DOI: 10.20514/2226-6704-2021-11-3-173-185

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ФИБРИЛЛЯЦИЯ ПРЕДСЕРДИЙ ПРИ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИИ

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Atrial Fibrillation in Hypertrophic Cardiomyopathy

Резюме

В настоящем обзоре представлены современные сведения об особенностях фибрилляции предсердий у лиц с гипертрофической кардиомиопатией. Приводятся данные о распространенности, патогенезе и осложнениях фибрилляции предсердий. В статье представлены современные клинические рекомендации авторитетных научных медицинских сообществ по обсуждаемой проблеме. Подробно освещаются факторы риска возникновения фибрилляции предсердий на фоне гипертрофической кардиомиопатии с демонстрацией результатов различных исследований, посвященных изучению взаимосвязи между факторами риска и вероятностью развития аритмии. Описываются методы выявления, клинические проявления и течение фибрилляции предсердий у больных с гипертрофической кардиомиопатией. Представлены современные литературные данные, посвященные тактике ведения пациентов с фибрилляцией предсердий, рассматриваются подходы к лечению с использованием антикоагулянтов, антиаритмических препаратов, показания для проведения радиочастотной транскатетерной аблации и результаты исследований, посвященные долгосрочной эффективности процедуры. Обсуждается ведение больных в случае невозможности восстановления и поддержания синусового ритма.

Ключевые слова: *гипертрофическая кардиомиопатия, нарушения ритма сердца, фибрилляция предсердий, факторы риска, антикоагулянтная терапия, антиаритмическая терапия, обструкция выносящего тракта левого желудочка, катетерная аблация*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 07.01.2021 г.
Принята к публикации 09.03.2021 г.

Для цитирования: Игнатенко Г.А., Тарадин Г.Г., Ватутин Н.Т. и др. ФИБРИЛЛЯЦИЯ ПРЕДСЕРДИЙ ПРИ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИИ. Архивъ внутренней медицины. 2021; 11(3): 173-185. DOI: 10.20514/2226-6704-2021-11-3-173-185

Abstract

The current information about features of atrial fibrillation in patients with hypertrophic cardiomyopathy is presented in this review. The data about prevalence, pathogenesis and its various complications in these patients are disclosed. The article contains updated clinical recommendations of authoritative medical societies on the discussing problem. There is detailed discussion of risk factors of atrial fibrillation onset in setting of hypertrophic cardiomyopathy with demonstration of results of different studies concerning to investigation of relationship between risk factors and probability

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of the arrhythmia development. There is description of detection methods, clinical manifestations, and the course of atrial fibrillation in patients with hypertrophic cardiomyopathy. The contemporary literature data are presented regarding to the management of patients with atrial fibrillation with use of anticoagulants, antiarrhythmic drugs, indications for performing of radiofrequency ablation and results of studies concerning long-term efficacy of such procedure are demonstrated. The discussion on the management of the patients in cases of sinus rhythm restoration or maintenance failure is described.

Key words: *hypertrophic cardiomyopathy, cardiac arrhythmias, atrial fibrillation, risk factors, anticoagulant therapy, antiarrhythmic therapy, left ventricular outflow tract obstruction, catheter ablation*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

Sources of funding

The authors declare no funding for this study

Article received on 07.01.2021

Accepted for publication on 09.03.2021

For citation: Ignatenko G.A., Taradin G.G., Vatutin N.T. et al. Atrial Fibrillation in Hypertrophic Cardiomyopathy. The Russian Archives of Internal Medicine. 2021; 11(3): 173-185. DOI: 10.20514/2226-6704-2021-11-3-173-185

ACC/AHA — American College of Cardiology / American Heart Association, AF — atrial fibrillation, ECG — electrocardiography, EF — ejection fraction, ESC — European Society of Cardiology, HCM — hypertrophic cardiomyopathy, HF — heart failure, HM — Holter monitoring, HR — heart rate, LA — left atrium, LGE — late gadolinium enhancement, LV — left ventricle, LVOT — left ventricular outflow tract, MRI — magnetic resonance imaging, NYHA — New York Heart Association, OSA — obstructive sleep apnea syndrome, Pmax — maximum P wave duration, PWD — P wave dispersion, RD — rhythm disturbances, SCD — sudden cardiac death

Introduction

Hypertrophic cardiomyopathy (HCM) is a disease with morphological expression only in the heart; it is primarily characterized by left ventricular (LV) hypertrophy with no other cardiac, systemic or metabolic diseases that can cause severe hypertrophy in a particular patient with sarcomere mutation that causes this disease, or with genetic etiology that remains unclear [1–5].

HCM prevalence is quite high and is approximately one case per 500 individuals [2–3, 6]. By some accounts, the prevalence of this disease in the United States is even higher, reaching a ratio of 1:200 [4]. HCM is an autosomal dominant disease; its causes include mutations of genes that encode regulatory, contractile and structural proteins of cardiac sarcomeres [7–9]. To date, at least 13 genes with more than 1,500 mutations expressed mainly or exclusively in heart tissues have been found in patients with HCM [5, 9–11].

Various clinical manifestations of HCM due to the severe hypertrophy of heart walls, obstruction of LV outflow tract (LVOT), mitral valve insufficiency and microvascular pathology include various rhythm disturbances (RD) [12–15]. Almost all types of arrhythmias are detected in association with HCM, particularly atrial fibrillation (AF), other supra- and ventricular RD, extrasystoles, Wolff–Parkinson–White syndrome and, to a lesser extent, bradyarrhythmia [11, 16].

