How should hypertrophic cardiomyopathy be classified?

Molecular Diagnosis for Hypertrophic Cardiomyopathy: Not Ready for Prime Time

Perry Elliott, MD; William J. McKenna, MD

Fifty years ago, Donald Teare,1 a well-known forensic pathologist in London, reported 8 cases of “asymmetrical hypertrophy or benign tumor” of the heart. Each had disproportionate hypertrophy of the interventricular septum, a coarse myocardial texture, and a bizarre arrangement of muscle fibers, separated by excessive connective tissue and clefts. At the time, numerous names for this entity were proposed, but after a relatively short period, the term hypertrophic cardiomyopathy (HCM) was adopted and has remained the accepted nomenclature to this day. In this issue of Circulation: Cardiovascular Genetics, Maron et al² propose a change to this convention by advocating a much more restrictive use of the term to describe myocardial hypertrophy caused by mutations in genes that encode sarcomere proteins. In our view, the rationale for this proposal is flawed and, following as it does on the tail of 2 recent updates of the cardiomyopathy classification, will result in increased confusion.

Response by Maron et al see p 89

What is a Cardiomyopathy?

In a remarkably prescient article published in 1957, Brigden3 observed that when describing heart muscle disease “adjectives such as isolated, idiopathic, nonspecific, specific, interstitial, diffuse, and circumscribed abound in the literature; others, such as acute, subacute, chronic pernicious, and malignant, relate to the clinical picture; while still others, such as eosinophilic, allergic, idiosyncratic, and granulomatous hint at etiology, as does familial cardiomegal.” His view at the time was that the term cardiomyopathy should be used to denote “isolated non-coronary myocardial disease.” In 1961, Goodwin4,5 observed that “no definition of the cardiomyopathies is entirely satisfactory,” but suggested that it would be appropriate to consider cardiomyopathies as disorders of heart muscle “of unknown or obscure etiology, often with endocardial, and sometimes with pericardial involvement, but not atheroscerotic in origin.” In subsequent publications, the concept of primary myocardial disorders, in which cardiomyopathies were defined as heart muscle diseases that were not the result of diseases in other parts of the body, was introduced. This was later simplified to “a disorder of cardiac muscle of unknown origin.”¹⁶ Cardiomyopathies defined in this way were then subdivided according to specific morphological and physiological features into hypertrophic, dilated, and restrictive subtypes.⁶⁻⁷

This method of describing heart muscle disease survived largely unchanged until 1995, when a joint World Health Organization/International Society and Federation of Cardiology panel met to update the scheme.⁷ The driving force behind this initiative was the considerable advance in understanding of etiology and pathogenesis of heart muscle disease, which the panel felt made the difference between cardiomyopathy and specific heart muscle disease indistinct. The panel’s solution was to preserve the existing morpholog-

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clinical subtypes, and to abandon the rigid distinction between primary and secondary, preferring instead to classify cardiomyopathies by the dominant pathophysiology and, when possible, by etiologic and pathogenetic factors.

In 2006 and 2008, independent expert committees of the American Heart Association (AHA) and the European Society of Cardiology, respectively, proposed updated classification schemes for cardiomyopathies. Both started with the historical concept that heart muscle disease caused by coronary artery disease, valvular dysfunction, or congenital malformations should be excluded from the definition. The two schemes also preserved the time-honored morphological and physiological approach to the classification of subtypes of cardiomyopathy. The major differences were the continued use of the terms primary and secondary and the inclusion of diseases with no macroscopic structural abnormalities (ion channelopathies) in the AHA scheme.

The chief contention of Maron et al is that the nomenclature applied to HCM has “persistently created a measure of confusion.” The first piece of evidence for this claim is the array of pseudonyms used to describe myocardial hypertrophy, but as the authors themselves acknowledge, most of the 80 or so terms were largely abandoned in the 1960s and 1970s and thus are of historical interest only. Their second argument is that current terminology is inconsistently applied to the large number of congenital and familial diseases that can present with left ventricular hypertrophy. It is, however, worthy of some consideration.

In the new AHA and European Society of Cardiology classifications, HCM is still defined by the presence of a hypertrophied ventricle in the absence of abnormal loading conditions, but they differ in their approach to hypertrophy caused by other systemic diseases. Historically, these were grouped under the heading of secondary or specific heart muscle diseases, but this terminology was never applied consistently in clinical practice. For example, hypertrophy associated with congenital disorders, such as Noonan and Costello syndrome, or multisystem disorders, such as Friedreich ataxia, are often included under the heading of HCM. The AHA panel’s solution was to reinvent the primary–secondary division, defining primary cardiomyopathies as diseases predominantly confined to heart muscle and secondary as cardiac disorders with pathological myocardial involvement as part of generalized systemic disorders. However, close examination of the disorders listed under each heading soon reveals the challenge of categorizing the diverse range of pathologies that cause myocardial disease in this way; for example, mitochondrial cytopathies, the embodiment of multisystem disease, are listed under the heading of primary disorders. The European Society of Cardiology Working Group’s strategy was to abandon the division of primary and secondary altogether, thereby avoiding the arbitrary definitions that have dogged previous classifications.

