, but it is extremely low, given the rare diagnosis and the absence of pathognomonic symptoms. In clinical practice, the criteria proposed by the American College of Rheumatology are used for making a diagnosis. A wide range of imaging diagnostic techniques plays a significant role. This article provides a literature review and a case report of Takayasu's arteritis in a patient admitted with an acute coronary syndrome.

Keywords: Takayasu's arteritis, nonspecific aortoarteritis, acute coronary syndrome, imaging diagnostic techniques.

Relationships and Activities: none.

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Nonspecific aortoarteritis (Takayasu's arteritis (TA), pulseless disease) is an autoimmune disease characterized by destructive-proliferative segmental aortitis and subaortic panarteritis of elastic-fiber-rich arteries with possible coronary and pulmonary artery involvement [1-3].

The true prevalence of the disease is unknown. TA is registered everywhere, but the number of cases in the population varies depending on the continent, race, sex and age [4]. The highest prevalence (40 cases per million population) is recorded in Japan, while the lowest (0,9 per million) one in the United States. Modern epidemiological studies register an increasingly widespread distribution of TA in Europe (from 0,4 to 1,5 cases per 1 million) [4]. There is evidence that in Russia its prevalence reaches 2,6 people per 1 million population [3]. The disease is most typical for young females with onset at the age of 15-35 years (according to various data, the woman-to-man ratio is from 2:1 in Western countries to 10:1 in Eastern ones) [1, 2].

The specific cause of the disease has not been established — the role of viruses, infections, in particular, mycobacterium tuberculosis, is being discussed. There is also information about the genetic predisposition. This theory is supported by the fact that one third of patients with TA has HLA-B52 allele [1, 2].

TA is characterized by multiple segmental damage to the aorta and aortic branches, followed by development of stenoses, occlusions, and aneurysms. First of all, the inflammatory process is localized in the media and adventitia, with further spread to the perivascular tissue. The intima involvement is of a secondary reactive-hyperplastic nature [3]. TA can be suspected after an objective examination of a patient, given the very specific localization of pathological process. As a rule, these are carotid and subclavian artery stenosis, the prevalence of which reaches 96% [1].

Depending on lesion localization, 6 types of TA are distinguished [2]:

- Type I — aortic arch and its branches;
- Type IIa — ascending aorta, aortic arch and its branches;
- Type IIb — ascending aorta, aortic arch and its branches, thoracic descending aorta;
- Type III — thoracic descending aorta, abdominal aorta, and/or renal arteries;
- Type IV — abdominal aorta and/or renal arteries;
- Type V — combined features of types IIb and IV.

When the coronary and/or pulmonary arteries are involved, C (+) or P (+) is added to the type of disease. The coronary and pulmonary artery involvement occurs in approximately equal numbers of cases, 5-20% and 7-18%, respectively. Right coronary artery involvement was the most common [1, 2].

Table 1

1990 American College of Rheumatology criteria for the classification of Takayasu arteritis [3]

№	Criterion
1	Age at disease onset <40 years
2	Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities
3	Decreased pulsation of 1 or both brachial arteries
4	Difference of >10 mm Hg in systolic blood pressure between arms
5	Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta
6	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

Table 2

General clinical manifestations in AT [1]

Manifestations	Prevalence
Weakness	40-70%
Fever	10-69%
Myalgia/arthralgia	25%
Weight loss	10-19%

On examination, the most characteristic sign is weak pulse in one or both of the radial arteries up to complete absence, due to the typical localizations described above [2, 3]. Attention is also drawn to the difference between systolic blood pressure (BP) on the right and left hands by more than 10 mm Hg. During auscultation, murmur in the projection of affected vessel can be detected [2].

At the moment, in clinical practice, the 1990 American College of Rheumatology criteria (Table 1) are used for diagnosis [2, 3]. The presence of three or more of any criteria in a patient makes it possible to diagnose TA with a specificity of 98% and a sensitivity of 91% [2].

The clinical performance, syndromes and symptoms described in the disease depend on its stage. The initial stage of TA is characterized by systemic inflammation in the form of low-grade fever, weakness, weight loss, myalgia and arthralgia (Table 2). As a rule, from 0,5 to 2 years is required to make diagnosis from the symptoms' onset. In most cases, when a patient turns to a physician, there is already late stage of disease [1, 2].

Table 3

Possible clinical manifestations [1]

Involvement level	Manifestations
Carotid and vertebral arteries	Dizziness, orthostatic reactions, headaches, visual impairment, syncope, stroke, transient ischemic attack
Subclavian artery	Raynaud's syndrome, subclavian steal syndrome, intermittent claudication
Aorta, aortic arch	Aortic regurgitation, heart failure
Pulmonary artery	Chest pain, shortness of breath, haemoptysis
Coronary arteries	Coronary artery disease, heart failure
Abdominal aorta, mesenteric arteries	Nausea, vomiting, abdominal pain, rectal bleeding
Renal arteries	Hypertension, renal failure
Iliac arteries	Intermittent claudication

Table 4

Ishikawa clinical classification of Takayasu arteritis [1]

Group	Clinical features
I	Uncomplicated disease, with or without pulmonary artery involvement
IIA	Mild/moderate single complication together with uncomplicated disease
IIB	Severe single complication together with uncomplicated disease
III	Two or more complications together with uncomplicated disease

In the late TA stage, the leading symptoms are prolapse and/or dysfunctions of organs due to stenoses, occlusions and thrombosis of the arteries supplying them. A wide variety of symptoms is due to the multilevel involvement of the aorta and its branches (Table 3). In one patient, signs of active and inactive TA phases may be present at the same time, given that the pathology is recurrent in nature [1-3].

It is worth mentioning the existing clinical classification of TA by K. Ishikawa (1978). This classification reflects the natural clinical course in the absence of therapy with the most serious complications, such as secondary hypertension, retinopathy, aortic regurgitation and aneurysms (Table 4) [1].

