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REVIEW TOPIC OF THE WEEK

New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is an important genetic heart muscle disease for which prevalence in the general population has not been completely resolved. For the past 20 years, most data have supported the occurrence of HCM at about 1 in 500. However, the authors have interrogated a number of relevant advances in cardiovascular medicine, including widespread fee-for-service genetic testing, population genetic studies, and contemporary diagnostic imaging, as well as a greater index of suspicion and recognition for both the clinically expressed disease and the gene-positive–phenotype-negative subset (at risk for developing the disease). Accounting for the potential impact of these initiatives on disease occurrence, the authors have revisited the prevalence of HCM in the general population. They suggest that HCM is more common than previously estimated, which may enhance its recognition in the practicing cardiovascular community, allowing more timely diagnosis and the implementation of appropriate treatment options for many patients. (J Am Coll Cardiol 2015;65:1249–54) © 2015 by the American College of Cardiology Foundation.

Hypertrophic cardiomyopathy (HCM) is a clinically and genetically heterogeneous disorder. It is characterized most commonly by left ventricular (LV) hypertrophy, with a range of potential outcomes including heart failure and sudden cardiac death, but also survival to normal life expectancy (1,2). HCM is a global disease (3) and is considered 1 of the most common genetic heart disorders, with an estimated prevalence of 1 in 500 people (4). Recognition of HCM is important, both for providing treatment and prevention strategies and in triggering the initiation of clinical and genetic surveillance of family members. In this commentary, we make the argument that HCM, including patients with clinically expressed disease and confirmed gene carriers, represents a much more common condition than previously thought.

REPORTED PREVALENCE OF HCM

The estimated prevalence of HCM of 1 in 500 is based on data originally collected almost 20 years ago in the landmark CARDIA (Coronary Artery Risk Development in Young Adults) cohort study, which reported standard echocardiographic analyses in 4,111 unrelated people 23 to 35 years of age (4). CARDIA was a biracial cohort established to longitudinally investigate life-style and other variables that influence the evolution of coronary risk factors during young adulthood. Subjects were randomly selected from the

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

G+ P− = genotype positive-phenotype negative

HCM = hypertrophic cardiomyopathy

LV = left ventricular

general population in community-based urban centers and census tracts (4).

This prevalence estimate was subsequently supported by a number of U.S. and international studies, including from China, Japan, and East Africa, with diverse study designs and variable ages of subjects, geography, and racial/ethnic composition (4-10) (**Table 1**). However, advances in HCM since the publication of these studies, including a more robust clinical experience, enhanced understanding of the underlying molecular and genetic substrate, the implementation of contemporary family screening, and more sensitive diagnostic cardiac imaging, contribute to the notion that the prevalence of this disease may have been underestimated.

GENETIC POPULATION STUDIES

Perhaps the most compelling avenue of evidence that supports the revised prevalence estimate for HCM, and the principle that this disease is more common than previously regarded, comes from the discovery of its molecular basis and the subsequent implementation of genetic testing, after publication of the CARDIA study almost 20 years ago (4). At least 11 genes have now been identified, which primarily encode more than 1,500 cardiac sarcomere and sarcomere-related single-nucleotide mutations, critical for the basic contractile function of the heart (**Figure 1**) (11,12).

Importantly, sarcomere protein mutations known to cause HCM are unexpectedly common in the general population. In 2012, Seidman and colleagues reported a relatively high frequency of pathogenic (disease-causing) mutations in a general community-based study designed to assess the burden of structural cardiovascular disease conferred by rare variants. In that unique investigation, 3,600 participants of both sexes (30 to 84 years of age) were studied, including 1,637 unrelated subjects in the offspring cohort of the Framingham Heart Study and 1,963 unrelated subjects from the Jackson Heart Study cohort (13). Screening the principal 8 HCM-causing sarcomere protein genes identified 1 or more rare nonsynonymous sarcomere variants (i.e., minor allele frequency <1%) in 11.2% of the general population, of which 0.6% were considered disease causing using stringent criteria for pathogenicity (Harvard Partners criteria) (12,14). It is possible that others of these variants could prove to be pathogenic (**Figure 1**).

