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

The 2006 American Heart Association Classification of Cardiomyopathies Is Not the Gold Standard

Perry Elliott, MBBS, MD, FRCP

The truth is rarely pure and never simple.
Oscar Wilde, *The Importance of Being Earnest*, Act I, 1895

Even a cursory examination of the medical literature from the past 100 years reveals that many proposed disease classifications were never adopted because they were too complex or irrelevant to everyday clinical practice; others fell victim to the onward march of medical knowledge. The term *cardiomyopathy* was first used more than 40 years ago to describe myocardial disorders that could not be explained by hemodynamic disturbances (such as valve disease and hypertension) or multisystem diseases; heart muscle disorders with an identifiable etiology were initially termed *specific heart muscle diseases* but were later renamed *specific cardiomyopathies*.1 Remarkably, this method of describing disorders of heart muscle has survived to the present day with only minor changes and remains a cornerstone of clinical practice and scientific research. Recently, expert committees of the American Heart Association (AHA) and the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases have proposed updated versions of the cardiomyopathy classification system.2,3 The aims of both groups were to resolve a number of ambiguities in the existing classification and to incorporate knowledge gleaned from recent advances in molecular genetics. Unfortunately, an unintended consequence of these independent initiatives is that attention will, for a time, be diverted toward debates on taxonomy rather than the advancement of knowledge. In this brief commentary, I have tried to avoid a polemic on the merits of one or the other classification and instead to focus on their similarities. The hope is that by emphasizing the common ground, this temporary breakdown in the consensus of the last half a century can be restored.

Response by Maron p 80

The AHA Classification

The AHA panel gave a number of reasons for revisiting the classification of cardiomyopathies.2 These include the following: “the identification of new disease entities, advances in diagnosis, and precise knowledge of causation; the rapid evolution of molecular genetics in cardiology; and the emergence of ion channelopathies as diseases predisposing to potentially lethal ventricular tachyarrhythmias.” The AHA panel concluded that, as a result of these developments, some disease definitions have become outdated, and the current classification system is obsolete. Despite this unequivocal position, the panel’s suggested replacement is still based on the time-honored division into primary and secondary cardiomyopathies—primary, in this instance, referring to diseases
solely or predominantly confined to heart muscle and secondary referring to cardiac disorders with “pathological myocardial involvement” as part of generalized systemic disorders. The first real departure from the existing convention is the subclassification of primary cardiomyopathies into genetic, mixed (genetic and nongenetic), and acquired forms. The second and more important innovation is the redefinition of ion channelopathies as primary, genetic cardiomyopathies.

The ESC Classification
The ESC working group’s proposal also recognized the limitations of the current classification system, in particular the fact that the distinction between primary and secondary heart muscle disease has become increasingly tenuous as the etiology of previously idiopathic disorders has been discovered. Their solution, however, is not to reconstruct the primary and secondary categorization but instead to abandon it altogether, thereby avoiding the arbitrary definitions that have dogged previous revisions. The existing morphological subtypes of cardiomyopathy (eg, hypertrophic, dilated, restrictive) are retained with some modifications, but they are separated into familial (or genetic) and nonfamilial (or nongenetic) subtypes (Figure). This is an explicit attempt to encourage a move away from the existing exclusion-based system toward a more logical and thorough search for diagnostic markers and, it is hoped, in time to more individually tailored therapies.

