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IN ISSUE:

Controversial and open issues of diagnosis and treatment of myocarditis (based on the discussion of Russian national recommendations)

Effectiveness of immunosuppressive therapy for lymphocytic myocarditis according: data from actual clinical practice

Right heart condition in patients with COVID-19 pneumonia

Comparative analysis of the concentrations of proinflammatory cytokines and glycosylated ferritin in patients with idiopathic recurrent pericarditis and adult-onset Still's disease

Evolution of diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy and their application in clinical practice

IN FOCUS:

Myocarditis, valvular and non-coronary diseases

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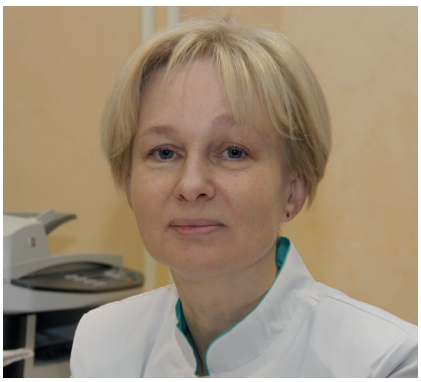
Dear readers!

Olga V. Blagova



Olga M. Moiseeva

The introduction of novel diagnostic methods based on intravital tissue biopsy, biomarkers and innovative imaging techniques opens up new opportunities in the treatment of patients with non-coronary heart disease.

Despite the increasing number of clinical and experimental studies, in actual clinical practice we are still faced with both the problem of examining patients with suspected myocarditis and the selection of optimal therapy. Mistakes in management of this category of patients, as a rule, are associated with a worse disease prognosis due to progressive myocardial dysfunction or the development of life-threatening arrhythmias.

In 2020, the National Guidelines for the Management of Patients with Myocarditis was approved by the Russian Ministry of Health. These are the only recommendations to date that regulate diagnosis and treatment of patients with myocarditis. Until recently, we were guided by the expert opinion of the European Society of Cardiology (2013) as the central document. Like any first document, the National Guidelines leave a number of unresolved issues that require further discussion. Therefore, in this issue an analysis of controversial problems in the diagnosis and treatment of myocarditis based on the National Guidelines is presented.

We will bring to your attention the results of single-center non-randomized clinical trials evaluating the effectiveness of immunosuppressive therapy in patients with documented myocarditis. Given the low availability of intravital endomyocardial biopsy, which is necessary to justify decisions on the appointment of specific therapy, as well as to confirm rare variants of myocarditis and viral etiology of the disease, it should be remembered that heart failure therapy remains the cornerstone in the treatment of patients with inflammatory myocardial diseases. In difficult cases, you can use the telehealth consulting services, which will allow not only to discuss the patient management, but also to promptly refer him to an expert center with a wide range of non-invasive and invasive diagnostics of myocarditis for the timely appointment of immunosuppressive, immunomodulatory and causal therapy.

Special attention should be paid to the study, which analyzed the common pathogenesis of idiopathic recurrent pericarditis and adult-onset Still's disease, which opens up new opportunities with the use of modern anticytokine therapy in the treatment of this disease.

In patients with COVID-19, there is high rate of cardiovascular complications due to the overproduction of proinflammatory cytokines, high tropism of SARS-CoV-2 to endothelium and the presence of prior cardiovascular pathology. Therefore, management of patients after acute COVID-19 should be further discussed.

Type 2 diabetes and obesity are well-known risk factors for heart failure and atrial fibrillation. The growing burden of these conditions, which have common pathophysiological mechanisms with cardiovascular pathology, is clearly demonstrated by the publications presented in the journal.

Of greatest interest is a publication devoted to new criteria for arrhythmogenic cardiomyopathy, the sensitivity and specificity of which have been verified on the basis of many years of clinical experience.

We hope that this issue of the journal devoted to diagnostics and treatment of patients with non-coronary heart disease will be interesting and useful for you in your practice.

Olga V. Blagova, Doctor of Medical Science
Olga M. Moiseeva, Doctor of Medical Science

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EDITORIAL
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Controversial and open issues of diagnosis and treatment of myocarditis (based on the discussion of Russian national recommendations)

Blagova O. V.[1], Moiseeva O. M.[2], Paleev F. N.[3]

In October 2020, the Russian Ministry of Health approved clinical guidelines for the management of patients with myocarditis. The aim of this review was to highlight controversial and open issues without unambiguous answer or those that were not described in the paper. The review highlights the objective factors that complicate the development of practical guidelines for the management of this category of patients. Comments on the definition and classification of inflammatory heart diseases are given. The approaches to the diagnosis of patients with suspected myocarditis are discussed. Particular attention is paid to the decision-making strategy in selecting optimal therapy in patients with documented myocarditis and the role of endomyocardial biopsy.

Keywords: myocarditis, clinical guidelines, open issues, diagnosis, treatment, expert comments.

Relationships and Activities: none.

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The last decades have been marked by numerous clinical and experimental studies, which have significantly changed our understanding of the pathogenesis of inflammatory myocardial diseases and served as the basis for a number of papers outlining the position of experts in the diagnosis and treatment of myocarditis [1-3]. A year ago (in October 2020) the Russian Ministry of Health approved the recommendations of the Russian Society of Cardiology on the myocarditis diagnosis and treatment (full text is available on the website of RSC scardio.ru) [4]. This event was preceded by a long period of discussion and amendments to the text of the recommendations by members of the expert group. In September 2020, the final stage of public discussion of the recommendation text took place at the Russian National Congress of Cardiology, which showed that an acceptable consensus was reached on many issues. However, a number of issues require further discussion.

The problem of myocarditis diagnostics and treatment in the practice of cardiologist, unlike other nosological forms, holds a unique position due to the lack of unambiguous decisions on a number of issues for objective reasons. They are related to the complexity and polyetiology of the pathological process itself, the absence of specific clinical manifestations of the disease, making its pre-test diagnosis difficult, the low availability of intravital endomyocardial biopsy (EMB), required to verify the diagnosis and choose the optimal treatment method, the unfavorable disease prognosis, associated with the development of systolic myocardial dysfunction, life-threatening rhythm and conduction disturbances, against the background of almost complete absence of randomized and, first of all, multicenter clinical trials, confirming the effectiveness and safety of currently available basic treatment methods. The only European document that outlines approaches to the management of patients with myocarditis remains the guideline (Current state of knowledge) 2013, to which we will refer more than once [1].

The year 2020, marked by a new coronavirus infection, has made the problem of myocarditis particularly urgent, bringing into our practice not only a very unique variant of SARS-CoV-2 induced myocarditis, but also new issues related to the management of patients suffering from acute and chronic forms of other etiologies. Thus, the circle of doctors who will be affected by these issues has undoubtedly expanded.

The purpose of this publication is to highlight controversial and unresolved issues that have not been answered unambiguously or have remained outside the scope of the published recommendations. Their final resolution is hardly possible without performing specially designed studies, but we hope that the introduction of domestic recommendations into real clinical practice will contribute to the accumulation of Russian experience and will make the algorithm for managing patients with myocarditis more effective.

Definitions and issues of myocarditis classification. During the discussion, the experts considered at least 5 different definitions of myocarditis, and even more diverse were the variants of classifications. These questions are not peripheral, because they are directly related to clinical practice (making and formulating a diagnosis, which largely determines the choice of treatment in each case).

The text of the recommendations included the following definition: "*Myocarditis — a group concept (a group of independent nosological units or a manifestation of other diseases), myocardial damage of an inflammatory nature, infectious, toxic (including medicinal), allergic, autoimmune or unclear etiology, with a wide spectrum of clinical symptoms: from asymptomatic course, mild shortness of breath and unexpressed pain in the chest, passing on their own, to heart failure, cardiogenic shock, life-threatening rhythm disturbances and sudden cardiac death*"[1]. The definition undoubtedly requires further revision, since myocarditis is not a concept, but "a group of diseases with inflammatory nature of myocardial lesions...". In contrast to the Russian recommendations, the European recommendations define inflammatory myocardial disease based solely on morphological signs (histological, immunological and immunohistochemical confirmation of inflammatory infiltrates in myocardium combined with signs of necrosis and degeneration of cardiomyocytes of non-ischemic genesis), which has several weaknesses: impossibility of diagnosis in patients with a mild course of the disease, in which EMB is not indicated, as well as difficulty in interpreting biopsy findings in comorbid patients (for example, ischemic damage of cardiomyocytes with secondary inflammatory reaction can not always be excluded). All of the above factors can make adjustments in the incidence and prevalence of myocarditis in the general population. On the contrary, the definition given in the Russian recommendations includes all basic characteristics (etiology, pathogenesis, clinical presentation, outcomes) of inflammatory myocardial disease and in general better meets the objectives of real clinical practice. However, the absence of morphological confirmation of the diagnosis can, on the one hand, lead to overdiagnosis of myocarditis, and on the other hand, make it difficult to decide on the prescription of specific therapy.

[1] Further, all quotations from the text of the national recommendations on myocarditis will be given in italics.

Along with the definition of various variants of myocarditis, the Russian recommendations provide an interpretation of other definitions that are widely used in English-language literature. In particular, the concept meaning of "inflammatory cardiomyopathy" as "myocarditis with myocardial dysfunction" is explained. Initially, this term reflected the stage of inflammatory myocardial damage with development of structural and functional changes characteristic of both acute and chronic myocarditis. However, if we turn to the definition of dilated cardiomyopathy (DCM) as left ventricular dilatation or biventricular dilatation with development of systolic dysfunction in the absence of risk factors (hypertension, valve pathology, ischemic heart disease), explaining impaired global myocardial contractility, we see that making a differential diagnosis between these similar in clinical manifestations nosological forms is impossible without performing EMB. In turn, confirmation of morphological criteria of active inflammation of non-ischemic nature forces us to make a diagnosis of acute or chronic myocarditis, which from a practical point of view will allow to discuss the prospects of specific therapy. Thus, the use of the term "inflammatory cardiomyopathy", which can be classified under ICD-10 headings I.42.8 (other cardiomyopathies) or I.42.9 (unspecified cardiomyopathy), does not significantly affect the management of a patient with recent myocardial systolic dysfunction, which traditionally is treated as DCM as a clinical diagnosis by practicing doctors until modern research methods are applied. In addition, it has been shown that previously silent recessive defects in genes not related to immunity but encoding the synthesis of cardiomyocyte structural proteins responsible for the development of cardiomyopathies increase susceptibility to viral infection as the most frequent cause of myocarditis [5]. This fact only confirms the theory of J. F. Goodwin on the polyethological nature of DCM syndrome [3, 6].

The issues of myocarditis classification cannot be considered secondary, because it is it that systematizes the doctor's thinking and largely determines the approaches to diagnosis and treatment. At the same time, there is no unified classification of myocarditis, which would meet the clinical requirements and make it possible to choose the optimal management tactics. This is probably why classification is one of the weakest points in the presented recommendations. Unfortunately, the Mayo Clinic classification, which emphasizes the nature of disease course depending on the variants of myocardial debut, and the clearly outdated clinical and morphological classification of Lieberman E. B., et al. are chosen as the main ones. In this regard, such variants of disease course as fulminant and subacute myocarditis are highlighted, but omitted is acute, which occurs much more often than fulminant and requires a special algorithm for decision-making. Such rare variants of myocarditis as gigantocellular and eosinophilic remained outside the classification tables, which cannot be diagnosed without EMB, although all of them, as a rule, have fulminant or acute course. Not only granulomatous myocarditis was lost in the classification, but also the most frequent morphological variant — lymphocytic myocarditis. According to the proposed classifications, the Russian recommendations divide chronic myocarditis into active and persistent, although it is not always possible to draw a parallel between the disease course and the morphological picture. In addition, myocarditis staging and, hence, diagnosis of chronic myocarditis is performed on the basis of detection of fibrous changes in myocardium at histological examination of EMB.

Prospects of using magnetic resonance imaging (MRI) of heart for differential diagnosis of chronic myocarditis are very doubtful, as sensitivity of Lake Louise criteria does not exceed 63% [7]. And only introduction of modern methods of T2-mapping, according to experts, allows to increase sensitivity of magnetic resonance criteria for detection of active inflammatory process up to 89% [8]. From the point of view of a practical physician, the domestic classification proposed and subsequently modified by N. R. Paleev and F. N. Paleev [9] is the closest to the optimal structure (etiology, pathogenesis, morphology, prevalence, nature of course, severity and variants of debut), but needs additional correction taking into account the results of modern clinical and morphological studies. Only this type of classification will allow a decision-making strategy to be developed regarding the choice of optimal therapy. As a result, the participants of the discussion agreed that for the next document revision, it is necessary to create a unified version of the classification, devoid of above-mentioned drawbacks, which will allow to avoid the wish of doctors "*to use any version of the classification*".

In the same section of the recommendations, one of the most fundamental issues is briefly discussed — indications for EMB in patients with suspected myocarditis. This question was discussed extensively when working on the text and essentially sounds like this: Does a doctor have the right to diagnose myocarditis and prescribe its treatment when a myocardial biopsy is not possible? European experts say no. The text of the national recommendations favors the more lenient American approach, which involves dividing the indications for EMB into absolute and other indications.

Absolute indications include hemodynamic instability in patients "*with a heart failure clinic of less than 2 weeks with normal or dilated left ventricle and first-onset heart failure lasting from 2 weeks to 3 months with dilated left ventricle, recurrent ventricular arrhythmias, grade II, III atrioventricular block (atrioventricular block) or lack of response to ongoing recommended therapy for 1-2 weeks*". Obviously, these indications cover a significant proportion of patients with fulminant and acute myocarditis of moderate to severe course.

The following section on "diagnosis" lists in more detail the clinical scenarios for EMB, taken from the 2007 guidelines [10]. The first four are mainly related to myocarditis — heart failure (HF) and/or dangerous rhythm and conduction disturbances of various prescription without a sufficient response to the optimal recommended therapy. However, given the cardiotoxic effects of antitumor drugs to exclude myocarditis in patients with a history of anthracycline therapy, and subsequently in patients receiving targeted or immune therapy for cancer, EMB may also be relevant.

In the course of discussion, it was suggested that EMB is insufficiently informative and has low sensitivity and specificity. In such cases, the question always arises — what is the diagnostic significance of EMB compared to, if it remains the "gold standard" in the diagnosis of myocarditis? We can only talk about the percentage of biopsies that allowed us to make (clarify) the clinical diagnosis and determine indications for treatment. But this percentage depends entirely on the principles of selection for biopsy and the capabilities (experience) of the center. In expert centers with extensive experience in EMB, its usefulness in making a diagnosis exceeds 90-95%. The question is not about the possibility of EMB performance (many centers have experience in such manipulations), but about the prospects for further immunohistochemical and molecular genetic analysis of biopsy material. To this end, it makes sense to create a network of expertise centers in which such research can be conducted.

The second no less important question is what does EMB offer in comparison to noninvasive diagnostic methods, which are generally more accessible to Russian doctors? The recommendations provide a very detailed review of the value of the individual history (primarily the association of symptoms with past infection) and the capabilities of currently available noninvasive methods for diagnosing myocarditis. It should be emphasized that none of them has an absolute value (although all methods were evaluated for their diagnostic significance in comparison with the "gold standard" — biopsy).

Insufficient specificity of radionuclide methods (except for diagnosis of cardiac sarcoidosis), low informative value of serological and molecular genetic studies in blood serum to confirm viral etiology of myocarditis were noted. It is emphasized that an increased level of cardio-specific autoantibodies serves as an additional indication of the autoimmune nature of the pathological process. At the same time, attention should be drawn to the lack of standardized kits for the evaluation of cardio-specific autoantibodies in the Russian Federation. The place of coronarography in the differential diagnosis of myocardial damage in patients with intermediate and high pretest probability is outlined. The issue of including computed coronary angiography in the algorithm of examination of a patient with suspected myocarditis remains open, because even in case of the disease onset as an acute coronary syndrome in a patient without traditional risk factors in some cases it is more justified to perform invasive coronarography to verify the diagnosis. During the discussion of clinical manifestations of myocarditis, it was suggested to create an algorithm describing the sequence and scope of diagnostic methods, quantitative (point) criteria for making a probable diagnosis of myocarditis, but such an algorithm was not included in the final recommendations.

The significance of biomarker determination in the diagnosis and monitoring of patients with myocarditis was unexpectedly discussed. This is probably due to the wider familiarity of these laboratory indicators and the experts' greater experience in their application. However, for myocarditis, there have been no randomized studies assessing the informative value of biomarkers, so all the provisions reflected in the text of the recommendations are only extrapolations from other areas of cardiology. In particular, the appropriateness of frequent determination of NT-proBNP level was questioned by experts. In the final text of the recommendations, this study is suggested for all patients with suspected myocarditis (as an objective tool to monitor the degree of decompensation over time), but it is clear that this biomarker is nonspecific and its increase cannot be directly used to diagnose myocarditis.

The most common alternative to EMB is contrast-enhanced cardiac MRI. Suffice it to say that even the European myocarditis registry included patients on the basis of either biopsy or MRI data (the experts really assessed the situation with biopsies in European countries) [11]. The Russian recommendations quite rightly note that while MRI has a high resolution and is useful in assessing myocardial disease, "*the method sensitivity decreases in patients with a long disease course and chronic myocarditis, especially out of exacerbation. Delayed contrast <...> does not allow to differentiate between acute and chronic phases of inflammation,*

i.e. the interpretation largely depends on clinical state of the patient". It should be noted that in patients with unstable hemodynamics who are on inotropic or circulatory support, MRI examination can be performed only after hemodynamics stabilization, i.e. when they are discharged from the hospital. Therefore, in order to exclude rare variants of myocarditis, for which the prescription of combined immunosuppressive therapy is recommended, the strategy of EMB is justified. In patients with acute myocarditis with the type of acute coronary syndrome or with the picture of recent HF but preserving hemodynamic stability, cardiac MRI can be diagnosed with diagnostic accuracy of ~85% [7]. However, it should be remembered that cardiac MRI has low diagnostic value for differential diagnosis between chronic myocarditis and DCM.

