European Heart Journal (2008) **29**, 144–146
doi:10.1093/eurheartj/ehm585

EDITORIAL

Revisiting definition and classification of cardiomyopathies in the era of molecular medicine

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Online publish-ahead-of-print 22 December 2007

This editorial refers to 'Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases' by P. Elliott *et al.*, on page 270

Primary myocardial diseases have always attracted the attention of the scientific community because of their obscure aetiopathogenesis, and for years there was confusion and controversy regarding their nosography and taxonomy. Since the first WHO official classification,[1] tremendous progress has been made.[2] Novel entities have been discovered, requiring an update of the classification in 1995,[3] and the aetiology of many forms has been clarified.

The Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology (ESC) recently published a position statement[4] different from the 2006 American Heart Association (AHA) scientific statement.[5]

The scope of the present editorial is to deal with the nosographic impact of the advances made since 1995 and to comment on the ESC position statement which has been designed to provide a valid tool for routine clinical practice.

Revision of the definition and classification of cardiomyopathies in 1995

The discovery of novel cardiomyopathies, namely arrhythmogenic right ventricular cardiomyopathy (ARVC), primary restrictive cardiomyopathy, and non-compacted myocardium, made a revision of the 1980 classification compulsory, and this led to many substantial, though often questionable, changes.[3] Moreover, taking into consideration that the aetiology was becoming clearer and clearer, the definition was changed from 'heart muscle disease of unknown aetiology' into 'myocardial disease associated with cardiac dysfunction', the term dysfunction meaning both mechanical and electrical abnormality. In the new classification, ARVC[6,7] and restrictive cardiomyopathy[8] were added to the primary forms, whereas the non-compacted myocardium was left in the limbo of 'unclassified cardiomyopathies'.

The secondary forms, which in the classification of the 1980s were called specific heart muscle diseases, were given the name of 'specific cardiomyopathies', and within this group myocarditis was added. Unfortunately, the concept of specific cardiomyopathy was widened too much, so as to include chronic ischaemic, valvular, and hypertensive diseases.

Although the 1995 classification made significant contributions (acknowledging new entities, unifying terminology, including myocarditis), nonetheless it introduced ambiguities by classifying the ischaemic and overload disorders among the cardiomyopathies.

Understanding the molecular mechanisms of cardiomyopathies

Besides taxonomic and nosographic improvements, mostly of an etymological and semantic nature, the great advances in the field of cardiomyopathies came from the rapid revolution of molecular biology in cardiology.

In inflammatory cardiomyopathy, the use of *in situ* hybridization and polymerase chain reaction (PCR) demonstrated that not only enteroviruses, but also adenoviruses are cardiotropic.[9]

Moreover, molecular biology made fundamental steps forward in understanding the genetics of cardiomyopathies. About one-third of dilated cardiomyopathies are heredo-familial, frequently

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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† doi:10.1093/eurheartj/ehm342

associated with skeletal muscle or neuromuscular disorders. Gene defects of familial dilated cardiomyopathy (either autosomal or X-linked) code for proteins such as dystrophin and associated glycoproteins, sarcoglycans, and destroglycans, all cytoskeleton proteins concerned with force transmission.[10] For this reason, familial dilated cardiomyopathy is reported as a disease of the cytoskeleton.[10,11] The same dilated cardiomyopathy, which results from enteroviral myocarditis, finds a molecular explanation as a sequela of the lytic action of viral protease 2A on the dystrophin complex.[12]

Hypertrophic cardiomyopathy, an heredo-familial disease with autosomal dominant Mendelian transmission, has been demonstrated to be essentially a sarcomere disease with a disorder of force generation, since the defective genes encode contractile proteins such as β-myosin heavy chain, myosin-binding protein C, α-tropomyosin, and troponin T and I.[13] Also primary restrictive cardiomyopathy, a dominant autosomal disease, has been proven to be a sarcomere disease, since troponin I gene mutations have been identified. It is reasonable that the abnormal protein impairs the relaxation of the myofilaments during diastole, accounting for restrictivity.

ARVC, an autosomal dominant but also a recessive disorder, was shown to be a cell junction disease, namely of the desmosomes ensuring mechanical attachments between cardiomyocytes.[14] Deletions or mutations have indeed been reported in the genes encoding desmoplakin, plakoglobin, plakophilin, desmoglein, and desmocollin. Mechanical stretch of the thin right ventricular wall may account for desmosomal disruption, cell injury, and repair with fibrofatty replacement.

