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ИНФЕКЦИОННЫЙ ЭНДОКАРДИТ У ПАЦИЕНТОВ С ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИЕЙ

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Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy

Резюме

Представлен обзор литературы, отражающий частоту возникновения, особенности этиологии, гемодинамики, локализации, клинических проявлений, исходов и лечения инфекционного эндокардита (ИЭ) у пациентов с гипертрофической кардиомиопатией (ГКМП). Несмотря на относительную редкость возникновения ИЭ у больных ГКМП, сочетание этих патологий характеризуется взаимным отягощением и неблагоприятным прогнозом. У больных с обструктивными формами ГКМП присоединение ИЭ усугубляет расстройства кровообращения и повышает вероятность неконтролируемого сепсиса и эмболий, увеличивая тем самым риск летального исхода. Консервативное лечение ИЭ у больных с ГКМП не отличается от такового без ГКМП. Необходимо междисциплинарное взаимодействие при ведении пациентов с ИЭ на фоне ГКМП в определении показаний к кардиохирургическому лечению и выборе оптимального метода. Антибактериальная профилактика ИЭ перед инвазивными медицинскими манипуляциями у пациентов с ГКМП не рекомендуется действующими согласительными документами, однако решение для каждого больного должно приниматься индивидуально с обязательной оценкой риска возникновения ИЭ, тяжести гемодинамических нарушений и прогноза.

Ключевые слова: *инфекционный эндокардит, гипертрофическая кардиомиопатия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

A literature review is presented, reflecting the incidence, etiology, hemodynamics, localization, clinical manifestations, outcomes and treatment of infective endocarditis (IE) in patients with hypertrophic cardiomyopathy (HCM). Despite the relative rarity of IE in patients with HCM, the

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combination of these pathologies is characterized by mutual aggravation and poor prognosis. The addition of IE increases the risk of death in patients with obstructive HCM, deteriorating circulatory disorders, increasing the likelihood of uncontrolled sepsis and embolism. Conservative treatment of IE in patients with HCM does not differ from that without HCM. Interdisciplinary interaction is needed in the management of patients with IE against the background of HCM in determining the indications for cardiac surgery and choosing the optimal method. Antibacterial prophylaxis of IE before invasive medical manipulations in patients with HCM is not recommended by the current consensus documents, however, the decision for each patient should be made individually, with a mandatory assessment of the risk of IE, the severity of hemodynamic disorders and prognosis.

Key words: *infective endocarditis, hypertrophic cardiomyopathy*

Conflict of interests

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AH — arterial hypertension, AV — aortic valve, SCD — sudden cardiac death, AF — atrial fibrillation, CI — confidence interval, CT — computed tomography, HCM — hypertrophic cardiomyopathy, HF — heart failure, IE — infectious endocarditis, IVS — interventricular septum, LA — left atrium, LV — left ventricle, LVOT — left ventricular outflow tract, MRI — magnetic resonance imaging, MV — mitral valve, OR — odds ratio, TTE — transthoracic echocardiography

Introduction

Despite significant progress in diagnosis and management, infective endocarditis (IE) has shown no decrease in morbidity for at least 30 years [1, 2] and is characterized by a serious prognosis and high mortality [1, 3]. The diagnosis of IE is often established late [4]. This is largely due to a significant variety of the onset and course of the disease, leading to diagnostic errors [1, 5]. Specific features of the IE course can be due to the etiological factor, conditions of development, previous heart damage, as well as extracardiac manifestations [3, 6]. Initial cardiac damage that results in IE is often caused by congenital or acquired valvular defects [6]. Much less often, such an unfavorable intracardiac background for IE is hypertrophic cardiomyopathy (HCM), which is also a pressing challenge facing cardiology today [7, 8]. Despite the relative rarity of IE in patients with HCM [7, 9], the combination of these pathologies is characterized by mutual complication and poor prognosis [9].

