Emergence of gene mutation carriers and the expanding disease spectrum of hypertrophic cardiomyopathy

Barry J. Maron1* and Christopher Semsarian2,3,4

1The Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, MN 55407, USA; 2Agnes Ginges Center for Molecular Cardiology, Centenary Institute, NSW, Australia; 3Sydney Medical School, University of Sydney, NSW, Australia; and 4Department of Cardiology, Royal Prince Alfred Hospital, NSW, Australia

This editorial refers to ‘Early identification of mutation carriers in familial hypertrophic cardiomyopathy by combined echocardiography and tissue Doppler imaging’, by E. Gandjbakhch et al., on page 1599

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, encompassing a particularly heterogeneous disease spectrum.1,2 The most recently defined subgroup, which has added considerably to this diversity,3 is a product of the molecular era in cardiovascular disease.4–9 i.e. mutation carriers without the HCM phenotype of left ventricular (LV) hypertrophy. These individuals, who carry mutations in genes encoding proteins of cardiac sarcomere judged to be disease causing, are usually asymptomatic relatives in HCM families, and variously described as ‘gene positive(+) phenotype negative(–)’, ‘mutation carriers’, or with ‘preclinical’ disease.10–16

Gandjbakhch et al.17 underscore the importance of this novel HCM subgroup with clinical studies in mutation carriers, utilizing echocardiographic and Doppler parameters. In the earliest days of molecular biology in HCM, a time period which now spans two decades, such family members were sporadically identified as part of specific pedigree studies and protocols performed in selected research laboratories in the USA, Europe, and Japan. However, more recently, molecular diagnosis has become much more available due to the evolution of commercial testing, currently available from four companies in the USA.

Since it is now generally conceded that the identification of specific mutations has little value in predicting prognosis in HCM patients, the primary role for such testing remains for the diagnosis of relatives in families with documented HCM, or possibly in probands for whom definitive diagnosis is ambiguous by standard clinical strategies, e.g. in distinguishing HCM from physiological ‘athlete’s heart’.

However, a complicating factor in this regard remains the substantial (and increasing) genetic heterogeneity attributable to HCM, now with >1000 mutations in 13 or more genes that encode proteins within and associated with the sarcomere, but nevertheless accounting for only ~50% of the HCM disease spectrum. β-Myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) genes are predominant and account for 80% of the genotyped patients. Furthermore, fully two-thirds of these mutations are ‘private’ (i.e. as yet reported in only one family), thereby limiting the prognostic weight that can be attributed to individual mutations, and giving rise to the possibility that many identified mutations are not truly disease causing. Indeed, the ‘variants of unknown significance’ issue is emerging as a significant limitation to the reporting of clinically relevant genetic testing data in HCM patients, requiring resolution by positive genetic testing in other family members, or by recognition that a specific mutation has previously been documented as pathogenic in other families. This is a relevant consideration for family members potentially designated as gene(+) phenotype(–).

Putting these considerations and concerns aside, it is obvious that we are nevertheless witnessing the identification of substantially increased numbers of preclinical mutation carriers, due largely to a greater accessibility to molecular diagnosis, and presumably this trend will only increase in the coming years.

However, while the genomics of HCM represent a powerful advance in diagnostics, it has also created a series of emerging clinical dilemmas. The natural history, risk of sudden death, general prognosis, and potential management strategies and decision-making related to mutation carriers is not only currently unresolved, but also essentially unknown given the youthful age of the affected relatives and the limited follow-up available in this subset—which requires substantial periods of longitudinal observation (probably encompassing decades). Also unknown is which (and how commonly) gene(+) phenotype(–) individuals will ultimately develop the HCM phenotype, or at what time in life.
Such uncertainty may impact on the question of eligibility vs. disqualification from intense competitive sports, as well as the wisdom of prophylactic implantation of cardioverter-defibrillators. First, the issue of disqualification from sports is particularly perplexing, given that the American College of Cardiology Bethesda Conference #36 did not recommend the withdrawal of gene (+) phenotype (−) individuals from competitive sports, while conversely the European Society of Cardiology considers HCM gene carriers to be at sufficient risk during sports to justify their removal from the competitive arena.19,20 However, there is no long-term follow-up evidence available at present to justify either view as absolutely correct. Secondly is the question of whether any (or which) gene carriers deserve consideration for primary prevention of sudden death with implantable defibrillators,21 particularly if there is a family history of HCM-related sudden death. Presently, conclusive answers to either of these new clinical questions are elusive, with evidence-based resolution remaining a long-term aspiration. For example, only very recently has the first report appeared in the literature of two gene carriers incurring sudden death events, offering support for the principle that the non-hypertrophied LV muscle in these individuals can represent an arrhythmogenic substrate.22