The main death causes in TA are stroke, heart failure, acute types of coronary artery disease, and renal failure. Given this, this classification is useful in determining the prognosis in this group of patients. In patients with or without one mild complication, vascular events are absent in 97% of cases within 5 years, whereas in patients with one or more severe complications, adverse vascular events develop in 40,3% of patients within the same time period [1].

For many years, angiography has been the gold standard in TA diagnosis, but given that this method is invasive, it has a higher risk of complications compared to non-invasive techniques [2]. The main reason for angiography at the moment are indications for percutaneous transluminal angioplasty and/or stenting [5].

In patients with suspected TA, magnetic resonance imaging (MRI) should be used as the first diagnostic test to assess the lesion. Magnetic resonance angiography and contrast-enhanced MRI make it possible to assess the degree of vascular stenosis and to identify tissue and morphological changes in the arteries. It has been proven that MRI has 100% sensitivity and specificity for TA diagnosis. But, given the cost of this diagnostic method, low availability, other imaging techniques are at the first lines of diagnostics [2].

An imaging technique that is widely used in clinical practice is multislice computed tomography (MSCT). Contrast-enhanced MSCT is the fundamental method in the description of TA anatomy, which allows visualizing the thickening of the aorta and its branches, as well as stenosis degree. This technique has high sensitivity and specificity in TA diagnosis [1, 2].

Duplex ultrasound plays an important role in visualization of the inflammatory process. Its main advantages are its availability, simplicity, cost, the ability to measure the carotid intima-media thickness [2].

The above methods are recommended for dynamic monitoring of structural vascular damage and assessing the therapy effectiveness [2].

^{18}F-fluorodeoxyglucose positron emission tomography is one of the TA diagnosis methods, which currently makes it possible to assess the disease activity and involvement. The accumulation of radiopharmaceuticals in areas with active inflammation demonstrates the degree and morphology of arterial damage [1].

TA is treated with glucocorticosteroid (GCS) therapy in order to achieve and maintain remission. With GCS monotherapy, remission can be achieved in 40-60% of cases. When patients are resistant to GCS therapy, cytostatic and/or biological agents are added to the treatment. The need for combination therapy of TA varies from 40 to 84% of cases, but only 40% of patients in this group can achieve stable remission [1].

Azathioprine and methotrexate are the most widely used cytostatics in TA treatment [1]. Increa-

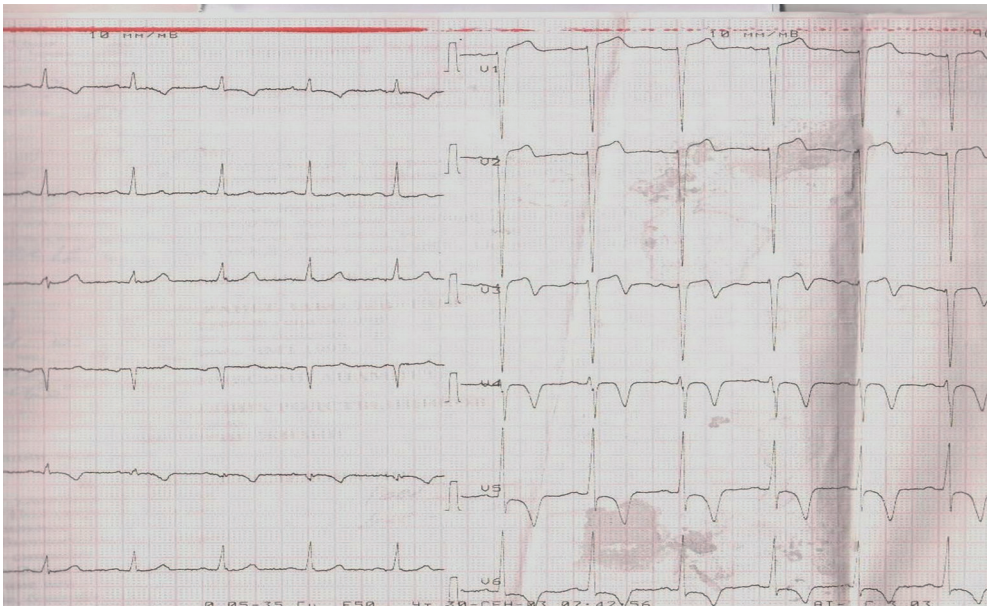

Figure 1. ECG of the patient upon admission to the hospital.

singly popular are biological agents — anti-IL-6 receptor monoclonal antibodies (tocilizumab) and anti-tumour necrosis factor-α antibodies (infliximab, certolizumab, etanercept). As mentioned earlier, this group of drugs is used in case of ineffectiveness of conventional immunosuppressive therapy [2].

However, the disease continues to progress and remains resistant to all possible options for drug therapy in 20% of patients with TA [1].

In addition, TA patients are diagnosed with an increased content of thrombin-antithrombin III complex, fibrinopeptide A and D-dimers. Considering the hypercoagulation with increased BP, the risk of vascular events in target organs significantly increases. Thus, antiplatelet therapy is necessary as the primary prevention of TA complications [1].

As mentioned above, it is recommended to use invasive interventions to correct stenosing and occlusive lesions of the arteries. Recently, percutaneous transluminal angioplasty with or without stenting has become the most popular [5]. The frequency of surgical interventions for TA varies from 12 to 70%. The indications should include manifestations of coronary artery disease, complicated renal artery stenosis, stroke, and aneurysms. In such situations, carrying out revascularizing procedures significantly increases survival and reduces the death risk [1].

It is worth mentioning the TA register launched in 2016 in East China. Given such a rare diagnosis, the standardization of the management of such patients is often difficult. Thus, researchers are trying to recruit as many TA patients as possible by creating a TA cohort for more professional and standardized patient management.

Case report

Forty-eight-year-old male patient was delivered by an ambulance team with non-ST-elevation acute coronary syndrome. Upon admission, he complains of pressing pain in chest with physical exertion (brisk walking, climbing 1-2 floors), shortness of breath and increased pain in the right chest half with a deep breath, low exercise tolerance, peripheral oedema.

