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Current opinion

Cardiomyopathies: is it time for a molecular classification?☆

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Primary myocardial diseases have always attracted the interest of the scientific community because of their obscure aetiopathogenesis. For years there was a confusion and controversy over their definition and classification. The 1995 WHO classification led to major advancements such as the introduction of a unified terminology, the official recognition of novel entities (arrhythmogenic right ventricular and idiopathic restrictive cardiomyopathies) and the definitive clarification that inflammatory heart disease has to be regarded as a cardiomyopathy. However, according to the new definition of cardiomyopathies as diseases of the myocardium associated with cardiac dysfunction, they should include not only forms with depressed contractility and impaired diastolic function, but also conduction and rhythm disturbances and enhanced arrhythmogenicity. Moreover, the recent development of molecular genetics, with the discovery of a genetic background in several forms previously defined of unknown origin, raises the need of a debate on a possible classification based on genomics.

Introduction

Primary myocardial diseases have always attracted the interest of the scientific community interest because of their obscure aetiopathogenesis. For years there was a confusion and controversy over their definition and classification: even cardiac tumours were for long considered ''cardiomyopathies''.[1] The interest was enhanced by the introduction in clinical practice of cardiac transplantation, by realizing that nearly half of the patients requiring such a procedure were affected by non-ischaemic myocardial disease.[2]

1980 WHO classification

In 1980 a Task Force was set up by the World Health Organization (WHO) and the International Society and Federation of Cardiology to establish a consensus on definition and nomenclature.[3] The report made a major contribution in clarifying the matter and was based upon two main principles: (1) heart muscle diseases should be distinguished according to the cause, whether known or unknown. The term *cardiomyopathy* was reserved for heart muscle disease of unknown cause, whereas *specific heart muscle diseases* were those in which the cause was known or were associated with disorders of other systems; (2) cardiac dysfunction caused by systemic or pulmonary hypertension, pericardial, coronary artery and valvular heart disease, or congenital cardiac anomalies

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Table 1 Cardiomyopathy definitions: 1980 vs. 1995

1980	1995
Cardiomyopathy Heart muscle disease of unknown cause	*Cardiomyopathy* Disease of the myocardium associated with cardiac dysfunction
Specific heart muscle disease Heart muscle disease of known cause or associated with disorders of other systems	*Specific cardiomyopathy* Heart muscle disease associated with specific cardiac or systemic disorders

were excluded, both from the group of cardiomyopathies and from specific heart muscle diseases.

Cardiomyopathies were then classified according to their own peculiar pathophysiological features, such as: (a) dilated, in the setting of dilatation and poor contractility of the ventricles; (b) hypertrophic, in the presence of unexplained hypertrophy of the left ventricle, either symmetric or asymmetric; and (c) restrictive, when endocardial thickening and cavity obliteration hinders diastolic ventricular filling (with or without eosinophilia).

A separate category of ''unclassified cardiomyopathies'' was forecast for those conditions which do not fit into any groups (i.e. endocardial fibroelastosis, hystiocytoid cardiomyopathy). Finally, specific heart muscle diseases were classified as infective, metabolic, general system diseases, heredofamilial, sensitivity and toxic reactions.

The need for a revision and the 1995 WHO classification

The new definition and classification as well as the novel terminology were well accepted within the scientific community and worked effectively for more than a decade.

Subsequently however, major advancements rapidly occurred casting doubts on the validity of the 1980 Task Force report.

First of all, new entities were discovered, which were not contemplated in the previous classification and thus fostered the need to update the classification.[4,5] A form of idiopathic restrictive cardiomyopathy was described with stiff ventricular wall and no endocardial thickening, in the absence of eosinophilic infiltrates.[6] A non-ischaemic fibro-fatty scarring of the right ventricular free wall was observed in young subjects and athletes dying suddenly, and was named arrhythmogenic right ventricular cardiomyopathy to underline the peculiar electrical instability of the right ventricular myocardium.[7,8]

Second, a definition of cardiomyopathy based upon unknown aetiology was groundless, taking into account the discovery of genetic defects in several forms.[9]

Third, there were ischaemic, hypertensive and valve diseases in which the ventricular dysfunction was not explained by the extent of coronary artery disease and abnormal loading conditions.

