

# Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

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In biology, classification systems are used to promote understanding and systematic discussion through the use of logical groups and hierarchies. In clinical medicine, similar principles are used to standardise the nomenclature of disease. For more than three decades, heart muscle diseases have been classified into primary or idiopathic myocardial diseases (cardiomyopathies) and secondary disorders that have similar morphological appearances, but which are caused by an identifiable pathology such as coronary artery disease or myocardial infiltration (specific heart muscle diseases). In this document, The European Society of Cardiology Working Group on Myocardial and Pericardial Diseases presents an update of the existing classification scheme. The aim is to help clinicians look beyond generic diagnostic labels in order to reach more specific diagnoses.

## Keywords

Cardiomyopathy • Classification • Position statement

## Introduction

In biology, classification systems are used to promote understanding and systematic discussion by arranging organisms into logical groups and hierarchies. In clinical medicine, similar principles are used to standardize the nomenclature of disease, grouping disorders on the basis of shared morphological appearances or particular biochemical and genetic abnormalities. For more than 30 years, the term *cardiomyopathies* has been used to describe disorders of the heart with particular morphological and physiological characteristics.<sup>1–4</sup> The purpose of this position statement is to update the classification system for cardiomyopathies in order to ensure its continued utility in everyday clinical practice.

## The rationale for a new classification

When the classification system for cardiomyopathies was originally conceived, the lack of knowledge about the underlying cause and pathophysiology of different types of cardiomyopathy was recognized, but there was an implicit assumption that they were distinct entities. Cardiomyopathies were defined as primary myocardial disorders of unknown cause; heart muscle disorders of known aetiology or associated with systemic disorders were classified as secondary or specific heart muscle diseases. With the passage of time, the distinction between primary and secondary heart muscle disease has become increasingly tenuous, as the aetiology of previously idiopathic disorders has been discovered. Recently,

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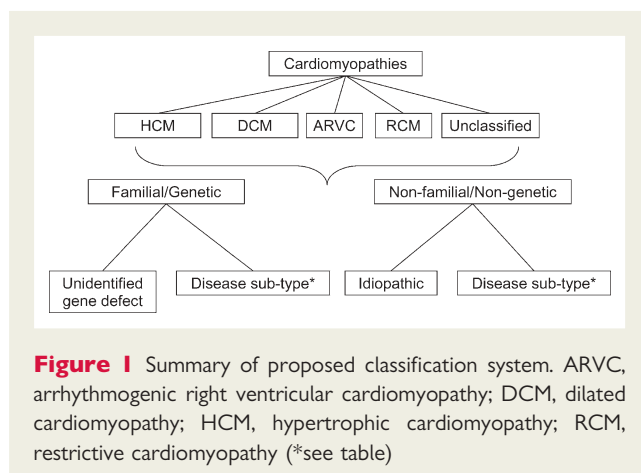
an expert committee of the American Heart Association proposed a new scheme in which the term primary is used to describe diseases in which the heart is the sole or predominantly involved organ and secondary to describe diseases in which myocardial dysfunction is part of a systemic disorder.<sup>5</sup> However, the challenge of distinguishing primary and secondary disorders in this way is illustrated by the fact that many of the diseases classified as primary cardiomyopathies can be associated with major extra-cardiac manifestations; conversely, pathology in many of the diseases classed as secondary cardiomyopathies can predominantly (or exclusively) involve the heart.

As many cardiomyopathies are caused by mutations in genes that encode various cardiac proteins, an alternative approach is to reclassify cardiomyopathies according to the causative genetic defect.<sup>6</sup> However, in clinical practice the pathway from diagnosis to treatment rarely begins with the identification of an underlying genetic mutation; more usually, patients present with symptoms or are incidentally found to have clinical signs or abnormal screening tests. Even when the genetic defect is known in a family, the identification of clinically relevant disease in gene-carriers still requires the demonstration of a morphological phenotype. Thus, we believe 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.

## Proposed new classification

In this statement we define a cardiomyopathy as: A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality.

Cardiomyopathies are grouped into specific morphological and functional phenotypes; each phenotype is then sub-classified into familial and non-familial forms (Figure 1). In this context, familial refers to the occurrence, in more than one family member, of either the same disorder or a phenotype that is (or could be) caused by the same genetic mutation and not to acquired cardiac or systemic diseases in which the clinical phenotype is



influenced by genetic polymorphism. Most familial cardiomyopathies are monogenic disorders (i.e. the gene defect is sufficient by itself to cause the trait). A monogenic cardiomyopathy can be sporadic when the causative mutation is *de novo*, i.e. has occurred in an individual for the first time within the family (or at the germinal level in one of the parents). In this classification system, patients with identified *de novo* mutations are assigned to the familial category as their disorder can be subsequently transmitted to their offspring.

