www.nature.com/clinicalpractice/cardio

Hypertrophic cardiomyopathy in the community: why we should care

Franco Cecchi*, Magdi H Yacoub and Iacopo Olivotto

F Cecchi is Head of and I Olivotto is a Staff Physician at the Referral Centre for Cardiomyopathies in the Cardiology Department of the Careggi University Hospital, Florence, Italy. MH Yacoub is a cardiac surgeon, Professor of Cardiac Surgery and Director of Research at the Heart Science Centre, Imperial College London, Harefield, UK.

Correspondence
*Via Iacopo
Nardi 30
Firenze, 50132
Italy
cecchif@
ao-careggi.toscana.it

Received 19 March 2005
Accepted 17 May 2005
www.nature.com/clinicalpractice
doi:10.1038/ncpcardio0248

Hypertrophic cardiomyopathy (HCM) is a model of genetic heart disease that fascinates clinical cardiologists, geneticists and scientists. Public and media interest, however, grows only briefly when HCM is identified as the cause of sudden death of a young competitive athlete.

HCM is an epidemiologically relevant, widespread yet frequently undiagnosed condition. The worldwide prevalence, based on left-ventricular wall thickness greater than 15 mm, is reported to be 0.2% (e.g. >100,000 individuals in the UK), but this value might be higher.[1] Diagnoses of HCM based on symptoms or cardiovascular complications represent the tip of the iceberg and many patients are asymptomatic and not aware of the risk inherent with HCM. Other conditions less common than HCM, such as multiple sclerosis and cystic fibrosis, benefit from raised awareness in the medical community and general public. Despite large gaps in our knowledge of the basic mechanisms of HCM, understanding is advancing at the clinical, molecular and community levels. We highlight some of the exciting new information in the field and its relevance to the community.

HCM was originally described and is still frequently perceived as a rare, malignant disease with a high incidence of sudden death, but community-based studies have begun to change this perception.[2] Patients with HCM might have normal life expectancy but often develop disease-related complications, such as ventricular or supraventricular arrhythmias, congestive heart failure, myocardial infarction in the absence of epicardial coronary artery disease, and endocarditis. Cardiovascular mortality, although lower than initially reported, is notable, with an average annual rate of about 1%. Sudden death accounts for about half of these events and for most deaths among young patients. Congestive heart failure and stroke account for the remaining half, occurring predominantly in adult and elderly patients. In the US, HCM is considered the most frequent cause of sudden death during sports activities. In Italy, though, where preparticipation screening for cardiovascular disease is mandatory in competitive sports, HCM rarely causes sudden death in young athletes.[3] Thus, early diagnosis of HCM is important.

The genetic basis of HCM is heterogeneous and is not yet completely clarified: as many as 10 genes, all encoding sarcomeric proteins, have been associated with cause.[4] Mutations in the *PRKAG2* and *LAMP2* genes, which account for rare forms of glycogenosis, can also result in phenotypes resembling typical HCM, and novel candidate genes are under investigation.[5] Screening for the five sarcomeric protein genes most commonly involved in HCM (myosin binding protein C [*MYBPC3*], β-myosin heavy chain [*MYH7*], cardiac troponin T and I [*TNNT2* and *TNNI3*], and regulatory myosin light chain [*MYL2*]) identifies HCM in 40–60% of affected patients. Unfortunately, because of molecular heterogeneity and the limited number of genotyped families, genotype–phenotype correlations and prediction of outcome based on one genetic defect have proved disappointing. We feel that further family screening studies are needed; an ongoing initiative at Careggi University Hospital, Florence will hopefully increase the yield of meaningful phenotypic correlations.

Knowledge of the genetic substrate is currently used to confirm diagnosis and screen patients' family members, as well as for research purposes.[6] Identification of HCM relatives who carry mutations before HCM phenotypes develop is essential if we are to understand the pathophysiology of myocardial hypertrophy. In individuals with no or mild disease expression, however, mutation identification could negatively impact on quality of life, affecting factors such as eligibility for sports, pregnancy and life insurance. Hence, genetic counseling must be offered to all patients and their families. The way in which clinical practice should be affected, however, also remains controversial. In our view, for example, routine prenatal testing in pregnant women with HCM is not justified, and the exclusion from competitive sports of mutation carriers with very mild HCM is debatable.