Finally, myocarditis was mostly ignored in the 1980 Task Force report, having been quoted only among unclassified cardiomyopathies and/or infective specific heart muscle disease.

Table 2 Cardiomyopathy classification: 1980 vs. 1995

1980	1995
Dilated	Dilated
Hypertrophic	Hypertrophic
Restrictive	Restrictive
	Arrhythmogenic right ventricular

The 1995 WHO classification

With a consensus meeting in Geneva, a new Task Force tried to answer each of the pending questions and introduced the following changes:[10]

(1) Definition and terminology. *Cardiomyopathies* were defined as ''disease of the myocardium associated with cardiac dysfunction'' and specific heart muscle diseases were named *specific cardiomyopathies* to describe ''heart muscle disease that are associated with specific cardiac or systemic disorders'', like amyloidosis or haemochromatosis (Table 1).

(2) Arrhythmogenic right ventricular cardiomyopathy[11] was acknowledged as a new separate entity, and added to the list. The idiopathic form of restrictive cardiomyopathy, characterised by interstitial fibrosis and myocardial disarray in the absence of endomyocardial disease,[12] was also recognized (Table 2).

(3) Within the unclassified cardiomyopathies, non-compacted myocardium,[13] mildly dilated cardiomyopathy[14] and mitochondrial cardiomyopathies were introduced (Table 3).

(4) Myocarditis in association with cardiac dysfunction was included within the specific cardiomyopathies and named ''inflammatory cardiomyopathy'' (Table 4).

(5) Ischaemic, valvular and hypertensive disorders were also regarded as ''specific cardiomyopathies'', when the severity of myocardial dysfunction largely exceeded the extent of basic defect (Table 4).

Table 3 Unclassified cardiomyopathy: 1980 vs. 1995

1980	1995
Endocardial fibroelastosis	Fibroelastosis
Histiocytoid cardiomyopathy	Non-compacted myocardium
Fiedler's myocarditis	Mildly dilated cardiomyopathy
	Mitochondrial cardiomyopathy

Table 4 Specific cardiomyopathy: 1980 vs. 1995

1980	1995
Specific heart muscle disease	*Specific cardiomyopathy*
Infective	Ischaemic cardiomyopathy
Metabolic	Valvular cardiomyopathy
General system disease	Hypertensive cardiomyopathy
Heredo-familial	Inflammatory cardiomyopathy
Sensitivity and toxic reaction	Metabolic cardiomyopathy
	Others

The new classification: pros and cons

The question is however, was the 1995 Task Force report a progress? The answer is mostly positive in view of the major advancements, namely the introduction of a unified terminology, the official recognition of novel entities (arrhythmogenic right ventricular and idiopathic restrictive cardiomyopathies) and the definitive clarification that inflammatory heart diseases (myocarditis)[15,16] have to be regarded as cardiomyopathies.

However, a major concern arises upon the opportunity to extend the concept of cardiomyopathy to damaged myocardium in the setting of coronary artery, valvular and hypertensive disease, which have been always considered secondary heart muscle diseases.[15] Although it is theoretically possible that some cardiomyopathic injury may be superimposed on, or be induced by, these disorders, it has never unequivocally been proven and may be merely coincidental. Accordingly, we fully agree with the 1980s Task Force that ''further extension of the classification to include these conditions'' would have so widened ''its scope as to render it useless''.[3] A recent clinical investigation indeed cast doubt on the existence of ischaemic cardiomyopathy.[17] In other words, all that was accomplished was taking three steps forward and one step backward (Table 5).