Collection of history revealed a BP increase for ~5 years up to 200/100 mm Hg. The current deterioration was within 1,5 months, characterised by shortness of breath, pressing pain in chest with intensification during exertion, puffiness, low exercise tolerance. He noted an increase in body temperature up to 37° C, a progressive weight loss of 25 kg in 6 months. He did not seek medical help. On the eve of admission, anginal pain became more frequent, intensified, dyspnoea increased. He turned to the local outpatient clinic. After electrocardiography (ECG), hospitalization was recommended to the cardiology department.

At the time of admission, the condition was of moderate severity, clear consciousness, skin of normal colour, moist, warm. Muffled heart sounds, regular heart rate of 80 beats per min. A significant difference in BP was found: 170/90 mm Hg on the right hand and 130/80 mm Hg on the left one. Lung auscultation revealed weakened vesicular sounds in the lower areas. The abdomen was soft and painless. The liver protrudes 1,5 cm below the costal margin. There was no costovertebral angle tenderness on both sides.

At admission, ECG showed incomplete left bundle branch block, low-amplitude R and deep negative T waves in I, AVL, V_3-V_6 leads (Figure 1).

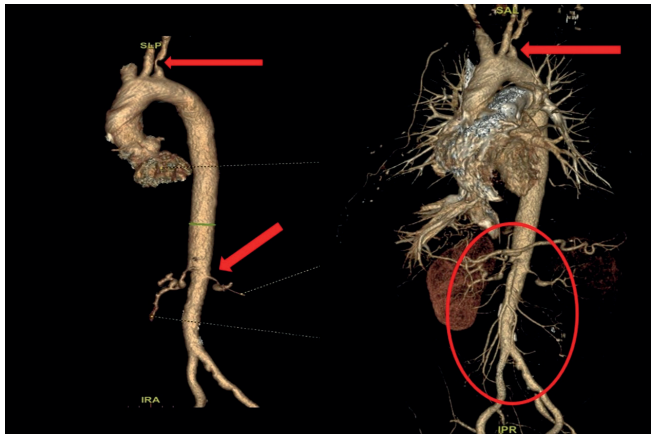

Figure 2. 3D reconstruction of the thoracic and abdominal aorta and their branches (arrows mark the lesions).

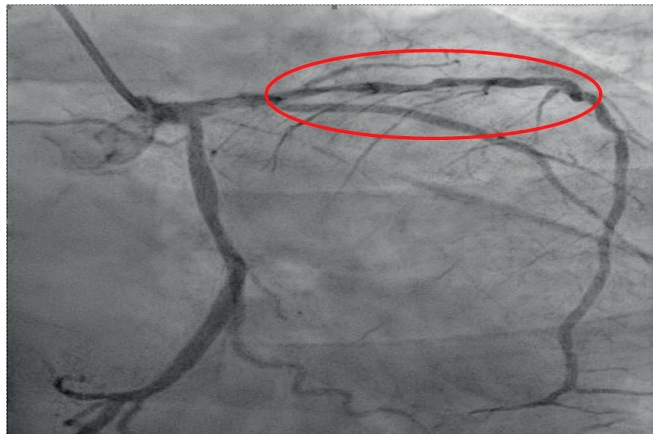

Figure 3. Extended stenosis of 50-75% from the orifice to proximal third of the 2nd segment (RAO 30°-Caudal 30°).

There were no significant changes in high-sensitivity troponin at admission and three hours later (0,008/0,014 ng/ml). There were following findings: white blood cells — $19{,}38\times10^9$/L, C-reactive protein — 62,8 mg/L (inflammatory markers); total platelet count — 642,0 10*3/ml, (thrombocytosis); red blood cells — $4{,}52\times10^{12}$/L; hemoglobin — 110,0 g/L (mild anemia); creatinine — 131,4 mmol/L, glomerular filtration rate — 53,8 ml/min/1,73 m^2 (reduced renal function); total cholesterol — 5,24 mmol/L, low-density lipoproteins — 3,23 mmol/L, high-density lipoproteins — 1,17 mmol/L (dyslipidemia).

According to echocardiography, the cardiac cavities were not dilated. Left ventricular (LV) ejection fraction was 59%. There were akinetic areas in apex, lower third of interventricular septum, anterior wall, and apical-lateral segment. Heart valves were normal. Left ventricular hypertrophy (interventricular septum — 13 mm, LV posterior wall — 15 mm) was revealed. The pericardium: above the right ventricle — 16 mm, the right atrium — 16 mm, along the LV posterior wall — 15 mm. Pleural cavity expansion: on the right — 26 mm, on the left — no.

According to the data obtained, the diagnosis of acute coronary syndrome raised doubts. Therefore, it was decided to conduct additional diagnostic tests.

Taking into account the increased body temperature, progressive weight loss, it was decided to perform chest, abdominal and pelvic MSCT. The MSCT revealed pronounced diffuse thickening of thoracic and abdominal aortic walls with infiltration of the paraaortic tissue. This process extended to left subclavian and both renal artery orifices, narrowing the lumen to 80% (Figure 2). There were no thrombotic masses in pulmonary artery and its branches. There were no abnormalities in the lung parenchyma. Also, worth noting is the thickening and infiltration of the perinephric tissue. The excretory renal function was sharply reduced.

The next stage of diagnosis was coronary angiography to assess the degree of coronary involvement, followed by decision on the need for myocardial revascularization. There was a right type of cardiac blood supply. The left coronary artery was with irregular contours. The left anterior descending artery was irregular contours and extended stenosis of 50-75% from the orifice to proximal third of the 2nd segment (Figure 3). Intermediate artery: occlusion from the orifice, distal areas are filled through intracoronary collaterals (Figure 3). The circumflex artery was with irregular contours, stenosis of 40% from the orifice, extended stenosis of 30% in the distal third of the 1st segment. The right coronary artery was with irregular contours and without hemodynamically significant stenoses (Figure 4). It was decided to perform stenting of affected artery segment using the Resolute Integrity (Medtronic) 3,0x30 mm stent (Figure 5).