Analysis of current practice in various regions of Russia with regard to myocarditis treatment shows that none of the noninvasive methods of diagnosing the disease, including cardiac MRI, usually gives the physician enough confidence to initiate specific therapy for myocarditis. There are three reasons for this: the mandatory biopsy to determine the scope and nature of drug therapy according to European experts, the insufficient evidence base regarding the effectiveness of immunosuppressive therapy, and the high risk of its side effects.

One of the main objectives of the Russian recommendations was to offer practitioners a simple algorithm for selecting a treatment for each individual case. During the discussion of treatment issues, a broad discussion unfolded. The difficulty in developing a therapeutic strategy was the fact that data from multicenter randomized trials, which have become indispensable in cardiology, are almost completely absent today. Therefore, the Russian recommendations, like their European predecessor in 2013, take into account only the opinion of experts who relied on a small number of single-center studies and data from the registry analysis.

The final recommendations included the following statement: "*Administration of glucocorticosteroids (H02AB) is not indicated in patients with acute myocarditis, with the exception of autoimmune, eosinophilic, granulomatous and giantcellular myocarditis*". It is important to note that this conclusion should equally apply to clinical cases of fulminant myocarditis. Unfortunately, when discussing the effectiveness of glucocorticosteroids in patients with acute myocarditis and unstable hemodynamics (p. 58), reference is made to the results of a single-center clinical trial of TIMIC, although the criteria for inclusion in the study refer to patients with a chronic HF clinic >6 months who do not respond to standard HF therapy, i.e. patients with chronic myocarditis or inflammatory cardiomyopathy, as this nosological form is commonly called in the English literature.

In patients with fulminant and acute myocarditis, the prevailing view is that immunosuppressive therapy is indicated only after histological confirmation that the clinical case belongs to rare variants of myocarditis (autoimmune, eosinophilic, granulomatous and giant cell). The recommendations for steroid therapy in viral-negative myocarditis also refer mainly to patients with chronic lymphocytic myocarditis, although the Russian recommendations also include rare myocarditis variants in this group. However, the evidence base for the efficacy of immunosuppressive therapy in acute myocarditis is insufficient.

The role of parvovirus infection in the development of myocarditis should be considered separately. Given the high prevalence of this viral infection in the general population and the frequent detection of the viral genome in myocardium in patients without inflammatory myocardial damage, there is an opinion that parvovirus B19 is present in myocardium in most cases as a non-specific myocarditis witness rather than as the main pathogen causing the disease [12]. Only the presence of a high titer of viral copies (>500 viral DNA copies per microgram of cardiac DNA) and confirmation of its replication are currently recognized as associated with the myocarditis development. Most of the EMB samples obtained from patients with acute or chronic myocarditis have a low abundance.

A number of studies have confirmed the efficacy of immunosuppressive therapy in patients with persistent parvovirus infection, regardless of abundance, as well as comparable efficacy of therapy in patients with myocarditis confirmed by biopsy and diagnosed without biopsy (among which there could be parvovirus-positive patients) [13, 14]. The situation is somewhat different with Ebstein-Barr virus and herpes virus type 6, reactivation of which is associated with a severe course of myocarditis. It has been shown that the genome of herpes virus type 6 can integrate into the DNA of somatic or embryonic cells. However, whether integrated viral particles can reactivate and induce myocarditis is still unclear.

During the on-line discussion, quite fair thoughts were expressed that the reasons for a strict ban on the use of steroids in severe forms of acute and fulminant myocarditis and the inability to immediately perform EMB are not enough — such an official ban would tie doctors' hands and deprive many patients of a chance for a more favorable disease course. However, it should be remembered that unjustifiably early prescription of steroids without verification of the diagnosis and using the reserve possibilities of additional (inotropic/

circulatory support) methods of treatment of acute HF may be associated with a high risk of septic complications development. Therefore, recommending telemedicine counseling and/or transferring such patients to specialized level 3 centers is important to indicate as an important step in medical care.

Regarding patients with chronic myocarditis, the recommendations on the use of immunosuppressive therapy agree with the opinion of most foreign experts: "*Immunosuppressive therapy may be considered in patients with moderate or severe heart failure, life-threatening rhythm and/or conduction disturbances with ineffective standard therapy only if histological and immunohistochemical confirmation of myocardial inflammatory disease and the absence of the viral genome in myocardial biopsy specimens are present*". To justify the alternative approach, a multicenter clinical trial is needed to confirm or refute the possibility of prescribing immunosuppressive therapy in virus-positive patients and to determine the therapy optimal dose and duration. Logically, the question was raised about the advisability of repeated myocardial biopsy to confirm the subsidence of inflammation or, conversely, in cases of ineffective treatment. However, this provision was not included in the final text of the recommendations, and the criteria for assessing the effectiveness of treatment of myocarditis and its discontinuation are not included in the document.

With regard to therapy with intravenous immunoglobulins and the use of immunosorption (selective and non-selective), the Russian recommendations are as cautious as the European recommendations issued seven years earlier (no fundamentally new studies have been added over the years): they are not recommended as mandatory treatment methods in adults. However, as noted in a recently published meta-analysis, the reason for such disappointing results was the study design and, in particular, the low representativeness of the study samples [15]. During the discussion, there were more positive statements regarding the use of plasmapheresis, therapy with intravenous immunoglobulin G (based on recent reviews), the appropriateness of using different (moderate or high) doses of immunosuppressive drugs was discussed, different regimens were proposed, but this has not yet been reflected in the document adopted.

The prescription for antiviral therapy is also not categorical: "*In real practice, where it is unlikely to obtain data on the presence of viral genome in myocardium, a consultation with infectious disease specialists will optimize the diagnostic decision and determine the advisability of initiating antiviral therapy*". But even with information about viral genome in myocardium, the choice of antiviral drugs is very limited. Recommendations reproduce the data on effectiveness of betaferon in some forms of viral myocarditis, but we have almost no own Russian experience of using this drug. And in general, the effectiveness of antiviral treatment in myocarditis is low, which is probably due not only to the lack of etiotropic drugs, but also to the complex pathogenesis of viral myocarditis (early start of autoimmune and autoinflammatory reactions). It should also be noted that in the Russian Federation, test systems originally developed for diagnosis of viral DNA by polymerase chain reaction (PCR) in serum are used for detection of viral genome in myocardium. Standardized kits to estimate the number of viral DNA copies per microgram of cardiac DNA are not currently available. In this regard, the prospects of prescribing antiviral therapy requiring at least 500 copies of viral genome in myocardium for its initiation or confirmation of viral replication by real-time reverse transcription PCR are rather dubious. The use of immunohistochemical analysis to detect VP-1 capsid protein of enterovirus in myocardium as an alternative to PCR with reverse transcription for diagnosis of enterovirus infection in myocardium in the Russian Federation does not allow to diagnose active enterovirus infection in myocardium, which also limits the use of beta interferon, proven to have a positive effect on enterovirus clearance.

Thus, the Russian recommendations are the first document regulating the management of patients with suspected myocarditis. And like any first basic document, it is not without flaws, which is primarily due to the complexity and insufficient study of the problem of inflammatory myocardial disease itself. But the accumulation of new knowledge about the etiology, pathogenesis and approaches to treatment of patients with myocarditis will allow adjustments to the presented recommendations. In particular, 2020-2021 forced us to deal with a very special form of myocarditis, coronavirus myocarditis — with prolonged persistence of the virus in the myocardium and simultaneously high immune activity, which largely determines the prognosis and requires active therapy. Note, incidentally, the provision of the national recommendations that "*vaccination against measles, rubella, mumps, influenza, poliomyelitis, and pneumococcus <...> is mandatory*". In turn, the feasibility and safety of vaccination against SARS-CoV-2 in patients with a history of myocarditis, including postvaccination myocarditis, remains an open question, which is likely to be reflected in the next revision of the recommendations.

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Effectiveness of immunosuppressive therapy for lymphocytic myocarditis according: data from actual clinical practice

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Aim. To compare the effectiveness of standard heart failure therapy with and without combined immunosuppressive therapy in patients with documented lymphocytic myocarditis (LM) based on data from actual clinical practice.
Material and methods. This observational study included 70 patients with documented LM, 40% (n=28) of whom received immunosuppressive therapy. All patients underwent standard echocardiographic and laboratory investigations, endomyocardial biopsy with histological, immunohistochemical and molecular genetic analysis. Contrast-enhanced cardiac magnetic resonance imaging was performed in 74% of patients. All patients received standard therapy for heart failure at baseline.
Results. The groups did not differ in demographic and echocardiographic characteristics. The appointment of immunosuppressive therapy was accompanied by an increase in ejection fraction by 12,2% compared to 6,4% (p=0,02). There were no significant differences in combined endpoints (survival and the need for heart transplantation) depending on therapy regimen (log-rank p=0,97).
Conclusion. The prognosis of patients with chronic LM depends on the process activity, the severity of impaired hemodynamics and ventricular arrhythmias, as well as on the presence of persistent viral infection. Compliance with patient selection algorithm before prescribing immunosuppressive therapy is associated with the improvement in myocardial global contractility.

Keywords: myocarditis, immunosuppressive therapy, prognosis.

Relationships and Activities. The study was carried out within the State Assignment of the Russian Ministry of Health "Transcriptomic biosignatures of peripheral blood cells for the prognosis of non-coronary myocardial disease course" № A20-120092490041-0.

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Myocarditis remains one of the most difficult diagnoses not only due to mosaic and nonspecific clinical manifestations of the disease, but also due to a rather complicated algorithm of diagnosis confirmation, often requiring a lifetime endomyocardial biopsy (EMB) for its verification and choice of optimal treatment method. Most patients diagnosed with acute myocarditis respond to standard therapy for heart failure (HF) and/or antiarrhythmic therapy. The analysis of two-year dynamic follow-up of patients with morphologically documented myocarditis in Charite clinic shows that left ventricular (LV) ejection fraction (EF) did not initially decrease in 26% of cases, in 27% of cases it recovered by the 2nd year of follow-up, and in 34% of patients it improved against standard therapy of HF [1]. However, the course of acute myocarditis can change rapidly. Therefore, patients with suspected myocarditis and elevated troponin levels or electrocardiogram changes should be hospitalized. Often, when hospitalized in patients with severe myocarditis, alternative therapies and, in particular, immunosuppressive therapy are used. However, most experts believe that immunosuppressive therapy in patients with acute and fulminant myocarditis should be discussed only after histological and immunohistochemical verification of the diagnosis of such rare forms of myocardial inflammatory diseases as giant cell, eosinophilic, granulomatous and autoimmune myocarditis [2]. The latter is usually associated with systemic connective tissue diseases. For other forms of inflammatory myocardial disease, the situation is more complicated. The results of the only multicenter clinical trial of MTT (Myocarditis Treatment Trial), which included 111 patients with systolic LV dysfunction and morphologically documented lymphocytic inflammation out of 2233 patients with suspected myocarditis, have not confirmed a positive effect of immunosuppression therapy on the combined endpoint (patient survival rate and need for heart transplant) and global myocardial contractility [3]. However, the active introduction of immunohistochemical and molecular genetic methods for the EMB analysis made it possible to formulate the basic principles of selecting patients for immunosuppressive therapy: disease duration ⩾3 months, presence of LV systolic dysfunction, histological and immunohistochemical criteria of myocarditis, as well as absence of viral genome. But in real clinical practice it is rarely possible to implement the proposed algorithm, which is clearly demonstrated by the discussion that has developed around the Russian recommendations for the management of patients with myocarditis.

The present study goal: on the basis of real clinical practice data, to carry out a comparative analysis of the efficacy of standard HF therapy without and in combination with combined immunosuppressive therapy in patients with morphologically documented lymphocytic myocarditis (LM).

Material and methods

Between 2017 and 2020, the observational study included 70 patients aged 18-64 years (66% men) with documented LM (number of $CD3^+$ cells in myocardial biopsy samples 18 [15; 22] per mm^2) and disease duration >3 months who were treated at the V.A. Almazov Scientific Research Center. The study protocol was approved by the Center's local ethics committee. All studies involving individuals was performed in accordance with the Declaration of Helsinki after signing informed consent. We used diagnostic criteria of myocardial inflammatory disease proposed by the European Society of Cardiology expert group for the enrollment [2].

All patients, according to the current recommendations, were treated for the correction of HF symptoms and/or rhythm disturbances [4, 5]. Along with basic therapy, immunosuppressive therapy, both as monotherapy with glucocorticosteroids and in combination with cytostatic drugs, was prescribed to 40 percent of patients, guided by history, clinical course and morphological analysis of EMB. In prescribing hormonotherapy, we followed the regimen proposed in the TIMIC study: prednisolone at 1 mg/kg per day for 1 month, followed by a decrease of 0,33 mg/kg for 5 months [6].

All patients underwent a standard echocardiographic (Echo) examination on Vivid 7 device (GE, USA) at the time of diagnosis verification and again after 7 [5; 12] months. Cardiac magnetic resonance imaging (MRI) with contrast enhancement (Gd-DO3A 0,2 ml/kg body weight) was performed on high-field Magnetom Trio A Tim 3.0T (Siemens) in 74% of patients. Every third patient subsequently underwent a control MRI examination. Lake Louise consensus criteria were used to assess inflammatory changes in myocardium: focal or global enhancement of MR signal intensity on T2-VI, increase of global early myocardial contrast enhancement coefficient and presence of late contrast enhancement foci in myocardium [7]. Patients with intermediate and high pretest probability underwent coronary angiography (n=42). As additional methods of investigation, the patients underwent daily electrocardiogram monitoring, determination of C-reactive protein level on automatic biochemical analyzer "CobasIntegra 400+" by turbidimetric method, assessment of serum concentration of N-terminal brain natriuretic propeptide (NT-proBNP) by electrochemiluminescent method on Elecsys analyzer (Roche Diagnostic) and troponin I by immunoassay method.

Table 1

Clinical characteristics of patients in the study groups

	Group with immunosuppressive therapy, n=28	Group without immunosuppressive therapy, n=42	
Age, years	38,7±14,0	40,4±11,9	0,59
Gender, m:w	15:13	31:11	0,08
Body mass index, kg/m^2	24,7±5,6	26,1±6,2	0,34
Smoking, n (%)	15 (54)	23 (55)	0,92
Infection suffered in the last 12 months, n (%)	16 (57)	23 (55)	0,84
Autoimmune diseases, n (%)	2 (7)	9 (21)	0,11
Time from the moment of the first clinical symptoms to the diagnosing, days	104 [24; 255]	93 [34; 295]	0,96
Disease onset			
Pain syndrome, n (%)	9 (32)	17 (41)	0,48
Symptoms of heart failure, n (%)	24 (86)	36 (86)	1,00
FC III/IV (NYHA), n (%)	22 (79)	29 (69)	0,38
Cardiogenic shock, n (%)	6 (21)	2 (5)	0,03
Systemic hypotension, n (%)	14 (50)	7 (17)	<0,01
Rhythm and/or conduction disturbances			
Atrial fibrillation/flutter, n (%)	6 (21)	12 (29)	0,50
Ventricular tachycardia, n (%):	19 (68)	27 (64)	0,76
— unstable, n (%)	6 (21)	18 (43)	0,06
— stable, n (%)	13 (46)	9 (21)	0,03
Echo parameters			
Longitudinal LA size, mm	45,1±8,2	46,5±7,3	0,48
LV EDD, mm	62,6±10,3	66,5±11,5	0,15
LV ESD, mm	52,9±9,5	54,5±14,4	0,62
LV ejection fraction, %	28,5±11,6	30,7±11,4	0,43
RV parasternalnaya position, mm	31,9±6,8	32,8±5,2	0,51
TAPSE, mm	16,9±4,7	18,3±3,2	0,17
Systolic pressure in pulmonary artery, mmHg	36,8±10,5	38,3±9,8	0,52
Heart MRI parameters:			
	n=21	n=31	
LV EF, n (%)	31,6±12,2	27,5±13,2	0,34
Myocardial edema by T2WI, n (%)	11 (52)	8 (26)	>0,05
LGE, n (%)	20 (95)	30 (97)	0,77
Drug therapy:			
BB + ACE inhibitors/AIIRA, n (%)	27 (96)	38 (91)	0,34
BB + ACE inhibitors/AIIRA + diuretics, n (%)	22 (79)	33 (79)	0,71
Inotropic drugs, n (%)	10 (36)	6 (14)	0,04
Immunoglobulins, n (%)	9 (32)	10 (24)	0,44
Disease outcomes:			
Heart transplantation, n (%)	5 (18)	2 (5)	0,07
Fatal outcome, n (%)	1 (4)	4 (10)	0,34

Abbreviations: AIIRA — angiotensin II receptor blocker, ACE inhibitors — angiotensin-converting enzyme inhibitors, BB — beta-blockers, EDD — end-diastolic dimension, ESD — end-systolic dimension, LV — left ventricle, LP — left atrium, MRI — magnetic resonance imaging, RV — right ventricle, EF — ejection fraction, FC — functional class, Echo — echocardiography, T2WI — T2 weighted image, LGE — late contrast enhancement, NYHA — New York Heart Association, TAPSE — tricuspid annular plane systolic excursion.

