Syncope, other risk factors, and the implantable defibrillator for sudden death prevention in hypertrophic cardiomyopathy

Hipertrofik kardiyomiyopatide senkop, diğer faktörler ve ani ölüm prevensiyonunda takılabilen defibrilatör

Delia Cotiga, Frederick Ehlert, Mark V. Sherrid*
Division of Cardiology, St. Luke's/Roosevelt Hospital Center
Columbia University, College of Physicians and Surgeons, New York City, NY, USA
*Current affiliation-New York Presbyterian Hospital, New York City, NY, USA

ABSTRACT

Sudden cardiac death is the most devastating complication of hypertrophic cardiomyopathy. Since HCM may present at young age, and since the risk period for sudden arrhythmic death may be long, decision-making in HCM patients may be difficult, and have lifelong implications. Community based studies show a sudden death mortality of approximately 1%/year. Certain patients can be identified by their clinical characteristics, and through testing, to have higher annual risk, as high as 4-5%/year. Risk factors for sudden cardiac death include: family history of HCM and sudden death, recurrent syncope, ventricular tachycardia, as detected by Holter monitoring or exercise testing, subnormal (<20 mmHg) increase in systolic blood pressure on maximal exercise testing and lastly marked (especially >30 mm) left ventricular hypertrophy. The implantable defibrillator has been shown to avert sudden death in selected HCM patients deemed to be at high risk. *(Anadolu Kardiyol Derg 2006; 6 Suppl 2: 55-60)*

Key words: Hypertrophic cardiomyopathy, syncope, sudden cardiac death, implantable defibrillator, risk assessment

ÖZET

Ani ölüm hipertrofik kardiyomiyopatinin (HKM) en yıkıcı komplikasyonudur. Hipertrofik kardiyomiyopatinin genç yaşta ortaya çıkması ve ani aritmik ölüm riskinin periyodunun uzun olması nedeni ile HKM hastalarda karar vermek çok zor olabilir ve etkileri hayat boyunca sürebilir. Toplum çalışmaları ani ölüm mortalitesini yaklaşık yılda %1 olarak göstermektedir. Yıllık %4-5'e kadar yüksek mortalite riski olan hastalar klinik özellikleri ve testler ile saptanabilirler. Hipertrofik kardiyomiyopatide ani kardiyak ölüm risk faktörleri sırası ile: ani ölüm ve HKM'nin ailesel hikayesi, tekrarlayan senkop, Holter monitorizasyonda veya egzersiz test sırasında saptanan ventriküler taşikardi, maksimal egzersiz sırasında sistolik kan basıncının subnormal (<20 mmHg) artışı ve belirgin (özellikle >30 mm) sol ventrikül hipertrofisi. Takılabilen defibrilatörün, seçilmiş yüksek risk taşıyan HKM li hastalarda ani ölümü önlediği gösterilmiştir. *(Anadolu Kardiyol Derg 2006; 6 Özel Sayı 2: 55-60)*

Anahtar kelimeler: Hipertrofik kardiyomiyopati, senkop, ani kardiyak ölüm, takılabilen defibrilatör, risk değerlendirmesi

Syncope and sudden death are the same - except that in one you wake up… Anonymous
As quoted in Zipes/Jalife
Cardiac Electrophysiology: From Cell to Bedside, 1990

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary disease of cardiac muscle characterized by a thickening of the left ventricular (LV) walls, most often the interventricular septum and the anterior wall. Hypertrophic cardiomyopathy is an inherited cardiac disease that often shows an autosomal dominant mode of inheritance; hypertrophy is otherwise unexplained clinically. Hypertrophy may present at any age. It exhibits pronounced phenotypic variability, including extent and location of hypertrophy, presence and severity of symptoms, and natural history. Early studies suggested that it was relatively uncommon but a malignant disorder, with annual mortality rates of 2-4% in adults and 6% in adolescents and children, the majority of deaths being sudden. Recently it has been found that HCM is in fact a common disorder, with a prevalence estimated from echocardiographic population screening of 0.2%. It is also now clear that HCM is much more benign, with an annual mortality rate in large unselected non-referred series of approximately 1.5%, more than half of these deaths being sudden, and the remainder largely caused by heart failure and stroke (1-6).