With regard to treatment, molecular level targets are nonexistent. The pathogenetic pathways by which hypertrophy develops, localizes and (occasionally) regresses to resemble dilated or restrictive cardiomyopathy are only just beginning to be investigated. Adequate medical therapy, based mostly on empirical data for β-blockers, such as nadolol, or calcium-blocking drugs, allows control of symptoms in most patients. In the past decade, clinical predictors of functional limitation and heart failure, such as left-atrial dilatation, atrial fibrillation, left-ventricular outflow tract obstruction, extreme hypertrophy and severe microvascular dysfunction, have been identified.[7,8]

Restoration of sinus rhythm in patients with paroxysmal atrial fibrillation can relieve symptoms and improve outcome. In patients with significant outflow obstruction and mitral regurgitation, surgical myectomy and mitral valve procedures can improve outcome. Alcohol septal ablation is an alternative approach but its long-term benefits are unknown; we advise alcohol ablation in patients older than 60 years who have hypertrophy selectively localized at the subaortic level, in the absence of moderate to severe mitral regurgitation, aortic valve disease or left-bundle-branch block. Surgery, which generally provides better hemodynamic improvements than ablation, is preferred for young patients with severe disease, although midventricular obstruction might be better treated by alcohol ablation. For other patients, randomized trials of these approaches are urgently needed.

Implantable cardioverter-defibrillators can prevent sudden death and lessen malignant arrhythmias, and are useful in patients with sustained ventricular tachycardia and survivors of cardiac arrest. The identification of HCM patients at high risk of sudden death, however, remains a challenge and matter of debate.[9] The degree of risk is difficult to predict and the decision to use an implantable cardioverter-defibrillator is often based on physicians' experience and patients' desires and risk perception. Young patients often refuse a lifelong implantable cardiac defibrillator, but if sudden death has occurred in a relative, they might demand one even in the absence of other risk factors.

Comprehensive management guidelines for HCM are now available.[10] Unfortunately, a nationwide survey in Italy has shown limited implementation of management options and poor access to optimum medical and surgical treatment for severely symptomatic HCM patients.[2] Access to tertiary centers, in which state-of-the-art management and optimum resources, such as surgery and invasive cardiology are available can benefit these patients.

In conclusion, HCM deserves attention in medical education and health-care planning. Increased awareness of the disease among patients, families and physicians will probably improve risk assessment and therapeutic efficacy in individuals. National registries could be invaluable for sharing disease knowledge and creating connections for HCM care and research. In Italy, a registry funded by the Istituto Superiore di Sanità, part of the Italian health service, has recruited over 1,600 patients with HCM, creating a network of 40 cardiology centers nationwide.[2] A similar project has also been presented in Egypt with the sponsorship of the reconstructed Bibliotheca Alexandrina library complex. Further research projects should be launched and could lead to national and international networks dedicated to HCM. In this exciting field, we feel it is time to look at the bigger picture.

Competing interests
The authors declared they have no competing interests.

References

1 Maron BJ (2004) Hypertrophic cardiomyopathy: an important global disease. *Am J Med* **116:** 63–65
2 Cecchi F *et al.*: The Italian registry for hypertrophic cardiomyopathy: a nationwide survey. *Am Heart J*, in press
3 Corrado D *et al.* (1998) Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* **339:** 364–369
4 Van Driest SL *et al*. (2005) Sarcomeric genotyping in Hypertrophic Cardiomyopathy. *Mayo Clin Proc* **80:** 463–469
5 Arad M *et al.* (2005) Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med* **352:** 362–372
6 Maron BJ *et al.* (2004) Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. *J Am Coll Cardiol* **44:** 2125–2132
7 Olivotto I *et al.* (2001) Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* **104:** 2517–2524
8 Cecchi F *et al.* (2003) Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med* **349:** 1027–1035
9 Maron BJ *et al.* (2000) Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* **342:** 365–373
10 Maron BJ *et al.*; American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines (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:** 1965–1991