How should hypertrophic cardiomyopathy be classified?

What’s in a Name? Dilemmas in Nomenclature Characterizing Hypertrophic Cardiomyopathy and Left Ventricular Hypertrophy

Barry J. Maron, MD; Christine E. Seidman, MD; Michael J. Ackerman, MD, PhD; Jeffrey A. Towbin, MD; Martin S. Maron, MD; Steve R. Ommen, MD; Rick A. Nishimura, MD; Bernard J. Gersh, ChB, MB, DPhil

A lmost 50 years of study have underscored the considerable heterogeneity in clinical presentation, natural history, morphology, and the genetic substrates that characterize inherited hypertrophic cardiomyopathy.1–5 Similarly, the nomenclature applied to this complex cardiac disease has persistently created a measure of confusion for both patients and physicians with regard to the definition and perceptions of the disease. This ambiguity has had, in turn, substantial impact on accurate diagnosis, full understanding of disease expression, and ultimately, decisions regarding management. At this juncture, it would seem appropriate and timely to conceptually revisit and clarify this important issue of names, consistent with the evolving knowledge of the cardiomyopathies.6

Response by Elliott and McKenna see p 86

Historical Context
The historical confusion over the names used to describe the entity of hypertrophic cardiomyopathy has arisen over the years in 2 fundamental areas. The first of these concerns the nomenclature used in prior efforts to characterize the disease. For example, at last count there are more than 80 individual names that have been used over the last 5 decades (most by early investigators) to describe the disease entity, which is the subject of this commentary (ie, hypertrophic cardiomyopathy)7 (Figure 1). It is likely that the confusing array of designations used to describe hypertrophic cardiomyopathy has also undoubtedly contributed to its relatively low visibility among the general public despite a prevalence (ie, 1:500), which greatly exceeds that of many other better known but less common cardiac or noncardiac diseases8,9 (Figure 2). Furthermore, nomenclature that was once popular in the 1960s and 1970s, such as idiopathic hypertrophic subaortic stenosis (IHSS) or hypertrophic obstructive cardiomyopathy (HOCM), are potentially confusing by virtue of their inference that obstruction to left ventricular (LV) outflow is an invariable and obligatory component of the disease, when in fact fully one-third of patients have the nonobstructive form.10 However, this particular issue has now been largely resolved. Although terms such as idiopathic hypertrophic subaortic stenosis and hypertrophic obstructive cardiomyop-
Asymmetrical hypertrophic cardiomyopathy
Asymmetrical hypertrophy of the heart
Asymmetrical septal hypertrophy
Brock’s disease
Diffuse muscular subaortic stenosis
Diffuse subvalvular aortic stenosis
Dynamic hypertrophic subaortic stenosis
Dynamic muscular subaortic stenosis
Familial hypertrophic subaortic stenosis
Familial hypertrophic cardiomyopathy
Familial muscular subaortic stenosis
Familial myocardial disease
Functional aortic stenosis
Functional hypertrophic subaortic stenosis
Functional obstructive cardiomyopathy
Functional obstruction of the left ventricle
Functional obstructive subvalvular aortic stenosis
Functional subaortic stenosis
Hereditary cardiovascular dysplasia
HYPERTROPHIC CARDIOMYOPATHY (HCM)
Hypertrophic constrictive cardiomyopathy
Hypertrophic hyperkinetic cardiomyopathy
Hypertrophic infundibular aortic stenosis
Hypertrophic nonobstructive cardiomyopathy
Hypertrophic obstructive cardiomyopathy (HOCM)
Hypertrophic stenosing cardiomyopathy
Hypertrophic subaortic stenosis
Idiopathic hypertrophic cardiomyopathy
Idiopathic hypertrophic obstructive cardiomyopathy
Idiopathic hypertrophic subaortic stenosis (IHSS)
Idiopathic hypertrophic subvalvular stenosis
Idiopathic muscular hypertrophic subaortic stenosis
Idiopathic muscular stenosis of the left ventricle
Idiopathic myocardial hypertrophy
Idiopathic stenosis of the flushing chamber of LV
Idiopathic ventricular septal hypertrophy
Irregular hypertrophic cardiomyopathy
Left ventricular muscular stenosis
Low subvalvular aortic stenosis
Muscular aortic stenosis
Muscular hypertrophic stenosis of LV
Muscular stenosis of the left ventricle
Muscular subaortic stenosis
Muscular subvalvular aortic stenosis
Non-dilated cardiomyopathy
Nonobstructive hypertrophic cardiomyopathy
Obstructive cardiomyopathy
Obstructive hypertrophic aortic stenosis
Obstructive hypertrophic cardiomyopathy
Obstructive hypertrophic myocardiopathy
Obstructive myocardiopathy
Pseudoaortic stenosis
Stenosing hypertrophy of the left ventricle
Stenosis of the ejection chamber of LV
Subaortic hypertrophic stenosis
Subaortic idiopathic stenosis
Subaortic muscular stenosis
Subvalvar aortic stenosis of the muscular type
Teare’s disease