Address for Correspondence: Mark V. Sherrid, MD, Professor, Clinical Medicine,
1000 10th Avenue, New York City, NY 10019 USA
E-mail: msherrid@chpnet.org

Presented in part at "Hypertrophic Cardiomyopathy Treatment: Medical, Surgical, Sudden Death Prevention and Newer Modalities" sponsored by St. Luke's/Roosevelt Hospital Center, Columbia University, College of Physicians and Surgeons, New York City. December, 2005

Differential diagnosis of syncope in HCM

In a given patient it can be challenging to determine the specific cause of a syncopal episode. Causes of syncope in hypertrophic cardiomyopathy include: LV outflow obstruction, which may cause a sudden reduction of cardiac output; sudden inappropriate vasodilatation; common vasovagal syncope; bradyarrhythmias and heart block; supraventricular arrhythmias and ventricular arrhythmias.

Syncope in HCM not due to ventricular tachycardia

Left ventricular outflow tract (LVOT) obstruction may cause a sudden reduction of cardiac output with resultant hemodynamic collapse. In vasovagal syncope (for example that caused by gastrointestinal stimulation) an abnormal reflex arc leads to sudden severe vasodilatation, and hypotension, accompanied paradoxically by bradycardia. Bradyarrhythmias: Sinus node dysfunction may be due to myocardial fibrosis or hypertrophy. Similarly, heart block may be caused by myocardial fibrosis, medication side effect, or as a complication of surgical septal myectomy or alcohol septal ablation. Supraventricular arrhythmias may have particularly severe effects when occurring in presence of diastolic dysfunction. They may also worsen the LV obstruction, leading to hypotension. It is always important to consider these causes in any patient, certainly before implantation of implantable cardioverter defibrillator (ICD). If overlooked, the patient will have unnecessary implantation, and syncope may recur with the device in place. Frequently, the cause of syncope may not be clear; in such cases considered physician judgment is needed.

Targeted specific treatments

Relief of LV outflow obstruction can be achieved with medical therapy. Vasodilator medications for hypertension uniformly worsen LV outflow obstruction. Simply stopping vasodilator medications may improve LV outflow obstruction. Then, if the patient is still hypertensive beta-blockade or verapamil or clonidine, or low dose diuretic may relieve hypertension. In patients who fail medical therapy, the gold standard for relieving LVOT obstruction is surgical septal myectomy. Sinus node dysfunction may require specific treatment, like the withdrawal of the offending medication or pacemaker insertion for sick sinus syndrome, or atrioventricular (AV) block. Treatment for supraventricular arrhythmias will include AV nodal blocking agents - beta blockers, calcium channel blockers to control ventricular response and may include antiarrhythmic agents and in some catheter ablation-pulmonary vein isolation may be offered. Anticoagulation with warfarin is generally prescribed for atrial fibrillation or flutter.