Table 2

Data of standard laboratory examination and results of histological, immunohistochemical and molecular biological examination of myocardial biopsy specimens

	Group with immunosuppressive therapy, n=28	Group without immunosuppressive therapy, n=42	p
Necrosis/dystrophy of cardiomyocytes, n (%)	24 (86)	18 (43)	<0,01
Fibrosis, n (%)	20 (71)	35 (83)	0,23
$CD3^+$ cells/mm^2, Me (Q25-Q75)	21 [16; 34]	17 [14; 20]	0,06
⩾30 $CD3^+$-cells, n (%)	7 (25)	2 (5)	0,01
$CD68^+$ T-lymphocytes, cells/mm^2, Me (Q25-Q75)	16 [7; 23]	17 [12; 24]	0,47
HLA-DR 1:4	3 (3; 4)	3 (3; 4)	0,48
Viral genome, n (%):	13 (46)	21 (50)	0,77
— Enterovirus, n (%) — Herpes virus type 6, n (%) — Parvovirus, n (%)	9 (32) 0 10 (36)	13 (31) 4 (10) 11 (26)	0,92 0,09 0,39
Laboratory data			
Increase in troponin I ng/ml, n (%)	10 (35)	7 (17)	0,09
NT-proBNP, pg/ml	2091 [678; 3861]	1490 [365; 4928]	0,81
C-reactive protein, mg/l	2,8 [1,2; 4,1]	4,2 [1,5; 16,0]	0,12

Abbreviations: HLA-DR — antigen of the main histocompatibility complex of class II, NT-proBNP — N-terminal brain natriuretic propeptide.

All patients underwent EMB before starting therapy. Repeated morphological examination was required in 14 patients receiving immunosuppressive therapy and one patient on standard HF therapy. Myocardial biopsy specimens were fixed with 10% buffered formalin. Paraffin sections of 2-3 microns were stained with hematoxylin-eosin, van Gieson with elastic trichrome to detect fibrotic changes in myocardium; toluidine was stained with blue and azure-eosin for qualitative and quantitative assessment of inflammatory infiltrates. Immunohistochemical analysis of myocardial biopsy specimens was performed using specific antibodies to major histocompatibility complex class II antigens (HLA-DR, cloneLN3, Leica, 1:300) and T-lymphocyte marker (CD-3, polyclonal antibodies, DAKO, 1:800). The HLA-DR expression of 3-4 points indicated the appearance of the antigen on non-hematopoietic cells, characteristic of the autoimmune genesis of the disease. Active myocarditis was diagnosed in the presence of cardiomyocyte necrosis/dystrophy and inflammatory infiltrate including ⩾7 $CD3^+$-cells per mm^2 [2]. Morphological forms of gigantocellular, eosinophilic, granulomatous inflammation, as well as LM in patients with systemic connective tissue diseases were the criteria for non-inclusion in the study. Also, patients with documented coronary artery stenosis ⩾50%, hemodynamically significant valve or clinically significant comorbidities were not included in the study.

DNA of cardiotropic viruses was detected by polymerase chain reaction. Diagnosis of RNA-containing enterovirus was made by immunohistochemical analysis of myocardial biopsy specimens for VP-1 capsid protein of the virus (monoclonal antibody, Clone 5-D8/1, DAKO).

Clinical characteristics of the groups depending on the volume and nature of the therapy are presented in Table 1.

Statistical analysis was performed using applied statistical softwares IBM SPSS 23, STATISTICA 64 v10.0. The descriptive indices with an approximate normal distribution are presented as arithmetic mean (M), standard deviation (σ) and the number of features in the group (n); in other cases, they are presented as median (Me) and quartiles. The unpaired Mann-Whitney U-criterion was used to statistically test the hypotheses on equality of numerical characteristics of the sample distributions in the compared groups. To compare binary and categorical measures, Fisher's exact two-sided criterion was used. The long-term follow-up period was up to 2 years: 350 [206; 593] days. Combined endpoint: survival and need for heart transplantation — was assessed by the Kaplan-Meier method. Survival in the two groups was compared using a log-rank test. Predictive models were built using binary logistic regression methods and ROC-analysis. Testing of statistical hypotheses was performed at the critical level of significance $p<0,05$.

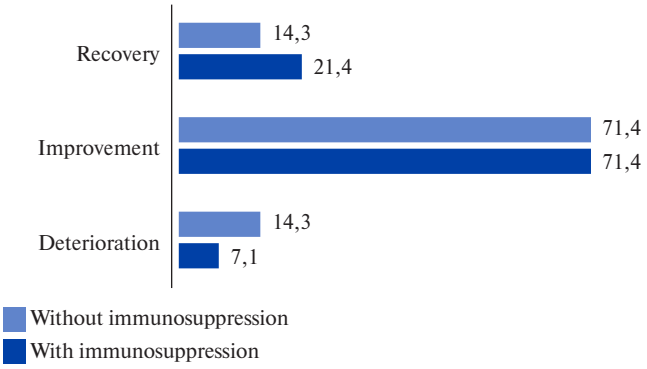

Figure 1. Dynamics of LV EF during follow-up depending on drug therapy nature.

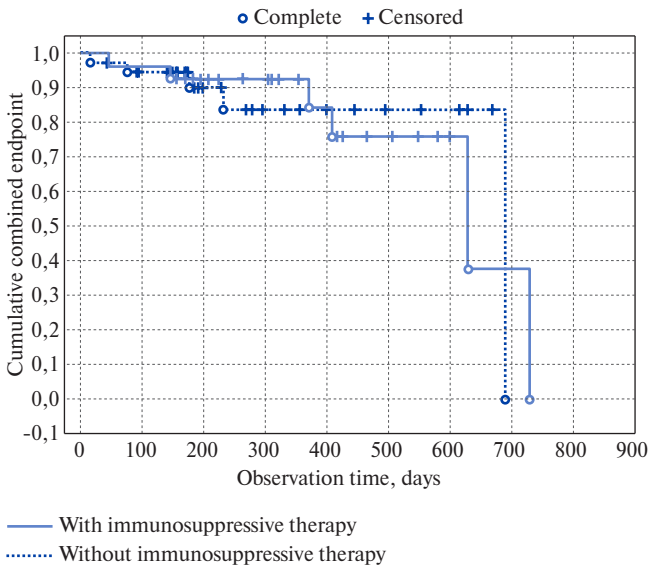

Figure 2. Cumulative survival and need for heart transplantation in patients with morphologically documented LM depending on drug therapy nature (Long-rank p=0,97).

Results

According to clinical and anamnestic data and instrumental examination data, episodes of sustained ventricular tachycardia, systemic hypotension and cardiogenic shock were registered more frequently in the group of patients with myocarditis who received immunosuppressive therapy at the disease onset. Patients with functional class IV (FC) of HF requiring inotropic support prevailed: 57% (n=16) in the immunosuppressive therapy group and 48% (n=20) in the comparison group.

At the same time, the groups did not differ in the initial Echo parameters and the cinema-MRI data (Table 1). In the group of patients on standard therapy, MR criteria of active inflammatory process in myocardium were confirmed less frequently, which is probably associated with a large number of patients with chronic myocarditis, in which the diagnostic value of cardiac MRI is reduced [8].

Necrosis and cardiomyocyte dystrophy, indicating, according to the Dallas criteria, the presence of active myocarditis, were detected in 86% of patients treated with immunosuppressive therapy, and only in 43% of patients in the standard therapy group. According to histological and immunohistochemical analysis of myocardial biopsy specimens, the groups differed in the number of inflammatory cells infiltrating the myocardium (Table 2). Taking into account fibrous changes in myocardium, the majority of examined patients had signs of chronic myocarditis.

The viral etiology of inflammatory myocardial damage was proven in 49% of cases. In the immunosuppressive therapy group, expression of VP-1 capsid protein of enterovirus on cardiomyocytes and vessel walls was detected in 3-30% of cases, whereas the presence of enterovirus genome reached 100% in the comparison group. In this regard, all patients from the immunosuppressive therapy group were preventively treated with immunomodulatory therapy with high doses of intravenous immunoglobulin G (daily dose 0,4 g/kg for 5 days) before the start of specific treatment. 10 patients (24%) received parenteral immunoglobulin therapy in the comparison group.

In addition, patients who received steroid therapy had elevated levels of the myocardial damage marker troponin I and higher values of NT-proBNP. Attention should be paid to the absence of an increase in the C-reactive protein level, which, as is known, does not exclude the diagnosis of myocarditis.

Initially, as part of a steroid-saving regimen, 57% of patients (n=16) received combination therapy with prednisolone combined with azathioprine 2 mg/kg (n=7) or with methotrexate 10-15 mg/week (n=5), or with mycophenolate mofetil 2 g/day (n=4). Due to the development of side effects in two patients, methotrexate and azathioprine were replaced by mycophenolate mofetil. In one case, given the high expression of $CD20^+$ (marker of B-lymphocytes) in the myocardium, rituximab (500 mg/m^2 on day 1 and 500 mg on day 14) was prescribed in addition to standard specific therapy. 12 patients received monotherapy with prednisolone. The variability of combined immunosuppressive therapy regimens did not fundamentally affect disease outcome (p=0,436).

The analysis of the total sample showed an increase in EF by an average of 8,3%. In the immunosuppressive therapy group, EF increased from 28,5±11,6% to 40,8±10,6% compared with the group of patients receiving only standard HF therapy: from 30,7±11,4% to 37,1±11,3%, p=0,02. Depending on the dynamics of myocardial contractility, patients were divided into three groups:

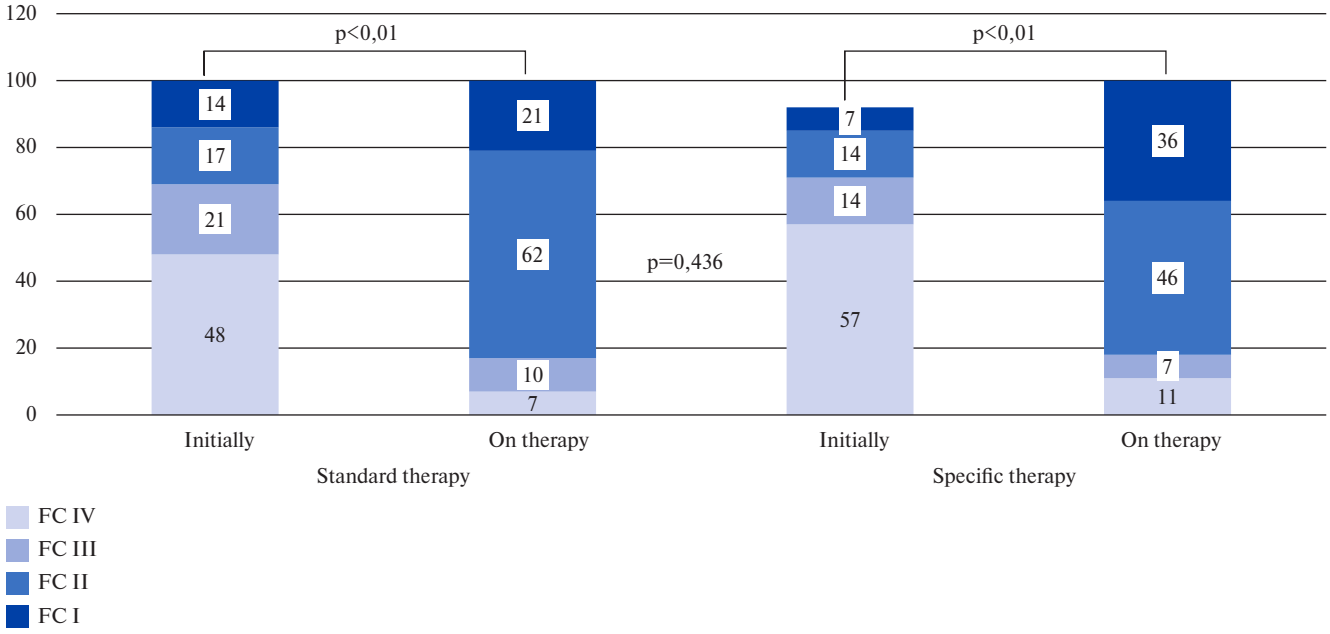

Figure 3. Dynamics of HF FC depending on therapy nature.
Abbreviation: FC — functional class.

Table 3

Logistic regression model for predicting a favorable increase in myocardial contractility

	V	Mean-squared error	Wald	Degrees of freedom	Significance	Exp (B)	95% confidence interval for EXP (B)	
							Lower	Upper
Immunosuppressive therapy	1,42	0,53	7,26	1	0,007	4,15	1,48	11,69
Active myocarditis	0,89	0,66	1,82	1	0,178	2,42	0,67	8,78
Virus	-0,64	0,47	1,88	1	0,171	0,53	0,21	1,32
Signs of chronization	-0,45	0,62	0,54	1	0,464	0,64	0,19	2,13

1) *recovery* was interpreted as an increase in EF of >50%; 2) *improvement* — if there is a positive dynamic, but without reaching EF >50%; 3) *deterioration* was defined as a decrease in EF in the process of observation (Figure 1).

The combined endpoint analysis (survival rate and need for heart transplantation) did not reveal any significant effect of immunosuppressive therapy on the long-term prognosis of patients with LM compared to standard therapy for HF (Figure 2). There was a more favorable prognosis in patients with EF >40% at the time of diagnosis, whereas patients with initially low fraction were more likely to have a severe course of the disease, leading to heart transplantation and/or death (p=0,04). In the course of treatment, HF FC decreased both in the group of standard therapy (p<0,01) and in the group of patients who received additional immunosuppressive therapy (p<0,01) (Figure 3).

Using ROC analysis, the threshold value of EF associated with a favorable prognosis of the myocarditis course was determined (AUC 0,77, 95% confidence interval 0,63-0,91, p=0,03). In our study, it was +12%. After step-by-step regression, the most informative risk factors were selected: immunosuppressive therapy, inflammatory activity, presence of viral genome and signs of chronic inflammatory process. Of the above factors, the use of immunosuppressive therapy proved to be the most significant predictor of a favorable outcome of LM (Table 3). The presence of active myocarditis positively correlated with an increase in EF during treatment, whereas the presence of fibrotic changes and persistent viral infection negatively influenced the long-term results of treatment.

Discussion

HF therapy remains the cornerstone of treatment of patients with inflammatory myocardial disease accompanied by systolic dysfunction. In foreign literature, this pathology is often referred to as "inflammatory cardiomyopathy" [1, 2]. To date, such disease-modifying drugs as angiotensin-converting

enzyme inhibitors/angiotensin II receptor antagonists and beta-adrenoblockers, due to their pleiotropic anti-inflammatory and anti-apoptotic effects, have proven effective as basic therapy for patients with myocarditis. This is also evidenced by the results of our study, in which the two-year survival rate without heart transplantation and the dynamics of functional status of patients did not depend on the regime of the chosen therapy. In contrast, in a recently published study by Merken J, et al, who analyzed the treatment outcomes of 209 patients with virus-negative LM, the administration of immunosuppressive therapy was accompanied by improved survival of patients without heart transplantation (Long-rank p=0,043, hazard ratio 0,34, 95% confidence interval 0,17-0,92) [9]. However, it should be noted that, unlike our sample, in this study, among patients with EF=33%, >60% of patients had CH FC I-II. This point is particularly important because it once again emphasizes the need to exploit the potential of standard therapy for CH before discussing the prescription of immunosuppressive drugs, especially when it comes to patients with chronic LM. The next equally important point — the detection of viral genome. It is still an open question whether a persistent viral infection is the initiator of the pathological process or a bystander. The literature often mentions latent infections caused by herpes viruses or parvovirus B19 [1]. The situation in real clinical practice in Russia is further complicated by the fact that there are no validated test systems designed for the quantification of viral copies in myocardial biopsy specimens. The qualitative assessment (immunohistochemical assay for VP-1 capsid protein of enterovirus), that was used in our study, does not warrant discussion of antiviral therapy before prescription of immunosuppressive drugs. In addition, the possibility of using a combination of antiviral and immunosuppressive drugs in selected patients with virus-positive inflammation is still the subject of debate. The only exception that allows discussing the use of immunosuppressive drugs without prior antiviral therapy may be parvovirus infection, especially when the viral load is low [10]. In this connection, preliminary results of CAPACITY (Cortisone in PArvovirus inflammatory cardiomyopathy) study, demonstrating resolution of inflammation and improvement of EF against the background of immunosuppressive therapy in patients with parvovirus inflammatory cardiomyopathy, look optimistic [11].

In recent years, the possibility of using intravenous immunoglobulins as an alternative approach for detecting latent viral infection has been increasingly discussed, focusing on the positive anti-inflammatory effects of the drugs, immune system activation and opsonization of infectious agents [12]. However, the Russian recommendations for the management of patients with myocarditis referred this class of drugs to level III.

Viral infection initiates autoreactive cellular and humoral immune response. Additional evidence of the autoimmune nature of myocarditis is the persistent myocardial inflammation in the absence of an infectious agent, increased titers of circulating cardiac-specific autoantibodies, and HLA-DR expression on nonhematopoietic cells. In the absence of a viral genome, the efficacy of immunosuppressive therapy also indicates the role of autoimmunity disorders in the pathogenesis of myocardial inflammatory diseases. The improvement of global LV contractility demonstrated in the present study and in a number of other publications once again emphasizes the promise of prescribing immunosuppressive therapy in patients with chronic LM [13]. However, the results of metaanalysis of 8 randomized clinical trials have shown that immunosuppressive therapy does not significantly affect mortality and the need for heart transplantation, but is accompanied after 1-3 months by a significant increase in LV EF by 7%, and in one study with long-term follow-up — by 13% [14]. The explanation should be sought in mosaic nature of myocarditis: the activity variability of pathological process, the influence of hemodynamic disorders and the presence of life-threatening rhythm disturbances on the outcome of the disease, as well as the role of latent viral infection in modulating the expression of genes involved in the pathological process of myocardial structural changes.