Arrhythmias usually aggravate the clinical picture of cardiomyopathy, increase the risk of stroke and overall mortality and contribute to the progression of heart failure (HF) [17–19]. AF is the most frequent persistent cardiac RD in patients with HCM that contributes to the worsening of the symptoms of the underlying disease and the quality of life [17, 20, 21].

The objective of this review was to summarize literature data on epidemiology, pathogenetic features, clinical manifestations, screening methods and management of AF associated with HCM.

1. Epidemiology and Relevance

AF is the most common persistent arrhythmia in patients with HCM found in 14–28% of cases [3, 14, 17, 21–27]; its incidence in people aged 70+ reaches 40% [25]. AF is found 4-6 times more often in patients with cardiomyopathy than in patients of the same age in the general population [5, 28]. In patients with non-valvular AF, HCM is detected in 1.1% of cases [29]. AF in patients with hypertrophic cardiomyopathy is hard to manage; its course is worse than in patients without this pathology since diastolic filling during the development of AF with HCM is even more disturbed; so, there is increased filling pressure and LV diastolic dysfunction due to the thickening and rigidity of myocardial walls [30]. Besides the absence of atrial systole, increased frequency of ventricular response in AF reduces the time of LV diastolic filling. Therefore, AF leads to decreased cardiac output, afterload and arterial hypotension, which, in turn, can contribute to LV myocardial hypercontractivity. As a result, the pressure gradient in LVOT increases, and, despite hypotension, LV filling pressure remains high, further aggravating diastolic dysfunction and symptoms of HF [28].

Diagnosing HCM in most cases precedes arrhythmia development; therefore, pathophysiological disorders such as diastolic dysfunction, myocardial ischemia and autonomic dysregulation predispose to AF [18, 21]. Patients with HCM and AF have an elevated risk of cardiovascular complications due to thromboembolic episodes, HF, as well as general and sudden cardiac death (SCD) [18, 28, 31]. The prevalence of thromboembolic complications in patients with HCM and AF reaches 30%, with an annual frequency of 3.75% per 100 patients per year. Patients with AF more often have acute cerebrovascular accidents than patients with sinus rhythm do (13.4% and 6.7%, p = 0.019) [18]. A systematic review that included 51 studies with a total of more than 20,000 patients with HCM showed that AF is associated with an elevated risk of thromboembolic complications seven times, HF — 2.8 times, SCD — more than 1.7 times, and death from other causes — 2.5 times [5]. In general, patients with HCM and AF have an unfavorable prognosis, especially in combination with LVOT obstruction and age below 50 years [24, 25].

2. Risk Factors

Size, volume and function of left atrium (LA). Increased size and volume of LA are directly related to the onset or relapse of AF [5, 21, 23, 32-35]. Increased LA size and increased ventricular dysfunction, associated with HCM, lead to an elevated risk of thrombosis in atria and, consequently, the risk of thromboembolic events. In a pooled cross-sectional study of patients with HCM and sinus rhythm, the mean LA diameter was 38 mm compared with 45 mm in patients with AF [18, 26]. However, it is still not clear whether LA increases before AF or dilation is secondary to arrhythmia [17].

LA remodeling associated with HCM represents a typical pattern with the impairment of all three atrial functions: reservoir, conduit (passing blood from pulmonary veins to LV) and pumping that increase as HCM progresses, which was demonstrated by Kowallick J. T. et al. (2017): LA dysfunctions are associated with the presence and severity of LV fibrosis but not with its hypertrophy [36]. Numerous studies with echocardiography and magnetic resonance imaging (MRI) of the heart revealed that the increased volume and impaired function of LA are independent and more reliable predictors of AF than the size of LA [37, 38].

In a prospective study of 427 patients with HCM, 41 of whom subsequently developed AF after enrollment in the study, LA ejection fraction (EF) and its end-diastolic volume were important markers of predisposition to AF [39]. End-diastolic volume of LA ≥118 ml and EF of LA ≤38% obtained via cardiac MRI independently predicted a new onset of AF with a negative predictive value of 95%. It is noteworthy that in 59% of patients with HCM and with AF first detected during the average 5-year follow-up period, LA diameter was <45 mm, which, in accordance with modern recommendations, is considered a factor related to low risk of AF [40]. Patients with LA size <45 mm and newly diagnosed AF had high values of LA volume and a more significant disturbance of its function compared with patients without AF [28].

Several reasons for the increased LA size and volume are considered. In particular, LV diastolic dysfunction typical for HCM leads to an increase in filling pressure, which, in turn, is accompanied by remodeling and dilatation of LA [41, 42]. Increased filling pressure in LV leads to increased pressure in LA, which is required to maintain adequate diastolic filling. This pathophysiological mechanism contributes to remodeling and increase of LA, creating a substrate for the development of arrhythmia and the formation of blood clots due to blood stagnation in LA. According to Zegkos T. et al. (2017), AF is the consequence of the progression of the underlying disease and severe impairment of LV diastolic function, which, in addition to its clinical manifestations, is a key event in the development of arrhythmia [18]. Also, increased LA size with HCM is due to primary sarcomere myopathy of LA myocardium, LVOT obstruction, increased myocardial stiffness, mitral regurgitation and other RD. Considering the established role of increased LA size and its dysfunction in the development of AF with HCM, it is recommended to annually monitor LA parameters and re-examine in case of new symptoms for all stable patients with this disease [28].

Atrial ischemia and myocardial infarction with HCM are caused by calcium metabolism disorders that lead to increased trigger activity due to delayed postdepolarization, hypertrophy of myocardial sleeves (myocardial fibers located outside the pulmonary vein transition zone in LA), which is responsible for triggers from pulmonary veins to LP, microvascular coronary dysfunction, and other causes [5].

