ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

РОССИЙСКИЙ КАРДИОЛОГИЧЕСКИЙ ЖУРНАЛ

Russian Journal of Cardiology

SCIENTIFIC, PEER-REVIEWED MEDICAL JOURNAL

RUSSIAN SOCIETY OF CARDIOLOGY

IN ISSUE:

IN FOCUS:

Non-coronarogenic heart lesions

№ 11 | 2020

РОССИЙСКОЕ КАРДИОЛОГИЧЕСКОЕ ОБЩЕСТВО

Russian Society of Cardiology

Scientific peer-reviewed medical journal

Mass media registration certificate № 017388 dated 06.04.1998

Periodicity — 12 issues per year
Circulation — 7 000 copies

The Journal is in the List of the leading scientific journals and publications of the Supreme Examination Board (VAK)

The Journal is included in Scopus, EBSCO, DOAJ

Russian Citation Index:
SCIENCE INDEX (2018) 3,054
Impact-factor (2018) 1,082

Complete versions of all issues are published: *www.elibrary.ru*

Instructions for authors: *https://russjcardiol.elpub.ru/jour/about/submissions#authorGuidelines*

Submit a manuscript: *www.russjcardiol.elpub.ru*

Subscription: *www.roscardio.ru/ru/subscription.html*

Open Access

Printed: OneBook, Sam Poligraphist, Ltd. 129090, Moscow, Protopopovsky per., 6. www.onebook.ru

Font's license №180397 от 21.03.2018

RUSSIAN JOURNAL OF CARDIOLOGY

№ 25 (11) 2020

founded in 1996

Editorial office:
119049, Moscow,
ul. Shabolovka, 23-254
e-mail: cardiojournal@yandex.ru
Tel. +7 (985) 768 43 18

Publisher:
Silicea-Poligraf
e-mail: cardio.nauka@yandex.ru

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-11

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

CONTENTS

ORIGINAL ARTICLES

CLINICAL AND INVESTIGATIVE MEDICINE

CLINICAL OBSERVATION

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3840

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Infectious-immune pericarditis: clinical assessment, diagnostics, and differentiated baseline therapy with hydroxychloroquine

Blagova O. V., Sorokin G. Yu., Sedov V. P., Kogan E. A., Sarkisova N. D., Nedostup A. V.

Aim. To study the clinical spectrum of infectious-immune pericarditis, the potential for their invasive and non-invasive diagnosis, as well as long-term treatment with hydroxychloroquine (in comparison with other baseline therapy options).
Material and methods. The study included 44 patients with infectious-immune pericarditis (28 women and 16 men aged 49,4±13,3 years). Patients with transudate and specific types of pericarditis were excluded. Levels of C-reactive protein and anticardiac antibodies were determined Multislice computed tomography of the lung (n=23) and heart (n=16), cardiac magnetic resistance tomography (n=9), scintigraphy (n=14), and if necessary — immunoelectrophoresis, DNA testing, Diaskin-test. Pericardio- and thoracentesis were performed in 3/3 patients, thoracoscopic pericardial biopsy — 1, endomyocardial biopsy — 7. The follow-up period was 14,5 [3; 39,5] months.
Results. Isolated pericarditis was diagnosed in 10 patients (22,7%), myopericarditis — in 34 (77,3%). In 38 patients, pericarditis was exudative: in 24 (63,2%) with a small effusion (⩽10 mm), in 10 (26,3%) — with a moderate (11-20 mm), in 4 (10,5%) — with a large (⩾20 mm). Fibrin was detected in 18,2% of patients. Pericardial effusion was assessed as acute in 4, subacute — in 8, chronic — in 26 patients. The connection between the disease onset and infection was found in 56,8% of patents, and inflammatory blood changes — in 59,1%. In 80%, the punctate was lymphocytic; endomyocardial biopsy confirmed active/borderline (5/2) lymphocytic myocarditis (virus-positive — in 3 patients). Anticardiac antibody titers were increased in 88,2%. Baseline therapy included NSAIDs (34,1%), colchicine (27,3%), hydroxychloroquine (43,2%), methylprednisolone (56,8%, 16 [16; 21] mg/day), azathioprine (20,5%). The treatment scheme was selected individually. In most cases, combined therapy was carried out. The results of treatment were assessed in 36 patients: an excellent effect was noted in 16 (44,4%) patients, stable effect — in 13 (36,1%), no stable effect — in 7 (19,4%). There were no cases of constrictive pericarditis, acute relapses, cardiac tamponade. Mortality of 6,8% was associated with myocardial injury.
Conclusion. Criteria for the diagnosis of infectious-immune pericarditis were proposed. An increase in the titer of anticardiac antibodies was noted in all types of the disease. Prescription of corticosteroids is justified in many cases, including in combination with colchicine, cytostatics, hydroxychloroquine. Hydroxychloroquine monotherapy is effective for subacute/chronic pericarditis with moderate effusion.

Key words: infectious-immune pericarditis, myocarditis, anticardiac antibodies, endomyocardial biopsy, corticosteroids, hydroxychloroquine.

Relationships and Activities: none.

I. M. Sechenov First Moscow State Medical University, Moscow, Russia.

Blagova O. V.* ORCID: 0000-0002-5253-793X, Sorokin G. Yu. ORCID: 0000-0002-1013-9706, Sedov V. P. ORCID: 0000-0003-2326-9347, Kogan E. A. ORCID: 0000-0002-1107-3753, Sarkisova N. D. ORCID: 0000-0002-5979-1180, Nedostup A. V. ORCID: 0000-0001-9587-6707.

*Corresponding author:
blagovao@mail.ru

Received: 13.04.2020
Revision Received: 20.04.2020
Accepted: 21.04.2020

For citation: Blagova O. V., Sorokin G. Yu., Sedov V. P., Kogan E. A., Sarkisova N. D., Nedostup A. V. Infectious-immune pericarditis: clinical assessment, diagnostics, and differentiated baseline therapy with hydroxychloroquine. *Russian Journal of Cardiology*. 2020;25(11):3840. (In Russ.) doi:10.15829/1560-4071-2020-3840

Pericarditis is a very heterogeneous group of diseases, the differential diagnosis of which is very difficult and does not always lead to a definite result. Difficulties begin already at the differentiation of exudate from transudate. Some pericarditis occurs without effusion (dry, constrictive) and can mimic myocardial infarction, restrictive cardiomyopathy, liver cirrhosis and other diseases. But the most difficult are the search for the etiology of effusive pericarditis and the determination of the optimal treatment strategy. According to the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases, in about half of cases, the etiology of pericarditis cannot be established [1]. At the same time, the ideologist of previous guidelines Maisch B from Marburg considers this percentage to be unjustifiably high and refers to his own unique experience in pericardioscopy and pericardial biopsy, which make it possible to establish diagnosis and carry out proper treatment in almost 100% of cases [2]. According to European experts and Maisch B and Ristic A group, the proportion of the established etiological factors are very close (bacteria, cancer, etc.), while 50% of European "idiopathic" types correspond to 12% of viral and 35% of the so-called autoreactive (lymphocytic) pericarditis [3].

Obviously, in both cases the issue is the most numerous groups of pericarditis, but without pericardial biopsy, pericardioscopy and even pericardiocentesis, cases of viral and lymphocytic pericarditis remain undiagnosed and considers as idiopathic. It seems to us justified to call this group "infectious-immune pericarditis", since even in the absence of a viral genome, it is highly probable that the starting role of infection in the development of autoreactive (lymphocytic) pericarditis can be assumed.

Therefore, a special study of infectious-immune pericarditis seems relevant, the results of which are presented in this work.

The aim was to study the infectious-immune pericarditis, potential of its invasive and non-invasive diagnosis, as well as long-term hydroxychloroquine therapy in comparison with other approaches.

Material and methods

Study sample. The study included 44 patients with infectious-immune pericarditis from 20 to 69 years (mean age, 49,4±13,3 years; 28 women and 16 men (53,2±10,3 and 42,9±15,4 years, respectively, $p<0,05$)). Inclusion criteria were the presence of inflammatory pericardial effusion or diagnostic criteria for dry pericarditis, as well as additional original criteria for infectious-immune pericarditis (see the Results section) with any disease duration. Patients with postpericardiotomy syndrome, purulent, tuberculous, post-traumatic pericarditis, cancer-related pericarditis (including after radiation and chemotherapy), systemic connective tissue diseases, vasculitis, amyloidosis, and sarcoidosis were excluded. The exclusion criteria were congestive pericardial effusion and hypothyroid effusion (i.e., hydropericardium).

Methods. All patients underwent chest X-ray, electrocardiography (ECG), echocardiography, 24-hour Holter monitoring, standard blood tests, determination of CRP and fibrinogen levels. Blood detection of cardiotropic viruses (Herpesviridae, Parvovirus B19), anti-cardiac antibody level by enzyme-linked immunosorbent assay, lung (n=23) and cardiac (n=16) multislice computed tomography (MSCT), cardiac magnetic resonance imaging (n=9), myocardial scintigraphy (n=14), coronary angiography (n=4). In order to rule out specific types of pericarditis, the blood was tested for antinuclear factor (ANF), rheumatoid factor (RF), complement, and, if necessary, anti-cyclic citrullinated peptide, antineutrophil cytoplasmic, anti-cardiolipin antibodies, extractable nuclear antigens. Blood and urine immunoelectrophoresis with determination of free light chains by immunofixation, genetic testing of the *MEFV* gene, Diaskin test and phthisiatrician examination, and cancer diagnostic tests were performed.

Diagnostic pericardiocentesis by a standard approach was performed by a cardiac surgeon in 3 patients, thoracentesis — in 3 patients. In one case, a thoracoscopic pericardial biopsy was performed, in 7 — right ventricular endomyocardial biopsy (EMB). Van Gieson's staining and polymerase chain reaction for viral infections (Herpesviridae, Parvovirus B19, Adenoviruses) were carried out. Three patients underwent a biopsy of subcutaneous fat with staining for amyloid (negative result).

Treatment and follow-up. Therapy for pericarditis will be described in the Results section. Therapy for heart failure and arrhythmias was carried out in accordance with European and Russian guidelines. Symptoms, laboratory parameters, and volume of pericardial effusion were monitored in 36 patients. The endpoints were the maintenance and recurrence of pericardial effusion, constriction and need for pericardial surgery, and all-cause mortality. The mean follow-up period was 14,5 [3; 39,5] months (maximum up to 10 years).

The study was approved by the local Ethics Committee.

Statistical processing was carried out using the SPSS Statistics 21 software. Quantitative characteristics are presented as M±δ (mean±one standard deviation) or as a median with 1st and 3rd quartiles. The distribution normality was assessed using the Kolmogorov-Smirnov test. The significance of dif-

ferences was assessed using the Student's test. Differences were considered significant at $p<0,05$.

Results

Clinical characteristics of patients (Table 1). Dry pericarditis (in all cases — acute or subacute) was made to 6 patients, while in other patients, pericarditis with effusion was diagnosed. In almost 2/3 of cases the effusion was minor (⩽10 mm), in 1/4 — moderate (11-20 mm) and only 1/10 — large (>20 mm). There was relatively infrequent detection of fibrin in pericardial effusion during echocardiography. In more than 2/3 of cases, pericarditis was chronic. General inflammatory changes in the blood were detected in almost 60% of patients, but leukocytosis — only in 6 patients; no one had leukopenia. In 20,5%, a relative blood lymphocytosis was detected.

The severity of symptoms and their clear connection with the previous infection was noted in more than half of the patients (n=25), while in 14 patients, there was definitely no such connection; in 5 more, it was possible. Fever was present at the disease onset in almost 1/3 of patients; in 11 of them, the body temperature reached 38° C. Sweat and cough were rare.

In addition to the association between the disease onset and respiratory infection, the infectious-immune nature of pericarditis was indicated:

1. The simultaneous presence of systemic immune manifestations and diseases that did not meet criteria for major immune diseases in 10 (22,7%) patients; these included the blood detection of elevated titers of ANF, RF, eosinophilia and an increase in eosinophilic cationic protein levels, arthritis/arthralgia, myasthenia, psoriasis, asthma. Signs of polyserositis were present in 3 patients.

2. High titers of anti-cardiac antibodies, which were detected in 88,2% of the examined patients (Figure 1). At the same time, there was also an increase in anti-endothelial cell and anti-conduction system antibodies, but also in anti-cardiomyocyte antibodies (1:160-1:320 in 8 patients), as well as antinuclear antibodies, which is normally absent, in 57,1% of patients (1:160-1:320 in 6 patients).

3. Clinical signs of myocardial involvement in the inflammatory process, which could be presented by arrhythmias, heart failure (HF) symptoms, as well as asymptomatic or oligosymptomatic ECG and imaging changes. In particular, HF was diagnosed in 21 patients (47,7%) in the absence of correlation with effusion volume, including stage I in 6 patients, stage IIA — in 16, stage IIB — in 7. Class 1 HF was registered in 6 patients, class 2 — in 14, and class 3 — in 9. In patients with stage IIB HF, pericardial effusion did not correlate with pleural and peritoneal effusion, did not respond to diuretic therapy, and could not be regarded as a manifestation of HF.

According to echocardiography, left ventricular (LV) mean end-diastolic dimension was 5,0 [4,6; 5,9] cm, LV end-diastolic volume — 98 [76; 124] ml, LV end-systolic volume — 41 [28,5; 70,5] ml, LV ejection fraction (EF) — 55 [41; 63]%, left atrial (LA) diameter — 4,2±0,9 cm, LA volume — 55,5 [37,75; 85,5] ml, right atrial volume — 47,3±18,6 ml, right ventricular dimension — 2,6±0,7 cm, pulmonary artery systolic pressure — 25 [20; 38] mm Hg. At the same time, LV dilatation was noted in 14 patients, LVEF decrease (range of 45-54%) in 4 patients, while in 13 patients, LVEF was <45%. Pulmonary hypertension was detected in 11 patients. There were no signs of cardiac tamponade in any case. Two patients had thickened pericardial layers without clear criteria for constriction.

Cardiac arrhythmias were represented mainly by ventricular premature contractions and unstable ventricular tachycardia, supraventricular premature contractions and atrial fibrillation, as well as atrial flutter, unstable supraventricular tachycardia (Table 1), first-degree atrioventricular block (n=5, 11,4%). One patient each had a complete left and right bundle branch blocks, sick sinus syndrome. The most characteristic ECG changes were a flattened or inverted T wave (n=16, 36,4%), transient ST segment depression or elevation (n=9, 20,5%), as well as signs of LV hypertrophy (n=8, 18,2%) and a QRS voltage decrease (n=5, 11,4%).

According to ^{99m}Tc scintigraphy, diffuse uneven impairment of myocardial perfusion in 6 patients (42,9%) was noted, as well as its combination with focal perfusion disorders in two more (14,3%). Intramyocardial, subepicardial delayed accumulation and their combination in 44,4% of MRI performances, signs of active contrast accumulation by the pericardium was revealed in one patient. Intramural, subepicardial and transmural delayed contrast accumulation in the myocardium according to MSCT (43,8%). Various types of lung fibrosis were detected in 55% of MSCT images, hilar lymphadenopathy — only in 3 patients.

4. The results of morphological and virological tests of the myocardium, which were obtained using EMB in 7 patients with suspicion of myocarditis, fully confirmed this diagnosis (Figure 2): active (according to Dallas criteria) lymphocytic myocarditis was detected in 5 cases, and borderline — in 2 cases. The viral genome in the myocardium was detected in 3 patients (in 2 — parvovirus B19, in 1 — the Epstein-Barr virus); the Epstein-Barr virus in the blood — in other 7 patients. The common pathogenesis of pericarditis in virus-positive and virus-negative patients was proved by an increase in

Table 1

Clinical characteristics and therapy in patients with various types of infectious-immune pericarditis

Parameter	All patients	Isolated pericarditis	Myoperi-/perimyocarditis
n	44	10	34
Age, years	49,4±13,3	54,1±14,7	47,9±12,7
Female/male	28/16	5/5	23/11
Acute /subacute/chronic	4/12/28	2/3/5	2/9/23
Dry/effusive	6/38	2/8	4/30
Minor/moderate/large effusion	24/10/4	3/3/2	21/7/2
Mean effusion volume, ml	200 [150; 450]	375 [200; 875]	200 [150; 450]
Onset association with infection	25 (56,8%)	5 (50%)	20 (58,8%)
Fever on the onset	14 (31,8%)	6 (60%)	8 (23,5%)
Sweat	4 (9,1%)	3 (30%)	1 (2,9%)
Cough	11 (25,0%)	4 (40%)	7 (20,6%)
Cardialgia	21 (47,7%)	5 (50%)	16 (47,1%)
HF	21 (47,7%)	7 (70%)	14 (41,2%)
PVC/unstable VT	18/5 (40,9/11,4%)	2/1 (20/10%)	16/4 (47,1/11,8%)
PSVC/SVT	14/9 (31,8/20,5%)	2/2 (20/20%)	12/7 (35,3/20,6%)
AF/AFL	10/6 (22,7/13,6%)	2/1 (20/10%)	8/5 (23,5/14,7%)
General inflammatory abnormalities	26 (59,1%)	10 (100%)	18 (52,9%)
Systemic immune manifestations	10 (22,7%)	4 (40%)	6 (17,6%)

Abbreviations: HF — heart failure, PVC — premature ventricular contractions, VT — ventricular tachycardia, PSVC — premature supraventricular contractions, SVT — supraventricular tachycardia, AF — atrial fibrillation, AFL — atrial flutter.

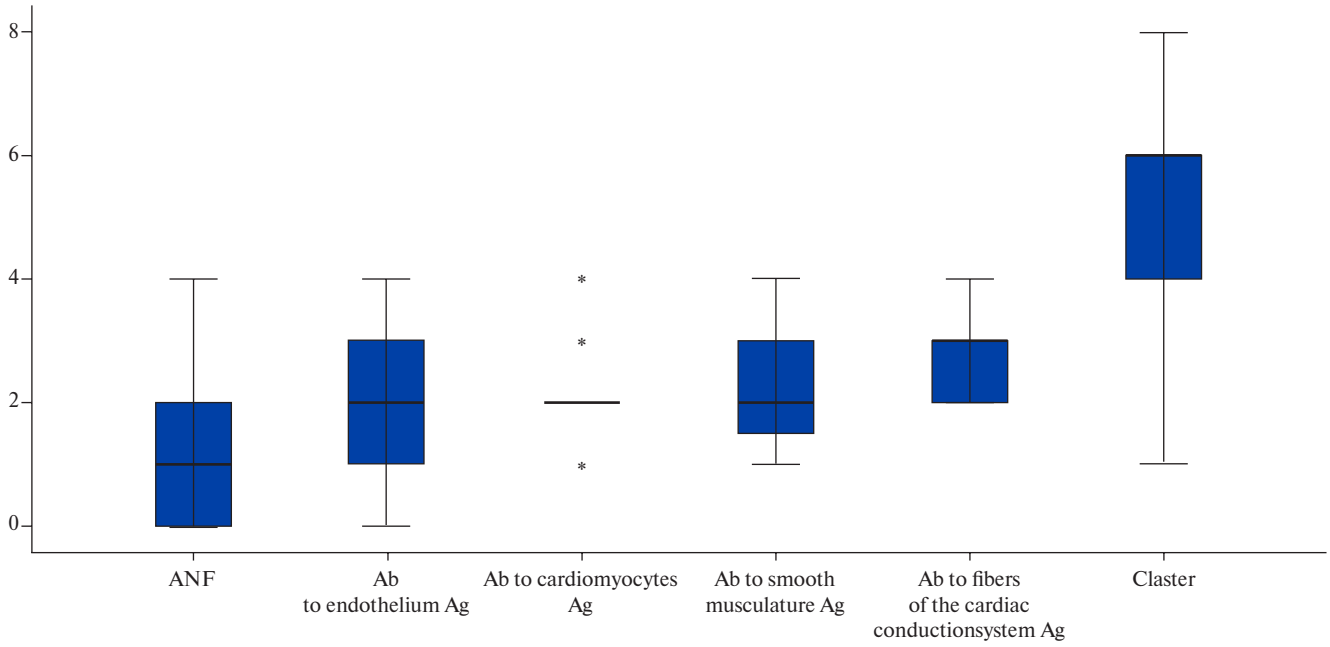


Figure 1. Concentration of various anticardiac antibodies in patients with infectious-immune pericarditis.
Note: ordinate is the level of titer increase (relative to the normal range).
Abbreviations: ANF — antinuclear factor, Ab — antibodies, Ag — antigens.

titers anticardiac antibodies and the simultaneous presence of myocarditis.

5. The results of a cytological examination of pericardial/pleural effusions, which were performed in patients with a sufficient fluid volume. In addition to confirming the inflammatory effusion nature (exudate in all cases), showed a significant (from 80 to 97%) prevalence of lymphocytes in 80% of tests. The viral genome was never detected. Due to the small number of examinations, the level of anticar-

diac antibodies in pericardial effusion was not analyzed.

6. The results of a pericardial biopsy, which was performed in a single case and showed a picture of active eukocytoclastic vasculitis (Figure 3).

Clinical types of infectious-immune pericarditis. Two main clinical types that were observed in patients of this group can be distinguished.

1. Isolated infectious-immune pericarditis. This type was diagnosed in a minority of patients (n=10, 22,7%). It was distinguished by acuity (in 70%), pronounced general inflammatory manifestations in all patients, as well as a significant volume of pericardial effusion (on average 375 [200; 875] ml, up to 1000 ml, with the exception of two cases of acute dry pericarditis), the presence of fibrin and resistance to treatment (which in half of the patients required the appointment of corticosteroids, see below). Fever was noted in 6 patients (>38° C). In 40% of cases, there were some systemic immune manifestations, including polyserositis (n=3).

Despite the absence of obvious signs of myocardial injury, a normal status of anticardiac antibodies was noted in only one patient, while in other cases, their increase was revealed (including ANF in 3 patients). The viral genome in the blood was not detected. An example is a 64-year-old, male patient (Figure 4), an Armenian, with an acute disease onset (fever >39° C), pericardial effusion up to 36 mm, neutrophilic leukocytosis up to 22 thousand, hyperfibrinogenemia, CRP of 168 mg/l, RF of 32 IU/ml, an increase in titers of specific ANP, anti-endothelial cell and anti-conduction system antibodies to 1:160, cardiolipin antibody IgM to 26,6 IU/ml. Pericardiocentesis removed 1,6 liters of serous fluid (neutrophils, 80%; lymphocytes, 20%). Immunoelectrophoresis revealed inflammatory dysproteinemia. No *MEFV* gene mutations in exon 10 were detected. Treatment with corticosteroids and colchicine was effective.

2. Pericarditis with simultaneous myocardial involvement (perimyo-/myopericarditis). This type was diagnosed in 34 (77,3%) patients: in 10 of them (29,4%), signs of myocarditis prevailed, in 17 (50%) — pericarditis; in 7 (20,6%), myo- and pericarditis had the same degree of severity. In a significant part of the patients, the symptoms were determined by myocarditis, which manifested itself not only in HF with EF decrease (44,1% of patients), arrhythmias, but also microvascular ischemia, an infarct-like signs (Figure 3). As noted earlier, in 7 cases the diagnosis of myocarditis was confirmed using EMB. Myocardium/blood of three-seven patients were virus-positive.

Pericarditis was exudative in 30 (88,2%) patients, in 2 cases was regarded as acute, in 9 as subacute and in 23 (67,6%) as chronic, mainly with small

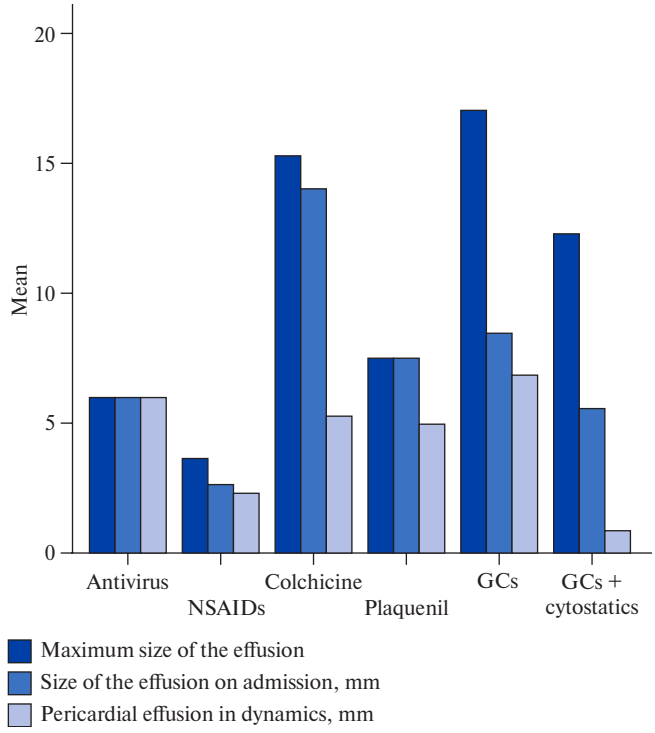


Figure 2. Changes in pericardial effusion volume depending on the type of initial therapy.
Abbreviations: GCs — glucocorticosteroids, NSAIDs — non-steroidal anti-inflammatory drugs.

effusion volume (on average 200 [140; 450] ml), general inflammatory blood abnormalities in 52,9% patients, systemic immune manifestations in 17,6%, fever at the onset in 23,5%, the absence of fibrin according to echocardiography in 86,7% of effusion pericarditis (Table 1). In general, it was less full-blown than isolated infectious-immune pericarditis.

As a special type, one should probably talk about the development of infectious-immune perimyocarditis in patients with primary cardiomyopathies. Thus, in one patient, perimyocarditis (with a predominance of pericarditis) developed against the background of severe obstructive hypertrophic cardiomyopathy, in the second — myopericarditis against the background of noncompact cardiomyopathy, and in the third — against the background of sarcomeric cardiomyopathy (MyBPC3 gene mutation). In two more patients, myopericarditis developed with arrhythmogenic right ventricular dysplasia (Figure 3). Two out of five patients were virus-positive (myocardium), which may indicate the viral tropism to genetically defective myocardium and its triggering role in pericarditis development.

Therapy of infectious-immune pericarditis, short-term and long-term outcomes. Therapy is presented in Table 2.

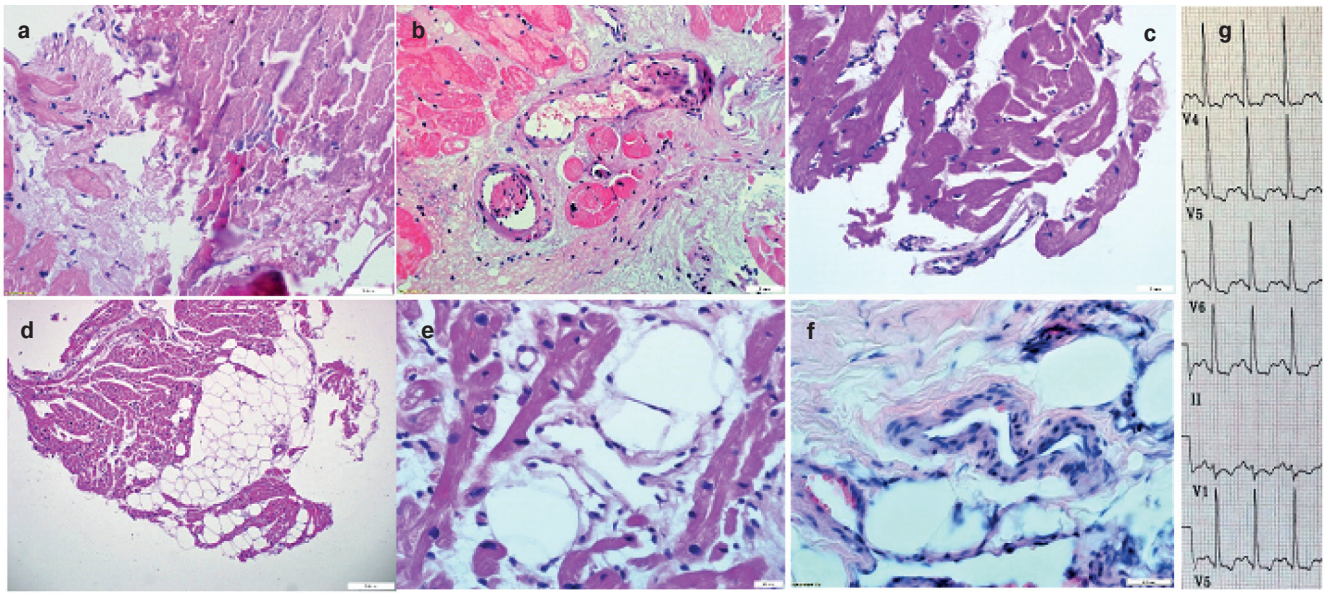


Figure 3. Results of biopsy of myocardium and pericardium in patients with infectious-immune myopericarditis (with ECG).
Note: a-e — right ventricular myocardial biopsy, **f** — pericardial biopsy, **a**, **d** — low-power magnification, **b**, **c**, **e**, **f** — high-power magnification; hematoxylin and eosin staining; dystrophy and necrosis of cardiomyocytes (**a**, **b**), interstitial (**a**, **d**, **e**) and perivascular (**b**, **c**) lymphohistiocytic infiltration, fatty myocardial replacement in a patient with arrhythmogenic right ventricular dysplasia (**d**, **e**), leucoclastic vasculitis (**f**); **g** — ECG during treadmill test, paper speed 25 mm/s (microvascular ischemia in a patient with vasculitis).