Conclusion

The analysis of real clinical practice showed the importance of following the recommendations of standard therapy of HF in patients with LM. Although the administration of immunosuppressive therapy had no effect on survival/need for heart transplantation, adherence to the algorithm for selecting patients for this type of therapy was accompanied by an improvement in global myocardial contractility. The use of intravenous immunoglobulins offers additional opportunities in the treatment of patients with LM. A multicenter clinical trial is needed to resolve a number of debatable issues that arise in prescription of immunosuppressive therapy to answer the question on place of this type of therapy in the treatment of patients with LM.

Relationships and activities. The study was performed within the State Assignment of the Ministry of Health of the Russian Federation "Transcriptomic biosignatures of peripheral blood cells for evaluation of prognosis of the course of noncoronary myocardial diseases" No. A20-120092490041-0.

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Right heart condition in patients with COVID-19 pneumonia

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Aim. To assess right heart condition in patients with coronavirus disease 2019 (COVID-19) pneumonia.

Material and methods. One hundred and five patients with COVID-19 pneumonia were divided into 3 groups depending on the involvement of lung parenchyma: group I — 0-25%, II — 25-50%, III — 50-75%. The clinical status of patients was assessed using the NEWS2 and SHOCS-COVID scales. A complete blood count and biochemical blood tests were performed to determine the level of N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin I. Echocardiography was performed to assess the right heart structural, hemodynamic and functional parameters.

Results. In patients with COVID-19 pneumonia, with an increase in lung parenchyma involvement, the intensity of systemic inflammatory response increased: C-reactive protein, group I — (4 [1,9; 35] mg/l), in III — (70,5 [33; 144] mg/l) (p_{I-III}=0,012); myocardial stress marker level increased: NT-proBNP, group I — 77 [48; 150] ng/l, group III — 165 [100; 287] ng/l (p_{I-III}=0,047). The dependence of NT-proBNP on C-reactive protein level was revealed (r=0,335, p=0,03). Intergroup comparison did not reveal significant differences between the main right heart functional parameters: TAPSE, Tei index (PW and TDI), FAC of the right ventricle (RV) (p>0,05). However, differences in the tricuspid annular peaks were found as follows: group I — 0,14 [0,12; 0,14] m/s, group II — 0,14 [0,12; 0,15] m/s, group III — 0,16 [0,14; 0,17] m/s (p_{I-II}=0,012, p_{I-III}=0,014) and RV global longitudinal strain: group I — 19,63±7,72%, group III — 27,4±5,93% (p_{I-III}=0,014). The relationship between the RV global longitudinal strain and SHOCS-COVID score was confirmed (r=0,381; p=0,024).

Conclusion. Patients with COVID-19 pneumonia showed no signs of right heart dysfunction. The development of RV hyperfunction was noted. Most likely, this is a compensatory mechanism in response to acute RV afterload. NT-proBNP increase under conditions of an inflammatory response may indicate myocardial stress. The results obtained allow to expand our understanding of the right heart condition in patients with COVID-19 pneumonia.

Keywords: COVID-19, echocardiography, NT-proBNP, right heart, global longitudinal strain.

Relationships and Activities: none.

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A new coronavirus infection (COVID-19) caused by the SARS-CoV-2 virus is characterized by multisystem complications, the leading one being respiratory system damage [1]. Cardiovascular damage occurs in patients with COVID-19 in 20-30% of cases. Several pathophysiological mechanisms of cardiac damage are discussed: hypoxia, direct viral myocardial damage, systemic inflammatory response syndrome, hypercoagulation [2, 3].

Special attention should be paid to right heart dysfunction in patients with COVID-19, the frequency of which, according to Insgro G, et al., is 20-39% and often remains undiagnosed [3]. The main concept of right heart dysfunction formation is the formation of a vicious circle — increase of post-load (pulmonary vascular resistance) on the right ventricle (RV) and increase of end-systolic RV volume [4].

The risk group for developing RV dysfunction includes patients with extremely severe COVID-19 complicated by acute respiratory distress syndrome and needing artificial lung ventilation [5, 6].

In the literature available to us, there is insufficient data characterizing the state of right heart in patients with COVID-19 viral pneumonia who have a mild, moderate, severe course and do not require treatment in the intensive care unit.

The study goal is to evaluate the state of right heart in patients with COVID-19-associated pneumonia.

Material and methods

A single-center prospective study enrolled 105 patients with COVID-19 (polymerase chain reaction "+") and viral pneumonia confirmed by chest spiral computed tomography (SCT). The age of the subjects ranged from 27 to 83 years (Me 52 years, IQR [44;61]), of whom 61 (58%) were men. Respiratory support for patients with acute respiratory failure (n=83) was performed in the volume of low-flow oxygenation, the average rate of oxygen mixture delivery was 8,6±2,4 l/min.

Enrollment criteria:

1. Presence of positive result of the polymerase chain reaction on SARS-CoV-2.

2. Presence of viral pneumonia, confirmed by SCT data.

Exclusion criteria from the study:

1. Systolic dysfunction of left ventricle (LV) according to echocardiography (Echo).

2. Severe concomitant pulmonary and cardiovascular pathology: chronic obstructive pulmonary disease, bronchial asthma, acute cerebrovascular accident with marked neurological deficit, postinfarction cardiosclerosis, permanent atrial fibrillation, severe impaired renal function.

The NEWS2 and SHOCS-COVID scales were used to assess the patients' clinical status [7, 8]. SCT with determination of the volume of pulmonary parenchyma damage using MULTI-VOX software was performed (the volume of pulmonary parenchyma lesion did not exceed 75%). General clinical blood test, biochemical blood test with determination of troponin I and N-terminal promoted natriuretic peptide (NT-proBNP) concentration, Echo on day 10±2,5 from the onset of symptoms (equipment Siemens SC2000, Germany), with in-depth assessment of structural (RV diameters, RV wall thickness, volumes of right atrium (RAP)), hemodynamic (systolic pulmonary artery pressure (SPAP), mean pulmonary artery pressure (mPAP), maximal gradient in pulmonary artery) and functional (systolic and diastolic function of RV with calculation of Tei indices and global longitudinal deformation (GLS) of RV and RA) parameters were performed.

Patients received combination drug therapy for SARS-CoV-2-associated infection according to the Provisional Guidelines of the Russian Ministry of Health Version 9 [9].

The study was approved by the Local Ethics Committee of N.I. Pirogov Russian National Research Medical University, Protocol No. 203 dated January 21, 2021. Written informed consent was obtained from all participants prior the enrollment.

According to the study design, patients were divided into 3 groups according to the severity of viral pneumonia according to SCT data. The volume of pulmonary parenchyma damage in group I was 0-25%, in group II — 25-50%, in group III — 50-75% (Table 1).

Statistical processing of the obtained data was performed using the application package IBM SPSS 26 for Windows (USA). Quantitative measures were assessed for normality using the Shapiro-Wilk test (for <50 subjects) or the Kolmogorov-Smirnov test (for >50 subjects). Quantitative indices with normal distribution were described using arithmetic mean (M) and standard deviations (SD), 95% confidence interval limits. In the absence of normal distribution, quantitative data were described using the median (Me) and the lower and upper quartiles [Q1;Q3]. Comparison of three or more groups for a quantitative indicator with a normal distribution was performed using a one-factor analysis of variance, a posteriori comparisons were made using Tukey's criterion (provided that the variances are equal). Comparisons of three or more groups for quantitative index whose distribution differed from normal were made using the Kruskel-Wallis test, a posteriori comparisons were made using the Dunn test with Hill's correction. Comparisons of

Table 1

Characteristics of patients depending on the volume of lung parenchyma damage

	Group I (n=12)	Group II (n=61)	Group III (n=32)	p
Age, years	48,9±17	51,6±13,1	53,1±10,3	0,807
Men, %	7 (58,35)	33 (54)	21 (65)	0,564
NEWS2, score	1,6±0,9	2,3±1	3,2±1,5	0,045*
SHOCS-COVID, score	7,5±3,7	9±2,4	12,8±2,2	0,001*
SpO_2, %	97 [95;98]	93 [92;94]	90 [86;91]	<0,001*
Laboratory data				
Leukocytes, thousands	5,6±2,3	7,7±4,1	8,6±3,4	0,006* p_{I-III}=0,006*
Lymphocytes, thousands	1,2 [0,9;1,7]	1,0 [0,6;1,2]	0,9 [0,7;1,3]	0,124
CRP, mg/l	4 [1,9;35]	48,2 [22,2;91,8]	70,5 [33;144]	0,012* p_{I-III}=0,012*
LDH, U/l	242,92 [215;245]	332 [278;378]	367 [250;420]	0,018* p_{I-II}=0,048* p_{I-III}=0,031*
Fibrinogen, g/l	4,3 [3,6;4,9]	5,8 [4,1;7,3]	5,5 [3,2;7,8]	0,046* p_{I-II}=0,048*
NT-proBNP, ng/l	77 [48;150]	96 [49;212]	165 [100;287]	0,045* p_{I-III}=0,047*
Troponin I, ng/ml	<0,02	<0,02	<0,02	>0,05

Note: data are presented as M±SD or Me [Q1;Q3], depending on type of value distribution of the indicator under study. * — differences in the indicators are statistically significant (p<0,05).

Abbreviations: LDH — lactate dehydrogenase, SHOCS-COVID — rating scale of clinical state of patients with COVID-19, CRP — C-reactive protein, NEWS2 — The National Early Warning Score, NT-proBNP — N-terminal brain natriuretic peptide, SpO_2 — oxygen saturation.

percentages in the analysis of multifield contingency tables was performed using Pearson's chi-square test. Direction and closeness of correlation between two quantitative indicators were assessed using Pearson correlation coefficient (with normal distribution of the compared indicators) and Spearman rank correlation coefficient (with distribution other than normal). A predictive model characterizing the dependence of a quantitative variable on factors was developed using the linear regression method. The differences between the groups were considered significant at p<0,05.

Results

The patients in the groups were comparable in age (p=0,807) and gender (p=0,564). Significant differences were obtained between the groups according to NEWS2 scores: in group I — 1,6±0,9, in group II — 2,3±1, in III — 3,2±1,5 (p=0,045); SHOCS-COVID scores: in group I — 7,5±3,7, in II — 9±2,4, in III — 12,8±2,2 (p=0,001); oxygen saturation (SpO_2): in group I — 97 [95;98]%, in II — 93 [92;94]%, in III — 90 [86;91]% (p<0,001).

In addition, the study of systemic inflammation markers revealed significant differences between the level of leukocytes in patients of groups I (5,6±2,3 thousand) and III (8,6±3,4 thousand) (p_{I-III}=0,006). There were no significant differences in absolute number of lymphocytes (p=0,124), but there was a tendency to lymphopenia in patients with a more severe course of coronavirus infection. There were significant differences in C-reactive protein levels between group I (4 [1,9;35] mg/l) and group III (70,5 [33;144] mg/l) (p_{I-III}=0,012), fibrinogen between group I (4,3 [3,6;4,9] g/l) and group II (5,8 [4,1;7,3] g/l) (p_{I-II}=0,048). The level of total lactate dehydrogenase, which indirectly reflects the pathological process intensity in lung tissue, also differed significantly between groups I (242,92 [215;245] U/l) and II (332 [278;378] U/l) (p_{I-II}=0,048), I and III (367 [250;420] U/l) (p_{I-III}=0,031).

The NT-proBNP level in patients in groups I and II were within normal limits, in contrast to patients in group III, where they were moderately outside normal limits (165 [100;287] ng/l) and were significantly higher than in patients in group I (p_{I-III}=0,047). The troponin I level in the three groups were within normal limits (Table 1).

Thus, the most severe patients, in terms of clinical status and severity of systemic inflammatory reaction (SIR), were in group III.

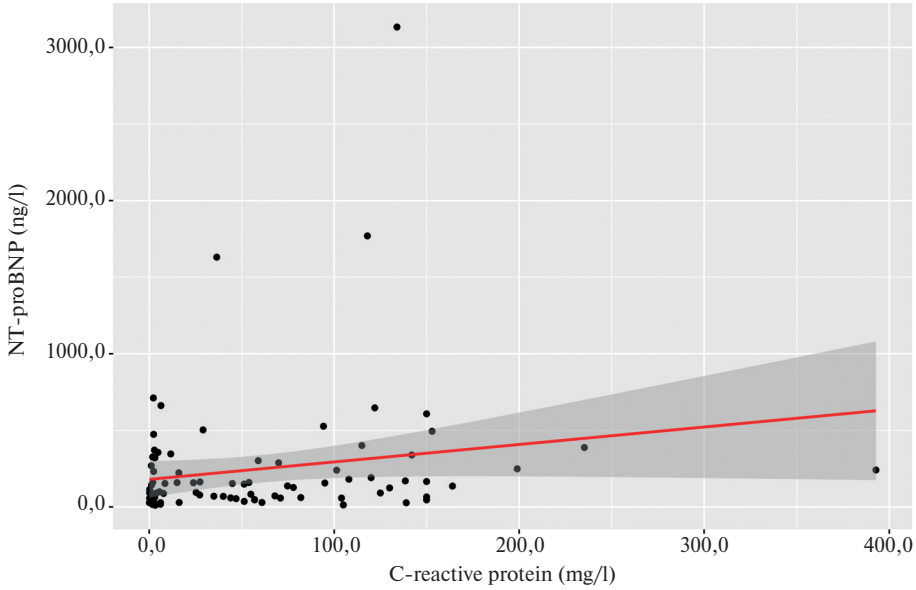

Figure 1. Dependence of myocardial stress marker (NT-proBNP) level on SIR's (CRP) marker in patients with COVID-19-associated pneumonia.
Abbreviation: NT-proBNP — N-terminal brain natriuretic peptide.

The relationship between level of the main marker of SIR — C-reactive protein (CRP) and the marker of myocardial stress — NT-proBNP was of interest. A statistically significant direct correlation of average strength between the above indicators was found (r=0,335, p=0,03). A prognostic model was built to describe the dependence of NT-proBNP level on the degree of SIR tension. The observed dependence is described by a pairwise linear regression equation: $Y_{NT\text{-}proBNP}=1,14\times X_{CRP}+178,702$. It was found that a 1-mg/l increase in CRP should be expected to increase NT-proBNP by 1,14 ng/l (Figure 1).

To assess the condition of the right parts of the heart, an Echo was performed, the results of which are presented in Table 2.

In all patients, LV ejection fraction (EF) was within normal limits (61±3,1%).

Comparison of the RV structural characteristics demonstrated that group III patients had a larger mean RV diameter than group I patients ($p_{I\text{-}III}=0,005$). Significant differences were revealed between all groups in terms of the minimum indexed volume of RA (p=0,038). Otherwise, there were no statistically significant differences in the structural characteristics of RV.

The study of hemodynamic parameters showed that SPAP reached the highest values in group III and was significantly higher than in patients of groups I and II ($p_{I\text{-}III}=0,001$, $p_{II\text{-}III}=0,001$). There was also an increase in mPAP with an increase in the volume of lung parenchyma damage. The values in group I significantly differed from those in groups II and III ($p_{I\text{-}II}=0,017$, $p_{I\text{-}III}=0,018$, respectively). The revealed differences are regular, taking into account the increase of hypoxemic vasoconstriction of the small circulatory circle vessels and dysregulation of vasoactive substances production in pulmonary vessels [10].

In the study of the right heart functional state, the peak s' rate — movement of the free wall of tricuspidal annulus tended to increase on tissue Doppler study. Significant differences in this parameter were found when comparing groups I and II, I and III ($p_{I\text{-}II}=0,012$, $p_{I\text{-}III}=0,014$, respectively). There were no differences in the parameters that most accurately determine the presence of right heart dysfunction: TAPSE, Tei index (PW and TDI), RV FAC (p>0,05).

When analyzing RV GLS as an index of RV systolic function, significant differences were obtained in comparison of groups I and III ($p_{I\text{-}III}=0,014$). Similar changes were revealed in the analysis of RA GLS values — the highest value was obtained in group III patients, and it was significantly higher than in group II patients ($p_{II\text{-}III}=0,002$).

Thus, there was no right heart dysfunction in patients with COVID-19-associated pneumonia. At the same time, higher RV and RA GLS values in group III patients may indicate right heart hyperfunction against the background of pronounced SIR. This observation is indirectly confirmed by the found direct correlation of average strength between the SHOCS-COVID score and RV GLS (r=0,381; p=0,024). The higher rate of peak s' of tricuspidal annulus in group III can be taken into account when discussing the formation of RV hypercontractility.