Subsequently, the patient underwent duplex ultrasound of brachiocephalic arteries: intima-media thickness — 1,3 mm and 1,2 mm on the left and right sides, respectively. There were following stenoses: left and right common carotid artery up to 55% and 60%, respectively; left and right internal carotid artery up to 28% and 30%, respectively; right external carotid artery up to 35%. Vertebral-subclavian steal syndrome.

It is worth noting the laboratory test dynamics during the follow-up period (Table 5).

The rest of blood test parameters were within the reference values and without negative dynamics. Blood tests for HIV, RW, hepatitis were negative.

According to repeated echocardiography, resolving hydropericardium and hydrothorax were shown.

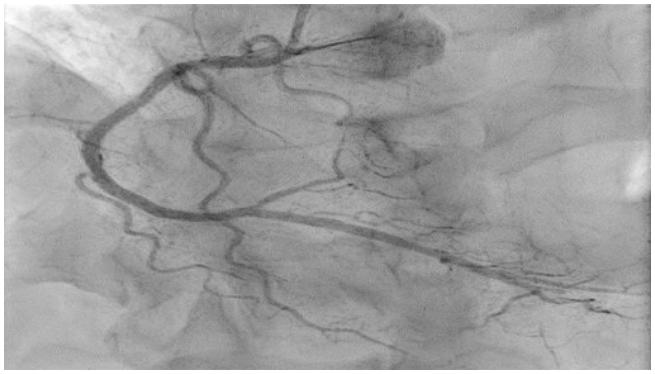

Figure 4. No abnormalities in the right coronary artery (RAO 30°-Caudal 30°).

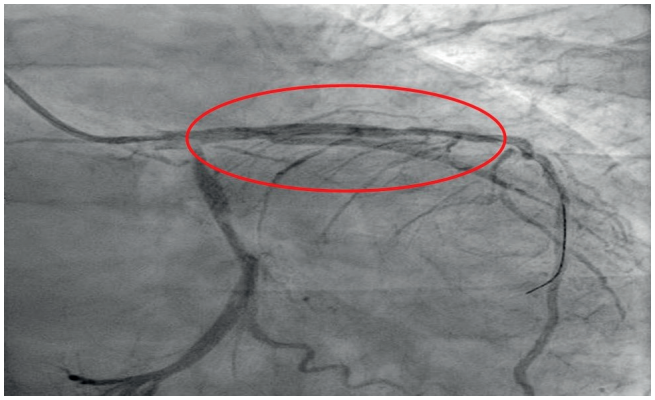

Figure 5. Left anterior descending artery after stenting surgery.

Table 5

Laboratory test dynamics during the follow-up period

Parameter	Result					
Hospitalization day	1	2	3	4	5	6
Creatinine (mmol/L)	131,4	189,4	193,4	169,2		
Platelets (10^3/ml)	642,0	586,0	540,0	505,0	651,0	367,0
White blood cells (10^9/L)	19,38	14,10	12,93	13,37	14,98	12,47

Thus, based on imaging and laboratory research methods indicating an inflammatory process in the walls of arteries of multiple localization, the patient was diagnosed as follows:

Non-specific type V C+ TA, with involvement of thoracic, abdominal aorta, coronary arteries (left anterior descending artery up to 75%), subclavian arteries, brachiocephalic arteries (left and right common carotid artery up to 55% and 60%, respectively; left and right internal carotid artery up to 28% and 30%, respectively; right external carotid artery up to 35%, left subclavian artery), renal arteries (up to 80%).

Unstable high-risk class 2 angina pectoris. Coronary angiography, left anterior descending artery stenting. Secondary hypertension. Left vertebral subclavian steal syndrome. Resolving moderate hydropericardium. Resolving bilateral mild hydrothorax. Stage 2A NYHA class 2 heart failure. During hospitalization, the patient received the following treatment: acetylsalicylic acid, clopidogrel, sartans, beta-blockers, calcium channel blockers, loop diuretics, verospiron, statins. After treatment, the patient noted a significant improvement

As discussed above, the cornerstone of TA therapy is immunosuppressive therapy, in particular — GCSs. Considering the need to take dual antiplatelet therapy, a positive history of gastrointestinal diseases (increased risk of bleeding), poorly controlled hypertension, the appointment of GCS therapy was postponed until a rheumatologist was consulted. Unfortunately, the period of hospitalization of our patient coincided with the introduction of COVID-19 restrictions and reprofiling of most departments in large hospitals in Samara, which did not allow a prompt consultation with a rheumatologist.

At discharge, the patient was given extended recommendations on the necessary follow-up examination and drug therapy.

The patient was invited for a consultation with a cardiologist 6 months after discharge from the hospital. During this period, the patient was not hospitalized in other hospitals. He noted lower limb oedema while taking amlodipine, as a result of which he independently cancelled it. Objective examination findings: BP on the right and left hands was 160/80 and 110/70 mm Hg, respectively. Complete blood count and biochemical blood test were without abnormalities. ECG was without negative dynamics compared to the early one. Taking into account the irrational therapy and not reaching the target BP levels, the treatment was adjusted. The patient was consulted by a rheumatologist and an additional examination was recommended: a biochemical blood test (rheumatoid factor, C-reactive protein, anti-double stranded DNA antibodies (anti-dsDNA), antinuclear factor, antinuclear antibodies (ana), ANCA), angiography of aorta and its large branches. According to available results, anti-dsDNA, ANA, ANCA IgG were within normal limits. Anti-inflammatory therapy was not prescribed. After the remaining examinations, a second consultation with a rheumatologist was recommended.

Thus, the clinical picture of acute coronary syndrome in some cases can be caused not only by

coronary atherosclerosis, but also be a consequence of occlusive-stenotic lesions of the aorta and its branches due to connective tissue diseases, which require differential diagnosis and alteration of management and therapy strategies with taking into account the identified conditions.

Relationships and Activities: none.