Antibiotic therapy was carried out mainly due to respiratory infections that developed at the onset of pericarditis or during treatment, much more often, with isolated pericarditis with a full-blown onset and general inflammatory changes. Antiviral drugs (acyclovir, ganciclovir) were prescribed only to virus-positive patients with myopericarditis. The relatively low percentage of NSAID use (mainly ibuprofen 1200-1600 mg/day for 1-2 months) is due to a small proportion of acute types of pericarditis. Colchicine was prescribed mainly for acute/subacute isolated pericarditis, while in the presence of myocarditis, preference was given to the immunosuppressive therapy.

Steroids was the basis of treatment in about half of cases of both isolated pericarditis and myopericarditis. The mean dose was low and corresponded to the standards of treatment of pericarditis rather than myocarditis. In the case of combined types, a cytostatic drug was added to the treatment (mainly azathioprine at a dose of 100-150 mg/day; in one case, mycophenolate mofetil 2 g/day). The combination of steroids with colchicine was prescribed to 6 patients, with hydroxychloroquine — 7; in 12 cases, monotherapy with hydroxychloroquine 200 mg/day was carried out. The choice of therapy was individual and depended on the clinical type of pericarditis, severity, effusion volume, previous treatment experience, the presence of contraindications or intolerance.

The effectiveness of pericarditis treatment was controlled primarily by changes of pericardial effusion volume. In patients with concomitant myocarditis, the goals of treatment were also relief of HF and arrhythmia symptoms, restoration of myocardial contractility (increase in EF), and improvement of other structural and functional disorders. In addition, decrease in anticardiac antibody titers was monitored.

The dynamics of pericardial effusion depending on the initial therapy is shown in Figure 2. Monotherapy with antiviral drugs was used in few patients and did not have a clear response in relation to effusion. With initially small-volume effusions, which differed in a chronic course and were not prone to spontaneous disappearance, hydroxychloroquine (Plaquenil) had a positive effect. At the same time, effusions >1 cm often required more aggressive therapy — not colchicine (used as monotherapy in isolated cases), but rather corticosteroids. In a significant part of patients, they were used in combination with cytostatic agents, which was due to the presence of clinically significant myocarditis.

In general, differentiated selection with a change in therapy made it possible to achieve good control of pericarditis in most patients. All cases of dry pericarditis resulted in complete resolution of symptoms without effusion formation. In 36 patients, an excellent effect (no effusion, relapses and constriction) was noted in 16 (44,4%), a stable effect (preservation of a small effusion, no congestive HF) — in 13 (36,1%). Absence of stable effect (presence or

Table 2

Characteristics of therapy for infectious-immune pericarditis

Parameter	All patients	Isolated pericarditis	Myoperi-/perimyocarditis
n	44	10	34
Antibiotic therapy	12 (27,3%)	6 (60%)	6 (17,6%)
Antiviral therapy	11 (25,0%)	-	11 (32,4%)
NSAIDs	15 (34,1%)	6 (60%)	9 (20,5%)
Colchicine	12 (27,3%)	7 (70%)	5 (14,7%)
Hydroxychloroquine	19 (43,2%)	3 (30%)	16 (47,1%)
Corticosteroids	25 (56,8%)	5 (50%)	20 (58,8%)
Mean dose of methylprednisolone, mg/day	16 [16; 21]	16 [14; 20]	16 [16; 22]
Azathioprine	9 (20,5%)	-	9 (26,5%)
Mycophenolate mofetil	1 (2,3%)	-	1 (2,9%)
β-blockers	31 (70,5%)	9 (90%)	22 (64,7%)
ACE inhibitors	23 (52,3%)	6 (60%)	17 (50,0%)
Mineralocorticoid receptor blockers	17 (38,6%)	2 (20%)	15 (44,1%)

Abbreviations: ACE — angiotensin-converting enzyme, NSAIDs — non-steroidal anti-inflammatory drugs.

increase in effusion, HF) — in 7 (19,4%). There were no cases of constrictive pericarditis, and acute recurrence. The frequency of different types of response to treatment in general and depending on the clinical type is shown in Figure 5.

Three patients died during the follow-up period. In all cases, this was caused by myocardial injury with severe HF and its complications: two patients with hypertrophic cardiomyopathy died in the early postoperative period from multiple organ failure. A third one had a stroke as the cause of death.

Criteria for infectious immune pericarditis. At the end of our analysis, we formulated criteria to diagnose infectious-immune pericarditis mainly by non-invasive methods and prescribe therapy:

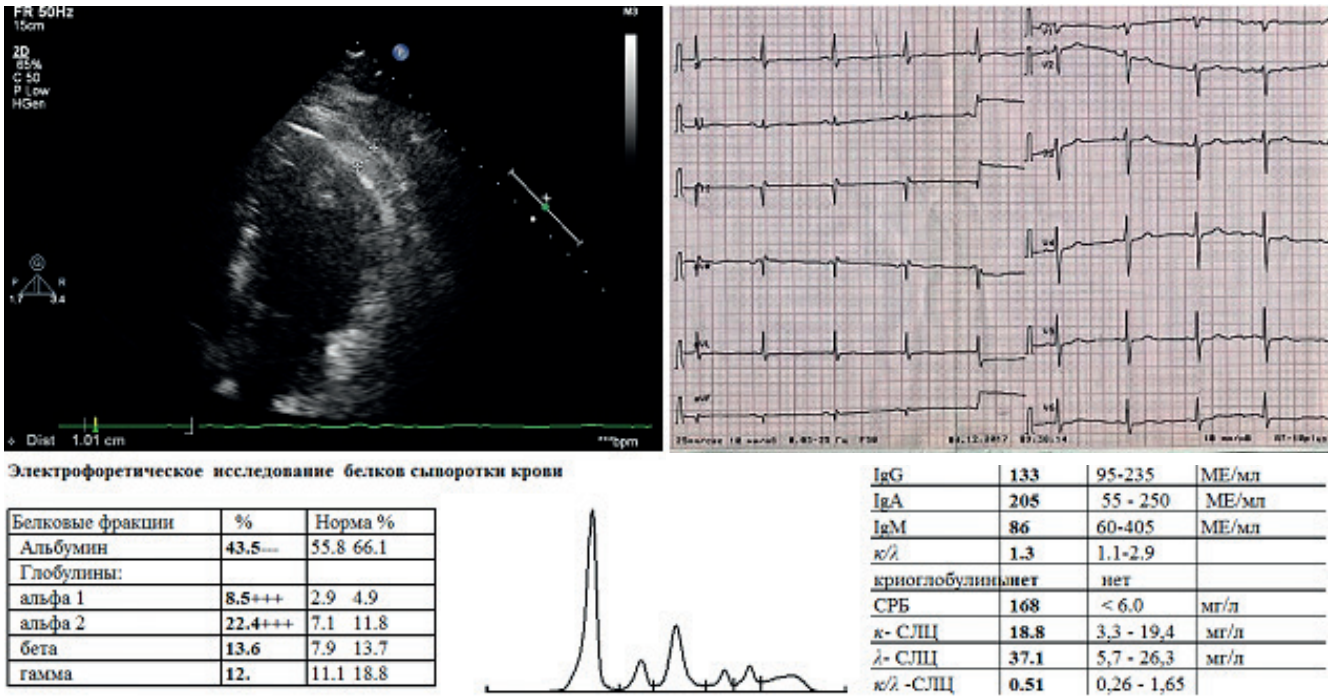
1. No prior cancer, tuberculosis, sarcoidosis, amyloidosis, systemic connective tissue diseases and vasculitis.
2. No history of radiation therapy, chemotherapy and any cardiac surgery less than six months old.
3. The relationship of disease onset with the previous infection (URTI, bronchitis, pneumonia, tonsillitis, etc.).
4. Concomitant myocarditis (including confirmed by EMB).
5. Three-four times increased titers of anticardiac antibodies in the blood (and, possibly, pericardial fluid).
6. Predominantly lymphocytic pericardial/pleural effusion.
7. Presence of the viral genome in the pericardial/pleural fluid/myocardium.
8. Small (up to 1 cm) or moderate (1-2 cm) volume of pericardial effusion.
9. Favorable course (without tamponade and constriction).
10. Positive effect of NSAID/colchicine/hydroxychloroquine/corticosteroid therapy during the first 3-6 months.

Discussion

One of the main aims of this study was to move away from the concept of idiopathic pericarditis. According to the Brucato A and Imazio M, up to 50-80% of patients with acute pericarditis remain without a definite diagnosis [5]. As these authors rightly point out, this is only due to lack of information. However, the first reason for the unjustifiably high proportion of idiopathic pericarditis is still underdiagnosis of tuberculosis, systemic diseases, cancer and other known causes of the disease.

Our experience shows that intensive diagnostics, including the repeated pericardiocentesis and invasive biopsy, is necessary in all cases of unclear pericarditis and gives results [6, 7]. It is interesting and quite natural that one of the few works on the diagnostic value of pericardioscopy and thoracoscopic biopsy of the pericardium in Russia was carried in tuberculosis institution, where it made it possible to diagnose tuberculous pericarditis in 44,4% of patients [8]. The present study included only those patients who had already undergone the necessary additional examination aimed at ruling out all known causes of pericarditis, and none of these causes was found.

As far as we know, the term “infectious-immune pericarditis” was not previously used, but there is nothing fundamentally novel. In the monograph



Электрофоретическое исследование белков сыворотки крови

Белковые фракции	%	Норма %
Альбумин	43.5---	55.8 66.1
Глобулины:		
альфа 1	8.5+++	2.9 4.9
альфа 2	22.4+++	7.1 11.8
бета	13.6	7.9 13.7
гамма	12.	11.1 18.8

IgG	133	95-235	МЕ/мл
IgA	205	55 - 250	МЕ/мл
IgM	86	60-405	МЕ/мл
κ/λ	1.3	1.1-2.9	
криоглобулины	нет	нет	
СРБ	168	< 6.0	мг/л
κ- СЛЦ	18.8	3,3 - 19,4	мг/л
λ- СЛЦ	37.1	5,7 - 26,3	мг/л
κ/λ -СЛЦ	0.51	0,26 - 1,65	

Figure 4. Diagnostic data on a patient with isolated infectious-immune pericarditis.

by Gogin RR (1979) the concepts of "infectious-allergic pericarditis", "acute benign or idiopathic pericarditis", "allergic pericarditis" were used [9]. The author discusses primarily the viral and allergic nature of acute benign pericarditis. The unifying features of this type include the absence of a microbial pathogen, a favorable outcome and a tendency to recurrence.

At present, two leading groups of European researchers offer similar, in our opinion, terms and consider idiopathic pericarditis in a similar way. The first group of authors (Maisch B and Ristic A, et al.) relies on their own unique experience of morphological and molecular diagnostics, which allows them, firstly, to distinguish a group of viral pericarditis and, secondly, to diagnose autoreactive (lymphocytic) viral-negative pericarditis [3]. The autoimmune nature of the latter is confirmed by the authors by detecting not only CD45-positive lymphocytes in the pericardium, but also anticardiac antibodies in the blood and pericardial fluid.

The second group of authors (Brucato A and Imazio M, et al.), without denying the role of viruses and even suggesting to term "presumed viral pericarditis", develops an interesting concept of "idiopathic" pericarditis as an autoinflammatory disease due to innate immune response [5]. Typical for autoinflammation is a recurrence, the onset in childhood, an acute inflammatory response with a high CRP level and subsequent regression of symptoms [10]. The key mediator of this response is interleukin-1, and the efficacy of anakinra in some patients with resistant pericarditis undoubtedly confirms the role of autoinflammation [11], as well as the proven anti-recurrent effect of colchicine, which modulates the innate immune response [4]. This concept is also supported by Russian authors [12].

Our data show that both concepts are true. Undoubtedly, isolated pericarditis with a supposed autoinflammatory nature is the most full-blown representative of this group of pericarditis. However, not all cases of infectious-immune pericarditis fit into this concept. It seems that the presence of concomitant myocarditis is a very clear indicator of a chronic autoimmune process, where viruses can be a trigger. Therefore, the algorithm proposed by Maisch B for the verification of myopericarditis with small effusion using EMB [3] looks very attractive, as we have seen from our own experience.

Concomitant detection of anticardiac antibodies in blood and pericardium makes it possible to use their determination in blood as a diagnostic marker of infectious-immune pericarditis. An increase in the titer of anticardiac anti-intercalated disk antibodies has already been shown in 67,5% of patients with recurrent pericarditis [13]. The results of our work indicate that the titers of antibodies to various cardiac structures were equally increased in patients with both isolated pericarditis and myopericarditis. This fact, as well as the association between the dis-

ease onset and prior respiratory infection in more than half of the patients, proves the common pathogenesis and the rationale of the concept of "infectious-immune pericarditis".

It also follows from our study that not all cases of infectious-immune pericarditis require therapy not only with anti-interleukin drugs, but also with colchicine. In most cases, more traditional treatment for immune diseases have been effective. First of all, this concerns chronic pericardial effusion, in which the effectiveness of colchicine (and, moreover, NSAIDs) has not been studied at all. The idea of the effect of colchicine on viral pericarditis remains controversial: after the catastrophic result of the experiment on mice with the treatment of Coxsackie-viral myocarditis (on the 3rd day of treatment, 50% of the mice died [14]), an opinion was expressed about too high doses used; the Tschöpe C group showed that colchicine improves the course of Coxsackie-viral myocarditis in mice by reducing the activity of inflammasomes [15]. In general, the presence of viruses in pericarditis is not given so much importance as in myocarditis.

On the other hand, there is evidence of greater efficacy of low doses of corticosteroids (0,2-0,5 mg/kg of prednisolone) in comparison with the standard for the treatment of myocarditis (1 mg/kg) [16]. The authors established long-term (86,7%) antirelapse efficacy of intrapericardial administration of triamcinolone (300 mg per 1 m^2 of body surface) for autoreactive pericarditis [3]. High efficacy of steroids in combination with azathioprine or mycophenolate mofetil in the treatment of idiopathic recurrent pericarditis has been shown [17]. We successfully used these regimens in patients with myopericarditis and achieved almost complete suppression of effusion (Figure 2), while in isolated pericarditis, the combination of corticosteroids with colchicine had the best effect. A similar regimen has been successfully used by other authors, who noted the insufficient effect of first-line drugs (NSAIDs and colchicine) in 62% of 276 patients [18].

Finally, the results of hydroxychloroquine use in our study deserve a separate analysis. We are not aware of special studies of this kind; there are only reports of its use for pericarditis in the framework of systemic diseases and rheumatism [19]. We have successfully used it to control pericardial effusion both in addition to maintenance doses of corticosteroids, and as monotherapy, at a minimum dose (200 mg/day). To date, hydroxychloroquine is used in patients with minor subacute and chronic effusions, which we attributed mainly to a slow onset of the effect. However, in the light of recent data on the

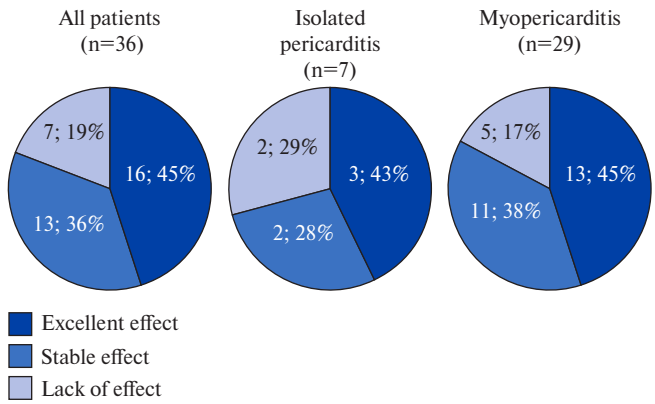


Figure 5. Results of treatment of infectious-immune pericarditis.

effectiveness of higher doses of hydroxychloroquine (800 mg/day with a switch to 400 mg/day) and its combinations with steroids and antiviral drugs in Coronavirus disease 2019, including leading to active myocarditis [20, 21], it is of particular interest to study its effectiveness in more acute and aggressive pericarditis types.

Conclusion

The concept of "infectious-immune pericarditis" and its clinical criteria were proposed. There are two main types of infectious-immune pericarditis (isolated pericarditis and myoperi-/perimyocarditis). It is analogous to autoreactive, lymphocytic pericarditis and underlies most cases of idiopathic pericarditis. Isolated pericarditis is more severe and characterize by more effusion. With myopericarditis, symptoms caused by myocardial injury may come to the fore. An increase in the titer of anticardiac antibodies is observed in all types of infectious-immune pericarditis and is a good marker of disease activity. Due to the relatively small volume of effusion, in most cases, pericardiocentesis is not possible and is not necessary for the diagnosis and choice of treatment. Anti-inflammatory/immunosuppressive therapy is determined by the severity, the volume of effusion, presence of concomitant myocardial injury, and the experience of previous treatment. The appointment of corticosteroids is justified in many cases of infectious-immune pericarditis, including in combination with colchicine in isolated pericarditis with significant effusion, with cytostatics — in myocarditis. The combination of steroids with hydroxychloroquine can be used for any option. Long-term monotherapy with hydroxychloroquine is quite effective in subacute/chronic pericarditis with moderate effusion. Further study of its effectiveness is necessary.

Relationships and Activities: none.

References

1. Adler Y, Charron P, Imazio M, et al. European Society of Cardiology (ESC). 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36(42):2921-64. doi:10.1093/eurheartj/ehv318.
2. Maisch B. European Society of Cardiology. [Progress or regress or both? ESC guidelines on pericardial diseases 2015]. Herz. 2015;40(8):1061-9. doi:10.1007/s00059-015-4395-z. (In German).
3. Maisch B, Rupp H, Ristic A, Pankuweit S. Pericardioscopy and epi- and pericardial biopsy — a new window to the heart improving etiological diagnoses and permitting targeted intrapericardial therapy. Heart Fail Rev. 2013;18(3):317-28. doi:10.1007/s10741-013-9382-y.
4. Imazio M, Belli R, Brucato A, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. Lancet. 2014;383(9936):2232-7.
5. Brucato A, Imazio M, Cremer PC, et al. Recurrent pericarditis: still idiopathic? The pros and cons of a well-honoured term. Intern Emerg Med. 2018;13(6):839-44. doi:10.1007/s11739-018-1907-x.
6. Blagova OV, Alijeva IN, Nedostup AV, et al. Exudative-constrictive tuberculous pericarditis in combination with arthritis in cardiologist practice: thoracoscopic biopsy as a diagnosis and treatment method. Ter Arkh. 2018;90(9):81-7. (In Russ.) doi:10.26442/terarkh201890981-87.
7. Blagova OV, Alieva IN, Senchikhin PV, et al. Massive tuberculous exudative pericarditis under the guise of hydropericardium in a patient with non-compaction cardiomyopathy: diagnosis and treatment. Russian Journal of Cardiology. 2019;24(11):55-62. (In Russ.). doi:10.15829/1560-4071-2019-11-55-62.
8. Dreval' PA, Vorob'ev AA, Vavilov PA. Surgical methods in the diagnosis and treatment algorithm in patients with exudative pericarditis of unknown etiology. Serdce. 2010;9(3):185-90. (In Russ.)
9. Gogin EE. The Pericarditis. M. "Medicina". 1979. 191 p. (In Russ.)
10. Brucato A, Emmi G, Cantarini L, et al. Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism. Intern Emerg Med. 2018;13(4):475-89. doi:10.1007/s11739-018-1842-x.
11. Imazio M, Andreis A, De Ferrari GM, et al. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis: The IRAP (International Registry of Anakinra for Pericarditis) study. Eur J Prev Cardiol. 2019:2047487319879534. doi:10.1177/2047487319879534.
12. Myachikova VYu, Titov VA, Maslyanskiy AL, Moiseeva OM. Idiopathic recurrent pericarditis — a paradigm shift? Russian Journal of Cardiology. 2019;24(11):155-63. (In Russ.) doi:10.15829/1560-4071-2019-11-155-163.
13. Caforio AL, Brucato A, Doria A, et al. Anti-heart and anti-intercalated disk autoantibodies: evidence for autoimmunity in idiopathic recurrent acute pericarditis. Heart. 2010;96(10):779-84. doi:10.1136/hrt.2009.187138.
14. Smilde BJ, Woudstra L, Fong Hing G, et al. Colchicine aggravates coxsackievirus B3 infection in mice. Int J Cardiol. 2016;216:58-65. doi:10.1016/j.ijcard.2016.04.144.
15. Van Linthout S, Pappritz K, Lin J, et al. Colchicine reduces NLRP3 inflammasome activity in murine Coxsackievirus B3-induced myocarditis. European Heart Journal. 2018;39(Supplement):594.
16. Imazio M, Brucato A, Cumetti D, et al. Corticosteroids for recurrent pericarditis: high versus low doses: a nonrandomized observation. Circulation. 2008;118(6):667-71. doi:10.1161/CIRCULATIONAHA.107.761064.
17. Peiffer-Smadja N, Domont F, Saadoun D, Cacoub P. Corticosteroids and immunosuppressive agents for idiopathic recurrent pericarditis. Autoimmun Rev. 2019;18(6):621-26. doi:10.1016/j.autrev.2019.04.001.
18. Perrone A, Castrovilli A, Piazzolla G, et al. Corticosteroids for Acute and Recurrent Idiopathic Pericarditis: Unexpected Evidences. Cardiol Res Pract. 2019;2019:1348364. doi:10.1155/2019/1348364.
19. Wilson NJ, Concannon A, Malcolm J, et al. The Treatment of Acute Rheumatic Fever: Novel Use of Hydroxychloroquine. Pediatr Infect Dis J. 2020. doi:10.1097/INF.0000000000002647.
20. Fantini J, Scala CD, Chahinian H, Yahi N. Structural and molecular modeling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents. 2020:105960. doi:10.1016/j.ijantimicag.2020.105960.
21. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020. doi:10.1001/jamacardio.2020.1096.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4108

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Cardiomyopathies: echocardiographic profiles based on principal component factor analysis in men and women

Vardugina N. G.[1], Medvedenko I. V.[2], Efimova N. M.[2]

Aim. To determine echocardiographic profiles and their prognostic value using factor analysis in men and women with various types of cardiomyopathies (CMP).

Material and methods. The study involved 100 people with CMP — 69 men with a median age of 53 years and 31 women with a median age of 58 years. Among the subjects, six nosological types corresponding to ICD 10 classification were revealed: dilated CMP (DCM), ischemic CMP (ICM), alcoholic CMP, mixed CMP, hypertrophic CMP (HCM) and myocarditis. All persons underwent an echocardiography. Echocardiography results as variables were included in factor analysis. The resulting two factors are presented as the first and second echocardiographic profiles.

Results. The first echocardiographic profile was characterized as the degree of myocardial contractile function reduction. A strong association of the first profile with DCM, alcoholic CMP and myocarditis in men (p=0,001) and DCM in women (p=0,05) was obtained. In some individuals with ICM and mixed CMP, there was no association with the first profile. The second echocardiographic profile reflected the degree of myocardial mass increase and had significant differences only in women (p=0,04). A strong correlation with the second profile was observed in HCM, in the majority of women with ICM and in some persons with mixed CMP. Fatal outcomes in men were recorded in patients with ICM (66,7%), alcoholic CMP and myocarditis, and in women with mixed CMP (11,1%).

Conclusion. For patients with DCM, myocarditis, and alcoholic CMP, the first echocardiographic profile with a risk of death is characteristic. The second echocardiographic profile was inherent in HCM and was associated with a protective effect in women with ICM. The revealed echocardiographic profiles can be extrapolated to nosological types of CMP in men and women in order to verify the diagnosis and prognosis.

Key words: cardiomyopathies, echocardiography, factor analysis, sex differences.

Relationships and Activities: none.

[1]South Ural State Medical University, Chelyabinsk; [2]Regional Clinical Hospital № 3, Chelyabinsk, Russia.

Vardugina N. G.* ORCID: 0000-0003-4526-8652, Medvedenko I. V. ORCID: 0000-0002-1568-9993, Efimova N. M. ORCID: 0000-0001-7105-2391.

*Corresponding author: centrproff@yandex.ru

Received: 14.09.2020
Revision Received: 18.09.2020
Accepted: 19.09.2020

For citation: Vardugina N. G., Medvedenko I. V., Efimova N. M. Cardiomyopathies: echocardiographic profiles based on principal component factor analysis in men and women. *Russian Journal of Cardiology*. 2020;25(11):4108. (In Russ.) doi:10.15829/1560-4071-2020-4108

Cardiomyopathies (CMP) are a large group of non-coronary myocardial diseases with various etiological and pathogenetic mechanisms. CMPs are widespread and often lead to heart failure, arrhythmias and sudden cardiac death [1, 2]. Recent international studies show that CMPs in men and women have different prevalence and frequency of complications [3-7]. This is due to the influence of sex on cardiac metabolism, different signaling pathways and gene expression [8]. Currently, verification of certain CMP types is possible only with molecular genetics and cellular testing, myocardial biopsy and modern visualization methods (magnetic resonance imaging, computed tomography and cardiac positron emission tomography), of which transthoracic echocardiography remains the leading technique in the diagnosis of CMPs. In order to obtain the qualitative characteristics of echocardiography in the differential diagnosis of CMPs, we used the factor analysis separately in men and women.

The aim was to determine echocardiographic profiles and their prognostic value using factor analysis in men and women with various types of cardiomyopathies.

Material and methods

We performed a retrospective analysis of medical records of 123 patients with CMP discharged from the hospital during 2018. According to the International Classification of Diseases 10th Revision (ICD-10), a total of 6 CMP types were registered: dilated CMP (DCM) (I42.0), ischemic CMP (ICM) (I25.5), alcoholic CMP (I42.6), mixed CMP (I43.1-43.8; I42.7-42.9), hypertrophic CMP (HCM) (I42.1-42.2) and myocarditis (I40.0-40.9). After hospitalization and examination, 111 patients were discharged with CMP, while 12 patients died. Of the 123 registered CMP cases, 100 medical records were available for analysis, of which 8 were lethal cases. There were 69 men with a mean age of 52,7±12,8 years and 31 women with a mean age of 58,6±14,7 years. Data on coronary angiography were available in 35 people out of 100 (35,0%). In all cases, no coronary artery stenosis was detected. Autopsy data were available in 6 of 8 deceased patients with CMP.

All patients underwent standard echocardiography. The following echocardiographic parameters were taken into account: ejection fraction (EF), left ventricular (LV) end diastolic dimension (EDD), LV end systolic dimension (ESD), LV end diastolic volume (EDV), LV end systolic volume (ESV), right ventricle dimension, interventricular septal thickness, LV posterior wall thickness, LV relative wall thickness, left atrial transverse diameter, right atrial transverse diameter, post-systolic shortening, pulmonary artery systolic pressure, LV mass index, presence of hypokinetic regions, and pericardial effusion.

Statistical analysis was carried out using the SPSS 17.0. Comparison of mean values was carried out according to Student's t-test. Differences were considered significant at $p<0,05$. The arithmetic mean was presented as M±SD, where M is the mean and SD is the standard deviation. The varimax rotated two-factor analysis was carried out. The obtained factor values for each case of CMP were ranged into 4 groups of percentiles depending on the trait t for men and women. The analysis of contingency table was carried out using the chi-squared test.

Table 1

Prevalence of different CMPs in men and women

		CMP types						Total
		DCM	ICM	Alcoholic CMP	Myocarditis	Mixed CMP	HCM	
Men	n	21	6	5	12	24	1	69
	%	30,4	8,7	7,2	17,4	34,8	1,4	100,0
	% CMP	91,3	46,2	100,0	85,7%	57,1	33,3	69,0
Women	n	2	7	0	2	18	2	31
	%	6,5	22,6	0,0	6,5	58,1	6,5	100,0
	% CMP	8,7	53,8	0,0	14,3	42,9	66,7	31,0
Total	N	23	13	5	14	42	3	100
	%	23,0	13,0	5,0	14,0	42,0	3,0	100,0
	% CMP	100,0	100,0	100,0	100,0	100,0	100,0	100,0
P		0,01*	0,05*	>0,5	>0,5	0,03*	>0,5	0,05*

Note: * — differences in the prevalence of CMP between men and women.

Abbreviations: HCM — hypertrophic cardiomyopathy, DCM — dilated cardiomyopathy, ICM — ischemic cardiomyopathy, CMP — cardiomyopathy.

Results

Among patients with CMP (n=100), there were more men (n=69) (69,0%) than women (n=31) (31,0%), which was significant (p<0,001). In men, compared with women, DCM was significantly more common (p=0,01), and in women, mixed CMP (p=0,03) and ICM were more often recorded (p=0,05). The distribution of CMP types by sex is presented in Table 1.

The group of CMP men was younger than women with CMP: the median age for men was 53 years, for women — 58 years (p=0,04). By age, the oldest among men and women were patients with ICM (66,3±4,0 years and 79,2±8,8 years, respectively), while the youngest were patients with myocarditis (45,9±10,6 years and 41,5±13,4 years, respectively). Comparative analysis of the groups of men (n=69) and women (n=31) revealed sex differences in almost all parameters of echocardiography, which coincide with other studies [9] (Table 2).