AF associated with HCM worsens coronary blood flow reserve, and the imbalance between myocardial oxygen supply and demand leads to the specific activation of redox signaling pathways and the formation of reactive oxygen forms, which, in turn, causes oxidative stress that plays a key role in ventricular remodeling. These mechanisms contribute to stable AF since myocardial ischemia creates a substrate for maintaining arrhythmia [43].

Myocardial fibrosis. In 2001, a small morphological study was conducted to analyze fragments of heart tissue in 10 patients with HCM (5 patients with AF and 5 with no arrhythmia) [44]. It was found that the extent

of fibrosis and the grade of stenosis in intramyocardial small arteries were more pronounced in the group of patients with AF. In patients with HCM, AF develops as a result of progressive atrial remodeling and fibrosis due to increased stretching of LA caused by LVOT obstruction, which leads to atrial myopathy [5]. The condition of "atrial standstill" is a severe form of atrial cardiomyopathy representing an arrhythmogenic substrate for AF. Atrial standstill can be associated with heterozygous mutations of SCN5A and connexin-40 genes [45].

With the latest advances in imaging diagnostic methods, cardiac MRI results dedicated to the identification of additional risk factors of AF were obtained. The detection of late gadolinium enhancement (LGE) in MRI indicates foci of myocardial fibrosis [46, 47]. To study the features of localization and extensiveness of LV myocardial fibrosis, cardiac MRI was performed in 67 patients with HCM, 17 of them with AF [48]. Results of this study revealed that AF was more often observed in patients with signs of LV myocardial fibrosis compared with individuals without it (42.1% and 3.4%, respectively). In a comparative study of two groups of patients with HCM with paroxysmal AF (n = 18) and without it (n = 27), Sivalokanathan S. et al. (2019) found the LGE phenomenon in the posterior LV wall when performing MRI in all patients with cardiomyopathy [47]. However, patients with paroxysmal AF had a greater LA volume, lower LA EF and larger LGE zones compared with the group of patients without AF.

Electrical remodeling of LA. Structural and functional remodeling of LA leads to its electrical instability and creates conditions for the development of various atrial arrhythmias, mostly AF.

Notably, in expanded LA, maximum diastolic potential decreases due to high pressure, and myocyte depolarization occurs faster, increasing susceptibility to arrhythmia. Interstitial fibrosis increases simultaneously with LA remodeling, changing the structure and function of the atria. Fibrosis impedes pulse conduction due to the interruption of the electrical integrity of myocytes, which leads to longer intra- and interatrial conduction time, and heterogeneous distribution of sinus impulses [49].

Predictors of AF in patients with HCM detected during electrocardiography (ECG) are being introduced into modern clinical practice and can help identify individuals with a high risk of AF. Maximum P wave duration (Pmax) and its dispersion (PWD) are easily calculated based on the standard ECG. Pmax reflects prolonged intra- and interatrial conduction. PWD is the difference between the longest (Pmax) and the shortest P (Pmin) wave according to ECG in 12 leads and reflects the heterogeneity of atrial conduction [28].

$$PWD = Pmax — Pmin$$

where PWD is P wave dispersion, ms; Pmax is the duration of the widest P wave, ms; Pmin is the duration of the narrowest P wave, ms

Ozdemir O., et al. (2004) analyzed ECG parameters in 27 patients with HCM and AF paroxysms compared with 53 patients selected by gender and age with no history of AF episodes [50]. Pmax of >134.5 ms and PWD of >52.5 ms determine AF with sensitivity of 92% and 96% and with specificity of 89% and 91%, respectively.

Köse S., et al. (2003) compared the morphological characteristics of P wave in 22 patients with HCM and history of AF and in 26 individuals without arrhythmia and found that PWD of >46 ms predicts AF with a sensitivity of 76% and a specificity of 82% [51]. In a study of 70 patients with HCM, 18 of whom developed AF in about 4.5 years, the authors found that PWD of >47.5 ms predicts AF with a sensitivity of 78% and a specificity of 72% [38].

Cardiac markers. It was previously found that highly sensitive cardiac troponin T (cTnT) has a predictive value for adverse outcomes with HCM [52, 53]. A small study demonstrated that cTnT levels were independent predictors of the presence and severity of AF [54]. The mechanism responsible for cTnT increase in such patients is not fully understood and requires further study. It is believed that it is based on pathological events such as remodeling of the heart, cardiomyocyte necrosis and atrial fibrosis. However, there is limited available information regarding cardiac marker value in assessing the relationship between AF and HCM [28].

It was shown that increased levels of B-type natriuretic peptide (BNP) with HCM are associated with AF [25]. N-terminal pro-BNP of 720 pg/ml predicts AF with a sensitivity of 72% and a specificity of 60% [38]. Overall, natriuretic peptides have a weak predictive power in relation to AF associated with this disease. Available data on using cardiac troponin and BNP levels to predict AF with HCM are insufficient. Therefore, most scientists do not recommend their clinical use for risk stratification in such patients [28].

LV hypertrophy and LVOT obstruction. The effect of LVOT obstruction on the development of AF is not fully understood since data from earlier studies are very contradictory. Moreover, the assessment of the presence and severity of LVOT obstruction in patients with HCM and heart RD can be very difficult. A positive correlation was confirmed by some studies [55, 56] but not found in others [21, 23]. Interesting results were obtained in a study of the relationship between the localization and severity of LV hypertrophy in patients with HCM with

clinical characteristics, a variant of RD, and the disease outcome during an average follow-up period of 6.1 years [57]. In the group of patients with more pronounced hypertrophy of the interventricular septum when hypertrophy covered more than half of the septum length from the heart apex to the base, various RD were observed significantly more often than in patients with local LV hypertrophy (50.1 % and 27.6%, respectively). AF was associated with a high incidence of interventricular septum lesion regardless of LVOT obstruction.

