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HYPERTROPHIC CARDIOMYOPATHY: HOW TO TREAT PATIENTS AT RISK?

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SUMMARY - Hypertrophic cardiomyopathy is a primary cardiac muscle disease with clinical manifestations that vary from a benign asymptomatic course to severe heart failure or cardiac arrest. Therefore, the identification of individual risk of sudden cardiac death is the first step in the treatment of patients with hypertrophic cardiomyopathy. The factors that best identify high risk patients include a history of cardiac arrest or syncope, inducible sustained ventricular tachyarrhythmia, nonsustained ventricular tachycardia in symptomatic patients, presence of ischemia associated with hypotension in children, and presence of mutations in the beta-myosin heavy chain along with family history of sudden cardiac death. The treatment of patients with hypertrophic cardiomyopathy depends on the symptoms and risk degree. Patients with cardiac arrest, sustained ventricular tachycardia, or inducible sustained ventricular tachyarrhythmia during programmed ventricular stimulation have an indication for implantable cardioverter-defibrillator. Patients with the symptoms of impaired consciousness and nonsustained ventricular tachycardia without inducible sustained ventricular tachyarrhythmias can be treated with amiodarone. Asymptomatic patients with nonsustained ventricular tachycardia do not need prophylactic drug therapy, because their prognosis is the same as the prognosis of asymptomatic patients without such tachycardia. Asymptomatic patients with two or more risk factors are candidates for electrophysiological testing and subsequent pharmacological or nonpharmacological therapy. On the other hand, asymptomatic patients free from risk factors have a good prognosis and should be allowed to lead a normal life. However, in young asymptomatic patients or athletes, discontinuation of competitive, high- and medium-grade physical activity is mandatory, because this measure significantly reduces their risk of sudden cardiac death.

Key words: *Cardiomyopathy, hypertrophic, complications; Cardiomyopathy, hypertrophic, therapy; Death, sudden, cardiac; Risk factors*

Introduction

Hypertrophic cardiomyopathy is a primary cardiac muscle disease, which is defined by ventricular left and/or right ventricular hypertrophy in the absence of any cardiac or systemic cause[1]. Although the cause of hypertrophic cardiomyopathy is not completely known, a majority of cases are caused by mutation of the genes that encode the proteins of the cardiac muscle sarcomere[2]. Clinically, two forms of hypertrophic cardiomyopathy may be distinguished: hypertrophic obstructive cardiomyopathy characterized by the presence of a resting or provocable gradient between the apex and the outflow tract in the left ventricle, and hypertrophic nonobstructive cardiomyopathy that has no intraventricular gradient at rest or on provocation (Table 1)[3]. Recent studies have shown that the prevalence of hypertrophic cardiomyopathy in the general population is between 0.2% and 0.02%[4,5]. The clinical

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Table 1. Hemodynamic classification of hypertrophic cardiomyopathy

Obstructive hypertrophic cardiomyopathy	
	subaortic obstruction
	midventricular obstruction
Nonobstructive hypertrophic cardiomyopathy	
	normal (supranormal) systolic function
	impaired systolic function (end-stage hypertrophic cardiomyopathy)

course of the disease is very variable. Many patients remain asymptomatic and unaware of their disease for years, some have cerebral symptoms on exertion, some have severe symptoms of heart failure or ischemia, and some die suddenly, without previous symptoms. Therefore, continuing efforts have been made in risk stratification and appropriate therapy for these patients.

The Incidence of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Sudden cardiac death is a significant cause of mortality in patients with hypertrophic cardiomyopathy, but its incidence depends on the study population (Table 2). Earlier hospital-based clinical investigations have reported on the annual incidence of sudden death of 2% to 4% in adults, and 4% to 6% in children and adolescents[8]. In recent outpatient and regionally selected population studies, the annual risk of cardiac mortality is about 1% (0.7% for sudden death), and hypertrophic cardiomyopathy does not significantly affect the overall life expectancy[9,10]. It is important to note that asymptomatic patients are at an even lower annual risk of sudden death (0.1%)[6].