Therefore, on the basis of these data, the minimal prevalence of HCM gene carriers could be estimated at 1 in 200 people or greater, and therefore 2.5-fold more common than reported in the original HCM phenotype-based echocardiographic CARDIA study (4). Although all gene carriers may not develop clinical HCM, the high frequency of HCM-causing pathogenic mutations strongly suggests a prevalence exceeding that reported in the CARDIA study (4).

RECOGNITION OF GENOTYPE-POSITIVE–PHENOTYPE-NEGATIVE PATIENTS

The availability of commercial genetic testing for HCM and recent advances in next-generation sequencing technologies are contributing to more comprehensive and less costly genetic testing. The value of a genetic diagnosis in an HCM family is immeasurable, allowing asymptomatic relatives to undergo predictive genetic testing to identify their carrier status, as well as contributing to an expansion of the HCM disease spectrum (15). Consequently, a new HCM subgroup has been identified, that is, asymptomatic gene carriers without LV hypertrophy, known as "genotype-positive-phenotype-negative" (G+ P−) (16-22). Such G+ P− subjects without the HCM phenotype were not identifiable or present in studies such as CARDIA, before the genetic era for HCM (11,12), which relied on echocardiographic diagnosis with recognition of LV wall thickening (4). Although these genetically affected subjects without clinical evidence of disease cannot be included in prevalence estimates

TABLE 1 Prior Estimates of HCM Prevalence With Echocardiography in 6 Populations

First Author (Ref. #)	Year	N	Age (yrs)	% Male	Maximal LV Thickness (mm)	Reported Prevalence (%)	Study Subjects
Maron et al. (4)	1995	4,111	25-35	71	17 ± 2	0.17	Random sampling from urban general population (CARDIA study)
Hada et al. (6)	1987	1,584	47*	76	17 ± 3	0.17	Annual health examinations
Maron et al. (8)	1999	15,137	57*	48	21 ± 4	0.19	Mobile echocardiography in rural communities
Maron et al. (9)	2004	3,501	60	50	21 ± 3	0.23	American Indian tribal communities†
Zou et al. (5)	2004	8,080	52	69	17 ± 6	0.16	Random sample from 9 communities in China
Maro et al. (10)	2006	6,680	55	68	21 ± 0.4	0.19	East African (Tanzanian) district regional hospitals

*For patients with HCM. †Derived from the Strong Heart Study, with subjects from Arizona, Oklahoma, North Dakota, and South Dakota.
CARDIA = Coronary Artery Risk Development in Young Adults; HCM = hypertrophic cardiomyopathy; LV = left ventricular.