Table 2

Echo parameters of RV in patients with COVID-19-associated pneumonia

RV indicators	Group I (n=12)	Group II (n=61)	Group III (n=32)	p
RV/LV	0,8 [0,79;0,86]	0,8 [0,73;0,9]	0,8 [0,74;0,85]	0,898
RV, parasternal access, cm	2,7 [2,48;2,82]	2,8 [2,6;3,0]	2,9 [2,68;3,02]	0,267
RV basal diameter, apical access, cm	3,5 [3,4;3,9]	3,8 [3,4;4,1]	3,9 [3,58;4,12]	0,279
RV middle segment, apical access, cm	2,75 [2,6;3,02]	3,1 [2,8;3,5]	3,25 [3,08;3,6]	0,007* p_{I-III}=0,005*
RV length, apical access, cm	6,6 [6,3;7,45]	6,9 [6,2;7,5]	6,7 [5,78;7,62]	0,809
RV wall thickness, cm	0,6 [0,58;0,65]	0,5 [0,49;0,6]	0,6 [0,5;0,64]	0,081
Maximum volume of RA ind., mm^3	28,4 [15,55;28,5]	25,1 [20,82;27]	24,9 [22,45;28,75]	0,743
Minimum volume of RA ind., mm^3	8,9 [7,1;10,9]	11,5 [8,78;14,97]	9,2 [6,75;12,3]	0,046*
Maximum gradient per PA, m/s	2,15 [1,98;2,45]	2,2 [1,8;2,8]	2,6 [1,95;2,9]	0,585
Diameter of PA trunk, cm	2,0 [1,9;2,1]	2,2 [2,0;2,3]	2,2 [2,1;2,3]	0,06
SPAP, mm Hg	27,5 [24,75;30,25]	30,0 [26,0;32]	34 [31,0;36,25]	<0,001* p_{I-III}=0,001* p_{II-III}=0,001*
mPAP, mm Hg	10,7 [10,0;14,07]	16,7 [13,8;23,10]	19 [12,7;23,1]	0,017* p_{I-II}=0,017* p_{I-III}=0,018*
TAPSE, cm	2,25 [2,18;2,38]	2,3 [2,1;2,6]	2,35 [2,1;2,5]	0,919
RV ESA ind., mm^2	5,3 [4,3;6,45]	6,0 [4,9;6,8]	5,5 [4,57;7,95]	0,654
RV EDA ind., mm^2	10,0 [8,85;11,65]	10,9 [9,7;12,5]	10,5 [9,0;13,05]	0,475
RV FAC, %	45 [36,0;47,4]	44 [39,1;51,5]	46,5 [39;51,95]	0,686
RV e', m/s	0,12 [0,1;0,15]	0,14 [0,11;0,17]	0,12 [0,11;0,14]	0,081
RV a', m/s	0,15 [0,14;0,18]	0,15 [0,12;0,18]	0,16 [0,14;0,2]	0,255
RV s', m/s	0,14 [0,12;0,14]	0,14 [0,12;0,15]	0,16 [0,14;0,17]	0,004* p_{I-III}=0,014* p_{II-III}=0,012*
RV E, m/s	0,45 [0,43;0,54]	0,55 [0,49;0,64]	0,55 [0,46;0,6]	0,041* p_{I-II}=0,036*
RV A, m/s	0,43 [0,38;0,47]	0,45 [0,4;0,51]	0,47 [0,4;0,5]	0,461
RV E/A	1,1 [0,97;1,2]	1,2 [0,92;1,5]	1,1 [1,0;1,3]	0,294
RV E/e'	4,05 [3,42;4,4]	4,0 [3,27;4,7]	4,12 [3,75;4,83]	0,657
RV DT, m/s	194 [182;220]	200 [162;227]	202 [170;224]	1,000
Tei index (PW)	0,21 [0,14;0,4]	0,2 [0,15;0,27]	0,21 [0,12;0,29]	0,803
Tei index (TDI)	0,3 [0,25;0,46]	0,33 [0,24;0,45]	0,38 [0,29;0,52]	0,308
RV e'/a'	0,8 [0,6;0,95]	0,8 [0,7;1,0]	0,7 [0,6;0,8]	0,029* p_{II-III}=0,025*
RV GLS, %	19,63±7,72	22,64±5,44	27,4±5,97	0,015* p_{I-III}=0,014*
RA GLS, %	30,07±8,98	26,72±9,47	35,13±8,37	0,003* p_{II-III}=0,002*
RA EF, %	61 [49,5;70]	50 [44,75;62]	59 [49,5;73,0]	0,028*

Note: data are presented as M±SD or Me [Q1;Q3], depending on type of value distribution of the indicator under study. * — differences in the indicators are statistically significant (p<0,05).

Abbreviations: ind. — indexed rate, PA — pulmonary artery, RV — right ventricle, RV/LV — ratio of basal diameter of right ventricle to basal diameter of left ventricle, RV EDA — right ventricle end-diastolic area, RV ESA — right ventricle end-systolic area, the RV FAC — fraction shortening of the right ventricle, RA — right atrium, SPAP — systolic pulmonary artery pressure, mPAP — mean pulmonary artery pressure, RA EF — right atrium ejection fraction, RV GLS — right ventricle global longitudinal strain, RA GLS — right atrium global longitudinal strain, TAPSE — tricuspid annular plane systolic excursion.

Discussion

A small number of publications devoted to the study of the right heart in patients with COVID-19-associated pneumonia have been found in the literature available to us.

In the study of Szekeley Y, et al. (2020) [11] conducted a comprehensive assessment of the cardiovascular system in patients hospitalized with COVID-19. 100 patients were divided into 3 groups depending on the conducted respiratory support. Group 1 included patients without respiratory insufficiency, group 2 included patients with moderate respiratory insufficiency who received non-invasive respiratory support, group 3 included patients on mechanical ventilation. The study of Echo parameters of RV revealed no differences in the end-diastolic area of RV (p=0,85), end-systolic area of RV (p=0,45), RV shortening fraction (p=0,08), systolic excursion of tricuspidal annulus (p=0,63), peak s' of tricuspidal annulus (p=0,55), Tei index (p=0,73). Thus, in patients with different severity of the disease there were no significant differences in structural and functional RV parameters, which coincides with the results we obtained, except for the rate of peak s' of tricuspidal annulus. Taking into account that in our study there were no patients with an extremely severe course of COVID-19, nevertheless there were higher values of this parameter.

The study by Bursi F, et al. (2020) [12] included 49 patients with COVID-19. The authors retrospectively analyzed Echo parameters of the right heart in surviving (n=33) and deceased patients (n=16). SPAP in the group of deceased patients corresponded to moderate pulmonary hypertension (39±11 mm Hg), but this index did not differ significantly from the values in the group of deceased patients (30±7 mm Hg, p=0,06). In addition, the deceased group showed RV dysfunction compared with the group of deceased patients, these are low TAPSE values of 18±3 mm (vs 21±5 mm, p=0,033) and RV GLS of 12±4% (vs 17±5%, p=0,008). In the present study, SPAP in patients with severe COVID-19-associated pneumonia (group III) was moderately elevated. It is interesting to note that in comparison with the study of Bursi F, et al. (2020), despite the severe course of COVID-19-associated pneumonia, there was no decrease in TAPSE in patients, and the GLS index increased, which can be interpreted as part of the development of RV hypercontractility.

Golukhova EZ, et al. (2020) [4] conducted an Echo study in 109 patients with COVID-19 in order to assess the right heart dysfunction in different variants of the course of COVID-19-associated pneumonia. 2 groups were identified — with stable (n=86) and progressive (n=23) COVID-19. In the group with progressive disease were observed moderate right heart dilatation: increase basal RV diameter — 44,3±6,6 mm (vs of 40,3±4,9 mm, p=0,002), the average RV diameter — 37,7 mm (vs 34,2±6,1 mm, p=0,032), indexed RA volume — 32,1 [26,3;42,2] ml/m^2 (vs 24,7 [19,4;33,7] ml/m^2, p=0,009). A number of functional indices of RV did not differ and remained within normal values: RV shortening fraction (p=0,937), TAPSE (p=0,167), Tei index (PW) (p=0,672), Tei index (TDI) (p=0,755). The only parameter that showed significant differences in the intergroup comparison was RV GLS (21,7% in group 1, 16,9% in group 2, p=0,001). The authors concluded that a decrease in this index may correspond to early systolic RV dysfunction.

The study of Li Y, et al. (2020) [13], in which RV GLS was studied as a possible predictor of death in patients with COVID-19, showed high prognostic value (cut-off point 23%, Se 94,4%, Sp 64,7%).

Myocardial GLS determination is a sensitive method for determining early systolic dysfunction of the right and left heart [14, 15]. At the same time, most methods of determining the RV functional state may not provide the necessary information on its systolic or diastolic function. Determination of RV GLS in combination with parameters of pulmonary hemodynamics [16] is the most valuable method for determination of RV function.

The main difference between the above studies and the present one is the examination of patients with an extremely severe and progressive course of COVID-19. Our study enrolled patients with a lung parenchyma damage volume of up to 75%. As a result, it was found not a decrease, but an increase in GLS of RV and RA in patients in the group with severe COVID-19-associated pneumonia. Most probably, this phenomenon is caused by compensatory RV hyperfunction in response to acutely increased postload. This was indirectly confirmed by an increase in NT-proBNP. It is known that NT-proBNP level increases as a result of atrial and/or ventricular distension, or increased myocardial postload, even when LV EF is normal [17].

Conclusion

This study demonstrates that patients with stable but severe COVID-19-associated pneumonia did not show Echo signs of right heart dysfunction. This is most likely due to the short duration of the disease at the time of investigation, absence of cardiomyocyte damage, which is confirmed by normal troponin I level and preserved LV EF in all examined patients. It was found that increase of RV GLS index (hypercontractility) with increasing severity of COVID-19-associated pneumonia and

its direct correlation with SHOCS-COVID scale may indicate the presence of compensatory RV hyperfunction in patients in response to acute post-loading. The NT-proBNP dynamics and its relationship with C-reactive protein (the main indicator of SVR severity) may indicate the presence of myocardial stress in systemic inflammatory response in COVID-19. These results can potentially be used in clinical practice in the comprehensive assessment of the cardiovascular system in patients with COVID-19-associated pneumonia outside the intensive care unit.

Relationships and Activities: none.

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Comparative analysis of the concentrations of proinflammatory cytokines and glycosylated ferritin in patients with idiopathic recurrent pericarditis and adult-onset Still's disease

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Idiopathic recurrent pericarditis (IRP) and adult-onset Still's disease (AOSD) are polygenic autoinflammatory diseases, in the pathogenesis of which proinflammatory cytokines from the interleukin-1 superfamily play a central role.

Aim. To compare serum concentrations of proinflammatory cytokines and glycosylated ferritin (GF) in patients with IRP and AOSD during an exacerbation.

Material and methods. The study included 15 patients with AOSD, 15 — IRP. The diagnosis of AOSD was established using the Yamaguchi criteria (1992). IRP was diagnosed in accordance with the 2015 European Society of Cardiology on the diagnosis and management of pericardial diseases. Blood sampling from all patients was carried out during the recurrence period prior to the anti-inflammatory therapy initiation.

The serum levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-18 (IL-18), procalcitonin, total ferritin and GF was assessed. The results obtained were compared with levels of biochemical parameters, high-sensitivity C-reactive protein (CRP), as well as with white blood cell (WBC) and neutrophil counts.

Results. The median age in the AOSD group was 28 years, and the IRP — 55 years. An increase WBC count >$10*10^9$/L was detected in 10 and 9 patients in the AOSD and IRP groups, respectively. The concentration of CRP was increased in all patients and did not differ in the study groups (p=0,836).

The highest values of ferritin and GF levels were found in the AOSD group (1416 ng/ml vs 408 ng/ml, p=0,008) and (12% vs 33,9%, p=0,067), respectively. In both groups, increased concentrations of IL-6 and IL-18 were determined. In the AOSD group, the concentration of IL-18 was higher than in the IRP group (2114 pg/ml vs 161,5 pg/ml, p<0,001). IL-6 concentrations in the study groups did not differ (33,9 pg/ml vs 24,9 pg/ml, p=0,4). IL-1β serum concentration in all subjects corresponded to normal values.

Correlation analysis in the AOSD group revealed a direct relationship between the IL-18 and ferritin concentrations (r_s=0,73, p=0,03).

Conclusion. The study established a similar pattern of changes in inflammatory biomarkers in patients with AOSD and IRI. The most informative marker of inflammation was IL-18.

Keywords: idiopathic recurrent pericarditis, adult-onset Still's disease, interleukin-1β, interleukin-6, interleukin-18, glycosylated ferritin.

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Idiopathic recurrent pericarditis (IRP) and adult Still's disease (AOSD) belong to a group of clinically similar rare polygenic autoinflammatory diseases (AID), united by similar pathogenesis [1]. It is assumed that they are based on dysregulation of innate immunity, leading to activation of NLRP3-inflammosome. The synthesis of interleukin-1 (IL-1) and interleukin-18 (IL-18) plays a central role. Due to the low incidence and prevalence, the diseases are included in the list of rare (orphan) diseases of the Russian Federation (edit dated June 23, 2021) [2]. Included in the register of rare nosologies in Europe — orphaned [3]. The prevalence of these diseases in Europe for IRP is 6-8 per 100 thousand [4], for AOSD — 0,16-0,4 per 100 thousand [5]. There are no publications assessing the prevalence of AOSD in Russia. The only article assessing the prevalence of IRP in the Russian Federation was published in January 2021 [6].

Currently, the globally recognized criteria used to confirm IRP are specified in the European Society of Cardiology recommendations on the diagnosis and management of patients with pericardial disease 2015 [4]. The diagnosis of recurrent pericarditis is verified if a recurrent episode of pericarditis occurs at least 4-6 weeks after the first episode of acute pericarditis has resolved. Confirmatory signs of pericarditis include clinical and instrumental data (typical retrosternal pain, new effusion into the pericardial cavity or worsening of the previous one, characteristic signs on the electrocardiogram), additional criteria of IRP, such as fever, pleurisy, increased acute phase values, neutrophilia, changes of liver values [7], are currently not obligatory, but serve as a clinical reference for IRP confirmation in disputed cases. However, it is possible to confirm the fact that recurrent pericarditis is *idiopathic* only by a broad differential search, which includes AOSD.

Due to the lack of diagnostic and pathognomonic markers in AOSD, >7 classifications of the disease criteria have been proposed, none of which has 100% sensitivity and specificity. Yamaguchi criteria with sensitivity of 96% and specificity of 92% are recognized as the most widely used classification criteria [8]. The criteria are divided into large and small. To confirm the AOSD diagnosis, 5 criteria should be scored, 2 of which are large, *provided* that other possible causes of pericarditis are excluded. Major criteria include fever >39° C, lasting more than <1 week, leukocytosis $10*10^9$/l, typical rash, and arthralgias for 2 weeks. Minor ones include sore throat, lymphoadenopathy and/or splenomegaly, altered liver tests, negative antinuclear factor and rheumatoid factor. Thus, if a patient's clinical picture is dominated by fever and serositis, and the laboratory parameters are dominated by neutrophilic leukocytosis, a slight increase in aminotransferases, negative indicators of antinuclear and rheumatoid factor, and the instrumental examination reveals moderate lymphoadenopathy, then even if there are no joint symptoms (arthralgia and arthritis) the AOSD diagnosis is legitimate.

Depending on the clinical picture, AOSD is usually subdivided into predominantly articular and predominantly systemic (including without damage to the musculoskeletal tract) forms, and according to the disease course, into monocyclic, polycyclic and chronic [9].

IRP and AOSD — diseases — exceptions. Paradoxically, in order to make a diagnosis of IRP, it is necessary to exclude AOSD, and vice versa. However, when we are talking about a systemic form of AOSD with serositis (as demonstrated in the example) — it becomes almost impossible.

Thus, the diagnosis of IRP and AOSD is complicated by a number of peculiarities:

1. Lack of specific biomarkers of the disease detected both during exacerbation and during remission.
2. Lack of known genetic mutations.
3. Non-specificity of symptoms (fever, serositis, arthralgia, myalgia).
4. Inability to confirm the diagnosis in the absence of signs of disease flare.
5. Presence of extracardiac manifestations in many patients with IRP, on the one hand, and manifestations of serositis in the structure of systemic variants of AOSD, on the other hand.

The above makes it urgent to carry out prospecting work to identify new markers of the disease.

Material and methods

The cross-sectional study included patients with IRP and AOSD over 18 years of age who were examined at the V.A. Almazov Scientific Research Center from 2018 to 2020. IRP was established according to the recommendations of the European Society of Cardiology for the Diagnosis and Management of Patients with Pericardial Diseases [4]. The AOSD diagnosis was confirmed on the basis of Yamaguchi classification criteria [8]. Patients was included during disease recurrence. The IRP recurrence was confirmed in the presence of all 3 symptoms — increase in C-reactive protein (CRP), new pericardial effusion or deterioration of the previous one and typical retrosternal pain. CRP was considered as recurrence when the CRP concentration was higher than the reference and at least 1 clinical symptom, which included arthritis, rash, pericarditis, and/or pleurisy. All participants signed voluntary informed consent to participate in the study. The study was approved by the Ethics

Table 1

Clinical and laboratory characteristics of patients with IRP and AOSD

Indicator (norms)	AOSD, n (%)	IRP, n (%)	p
Number of patients	15 (100%)	15 (100%)	
Gender (female/male)	12/3	11/4	
Age, years	28 [25;42]	55 [44;66]	
Fever	15 (100%)	15 (100%)	1
Pericarditis	6 (40%)	15 (100%)	<0,001
Pleurisy	5 (33,3%)	14 (93,3%)	0,001
Arthritis	13 (86,6%)	3 (20%)	<0,001
Arthralgia	13 (86,6%)	9 (60%)	0,099
Rash	12 (80%)	1 (6,6%)	<0,001
Lymphadenopathy	11 (73,3%)	4 (26,6%)	0,011
Splenomegaly	8 (53,3%)	0 (0%)	0,001
Hepatomegaly	5 (33,3%)	5 (33,3%)	1
Pharyngalgia	11 (73,3%)	4 (26,6%)	0,011
Leukocytes, $*10^9$/l, (4,0-9,0)	13,5 [8,4;17,4]	9,7 [8,2;12,8]	0,158
Neutrophils, $*10^9$/l, (2,00-5,80)	8,8 [4,8;13,4]	6,1 [5,0;9,0]	0,217
AST, U/l, (5,0-34,0)	24 [14;52,5]	26,0 [20,5;45,5]	0,650
ALT, U/l, (0,0-33,0)	61,3 [12;82]	41,0 [29,5;50,0]	0,801
CRP, mg/l, (0,0-5,0)	90 [25;160]	104,0 [57,0;170,0]	0,836
Ferritin, ng/ml, (13,0-150,0)	1416,5 [591;2000]	408 [239;643]	0,008
ESR, mm/h, (2-25)	47 [22;65]	55 [32;65]	0,684
Fibrinogen, g/l, (1,9-4,3)	4,5 [2,8;6,1]	4,6 [4,0;6,1]	0,442
GF, %, (⩾78,3% — normal, 30,5-78,2% — moderate decrease, ⩽30,4% — pronounced decrease)	12,0 [0,1;29,1]	33,9 [29;38]	0,067
IL-6, pg/ml, (0,0-10,0)	33,9 [10,7;56,7]	24,9 [9,9;43,3]	0,4
IL-18, pg/ml, (104,0-270,0)	2114 [1994;2127]	161,5 [120,8;285,2]	<0,001
IL-1, pg/ml, (0,0-11,0)	0,01 [0,01;0,77]	0,39 [0,01;1,03]	0,362
PCT, ng/ml, (0,0-0,05)	0,08 [0,03;0,22]	0,06 [0,05;0,09]	0,541

Abbreviations: AST — aspartate aminotransferase, ALT — alanine aminotransferase, AOSD — adult Still's disease, GF — glycosylated ferritin, IRP — idiopathic recurrent pericarditis, PCT — procalcitonin, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, IL-1 — interleukin-1, IL-6 — interleukin-6, IL-18 — interleukin-18.