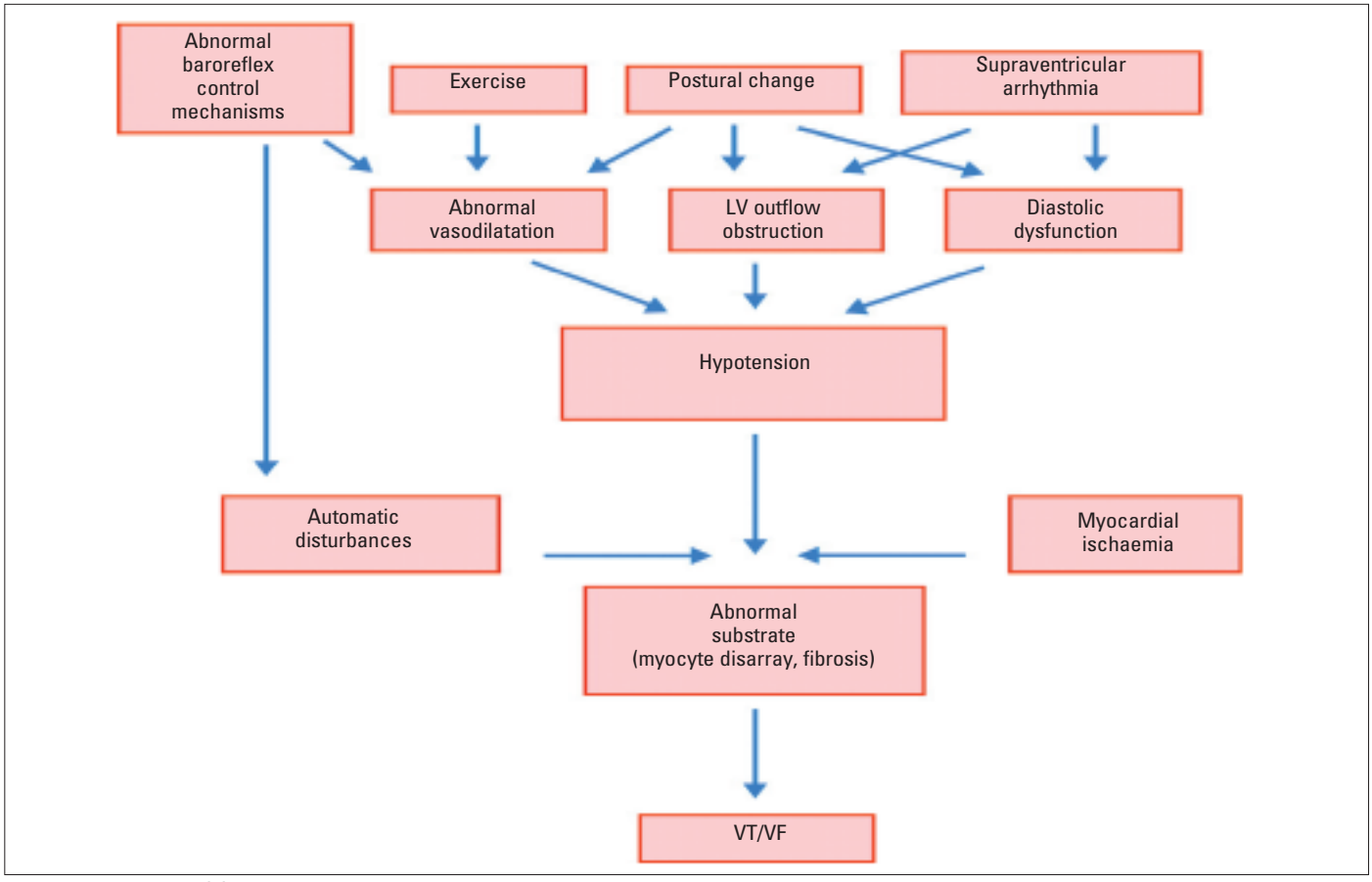

Figure 1. Mechanism(s) of sudden cardiac death in hypertrophic cardiomyopathy: current concepts

LV- left ventricular, VF- ventricular fibrillation, VT- ventricular tachycardia

(Reproduced from Frenneaux MP. Assessing the risk of sudden cardiac death in patient with hypertrophic cardiomyopathy. Heart 2004;90:570-5, Copyright (2004) with permission of BMJ Publishing Group Ltd)

Sudden death from ventricular fibrillation

In contrast, the terminal event in patients who die suddenly from HCM is almost always ventricular fibrillation (VF) . The development of a malignant arrhythmia requires the presence of critically-timed triggers, occurring in an abnormal LV with pro-arrhythmic substrate (most likely myocyte disarray and/or fibrosis). Possible triggers to malignant arrhythmia are myocardial ischemia, hypotension, or paroxysmal atrial fibrillation (Fig. 1). Because ventricular arrhythmia is the cause of syncope of most direct concern, such patients require risk stratification as described below, to assess their risk for sudden cardiac death (SCD) and consideration of an implantable defibrillator if risk is deemed to be high (1-8). In some patients, syncope with unexplained cause is an indication for ICD even in the absence of other risk factors.