Maron et al’s definition of HCM is essentially a rewrite of that proposed in the AHA classification. They define HCM as myocardial hypertrophy that “based on careful clinical examination” appears to be confined to the heart and is either caused by a mutation in a sarcomere-encoding gene or “alternatively is unresolved.” This definition differs little from the historical construct in that “unresolved hypertrophy” is simply another way of saying unknown etiology and “careful clinical examination” is a reference to the exclusion of hypertrophy caused by systemic diseases. The only major innovation in this proposal is the inclusion for the first time, of a specific etiology, namely hypertrophy caused by sarcomere protein gene mutations. The authors’ rationale is that the majority of people with otherwise unexplained hypertrophy have mutations in cardiac sarcomeric protein genes. The problem is that the evidence to support this contention comes from studies in highly selected cohorts with a bias toward patients with familial disease. When unselected community populations are screened for sarcomere protein gene mutations, the yield is <20%. It seems irrational, therefore, to make this a defining feature of the disease.

The current debate on the taxonomy of heart muscle disorders centers on the relative merits of systems based on etiology (genetics) compared with the traditional approach based on clinical phenotypes (ventricular morphology and physiology). The emergence of new information from genetic studies means that much of what was previously unexplained myocardial disease can now be attributed to mutations in genes encoding structural and regulatory cardiac proteins. Theoretically, therefore, myocardial disease could be redefined according to the underlying genetic defect. However, patients present not as genetic defects but as clinical phenotypes that determine not only disease management but also any subsequent genetic screening strategy. Even when a genetic mutation is identified, the fact that mutations in different genes can give rise to the same morphology and conversely, the same mutation, can cause different disease phenotypes, means that a molecular classification has little resonance or relevance to everyday clinical practice.

In their attempt to make the case for a change in the definition of HCM, Maron et al somewhat overstate the problems that clinicians and researchers have encountered over the past 50 years. The publication of many thousands of articles on the subject suggests that the terminology works well in most circumstances. It is our view that the imperfections in the definition of HCM are best resolved by adoption of the approach outlined in the European Society of Cardiology classification, which begins with a careful assessment of the disease phenotype (cardiac and extracardiac) and then proceeds in a logical way to the elucidation of the etiology. We believe that this approach is more likely to benefit patients than a protracted debate on semantics and a theoretical nosological construct that will be almost impossible to apply in everyday clinical practice.

Disclosures
Dr Elliott is Vice-chairman of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. Drs Elliott...
and McKenna are authors of the European Society of Cardiology Working Group’s position statement on the classification of cardiomyopathies.

References

Response to Elliott and McKenna

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We have carefully read the rebuttal to our editorial by Elliott and McKenna, and we take great exception to their argument, as well as to the general tone of their critique. Furthermore, their objection to characterizing hypertrophic cardiomyopathy (HCM) in genomic terms is surprising in that it simply does not take into account the incremental information obtained over the last decade, nor is their persistent and self-serving comparison to a separate controversy concerning the classification of cardiomyopathies relevant. In the process of converting this rebuttal into yet another contentious “us versus them” (European versus United States) debate, we believe Elliott and McKenna have basically misunderstood and mischaracterized our editorial and motives for writing. Here are our specific responses regarding the nomenclature of HCM, based on clinical and genetic investigations, which have advanced our understanding of this disease over the last 20 years. In this context, the clinical diagnosis of HCM is most appropriate for those patients in whom overt disease expression (ie, left ventricular [LV] hypertrophy) is confined to the heart, particularly when mutations encoding proteins of the cardiac sarcomere are identified (or when the genetic substrate is unresolved, which is often the case at present). Therefore, HCM is a disease of LV hypertrophy, which is independent of (and not explained by) overt systemic processes. We exclude from this clinical diagnosis those systemic, metabolic, or multiorgan syndromes that can mimic true HCM (due to increased LV wall thickness), but which often require substantially different management strategies. In other words, not all examples of LV hypertrophy are in fact HCM, and clinical genetics provides a rigorous strategy for structuring the classification of otherwise unexplained LV hypertrophy. Although HCM has been an identifiable clinical entity for 5 decades, we nevertheless recognize the contribution of molecular genetics to this diagnosis. Indeed, what is the point in turning back the clock on this area of science? These are the views that this group of authors (with an accumulated experience of 175 years in HCM and cumulatively more than 1,500 reviewed publications) believe to be both prudent and reasonable, but hardly “irrational,” as unfairly and remarkably characterized by Elliott and McKenna.
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