Figure 1. The multitude of names used to describe hypertrophic cardiomyopathy in the literature. Many of these traditional terms, such as idiopathic hypertrophic subaortic stenosis, hypertrophic obstructive cardiomyopathy, and muscular subaortic stenosis, emphasize obstruction to left ventricular outflow to the exclusion of the nonobstructive form of the disease.

Figure 2. The prevalence of hypertrophic cardiomyopathy in the general population substantially exceeds that of several other cardiac and noncardiac diseases, which paradoxically have achieved greater recognition in the public sphere.

The Problem
The second nomenclature issue, and the focus of this discussion, relates to the differential diagnosis of hypertrophic cardiomyopathy with other congenital and familial diseases (largely of childhood) in which increased LV wall thickness is a prominent clinical feature. Some of these diseases harbor cardiac phenocopies in which the pattern and magnitude of LV hypertrophy clinically mimics hypertrophic cardiomyopathy due to sarcomere protein mutations. Perhaps the most common example is Noonan syndrome, an autosomal dominant cardiofacial condition also associated with pulmonary valve dysplasia and septal defects, which is caused by mutations in the PTPN11 gene, as well as those that encode protein components of tyrosine kinase signal-transduction pathways (RAF1, KRAS, SOS1).6,11

Other rare conditions that fall under this umbrella of sarcomere-related cardiomyopathies10 are mitochondrial myopathies caused by mutations encoding mitochondrial DNA (including Kearns-Sayre syndrome) or mitochondrial proteins associated with ATP electron transport chain enzyme defects altering mitochondrial morphology; metabolic myopathies representing ATP production and utilization defects involving abnormalities of fatty acid oxidation (acyl CoA dehydrogenase...
deficiencies); carnitine deficiency; infiltrative myopathies, ie, glycogen storage diseases (type II; autosomal recessive Pompe disease); as well as Hunter and Hurler diseases, and the transient nonfamilial cardiomyopathy, which is part of a generalized organomegaly occurring in infants of insulin-dependent diabetic mothers. In addition, disorders such as Danon disease, due to abnormalities of lysosomal membrane, Barth syndrome, and the glycogen storage-like disease caused by AMP-kinase deficiency have more recently been described. In older patients, systemic diseases associated with LV hypertrophy include Friedreich ataxia, pheochromocytoma, neurofibromatosis, lentiginosis, and tuberous sclerosis, as well as Fabry disease, an X-linked recessive disorder of glycosphingolipid metabolism caused by a deficiency in the lysosomal enzyme α-galactosidase A, resulting in intracellular accumulation of glycosphingolipids.

The Clinical Definition
The generally accepted clinical definition of hypertrophic cardiomyopathy, independent of age, is a disease state characterized by unexplained LV hypertrophy associated with a nondilated ventricular chamber, in the absence of another cardiac or systemic disease, which itself would be capable of producing the magnitude of hypertrophy evident in a given patient. The diagnosis of hypertrophic cardiomyopathy in the clinical arena may be buttressed by other characteristic non–morphological features such as family history of the disease, symptoms, and ECG abnormalities.

Therefore, use of the term hypertrophic cardiomyopathy to describe patients with LV hypertrophy in whom the aforementioned syndromes or conditions, including the relatively common Noonan syndrome, are known to be present (or are strongly suspected) is inconsistent with this nomenclature.

Impact of Genetics
This inadvisable practice of assigning the term hypertrophic cardiomyopathy to many diseases associated with LV hypertrophy, including even systemic hypertension, precedes the genomic era for cardiomyopathies. The advent of molecular diagnosis has raised the level of complexity regarding the most appropriate nomenclature for such diseases. In this regard, genetic testing has contributed both valuable insights into the molecular basis of the diverse hypertrophic cardiomyopathy disease spectrum and has now become a powerful diagnostic aid through commercially available (ie, non–research-laboratory) DNA-based testing for disease-causing mutations.

