Ventricular arrhythmias complicating hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is the most common genetic cardiovascular disorder and the leading cause of sudden cardiac death in the young. This article reviews the ventricular arrhythmias associated with hypertrophic cardiomyopathy, the difficulties in risk stratification, and current and future therapeutic strategies.

Hypertrophic cardiomyopathy is an autosomal dominant genetic disorder. The underlying mutations causing hypertrophic cardiomyopathy primarily affect myofilament 'contractile machinery' proteins of cardiac myocytes (Marian and Roberts, 2001). It is defined as a condition of unexplained left ventricular hypertrophy, in the absence of dilatation of cardiac chambers or any other condition that could cause hypertrophy (Gersh et al, 2011). It is the commonest cause of sudden cardiac death in those aged <35 years (Gersh et al, 2011), and its prevalence of 1 in 500 in the general population also makes it the most common genetic cardiovascular disease (Maron et al, 1995). Sudden cardiac death caused by ventricular arrhythmias is the most common cause of mortality in this condition especially (although not exclusively) in late teenage years and early adulthood, whereas stroke associated with atrial fibrillation and heart failure also contributes to mortality and morbidity in the latter years of life (Maron et al, 2000a, b).

The myofilament proteins most commonly involved in mutations include myosin heavy chain β (MYH7), cardiac myosin binding protein C (MYBPC3), the cardiac troponins (T, C, I) and tropomyosin. Alterations in genes MYH7 and MYBPC3 account for about 75% of hypertrophic cardiomyopathy cases with a genetic diagnosis. Over the last two decades, mutations causing hypertrophic cardiomyopathy have been identified in 23 different sarcomeric or sarcomere-associated proteins (>900 individual mutations) but mutations have not yet been identified in as many as 25% of hypertrophic cardiomyopathy cases (Ho, 2010; Frey et al, 2012). Hypertrophic cardiomyopathy is a complex genetic disorder to study. It has incomplete penetrance and large variability in the degree of disease severity (even for the same mutation) (Bos et al, 2009). This has lead to speculation that environmental influences play a considerable role in the onset and progression of the disease (Ashrafian et al, 2011).

Dr David C Hutchings *is NIHR Academic Clinical Fellow and Specialist Registrar in Cardiology, Department of Cardiac Physiology, University of Manchester, Manchester M13 9NT,* **Dr Rajiv Sankaranarayanan** *is Cardiology Speciality Registrar in Electrophysiology and British Heart Foundation Clinical Research Fellow, University of Manchester, Manchester and* **Dr Luigi Venetucci** *is British Heart Foundation Intermediate Clinical Fellow, University of Manchester, Manchester*

Correspondence to: Dr DC Hutchings (dhutchings@doctors.org.uk)

Epidemiology of ventricular arrhythmias

Ventricular ectopics occur in the majority of hypertrophic cardiomyopathy patients (80–90%, with up to 24% having >30 ventricular ectopics/hour) whereas ventricular couplets have been found in 30–40% of patients, and non-sustained ventricular tachycardia in about a quarter in studies using Holter electrocardiogram monitoring (reviewed by Adabag and Maron (2007)). Of these, only non-sustained ventricular tachycardia is a risk marker for sudden cardiac death (Adabag and Maron, 2007). Similarly, absence of non-sustained ventricular tachycardia on Holter monitoring has a high negative predictive value (Adabag et al, 2005).

Studies have also found that non-sustained ventricular tachycardia episodes were relatively infrequent (1–3 runs over 24 hours) and did not lead to clinical symptoms (Adabag and Maron, 2007). Non-sustained ventricular tachycardia prevalence varies according to age, being low in children and adolescents but can affect up to 25% of hypertrophic cardiomyopathy patients aged >40 years (Monserrat et al, 2003). Extreme left ventricular thickness (>30 mm) predicts increased incidence of non-sustained ventricular tachycardia (Adabag et al, 2005).

Internal cardioverter-defibrillator interrogation data give more prolonged monitoring than Holter data and also provide crucial insights into the mechanism of initiation of sustained ventricular arrhythmias in hypertrophic cardiomyopathy patients. A recent internal cardioverter-defibrillator study in hypertrophic cardiomyopathy patients by O'Mahony et al (2012b) reported that the underlying rhythm triggering internal cardioverter-defibrillator therapy was monomorphic ventricular tachycardia in 86% of cases, ventricular fibrillation or ventricular flutter in 9% and polymorphic ventricular tachycardia in 5%. In the majority of cases (72%), the arrhythmia was secondary to a preceding ventricular ectopic; it was spontaneous in 26% and pause-dependent in 2%. In patients with multiple arrhythmias within 24 hours, a majority (69%) had arrhythmias initiated by one or more mechanisms, in keeping with the multitude

of different underlying substrates. None of the episodes of ventricular fibrillation were potentiated by degeneration of preceding ventricular tachycardia or atrial fibrillation in this study.