Sudden cardiac death has been the most visible and devastating consequence of hypertrophic cardiomyopathy. Its incidence is as high as 4-6% in selected referred populations but only 1% in non-referral centers (4). Community based, more recent series, have shown an overall yearly HCM-related mortality of 1.5%/year, with SCD mortality of 1%/year. Sudden cardiac death from HCM may affect young adults and adolescents who may be asymptomatic; sudden cardiac death occurs in otherwise healthy individuals, and accounts for nearly 35% of all sudden deaths that occur in this group (5,6). Although there is a predilection for SCD in young HCM patients (<30 years), SCD can also occur in middle-age and beyond; therefore, achieving a particular age does not confer immunity to sudden death. Though the average annual risk of sudden death in HCM is 1%/year, certain patients can be identified who have higher annual risk (7-10).

Since HCM patients may present at young age and since the risk period for sudden arrhythmic death may be long and cumulative, decision making about primary prevention may be difficult and have lifelong implications (2,3,7,8).

Ability to predict which patients with HCM will suffer sudden death has long been a clinical goal. The need for risk stratification has become even more focused since the advent of sudden death prevention with the implantable cardioverter defibrillator (ICD) for both primary and secondary prevention (2,7,8). The benefit of ICD implantation in high risk patients is sudden death prevention: appropriate shock rates of 4.5%/year occur for primary prevention and 11%/year for secondary prevention of those who have already experienced prior symptomatic ventricular tachycardia or who have been resuscitated from ventricular fibrillation (2).

Risk factors for SCD

The most important risk factors (8-24) for sudden cardiac death in HCM are:

1. Prior cardiac arrest: ventricular fibrillation or symptomatic ventricular tachycardia (15-16);

2. Unexplained syncope, particularly if recurrent, exertional, or in the young (3,18);

3. Massive LV hypertrophy (LVH) (maximum LV thickness ≥30 mm from echocardiogram or MRI) (8,9);

4. Sudden death due to HCM in the family (particularly in a first degree relative and/or multiple deaths), or SCD in first degree family member the relative dying age ≤ 40 years (3,10);

5. Nonsustained ventricular tachycardia (NVST) on 24 or 48 hour ECG, defined as ≥3 beats of NSVT at ≥120 bpm (especially if frequent, repetitive, or prolonged) (11,12,23);

6. Abnormal blood pressure response with exercise (a frank fall or sustained failure to rise ≥20 mm Hg during exercise or recovery, in patients <40 years of age) (13,14,20,21) .

Secondary prevention

Prior cardiac arrest is considered the most important risk factor for future risk of SCD (15,16). Hypertrophic cardiomyopathy patients who have survived a cardiac arrest and who were treated with conventional medical therapy and/or with surgery had a high seven year mortality rate of approximately 33%. The appropriate ICD discharge rate in HCM patients implanted for secondary prevention because of prior cardiac arrest caused by documented VT or VF was approximately 11% per year (2). In patients who have experienced SCD or sustained ventricular tachycardia, the judgment to implant an ICD for secondary prevention is straightforward because of subsequently high annual rates of recurrent malignant arrhythmia. However, this subset of patients is a small proportion of the at-risk population.

Family history of SCD. A family history of one or more SCDs was also associated with an increased risk of SCD, as described by McKenna et al, sensitivity 42%, specificity 79%, positive predictive accuracy 28%, and negative predictive accuracy 88% (17).

Unexplained or recurrent syncope. Unexplained syncope, particularly when it occurs on exertion, is associated with an increased risk of SCD (3,8). However, the majority of patients who die suddenly do not have a history of syncope. A recent community based study of a population of 225 consecutive patients with HCM, showed that the overall annual SCD rate was 0.8%; a history of syncope was the only independent predictor of SCD in a multivariate model which also included family history of SCD due to HCM, presence of non-sustained VT on Holter monitoring, atrial fibrillation, resting left ventricular outflow tract obstruction > 50 mm Hg, and maximum wall thickness > 25 mm (18). In a larger (368 patients) tertiary referred population followed for a mean of 3.6 years, the annual rate of SCD was approximately 1.5%. On univariate analysis, the relative risks of syncope and family history for SCD during follow up were 2.0 and 1.9, respectively. In a multivariate model the combination had an additive predictive risk of SCD (relative risk (RR) 5.3, 95% confidence interval (CI) 1.9 to 14.9) (3).

Prognostic impact of a family history of SCD should be interpreted in the context of the number of family members affected by HCM. A single SCD in a large family with multiple affected members carries less weight than such a death in a small family.

