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Journal of the Cardioprogress Foundation

Myocarditis: expert opinions and new research opportunities

Hyporesponse to statin therapy in patients with carbohydrate metabolism disorders following acute coronary syndrome

Comparison of conventional and developed echocardiographic criteria of pulmonary embolism

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International Heart and Vascular Disease Journal

Journal of the «Cardioprogress» Foundation

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Contents

Editor's Welcome

Dear colleagues!

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

The "Leading Article" section provides a systematic review of various aspects of the etiology, diagnosis, and treatment of myocarditis. The potential of cardiovascular imaging and endomyocardial biopsy in diagnostic decision making is reviewed. Although priorities for the treatment of myocarditis have been identified in the form of treatment of heart failure and rhythm/conduction disturbances, researchers continue to investigate the efficacy of specific therapies.

Three papers are presented in the "Original Articles" section. The first article studied the incidence of hyporesponse to statin therapy in patients with carbohydrate metabolism disorders after acute coronary syndrome in short-term follow-up. In a study that analyzed data from 400 patients, the rate of hyporesponse to atorvastatin at a daily dose of 40 mg or greater was 26.75 %. Lower baseline low-density lipoprotein levels increase the likelihood of hyporesponse to statins. Characteristics of heart failure course in patients with chronic myocarditis and the background of left bundle branch block are discussed in the second article. According to the results obtained, the complete left bundle branch block in patients with chronic myocarditis leads to the earlier cardiac remodeling with pronounced impairment of systolic and diastolic myocardial functions. In the third article the experts compared the generally accepted and developed echocardiographic criteria of severity of the course and prognosis of pulmonary embolism, establishing the most important of them.

The "Review Articles" section contains an article where the modern conditions that may lead to dysregulation of diurnal BP fluctuations — shift work, obstructive sleep apnea, and restless legs syndrome were discussed. Patients need continuous BP monitoring, including at night, to detect nocturnal hypertension and prescribe appropriate therapy to prevent disease progression and increased cardiovascular risk.

This issue presents the clinical case of a patient with a history of atrial septal defect and heart failure. The patient developed symptomatic heart failure with left ventricular ejection fraction ≥50 % as well as the right atrial and right ventricular dilatation. A response to treatment was observed in terms of a reduction in symptoms and an improvement in quality of life. According to the authors, the patient developed heart failure due to untimely diagnosis of congenital heart disease.

Traditionally, our journal publishes the results of the annual of the European Society of Cardiology Congress 2023. The event was attended by approximately 31,000 specialists from 150 countries. Five new clinical guideline texts and the results of 29 large randomized trials were presented.

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

Mekhman N. Mamedov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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International medical review

Researchers compared the efficacy and safety of apixaban and aspirin in patients with subclinical atrial fibrillation (AF).

During 3.5 years of follow-up, the incidence of stroke or systemic embolism was 0.78 % per patient-year in the apixaban group and 1.24 % per patient-year in the aspirin group. The risk of these complications was reduced by 37 % with apixaban.

Data were analyzed from 4012 patients with subclinical AF lasting from 6 minutes to 24 hours. The mean age of the participants was 77 years. All patients were divided into two groups according to the prescribed treatment: oral apixaban at a dose of 2.5-5 mg twice daily or aspirin at a dose of 81 mg daily. The average follow-up period was 3.5 years.

According to The New England Journal of Medicine

Researchers assessed the health risks associated with prolonged sedentary time at work and determined whether there was a threshold of physical activity that could reduce them.

The analysis showed that people with mostly sedentary jobs had a 34 % higher risk of cardiovascular disease mortality and a 16 % higher risk of all-cause mortality compared with participants with mostly active, non-sitting jobs.

The authors concluded that for people with predominantly sedentary jobs, increasing the amount or intensity of daily physical activity may be beneficial in reducing the risk of cardiovascular and all-cause mortality.

According to the JAMA Network Open

Cardiac surgeons at the Mariinsky Hospital combined and modified two methods known in world clinical practice to restore the aortic valve function and performed the first operation. The procedure was called FLOZ.

The intervention was required for a 76-year-old patient who had a significantly enlarged aortic root and aortic stenosis, making it difficult to find a mechanical or biological prosthesis of the appropriate size.

According to experts, after such a complex surgical procedure, recovery is quite fast and the valve functions as a native one on the first day after surgery.

According to the materials of the press service of the St. Petersburg Health Care Committee

A new approach has been developed to predict the progression of aortic aneurysms based on the assessment of vessel wall fluctuations.

Scientists have developed a new method of assessing aortic aneurysms using a physiomarker — the stability of vessel wall fluctuation.

Abnormal dilation of the aorta leads to the appearance of unstable fluctuations of the vessel wall. In this case, the transition from stable blood flow to unstable depends on the pressure level, aortic size, flow shear stress and rigidity of the vascular wall.

The analysis showed that the appearance of unstable vessel wall fluctuations serves as a physiomarker of aneurysm progression in the ascending thoracic aorta, which predicts aneurysm growth over the next 3 years with 98 % accuracy.

According to the Nature Biomedical Engineering Journal

Experts at the University of Glasgow have studied the effect of the presence of gout on the risk of developing cardiovascular diseases.

The results of the study show that patients with gout had a 58 % higher overall risk of cardiovascular disease than participants in the control group.

When assessing the morbidity by age group, patients with gout younger than 45 years of age were most at risk: they had a 2.22-fold increased risk of cardiovascular disease.

According to The Lancet

Researchers at Harvard Medical School studied 24 plasma biomarkers in patients with rheumatoid arthritis to determine how their levels relate to arterial wall inflammation, an indicator of cardiovascular risk.

The analysis showed that changes in the levels of six of 24 plasma markers — serum amyloid protein A, C-reactive protein, tumor necrosis factor receptor type 1, adiponectin, osteoprotegerin, and chitinase-3-like protein 1 (also known as YKL-40) — were associated with arterial inflammation.

The authors concluded that the six new biomarkers could be used to predict cardiovascular risk in patients with rheumatoid arthritis.

According to the JAHA

Myocarditis: expert opinions and new research opportunities

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Analysis of data from the contemporary literature confirms a number of gaps in the diagnosis and treatment of myocarditis. Sufficiently accurate data on the prevalence of myocarditis are available only for individual clinical situations, as endomyocardial biopsy and viral genome testing are rarely performed in routine clinical practice. The pathways that determine the transition from myocardial inflammation to chronic ventricular dysfunction have not been definitively established in viral infections. Therapy with immune checkpoint inhibitors in oncology, vaccination, and genetic predisposition to myocarditis are the subject of active research. Cardiovascular imaging, particularly magnetic resonance imaging, plays an important role in diagnostic and therapeutic decisions. Endomyocardial biopsy may be considered on a case-by-case basis depending on the likelihood of finding treatable disease. Current clinical guidelines for the management of patients with myocarditis, based on expert opinion alone, include treatment of heart failure, rhythm and conduction disorders. Specific therapies, particularly immunosuppression, continue to be evaluated in randomized trials. Ongoing clinical trials will contribute to the development of standardized treatment regimens for patients with acute myocarditis.

Keywords: myocarditis, pathogenesis, magnetic resonance imaging, endomyocardial biopsy, heart failure, treatment, immunosuppression.

Conflict of interests: none declared.

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Introduction

Myocarditis is an inflammatory disease of the myocardium that has traditionally been diagnosed based on established histologic, immunologic, and immunohistochemical criteria [1]. Since the introduction of the Dallas criteria for myocarditis, endomyocardial biopsy has been the standard method of diagnosis [2]. However, the diagnostic workup has changed over the last two decades due to the availability of new tools, mainly the determination of cardiac troponin concentration in blood by a highly sensitive method and cardiac magnetic resonance imaging (MRI) [3]. In routine clinical practice, a combination of symptoms and signs, laboratory tests and imaging studies is often sufficient to make the diagnosis of myocarditis.

In recent years, diagnostic criteria for myocarditis associated with coronavirus infection (COVID-19) or COVID-19 vaccination have been adapted from those established by the Centers for Disease Control and Prevention and the Brighton Collaboration [4, 5]. As a result, the definition and diagnostic methods for myocarditis are not uniform and can vary widely. The lack of simple and widely available diagnostic methods, as well as a universal definition of myocarditis, largely explains the lack of development of treatment options for myocarditis compared to other cardiac pathologies.

The aim of the review article is to analyze the data of modern literature on epidemiology, etiology, pathogenesis, clinical manifestations, diagnosis and treatment of myocarditis, to identify existing gaps and contradictions in scientific data, to substantiate the feasibility and methodology of further research on this topic.

Principles of literature search

In accordance with the principles of the PRISMSA systematic review [6], we searched literature sources in eLIBRARY and MEDLINE/PubMed databases using the keywords "myocarditis", "epidemiology", "etiology", "pathogenesis", "clinical presentation", "COVID-19", "diagnostics", "treatment" with selection of the type of articles "Clinical Trial", "Meta-Analysis", "Randomized Controlled Trial", "Review", "Systematic Review" published for the period from January 1, 2013. to June 20, 2023 in English and Russian languages. After screening 10626 literature sources, 1771 most relevant articles available in full-text format were selected and analyzed, 59 of them were included in the article.

Etiology and pathogenesis

Myocarditis can be caused by a variety of infectious or non-infectious agents, including viruses, activation of the immune system (e.g., autoimmunity in sarcoidosis, Sjögren's disease, systemic lupus erythematosus, and vasculitis, immune stimulation by vaccination or cancer treatment), or exposure to toxins and drugs, including endogenous biochemical compounds produced in amyloidosis and thyrotoxicosis. In infectious forms of myocarditis, viruses are the most common etiologic factor. In certain populations, non-viral pathogens (e.g., bacteria Corynebacterium diphtheriae, Borrelia burgdorferi, and parasites Trypanosoma cruzi) and streptococcal autoimmune rheumocarditis remain significant [7].

Data on the true prevalence of viral myocarditis are not available because endomyocardial biopsy and viral genome testing are rarely performed in routine clinical practice. In addition, seasonal, geographic, and socioeconomic differences, as well as different attitudes toward vaccination, must be taken into account. Virus-mediated myocarditis can be caused by cardiotropic viruses such as adenoviruses and enteroviruses (e.g., coxsackievirus), vasculotropic viruses (e.g., parvovirus B19 — PVB19), lymphotropic viruses (e.g., cytomegalovirus, Epstein-Barr virus, and herpes virus 6 — HHV-6), cardiotoxic viruses (e.g., hepatitis C virus, human immunodeficiency virus — HIV-1), hepatitis C virus, human immunodeficiency virus, and influenza virus), and potentially cardiotoxic angiotensin-converting enzyme 2-tropic viruses (e.g., coronaviruses, including the novel SARS-CoV-2 coronavirus) [8]. The epidemiologic shift from traditional cardiotropic viruses to PVB19 and HHV-6 has been evident over the past 30 years. However, since PVB19 and HHV-6 are also found in the normal heart or in other diseases, it has been proposed to consider the cause of myocarditis as exceeding the threshold of 500 copies of viral DNA per microgram of biopsy tissue [9]. Unfortunately, in Russia there are no validated test systems designed for quantitative assessment of viral copies in myocardial biopsy specimens to evaluate viral replication.

The current understanding of the pathophysiology of viral myocarditis is mainly based on the results of experimental studies of cardiotropic viruses in mice with three phases:

1) viral entry into cardiomyocytes via transmembrane receptors with necrosis, apoptosis, and activation of innate immunity (1 to 7 days);

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2) viral replication, activation of acquired immune responses with T-cell infiltration and autoantibodies (1 to 4 weeks);

3) viral clearance or progression to dilated cardiomyopathy (months to years) [10].

The notion that non-major cardiotropic viruses cause direct tissue damage or act as triggers of immune-mediated damage remains controversial. The latter mechanism is likely to occur in myocarditis associated with SARS-CoV-2 and other respiratory viruses [11]. However, the regulatory switch between inflammatory and reparative responses in the heart in response to viral infection is poorly understood. In addition, the pathways that determine the transition from myocardial inflammation to chronic ventricular dysfunction have not been definitively identified, i.e., it is unknown why some patients recover from myocarditis and others do not.

In the context of COVID-19, the mechanisms of cardiac damage may be multifactorial and include not only endotheliitis or myocarditis, but also myocardial damage due to mismatch between oxygen demand and supply, microvascular thrombosis, systemic hyperinflammatory response, and myocardial ischemia [12].

The use of several groups of pharmacological agents (neuroleptics, cytostatics, salicylates, immunotherapy agents, vaccines) has been recognized as a cause of myocarditis [13]. Recently, myocarditis has been proven to be a rare complication of COVID-19 vaccination when an mRNA-based vaccine is used [8]. In such cases, the vaccine is not necessarily the sole cause, and myocarditis may be caused by promotion, reactivation, or acceleration of naturally occurring myocarditis by viral or immune-mediated mechanisms [14].

Immune checkpoint inhibitor therapy is a novel treatment option for advanced cancer in which antibodies targeting cytotoxic T-lymphocyte antigen 4, cell apoptosis stimulator 1, or programmed cell death ligand 1 are used to enhance a T-cell-mediated immune response against tumor cells. However, systemic immune-mediated adverse events, including potentially life-threatening myocarditis, have been observed with increasing frequency, especially when combined with immune checkpoint inhibitors [15].

The role of genetic predisposition as a contributing factor in the development of myocarditis has now been documented, with putative pathogenic variants in genes related to cardiomyocyte structure and function occurring in up to 16 % of cases. According to the "two-hit" hypothesis, the genetic substrate may play a critical role in the phenotypic outcome in patients exposed to infectious or toxic factors. Genetic testing may be considered in all familial forms of myocarditis, not just familial cardiomyopathy [16].

The gut microbiome is a potential risk modifier for myocarditis. Mimetic peptides of commensal gut bacteria may contribute to inflammatory cardiomyopathy in genetically predisposed individuals [17].

Clinical manifestations

Myocarditis has different clinical manifestations depending on the degree of organ damage [18]. In an uncomplicated clinical picture (preserved left ventricular ejection fraction (LVEF) and absence of ventricular arrhythmias), the main symptoms of myocarditis are chest pain, dyspnea and tachycardia. New or worsening heart failure, critical hemodynamic disturbances (fulminant myocarditis with cardiogenic shock and severe LV dysfunction), and life-threatening arrhythmias or conduction disturbances (sustained ventricular arrhythmias, grade III atrioventricular block, and sudden death) may occur. Irregular, polymorphic ventricular arrhythmias are typical of active myocarditis and regular, monomorphic arrhythmias are typical of chronic myocarditis [19].

In the past, the diagnosis of myocarditis was based on the results of endomyocardial biopsy, which was mainly performed in patients with a moderate or high risk of complications. The use of new non-invasive diagnostic tools has led to the identification of a larger population of patients with clinical suspicion of myocarditis, including those with a more favorable prognosis [20].

An analysis of data from an Italian registry of acute myocarditis cases showed that most patients were without complications, but with chest pain in 97 % and ST-segment elevations on the electrocardiogram (ECG) in 62 % of cases, without death or heart transplantation at 5-year follow-up [21]. Heart transplantation or death from cardiac causes has been reported almost exclusively in patients with LVEF <50 %, sustained ventricular arrhythmias, hemodynamic instability on hospital admission, or with a combination of these manifestations. In this complicated course of myocarditis, the incidence of death or heart transplantation was 10.4 % at 30 days and 14.7 % within 5 years [21]. Analysis of data from a multicenter registry of

endomyocardial biopsies confirming acute myocarditis showed a prognostic effect of systolic dysfunction (LVEF <50 %) and hemodynamic disturbances during hospitalization on the rate of death or heart transplantation — 27.8 % within 60 days in patients with cardiogenic shock compared to 1.8 % in the absence of shock [22]. The prognostic value of histologic characterization of the inflammation with the highest risk of adverse outcome in confirmed giant cell myocarditis has been convincingly demonstrated [23]. An unfavorable effect on long-term survival after myocarditis of female gender and high myocardial antibody titer has also been reported [24].

Giant cell myocarditis should always be suspected in patients with rapidly progressing heart failure, cardiogenic shock with or without conduction disturbances, when there is no positive response to conventional therapy. The prognosis in such cases is unfavorable, with a mortality or heart transplantation rate within next 3 years of approximately 85 % [25]. However, early diagnosis, rapid initiation of aggressive immunosuppressive therapy and/or mechanical hemodynamic support can reduce the risk of death or the need for heart transplantation [26].

The rates of mortality or heart transplantation in patients with fulminant eosinophilic myocarditis is more than 1/4 of cases at 60 days of follow-up [23]. The use of glucocorticoids in this setting has been shown to reduce in-hospital mortality, but the data supporting this treatment option and the randomized trials themselves are still insufficient [27].

Patients with cardiac sarcoidosis may have conduction abnormalities and heart failure. Such patients are at risk of sudden death and may require an implantable cardioverter-defibrillator [28].

Myocarditis associated with COVID-19

Myocarditis is thought to be relatively rare in COVID-19, but in nearly 40 % of cases where it is considered a definite or probable diagnosis, the disease has a fulminant course [11]. Hemodynamic instability, the need for temporary mechanical circulatory support, and a fatal outcome are more likely in patients with concomitant pneumonia than in those without [29]. Patients with COVID-19 have a more than 5-fold increased risk of myocarditis within one year of infection [30].

Apparently, SARS-CoV-2 is one of the etiologic factors of both acute myocarditis in the initial (actually infectious) phase of the disease and subacute (within 1 to 3 months), as well as of the chronic post-infection myocarditis, caused not only by viral persistence in the myocardium up to 9 months, but primarily by severe autoimmune reactions, which requires determination of the indications for immunosuppressive therapy, its extent and duration [31].

Myocarditis associated with COVID-19 vaccines

The analysis of retrospective data from large populations showed that myocarditis following administration of the mRNA vaccine BNT162b2 (Pfizer-BioNTech) was very rare, most commonly in males aged 16–29 years (10.7 cases per 100,000), occurring 1–7 days after the second dose and usually resolving spontaneously within a few days [32]. An increased risk of myocarditis after COVID-19 vaccination with mRNA vaccines (e.g., BNT162b2 or mRNA-1273 [Moderna]) has also been reported in adolescent boys and young men after the second dose. In 87 % of cases, myocarditis symptoms resolved by hospital discharge [33].