The Mechanisms of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

There are many potential mechanisms of sudden cardiac death in patients with hypertrophic cardiomyopathy. A sudden onset of any supraventricular tachyarrhythmia can be associated with severe hypotension, especially if there is a concurrent left ventricular outflow obstruction, impaired diastolic function, or myocardial ischemia. Atrial fibrillation, alone or associated with preexcitation syndrome, can induce highly devastating hemodynamic sequels and precipitate sudden death due to rapid heart rate, loss of atrial contribution to cardiac output, and irregular filling and emptying of the left ventricle. Acute myocardial ischemia or even myocardial infarction is rarely the cause of sudden death, but they can precipitate ventricular tachyarrhythmia causing cardiac arrest. Complete heart block has also been reported as a potential cause of sudden death, but it occurred in a few cases only[11].

The available data suggest that ventricular tachyarrhythmias are the cause of sudden death in most patients with hypertrophic cardiomyopathy, either as a primary event related to an arrhythmogenic substrate (disarray or myocardial scarring) or as a secondary phenomenon triggered by myocardial ischemia, diastolic dysfunction, outflow obstruction, or supraventricular tachyarrhythmias[12].

Evaluation of Patients at Risk

One of the main aims on assessing patients with hypertrophic cardiomyopathy is the identification of individual risk for sudden cardiac death. A number of identifiable risk factors have been proposed: family history of sudden death, exercise-induced hypotension, history of syncope, nonsustained ventricular tachycardia on 24- or 48-hour Holter monitoring, and inducible ventricular tachycardia or ventricular fibrillation (Table 3). In children

Table 2. Clinical presentation and prognosis (follow-up, 7-10 years)

	Asymptomatic[6] (n=58)	Symptomatic[6] (n=70)	Cardiac arrest survivors[7] (n=33)
Mean age (yrs)	42.8	50.4	32
Family history of hypertrophic cardiomyopathy	16%	7%	51%
Sudden death	2%	11%	24%
All-cause mortality	9%	24%	33%

Table 3. Hypertrophic cardiomyopathy - predictive value of risk factors for sudden cardiac death

	Predictive accuracy	
	positive	negative
Family history of sudden cardiac death[13]	28	88
Exercise-induced hypotension[14]	15	97
Syncope[12]	25	86
Nonsustained ventricular tachycardia[8]	22	97
Inducible ventricular tachycardia/ventricular fibrillation[15]	18	97

and adolescents, only the first three factors are used, knowing that syncope, rare though, carries a very poor prognosis. In older patients aged up to 40, all five factors are valid for risk stratification. Unfortunately, all the risk factors proposed have a low positive predictive value, because a majority of patients with one of these factors will never have sudden death. On the other hand, their negative predictive value for sudden death is very high. Therefore, a patient with none of these factors has a favorable prognosis and should be allowed to lead normal life. The risk is considered to be higher when two or three of the factors are associated. In children and adolescents with hypertrophic cardiomyopathy, syncope on exertion is an ominous symptom, but the risk is higher when it occurs in individuals with a family history of sudden cardiac death[13]. A similar logic should be used in patients with hypertrophic cardiomyopathy who have nonsustained ventricular tachycardia. In these patients, the risk of nonsustained ventricular tachycardia is significantly higher when tachycardia occurs in combination with the symptoms of impaired consciousness[15]. New possibilities in the risk stratification have been offered by the finding that some gene mutations, such as cardiac troponin T and beta cardiac myosin heavy chain mutations causing hypertrophic cardiomyopathy, indicate a particularly high risk of sudden cardiac death[16]. However, this genetic stratification has not yet become available in routine clinical practice.

Therapy to Prevent Sudden Cardiac Death

A number of factors limit our ability to effectively prevent sudden cardiac death in an individual. These factors include low prevalence of hypertrophic cardiomyopathy, low incidence of death among affected patients, and a variety of clinical conditions that may cause death. In one of the largest groups of prospectively investigated hypertrophic cardiomyopathy patients, the loss of consciousness was the only independent clinical predictor of future events during follow-up[15]. Although the mortality rate in this subgroup was still low (about 13% at 5 years), it seems reasonable to assess the risk by subdividing the affected patients into asymptomatic or mildly symptomatic patients and those with the symptoms of impaired consciousness.