Should Ion Channelopathies Be Reclassified as Cardiomyopathies?
Perhaps the most controversial aspect of the AHA classification is its redesignation of ion channelopathies. The rationale behind this bold notion is that mutations in genes encoding ion channel proteins “are responsible for altering biophysical properties and protein structure, thereby creating structurally abnormal ion channel interfaces and architecture.” This proposal has already stimulated considerable debate, with protagonists and antagonists lining up on either side of the argument, armed with data supporting their respective views. The ESC working group was unanimously against this proposal, if only because its members felt that it would be inappropriate (and of limited clinical utility) to reclassify a whole group of diseases that have little or no clinically detectable (or relevant) effect on cardiac morphology and hemodynamics. Having reflected on this issue, I wonder if the problem is not the concept of reclassification per se but the ambiguity of the phrase ion channelopathy. For most cardiologists, this term is used as shorthand for a group of syndromes that are defined with the use of specific ECG criteria, for example, prolongation of the QT interval in long QT syndrome. To a molecular biologist, however, ion channelopathy refers to the biophysical consequences of an alteration in protein structure. Although these 2 concepts are clearly related, they are not synonymous. The clinical syndromes are not always caused by ion channel gene mutations, and, conversely, ion channel gene mutations may not result in a recognizable clinical phenotype. This is a perfect illustration of the problem encountered when one attempts to meld a molecular taxonomy with a clinical classification. The difficulty with the AHA proposal is not the concept that ion channel gene mutations might be a rare cause of heart muscle disease but rather the confusion that will be created by suggesting that all ion channelopathies are cardiomyopathies, when (as is the case) the term is used to describe syndromes defined exclusively by their electrophysiological characteristics. For this reason, it is probably wiser, once further studies have corroborated the link between ion channel gene mutations and structural heart disease, to consider ion channel gene mutations as one of the many causes of existing cardiomyopathy subtypes (in the same way that sarcomeric protein gene mutations are a cause of hypertrophic cardiomyopathy) rather than to create a whole new class of arrhythmogenic cardiomyopathies.

Figure. Summary of the ESC Working Group on Myocardial and Pericardial Diseases classification of cardiomyopathies. The division into primary and secondary causes is abandoned, and diseases are grouped according to whether they are familial (genetic) or nonfamilial (nongenetic). Disease subtype refers to individual genetic or nongenetic causes of specific morphological phenotypes. HCM indicates hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; and RCM, restrictive cardiomyopathy. Adapted from Elliott et al with permission from Oxford University Press. Copyright 2008 European Society of Cardiology.

Are Genetics Relevant to Classification?
As already stated, an inspiration for the revision of the classification of cardiomyopathies was the recognition that many of them are familial. This has led to a call for a classification system based on the underlying genetic or molecular pathology to replace the existing clinical model. Such an approach would (it is argued) promote greater awareness of the molecular basis of disease and provide a framework for the study of disease mechanisms. Despite appearances to the contrary, neither the AHA nor the ESC proposal fully endorses this philosophy. The AHA document states that “it probably is premature and inadvisable at this time to preferentially formulate a classification that is entirely dependent on genomics.” A very similar view was taken by the ESC working group, which felt that a “clinically oriented classification system in which heart muscle disorders are...
grouped according to ventricular morphology and function remains the most useful method for diagnosing and managing patients and families with heart muscle disease.” The starting point for the AHA and ESC proposals is essentially the same as that used in all previous versions of the classification, namely, the identification of specific patterns of abnormal ventricular function and morphology. The important role of genetics in the etiology of many cardiomyopathies is acknowledged by the creation of subsidiary categories of genetic, mixed, and acquired in the AHA system and familial and nonfamilial in the ESC scheme. An obvious question that arises from this approach is why, despite the great emphasis on genomics in both documents, did the AHA and ESC groups shy away from a more radical reworking of the classification system? The explanation, at least for the ESC working group, was the desire to ensure that the classification system remains relevant to everyday clinical practice. Consider, for a moment, the pathway that patients follow on their journey to a diagnosis of cardiomyopathy: Most will present with symptoms of cardiac dysfunction that result in referral to a clinician; after an evaluation of symptoms, family history, and physical signs, patients are then subjected to a series of investigations that describe the morphology and physiology of their hearts; identification of a cardiac morphology corresponding to one of the classic phenotypes results in a diagnosis of cardiomyopathy; and finally, genetic investigation of the patient and their family is performed, guided by the clinical findings and family pedigree. In this model, it is the phenotype that drives the search for a particular genotype and not the other way around. It could be argued that the greater use of predictive genetic testing in the relatives of patients with an identified mutation radically changes this approach to diagnosis, but even in this scenario the detection of clinically relevant disease in gene carriers usually requires the demonstration of a clinical phenotype. Thus, although ongoing efforts to understand the genetic basis of cardiomyopathies will continue to provide valuable insights into disease mechanisms, it seems premature to call for a purely molecular classification.