Immune Checkpoint Inhibitors-Related Myocarditis

Analysis of follow-up data from the largest series of patients with myocarditis associated with immune checkpoint inhibitor therapy in oncology practice showed early onset of symptoms (median time interval after initiation of therapy was 34 days) and high mortality (50 % of cases) [34]. The growing understanding of the severity of this complication, as well as the increasing number of patients receiving combination therapy with immune checkpoint inhibitors, has led to recommendations to record ECGs and determine troponin levels initially and weekly during the first six weeks of treatment, although there is still no convincing evidence of the efficacy and value of such monitoring [35].

Diagnostic instruments

Given the non-specific and variable clinical presentation of patients with myocarditis, cardiovascular imaging plays an important role in diagnostic and therapeutic decisions. According to the European Society of Cardiology (ESC) Working Group [36], non-invasive diagnostic tests help to establish the diagnosis of "suspected myocarditis" in the presence of clinical manifestations and criteria in four categories:

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1) laboratory tests;

2) electrocardiography, Holter ECG monitoring and exercise testing;

3) functional and structural assessment of the heart with imaging studies (echocardiography, angiography, MRI);

4) detailed tissue characterization with cardiac MRI.

Standard transthoracic echocardiography serves as the initial cardiac imaging modality and plays a role in assessing the likelihood of myocarditis because of its availability and ability to be used as a bedside technique in the acute care setting. However, echocardiography is not sensitive enough to detect inflammation in the absence of wall motion abnormalities not due to acute ischemia, which limits its clinical utility. This imaging modality can be used to dynamically monitor structural and functional changes in the heart. Speckle-tracking echocardiography allows the assessment of global longitudinal and radial myocardial deformation, more accurately diagnosing LV dysfunction, but has limited application due to high cost.

The ESC experts recommended selective coronary angiography and endomyocardial biopsy for all patients meeting the diagnostic criteria for clinically suspected myocarditis [36]. More recently, a risk-based approach to diagnostic testing and emergency management of clinically suspected myocarditis has been proposed by expert consensus [37]. It is suggested that endomyocardial biopsy should be performed in patients with clinical suspicion of myocarditis and the following features:

1) Cardiogenic shock or acute heart failure requiring inotropic or mechanical circulatory support; ventricular arrhythmias or Mobitz grade II or III atrioventricular block, especially with recent onset of symptoms, with or without moderate LV dilatation, peripheral blood eosinophilia, or associated systemic inflammatory disease;

2) Persistent or recurrent release of necrosis markers, especially in the setting of probable autoimmune disease or ventricular arrhythmias and high-degree atrioventricular block;

3) Heart failure in patients receiving therapy with immune checkpoint inhibitors.

In other clinical situations, cardiac MRI should be considered as an initial diagnostic test to detect inflammation, and endomyocardial biopsy may be considered on a case-by-case basis depending on the likelihood of detecting a treatable condition [37].

According to authoritative domestic researchers, if biopsy cannot be performed, complex non-invasive diagnostics allows to diagnose myocarditis of severe and moderate course with different degrees of probability, as well as to perform effective immunosuppressive therapy, the refusal of which is not justified in many cases [38].

Cardiac MRI

In case of clinical suspicion of myocarditis, cardiac MRI is a valuable diagnostic tool and has the highest sensitivity when performed within 2-3 weeks of the onset of clinical manifestations. Cardiac MRI is also useful for dynamic follow-up of disease progression after 6-12 months. The MRI markers for the diagnosis of myocarditis proposed in 2009 (Lake Louise Criteria) were updated in 2018 to include T2-mapping techniques, increasing their sensitivity and specificity for detecting active inflammation to 88 % and 96 %, respectively [39].

Exclusion of pathology on MRI in a patient with clinical suspicion of myocarditis is associated with a good prognosis. In contrast, late gadolinium enhancement in the middle layer of the interventricular septum and low LVEF are recognized as strong predictors of an unfavorable outcome. Late gadolinium enhancement and disappearance of edema on dynamic imaging are negative predictors compared to not only complete resolution of the pathological process, but also simultaneous preservation of late gadolinium enhancement and edema, as the latter data indicate preservation of process activity with potential for recovery [40].

Endomyocardial biopsy

Myocarditis is diagnosed when histologic examination of at least three 1–2 mm tissue samples obtained by endomyocardial biopsy reveals an inflammatory infiltrate with necrosis or degeneration of adjacent myocytes. Subtypes such as lymphocytic, eosinophilic, giant cell myocarditis and cardiac sarcoidosis can be identified, each with specific prognostic and therapeutic implications [41].

Quantitative criteria for inflammation were specified in the 2013 ESC guidelines [36], but they have not been validated in a population of non-European origin. The diagnostic utility of endomyocardial biopsy is maximized when performed within 2 weeks of symptom onset. Its sensitivity can be improved by in-

creasing the number of biopsy specimens and by performing endomyocardial biopsy under imaging guidance or electroanatomic mapping [41]. The availability of immunohistochemical staining to characterize inflammatory cells leads to an increase in positive endomyocardial biopsy results.

In addition to histological and immunohistochemical evaluation of biopsy specimens, polymerase chain reaction or in situ hybridization analysis is recommended to detect the presence of viruses, although the causal relationship between viral infection and cardiac injury is still being studied. Standardization of methods for identification and quantification of the viral genome is needed [7]. Meanwhile, the presence of viral genome in the absence of inflammatory cells is not a criterion for the diagnosis of myocarditis.

Other tests

In routine practice, markers of myocyte inflammation such as erythrocyte sedimentation rate and C-reactive protein levels are commonly evaluated, although they are not specific and are not necessarily elevated in myocarditis [18, 36]. Cardiac troponin is a more sensitive marker than creatine kinase and its MB fraction [36]. Russian experts recommend the study of troponins I, T levels in the blood of all patients with myocarditis as part of the initial examination and in the course of dynamic follow-up [42]. Determination of troponin levels by a highly sensitive method is a valuable tool that helps to identify myocarditis more accurately than the conventional troponin test. Russian experts also recommend testing the level of natriuretic peptides, such as the N-terminal precursor of brain natriuretic peptide, in the blood of all patients with myocarditis as part of the initial examination and during dynamic follow-up [42]. However, changes in this parameter are not specific for myocarditis, and normal levels do not exclude myocarditis [36].

The recommendation to determine the level of serum cardiac autoantibodies specific for myocardial tissue in all patients with myocarditis [42] is unfortunately not feasible due to the lack of standardized kits for such a study in the Russian Federation.

MicroRNA profiling in blood and endomyocardial biopsy samples in search of disease biomarkers at the whole transcriptome level has been studied with encouraging results, but there was no correlation between tissue and blood marker levels [43]. It has been shown that circulating RNA synthesized by type 17 helper T cells (hsa-miR-Chr8:96) can be used to differentiate patients with myocarditis from those with myocardial infarction [44].

Treatment

No large-scale prospective controlled trials have been conducted to assess the efficacy of myocarditis treatment and its impact on prognosis. Existing guidelines are based only on expert opinion [36, 42]. Therefore, myocarditis therapy includes urgent correction of life-threatening conditions (refractory circulatory failure, cardiac rhythm and conduction disturbances), treatment of chronic heart failure according to current recommendations [28, 45, 46], and, if possible, specific etiopathogenetic intervention on viral infection and immune inflammation [18, 42].

Conventional therapy

Patients with heart failure who remain hemodynamically stable should be treated with diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and beta-adrenergic blockers. Additional treatment with mineralocorticoid receptor antagonists should be considered in patients with persistent heart failure despite adequate therapy. Whether early treatment of patients with preserved LVEF to reduce myocardial inflammation, remodeling and scarring is appropriate remains unclear.

Patients with heart failure and hemodynamic instability require the use of inotropic agents. Their care should be managed in the intensive care unit with the possibility of respiratory and mechanical cardiopulmonary support; referral of such patients to a specialized cardiac center should be considered. In patients with cardiogenic shock, severe ventricular dysfunction refractory to drug therapy, mechanical circulatory support with a mechanical assist device or extracorporeal membrane oxygenation (ECMO) may be required [47].

The main goals of treating severe myocarditis are to achieve hemodynamic ventricular unloading, adequate systemic and coronary perfusion, and relief of venous congestion to prevent multiorgan dysfunction and allow recovery, heart transplantation, or the use of an implantable circulatory support device. Temporary use of intra-aortic balloon counterpulsation, veno-arterial ECMO, centrifugal pump, and axial-rotary pump should be considered.

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The use of devices that reduce LV afterload, such as extracorporeal left ventricular bypass or intra-aortic left ventricular bypass with an axial pump, alone or in combination with ECMO, is more likely to promote myocardial recovery than ECMO alone [48]. In recent years, LV unloading with a percutaneously placed axial pump (Impella; Abiomed) has been used as a treatment option in patients with cardiogenic shock, either as sole LV support with preserved right ventricular function or in combination with extracorporeal hemodynamic support or with right-sided placement of such a pump. If the patient cannot be withdrawn from mechanical circulatory support after 2–3 weeks, the implantation of a mechanical LV support device or heart transplantation should be considered [18].

There are no specific guidelines for the management of rhythm and conduction disturbances in patients with myocarditis. After the acute phase of the disease, treatment should be in accordance with current recommendations for the management of patients with arrhythmias and the use of electronic cardiac devices [45, 46]. Because myocarditis is a potentially reversible condition, a step-by-step approach to therapy during the acute phase is suggested. In cases of complete atrioventricular block, electrocardiostimulation may be required. The use of an implantable cardioverter-defibrillator should be delayed until after the acute phase of myocarditis, usually within 3-6 months of onset; if necessary, the use of a portable cardioverter-defibrillator may be considered.

In competitive athletes, physical activity should be restricted during the acute phase of myocarditis and for a period of 3 to 6 months thereafter, depending on the clinical severity and duration of the acute phase of the disease [49]. After resolution of myocarditis, reassessment of clinical status is indicated prior to resumption of competitive sports participation. Survivors of myocarditis should be followed every 6 months [36, 42].

Specific therapy

After eliminating the causes of eosinophilia, such as the effects of drugs or parasites, the main therapy for eosinophilic giant cell myocarditis and cardiac sarcoidosis is the administration of immunosuppressants (glucocorticoids alone or together with azathioprine and/or cyclosporine) [50, 51]. There is no specific therapy for acute lymphocytic myocarditis, except for forms associated with systemic disease and therapy with immune checkpoint inhibitors [36, 52].

Although there is a rationale for immunosuppressive therapy in the acute phase of myocarditis in patients at high risk of adverse outcomes, there are no data from large prospective multicenter trials focused on this issue. In a few small single-center studies in patients with virus-negative chronic inflammatory cardiomyopathy confirmed by endomyocardial biopsy, treatment with prednisolone and azathioprine showed favorable results, including a significant increase in LVEF [53]. The authors of the first of these studies recently reported long-term (up to 20 years) clinical outcomes in 85 patients originally enrolled in the TIMIC trial (group A), compared with outcomes in the control group of patients matched by pseudorandomization (statistical technique of propensity score matching) and not treated according to the TIMIC protocol (group B). In group A, immunosuppressive therapy reduced the risk of a combination of adverse outcomes (cardiovascular death, heart transplantation) by 6.77 times wuth the background of persistent improvement of LVEF compared with group B, in which implantation of a cardioverter-defibrillator was also performed more frequently [54]. The potential efficacy of an inexpensive and sufficiently safe immunosuppressive therapy in targeted use after assessment of morphomolecular characterization of myocardial tissue should be confirmed or refuted in a multicenter, randomized, double-blind, placebo-controlled trial.

Current European and Russian guidelines do not recommend the widespread use of immunosuppressive therapy in patients with myocarditis; non-steroidal anti-inflammatory drugs (in the absence of pericarditis), glucocorticoids also are not indicated (except for autoimmune, eosinophilic, granulomatous and giant cell acute myocarditis). For the safe use of immunosuppressive therapy, histochemical analysis of the viral genome from endomyocardial biopsy specimens is recommended to confirm active viral-negative myocarditis [36, 42]. The American Heart Association document on the management of fulminant myocarditis [55] recommends immediate intravenous administration of 1 g of methylprednisolone, even before endomyocardial biopsy or other investigations are performed, if there is reasonable suspicion of an immune-mediated form of myocarditis. If the diagnosis of giant cell myocarditis is confirmed,

immunosuppressive agents should be added to the treatment regimen.

Recently, empiric treatment with intravenous glucocorticoids has been proposed for patients with cardiogenic shock or acute myocarditis complicated by heart failure, ventricular arrhythmias, or high-degree atrioventricular block [18]. Supportive glucocorticoid therapy is appropriate in patients with eosinophilic or giant cell myocarditis, cardiac sarcoidosis, or confirmed autoimmune disease. In rare cases where enterovirus, cytomegalovirus, or adenovirus are detected, immunosuppressive therapy may be canceled [56]. In patients who test positive for PVB19 or HHV-6, maintenance of immunosuppression depends on the initial response to therapy and viral load [9, 18].

Alternative treatments for specific conditions in patients with virus-negative or autoimmune inflammatory cardiomyopathy include removal of autoantibodies (immunoadsorption) followed by intravenous immunoglobulin therapy [57]. This treatment is currently being evaluated in a large multicenter trial in patients with dilated cardiomyopathy. Intravenous immunoglobulin therapy is widely used in pediatrics, but the use of such treatment in adults with lymphocytic myocarditis is limited.

There are insufficient data to support antiviral therapy for acute myocarditis. Beneficial effects of interferon treatment with virus elimination and the improvement of the functional class of heart failure according to the New York Heart Association classification have been demonstrated only in chronic inflammatory cardiomyopathy caused by adenovirus, enterovirus, and PVB19 confirmed by endomyocardial biopsy [7]. Treatment with anti-herpes viral drugs may be considered in patients with Epstein-Barr virus, cytomegalovirus, or HHV-6 infection [58]. Whether a combination of antiviral and immunosuppressive therapy can be used in some patients with virus-positive inflammatory cardiomyopathy at a certain stage of the disease remains to be studied.

Ongoing clinical trials are evaluating the role of high-dose methylprednisolone (The Myocarditis Therapy with Steroids trial — MYTHS); the interleukin-1 receptor antagonist anakinra (The Anakinra versus Placebo for the Treatment of Acute Myocarditis — ARAMIS) in patients with acute myocarditis complicated by heart failure or cardiogenic shock, while excluding patients with hemodynamic instability; and abatacept (a protein that selectively modulates the key co-stimulatory signal required for full activation of T lymphocytes) for the treatment of myocarditis associated with immune checkpoint inhibitor therapy (Abatacept for the Treatment of Immune-Checkpoint Inhibitors Induced Myocarditis (ACHLYS)) [59].

Conclusion

Myocarditis remains an understudied pathology compared to other common diseases of the cardiovascular system. The variety of clinical manifestations of myocarditis, different criteria of its histological and imaging diagnostics make it difficult to determine useful therapeutic interventions.

Studies to identify the factors that determine the progression of acute viral myocarditis to autoimmune cardiomyopathy are now urgently needed. Standardization and integration of endomyocardial biopsy, imaging, laboratory and clinical criteria are needed to better understand the phenotype of myocarditis and optimize the management of patients. New diagnostic tools, including single cell sequencing, coupled with in-depth clinical phenotyping, are needed to identify novel targets potentially amenable to therapeutic intervention. Prospective multicenter studies of the role of genetics in susceptibility to myocarditis are needed to determine its impact on disease severity and long-term outcomes.

Determination of the indications for immunosuppressive therapy for post-void myocarditis, its amount and duration is required. Understanding the pathogenesis of mRNA vaccine-induced myocarditis is important for public health. A better understanding of the cardiac damage associated with immune checkpoint inhibitor therapy in oncology, determination of susceptibility to such myocarditis, and identification of biomarkers for its early diagnosis should be researchers' priority.

Clinical trials of treatment options for myocarditis that combine knowledge of genetics, single-cell tissue analysis and cardiac imaging with patient phenotyping are needed to develop standard regimens for the treatment of patients with acute myocarditis and to ensure that the burden of myocarditis on society is reduced.

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Hyporesponse to statin therapy in patients with carbohydrate metabolism disorders following acute coronary syndrome

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The aim of the study was to investigate the frequency of hyporesponse to statin therapy among patients with impaired carbohydrate metabolism after acute coronary syndrome (ACS) in short-term follow-up.

Methods. A retrospective analysis of the medical records of 1500 patients admitted for cardiologic follow-up after ACS was performed. The data of patients who did not receive statins before the development of ACS (400 patients; mean age — 63.42±9.64 years, including 286 (71.5%) men) were included in the analysis. Carbohydrate metabolism disorders (CMD) according to WHO and Russian Association of Endocrinologists criteria were present in 124 patients (type 2 diabetes mellitus (type 2 DM) — in 71 patients; prediabetes — in 53 patients). All patients were prescribed high-dose statin therapy, namely atorvastatin (40 mg or more daily). Low-density lipoprotein (LDL) cholesterol was assessed at baseline and after 1 month of therapy. Hyporesponse to statins was defined as the percentage reduction in LDL cholesterol of <15% from baseline during 1 month of therapy. Suboptimal response was defined as an LDL reduction of less than 50% after 1 month of therapy.

Results. The frequency of hyporesponse was 26.75% (n=107). Depending on the history of carbohydrate me-

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tabolism disorders (type 2 DM, prediabetes), patients were divided into 2 groups: group 1 (CMD, n=124), group 2 (without CMD, n=276). After 1 month of follow-up in the total group, the rate of hyporesponse was 26.75%. In group 1 and group 2, the rate of hyporesponse to statin therapy was 25.81% and 27.54%, respectively (p=0.719). The frequency of suboptimal response in the CMD group was 56.45%. Patients with CMD and hyporesponse to statins were characterized by lower baseline LDL levels.
Conclusion. The absolute majority of patients with CMD after ACS do not achieve the LDL-lowering goal after 1 month of high-intensity statin therapy. Hyporesponse to statins is seen in a quarter of this group. Lower baseline LDL levels increase the likelihood of hyporesponse to statins.