The rare development of IE in patients with HCM is why the combination of these diseases is presented primarily as a description of individual cases [10–13] and small serial observations in the literature [14]. There are not enough extensive retrospective and prospective studies on this issue [9, 15]. An analysis of literature data on this problem was published by one of the co-authors of this paper in 2013 [16]. During this time, new versions of consensus papers were published and implemented both for IE [1, 17, 18] and HCMP [7, 19, 20]. Changes in the study of the combination of these pathologies over the past decade are of interest, particularly treatment approaches, including cardiac surgery and the prevention of IE in patients with HCM.

When preparing this review, literature sources on Pubmed, MEDLINE, Embase, Cochrane, Scopus, Web of Science databases were analyzed. They include consensus papers, case series descriptions and individual observations, guidelines and monographs published over the past ten years. Several fundamental sources on this issue that were written earlier were also included. The search keywords were “infective endocarditis” and “hypertrophic cardiomyopathy” in the title or abstract.

Brief Description of Hypertrophic Cardiomyopathy: Definition, Clinical Picture, Diagnostic Methods, Complications, Treatment

HCM is a genetic disease (usually autosomal dominant, less often due to mutations *de novo*, and in some cases, an autosomal recessive disease). It is characterized by massive (> 15 mm) myocardial hypertrophy, predominantly of the left ventricle (LV), more often of an asymmetric nature due to the thickening of the interventricular septum (IVS), sometimes with the development of obstruction (systolic pressure gradient) of LV outflow tract (LVOT), in the absence of reasons that can cause such severe hypertrophy [7, 19–22].

Causes of HCM include mutations in genes that encode regulatory, contractile and structural proteins of cardiac sarcomeres [19, 23]. Today, HCM is found in about one out of 200–500 people [24]. The disease is characterized by severe hypertrophy of various parts of the LV, most often IVS, which creates an obstacle to blood ejection from LV (obstructive form of HCM) along with

the systolic displacement of the anterior mitral valve (MV) [7, 19].

Clinical manifestations of HCM primarily accompany obstructive forms of the disease [19, 25]. In patients with HCM, chest pains of ischemic origin occur due to a decrease in coronary blood flow (hemodynamic angina) [7, 19]. LVOT obstruction may cause fainting, especially after exercise. Pre- and syncope conditions develop as a result of LVOT obstruction, disturbances in the mechanisms of vascular regulation that lead to episodes of arterial hypotension due to inadequate vasodilation or diastolic dysfunction, as well as various disturbances in rhythm and conduction [19, 24–26]. Heart failure (HF) (dyspnea, cardiac asthma, orthopnea) gradually occurs and progresses due to progressive diastolic dysfunction with preserved or increased ejection fraction [25]; systolic dysfunction develops only in the later stages of this disease [7, 19].

HCM is diagnosed using imaging techniques (echocardiography, magnetic resonance imaging (MRI) of the heart) that reveal maximum end-diastolic wall thickness of ≥ 15 mm anywhere in the LV in the absence of another cause of hypertrophy of this degree [20]. Although HCM in most patients can be associated with a normal life expectancy without limiting its quality and/or the need for cardiac surgery, 30–40% of patients may experience serious consequences associated with the disease [7, 20]. The causes of death in HCM cases are: progressive circulatory failure, life-threatening tachyarrhythmias, including ventricular fibrillation, sudden cardiac death (SCD), embolism of systemic circulation, mainly cerebral vessels [27]. Atrial fibrillation (AF) with HCM occurs in 14–28% of patients. It is poorly tolerated, difficult to treat [28], and is associated with an increased risk of thromboembolic complications (AF increases the risk of ischemic stroke eightfold (!)), HF, SCD and death from all causes [29, 30]. HCM can be combined with another cardiovascular pathology (coronary heart disease, AH, diabetes mellitus) [31], especially with the increasing age of patients [32].