Committee of the V.A. Almazov National Medical Research Center in St. Petersburg (No. 28, version 1.0 dated February 12, 2018).

Blood draw in all patients was performed in the morning in fasting state during recurrence of the main disease before the start of contradictory therapy.

The change in concentrations of IL-1, IL-6, IL-18, procalcitonin was performed using enzyme immunoassay (commercial kits manufactured by Vector-Best, Russia). Ferritin — by immunoturbidimetry on an AU-480 analyzer (Beckman Coulter, USA). The determination methodology for glycolized ferritin (GF) is described in the article by Potapenko VG, et al. 2018 [10]. Clinical blood tests, CRP and aminotransferases using standard commercial reagents.

Statistical analysis of the results was performed using Statistica 10.0 for Windows (StatSoft Inc., USA) and Prisma GraphPad 6.0 (GraphPad Software, USA). If an abnormal distribution was detected, the results were described as median and 25^{th};75^{th} percentiles. Mann-Whitney U-criterion was used to compare quantitative signs. Correlation analysis between the studied attributes was performed using Spearman's rank correlation coefficient (r_s). The significance criterion was set at the level of $p<0,05$.

Results

The study included 15 patients with AOSD, 15 with IRP. The median age in patients with AOSD was 28 years [25;42], IRP — 55 years [44;66]. Clinical and laboratory characteristics of the groups,

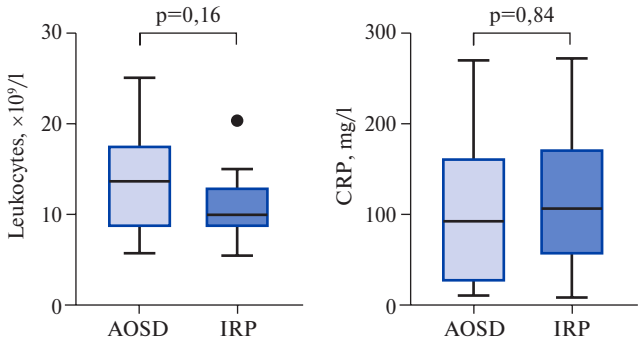

Figure 1. CRP concentration and the number of leukocytes in patients with AOSD and IRP.
Abbreviations: AOSD — adult Still's disease, IRP — idiopathic recurrent pericarditis, CRP — C-reactive protein.

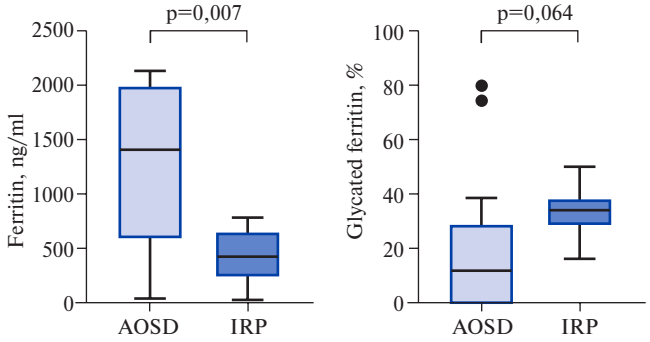

Figure 2. Comparison of ferritin concentration and percentage of GF in serum in patients with AOSD and IRP.
Abbreviations: AOSD — adult Still's disease, IRP — idiopathic recurrent pericarditis.

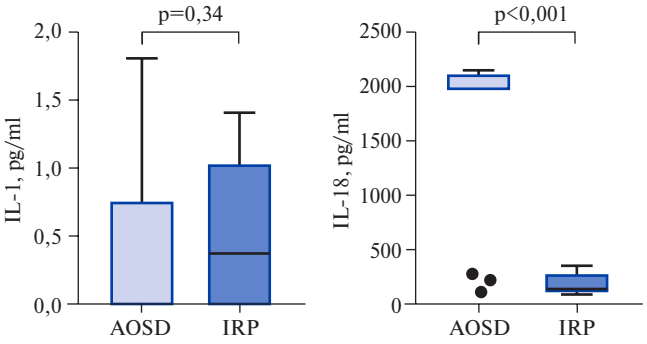

Figure 3. Comparison of IL-18 and IL-1 serum concentrations in patients with AOSD and IRP.
Abbreviations: AOSD — adult Still's disease, IRP — idiopathic recurrent pericarditis, IL-1 — interleukin-1, IL-18 — interleukin-18.

medians of analyzed parameters are presented in Summary Table 1.

Neutrophilic leukocytosis >10*10>⁹/l was detected in 10 patients with AOSD and in 9 patients with IRP. Median concentrations of acute phase markers, aspartate aminotransferase, alanine aminotransferase were elevated in all patients and were not statistically different in the studied groups. The CRP concentration and the number of leukocytes in the study groups are shown in Figure 1. Differences were found in the following indices — median age, ferritin concentration, GF and degree of IL-18 elevation.

Ferritin concentration is increased in both groups. In the AOSD group, the increase in ferritin concentration was statistically more significant (1416 pg/ml vs 408 pg/ml, p=0,008), as was the decrease in its glycosylated fraction (12% vs 33,9%, p=0,067) (Figure 2). The IL-6 and IL-18 concentrations were elevated in both groups, but the IL-18 concentration was statistically significantly higher in the AOSD group (2114 pg/ml vs 161,5 pg/ml, p⩽0,001) (Figure 3). The IL-1 concentration did not exceed the reference values and did not differ in the study groups (Figure 3).

In the correlation analysis, there was a direct correlation between IL-18, ferritin levels (r_s=0,73, p=0,03) in the AOSD group. No other correlations between clinical and laboratory parameters were found, probably due to the small sample size.

Discussion

According to the data obtained during the study, there were no differences in such indices as leukocyte count, absolute neutrophil count, erythrocyte sedimentation rate, CRP, and aminotransferases between the groups. This confirms the fact that it is impossible to distinguish between IRP and AOSD using standard diagnostic approaches. In the absence of established genetic predisposition, informative diagnostic laboratory tests, it is of interest to consider a broader panel of inflammatory biomarkers in order to assess their diagnostic significance.

Ferritin and GF. Normally, >78% of ferritin exists in glycosylated form. With increased synthesis of ferritin by cells (macrophages, Kupffer cells, hepatocytes, endothelium), glycosylation of the protein decreases, which leads to a change in the ratio of free ferritin and its glycosylated form in blood serum. In 2002, Fautrel B, et al. [11] proposed to use GF expressed as a percentage of total ferritin as a laboratory criterion for AOSD. The GF indicator ⩽20% is taken as a diagnostic value. The GF determination has not been performed in other AID. In the present study, the GF percentage in patients with IRP was investigated in a scientific first. According to the results obtained in the course of work, the percentage of GF in patients with IRP is reduced, a median rate was 33,9%. The decrease was less significant than in the AOSD group, where the GF median was 12%, which may be explained by fewer symptoms and less pronounced leukocytosis.

Cytokines. The IL-1 cytokine superfamily has 11 representatives. They are the most important regulators of inflammation, controlling various processes of innate immunity [12]. IL-1β and IL-18 synthesized in response to the inflammasome activation, a key mechanism in the development of AOSD and IRP, are of most interest. Blocking these targets in practice proved to be effective and formed the basis of anticytokine therapy [13, 14] in the treatment of both AOSD and IRP.

IL-1. IL-1 is divided into 2 independent cytokines — IL-1α and IL-1β, united by a common receptor (IL-1R1) and performing similar biological functions.

IL-1β has a central role in AID pathogenesis. Its importance has been confirmed by clinical studies in various AID using IL-1 blockers, where the percentage of responders exceeded 90% [13, 14].

Based on the data obtained in this study, no increase in serum IL-1β concentration was detected in either group. We can assume that the obtained results are underestimated for a number of reasons: first, the existing test systems work incompletely within the low IL-1β concentrations, and second, the cytokine's short half-life.

IL-18. IL-18 is one of the key cytokines synthesized in response to monocytic cell activation. Its significant increase was noted in diseases such as AOSD [15, 16], recurrent macrophage activation syndrome, macrophage activation syndrome associated with loss of NLRC4 function (NLRC4/MAS) [17] pyogenic arthritis, gangrenous pyoderma and acne (PAPA) [18]. A moderate increase was detected in infectious processes such as COVID-19 [19], sepsis [15].

There are no studies evaluating IL-18 concentrations in IRP, and the present study is the first to investigate IL-18 concentrations in patients with IRP. An increase in IL-18 concentration was detected in the studied groups, the concentration was higher in patients with AOSD, which correlated with the ferritin concentration. Our data are comparable with those of Priori R, et al. (2014) [15], where a correlation was found between IL-18 concentrations and ferritin. Her work also noted a correlation between disease activity and IL-18. This was not demonstrated in our cohort, which may be due to a smaller sample.

Colafrancesco S, et al. (2012) [16] demonstrated the relationship between IL-18 concentration and worse prognosis, disease activity, risk of macrophage activation syndrome.

Some authors hypothesized the possibility of using IL-18 as an additional AOSD diagnostic marker [20]. However, the accumulated data do not support this hypothesis. Probably, the determination of IL-18 concentration will find its application when using composite scales.

IL-6. Since the late 1990s, the study of IL-6 as a marker of AOSD activity began [21]. It was not considered as a diagnostic marker, because its increase was noted both in autoimmune diseases and in AID. Similar concentrations of this cytokine in infectious diseases have been shown, and its correlation with CRP level is known. This marker has not been studied in IRP.

In the cohorts we studied, IL-6 concentrations were comparable and correlated with CRP levels in both groups. Its determination in routine clinical practice is not justified due to insufficiently high specificity, but the study of its concentrations is valuable in terms of pathogenesis and prediction of response to therapy with IL-6 blockers.

Conclusion

As part of the study, we established a similar pattern of changes in inflammatory biomarkers in patients with AOSD and IRP, which is expressed in an increase in cytokines (IL-18, IL-6), ferritin. It was noted that the increase in IL-18 concentration was higher in the AOSD group, which may be explained by a more generalized inflammatory process.

If to consider AOSD and IRP on a continuum, a certain pattern can be observed: the younger the patient, the more systemic manifestations (arthritis, rash, splenomegaly), higher levels of ferritin and IL-18.

The obtained data are not sufficient to make an unequivocal statement about the general classification, molecular genetic and epigenomic studies in these conditions are required.

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LITERATURE REVIEW
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Evolution of diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy and their application in clinical practice

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This article describes evolution of criteria for arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). The novel diagnostic criteria for ARVD/C published in 2020 are analyzed in detail, among which biventricular and left-dominant arrhythmogenic cardiomyopathy are identified for the first time. The need to develop novel criteria was fed on the accumulation of new data on ARVD/C, in particular, significant advances in magnetic resonance imaging technologies. The novel criteria retained high sensitivity and specificity in relation to traditional right ventricular disease form and became more sensitive in relation to the biventricular and left-dominant arrhythmogenic cardiomyopathy.
Nevertheless, the addition of left-dominant disease forms reduces the criteria specificity in general, since left ventricle involvement with a similar clinical performance can have different etiology that goes beyond the ARVD/C, even when mutations are detected in typical genes, which is demonstrated by case reports described in the article. Like the previous two versions, the novel criteria will be fully assessed only with a large sample of patients after their introduction into the routine cardiology clinical practice.

Keywords: diagnostic criteria, arrhythmogenic right ventricular dysplasia/cardiomyopathy, myocardial noncompaction, ventricular premature beats, ventricular tachycardia, myocarditis.

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Arrhythmogenic dysplasia/right ventricle cardiomyopathy (ARVD/C) in classical version is a hereditary myocardial disease characterized by fibroadipose myocardial replacement of the right ventricle (RV) and manifested by aggressive ventricular rhythm disorders [1]. This is how G. Fontaine described this disease in 1977 [2]. At that time, ARVD/C was considered a rare disease, but with the expansion of clinical and morphological beliefs about this nosology, the appearance of magnetic resonance imaging (MRI) of heart and the development of DNA diagnostics, information on the prevalence of this cardiomyopathy has changed: today, the frequency of ARVD/C, depending on population, varies from 1:1000 to 1:5000 [3, 4]. ARVD/C accounts for up to 20% of sudden cardiac death (SCD) cases in young individuals [5], which makes timely diagnosis and competent treatment of this disease extremely relevant.

The first criteria for diagnosis of ARVD/C were proposed by a group of experts in this field in 1994 [6]. They were successfully used for >10 years, but later it became clear that the criteria, while highly specific, lacked sufficient sensitivity and did not take into account recent advances in imaging and genetic testing. They underwent revision, and in 2010, the Modified Diagnostic Criteria for ARVD/C (TFC-2010) was published [7]. Since about 2017, the professional community began to actively discuss the refinement of these criteria taking into account the accumulation of data on biventricular and left ventricular forms of ARVD/C. As a result, in 2020, a group of leading experts developed updated (called Padua criteria) criteria for ARVD/C [8], which are analyzed in detail using clinical cases as examples in this article.

ARVD/C diagnosis is complex and requires a complex approach, because there is no diagnostic method that can unequivocally confirm or exclude this diagnosis. Even endomyocardial biopsy (EMB) and DNA diagnostics are not absolute in ARVD/C. Since myocardial fibrotic-fatty replacement is focal and localized subepicardially at early stages of the disease, EMB sensitivity in ARVD/C diagnosis does not exceed 70% [9]. As for DNA diagnostics, despite significant progress in this field, not all genes responsible for the development of this cardiomyopathy have been described, so a negative result has no excluding power.

The first criteria for diagnosing ARVD/C, proposed in 1994, included structural, histological, electrocardiographic, arrhythmic and hereditary signs of the disease [6]. There are large and small criteria in each category, depending on their specificity to ARVD/C. Based on the number of large and small criteria, the diagnosis is understood as reliable, probable or possible. These criteria had high specificity, but were not without a number of drawbacks. Firstly, they focused exclusively on the right ventricular variant of ARVD/C, which was considered to be the main one at that time. Secondly, due to insufficiently high sensitivity, the criteria often did not "work" in early forms of the disease [7]. In the TFC-2010 criteria, which we have used up to now (Table 1), several fundamental differences appeared: quantitative parameters were introduced (volume and RV systolic function, percentage of preserved cardiomyocytes at fibrous replacement), and the presence of fat in RV myocardium was no longer considered mandatory due to its insufficient specificity for ARVD/C. TFC-2010 has been shown to be more sensitive than the criteria in 1994, but not inferior in specificity [7, 10].

A paper on arrhythmogenic cardiomyopathies in a broad sense was published in 2019 [11]. It summarizes data on diagnosis, SCD risk stratification and management of patients with any cardiomyopathy for which rhythm disturbances are typical, in the absence of myocardial ischemia, significant hypertension and valve lesion. In addition to ARVD/C, this included hypertrophic and restrictive cardiomyopathies, left ventricular (LV) noncompact myocardium (NCM), storage diseases, mitochondrial diseases, including Kearns-Seir syndrome, and also canalopathies. In our opinion, combining such heterogeneous diseases under a single term "arrhythmogenic cardiomyopathies" is inappropriate, since their genetic basis, pathogenesis, clinical manifestations, treatment, and prognosis are fundamentally different. Thus, further improvement of diagnostic criteria of classical ARVD/C taking into account left ventricular and biventricular variants is still relevant.

Such criteria were proposed by a group of scientists from Padua in 2020 (Table 2) [8]. Specialists from Italy have the most experience in ARVD/C, since Veneto, where Padua is located, is the endemic region for this cardiomyopathy [12]. In addition, the expert board included other recognized experts from Great Britain, Greece, Germany, the United States, Norway, and Switzerland.