Keywords: statins, hyporesponse, diabetes mellitus, prediabetes.

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Introduction

The amount of cases of type 2 diabetes mellitus (T2DM) is increasing at an alarming rate worldwide. As a prevalent and serious disease, T2DM places a significant burden on patients, their families and the healthcare system. T2DM is a significant risk factor (RF) for cardiovascular diseases (CVD) such as: coronary heart disease (CHD), stroke, peripheral arterial disease (PAD), heart failure (HF). Patients with T2DM have a 2–4 times higher risk of developing CVD than patients without diabetes [1]. Prediabetes is an independent risk factor for cardiovascular morbidity and mortality [2]. A meta-analysis of 102 prospective studies found that patients with a glycemic level of 6.1–7.0 mmol/L had a 17% higher risk of CHD, and those with a glycemic level of 5.6–6.1 mmol/L had an 11% higher risk of CHD than those with a glycemic level < 5.6 mmol/L [3].

According to current guidelines, the first-line therapy for patients of very high cardiovascular risk is high-intensity statin therapy with a target low-density lipoprotein cholesterol (LDL-C) level of ⩾50% of baseline, with a goal of <1.4 mmol/L achieved [4]. Indeed, "there is no longer a 'hypothesized role for LDL-C,' but rather an established fact that elevated LDL-C levels have a causal relationship with CVD of atherosclerotic etiology and that the maximal reduction of LDL-C and other apoliprotein B (apoB)-containing lipoproteins leads to a reduction in cardiovascular mortality" [4].

Some data suggest that the use of statins may be associated with the prevention of HF in patients after acute coronary syndrome (ACS) [5, 6]. The benefit of statin therapy in terms of impact on the prognosis of HF remains controversial. Further investigation of the role of statins in preventing the development or progression of HF is all the more interesting because of the variable hypolipidemic response to drug administration. For example, a recent retrospective observational study (4.4 years of follow-up) showed that hyporesponse to statins increased the risk of HF in patients after myocardial infarction (MI) [7]. In this observational study, hyporesponse to statins was more frequent in patients with dyslipidemia and in patients with T2DM. Assessing the prevalence of hyporesponse to statin therapy in patients with CMD after ACS may be the first step in assessing the clinical significance of this phenomenon in relation to the development of HF and a step towards optimizing lipid-lowering therapy.

Methods

We retrospectively analyzed the medical records of ACS patients admitted to the outpatient phase of cardiac rehabilitation. From January 1, 2020 to January 1, 2021, 1500 patients who underwent ACS and coronary stenting were admitted for observation in the first 3 days after discharge from hospital vascular departments. Patients received medical therapy including dual antiplatelet therapy, high-dose statin therapy, beta-adrenergic blockers, renin-angiotensin-aldosterone system antagonists, and diuretics. Inclusion criteria were: history of ACS of 1 month or less, no statin use before the cardiovascular event, no con-

traindications to statin prescription. Exclusion criteria were: use of statins in any therapeutic dose before the cardiovascular event, incomplete information from outpatient records. Parameters studied included: LDL-C, recurrent cardiovascular events and HF. The study protocol was approved by the ethics committees of our institutions. Atorvastatin was started within 24 hours after coronary stenting. The choice of atorvastatin dose was made by the treating physician. LDL-C levels were measured on admission and 1 month after initiation of statin therapy in all patients. Hyporesponse to statins was defined as a percent decrease in LDL-C levels <15% of baseline before 1 month after initiation of statins. High-intensity statin therapy was defined as atorvastatin ⩾40 mg daily.

All analyses were performed using the program Statistica 13.3 (StatSoft Russia). In case of non-normal distribution, data were presented as median (Me), lower (LQ) and upper quartiles (UQ), in case of normal distribution — as sample mean and standard deviation. The Mann-Whitney test was used when two independent samples were compared quantitatively, and the χ^2 test for independent samples was used when groups were compared qualitatively. In all cases, the critical p level was considered to be < 0.05.

Results

According to the inclusion/exclusion criteria, data from 400 patients (mean age 63.42±9.64 years, 286 (71.5%) men) were included in the retrospective analysis. More than 50% of the patients had a history of MI. Coronary revascularization was performed in almost all cases. The majority of patients had arterial hypertension (AH) — 383 patients (95.75%). More than half of the patients were diagnosed with HF — 269 patients (67.25%), with a prevalence of preserved ejection fraction (EF), functional class (FC) 2 (Table 1).

All patients were prescribed antiplatelet and hypolipidemic therapy in the form of atorvastatin. Most patients were taking beta-adrenergic blockers (89.75%), renin-angiotensin system inhibitors, mostly angiotensin-converting enzyme inhibitors (ACEi) (75.25%), and diuretics in 18.25% of patients. LDL–C was assessed at baseline using medical records provided to patients at discharge and again at 1 month. Hyporesponse to statins was defined as the percentage of LDL-C reduction <15% from baseline within 1 month of statin treatment. When LDL-C was analyzed in the entire group, the prevalence of hyporesponse after 1 month of therapy was 26.75% (107/400) (Figure 1). The majority were men (n=71; 66.35%). The baseline LDL-C level in patients with a hyporesponse to statins was 2.66 mmol/L (2.2; 3.3) and was lower than in patients with a greater reduction in LDL-C (3.3 (2.5; 4.0); p=0.000).

Table 1. **Clinical characteristics of the group**

Characteristic	Values
Age, years	63.42±9.64 years
Male gender	286/71.5
MI	296/74
Unstable angina pectoris	104/26
Revasculzrization	384/96
Coronary artery bypass surgery	35/9
Stenting	349/91
AH	383/95.75
Atrial fibrillation	40/10
Supraventricular arrhythmias	79/19.75
Ventricular arrhythmias	74/18.5
Sick sinus syndrome	3/0.75
Conduction disorders of the atrioventricular or sinoatrial block type	16/4
Bundle branch block	50/12.5
Chronic HF (CHF), total	269/67.25
CHF with preserved LV EF	188/69.88
CHF with reduced LV EF	16/5.94
CHF with mid-range LV EF	65/24.16
FC 1	98/36.43
FC 2	146/54.27
FC 3	25/9.29
T2DM	71/17.75
Pre-diabetes	53/13.25

Note. Data are presented as N (%) or mean ± standard deviation.

Carbohydrate metabolism disorders were present in 124 patients (31.00%; group 1), carbohydrate metabolism disorders (CMD) were absent in 276 patients (group 2). Patients with CMD were older and had a higher body mass index (BMI) (Table 2).

Initial levels of TC, LDL-C, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) did not differ between groups (Table 3). After 1 month, patients in group 1 had higher TG levels and hypertriglyceridemia was more frequent. After 1 month of follow-up, LDL-C levels <1.4 mmol/L were observed in a minority of patients in both groups; achievement of the hypolipidemic therapy goal (LDL-C <1.4 mmol/L or LDL-C reduction by ⩾50%) was equally frequent in groups 1 and 2 (23% and 16%, respectively; p=0.092). Hyporesponse to statins was observed in 32 patients in group 1 (25.81%) and 76 patients in group 2 (27.54%; p=0.719). Suboptimal response (< 50% LDL-C reduction) was observed in every second pa-

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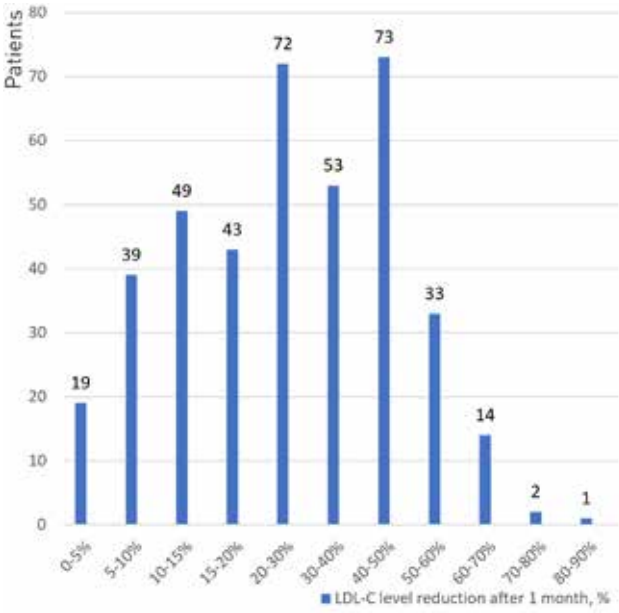

Fig. 1. Distribution of percent change in LDL–C levels in all subjects after 1 month

Table 2. **Clinical characteristics of patient groups**

Characteristic	Group 1, n=124	Group 2, n=276	p
Age, years	64.99±8.25	62.72±10.14	0.024
BMI, kg/m^2	30.05±5.36	28.33±4.86	0.002
Male gender	77 (62.1)	209 (75.7)	0.005
MI	40 (32.26)	84 (30.44)	0.715
Revascularization	117/94.35	268 (97.10)	0.181
Coronary artery bypass surgery	12/10.25	12 (4.48)	0.038
Stenting	112/84.67	256 (95.52)	0.407
AH	121 (97.58)	262 (94.93)	0.224
Atrial fibrillation	14 (11.29)	26 (9.42)	0.564
Obesity/overweight	102 (82.26)	215 (77.9)	0.320
CHF, total	85/68.54	181 (65.58)	0.561
CHF with preserved LV EF	60/70.58	140 (77.34)	0.665
CHF with reduced LV EF	1/1.17	11 (6.08)	0.085
CHF with mid-range LV EF	24/28.23	30 (16.57)	0.022
FC 1	31/36.47	68 (37.57)	0.938
FC 2	50/58.82	94 (51.93)	0.227
FC 3	4/4.70	17 (9.39)	0.224
LV EF (%)	57.5 (50; 64)	57 (51.8; 63)	0.598
Atorvastatin, 40 mg	8 (6.45)	7 (3.26)	0.057
Atorvastin, 80 mg	116 (93.54)	269 (96.74)	0.057
β-blockers	117 (94.35)	243 (88.04)	0.052
ACEi or ARBs	118 (95.16)	257 (93.12)	0.434
Slow calcium channel blockers	34 (37.42)	60 (21.74)	0.215
Diuretics	26 (20.97)	47 (17.03)	0.346
DAPT, double antiplatelet therapy	110 (88.70)	250 (90.58)	0.564
Oral anticoagulant.	14 (11.29)	26 (9.42)	0.564
Metformin	66 (53.22)	—	—
Gliclazide	58 (46.77)	—	—
Insulin	22 (17.74)	—	—

Note. Data are presented as N (%) or mean ± standard deviation.

Table 3. **Characterization of lipid metabolism baseline and response to statin therapy in the groups**

Parameter	Group 1, n=124	Group 2, n=276	p
Baseline lipid levels			
TC, mmol/l	4.79 (4.0;5.56)	4.7 (4.0; 5.58)	0.881
LDL–C, mmol/l	3.2 (2.48; 3.80)	3.15 (2.5; 3.91)	0.639
TG, mmol/l	1.65 (1.1; 2.30)	1.50 (1.09; 2.0)	0.095
HDL–C, mmol/l	1.09 (0.92; 1.22)	1.10 (0.90; 1.36)	0.096
Hypertriglyceridemia	53 (42.7)	95 (34.4)	0.111
Lipid levels after 1 month			
TC, mmol/l	3.78 (3.20;4.50)	3.80 (3.32; 4.21)	0.535
LDL–C, mmol/l	2.10 (1.62; 2.62)	2.20 (1.80; 2.60)	0.226
TG, mmol/l	1.41 (1.10; 1.90)	1.40 (0.99; 1.60)	0.023
HDL–C, mmol/l	1.00 (0.80; 1.17)	1.03 (0.90; 1.20)	0.069
Hypertriglyceridemia	37 (29.8)	56 (20.3)	0.036
LDL–C <1,4 mmol/l	13 (10.48)	17 (6.16)	0.129
Decrease in LDL–C level after 1 month of therapy			
0-5 %	3 (2.42)	15 (5.43)	0.179
5-10 %	14 (11.29)	25 (9.06)	0.486
10-15 %	15 (12.09)	36 (13.04)	0.793
15-20 %	9 (7.26)	32 (11.59)	0.186
20-30 %	27 (21.77)	47 (17.03)	0.258
30-40 %	17 (13.71)	35 (12.68)	0.777
40-50 %	17 (13.71)	54 (19.56)	0.156
50-60 %	14 (11.29)	21 (7.61)	0.228
60-70 %	8 (6.45)	8 (2.89)	0.093
70-80 %	0	2 (0.72)	0.854
80-90 %	0	1 (0.36)	0.681
≥50 %	22 (17.74)	29 (10.51)	0.045
LDL–C <1.4 mmol/l or decrease in LDL–C by ≥ 50 %	29 (23.39)	45 (16.30)	0.092

Note. Data are presented as N (%) or median (interquartile range).

tient with CMD (56.45 %) and in 39.13 % of cases in group 2 (p=0.405).

In group 1, baseline LDL-C in the hyporesponders was 2.7 (2.1; 3.30) mmol/l and was significantly lower than in the responders (3.28 mmol/l (2.7; 3.9), p=0.006). Consistently, TC was also lower: 4.1 (3.5; 4.83) and 5.0 (4.2; 5.7) respectively; p=0.001. In group 1, the frequency of atorvastatin 40 mg and atorvastatin 80 mg/day did not differ between responders and hyporesponders. Particularly, atorvastatin 40 mg was used in 12.5 % of hyporesponders and 4.35 % of responders (p=0.230). In group 2, the baseline LDL-C level in hyporesponders was 2.6 (2.27; 3.19) mmol/l and was also significantly lower than in responders (3.4 mmol/l (2.80; 4.09)), p=0.000. In group 2, atorvastatin 40 mg was used more frequently in hyporesponders (7.89 % vs. 2.0 %, respectively, p=0.001).

Discussion

Achieving target lipid levels is aimed at reducing the risk of atherosclerotic CVD. HMG-CoA reductase inhibitors (statins) have been shown to reduce the incidence of CHD in patients with and without diagnosed CVD [8, 9]. Numerous data suggest that the use of statins may be associated with the prevention of HF in patients after ACS [10]. The results of a large meta-analysis of 17 randomized clinical trials (RCTs) (n=132,568, mean age 63 years, 29 % women) showed that statin therapy was associated with a reduced risk of hospitalization for HF [11]. A combined analysis of the data showed a reduction in the incidence of hospitalization for HF and a reduction in the incidence of MI if statins are used [12]. A recently published retrospective cohort study in a group of patients with atrial fibrillation showed a reduction in the risk of HF, HF-related death, and all-cause mortality independent of LDL-C cholesterol levels [13]. At the same time, an observational study using data from the Swedish nationwide MI registry showed that patients with a larger reduction in LDL-C (1.85 mmol/l) compared with a smaller reduction (0.36 mmol/l) had lower risk ratios for all outcomes assessed, and in particular for hospitalization due to HF (OR: 0.73; 95 % CI 0.63–0.85) [14]. A RCT in patients with ACS and dyslipidemia showed that hospitalization for HF was significantly reduced in the intensive therapy group (pitavastatin + ezetimibe) compared with pitavastatin monotherapy [15]. ESC experts recommend the use of statins for the prevention of HF in high-risk individuals [16].

It is well known that there is a large variability in the response to statins as well as in the % reduction of LDL-C. According to the Russian registry (REGION-IM) of patients with MI, LDL-C ⩽1.4 mmol/l was achieved in 23 % of cases on hypolipidemic therapy. In addition, the target LDL-C level was achieved in 21 % of patients receiving statin monotherapy and in 44 % of patients receiving statin + ezetimibe combination therapy. [17]. In another European study, despite the use of high-intensity statin monotherapy, more than half of the patients hospitalized with ACS (82.9 %) did not achieve target LDL-C levels [18]. The mechanisms that increase cardiovascular risk in this group of patients may be not only higher LDL-C levels, but also decreased pleiotropic effects such as the anti-inflammatory one [19, 20].

In a retrospective observational study (follow-up period — 4.4 years), hyporesponse to statins was shown to increase the risk of HF in post-MI patients [7]. A study by Kuyama N. et al. showed that baseline levels of mature PCSK9 (proprotein convertase subtilisin/kexin type 9) were associated with hyporesponse to statins. This suggests that mature PCSK9 may be a potential determinant of statin hyporesponse [21]. Statin-mediated increases in circulating PCSK9 levels may contribute to inflammation and impair endothelial permeability, including nitric oxide production [22]. Since systemic inflammation is a known component of HF pathogenesis, mediated by increased expression of endothelial adhesion molecules and production of reactive oxygen species [23], an unfavorable inflammatory activity profile may be another factor in the occurrence of HF in statin hyporesponders. According to some data, circulating PCSK9 levels are a significant predictor of the combined endpoint of all-cause death and hospitalization in patients with HF [24].

Other individual characteristics, including age, sex, body weight, cigarette smoking, inflammation, chronic kidney disease, DM, baseline lipid levels, and some genetic variations, may also be possible the determinants of poor response to statins [25–27].

In our observation, the hyporesponse (LDL-C reduction ⩽ 15 %) to high-dose atorvastatin therapy was registered in 28 % of cases in patients after ACS and coronary revascularization after 1 month of therapy. The frequency of hyporesponse registered in our observation was higher than in the previous study by Tsuda K. et al. (2020). According to the results of the Japanese study, hyporesponse was observed in 15.2 % of cases (77/505) of statin therapy [7]. Similarly, we found no evidence of a greater rate of hyporesponse or suboptimal response to statins in the group of patients with CMD. A significantly lower baseline LDL-C level was observed in the group of patients with CMD and in group 2 of hyporesponders, which is consistent with the results of previous studies [7, 18].

Conclusion

According to the data of the retrospective analysis of the outpatient records of patients who were followed up in the clinic after ACS and had CMD (T2DM, prediabetes), hyporesponse to statin therapy was observed in 25.81 % of cases, suboptimal response to statins in 56.45 % of cases. There was no evidence of a higher frequency of hyporesponse and subop-

timal response to statin therapy in the group of patients with CMD compared to patients without CMD. Hyporesponders with CMD had significantly lower baseline LDL–C levels.

Conflict of interests: none declared.