Comparative analysis of echocardiographic data in patients with the same type of CMP between men and women revealed that among those with DCM, myocarditis and HCM, there were no sex differences in any echocardiographic parameter (p>0,5), while there were significant differences between men and women only with ICM and mixed CMP (Table 3).

Among men (n=69), there were 6 deaths (8,7%): 4 (66,7%) patients with ICM (n=6), 1 (20,0%) patient with alcoholic CMP (n=5) and 1 (8,3%) patient with myocarditis (n=12). The difference in mortality with ICM in men (n=6) compared to women with ICM (n=7) was significant: 66,7% and 0% (p=0,009). The deceased and surviving men with ICM did not differ in age (p>0,5) and echocardiographic parameters (p>0,5).

Among women (n=31), 2 (6,5%) people with mixed CMP died, which amounted to 11,1% in the mixed CMP group of women (n=18). The 2 women who died differed from the surviving women with mixed CM by lower ejection fraction (p=0,002), LV reduced contractility fraction (p=0,001) and the presence of hypokinetic regions (p=0,024). There were no differences in mortality in patients with mixed CMP and in general between women and men (8,7% and 6,5%) (p>0,5).

Principal factor analysis was carried out separately for men and women. Three factors have been identified that explain 83,7% of the total variance of studied variables in men, of which the first factor explained 45,9%, the second factor — 21,9% and the third factor — 15,8% of the variance. In women, the total variance was 80,8%, where the first factor explained 43,1% of the total variance, the second factor — 19,4%, and the third factor — 18,3%. Fac-

Table 2

Comparative analysis of echocardiographic data in CMP among men and women

Parameters	Men (n=69) M±SD	Women (n=31) M±SD	p
EF (%)	47,3±14,8	53,4±12,1	0,046
LA (cm)	4,8±1,0	4,5±0,8	>0,5
RA (cm)	4,5±0,8	4,2±0,9	>0,5
RV (cm)	3,8±0,7	3,3±0,6	0,001
CF (%)	24,8±8,6	28,7±7,5	0,032
RWT	0,31±0,08	0,37±0,10	0,002
EDD (cm)	6,0±1,0	5,2±0,8	0,001
ESD (cm)	4,6±1,2	3,9±0,8	0,004
EDV (ml)	189,3±77,5	146,7±45,3	0,008
ESV (ml)	107,9±71,9	63,1±34,8	0,002
IVS (cm)	0,9±0,2	1,0±0,3	0,028
LVPW (cm)	0,9±0,1	0,9±0,2	>0,5
LVMI	125,5±45,2	123,9±43,6	>0,5
RVSP (mm Hg)	41,2±11,5	39,1±8,2	>0,5
Pericardial fluid (n)	3 (5,4%)	5 (16,1%)	0,06
Hypokinesia (n)	31 (52,5%)	9 (29,0%)	>0,5

Abbreviations: LVPW — left ventricular posterior wall, LVMI — left ventricular mass index, EDV — end-diastolic volume, ESV — end-systolic volume, EDD — end-diastolic dimension, ESD — end-systolic dimension, LA — left atrium, IVS — interventricular septum, RWT — relative wall thickness, RV — right ventricle, RA — right atrium, RVSP — right ventricular systolic pressure, EF — ejection fraction, CF — contractility fraction.

Table 3

Comparative analysis of echocardiographic data in men and women with ICM and mixed CMP

CMP type	Parameters	Men, M±SD	Women, M±SD	p
ICP	RV (cm)	4,0±0,6, n=6	3,2±0,5, n=7	0,04
	EDD (cm)	6,7±0,7, n=6	5,8±0,7, n=7	0,07
Mixed CMP	RV (cm)	3,6±0,6, n=24	3,2±0,5, n=18	0,02
	EDD (cm)	5,7±0,6, n=24	5,1±0,6, n=18	0,01
	ESV (ml)	79,8±50,6, n=24	51,4±21,5, n=18	0,04

Abbreviations: ICM — ischemic cardiomyopathy, EDD — end-diastolic dimension, CMP — cardiomyopathy, ESV — end-systolic volume, RV — right ventricle.

Table 4

Rotated factor matrix in men and women with CMP

Factor loadings							
Variables	Units	Men			Women		
		Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
LA	cm			0,801			0,872
RA	cm			0,953			0,953
EF	%	-0,892			-0,875		
CF	%	-0,878			-0,879		
EDD	cm	0,870			0,864		
ESD	cm	0,948			0,773		
EDV	ml	0,834			0,898		
ESV	ml	0,901			0,929		
IVS	cm		0,910			0,859	
LVPW	cm		0,936			0,895	
LVMI	n		0,692			0,789	
Hypokinesia	n	0,780			0,788		

Abbreviations: LVPW — left ventricular posterior wall, LVMI — left ventricular mass index, EDV — end-diastolic volume, ESV — end-systolic volume, EDD — end- diastolic dimension, ESD — end-systolic dimension, LA — left atrium, IVS — interventricular septum, RA — right atrium, EF — ejection fraction, CF — contractility fraction.

Table 5

Contingency table of Factor 1 with different CMP types in men

CMP type		Factor 1: reduced MCF				Total
		No	Mild	Strong	Very strong	
DCM	n	1	0	6	8	15
	%	6,7%	0,0%	40,0%	53,3%	100,0%
ICM	n	1	3	2	2	8
	%	12,5%	37,5%	25,0%	25,0%	100,0%
Alcoholic CMP	n	0	0	2	0	2
	%	0,0%	0,0%	100,0%	0,0%	100,0%
Myocarditis	n	0	0	0	1	1
	%	0,0%	0,0%	0,0%	100,0%	100,0%
Mixed CMP	n	9	12	5	3	29
	%	31,0%	41,4%	17,2%	10,3%	100,0%
HCM	n	3	0	0	0	3
	%	100,0%	0,0%	0,0%	0,0%	100,0%
Total	n	14	15	15	14	58
	%	24,1%	25,9%	25,9%	24,1%	100,0%

Abbreviations: HCM — hypertrophic cardiomyopathy, DCM — dilated cardiomyopathy, ICM — ischemic cardiomyopathy, CMP — cardiomyopathy.

tor analysis created a rotated matrix of factor loadings with three main components (Table 4).

The first component (Factor 1) included variables same for men and women: EF, post-systolic shortening, EDD, ESD, EDV, ESV, hypokinetic myocardium. Factor 1 had a strong inverse relationship with EF and contractility fraction variables and a strong direct relationship with LV dimension, volume, and hypokinesis, as a result of which Factor 1 was characterized as *the first echocardiographic profile with reduced myocardial contractile function* (MCF). The second component (Factor 2) in men and women consisted of the variables of the interventricular septum, LV posterior wall, LV mass index, reflecting the LV myocardium walls' thickness and was designated as *the second echocardiographic*

Table 6

Contingency table of Factor 1 with different CMP types in women

CMP type		Factor 1: reduced MCF				Total
		No	Mild	Strong	Very strong	
DCM	n	0	0	0	2	2
	%	0,0%	0,0%	0,0%	100,0%	100,0%
ICM	n	0	2	1	2	5
	%	0,0%	40,0%	20,0%	40,0%	100,0%
Mixed CMP	n	2	3	4	1	10
	%	20,0%	30,0%	40,0%	10,0%	100,0%
HCM	n	2	0	0	0	2
	%	100,0%	0,0%	0,0%	0,0%	100,0%
Total	n	4	5	5	5	19
	%	21,1%	26,3%	26,3%	26,3%	100,0%

Abbreviations: HCM — hypertrophic cardiomyopathy, DCM — dilated cardiomyopathy, ICM — ischemic cardiomyopathy, CMP — cardiomyopathy.

Table 7

Contingency table of Factor 2 with different CMP types in women

CMP type		Factor 2: increased MM				Total
		No	Mild	Strong	Very strong	
DCM	n	2	0	0	0	2
	%	100,0%	0,0%	0,0%	0,0%	100,0%
ICM	n	0	1	3	1	5
	%	0,0%	20,0%	60,0%	20,0%	100,0%
Mixed CMP	n	2	4	2	2	10
	%	20,0%	40,0%	20,0%	20,0%	100,0%
HCM	n	0	0	0	2	2
	%	0,0%	0,0%	0,0%	100,0%	100,0%
Total	n	4	5	5	5	19
	%	21,1%	26,3%	26,3%	26,3%	100,0%

Abbreviations: HCM — hypertrophic cardiomyopathy, DCM — dilated cardiomyopathy, ICM — ischemic cardiomyopathy, CMP — cardiomyopathy.

profile with increased myocardial mass (MM). The third component (Factor 3) is defined as the degree of *atrial load*, since in men and women this factor included the variables of the left and right atria.

When analyzing contingency tables with analysis of relationship strength of factor values of *the first echocardiographic profile* with individual CMP types, the chi-squared test in men was significant at the level of p=0,001, and in women it was equal to p=0,05. Among men, association with *the first echocardiographic profile* were obtained for alcoholic CMP, myocarditis, DCM, ICM, and mixed CMP (Table 5).

In women, the relationship of *the first echocardiographic profile* with DCM, ICM and mixed CMP (Table 6).

The second echocardiographic profile with increased MM among men did not have a significant relationship with CMP (p>0,5). On the contrary, in women, *the second echocardiographic profile* had a significant difference (p=0,04) with HCM and ICM (Table 7).

Factor 3 (*degree of atrial load*) showed no differences either in men (p>0,5) or in women (p>0,5), which indicated a comparatively equal atrial load in all types of CMP in both sexes.

Discussion

The first echocardiographic profile with reduced MCF was characteristic of patients with DCM, alcoholic CMP, myocarditis and, in general, corresponded to morphological abnormalities in these

CMPs. Among these individuals, deaths were reported in men. *The second echocardiographic profile with increased MM* was present in women with HCM, since they did not have *the first echocardiographic profile*. There were no sex differences in the echocardiographic parameters (p>0,5) in DCM, myocarditis and HCM, which may indicate the dominance of etiological and genetic mechanisms of the development of these CMP types over sex influence. To confirm these conclusions, it is necessary to study a large population of patients with CMP due to the differences between our results and a number of other studies [5-7].

With ICM, the majority of men had an association with *the first echocardiographic profile* and high mortality (66,7%) compared with women (p=0,009). This confirms the literature data [8] about a poor prognosis in men with ICM. There were no differences in echocardiographic parameters between the deceased and surviving men with ICM (p>0,5), which indicates the morphological homogeneity of this group. Comparison of men with ICM with women with ICM revealed sexual dimorphism of echocardiographic parameters with a significant increase in heart chambers among men (p<0,05). All women with ICM, as well as men, had an association with *the first echocardiographic profile*, but women also had a significant association with *the second echocardiographic profile*. It can be assumed that *second echocardiographic profile* had a protective effect in women with ICM and prevented deaths among them. This conclusion is supported by other studies [8, 10] on the prevalence of concentric myocardial remodeling in women with cardiac hypertrophy, which prevents a decrease in myocardial contractility. All lethal cases in women were registered with mixed CMP, as other papers [8], which revealed a high mortality rate in women with metabolic (mixed) CMP in comparison with men. In our study, in some women with this CMP type, there was an association with *the first echocardiographic profile* and less often there was an association with *the second echocardiographic profile* compared with women with ICM.

Thus, factor analysis of a large number of echocardiographic variables reduces them to complex factors and allows classification by selection of several echocardiographic profiles. Two echocardiographic profiles with different prognostic values revealed in our study indicate associations of different strength with certain CMP types. The results obtained can be extrapolated to patients with CMP in order to verify the diagnosis and determine the prognosis.

Conclusion

1. Among patients with CMP, there were 2 main echocardiographic profiles: *first profile with reduced MCF* and *the second profile with increased MM*.

2. *The first echocardiographic profile* in men had significant differences (p=0,001) and was closely associated with DCM, myocarditis, alcoholic CMP and was present in the majority of patients with ICM and mixed CMP.

3. Among women, a clear relationship (p=0,05) with *the first echocardiographic profile* was in all individuals with DCM and in some with ICM and mixed CMP.

4. *The second echocardiographic profile* with increased MM in women had a strong relationship with HCM and the majority of individuals with ICM (p=0,04).

5. High mortality was found in men with ICM (66,7%) and among women with mixed CMP (11,1%).

6. Comparative analysis of echocardiographic profiles and outcomes in patients with ICM and mixed CMP suggests a protective effect of *the second echocardiographic profile* in women with ICM.

Relationships and Activities: none.

References

1. Cardiology: national guideline. Ed. Shlyakhto EV. 2-nd edition. M.: GEOTAR-Media, 2019. p. 800. (In Russ.) ISBN: 978-5-9704-4810-6.
2. Braunwald E Cardiomyopathies: An Overview. Circulation Research. 2017;121(7):711-21. doi:10.1161/CIRCRESAHA.117.311812.
3. Seyler C, Meder B, Weis T, et al. TranslatiOnal Registry for CardiomyopatHies (TORCH) — rationale and first results. ESC Heart Fail. 2017;4(3):209-15. doi:10.1002/ehf2.12145.
4. Masarone D, Kaski JP, Pacileo G, et al. Epidemiology and Clinical Aspects of Genetic Cardiomyopathies. Heart Fail Clin. 2018;14(2):119-28. doi:10.1016/j.hfc.2017.12.007.
5. Meyer S, van der Meer P, van Tintelen JP, et al. Sex-related differences in cardiomyopathies. European Journal of Heart Failure. 2014;16(3):238-47. doi:10.1002/ejhf.15.
6. Pelliccia F, Limongelli G, Autore C, et al. Sex-related differences in cardiomyopathies. Int J Cardiol. 2019;286:239-43. doi:10.1016/j.ijcard.2018.10.091.
7. Norris CM, Yip CYY, Nerenberg KA, et al. State of the Science in Women's Cardiovascular Disease: A Canadian Perspective on the Influence of Sex and Gender. J Am Heart Assoc. 2020;9(4):e015634. doi:10.1161/JAHA.119.015634.
8. Murphy E, Amanakis G, Fillmore N, et al. Sex differences in metabolic cardiomyopathy. Cardiovasc Res. 2017;113(4):370-7. doi:10.1093/cvr/cvx008.
9. Filatova OV, Chursina VI. Characteristic features of Echo parameters in men and women with different geometric configurations. Human Physiology. 2016;42(5):63-72. (In Russ.) doi:10.7868/s0131164616050064.
10. Phua AlH, Le T-T, Tara SW, et al. Paradoxical Higher Myocardial Wall Stress and Increased Cardiac Remodeling Despite Lower Mass in Females. J Am Heart Assoc. 2020;9(4):e014781. doi:10.1161/JAHA.119.014781.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4165

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

International register "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV SARS-CoV-2): analysis of 1,000 patients

Arutyunov G. P., Tarlovskaya E. I., Arutyunov A. G., Belenkov Y. N., Konradi A. O., Lopatin Y. M., Tereshchenko S. N., Rebrov A. P., Chesnikova A. I., Fomin I. V., Grigorieva N. U., Boldina M. V., Vaisberg A. R., Blagonravova A. S., Makarova E. V., Shaposhnik I. I., Kuznetsova T. Yu., Malchikova S. V., Protsenko D. N., Evzerikhina A. V., Petrova M. M., Demko I. V., Saphonov D. V., Hayrapetyan H. G., Galyavich A. S., Kim Z. F., Sugraliev A. B., Nedogoda S. V., Tsoma V. V., Sayganov S. A., Gomonova V. V., Gubareva I. V., Sarybaev A. Sh., Koroleva E. V., Vilkova O. E., Fomina I. Y., Pudova I. A., Soloveva D. V., Kiseleva N. V., Zelyaeva N. V., Kouranova I. M., Pogrebetskaya V. A., Muradova F. N., Badina O. Y., Kovalishena O. V., Galova E. A., Plastinina S. S., Lyubavina N. A., Vezikova N. N., Levankova V. I., Ivanova S. Yu., Ermilova A. N., Muradyan R. G., Gostishev R. V., Tikhonova E. P., Kuzmina T. Y., Soloveva I. A., Kraposhina A. Yu., Kolyadich M. I., Kolchinskaya T. P., Genkel V. V., Kuznetsova A. S., Kazakovtseva M. V., Odegova A. A., Chudinovskikh T. I., Baramzina S. V., Rozanova N. A., Kerimova A. Sh., Krivosheina N. A., Chukhlova S. Y., Levchenko A. A., Avoyan H. G., Azarian K. K., Musaelian Sh. N., Avetisian S. A., Levin M. E., Karpov O. V., Sokhova F. M., Burygina L. A., Sheshina T. V., Tiurin A. A., Dolgikh O. Yu., Kazymova E. V., Konstantinov D. Yu., Chumakova O. A., Kondriakova O. V., Shishkov K. Yu., Fil T. S., Prokofeva N. A., Konoval M. P., Simonov A. A., Bitieva A. M., Trostianetckaia N. A., Cholponbaeva M. B., Kerimbekova Zh. B., Duyshobayev M. Y., Akunov A. Ch., Kushubakova N. A., Melnikov E. S., Kim E. S., Sherbakov S. Y., Trofimov D. A., Evdokimov D. S., Ayipova D. A., Duvanov I. A., Abdrahmanova A. K., Aimakhanova G. T., Ospanova Sh. O., Dabylova G. M., Tursunova A. T., Kaskaeva D. S., Tulichev A. A., Ashina E. Yu., Kordukova V. A., Barisheva O. Yu., Egorova K. E., Varlamova D. D., Kuprina T. V., Pahomova E. V., Kurchugina N. Yu., Frolova I. A., Mazalov K. V., Subbotin A. K., Kamardina N. A., Zarechnova N. V., Mamutova E. M., Smirnova L. A., Klimova A. V., Shakhgildyan L. D., Tokmin D. S., Tupitsin D. I., Kriukova T. V., Rakov N. A., Polyakov D. S.

COVID-19 is a severe infection with high mortality. The concept of the disease has been shaped to a greater extent on the basis of large registers from the USA, Spain, Italy, and China. However, there is no information on the disease characteristics in Caucasian patients.

Therefore, we created an international register with the estimated capacity of 5,000 patients — Dynamics Analysis of Comorbidities in SARS-CoV-2 Survivors (AKTIV SARS-CoV-2), which brought together professionals from the Russian Federation, Republic of Armenia, Republic of Kazakhstan, and Kyrgyz Republic. The article presents the first analysis of the register involving 1,003 patients. It was shown that the most significant difference of the Caucasian population was the higher effect of multimorbidity on the mortality risk vs other registers. More pronounced effect on mortality of such diseases as diabetes, obesity, hypertension, chronic kidney disease, and age over 60 years was also revealed.

Key words: AKTIV register, SARS-CoV-2, COVID-19, multimorbidity.

Relationships and Activities: none.

Arutyunov G. P.* ORCID: 0000-0002-6645-2515, Tarlovskaya E. I. ORCID: 0000-0002-9659-7010, Arutyunov A. G. ORCID: 0000-0003-1180-3549, Belenkov Y. N. ORCID: 0000-0002-6180-2619, Konradi A. O. ORCID: 0000-0001-8169-7812, Lopatin Y. M. ORCID: 0000-0003-1943-1137, Teresh-

chenko S. N. ORCID: 0000-0001-9234-6129, Rebrov A. P. ORCID: 0000-0002-3463-7734, Chesnikova A. I. ORCID: 0000-0002-9323-592X, Fomin I. V. ORCID: 0000-0003-0258-5279, Grigorieva N. U. ORCID: 0000-0001-6795-7884, Boldina M. V. ORCID: 0000-0002-1794-0707, Vaisberg A. R. ORCID: 0000-0003-3658-5330, Blagonravova A. S. ORCID: 0000-0002-1467-049X, Makarova E. V. ORCID: 0000-0003-4394-0687, Shaposhnik I. I. ORCID: 0000-0002-7731-7730, Kuznetsova T. Yu. ORCID: 0000-0002-6654-1382, Malchikova S. V. ORCID: 0000-0002-2209-9457, Protsenko D. N. ORCID: 0000-0002-5166-3280, Evzerikhina A. V. ORCID: none, Petrova M. M. ORCID: 0000-0002-8493-0058, Demko I. V. ORCID: 0000-0001-8982-5292, Saphonov D. V. ORCID: none, Hayrapetyan H. G. ORCID: 0000-0002-8764-5623, Galyavich A. S. ORCID: 0000-0002-4510-6197, Kim Z. F. ORCID: 0000-0003-4240-3329, Sugraliev A. B. ORCID: 0000-0002-8255-4159, Nedogoda S. V. ORCID: 0000-0001-5981-1754, Tsoma V. V. ORCID: 0000-0002-0662-1217, Sayganov S. A. ORCID: 0000-0001-7319-2734, Gomonova V. V. ORCID: 0000-0002-9816-9896, Gubareva I. V. ORCID: 0000-0003-1881-024X, Sarybaev A. Sh. ORCID: 0000-0003-2172-9776, Koroleva E. V. ORCID: none, Vilkova O. E. ORCID: 0000-0002-1129-7511, Fomina I. Y. ORCID: none, Pudova I. A. ORCID: none, Soloveva D. V. ORCID: 0000-0001-5695-0433, Kiseleva N. V. ORCID: 0000-0002-0935-8717, Zelyaeva N. V. ORCID: none, Kouranova I. M. ORCID: none, Pogrebetskaya V. A. ORCID: none, Muradova F. N. ORCID: 0000-0002-2723-8081, Badina O. Y. ORCID: 0000-0001-9068-8088, Kovalishena O. V. ORCID: 0000-0002-9595-547X, Galova E. A. ORCID: 0000-0002-9574-2933, Plastinina S. S. ORCID: 0000-0002-0534-5986, Lyubavina N. A. ORCID: 0000-0002-8914-8268, Vezikova N. N. ORCID: 0000-0002-8901-3363, Levankova V. I. ORCID: 0000-0002-0788-4449, Ivanova S. Yu. ORCID: 0000-0002-0720-6621, Ermilova A. N. ORCID: 0000-0002-5704-697X, Muradyan R. G. ORCID: none, Gostishev R. V. ORCID: 0000-0002-2379-5761, Tikhonova E. P. ORCID: 0000-0001-6466-9609, Kuzmina T. Y. ORCID: 0000-0002-0105-6642, Soloveva I. A. ORCID: 0000-0002-1999-9534, Kraposhina A. Yu. ORCID: 0000-0001-6896-877X, Kolyadich M. I. ORCID: 0000-0002-0168-1480, Kolchinskaya T. P. ORCID: none, Genkel V. V. ORCID: 0000-0001-5902-3803, Kuznetsova A. S. ORCID: 0000-0002-1136-7284, Kazakovtseva M. V. ORCID: 0000-0002-0981-3601, Odegova A. A. ORCID: 0000-0001-9691-6969, Chudinovskikh T. I. ORCID: 0000-0002-7515-2215, Baramzina S. V. ORCID: none, Rozanova N. A. ORCID: none, Kerimova A. Sh. ORCID: 0000-0002-2806-5901, Krivosheina N. A. ORCID: none, Chukhlova S. Y. ORCID: none, Levchenko A. A. ORCID: none, Avoyan H. G. ORCID: 0000-0002-3335-7255, Azarian K. K. ORCID: none, Musaelian Sh. N. ORCID: none, Avetisian S. A. ORCID: none, Levin M. E. ORCID: 0000-0002-9197-1691, Karpov O. V. ORCID: 0000-0001-7909-0675, Sokhova F. M. ORCID: 0000-0002-6208-2908, Burygina L. A. ORCID: 0000-0002-2613-8783, Sheshina T. V. ORCID: none, Tiurin A. A. ORCID: none, Dolgikh O. Yu. ORCID: none, Kazymova E. V. ORCID: none, Konstantinov D. Yu. ORCID: 0000-0002-6177-8487, Chumakova O. A. ORCID: none, Kondriakova O. V. ORCID: 0000-0002-4092-6612, Shishkov K. Yu. ORCID: 0000-0003-2942-6200, Fil T. S. ORCID: none, Prokofeva N. A. ORCID: 0000-0002-7679-413X, Konoval M. P. ORCID: 0000-0002-8187-6105, Simonov A. A. ORCID: 0000-0002-7915-3880, Bitieva A. M. ORCID: 0000-0002-5383-2367, Trostianetckaia N. A. ORCID: none, Cholponbaeva M. B. ORCID: none, Kerimbekova Zh. B. ORCID: none, Duyshobayev M. Y. ORCID: none, Akunov A. Ch. ORCID: none, Kushubakova N. A. ORCID: 0000-0001-6874-7125, Melnikov E. S. ORCID: 0000-0002-8521-6542, Kim E. S. ORCID: none, Sherbakov S. Y. ORCID: none, Trofimov D. A. ORCID: 0000-0001-7613-7132, Evdokimov D. S. ORCID: 0000-0002-3107-1691, Ayipova D. A. ORCID: none, Duvanov I. A. ORCID: 0000-0003-0789-429X, Abdrahmanova A. K. ORCID: none, Aimakhanova G. T. ORCID: none, Ospanova Sh. O. ORCID: none, Dabylova G. M. ORCID: none, Tursunova A. T. ORCID: none, Kaskaeva D. S. ORCID: 0000-0002-0794-2530, Tulichev A. A. ORCID: 0000-0002-3157-2218, Ashina E. Yu. ORCID: 0000-0002-7460-2747, Kordukova V. A. ORCID: none, Barisheva O. Yu. ORCID: 0000-0001-6317-1243, Egorova K. E. ORCID: 0000-0003-4233-3906, Varlamova D. D. ORCID: 0000-0002-4015-5109, Kuprina T. V. ORCID: 0000-0002-1176-7309, Pahomova E. V. ORCID: 0000-0002-8335-4626, Kurchugina N. Yu. ORCID: 0000-0003-2988-7402, Frolova I. A. ORCID: none, Mazalov K. V. ORCID: none, Subbotin A. K. ORCID: none, Kamardina N. A. ORCID: none, Zarechnova N. V. ORCID: none, Mamutova E. M. ORCID: none, Smirnova L. A. ORCID: 0000-0002-2083-0373, Klimova A. V. ORCID: 0000-0002-3176-7699, Shakhgildyan L. D. ORCID: 0000-0003-3302-4757, Tokmin D. S. ORCID: none, Tupitsin D. I. ORCID: none, Kriukova T. V. ORCID: none, Rakov N. A. ORCID: none, Polyakov D. S. ORCID: 0000-0001-8421-0168.

*Corresponding author: arut@ossn.ru

Received: 28.10.2020
Revision Received: 05.11.2020
Accepted: 11.11.2020

For citation: Arutyunov G. P., Tarlovskaya E. I., Arutyunov A. G., Belenkov Y. N., Konradi A. O., Lopatin Y. M., Tereshchenko S. N., Rebrov A. P., Chesnikova A. I., Fomin I. V., Grigorieva N. U., Boldina M. V., Vaisberg A. R., Blagonravova A. S., Makarova E. V., Shaposhnik I. I., Kuznetsova T. Yu., Malchikova S. V., Protsenko D. N., Evzerikhina A. V., Petrova M. M., Demko I. V., Saphonov D. V., Hayrapetyan H. G., Galyavich A. S., Kim Z. F., Sugraliev A. B., Nedogoda S. V., Tsoma V. V., Sayganov S. A., Gomonova V. V., Gubareva I. V., Sarybaev A. Sh., Koroleva E. V., Vilkova O. E., Fomina I. Y., Pudova I. A., Soloveva D. V., Kiseleva N. V., Zelyaeva N. V., Kouranova I. M., Pogrebetskaya V. A., Muradova F. N., Badina O. Y., Kovalishena O. V., Galova E. A., Plastinina S. S., Lyubavina N. A., Vezikova N. N., Levankova V. I., Ivanova S. Yu., Ermilova A. N., Muradyan R. G., Gostishev R. V., Tikhonova E. P., Kuzmina T. Y., Soloveva I. A., Kraposhina A. Yu., Kolyadich M. I., Kolchinskaya T. P., Genkel V. V., Kuznetsova A. S., Kazakovtseva M. V., Odegova A. A., Chudinovskikh T. I., Baramzina S. V., Rozanova N. A., Kerimova A. Sh., Krivosheina N. A., Chukhlova S. Y., Levchenko A. A., Avoyan H. G., Azarian K. K., Musaelian Sh. N., Avetisian S. A., Levin M. E., Karpov O. V., Sokhova F. M., Burygina L. A., Sheshina T. V., Tiurin A. A., Dolgikh O. Yu., Kazymova E. V., Konstantinov D. Yu., Chumakova O. A., Kondriakova O. V., Shishkov K. Yu., Fil T. S., Prokofeva N. A., Konoval M. P., Simonov A. A., Bitieva A. M., Trostianetckaia N. A., Cholponbaeva M. B., Kerimbekova Zh. B., Duyshobayev M. Y., Akunov A. Ch., Kushubakova N. A., Melnikov E. S., Kim E. S., Sherbakov S. Y., Trofimov D. A., Evdokimov D. S., Ayipova D. A., Duvanov I. A., Abdrahmanova A. K., Aimakhanova G. T., Ospanova Sh. O., Dabylova G. M., Tursunova A. T., Kaskaeva D. S., Tulichev A. A., Ashina E. Yu., Kordukova V. A., Barisheva O. Yu., Egorova K. E., Varlamova D. D., Kuprina T. V., Pahomova E. V., Kurchugina N. Yu., Frolova I. A., Mazalov K. V., Subbotin A. K., Kamardina N. A., Zarechnova N. V., Mamutova E. M., Smirnova L. A., Klimova A. V., Shakhgildyan L. D., Tokmin D. S., Tupitsin D. I., Kriukova T. V., Rakov N. A., Polyakov D. S. International register "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV SARS-CoV-2): analysis of 1,000 patients. *Russian Journal of Cardiology*. 2020;25(11):4165. (In Russ.) doi:10.15829/1560-4071-2020-4165

Coronavirus disease 2019 (COVID-19) is a severe infectious disease with a high death risk. At the time of preparing article, according to the World Health Organization (October 25, 2020), the disease has spread to 235 countries and there were 42,512,186 documented cases of infection and 1,147,301 related deaths [1]. The concept of the disease is based on large registries made in the USA, Spain, Italy, and China. However, to date, there is no data on the characteristics of the disease course in Eurasian patients. In this regard, an international AKTIV SARS-CoV-2 register was created, in which specialists from the Russian Federation, the Republic of Armenia, the Republic of Kazakhstan and the Kyrgyz Republic united. The design and prerequisites for register creation are described in article [2]. The main aim of the register with estimated capacity of 5 thousand patients, in addition to assessing the influence of individual risk factors (RFs) (obesity, smoking, hypertension (HTN), age over 60 years) and chronic non-infectious diseases on the risk of severe disease course and death, was the analysis of the infection influence on the course of chronic non-communicable diseases and cancer, as well as on the incidence of new cases of heart failure (HF), diabetes, acute coronary syndrome and cerebrovascular disease within 2 years.