The treatment of HCM patients consists in using drugs with a negative inotropic effect (β-blockers and calcium channel blockers), correction of rhythm disorders (disopyramide, amiodarone) and HF [7, 19, 25, 28]. Treatment with nitrates, diuretics and angiotensin-converting enzyme inhibitors should be avoided since vasodilation mediated by these drugs or the decreased volume of circulating blood leads to increased obstruction in LVOT [19, 24, 25]. A cardioverter-defibrillator is implanted in case of syncope, sudden cardiac arrest, confirmed life-threatening arrhythmias [19, 28, 33]. The possibility of implanting cardioverter-defibrillators for the primary prevention of SCD (based on effective risk stratification) reduces mortality in patients with HCM to 0.5% per year [27]. Based on the corresponding indications (symptoms of LVOT obstruction with pressure gradient of ≥ 50 mm Hg, ineffectiveness of drug therapy), cardiac surgery is used: mainly septal myectomy and percutaneous catheter alcohol septal ablation [7, 24, 34].

Incidence, Hemodynamic Conditions and Localization of Valvular Lesions in Infective Endocarditis with Underlying Hypertrophic Cardiomyopathy

According to the most complete, albeit relatively old study (1999) that included 810 patients with HCM, including 681 patients with long-term (over 55 months) follow-up, the incidence of IE was 1.4 per 1,000 person-years [35]. In individuals with LVOT obstruction, the incidence of IE increased to 3.8 per 1,000 person-years, and with dilatation of the left atrium (LA) over 50 mm, the incidence of IE reached 9.2 per 1,000 person-years [35]. In a recently published large single-center study with extensive patient coverage over 12 years of follow-up, the percentage of patients with HCM with IE was 0.19%, with an estimated frequency of 0.15/1,000 person-years among patients with HCM [36]. In another study with 640 patients with HCM who were followed up over a ten-year period, only three patients had IE (IE incidence of 0.5%) [9]. Therefore, IE is a relatively rare disease in patients with HCM, even in the presence of LVOT obstruction [35, 36]. Most researchers cite IE mostly in patients with obstructive HCM [10, 11, 35, 36]; some sources indicate a similar incidence of IE in both obstructive and non-obstructive forms of the disease [15, 37]. The development of left-sided IE in HCM, especially in its obstructive form, is facilitated by hemodynamic disorders typical for this pathology. Hypertrophied IVS with repeated abnormal systolic movement of the anterior cusp of the mitral valve (MV) [7, 19], aortic regurgitation in some patients, and the centrifugal effect of turbulent blood flow in LVOT cause permanent microtraumatization (erosion) of the endocardium [12, 35, 38], which, under conditions of bacteremia, facilitates the fixation of microorganisms and the formation of microbial vegetations — an indispensable morphological attribute of IE and its "major" diagnostic criterion [1, 3, 4, 6]. As a result, in cases of HCM, IE is predominantly of mitral localization and parietal endocardium of IVS [11, 16, 39]. Other hemodynamic prerequisites for IE in obstructive HCM are elevated intracardiac pressure, lengthening of MV cusps [15], abnormal attachment of papillary muscles, as well as thinning of the myocardium, dilatation of LA and LV (sometimes with aneurysmal dilation of the heart apex), which is observed at the late stage of HCM [35]. All