There is clinical consensus that an asymptomatic patient without previously outlined clinical risk factors is at a low risk of sudden cardiac death. Most adult patients with such a profile can be reassured and do not require prophylactic therapy, but should be reassessed at intervals, at least until they have completed adolescent growth[1]. Recently, Corrado et al.[5] investigated the impact of disqualification from intense physical activity on the future risk of sudden cardiac death in patients with identified hypertrophic cardiomyopathy. During the study period, the incidence of sudden death was 1.6 *per* 100,000 per year among competitive athletes and 0.75 *per* 100,000 per year among nonathletes aged (35. Out of 337735 competitive athletes undergoing preparticipation screening, 22 were found to have hypertrophic cardiomyopathy and were disqualified from further physical activity. During the follow-up, hypertrophic cardiomyopathy caused only one (2%) sudden death among the athletes, whereas in the nonathlete population it caused 16 (7.3%) sudden deaths. None of the 22 athtletes who were disqualified from sports activities for hypertrophic cardiomyopathy died during the follow-up. These data support the opinion that the identification and disqualification from further physical activity of patients with asymptomatic or mildly symptomatic hypertrophic cardiomyopathy may significantly reduce their risk of sudden cardiac death.

Asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia on ambulatory Holter have a low risk of sudden cardiac death and the same prognosis as the patients with this disease without nonsustained ventricular tachycardia[15,17]. Accordingly, episodes of nonsustained

ventricular tachycardia should not be considered an indication for prophylactic antiarrhythmic treatment in asymptomatic patients.

In patients with symptoms of impaired consciousness, the conventional risk factor stratification may identify the subgroup of patients with hypertrophic cardiomyopathy who are at an increased or high risk of sudden cardiac death (Table 4). In approximately 30% of these patients, a probable initiating mechanism that is amenable to specific therapy can be identified. Paroxysmal atrial fibrillation can be effectively prevented with amiodarone, rapid atrioventricular conduction *via* an accessory pathway by radiofrequency catheter ablation, ischemia with high dose verapamil or beta-blockers, and left ventricular obstruction by dual chamber pacing or myectomy.

In other patients, who are considered to be at a particularly high risk of life-threatening tachyarrhythmias, the available therapeutic options for prevention of sudden cardiac death include amiodarone, implantable cardioverter defibrillator, or myectomy.

Table 4. Hypertrophic cardiomyopathy - patients at high risk of sudden cardiac death

- history of cardiac arrest or syncope
- episodes of sustained monomorphic or polymorphic ventricular tachycardia
- induction of sustained ventricular tachycardia/ventricular fibrillation on electrophysiological testing
- nonsustained ventricular tachycardia associated with presyncope or syncope
- myocardial ischemia associated with hypotension
- gene mutation associated with high incidence of sudden death
- severe left ventricular outflow obstruction

Antiarrhythmic Drug Therapy

To date, amiodarone is the only prophylactic drug therapy that has been tested in high risk patients without a history of sudden cardiac death (Table 5). McKenna et al.[18] report that patients treated with amiodarone for nonsustained ventricular tachycardia had a more favorable outcome on Holter than those treated with conventional antiarrhythmics. The 3-year survival was 100% and 82% for patients on amiodarone and those on conventional therapy, respectively. In the study of Fananapazir et al.[19],

Table 5. Hypertrophic cardiomyopathy - amiodarone in prevention of nonsustained ventricular tachycardia (3-year follow-up)

	No. of patients	Mortality (%)
McKenna (1985)		
Ventricular tachycardia	21	0
Ventricular tachycardia - disopyramide, mexiletine, or quinidine	24	20
No ventricular tachycardia - no antiarrhythmic	123	4
Fananapazir (1991)		
Ventricular tachycardia - amiodarone	21	38
No ventricular tachycardia - amiodarone	29	3