Obstructive Sleep Apnea Syndrome (OSAS) is the most common type of respiratory failure during sleep and is characterized by recurring episodes of upper airway obstruction, leading to hypopnea or apnea associated with periods of hypoxia, activation of the sympathetic nervous system with increased heart rate, increased blood pressure and awakening.

The prevalence of OSAS among patients with AF is extremely high — approximately 50%. When OSAS is associated with HCM, it worsens the severity of the underlying disease and increases mortality due to a 2-4-fold increase in AF incidence, increased diastolic dysfunction, LA dilatation, a more severe functional class of HF according to the classification of the New York Heart Association (NYHA), and deterioration in the quality of life despite optimal therapeutic management of patients [58]. Numerous studies demonstrated a higher prevalence of AF among patients with HCM and OSAS compared with subjects without it, as well as a larger LA and worse diastolic function with increased severity of OSAS [28, 58].

The pathophysiological mechanisms underlying the association of OSAS and HCM are likely to be associated with catecholaminergic activation observed in OSAS, which increases arrhythmogenicity, LV hypertrophy, filling pressure, reduces cardiac output, potentially initiating or worsening LVOT obstruction gradient and mitral regurgitation [28].

Other factors affecting the development of AF with HCM include the severity of LV hypertrophy, certain genetic mutations, insulin resistance, female gender, more severe NYHA class of HF, LVEF, severe mitral regurgitation, history of syncope, etc. [30, 34, 35, 46, 59–61].

3. Detection of Atrial Fibrillation

ECG is an available and informative method of detecting AF, especially in cases of long-term monitoring (24-48 hours) [62].

According to recommendations of the European Society of Cardiology (ESC) for the diagnosis and management of HCM [3], patients with sinus rhythm and anteroposterior LA size ≥45 mm should undergo 48-hour Holter monitoring (HM) ECG every 6-12 months. As per the recommendations of the American College of Cardiology / American Heart Association (ACC/AHA)-2011, one-time 24-hour outpatient ECG monitoring for adult patients with HCM should be carried out to detect asymptomatic flutter or AF [2]. According to the Russian clinical guidelines for HCM, ECG (in 12 leads) is recommended during the initial examination of all patients with suspected HCM and during follow-up. HM ECG (optimally for 48-72 hours) is recommended during the initial clinical examination and every 12-24 months. According to the comments to this paragraph, indications for HM ECG include the patient's complaints of palpitations and/or dizziness [63].

According to retrospective analysis, daily HM ECG allowed to detect AF in 9% of patients among the elderly population, who had severe HF and increased LA compared to the patients with sinus rhythm [12].

In late 2020, updated ACC/AHA recommendations [4] were issued with proposals in the «Assessment of heart rhythm» section that are given in Table 1.

Table 1. *ACC/AHA 2020 guidelines for the assessment of heart rhythm in patients with hypertrophic cardiomyopathy*

COR	LOE	Recommendations
I	B-NR	In patients with HCM who develop palpitations or lightheadedness, extended (>24 hours) electrocardiographic monitoring or event recording is recommended, which should not be considered diagnostic unless patients have had symptoms while being monitored
2a	B-NR	In patients with HCM who have additional risk factors for atrial fibrillation (AF), such as left atrial dilatation, advanced age, and NYHA class III to class IV heart failure (HF), and who are eligible for anticoagulation, extended ambulatory monitoring is reasonable to screen for AF as part of initial evaluation and periodic follow-up (every 1 to 2 years)
2b	B-NR	In adult patients with HCM without risk factors for AF and who are eligible for anticoagulation, extended ambulatory monitoring may be considered to assess for asymptomatic paroxysmal AF as part of initial evaluation and periodic follow-up (every 1 to 2 years)

Abbreviations: COR — class of recommendation; LOE — level of evidence; B-NR — moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, meta-analyses of such studies; ECG — electrocardiography; HCM — hypertrophic cardiomyopathy; AF — atrial fibrillation; HF — heart failure; NYHA — New York Heart Association. Adapted from S.R. Ommen et al. [4]

The accompanying text to this section includes the following: «Although some studies show that the incidence of asymptomatic AF can be as high as 50%, it remains unclear whether asymptomatic episodes, especially short ones, have an effect on an adverse outcome. AF predictors include LA dilatation, elderly age, HF grade III–IV according to NYHA. Therefore, patients with these characteristics should be examined more often, including extended ECG screening on an outpatient basis» [4].

According to Zegkos T. et al. (2017), who noted a smaller LA size among individuals with AF, there is no reliable indicator of the size of LA, which is important for screening patients with HCM for arrhythmia and timely administration of anticoagulant agents [18]. In this context, physicians should bear in mind the possibility of AF in any patient with HCM, even in an asymptomatic patient without risk factors for this atrial arrhythmia.

In recent years, with the development of digital and portable devices, it has become possible to use new mobile systems designed primarily to detect AF paroxysms. Table 2 shows sensitivity and specificity values of some devices for AF screening considering ECG in 12 standard leads as the «gold standard» [19].