Results

The first analysis of the register included data from 1,003 patients (Table 1): women — 55,2%, mean age — 57,9 [49, 67] years. Patients were hospitalized in 91,6% of cases. The distribution of patients according to the lung damage degree based on computed tomography data is presented as follows: grade 1 — 35,87%, grade 2 — 40,95%, grade 3 — 14,45% and grade 4 — 2,77%. Among hospitalized patients, the mortality rate was 3,8%, in the general cohort — 3,7%. Invasive mechanical ventilation was required in 5,9% of patients, while cytokine storm was observed in 12% of cases. Pulmonary embolism was diagnosed in 0,7% of patients, deep vein thrombosis — in 0,1%.

Impact of prior diseases and RFs. The most common RF was hypertension (Table 1), which occurred in 59,4% and 48,8% of in- and outpatients, respec-

Table 1

Characteristics of in- and outpatients included in the AKTIV register

Parameter	Inpatients	Outpatients	Total
n	919	84	1003
Age, years	58,2 [49, 67,2]	54,1 [44,5, 64,7]	57,9 [49, 67]
Women, %	55,6	51,2	55,2
Deceased patients, %	3,8	2,7	3,7
HTN, %	59,4	48,8	58,5
Obesity, %	42,2	34,2	41,2
Smoking, %	3,9	21,3	5,5
Grade 1, %	35,5	42,0	35,9
Grade 2, %	42,2	20,0	40,9
Grade 3, %	14,9	6,0	14,4
Grade 4, %	2,8	2,0	2,8
CAD, %	21,5	21,5	21,5
Prior MI, %	7,7	2,5	7,3
Type 2 diabetes, %	18,3	12,7	17,9
Class I-II HF, %	12,0	6,3	11,5
Class III-IV HF, %	2,3	0,0	2,1
CKD, %	7,0	19,0	8,0
COPD, %	6,1	1,3	5,7
Cerebrovascular disease, %	3,6	3,8	3,6
Active cancer, %	1,8	5,1	2,1
Type 1 diabetes, %	0,3	1,3	0,4

Abbreviations: HTN — hypertension, CAD — coronary artery disease, MI — myocardial infarction, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, HF — heart failure.

Table 2

Characteristics of surviving and deceased patients included in the AKTIV register

Parameter	Surviving patients N=975	Deceased patients N=28	p
Age, years	58 [48,75, 66,0]	72 [63,5, 82,0]	0,001
Lymphocytes, %	23,4 [16,0, 31,85]	14,0 [8,45, 19,05]	0,001
CRP, mg/L	29,15 [12,0, 82,70]	98,98 [42,7, 192,5]	0,001

Abbreviation: CRP — C-reactive protein.

tively. The second most common RF was obesity, which was observed in 42,2% and 34,2% of in- and outpatients, respectively. Smoking was more common among outpatients (24,1%) than among hospitalized patients (3,9%). Among chronic noncommunicable diseases in patients with COVID-19, coronary artery disease (CAD) was most common, which was observed with the same frequency in in- and outpatients (21,5%). Prior myocardial infarction was noted in 7,7% of hospitalized patients and only 2,5% of outpatients. Type 2 diabetes occurred in 18,3% of inpatients and 12,7% of outpatients. Class I-II HF was observed in 12,0% and 6,3% of in- and outpatients, respectively. Class III-IV HF occurred only in hospitalized patients (2,3%). Chronic kidney disease (CKD) was diagnosed in 8% of patients — in 7,0% and 19,0 of in- and outpatients, respectively. Chronic obstructive pulmonary disease (COPD) was observed in 6,1% and 1,3% of in- and outpatients, respectively. Prior cerebrovascular disease was in 3,6% and 3,8% of in- and outpatients, respectively. Active cancer was in 1,8% and 5,1% of in- and outpatients, respectively. Type 1 diabetes was observed in 0,3% and 1,3% of in- and outpatients, respectively.

Comparison of survived and deceased patients is shown in Table 2. It was found that the deceased patients were older (72 [63,5, 82,0] vs 58 [48,75, 66,0] years, p=0,001) (Table 2). Age 60 years and older (60+) increased the mortality risk more than 7 times (odds ratio (OR), 7,523 [95% confidence

Table 3

Characteristics of surviving and deceased patients included in the AKTIV register

Parameter	Surviving patients N=975	Deceased patients N=28	p	OR (95% CI)
Men, %	44,6	46,4	NA	
Age 60+, %	44,3	85,7	0,001	7,523 (2,584-21,898)
Grade 3-4, %	15,9	56,5	0,0001	6,880 (2,940-16,099)
HTN, %	57,3	82,1	0,016	3,428 (1,289-9,117)
Obesity, %	38,8	63,6	0,001	2,736 (1,137-6,680)
Obesity, inpatients, %	39,3	70,0	0,01	3,605 (1,362-9,545)
AF, inpatients, %	6,5	19,2	0,04	3,394 (1,220-9,443)
CAD, %	21,6	39,3	0,049	2,345 (1,076-5,109)
Type 2 diabetes, %	15,7	35,7	0,01	2,982 (1,342-6,627)
CKD, %	7,3	28,6	0,0001	5,079 (2,136-12,079)
CKD, patients >60 years of age, %	13,0	33,3	0,02	3,333 (1,344-8,269)
Comorbidities (⩾2), %	46,8	89,3	0,001	9,461 (2,831-31,613)
Comorbidities (⩾2), patients >60 years of age, %	70,2	91,7	0,04	4,673 (1,077-20,263)
Comorbidities (⩾2) and obesity, %	19,0	45,5	0,01	3,544 (1,490-8,427)
Diabetes + obesity + CVD*, %	8,7	41,7	0,001	7,473 (2,076-26,901)
Diabetes + obesity + CVD*, patients >60 years of age, %	13,6	45,5	0,04	5,278 (1,329-20,966)

Note: * — HTN, CAD, MI, cerebrovascular disease, DVT, HF.

Abbreviations: HTN — hypertension, CI — confidence interval, CAD — coronary artery disease, MI — myocardial infarction, OR — odds ratio, CVD — cardiovascular diseases, DVT — deep vein thrombosis, AF — atrial fibrillation, CKD — chronic kidney disease, HF — heart failure.

Table 4

Hospital mortality (%) of patients depending on drug intake

Drug	Intake+	Intake-	p	OR (95% CI)
ACE inhibitors/ARBs, patients with HTN	2,20	5,50	0,166	0,382 (0,118-1,241)
Statins, patients with CAD	3,50	10,00	0,269	0,397 (0,067-1,603)
Anticoagulants, patients >60 years of age	3,00	10,60	0,049	0,259 (0,078-0,855)

Abbreviations: HTN — hypertension, ARBs — angiotensin receptor blockers, ACE — angiotensin-converting enzyme, CI — confidence interval, CAD — coronary artery disease, OR — odds ratio.

interval (CI), 2,584-21,898] p=0,001) (Table 3). The degree of lung damage significantly influenced the prognosis of the disease. Grade 3-4 increased the risk of death in comparison with grade 1-2 by almost 7 times (OR, 6,880 [95% CI, 2,940-16,099] p=0,0001).

Among comorbidities, CKD had the greatest negative impact on prognosis. The presence of CKD increased the risk of death, regardless of the patient age, by 5 times (OR, 5,079 [95% CI, 2,136-12,079] p=0,0001). The presence of obesity (body mass index ⩾30 kg/m^2) was the RF for death in hospitalized patients (OR, 3,605 [95% CI, 1,362-9,545] p=0,01). Atrial fibrillation (AF), type 2 diabetes, and CAD increased the risk of death in hospitalized patients by 3,4, 3,0 and 2,3 times, respectively (OR, 3,394 [95% CI, 1,220-9,443] p=0,04; OR, 2,982 [95% CI, 1,342-6,627] p=0,01; OR, 2,345 [95% CI, 1,076-5,109] p=0,049).

Among the deceased patients, multimorbidity was significantly more common, which negatively affected the prognosis. Among the deceased patients, 2 or more chronic diseases were observed in 89,3% vs 46,8% among the survivors (p=0,001). The presence of 2 or more comorbidities in comparison with those with no more than 1 disease increased the risk of death by more than 9 times (OR, 9,461 [95% CI, 2,831-31,613] p=0,001). The combination of 2 or more comorbidities with obesity (OR, 3,544 [95% CI, 1,490-8,427] p=0,01) and the combination of diabetes with obesity and cardiovascular disease (OR, 7,473 [95% CI, 2,076-26,901] p=0,001).

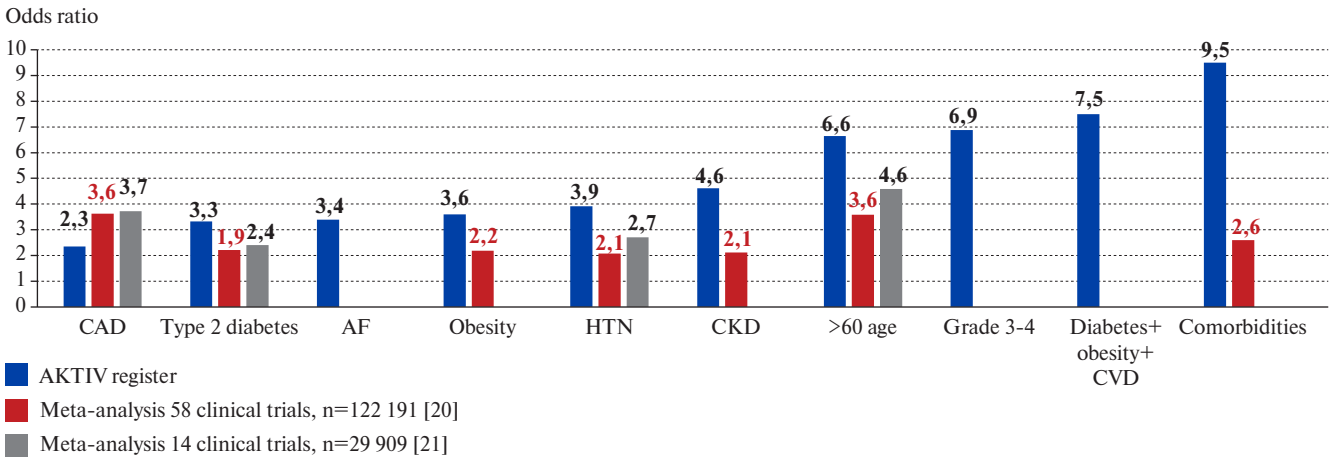


Figure 1. Risk factors for death in hospitalized patients with COVID-19 (ID ClinicalTrials.gov: NCT04492384, https://ACTIV.euat.ru, [20, 21]). **Abbreviations:** HTN — hypertension, CAD — coronary artery disease, CVD — cardiovascular diseases, AF — atrial fibrillation, CKD — chronic kidney disease.

Comparison of a large array of routine laboratory parameters in the population of deceased and surviving patients showed that significant differences were achieved in the levels of C-reactive protein (CRP) (98,98 [42,7, 192,5] vs 29,15 [12,0, 82, 70] mg/l, p=0,001) and the level of lymphocytes. In the population of deceased patients, the level of lymphocytes was significantly lower (14,0 [8,45, 19,05]% vs 23,4 [16,0, 31,85]%, p=0,001).

Analysis of the effect of individual drugs on the risk of death showed that:

– In patients over 60 years of age who received anticoagulant therapy, the death risk was lower than in patients who did not receive it (3,0% vs 10,6%, p=0,049, OR, 0,259 [0,078-0,855]) (Table 4).

– Statin therapy (not adjusted for dose and achievement of target low-density lipoprotein level) did not lead to a decrease in mortality, but significantly reduced the level of CRP by ⩾50% at 7-12 days in 82,9%, while in patients not receiving statins, such CRP changes was observed only in 48,1% (OR, 5,205 [1,634-16,582] p=0,009).

Discussion

Comparison of AKTIV register data with large registers performed in Great Britain, China, Italy, Spain is of great interest. The analysis showed that the patients in the AKTIV register reflecting the Eurasian cohort of patients were 5-15 years younger (mean age, 58 years vs 73 (UK [3]), 64 (China [4]), 63 (USA [5]), 69 (Spain [6]), 63 (Italy [7]). The proportion of women was significantly higher.

Thus, the proportion of women in the AKTIV register was 55%, which exceeds that in UK (40%) [3], China (51%) [4], the USA (40%) [5], Spain (43%) [6] and Italy (18%) [7].

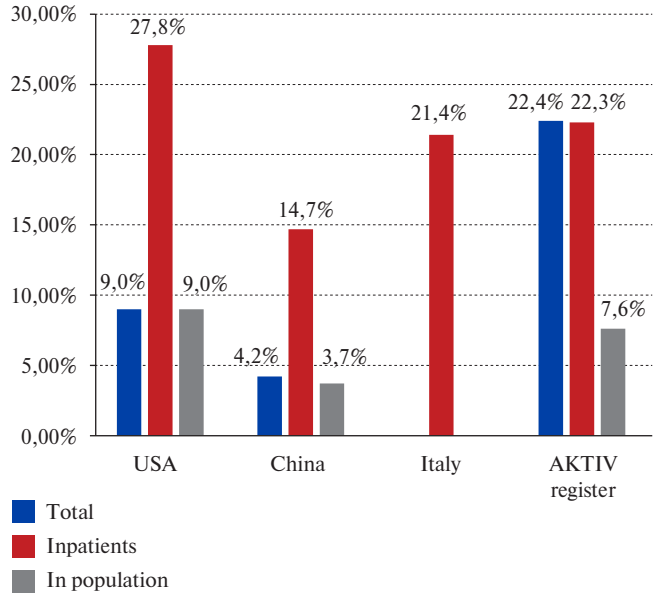


Figure 2. Incidence of CHD in COVID-19 in different regions, depending on the severity of the course [Kang Y, Chen T, Mui D, et al. Cardiovascular manifestations and treatment considerations in COVID-19. Heart. 2020;106(15):1132-41. doi:10.1136/heartjnl-2020-31, [17]).

The mortality rate in the AKTIV register was 3,7% and was lower than in the Italian register (7,2%) [8] and approximately corresponded to the Chinese ones (2,3% and 3,2%) [9, 10] and meta-analysis of Chinese and US studies (4,8%) [11] (Figure 1).

According to various studies, it was found that patients with concomitant diseases such as HTN, CAD, diabetes, HF, CKD, cancer, COPD, asthma, obesity are prone to a more severe course of COVID-19 and have a high death risk [12-16].

According to the AKTIV register, HTN was more common in the Eurasian population (58,5% vs 30,5% (China) [4], 56,6% (USA) [5], 50,9% (Spain) [6] and 49 % (Italy)) [7]. Almost half of the patients in the AKTIV register were obese (41,2%), which coincided with US data (41,7%) [5] and exceeded the obesity rate in the Spanish register (21,2%) [6] almost 2 times.

The CAD rate in patients of the AKTIV register (21,5%) was more than in the population (7,6%) (Figure 2) [17] and was comparable with data from Italian (21%) [7] and Spanish (19,9%) registers [6]. The CAD rate in registers from the USA (11,1%) [5] and China (10,6%) [4] was significantly lower in comparison with AKTIV register.

Diabetes occurred among the patients of the AKTIV register (17,9%) as often as in the register from Italy (17%) [7] and Spain (19,4%) [6] and less frequently than in UK (29, 9%) [3] and US (33,8%) registers [5]. In the Chinese register, diabetes was somewhat less common than in the AKTIV register (14,4%) [4].

The HF prevalence in the AKTIV register (13,6%) was higher than in the US (6,9%) [5] and Spainish (9,2%) registers [6]. In the AKTIV register, class I-II HF was observed in 11,5%, while class III-IV HF — in 2,1%.

CKD in patients of the AKTIV register (8%) was observed approximately as often as in the Spanish register (6,1%) [6] and significantly less frequently than in the UK register (16%) [3]. In registers of USA (5%) [5], China (3,4%) [4] and Italy (3%) [7], CKD was observed somewhat less frequently than in the AKTIV register.

Among patients in the AKTIV register, the COPD rate was small and amounted to 5,7%, which was comparable with data from the USA (5,4%) [5], Spain (5,3%) [6] and Italy (4%) [7]. The prevalence of COPD in UK patients (18,3%) [3] was higher, while in the Chinese ones (2,9%) [4] — lower than in the AKTIV register.

The smoking prevalence among patients of the AKTIV register was also low (5,5%), which is comparable to data from the UK (6,4%) [3] and Spain (5,3%) [6], but significantly lower, than in the US register (15,6%) [5].

The cancer rate in patients of the AKTIV register was low (2,1%) and corresponded to the Russian population (2,56%) [18]. A similar low incidence of cancer was in the Chinese register (2,2%) [4]. In other registries, the cancer prevalence was slightly higher: USA — 6% [5], Italy — 8% [7], Spain — 10,7% [6], Great Britain — 10,8% [3].

In deceased patients of the AKTIV register, hypertension was registered in 82,1%, which was more often than among deceased patients in the Italian register (73%) [19]. Among the deceased patients of the AKTIV register, CAD (39,3% vs 30%), CKD (28,6% vs 20%), type 2 diabetes (35,7% vs 33%) were more common than in the Italian register [19]. Comorbidities such as AF (19,2% vs 22%) and prior cerebrovascular disease (10,7% vs 11,2%) were observed in the AKTIV and Italian registers with approximately the same frequency [19]. In the AKTIV register, among the deceased patients, there were fewer patients with COPD (3,6% vs 13,7%) and cancer (10,7% vs 19,5%) than in the Italian register [19].

Comparison of RFs for death in the AKTIV register with the meta-analysis by the Noor FM, et al. [20] with58 studies involving 122,191 patients and the meta-analysis by Parohan M, et al. [21], with 14 studies involving 14,909 patients (Figure 1) found number of differences. Thus, in the AKTIV register, type 2 diabetes, obesity, HTN, CKD, age over 60 and multimorbidity had the most significant negative influence, higher than in above-mentioned meta-analyzes (Figure 1). Multimorbidity had the most significant negative impact on the prognosis in the Eurasian population of COVID-19 patients: 2 or more chronic diseases increased the risk of death by 9,5 times, while in the meta-analysis by the Noor FM, et al. [20], only by 2,6 times.

A number of RFs (male sex, COPD, cancer, asthma, cerebrovascular diseases, chronic liver diseases), which was associated with death in other studies [20, 21], with a pronounced trend, did not achieve significance in the AKTIV register. This can be explained by different sample sizes.

In the AKTIV register, deceased patients had a higher CRP level and a lower lymphocyte count, which is consistent with other studies [22-25].

According to the AKTIV register, the mortality rate was lower in patients over 60 years old who received anticoagulant therapy than in patients who did not receive it. The positive effect of anticoagulant therapy on the severity of COVID-19 course and the death risk was also shown in the study by Paranjpe I, et al. [26]. In this study, long-term anticoagulant therapy was associated with in-hospital mortality reduction by a 14% (hazard ratio, 0,86 [95% CI, 0,82-0,89] p<0,001). According to the study by Lemos AC, et al. [27], therapeutic-dose anticoagulation has advantages over prophylactic doses. The rationale for the widespread use of anticoagulant therapy for COVID-19 patients is the high risk of thrombotic events [28, 29].

Currently, anticoagulant therapy is recommended for COVID-19 pneumonia of any severity [30, 31].

According to the AKTIV register, the statin therapy in CAD patients contributed to a decrease in CRP level in comparison with patients not receiving these drugs. A similar beneficial effect of statins

on inflammatory markers was demonstrated in the study by Zhang XJ, et al. [32]. It is now known that, in addition to the anti-inflammatory effect, statins can inhibit the penetration of SARS-CoV-2 into host cells. Statins, activating autophagy, can regulate viral replication or degradation, providing protective effects in COVID-19 [32, 33]. According to the meta-analysis by the Kow CS and Hasan SS with 8,990 patients [34], the all-cause mortality and/or disease severity in patients with COVID-19 was reduced by 30% in patients taking statins.

Conclusion

The Eurasian population of COVID-19 patients differs from the populations in the European, US and Chinese registers, primarily in terms of the age and sex. The population of the AKTIV register is characterized by a younger age and female predominance. HTN and HF were observed more often than in other registers.

The most significant difference of the Eurasian population was the higher effect of multimorbidity on the mortality risk vs other registers. More pronounced effect on mortality of such diseases as diabetes, obesity, hypertension, chronic kidney disease, and age over 60 years was also revealed.

The mortality rate in the AKTIV register was 3,7%, which is lower than in the Italian register and approximately corresponds to the mortality rate in the Chinese and US registers.

Relationship and Activities: none.

References

1. World Health Organization (WHO). https://www.who.int.
2. Arutyunov GP, Tarnovskaya EI, Arutyunov AG, et al. International registry "Analysis of the dynamics of Comorbid diseases in patients who have been infected with SARS-CoV-2 (active SARS-CoV-2)": methodology and design. Kardiologiia. 2020;60(11):35-7. (In Russ.)
3. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985. doi:10.1136/bmj.m1985.
4. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-10. doi:10.1001/jamacardio.2020.0950.
5. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area [published correction appears in doi:10.1001/jama.2020.7681]. JAMA. 2020;323(20):2052-9. doi:10.1001/jama.2020.6775.
6. Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry [Características clínicas de los pacientes hospitalizados con COVID-19 en España: resultados del Registro SEMI-COVID-19] [published online ahead of print, 2020 Sep 9]. Rev Clin Esp (Barc). 2020; doi:10.1016/j.rceng.2020.07.003.
7. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-81. doi:10.1001/jama.2020.5394.
8. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020;323(18):1775-6. doi:10.1001/jama.2020.4683.
9. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42. doi:10.1001/jama.2020.2648.
10. Hu Y, Sun J, Dai Z, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Virol. 2020;127:104371. doi:10.1016/j.jcv.2020.104371.
11. Sun P, Qie S, Liu Z, et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. J Med Virol. 2020;92(6):612-7. doi:10.1002/jmv.25735.
12. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality of COVID-19 patients in Wuhan, China. Clinical Microbiology and Infection. 2020;26:767-72.
13. Yu C, Lei Q, Li W, et al. Clinical characteristics, associated factors, and predicting COVID-19 mortality risk: A retrospective study in wuhan, China. American Journal of Preventive Medicine. 2020;59:168-75.
14. Cen Y, Chen X, Shen Y, et al. Risk factors for disease progression in mild to moderate COVID-19 patients–a multi-center observational study. Clinical Microbiology and Infection. 2020;26:1242-7. doi:10.1016/j.cmi.2020.05.041.
15. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. The Lancet. 2020;395:1054-62.
16. Rocio LG, Alberto UR, Paloma T, et al. Interleukin-6-based mortality risk model for hospitalised COVID-19 patients. Journal of Allergy and Clinical Immunology. 2020;6749(20):31027-37.
17. Imaeva AE, Tuaeva EM, Shalnova SA, Kiseleva NV. Coronary heart disease and risk factors in elderly population. Cardiovascular Therapy and Prevention. 2016;15(2):93-9. (In Russ.) doi:10.15829/1728-8800-2016-2-93-99.
18. Malignant neoplasms in Russia in 2018 (morbidity and mortality). Ed. A.D. Kaprin, V.V. Starinsky, G.V. Petrova. M.: p. A. Herzen Moscow state medical research Institute, branch of the Federal state budgetary institution "NMIC of radiology" of the Ministry of health of Russia. 2019. 250 p. (In Russ.) ISBN: 978-5-85502-251-3.
19. Characteristics of COVID-19 patients dying in Italy Report based on available data on March 20th, 2020 https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf.
20. Noor FM, Islam MM. Prevalence and Associated Risk Factors of Mortality Among COVID-19 Patients: A Meta-Analysis. J Community Health. 2020. doi:10.1007/s10900-020-00920-x.
21. Parohan M, Yaghoubi S, Seraji A, et al. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. Aging Male. 2020. doi:10.1080/13685538.2020.1774748.
22. Ghahramani S, Tabrizi R, Lankarani KB, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. Eur J Med Res. 2020;25(1):30. doi:10.1186/s40001-020-00432-3.
23. Bonetti G, Manelli F, Patroni A, et al. Laboratory predictors of death from coronavirus disease 2019 (COVID-19) in the area of Valcamonica, Italy. Clin Chem Lab Med. 2020;58(7):1100-5. doi:10.1515/cclm-2020-0459.
24. Elshazli RM, Toraih EA, Elgaml A, et al. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: A meta-analysis of 6320 patients. PLoS One. 2020;15(8):e0238160. doi:10.1371/journal.pone.0238160.
25. Soraya GV, Ulhaq ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis. Med Clin (Barc). 2020;155(4):143-51. doi:10.1016/j.medcli.2020.05.017.
26. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19. MPH PII: S0735-1097(20)35218-9. doi:10.1016/j.jacc.2020.05.001.
27. Lemos ACB, do Espírito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thromb Res. 2020;196:359-66. doi:10.1016/j.thromres.2020.09.026.
28. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149. doi:10.1177/1076029620938149.
29. Bilaloglu S, Aphinyanaphongs Y, Jones S, et al. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA. 2020. doi:10.1001/jama.2020.13372.
30. Shlyakhto YV, Arutyunov GP, Belenkov YuN, et al. Use of Statins, Anticoagulants, Antiaggregants and Antiarrhythmic Drugs in Patients With COVID-19. The Agreed Experts' Position. Kardiologiia. 2020;60(6):4-14. (In Russ.) doi:10.18087/cardio.2020.6.n1180.
31. Prevention, diagnosis and treatment of new coronavirus infection (2019-nCoV). Temporary guidelines of the Ministry of health of Russia, Version VIII. (In Russ.) https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/051/777/original/030902020_COVID-19_v8.pdf.
32. Zhang XJ, Qin JJ, Cheng X, et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19 [published online ahead of print, 2020 Jun 24]. Cell Metab. 2020;S1550-4131(20)30316-8. doi:10.1016/j.cmet.2020.06.015.
33. Reiner Ž, Hatamipour M, Banach M, et al. Statins and the COVID-19 main protease: *in silico* evidence on direct interaction. Arch. Med. Sci. 2020;16:490-6.
34. Kow CS, Hasan SS. Meta-analysis of Effectiveness of Statins in Patients with Severe COVID-19. The American Journal of Cardiology. 2020;134:153-5. doi:10.1016/j.amjcard.2020.08.004.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3915

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Combination of chronic myocarditis and progressive coronary artery disease: differential diagnosis and stepwise treatment

Lutokhina Yu. A.[1], Blagova O. V.[1], Sedov V. P.[1], Zaydenov V. A.[2], Nedostup A. V.[1]

Aim. To assess the differential diagnosis in a patient with a combination of coronary artery disease and myocarditis and the results of stepwise treatment (including immunosuppressive therapy (IST), and coronary stenting).

Material and methods. A 56-year-old female patient with hypertension, obesity (body mass index, 31,6 kg/m^2), diabetes and psoriasis developed shortness of breath after a respiratory viral infection. Primary echocardiography revealed left heart dilatation, ejection fraction (EF) of 21%. Coronary angiography revealed anterior descending artery stenosis of 75%, circumflex artery — 80%, right coronary artery (RCA) — 70%. RCA stenting was performed and cardiovascular and diuretic therapy was started. However, shortness of breath and low exercise tolerance persisted.

Results. In the blood test, anti-endothelial cell antibodies were 1:320, anti-cardiomyocyte and anti-smooth muscle antibodies — 1:80, anti-cardiac conduction system fibers — 1:320 (N≤1:40). During myocardial perfusion scintigraphy with computed tomography, an uneven distribution of the indicator was noted. Signs of myocardial scarring and indications for further revascularization were not revealed. Cardiac magnetic resonance imaging confirmed a decrease in left ventricular (LV) contractility (LVEF 37%) and moderate dilatation. Biopsy was not performed due to dual antiplatelet therapy. The condition is regarded as infectious-immune myocarditis. IST was started with azathioprine 150 mg/day. We noted dyspnea relief and a stable increase in LVEF to 50-52%. The clinical course was complicated by sick sinus syndrome with pauses up to 6 seconds and presyncope; a pacemaker was implanted. After 5 years from the onset of IST, dyspnea episodes reappeared without exacerbation of myocarditis. As their cause, ischemia was diagnosed due to the progression of coronary atherosclerosis. Symptoms regressed after repeated coronary stenting.