Molecular pathogenesis

The high arrhythmic risk in hypertrophic cardiomyopathy is the result of the complex interplay of substrate abnormalities (ventricular hypertrophy, fibrosis, myocyte disarray) (Varnava et al, 2000), myocyte calcium hypersensitivity as well as mis-handling, and cardiomyocyte energy inefficiency, acting in concert with triggering factors such as physical exertion, autonomic dysfunction and ischaemia, as described below and in *Figure 1*. Although exact triggering mechanisms for the arrhythmogenesis in hypertrophic cardiomyopathy are not precisely known, there are several known substrates which act synergistically to create a pro-arrhythmic state in hypertrophic cardiomyopathy that presents a considerable therapeutic challenge. These substrates can be classified as intracellular or structural in their nature.

Anatomical and structural substrate abnormalities

At the structural level, the widespread fibrosis seen in hypertrophic cardiomyopathy is strongly implicated as a substrate for arrhythmias. Arrhythmia origin (as assessed by electrocardiogram criteria) correlates with regions of fibrosis (demonstrated as late gadolinium enhancement) on cardiac magnetic resonance imaging (van Rijsingen et al, 2011). It is typically patchy, often occurring in regions of increased wall thickness, but may occur in very early stages of disease when pathological hypertrophy is not apparent (O'Hanlon et al, 2010; Teekakirikul et al, 2010). It arises when myocytes die (from a combination of energy depletion, microvascular ischaemia and hypertrophy) and are replaced by fibroblasts (Frey et al, 2012).

In contrast, the myocyte disarray of hypertrophic cardiomyopathy (a characteristic histological feature) has been suggested to exist before birth, whereas fibrosis manifests subsequently (Dimitrow et al, 2010). Myocyte disarray (Varnava et al, 2001) also acts in concert with fibrosis to potentiate arrhythmogenesis. By disrupting cell to cell alignment, it impairs cardiac conduction leading to conduction delay and unidirectional block which predisposes to re-entry arrhythmias such as monomorphic ventricular tachycardia (Elliott and Spirito, 2008; Michels, 2012). Such effects are further exacerbated by microvascular dysfunction seen in hypertrophic cardiomyopathy, as a result of arteriole luminal wall thickening, which can lead to myocardial ischaemia (Basso et al, 2000). Myocardial perfusion studies and pathological examination have implicated bouts of asymptomatic ischaemia as further exacerbating the electrical instability of the chaotic myocyte architecture in hypertrophic cardiomyopathy and leading to arrhythmias (O'Gara et al, 1987; Basso et al, 2000). Proposed mechanisms include small vessel disease or systolic compression of epicardial coronary arteries caused by hypertrophied myocardium (Basso et al, 2000).

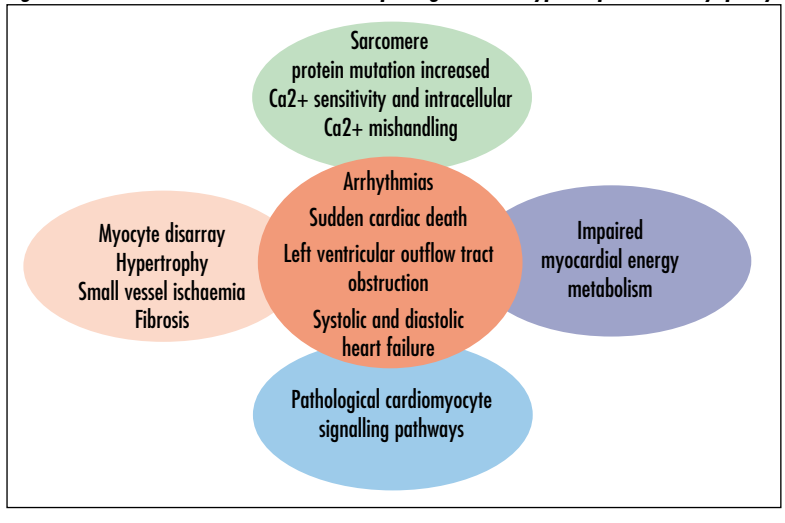
Alcohol septal ablation, used to alleviate left ventricular outflow tract obstruction in hypertrophic cardiomyopathy patients, can actually potentiate sustained ventricular arrhythmias in about 3–10% of patients and even cause sudden cardiac death because of the resulting myocardial scar formation (Ten Cate et al, 2010).