amiodarone was given to 50 patients for the symptoms refractory to conventional therapy, 21 of them with nonsustained ventricular tachycardia on Holter monitoring. Seven deaths were recorded during a mean follow-up, six within 5 months of therapy initiation. Among 21 patients with nonsustained ventricular tachycardia prior to amiodarone therapy, the survival rate at 2 years was only 62%. It should be noted that the dosage of amiodarone used in this study was higher (loading dose of up to 1600 mg/day and maintenance dose of 400 mg/day) than usual, and that the proarrhythmic action of amiodarone could not be excluded in some cases. In a later study in 35 patients undergoing electrophysiological testing, amiodarone was shown to facilitate ventricular tachycardia or fibrillation induction in about 50% of patients with hypertrophic cardiomyopathy[20]. This group of patients had a significantly higher risk of arrhythmic events during follow-up than the patients in whom ventricular tachycardia was rendered noninducible or more difficult to induce after amiodarone therapy. The data reported from these studies show that amiodarone is not as effective in hypertrophic cardiomyopathy as it was previously thought to be, and that asymptomatic patients with nonsustained ventricular tachycardia should not be administered amiodarone as prophylactic therapy. However, in symptomatic patients with nonsustained ventricular tachycardia, electrophysiological testing of amiodarone should be performed before starting prophylactic therapy with this drug. In a recent study, Elliott et al. obtained some evidence for the beneficial effect of amiodarone in patients

at high risk[21]. They stratified 474 consecutive patients according to the presence of one or no risk factor (low risk group, n=284), or two or more risk factors (high risk group, n=109). During the mean follow-up of 1121 days, 81 patients received amiodarone as monotherapy. In the patients who did not receive amiodarone, the annual rate of sudden death was 2.5% in the high risk group, and 1.3% in the low risk group. None of the treated patients on amiodarone died during the follow-up period. Therefore, although unequivocal evidence in support of amiodarone is lacking, the weight of evidence strongly favors the use of amiodarone in high risk groups of patients.

Recently, Elliott et al. compared the efficacy of amiodarone and implantable cardioverter-defibrillator therapy in 16 patients with hypertrophic cardiomyopathy who survived cardiac arrest[22]. The choice of treatment was based on the failure of low dose amiodarone, availability of appropriate devices, and individual patient preference. Eight patients were on low dose amiodarone (200 to 300 mg), six patients underwent implantation of implantable cardioverter-defibrillator, and two patients declined any prophylactic therapy. During a mean follow-up of 6 years, two patients died while taking amiodarone, and one patient died who had refused drug and device prevention. Of six patients with implantable cardioverter-defibrillator, three had appropriate discharge for ventricular tachycardia or ventricular fibrillation. In two patients, interrogation of the implantable cardioverter-defibrillator revealed several episodes of atrial fibrillation degenerating into polymorphic ventricular tachydardia and sinus tachycardia followed by ventricular tachycardia. Although the number of study patients was small, the authors conclude that the patients with hypertrophic cardiomyopathy who survive cardiac arrest should preferentially be treated with implantable cardioverter-defibrillator.

Implantable Cardioverter-Defibrillator

There are only a few retrospective studies on the efficacy of implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy, and the indications of its use, especially for primary prevention, have not yet been established. In a study of Silka et al.[23], a cardioverter-defibrillator was implanted in 44 patients (age <20 years) with hypertrophic cardiomyopathy. The indications for implantation included cardiac arrest in personal history, drug-refractory ventricular tachycardia, and syncope with inducible ventricular tachyarrhythmias. During a mean follow-up of 31 months, the implantable cardioverter-defibrillator had an appropriate discharge in 25 (57%) patients. In a study of Tripodi et al.[24], a cardioverter-defibrillator was implanted in 31 patients with hypertrophic cardiomyopathy, and the rate of appropriate discharge was 32% during a 33-month period. Borggreffe et al.[12] report on 14 patients with hypertrophic cardiomyopathy and implantable cardioverter-defibrillator. An appropriate implantable cardioverter-defibrillator discharge during a mean follow-up of 48 months was recorded in 43% of patients. Primo et al.[25] report on the occurrence of cardiac events during follow-up in 13 patients with hypertrophic cardiomyopathy who received an implantable cardioverter-defibrillator because of aborted sudden death (n = 10) or sustained ventricular tachycardia (n = 3). The results were compared with those in 215 patients with an implantable cardioverter-defibrillator and other structural heart diseases or idiopathic ventricular fibrillation. After a mean follow-up period of 26 months, only two of 13 patients received appropriate shocks. At 40 months, the calculated cumulative incidence of shocks was 21% in patients with hypertrophic cardiomyopathy and 66% in the rest of patients. No lethal outcome was recorded in patients with hypertrophic cardiomyopathy, however, 11 of them were medicamentously treated. The authors conclude that the implantable cardioverter-defibrillators have a less important impact on the prognosis in patients with cardiomyopathy than in those with other etiologies of aborted sudden death.