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Difficult diagnostics of a rare cause of pulmonary hypertension: a case report

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Pulmonary hypertension is a syndrome difficult for differential diagnosis, which is the outcome of various pathological conditions. With the exclusion of the most common causes of pulmonary hypertension (left heart disorders and pulmonary embolism), further search for cause often becomes an insoluble problem. Sezary syndrome is classified as a rare type of cutaneous T-cell lymphomas. Early diagnosis of this syndrome is important for the initiation of adequate therapy, since cases of complete recovery or long-term remission in patients with Sezary syndrome are very rare. A case report of Sezary syndrome verification in cardiology practice is described.

Keywords: pulmonary hypertension, Sezary syndrome, T-cell lymphoma.

Relationships and Activities: none.

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Interest in studying the causes of development and approaches to treatment of pulmonary hypertension (PH) has significantly increased in the last 2 decades. This is due to the expansion of both diagnostic techniques and therapeutic strategies, which contributed to significant progress in improving the quality and duration of life of PH patients. According to comprehensive clinical classification of PH by the European Society of Cardiology (2015), there are 5 main groups [1]:

1) Pulmonary arterial hypertension (PAH);
2) PH due to left heart disease;
3) PH due to lung diseases and/or hypoxia;
4) Chronic thromboembolic PH and other pulmonary artery (PA) obstructions;
5) PH with unclear and/or multifactorial mechanisms.

The last (fifth) group is a fairly heterogeneous set of diseases that are rarely found in the practice of a cardiologist.

The presented paper describes a stepwise diagnostic analysis of an extremely rare case of PH in a patient with myeloproliferative disease.

Case report

Fifty-years-old female patient, was admitted to the clinic with complaints of severe weakness, shortness of breath with minimal exertion and at rest, palpitations, increased blood pressure up to 160-170/95 mm Hg, abdominal distention, joint pain, dry and flaky skin.

The described complaints were present for one year with a progressive decrease in exercise tolerance. Two years ago, the patient was examined by a gynaecologist for uterine fibroids, during which anaemia, leucocytosis, and thrombocytosis were revealed. Within 2 years she lost 18 kg. For about 1 year, there are pains in different joints, severe weakness, and peripheral lymph node enlargement (cervical, occipital, inguinal, axillary nodes). She was consulted by a rheumatologist and haematologist, and foot arthrosis was diagnosed. A hypothesis was made about a lymphoproliferative disease, in connection with which sternal puncture and lymph node biopsy were performed, according to which no signs of acute and chronic hemoblastosis were obtained. Therapy with vitamin B_{12} and folic acid was prescribed, against which the haemoglobin level increased.

Physical examination. Status: severe. Asthenic type, debilitated. Height — 160 cm, weight — 40 kg. Body mass index — 15,62 kg/m^2. Skin: dry; hyperpigmentation, sloughing; moderate acrocyanosis (Figure 1). Submandibular and axillary lymph nodes were enlarged. Visible mucous membranes: pale, cyanotic. Subcutaneous tissue was practically absent. Lower leg and foot swelling; anterior abdominal wall swelling, ascites. Cardiovascular system: regular heart rate (HR) of 98 beats per min. Loud second heart sound at pulmonic area, soft systolic murmur at the apex; pulse of 98 beats per min, regular, weak, blood pressure: 100/60 mm Hg. Respiratory system: chest — right shape; vesicular breathing, weakened; no wheezing; respiratory rate of 20 per minute. Digestive system: tongue — dry, white. The abdomen is enlarged, right upper quadrant discomfort on palpation, free fluid in the abdominal cavity. Liver: enlarged — 2,5-3 cm below the right costal margin; the edge is dense, even, the size of 12×10×9 cm according to Kurlov's method. The musculoskeletal system: joint deformity (Figure 2). Genitourinary system: Murphy's punch sign is negative on both sides.

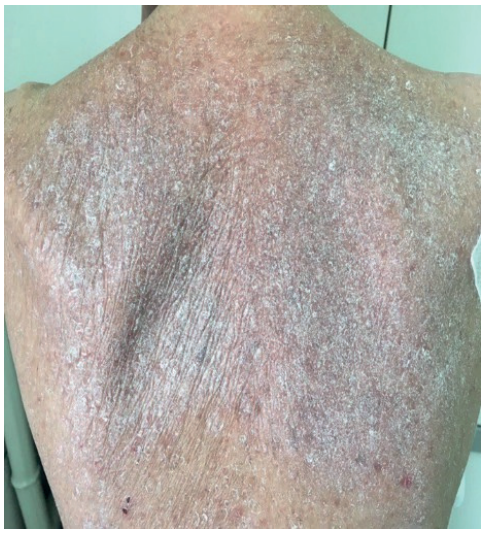

Figure 1. Keratosis of back skin of 50-years-old female patient.

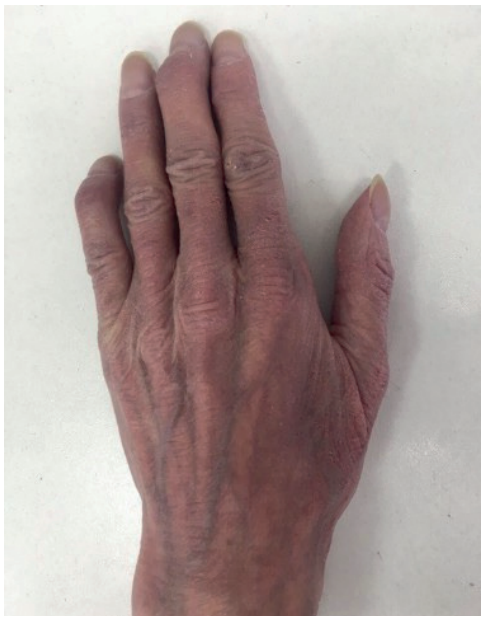

Figure 2. Hand joint deformities of 50-years-old female patient.