The definition as diseases of the myocardium associated with cardiac dysfunction widens the concept of cardiomyopathies. Classically, dysfunction of the cardiomyocyte was thought to be contractile in nature: this is the case for dilated cardiomyopathy, with systolic pump failure; hypertrophic cardiomyopathy, with even enhanced systolic contractility; and restrictive cardiomyopathy, with impaired diastolic relaxation. However, myocardial dysfunction can be purely electric, as is the case for both structural (i.e. myocarditis, ARVC) and non-structural heart muscle disease (i.e. ion channel diseases), in the absence of any contractile impairment.[11]

Long and short QT syndromes are mostly characterized by mutation of K^+ channel genes; Brugada syndrome and Lenègre disease by mutations of the Na^+ channel gene (SNC5A); and catecholaminergic polymorphic ventricular tachycardia by mutations of ryanodine receptor 2, which controls the Ca^{2+} release from the sarcoplasmic reticulum. With the exception of Lenègre disease, an elective cardiomyopathy of the specialized conduction system, all these syndromes are associated with a structurally normal heart, and the patient's vulnerability resides in the electrical instability at the myocyte membrane. The alteration is seen only on the ECG: QT lengthening or shortening, ST segment elevation, or effort-induced ventricular tachycardia, respectively. The substrate is at the molecular level where a simple missense mutation may determine an abnormal sequence of the nucleotide triplet encoding an amino acid, with a change in the corresponding protein.

Thus primary inherited cardiomyopathies might be distinguished into two categories:[11] (i) cardiomyopathies with structural abnormalities (dilated, hypertrophic, restrictive, and arrhythmogenic) = cytoskeleton, sarcomeric, cell junction diseases; and (ii) cardiomyopathies without structural abnormalities (short and long QT, Brugada, and catecholaminergic polymorphic ventricular tachycardia) = channelopathies.

By accepting the view that cardiomyopathy may manifest only with an electric disorder, in the absence of structural abnormalities, we recognize that these cardiomyopathies can be diagnosed more by ECG than by echo or other cardiac imaging techniques.

2006 AHA scientific statement

The AHA has recently incorporated these ideas in a Scientific Statement,[5] advancing a new definition and classification. If cardiac dysfunction can be both mechanical and electrical, then a cardiomyopathic heart does not necessarily appear dilated or hypertrophic, and the causes are several, both genetic and acquired. Accordingly, the following definition has been put forward. 'Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic'.

The original distinction into primary and secondary forms was reintroduced, considering *primary* cardiomyopathies 'those solely or predominantly confined to heart muscle' and *secondary* those with 'myocardial involvement as part of generalized systemic (multiorgan) disorders'. Primary cardiomyopathies have been divided into three main categories (genetic, acquired, and mixed), incorporating among genetic also primary electrical disorders with a structural normal heart (channelopathies). Lenègre disease was considered a cardiomyopathy, and the group of unclassified cardiomyopathies was abolished. A subclassification of cardiomyopathies into familial/genetic and non-familial/non-genetic was considered of help in orienting towards genetic mutational analysis and screening. Thus, the concept of cardiomyopathy has evolved into the current perspective of a larger group of genetically determined diseases of the myocyte, that includes not only the previously recognized conditions manifesting as overt morphofunctional cardiac abnormalities, but also new conditions showing a primarily arrhythmic phenotype, in the absence of structural changes. There is growing evidence that these 'primarily electrical' cardiomyopathies often show an overlap with phenotypic manifestations of 'traditional structural' cardiomyopathies.[15] The AHA Task Force proposed a 'beyond of phenotype' classification of cardiomyopathies, that groups under such a designation all myocardial diseases, whose common denominator is a genetic defect, consisting of mutant genes encoding sarcomeric, cytoskeletal, desmosomal, or ion channel proteins.

2007 ESC position statement

An update of the 1995 WHO/ISFC classification has also been proposed as a position statement of the ESC Working Group on Myocardial and Pericardial diseases and recently published.[4] In the definition, it is clearly stated that cardiomyopathy is 'a myocardial disorder in which heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart diseases'.

While accepting and reinforcing the idea advanced by the AHA statement to divide cardiomyopathies into familial/genetic and non-familial/non-genetic, the traditional division of primary and secondary (specific) cardiomyopathies was abolished, probably with the erroneous belief that primary means idiopathic and secondary means of known aetiology. Moreover, the concept of pure electrical dysfunction was denied, thus ruling out ion channel and conduction system diseases from the umbrella of cardiomyopathies.

Basically, five types of cardiomyopathies are recognized according to the morphofunctional phenotype (hypertrophic, dilated, arrhythmogenic, restrictive, and unclassified), either familial or non-familial, whether or not the heart is the only target of the disease.