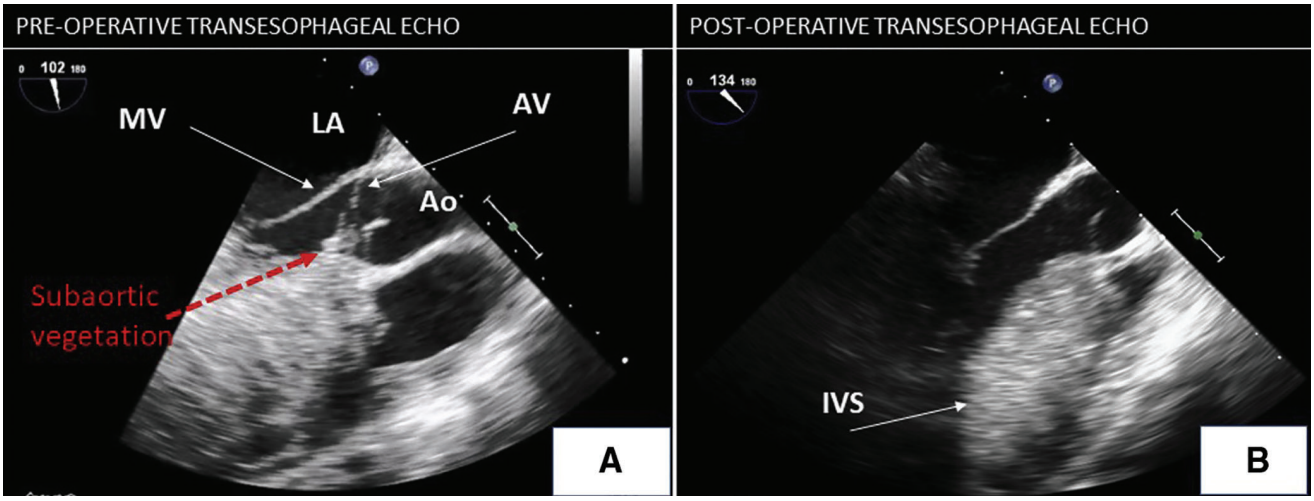

Figure. *Image of a vegetation in infective endocarditis in a patient with hypertrophic cardiomyopathy during transesophageal echocardiography*

Description: A. Preoperative echocardiography shows a subaortic vegetation (indicated by the dashed red line) and marked septal (IVS) hypertrophy. B. On the postoperative image, the vegetation was removed, the patency of the left ventricle outflow tract was improved, severity of IVS hypertrophy after septal myectomy became less significant. MV — mitral valve; LA — left atrium; AV — aortic valve; Ao — aorta. The picture was kindly provided by Madonna Lee (Congenital Cardiac Surgery Department, Seattle Children's Hospital, WA, USA) [13] and permitted for reproduction on conditions of the licence Creative Commons CC-BY-NC-ND

these conditions contribute to permanent hemodynamic damage to the MV valve, the formation of loose and fragile vegetations, and, consequently, embolism and HF progression [11, 16, 35, 39]. Predominant localization of microbial vegetations in patients with HCM is observed on the ventricular side of the anterior MV cusp [35] and on the parietal endocardium of IVS, mainly in its upper third (Fig.) [13]. According to the study by F. Dominguez et al. [15] that included 34 patients with HCM complicated by IE, the incidence of aortic and MV lesions was 71% and 35%, respectively, while in two cases, there was combined damage of two valves. J. R. Sims et al. [37] found a comparable incidence of aortic and MV damage among 30 examined patients with HCM: 47% and 53%, respectively, while there was no effect of LVOT obstruction on the localization of endocarditis. Combined lesions of ≥ 2 valves in IE are not uncommon [15, 37]. There is a report [40] about a severe course of IE with damage to all four valves in a patient with HCM. It should be noted that when performing transthoracic echocardiography (TTE), new valve regurgitation or vegetation on any of the valves could not be detected. Transesophageal echocardiography demonstrated vegetations on four valves and atrial septal defect.

Etiology, Clinical Picture, Diagnosis of Infective Endocarditis in Hypertrophic Cardiomyopathy

Analysis of literature data does not allow to identify significant features that distinguish IE in HCM from other types of this disease in the etiological aspect. Therefore, the most common causative agents of IE in patients with HCM are gram-positive cocci: staphylococci, streptococci and enterococci are etiological agents typical for IE in general [1, 41], much less often — other types of microorganisms [16, 37]. The etiological role of Staphylococcus aureus in IE is associated with a poor prognosis [3].