Severe left ventricular hypertrophy. Two groups recently reported that extreme LVH (maximum wall thickness > 30 mm) was associated with an increased risk of SCD during follow up (8,9). Patients with maximum wall thickness > 30 mm had a higher probability of SCD or ICD discharge than those with maximum wall thickness < 30 mm (RR 2.07, 95% CI 1.00 to 4.25). However, approximately 75% of those who died suddenly had a maximum wall thickness < 30 mm. Also the five year risk of sudden death or ICD discharge was only 5% in patients with extreme LVH as their only risk factor. Also, two recent smaller studies have not confirmed the association between severe LVH and increased SCD risk. In

summary, severe LVH is a risk factor for SCD but its predictive accuracy is low-sensitivity 26%, specificity 88%, positive predictive accuracy 13%, and negative predictive accuracy 95% (9).

The presence of extreme LVH alone in a young individual should prompt consideration of an ICD. However, some patients with HCM who die suddenly have minimal hypertrophy; this is particularly true of those with troponin mutations

Therefore, the presence of mild LVH alone does not necessarily provide reassurance.

Abnormal blood pressure response during exercise is thought secondary to exaggerated fall in systemic vascular resistance (20). In some patients an impaired stroke volume caused by ischemia or obstruction may be the predominant mechanism (14). During stress testing blood pressure must be measured each minute during exercise and at peak exercise, because blood pressure drops can occur abruptly.

About a third of patients with HCM have abnormal blood pressure responses (ABPRs) during maximal treadmill exercise-with a flat blood pressure response, or uncommonly a fall in blood pressure. Abnormal blood pressure responses are more frequent in younger than older patients (20). Interest in this risk factor is highlighted by the observation that approximately half of SCDs occur during or soon after exercise.

In a tertiary population of 161 HCM patients, Sadoul et al showed that ABPR in patients less than 40 years was associated with an increased risk of SCD (12). The positive predictive accuracy of ABPR was low (15%), but the negative predictive accuracy was high (97%). A larger study - 368 patients followed for mean 3.6 years-reported that ABPR was only of prognostic significance in patients in patients < 40 years. An increase in systolic blood pressure < 25 mm Hg (from baseline to end of exercise) or a > 15 mm Hg drop in systolic blood pressure (from peak recorded to end of exercise) were the best predictive values (3). Olivotto et al studied 126 patients from a community based population and found that ABPR had an adverse effect on prognosis as well, but also found a low predictive accuracy, 14% (13). A Japanese study of 309 consecutive patients also reported a flat blood pressure response to be associated with an independently higher SCD risk on multivariate analysis during (mean) 10 year follow up (21).

The abnormal vascular response may also cause hypotension in other settings-for example, spontaneously or during upright posture or in response to arrhythmia such as paroxysmal atrial fibrillation.

Non-sustained ventricular tachycardia. Approximately 15-20% of adult patients with HCM demonstrate NSVT (defined as a run of three or more ventricular beats at a rate of at least 120 bpm) during 48 hour ambulatory ECG recording (6,11,22,23). In adult patients NSVT was an insensitive but relatively specific marker of risk (sensitivity 35%, specificity 82%, PPV 25%, NPV 85%). Elliot et al showed that in a 368 patients age 14-65 years, the overall multivariate risk ratio of NSVT for SCD was 1.9 (3). In contrast to the adult HCM population, NSVT is uncommon, but relatively dangerous, in children and adolescents with HCM. Monserrat et al showed a difference in the risk of sudden death between older and younger patients. The odds ratio of sudden death in patients < 30 years of age with NSVT was 4.35 (95% CI: 1.54 to 12.28; p = 0.006) compared with 2.16 (95% CI: 0.82 to 5.69; p = 0.1) in patients >30 years of age. So, in patients > 30 years there is a trend towards increased risk that does not meet statistical significance (11,22,23). Thus, in older patients non-sustained ventricular tachycardia, has limited weight, when it occurs in isolation. In the young it is a potent risk factor and may alone warrant discussion of ICD implantation.