Recently, Maron et al.[26] investigated the efficacy of cardioverter-defibrillator in 128 patients with hypertrophic cardiomyopathy, mean age 40 years. In 43 patients, defibrillators were implanted for secondary prevention after either resuscitation from cardiac arrest (with documented ventricular fibrillation) or sustained ventricular tachycardia. In the remaining 85 patients, defibrillators were implanted as a prophylaxis for primary prevention of sudden cardiac death. The main clinical reasons for these implantations, either alone or in combination, were syncope (n = 41), family history of one or more sudden deaths due to hypertrophic cardiomyopathy (n = 39), nonsustained ventricular tachycardia on Holter monitoring (n = 32), and left-ventricular wall thickness of at least 30 mm (n = 10). In addition, 56 patients had inducible ventricular tachycardia or fibrillation on electrophysiological testing. Appropriate defibrillator discharge was recorded in 29 (23%) of 128 patients during a mean follow-up period of 3 years. In each of 21 patients with stored electrocardiography records, ventricular tachycardia or fi-

brillation was the rhythm that activated the device. Discharges were most frequent (about 11% *per* year) in the patients who received defibrillators for secondary prevention. In this group, the device failed to prevent death in two patients who had end-stage hypertrophic cardiomyopathy with severe systolic dysfunction and heart failure. The rate of appropriate discharge was about 5% *per* year in the group of patients who had received defibrillators solely for primary prevention. Data from this study support the view that implantable defibrillator can be lifesaving in patients with hypertrophic cardiomyopathy, supporting its use for both secondary and primary prevention.

The decision to implant a cardioverter-defibrillator is quite clear for patients who had cardiac arrest, symptomatic sustained ventricular tachycardia, or sustained ventricular tachyarrhythmia induced during electrophysiological testing (Fig. 1). Does the current evidence justify implantation of these devices for primary prevention in high risk patients, many of them young people? The question could only be definitely answered by an appropriately designed, randomized trail of defibrillator *versus* amiodarone, however, it would be difficult to conduct because of ethical considerations, relatively low prevalence of the disease, and relatively low rate of events.

The Role of Myectomy

In a prospective study by Borggreffe et al.[27], ten cardiac arrest survivors underwent myectomy for hypertrophic obstructive cardiomyopathy. Eight of ten patients had inducible sustained ventricular tachycardia or fibrillation before the operation. After myectomy, ventricular tachycardia was rendered noninducible in all ten patients by use of an aggressive protocol stimulation with up to three extrastimuli. During a mean follow-up of 4.5 years, no ventricular tachyarrhythmias occurred in any of these patients. This preliminary observation could be explained by surgical removal of the arrhythmogenic substrate, and may support a potential mechanism of the beneficial long-term postoperative results. Therefore, in some patients with cardiac arrest and inducible ventricular tachyarrhythmias, myectomy may be the treatment of choice, because it represents a curative approach for these arrhythmias.