Non-familial cardiomyopathies are clinically defined by the presence of a cardiomyopathy in the index patient and the absence of disease in other family members (based on pedigree analysis and clinical evaluation). They are subdivided into idiopathic (no identifiable cause) and acquired cardiomyopathies in which ventricular dysfunction is a complication of the disorder rather than an intrinsic feature of the disease. In a departure from the 1995 WHO/ISFC classification, we exclude left ventricular dysfunction secondary to coronary artery occlusion, hypertension, valve disease, and congenital heart disease because the diagnosis and treatment of these disorders generally involves clinical issues quite different from those encountered in most cardiomyopathies.

The expert panel of the American Heart Association has suggested that ion channelopathies and disorders of conduction should also be considered as cardiomyopathies. This suggestion was predicated on the fact that these genetic disorders 'are responsible for altering biophysical properties and protein structure, thereby creating structurally abnormal ion channel interfaces and architecture'.<sup>5</sup> However, recent studies suggesting that genes encoding ion channels may be implicated in subgroups of patients with dilated cardiomyopathy (DCM), conduction disorders, and arrhythmias<sup>7</sup> do not provide an argument for the redesignation of channelopathies as cardiomyopathies at the present time.

## Implications for clinical practice

The most important principle underlying this proposed classification system is its relevance to everyday clinical practice. The division of cardiomyopathies into familial and non-familial forms is designed to raise awareness of genetic disease as a cause of heart muscle dysfunction and to provide a logical framework on which to base further investigations. Importantly, the classification system does not provide guidance on the diagnostic algorithm that should be followed whenever a cardiomyopathy is diagnosed, but it is our intention to provide such advice in subsequent statements.

## Cardiomyopathy subtypes

Historically, most cardiomyopathies have been defined by the absence of particular features or associated disorders, but it is increasingly apparent that many patients with unexplained heart muscle disease in fact have rare, but well described diseases that can involve the myocardium. In this new classification system, we propose a move away from the concept of diagnosis by exclusion and focus solely on the morphology and function of the heart. This simple but radical departure from the existing convention means that the differentiation between cardiomyopathies and specific heart muscle diseases is abandoned (with the exceptions of

hypertension, coronary artery disease, valve disease, and congenital heart anomalies). The aim is to promote a greater appreciation of the broad spectrum of diseases that can cause cardiomyopathies in everyday clinical practice.

### Hypertrophic cardiomyopathy

Historically, hypertrophic cardiomyopathy (HCM) has been defined by the presence of myocardial hypertrophy in the absence of haemodynamic stresses sufficient to account for the degree of hypertrophy and systemic diseases such as amyloidosis and glycogen storage disease.<sup>1–4,8,9</sup> The aim of this distinction was to separate conditions in which there is myocyte hypertrophy from those in which left ventricular mass and wall thickness are increased by interstitial infiltration or intracellular accumulation of metabolic substrates. In everyday clinical practice, however, it is frequently impossible to differentiate these two entities using non-invasive techniques such as echocardiography or magnetic resonance imaging. One approach to this conundrum is to include the histological demonstration (on myocardial biopsy) of myocyte hypertrophy in the definition of HCM; unfortunately, the patchy and complex nature of most myocardial pathologies means that this distinction can only be reliably made at post-mortem. In order to provide a common starting point for clinical investigation, the presence of intramyocardial storage material is not an exclusion criterion for HCM in this classification scheme. Instead, hypertrophic cardiomyopathies are simply defined by the presence of increased ventricular wall thickness or mass in the absence of loading conditions (hypertension, valve disease) sufficient to cause the observed abnormality.

Inevitably, this approach will be controversial, but it reflects the terminology that is already in use in paediatric practice and avoids the circular arguments and contradictions that arise when trying to confine the term HCM to one narrow phenotype and aetiology (i.e. sarcomere protein disease). The potential inaccuracy (in a pathological sense) of the term 'hypertrophic' in some clinical settings is, in our view, outweighed by a shift in the clinical emphasis towards the development of appropriate diagnostic strategies based on clues from the history, physical examination, and non-invasive investigations.