Based on available genotype-phenotype data, hypertrophic cardiomyopathy has been generally regarded as a disease entity caused by dominant mutations in genes encoding protein com-

---

**Figure 3.** Summary of nomenclature that distinguishes hypertrophic cardiomyopathy from other genetic diseases associated with LV hypertrophy. At this time, the overwhelming evidence links the clinical diagnosis of hypertrophic cardiomyopathy with a variety of genes encoding protein components of the cardiac sarcomere. However, it is possible that in the future other nonsarcomeric (but also nonmetabolic) genes may prove to cause hypertrophic cardiomyopathy.
ponents of the sarcomere and its constituent myofilament components.\textsuperscript{1,5,16,17} Indeed, at present, the weight of evidence supports the concept that the majority of genes and mutations, which are responsible for clinically diagnosed hypertrophic cardiomyopathy in adult patients, encode proteins of the sarcomere.\textsuperscript{1,3,16,17} However, it is unresolved as to whether these sarcomere protein mutations are primarily causative, or alternatively act as triggers for a cascade of protein-protein interactions resulting in the final common pathway of sarcomeric dysfunction\textsuperscript{18} is unresolved.

Eleven genes of the sarcomere have been identified as responsible for this disease, but with a wide range in frequency, most commonly the \(\beta\)-myosin heavy chain (the first identified) and myosin-binding protein C genes. The other 9 genes appear to account for far fewer cases and include troponin T and I, \(\alpha\)-tropomyosin, regulatory and essential myosin light chains, titin, \(\alpha\)-actin, \(\alpha\)-myosin heavy chain, and muscle LIM protein (MLP). This intergenic diversity is compounded by considerable intragenic heterogeneity, with >400 mutations identified among the 11 genes (http://cardiogenomics.med.harvard.edu).

Several other mutant genes have been promoted as disease-causing for hypertrophic cardiomyopathy, although with lower levels of evidence.\textsuperscript{5,19,20}

However, the presentation of LV hypertrophy may be based on very different mechanisms. It is now evident that metabolic or storage disorders in older children and young adults can mimic hypertrophic cardiomyopathy due to sarcomere protein mutations, eg, conditions involving the gene encoding \(\gamma\)-2-regulatory subunit of the AMP-activated protein kinase (PRKAG2) and the X-linked lysosome-associated membrane protein gene (LAMP2; Danon disease).\textsuperscript{10,12,13}

In both PRKAG2 and LAMP2, clinical manifestations predominantly (but not solely) involve the heart, with variable degrees of LV hypertrophy, and frequently ventricular preexcitation. PRKAG2 is an infiltrative glycogen storage disease of children and young adults, as is Pompe disease, which is a glycogen storage disease of infants due to \(\alpha\)-1,4 glycosidase (acid maltase) deficiency.\textsuperscript{13}

Penetration of genetic testing into routine cardiovascular practice, although increasing, is presently incomplete, all mutations responsible for unexplained LV hypertrophy are not yet known, and only a small proportion of patients with clinically diagnosed hypertrophic cardiomyopathy have been genotyped. Consequently, it should be underscored that the present discussion of nomenclature does not advocate for clinical diagnosis based solely on genetic analysis. It is also apparent that the perspective presented here is perhaps best regarded as a “snapshot” in time for a potentially dynamic process that is likely to evolve further. Undoubtedly, patients with both LV hypertrophy and clinical findings consistent with hypertrophic cardiomyopathy will be identified with other mutant genes that encode either non-myofilament sarcomere protein components or proteins regulating calcium homeostasis, metabolic diseases (other than LAMP2 or PRKAG2), and mitochondrial cardiomyopathies,\textsuperscript{12,13} but nevertheless recapitulate the basic underlying pathology created by the known disease-causing sarcomeric mutations.

