Is the 2006 American Heart Association classification of cardiomyopathies the gold standard?

The 2006 American Heart Association Classification of Cardiomyopathies Is the Gold Standard

Barry J. Maron, MD

The cardiomyopathies are an important and complex group of heart muscle diseases with multiple etiologies and heterogeneous phenotypic expression. Awareness and knowledge of these diseases in both the public and medical communities have historically been impaired by periodic confusion surrounding definitions and nomenclature. Therefore, formal and systematic classifications have traditionally been viewed as useful exercises promoting greater understanding of the heart muscle diseases. Indeed, a multitude of such cardiomyopathy classifications have been advanced over the years by individual investigators and consensus panels sanctioned by medically related organizations such as the World Health Organization (WHO). These classification schemes have evolved in concert with the level of scientific understanding.

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Historical Context to the Debate

Remarkably, it was not until 50 years ago (1957) that the term cardiomyopathy was used for the first time. Over the next 25 years, a number of definitions for cardiomyopathies were advanced. Indeed, in the original 1980 WHO classification, cardiomyopathies were defined only as “heart muscle diseases of unknown cause,” reflecting a general lack of available information about basic disease mechanisms. In 1968, the WHO defined cardiomyopathies as “diseases of different and often unknown etiology in which the dominant feature is cardiomegaly and heart failure.” The final WHO classification published in 1995 proposed “diseases of myocardium associated with cardiac dysfunction” and included for the first time arrhythmogenic right ventricular cardiomyopathy/dysplasia, as well as primary restrictive cardiomyopathy.

Therefore, why was it necessary to offer yet another classification scheme for cardiomyopathies in 2006 under the auspices of the American Heart Association (AHA)? In fact, the international expert consensus panel (and writing group) found several very important reasons to take on this project. The last formal effort at developing a consensus for the classification of cardiomyopathies had been published 12 years previously in the form of a very brief and rudimentary document. Most importantly, it was apparent that with the identification of several new disease entities over the prior decade and a virtual explosion in diagnostic capability with the introduction and penetration of modern molecular biology into cardiovascular medicine and more precise knowledge of the basic causes and phenotypic expression of cardiomyopathies, the WHO classification had been rendered obsolete.
Indeed, out of this genomic revolution the ion channelopathies emerged as important causes of sudden death in the young, caused by mutations in proteins leading to dysfunctional sodium, potassium, and calcium ion channels and predisposed to potentially lethal ventricular tachyarrhythmias. These are, by definition, molecular diseases of heart muscle and without gross structural abnormalities.

**Old Ideas**

By virtue of these novel insights into the morphological and functional expression of the heart muscle diseases, older entrenched disease definitions and classifications are no longer relevant. In particular, the popular clinical classification for cardiomyopathies of “hypertrophic-dilated-restrictive” poses major limitations by mixing anatomic designations (ie, hypertrophic and dilated) with a functional one (ie, restrictive) into the same construct, and this classification probably should be abandoned. An example of confusion in nomenclature caused by “mixed phenotypes” arises with regard to hypertrophic cardiomyopathy (the most common of the purely genetic cardiomyopathies), given that this disease may appear in 2 or all 3 of the categories.

Hypertrophic cardiomyopathy is characterized by left ventricular hypertrophy, is usually restrictive in the sense that impaired diastolic filling is a common and important disease component, and furthermore may evolve into a dilated phase with systolic dysfunction as part of a remodeling process.

Similarly, amyloid and other infiltrative cardiomyopathies do not adopt uniformly static phenotypic expression, and as part of their natural history they may evolve from a nondilated (often hyperdynamic) state with ventricular stiffness to a dilated form with systolic dysfunction and heart failure.

In addition, it is often difficult to reliably distinguish dilated from nondilated forms of cardiomyopathy given that quantitative assessments of ventricular chamber size represent a continuum and patients can vary widely in their degree of cavity enlargement (often deviating only slightly from the upper limits of normal). Indeed, such ambiguities may also arise with regard to some rare and/or newly identified cardiomyopathies for which few quantitative cardiac dimensional data are available.