Intracellular substrate abnormalities

The activity of cardiac myofilaments is controlled by cytosolic calcium levels and contraction is initiated by a transient increase in cytosolic calcium concentration (systolic Ca transient). Knollman et al (2003) studied cardiomyocytes from transgenic mice which expressed mutations of troponin T and demonstrated increased myofilament calcium sensitivity and increased susceptibility to stress-induced ventricular tachycardia. Increase in myofilament Ca2+ sensitivity, one of the hallmark features of hypertrophic cardiomyopathy, correlates closely with ventricular arrhythmia burden (Baudenbacher et al, 2008). The increased myofilament Ca sensitivity leads to increased cytosolic Ca binding affinity and this, through complex mechanisms, leads to delayed afterdepolarizations, triggered activity and ventricular arrhythmias (Schober et al, 2012). Increased cytosolic Ca binding can also cause variations in action potential duration (with reduction in effective refractory period), and dispersion of cardiac conduction velocities, which can cause ventricular arrhythmias even in the absence of other substrates for arrhythmia such as fibrosis (Watkins et al, 1995).

Myocyte hypertrophy leads to electrical remodelling, largely through a down-regulation of K+ channels (Yang et al, 2012), resulting in pro-arryhythmic prolongation and heterogeneity or dispersion of cardiac

Figure 1. Factors involved in the molecular pathogenesis of hypertrophic cardiomyopathy.



repolarization (Mayet et al, 1996; McIntyre and Fry, 1997), ultimately increasing the propensity to develop triggered arrhythmias.

Sarcomere mutations can also lead to inefficient utilization of energy and increased energy cost of contraction (Frey et al, 2012). Cardiac magnetic resonance studies have demonstrated that this results in a ~30% reduction in phosphocreatine:ATP ratio in hypertrophic cardiomyopathy cardiac myocytes (Crilley et al, 2003), a marker of cell energy status. Under conditions of increased demand such as exercise, this can cause severe energy depletion and profound alteration of cell electrical properties. This could explain the pathogenesis of exercise-induced arrhythmias (Frey et al, 2012). The impaired myocardial energetics in combination with the microvascular dysfunction causes the increased rate of myocyte death and replacement with fibroblasts that is characteristic of hypertrophic cardiomyopathy.

Clinical features

Hypertrophic cardiomyopathy is the commonest cause of sudden cardiac death in the young (Gersh et al, 2011). While the incidence of sudden cardiac death is relatively infrequent in hypertrophic cardiomyopathy with annual event rates quoted to be ≤1%, it is still the most catastrophic complication of the disease (Maron et al, 2000a; Adabag and Maron, 2007). Sudden cardiac death can be the first manifestation of hypertrophic cardiomyopathy and can affect up to two-thirds of hypertrophic cardiomyopathy patients, the cause usually being ventricular tachycardia (Maron et al, 2000b).

Table 1. Risk markers for sudden cardiac death in hypertrophic cardiomyopathy and recommendations

Risk markers	Class (level of evidence)*
Previous cardiac arrest, ventricular fibrillation or haemodynamically significant ventricular tachycardia	1(B)
Unexplained syncope	1(B)
Positive family history of sudden cardiac death or appropriate internal cardioverter-defibrillator therapy	1(B)
Severe left ventricular hypertrophy on echo (>30 mmHg)	1(B)
Abnormal blood pressure response on exercise	2a(B)
Non-sustained ventricular tachycardia	1(B)
Cardiac magnetic resonance imaging with late gadolinium enhancement	2b(C)
Double and compound mutations	2b(C)
Marked left ventricular outflow tract obstruction	2b(C)
Invasive electrophysiological testing	3(C)

From American College of Cardiology Federation/American Heart Association guidelines (Gersh et al, 2011). *Class measure describes the size of treatment effect: class I – procedure should be performed/administered; class IIa – it is reasonable to perform procedure/administer treatment; class IIb – procedure/treatment may be considered; class III – no benefit or harmful. Level of evidence estimates the certainty of the treatment effect: level A – multiple populations evaluated; level B – limited populations evaluated; level C – very limited populations evaluated.

Ventricular ectopics, couplets or non-sustained ventricular tachycardia can be associated with palpitations, pre-syncope or syncope, although they frequently do not lead to symptoms in hypertrophic cardiomyopathy patients (Adabag and Maron, 2007). Both ventricular arrhythmias and sudden cardiac death can be precipitated by exercise in hypertrophic cardiomyopathy patients (Gimeno et al, 2009). While ventricular arrhythmias during exercise are rare, they can lead to sudden cardiac death (Gimeno et al, 2009).

A recent study that explored the relationship between circadian rhythm and ventricular arrhythmias seen on internal cardioverter-defibrillator interrogation found a peak incidence at midday, followed by a second peak at late afternoon (O'Mahony et al, 2012b). This peaked on a weekly basis on Sundays and on a monthly basis in May. These times are likely to be associated with increased metabolic activity and consequent autonomic imbalance which potentiates arrhythmias. This circadian variation is in contrast to ventricular arrhythmias in ischaemic cardiomyopathy which tend to occur mostly during morning hours and associated with peaking of factors potentiating ischaemia (Lampert et al, 1994). The younger age of hypertrophic cardiomyopathy patients likely results in differences in lifestyles and activity levels, further contributing to this circadian variation (O'Mahony et al, 2012b). Another interesting explanation is that sarcomeric mutations causing hypertrophic cardiomyopathy can also blunt normal cardiomyocyte circadian regulation (O'Mahony et al, 2012b). Younger patients developed ventricular arrhythmias with faster ventricular rates, potentially explaining why younger patients also have a higher incidence of mortality caused by ventricular arrhythmias (O'Mahony et al, 2012b).