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Characteristics of heart failure course in patients with chronic myocarditis

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The aim of this study is to investigate the features of chronic heart failure (CHF) in patients with chronic myocarditis (CM) in the setting of left bundle branch block (LBBB).

Methods. To assess the severity of CHF depending on the degree of LBBB, 51 CM patients with signs of CHF were studied. Patients were divided into 2 groups. The first group consisted of 21 patients (mean age, 36.7±1.1 years) with LBBB and the second group consisted of 30 patients (mean age, 32.5±1.0 years) without conduction disturbances. All patients underwent resting electrocardiography and transthoracic echocardiography.

Results. As CHF progresses, patients with LBBB have statistically significant increases in left ventricular (LV) posterior wall and interventricular septum thickness, left ventricular myocardial mass index (LVMMI), and left atrial (LA) size compared to patients without conduction disturbances. End-diastolic size and end-diastolic volume were not significantly different between groups. A more pronounced deterioration of systolic cardiac function was observed in group 1 patients. In patients with functional class (FC) II CHF without LBBB, LV ejection fraction (EF) remained at the lower limit of normal (58.9±2.3%), whereas in patients with LBBB, LV EF decreased (47.1±1.0%). Patients in group 1 showed more pronounced signs of diastolic dysfunction at an early stage of CHF compared to patients in group 2. Thus, the pseudonormal type of diastolic dysfunction is diagnosed in the majority of group 1 patients with I FC CHF and the restrictive type in group 1 patients with II–III FC CHF.

Conclusion. Thus, complete block of LBBB in CM patients leads to earlier cardiac remodeling with marked impairment of myocardial systolic and diastolic functions.

Keywords: myocarditis, heart failure, left bundle branch block.

Conflict of interests: none declared.

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Introduction

Cardiovascular diseases are one of the main causes of early disability and high mortality worldwide. Despite the fact that cardiovascular diseases associated with atherosclerosis take the leading position in the development of complications, still myocardial inflammatory diseases are important factors of cardiovascular morbidity and mortality [1-3]. In primary health care, verification of the causes, diagnosis and treatment of inflammatory myocardial diseases are challenging tasks [3-5].

Epidemiological studies have shown a steady increase in both non-coronary myocardial disease and chronic infections in young adults [3, 6]. Their late recognition leads to chronic inflammatory myocardial damage, progression of arrhythmias, and the development of chronic heart failure (CHF) [5, 7, 8]. There is no universally accepted scientific concept explaining the mechanisms of the onset and development of inflammatory myocardial diseases associated with chronic infections, which negatively affects treatment tactics [1, 4, 5].

Chronic myocarditis is a key pathology in the group of diseases called "inflammatory cardiomyopathy". Publications in recent years prove that the course and outcome of chronic inflammatory myocardial damage serve as the main pathogenetic mechanism for the development of congestive heart failure in young people [3, 8]. In recent years, special attention has been paid to the etiology of chronic myocarditis (CM), since the further management of the patient and the success of therapeutic measures largely depend on it [2, 4]. It is well known that the progression of CHF often leads to the development of dilated cardiomyopathy with the phenomenon of congestive CHF, which is resistant to optimal medical therapy and serves as an indication for heart transplantation [7, 8].

Despite its low sensitivity, electrocardiography (ECG) is widely used as a screening method. ECG changes in patients with myocarditis range from non-specific T-wave and ST segment changes to infarction-like ST elevations [1, 4]. Along with the development of CHF, arrhythmias and conduction disturbances become common and serious complications of CM [7, 9]. The presence of an abnormal Q wave and/or left bundle branch block (LBBB) is known to be associated with a higher incidence of fatal outcome in this group of patients [9–11].

The influence of intraventricular conduction disturbances on the course and outcome of CHF has been investigated in only a few studies [12, 13], and according to different authors, they are observed in 10–37 % of patients. At the same time, most attention has been paid to atrioventricular block, and complete LBBB, as well as the relationship of intraventricular conduction disturbances with the etiology and severity of CHF and with the contractile and diastolic function of the heart, have practically not been considered. According to some authors, LBBB is an independent predictor of death in patients with CHF [11-14]. Thus, the presence of complete LBBB, even in the absence of structural heart disease, has been shown to be an independent risk factor for the development and prognosis of CHF.

The pathogenetic role of interventricular dyssynchrony caused by right ventricular apical pacing, which resembles the morphology of complete LBBB on ECG, is also known to contribute to the development of pacemaker cardiomyopathy with CHF phenomenon [15]. Obviously, in patients with CM, the risk of development/progression of CHF and the high incidence of fatal outcome are not only due to the presence of LBBB, but also to severe myocardial morphofunctional changes [1, 4, 5]. Thus, given the unfavorable prognostic value of complete LBBB in CM, the study of the hemodynamic mechanisms of CHF development and progression is relevant to justify the choice of therapeutic tactics, including the use of electrocardiotherapy.

The aim of the present study was to compare the characteristics of morphofunctional cardiac remodeling in patients with chronic myocarditis in relation to the presence of LBBB.

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Methods

Fifty-one patients (32 males and 19 females) diagnosed with CM with varying degrees of CHF severity were enrolled in an open-label, comparative clinical trial. The age of the patients ranged from 28 to 37 years (mean 34.2±1.4 years). Patients were divided into two groups according to the presence of LBBB: group 1 included 21 patients with LBBB and group 2 included 30 patients with normal QRS complex duration, i.e. without LBBB.

All patients underwent clinical examination (analysis of complaints and physical examination data), resting ECG recording in 12 standard leads, and Doppler echocardiography. Ultrasound examinations were performed with a color diagnostic scanner "Aloka SSd-2000" (Hitachi Aloka Medical, Japan) in M-mode with a 3.5 MHz pulse transducer in the left lateral position of the patient. Echocardiographic parameters characterizing chamber dimensions, wall thickness, and left ventricular (LV) systolic and diastolic function were calculated. LV diastolic function was assessed using transmitral diastolic flow and the following types of diastolic dysfunction were verified: hypertrophic, pseudonormal and restrictive.

Tolerance to physical activity was assessed by a standardized 6-minute walk test. Quality of life was assessed in scores using the Minnesota Questionnaire. The Clinical Status Assessment Scale (CSAS) modified by V.Y. Mareev was used to assess the clinical status of patients with CHF. Functional classes (FC) of CHF were determined according to the New York Heart Association classification.

Statistical analysis of the obtained data was performed in the system of statistical analysis IBM SPSS 20.0. Data input was carried out in Excel system of MS Office package. Qualitative parameters were described by relative frequencies in percentages. Normality of distribution of variables was determined by Kolmogorov-Smirnov test. Quantitative parameters were described by means and errors of means (M±m). The Student's t-test was used to evaluate differences between two independent samples for continuous parameters. For correlations, the Spearman rank correlation method was used. Differences were considered significant at $p<0.05$.

Results and the discussion

According to the clinical course of CHF, group 1 had 6 patients with I FC, 9 patients with II FC, and 6 patients with III FC. There were 10, 12, and 8 patients, respectively in group 2 (Table 1). Group 1 was predominantly presented by women. It should be noted that the mean age of the patients was not significantly different between the groups. However, the duration of the QRS complex width was significantly longer in group 1 than in group 2, which can be explained by the feature of this group — the presence of LBBB. In addition, group 1 was characterized by the predominance of cardiac rhythm disturbances, mainly in the form of supraventricular and ventricular extrasystoles or the presence of various atrial tachyarrhythmias. At the same time, the difference is not statistically significant, which is probably explained by the small sample in the study.

Table 1. **Clinical characteristics of patients in the compared groups**

Parameters	Group 1 (n = 21)	Group 2 (n = 30)
Males/females, n	18 / 3	14 / 16
Age, years (M ± m)	36.7±1.1	32.5±1.0
I FC CHF, n/%	6 (28.6)	10 (33.3)
II FC CHF, n/%	9 (42.8)	12 (40.0)
III FC CHF, n/%	6 (28.6)	8 (26.7)
QRS complex width, m/s (M ± m)	138.5±4.7	90.2±2.6
Rhythm and conduction disorders, n/%	6 (28.6)	5 (16.7)

Our findings in severe CHF may be explained by the fact that patients with complete LBBB are more likely to decompensate, require hospitalization or outpatient care, and have greater limitations in physical activity. Patients with early-stage CHF do not differ significantly in clinical manifestations, but in the absence of LBBB, they achieve compensation more quickly and have relatively high levels of quality of life indices. Table 2 shows the parameters of the morphofunctional state of the heart depending on the presence of LBBB, but without taking into account the FC of CHF. In this case, LV parameters were significantly larger in patients with complete LBBB than in patients without LBBB. In addition, the thickness of LV posterior wall and interventricular septum thickness was greater in group 1 than in group 2, although the difference was not significant ($p>0.05$). Importantly, the mean LV EF in group 1 was less than 40 % and significantly lower than in group 2: 29.3 % less on average ($p<0.001$).

With the progression of CHF, there is a statistically significant values increase in LV posterior wall and

Table 2. **Morphofunctional parameters of intracardiac hemodynamics in myocarditis patients depending on the presence of LBBB (M ± m)**

Parameters	Patients with LBBB (group 1)	Patients without LBBB (group 2)
LA, mm	4.5±1.3	4.3±0.9
LA volume index, ml/m^2	33.2±6.1	33.0±5.2
End diastolic diameter (EDD), mm	6.8±0.6	5.8±0.5*
End systolic diameter (ESD), mm	4.7±0.5	3.9±0.7*
End diastolic volume (EDV), ml	193±9.0	138±11.9*
End systolic volume (ESV), ml	120±6.9	69±9.0*
Indexed EDV (iEDV), ml/m^2	107±11.3	75.9±10.8*
Indexed ESV (iESV), ml/m^2	63.5±10.2	39.3±9.8*
Interventricular septum thickness, mm	10.1±0.4	9.2±0.4
LV posterior wall thickness, mm	11.2±0.3	10.2±0.3
LV EF, %	38.3±3.2	54.2±4.1*
Relative wall thickness (RWT)	0.35±0.04	0.35±0.03
Sphericity index	0.72±0.14	0.66±0.12
Pulmonary artery systolic pressure, mmHg	35±2.4	31.8±1.9

Note. * p<0,05 — statistically significant difference.

interventricular septum thickness, LVMMI and LA size, as well as of EDD and EDV indices in patients with LBBB compared to patients without conduction disturbances (Table 3). It should be noted that the severity of LV posterior wall hypertrophy increases with the FC of CHF, and LV posterior wall thickness directly correlates with the FC of CHF: r=0.49 (p=0.026).

Furthermore, a regular deterioration of LV systolic and diastolic function indices was observed with the progression of CHF. Thus, a physiological predominance of LV systolic function over RV systolic function is observed in I FC CHF in group 1 patients, regardless of the presence of LBBB. In addition, in patients with initially preserved LV systolic function (EF > 50 %), no significant difference was found. However, in II–III FC CHF, LV EF is moderately reduced or low (≤40 %), and RV EF is practically unchanged.

The evaluation of diastolic function of the heart taking into account the FC of CHF showed that patients with LBBB have more pronounced signs of diastolic dysfunction already in the early stage of CHF than patients without LBBB. Thus, "pseudo-normal" diastolic dysfunction was observed in group 1 patients at I FC CHF, and diastolic dysfunction worsened and became restrictive at II FC CHF. These marked disturbances in diastolic function associated with impaired active myocardial relaxation or a significant increase in ventricular diastolic pressure may characterize diastolic heart failure [7, 11]. Furthermore, it confirms the generally accepted hypothesis that diastolic dysfunction is a precursor or risk factor for the development of systolic heart failure in most cases of systolic heart failure [4, 12, 13].

When assessing the clinical status of patients according to the CSAS scale, no significant differences were found depending on the presence of LBBB (p>0.05). However, with the progression of hemodynamic disturbances, taking into account the FC of CHF, there was a regular and reliable increase in the average score of the CSAS scale, especially in pa-

Table 3. **Comparison of structural and functional parameters of the heart depending on the severity of CHF in groups (M ± m)**

Parameters	I FC CHF		II FC CHF		III FC CHF	
	1 group	2 group	1 group	2 group	1 group	2 group
LA, mm	42.6±1.3	44.5±1.1	44.3±1.1	41.8±1.2	47±1.5	40±2.0*
ESD, mm	37.2±1.7	35.0±2.1	43.5±1.9	40.2±1.6	48.0±1.4	45.4±2.1
EDD, mm	48.5±3.9	50.8±3.4	54.6±2.8	52.0±3.3	58.3±3.5	63.0±3.0
LV EDV, ml	113.5±14.2	113±15.2	173.0±3.2	160±3.41*	192.3±9.1	173.13±8.8*
LV ESV, ml	52.3±7.9	42.7±5.3	65.2±2.5	61.8±2.2*	91.8±5.7	79.3±4.5*
LV posterior wall, mm	10.1±1.0	9.7±0.8	13.7±0.9	12.2±0.8*	16.4±1.5	14.0±0.9*
Interventricular septum, mm	9.1±0.5	9.2±0.7	11.6±0.7	10.1±0.9*	12.9±1.4	11.1±1.12*
RV EF, (%)	56.3±2.9	56.1±1.3	52.8±2.8	53.6±1.9	58.9±1.9	53.3±1.9*
LV EF (%)	65.0±3.3	66.2±1.2	47.1±1.0	58.9±2.3*	40.6±0.9	43.2±1.5
LVMMI, (g/m^2)	105.7±4.5	102.4±4.9	132.5±5.9	121.3±4.1*	156.4±3.9	135.1±4.1*
E/A	0.98±0.02	0.51±0.03*	0.96±0.04	0.99±0.02	1.11±0.01	0.98±0.01
IVRT, m/s	112.3±1.3	114.2±2.0	112.2±1.7	112.2±1.5	113.2±1.8	112.2±1.9
DT, m/s	242.0±7.2	228.2±7.0*	255.0±7.2	242.7±7.0	265.0±6.9	245.9±6.6*
CSAS, score	3.9±0.1	3.6±0.3	4.7±1.6	4.1±1.9	6.7±0.5	6.0±0.4

Note. * p<0,05 — statistically significant differences between groups 1 and 2: E/A — is the ratio of the early to lateventricular filling velocities; IVRT — isovolumic relaxation time; DT — deceleration time of early diastolic filling.

tients with the presence of LBBB. This means that the quality of life, including tolerance to physical activity, is reduced in patients of group 1 compared to group 2.

It should be noted that in patients with LBBB some patterns were revealed depending on the QRS complex duration. In group 1, out of 21 patients with LBBB, 8 patients had QRS complex width from 120 m/s to 150 m/s and 13 patients — more than 150 m/s. It is shown that LV EF value is inversely correlated with QRS complex duration: r = –0.53 (p=0.007). Moreover, in group 1, among patients with QRS complex duration more than 150 m/s, cases of severe CHF predominate: out of 15 patients, 12 patients were diagnosed with II–III FC CHF.

The data obtained by the authors confirm the underlying pathophysiological mechanisms of the development and progression of CHF caused by electromechanical dispersion due to complete LBBB, leading to mechanical interventricular dyssynchrony and global systolic dysfunction. In this regard, it is important to note that the therapeutic tactics of CHF treatment in the presence of LBBB with QRS complex duration greater than 150 m/s justified the introduction into clinical practice of cardiac resynchronization therapy as a highly effective method of biventricular electrical stimulation in patients with symptomatic CHF. It allows to improve the quality of life and the prognosis [16]. This method contributes to restoration of interventricular synchronization, improvement of systolic and diastolic functions of the heart, resolution/relief of CHF symptoms, especially with low LV EF. It should be noted that cardiac resynchronization therapy has shown particularly high efficacy in patients with CHF of non-ischemic genesis, including the fibrosis after myocarditis.

Conclusion

Thus, the characteristics of morphofunctional remodeling of the heart in patients with chronic myocarditis in relation to the presence of LBBB, as well as clinical and hemodynamic features of the course of CHF, which are important for predicting the outcome of the disease and choosing appropriate therapeutic strategies, were demonstrated.

Considering the leading role of conduction disturbances in the His-Purkinje system caused by chronic myocarditis in the development of CHF, in addition to the commonly used method of transthoracic echocardiography, it is advisable to use the method of tissue Doppler cardiac imaging to detect interventricular dyssynchrony, which causes disturbances in local myocardial contractility and a decrease in contractile and/or pumping function of the left ventricle. Diffuse inflammatory damage to the heart caused by myocarditis, especially in the case of complete LBBB, serves as the pathogenetic mechanism for the development of dilated cardiomyopathy, the adequate treatment of which requires the use of a wide range of therapeutic measures, including heart transplantation.

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Comparison of conventional and developed echocardiographic criteria of pulmonary embolism

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The aim of the study was to compare the conventional and developed echocardiographic (EchoCG) criteria of severity of the course and prognosis of pulmonary embolism (PE) outcomes and to establish the most significant of them.

Methods. The study included 428 patients with PE, of whom 42 died and 51 had hemodynamically significant course of the disease. The remaining patients were hemodynamically stable. Of these, 193 had evidence of right heart overload on echocardiography and 142 did not. The prevalence of commonly accepted and developed EchoCG criteria was assessed in the study groups with subsequent comparative analysis and determination of the significance of each parameter.

Results. The significance of such common EchoCG criteria of right heart overload as the presence of interventricular septal flattening (74.1% and 82.6%, respectively) and right ventricular free wall dyskinesia (67.3% and 88.2%, respectively), which have the highest diagnostic sensitivity and specificity for determining the severity of the disease course and fatal outcome, was confirmed. It has been proved that it is more informative to estimate not the level of pressure in the pulmonary artery, but to calculate the pressure gradient on its valve. Decrease of this parameter less than 16 mmHg is highly (r=0.99) associated with hemodynamically significant course of the disease, and less than 12 mmHg — with death. The calculated volume of tricuspid regurgitation, especially in correlation with the right atrial volume, more clearly and informatively reflects the overload of the right heart chambers than the degree of tricuspid regurgitation, and allows to assess its dynamics during therapy.

Conclusion. The determined generally accepted and developed EchoCG criteria allow to optimize the stratification of patients according to the severity of PE course and prediction of its outcomes.