Table 2. *Sensitivity and specificity of various AF screening tools*

Screening tools	Sensitivity	Specificity
Pulse taking	87-97 %	70-81 %
Automated BP monitors	93-100 %	86-92 %
Single lead ECG	94-98 %	76-95 %
Smartphone apps	91,5-98,5 %	91,4-100 %
Smartwatch	97-99 %	83-94 %

Notes: BP — blood pressure; ECG — electrocardiogram. Adapted from G. Hindricks et al. [19]

When determining AF using modern mobile and portable devices, an ECG should be recorded in one (≥30 sec) or 12 leads with the interpretation of results by a physician experienced in interpreting heart RD in order to make a final diagnosis [19].

4. Clinical Manifestations and Course

AF in some patients with HCM may not be accompanied by any complaints or symptoms, and in such cases, arrhythmia is detected during routine ECG. In some patients, AF is manifested by a variety of complaints of palpitations, pre- and syncopal conditions, onset or intensification of pain in the left half of the chest, shortness of breath at rest or during physical activity; there may be decreased exercise tolerance or blood pressure [62, 64].

According to the study by Zegkos T. et al. (2017), patients with HCM and AF had more pronounced clinical manifestations of HF than patients with no AF did [18]. In the study conducted by Siontis K., et al. (2014), a significant decrease in the functional ability of patients with HCM and AF was registered during a cardiopulmonary exercise test [25]. This was because LV diastolic dysfunction is initially observed in the cases of HCM, and, with the onset of AF, i.e., the loss of coordinated atrial systole, LV filling worsens significantly, which aggravates HF, especially during physical exertion. Thus, both AF and increased HF can be the result of progressive structural and functional impairment due to HCM. Therefore, ESC experts consider it appropriate to include a cardiopulmonary exercise test in the initial assessment program of such patients [2].

According to the current hypothesis, decreased cardiac output due to atrial systole loss and decreased stroke volume are taken into consideration in relation to the mechanisms by which AF is associated with decreased exercise tolerance in patients with HCM. Although, according to Azarbal F. et al. (2014) [65], who found that the paroxysmal form of AF is significantly associated with decreased exercise tolerance in patients with sinus rhythm at the time of the study and with no active hemodynamic consequences of arrhythmia, there are probably other non-arrhythmogenic causes of physical exercise intolerance. Diastolic dysfunction, ventricular remodeling, atrial enlargement, systemic vasodilation, or decreased intravascular volume predisposing to arterial hypotension, as well as increased adrenergic tone, are considered possible causes of decreased exercise tolerance in patients with HCM and AF [65].

The most common complication of AF associated with HCM is systemic thromboembolism [29, 31]. In particular, this arrhythmia increases the risk of ischemic stroke eightfold [21]. It should be noted that the increased risk does not depend on the form of arrhythmia (paroxysmal/persistent for a long time/permanent) or the number of AF paroxysms.

5. Management

Modern methods of managing AF with anticoagulants, antiarrhythmic agents, catheter ablation, and maze procedure have demonstrated their high efficiency, which has helped reduce the mortality rate of patients with HCM and AF to the level of patients with no AF [28, 31].

Anticoagulant therapy. AF in a patient with HCM is a direct indication for oral anticoagulant therapy. According to the ESC-2014 [3], ACC/AHA 2014 [66] and 2019 recommendations [67], the CHA_2DS_2-VASc scale is

not recommended for stroke risk assessment. According to Alphonse P. et al. (2020), based on the results of a meta-analysis and taking into consideration the multifold increase in the risk of thromboembolic complications, HCM itself should be included in the CHA_2DS_2-VASc scale as an independent risk factor [5].

The ACC/AHA 2011 guide for the diagnosis and management of HCM offers recommendations for anticoagulant therapy with oral anticoagulants, including vitamin K antagonists with a target range of the international normalized ratio of 2.0–3.0 [2] for patients who developed paroxysmal, persistent or permanent AF. Unfortunately, there are currently no randomized clinical trials of anticoagulant therapy in patients with this form of cardiomyopathy [5]. However, numerous retrospective studies demonstrated a decrease in the level of embolic complications in patients taking warfarin. Therefore, anticoagulant therapy is justified if AF persists for more than 48 hours or if there is a high probability of its relapse [2, 21]. Warfarin should be prescribed literally after the first AF episode [21].

Direct oral anticoagulants — direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivaroxaban and apixaban) — can be successfully used in patients with HCM and AF [46, 63, 68]. According to the Russian recommendations on HCM, in the cases of side effects of warfarin or the inability to reach target INR, dabigatran etexilate, or rivaroxaban, or apixaban is recommended. In all cases of HCM complicated by AF, life-long therapy with warfarin (INR 2–3.0) or direct anticoagulant agents is recommended, even if sinus rhythm has been restored [63]. Patten M. et al. (2018) [64] recommend life-long oral anticoagulant therapy in cases of documented AF regardless of the individual score according to CHA_2DS_2-VASc in order to reduce the risk of stroke.

Antiarrhythmic therapy. Relative benefits of rhythm control compared with heart rate (HR) control in the management of AF in patients with HCM are not yet clear [30, 69]. This is partly because there are very limited data on the safety and efficacy of drug therapy for AF rhythm control in individuals with HCM. However, in some patients, especially with severe LVOT obstruction and increasing severity of HF and ventricular tachysystole, restoration of sinus rhythm is justified. Clinical guidelines of the Ministry of Health of the Russian Federation on AF and atrial flutter recommend restoration of sinus rhythm by electric or pharmacological cardioversion to improve symptoms for all patients with HCM and onset of symptomatic AF for the first time [62].