Risk predictors and investigations

Owing to the mortality risk in hypertrophic cardiomyopathy, risk stratification for sudden cardiac death is mandatory according to the American College of Cardiology and European Society of Cardiology guidelines (Maron et al, 2003; Gersh et al, 2011). These recommend six major risk factors (*Table 1*) as risk predictors for sudden cardiac death in hypertrophic cardiomyopathy (Gersh et al, 2011):

1. Previous cardiac arrest, ventricular fibrillation or haemodynamically significant ventricular tachycardia
2. Unexplained syncope
3. Family history of sudden cardiac death (presumably caused by hypertrophic cardiomyopathy) or internal cardioverter-defibrillator therapy in one or more first degree relatives
4. Abnormal blood pressure response to exercise (defined as lack of increase of blood pressure by at least 20 mmHg or a drop by similar value during exercise)
5. Extreme left ventricular hypertrophy (left ventricular wall thickness ≥30 mm)
6. Non-sustained ventricular tachycardia.

Of these, patients with previous cardiac arrest, ventricular fibrillation or haemodynamically significant ventricular tachycardia have the highest risk of sudden cardiac death with an annual arrhythmia recurrence rate of 10%. The other listed risk factors have a low positive predictive value (10–20%) and the negative predictive value is high but not absolute (80–95%) (Gersh et al, 2011).

A systematic review showed that each of these risk factors strongly predicted sudden cardiac death risk (Christiaans et al, 2010). Other studies have varied in their interpretation of the 'primary prevention' as risk markers of sudden cardiac death in hypertrophic cardiomyopathy patients. Cardiac syncope as a symptom can be difficult to elicit and requires detailed history-taking. Elliott et al (2000) reported from their referral centre registry data of 368 hypertrophic cardiomyopathy patients that syncope and family history of sudden death reach prognostic significance only when considered together as risk markers. Elliott et al (2000) also found that only blood pressure response to exercise (especially if age <40 years) and severe left ventricular hypertrophy significantly predicted increased sudden cardiac death risk on univariate analysis. Surprisingly, however, most sudden cardiac death cases in this study occurred in patients with mild or moderate hypertrophy, illustrating the low negative predictive value of this marker. Abnormal blood pressure response as a risk marker has been corroborated by other studies (Olivotto et al, 1999). However, this marker has the weakest recommendation of the major risk markers in the guidelines (Gersh et al, 2011). The strength of non-sustained ventricular tachycardia as a risk marker is particularly robust in patients less than 30 years old but this risk prediction is not uniform in all studies (Monserrat et al, 2003; Gersh et al, 2011).

Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy has been a considerable challenge for more than a decade and remains far from perfect, especially because of the low positive predictive value in the modern treatment era of internal cardioverter-defibrillators. Event rates are only 5% even in the presence of more than three risk factors (Maron et al, 2007). However, life-saving internal cardioverter-defibrillator therapy could first occur even as late as 10 years after implant and thus the duration of follow up is also particularly relevant while analysing internal cardioverter-defibrillator efficacy in hypertrophic cardiomyopathy (Maron et al, 2000b).

Evidence that appropriate internal cardioverter-defibrillator therapy in hypertrophic cardiomyopathy patients is exceeded by inappropriate shocks and complications is another indication of the inadequacy of risk stratification measures in hypertrophic cardiomyopathy (Maron et al, 2007; Lin et al, 2009). O'Mahony et al (2012a) looked at the outcome of internal cardioverter-defibrillator implant in 334 consecutive hypertrophic cardiomyopathy patients managed at the Heart Hospital, London and reported appropriate shocks in 8% of patients (2.3%/year) compared to inappropriate shocks in 16% of patients (4.6%/year) in addition to 18% of patients who experienced internal cardioverter-defibrillator-implant related complications (two deaths). Secondary prevention internal cardioverter-defibrillator implants led to a better outcome than primary prevention internal cardioverter-defibrillators implanted in this study. The rate of appropriate internal cardioverter-defibrillator discharge when used for secondary prevention is 10%/year compared to 4%/year when used for primary prevention, again reflecting the low positive predictive value of existing risk predictors (Spirito et al, 2009). Worryingly, the negative predictive value of the lack of risk factors has also been questioned, because of the occurrence of sudden cardiac death in hypertrophic cardiomyopathy patients without any conventional high-risk features (Maron et al, 2008).