The working group considered at some length the issue of cardiac amyloid, historically regarded as an exemplar of restrictive cardiomyopathy (RCM), in spite of the fact that, in strict morphological terms, it frequently fails to fulfil most of the features listed in previous definitions. The arguments for continuing with this convention are that interstitial (rather than intracellular) accumulation of amyloid protein precludes use of the term 'hypertrophy' and that, unlike other causes of myocardial thickening, amyloid has distinct features on electrocardiography and cardiac imaging that suggest the diagnosis. The counterargument is that the logic of a morphological classification dictates that increased ventricular wall thickness caused by amyloidosis should be listed as HCM. The final consensus was that amyloidosis should be listed in the differential diagnosis of both HCM and RCM, acknowledging that this still leaves a degree of nosological ambiguity.

Left ventricular hypertrophy in the absence of hypertension and valve disease occurs in approximately 1:500 of the general population.<sup>8,9</sup> Many individuals have familial disease with an autosomal

dominant pattern of inheritance caused by mutations in genes that encode different proteins of the cardiac sarcomere. The majority of patients with sarcomeric protein gene mutations have an asymmetrical pattern of hypertrophy, with a predilection for the interventricular septum and myocyte disarray. Left ventricular cavity size is usually diminished and fractional shortening typically higher than normal. Progression to left ventricular dilatation and systolic failure occurs in a minority of patients (up to 10% in some series). All patterns of hypertrophy are consistent with the diagnosis of sarcomeric protein disease, but concentric hypertrophy is more frequent in patients with metabolic disorders such as Anderson–Fabry disease, mitochondrial cytopathy, and glycogen storage disease. Additional diagnostic clues in these patients include the inheritance pattern (X-linked, autosomal recessive) and the presence of signs and symptoms of multi-system disease. Athletic training to national or international level is associated with physiological changes in left ventricular morphology that can be confused with a pathological phenotype, but myocardial thickness similar to those seen in patients with HCM are rare (less than 2% of male athletes).<sup>8</sup> In the young, HCM is often associated with congenital syndromes, inherited metabolic disorders, and neuromuscular diseases. In familial cases, various patterns of inheritance are observed; autosomal disorders that present in the young include Noonan and LEOPARD syndrome (dominant) and Friedreich's ataxia (recessive).<sup>9</sup>

### Dilated cardiomyopathy

DCM is defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment. Right ventricular dilation and dysfunction may be present but are not necessary for the diagnosis.

The prevalence of DCM in the general population is unknown, but it clearly varies with age and geography. At least 25% of patients in Western populations have evidence for familial disease with predominantly autosomal dominant inheritance.<sup>10–12</sup> Familial disease should also be suspected when there is a family history of premature cardiac death or conduction system disease or skeletal myopathy. Autosomal dominant forms of the disease are caused by mutations in cytoskeletal, sarcomeric protein/Z-band, nuclear membrane and intercalated disc protein genes. X-linked diseases associated with DCM include muscular dystrophies (e.g. Becker and Duchenne) and X-linked DCM. DCM may also occur in patients with mitochondrial cytopathies and inherited metabolic disorders (e.g. haemochromatosis). Examples of acquired causes of DCM include nutritional deficiencies, endocrine dysfunction, and the administration of cardiotoxic drugs (Table 1).

DCM can occur at a late stage following cardiac infection and inflammation. In contrast to active or fulminant myocarditis, which is by definition, an acute inflammatory disorder of the heart, often with preserved left ventricular size, inflammatory DCM is defined by the presence of chronic inflammatory cells in association with left ventricular dilatation and reduced ejection fraction; histology and/or immunocytochemistry are, therefore, necessary for the diagnosis. A proportion of individuals with inflammatory DCM have persistence of viral proteins in the

**Table 1** Examples of different diseases that cause cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations $\beta$ myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin-T $\alpha$ -tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin $\alpha$ -myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedemann syndrome Swyer's syndrome Other Phospholamban promoter Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy	Familial, unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor- $\beta$ 3 (TGF $\beta$ 3)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/- HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desminopathy Pseuxanthoma elasticum Haemochromatosis Anderson–Fabry disease Glycogen storage disease	Left ventricular non-compaction Barth syndrome Lamin A/C ZASP $\alpha$ -dystrobrevin
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid (AL/prealbumin)	Myocarditis (infective/toxic/immune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chromosomal cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (anthracyclines)	Tako Tsubo cardiomyopathy

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

myocardium; viral persistence can also be observed in the absence of inflammation.