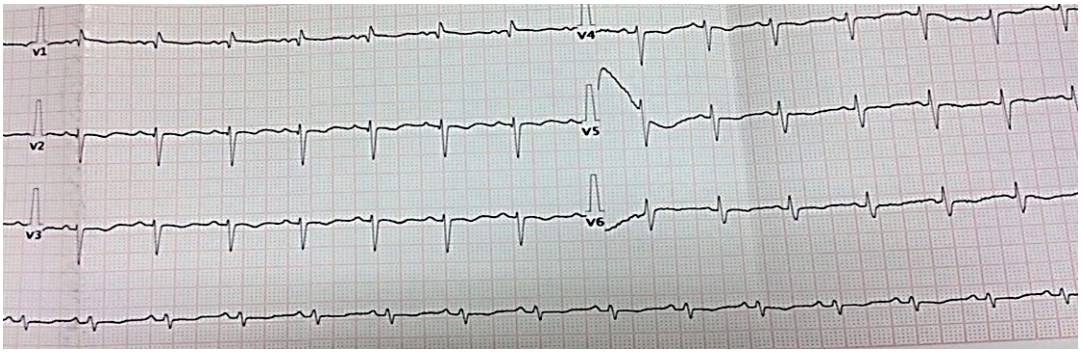

Figure 3. Electrocardiogram upon admission of 50-years-old female patient: sinus rhythm, heart rate of 86 bpm. QT length of 400 ms. Right axis deviation. Low wave voltage. Incomplete right bundle branch block.

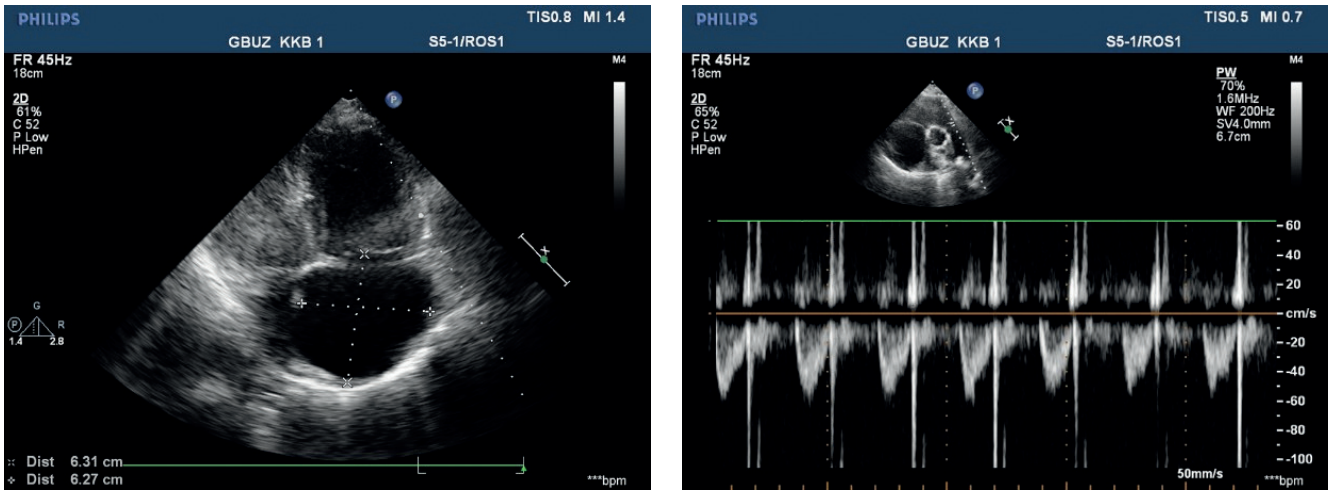

Figure 4, 5. Echocardiography upon admission of 50-years-old female patient: severe PH. Severe TV regurgitation. Right heart dilation.

Thus, the patient had the following symptom complexes: 1) oedema (ascites, lower limb oedema); 2) hepatomegaly; 3) skin; 4) articular; 5) respiratory failure; 6) lymphadenopathy.

According to diagnostic tests, there were following findings:

Electrocardiography — sinus tachycardia with a heart rate of 100 bpm. Right axis deviation. Low wave voltage. Incomplete right bundle branch block. Signs of right ventricular (RV) overload (Figure 3).

Echocardiography — ascending aorta 30 mm. Aortic regurgitation: ++. Left atrium: 29 mm. Left ventricular (LV) end diastolic dimension: 38 mm, interventricular septum (IVS), 9 mm, LV posterior wall, 10 mm. LV ejection fraction: 43%. LV diffuse hypokinesis with paradoxical septal motion. Mitral valve Doppler ultrasound: +. No pronounced response to respiratory phases. Right atrium (RA): 55×58 mm. RV: 32 mm. Right ventricular inflow tract: 53 mm. Diffuse RV hypokinesis. Tricuspid valve (TV) leaflets: sealed, thickened. TV prolapse. TV Doppler ultrasound: +++, (+++/++++). LA: with signs of severe hypertension. Diastolic pressure: 25 mm Hg. Systolic pressure: 90 mm Hg. LA

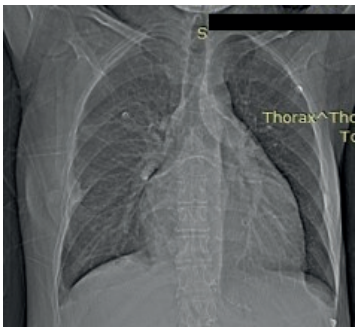

Figure 6. Chest X-ray of 50-years-old female patient. no focal and infiltrative abnormalities. Sinuses are clear. The left heart is enlarged. Cardiothoracic ratio is 0,52.

Doppler ultrasound: ++. Inferior vena cava: 20 mm, inadequate response, with spontaneous contrast enhancement effect. Echo-free space along the entire heart perimeter: in front of RV from the epigastric view, 12 mm; above the RV, 5 mm; at the LV apex, 5 mm; behind the lateral wall, 12 mm; behind the LV, 17 mm (Figure 4, 5).

Chest X-ray — no focal and infiltrative abnormalities. Grade 3 cardiomegaly. Cardiothoracic ratio was 0,52 (Figure 6).