In other conditions, such as stress (tako-tsubo) cardiomyopathy and the transient cardiomyopathy in infants of diabetic mothers, the dynamic remodeling that occurs with clinical recovery substantially changes (and normalizes) cardiac morphology. Finally, the pure form of restrictive (nonhypertrophied) cardiomyopathy is extraordinarily rare and should not be confused with the myriad of myocardial diseases that have a component of restrictive physiology, usually with associated left ventricular hypertrophy (such as hypertrophic cardiomyopathy).

**AHA Definition**

The proposed definition of cardiomyopathies offered by the AHA expert consensus panel is as follows: a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation, due to a variety of etiologies that frequently are genetic. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, and often lead to cardiovascular death or progressive heart failure–related disability. This definition of cardiomyopathies, similar to that reported by the European Society of Cardiology (ESC), under the auspices of the Working Group on Myocardial and Pericardial Diseases, excludes myocardial involvement secondary to coronary artery disease, systemic hypertension, and valvular and congenital heart disease. Primary cardiomyopathies (ie, those solely or predominantly confined to heart muscle) are shown in the Figure from the AHA classification.

**Points of Departure With ESC**

Three major considerations relevant to the AHA cardiomyopathy definitions and classification will be addressed here because they have been the source of controversy and also some criticism from the writing panel of the recent ESC classification of cardiomyopathies, in an unpublished letter to the editor of Circulation, which in part triggered the present debate.

**Genetic Diagnosis**

It seemed self-evident and unavoidable to the AHA panel that contemporary definitions and a classification for heart muscle diseases should rely substantially on a genetic model, taking into account encoded protein expression and underlying gene mutations. Nevertheless, the panel also recognized that the penetration of commercial diagnostic genetic testing into routine clinical practice is far from complete, and molecular biology of the cardiomyopathies will also evolve considerably over the next several years.

Indeed, the AHA recommendations represent (and function as) a robust but flexible “living document” that will continue to be largely relevant in the future as new data emerge and genetic testing becomes more routine. The ESC inference (in 2008) that contemporary understanding of the cardiomyopathies is only confused by genetic diagnostic labeling seems to be a reversion to the old 1995 WHO classification. Furthermore, the ESC classification itself segregates the cardiomyopathies into “familial/genetic” and “nonfamilial/nongenetic” categories seemingly indistinguishable from the AHA nomenclature, which also uses “genetic/acquired (nongenetic).” Therefore, at least in this respect, the AHA and ESC presentations do not appear to differ significantly.

**Clinical Utility**

Neither the AHA nor the ESC presentations represent comprehensive guides that dictate precise, clinical diagnostic strategies for each of the cardiomyopathies. Nevertheless, the ESC promotes their document as an improved “clinically oriented” classification with “utility for “everyday practice,” which serves as an improved guide for diagnosis emphasizing specific morphological and functional phenotypes.
ever, on close inspection, the ESC\textsuperscript{10} and AHA\textsuperscript{1} do not differ substantially in this regard because both in fact rely on specific structural disease states (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia) as the basis for the classification.

**Inclusion of Ion Channelopathies**

Given the basic definition for cardiomyopathies established by the AHA consensus panel,\textsuperscript{1} inclusion of ion channelopathies (ie, clinically expressed long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia)\textsuperscript{14–16} in the classification scheme seems reasonable and appropriate (if not unavoidable), although admittedly a distinct departure from prior efforts. Within the AHA definition, cardiomyopathies are associated with failed myocardial performance that may be either mechanical (eg, diastolic or systolic dysfunction) or electrical. Indeed, the ion channelopathies are a constellation of related primary electrical diseases that do not express gross or histopathological abnormalities, in which the structural and functional myocardial abnormalities responsible for arrhythmogenesis exist at the molecular level within the cell membrane.\textsuperscript{14} Therefore, the basic pathological abnormality in this group of diseases cannot be identified by conventional noninvasive imaging or myocardial biopsy, or by autopsy examination of tissue.