In view of the limitations of traditional risk markers for sudden cardiac death in hypertrophic cardiomyopathy, there have been continuing attempts to identify new risk predictors. Patients who inherit multiple sarcomere mutations have an increased risk of sudden death even without other traditional risk factors (Maron et al, 2012). Some sarcomeric mutations such as those affecting troponin T, which can account for up to 15% of cases of familial hypertrophic cardiomyopathy, confer a disproportionately higher risk of sudden cardiac death despite a lesser degree of hypertrophy (Watkins et al, 1995). However, in view of the diversity of mutations causing hypertrophic cardiomyopathy as well as the low specificity of different mutations for sudden cardiac death, the role of genetic testing in risk stratification for sudden cardiac death is far from certain and thus is not strongly indicated in terms of risk stratification for sudden cardiac death (Gersh et al, 2011).

While the 12-lead electrocardiogram is abnormal in up to 95% of hypertrophic cardiomyopathy patients and electrocardiogram abnormalities may even precede echocardiographic evidence of wall thickening, this test is a poor investigational modality to predict risk of sudden cardiac death itself (Maron, 2002; Sherrid et al, 2009). Although other markers such as T wave alternans have been useful in assessing for post-ischaemic ventricular arrhythmias, they have minimal use in risk stratifying hypertrophic cardiomyopathy patients (Fuchs and Torjman, 2009). Ambulatory (Holter) monitoring has an important role especially in patients younger than 30 years of age, in whom identification of non-sustained ventricular tachycardia independently portends risk of sudden cardiac death (Monserrat et al, 2003). Ambulatory monitoring is therefore recommended in both symptomatic as well as asymptomatic patients for risk stratification and should be repeated annually (Gersh et al, 2011).

Exercise-induced non-sustained ventricular tachycardia or ventricular fibrillation increase the risk of subse-

quent sudden cardiac death or haemodynamically significant ventricular tachycardia about four-fold (Gimeno et al, 2009). Treadmill testing with monitoring of electrocardiogram and blood pressure is reasonable for sudden cardiac death risk stratification in patients with hypertrophic cardiomyopathy (Gersh et al, 2011). It has also been suggested that left ventricular outflow tract obstruction should be included in the risk stratification process (Christiaans et al, 2010) but this can be dynamic and variable in hypertrophic cardiomyopathy patients and lacks sufficient specificity or sensitivity for sudden cardiac death prediction. Invasive electrophysiological studies using programmed stimulation have been largely abandoned as the most common induced arrhythmia, polymorphic ventricular tachycardia, offers minimal prognostic information for risk stratification (Behr et al, 2002).

A raised plasma level of metalloproteinase-3 is also an independent marker of ventricular arrhythmia especially in adolescent hypertrophic cardiomyopathy patients (Zachariah et al, 2012). Assessing the extent of myocardial fibrosis or scarring using late gadolinium enhancement on contrast-enhanced cardiac magnetic resonance is a useful tool to independently predict risk of ventricular arrhythmias (Appelbaum et al, 2012), cardiac death and also possibly sudden death or aborted sudden death (Green et al, 2012). There have therefore been calls to include this investigation as one of the risk predictors for sudden cardiac death in hypertrophic cardiomyopathy, and American guidelines recommend cardiac magnetic resonance when echocardiography is not conclusive for diagnosis, but it is not currently recommended for risk stratification (Maron et al, 2008; Gersh et al, 2011).

Table 2. Indications for internal cardioverter-defibrillator implant and strength of evidence

Risk factor	Internal cardioverter-defibrillator implant	Class (level of evidence)*
Previous cardiac arrest	Recommended	1(B)
One or more recent unexplained syncopal episodes	Reasonable	2a(C)
Sudden death presumably caused by hypertrophic cardiomyopathy in one or more first degree relative(s)	Reasonable	2a(B)
Severe left ventricular hypertrophy (≥30 mm)	Reasonable	2a(B)
Non-sustained ventricular tachycardia (especially if age <30 years) in presence of other risk factors	Reasonable	2a(B)
Abnormal blood pressure response to exercise in presence of other risk factors	Can be useful	2a(B)
High risk children (unexplained syncope, severe left ventricular hypertrophy, family history of sudden cardiac death)	Reasonable	2a(B)
Isolated bursts of non-sustained ventricular tachycardia	Usefulness uncertain	2b(C)
Abnormal blood pressure response on exercise in absence of other risk factors	Usefulness uncertain	2b(C)
No risk factors	Harmful	3(C)
Internal cardioverter-defibrillator implant as strategy to enable participation in competitive sport	Harmful	3(C)
Positive hypertrophic cardiomyopathy genotype but no clinical manifestations	Harmful	3(C)

From Gersh et al (2011). *Class measure describes the size of treatment effect: class I – procedure should be performed/administered; class IIa – it is reasonable to perform procedure/administer treatment; class IIb – procedure/treatment may be considered; class III – no benefit or harmful. Level of evidence estimates the certainty of the treatment effect: level A – multiple populations evaluated; level B – limited populations evaluated; level C – very limited populations evaluated.