Analysis of papers published in the late 20th century suggested IE with underlying HCM as a disease of primarily young people. The average age of patients with IE with this pathology in the previously mentioned multicenter study by P. Spirito et al. was 39 years old [35]. However, the average age of patients with IE tends to increase in almost all categories of patients with this disease [1, 3, 4]. This is also true for patients with IE with underlying HCM because the life expectancy of persons with HCM also gradually increases [7, 32]. The combination of HCM and IE in young and middle-aged patients is more common in men [12, 15, 35, 37].

IE with underlying HCM demonstrates all the clinical features inherent in IE of native valves of left-sided localization [10–12, 25, 35]. Besides febrile wave-like or persistent fever with chills, intoxication and blood systemic inflammatory reaction syndrome, patients experience a rapid formation of a defect of insufficiency type (mitral or aortic), left ventricular circulatory failure, systemic embolism, and with a longer course of IE — visceral lesions of immunocomplex origin [1, 3–5]. In the above descriptions of IE cases in patients with HCM, cardioembolic strokes are often cited, which is associated with an unfavorable outcome [11, 12, 25]. Mutual aggravation of these diseases is manifested by the rapid development and progression of HF, and

arrhythmias [15, 16, 39]. Also, among the consequences of IE in patients with HCM, uncontrolled sepsis is more often observed [15], which is associated with persistent hemodynamic damage to MV cusps and resistance to antibiotic therapy.

TTE remains the basic method for diagnosing IE with underlying HCM. It allows detecting vegetations on valve structures and parietal endocardium, destruction of valves, perivalvular changes, and the formation of regurgitation [1, 4, 6]. Using TTE, structural and hemodynamic features caused by HCM are also revealed: wall thickness of the right and left ventricle (including IVS), MV features, pressure gradient in the middle and LVOT, diastolic dysfunction, LA size [7, 19] are signs that have prognostic value in both diseases in the case of IE with underlying HCM [35, 37]. Since its introduction into clinical practice, high diagnostic capabilities of transesophageal echocardiography were identified due to the proximity of the ultrasound sensor to the heart and the ability to obtain high-quality images due to the use of high-frequency sensors. Other modern methods of cardiac imaging in IE (single-photon emission and positron-emission computed tomography (CT), cardiac MRI, etc.) used in the diagnostic process have not been sufficiently studied in IE with underlying HCM, although, undoubtedly, they should be applied where possible and for corresponding indications.

Another "major" diagnostic criterion for IE that is critical for the choice of antibiotic therapy is the isolation of the pathogen from blood [1, 3, 41]. Results of routine laboratory and instrumental studies usually indicate a systemic inflammatory reaction (leukocytosis with a neutrophilic shift, increased level of C-reactive protein, procalcitonin and other markers of inflammation), immune shifts (rheumatoid factor, circulating immune complexes), as well as the presence of visceral lesions that are typical for IE (nephropathy, splenomegaly, etc.) [1, 4, 5]. To detect embolic events, primarily of cerebral vessels, including asymptomatic ones, brain MRI or CT is indicated. Thromboembolism develops in 2–9% of patients with HCM in the absence of IE [7], accounting for 2–11% of death causes for patients with HCM [27]. AF in patients with HCM is associated with a significant risk of cardioembolic stroke [20, 28–31]. With IE with underlying HCM, such a complication can develop along with sinus rhythm [11]. Thromboembolism in HCM can be caused by intracardiac thrombi localized on the thickened endocardium of IVS at the point of contact with the anterior cusp of MV, in the dilated LA [7, 27], and in cases of IE — fragments of microbial vegetations of the valves of the left heart [1, 12, 25, 35]. When describing cases of IE with underlying HCM, clinical signs of circulatory failure are often reported [12, 15, 35]. The addition of left-sided IE to HCM either causes valvular regurgitation or makes the existing one worse [16], leading to the development of HF in patients with previously asymptomatic forms of the disease [42].