Currently, amiodarone is the most effective agent that reduces the frequency of AF paroxysms [17, 46, 63]. Amiodarone is recommended for patients with recent AF (<48 h) [63]. The minimum effective dose of this drug is 200 mg 5-7 times a week with regular monitoring of thyroid, hepatic and pulmonary functions [70, 71]. In one study involving 52 patients with HCM and AF, amiodarone was associated with more rare episodes of AF and embolic events compared with class I antiarrhythmic drugs [72]. In patients who initially received standard therapy (including digoxin, β blockers, calcium channel blockers, quinidine and disopyramides), sinus rhythm maintenance was achieved in 22 out of 38 (58%) compared with 7 out of 8 (87%) patients on amiodarone. Over time, 20 (39%) patients receiving conventional treatment switched to amiodarone, which significantly reduced the number of cardioversions [72]. Despite the high effectiveness of amiodarone in preventing AF relapse, this antiarrhythmic drug is considered not ideal for the group of patients with HCM due to the need for long-term use and high frequency of side effects [17, 46]. According to the results of another study with 98 participants, 19.1% of patients taking amiodarone developed side effects, which was the reason for the discontinuation of the drug, once again confirming the limited use of amiodarone among patients, especially young ones. At the same time, amiodarone was found to be highly effective in rhythm control: the drug was discontinued due to inefficiency (no sinus rhythm along with amiodarone intake) in 8.5% of patients [30]. The probability of taking amiodarone after 1 and 3 years was 51.4% and 29.2%, respectively, indicating poor tolerability of this drug in most patients.

Sotalol and disopyramide are alternative antiarrhythmic drugs for managing AF in patients with HCM. [30, 73–75]. Besides a direct antiarrhythmic effect, disopyramide also has a negative inotropic effect, which is especially important in cases of LVOT obstruction [19]. According to a retrospective analysis, using disopyramide was not associated with an increased risk of ventricular arrhythmia or SCD in patients with HCM [74]. Considering that monotherapy with disopyramide is potentially dangerous due to increased atrioventricular conduction, which accelerates ventricular response in AF [3], this agent is mainly used in emergency care. In such cases, disopyramide is administered simultaneously with rhythm control drugs along with continuous monitoring of the QTc interval [2]. When the QTc interval value reaches ≥480 ms, the dose of the drug should be immediately reduced, or the drug should be completely withdrawn [3]. Along with this, other drugs that extend QT interval should be avoided. The small number of examined patients with HCM does not provide a complete picture of the efficacy and safety of disopyramide and dofetilide in this population [30].

Sotalol, as a class III antiarrhythmic drug, demonstrated its efficacy in patients with structural heart diseases.

A recent study by Miller C. A. S. et al. (2019) showed that sotalol is effective for rhythm control with AF (27.2% of patients had to stop taking sotalol due to its inefficiency) [30]. At the same time, the probability of taking sotalol after 1 and 3 years was 74.4% and 50%, respectively, which indicates good tolerability of this drug. Based on the results of the then-largest study of the group of patients with HCM and AF who were taking sotalol (45 patients observed for 2.3 ± 2.3 years), the authors believe that sotalol may be the drug of choice in the treatment of such patients considering the absence of serious side effects [30].

In the study, there were no cases of SCD and no serious side effects among patients receiving amiodarone and sotalol. In the group of patients taking disopyramide, three cases of side effects were registered: anaphylaxis in one patient, stable form of ventricular tachycardia in one patient and QTc prolongation according to ECG data in one patient as well [30]. Three patients who received dofetilide developed side effects: symptomatic bradycardia in one patient and syncope in two patients. In one case, stable ventricular tachycardia was detected in a 50-year-old patient with HCM who received disopyramide. Due to a family history of SCD, a cardioverter-defibrillator was implanted for secondary prevention. During the administration of disopyramide (200 mg twice a day), the patient received three shocks of a cardioverter-defibrillator due to polymorphic ventricular tachycardia [30].

Experts from the ACC/AHA Working Group for the study of HCM in 2011 assigned amiodarone and disopyramide class IIa as agents for rhythm control (Fig. 1) [2].