Treatment

Before widespread availability of internal cardioverter-defibrillators, a variety of pharmacological agents (verapamil, beta-blockers, disopyramide, amiodarone and procainamide) were tried to prevent sudden cardiac death in hypertrophic cardiomyopathy patients. While older studies suggested that amiodarone could protect against sudden cardiac death in hypertrophic cardiomyopathy (Cecchi et al, 1998), others have raised doubts about this. In a large unselected cohort of hypertrophic cardiomyopathy patients (approximately 750), 15% of patients who experienced sudden cardiac death were prophylactically on amiodarone (Maron et al, 2000a). Amiodarone can also lead to significant side effects following chronic administration. There is more evidence that antiarrhythmics lack efficacy against sudden cardiac death in hypertrophic cardiomyopathy patients (Melacini et al, 2007).

In view of the lack of clear efficacy data, significant side effects of medications, and the superior protection offered by internal cardioverter-defibrillators, the use of pharmacological agents as sole therapy to reduce risk of sudden cardiac death in hypertrophic cardiomyopathy patients has declined significantly.

While there is no approved therapy to retard disease progression in hypertrophic cardiomyopathy, internal cardioverter-defibrillator therapy is the most effective strategy to abort sudden death as a result of lethal ventricular arrhythmias in high risk patients (Maron et al, 2007). However, internal cardioverter-defibrillator implantation not without complications. Frequent internal cardioverter-defibrillator shocks can affect quality of life and have adverse psychological consequences, especially in young hypertrophic cardiomyopathy patients. Therefore the decision to implant an internal cardioverter-defibrillator should be made after detailed discussion of risks *vs* benefits with the patient. Recommendations for internal cardioverter-defibrillator implant based on risk factors are shown in *Table 2*. Epicardial ventricular tachycardia mapping and catheter ablation are effective in eliminating ventricular tachycardia in up to three quarters of cases of hypertrophic cardiomyopathy followed up for nearly 2 years (Santangeli et al, 2010). However, as opposed to ischaemic ventricular tachycardia where there exists a discrete substrate (in the form of a scar), the

abnormal substrate in hypertrophic cardiomyopathy is more extensive and heterogeneous. Thus, it is difficult to foresee a widespread role for catheter ablation in the treatment of ventricular tachycardia in hypertrophic cardiomyopathy.

Future directions

There is increasing evidence supporting a role for incorporation of late gadolinium enhancement detection on cardiac magnetic resonance to be included as one of the risk factors for sudden cardiac death in hypertrophic cardiomyopathy. However, there is a need for further evidence from large scale studies, and a consensus needs to be reached regarding imaging protocols and threshold for detection to validate this investigation as a risk marker (Gersh et al, 2011). With improving understanding of the link between the genotypic and phenotypic features of hypertrophic cardiomyopathy, there could be a role in the future for the incorporation of 'malignant' gene mutations among risk factors. Use of gene therapy to dilute the consequences of the mutation could be another novel approach (Jagatheesan et al, 2007).

Understanding the underlying molecular basis of hypertrophic cardiomyopathy is also important to devise novel approaches to prevent malignant ventricular arrhythmias. For instance, blebbistatin is a novel drug that reduces myofilament calcium sensitivity and could reduce susceptibility to arrhythmia (Baudenbacher et al, 2008). Targeting the proteins involved in calcium mishandling such as SERCA2a or phospholamban or even using calcium-channel blockers such as diltiazem can also prevent fibrosis or hypertrophy if used prophylactically in genotype positive phenotype negative hypertrophic cardiomyopathy patients (Ashrafian et al, 2011). Perhexiline (a metabolic modulator) has shown promise in helping to retard disease progression in hypertrophic cardiomyopathy (Abozguia et al, 2010).

Conclusions

Hypertrophic cardiomyopathy has considerable phenotypic and genotypic heterogeneity. While sudden death is relatively uncommon, it can be a catastrophic and unpredictable event in a young asymptomatic patient. Risk stratification for sudden cardiac death continues to be challenging because of the low positive predictive value of certain risk factors, the diverse phenotypic manifestations of the disease and the fact that sudden cardiac death can affect patients without any traditional risk factors. Emergence of new risk predictors may improve the predictive value of risk stratification in the future. Understanding the molecular basis of this genetic cardiomyopathy is also crucial to develop novel substrate-based strategies to prevent ventricular arrhythmias. BJHM

Conflict of interest: none.