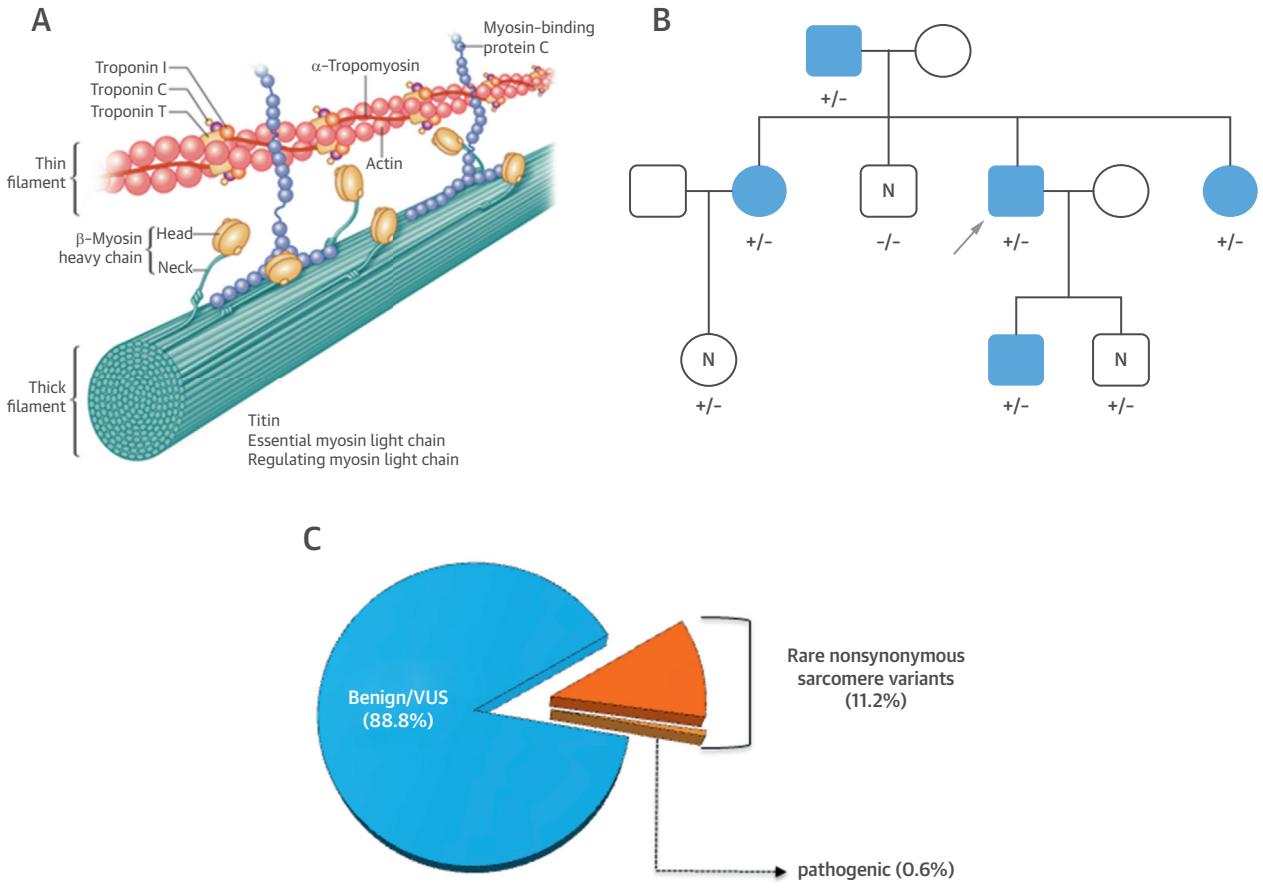
on the basis of the HCM phenotype, they nonetheless represent a distinct subgroup at some risk for developing disease, requiring ongoing assessment and possible management considerations.

It should be emphasized that the natural history of this group of family members over time remains largely unresolved and that caution should be exercised before regarding such subjects as harboring a true disease state requiring restrictions in lifestyle, such as exclusion from competitive sports or employment (23). G+ P− status would add considerably to the prevalence of HCM. As evidence for this assertion, a review of genetically tested families with HCM enrolled in the Australian Genetic Heart Disease Registry (24) identified an average of 1.5 G+ P− (range: 0 to 3) subjects in each genetically tested HCM family.

CLINICAL SCREENING OF HCM FAMILIES

Not accounted for in the CARDIA and other study designs are the multiple clinically expressed relatives in most HCM families (1,2,11,12,25,26). Although HCM is inherited as an autosomal-dominant trait, with first-degree relatives having a 50% chance of inheriting the disease, the CARDIA study included only a specific adult age group, and most importantly, none of the 4,111 participants were related (4). Given that