Left ventricular outflow tract obstruction. Maron et al (19) reported that patients with a resting peak instantaneous outflow tract gradient > 30 mm Hg were at increased risk of total mortality (RR 2.0, 95% CI 1.3 to 3.0), of death from heart failure or stroke (RR 4.4, 95% CI 3.3 to 5.9), and of SCD (RR 2.1, 95% CI 1.1 to 3.7). There was no higher risk with higher gradients. The negative predictive accuracy for SCD was very high (95%) but the positive predictive accuracy was very low (7%). Thus, LVOT obstruction alone is not an indication for ICD implantation (19). Syncope occurring during dehydration, acute anemia, after standing or other LV obstruction-exacerbating situations may be judged as due to obstruction and not ventricular tachycardia.

Decision-making about implantation of an ICD

The problem with risk stratification that each risk factor has relatively low positive predictive value for SCD. Absence of any risk factor offers the patient and clinician some measure of assurance that the risk of SCD is low. However, the risk of dying suddenly in the absence of risk factors is not zero. The presence of one risk factor is very common in HCM (45%) while sudden death is uncommon. Overall, no risk factors are found in 55% of patients, 1 risk factor is found in 33%, 2 risk factors are found in 10%, and 3 are found in 2% (8). At present, most clinicians would agree that the presence of 2 risk factors would be enough to consider implantation of an ICD (7,8,24), and would individually tailor therapy depending on age and patient circumstances. For example, the low incidence of SCD after myectomy would make the necessity of ICD implantation debatable for patients undergoing surgery. Implantation of an ICD in patients with one risk factor is open to considered physician judgment and patient choice (7,8,24) (Fig. 2). Regardless, there should be discussion with the patient of the benefits and risks of the ICD, and the pros and cons of implantation, and the reason for the physician's considered recommendation

Not proven clinical utility

Electrophysiological testing (EPS) with programmed ventricular stimulation has been largely abandoned as a routine strategy in HCM because of the non-specificity of provoked ventricular tachyarrhythmias. Electrophysiological testing has a poor predictive value in patients with HCM and its role in identifying patients with at risk for sudden cardiac death is limited. The largest published series by Fananapazir et al. (25) examined a strategy of utilizing clinical, Holter, hemodynamic and electrophysiological findings for risk stratification in patients with HCM. They showed that patients with inducible ventricular arrhythmias were at increased risk of sudden cardiac death. However, the patients studied were those already thought clinically to be at high risk, and the positive predictive accuracy of induced sustained ventricular arrhythmia of any type was less than 20%. Thus, at present, existing data does not support the routine use of EPS for risk stratification (25,26). The presence of a myocardial bridge of

epicardial coronary arteries at coronary angiography was associated with an increased risk of death in children (27) but this observation has been questioned by others.

To date genotype analysis has not been yet fruitful in predicting high risk. Initially, families with thin myofilament disease, troponin and alpha tropomyosin mutations were thought be at higher risk. These mutations are uncommon, occurring in less than 5% of patients. However, recent data in consecutive referred patients indicates that definite prognostic characteristics have not yet been defined (28-31). Because HCM may be caused by any of many mutations on each individual gene, a myriad number of disease-causing mutations have been discovered. Thus, there is yet limited prognostic information collected on individual mutations (though this work is ongoing, see www.cardiogenomics.org). In addition, there are modifier genes that may accentuate or attenuate the individual prognostic effect of particular mutations (32-33).

Risks of ICD implantation and ICD management in HCM

Risks of ICD implantation may be communicated to patients as, 4 "I's", implantation risk, infection, inappropriate shock and never using the device - insurance risk. Implantation risks include perforation of the great vessels with bleeding, lung and cardiac chambers and the infrequent need for surgery to correct perforation. An ICD implantation extends a trail of risk into the patient's future as they require generator replacements roughly every 5 or 7 years and may require lead removal because of fracture or infection. Lead infection is particularly problematic because it requires removal of infected leads that may be fixed in situ at the superior vena cava, right ventricle, or right atrium. Removal of leads may require specialized laser technology, and has a > 1% potential for major complications, including death. Inappropriate shock occurs frequently in young HCM patients if they overexert or develop atrial fibrillation; most young patients receiving an ICD should be maintained on beta-blockade.