Abozguia K, Elliott P, McKenna W et al (2010) Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. *Circulation* **122**(16): 1562–9

Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ (2005) Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. *J Am Coll Cardiol* **45**(5): 697–704

Adabag AS, Maron BJ (2007) Implications of arrhythmias and prevention of sudden death in hypertrophic cardiomyopathy. *Ann Noninvasive Electrocardiol* **12**(2): 171–80

Appelbaum E, Maron BJ, Adabag S et al (2012) Intermediate-signal-intensity late gadolinium enhancement predicts ventricular tachyarrhythmias in patients with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging* **5**(1): 78–85

Ashrafian H, McKenna WJ, Watkins H (2011) Disease pathways and novel therapeutic targets in hypertrophic cardiomyopathy. *Circ Res* **109**(1): 86–96

Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A (2000) Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. *Hum Pathol* **31**(8): 988–98

Baudenbacher F, Schober T, Pinto JR et al (2008) Myofilament Ca2+ sensitization causes susceptibility to cardiac arrhythmia in mice. *J Clin Invest* **118**(12): 3893–903

Behr ER, Elliott P, McKenna WJ (2002) Role of invasive EP testing in the evaluation and management of hypertrophic cardiomyopathy. *Card Electrophysiol Rev* **6**(4): 482–6

Bos JM, Towbin JA, Ackerman MJ (2009) Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. *J Am Coll Cardiol* **54**(3): 201–11

Cecchi F, Olivotto I, Montereggi A, Squillatini G, Dolara A, Maron BJ (1998) 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* **79**(4): 331–6

Christiaans I, van Engelen K, van Langen IM, Birnie E, Bonsel GJ, Elliott PM, Wilde AA (2010) Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers. *Europace* **12**(3): 313–21

Crilley JG, Boehm EA, Blair E et al (2003) Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy. *J Am Coll Cardiol* **41**(10): 1776–82

Dimitrow PP, Chojnowska L, Rudzinski T et al (2010) Sudden death in hypertrophic cardiomyopathy: old risk factors re-assessed in a new model of maximalized follow-up. *Eur Heart J* **31**(24): 3084–93

Elliott P, Spirito P (2008) Prevention of hypertrophic cardiomyopathy-related deaths: theory and practice. *Heart* **94**(10): 1269–75

Elliott PM, Poloniecki J, Dickie S et al (2000) Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* **36**(7): 2212–18

Frey N, Luedde M, Katus HA (2012) Mechanisms of disease: hypertrophic cardiomyopathy. *Nat Rev Cardiol* **9**(2): 91–100

KEY POINTS

- Deaths from ventricular tachycardia and fibrillation are the single biggest cause of mortality in hypertrophic cardiomyopathy.
- Hypertrophic cardiomyopathy is the biggest cause of sudden cardiac death in the young.
- Hypertrophic cardiomyopathy patients with previous cardiac arrest, ventricular fibrillation or haemodynamically significant ventricular tachycardia have the highest risk of sudden cardiac death.
- Internal cardioverter-defibrillator implantation is the most effective strategy to reduce sudden cardiac death.
- Risk stratification of hypertrophic cardiomyopathy patients before internal cardioverter-defibrillator insertion is complex, challenging and evolving rapidly.

Fuchs T, Torjman A (2009) The usefulness of microvolt T-wave alternans in the risk stratification of patients with hypertrophic cardiomyopathy. *Isr Med Assoc J* **11**(10): 606–10

Gersh BJ, Maron BJ, Bonow RO et al (2011) 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* **58**(25): e212–e260

Gimeno JR, Tome-Esteban M, Lofiego C et al (2009) Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. *Eur Heart J* **30**(21): 2599–605

Green JJ, Berger JS, Kramer CM, Salerno M (2012) Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging* **5**(4): 370–7

Ho CY (2010) Genetics and clinical destiny: improving care in hypertrophic cardiomyopathy. *Circulation* **122**(23): 2430–40

Jagatheesan G, Rajan S, Petrashevskaya N et al (2007) Rescue of tropomyosin-induced familial hypertrophic cardiomyopathy mice by transgenesis. *Am J Physiol Heart Circ Physiol* **293**(2): H949–H958

Knollmann BC, Kirchhof P, Sirenko SG et al (2003) Familial hypertrophic cardiomyopathy-linked mutant troponin T causes stress-induced ventricular tachycardia and Ca2+-dependent action potential remodeling. *Circ Res* **92**(4): 428–36

Lampert R, Rosenfeld L, Batsford W, Lee F, McPherson C (1994) Circadian variation of sustained ventricular tachycardia in patients with coronary artery disease and implantable cardioverter-defibrillators. *Circulation* **90**(1): 241–7

Lin G, Nishimura RA, Gersh BJ, Phil D, Ommen SR, Ackerman MJ, Brady PA (2009) Device complications and inappropriate implantable cardioverter defibrillator shocks in patients with hypertrophic cardiomyopathy. *Heart* **95**(9): 709–14

Marian AJ, Roberts R (2001) The molecular genetic basis for hypertrophic cardiomyopathy. *J Mol Cell Cardiol* **33**(4): 655–70