The Future

So how do the AHA and ESC systems compare? They are based on the same premise, that the purpose of the classification system is to assist diagnostic (and therapeutic) decision making; they use similar morphological and physiological parameters to codify subtypes of cardiomyopathy; and they each subclassify disease into genetic and nongenetic forms. The handling of ion channel disease is a major difference, but it is likely that time and further research will resolve this issue. In the final analysis, neither the AHA nor the ESC classification should be elevated to the contrived status of “a gold standard” because neither proposal fully describes the complexity of this heterogeneous group of disorders. Classification systems should be subject to constant review to ensure that they reflect new information and different ways of thinking. The current situation in which we have 2 classifications is unfortunate, and in the short term, clinicians will have to choose the system that is most applicable to their everyday practice. It is hoped that the common principles at the heart of both classifications will provide the basis for a joint revision in the not too distant future.

Disclosures

Dr. Elliott is secretary to the ESC Working Group on Myocardial and Pericardial Disease and an author of the ESC Working Group’s position statement on the classification of cardiomyopathies.

References

Response to Elliott

Barry J. Maron, MD

On behalf of the expert consensus panel, my answer to the question addressed here: “Is the 2006 American Heart Association classification of cardiomyopathies the new gold standard?” remains as follows: The AHA classification is the most contemporary and compelling version available. The AHA writing panel believes that they fulfilled their objective to be modern, relevant, and clear in the course of this endeavor. However, we must also acknowledge Dr Elliott’s point that this fundamental question itself may not be entirely appropriate, in the sense that no classification of heart muscle disorders can completely satisfy all interested parties and diverse perspectives, largely because of the heterogeneity of the diseases involved. Therefore, by inference, probably no classification of cardiomyopathies can be regarded as a true gold standard to the exclusion of all others. However, Dr Elliott is not entirely correct in asserting that this controversy is simply an exercise in semantics. The precise language used to describe each of these complex diseases can often take on profound importance. Furthermore, despite his eloquent discussion, it remains unclear why Dr Elliott’s report from the ESC Working Group on Myocardial and Pericardial Diseases should be considered more relevant to “everyday clinical practice” than would the AHA statement. Indeed, this argument is a mystery because both documents do not serve (and are not designed to serve) as “cookbook” guides to clinical diagnosis. After all, it is not as if physicians will approach the patient’s bedside with either the ESC or AHA classification in hand. In addition, it is difficult to understand the ESC reticence to fully embrace genomics in their current classification, given that all parties agree that the majority of cardiomyopathies have a genetic etiology. On the other hand, we are in accord with Dr Elliott that a pure molecular model is premature at this time. The unanimous agreement of the ESC panel to exclude ion channelopathies from the cardiomyopathies (because they are not associated with a detectable effect on cardiac structure) represents a bias favoring traditional morphological definitions, a position the AHA panel considered outdated and obviously rejected. Alterations in protein structure creating abnormal ion channel interfaces and architecture are undoubtedly responsible for primary electric and molecular diseases such as long QT syndrome and Brugada syndrome, although this pathology cannot be directly visualized or imaged. Dr Elliott has touched on an interesting point that rings true, ie, that we have here 2 new classifications of cardiomyopathies, 1 from the United States (although with an international writing group) and 1 that is purely European. This is consistent with the increasing appearance over the last few years of many parallel guidelines coming independently from the AHA/American College of Cardiology (and/or Heart Rhythm Society) on the one hand and the ESC on the other. These documents often address the same management issues, usually without major contradictions. Similarly, with the 2 cardiomyopathy classifications discussed and dissected here, 2 literatures have been created when a joint effort might well have lessened the inevitable confusion created for the cardiovascular community.
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