Table 5 The new 1996 WHO classification of cardiomyopathies

Step forwards	Step backwards
Unified terminology	Coronary, valvular and hypertensive disease listed among cardiomyopathies
Recognition of new entities	
Myocarditis acknowledged as heart muscle disease (inflammatory cardiomyopathies)	

Another criticism resides on the new definition of cardiomyopathies, namely diseases of the myocardium associated with cardiac dysfunction as opposite to the previous one of heart muscle diseases of unknown cause. While we concur on the need to avoid a definition of an entity based on its cryptogenicity, we believe that the term cardiac dysfunction should include not only depressed contractility and impaired diastolic function, but also conduction and rhythm disturbances and enhanced arrhythmogenicity.

If we accept that arrhythmias are *per se* a sign of cardiac dysfunction, regardless of mechanical cardiac behaviour, then we have also to realize that myocardial electrical diseases do exist which do not have structural abnormalities as features. We refer to inherited ventricular arrhythmias, such as long or short QT syndromes, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia in which the genetic defect leads to ion channel disorders at risk of electrical apoplexy of the heart.[18–22]

These defects are invisible even under electron microscopy and are considered purely functional and not structural. Nonetheless, the myocyte is abnormal, even though the heart is apparently intact. Should these non-structural life-threatening cardiac dysfunctions, causing a high risk of arrhythmic sudden death, be regarded as cardiomyopathies as well?

Time for a genomic/post-genomic classification of cardiomyopathies

Many cardiomyopathies are the consequences of a single gene defect and are thus inherited according to Mendelian law. The extraordinary advances accomplished in the last two decades in molecular genetics has allowed the identification of the gene defect for some forms of dilated cardiomyopathy,[23] hypertrophic cardiomyopathy,[24] restrictive cardiomyopathy[25] and arrhythmogenic right ventricular cardiomyopathy.[26–28] These are clearly structural heart diseases, with or without arrhythmias.

Familiar dilated cardiomyopathies have been found to be due to defects of the cytoskeleton impairing force transmission.[23] Familiar hypertrophic and restrictive cardiomyopathies have been related to defective sarcomere proteins impairing force production.[24,25] The genetic basis of arrhythmogenic right ventricular cardiomyopathy has recently been found to be linked to abnormal cytoskeleton proteins regulating cell junctions, both in the autosomal[28] and recessive (Naxos disease)[29] forms. Mutations in the genes encoding for intercellular junctions have been also discovered to account for the other cardiocutaneous syndromes which are characterised by the association of cardiomyopathy and skin abnormalities.[30–32] On the other hand, non-structural heart disease manifesting with arrhythmias or conduction disturbances are mostly the consequence of ion channel gene mutations, either at the level of the cell membrane

Table 6 A genomic/post-genomic classification of inherited cardiomyopathies

Cytoskeletal cardiomyopathy (''cytoskeletalopathy'')	Dilated cardiomyopathy, Arrhthmogenic right ventricular cardiomyopathy, Cardiocutaneous syndromes
Sarcomeric cardiomyopathy (''sarcomyopathy'')	Hypertrophic and restrictive cardiomyopathy
Ion channel cardiomyopathy (''channelopathy'')	Long and short QT syndromes, Brugada syndrome, catecholaminergic polymorphic VT

or intracellular organelles. Long and short QT syndrome are sodium or potassium ion channel diseases of the cell membrane,[18–20] Brugada syndrome is a sodium ion channel disease,[21] and polymorphic ventricular tachycardia is related to an abnormal ryanodyne receptor 2 regulating calcium release from the sarcoplasmic reticulum for electromechanical coupling.[22,27]

Thus, if we want to reconsider the classification of inherited cardiomyopathies, which is currently based upon the phenotypic expression, a genomic/post-genomic classification could be postulated taking into account the underlying gene mutations and the cellular level of expression of encoded proteins, thus distinguishing cytoskeleton (cytoskeletalopathies), sarcomeric (sarcomyopathies) and ion channel (channelopathies) cardiomyopathies (Table 6).[33]

What was considered for years as idiopathic and was at the base of early classification (of unknown cause), was recently largely elucidated by finding a genetic background.

This should be taken into account for a newly necessary revision of the WHO classification of cardiomyopathies.

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