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Introduction

Pulmonary embolism (PE) is the sudden complete or partial occlusion of a branch of the pulmonary artery by a thrombotic mass that obstructs normal blood flow, resulting in increased pressure and enlargement of the right ventricle (RV) [1, 2]. In patients with significant RV overload due to functional insufficiency of the tricuspid valve, there may be increased severity of blood regurgitation into the right atrium with dilation of the inferior vena cava more than 20 mm and reduction of its collapse during breathing, as well as development of dyskinesia zones, usually of the RV free wall with preserved mobility of the apex [3, 4]. All these signs can be diagnosed by echocardiography (EchoCG), which is the most widespread and accessible method to evaluate morphological and functional changes of the heart and its valvular apparatus. The convenience of cardiac ultrasound in PE lies, first of all, in the possibility to evaluate all changes in real time at the patient's bedside, and in case of severe condition helps to diagnose the disease quickly [5, 6].

According to modern concepts, EchoCG plays a significant role in determining the severity of disease progression and the probability of death in patients with PE. In a hemodynamically unstable patient with suspected PE, incontrovertible signs of pressure overload or RV dysfunction become the basis for urgent initiation of reperfusion therapy in the absence of CT-angiography [1, 6, 7].

However, taking into account the features of RV geometry, there is no single EchoCG parameter to rapidly and reliably detect RV dysfunction, and the course of the disease is not always accompanied by typical signs [8, 9]. Therefore, EchoCG diagnosis of PE is difficult, and the significance of EchoCG criteria varies in different studies [10, 11]. All this determines the importance of searching for new, more accurate criteria reflecting the degree of RV dysfunction [12, 13].

The aim of the study was to compare the conventional and developed echocardiographic (EchoCG) criteria of severity of the course and prognosis of PE outcomes and to establish the most significant of them.

Methods

The course of PE was analyzed in 428 patients hospitalized between 2010 and 2022. Of these, 42 died despite treatment (fatal PE). They formed the first comparison group. There were 18 men and 24 women. The age of the patients ranged from 34 to 92 years, with a mean age of 66.5±12.0 years. According to the Pesi scale of early PE-associated death, 38.1 % of patients had class 4 and 61.9 % class 5.

Hemodynamically significant PE was present in 51 patients who constituted the second group. There were 23 men and 28 women. The age of the patients ranged from 27 to 84 years with a mean age of 62.6±11.8 years. According to the Pesi scale of early PE-associated death, 17.7 % of the patients had class 3, 72.5 % class 4, and 9.8 % class 5.

The third group, PE patients with hemodynamically stable course and presence of EchoCG criteria for RV overload, consisted of 193 patients. There were 108 men and 85 women. The age of the patients ranged from 23 to 95 years, with a mean age of 64.7±13.6 years. According to the Pesi scale, 48.2 % of the patients had class 3, 40.9 % class 4 and 10.9 % class 5 early PE-associated death.

The fourth, additional control group consisted of 142 patients aged 28 to 80 years with a mean age of 55.5±16.2 years. This group was used to determine the thresholds of the developed EchoCG parameters in patients without evidence of right heart overload. There were 70 males and 72 females. The first class of early PE-associated death according to the Pesi

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scale was found in 37.3% of patients in this group, the second class — in 62.7% of patients.

The groups were comparable by PE duration and comorbidities. Patients were treated according to the European Society of Cardiology risk stratification for early death from PE.

Inclusion criteria: age 18 years and older; presence of PE reliably confirmed by CT-angiopulmonography; general clinical and biochemical blood tests with determination of plasma concentration of troponin and D-dimer, electrocardiography, EchoCG, ultrasound angioscan of the lower limb veins on the first day of hospitalization.

The severity of the disease course was assessed using the Pesi index, which includes a large number of clinical characteristics. The probability of early PE-associated death was evaluated according to the European Society of Cardiology criteria.

Exclusion criteria of patients from the study were: death or discharge from the hospital before completion of all necessary investigations.

Statistical analysis

The volume of tricuspid regurgitation (V_{tr}) and the pressure gradient on the pulmonary artery valve (ΔP_{pa}) were calculated on the basis of the formula of elementary physics for the volume of fluid flowing through an orifice of a certain diameter under a pressure gradient on its different sides (1) [14, 15].

$$V = \eta x S \sqrt{\frac{2 x_{\Delta} P}{\rho}} \qquad (1),$$

where:

V — the volume of blood flowing through the orifice during one systole;

μ — jet compression coefficient, equal to 0.62 for small orifices;

ΔP — pressure gradient on different sides of the orifices;

ρ — blood density of 1060 kg/m^3;

S — cross-sectional area of fluid flow through the orifices.

The formula (2) was used to calculate the pulmonary artery pressure (P_{pa}):

$$P_{pa} = P_{RV} - \Delta P_{pa} \qquad (2),$$

where:

P_{pa} — calculated pulmonary artery pressure;

P_{RV} — Right ventricular pressure, which is currently calculated as "systolic pulmonary artery pressure" during EchoCG;

ΔP_{pa} — the difference of pressure in the right ventricle and pulmonary artery, which was calculated according to the formula established earlier.

Based on these formulas, we determined the volume of tricuspid regurgitation and its ratio to the right atrial volume (V_{tr}/V_{RA}), as well as the pressure gradient across the pulmonary artery valve and the pressure in the pulmonary trunk. Thresholds were established for each of these parameters.

The methods of descriptive statistics were used to evaluate the prevalence of conventional and developed EchoCG criteria in the studied groups, to establish the correlation dependence of each conventional and advanced parameter with the severity of the disease course and mortality, to determine their diagnostic characteristics with subsequent comparative analysis.

Statistica 10.0 (Stat Soft Inc., USA) was used for statistical processing and analysis of the results. Data are presented as: absolute number of cases (n), prevalence of the trait (%), mean (M), and standard deviation (SD). Quantitative data were assessed for conformity to a normal distributionΔ using the Shapiro-Wilk test (when n was less than 50) or the Kolmogorov-Smirnov test (when n was greater than 50). All distributions were normal. Statistical significance of differences was evaluated using Student's t-test. The significance of each parameter and its diagnostic characteristics were determined using Pearson's correlation (r) and the odds ratio method. Differences were considered statistically significant at $p < 0.05$.

Results

In PE patients of the first, second and third comparison groups, the prevalence of conventional EchoCG criteria such as: increase in the ratio of basal sizes of the right and left ventricles more than 0.9, which was 61.8%, 58.8% and 58% of patients, respectively; presence of RV free wall dyskinesia, which was registered in 4.8%, 9.8% and 6.2% of patients, respectively; flattening of the interventricular septum — in 31%, 15.7% and 25.4% of patients, respectively. No statistically significant difference ($p>0.05$) was found when the data were compared. However, a high correlation was found with the severity of the disease ($r=0.76$) according to the Pesi scale, with the moder-

ate-high (r=0.71) and high (r=0.70) risk of early PE-related death according to the European Society of Cardiology criteria, and with the fatal outcome (r=0.79) for the presence of interventricular septal flattening on EchoCG. A moderate correlation was found between the same data and visualization of RV free wall dyskinesia, with correlation coefficients of 0.67, 0.53, 0.59, and 0.54, respectively. The diagnostic values of interventricular septal flattening and RV free wall dyskinesia were among the highest among the compared conventional parameters and were as following: sensitivity — 74.1 % and 67.3 %, respectively, specificity — 82.6 % and 88.2 %, respectively.

The next widely used criterion for diagnosis and severity assessment in patients with PE is the increase in pulmonary artery systolic pressure. We confirmed a significant correlation (r=0.58) between the increase in pulmonary artery systolic pressure of more than 55 mm Hg and class 5 severity of the disease course according to the Pesi scale, as well as high (r=0.69) and moderately high (r=0.68) risk of early PE-associated death according to the criteria of the European Society of Cardiology. However, considering the diagnostic sensitivity (66.1 % and 71.2 %, respectively) and specificity (57.5 % and 68.3 %, respectively), which are not very high for predicting mortality and patient severity, we attempted to develop a new method for calculating pulmonary artery pressure. Nearly identical physiological data were obtained. In the absence of right heart overload, the calculated pressure in the pulmonary trunk ranged from 2 to 12 mmHg, and the higher this index was, the more severe was the disease. At Ppa values higher than 35 mmHg, PE was hemodynamically significant in 68.6 % of patients, and at the level of more than 45 mmHg — resulted in death in 83.3 % of patients. This was confirmed by correlation analysis, which showed a high correlation with the severity of the disease (r=0.79) according to the Pesi scale and a high risk of early death associated with PE according to the ESC criteria (r=0.93). When comparing the results obtained, it was found that the increase in pulmonary artery pressure according to the developed method correlates better with the severity of the disease and the outcome than the calculation of systolic pulmonary artery pressure. Moreover, the latter is not a real method, but the determination of the pressure in the RV cavity, while the proposed method is a variant of the calculation of the pressure in the pulmonary artery trunk. However, when comparing the diagnostic characteristics of the proposed method of calculating the pressure in the pulmonary trunk and the generally accepted measurement of systolic pressure in the pulmonary artery, no significant increase was found. Diagnostic sensitivity and specificity were also not high, at 66.7 % and 78.3 %, respectively. This is most likely due to the fact that the pressure in the right ventricular cavity (pulmonary artery systolic pressure with its measurement errors) was used to calculate the pressure in the pulmonary artery trunk, according to generally accepted principles. Calculated determination of pressure gradient across the pulmonary artery valve, free from calculation of pulmonary artery systolic pressure, had more reliable diagnostic characteristics.

The mean calculated pressure gradient across the pulmonary artery valve in patients without evidence of RV overload was 24.1±2.8 mmHg. This parameter was lower in patients with more severe course of the disease and hemodynamic instability. In all patients with fatal outcome it did not exceed 12 mmHg, in 94.1 % of patients with hemodynamic instability it was in the range of 12 to 16 mmHg, and in 96.9 % of patients with hemodynamic stability it was higher than 16 mmHg. These data were confirmed by correlation analysis, which showed a strong correlation with the severity of disease progression. The calculated pressure gradient across the pulmonary artery valve at its values from 4 to 12 mmHg highly correlated with class 4 (r=0.72) and very highly — with class 5 (r=0.99) of disease severity according to the Pesi scale, high probability of early PE-associated death according to ESC criteria (r=0.96), and fatal outcome (r=1). The disease tended to be hemodynamically significant (r=0.78) with ΔP_{pa} values between 12 and 16 mmHg, and at values greater than 16 mmHg the course of PE was stable (r=0.77).

The sensitivity and specificity of this parameter are quite high. They are 92.7 % and 97.8 %, respectively, for the severity of the disease course and 100 % and 98.7 %, respectively, for mortality. This indicates the greater importance of pressure gradient calculation in determining the severity of pulmonary embolism and prognosis compared with the determination of systolic blood pressure or pressure in the pulmonary artery trunk according to the proposed formula.

Determining the calculated volume of tricuspid regurgitation per one systole, it was found that it fully

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corresponded to the degree of tricuspid regurgitation according to literature sources, namely, in patients with the 1st degree of regurgitation it did not exceed 30 ml, in the 2nd degree it ranged from 30 to 60 ml, and in the 3rd degree it was more than 60 ml. At the same time, of course, it was found out that the greater the volume of regurgitation, the more often it is associated with dilatation of the inferior vena cava more than 2 cm and absence of its collapse during inspiration by 50 % and more. Thus, at values of tricuspid regurgitation volume less than 30 ml, dilatation of inferior vena cava more than 2 cm and absence of its collapse during inspiration by 50 % and more occurred in 12.6 % and 2.6 % of patients, respectively, at values from 30 to 60 ml — in 29.4 % and 19.6 %, respectively, and at regurgitation volume more than 60 ml — in 86.4 % and 68.3 % of patients, respectively.

When comparing the values of the estimated volume of tricuspid regurgitation per systole, no differences were found in the severity of the patients' condition in the compared groups, as well as in the prevalence of the degree of tricuspid regurgitation, dilatation of the inferior vena cava by more than 2 cm and absence of its collapse during inspiration by 50 % or more.

To assess the severity of tricuspid regurgitation, it is important to evaluate not only the volume of tricuspid regurgitation, but also its ratio to the volume of the right atrial cavity, which is similar to the method used to determine the degree of tricuspid regurgitation. Equivalent values were obtained between the area and volume ratios. Thus, in the absence of pathological changes, V_{tr}/V_{RA} was not higher than 0.36, which is comparable to the first degree of regurgitation, and clinically manifested PE was at values higher than 0.6, which is comparable to the second degree and higher. However, the determination of V_{tr}/V_{RA} is clearer and more informative and allows us to assume that the blood volume exits the right atrium, resulting in dilatation of the inferior vena cava by more than 2 cm and the absence of its collapse during inspiration by 50 % or more due to volume and pressure overload. This is confirmed by the correlation analysis, which showed a high correlation between V_{tr}/V_{RA} and inferior vena cava dilation of more than 2 cm (r=0.79) and the absence of its collapse on inspiration by 50 % and more (r=0.76). The above indicates the possibility of estimating the volume of tricuspid regurgitation and its relation to the volume of the right atrium with greater informative value than dilatation of the inferior vena cava more than 2 cm and absence of its collapse on inspiration by 50 %.

When comparing the mean values of Vtr/VRA, it was found that in patients with fatal outcome and hemodynamically unstable patients they were statistically significantly higher ($p<0.01$) than in patients with stable hemodynamics: 0.57±0.2 and 0.66±0.31 versus 0.48±0.18, respectively, and when comparing the prevalence of the degree of tricuspid regurgitation in all groups, no statistically significant differences were obtained ($p>0.05$). This confirms the usefulness of using the calculated numerical parameters of regurgitation and Vtr/VRA compared to the degree of tricuspid regurgitation both at the initial contact and, to a greater extent, to assess the dynamics of changes on the background of treatment.

When estimating the correlation dependence of the currently used method of determining the degree of tricuspid regurgitation, it was found that its increase more than the second degree weakly reflects the severity of the disease course and moderately (r=0,31) correlates with the onset of fatal outcome, and V_{tr}/V_{RA} significantly correlates with 4 (r=0,52) and 5 (r=0,69) classes of the severity of the disease course according to the Pesi scale and with mortality (r=0,68). The diagnostic sensitivity and specificity of the degree of tricuspid regurgitation and V_{tr}/V_{RA} were practically equal and amounted to 71.5 % and 76.4 % for the mortality (sensitivity — 71.5 % and 76.4 %, specificity — 59.4 % and 54.1 %, respectively) and for the severity of the disease course (70.7 % and 64.3 %, sensitivity — 57 % and 53.6 %, respectively).

Discussion

We demonstrated that among the currently widely used EchoCG criteria of RV dysfunction in patients with PE, the most significant in determining the severity of the disease course are flattening of the interventricular septum and dyskinesia of the RV free wall, which is consistent with literature sources [1, 10, 11].

Such EchoCG criteria as the increase in systolic pressure in the pulmonary artery and the degree of tricuspid regurgitation, regardless of its severity, are less informative in determining the severity of the course of PE and predicting its outcome than the proposed calculation of the pressure gradient across the pulmonary artery valve and determination of the ratio of the volumes of tricuspid regurgitation and the right atrium [3, 5, 6].

The calculated volume of tricuspid regurgitation per systole does not have a strong diagnostic and prognostic significance, but in contrast to the determination of the degree of tricuspid regurgitation, which is currently used for indirect assessment of right atrial overload, it allows for a clear and informative assessment of the dynamics of blood flow through the tricuspid valve during systole [8, 9].

Conclusion

To determine the severity of the PE course, it is most effective to use such conventional EchoCG criteria of right ventricular overload as flattening of the interventricular septum and right ventricular free wall dyskinesia, while the determination of the level of systolic pressure in the pulmonary artery and the degree of tricuspid regurgitation should be replaced by the calculation of the pressure gradient across the pulmonary valve and the ratio of tricuspid regurgitation to right atrial volume.

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Shift work, obstructive sleep apnea syndrome and restless legs syndrome: effects on nocturnal blood pressure

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The prevention of cardiovascular diseases (CVD) has been one of the most important issues in cardiology practice for many years. For this reason, active research is being conducted worldwide to identify new risk factors that lead to damage to the cardiovascular system. One such factor is impaired nocturnal arterial blood pressure (NBP) regulation, which is associated with an increased risk of CVD and premature death. This article reviews the current conditions that may lead to dysregulation of diurnal BP fluctuations: shift work, obstructive sleep apnea syndrome (OSAS), and restless legs syndrome (RLS). The literature review revealed a correlation between the occurrence of nocturnal arterial hypertension (AH) and the presence of OSAS or RLS in the patient, as well as the predisposing factors for nocturnal BP elevation in patients with shift work. It is obvious that patients with OSAS, RLS and shift workers need continuous BP control, including at night, to detect nocturnal AH and prescribe appropriate therapy to prevent disease progression and the increase of the cardiovascular risk.

Keywords: shift work, obstructive sleep apnea syndrome, restless legs syndrome, nocturnal arterial hypertension.

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Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVD) are the leading cause of death today. Because of its social and economic importance, research is underway worldwide to identify new risk factors for CVD. One such factor is impaired nocturnal blood pressure (BP) regulation, which is associated with an increased risk of fatal cardiovascular events and premature death. However, most studies and meta-analyses addressing this issue have examined only a limited spectrum of non-cardiac nosologies that lead to inadequate reduction or increase in sleep BP, such as diabetes mellitus (DM), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and rheumatoid arthritis (RA). This paper reviews current conditions that can potentially lead to impaired regulation of diurnal BP fluctuations: shift work, obstructive sleep apnea, and restless legs syndrome.

Shift work

Shift work is important in the implementation of 24-hour work functions, including emergency and security services, industry, food and some others. According to statistics, approximately 2.5 billion people around the world work in shifts, with 20 % of the workforce in Europe working in shifts [1]. Shift work refers to a type of activity that requires the performance of work functions outside of traditional working hours (e.g., 8:00 to 18:00, 9:00 to 17:00, etc.) [2].