Conclusion. The presence of moderate coronary atherosclerosis without signs of ischemia and myocardial infarction should not be considered as the only cause of severe systolic myocardial dysfunction. Diagnosis and treatment of myocarditis in combination with coronary artery disease is carried out according to the standard principles and can improve LV systolic function and control the heart failure symptoms.

Key words: coronary artery disease, myocarditis, anticardiac antibodies, heart failure, immunosuppressive therapy.

Relationships and Activities: none.

[1]I. M. Sechenov First Moscow State Medical University, Moscow; [2]City Clinical Hospital № 52, Moscow, Russia.

Lutokhina Yu. A.* ORCID: 0000-0002-7154-6794, Blagova O. V. ORCID: 0000-0002-5253-793X, Sedov V. P. ORCID: 0000-0003-2326-9347, Zaydenov V. A. ORCID: 0000-0002-0102-9740, Nedostup A. V. ORCID: 0000-0002-5426-3151.

*Corresponding author: lebedeva12@gmail.com

Received: 18.05.2020
Revision Received: 06.06.2020
Accepted: 29.06.2020

For citation: Lutokhina Yu. A., Blagova O. V., Sedov V. P., Zaydenov V. A., Nedostup A. V. Combination of chronic myocarditis and progressive coronary artery disease: differential diagnosis and stepwise treatment. *Russian Journal of Cardiology*. 2020;25(11):3915. (In Russ.) doi:10.15829/1560-4071-2020-3915

In modern cardiology, in recent years, special attention has been paid not only to a comprehensive study of certain diseases, but also to a combination of several disorders. At the same time, the combination of various cardiovascular diseases (CVD) often significantly changes the approach to the diagnosis and treatment of a patient, and also has an important effect on the prognosis. Angina is the most common type of coronary artery disease (CAD). Its prevalence increases in the population with age: from 5-7% among women 45-64 years old to 10-12% among women aged 65-85 years, and from 4-7% among men 45-64 years old to 12-14% among men aged 65-85 [1]. Myocarditis is the most common myocardial disease. According to some estimates, it accounts for up to 10% of patients with CVD in the Russian Federation [2]. Thus, the combination of CAD and myocarditis is quite likely to occur, and it is extremely important to take into account both of these diseases when managing such patients. This will be discussed in the article.

Case report

Female patient, 56 years old, first entered the hospital in December 2013 with complaints of shortness of breath with minimal exercise, pain in the left shoulder with moderate exercise, stopping at rest within 15 minutes, episodes of increased blood pressure (BP) to 170/110 mm Hg, pronounced weakness, and anxiety.

Family history of CVD was negative.

Past history. From childhood to 50 years, the patient suffered from frequent tonsillitis and bronchitis. Since 1986, there has been a wave-like course of psoriasis. In 2007 (at the age of 50), type 2 diabetes (T2D) was diagnosed for the first time, and therefore receives oral hypoglycemic therapy, however, glycated hemoglobin was 9% (with a target range of HbA_{1c} value <7,5%). An architect by profession, currently retired. The patient did not smoke and not abuse alcohol.

Medical history. From about 42 years of age episodes of BP rises to a maximum of 160-170/110 mm Hg was noted. She occasionally took antihypertensive drugs (prestarium, concor) with incomplete effect. Since autumn 2012, for the first time, short episodes of shortness of breath with moderate exercise and left shoulder pain appeared. The patient was not examined. In March 2013, she suffered an acute upper respiratory tract infection with low-grade fever that lasted for 3 weeks. After a course of antibiotic therapy, the temperature returned to normal, but shortness of breath appeared, which then independently regressed within a few weeks. Echocardiography was performed, in which a slight left ventricular (LV) dilation was found; the ejection fraction (EF) was 51%.

There was a worsening since September 22, 2013, when after drinking a large amount of liquid, severe shortness of breath appeared. Chest computed tomography revealed a small amount of fluid in the right pleural cavity, calcification of aorta and coronary arteries. The patient was hospitalized in respiratory medicine unit, the cardiogenic nature of shortness of breath was suspected. Repeated echocardiography revealed EF of 21%, hypoakinetic areas in the anterior septum, left heart dilatation. Coronary angiography revealed 75% stenosis of the anterior descending artery (ADA) throughout, 80% stenosis of left circumflex artery (LCA) orifice, 70% stenosis of the right coronary artery (RCA) in the proximal third. On October 14, 2013, RCA stenting was performed. The patients received furosemide, digoxin, rosuvastatin, ticagrelor, aspirin, perindopril. At discharge, the EF was 33%. After hospitalization, shortness of breath persisted, exercise tolerance remained low, and episodes of left shoulder pain remained unrelated to exercise. The patient turned to cardiology unit for further examination and treatment.

Physical examination. Height was 164 cm, weight — 85 kg, body mass index — 31,6 kg/m^2. Hypersthenic type. Psoriatic plaques located on the elbows and dorsal feet surfaces. There was swollen legs and feet. Respiratory rate of 28 bpm. According to auscultation, breathing was harsh and withoit crackles. Muffled heart tones, no cardiac murmur. Heart rate (HR) of 80 bpm. BP was 150/90 mm Hg. The liver was 1 cm below the costal margin. The spleen was not enlarged.

Parameters of complete blood count, biochemical blood tests, coagulation testing, and urine tests were without findings. Anticardiac antibodies (ACA) were as follows: antinuclear antibody (ANA) — no, antiendothelial cell antibodies — 1:320, anticardiomyocyte antibodies 1:80, anti-smooth muscle antibodies — 1:80, and antibodies to cardiac conduction system fibers — 1:320 (normal range, below 1:40). The genome of cardiotropic viruses (herpes viruses, parvovirus B19) was not detected.

Electrocardiography (ECG) (Figure 1) revealed first-degree atrioventricular block (PQ, 240 ms), signs of left atrial and LV hypertrophy, poor progression of R wave in V_1-V_3. Attention was paid to QS complexes in III and aVF (no negative alteration compared with previous ECGs, including from 1987). Twenty-four hour Holter monitoring revealed a constant first-degree atrioventricular block with a maximum PQ lengthening up to 260 ms, ST segment depression up to 1 mm without diagnostically significant dynamics.

Echocardiography showed a slight left heart dilation (LV end diastolic dimension (EDD), 5,9 cm; LV

end diastolic volume (EDV), 152 ml; left atrial end diastolic volume, 80 ml) and LVEF of 39%. No local contractility disorders were found. According to single-photon emission computed tomography, the indicator inclusion into the LV myocardium with a diffusely uneven distribution was visualized, which is characteristic of non-coronary myocardial damage. Signs of cicatricial myocardial damage were not identified. According to cardiac multislice computed tomography (MSCT), the stent was patient, while in the area of the LV lateral wall, increased trabecularity was determined without myocardial noncompaction. The myocardial enhancement in the arterial phase was uneven, especially in the lateral wall area, while in the delayed phase, there were no areas of contrast accumulation.

To rule out myocardial noncompaction and scarring, contrast-enhanced cardiac magnetic resonance imaging (MRI) was performed: LV moderate dilatation (EDD, 5,8 cm; EDV, 111 ml/m^2 up to 92 ml/m^2) and decreased contractility (EF, 37%) without clear areas of delayed contrasting. No evidence in favor of non-compact myocardium were obtained. There was no myocardial hypertrophy (interventricular septal thickness, 11-12 mm; posterior wall thickness, 10 mm). Myocardial mass was at the upper normal limit.

The previous coronary angiograms were studied by professor V.A. Sulimov: the stenoses were significantly overestimated before; stenosis degree of ADA and LCA did not exceed 50-60% and further revascularization was not required. Moreover, RCA stenosis also did not exceed 50-60%, and therefore the indications for its stenting were dubious, and the procedure did not lead to an improvement in the patient's condition.

Thus, CAD in the presence of significant coronary atherosclerosis was highly probable. Left shoulder pain arising during exercise and stopping at rest was regarded as angina. It was not possible to carry out stress tests due to severe heart failure (HF). According to scintigraphy, echocardiography, MSCT and MRI, there was no evidence in favor of myocardial infarction (MI).

Taking into account the relatively old age for primary cardiomyopathy decompensation, a clear connection between the increase in HF symptoms and the previous upper respiratory tract infection, low immune status (psoriasis), the rapid development of diffuse myocardial dysfunction with a EF decrease to 21%, high titers of antiendothelial antibodies and antibodies to cardiac conduction system, uneven myocardial contrasting in the arterial phase according to cardiac MSCT, diffuse uneven perfusion disorders according to myocardial scintigraphy, the condition was regarded as infectious-immune myocarditis. Due to the need to continue dual antiplatelet therapy until October 2014, myocardial biopsy was associated with a high risk. There was no clear evidence for primary cardiomyopathy (in particular, myocardial non-compaction) with MSCT and MRI. The absence of delayed accumulation did not exclude myocarditis.

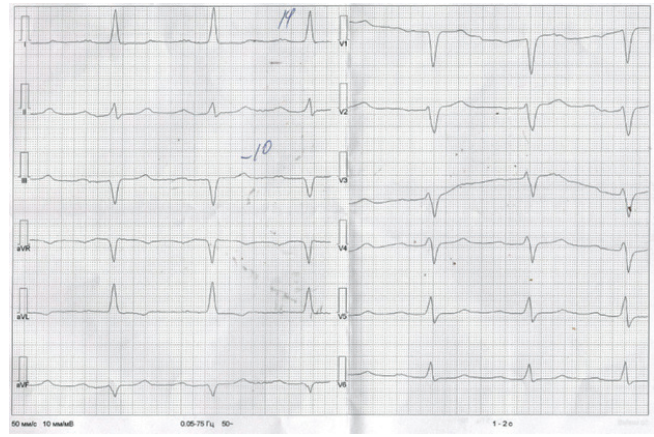


Figure 1. ECG of the patient (description in the article).

Taking into account the moderate degree of myocarditis activity and presence of relative contraindications to steroid therapy (obesity, subcompensated diabetes), azathioprine monotherapy (150 mg/day) was started. Optimal doses of angiotensin-converting enzyme inhibitors and β-blockers (fosinopril 20 mg/day, bisoprolol 2,5 mg/day), diuretics (spironolactone 50 mg/day, furosemide 40 mg/day intravenously with a switch to torasemide 10 mg/day). As a result of treatment, there was a decrease in shortness of breath with a stable positive diuresis, an increase in exercise tolerance, and a significant improvement in general well-being.

Since the beginning of 2014, episodes of dizziness and rare lightheadedness have appeared. In May 2014 she applied to the hospital. There was a clear positive dynamics: a decrease in shortness of breath, an EF increase to 46-48%, a decrease in LV EDD to 5,3 cm, despite an increase in weight of 9 kg. Holter monitoring while taking 2,5 mg of bisoprolol revealed 49 pauses >2 seconds (maximum, 2,3 sec), frequent episodes of postextrasystolic depression of the sinus node. The dose of bisoprolol was reduced to 1,25 mg/day, against the background of which only isolated episodes of sinoatrial block were recorded at night. Signs of moderate myocarditis activity persisted (Table 1) and therapy with azathioprine was continued at the same dose. Doppler ultrasound revealed hemodynamically significant stenosis of the internal carotid arteries (right, 50%; left, 60%). In December 2014, a decrease in antibodies' titers was noted. Therefore, the azathioprine dose was reduced

Table 1

Results of dynamic follow-up of the patient

Parameter	December 2013	May 2014	December 2014	December 2015	May 2016	November 2017	May 2018	May 2019
ANA (no)	нет	нет	нет	1:320	1:80	1:160	1:40	1:40
AECA (1:40)	1:320	1:80	1:80	1:80	1:80	1:160	1:80	1:80
ACA (1:40)	1:80	1:160	1:80	1:160	1:80	1:80	1:80	1:80
ASMA (1:40)	1:80	1:160	1:80	1:160	1:160	1:80	1:80	1:80
CCSA (1:40)	1:320	1:320	1:160	1:160	1:160	1:80	1:80	1:80
Shortness of breath	+++	++	+	++	–	–	–	++
LVEF, %	21→39	47	49	41	52	50	51	41→50
Azathioprine dose (mg/day)	150	150	50	150	150	150	100	150

Abbreviations: ANA — antinuclear antibodies, AECA — antiendothelial cell antibodies, ACA — anticardiomyocyte antibodies, ASMA — antibodies to anti-smooth muscles, CCSA — antibodies to cardiac conduction system fibers, LVEF — left ventricular ejection fraction.

to 50 mg/day. Holter monitoring revealed 195 pauses (maximum, 3,78 sec), in connection with which bisoprolol was completely canceled. The patient felt satisfactory for the next year.

In December 2015, shortness of breath appeared and gradually increased, exercise tolerance decreased, and the patient was hospitalized. Echocardiography revealed a decrease in EF to 41% without LV dilatation. Exercise tests were not performed due to shortness of breath. The patient refused to perform stress transesophageal echocardiography. Holter monitoring without β-blockers' intake revealed episodes of second-degree sinoatrial block with pauses of up to 2,5 seconds in combination with sinus tachycardia. Considering the need for therapy with β-blockers (HF, hypertension, CAD), a maximum pause of 3,78 seconds and a history of syncope, the implantation of a pacemaker was recommended. Taking into account a significant increase in antibodies' titers (Table 1), the deterioration of the condition was regarded as a consequence of myocarditis exacerbation. Therefore, azathioprine dose was again increased to 150 mg/day.

In January 2016, a pacemaker was implanted. Before the implantation, Holter monitoring revealed pauses of up to 6,25 seconds (Figure 2). After implantation of the pacemaker, therapy with bisoprolol 2,5 mg was resumed. The state of health improved: there were no episodes of dizziness, shortness of breath decreased, exercise tolerance increased, and EF stabilized at the level of 50-52%.

The patient's condition remained stable until December 2018 (Table 1), when she noted an increase in shortness of breath, a feeling of "globus behind the breastbone" without a clear connection with physical activity. According to echocardiography in January 2019, LVEF was 41%. In May 2019, she was again hospitalized to rule out an exacerbation of myocarditis. According to the echocardiography performed in the clinic, the EF was 50%. There was no increase in the antibodies' titer, which required the search for other causes of deterioration. Due to the presence of risk factors for CAD and verified coronary atherosclerosis, a stress test was performed (positive results). During the test, a feeling of heaviness behind the sternum appeared, accompanied by ECG changes: horizontal ST segment depression in II, III, aVF, V_5-V_6 up to 0,16 mV). The increase in episodes of shortness of breath is regarded as equivalent to angina.

In November 2019, coronary angiography revealed 75% stenosis of the left coronary artery, 50% stenosis of the proximal third of ADA, 30% stenosis in the proximal third of RCA, while LCA was without significant stenosis. Stent in the middle third was without signs of restenosis. Coronary artery bypass grafting was recommended, which the patient refused, and therefore, in December 2019, bifurcation stenting was successfully performed using the culotte technique. After that, she noted a significant improvement in well-being in the form of a decrease in shortness of breath and the disappearance of discomfort behind the breastbone.

Discussion

In the presented case report, the simultaneous presence of two diseases in the patient was demonstrated: moderate chronic infectious-immune myocarditis and CAD. Both diseases determine the patient's prognosis equally. At the same time, either myocarditis or the progression of CAD played a leading role in the formation of clinical performance at different times.

Initially, the HF symptoms in the patient were regarded precisely as a manifestation of CAD, despite the clear connection between the onset of

symptoms and the previous infection, a rapid EF decrease and left heart dilatation, a moderate coronary artery stenosis and the absence of verified ischemia. The patient underwent RCA stenting, but there was no significant positive dynamics in condition. Only after the start of basic therapy a significant increase in EF (from 21-39% to 52%), normalization of the heart size, and control over HF symptoms were achieved. The restored blood flow through the RCA, a simultaneous decrease in EF and an increase in antibodies' titers make myocarditis a more likely cause of the progression of conduction disorders. In any case, the nature of the pauses did not influence the treatment tactics.

As for the last deterioration in the patient's condition, her long history of myocarditis forced the doctors, who initially diagnosed CAD, to regard the negative dynamics as an increase in the activity of myocarditis. She was again referred to our hospital to determine further management tactics. The stress test revealed myocardial ischemia due to the progression of coronary atherosclerosis in the patient with hypertension, obesity and not fully controlled diabetes. Timely pathogenetic treatment (revascularization) again made it possible to stabilize the condition.

Given the high prevalence of both myocarditis and CAD, a combination of these two diseases is quite likely. However, there is very little data in the literature. There are many publications about the infarct-like acute myocarditis, however, only a few publications were found about the combination of myocarditis and "classical" CAD. A group of Japanese scientists described a patient with a long history of multivessel CAD; this patient had an acute decompensated HF, the cause of which was morphologically verified lymphocytic fulminant myocarditis, first regarded as ACS [3]. The main message of the authors coincides with ours: the presence of a verified CAD in a patient may complicate the timely diagnosis of myocarditis and one should bear in mind the addition of myocarditis as one of the deterioration reasons.

In 1999, Italian researchers described 7 patients with advanced coronary atherosclerosis, biventricular heart failure, and right ventricular and LV dilatation without prior MI. In all of these patients, myocardial biopsy was diagnosed with active lymphocytic myocarditis. In addition, an increase in antibodies' titers was noted in two patients. In addition to the conventional treatment of HF, two patients were prescribed immunosuppressive therapy for myocarditis with a combination of prednisolone and azathioprine, and 8 months after they had a significant increase in LVEF (from 15% to 50% and from 20% to 38%), while in 5 patients without immunosuppressive therapy, EF remained low and one of them died [4].

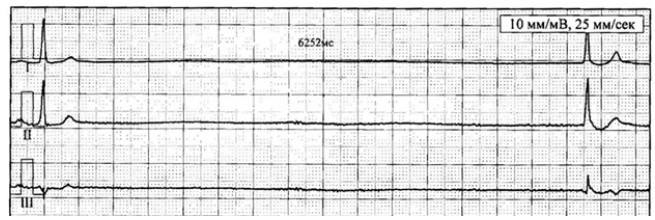


Figure 2. Fragment of 24-hour ECG monitoring (description in the article).

We have repeatedly observed cases of a combination of various types of CAD and myocarditis. When observing more than 600 patients with myocarditis, we identified two variants of infarct-like myocarditis (favorable and unfavorable) and described numerous forms of microvascular ischemia within myocarditis without necrosis [5, 6] and cases of a true combination of CAD with morphologically verified myocarditis, as well as cases of myocarditis after MI [7].

We also repeatedly noted about the ambiguity and often unjustified use of the clinical term "ischemic cardiomyopathy", which, unfortunately, began to be used by pathologists instead of the much more correct and understandable diagnosis of "small focal cardiosclerosis". Today, ischemic cardiomyopathy is most often understood as a pronounced postinfarction LV remodeling with its dilatation and a progressive EF decrease. However, in 1970 this term was proposed to denote the dilated cardiomyopathy in patients with multivessel CAD, regardless of a history of myocardial infarction. At the same time, the reasons for the development of cardiomyopathy in only a small part of patients with CAD remain unclear. Obviously, in addition to chronic ischemia, there must be special factors that are not present in everyone, probably genetic.

In the presented case report, we have no reason to suspect true ischemic cardiomyopathy for a number of reasons: initially there was not only myocardial infarction and severe multivessel lesion, but also verified ischemia. Significant improvement in the condition and increase in LV systolic function were achieved in the absence of complete myocardial revascularization. Before pacemaker implantation, β-blockers were used only in a minimal dose and then were canceled, which does not meet the optimal medical therapy for CAD and HF. Pronounced clinical effect was achieved by use of azathioprine.

Thus, when patients with coronary atherosclerosis develop unexplained biventricular HF without myocardial infarction, one should always remember about the need to actively diagnose and treat myocarditis.

Conclusion

The presence of moderate coronary atherosclerosis without signs of ischemia and myocardial infarction should not be considered as the only cause of severe systolic myocardial dysfunction. In patients with verified CAD, increase in HF symptoms with a significant decrease in EF and cardiac dilatation may be due not only to coronary atherosclerosis progression, but also to the presence of myocarditis. Diagnosis and treatment of myocarditis in combination with CAD is carried out according to the standard principles and can improve LV systolic function and control the heart failure symptoms. Active myocarditis and CAD equally specify the patient's prognosis and equally require treatment. With such a combination, the causes of deterioration and the indications for various types of treatment should be differentially re-evaluated at each stage of the disease.

Relationships and Activities: none.

References

1. For citation: 2020 Clinical practice guidelines for Stable coronary artery disease. Russian Journal of Cardiology. 2020;25:4076. (In Russ.) doi:10.15829/1560-4071-2020-4076.
2. Paleyev NR, Paleyev FN. Non-coronarogenic myocardial diseases and their classification. Russ J Cardiol. 2009;(3):5-9. (In Russ.) doi:10.15829/1560-4071-2009-3-5-9.
3. Fujita S, Okamoto R, Takamura T, et al. Fulminant myocarditis in a patient with severe coronary artery disease. J Cardiol Cases. 2014;9(1):15-7. doi:10.1016/j.jccase.2013.08.010.
4. Frustaci A, Chimenti C, Maseri A. Global biventricular dysfunction in patients with asymptomatic coronary artery disease may be caused by myocarditis. Circulation. 1999;99(10):1295-9. doi:10.1161/01.cir.99.10.1295.
5. Nedostup AV, Blagova OV, Kogan EA, et al. Myocardial vasculitis: nosologic unit, clinical picture, diagnostics, treatment. Kardiologija i Cardiovasc Surg. 2011;4(3):85-92. (In Russ.)
6. Blagova OV, Nedostup AV. Contemporary masks of the myocarditis (from clinical signs to diagnosis). Russ J Cardiol. 2014;19(5):13-22. (In Russ.) doi:10.15829/1560-4071-2014-5-13-22.
7. Blagova OV, Nedostup AV, Kogan EA, et al. Myocardial and pericardial diseases: from syndromes to diagnosis and treatment. Msk.: Geotar-Media, 2019. p. 884. (In Russ.)

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-4046

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Differential diagnosis of acute myocardial injury: a case report and discussion

Boldueva S. A., Evdokimov D. S., Evdokimova L. S., Khomulo A. D., Rozhdestvenskaya M. V.

The article describes a case report of acute myocardial injury developed against the background of systemic inflammatory response in a patient with chronic tonsillitis exacerbation, who had no signs of coronary artery atherosclerosis and pathological changes according to cardiac magnetic resonance imaging. The differential diagnosis and discussion of the problem of acute non-ischemic myocardial injury are presented.

Key words: acute coronary syndrome, acute myocardial injury, magnetic resonance imaging, myocarditis.

Relationships and Activities: none.

I. I. Mechnikov North-Western State Medical University, St. Petersburg, Russia.

Boldueva S. A.* ORCID: 0000-0002-1898-084X, Evdokimov D. S. ORCID: 0000-0002-3107-1691, Evdokimova L. S. ORCID: 0000-0002-7731-0109, Khomulo A. D. ORCID: 0000-0002-1918-5661, Rozhdestvenskaya M. V. ORCID: 0000-0002-6298-547X.

*Corresponding author:
svetlanaboldueva@mail.ru

Received: 04.08.2020
Revision Received: 10.08.2020
Accepted: 07.09.2020

For citation: Boldueva S. A., Evdokimov D. S., Evdokimova L. S., Khomulo A. D., Rozhdestvenskaya M. V. Differential diagnosis of acute myocardial injury: a case report and discussion. *Russian Journal of Cardiology*. 2020;25(11):4046. (In Russ.) doi:10.15829/1560-4071-2020-4046

According to the fourth universal definition of myocardial infarction (MI), there are many causes of acute myocardial injury associated both directly with myocardial ischemia and other non-ischemic causes, such as myocarditis, sepsis, chronic kidney disease, and others [1]. It can be quite difficult to establish the cause of myocardial injury. High-tech diagnostic methods are required, which also cannot always give a clear answer to the question of injury cause. We present a case report of acute myocardial injury caused by a systemic inflammatory response syndrome (SIRS), which developed due to chronic tonsillitis exacerbation.

Male patient, 44 years old, was admitted on February 9, 2020 to cardiac intensive care unit with non-ST segment elevation acute coronary syndrome (ACS) and lacunar tonsillitis.

Upon admission, he complained of general weakness, chills, sore throat.

He consider oneself sick since the evening of February 5, 2020, when at about 7 pm he felt a sharp weakness, chills, the body temperature rose to 37,4° C. Two hours later, complaints arose of severe sore throat, aggravated by swallowing, muscle pain; body temperature rose to 40,5° C. The patient receive antiseptics and paracetamol. While taking paracetamol (500 mg), the temperature dropped for several hours to 39,2° C. From February 7, 2020, taking into account the persisting sore throat and an increase in body temperature to 39-40° C, intense knee pain, he independently began to take amoxiclav 500 mg twice a day. On February 9, 2020, he noted a sharp decrease in body temperature to 37,4° C. Then the temperature above 38° C was not noted. On the same day, at about 3 pm, there suddenly appeared a burning pain behind the sternum of moderate intensity, spreading to the left shoulder, left arm and interscapular area. The patient took two Nurofen tablets, after which the pain intensity decreased slightly. At 6 pm, after a daytime sleep and slight exercise, squeezing pain resumed behind the sternum, spreading to the left shoulder and left arm, the interscapular area. An ambulance was called. Electrocardiography did not reveal abnormalities. Repeated intake of sublingual nitrates did not stop the pain syndrome and the patient was admitted to the S. P. Botkin Clinical Infectious Diseases Hospital diagnosed with lacunar tonsillitis. The chest pain had passed by the time of hospitalization and did not recur. The patient was examined by an otorhinolaryngologist. The diagnosis of chronic tonsillitis exacerbation was confirmed. Smears for diphtheria were negative. Considering complaints of chest pain, the patient was examined by a cardiologist. Troponin T was elevated — 750 pg/ml. Therefore, the patient was transferred to the cardiac intensive care unit of the I. I. Mechnikov North-Western State Medical University with non-ST segment elevation ACS lacunar tonsillitis.

Collection of medical history revealed that in the last years 4-5 times a year he had tonsillitis. About 3 years, the patient also had hypertension with maximum blood pressure values of 150/90 mm Hg and did not receive constant antihypertensive therapy. Cardiovascular family history is negative. There were following bad habits: 24-year smoking, 1 pack per day (smoking index — 24), moderate alcohol consumption.

Objectively, the condition was moderate. Clear consciousness. The body temperature was 37,3° C. Hypersthenic type, class 1 obesity (body mass index — 31,6 kg/m^2). Blood pressure of 130/80 mm Hg. Symmetrical regular pulse of 80 bpm. Clear heart tones, no cardiac murmur. Respiratory rate of 16 bpm. According to auscultation, breathing was harsh and without crackles. Pronounced hyperemia of the pharynx was revealed. The tonsils were enlarged and covered with a white lump. Other systems were without findings.

Upon admission to the cardiac intensive care unit, the ECG revealed sinus rhythm, heart rate (HR) of 86 bpm. In I, II, aVL, aVF, V4-6, smoothed T waves were recorded (Figure 1). Troponin T of 903,3 pg/ml was revealed, followed by a natural decrease and normalization by 7 days. According to echocardiography, ejection fraction was 57,6%, left ventricular (LV) end-diastolic dimension — 51 mm, LV end-systolic dimension — 33 mm, LV mass — 140,5 g, left atrial volume — 35 ml, inferior vena cava diameter — 11 mm, pulmonary artery pressure — 22 mm Hg. Areas of impaired local contractility were not identified. The valves were without significant abnormalities. Pericardial effusion was not revealed.

Given the absence of chest pain on admission, typical ECG changes and areas of impaired contractility according to echocardiography, as well as the presence of an acute infectious disease, it was decided not to perform coronary angiography on the day of admission.

Complete blood count revealed neutrophilic leukocytosis: WBC — 12,2*10^9/l, neutrophils — 9,2*10^9/l, Also, attention was drawn to an increase in the following indicators: aspartate aminotransferase — 78 U/L, creatine phosphokinase — 540 U/L, creatine phosphokinase–MB — 55 U/l, C-reactive protein — 138,8 mg/ l. Blood glucose was 6,1 mmol/ l, creatinine — 95 μmol/ l, urea — 5,9 mmol/ l. Lipid profile was as follows: total cholesterol — 4,7 mmol/l, triglycerides — 3 mmol/l, high–density lipoprotein cholesterol — 0,4 mmol/l, low-density lipoprotein cholesterol — 2,92 mmol/l; atherogenic coefficient — 10,7. Chest X-ray was without findings.

According to clinical urine tests, relative density was 1,015, protein — 0,58 g/l, RBC — 87/μl, WBC — 27/μl, transitional epithelium — 6/μl, granular casts — 3 U/ml.