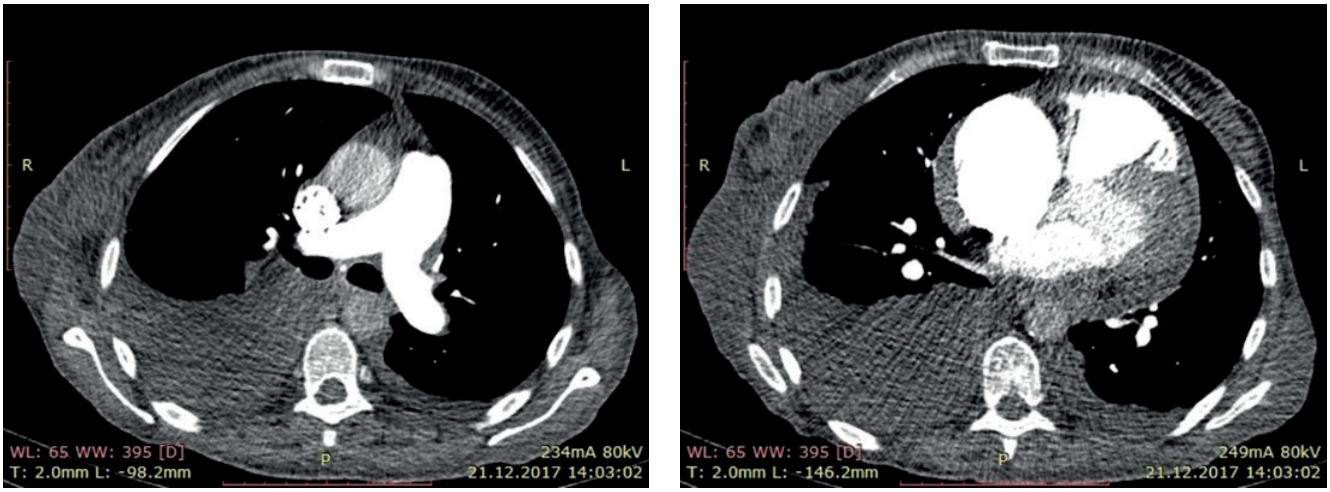

Figure 7. CT of 50-years-old female patient: axillary lymphadenopathy. Hydropericardium. Bilateral hydrothorax.

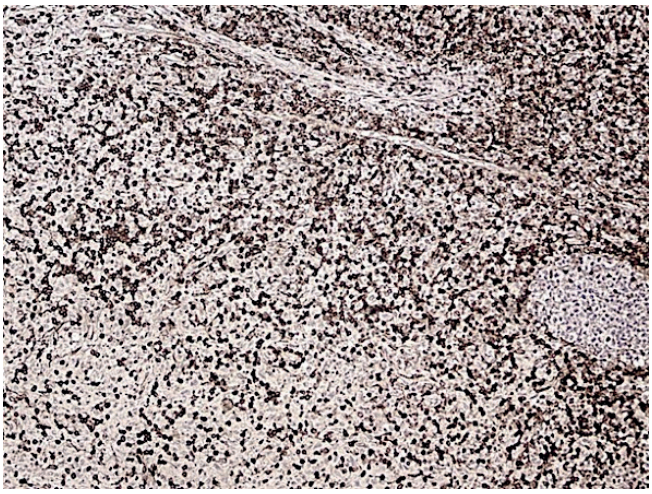

Figure 8. CD4, clone 4B12. Positive reaction is in most tumour cells.

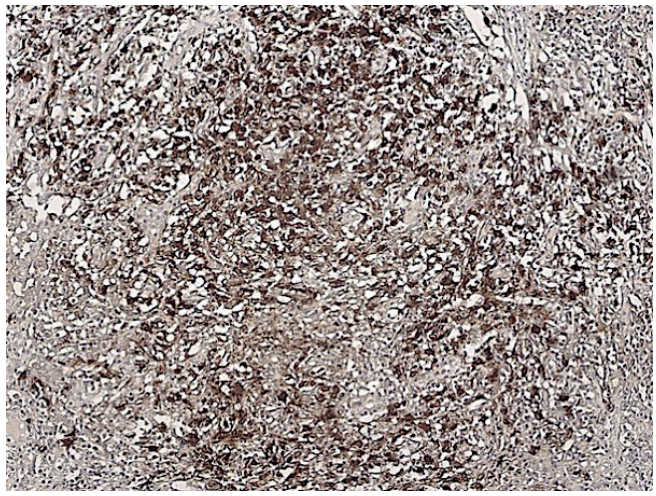

Figure 9. CD8, Clone C8/144B. Positive reaction is in some tumour cells

Based on the above data, the differential diagnosis included: cancer with paraneoplastic syndrome, cardiovascular disease, pulmonary disorder with development of pulmonary heart disease and heart failure. A combination of several diseases was not ruled out.

The patient underwent esophagogastroduodenoscopy, colonoscopy, transvaginal ultrasound. There were no data suggestive of cancer.

When analysing the echocardiography, attention was drawn to the high PA pressure and right heart enlargement without left heart structural pathology.

According to clinical guidelines for the diagnosis and treatment of patients with PH, PH is most common due to left heart disease [1].

To rule out the left heart disease as a possible cause of PH, a Swan-Ganz catheter was placed, according to which the pulmonary wedge pressure was 13 mm Hg, PA systolic pressure — 48 mm Hg, and pulmonary vascular resistance — 380 mm. Pulmonary vascular resistance index was 412, which militates in favour of precapillary PH.

In order to rule out pulmonary disease, chest computed tomography (CT) and pulmonary function test (PFT) were performed. According to chest CT, no structural lung pathology was revealed. According to PFT, moderate restrictive impairment was shown. Also, the contrast-enhanced PA CT was performed, according to which there were no data suggestive of thrombosis (Figure 7).