FIGURE 1 Genomics and Prevalence of HCM



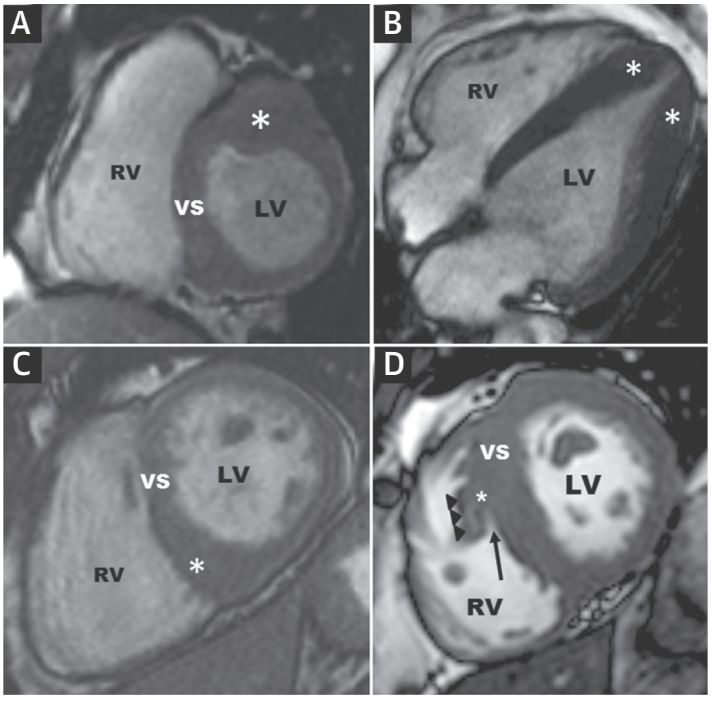
(A) Molecular structure of the sarcomere showing the location of genes encoding the principal proteins of the thick and thin filaments involved in the pathogenesis of hypertrophic cardiomyopathy (HCM). **(B)** Pedigree of an HCM family showing the impact of predictive testing. After the identification of a gene mutation (+/−) in the proband **(arrow)**, clinical and predictive testing identified 4 other clinically affected patients with HCM **(solid symbols)** with the gene mutation (+/−). Two relatives, the other son, and niece of the proband have no left ventricular hypertrophy as adults (N) but carry the pathogenic mutation (genotype-positive-phenotype-negative). **(C)** Genetic analyses from the Framingham Heart Study and Jackson Heart Study cohorts, in 3,600 unrelated subjects (13). The prevalence of rare variants is 11.2%, of which 0.6% are likely pathogenic sarcomere gene variants, providing an estimate for the prevalence of those variants known to cause HCM in the general population (i.e., 1 in 200). VUS = variant of uncertain significance.

HCM is a familial disease, this is another source of underestimating the true prevalence of HCM in the general population.

ENHANCED DETECTION OF HCM PHENOTYPE BY ADVANCED IMAGING

CARDIA and all other HCM clinical prevalence studies used conventional 2-dimensional echocardiography to identify the HCM phenotype (27). However, cardiac magnetic resonance (CMR) imaging has recently emerged as a more precise diagnostic tool in some patients with HCM (28-31) (**Figure 2**). Although echocardiography remains the cornerstone of cardiac assessment in HCM, recent comparative studies have shown CMR to have the high-resolution tomographic imaging capability for identifying not only myriad patterns of LV wall thickening but also the HCM phenotype in some patients in whom hypertrophy is confined to the apical, anterolateral, or posterior (inferior) septal regions of the LV chamber, often not reliably visualized with standard echocardiographic cross-sectional planes (28,29,31). Furthermore, CMR is also capable of clarifying diagnosis when the extent of LV hypertrophy is considered borderline or ambiguous by echocardiography (**Figure 2**) (1,2,28,29,31). Patients with such morphologic imaging considerations are unavoidably excluded from current prevalence figures, thereby further supporting the likelihood that clinically expressed HCM was underestimated in the earlier echocardiographic era (27) and in HCM population studies (4-10).

FIGURE 2 CMR Images Demonstrating Diversity of the HCM Phenotype



(A–C) Segmental areas of hypertrophy within the left ventricular chamber not reliably detected by 2-dimensional echocardiography (i.e., "echo-blind"), potentially responsible for underdiagnosis of hypertrophic cardiomyopathy (HCM). **(A)** Segmental hypertrophy of 18 mm confined to the anterolateral free wall **(asterisk)**, sparing the ventricular septum. **(B)** Hypertrophy localized to the left ventricular apex **(asterisk)**, that is, apical HCM. **(C)** Wall thickening confined to the posterior (inferior) septum **(asterisk)**. **(D)** Crista supraventricularis muscle **(arrowheads)**, a prominent right ventricular structure that inserts directly on the anterior ventricular septum and can be inappropriately included in the measurement of wall thickness, resulting in overdiagnosis of HCM. With cardiac magnetic resonance (CMR) imaging, the crista supraventricularis is recognized moving away from the septum during systole, leaving a small blood pool between the crista and septum **(arrow)** and allowing a more accurate delineation of the endocardial border of the septum **(asterisk)**. LV = left ventricle; RV = right ventricle; VS = ventricular septum.