Shift work and health effects

Irregular work schedules can have a negative impact on a person's health. An analysis of 38 meta-analyses and 24 systematic reviews by Göran Kecklund et al. (2016) showed an association between shift work and accidents, type 2 DM, weight gain, stroke, coronary heart disease (CHD), acute sleep disturbance, cancers such as prostate and breast cancer, infectious diseases, and increased risk of cognitive and cardiometabolic disorders to the same extent as sleep deprivation [3–5]. However, the association between cancer and night shift work is not evident from a meta-analysis of 57 articles by Aishe Dun et al. (2020) [6], despite the previously observed association. A study by Bette Loef et al. (2019) of blood tests from 254 participants working night shifts (experimental group) and 57 participants in a control group (not associated with shift work) suggested an effect of the night shifts on the immune system of the respondents [4].

Circadian Rhythms and BP Regulation

It is known that the shift work leads to disruption of circadian rhythms, which control not only the sleep-wake cycle, but also many metabolic processes, including BP [7, 8]. Circadian rhythms of BP are characterized by an increase of its values in the morning, 1 hour before awakening, and its decrease ("dipping") by 10-20 % at night and during sleep [2, 9]. The main component of the physiological regulation of blood pressure is the phosphorylation of glycogen synthase kinase-3ß (pGSK-3ß), which activates the WNT/B-catenin signaling pathway. The released B-catenin translocates from the cytoplasm to the nucleus of astrocytes in the supraoptic nucleus of the hypothalamus, where it induces the expression of the glutamate transporter EAAT2 and glutamine synthetase. At the next stage, the concentration of glutamate in the synaptic clefts of glutamatergic neurons decreases as a result of the function of EAAT2 and the conversion of glutamate into glutamine due to the activity of glutamine synthetase. The activity of AMPA-R and NMDA-R receptors is reduced, including on the membranes of neurons of the nucleus of the solitary tract. The intensity of signal impulses from the nucleus of the solitary tract to the neurons of the caudal part of the ventrolateral parts of the medulla oblongata inhibiting the rostral part of the ventrolateral parts of the medulla oblongata decreases, which results in suppression of the sympathetic nervous system and activation of the parasympathetic nervous system. As a result of the described process, there is an increase in BP when photons hit the retina, especially in the morning upon awakening [10]. This describes the central regulation of BP by circadian rhythms.

However, there is also a peripheral regulation, which has been linked at the molecular level to the interaction of the clock proteins CLOCK (circadian locomoter output cycles protein kaput), BMAL1 (for brain and muscle aryl hydrocarbon receptor nuclear translocator (ARNT)-like protein 1), period and cryptochrome: CLOCK and BMAL1 heterodimerize as transcription factors and bind to the promoter regions of tissue-specific target genes involved in the regulation of physiological functions, as well as to the promoter regions of the period and cryptochrome genes, which encode the proteins of the same name,

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via an E-box. According to the negative feedback mechanism, accumulation and penetration of period and cryptochrome protein molecules into the nucleus under the influence of RORα/β/γ and REV-ERBα/β proteins (retinoic acid-related orphan receptors and nuclear receptor subfamily 1 group D member, respectively) inhibits CLOCK and BMAL1, thus stopping the transcription process. The described process has a 24-hour rhythm and is found in cells of smooth muscle tissue, perivascular adipose tissue, liver, adrenal glands, and kidneys, where active substances (serotonin, phenylephrine, angiotensinogen, beta-hydroxybutyrate, IGF, corticosterone, aldosterone, and others) are released, causing changes in vascular wall tone and physiological blood pressure fluctuations [11, 12].

Disruption of such a complex mechanism of regulation of diurnal BP variation leads to the launch of an equally complex pathogenetic mechanism of AH, including both central and peripheral changes in circadian rhythms [11]. In particular, it is of interest to study the relationship between circadian rhythm disturbances and the development of nocturnal arterial hypertension (NAH).

Shift work and AH

AH is one of the pathological conditions caused by shift work. Compared to people with regular work schedules, AH and its progression from mild to severe stage are more common in shift workers [13, 14]. A meta-analysis of 45 studies by Sara Gamboa Madeira et al. (20–21) [1] also found significant increases in systolic (by 2.52 mm Hg, 95 % CI 0.75–4.29) and diastolic BP (1.76 mm Hg, 95 % CI 0.41–3. 12) in participants with regular night shifts, but did not show a significant increase in the risk of developing AH in such participants, in contrast to previous studies, which may be explained by the larger sample size in some previous studies, the age of the participants, the presence of specific conditions in individuals in the study population (pregnancy, sleep disorders, etc.), and differences in the definition of AH. The importance of considering the last factor, the definition of AH, was also noted in a study by Masoud Khosravipour et al. (2021), where the characteristics of AH (ACC/AHA and ESC/ESH criteria) were selected and different results were obtained regarding the incidence of AH development among workers with a 12-hour night shift, depending on the characteristics of the definition. However, despite the differences described, the results of the study showed a higher incidence of AH among "night workers" compared to workers with regular schedules [15].

Shift work and NAH. Shift work is a factor that leads to changes in BP variability and sympathetic nervous system transformation from dipper to non-dipper type [16]. There are data showing that patients with AH who are accustomed to sleeping less than 6 hours (short sleepers) are twice as likely to develop resistance to the antihypertensive drug they are taking than patients with longer sleep duration [24]. In the AAC (American Association of Cardiology) guidelines, night work is considered a factor leading to inadequate nocturnal BP reduction [17]. The development of drug resistance in certain subgroups of patients and inadequate nocturnal BP reduction are characteristics of nocturnal hypertension [17], but no studies were found that examined nocturnal BP levels and the extent of nocturnal BP reduction in this cohort of patients. Given the lack of consensus, it seems reasonable to conduct studies aimed at assessing the risk of developing NAS in patients working shifts and suffering from sleep deprivation.

Cardiovascular risk, circadian disruption and shift work

Circadian disruption due to shift work is associated with an increased cardiovascular risk, which has been repeatedly demonstrated in studies [18, 19]. The first meta-analysis demonstrating the association between shift work and increased likelihood of CVD, including 34 research papers and a total of 2,011,935 participants, was conducted by Manav V. Vyas et al. (2012) in 2012 [19]. The meta-analysis found that shift work was associated with the development of myocardial infarction (OR 1.23, 95 % CI 1.15–1.31), ischemic stroke (OR 1.05, CI 1.01–1.09), and increased risk of vascular events (OR 1.24, CI 1.10–1.39).

Since the work of Manav V. Vyas. et al. (2012) was limited to studies conducted before 2006, Torquati L. et al. (2018) [18] included scientific articles from 2006 to 2016 in their meta-analysis to update the association of shift work with increased cardiovascular risk. The authors assessed cardiovascular risk in 173,010 participants with regular and irregular work schedules in an analysis of 21 studies. The meta-analysis supported the assessment of higher

cardiovascular risk (likelihood of developing cardiovascular disease, including CHD, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism) among people who worked shifts (CI 1.10–1.43), although the definitions of shift work varied among the studies included in the meta-analysis.

Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) is a sleep-related chronic respiratory disorder with a high prevalence worldwide, characterized by airway obstruction during sleep [20]. A recent study showed that nearly 1 billion people worldwide have manifestations of this pathology, indicating the need for further study of this condition [21]. If left untreated, OSAS can lead to the development of other pathological conditions, including AH [21]. OSAS and AH influence each other in terms of clinical presentation, therapy, and prognosis. Currently, the concept of "OSAS-associated hypertension" is used in the foreign literature.

Etiology and possible pathogenesis of OSAS

The pathophysiological mechanism of OSAS development is multifactorial and variable, involving many factors, most of which are individualized for each patient. Based on our studies, the most important anatomical and functional mechanisms of OSAS development have been identified and summarized in the general concept of "PALM": P (Pcrit) — critical pharyngeal closure pressure, this term refers to anatomical features that can lead to upper airway collapse; A (Arousal threshold) — reduced respiratory arousal threshold or tendency to night arousals due to respiratory stimuli; L (Loop gain) — instability of ventilation control; M (Muscle responsiveness) — insufficient activity of the muscles that dilate the upper airway [22]. Taken together, these factors can lead to recurrent upper airway spasms, resulting in a marked decrease or complete cessation of airflow. As a result, blood oxygenation decreases, leading to sympathetic nervous system activation, catecholamine release, and sleep fragmentation.

OSAS-associated hypertension

OSAS-associated hypertension occurs as a latent nocturnal hypertension with non-dipper type and pathological variability, more often resistant to drug therapy (45 %). The presence of moderate to severe obstructive apnea in a patient increases the risk of target organ damage [23, 24]. The increase in inflammatory factors in the blood that occurs with OSAS causes oxidative stress, which also increases cardiovascular risk [25]. Thus, the combination of OSAS and AH significantly worsens the patient's prognosis and requires careful evaluation for diagnosis and treatment.

OSAS is more common in patients with AH than in the general population. AH and OSAS share common risk factors, including obesity, high salt intake, advanced age, sedentary lifestyle, and diabetes [25]. Some studies have questioned the causal relationship between OSAS and AH, suggesting that the development of AH is not due to OSAS but to the same risk factor, such as obesity or diabetes [26]. A meta-analysis by Han B. et al. (2017), which included 54 original studies, found a significant association between OSAS and AH (OR = 1.798, 95 % CI 1.355–2.384). Furthermore, in a cross-sectional study group, pooled results showed that OSAS was significantly correlated with AH (OR = 1.980, 95 % CI 1.312–2.987) [27].

The common pathophysiological mechanisms for the development of OSAS and AH involve the activation of the renin-angiotensin-aldosterone system (RAAS). The hypoxemia that develops due to the sleep obstruction leads to increased synthesis and release of renin into the blood, resulting in RAAS activation, vascular constriction, and nocturnal blood pressure elevation. In addition, in the supine position, there is a distribution of fluid in the human body from the lower extremities to the neck, leading to edema of the tissues of the nasopharynx and upper airways, their obstruction and increase in BP, which is exacerbated by the activation of the RAAS by the mechanism described above and an increase in the concentration of aldosterone in the blood, which retains fluid and increases the volume of circulating blood [24]. A meta-analysis by Ze-Ning Jin et al (2016) found an increase in blood aldosterone and angiotensin II in people with OSAS and AH [28].

The impact of OSAS on nocturnal blood pressure

As described above, the pathogenesis of OSAS involves factors that have a significant impact on the cardiovascular system, such as oxidative stress, hypoxia, metabolic acidosis, and excessive activation of

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the sympathetic nervous system. As a result of these factors, there may be a sustained increase in blood pressure and an increase in its diurnal variability. The most significant changes in blood pressure occur at night. During airway obstruction, the phenomenon of "paradoxical" pulse occurs, i.e., a decrease in BP ⩾ 10 mm Hg and a decrease in heart rate as a result of excessive inspiratory effort [29]. After the obstruction ceases, there is a sharp peak in BP for a few seconds, after which the BP values return to normal [29]. Based on this, we can conclude that the variability of nocturnal BP depends on the number of apnea/hypopnea attacks, but the amplitude of BP peaks depends on individual characteristics of the organism and drug therapy. Confirmation of the direct effect of OSAS on nocturnal BP peaks and their variability can be found in numerous studies [30–32], where BP values and their variability returned to normal after the application of CPAP therapy, but not all results were consistent, indicating the need for more thorough study of this problem. In addition to these findings, the CARDIA (2020) study found a pattern: a higher likelihood of having OSAS increases the likelihood of developing comorbid nocturnal hypertension (CI 1.00-1.75) [33].

Restless legs syndrome

Restless legs syndrome (RLS) or Willis-Ekbom disease is a sensorimotor neurological disorder in which the need to move the lower extremities at rest, more often in the evening or at night during sleep, that disappears or diminishes with movement [34]. The estimated epidemiology is 5–8.8 % of the general population [35]. Periodic limb movement syndrome of sleep (PLMS) is known to occur in people with RLS. The main role in the pathogenesis of the primary form of RLS is attributed to genetically determined disorders of the dopaminergic system and iron metabolism in the brain. However, secondary forms have also been identified in the context of iron deficiency anemia, pregnancy, terminal renal failure, and vitamin B12 deficiency [36].

The impact of RLS on nocturnal blood pressure

RLS, PLMS, and OSAS are the most common sleep disorders that induce nocturnal BP elevation through activation of the sympathoadrenal system and RAAS, development of oxidative stress, and further endothelial dysfunction, and thus resulting in NAH [37, 38].

A meta-analysis by Giuseppe Maiolino et al. (2021), including 7 studies and 442 patients, showed that RLS was associated with higher BP during sleep compared to controls. It should be noted that the highest BP values occurred during both periodic and non-periodic limb movements, and the duration of nocturnal BP peaks during non-periodic movements was longer in some studies included in the meta-analysis [37]. In addition, NAH in patients with RLS was more frequently observed in the elderly and was also associated with a later onset of RLS. The severity of NAH correlates with the severity of RLS, but this statement is true only for patients with diastolic non-dipper type of diastolic BP diurnal curve [39].

However, the pathogenesis of nocturnal BP elevation in patients with sleep disorders is still under study. Exploring two main hypotheses (sleep fragmentation and the presence of periodic limb movements during sleep), Mariusz Sieminski et al (2017) concluded that sleep fragmentation is not a necessary component for the development of nocturnal BP in patients with RLS. They found a strong association between nocturnal increases in both diastolic BP and systolic BP during bouts of periodic limb movements during sleep [40]. Considering the different data obtained, the authors suggest the need for more detailed study of PLMS on the pathogenesis of nocturnal AH.

Thus, RLS, both in combination with and without PLMS, leads to increased cardiovascular risk, and therefore more careful monitoring of BP, including nocturnal BP, in these patients is required.

Conclusion

Thus, there are data suggesting an association between the occurrence of NAH and common conditions such as OSAS and RLS, as well as an increase in nocturnal BP in individuals with shift work. Studying the influence of these factors on nocturnal BP will help to clarify the specific pathogenetic links that can be acted upon to prevent the development of NAH. It is clear that patients with OSAS, RLS, and shift workers need continuous BP control, including at night, for earlier detection of NAH and prescription of appropriate therapy to prevent disease progression and increased cardiovascular risk. The issues of optimal correction of nocturnal BP levels in combination with the impact on comorbidities (RLS, OSAS, or shift work) are an ur-

gent scientific and practical task that requires further comprehensive studies.

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Congestive heart failure in children with atrial septal defect: a case report

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The aim of this study is to present a clinical case referred to a 12-year-old boy with history of atrial septal defect (ASD) and HF shows a response to treatment with improved symptoms and quality of life. The patient's laboratory studies shown increasing of neutrophil lymphocyte ratio. Chest X-ray showed a cardiomegaly. The patient had no peripheral oedema. The echocardiography identified there were a 1.88-cm ostium secundum atrial septal defect with right atrium, and right ventricle dilatation. This case highlights the associated between congenital heart disease and heart failure in paediatrics. It also illustrates exercise intolerance could be a presentation of undiagnosed atrial septal defect with heart failure. The conclusion is the patient had developed symptomatic HF with LVEF ⩾ 50 % as well as RA and RV dilatation. Most likely this patient developed HF due to the delayed diagnosis of ASD.

Keywords: heart failure, child, atrial septal defect, congenital heart defects.

Conflict of interests: none declared

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Introduction

Atrial septal defect (ASD) is condition of the wall (septum) that divides atrium are opened [1]. Those condition are one of the most common congenital heart defects (CHD) occurred in about 25 % children and estimated incidence of 56 per 100,000 live births [2–4]. Small defects on atrial septal usually can be closed spontaneously in childhood, whereas large de-

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fects can cause complications such as heart failure, dysrhythmias, and pulmonary hypertension. Doing a surgical intervention is necessary to prevent those complications in children [1].

Congestive heart failure (CHF) sometimes known as heart failure (HF). HF is defined as the clinical syndrome associated by the cardiac structure or function abnormalities. Paediatrics HF is rare than HF in adult. Although relatively rare, CHD and cardiomyopathies are the most common aetiologies of HF in children [5]. Epidemiology of HF in children isn't well characterized, but in United States (US) the incidence of HF occurred in children is 0.97 to 7.4 per 11,000–14,000. [6] The aetiologies of HF in CHD can be divided into 2 conditions of pathophysiology, there are: (1) over circulation failure; and (2) pump failure [7].

HF intervention in the setting of CHD is challenged. The aim of this research is to present a clinical case referred to a 12-year-old boy with history of ASD and HF shows the response to treatment with improved symptoms and quality of life.

Case Report

A 12-year-old-boy was admitted on the emergency department (ED) complaining of the sudden onset of dyspnoea that appeared after activity and lasted for several hours. Dyspnoea appeared suddenly and lasts continuously before entering the hospital. His complaint didn't improve at rest. There were minimal intercostal retractions, but there are no abnormal breath sounds were described on admission. On examination, there was a soft mid-systolic murmur at his upper left sternal. The patient was an elementary school's student and reported his activity more fully than before. There were no chest tightness or palpitation, and respiratory symptoms. Previously, the patient presented with the sudden onset of shortness of breath after doing sport, but it was improved at rest. In addition, he also complained of considerable orthopnea while lying down, which was relieved by sleeping prone, and frequent shortness of breath and colds. There was no family history of cardiovascular events or deaths in young people.