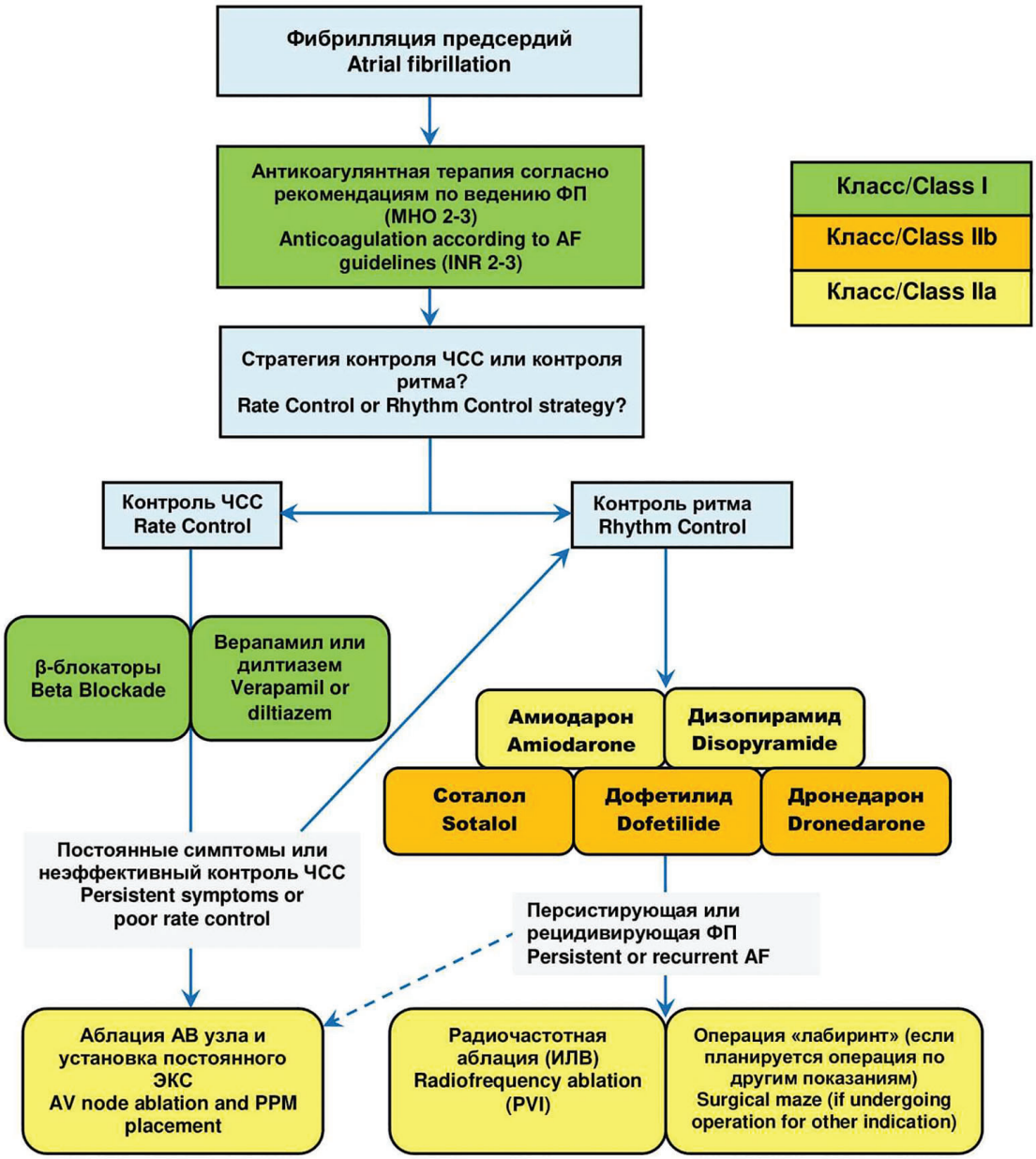

Figure 1. *Management of atrial fibrillation in hypertrophic cardiomyopathy*

Table 3. *ACC/AHA 2020 guidelines for the management of atrial fibrillation in patients with hypertrophic cardiomyopathy*

COR	LOE	Recommendations
I	B-NR	In patients with HCM and clinical AF, anticoagulation is recommended with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option, independent of CHA2DS2-VASc score
I	C-LD	In patients with HCM and subclinical AF detected by internal or external cardiac device or monitor of >24 hours' duration for a given episode, anti-coagulation is recommended with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option, independent of CHA2DS2-VASc score
I	C-LD	In patients with AF in whom rate control strategy is planned, either beta blockers, verapamil, or diltiazem are recommended, with the choice of agents according to patient preferences and comorbid conditions
2a	C-LD	In patients with HCM and subclinical AF detected by internal or external device or monitor, of >5 minutes' but <24 hours' duration for a given episode, anticoagulation with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option can be beneficial, taking into consideration duration of AF episodes, total AF burden, underlying risk factors, and bleeding risk
2a	B-NR	In patients with HCM and poorly tolerated AF, a rhythm control strategy with cardioversion or antiarrhythmic drugs can be beneficial with the choice of an agent according to AF symptom severity, patient preferences, and comorbid conditions.
2a	B-NR	In patients with HCM and symptomatic AF, as part of an AF rhythm control strategy, catheter ablation for AF can be effective when drug therapy is ineffective, contraindicated, or not the patient's preference
2a	B-NR	In patients with HCM and AF who require surgical myectomy, concomitant surgical AF ablation procedure can be beneficial for AF rhythm control

Abbreviations: COR — class of recommendation; LOE — level of evidence; B-NR — moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, meta-analyses of such studies; C-LD — randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, physiological or mechanistic studies in human subject; HCM — hypertrophic cardiomyopathy; AF — atrial fibrillation.
Adapted from S.R. Ommen et al. [4]

Sotalol, dofetilide, and dronedarone belong to class IIb and can be used in the rhythm control strategy in patients with HCM [66, 67], but with the note that their use should be carefully considered in patients with implanted cardioverter-defibrillators. Flecainide and propafenone are undesirable due to possible proarrhythmic effects and hemodynamic deterioration [2, 3].

Thus, to date, the exact risks and benefits of using antiarrhythmic agents in patients with HCM and AF are unclear. Therefore, the decision on the choice of rhythm control tactics should be made in each case individually with discussion between the physician and the patient [30].

There are interesting recent recommendations for the management of patients with HCM and AF developed by AHA/ACC and published in 2020. [4].

If sinus rhythm cannot be maintained, β blockers or calcium channel blockers (verapamil, diltiazem) are prescribed to control the frequency of ventricular response [2, 62, 63]. Atenolol, nadolol, metoprolol succinate are justified in cases of preserved LV EF, and bisoprolol or carvedilol — in cases of systolic dysfunction. Verapamil or diltiazem should be used only with preserved LV EF [70]. Digoxin is actually not used for AF in patients with "classical" HCM. However, its use can be considered for patients with severe LV dysfunction in order to control heart rate. The Russian Guidelines for HCM recommend considering the use of digoxin in low doses for patients with non-obstructive HCM with persistent AF and chronic NYHA functional class II-IV with EF <50% in order to control ventricular contraction rate [63].