Maron BJ (2002) Hypertrophic cardiomyopathy: a systematic review. *JAMA* **287**(10): 1308–20

Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE (1995) Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation* **92**(4): 785–9

Maron BJ, Olivotto I, Spirito P et al (2000a) Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation* **102**(8): 858–64

Maron BJ, Shen WK, Link MS et al (2000b) Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* **342**(6): 365–73

Maron BJ, McKenna WJ, Danielson GK et al (2003) 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. *Eur Heart J* **24**(21): 1965–91

Maron BJ, Spirito P, Shen WK et al (2007) Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA* **298**(4): 405–12

Maron BJ, Maron MS, Lesser JR et al (2008) Sudden cardiac arrest in hypertrophic cardiomyopathy in the absence of conventional criteria for high risk status. *Am J Cardiol* **101**(4): 544–7

Maron BJ, Maron MS, Semsarian C (2012) Double or compound sarcomere mutations in hypertrophic cardiomyopathy: a potential link to sudden death in the absence of conventional risk factors. *Heart Rhythm* **9**(1): 57–63

Mayet J, Shahi M, McGrath K et al (1996) Left ventricular hypertrophy and QT dispersion in hypertension. *Hypertension* **28**(5): 791–6

McIntyre H, Fry CH (1997) Abnormal action potential conduction in isolated human hypertrophied left ventricular myocardium. *J Cardiovasc Electrophysiol* **8**(8): 887–94

Melacini P, Maron BJ, Bobbo F et al (2007) Evidence that pharmacological strategies lack efficacy for the prevention of sudden death in hypertrophic cardiomyopathy. *Heart* **93**(6): 708–10

Michels M (2012) Appropriate implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: what happens on Sunday afternoons in May? *Europace* **14**(5): 621–2

Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ (2003) Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol* **42**(5): 873–9

O'Gara PT, Bonow RO, Maron BJ et al (1987) Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. *Circulation* **76**(6): 1214–23

O'Hanlon R, Grasso A, Roughton M et al (2010) Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol* **56**(11): 867–74

Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F (1999) Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. *J Am Coll Cardiol* **33**(7): 2044–51

O'Mahony C, Lambiase PD, Quarta G et al (2012a) The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. *Heart* **98**(2): 116–25

O'Mahony C, Lambiase PD, Rahman SM et al (2012b) The relation of ventricular arrhythmia electrophysiological characteristics to cardiac phenotype and circadian patterns in hypertrophic cardiomyopathy. *Europace* **14**(5): 724–33

Santangeli P, Di BL, Lakkireddy D et al (2010) Radiofrequency catheter ablation of ventricular arrhythmias in patients with hypertrophic cardiomyopathy: safety and feasibility. *Heart Rhythm* **7**(8): 1036–42

Schober T, Huke S, Venkataraman R et al (2012) Myofilament ca sensitization increases cytosolic ca binding affinity, alters intracellular ca homeostasis, and causes pause-dependent ca-triggered arrhythmia. *Circ Res* **111**(2): 170–9

Sherrid MV, Cotiga D, Hart D et al (2009) Relation of 12-lead electrocardiogram patterns to implanted defibrillator-terminated ventricular tachyarrhythmias in hypertrophic cardiomyopathy. *Am J Cardiol* **104**(12): 1722–6

Spirito P, Autore C, Rapezzi C et al (2009) Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation* **119**(13): 1703–10

Teekakirikul P, Eminaga S, Toka O et al (2010) Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires Tgf-beta. *J Clin Invest* **120**(10): 3520–9

Ten Cate FJ, Soliman OI, Michels M, Theuns DA, de Jong PL, Geleijnse ML, Serruys PW (2010) Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. *Circ Heart Fail* **3**(3): 362–9

van Rijsingen IA, Bekkers SC, Schalla S et al (2011) Exercise related ventricular arrhythmias are related to cardiac fibrosis in hypertrophic cardiomyopathy mutation carriers. *Neth Heart J* **19**(4): 168–74

Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ (2000) Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. *Heart* **84**(5): 476–82

Varnava AM, Elliott PM, Mahon N, Davies MJ, McKenna WJ (2001) Relation between myocyte disarray and outcome in hypertrophic cardiomyopathy. *Am J Cardiol* **88**(3): 275–9

Watkins H, McKenna WJ, Thierfelder L et al (1995) Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* **332**(16): 1058–64

Yang KC, Jay PY, McMullen JR, Nerbonne JM (2012) Enhanced cardiac PI3Kalpha signalling mitigates arrhythmogenic electrical remodelling in pathological hypertrophy and heart failure. *Cardiovasc Res* **93**(2): 252–62

Zachariah JP, Colan SD, Lang P et al (2012) Circulating matrix metalloproteinases in adolescents with hypertrophic cardiomyopathy and ventricular arrhythmia. *Circ Heart Fail* **5**(4): 462–6