This approach is certainly a simplification of a complex nosographic puzzle, but does not yet fully answer the question raised by emerging evidence. While removal of specific cardiomyopathies such as ischaemic, hypertensive, and valvular should be greeted with cheers, as the AHA document first did in 2006, it is not convincing at all why myocarditis should be grouped 'tout court' among dilated cardiomyopathies. What about acute/fulminant myocarditis or those presenting only with arrhythmias and chest pain? The AHA position statement abolished the so-called non-classified cardiomyopathies, whereas the ESC position statement still regards forms such as non-compaction and Tako Tsubo in search of a room. Finally, only cardiomyopathies with structural deformities were included, renewing the purely morphofunctional approach, without considering the problem of possible evolution of a disease phenotype into another during the natural history and leaving electrical disorders without a taxonomic location.

Conclusions

Both the AHA and ESC statements are commendable contributions which certainly help to clarify this complex field. The concept of electrical cardiomyopathy due to ion channel diseases remains a major concern, because theoretically it might be extended from ventricles to atria so as to include familial atrial fibrillation among inherited cardiomyopathies.

We are well aware of the complexity of disease phenotype in the setting of a nosographic framework and of the risk of overlap among categories. However, an agreement to update the 1995 WHO/ISFC classification is deemed necessary, with merging views of worldwide scientists, based upon the breaking news coming from genomics and proteomics of molecular cardiovascular medicine.

Competing interests: none declared.

Funding

Funding to pay the Open Access publication charges for this article was provided by the Ministry of Health, Rome, Italy.

References

1. Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. *Br Heart J* 1980;**44**:672–673.
2. Thiene G, Basso C, Calabrese F, Angelini A, Valente M. Twenty years of progress and beckoning frontiers in cardiovascular pathology: cardiomyopathies. *Cardiovasc Pathol* 2005;**14**:165–169.
3. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J, Gyarfas I, Martin I, Nordet P. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996;**93**:841–842.
4. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Khul U, Maisch B, McKenna WJ, Monserrat L, Oankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008;**29**:270–276. First published on October 4, 2007, doi:10.1093/eurheartj/ehm342.
5. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies. An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups, and council on epidemiology and prevention. *Circulation* 2006;**113**:1807–1816.
6. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med* 1988;**318**:129–133.
7. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, Grosgogeat Y. Right ventricular dysplasia: a report of 24 adult cases. *Circulation* 1982;**65**:384–398.
8. Angelini A, Calzolari V, Thiene G, Boffa GM, Valente M, Daliento L, Basso C, Calabrese F, Razzolini R, Livi U, Chioin R. Morphologic spectrum of primary restrictive cardiomyopathy. *Am J Cardiol* 1997;**80**:1046–1050.
9. Calabrese F, Thiene G. Myocarditis and inflammatory cardiomyopathy: microbiological and molecular biological aspects. *Cardiovasc Res* 2003;**60**:11–25.
10. Bowles NE, Bowles KR, Towbin JA. The 'final common pathway' hypothesis and inherited cardiovascular disease. The role of cytoskeletal proteins in dilated cardiomyopathy. *Herz* 2000;**25**:168–175.
11. Thiene G, Corrado D, Basso C. Cardiomyopathies: is it time for a molecular classification? *Eur Heart J* 2004;**25**:1772–1775.
12. Badorff C, Lee GH, Lamphear BJ, Martone ME, Campbell KP, Rhoads RE, Knowlton KU. Enteroviral protease 2A cleaves dystrophin: evidence of cytoskeletal disruption in an acquired cardiomyopathy. *Nat Med* 1999;**5**:320–326.
13. Ashrafian H, Watkins H. Reviews of translational medicine and genomics in cardiovascular disease: new disease taxonomy and therapeutic implications cardiomyopathies: therapeutics based on molecular phenotype. *J Am Coll Cardiol*. 2007;**49**:1251–1264.
14. Marcus FI, Nava A, Thiene G, eds. *Arrhythmogenic RV Cardiomyopathy/Dysplasia—Recent Advances*. Milano: Springer; 2007.
15. Lehnart SE, Ackerman MJ, Benson DW Jr, Brugada R, Clancy CE, Donahue JK, George AL Jr, Grant AO, Groft SC, January CT, Lathrop DA, Lederer WJ, Makielski JC, Mohler PJ, Moss A, Nerbonne JM, Olson TM, Przywara DA, Towbin JA, Wang LH, Marks AR. Inherited Arrhythmias: A National Heart, Lung, and Blood Institute and Office of Rare Diseases Workshop Consensus Report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 2007;**116**:2325–2345.