How should hypertrophic cardiomyopathy be classified?

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

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Almost 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 myocardialopathy
Obstructive myocardialopathy
Pseudoaortic stenosis
Stenosing hypertrophy of the left ventricle
Stenosis of the ejection chamber of LV
Subaortic hypertrophic stenosis
Subaortic idiopathic stenosis
Subaortic muscular stenosis
Subvalvular 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.

Asymptomatic hypertrophic cardiomyopathy persist occasionally in informal usage, they rarely appear any longer in the literature, whereas hypertrophic cardiomyopathy (which allows for both the obstructive and nonobstructive hemodynamic forms) has predominated as the formal designation for this disease since it was initially promoted in 1979. 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). Other rare conditions that fall under this umbrella of sarcomere-related cardiomyopathies 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

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.
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-

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**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 com-
ponents. 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 sarco-
mere. However, it is unresolved as to whether these
sarcomere protein mutations are primarily causative, or alterna-
tively act as triggers for a cascade of protein-protein interactions
resulting in the final common pathway of sarcomeric dysfunc-
tion 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 β-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,
α-tropomyosin, regulatory and essential myosin light chains,
titin, α-actin, α-myosin heavy chain, and muscle LIM protein
(MLP). This intergenic diversity is compounded by consid-
erable intragenetic 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.

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 sarco-
mere protein mutations, eg, conditions involving the gene
coding γ-2-regulatory subunit of the AMP-activated pro-
tein kinase (PRKAG2) and the X-linked lysosome-associated
membrane protein gene (LAMP2; Danon disease).

In both PRKAG2 and LAMP2, clinical manifestations
predominantly (but not solely) involve the heart, with vari-
dable 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 α-1,4
glycosidase (acid maltase) deficiency.

Penetration of genetic testing into routine cardiovascular
practice, although increasing, is presently incomplete, all muta-
tions 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 discus-
sion 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 “snap-
shot” 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 cardiomyop-
athy 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,
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 sce-
nario 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. Among this
group, a variety of phenotypic expressions (with LV hyper-
trophy) have been regarded as examples of hypertrophic
cardiomyopathy, even in those circumstances in which pa-
tients are clearly afflicted by a variety of other syndromic
conditions. This approach not only splits hypertrophic
cardiomyopathy into a multitude of diverse diseases, many of
which are presently known to have different genetic sub-
strates, 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). To abandon that half-century old con-
struct 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 cham-
ber 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 cardiomyop-
athy,” is discouraged, whereas “Noonan syndrome with cardio-
mopathy” 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 cardiomyop-
athy (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 hyper-
trophy is known, and it is possible and clinically convenient to
universally determine the genetic and etiologic basis for other-
wise unexplained cardiac hypertrophy, will the uncertainty
surrounding the evolving nomenclature of hypertrophic cardio-
mypathy be definitively resolved.
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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.
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