The 44-year-old patient with metabolic syndrome against the background of chronic tonsillitis exacerbation developed a long-term chest pain, similar to anginal, but not accompanied by typical ECG changes and LV contractility disorders, but combined with an increased troponin, studied in dynamics. It is necessary to carry out a differential diagnosis between acute rheumatic fever (ARF) (angina, arthralgia, systemic inflammatory response syndrome, chest pain, which may be a manifestation of myopericarditis, which developed, however, in the first days of the disease, which is not typical for ARF), non-ST elevation ACS and acute myocardial injury against the background of an infectious process. To clarify the nature of kidney injury, additional examination was required.

Oropharyngeal and tonsillar swabs were positive for *Streptococcus viridans* and *Staphylococcus epidermidis*. Antistreptolysin O antibodies were not detected. The level of complement-C3 was 1,3 g/l (normal range, 0,9-1,8 g/l). Venous blood circulating immune complexes level was 14 U (normal range, 50-80 U).

ECG on the second day of hospitalization revealed sinus rhythm with a heart rate of 86 bpm. There were no significant changes in comparison with the ECG from the first day. Repeated echocardiography 3 days after admission were without dynamics.

Repeated urine tests on the third day of hospitalization revealed a relative density of 1,020, protein — 0,3 g/l, RBC — 138/μl, erythrocyte clots — 5/μl, WBC — 19/μl, transitional epithelium — 4/μl, hyaline casts — 2 U/ml. Parameters of urine analysis on the 5th day were normal. According to Nechiporenko's test, WBC was 300 cells/ml, RBC — 675 cells/ml, casts — 10 U/ml. The daily protein loss was 0,95 g/l.

Kidney ultrasound revealed the following data: renal parenchyma was homogeneous, echogenicity was not changed, corticomedullary differentiation was preserved. The pyelocaliceal complex was not expanded. There were no concrements.

Thus, according to the diagnostic tests, data for ARF were not obtained: from the major criteria, the suspicion of myopericarditis was not confirmed, which will be discussed in more detail below; minor criteria — arthralgia, fever, increased C-reactive protein were present, but group A β-hemolytic streptococcus and antistreptococcal antibodies was not detected. There were no evidence in favor of acute glomerulonephritis (no acute nephritic syndrome),

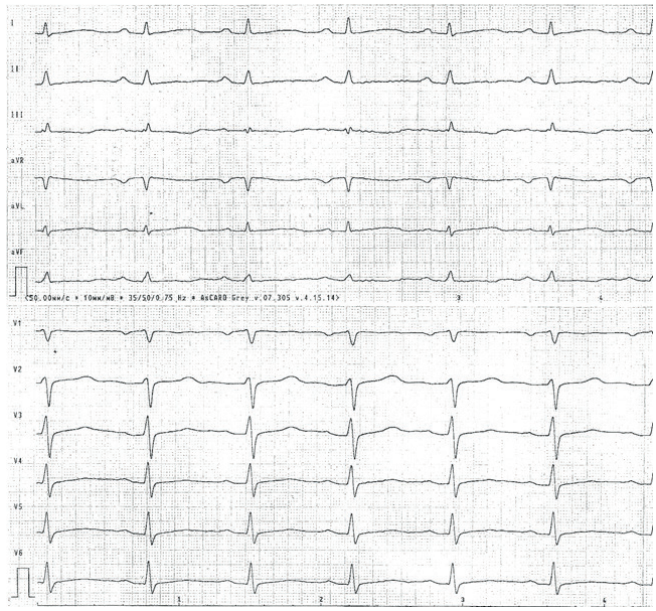


Figure 1. ECG on admission to the cardiac intensive care unit.

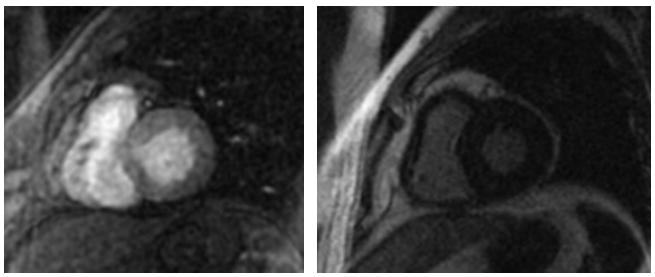
normal complement values, rapid normalization of urine parameters. Evidence in favor acute interstitial nephritis (adequate diuresis, normal relative urine density and creatinine levels, rapid normalization of urinary sediment) was also absent. Transient changes in urine tests fit into the picture of SIRS.

In connection with suspected non-ST-elevation ACS in the patient with signs of metabolic syndrome and cardiovascular risk factors, after normalization of body temperature, coronary angiography was performed, in which no changes were found.

To rule out myocarditis and ischemic myocardial necrosis, on February 17, 2020, contrast-enhanced cardiac magnetic resonance imaging (MRI) was performed: ejection fraction was 69%, heart chambers were not dilated, contractility was preserved, and no local contractility disorders were detected. No MRI signs of myocardial edema were found (Figure 2, 3). On delayed post-contrast images, no pathological accumulation of contrast agent in the LV myocardium was detected. According to conclusion, MRI evidence in favor of LV myocardial edema were not obtained. Inflammatory and postischemic changes were not detected.

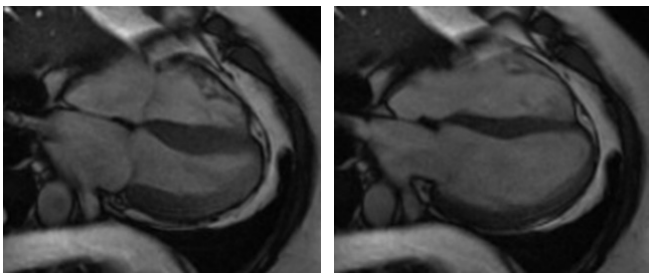
Thus, after rolling out myocarditis and myocardial infarction, the most likely explanation for the increase in troponin was acute reversible myocardial injury due to SIRS in the presence of severe bacterial tonsillitis.

In the hospital, the patient received the following therapy: amoxicillin + clavulanic acid, dual antiplatelet therapy (before coronary angiography), statins, β-blockers, angiotensin-converting enzyme



A **B**

Figure 2. Cardiac MRI, short axis. Myocardial perfusion (**A**), no impaired perfusion areas and delayed contrasting (**B**), no areas of contrast accumulatio.



A **B**

Figure 3. Cardiac MRI, four-chamber view. Systolic (**A**) and diastolic (**B**) phases, no areas of impaired contractility.

inhibitors. With treatment, the patient's condition improved: there was no fever, chest pain did not recur; shortness of breath, heart failure, and weakness wan not established. Tonsillitis was resolving. Complete blood count, C-reactive protein, and transaminases returned to normal value by the 5th day of hospitalization. At discharge, the patient was recommended an additional examination for steatohepatitis, control of urine tests against a background of fever to rule out Berger's disease, and intake of statins and antihypertensive drugs, as well as modification of cardiovascular risk factors.

Discussion

The patient with severe chronic tonsillitis exacerbation was admitted to the cardiac intensive care unit with a diagnosis of non-ST-segment elevation ACS due to chest pain and elevated troponin. The pain developed against the background of pronounced arthralgia and intoxication, responded to non-steroidal anti-inflammatory drugs, not nitrates. It also lasted a long time (about 6 hours) and there were no typical ECG changes and echocardiographic local contractility disorders. Coronary angiography showed no signs of atherosclerosis. According to the results of cardiac MRI, no evidence was obtained in favor of MI.

The assumption of ARF with myopericarditis was not very convincing from the very beginning due to the early pain onset (on the 3rd day of illness) and subsequently was not confirmed by laboratory data. There were no pericardial friction rub and no ECG changes specific to pericarditis. Finally, no myocarditis was detected by contrast-enhanced cardiac MRI. Thus, the pain could be explained by muscle pain against the background of fever and an acute infectious process.

Then the question remains, what was the reason for the troponin turn observed in the patient? In our opinion, this phenomenon can be explained by acute myocardial injury against the background of SIRS, which developed as a result of bacterial infection. The severity of SIRS, in addition to long-term fever, neutrophilic leukocytosis and high C-reactive protein, was also evidenced by urine changes and increased transaminases upon admission.

As follows from recent European and Russian literature, an increase in troponin levels does not always indicate ACS and, in the absence of other ischemia signs, may reflect acute or chronic myocardial injury, which, in turn, develops for various reasons [1].

Differential diagnosis of acute myocardial injury and ACS can be difficult. In addition to troponins, first of all, the presence of acute myocardial ischemia signs should be taken into account: clinical performance, ECG alterations, areas of impaired local myocardial contractility, and, of course, coronary angiography data. In the case of coronary artery thrombosis with pronounced atherosclerotic changes according to angiography, as a rule, there are no diagnostic problems, and type 1 MI is diagnosed.

In the absence of significant (>50%) coronary artery changes and acute thrombosis, but with *ischemia signs and increased troponin*, myocardial infarction with nonobstructive coronary arteries (MINOCA) is suspected. MINOCA is a working diagnosis that requires a search for the cause of myocardial infarction or disorders masking it: myocarditis, takotsubo syndrome, etc. [2].

It should be borne in mind that one of MINOCA causes may be a small plaque damage with the development of thrombosis, the signs of which, according to coronary angiography, may be absent due to spontaneous thrombolysis. In this case, the diagnosis is confirmed by intracoronary imaging methods. With this data, a working diagnosis of MINOCA should be transformed into a type 1 MI. Another variant of MINOCA occurs when there are no significant atherosclerotic changes and/or signs of thrombosis in the suspected infarct-related artery, but ischemia can be explained by an acute discrepancy between myocardial oxygen demand and its delivery, arising, for example, due to coronary artery spasm, arrhythmias,

severe hypertensive crisis, etc. In this situation, the final diagnosis will be type 2 MI [1].

It is far from always possible to immediately establish the cause of MINOCA, given insufficiently available intracoronary imaging methods. In this case, the key diagnostic method is cardiac MRI, which allows visualizing the area of ischemic necrosis in MI, including hemodynamically insignificant atherosclerotic plaque, and also to rule out myocarditis and other causes of myocardial injury, for example, Takotsubo syndrome, amyloidosis, sarcoidosis, etc. [1, 2].

If there are no clinical symptoms of ACS and no signs of ischemic injury according to ECG and echocardiography, an increased troponins can be explained by acute or chronic myocardial injury that can occur with sepsis, end-stage chronic kidney disease, severe respiratory failure, etc. [1]. Also, in patients with COVID-19 and severe lung injury, cases of acute myocardial injury have been described, aggravating the prognosis of the disease [3].

In presented case, the patient had a bacterial infection accompanied by SIRS. According to experts, such a body response with sepsis and other infectious processes can be an independent cause of myocardial injury. As is known, the main mediators of inflammation with a direct cytotoxic effect are tumor necrosis factor alpha, interleukins 1 and 6, which are present in large quantities in the blood of patients with sepsis and other severe infections [4]. Increased blood troponin may be associated not only with cardiomyocyte necrosis, accompanied by myofilament rupture, but also with the leakage of cytosolic troponin due to an increase in the sarcolemma permeability associated with an action of endotoxins, cytokines, and also reactive oxygen species [5].

The issue of ischemic and non-ischemic myocardial injury is relatively new for modern cardiology and not all questions have been resolved by now. So, for example, how sensitive is the MRI in detecting acute ischemic myocardial injuries and their differential diagnosis with myocarditis? So, according to a number of authors, in 10-20% of patients with MINOCA, no changes were found on cardiac MRI [6]. Perhaps the timing of MRI is important [6].

Even less studied is the question of whether it is possible to visualize myocardial injury in sepsis and SIRS with the help of cardiac MRI? When is troponin elevated? What is the nature of this injury? In the study by Siddiqui Y, et al. (2013), group of patients with elevated troponin I on the background of sepsis or SIRS was studied, authors found an increased T2 relaxation time of the epicardium, which indicates a nonischemic reversible mechanism of myocardial injury due to inflammation or the development of tissue acidosis [7]. Similar results were obtained by Takasu O, et al. (2013) during analysis of the hearts of deceased patients with sepsis. The authors found that “septic hearts” did not have signs of irreversible acute injury and cell death, i.e., signs of necrosis, but there was focal potentially reversible damage to cardiomyocyte mitochondria [8].

Thus, the issues of differential diagnosis of ACS and acute myocardial injury, as well as the mechanisms of the latter, including with a SIRS, require further study.

Relationships and Activities: none.

References

1. Averkov OV, Barbarash OL, Boytsov SA, et al. Differentiated approach in diagnostics, diagnosis formulation, case management and statistical accounting of type 2 myocardial infarction (Position Paper). Russian Journal of Cardiology. 2019;6:7-21. (In Russ.) doi:10.15829/1560-4071-2019-6-7-21.
2. Boldueva SA, Feoktistova VS. Myocardial infarction with no obstructive coronary atherosclerosis (MINOCA): review (part 1): definithion, epidemiology, main clinical forms. Emergency Cardiology. 2019;3-4:4-14. (In Russ.) doi:10.25679/EMERGCARDIOLOGY.2020.82.51.001.
3. The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESCCOVID-19-Guidance. (Last update: 28 May 2020).
4. Kumar A, Kumar A, Paladugu B, et al. Transforming growth factor-beta 1 blocks in vitro cardiac myocyte depression induced by tumour necrosis factor-alpha, interleukin-1 beta, and human septic shock serum. CritCareMed. 2007;35(2):358-64. doi:10.1097/01.CCM.0000254341.87098.A4.
5. Favory R, Neviere R. Significance and interpretation of elevated troponin in septic patients. CritCare. 2006;10(4):224. doi:10.1186/cc4991.
6. Collste O, Sorensson P, Frick M, et al. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. J Int Med. 2013;273:189-96. doi:10.1111/j.1365-2796.2012.02567.x.
7. Siddiqui Y, Crouser ED, Raman SV. Nonischemic myocardial changes detected by cardiac magnetic resonance in critical care patients with sepsis. Am J RespirCrit Care Med. 2013;188(8):1037-9. doi:10.1164/rccm.201304-0744LE.
8. Takasu O, Gaut JP, Watanabe E, et al. Mechanisms of cardiac and renal dysfunction in patients dying of sepsis. American journal of respiratory and critical care medicine. 2013;187(5):509-17. doi:10.1164/rccm.201211-1983OC.

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3942

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Atrial cardiomyopathy — a new concept with a long history

Vaikhanskaya T. G.[1], Kurushko T. V.[1], Persianskikh Yu. A.[1], Sivitskaya L. N.[2]

Atrial cardiomyopathy (ACM) is a relatively common but clinically underestimated disorder, which is characterized by an increased atrial size and dysfunction. Previously, ACM was considered a primary disorder, but in 2016 this concept was revised by European Heart Rhythm Association (EHRA) working group with inclusion of secondary atrial remodeling. The EHRA document details aspects of atrial anatomy and pathophysiology, proposes definitions of ACM, histological classification, outlines the molecular mechanisms of atrial arrhythmia and the problems of personalized treatment and optimization of indications for catheter ablation.

Practical application of the proposed ACM classification system, the clinical significance of novel ACM concept and the potential role of this information for a practitioner are presented in this article. Two clinical cases of ACM with "primary" (familial form of ACM due to *NPPA* gene mutation with primary defect in atrial structure and function) and "secondary" atrial remodeling (ACM caused by a long-term supraventricular tachyarrhythmias due to *SCN1B* gene mutation).

Key words: atrial remodeling, atrial cardiomyopathy, atrial fibrillation, atrial electromechanical dysfunction, *NPPA* gene.

Relationships and Activities: none.

[1]Republican Science-Practical Centre "Cardiology", Minsk; [2]Institute of Genetics and Cytology, Minsk, Belarus.

Vaikhanskaya T. G.* ORCID: 0000-0002-2127-8525, Kurushko T. V. ORCID: 0000-0001-5727-3219, Persianskikh Yu. A. ORCID: 0000-0003-0279-912X, Sivitskaya L. N. ORCID: 0000-0001-6359-4967.

*Corresponding author:
tat_vaikh@mail.ru

Received: 02.06.2020
Revision Received: 02.07.2020
Accepted: 09.07.2020

For citation: Vaikhanskaya T. G., Kurushko T. V., Persianskikh Yu. A., Sivitskaya L. N. Atrial cardiomyopathy — a new concept with a long history. *Russian Journal of Cardiology*. 2020;25(11):3942. (In Russ.) doi:10.15829/1560-4071-2020-3942

In recent years, the structural and electromechanical atrial abnormalities as markers of unfavorable clinical prognosis in various groups of patients with cardiovascular diseases has been actively studied. The issues of atrial cardiomyopathy are today the subject of scholarly discussion. However, the fact that atrial cardiomyopathy (ACM) is a fairly common, but still clinically underestimated pathology, is beyond doubt by most researchers.

The first report of a familial fibrotic ACM (FACM) was provided by Williams D, et al. (1972) during long-term follow-up of family members with atrial ectopic beats and atrioventricular (AV) block, when three out of five brothers and sisters had progressive symptoms of chrono-, dromo- and inotropic atrial dysfunction [1]. Later, many researchers reported on histopathological changes in the atria (inflammation, interstitial or focal fibrosis) that were observed in patients with atrial fibrillation (AF) in the absence of structural causes of arrhythmia, such as valvular heart disease or heart failure (HF) [2, 3]. Kottkamp H, et al. (2012) for the first time defined FACM as an independent and progressive ACM with atrial fibrotic lesion, which cannot be caused by age, heart disease, or the presence of atrial fibrillation [4]. The authors suggested that a specific form of FACM is a common pathological manifestation of all AF types, but is caused by a primary process in atrial myocytes, regardless of arrhythmia. In 2016, experts of the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), the Asia-Pacific Heart Rhythm Society (APHRS) and the Latin American Society of Cardiac Pacing and Electrophysiology (SOLAECE) proposed new definitions of ACM as any complex of structural, contractile or electrophysiological abnormalities affecting the atria and contributing to the clinically significant manifestations [5]. This definition resembles the concept of arrhythmogenic atrial remodeling, defined as any change in the structure or function of the atria that contributes to atrial arrhythmias [6]. However, a new element of ACM definitions reflects a potentially important position — the adverse consequences of atrial electromechanical disturbances may be completely independent of atrial arrhythmias. This is a very important aspect, emphasizing the fact that the risk of cerebral thromboembolic events (CTEs) in the presence of ACM may not depend on the onset/development of AF. The second difference is that the terminological subtext of atrial remodeling includes the assumption that the atria were normal before they were exposed to any external influences. Thus, ACM can be caused by primary processes in the atria — structural, electrical and functional disorders characteristic of some genetic diseases (for example, due to *MYL4* or *NPP*A gene mutations) [7, 8]), as well as secondary arrhythmogenic changes caused by isolated AF and other risk factors for AF causing structural myocardial remodeling [9, 10].

ACM — orphan or common disorder?

It is known that many diseases (hypertension valvular heart disease, heart failure, diabetes, myocarditis) or conditions (aging, smoking, obesity, metabolic disorders) cause or contribute to the development of ACM [11]. However, changes in the atria caused by these diseases are not specific for ACM — the localization, prevalence and degree of pathological atrial remodeling depend on the duration and severity of disease, on the modification of many other concomitant factors that cause significant individual differences. The progression of the remodeling substrate depends on many factors that influence the cardiomyocyte reaction in response to electrical, mechanical, hemodynamic, and metabolic stress. Some components of atrial remodeling are reversible (adaptive), while others are permanent (maladaptive). The progression of atrial injury due to underlying heart disease is a major pathogenic factor. Recent studies have demonstrated the effectiveness of AF prevention by successful management of such modifiable risk factors as obstructive sleep apnea syndrome, obesity, hypertension (HTN), hyperglycemia and dyslipidemia [12-15]. Elimination of these abnormalities contributed to the prevention of further atrial damage, and conversely, additional risk factors was associated with recurrence and persistence of AF with progression of the pathological substrate, which supports the Wijffels-Allessie postulate that AF begets AF [16].

However, in addition to the fact that some pathological processes can affect the atria very selectively (for example, AF-related remodeling), there are other less specific mechanisms that cause changes not only in the atria, but also in the ventricles to a greater or lesser extent (primary cardiomyopathies, HTN, muscular dystrophies (MD), amyloidosis, myocarditis) [17].

Thus, ACM is associated with a variety of causes that contribute to pathological atrial remodeling. The most common causes are isolated AF, HF, HTN, myocarditis, valvular heart disease, diabetes, obesity, amyloidosis, hereditary MD. The main etiological, clinical and morphometric features of atrial remodeling leading to electromechanical dysfunction and ACM are presented in Table 1 [5].

In 2016, experts of the EHRA/HRS/APHRS/SOLAECE working group developed a consensus document with a detailed presentation of atrial anatomy, physiology and pathology, definitions with histological classification of ACM, molecular mechanisms affecting the development of arrhyth-

mias, imaging and mapping methods, where they also identified problematic issues of personalized treatment and optimization of indications for catheter ablation. The authors proposed a histological (pathophysiological) classification using the EHRAS abbreviation (E — EHRA, HR — HRS, A — APHRS, S — SOLEACE) to define 4 classes of ACM [1]: I — primarily cardiomyocyte-dependent; II — primarily fibroblast-dependent; III — mixed cardiomyocyte-fibroblast-dependent; IV — primarily non-collagen deposits (Table 2) [5].

This simple classification reflects the dominant morphological pathology in various clinical and pathophysiological situations. These EHRAS classes correspond to their histopathological characteristics. However, at least two problems limit the application of this classification in clinical practice. First, the system is based on histological interpretation, requiring analysis of atrial tissue samples for verification, which in most cases is technically impossible. Second, there is significant overlap between EHRAS classes within almost every etiological category of ACM (Table 1). For example, the histopathological characterization of valvular heart disease can have features of all four classes; pathomorphological signs of HTN, diabetes and MD will overlap within three classes. Only atrial amyloidosis will be in one class (class IV). While class I is often seen in patients with hereditary AF and diabetes, class II is characteristic of atrial remodeling with aging and smoking (Table 1). In patients with HF, the remodeling type corresponds to class III or II, while class IV is often observed in isolated atrial lesions [5].

Clinical application of a novel concept with a long history

At first glance, the ACM classification seems to be not suitable for a practitioner, since for most patients it is impossible to unambiguously determine the EHRAS class without histopathological assessment. But even if the patient's phenotype is unambiguously assigned to a certain I or IV class, it is not fully clear what to do in the future and how to use this information correctly.

However, considering all of the listed ACM classes have one common feature (electromechanical atrial dysfunction caused by structural, mechanical and electrical remodeling) and these changes most often lead to AF [5-7], which is associated with an increased risk of thromboembolic events (TEE), decompensated HF and mortality due to stroke [11, 13-20], it is quite expected that the analysis of ACM etiology, assessment of atrial hemodynamic parameters (speckle tracking, tissue Doppler imaging), macroscopic determination of atrial fibrosis degree using contract-enhanced magnetic resonance imaging (MRI) and the identification of patient procoagulant status will have important prognostic and therapeutic value.

Figure 1 shows the main thromboembolic risk factors that are used for risk stratification in patients with AF before oral anticoagulant (OAC) therapy.

Today, the CHA_2DS_2-VASc score is widely used in practice, including predictors (HF, HTN, age from 65 to 74 years, age 75 years and older, female sex, diabetes, prior stroke or transient ischemic attack, TEE, vascular diseases), which determine the decision to use OAC therapy in accordance with generally accepted guidelines [20, 21]. It is known that all these predictors of TEE are also independent risk factors and the main causes of ACM. Logically, clinicians do not make clinical decisions about prescribing OAC therapy on the basis of AF as such, but rather taking into account concomitant conditions and diseases associated, including with ACM.

This hypothesis is supported by the results of studies showing the absence of absolute synchronization of episodes of AF and stroke [21-25]. The authors' conclusions that ACM is an independent risk factor for cerebral TEE contradict the classical scenario of stroke due to embolization by thrombi from the left atrial (LA) appendage. The ASSERT study revealed that AF were observed within 30 days before stroke in only 8% of patients, and in 16% of patients with cerebral TEE, paroxysmal AF developed after cerebrovascular accident, while in 49%, subclinical episodes of AF were not observed [24, 25]. The absence of a temporal relationship between the AF and cerebral TEE was also demonstrated in the IMPACT study [26]. One of the possible explanations for this phenomenon is the structural mechanisms of atrial remodeling with inotropic and endothelial atrial dysfunction, which increases the risk of stroke even without AF. The well-known diseases with a predominant atrial lesion (cardiac amyloidosis and Fabry disease) associated with an increased risk of TEE, including stroke, which are caused by serious atrial contractile dysfunction, confirm the direct association between ACM and cerebral TEE [27]. Mutations in the *MYL4* gene also cause ACM with severe atrial contractile dysfunction [7-9] and a high risk of stroke [8]. ACM with an autosomal recessive inheritance has been well studied in patients with a homozygous *NPPA* gene mutation (p.Arg150Gln), leading to structural damage to atrial natriuretic peptide (ANP) [28]. The phenotype is characterized by significant biatrial dilatation, supraventricular arrhythmias with progressive loss of sinus and atrial electrical activity with stable normal left ventricular (LV) contractile function. These patients often require pacemaker implantation and long-term anticoagulant therapy due to the high risk

Table 1

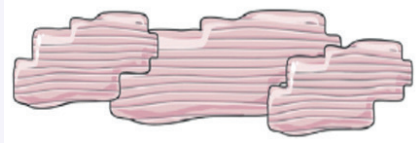
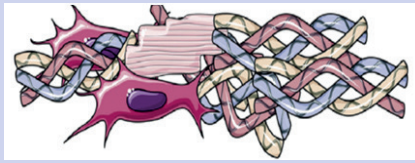
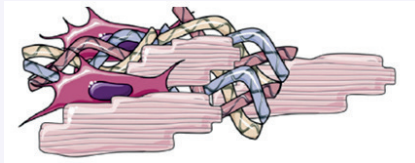
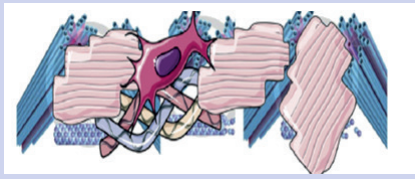
Etiology, structure and characteristics of the main ACM phenotypes

Etiological category of ACM	Clinical and/or morphometric features of atrial remodeling	EHRAS class
AF (isolated)	Atrial morphometry in longstanding persistent AF: cardiomyocyte hypertrophy, myocytolysis, interstitial fibrosis, and decreased expression of connexin-43	I, II, III
Obesity	An increase in body mass index per unit is associated with an increased risk of AF by 3,5-5,3%	III, IV
HF	HF-related phenotype is characterized by the early development of atrial fibrosis. Remodeling components (ionic current changes, connexin), in contrast to AF-induced remodeling, are not accompanied by a decrease in the action potential and slow conduction	II, III, IV
Valvular heart disease	Mitral stenosis and/or insufficiency, aortic stenosis are associated with structural atrial remodeling and a tendency to AF	I, II, III, IV
Myocarditis	AF in about 30% of cases is part of the clinical picture of myocarditis	III, IV
Obstructive sleep apnea	Adverse effect on conduction (slowing atrial conduction) with increased susceptibility to AF	I, III
Diabetes	Diabetes is an independent risk factor for the development and progression of AF	I, III, IV
HTN	HTN is associated with left atrial enlargement and ECG P-wave changes, which are predictors of AF risk	I, II, III
Aging	Conduction abnormalities, increased refractory period due to atrial fibrosis	II
Mutations in the *NPPA* gene	Phenotype of biatrial dilatation with atrial ectopia and AF (Arg150Gln mutation in the *NPPA* gene). Association of *NPPA* variants (S64R and A117V) with AF	I, II, III
Isolated atrial amyloidosis	The most common type of age-related amyloidosis, which is limited to atrial involvement	IV
Genetic repolarization disorders	Combined heterozygous mutations in the sodium channel protein type 5 subunit alpha (*SCN5A*) and connexin-40 (*GJA5*) genes. Mutations in potassium channel subunits (*KCNQ1*, *KCNH2*, *KCND3*, and *KCNE5*) and loss-of-function mutation in the *SCN5A* gene have been identified in patients with AF. Gain-of-function mutations in the *KCNJ8* gene are associated with AF and early repolarization	I
Drug-induced atrial fibrillation	— Bisphosphonates (alendronate, zoledronic acid) — Inotropic agents (dopamine, dobutamine, dopexamine, arbutamine, enoximone, milrinone, levosimendan) — Vasodilators (isosorbide, losartan, flosequinan) — Acetylcholine and anticholinergics (atropine) — Diuretics (thiazides) — Sympathomimetics (pseudoephedrine, albuterol, salbutamol, salmeterol) — Xanthines (aminophylline, theophylline) — Anticonvulsants (lacosamide, paliperidone) — Antidepressants (fluoxetine, tranylcypromine) — Anti-migraine drugs (ondansetron, sumatriptan) — Antipsychotic agents (clozapine, loxapine, olanzapine) — Cholinomimetics (physostigmine, donepezil) — Dopamine agonists (apomorphine) — Anthracyclines (doxorubicin, mitoxantrone) — Antimetabolites (capecitabine, 5-fluorouracil, gemcitabine) — Tyrosine kinase (cetuximab, sorafenib, sunitinib) and topoisomerase (amsacrine, etoposide) inhibitors — Monoclonal antibodies (alemtuzumab, bevacizumab, rituximab, trastuzumab) — Cytokines and immunomodulatory drugs (azathioprine, interferon-gamma, interleukin-2, lenalidomide) — Drugs for erectile dysfunction treatment (sildenafil, tadalafil, vardenafil) — Anabolic androgenic steroids	I, II, III, IV
Hereditary MD	With hereditary MD, caused by degeneration of myocytes with fatty or fibrous replacement, the heart is involved in the pathological process: — Duchenne MD and Becker MD (DCM, dystrophin gene); — Type 1 myotonic dystrophy (conduction defects, *DMPK* gene); — Emery-Dreifuss MD (DCM with conduction defects, emerin and lamin A/C genes); — Limb-girdle MD (DCM with conduction defects, lamin A/C and sarcoglycan genes)	I, II, III, IV

Abbreviations: DCM — dilated cardiomyopathy, MD — muscular dystrophy, ACM — atrial cardiomyopathy, HF — heart failure, AF — atrial fibrillation, ECG — electrocardiography.