He had a heart rate of 103 bpm, blood pressure of 93/57 mmHg, a respiratory rate of 23 breaths per minute, an oxygen saturation of 100 % on 2 lpm of oxygen. Examination revealed clean lungs and a faint mid-systolic murmur at his upper left sternal. There weren't both of ascites, and oedema on his extremities. The result of his laboratory studies shown increasing of neutrophil lymphocyte ratio (NLR). Chest X-ray (CXR) on anteroposterior view (Figure 1). Based on the CXR results, the patient did an echocardiography examination, and the result shown in (Figure 2, and 3). CXR,

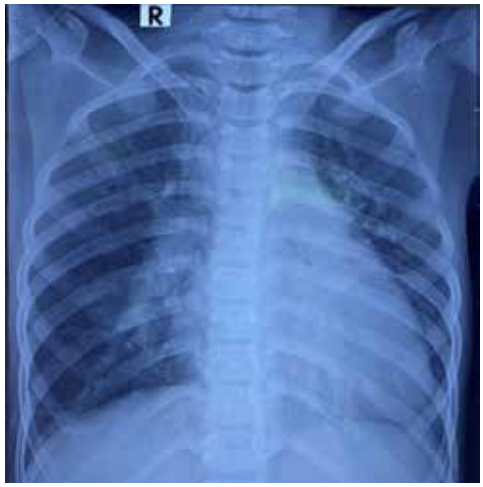

Fig. 1. Chest X-Ray P/A view showing cardiomegaly with Cardiothoracic ratio (CTR) 0.59

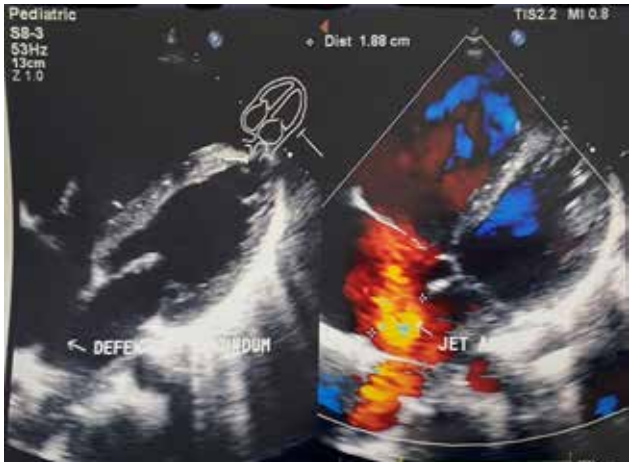

Fig. 2. Echocardiography showing the ostium secundum ASD (Diameter 1.88 cm)

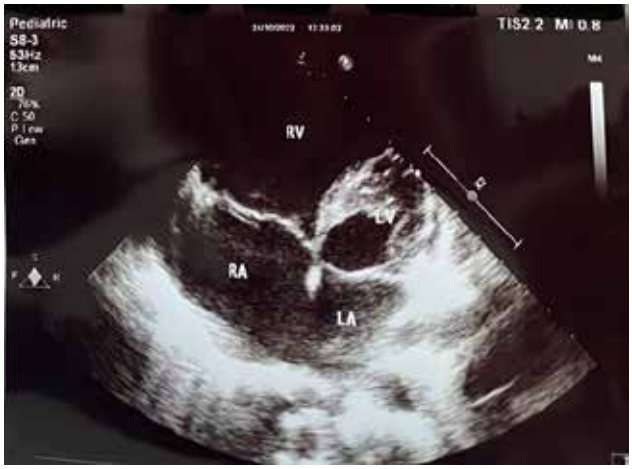

Fig. 3. Echocardiography showing RA-RV dilatation

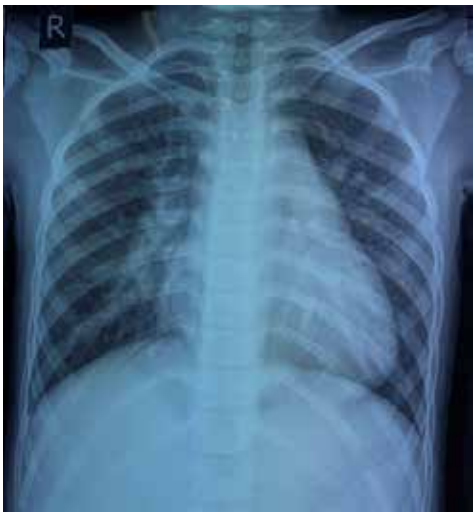

Fig. 4. Chest X-Ray P/A view showing cardiomegaly improvement with cardiothoracic ratio (CTR) 0.55

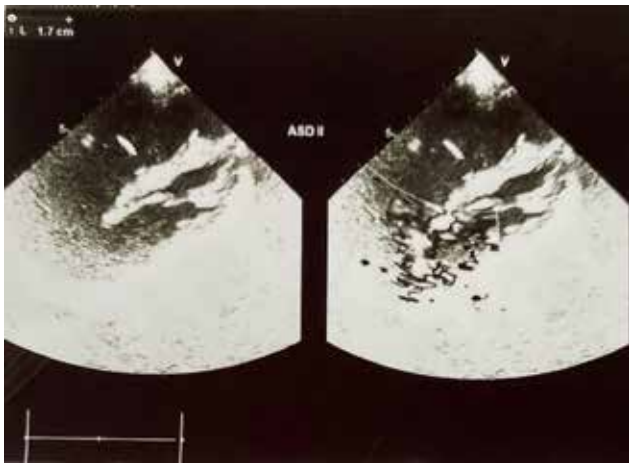

Fig. 5. Echocardiography showing the ostium secundum ASD (Diameter 1.7 cm)

and echocardiography examination were performed, a cardiomegaly and ASD, respectively were identified. The echocardiography revealed an ASD 1.88 cm with a left-to-right shunt (Figure 2). Echocardiography showed LVEF of 73.1 %, and a sign of right atrium, and right ventricle (RV) dilatation (Figure 2, and 3), respectively. Based on this case, a diagnosed of Heart failure et causa ASD was made. The patient treatment was commenced on furosemide, and spironolactone. He was receiving furosemide 5 mg, and spironolactone 6,25 mg. After 3 months of evaluation, there is a clinical improvement and improved result of CXR, echocardiography and electrocardiography (ECG) (Figure 4, 5 and 6), respectively. The CXR shown CTR 0.55 (Figure 4). The echocardiography had shown that the hole of secundum ASD have gotten smaller than before (Figure 5). An ECG had shown a right ventricular hypertrophy (RVH), the heart rate of 89 bpm, PR interval of 176 ms, QRS duration of 120 ms, right axis deviation (Figure 6).

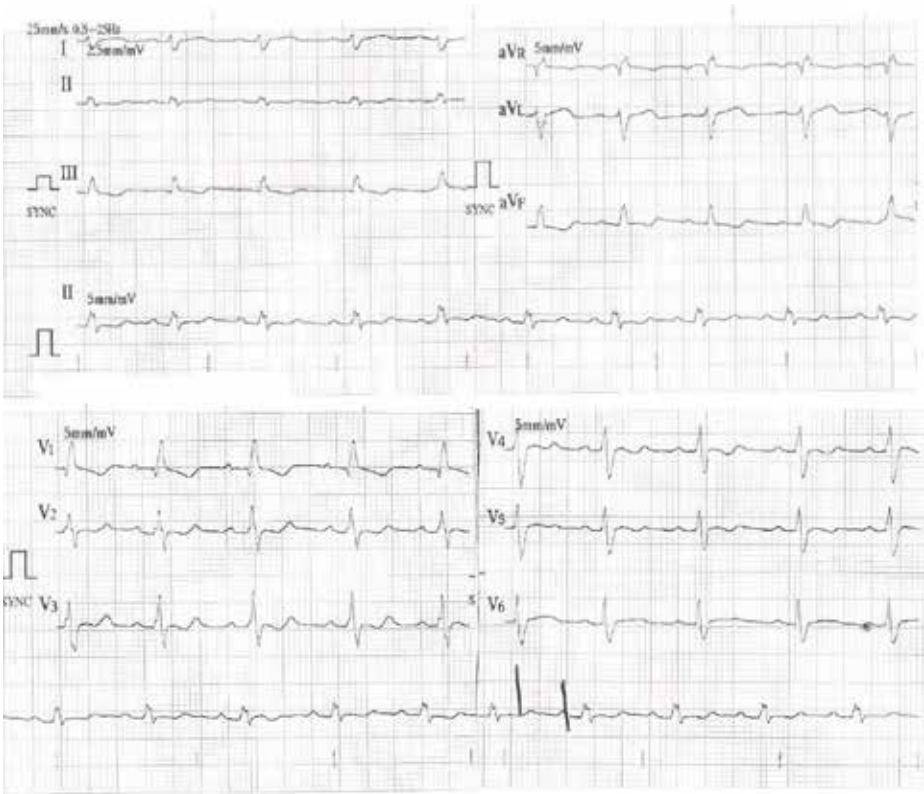

Fig. 6. Electrocardiography showing right ventricular hypertrophy (RVH)

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Discussions

This case describes a 12-year-old boy previous undetected ASD attended an ED due to sudden onset of dyspnoea that didn't improve at rest. Heart failure (HF) on paediatric is defined as a complex clinical syndrome that caused by cardiac structure or function abnormalities. It was an important thing that caused of morbidity and mortality not only in adult, but also in childhood [8]. Children whose history of HF have more than 20 times risk of death. The American Heart Association (AHA) estimated more than 8 million people in the United States (US) will be able to has HF, and the cost of treating patients whose HF around $160 billion on 2030 [9]. Impairing of ventricular filling or blood ejection fraction, or combination of both to systemic was important thing that can cause of HF [10].

Heart failure has been classified according to left ventricular ejection fraction (LVEF) (table 1). It is important to classify patients with HF because the difference prognosis and response to interventions. LVEF classified into 4 type: (1) heart failure with preserved ejection fraction (HFpEF, LVEF≥50 %); (2) heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 41 %-49 %); (3) heart failure with improved ejection fraction (HFimpEF, previous LVEF ⩽ 40 % and a follow-up measurement LVEF > 40 %); and (4) heart failure with reduced ejection fraction (HFrEF, the LVEF is ⩽40 %) [11]. Children whose HF may have sign and symptom include recurrent dyspnoea, fatigue, growth failure, and exercise intolerance [8,12]. The NYHA is a subjective HF classification by a clinician used to characterized symptoms of patients with symptomatic or asymptomatic HF (table 2) [8]. The NYHA HF classification isn't easily applicable to younger children. Meanwhile, the modified ross classification is used for HF in younger children (table 3) [8, 13, 14].

The diagnose of HF was made based on framingham diagnostic criteria for heart failure. It must presence of 2 major or 1 major and 2 minor criteria were required to make the diagnosis of HF [15]. The criteria of framingham diagnosis are as follow: (1) major criteria; and (2) minor criteria. Major criteria consist of: acute pulmonary oedema; radiographic cardiomegaly; paroxysmal nocturnal dyspnoea; pulmonary rales; neck vein distension; hepatojugular reflex; third heart sound (S3 Gallop). Minor criteria consist of; ankle oedema; dyspnoea on exertion; hepatomegaly; pleural effusion; nocturnal cough; tachycardia (>120 beats per minute) [15].

Table 1. **Classification of HF by LVEF [8]**

Type of HF According to LVEF	Criteria
HFrEF (HF with Reduced EF)	LVEF ⩽40 %
HFimpEF (HF with improved EF)	Previous LVEF ⩽40 % and a follow-up measurement of LVEF >40 %
HFmrEF (HF with mildly reduced EF)	LVEF 41–49 % Evidence of spontaneous of provokable increased LV filling pressures (eg, elevated natriuretic peptide, non-invasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF >50 %

Table 2. **Classification of HF by NYHA (13)**

	Class	Functional Capacity
NYHA Functional Classification System	I	Patients with heart disease but not causing physical activity restriction. Regular physical activity does not cause excessive fatigue, palpitation, dyspnea, or anginal pain.
	II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity result in fatigue, palpitation, dyspnoea, or anginal pain.
	III	Patients with heart disease who have limited physical activity. They feel comfortable at rest. Less activity than ordinary causes fatigue, palpitation, dyspnoea, or anginal pain.
	IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Even while at rest, HF or the anginal syndrome symptoms may be present. If any physical activity is undertaken, discomfort increases.

Table 3. **Classification of Modified Ross (14)**

Modified Ross Classification for Paediatric Heart Failure	
Class I	Asymptomatic
Class II	Mild tachypnoea or diaphoresis with feeding in infants
Class III	Marked tachypnoea or diaphoresis with feeding in infants. Prolonged feeding times with growth failure Marked dyspnoea on exertion in older children
Class IV	Symptoms such as tachypnoea, retractions, grunting, or diaphoresis at rest

Congenital heart disease (CHD) is one of predisposing factor that can be triggering HF on paediatrics [2, 3, 10, 16]. ASD is one of CHD that defined as a defect in the septum that divided atria of the heart, it was occurred at birth[16]. ASD cause left-to-right shunting that may result in right heart enlargement and right ventricle (RV) dysfunction. It will lead diastolic dysfunction [13]. The defect in cardiac septum

can also reduce stroke volume and would make inability to maintain cardiac output (CO). It will trigger sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) to be activated. The result of those are sodium and fluid retention occur in attempt to sustain preload and CO[17]. SNS, and RAAS were able to stimulate peripheral vascular vasoconstriction, so the blood pressure will increase to adequate organ perfusion. The effects of afterload changing and stress on blood vessels lead myocardial cell growth and adaptation. Those reaction will increase myocardial oxygen consumption, ventricular afterload which causes haemodynamic derangements such as abnormal pressure or volume loading, ventricular hypertrophy, myocardial ischemia, fibrosis interstitial, and decreases the density of cardiac capillaries. So that, it can cause cardiac toxicity and progression of HF [12]. HF in paediatrics can down-regulation both of β1 and β2-adrenergic receptors. In the Woulfe studied explained, that there was a difference occurrence of fibrosis and fibrotic gene expression in adult HF compared to paediatrics HF. Paediatrics HF showed less fibrosis and fibrotic gene expression than adult HF [18].

The clinical manifestation of HF in paediatrics whose CHD may vary significantly by their defect or age. Dyspnoea, fatigue, orthopnoea, fluid retention, falling asleep when feeding or becoming too tired to eat, malnutrition, failure to gain weight, and pulmonary & systemic congestion are clinical manifestations of HF in paediatrics, however each child may have experience symptoms differently [19]. Therefore, the application of general HF classifications in paediatrics such as the NYHA categories or the ross classification are important to provide a global assessment of HF severity in paediatrics [20].

The patient in this case presented with sudden onset of dyspnoea triggered by moderate exercise, which characterized him class II according to the NYHA, and Ross classification. Dyspnoea and fatigue can cause exercise intolerance among children with HF related to cardiac dysfunction. Exercise intolerance is a major cause of reduced quality of life in patients of HF. It could be happened because there was hypoperfusion of the lung, and skeletal muscular pathology significantly present in HF. Those mechanism leads to recurrent dyspnoea, as result of excessive activity more fully than before [20]. The patient has history of presence orthopnea, the presence of that has a positive predictive for HF. Orthopnea is the shortness of breath while supine brought on by an increase in the amount of blood flowing from the heart and pooling in the legs. While lying with prone position has an improve on orthopnea [21].

Making a diagnosis is a challenge when the clinical assessment does not correlate with clinical findings of investigation. Not only a comprehensive history, but also critical analysis of the symptom at the clinical findings are vital to make any diagnosis. The first step in diagnostic procedure in children of HF is based on non-invasive clinical investigations[13]. In this case, patient has a history of orthopnoea and radiographic cardiomegaly, so this patient have 2 major Framingham leading to HF. Further investigation is needed to determine the cause of HF. Echocardiography is the primary imaging modality in paediatric cardiology used for initial diagnosis especially in HF [12]. It provides an excellent image of cardiac structural and functional among children. In this case, the echocardiography showing the ostium secundum ASD (Figure 2). Patients with ostium secundum defect commonly asymptomatic during childhood. The diameter of defect smaller than 8 mm can be closed spontaneously, but the probability of spontaneous closure become poor if the diameter over than 10 mm. So that, it can cause a probability of HF, and the prevalence has been estimated around 10 %. In this case, the patient has diameter of defect 18.8 mm, it can increase the risk of HF occurrence.

The septum secundum is formed by the atrial roof to the right of the septum primum. As it is going to grow caudally and will cover the ostium secundum, the space between septum primum and septum secundum is known as the foramen ovale. The foramen ovale in the fetus allows blood that rich of oxygen pass the lung by flowing from right atrium to the left atrium. The Foramen is going to close spontaneously when the neonates was born and began to breathe. It caused by the change of pulmonary vascular resistance. So that, an ostium secundum ASD will cause left-to-right shunting that may result in chronic right ventricular volume overload, right heart enlargement and RV dysfunction. It will lead reverse-bernheim effect. This phenomenon was referred to characterized a syndrome of HF and usually present with cardiomegaly [3,22].

Cardiomegaly means enlargement of heart, it can happens due to ASD [23]. ASD has been found as-

sociated Gly247Asp ACTC1 mutation leading dilated hypertrophy, fibrosis, and contractile disfunction that cause dilatated cardiomyopathy (DCM) [24]. Chest X-ray (CXR) is one of basic investigation to detect cardiomegaly. Cardiomegaly in children suggested by the cardiothoracic ratio (CTR) > 55 %[25]. Therefore, the findings cardiomegaly in this case is associated with heart failure (Figure 1).

Medical therapy of HF in children focuses on 3 main goals: (1) reduce of pulmonary pressure; (2) increase of cardiac output & the improvement of organ perfusion; and (3) progression of HF is delayed [14]. The NYHA class of HF stage serves as the foundation for the management recommendations in the American College of Cardiology Foundation/American Heart Association guidelines [8]. Pharmaceutical treatments for HF patients with CHD aim to decrease pulmonary and systemic congestion by employing diuretics to increase contractility with inotropes and decrease afterload pressure. The other drug that routinely used in the pharmacological therapies of paediatric HF include angiotensin-converting enzyme inhibitors (ACEIs), spironolactone, and β-blockers [8,25].

Based on this case, patients used furosemide and spironolactone as his medical therapy. Furosemide is one of loop diuretics. The majority of HF patients should utilize diuretics instead. It will inhibit the reabsorption of sodium or chloride at the loop of henle, whereas spironolactone is one of aldosterone receptor antagonists (potassium sparing diuretics) act in the collecting duct [8,20]. The purpose of diuretic treatment is to reduce clinical manifestation of recurrent dyspnoea that caused by fluid retention using the lowest dose possible [8]. Tsujimoto studied showed spironolactone was an effective add-on therapy for patients with HF taking ACEIs, β-blockers, Calcium channel blockers, and diuretics. It blocks the RAAS pathway to prevent remodelling that will leading myocardial fibrosis [26].

Conclusions

This case described symptoms of HF due to CHD, particularly ASD. Currently, because of effective drug therapy, symptoms of HF due to ASD is able to reduce. However, it is still necessary to pay attention to the fact that heart failure in younger people can result from untreated CHD. In this case report, the patient had developed symptomatic HF with LVEF ⩾ 50 % also RA and RV dilatation. Most likely this patient developed HF due to the delayed diagnosis of ASD.