Nevertheless, the AHA panel was justified in including ion channelopathies in a contemporary classification of cardiomyopathies on the basis of the scientific assertion that ion channel mutations are responsible for altering biophysical properties and protein structure, thereby creating structurally abnormal ion channel interfaces and architecture. The fact that mutations in genes encoding ion channel proteins have been reported in patients with other cardiac diseases, a criticism made by the ESC,\textsuperscript{10} is not a particularly compelling argument against our inclusion of the ion channelopathies.

**Conclusions**

As stated in the abstract summary of the AHA document,\textsuperscript{1} formal classifications of heart muscle diseases have proved to be exceedingly complex and, in many respects, contradictory. Indeed, given the heterogeneous nature of the cardiomyopa-
thies, there probably is no single classification that can be regarded as generally acceptable to all interested parties from diverse disciplines, including clinical and research physicians, epidemiologists, molecular biologists, and other basic scientists. Nevertheless, the precise language used to describe each of these diseases remains profoundly important. The AHA reference document affords a rigorous framework and contributes a large measure of clarity to the understanding of these heart muscle diseases. In particular, this classification scheme represents a contemporary model relying substantially on the contribution of molecular biology to the cardiomyopathies and is notable for the inclusion of the ion channelopathies in this group of diseases for the first time.

Disclosures

None.

References


Response to Maron

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It is reassuring that Dr Maron agrees that the ESC and AHA classifications share a great deal in their philosophy and design. Perhaps the most perplexing disagreement relates to the core foundation of both classification systems. Dr Maron’s contention is that advances in molecular medicine have made the old morphological classification “obsolete.” He describes the shortcomings, as he sees them, of terms such as hypertrophic and dilated cardiomyopathy and concludes that the existing anatomic nosology “probably should be abandoned” in favor of a molecular system. Later in his commentary, he points out that the ESC and AHA classifications are very similar in that they “both in fact rely on specific structural disease states (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia) as the basis for the classification”—a statement that I fully endorse but that completely contradicts his earlier argument. The aim of both the AHA and ESC classifications is to provide cardiologists with a terminology that helps them to describe what they see in the clinic. I agree that there are some shortcomings of an anatomic system, but these are, in my view, considerably overstated. The real challenge, which will be addressed by the ESC working group in subsequent position statements, is the diagnostic process that follows the recognition of a clinical phenotype. Inevitably, we continue to disagree about the issue of ion channel disease. The counterargument is quite clear. If one accepts the AHA panel’s definition of cardiomyopathies as “diseases of the myocardium associated with mechanical and/or electrical dysfunction,” then logic dictates that virtually every disorder that affects the heart should be regarded as a cardiomyopathy. I am sure that the AHA panel would not endorse such a clearly absurd idea, but it illustrates the confusion that can arise when theory and the practicalities of real-life clinical medicine diverge. As stated in my commentary, the ESC panel was content with the idea that specific ion channel gene mutations might be a rare cause of cardiomyopathy but found the notion that the terms channelopathy and cardiomyopathy are interchangeable unhelpful. Finally, I agree with Dr Maron’s view that “precise language” is very important. Both classifications are a little fuzzy in some areas, reflecting a lack of hard data and the inevitable limitations of a biological taxonomy. However, it is very likely that some of the terminology used in the AHA proposal will be difficult to translate into the clinical setting. For example, the term predominant, which is used to define primary heart muscle disease, is entirely subjective. Similarly, the term mixed, used to categorize cardiomyopathies that can be either genetic or acquired, is vague and of little clinical utility. A clinical classification should be simple and relevant to everyday medical practice. The ESC working group’s classification achieves this goal and, by highlighting the importance of familial disease, will result in more accurate diagnoses and better outcomes for patients.
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