There has also been substantial interest in using non-invasive ECG, echocardiography, and Doppler parameters to identify abnormalities of LV myocardium in gene carriers preceding the appearance of hypertrophy, i.e. LV diastolic dysfunction, remodelling, or tissue characterization.3,10,11 Indeed, evidence that the non-hypertrophied LV muscle of gene (+) phenotype (−) family members may be electrically and functionally altered is evident in these studies which report abnormal ECG patterns in ~50%, and diastolic dysfunction with varied sensitivity (44–100%) and specificity (93–100%) for predicting the affected genotype.3,10,11

Gandjbakhch et al.17 propose a novel approach to defining such abnormalities in mutation carriers with a combined echocardiographic and Doppler strategy that integrates tissue Doppler imaging (TDI), ventricular sepal E/Ea ratio, the ventricular septum to LV free wall ratio, and also relative wall thickness. The authors report an ‘echo/TDI’ score which identified affected mutation carriers [i.e. with MYH7, MYBPC3, and troponin T (TNNT2) genes] with 67% sensitivity and 96% specificity. However, such non-invasive clinical approaches, such as ‘echo/ TDI score’, cannot be regarded as sufficiently diagnostic to supplant genetic testing. Furthermore, it is unknown whether such findings in mutation carriers predict the eventual development of LV wall thickening.

In conclusion, the expanding preclinical genotype (+) phenotype (−) HCM subgroup represents a major challenge to clinicians. Answers to the prevailing important questions concerning management decisions for such individuals will unavoidably require many years of careful assembly of data in large cohorts with longitudinal and substantial follow-up. In addition, studies such as that of Gandjbakhch et al., targeting the pathophysiology and clinical recognition of gene carriers, represent an important advance in this rapidly evolving area.

Conflict of interest: none declared.

References


CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehq086
Online publish-ahead-of-print 12 April 2010

Aneurysm of the right sinus of Valsalva in a four-and-a-half-year-old boy successfully treated with a ‘Hemi-David’ operation

Andreas Kühn1, Christian Schreiber2, and Manfred Vogt1*

1Deutsches Herzzentrum München, Klinik an der Technischen Universität München, Klinik für Kinderkardiologie und angeborene Herzfehler, Lazarettstr. 36, D 80636 Munich, Germany and 2Deutsches Herzzentrum München, Klinik für Herz- und Gefäßchirurgie, Munich, Germany

* Corresponding author. Tel: +49 89 1218 1363, Fax: +49 89 1218 3013, Email: drvogt@dhm.mhn.de

Dilatation of the aortic root and aneurysms of the sinus of Valsalva can occur in different circumstances such as Marfan syndrome, Loeys-Dietz syndrome, or bicuspid aortic valve. Even though in most of these cases this process begins already in childhood, treatment before adulthood is rarely needed. We report on a four-and-a-half-year-old-year-old boy with a functional bicuspid aortic valve. His aneurysm of the right sinus of Valsalva was followed since birth. Clinical findings did not support the diagnosis of Marfan syndrome. Gene analysis showed no mutation in the genes representing a Loeyes–Dietz syndrome. Therefore, the tentative explanation for the aneurysm formation remained his functional bicuspid valve. Since there was a rapid progression of the size of the aneurysm, up to a diameter of 38 mm, the decision was taken to operate (Panel A depicts transoesophageal echo and Panel B angiographic finding). Surgery was performed using a valve sparing technique with implantation of a Goretext patch at the site of the resected aneurysm (Panel C intraoperative finding). The right coronary artery was re-implanted after mobilization. One year after the operation, the function of the aortic valve is normal, without any further abnormal dilatation of the aortic root (Panel D postoperative transoesophageal echo).

Panel A: Transoesophageal echocardiogram, 110° view demonstrating the aneurysm of the right sinus of Valsalva.

Panel B: Corresponding angiography of the aortic root.

Panel C: Intraoperative finding; marked dilatation of the right sinus of Valsalva.

Panel D: Postoperative transoesophageal echocardiogram, 110° view showing the postoperative result.

Asterisk indicates the aneurysm of the right sinus of Valsalva. LA, left atrium; LV, left ventricle; Ao, Aorta; AoV, Aortic valve; arrows indicates the Goretext patch after resection of the aneurysm.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oxfordjournals.org.