Table 2

EHRAS classification of ACM

EHRAS classes	Scheme of atrial substrate	Histological characteristics
I. Primarily cardiomyocyte-dependent (AF, diabetes, K- and Na-channel-related genetic disorders).		Morphological changes in cardiomyocytes (hypertrophy, myocytolysis); without fibrosis and interstitial changes.
II. Primarily fibroblast-dependent (aging, smoking).		Mostly fibrotic changes; cardiomyocytes are not changed.
III. Mixed cardiomyocyte-fibroblast-dependent (HF, valve defects).		Combination of cardiomyocyte (hypertrophy, myocytolysis) and fibrotic changes.
IV. Primarily non-collagen deposits (amyloid deposits, glycosphingolipids, granulomas and inflammatory infiltrates).		Alteration of interstitial matrix without prominent collagen fibre accumulation: IVa — accumulation of amyloid IVf — fatty infiltration IVi — inflammatory cells IVo — other interstitial alterations.

Abbreviations: ACM — atrial cardiomyopathy, HF — heart failure, AF — atrial fibrillation.

of TEE. Dilation and structural changes (fibrosis) of the atria are associated with the loss of ANP antihypertrophic effect [28].

The study of the potential causes of ACM, a better understanding of the pathogenesis and interrelationships of arrhythmogenic conditions with the atrial anatomy, structure and function may already be in demand today for predicting unfavorable outcomes and preventing cerebral TEE in patients with AF. For this, it is necessary to develop clinical tools for conducting the research, which will determine the practical and predictive value of ACM concept. The search for clinical tools and tactics for ACM treatment is presented below on two case reports: 1) a case of familial ACM due to mutation in the *NPPA* gene, causing a "primary" genetic defect in the atrial structure and function, and 2) a case of "secondary" atrial remodeling, associated with a long-term arrhythmic factor — supraventricular (SV) tachyarrhythmia, including AF associated with a *SCN1B* gene mutation.

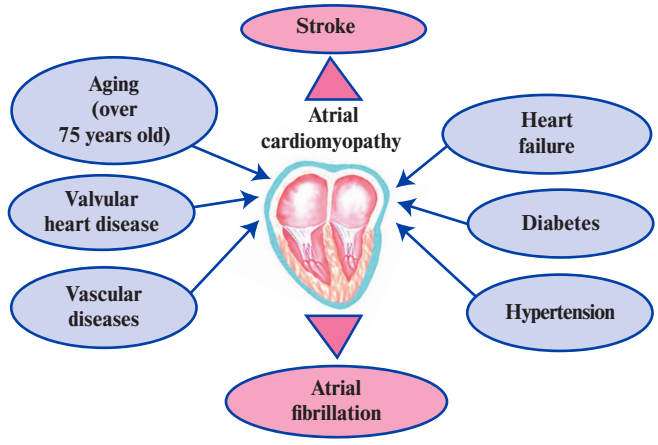


Figure 1. Schematic representation of the main risk factors for stroke (risk factors are included in the $CHADS_2$ and CHA_2DS_2-VASc scores and coincide with risk factors and causes of ACM).

Case report 1

Female patient, born in 1993, first consulted a cardiologist in 2019 with complaints of heart palpitations and shortness of breath with brisk walking. Cardiac examination was initiated by a gynecologist as a search for disorders of the patient's reproductive system.

As a result of electrocardiography (ECG), the following data were obtained: sinus rhythm with a heart rate (HR) of 73 bpm and first-degree AV

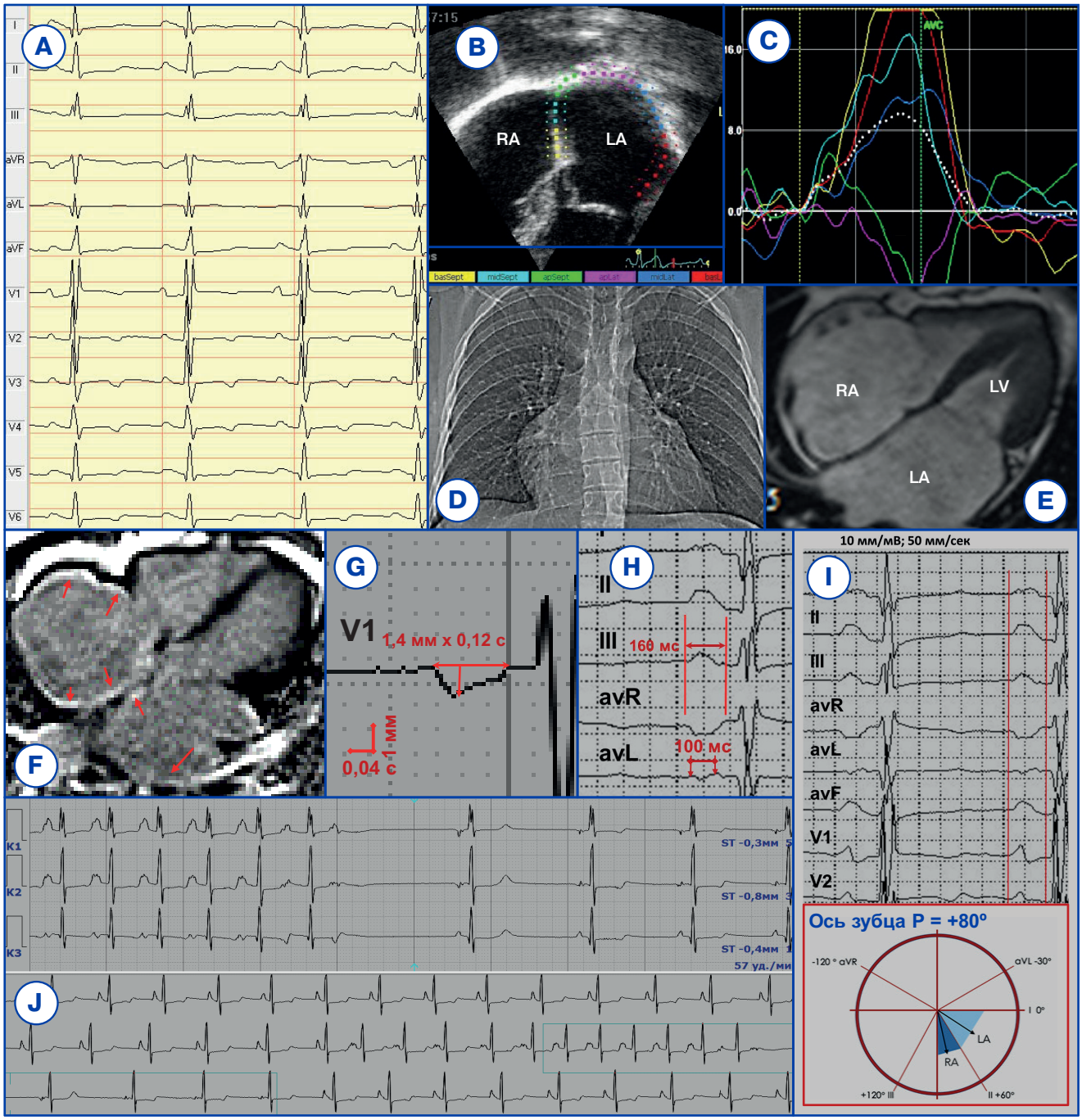


Figure 2. Representative fragments of ECG, HM, pre- and post-contrast MRI, x-ray signs of biatrial cardiomegaly in proband (case 1): **A)** abnormal ECG: wide and biphasic P wave with signs of interatrial block and biatrial dilatation, fragmentated QRS; **B)** speckle-tracking echocardiography of LA; **C)** signs of a significant decrease in peak atrial longitudinal strain (9,8%); **D)** X-ray signs of biatrial cardiomegaly; **E)** MRI movie in a 4-chamber view along the long axis in late diastolic phase with signs of pronounced biatrial dilatation; **F)** accumulation of contrast agent in the walls of both atria and interatrial septum during the delayed phase of MRI scanning (zones of atrial fibrosis are indicated by arrows); **G)** increased integral area of terminal P wave activity to 0,168 mm*s (negative component of the P wave ∫P-V1=1,4 mm×0,12 s=0,168 mm*s); **H)** increased duration of the abnormal P wave to 160 ms in III; biphasic P-waves in I, II, III, aVL; duration of 100 ms between two peaks of the biphasic P wave in aVL; **I)** six-axis system (I — 0°, II — +60°, aVF — +90°, aVR — -150°, aVL — -30°), representing the normal P wave axis (0-75°); the abnormal P wave axis on the ECG of the proband is equal to +80°; **K)** HM fragment with an episode of unstable atrial tachycardia and postectopic depression of the sinus node function with escaping/replacing ectopic atrial rhythm.
Abbreviations: LV — left ventricle, LA — left atrium, RA — right atrium.

block (PQ interval, 210 ms), signs of biatrial dilatation with third-degree interatrial block (Figure 2 A), counterclockwise rotation of the electrical axis in the frontal plane (qR in I and aVL), signs of incomplete right bundle branch block.

Echocardiography revealed severe biatrial dilatation without a decrease in the venricular systolic function: LA anteroposterior dimension — 44/68 mm, LA volume indexed to body surface area (BSA) — 73,5 ml/m^2; right atrial (RA) anteroposterior dimension — 47/68 mm, RA volume — 129 ml, RA volume index (RAVI) — 74 ml/m^2; LV end-diastolic dimension — 42 mm, LV end-systolic dimension — 31 mm, LV end-diastolic volume — 83 ml, LV end-systolic volume — 36 ml, LV ejection fraction (EF) — 56%, LV mass index — 85,7 g/m^2, grade 1-2 mitral regurgitation; right ventricular (RV) fractional area change — 41%, TAPSE — 14 mm, grade 2 tricuspid regurgitation, volume and gradient of tricuspid regurgitation — 18 ml and 30 mm Hg, respectively; pulmonary artery pressure (mean/systolic) — 32,5/50 mm Hg. The patient had signs of a slight local contractility decrease in the basal and middle anteroseptal LV segments (GLS= -14,9%) and restrictive LV diastolic dysfunction: early diastolic transmitral flow velocity — 0,87 m/s, late diastolic transmitral flow velocity (A) — 0,29 m/s, E/A ratio — 3; deceleration time of early filling (DT) — 105 ms; annular early diastolic velocity (e`) — 12 cm/s; E/e` ratio — 7,25. To analyze the atrial systolic function using the tissue speckle-tracking echocardiography, a quantitative assessment of longitudinal strain rate and atrial systolic dynamics was carried out. LA peak systolic strain was 9,8% (reference values — 53,1±12,0%), peak systolic strain rate — 0,3 s-1 with reference values of 1,7±0,3 s-1 (Figure 2 B, C).

Signs of biatrial cardiomegaly were revealed by chest x-ray (Figure 2 D). Pronounced atrial dilation with normal ventricular contractile function (LVEF, 72%, RV ejection fraction, 64%) were confirmed by cardiac MRI: longitudinal-transverse dimensions of LA (3,8/3,4 cm/m^2) and RA (4,0/3,5 cm/m^2) indexed to BSA (Figure 2 E). When assessing the pre- and post-contrast cardiac, no signs of edema and criteria for accumulation diseases were revealed. The tissue characteristics of LV and RV myocardium were without abnormalities. The accumulation of contrast agent (sign of fibrosis) was found in the walls of both atria (50% of the RA, 30% of the LA) and in the interatrial septum during the delayed phase (Figure 2 F).

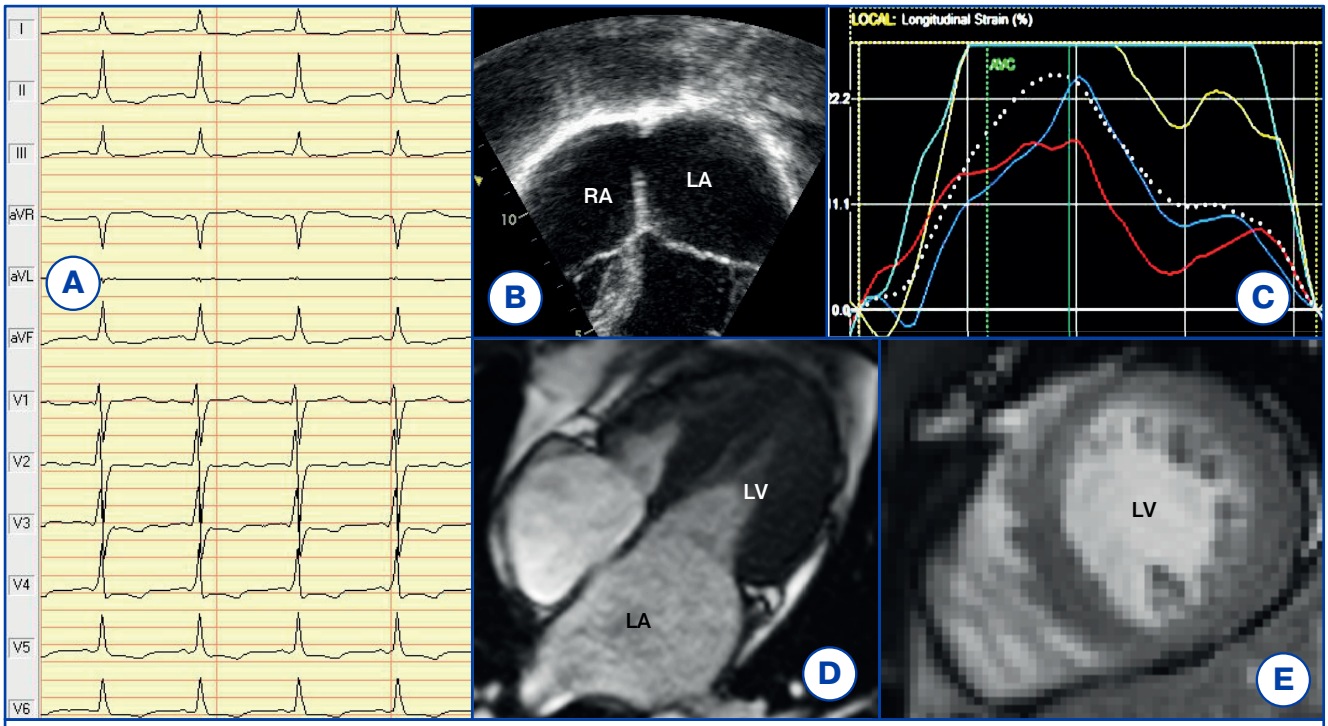
Holter monitoring (HM) recorded SV premature contractions (ectopic index, 9-17% per day) — isolated, coupled and group with postectopic suppression of the sinoatrial node and escaping contractions (Figure 2 J). The mean 24-hour heart rate did not exceed 65-67 bpm. Episodes of intermittent first-degree AV block (PQ, 210-270 ms) and transient changes in the terminal part of ventricular complex (ST-T depression) were recorded. No hypoplastic and other abnormalities of the coronary system were found.

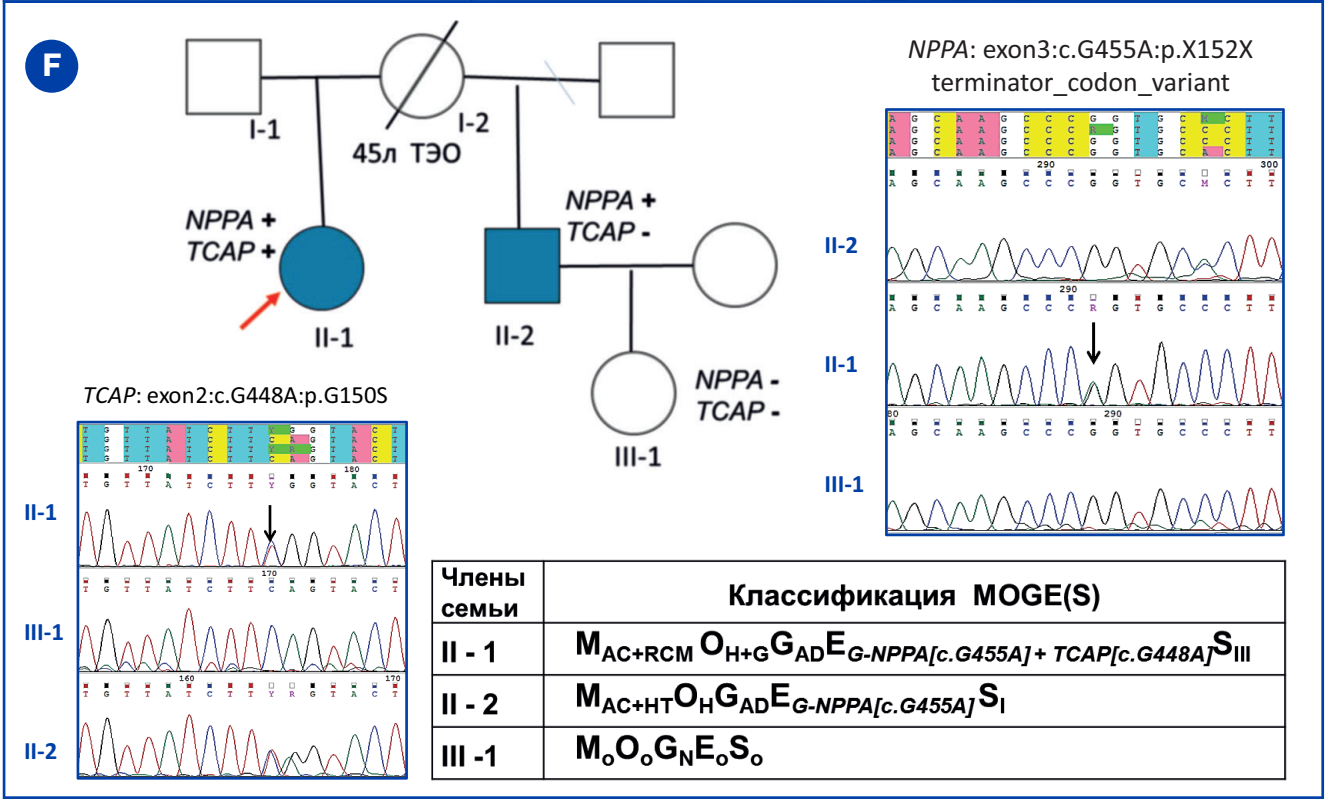
Thus, the patient showed signs of pronounced structural atrial remodeling (significant LA and RA dilatation and fibrosis), electromechanical atrial dysfunction with Bayes syndrome [29] (third-degree interatrial block and supraventricular arrhythmia): the duration of the P wave was 160 ms (normal to 120 ms); biphasic P wave, visualized in all leads, with a maximum duration of 100 ms between two P peaks in aVL (Figure 2 H); the duration of the terminal negative phase of the P wave in V1 was 120 ms (0,12 s), the amplitude — 1,4 mm. The integral area of terminal P wave activity was 0,168 mm*s: the negative component of the P wave $\int P^-_{V1}$=1,4 mm×0,12 s=0,168 mm*s (Figure 2 G), which is a significant deviation, indicating LA dilatation. Normally, the integral area of the negative P wave does not exceed 0,04 mm*s. P-wave axis was +80° as shown in Figure 2 I and, normally the angle of the P axis varies from 0° to 75°.

In the patient's blood plasma, an increase in the level of myocardial stress biomarker NT-proBNP (N-terminal pro-brain natriuretic peptide) up to 326 pg/ml and a decrease in the level of pro atrial natriuretic peptide — 0,67 nmol/ml.

Taking into account the presence of electromechanical dysfunction of significantly dilated atria with signs of ACM (differential diagnosis with restrictive cardiomyopathy) and burdened heredity (recurrent cerebral TEE in the mother from 45 years of age and development of heart failure with AF and fatal stroke at the age of 49), family cascade screening and genetic testing was performed.

Genotyping of proband (II:1) and family members available for examination was carried out in accordance with the Declaration of Helsinki. The patients signed written informed consent. Sequence analysis of 174 genes of the target panel (NGS) in the patient revealed two variants of unknown clinical significance were identified and confirmed by Sanger sequencing: c.G448A (rs762850913) in the 2nd exon of the teletonin gene (*TCAP*) and c.G455A (rs755829943) in the 3rd exon of the atrial natriuretic peptide (*NPPA*) gene. Carriage of an identical mutation in the *NPPA* gene with a similar phenotype of biatrial dilatation and Bayes syndrome was found in the half-brother of the proband — a positive result of the genotype-phenotype segregation. Typical ECG, echocardiography and MRI signs of ACM in the proband's brother are shown in Figure 3. The family





Члены семьи	Классификация MOGE(S)
II - 1	$M_{AC+RCM}\,O_{H+G}G_{AD}E_{G\text{-}NPPA[c.G455A]+\,TCAP[c.G448A]}S_{III}$
II - 2	$M_{AC+HT}O_{H}G_{AD}E_{G\text{-}NPPA[c.G455A]}S_{I}$
III -1	$M_{o}O_{o}G_{N}E_{o}S_{o}$

Figure 3. Representative fragments of ECG, echocardiography and MRI of a relative of proband (case 1), pedigree of family, results of *NPPA* sequencing, *TCAP* genes and diagnoses in the MOGE(S) classification:
A) 12-lead ECG of the proband's brother with an extended and biphasic P wave in II, III, aVF; **B)** signs of predominant LA dilatation according to echocardiography; **C)** LA according to speckle tracking echocardiography: signs of a slight decrease in peak atrial longitudinal strain (22,4%); **D)** MRI movie in a 4-chamber view along the long axis in late diastolic phase with signs of pronounced LA dilatation; **E)** postcontrast T1-weighted MRI image in a two-chamber view along the short axis demonstrates normal LV and RV dimensions without signs of delayed accumulation of contrast and signs of increased LV trabecularity (without criteria for myocardial non-compaction) in the proband's brother; **F)** family tree and results of sequencing of *NPPA* and *TCAP* genes in family members and diagnoses according to the MOGE(S) classification.
Abbreviations: LV — left ventricle, LA — left atrium, RA — right atrium.

tree, the results of Sequence analysis of the 2nd exon of the *TCAP* gene, the 3rd exon of *NPPA* gene in members of the proband's family and the clinical diagnosis in the MOGE (S) classification are shown in Figure 3 F.

The *NPPA* gene encodes the synthesis of atrial natriuretic peptide (ANP), which plays a key role in maintaining homeostasis by regulating the natriuresis, diuresis and vasodilation. Along with the regulation of intravascular volume and vascular tone, it takes part in modifying the ion channels and helps prevent atrial electrical remodeling [28]. ANP also participates in the development and onset of pregnancy, promoting trophoblast invasion and remodeling of the uterine spiral artery. *NPPA* gene mutations, leading to a decrease in the ANP level, disrupt all of these mechanisms. *In vivo* models (knockout mice) with long-term exposure to low ANP levels resulted in damage to myocytes with the development of extensive fibrotic areas and significant atrial dilatation [30].

In the presented case, the proband had severe manifestations of *NPPA* mutation — atrial cardiomyopathy with severe dilatation and biatrial fibrosis, SV arrhythmia and reproductive dysfunction (without anatomical, hormonal, immunological, endocrine and other causes). Taking into account the genetic status, low systolic function of significantly dilated atria, endothelial atrial dysfunction with prothrombotic changes (increased von Willebrand factor level) and increased HF signs (mild contractile and severe LV diastolic dysfunction, CHA_2DS_2-VASc score of 2), the patient was prescribed OACs together with HF therapy.

Case report 2

Male patient, born in 1965, without concomitant hypertension, coronary artery disease, diabetes and obesity, without a history of bad habits. From the age of 30, the patient had asymptomatic SV arrhythmias (moderate sinus bradycardia with escape atrial and junctional beats, SV premature beats) and grade 2 mitral valve prolapse. Symptomatic arrhythmias in the form of paroxysmal AF appeared at the age of 53, and in 2019 the patient sought medical help with complaints of rapidly developing resistance to the "pill-in-the-pocket" strategy with the use of class 1C antiarrhythmic agents and to parenteral antiarrhythmic drugs with the need for repeated electrical cardioversion. Examination of the patient for the first time (at the age of 54) revealed signs of LA dilatation with impaired atrial systolic dynamics and electrical (Bayes syndrome) criteria for LA remodeling, characteristic of ACM.

The ECG admission showed a sinus rhythm with a heart rate of 82 bpm, first-degree AV block (PQ interval, 240 ms), signs of LA dilation with third-degree interatrial (Figure 4 A) and the biphasic P wave duration in I, II, III, aVF >195 ms, left axis deviation, terminal negative P wave integral in V1 was 0,144 mm*s (P negative amplitude — -1,2 mm, duration — 0,11 s).

Holter monitoring revealed episodes of first-degree AV block and transient right bundle branch block, episodes of stable and unstable junctional rhythm against the background of moderate chronotropic sinus node dysfunction, multifocal atrial ectopic activity (ectopic index — 30-45% per day) — isolated, coupled, and group SV premature beats with episodes of atrial Galavardin's tachycardia (Figure 4 B) and unstable paroxysmal AF (Figure 4 C).

Echocardiography revealed signs of significant LA dilatation (Figure 4 D): LA anteroposterior dimension — 50/55 mm, LA volume indexed to BSA — 57 ml/m^2; RA anteroposterior dimension — 40/47 mm, RAVI — 28 ml/m^2; LV end-diastolic dimension — 58 mm, LV end-systolic diameter — 39 mm, LV end-diastolic volume — 156 ml, LV end-systolic volume — 70 ml, LV volume index — 91 ml/m^2, LV mass index — 98,3 g/m^2, grade 2 mitral valve prolapse with grade 2-3 mitral regurgitation; RV fractional area change — 47%, TAPSE — 22 mm, grade 1 tricuspid regurgitation; pulmonary artery pressure (mean/systolic) — 17/25 mm Hg; no local and global ventricular myocardial contractility disorders were detected (GLS — -17,6%, LVEF — 56%), moderate LV diastolic dysfunction: E — 0,64 m/s, A — 0,29 m/s, E/A ratio =2,21; DT — 231 ms; e` — 16 cm/s; E/e` ratio =4. A quantitative assessment of longitudinal strain and atrial systolic dynamics (Figure 4 D, E, F, G) revealed a decrease in LA contractile function: LA peak systolic strain was 11% (reference values — 53,1±12,0%), peak systolic strain rate — 0,7 s^{-1}.

According to MRI, atrial dilation was revealed, mainly the LA (Figure 4 H, I): longitudinal-transverse dimensions of LA (3,7/3,5 cm/m^2) and RA (3,4/2,9 cm/m^2) indexed to BSA. No contrast agent accumulation in the ventricles and atria was detected. The myocardial tissue characteristics, local and global ventricular contractility (LVEF, 58%, RVEF, 69%) were normal.

According to selective angiography, atherosclerotic coronary lesions and right coronary artery hypoplasia were not found.