The basis of the Paduan criteria for ARVD/C is still morphofunctional and structural changes, disorders of repolarization, depolarization, ventricular arrhythmias and family history in combination with genetic data. Unlike TFC-2010, there are categories that include only large or only small criteria. The approach to varying measure of diagnosis confidence was preserved. This is of great clinical importance, because patients with a probable and possible diagnosis also require careful follow-up, and often treatment, since they are at risk of SCD

Table 1

Criteria for ARVD/C diagnostics (revision 2010) [7]

	Large criteria	Small criteria
I. Global/regional dysfunction and structural changes	**in Echo:** 1) regional akinesia, dyskinesia or RV aneurysm 2) *and* one or more signs (end of diastole): • RV (long axis) ⩾32 mm (index ⩾19 mm/m^2) • RV (short axis) ⩾36 mm (index ⩾21 mm/m^2) • *or* regional violations ⩽33% **in MRI:** 1) regional akinesia or dyskinesia, or dissynchrony of RV contraction 2) *and* one or more signs: • ratio of RV EDV to the body surface area ⩾110 ml/m^2 (in men) and ⩾100 ml/m^2 (in women) • *or* RV EF ⩽40% **in RV ventriculography:** regional akinesia, dyskinesia or RV aneurysm	**in Echo:** 1) regional akinesia or RV dyskinesia 2) *and* one or more signs (end of diastole): • RV (long axis) 29-31 mm (index 16-18 mm/m^2) • RV (short axis) 32-35 mm (index 18-20 mm/m^2) • *or* regional violations 34-40% **in MRI:** 1) regional akinesia or dyskinesia, or dissynchrony of RV contraction 2) *and* one or more signs: • ratio of RV EDV to the body surface area ⩾100-109 ml/m^2 (in men) and ⩾90-99 ml/m^2 (in women) • *or* RV EF 41-45%
II. Histology	preserved myocytes <60% on morphometric analysis (or <50% on accurate assessment) with fibrous myocardial replacement of the free RV wall in ⩾1 area, with or without fatty tissue replacement (in EMB)	preserved myocytes 60-75% in morphometric analysis (50-65% on accurate assessment) with fibrous myocardial replacement of the free RV wall in ⩾1 area, with or without fatty tissue replacement (in EMB)
III. Repolarization disorders	inversion of T deflections in the right thoracic leads (V_1-V_3) or further in persons over 14 years of age (in the absence of complete RBB block with a QRS width ⩾120 ms)	• inversion of T deflections in leads V_1-V_2 in persons over 14 years of age (in the absence of complete RBB block) or in V_4-V_5 or in V_6 • inversion of T deflections in leads V_1-V_4 in persons over 14 years of age in the presence of complete RBB block
IV. Depolarization/ conduction disorders	epsilon wave (reproducible low-amplitude signal between the end of the QRS complex and the beginning of T deflection) in the right thoracic leads (V_1-V_3)	1) late ventricular potentials (1-3 parameters) on signal-averaged Echo in absence of QRS expansion ⩾110 ms on standard Echo: • filtered QRS duration ⩾114 ms • duration of the final part of QRS (low-amplitude signal duration) ⩾38 ms • RMS voltage of the final part of QRS ⩽20 mV 2) duration of final activation of QRS ⩾55 ms (from the top of S deflection to the end of QRS, including R' in leads V_1, V_2 or V_3 in the absence of complete RBB block)
V. Arrhythmias	unstable or sustained ventricular tachycardia with morphology of left bundle branch block and superior axis (negative or uncertain QRS complexes in leads II, III, aVF and positive in aVL lead)	• unstable or sustained ventricular tachycardia from the LV outlet tract or with morphology of left bundle branch block and inferior axis (positive QRS complexes in leads II, III, aVF and negative in aVL lead) or unknown axis • >500 VES per day (Holter monitoring)
VI. Family history	• ARVD/C in relatives of the first degree (according to diagnosis criteria) • ARVD/C, confirmed morphologically, in relatives of the first degree • identification of pathogenic mutations in the patient with a proven or probable link to ARVD/C	• ARVD/C in relatives of the first degree (when it cannot be determined whether family members meet the diagnosis criteria) • sudden cardiac death (under the age of 35) due to suspected ARVD/C in relatives of the first degree • ARVD/C, confirmed morphologically or according to diagnosis criteria in relatives of the second degree

Note: *reliable diagnosis*: 2 large criteria or 1 large + 2 small criterion (from various categories), or 4 small (from various categories); *probable diagnosis*: 1 large criteria + 1 small or 3 small criteria (from various categories); *possible diagnosis*: 1 large criterion or 2 minor criteria (from various categories).

Abbreviations: ARVD/C — arrhythmogenic dysplasia/right ventricular cardiomyopathy, VES — ventricular extrasystole, EDV — end-diastolic volume, MRI — magnetic resonance imaging, RV — right ventricle, RBB — right bundle branch, EF — ejection fraction, Echo — electrocardiography, EMB — endomyocardial biopsy of right ventricle, Echo — echocardiography.

Table 2

Padua criteria for ARVD/C diagnosis (revision 2020) [8]

	RV (updated TFC-2010 criteria)	LV
I. Morpho-functional changes of ventricles	*Echo, MRI or ventriculography* **Large** • local akinesis, dyskinesis or RV heave *plus one* of the following manifestations: — RV dilation (increase in EDV in accordance with nomograms for a specific imaging method) — systolic RV dysfunction (decrease in EF in accordance with nomograms for a specific imaging method) **Small** • local akinesis, dyskinesis or aneurysm of RV free wall	*Echo, MRI or ventriculography* **Small** • LV systolic dysfunction (reduction of LV EF or reduction of global longitudinal deformation in echocardiography), with or without LV dilation (increase in EDV in accordance with nomograms for a specific imaging method, taking into account age, gender and body surface area) **Small** • local akinesis or dyskinesis of the free LV wall and/or septum
II. Myocardium structural changes	*MRI* **Large** • Transmural LGE (band pattern) in ⩾1 region of RV (input, output tracts and apex in 2 orthogonal projections) *EMB (limited indications):* **Large** • fibrous myocardial replacement in ⩾1 sample, with or without adipose tissue	*MRI* **Large** • LGE in LV (band pattern) in ⩾1 segment (bovine eye in 2 orthogonal projections) of the free wall (subepicardially or intramiocardially) and/or septum (except LGE in the area of interventricular septum junction with the free wall)
III. Repolarization disorders	**Large** • inversion of T deflections in the right thoracic leads (V_1-V_3) or further in persons over 14 years of age (in the absence of complete RBB block) **Small** • inversion of T deflections in leads V_1-V_2 in persons over 14 years of age (in the absence of complete RBB block) • inversion of T deflections in leads V_1-V_4 in persons over 14 years of age in the presence of complete RBB block	**Small** • inversion of T deflections in the left thoracic leads V_4-V_6 (in the absence of complete LBB block)
IV. Depolarization disorders	**Small** • epsilon wave (reproducible low-amplitude signal between the end of the QRS complex and the beginning of T deflection) in the right thoracic leads (V_1-V_3) • duration of final activation of QRS ⩾55 ms (from the top of the S deflection to the end of the QRS, including R' in leads V_1, V_2 or V_3 in the absence of complete RBB block)	**Small** • low voltages of the QRS complex (<0,5 mV) in limb leads (in the absence of obesity, emphysema, or pericardial effusion)
V. Ventricular rhythm disorders	**Large** • frequent VES (>500/day), unstable and/or stable VT with the morphology of LBB block (except VES and VT from VT outflow tract) **Small** • frequent VES (>500/day), unstable and/or stable VT from RV outflow tract (morphology of LBB blockade, lower axis)	**Small** • frequent VES (>500/day), unstable and/or stable VT with the morphology of RBB block (with the exception of fascicular tachycardia)
VI. Family history and genetics	**Large** • ARVD/C in relatives of the first degree of kinship (according to diagnosis criteria) • ARVD/C, confirmed morphologically, in relatives of the first degree of kinship • identification of pathogenic mutations in the patient with a proven or probable link to ARVD/C **Small** • ARVD/C in relatives of the first degree of kinship (when it cannot be determined whether family members meet the diagnosis criteria) • sudden cardiac death (under the age of 35) due to suspected ARVD/C in relatives of the first degree of kinship • ARVD/C, confirmed morphologically or according to diagnosis criteria in relatives of the second degree of kinship	

Abbreviations: ARVD/C — arrhythmogenic dysplasia/right ventricular cardiomyopathy, VT — ventricular tachycardia, VES — ventricular extrasystoles, EDV — end-diastolic volume, LV — left ventricle, LBB — left bundle branch, MRI — magnetic resonance imaging, RV — right ventricle, RBB — right bundle branch, EF — ejection fraction, EMB — endomyocardial biopsy of right ventricle, Echo — echocardiography, LGE — late gadolinium enhancement.

along with patients with a reliable ARVD/C diagnosis. The fundamental difference in criteria structure is a separate part devoted to the diagnosis of left ventricular forms of ARVD/C.

Let us briefly discuss the new aspects in each of the categories.

When assessing **morphofunctional changes**, it was decided once again to abandon quantitative assessment of the degree of dilatation and systolic dysfunction of RV. This is due to the fact that in TFC-2010, the average MRI parameters of the control group (462 people) from the 2006 MESA atherosclerosis study were taken as reference values [8, 13], when the assessment of heart chambers volume was carried out using outdated techniques that are far from perfect. The updated criteria are recommended to be based on nomograms used in this population, which take into account the patient's gender, age and anthropometric indicators. In addition, RV hypo-/akinesis has been added as a separate small criterion, which makes it possible to diagnose ARVD/C at the early stages, when there has not yet been a RV dilation and a decrease in its ejection fraction (EF). A similar approach is provided for left ventricular forms of ARVD/C.

Structural changes imply the degree of myocardial fibrotic-fatty replacement. In this category, there are only large criteria based on EMB or MRI data. Due to the relatively low sensitivity of EMB [9] in the new criteria, it is recommended to perform it only in non-familial forms of ARVD/C in combination with negative results of DNA diagnostics within differential diagnosis with myocarditis, sarcoidosis. In addition, in doubtful cases, EMB will reveal a combination of ARVD/C and myocarditis, which, according to our data, occurs in more than 70% of patients with ARVD/C [14]. The histological criterion is counted in the presence of fibrous substitution in at least one sample. At the same time, the percentage of preserved cardiomyocytes that was present in TFC-2010 is not stipulated, and the presence of fat is still not considered mandatory. Fibrosis according to the LV EMB results is not considered as a criterion due to its low specificity, in addition, LV EMB is performed less frequently than RV.

As for MRI signs of fibrous replacement, the resolution of modern tomographs and special study protocols allow to estimate even tissue characteristics of the thinned RV wall [15, 16]. In this regard, transmural late gadolinium enhancement (LGE) in RV is attributed to the large criteria of ARVD/C. For the left ventricular form, it was proposed to treat only subepicardial or intramyocardial LGE in LV as a major criterion. Nevertheless, LGE in LV should be interpreted with caution and taking into account the clinical context, since this sign is not specific enough and often occurs not only in ARVD/C, but also in myocarditis, dilated and hypertrophic cardiomyopathies, LV NCM, sarcoidosis and amyloidosis [17-20]. The variety of causes for LGE is fully demonstrated in the work of Japanese scientists, where MRI data were compared with the results of myocardial morphological study [21].

Depolarization abnormalities in TFC-2010 included the presence of an epsilon wave as a major criterion, and the presence of late ventricular potentials on a high-resolution electrocardiogram (Echo) and increased QRS terminal activation duration $\geqslant$55 ms as minor ones. In the updated version, there are no large criteria in this category. Epsilon wave was decided to "downgrade" to a small criterion. This sign is typical for ARVD/C, although it is not pathognomonic, but there are often difficulties with its unambiguous interpretation. In 2016, an extravagant study was conducted in which the authors of TFC-2010 were asked directly to analyze a number of cardiograms of patients with ARVD/C and to conclude whether there was an epsilon wave: the experts' opinion fully coincided only in one third of cases [22]. The increase in duration of terminal QRS activation is still considered to be a small criterion, and high-resolution Echo data were decided to be excluded altogether, because this method was rarely used in practice and, according to the authors of the Padua criteria, it is not specific enough. For diagnostics of left ventricular forms, it was suggested to consider a decrease in QRS voltages in limb leads as a small criterion. Previously, it was shown that low voltages are a predictor of heart failure development in patients with ARVD/C, including due to left-sided lesions [23]. Nevertheless, low Echo voltages are not specific for left ventricular ARVD/C. This sign can occur in widespread lesions of RV as part of ARVD/C, other cardiomyopathies (dilated, NCM), a number of accumulation diseases (especially in amyloidosis), and due to extracardiac causes.

As for **repolarization disorders**, this category underwent minimal changes: the criteria for ARVD/C with predominant involvement of RV remained the same, and for the diagnosis of left ventricular forms, a small criterion in the form of negative T waves in V_4-V_6 leads was added. Nevertheless, the negative T teeth in the left leads may also be a reflection of pronounced dilation and fibrous-fat replacement of RV [17].

The approach to assessing the main ARVD/C manifestation — **ventricular arrhythmias** — has changed slightly. If in the previous version of the criteria only ventricular tachycardia (VT) topology was important, in the Padua criteria, the source of ventricular extrasystoles (VES) is proposed to be

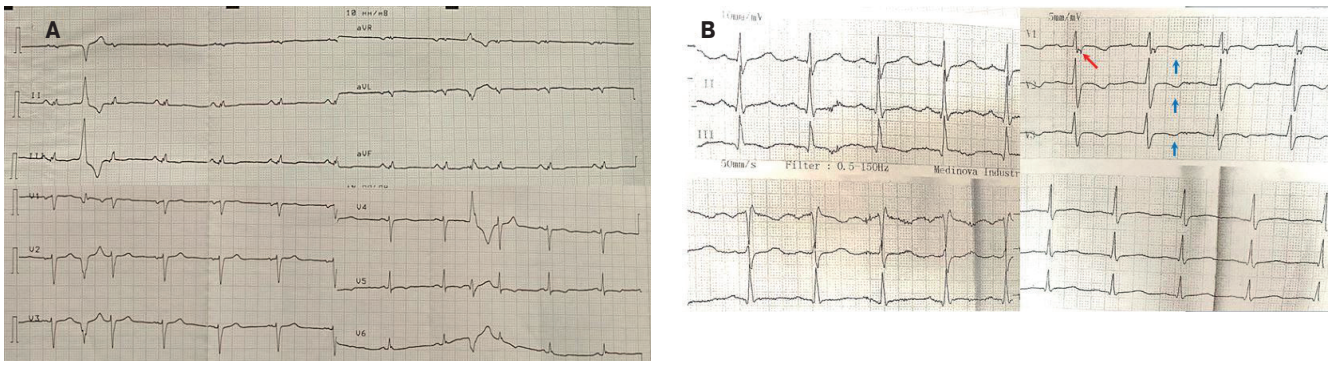

Figure 1. Cardiograms of patient E. (clinical example No. 1). **A** — Echo in 2020; **B** — Echo in 2010.
Note: red arrow shows epsilon wave, blue arrows show negative T deflections. Explanations in the text.

determined as well. The major criterion for right ventricular forms is >500 VES/day and/or VTs with morphology of left bundle branch block (LBB), and the minor criterion is >500 VES/day and/or VTs from the RV outflow tract. A small criterion for the left ventricular ARVD/C form is >500 VES/day and/or VT with the morphology of right bundle branch block (RBB).

The last category, **family history and DNA diagnostic data**, remained the same. The criteria are common for right ventricular and left ventricular forms.

The determination of the degree of diagnosis reliability by total number of large and small criteria from various categories has also not changed, but the approach to the diagnosis of various forms has changed. So, for an *isolated right ventricular form*, it is necessary to have at least one morphofunctional or structural criterion, in addition, there should be no signs of LV involvement. For the *biventricular variant*, there should be at least one morphofunctional or structural criterion of lesion of both LV and pancreas. Finally, for the form with *predominant LV damage*, the presence of structural criterion and mutations in genes typical for ACL, in the absence of changes in RV, are mandatory. The presence of mutation is particularly important because, according to the authors, it is the one that excludes other, more typical, causes of LV damages. Nevertheless, even the detection of mutations is not entirely unambiguous, because the genetics of cardiomyopathies is much more complex and numerous crossings of genotypes and phenotypes are described: mutations typical for ARVD/C can occur in NCM, in dilated, hypertrophic, and even in restrictive (for example, mutations in desmin gene) cardiomyopathies [24]. It is by adding left ventricular forms that the criteria to some extent lose their high specificity as a whole, retaining it only for the classic right ventricular form.

Clinical example 1

Patient E., 39 years old, was admitted to the Department of Cardiology of the Faculty Therapeutic Clinic n.a. V. N. Vinogradov (FTC) in January 2021 due to an episode of discomfort behind the sternum, accompanied by a feeling of compression, suffocation, presyncopal state lasting ~5 minutes, which developed at the end of November 2020. On ambulatory examination after the attack, the Echo showed changes in the form of a sharp decrease of QRS voltages in the limb leads, QS complexes in V_1-V_3 (Figure 1 A), Holter monitoring recorded 3,7 thousand VES, therefore, the patient was referred to the FTC with suggestion of myocarditis. For the first time, VES was detected 10 years ago after the first pregnancy (~1000/day), no treatment was prescribed. Already at that time the Echo showed typical changes for ARVD/C: epsilon wave and negative T waves in the leads V_1-V_3 in the absence of RBB block (Figure 1 B), but the diagnosis was not made. It is known that in February 2020, upon return from Italy, the whole family had an episode of unspecified infectious disease with fever, which does not allow to rule out a non-serious COVID-19. A new coronavirus infection (COVID-19) could be both a cause of myocarditis accession and a trigger for genetic cardiomyopathy progression.

When studying the level of anti-cardiac antibodies in the blood, an increase in the titers of antibodies to antigens of cardiomyocyte nuclei to 1:160 (normally absent), smooth muscles and the conducting system (1:160 at normal to 1:40) was obtained. On Echo at rest, the picture is similar to Echo after an attack of discomfort behind the sternum. High-resolution Echo revealed late ventricular potentials according to two out of three criteria (Std QRS 90 ms at 114 ms norm, LAS 40-60 ms at 29 ms norm), which serves as an additional confirmation of the ARVD/C diagnosis. Echocardiography (Echo)

showed a moderate decrease of LV EF (47%), other parameters were normal.