**Final Perspectives and Recommendations**

In clinical practice, 2 perspectives on the nomenclature for hypertrophic cardiomyopathy have evolved. The first scenario most commonly arises in pediatric cardiology, where a sizable proportion of younger patients with cardiomyopathy and LV hypertrophy (including some with a positive family history) do not carry sarcomeric mutations.\textsuperscript{21} Among this group, a variety of phenotypic expressions (with LV hypertrophy) have been regarded as examples of hypertrophic cardiomyopathy, even in those circumstances in which patients are clearly afflicted by a variety of other syndromic conditions.\textsuperscript{22,23} This approach not only splits hypertrophic cardiomyopathy into a multitude of diverse diseases, many of which are presently known to have different genetic substrates, but also ignores the voluminous literature published over 50 years, which describes the specific disease entity known as hypertrophic cardiomyopathy in thousands of patients (most of whom are adults and likely with sarcomere protein mutations).\textsuperscript{1} To abandon that half-century old construct would potentially create even more confusion for both patients and clinicians.

Consequently, it would seem preferable that the myriad of clinically diverse genetic syndromes associated with LV chamber hypertrophy (most of which are identified in the pediatric age group) should not be designated as part of the hypertrophic cardiomyopathy disease spectrum. For example, nomenclature that describes patients with “Noonan hypertrophic cardiomyopathy,” is discouraged, whereas “Noonan syndrome with cardiomyopathy” or “Noonan cardiomyopathy” seem most prudent and are preferred, enabling clinicians to communicate effectively regarding clinical phenotypes.

Therefore, we support an alternative nomenclature that comes closest to the reality of contemporary clinical practice, by recognizing the important impact that genetic substrates have on the names used to describe heart muscle diseases with LV hypertrophy. To minimize confusion, we believe the most prudent recommendation should be that hypertrophic cardiomyopathy (and the acronyms HCM or HC) remains a clinical diagnosis limited to those patients in whom: (1) overt disease expression with LV hypertrophy, based on careful clinical examination, appears to be confined to the heart and (2) the disease-causing mutation is either known to be sarcomeric or is unresolved (Figure 3).

This definition would exclude systemic, metabolic, or multi-organ syndromes associated with increased LV wall thickness that may mimic hypertrophic cardiomyopathy. However, only when the full compliment of genes responsible for LV hypertrophy is known, and it is possible and clinically convenient to universally determine the genetic and etiologic basis for otherwise unexplained cardiac hypertrophy, will the uncertainty surrounding the evolving nomenclature of hypertrophic cardiomyopathy be definitively resolved.
Sources of Funding
This study was supported by the Howard Hughes Medical Institute (Dr Seidman) and The Hearst Foundations (Dr Maron).

Disclosures
None.

References
Response to Maron et al

Perry Elliott, MD; William J. McKenna, MD

The rationale for the definition proposed by Maron et al is that persistent confusion with regard to the definition of hypertrophic cardiomyopathy has hampered accurate diagnosis and patient management. If this were true, it is difficult to understand how several generations of clinical and basic scientists have been able to produce erudite observations on etiology, pathophysiology, clinical outcomes, and treatment of the disease. In essence, the “controversy” can be distilled to a single question—whether heart muscle disease caused by systemic disorders with extracardiac manifestations should be included under the rubric of hypertrophic cardiomyopathy. The position taken by Maron et al is that it is inappropriate to do so. In an attempt to refine the clinical definition of hypertrophic cardiomyopathy, they suggest that the term should only be used in patients with ventricular hypertrophy and a definite disease causing mutation in a cardiac sarcomeric protein gene or in patients in whom the etiology cannot be determined. However, this definition adds very little to that first proposed 50 years ago in that it simply excludes patients with systemic diseases. The emphasis on sarcomeric protein gene mutations gives the semblance of a more precise diagnosis, but as work by some of the authors of this article has shown, the fact that only a minority of patients in the community with unexplained left ventricular hypertrophy have such mutations means that it has little relevance to everyday clinical practice. Our view is that it is far better to abandon the tortuous efforts to constrain hypertrophic cardiomyopathy into a single entity in favor of a concerted effort to develop new methods for the elucidation of the cause of ventricular hypertrophy in individual patients.
How should hypertrophic cardiomyopathy be classified?: What's in a Name? Dilemmas in Nomenclature Characterizing Hypertrophic Cardiomyopathy and Left Ventricular Hypertrophy

Barry J. Maron, Christine E. Seidman, Michael J. Ackerman, Jeffrey A. Towbin, Martin S. Maron, Steve R. Ommen, Rick A. Nishimura and Bernard J. Gersh

doi: 10.1161/CIRCGENETICS.108.788703

_Circulation: Cardiovascular Genetics_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circgenetics.ahajournals.org/content/2/1/81

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Genetics_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Genetics_ is online at:
http://circgenetics.ahajournals.org/subscriptions/