The term mildly dilated congestive cardiomyopathy (MDCM) has been used to describe patients with advanced heart failure and severe left ventricular systolic dysfunction occurring with neither restrictive haemodynamics nor significant left ventricular dilatation (less than 10–15% above normal range). A family history of DCM is present in over 50% of patients. Although some pathological findings differ, the clinical picture and prognosis of MDCM are very similar to those of typical DCM.<sup>13</sup>

Peripartum cardiomyopathy (PPCM) is a form of DCM that presents with signs of cardiac failure during the last month of pregnancy or within 5 months of delivery.<sup>14</sup> Suggested aetiological factors in PPCM include myocarditis, autoimmunity caused by chimerism of haematopoietic lineage cells from the foetus to the mother and the haemodynamic stress of pregnancy. PPCM can occur at any age but is more common in women older than 30 years. It affects women of all ethnic groups, is almost equally associated with first/second and multiple pregnancies and is strongly associated with gestational hypertension, twin pregnancy and tocolytic therapy.

### Restrictive cardiomyopathy

Restrictive left ventricular physiology is characterized by a pattern of ventricular filling in which increased stiffness of the myocardium causes ventricular pressure to rise precipitously with only small increases in volume. Restrictive cardiomyopathy (RCM) has always been difficult to define because restrictive ventricular physiology occurs in a wide range of different pathologies.<sup>15</sup> In this classification system, restrictive cardiomyopathies are defined as restrictive ventricular physiology in the presence of normal or reduced diastolic volumes (of one or both ventricles), normal or reduced systolic volumes, and normal ventricular wall thickness. Historically, systolic function was said to be preserved in RCM, but is rare for contractility to be truly normal. Restrictive physiology can occur in patients with end-stage hypertrophic and DCM but we do not believe that these entities require their own sub-category.

The exact prevalence of RCM is unknown but it is probably the least common type of cardiomyopathy. RCM may be idiopathic, familial, or result from various systemic disorders, in particular, amyloidosis, sarcoidosis, carcinoid heart disease, scleroderma and anthracycline toxicity. Familial RCM is often characterized by autosomal dominant inheritance, which in some families is caused by mutations in the troponin I gene; in others, familial RCM is associated with conduction defects, caused by mutations in the desmin gene (usually associated with skeletal myopathy). Rarely, familial disease can be associated with autosomal recessive inheritance (such as haemochromatosis caused by mutations in the HFE gene, or glycogen storage disease), or with X-linked inheritance (such as Anderson–Fabry disease).

Restrictive ventricular physiology can also be caused by endocardial pathology (fibrosis, fibroelastosis, and thrombosis) that impairs diastolic function. These disorders can be sub-classified according to the presence of eosinophilia into *endomyocardial diseases with hypereosinophilia* [now grouped under hypereosinophilic syndromes (HES)] and *endomyocardial disease without*

*hypereosinophilia* [e.g. endomyocardial fibrosis (EMF)]. Parasitic infection, drugs such as methysergide, and inflammatory and nutritional factors have been implicated in acquired forms of EMF. Fibrous endocardial lesions of the right and/or left ventricular inflow tract cause incompetence of the atrioventricular valves. Isolated left ventricular involvement results in pulmonary congestion and predominant right ventricular involvement leads to right heart failure.

EMF should be distinguished from endocardial fibroelastosis, occurring in early childhood, characterized by thickening of mural endocardium mainly of the left ventricle, secondary to proliferation of fibrotic and elastic tissues. It is often associated with congenital malformations and some data suggest an aetiological role for viral infection, in particular, mumps virus.

### Arrhythmogenic right ventricular cardiomyopathy

Unlike HCM, DCM, and RCM, arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined histologically by the presence of progressive replacement of right ventricular myocardium with adipose and fibrous tissue often confined to a ‘triangle of dysplasia’ comprising the right ventricular inflow, outflow, and apex. While these pathologic abnormalities can result in functional and morphological right ventricular abnormalities, they also occur in the left ventricle, producing a DCM phenotype, or can be present in the absence of clinically detectable structural changes in either ventricle. For the purposes of this classification, ARVC is defined by the presence of right ventricular dysfunction (global or regional), with or without left ventricular disease, in the presence of histological evidence for the disease and/or electrocardiographic abnormalities in accordance with published criteria.<sup>16</sup>

Although uncommon (estimated prevalence 1:5000), ARVC is a frequent cause of sudden death in young people in some areas of Europe. Autosomal recessive forms of ARVC (e.g. Naxos and Carvajal syndromes caused by mutations in genes encoding plakoglobin and desmoplakin, respectively) are recognized, but the majority of cases are caused by autosomal dominantly inherited mutations in genes encoding plakophilin 2 and other proteins of the desmosome of cardiomyocytes (Table 1). Mutations in TGF- $\beta$  and Ryanodine receptor genes may be associated with an ARVC phenotype.