Management of infective endocarditis in the presence of hypertrophic cardiomyopathy

is carried out in accordance with the general principles articulated in modern consensus recommendations on IE [1, 43]. Antibiotic therapy is carried out depending on the established or suspected pathogen [1, 3, 41]. Cardiac surgery for IE is used in the presence of conventional indications: progressive HF, uncontrolled infection (including intracardiac abscesses) and for the prevention of embolism [1, 3, 6]. A specific feature of cardiac surgical tactics in IE with underlying HCM is, besides the prosthetics of MV or AV, the possibility of simultaneous Morrow myectomy [9, 10, 15, 37, 44]. Successful transcatheter aspiration of a septic embolus of a coronary artery with subsequent surgical replacement of MV and septal myectomy was described [45]. Such interventions require certain experience and conditions; otherwise, the procedure is associated with a high risk of death [37]. There are isolated cases of IE after alcoholic septal ablation — one of the methods of surgical treatment of HCM today [46]. After successful cardiac surgery, not only foci of valvular infection are eliminated but also LVOT obstruction, which is manifested by an improvement in well-being and hemodynamic parameters (disappearance of fainting, dyspnea, etc.) [9, 15, 36]. Therefore, some researchers prefer cardiac surgical treatment of IE in patients with HCM [9, 10, 36, 47]. The advantages of using cardiac surgery are the possibility of simultaneous sanitation of valve infection and the correction of hemodynamic defect, a decrease in the incidence of thromboembolism, HF, sepsis, and decreased mortality. Interdisciplinary interaction between professionals is crucial when selecting the optimal treatment strategy for patients with IE and HCM, especially in the presence of indications for cardiac surgery [1].

Implantation of intracardiac devices (cardioverter-defibrillators) for the management of rhythm disturbances in patients with HCM is an additional factor that increases the risk of IE associated with intracardiac devices [47]. In terms of incidence, this type of IE is only slightly inferior to the left-sided IE of native valves in patients with HCM. It occurs in cases of the obstructive form, and management strategy requires the mandatory removal of the implanted intracardiac device [47] in accordance with consensus papers [1]. A major British study [48] that assessed the risk of IE in persons with

predisposing cardiac factors showed a significant risk of IE in patients with HCM. Among 4,418 patients with HCM, there were 37 hospitalizations due to IE; odds ratio (OR) 32.8, 95% confidence interval (CI) 23.3–44.6, $p < 0.0001$. The risk of an unfavorable outcome (mortality) was low: among 37 cases of IE in patients with HCM, one death was reported (OR 4.0, 95% CI 0.2–17.5, $p = 0.17$). The presence of implanted cardioverter pacemakers in HCM patients was associated with both a significant risk of IE (OR 9.7, 95% CI 9.0–10.6, $p < 0.0001$), and death associated with IE (OR 10.1, 95% CI 8.6–11.7, $p < 0.001$) [48].

Antibacterial Prophylaxis of Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy

When it comes to the preventive prescription of antibiotics before invasive procedures to prevent IE, there is some contradiction between consensus papers approved at different times. When assessing the need for antibacterial prophylaxis of this disease, previous recommendations on IE assign patients with HCM to the group of intermediate or moderate risk of developing IE. However, the revision of some provisions on the antibacterial prophylaxis of IE in the latest editions by experts at the European Heart Society [1] and the American College of Cardiology/American Heart Association [18], suggests the use of antibacterial prophylaxis only in patients with a very high cardiogenic risk of developing IE; HCM does not apply here. According to researchers who have been studying the problem for many years, the "softening" of the stance on preventive antibacterial prophylaxis of IE and its optionality before invasive procedures in patients outside the high-risk group of IE should not apply to patients with HCM [9, 35, 49]. Undoubtedly, good oral hygiene and regular dental check-ups, as well as avoidance of intravenous drug use, piercings, tattoos, etc., play a critical role in the prevention of episodes of bacteremia and reducing the likelihood of IE in patients with cardiogenic risk factors [1, 48], including patients with HCM. However, in some clinical situations (severe obstruction of LVOT, symptoms of circulatory failure), when IE, in addition to obstructive HCM, can seriously worsen the patient's prognosis, patients with HCM should still be assigned to a high-risk group [25]. Therefore, for such patients, antibacterial prophylaxis of IE is required, and its potential benefit (prevention of IE) exceeds the risk of developing adverse events (anaphylactic shock, resistance to antibiotic therapy, etc.) [49, 50]. IE is a life-threatening condition [1, 4, 6], and its prevention is preferable to its subsequent management.