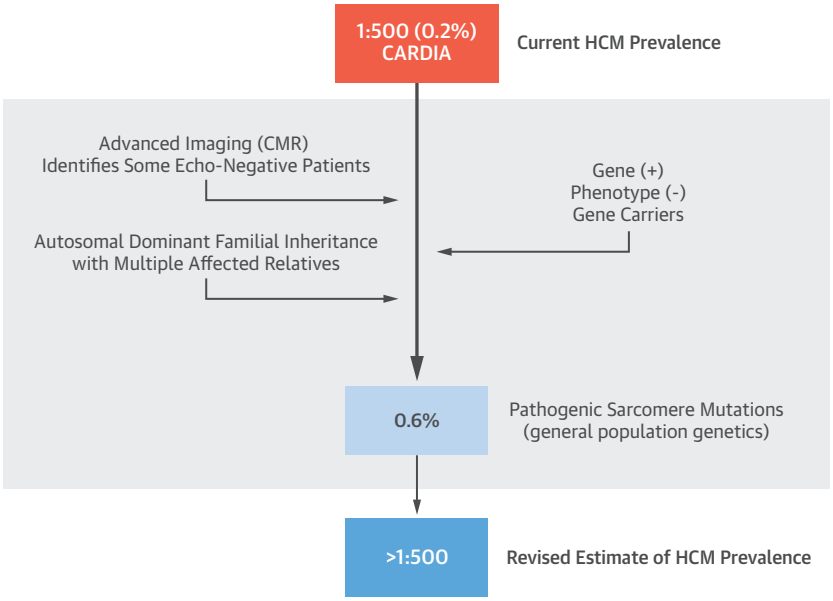
IMPLICATIONS AND CONCLUSIONS

Over the past 10 to 20 years, investigators committed to HCM have been able to rapidly assemble large patient cohorts with ease, exceeding expectations on the basis of earlier perceptions of disease frequency. Indeed, HCM would now appear to be the most common of the genetic heart diseases. With these clinical intuitions as a starting point, we have constructed a viewpoint on the basis of contemporary principles and data, which supports the principle that HCM may well be more common than the prevalence of 1 in 500 initially established by the CARDIA study (4) but now potentially outdated.

Several avenues of evidence support this hypothesis: 1) pathogenic sarcomere genes are more common in the general population than previously thought; 2) genetic testing has defined a new subset of patients without clinical expression and LV hypertrophy (G+ P–); 3) recognition of some HCM phenotypes is enhanced by advanced imaging (i.e., CMR); and 4) prior prevalence studies do not account for the familial nature of the disease (**Central Illustration**).

When these contemporary clinical and genetic principles are considered, it is possible to make the case for a revised estimate of the combined prevalence of clinically expressed HCM and gene carriers (at risk for developing the disease phenotype), which we place at about 1 in 200 (32). This revised prevalence estimate is based on the assimilation of diverse and currently available data. It is unlikely that a comprehensive, large, population-based, epidemiologically sound study with genetic testing and echocardiographic and CMR imaging for the purpose of establishing the prevalence of HCM will occur.

CENTRAL ILLUSTRATION **Factors Contributing to the Revised Estimate for the Prevalence of HCM**



Semsarian, C. et al. J Am Coll Cardiol. 2015; 65(12):1249–54.

The initial estimate of the prevalence of hypertrophic cardiomyopathy (HCM) came largely from the CARDIA (Coronary Artery Risk Development in Young Adults) study, which relied on echocardiographic identification of probands. Among the factors contributing to the revised estimate of more common than 1 in 500 were the identification of gene carriers who are negative for the HCM phenotype; enhanced clinical identification of the HCM phenotype with advanced imaging; recognition that because of the autosomal-dominant inheritance pattern, multiple relatives of probands (and carriers) would be affected by HCM; and recognition that up to 0.6% of the population may carry HCM-causing sarcomere mutations. CMR = cardiac magnetic resonance.

Recognition of a higher, more accurate prevalence figure for HCM may be important to the patient population and practicing cardiovascular community for a number of reasons. If HCM is more common and has higher visibility in the medical consciousness, it is more likely that this disease will be considered in cardiology practice. Increased awareness and recognition of HCM among cardiologists and allied health professionals will, in turn, enhance the overall index of suspicion and increase the frequency of diagnosis in family members and in the general population. This will promote more timely and contemporary treatment options for many patients, with the capability of reducing adult HCM-related mortality to 0.5%/year, similar to that expected in the general U.S. population (33). Together, all these considerations ultimately dispel the historical myth that HCM is a rare and untreatable genetic heart disease, which has in the past suppressed its visibility, recognition, and understanding within cardiovascular medicine.

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