In addition, PH can most often be caused by congenital heart defects (atrial septal/IVS defects, patent ductus arteriosus, partial anomalous pulmonary venous return), as well as HIV infection and portal hypertension. According to transesophageal echocardiography, contrast-enhanced cardiac CT,

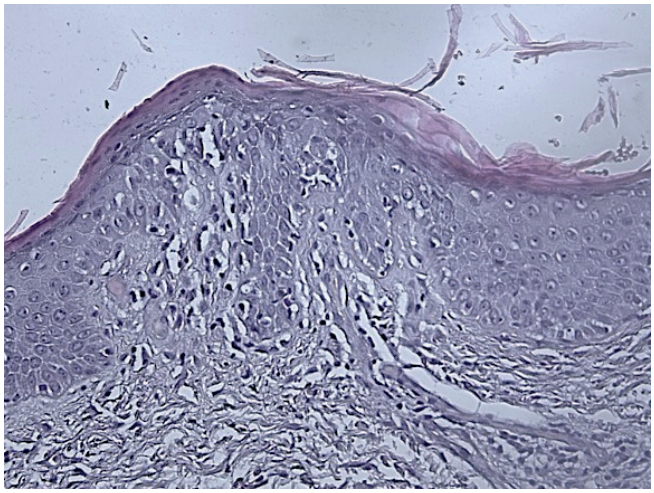

Figure 10. Skin biopsy of 50-years-old female patient.

abdominal ultrasound, and laboratory tests, these reasons were ruled out and HIV infection was not detected.

The patient's age at the onset and the presence of concomitant systemic syndromes made it unlikely that PH was hereditary.

Subsequently, the diagnostic search was aimed at identifying pathologies included in the PH group with unclear and/or multiple mechanisms. The presence of lymphadenopathy, articular syndrome, hepatomegaly made it possible to suspect the lymphoproliferative disease.

Morphological and immunohistochemical analysis of biopsy specimens:

Morphology: skin — epidermis with hyperkeratosis, thinned; in the basal layer, the lymphoid infiltrate with a pagetoid growth, pronounced exocytosis, which is represented by medium-sized cells with abnormal nuclear shape and pronounced nuclear folds. Lymph nodes — the lymph node structure is disturbed due to a sharp paracortical expansion, infiltrated by polygonal cells with abnormal nuclear shape and nuclear folds. The pre-existing follicles are small with a thinned mantle zone and are pushed aside by tumour infiltrate. The sinuses are dilated. Inner layer with lipomatosis (Figures 8-10). Conclusion: the immunomorphological picture of Sezary syndrome with lymph node involvement. Diagnosis: Sezary disease — T-cell lymphoma with lymph node involvement.

Final diagnosis: Sezary disease (grade III). Severe PAH associated with lymphoproliferative disease (Sezary disease). Pulmonary heart disease, stage II B heart failure.

With diuretic and heart rate reduction therapy, exercise tolerance increased and oedema regressed. After 4 years of follow-up, the patient is alive, feels satisfactory, and receives the recommended therapy.

Sezary disease is an extremely rare disease — 3 cases per 1 million population [2, 3], which is a type of T-cell lymphoma (peripheral CD4+ T-cells are involved) and is characterized by generalized erythroderma, lymphadenopathy and presence of Sezary cells in the skin, lymph nodes and peripheral blood [3, 4].

Early diagnosis of this disease is important in order to initiate adequate therapy, since cases of complete recovery or long-term remission in these patients are rare [5].

According to the literature, cases of sever PH are described in patients with B-cell lymphoma. Such cases are extremely rare in T-cell lymphomas [4, 5].

Discussion

The presented case, according to the latest classification, belongs to the fifth group of PH causes.

According to the 2008 WHO classification of lymphomas, mycosis fungoides/Sezary disease refers to primary T-cell lskin lymphomas from mature (peripheral) cells [2]. The disease was first described by the French dermatologist Alibert in 1806. In 1832, he proposed the name, emphasizing the clinical manifestations — fungous tumors. In 1879, the French dermatologist Bazin described in detail the clinical performance of the disease, and since then it bears the name of Alibert-Bazin. The first description of the disease in Russia was made by A. M. Stukovenkov in 1889 [1, 5]. In 1938, the French dermatologist Cesari first described a 59-year-old woman with generalized erythroderma, lymphadenopathy, intense itching, and abnormal monocytoid cells in the peripheral blood [1]. Sezary disease accounts for 2-3% of all lymphomas [2]. It is considered as a leukemic type of disease, characterized by chronic erythroderma with diffuse lymphoid dermal infiltration, release of abnormal lymphocytes into the blood, and damage to the bone marrow [4]. Classic Sezary cells have large folded nuclei similar to the brain. They are mainly localized in the upper layers of the dermis and epidermis and have an immunological phenotype of T-helpers (CD2+, CD3+, CD4+, CD5+) [2].

This diagnosis is established by comprehensive assessment of clinical picture, histological and immunophenotypic studies of skin biopsies, and determination of the T-cell receptor gene rearrangement. It should be noted that currently there are no uniform generally accepted diagnostic criteria for mycosis fungoides, and clinical guidelines differ significantly in the amount of recommended diagnostic tests. Clinical examination of the patient remains the fundamental method in diagnosis, because makes it

possible to determine the type and stage of this disease, but with the leukemic type of cutaneous T-cell lymphoma, the importance of complete blood count increases [5].

Lung involvement in T-cell lymphomas occurs in about 10% of cases [6]. The main mechanism of LH development in these patients is considered to be the stimulation of vascular endothelial cells by factors associated with platelets, primarily serotonin and growth factor [7]. Other probable reasons are considered to be increased blood viscosity with abnormal immunoglobulin function [8, 9] and tumour microembolism [8].

Conclusion

In the presented case report, a sequential diagnostic algorithm was demonstrated, which made it possible to establish a rare cause of PH. Given the infrequent reference of Sezary disease in cardiology literature, the unification of dissociated syndromes into a single disease is difficult.

The absence of guidelines on PH treatment in patients with lymphoproliferative diseases requires an individual approach to PAH-targeted therapy in each case.

Relationships and Activities: none.

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