Catheter ablation. Indications for radiofrequency catheter ablation include symptomatic AF that is refractory to drug treatment and intolerance to drug therapy [66, 67]. The procedure should be carried out as soon as possible after the onset of AF while the arrhythmogenic substrate remains pliable for external exposure [70]. The 2014 ACC/AHA/Heart Rhythm Society guidelines include catheter ablation on the list of therapeutic methods for heart rate control [66]. However, most studies revealed a high frequency of repeated procedures to achieve long-term control AF [76]. Rhythm restoration and relapse rate reduction can be achieved in 2/3 of patients with HCM in two years [77]. The lower efficiency of stopping AF in patients with HCM (varying from 45 to 82% in the long-term) is due to pronounced remodeling of LA — its hypertrophy/dilation [22] and the presence of fibrotic zones (Fig. 2) [17, 76].

The need for re-ablation often occurs in elderly people with a large LA and high functional class of HF, according to NYHA [77]. With paroxysmal AF, the probability of successful relief is higher (77%) than with its permanent form (50%) [78].

Therefore, AF is the most common persistent arrhythmia that complicates the course of HCM. AF leads to the aggravation of the clinical manifestations of the disease, progression of HF, and an elevated risk of cardiovascular complications and mortality. In this regard, patients

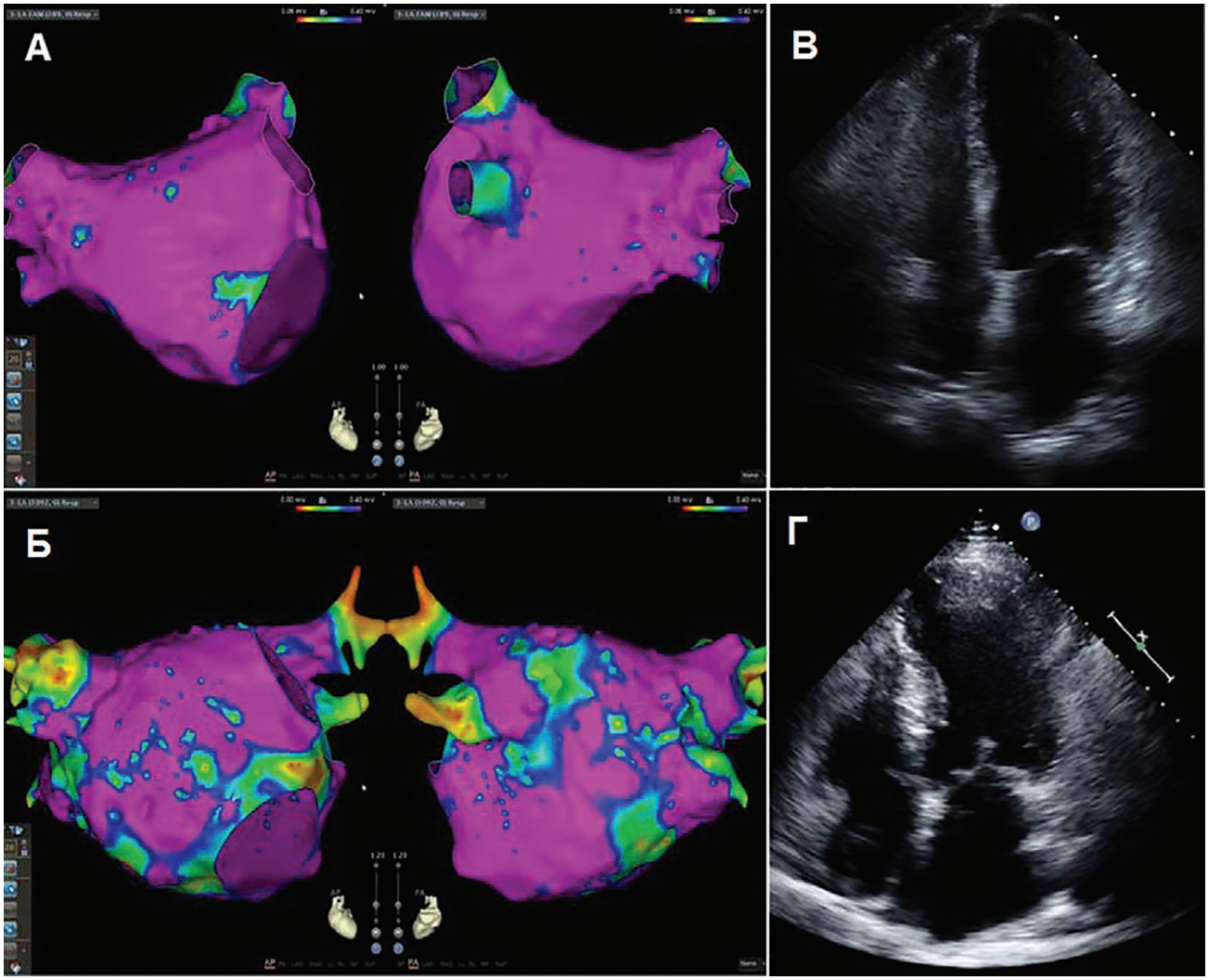

Figure 2. *Bipolar stress maps and echocardiographic data in patients with hypertrophic cardiomyopathy and atrial fibrillation*

with HCM should be examined for risk factors and AF. In the event of AF, a strategy for rhythm control or heart rate control should be carefully chosen based on existing experience with antiarrhythmic drugs and current recommendations. Anticoagulant therapy deserves special attention; its prescription is justified for all patients with HCM and AF in order to prevent thromboembolic complications.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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