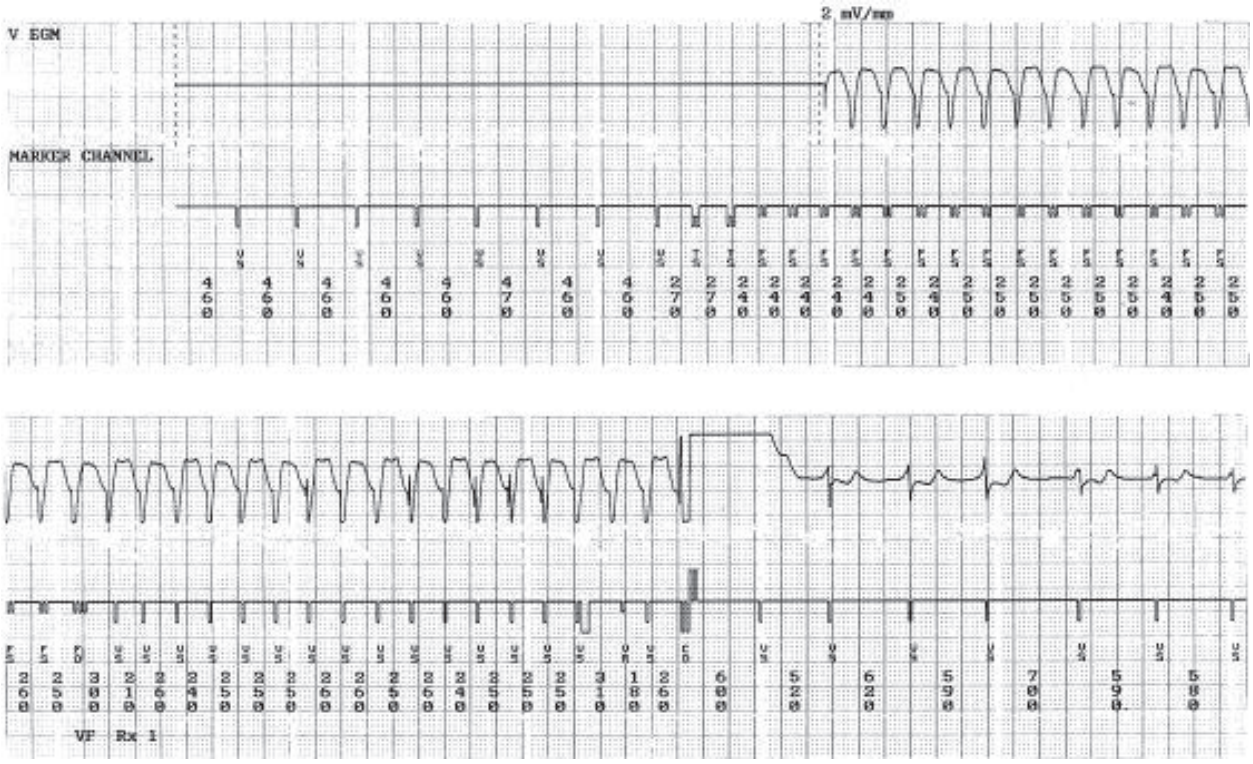

Fig. 1. Stored ventricular electrogram of a patient with hypertrophic cardiomyopathy who received a cardioverter-defibrillator because of syncope and inducible sustained ventricular tachycardia. On physical activity (length of sinus cycle, 460 ms; upper panel), fast ventricular tachycardia occurred with a mean cycle length of 260 ms. The device records ventricular tachycardia, discharges shock (CD), and restores sinus rhythm (lower panel).

Recommendations

The treatment of patients with hypertrophic cardiomyopathy and ventricular tachyarrhythmias depends on the clinical presentation, type of cardiomyopathy (obstructive or nonobstructive), age, and risk level. Patients who have survived cardiac arrest or have sustained ventricular tachycardia without any evident precipitating cause that can be eliminated, have an indication for implantable cardioverter-defibrillator. In some cases with hypertrophic obstructive cardiomyopathy and such ventricular tachyarrhythmias, myectomy with pre- and postoperative electrophysiological testing may be performed, however, it can only be done at highly specialized cardiosurgical centers. The patients with symptoms of impaired consciousness and nonsustained ventricular tachycardia are candidates for programmed ventricular stimulation (Fig. 2). Patients with inducible sustained ventricular tachycardia or fibrillation have an indication for implantable cardioverter-defibrillator, while those with noninducible ventricular tachyarrhythmias may be treated by amiodarone.

Asymptomatic patients with nonsustained ventricular tachycardia should not be prophylactically treated with amiodarone, because their prognosis does not differ from the prognosis of asymptomatic patients without nonsustained ventricular tachycardia. However, asymptomatic patients who have two or more risk factors for sudden cardiac death are also candidates for programmed ventricular stimulation with subsequent pharmacological or nonpharmacological treatment. Genetic testing may be especially important to determine therapy in this group of patients. Early identification of hypertrophic cardiomyopathy and subsequent discontinuation of competitive, high- and medium-grade physical activity are mandatory in competitive athletes or other asymptomatic or mildly symptomatic young patients, because these measures result in a substantial reduction in the risk of sudden cardiac death in these individuals.