To clarify the nature of myocardial damage, cardiac MRI was performed (Figure 2): dyskinesia of RV in the area of "dysplasia triangle" was described, otherwise RV was unchanged; there were also convincing data in favor of ARVD/C with LV damage: "creeping" of fat on myocardium in the area of interventricular septum, which corresponds to the zone of disappearance of R deflections on Echo, moderate decrease of LV contractility (EF 54%) with its dilatation (ratio of end-diastolic volume/body surface area to LV 107 ml/m^2 with normal 41-81 ml/m^2), pronounced LGE subepicardial localization in LV and interventricular septum. In addition, noncompact myocardial layer in LV (ratio with compact one up to 2,1) attracted attention, which does not reach the criteria of noncompact cardiomyopathy (>2,3 according to Petersen [25]), but indicates in favor of primary cardiomyopathy. Magnetic resonance signs of LV myocardial edema were noted, which, along with a history of infection and a significant increase in the titers of anticardial antibodies, confirms the presence of concomitant myocarditis; hydroxychloroquine 400 mg/day was prescribed. Daily Echo monitoring by Holter on a "clean" background recorded 1300 VES, sotalol was administered without significant effect. Due to the small amount of VES, the latter was replaced with bisoprolol 5 mg/day. No indication for cardioverter-defibrillator implantation was found. The patient was consulted by a geneticist, and DNA diagnostics revealed a mutation and a variants of uncertain clinical significance (VUCS) in the gene *DSP*, which confirmed the diagnosis and was fully consistent with the clinical performance, since mutations in desmoplakin are characterized by left-sided involvement [8], as well as the presence of NCM [26]. The patient's diagnosis criteria are summarized in Table 3: biventricular form of ARVD/C was diagnosed, but LV damage has more complex character and seems to be caused by ARVD/C combination, myocarditis and increased LV trabecularity.

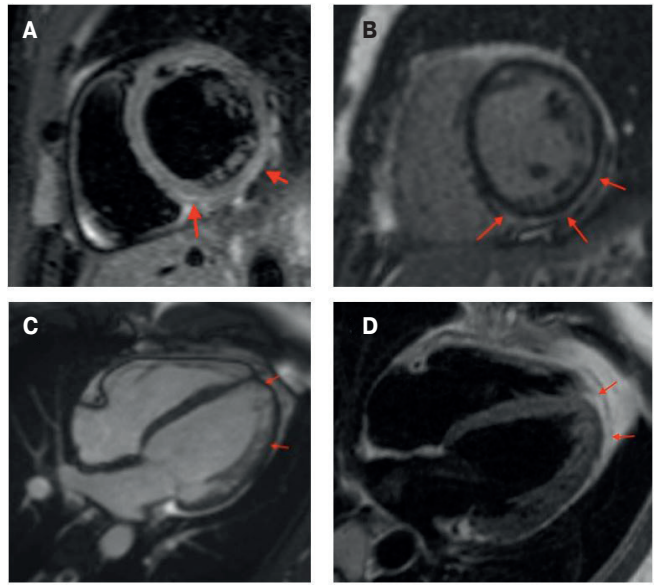

Figure 2. Cardiac MRI of patient E. (clinical example No. 1). **A** — TIRM sequence (T2 FS), short axis at the basal level, increased intensity of magnetic resonance signal from the posterior septal and posterolateral segments is visualized; **B** — PSIR sequence, short axis at the basal level, areas of delayed contrast agent accumulation (LGE) are visualized along the posterolateral segment with spreading to the posterior segment and along the posterior septal segment; **C** — cinema sequence (SSFP), 4-chamber plane, diastole, trabecular enhancement is visualized; **D** — T2-weighted sequence, 4-chamber plane, epicardial fat thickening with signs of spreading to LV myocardium and cardiac apex is visualized.

Clinical example 2

Patient I., 35 years old, was first admitted to the FTC department in September 2018 due to ventricular rhythm disorders persisting on amiodarone and bisoprolol therapy, moderate heart failure. Rhythm disorders were recorded for >10 years, at the age of 29 for frequent ventricular ectopy (6 thousand extrasystoles and 153 runs of unstable VT), an attempt of radiofrequency ablation of arrhythmogenic focus in LV was performed in the center n.a. V. A. Almazov without significant effect, EMB showed a picture of active lymphocytic myocarditis, which was not treated. There was a history of syphilis treated in 2008, which stopped doctors from prescribing immunosuppressive therapy (its etiological role in the development and maintenance of myocarditis was not excluded). The arrhythmia was only partially suppressed with amiodarone, but the presence of untreated myocarditis made it difficult to determine the indication for implantation of a cardioverter-defibrillator. He was sent to the FTC to decide on the baseline therapy of myocarditis and the advisability of interventional treatment.

The association of subsequent exacerbations of the disease (increase in dyspnea with a fall in EF up to 33%, appearance of persistent paroxysms of VT) with infections (chickenpox, whooping cough, acute respiratory viral infection) was evidence in favor of preserving myocarditis activity. Nevertheless, as a result of complex examination of the patient and analysis of medical records, ARVD/C appears to be the main cause of ventricular arrhythmias. As early as the Echo taken at the age of 21 during the preventive medical examination, there were negative T deflections in all thoracic leads, which

Table 3

Diagnosis criteria of patient E. in the clinical example 1

Padua Criteria 2020	RV	LV	Could it be for myocarditis?
I. Morpho-functional changes of ventricles (MRI)	• RV dyskinesis	• LV EF (MRI) 54% • EDV/body surface area to LV 107 ml/m² at N 41-81 ml/m²	yes
II. Myocardium structural changes	no	• **subepicardial LGE**	yes
III. Repolarization disorders	• **inversion of T deflections in the right thoracic leads (V_1-V_3)**	no	yes
IV. Depolarization disorders	• epsilon wave	• low voltage of the QRS complex in leads from limbs	not typical
V. Ventricular rhythm disorders	• frequent VES (>500/day)	• frequent VES (>500/day)	yes
VI. Family history and genetics	**mutation and VUCS in the gene *DSP***		may be the background for the attachment of myocarditis

Note: large criteria are highlighted in bold.

Abbreviations: VES — ventricular extrasystole, EDV — end-diastolic volume, LV — left ventricle, MRI — magnetic resonance imaging, RV — right ventricle, EF — ejection fraction, LGE — late gadolinium enhancement, VUCS — variants of uncertain clinical significance.

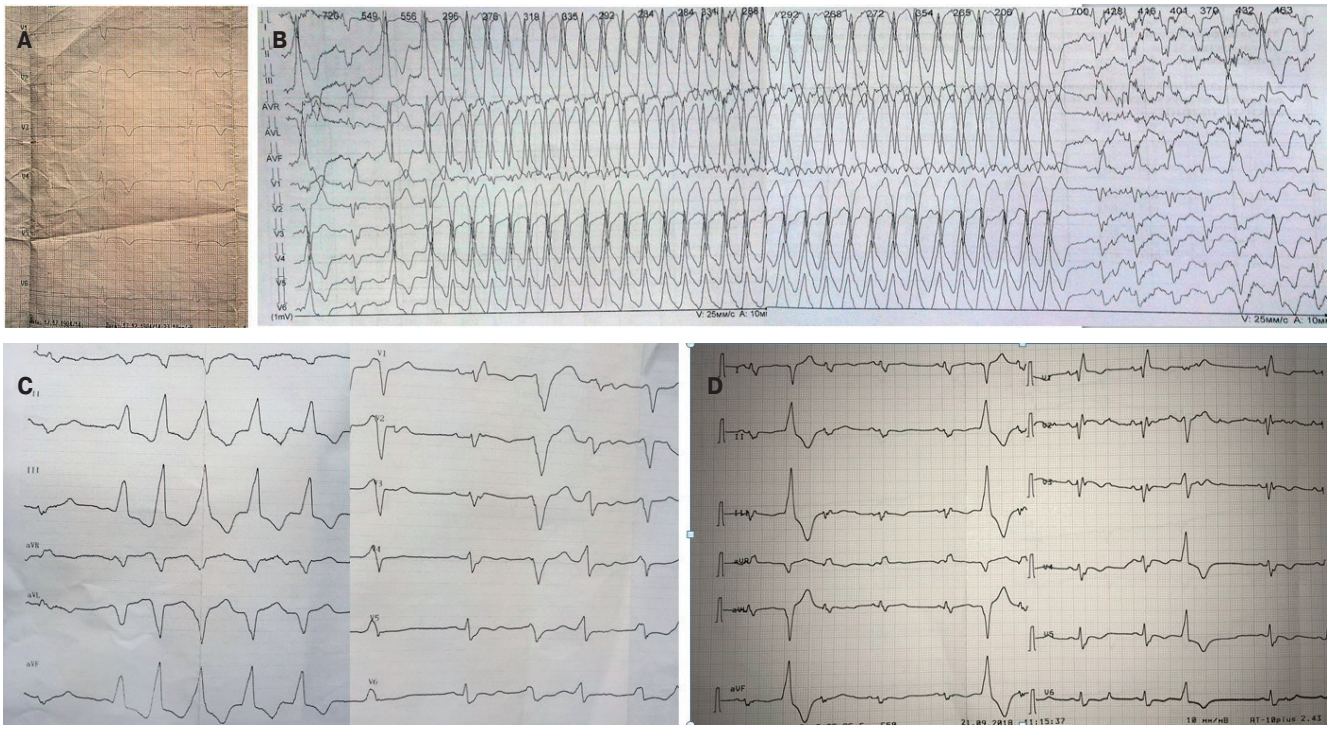

Figure 3. Cardiograms of patient I. (clinical example No. 2). **A** — Echo for medical examination at the age of 21; **B**, **C** — VT paroxysms; **D** — Echo upon admission to the clinic.

were regarded as nonspecific changes (Figure 3 A), later there was VT with the morphology of LBB block with a lower axis (Figure 3 B, C). On the Echo recorded at admission to the FTC, attention was drawn to a pronounced decrease in the voltage of QRS complexes in standard leads (Figure 3 D). It was not possible to assess the presence of an epsilon wave due to the development of complete RBB block. In Holter Echo monitoring performed during amiodarone therapy, >25 thousand Echos were recorded. VES per day, frequent episodes of unstable VT persisted. Myocardial biopsy data were requested — lipomatosis sites were mentioned in the received conclusion (attempts to obtain initial morphological material were unsuccessful).

With Echo, moderate LV dilation up to 6,2 cm was noted, with a decrease in its LV to 52%, RV — 3,4 cm. According to the MRI data, the indexed volume of

RV was >110 ml back in 2012 at 29 years old, LV EF 40% was registered in 2012 and with repeated MRI in the FTC, there were RV dyskinesis, LV EF was reduced to 40%. In addition, the last MRI revealed reliable signs of NCM (Figure 4). The addition of myocarditis is typical for both ARVD/C [14] and non-compact myocardium [27]. Blood antibody titers to endothelial, smooth muscle, and conduction system antigens increased to 1:160 (normal to 1:40), for which reason methylprednisolone 16 mg (with subsequent dose reduction to 4 mg) in combination with azathioprine 150 mg/day was added to the treatment (with subsequent replacement with hydroxychloroquine 200 mg/day). After 6 months, a positive dynamics in the titers of anticardial anti-

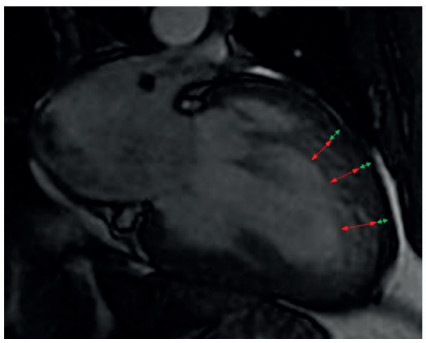

Figure 4. Cardiac MRI of patient I. (clinical example No. 2).
Note: cinema sequence (SSFP), 4-chamber plane, diastole, signs of non-compact LV myocardium are visualized (green arrows show compact layer, red arrows — non-compact layer).
Abbreviation: LV — left ventricle.

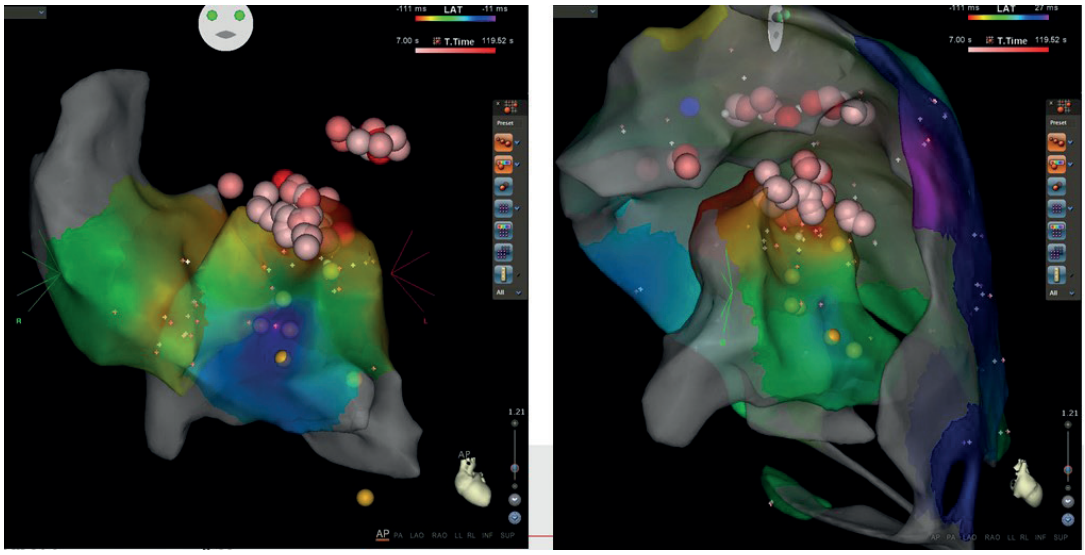

Figure 5. Mapping scheme for radiofrequency ablation in patient I. (clinical example No. 2).

Table 4

Diagnosis criteria of patient I. in the clinical example 2

Padua Criteria 2020	RV	LV	Could it be for myocarditis?
I. Morpho-functional changes of ventricles (MRI)	• **RV EF 33%** • **EDV**/body surface area **97 ml/m²**	• LV EF (MRI) 40% • LV EDD 6,4 cm	yes
II. Myocardium structural changes	no	no	yes
III. Repolarization disorders	• **inversion of T deflections in the right thoracic leads (V_1-V_3)**	• inversion of T deflections in the left thoracic leads (V_4-V_6)	yes
IV. Depolarization disorders	no	• low voltage of the QRS complex in leads from limbs	not typical
V. Ventricular rhythm disorders	• frequent VES (>500/day), unstable and stable VT (?) with a lower axis	no	aggressive and therapy-resistant ventricular rhythm disorders are not so characteristic
VI. Family history and genetics	VUCS in the genes *DSP* and *TMEM43*		may be the background for the attachment of myocarditis

Note: large criteria are highlighted in bold.
Abbreviations: VT — ventricular tachycardia, VES — ventricular extrasystoles, EDV — end-diastolic volume, EDV — end-diastolic volume, LV — left ventricle, MRI — magnetic resonance imaging, RV — right ventricle, EF — ejection fraction, LGE — late gadolinium enhancement, VUCS — variants of uncertain clinical significance.

bodies was noted, EF was steadily maintained at 55%, dyspnea was almost completely eliminated, the number of VES decreased to 510. Gradually (by the end of 2020) immunosuppressive therapy was completely abolished.

However, frequent ventricular ectopy persisted: >18 thousand were recorded during amiodarone withdrawal VES, 33 episodes of unstable VT with a heart rate of up to 130/min. Repeated radiofrequency ablation of the arrhythmogenic focus in the upper third of the anterior interventricular sulcus was performed by combined endo- and epicardial access (Figure 5), however, the procedure was ineffective: frequent (up to 15 thousand) VES, episodes of unstable VT persisted, and therefore amiodarone therapy was resumed.

DNA diagnostics was performed: VUCS were detected in the *DSP* gene, which is typical for a combination of ARVD/C and NCM [26, 28], as well as in the gene *TMEM43*, mutations in which are associated with a high risk of SCD [29, 30]. The clinical significance of VUCS needs further clarification, but bioinformatic analysis of the PolyPhen-2 variants detected considered both variants as pathogenic with a high probability. Taking into account the phenotype of two genetically determined cardiomyopathies, resistant to interventional treatment of aggressive ventricular rhythm disturbances, additional risk factors of SCD (VUCS in *DSP* and *TMEM43*, myocarditis accession, low voltages of QRS complexes), as a primary prevention of SCD, at the Transplant Center n.a. V. I. Shumakov, CRT-D was implanted (without connection of ventricular electrode). At the moment the patient is stable, receives sotalol 240 mg/day, eplerenone 50 mg/day, perindopril 2,5 mg/day. No defibrillator triggers have been recorded yet. In December 2020, had a mild form of COVID-19, no increase in shortness of breath or rhythm disturbances was noted.

As we can see from the above clinical case, despite the presence of obvious criteria of ARVD/C (Echo changes, decreased RV EF in combination with dyskinesia according to MRI back in 2012, ventricular rhythm disorders), the diagnosis was not made in time. Myocardial biopsy revealed lymphocytic myocarditis (the etiological role of syphilis was assumed), immunosuppressive therapy was not administered. Only as a result of combination of baseline therapy for myocarditis and antiarrhythmic drugs, state stabilization was achieved. According to the updated 2020 criteria, the patient has a reliable diagnosis of biventricular ARVD/C (Table 4). Nevertheless, as in the previous case, LV changes cannot be unambiguously assessed, because in addition to undoubted ARVD/C, NCM and myocarditis are present.

Conclusion

The Paduan criteria include clinical manifestations of ARVD/C, the sensitivity and specificity of which have been verified by long-term practice. At the same time, the criteria are modified to take into account new diagnostic possibilities and data obtained in the study of this cardiomyopathy during the last decade, which makes them more sensitive for biventricular and left ventricular forms of ARVD/C. Nevertheless, the addition of left ventricular forms reduces the criteria specificity as a whole, since LV lesions with a similar clinical picture can have a variety of etiologies beyond ARVD/C, even when mutations in typical genes are found. Like the previous two versions, the new criteria will be fully evaluated only prospectively on a large sample of patients, i.e. as a result of their introduction into the daily clinical practice of cardiologists.

Relationships and Activities: none.

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