Given the low efficiency of non-invasive interventions to control the rhythm and the presence of structural and electromechanical signs of ACM, endocardial pulmonary vein radiofrequency ablation (RFA) was considered. Before RFA, a transesophageal echocardiography was performed: there were no signs of LA appendage thrombi, but there

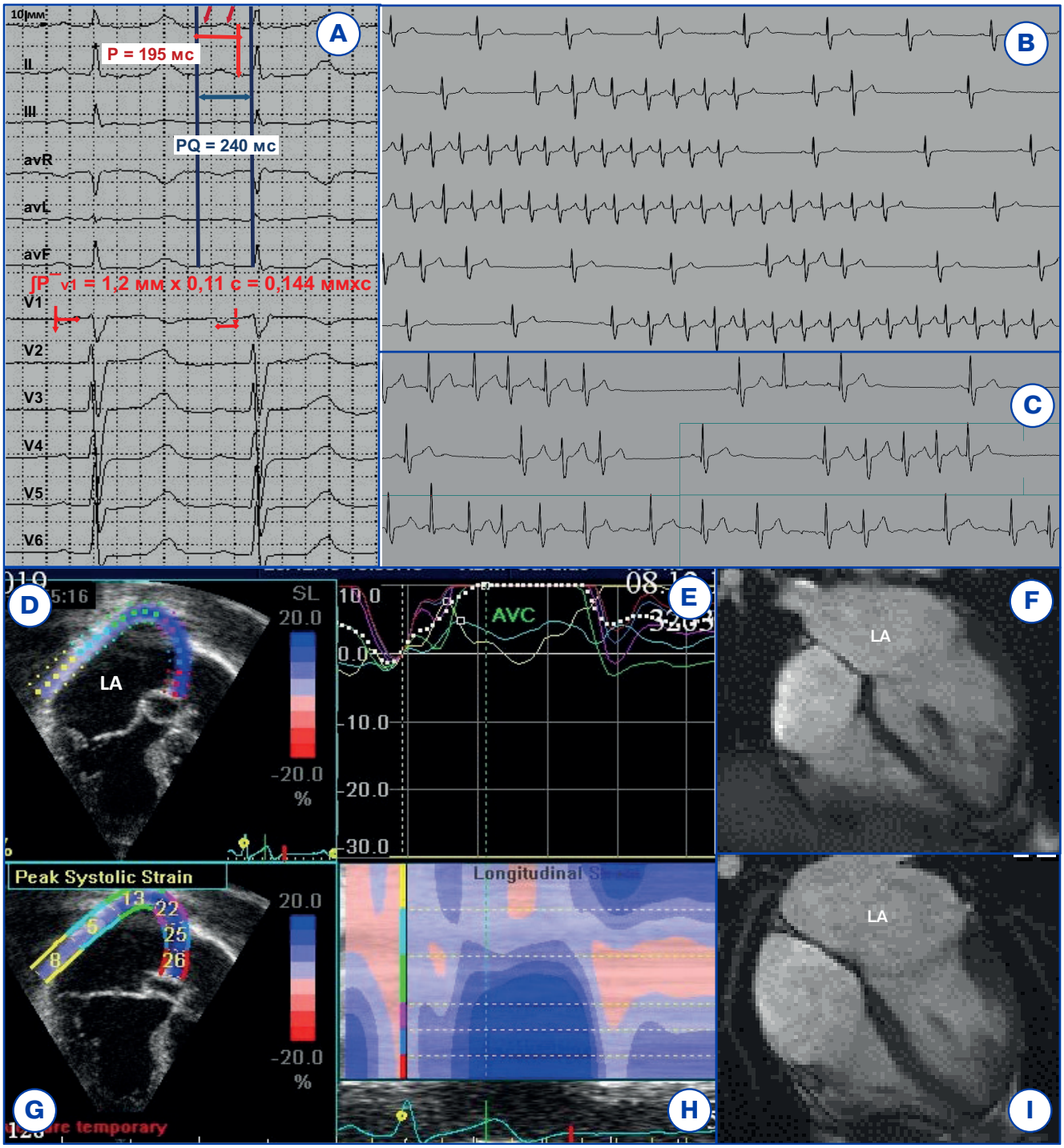


Figure 4. Representative ECG and HM fragments with signs of Bayes syndrome, echocardiographic and MRI features characteristic of ACM in proband (case 2): **A)** 12-lead ECG with an extended and biphasic P wave in I, II, III, aVF; with an increased terminal negative P wave integral in V1 to 0,144 mm*s; **B)** HM fragment with recurrent atrial tachycardia; **C)** HM fragment with paroxysmal AF; (**D, E, F, G**) signs of predominant LA dilatation with decreased systolic peak longitudinal strain of LA free wall according to speckle-tracking echocardiography; **H)** MRI movie along the long axis in 4-chamber view in late atrial systolic and atrial diastolic phases (**I**) with signs of LA dilatation.
Abbreviation: LA — left atrium.

was a pronounced (grade 3) spontaneous contrasting; LA appendage area was 7,8 cm^2, peak blood flow velocity — 0,47 m/s. Frequency and rhythm control following a successful invasive procedure was achieved with a prophylactic dose of a beta-blocker. Taking into account the CHA_2DS_2-VASc score of 2 and increased von Willebrand factor, a history of varicose veins and recurrent lower limb

Table 3

Comparative characteristics of echocardiographic, ECG and laboratory biomarkers in patients with EHRAS type I and III ACM

Parameter	Proband N. (*NPPA*)	Family member (*NPPA*)	Proband S. (*SCN1B*)
Diastolic echocardiographic parameters of transmitral hemodynamics			
Early diastolic transmitral flow velocity (E), m/s	0,87	0,72	0,64
Late diastolic transmitral flow velocity (A), m/s	0,29	0,37	0,24
E/A ratio (normal range <2)	3	1,95	2,21
Deceleration time of early filling, ms	105	146	231
Septal annular early diastolic velocity (e`), cm/s (normal range <7 cm/s)	12	9	16
Lateral annular early diastolic velocity (e`), cm/s (normal range, 10 cm/c)	14	9	20
E/e` ratio (normal range <14)	6,7	8	4
RA volume index, ml/m^2 (normal range <34 ml/m^2)	73,5	44	57
LA volume index, ml/m^2 (normal range <34 ml/m^2)	74	32	28
Speckle-tracking echocardiographic data			
Global longitudinal strain, -% (normal range, -21,5±2,1%)	-14,9	-17,2	-18,1
LA peak systolic strain rate, s-1 (normal range, 1,7±0,3 s-1)	0,2	0,9	0,5
LA peak systolic strain, % (normal range 53±12%)	9,8	22,4	10,1
ECG signs of LA dilation and interatrial block (Bayes syndrome)			
PQ interval, ms	210	180	240
Biphasic P wave duration P, ms	180	135	195
P-wave axis, degree (normal range 0-75°)	80	-30	-33
Terminal negative P wave integral, mm*s (normal range ⩽0,04 mm*s)	0,158	0,088	0,144
Biomarkers of myocardial stress and endothelial dysfunction			
NT-proBNP, pg/ml (normal range <125 pg/ml)	326	107	115
proANP, nmol/ml (normal range, 1,1-2,0 nmol/ml)	0,67	0,84	3,13
Von Willebrand factor, IU/dl (50-150 IU/dl)	165	-	179
CHA_2DS_2-VASc score	2	0	2

Abbreviations: LA — left atrium, RA — right atrium, ECG — electrocardiogram.

venous thromboembolism, the patient underwent endovenous laser coagulation of great saphenous vein branches and was prescribed prophylactic OAC therapy.

Due to presence of familial ACM with arrhythmia (positive family history: in maternal grandmother, sinus node dysfunction with implantation of pacemaker, AF, LA dilation and dysfunction, arrhythmias and fatal stroke in a grandmother at the age of 50), a family cascade screening and genetic testing were performed.

Genotype test of proband (II: 1) and family members available for examination was carried out in accordance with the Declaration of Helsinki. All patients signed written informed consent. Sequence analysis of 174 genes of the target panel (NGS) in the patient revealed c.C35A variant (p.A12E, NM_001037) in the first exon of the *SCN1B* gene. An identical mutation was found in the mother of the proband. The *SCN1B* gene encodes the sodium channel beta-1 subunit. Mutations in this gene are associated with cardiac arrhythmias (AF that were observed in the family of proband.

Thus, in clinical practice, it is extremely important to take into account the possible etiological factors of ACM, since the causes of ACM can have clear diagnostic, prognostic and therapeutic consequences. For example, mutations in the *MYL4* and *NPPA* genes lead to specific ACM — rapidly progressive, with chrono-, dromo- and inotropic atrial dysfunction, with a high risk of AF, cerebral TEE and the need for OAC therapy or pacing [6-9, 28].

Comparative characteristics of atrial electromechanical dysfunction, parameters of LV diastolic and contractile function, laboratory biomarkers in family members of proband with EHRAS class III ACM (*NPPA* mutation carriers) and a patient with EHRAS class I ACM (*SCNB1* mutation carrier) are presented in Table 3.

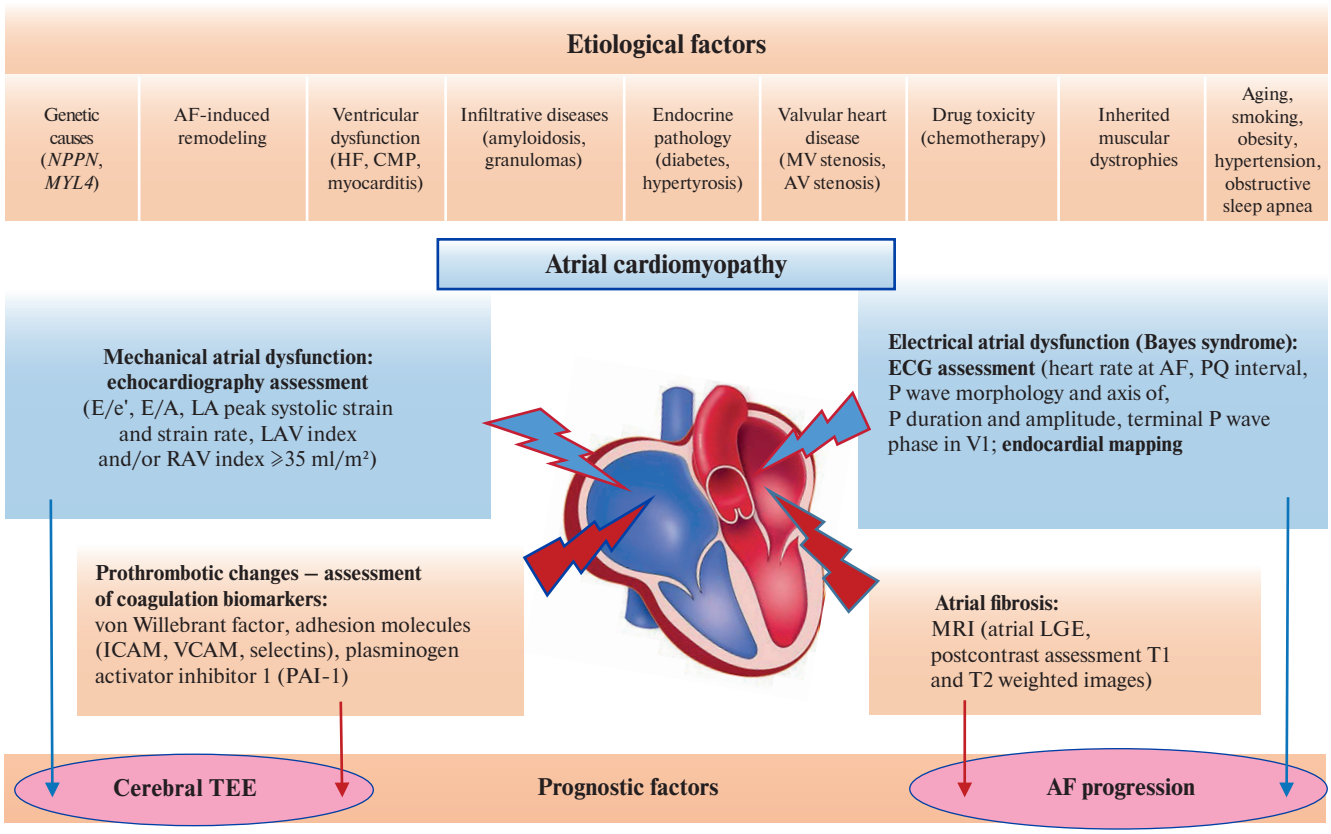


Figure 5. Etiological, clinical and prognostic factors of ACM.
Abbreviations: HTN — hypertension, AV — aortic valve, CMP — cardiomyopathy, LA — left atrium, LAV — left atrial volume, MV — mitral valve, MRI — magnetic resonance imaging, RAV — right atrial volume, TEE — thromboembolic events, AF — atrial fibrillation, HF — heart failure, HR — heart rate, ECG — electrocardiography.

The main clinical and prognostic factors of ACM in the presented clinical observations (Table 3) are specified by the severity of mechanical and electrical atrial dysfunction, their structural remodeling (fibrosis), procoagulation status, and atrial endothelial dysfunction. Thus, a more severe ACM phenotype with an early manifestation of the disease was observed in the 1st case with primary atrial remodeling caused by *NPPA* gene mutation. The following were used as a non-invasive clinical tool for assessing ACM: echocardiography with LA function analysis (determination of E/e`, atrial volume indexes, assessment of atrial tissue using speckle tracking echocardiography with determination of peak systolic strain and strain rate), 12-lead surface ECG with analysis of atrial electrical dysfunction markers and MRI (assessment of fibrosis), which have important diagnostic and predictive value for assessing the risk of developing SV arrhythmias, including AF.

Atrial endothelial dysfunction with coagulation system activation and increased synthesis of prothrombotic tissue factors in the LA endocardium (plasminogen activator inhibitor (PAI) 1, von Willebrand factor (vWF), adhesion molecules (ICAM, VCAM, selectins) and changes in the tumor necrosis factor receptor superfamily such as CD40/CD154, which control interactions between platelets, leukocytes and endothelial cells [31, 32]) are important additional risk factors for ACM-related cerebral TEE.

Thus, Figure 5 shows the main diagnostic elements that can be used in research and practice for verification, classification, treatment and prediction of ACM complications.

As practice shows, a strategically important clinical task in choosing treatment tactics and in determining the prognosis is the etiological verification of ACM. Thus, mutations in the *MYL4* or *NPPA* genes determine severe, rapidly progressive types of ACM with a high risk of AF, HF and cerebral TEE [6-9, 28]; it is also important to take into account/control the toxicity of certain drugs and their adverse effects (Table 1). Treatment of obesity, endocrine disorders (diabetes, hypo- and hyperthyroidism) and infiltrative disorders (amyloidosis) is an equally important factor contributing to an improvement in the ACM prognosis. The beneficial effects of weight loss in

obesity and modification of other AF risk factors have been demonstrated in the randomized trials REVERSE-AF and HUNT [33, 34].

Thus, the individual prognosis of a patient with AF is influenced, on the one hand, by the risk factors for TEE, and on the other hand, by factors that cause or maintain an abnormal heart rhythm (Figure 5). The main reason for the progression of AF from paroxysmal to permanent or longstanding persistent is usually the arrhythmia itself. In addition to focal triggers, which are often located at the pulmonary vein orifices, multiple-loop reentry and electrical dissociation between the epicardial and endocardial layers influence the onset and maintenance of AF [35, 36]. The common of these mechanisms is that they depend on electrical and structural atrial changes that are observed in ACM.

Thus, an important clinical, highly sensitive tool for assessing atrial dysfunction is ECG (PQ interval prolongation [37], an increased P wave duration, increased terminal negative P wave in V1, and an abnormal P-wave axis [38]), and also the low voltage in endocardial mapping [39]. Echocardiography is a highly specific method for assessing the atrial structure and function: transmitral spectral and tissue Doppler with E/e` determination, atrial volume indexes, 3D speckle tracking assessment of fibrous tissue with determination of peak systolic strain and strain rate [40]. Non-invasive quantification of atrial fibrosis, which plays an important role in the pathophysiology of AF and is closely associated with recurrent AF, can be performed with contrast-enhanced MRI [41, 42]. In addition to the technique for assessing delayed contrast accumulation to detect replacement fibrosis, pre- and post-contrast T1 mapping can be used to quantify diffuse interstitial fibrosis. Typically, these techniques are widely used for ventricular imaging, while the assessment of thin-walled atria is somewhat limited by technical problems. However, a multicenter study revealed that quantitative MRI assessment of atrial fibrosis can play a key role in the selection of patients for catheter ablation of AF [43-45]. Thus, the risk of recurrent AF increased by 15% in stage I fibrosis (<10% of the atrial wall) and up to 69% in stage IV fibrosis (⩾30% of the atrial wall) [43].

Discussion

To conduct studies that determine the practical and prognostic value of the ACM concept, highly sensitive and specific clinical tools are in demand today for the early diagnosis of atrial electromechanical dysfunction and the determination of clear prognostic risk factors for cardiovascular events.

If ACM is a significant risk factor for stroke, irrespective of AF, how to identify patients at increased risk of TEE (without history of AF) for OAC therapy? In the study by Wolsk E, et al. (2015), the CHA_2DS_2-VASc score was defined as an independent risk factor for TEE in the absence of any history of AF in patients with heart failure [46]. Similar results in assessing the predictive value of the CHA_2DS_2-VASc scale were demonstrated by the studies of Belen E, et al. (2016) when assessing spontaneous LA contrasting in patients with rheumatic mitral stenosis and without AF history, who had a high risk of LA thrombus formation and TEE, despite sinus rhythm [47]. It is known that patients with mechanical valve prostheses and significant mitral stenosis are not adequately protected by a direct OAC and require anticoagulant therapy with warfarin [22]. Could there be other groups of patients who should be given warfarin to prevent TEE when specific signs of ACM are detected? [48]. Is it possible to identify patients who require more aggressive approaches to TEE prevention, such as the combination of an antiplatelet agent with OAC or the use of LA appendage occluders? The study, analysis and potential of using ACM-specific characteristics for assessing the high risk of TEE and OAC therapy in patients with sinus rhythm should be carried out in prospective randomized multicenter studies.

A combined assessment of etiological factors and signs associated with ACM can be useful information in the selection of initial drug therapy, while analysis of fibrosis severity, LA electrical characteristics and function can be critical in choosing invasive interventions. Thus, electromechanical and structural (fibrosis) markers of ACM have demonstrated prognostic value in assessing the risk of AF recurrence after catheter RFA in a number of studies [49-51].

Could these predictors be used to predict outcomes in patients for whom RFA would not be warranted and thereby eliminating the risk of unnecessary procedures? Can the characteristic features of ACM be used to select the optimal catheter ablation technique for a particular patient?

In accordance with current guidelines, RFA is recommended as a second-line treatment for antiarrhythmic drug intolerance or ineffectiveness. As a first-line treatment, indications are limited to paroxysmal AF only. According to these guidelines, RFA is generally considered by clinicians after a longer period of conservative therapy for AF. The development of tools and methods for the identification of ACM markers can allow avoiding the discrepancy between the optimal period for RFA and its time in accordance with a substrate-oriented diagnosis and treatment of AF.

Conclusion

Thus, further randomized prospective studies are required for a comprehensive and individua-

lized approach to treatment, including optimal OAC therapy, ablation (taking into account the type and severity of ACM), and, possibly, genetics-based approaches in the future.

Conceptual reevaluation and classification of ACM are important for predicting and personalizing treatment strategies, taking into account etiology, morphology, pathogenesis, geno- and phenotype. Although the genetic determinants of ACM are poorly understood today, significant efforts have been made in the last decade to identify the genetic causes of AF, which is both a complication of ACM and its common cause. Study of the genetic basis of primary defects in the atrial structure and function, as well as the genetic contribution of other cardiac pathology and concomitant diseases, adverse environmental and lifestyle factors that lead to secondary atrial remodeling, improvement of invasive and non-invasive technologies for visualization of atrial remodeling will contribute to the creation of new risk stratification approaches for complications such as AF, heart failure and TEE.

Relationships and Activities: none.

References

1. Nagle RE, Smith B, Williams DO. Familial atrial cardiomyopathy with heart block. Br Heart J. 1972;34(2):205.
2. Hensey M, O'Neill L, Mahon C, et al. A review of the anatomical and histological attributes of the left atrial appendage with descriptive pathological examination of morphology and histology. J Atr Fibrillation. 2018;10(6):1650-5. doi:10.4022/jafib.1650.
3. Mueller KL, Heinzmann D, Klingel K, et al. Histopathological and immunological characteristics of tachycardia-induced cardiomyopathy. J Am Coll Cardiol. 2017;69:2160-72. doi:10.1016/j.jacc.2017.02.049.
4. Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. J Cardiovasc Electrophysiol. 2012;23(7):797-9. doi:10.1111/j.1540-8167.2012.02341.X.
5. Goette A, Kalman JM, Aguinaga L, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace. 2016;18(10):1455-90. doi:10.1093/europace/euw161.
6. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol. 2014;63(22):2335-45. doi:10.1016/j.jacc.2014.02.555.
7. Nattel S. Close connections between contraction and rhythm: a new genetic cause of atrial fibrillation/cardiomyopathy and what it can teach us. Eur Heart J. 2017;38:35-7. doi:10.1093/eurheartj/ehw457.
8. Gudbjartsson DF, Holm H, Sulem P, et al. A frameshift deletion in the sarcomere gene MYL4 causes early onset familial atrial fibrillation. Eur Heart J. 2017;38:27-34. doi:10.1093/eurheartj/ehw379.
9. Fatkin D, Santiago CF, Huttner IG, et al. Genetics of atrial fibrillation: state of the art in 2017. Heart Lung Circ. 2017;26:894-901. doi:10.1016/j.hlc.2017.04.008.
10. Pérez-Serra A, Campuzano O, Brugada R. Update about atrial fibrillation genetics. Curr Opin Cardiol. 2017;32(3):246-52. doi:10.1097/hco.0000000000000387.
11. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. Circulation. 2017;136(6):583-96. doi:10.1161/CIRCULATIONAHA.116.023163.
12. Mahajan R, Lau DH, Brooks AG, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. J Am Coll Cardiol. 2015;66:1-11. doi:10.1016/j.jacc.2015.04.058.
13. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014;64:2222-31. doi:10.1016/j.jacc.2014.09.028.
14. Mohanty S, Mohanty P, Di Biase L, et al. Long-term outcome of catheter ablation in atrial fibrillation patients with coexistent metabolic syndrome and obstructive sleep apnea: impact of repeat procedures versus lifestyle changes. J Cardiovasc Electrophysiol. 2014;25:930-8. doi:10.1111/jce.12468.
15. Miller JD, Aronis KN, Chrispin J, et al. Obesity, exercise, obstructive sleep apnea, and modifiable atherosclerotic cardiovascular disease risk factors in atrial fibrillation. J Am Coll Cardiol. 2015;66(25):2899-906. doi:10.1016/j.jacc.2015.10.047.
16. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation. 1995;92:1954-68. doi:10.1161/01.cir.92.7.1954.
17. Melenovsky V, Hwang SJ, Redfield MM, et al. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015;8:295-303. doi:10.1161/circheartfailure.114.001667.
18. Berg DD, Ruff CT, Jarolim P, et al. Performance of the ABC scores for assessing the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in ENGAGE AF-TIMI 48. Circulation. 2019;139:760-71. doi:10.1161/CIRCULATIONAHA.118.038312.
19. Gebreyohannes EA, Tegegn HG, Bhagavathula AS, et al. Poor outcomes associated with antithrombotic potential undertreatment in patients with atrial fibrillation: a retrospective cohort study. Value in Health. 2017;20(9):A625-A626. doi:10.1016/j.jval.2017.08.1377.
20. Habibi M, Zareian M, Ambale Venkatesh B, et al. Left atrial mechanical function and incident ischemic cerebrovascular events independent of AF: insights from the MESA study. J Am Coll Cardiol Img. 2019;12:2417-27. doi:10.1016/j.jcmg.2019.02.021.
21. D'Souza M, Carlson N, Fosbøl E, et al. CHA_2DS_2-VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. Eur J Prev Cardiol. 2018;25(6):651-8. doi:10.1177/2047487318759858.
22. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal. 2016;37(38):2893-962. doi:10.1093/eurheartj/ehw210.
23. Turakhia MP, Ziegler PD, Schmitt S, et al. Atrial fibrillation burden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. Circ Arrhythm Electrophysiol. 2015;8:1040-7. doi:10.1161/circep.114.003057.
24. Brambatti M, Connolly SJ, Gold MR, et al. ASSERT Investigators Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation. 2014;129:2094-9. doi:10.1161/circulationaha.113.007825.
25. Van Gelder IC, Healey JS, Crijns HJGM, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J. 2017;38:1339-44. doi:10.1093/eurheartj/ehx042.
26. Martin DT, Bersohn MM, Waldo AL, et al. IMPACT Investigators Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. Eur Heart J. 2015;36:1660-8. doi:10.1093/eurheartj/ehv115.

27. Hausfater P, Costedoat-Chalumeau N, Amoura Z, et al. AL cardiac amyloidosis and arterial thromboembolic events. Scand J Rheumatol. 2005;34:315-9. doi:10.1080/03009740510015203.
28. Disertori M, Quintarelli S, Grasso M, et al. Autosomal recessive atrial dilated cardiomyopathy with standstill evolution associated with mutation of natriuretic peptide precursor A. Circ Cardiovasc Genet. 2013;6:27-36. doi:10.1161/circgenetics.112.963520.
29. Bayés de Luna A, Platonov P, Cosio FG, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol. 2012;45(5):445-51. doi:10.1016/j.jelectrocard.2012.06.029.
30. Cheng C, Liu H, Tan C, et al. Mutation in NPPA causes atrial fibrillation by activating inflammation and cardiac fibrosis in a knock-in rat model. FASEB J. 2019;33(8):8878-91. doi:10.1096/fj.201802455RRR.
31. Pellegrino PL, Brunetti ND, De Gennaro L, et al. Inflammatory activation in an unselected population of subjects with atrial fibrillation: links with structural heart disease, atrial remodeling and recent onset. Intern Emerg Med. 2013;8:123-8. doi:10.1007/s11739-011-0557-z.
32. Freestone B, Chong AY, Nuttall S, et al. Impaired flow mediated dilatation as evidence of endothelial dysfunction in chronic atrial fibrillation: relationship to plasma von Willebrand factor and soluble E-selectin levels. Thromb Res. 2008;122:85-90. doi:10.1016/j.thromres.2007.09.008.
33. Middeldorp ME, Pathak RK, Meredith M, et al. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. Europace. 2018;20(12):1929-35. doi:10.1093/europace/euy117.
34. Feng T, Vegard M, Strand LB, et al. Weight and weight change and risk of atrial fibrillation: the HUNT study. Eur Heart J. 2019;40:2859-66. doi:10.1093/eurheartj/ehz390.
35. AlTurki A, Marafi M, Russo V, et al. Subclinical atrial fibrillation and risk of stroke: past, present and future. Medicina. 2019;55:611-29. doi:10.3390/medicina55100611.
36. Bisbal F, Baranchuk A, Braunwald E, et al. Atrial Failure as a Clinical Entity. J Am Coll Cardiol. 2020;75(2):222-32. doi:10.1016/j.jacc.2019.11.013.
37. Park J, Kim TH, Lee JS, et al. Prolonged PR interval predicts clinical recurrence of atrial fibrillation after catheter ablation. J Am Heart Assoc. 2014;3:e001277. doi:10.1161/jaha.114.001277.
38. Chen LY and Soliman EZ. P Wave Indices Advancing Our Understanding of Atrial Fibrillation-Related Cardiovascular Outcomes. Front Cardiovasc Med. 2019;6:53-9. doi:10.3389/fcvm.2019.00053.
39. Müller P, Makimoto H, Dietrich JW, et al. Association of left atrial low-voltage area and thromboembolic risk in patients with atrial fibrillation. Europace. 2018;20(FI_3):f359-f365. doi:10.1093/europace/eux172.
40. Lim DJ, Ambale-Ventakesh B, Ostovaneh MR, et al. Change in left atrial function predicts incident atrial fibrillation: the Multi-Ethnic Study. Eur Heart J: Cardiovascular Imaging. 2019;20(9):979-87. doi:10.1093/ehjci/jez176.
41. Siebermair J, Kholmovski EG, Marrouche N, et al. Assessment of Left Atrial Fibrosis by Late Gadolinium Enhancement Magnetic Resonance Imaging: Methodology and Clinical Implications. JACC: Clinical Electrophysiology. 2017;3(8):791-802. doi:10.1016/j.jacep.2017.07.004.
42. Higuchi K, Cates J, Gardner G, et al. The spatial distribution of late gadolinium enhancement of left atrial magnetic resonance imaging in patients with atrial fibrillation. JACC: Clinical Electrophysiology. 2018;4(1):49-58. doi:10.1016/j.jacep.2017.07.016.
43. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311:498-506. doi:10.1001/jama.2014.3
44. Blandino A, Bianchi F, Grossi S, et al. Left atrial substrate modification targeting low-voltage areas for catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Pacing Clin Electrophysiol. 2017;40:199-212. doi:10.1111/pace.13015.
45. Cochet H, Dubois R, Yamashita S, et al. Relationship between fibrosis detected on late gadolinium-enhanced cardiac magnetic resonance and re-entrant activity assessed with electrocardiographic imaging in human persistent atrial fibrillation. JACC: Clinical Electrophysiology. 2018;4(1):17-29. doi:10.1016/j.jacep.2017.07.019.
46. Wolsk E, Lamberts M, Hansen ML, et al. Thromboembolic risk stratification of patients hospitalized with heart failure in sinus rhythm: a nationwide cohort study. Eur J Heart Fail. 2015;17:828-36. doi:10.1002/ejhf.309.
47. Belen E, Ozal E, Pusuroglu H. Association of the CHA_2DS_2-VASc score with left atrial spontaneous echo contrast: a cross-sectional study of patients with rheumatic mitral stenosis in sinus rhythm. Heart Vessels. 2016;31:1537-43. doi:10.1007/s00380-015-0759-9.
48. Baranchuk A, Alexander B, Cinier G, et al. Bayes' syndrome: time to consider early anticoagulation? North Clin Istanb. 2018;5:370-8. doi:10.14744/2Fnci.2017.60251.
49. Yagishita A, Sparano D, Cakulev I, et al. Identification and electrophysiological characterization of early left atrial structural remodeling as a predictor for atrial fibrillation recurrence after pulmonary vein isolation. J Cardiovasc Electrophysiol. 2017;28:642-50. doi:10.1111/jce.13211.
50. King JB, Azadani PN, Suksaranjit P, et al. Left atrial fibrosis and risk of cerebrovascular and cardiovascular events in patients with atrial fibrillation. J Am Coll Cardiol. 2017;70:1311-21. doi:10.1016/j.jacc.2017.07.758.
51. Pranata R, Chintya V, Raharjo SB, et al. Longer diagnosis-to-ablation time is associated with recurrence of atrial fibrillation after catheter ablation. Systematic review and meta-analysis. J Arrhythm. 2019;36(2):289-94. doi:10.1002/joa3.12294.