Young HCM patients should understand that having an ICD is like buying an insurance policy. Though, there is a 4%/year chance of appropriate shock and prevention of cardiac death, it is also possible that malignant arrhythmia will never occur in their case. They may never need device intervention. After discussing the risks and benefits of ICD implantation, most patients will decide to have implantation done. Families are encountered who have suffered multiple sudden deaths (10). In this circumstance it would seem prudent to consider ICD implantation for all first degree relatives who are diagnosed with HCM.

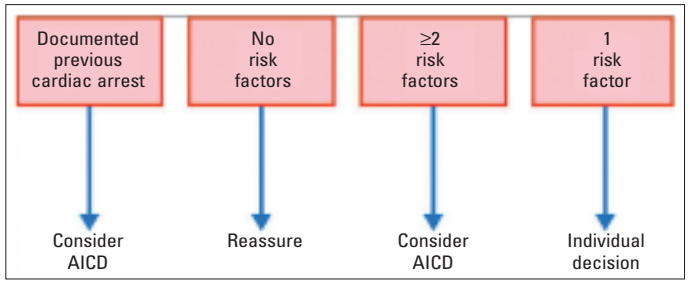

Figure 2. Targeting prevention of sudden cardiac death in hypertrophic cardiomyopathy

AICD-automatic implantable cardioverter-defibrillator

(Reproduced from Frenneaux MP. Assessing the risk of sudden cardiac death in a patient with hypertrophic cardiomyopathy. Heart 2004;90:570-5, Copyright (2004) with permission of BMJ Publishing Group Ltd)

Recommendation to avoid competition

In Teare's pathologic case reports that formed the modern description of HCM the association of vigorous activity and sudden death in the young was apparent. Athletes that die suddenly on the playing field most often are found to have structural heart disease. At autopsy HCM is the most common structural heart disease found (34). Because of these and other clinical observations, it is recommended that patients with HCM should avoid competition and extremes of exertion (35). The elderly and severely symptomatic limit themselves. However, in the young, or in asymptomatic this recommendation to avoid competition may be unsettling. Sport occupies a central role in many patient's lifestyles. In some, athletic success has been a long-term primary goal (36). The guidelines allow recreational sports activity to maintain muscular tone. There may be ambiguity in the intensity of activity allowed. We clarify by pointing out that in competition athletes will often push beyond limiting symptoms to win and that this is to be specifically avoided. We recommend that patients not lift more than 40 lbs. We also recommend avoiding activities where syncope would have disastrous effect such as scuba diving or surfing.

Conclusions

The most important challenge in clinical HCM management is more precise identification of those HCM patients who should be targeted for primary prevention. Prudent management decisions concerning ICD implantation should be based on the known risk factors and in many instances are made by integrating all relevant clinical data with physician judgment and in accord with the risk level acceptable to patient and family.

References

1. Frenneaux MP. Assessing the risk of sudden cardiac death in a patient with hypertrophic cardiomyopathy. Heart 2004;90:570-5.
2. Maron BJ, Shen WK, Link MS, Almquist AK, Daubert JP, Bardy GH, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 2000;342:365-73.
3. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212-8.
4. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA 1999;281:650-5.
5. McKenna WJ, Monserrat Iglesias L. Sudden death (V). Identification and treatment of patients with hypertrophic cardiomyopathy at risk of sudden death. Rev Esp Cardiol 2000;53:123-30.
6. Thaman R, Firoozi S, Hamid MS, McKenna WJ. Hypertrophic cardiomyopathy: management issues in the new millennium. Curr Cardiol Rep 2002;4:226-32.
7. Maron BJ, Estes NA, 3rd, Maron MS, Almquist AK, Link MS, Udelson JE. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. Circulation 2003;107:2872-5.

8. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet 2001;357:420-4.
9. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000;342:1778-85.
10. Maron BJ, Lipson LC, Roberts WC, Savage DD, Epstein SE. "Malignant" hypertrophic cardiomyopathy: identification of a subgroup of families with unusually frequent premature death. Am J Cardiol 1978;41:1133-40.
11. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol 2003;42:873-9.
12. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation 1997;96:2987-91.
13. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. J Am Coll Cardiol 1999;33:2044-51.
14. Ciampi Q, Betocchi S, Lombardi R, Manganelli F, Storto G, Losi MA, et al. Hemodynamic determinants of exercise-induced abnormal blood pressure response in hypertrophic cardiomyopathy. J Am Coll Cardiol 2002;40:278-84.
15. Cecchi F, Maron BJ, Epstein SE. Long-term outcome of patients with hypertrophic cardiomyopathy successfully resuscitated after cardiac arrest. J Am Coll Cardiol 1989;13:1283-8.
16. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 1999;33:1596-601.
17. McKenna WJ, Behr ER. Hypertrophic cardiomyopathy: management, risk stratification, and prevention of sudden death. Heart 2002;87:169-76.
18. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. J Am Coll Cardiol 2003;41:987-93.
19. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303.
20. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. Circulation 1990;82:1995-2002.
21. Maki S, Ikeda H, Muro A, Yoshida N, Shibata A, Koga Y, et al. Predictors of sudden cardiac death in hypertrophic cardiomyopathy. Am J Cardiol 1998;82:774-8.
22. McKenna WJ, Firoozi S, Sharma S. Arrhythmias and sudden death in hypertrophic cardiomyopathy. Card Electrophysiol Rev 2002;6:26-31.
23. Cecchi F, Olivotto I, Montereggi A, Squillatini G, Dolara A, Maron BJ. Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: assessment in an unselected non-referral based patient population. Heart 1998;79:331-6.
24. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687-713.
25. Fananapazir L, Chang AC, Epstein SE, McAreavey D. Prognostic determinants in hypertrophic cardiomyopathy. Prospective evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic, and electrophysiological findings. Circulation 1992;86:730-40.
26. Kuck KH, Kunze KP, Schluter M, Nienaber CA, Costard A. Programmed electrical stimulation in hypertrophic cardiomyopathy. Results in patients with and without cardiac arrest or syncope. Eur Heart J 1988;9:177-85.
27. Yetman AT, McCrindle BW, MacDonald C, Freedom RM, Gow R. Myocardial bridging in children with hypertrophic cardiomyopathy--a risk factor for sudden death. N Engl J Med 1998;339:1201-9.
28. Van Driest SL, Ellsworth EG, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy. Circulation 2003;108:445-51.
29. Mogensen J, Murphy RT, Kubo T, Bahl A, Moon JC, Klausen IC, et al. Frequency and clinical expression of cardiac troponin I mutations in 748 consecutive families with hypertrophic cardiomyopathy. J Am Coll Cardiol 2004;44:2315-25.
30. Ackerman MJ, Van Driest SL, Ommen SR, Will ML, Nishimura RA, Tajik AJ, et al. Prevalence and age-dependence of malignant mutations in the beta-myosin heavy chain and troponin T genes in hypertrophic cardiomyopathy: a comprehensive outpatient perspective. J Am Coll Cardiol 2002;39:2042-8.
31. Van Driest SL, Ackerman MJ, Ommen SR, Shakur R, Will ML, Nishimura RA, et al. Prevalence and severity of "benign" mutations in the beta-myosin heavy chain, cardiac troponin T, and alpha-tropomyosin genes in hypertrophic cardiomyopathy. Circulation 2002;106:3085-90.
32. Marian AJ, Yu QT, Workman R, Greve G, Roberts R. Angiotensin-converting enzyme polymorphism in hypertrophic cardiomyopathy and sudden cardiac death. Lancet 1993;342:1085-6.
33. Lechin M, Quinones MA, Omran A, Hill R, Yu QT, Rakowski H, et al. Angiotensin-I converting enzyme genotypes and left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. Circulation 1995;92:1808-12.
34. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA 1996;276:199-204.
35. Maron BJ, Isner JM, McKenna WJ. 26th Bethesda conference: recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities. Task Force 3: hypertrophic cardiomyopathy, myocarditis and other myopericardial diseases and mitral valve prolapse. Med Sci Sports Exerc 1994;26:S261-7.
36. Maron BJ, Mitten MJ, Quandt EF, Zipes DP. Competitive athletes with cardiovascular disease--the case of Nicholas Knapp. N Engl J Med 1998;339:1632-5.