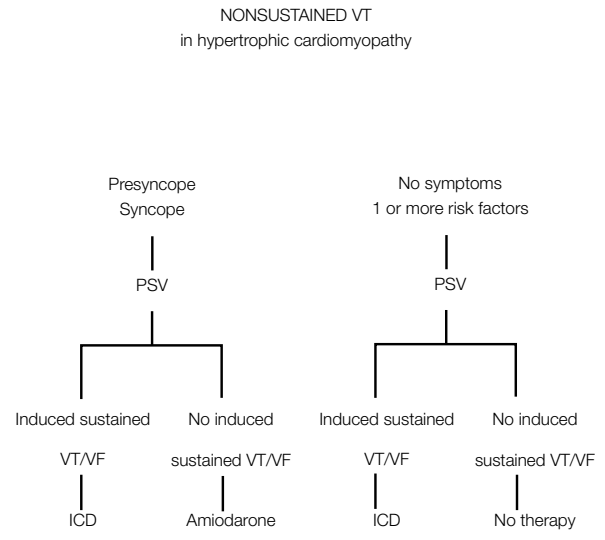

Fig. 2. Our algorithm for the management of patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. PVS = programmed ventricular stimulation; VT = ventricular tachycardia; VF = ventricular fibrillation.

Conclusion

The low prevalence of hypertrophic cardiomyopathy, low incidence of sudden cardiac death among affected patients, and different potential causes of death make it difficult to provide evidence-based criteria for effective prevention of sudden cardiac death in an individual case. In high risk patients, curative or palliative therapy should be directed toward elimination or treatment of the precipitating cause. In these patients with proved ventricular electric vulnerability due to an arrhythmogenic substrate, an implantable cardioverter-defibrillator is indicated. The value of these devices in primary prevention has yet to be established in the future.

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Sažetak

HIPERTROFIČNA KARDIOMIOPATIJA: KAKO LIJEČITI RIZIČNE BOLESNIKE?

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Hipertrofična kardiomiopatija je primarna bolest srčanog mišića, čije kliničko očitovanje varira od benignog, asimptomatskog tijeka do teške srčane dekompenzacije ili srčanog aresta. Stoga je otkrivanje pojedinačnog rizika od nagle srčane smrti prvi korak u liječenju bolesnika s hipertrofičnom kardiomiopatijom. Čimbenici koji najbolje otkrivaju visoko rizične bolesnike su srčani arest ili sinkopa u povijesti, mogućnost izazivanja postojane ventrikulske tahiaritmije, prisutnost nepostojane ventrikulske tahikardije u simptomatskih bolesnika, ishemija povezana s hipotenzijom u djece, te prisutnost mutacija teškog lanca beta-miozina zajedno s obiteljskom poviješću nagle srčane smrti. Liječenje bolesnika s hipertrofičnom kardiomiopatijom ovisi o simptomima i visini rizika. Bolesnici s preživjelim srčanim arestom ili postojanom ventrikulskom tahikardijom, te bolesnici s izazvanom postojanom ventrikulskom tahiaritmijom tijekom programirane stimulacije ventrikla imaju indikaciju za ugradnju kardioverter-defibrilatora. U bolesnika s poremećajem svijesti i nepostojanom ventrikulskom tahikardijom bez mogućnosti izazivanja ventrikulskih tahiaritmija dolazi u obzir liječenje amjodaronom. Asimptomatski bolesnici s nepostojanom ventrikulskom tahikardijom ne trebaju profilaktičnu terapiju lijekovima, jer je njihova prognoza jednaka kao i prognoza asimptomatskih bolesnika bez takve tahikardije. Asimptomatski bolesnici s dva ili tri rizična čimbenika kandidati su za programiranu ventrikulsku stimulaciju i susljedno farmakološko ili nefarmakološko liječenje. S druge strane, asimptomatski bolesnici bez rizičnih čimbenika imaju dobru prognozu i treba ih pustiti da vode normalan život. Međutim, u mladih asimptomatskih bolesnika ili športaša treba ukinuti natjecateljske, teške i srednje teške tjelesne aktivnosti, jer se na taj način znatno smanjuje njihov rizik od nagle srčane smrti.

Ključne riječi: *Kardiomiopatija, hipertrofična, komplikacije; Kardiomiopatija, hipertrofična, terapija; Smrt, nagla, srčana; čimbenici rizika*