Outcomes and Prognosis of Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy

According to studies dating back to the 1980s, IE was the cause of death in about 5–7% of patients with HCM [37, 51]. With the improvement of the quality of diagnosis and treatment of such patients, mortality from IE with underlying HCM has decreased, which is confirmed by studies today [37]. IE is inferior in the incidence of such causes of death in patients with HCM as SCD and embolism. However, the comorbidity of IE is certainly a factor that worsens the condition and prognosis of patients with HCM [15].

Our Data on the Incidence of Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy

When analyzing the observations of 340 patients with IE admitted to the Saratov Regional Clinical Hospital from 2006 to 2019, we recorded three cases of IE in patients with obstructive HCM (incidence of IE with underlying HCM among all patients with IE was 0.8%). During this period, we observed 136 patients with HCM, 61 of them with an obstructive form of the disease; therefore, according to our observations, the incidence of IE among patients with HCM was 2.2%. Two observations were described earlier [12]. In one case of IE with underlying HCM, the course of this disease was complicated by cerebral embolism with the development of stroke. HCM was diagnosed for the first time during hospitalization of the patient, simultaneously with IE. As a result of antibiotic therapy in the hospital, body temperature returned to normal, HF manifestations decreased, and neurological functions were partially restored. Second observation: IE of mitral and aortic valves in a 33-year-old patient with obstructive HCM was diagnosed five years earlier, with underlying intravenous drug addiction and HIV infection, stage IVB (AIDS) with a fatal outcome. The third patient, male, 57, with mitral IE and obstructive HCM, successfully received surgical treatment (septal myectomy and MV prosthetics), but there was no further information on him after changing his place of residence.

Among 278 patients with HCM admitted to the cardiology departments of Donetsk Clinical Territorial Medical Association, Central Clinical Hospital No. 1, State Clinical Hospital No. 2 and the State Institution "V. K. Gussak Institute of Emergency and Reconstructive Surgery", Donetsk, from 2001 to April 2021, 68 (25%) of these patients had an obstructive form at rest, and two patients reliably had IE (0.72%). IE of MV developed in

one patient, IE of MV and AV — in the second patient who was referred for cardiac surgery. Along with prosthetics of AV and MV, surgical myectomy was performed, which made it possible to reduce LVOT gradient twofold (from 40 to 20 mm Hg).

Conclusion

IE with underlying HCM, even in its obstructive form, is a relatively rare disease. In turn, HCM cannot be considered a frequent factor of cardiogenic risk of IE among others. However, due to the peculiarities of hemodynamics, the comorbidity of IE significantly increases the risk of complications and death in patients with HCM, mainly its obstructive form, due to the aggravation of circulatory disorders and increased likelihood of uncontrolled sepsis and fatal embolisms. In this regard, early diagnosis of IE in patients with HCM is required, as well as interdisciplinary interaction in the management of these patients, timely determination of indications for cardiac surgery and the choice of an optimal method. The decision on antibacterial prophylaxis of IE before invasive medical procedures in patients with HCM should be made on a case-by-case basis, with a mandatory assessment of the risk of IE and the severity of hemodynamic disorders and prognosis.

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