Conflicts of interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Main results of the European Society of Cardiology Congress 2023

From August 25 to 28, 2023, the regular Congress of the European Society of Cardiology was held in a hybrid format (onsite and online) in Amsterdam (the Netherlands). The event was attended by about 31,000 specialists from 150 countries.

Congress participants reviewed 5 new clinical guideline texts:

- on the treatment of endocarditis;
- on the treatment of cardiovascular diseases in diabetic patients;
- on the treatment of cardiomyopathies;
- on the treatment of acute coronary syndromes;
- the targeted update of the European Society of Cardiology 2021 guidelines on the diagnosis and treatment of acute and chronic heart failure.

The full texts of these documents are available at www.escardio.org/Clinical Practice Guidelines.

The most interesting events of the Congress are traditionally recognized as HOT LINE scientific sessions, where the results of the most important clinical trials are presented for the first time. This time the participants of the event had an opportunity to get acquainted with 29 specially selected randomized trials in 9 sessions during 4 days. Their most important results are summarized below.

STEP-HFpEF. In patients with heart failure with preserved ejection fraction and obesity, treatment with semaglutide at a dose of 2.4 mg subcutaneously once weekly for 52 weeks was associated with a significant improvement in quality of life (by 7.8 points on the Kansas City Cardiomyopathy Questionnaire), reduction in body weight (by 10.7%), increase in 6-minute walk distance (by 20.3 m), and reduction in C-reactive protein levels, compared with placebo.

NOAH-AFNET 6. Elderly patients with episodes (at least 6 minutes) of frequent (≥170 beats per minute) atrial pacing detected by implantable devices and at least one risk factor for stroke were assigned to standard treatment with edoxaban or placebo. The trial was stopped early due to safety concerns after a mean follow-up of 21 months. The incidence of stroke was approximately 1% per patient-year in both groups. There was no significant reduction in the incidence of cardiovascular death, stroke or systemic embolism with edoxaban compared to placebo, but a significant increase in the incidence of death from any cause or major bleeding (p=0.03).

COP-AF. Patients undergoing major non-cardiac thoracic surgery (lung lobe resection and others) received colchicine 0.5 mg or placebo 4 hours prior to surgery and twice daily for 10 days. Clinically significant perioperative atrial fibrillation was observed in 6.4% and 7.5% (p=0.22), and myocardial damage in 18.3% and 20.3% (p=0.16) of patients receiving colchicine and placebo, respectively. Sepsis or infection was reported in 6.4% of patients in the colchicine group and 5.2% in the placebo group. Colchicine administration was significantly more associated with the development of non-infectious diarrhea (8.3% of cases vs. 2.4% with placebo).

QUEST. The combination herbal medicine qiliqiangxin capsules or placebo were added to standard therapy for chronic heart failure with reduced left ventricular ejection fraction (≤40%). During a medi-

an follow-up of 18.3 months, the primary endpoint (rehospitalization for heart failure decompensation or cardiovascular death) was observed in 25.02% of patients in the qiliqiangxin group versus 30.03% in the placebo group (p<0.001). There were no significant differences between groups in all-cause mortality and adverse events, including gastrointestinal symptoms, worsening renal function, and elevated liver enzymes.

BUDAPEST-CRT Upgrade. The study included patients with an implantable cardioverter defibrillator and intermittent or continuous right ventricular pacing with a stimulated QRS complex duration of at least 150 m/s. The addition of a left ventricular stimulation lead implanted in the lateral branch of the coronary sinus resulted in a reduced risk of the primary endpoint of hospitalization for heart failure, all-cause death or no reverse myocardial remodeling (32.4% vs. 78.9%; p<0.001). The hospitalization rate for heart failure or all-cause mortality was 10.2% vs. 34.7% (p<0.001) compared to the control group during 12 months of follow-up.

HEART-FID. Intravenous iron carboxymaltose or placebo was added to the treatment regimen for chronic heart failure with reduced (≤40%) left ventricular ejection fraction in iron-deficient patients. At 12 months, there were no significant differences in the all-cause mortality(8.6% vs. 10.3% of cases) and hospitalization for heart failure (13.3% vs. 14.8%) in the iron carboxymaltose and placebo groups, respectively, although the 6-minute walk distance increased by 8 m in the carboxymaltose group and by 4 m in the placebo group at 6 months (p=0.02). The incidence of serious adverse events during treatment was not significantly different between groups.

FIRE. Patients aged ≥75 years with myocardial infarction and multivessel coronary stenoses underwent percutaneous coronary intervention (PCI) with stenting of all arteries with hemodynamically significant narrowing or only of the infarct-related artery. The combined primary endpoint of death, myocardial infarction, stroke, or any revascularization procedure at one year was less frequent in the complete revascularization group (15.7% vs. 21.0% in the culprit artery stenting group), and the safety of the procedure (composite of stroke, bleeding, or contrast-related acute kidney injury) was comparable (p=0.37).

ECLS-SHOCK. Patients with myocardial infarction complicated by cardiogenic shock who were scheduled for early revascularization were treated with venoarterial extracorporeal membrane oxygenation plus conventional medical therapy or conventional medical therapy alone (control group). The primary efficacy endpoint, death from any cause at 30 days, was observed in 47.8% versus 49.0% of patients in the full extracorporeal support and control groups, respectively (p=0.81). In the first group, moderate or major bleeding was 2.44 times more frequent and peripheral vascular complications requiring intervention were 2.86 times more frequent.

STOPDAPT-3. Patients with acute coronary syndromes and a high risk of bleeding after PCI were randomized to antiplatelet monotherapy with prasugrel or a combination of aspirin (for 1 month) with prasugrel. The 30-day cumulative incidence of cardiovascular death, myocardial infarction, definite stent thrombosis, or ischemic stroke (4.12% vs. 3.6–9%) and the risk of Academic Research Consortium type 3 or 5 bleeding (4.71% vs. 4.47%) were not significantly different between the monotherapy and dual therapy groups. Antiplatelet monotherapy increased the risk of subacute definite or probable stent thrombosis by 3.4-fold and the risk of unplanned coronary revascularization by 83%.

ILUMIEN IV. Percutaneous coronary intervention in patients with complex coronary artery lesions was performed under control of optical coherence tomography or conventional angiography. There was a significant difference in the minimum stent area (5.72±2.04 mm^2 vs. 5.36±1.87 mm^2; p<0.001) with a similar cumulative incidence of adverse outcomes — death from cardiac causes, myocardial infarction or revascularization due to ischemia in the target artery area at 2 years (7.4% and 8.2% of cases; p=0.45) in the optical coherence tomography and angiography groups, respectively. The stent thrombosis at 2 years occurred in 0.5% vs. 1.4% of cases (p=0.02).

OCTOBER. Patients with clinical indications for percutaneous coronary intervention and complex bifurcation lesions underwent revascularization with optical coherence tomography or conventional angiography. At a mean follow-up of 2 years, the composite of the primary endpoint — cardiac death, myocardial infarction, or target artery revascularization for ischemia — occurred in 10.1% of patients in the optical coherence tomography group and 14.1% in the angiography group (p=0.035). Procedural complications were similar in both groups.

OCTIVUS. Patients with significant coronary artery lesions underwent percutaneous coronary intervention under optical coherence tomography or intravascular ultrasound guidance. After one year of follow-up, the event rate of the primary endpoint, death from cardiac causes, myocardial infarction or revascularization due to ischemia in the target artery area, was 2.5% in the optical coherence tomography group and 3.1% in the intravascular ultrasound group (p<0.001 for no less efficacy). The risk of contrast-induced nephropathy was similar in the two groups (p=0.85).

ATTRibute-CM. Elderly patients with transthyretin amyloid cardiomyopathy were prescribed akoramidis 800 mg twice daily or placebo twice daily for 30 months, with open-label tafamidis allowed after 12 months at the discretion of the physician. The akoramidis group demonstrated a statistically significant superiority in the risk of the primary combined endpoint.with a hazard ratio of 1.772 (p<0.0001). Hierarchical analysis prioritized the endpoints in the following order: all-cause mortality, the incidence of cardiovascular-related hospitalizations, the change from baseline in the N-terminal precursor of brain natriuretic peptide, the change from baseline in 6-minute walk distance. In addition, acoramidis was associated with a 50% reduction in the relative risk of cardiovascular hospitalization (p<0.0001).

ARREST. Patients with spontaneous circulatory recovery after out-of-hospital cardiac arrest without ST-segment elevation were transported by London ambulance services to one of 7 cardiac arrest centers or to the geographically closest emergency department. The primary endpoint, 30-day all-cause mortality, was 63% in the cardiac arrest center group and 63% in the standard of care group (unadjusted hazard ratio 1.00; p=0.96).

ADVENT. Patients with paroxysmal atrial fibrillation refractory to antiarrhythmic drugs underwent pulsed field catheter ablation or conventional radiofrequency or cryoballoon (thermal) catheter ablation to isolate the pulmonary vein orifices. At 1 year of follow-up, the primary efficacy endpoint of freedom from primary procedure failure, documented atrial tachyarrhythmia after a 3-month blinded period, antiarrhythmic drug use, cardioversion, or repeat ablation was reported in 73.3% versus 71.3% of cases in the pulsed field and thermal ablation groups, respectively. The incidence of serious adverse events was similar in both groups.

MULTISTARS AMI. Hemodynamically stable patients with ST-segment elevation myocardial infarction and multivessel coronary heart disease underwent either immediate multivessel PCI (emergency group) or first intervention on the "culprit" artery followed by staged multivessel intervention on the "non-culprit" arteries within 19–45 days after the index procedure (staged group). During one year of follow-up, the composite of primary endpoint events — all-cause mortality, non-fatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure — was 8.5% in the immediate treatment group versus 16.3% in the staged treatment group (p<0.001 for no less effective and p<0.001 for superior).

CASTLE HTx. Patients with symptomatic atrial fibrillation and end-stage heart failure (ejection fraction ⩽35%) received catheter ablation to restore sinus rhythm and drug therapy or drug therapy alone. At a median follow-up of 18 months, the primary endpoint of death from any cause, left ventricular assist device implantation or urgent heart transplantation was observed in 8% of the ablation group and 30% of the drug therapy alone group (p<0.001).

FRAIL-AF. Patients with non-valvular atrial fibrillation and frailty aged ⩾75 years with a glomerular filtration rate ⩾30 ml/min/1.73m^2 were switched to direct oral anticoagulants or continued on vitamin K antagonists. After 12 months of follow-up, major and clinically significant bleeding (primary endpoint) occurred in 15.3% vs. 9.4% of cases (p=0.00112), and the incidence of thromboembolic complications was 2.4% vs. 2.0% in the direct oral anticoagulant and vitamin K antagonist groups, respectively.

OPT-BIRISK. Patients undergoing PCI for acute coronary syndromes at high bleeding risk and high ischemic risk received dual antiplatelet therapy (clopidogrel plus aspirin) for 9–12 months, then 9 months of clopidogrel plus aspirin or clopidogrel plus placebo, followed by 3 months of aspirin alone. The risk of type 2, 3, or 5 bleeding according to the Bleeding Academic Research Consortium classification was lower in the group without aspirin (2.5% vs. 3.3%; p=0.03) after 9 months of the different therapies. The cumulative risk of all-cause death, myocardial infarction, stroke or clinically driven revascularization was also lower in the aspirin-free group (2.6% vs. 3.5%; p=0.02).

ARAMIS. The subcutaneous administration of the interleukin-1 receptor antagonist anakinra 100 mg

once daily was compared with placebo in hospitalized patients with symptomatic acute myocarditis and elevated cardiac troponin levels receiving standard therapy. The primary efficacy endpoint, the number of days free of myocarditis complications after hospital discharge, averaged 30 days in the anakinra group and 31 days in the placebo group. The safety endpoint, the number of serious adverse events within 28 days of discharge, was observed in 12.1% of patients receiving anakinra and 10.2% of patients receiving placebo, with no significant differences between groups.

DANPACE II. Patients with sick sinus syndrome were initially implanted with pacemakers programmed to a baseline rate of 60 beats per minute with rate-adaptive pacing (DDDR-60) or a baseline rate of 40 beats per minute without rate-adaptive pacing (DDD-40). After 2 years of remote monitoring, there were no differences between the groups in the number of atrial fibrillation episodes lasting longer than 6 minutes (46% of cases each), longer than 6 hours or longer than 24 hours. There were no significant differences in frequency of progression to persistent or permanent atrial fibrillation, cardioversion for atrial fibrillation, and all-cause mortality. In addition, quality of life and 6-minute walk test results at 12 months were similar in both groups.

RED–CVD. Patients with chronic obstructive pulmonary disease and/or diabetes mellitus in primary care were compared in a diagnostic intervention consisting of three steps:

- assessment of symptoms using a questionnaire;
- physical examination, determination of N-terminal brain natriuretic peptide precursor levels, as well as an electrocardiogram recording;
- at the discretion of the primary care physician, referral to a cardiologist if abnormalities were detected, as well as usual care.

Patients progressed to the next stage if they scored above a certain threshold. At one year, new diagnoses of cardiovascular disease (8.0% vs. 3.0%), heart failure (4.5% vs. 1.5%), atrial fibrillation (2.1% vs. 0.8%), and coronary heart disease (2.6% vs. 1.4%) were higher in the intervention group than in the usual care group.

NITRATE-CIN. In patients with acute coronary syndrome without ST-segment elevation referred for invasive coronary angiography and at risk for contrast-induced nephropathy, the efficacy of once-daily potassium nitrate (12 mmol) was compared with placebo (potassium chloride) in a capsule form for 5 days. There was a significant reduction in the risk of contrast-induced nephropathy (elevation of creatinine levels ≥26.5 μmol/L within 48 hours or ≥1.5 times within a week) of 9.1% vs. 30.5%, (p<0.0001), procedural myocardial infarction (2.7% vs. 12.5%; p=0.003) and major cardiovascular complications within one year (9.1% vs. 18.1% of cases; p=0.001) in the inorganic nitrate group, compared with placebo.

DICTATE-AHF. Patients with type 2 diabetes mellitus and a calculated glomerular filtration rate of at least 25 ml/min/1.73 m^2 hospitalized for acute decompensated heart failure with hypervolemia and receiving intravenous loop diuretics were randomized to receive dapagliflozin 10 mg/day or standard therapy for the first 24 hours. After 5 days or up to the day of discharge, there was no advantage of dapagliflozin in affecting the ratio of weight change in kg/dose of loop diuretic in mg. However, dapagliflozin significantly increased 24-hour natriuresis (p=0.025) and 24-hour diuresis (p=0.005), and shortened the time to completion of intravenous diuretic therapy (p=0.006) and time to hospital discharge (p=0.007).

PUSH-AHF. Treatment of acute heart failure with natriuresis testing at 2, 6, 12, 18, 24 and 36 hours after initiation of intravenous loop diuretics with possible dose adjustment was compared with standard therapy. During the first 24 hours, natriuresis was significantly higher in the natriuresis control group (p=0.0061), but the risk of all-cause mortality or hospitalization for heart failure at 180 days was the same as in the conventional treatment group (31% in both groups; p=0.70).

RIGHT. Patients undergoing primary PCI with bivalirudin for ST-segment elevation myocardial infarction received anticoagulant therapy within 4 hours of the procedure:

1) unfractionated heparin at 10 units/kg/hour intravenously with dose adjustment to maintain an activated clotting time of 150–220 s enoxaparin at a dose of 40 mg once daily subcutaneously OR

3) bivalirudin 0.2 mg/kg/hour intravenously or placebo (ie, no anticoagulant therapy) for ≥48 hours.

At 30 days, there was no difference in the cumulative incidence of the primary efficacy endpoint (all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, definite stent thrombosis, or urgent revascularization of any vessel at 30 days) between the anticoagulation and placebo groups (p=0.988).

However, there was a significant relationship between the primary efficacy endpoint and the type of anticoagulant used. Enoxaparin reduced the risk of adverse outcomes by 54 % compared to placebo, while unfractionated heparin increased the risk by 3.71-fold and bivalirudin by 1.24-fold. The incidence of the primary safety endpoint (major bleeding) was not different between the two groups (p=0.511) and there was no significant interaction between the three anticoagulants (p for interaction=0.679).

ONCO DVT. Cancer patients with isolated distal deep vein thrombosis were treated with edoxaban for 12 or 3 months. At one year, the primary endpoint of symptomatic recurrent venous thromboembolism or VTE-related death was reported in 1.0 % vs. 7.2 % of cases (p<0.001) and major bleeding according to International Society on Thrombosis and Hemostasis criteria was in 9.5 % vs. 7.2 % of cases in the 12-month and 3-month therapy groups, respectively.

A meta-analysis of the **DARE-19**, **RECOVERY** and **ACTIV-4A** studies. Participants in the three trials who were hospitalized for COVID-19 received either sodium-glucose cotransporter type 2 inhibitors (n=3025) or conventional treatment/placebo alone (n=3071) after randomization. The primary endpoint of all-cause mortality within 28 days occurred in 11.7 % and 12.4 % of patients in the sodium-glucose cotransporter type 2 inhibitor and conventional treatment/placebo groups, respectively. There were also no significant differences in the risk of progression to acute kidney injury, need for dialysis, conversion to invasive mechanical ventilation, or extracorporeal membrane oxygenation within 28 days. These results do not support the use of type 2 sodium-glucose cotransporter inhibitors as standard therapy in this clinical setting, but routine withdrawal of these drugs prescribed for other indications (heart failure, chronic kidney disease or type 2 diabetes mellitus) during COVID-19 does not seem justified.

The next Congress of the European Society of Cardiology is planned to be held in the United Kingdom (onsite and online) in London from August 30 to September 2, 2024.

The material was prepared by Professor Kanorsky S.G. and reviewed by Professor Mamedov M.N.

Author Guidelines

Manuscript publication rules
in the International heart and vascular disease journal

Edit from December, 2021

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Book:

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

Chapter:

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

Russian chapter:

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

Webpage:

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

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

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XIII. Journal subscription

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XIV. Journal subscription

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

Official sites where information about the journal is placed:

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

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

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