### Unclassified cardiomyopathies

#### Left ventricular non-compaction

Left ventricular non-compaction (LVNC) is characterized by prominent left ventricular trabeculae and deep inter-trabecular recesses.<sup>17</sup> The myocardial wall is often thickened with a thin, compacted epicardial layer and a thickened endocardial layer. In some patients, LVNC is associated with left ventricular dilatation and systolic dysfunction, which can be transient in neonates.

It is not clear whether LVNC is a separate cardiomyopathy, or merely a congenital or acquired morphological trait shared by many phenotypically distinct cardiomyopathies. LVNC occurs in isolation and in association with congenital cardiac disorders such as Ebstein’s anomaly or complex cyanotic heart disease and

some neuromuscular diseases. The population prevalence of isolated LVNC is not known, but it is reported in 0.014% of consecutive echocardiograms. In large paediatric series, LVNC is reported to be the commonest cause of unclassified cardiomyopathies.<sup>18</sup> LVNC is frequently familial, with at least 25% of asymptomatic relatives having a range of echocardiographic abnormalities. Genes in which causative mutations have been identified include G 4.5 encoding taffazin (X-linked), alpha dystrobrevin, ZASP, actin, lamin A/C and a locus on chromosome 11 p 15.

### Takotsubo cardiomyopathy

Transient left ventricular apical ballooning syndrome or takotsubo cardiomyopathy is characterized by transient regional systolic dysfunction involving the left ventricular apex and/or mid-ventricle in the absence of obstructive coronary disease on coronary angiography. Patients present with an abrupt onset of angina-like chest pain, and have diffuse T-wave inversion, sometimes preceded by ST-segment elevation, and mild cardiac enzyme elevation.<sup>19</sup> Originally described in Japan, the condition is reported in Caucasian populations in Europe and North America. Most reported cases occur in post-menopausal women. Symptoms are often preceded by emotional or physical stress. Norepinephrine concentration is elevated in most patients and a transient, dynamic intraventricular pressure gradient is reported in 16% of cases. Left ventricular function usually normalizes over a period of days to weeks and recurrence is rare. The same kind of reversible myocardial dysfunction is occasionally encountered in patients with intracranial haemorrhage or other acute cerebral accidents (neurogenic myocardial stunning).

### Limitations

Inevitably there are circumstances in which this classification system fails to describe fully the complexity of some disease phenotypes. Some of the most commonly encountered clinical problems include the occurrence of different cardiomyopathies caused by the same genetic mutation (in unrelated and related individuals); the same cardiomyopathy resulting from many different mutations, and the evolution of one disease phenotype into another over time. A further limitation of the proposed scheme is the problem of the 'mixed phenotype' as, for example, in patients with dilated and hypertrophied ventricles. Rather than attempt to construct complex sub-categories that are difficult to apply in clinical practice, our solution is to modify the definitions of individual cardiomyopathies in such a way that raises awareness of the possible spectrum of abnormalities in patients (and families) with heart muscle diseases. We hope that subsequent revisions of the classification based on emerging data will resolve any remaining ambiguities.

### Conclusions

This position paper proposes a new classification of cardiomyopathies that is designed to provide a valid tool for routine clinical practice. The proposal differs in several ways from the 1995 WHO/ISFC classification and the system drawn

up by the expert panel of the American Heart Association. Specific features of the proposal include:

- A classification based on groupings of specific morphological and functional phenotypes (rather than putative pathophysiological mechanisms, which may be more suited to research purposes than to everyday practice).
- Further sub-classification into familial and non-familial forms so as to raise awareness of genetic determinants of cardiomyopathies and to orient diagnostic tests (including the search for specific mutations, when appropriate).
- Abandonment of the distinction between primary and secondary cardiomyopathies.
- A move away from the predominantly exclusion-based diagnostic work-up towards a positive, logical search for diagnostic indicators.

The aim of these proposals is to help clinicians look beyond generic diagnostic labels in order to reach more specific diagnoses that may be useful for tailored clinical management of patients and their families.

**Conflict of interest:** none declared.

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