Review article

Clinical and molecular classification of cardiomyopathies

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ABSTRACT

The term "cardiomyopathies" was used for the first time 55 years ago, in 1957. Since then awareness and knowledge of this important and complex group of heart muscle diseases have improved substantially. Over these past five decades a large number of definitions, nomenclature and schemes, have been advanced by experts and consensus panel, which reflect the fast and continued advance of the scientific understanding in the field.

Cardiomyopathies are a heterogeneous group of inherited myocardial diseases, which represent an important cause of disability and adverse outcome. Although considered rare diseases, the overall estimated prevalence of all cardiomyopathies is at least 3% in the general population worldwide. Furthermore, their recognition is increasing due to advances in imaging techniques and greater awareness in both the public and medical community.

Cardiomyopathies represent an ideal translational model of integration between basic and clinical sciences. A multidisciplinary approach is therefore essential in order to ensure their correct diagnosis and management.

In the present work, we aim to provide a concise overview of the historical background, genetic and phenotypic spectrum and evolving concepts leading to the various attempts of cardiomyopathy classifications produced over the decades.

Keywords: classification, cardiomyopathies, myocardial disease
INTRODUCTION
Cardiomyopathies (CM) are a fascinating group of myocardial diseases, which constitute an important cause of disability and adverse outcome due to heart failure or sudden and unexpected death. Their recognition is increasing due to advances in imaging techniques and greater awareness in the medical community, although the majority of patients are still likely to be undiagnosed or misdiagnosed with more prevalent cardiac conditions. Population cross-sectional studies show that the overall estimated prevalence of all cardiomyopathies is at least 3% in the general population worldwide. They are often inherited heart muscle diseases, generally with an autosomic dominant, more rarely recessive or X-linked transmission. As a variety of gene abnormalities are identified as the cause of cardiomyopathies, the need for a close cooperation among clinicians, geneticists and molecular biologists, in addition to imaging experts, pathologists, neurologists, nephrologists and paediatricians is well recognized: a multidisciplinary approach is essential in order to ensure their correct diagnosis and management. Furthermore, cardiomyopathies represent an ideal translational model of integration between basic and clinical sciences. In the present work, we aim to provide a concise overview of the historical background, genetic and phenotypic spectrum and evolving concepts leading to the various attempts of cardiomyopathies classifications produced by experts over the decades.

HISTORY
The term ‘cardiomyopathy’ was first used in 1957 by Brigden, who described a group of uncommon, non-coronary myocardial diseases [1]. In 1961 Goodwin defined cardiomyopathies as “myocardial diseases of unknown cause” [2]. He described three different entities, namely “dilated, hypertrophic and restrictive”, terms which are still in use today. In the 70s, the expanding clinical use of non-invasive imaging, such as m-mode and 2D echocardiography, allowed cardiologists and internists to easily measure left ventricular (LV) wall thickness, cavity dimension and systolic function. Cardiomyopathies began to be recognized with increasing frequency in different populations. In an attempt to provide a useful intellectual framework for clinicians involved in the care of these patients, the first classification of cardiomyopathies was published in 1980, by the World Health Organization (WHO) and International Society and Federation of Cardiology (ISFC), and included the three subgroups proposed by Goodwin [3]. The definition of “myocardial diseases of unknown cause” was maintained to define cardiomyopathies, which were distinguished from “specific heart muscle diseases”, the latter comprising heart diseases with similar phenotypes, but due to an identifiable cause.

In the last 30 years, intensive genetic investigation carried out with linkage analysis on large affected families lead to major breakthroughs in the identification of genes associated with familial cardiomyopathies [4,5]. Meanwhile, new nosologic entities were described and the new revision of the classification was carried out in 1996 by the WHO and ISFC [6].

Representing a major advancement, both “arrhythmogenic right ventricular dysplasia” (with the inappropriate term “dysplasia” later changed to “cardiomyopathy”) and a group of “unclassified cardiomyopathies”, defined as “those that do not fit in any group”, were added to the three original subgroups. The definition of cardiomyopathy was changed to “diseases of the myocardium associated with myocardial dysfunction”. Moreover, three additional subgroups termed “hypertensive”, “valvular” and “ischemic” cardiomyopathies were – somewhat confusingly – added to the group of “specific heart muscle diseases” in order to resolve a terminology controversy between US and European experts [6]. These were defined as cardiac conditions characterized by the presence of hypertension, coronary or valvular disease, in a degree that would not explain the magnitude of LV dysfunction observed. Nevertheless, a substantial difference in terminology persisted on the two sides of the Atlantic, reflecting the refusal of these fine distinctions by US experts [7].

In 2006, an American Historical Association (AHA) panel of experts published a scientific statement on the “Contemporary classification and definitions of Cardiomyopathies” [7]. They proposed a novel approach, by which “Primary” cardiomyopathies were defined as those “involving only the heart”, as opposed to the “secondary”, characterized by a “generalized multiorgan involvement”. Primary cardiomyopathies for the first time also included “ion channel diseases” and were differentiated in three subgroups based on their etiology as “genetic, mixed and acquired” [Fig. 1]. The radical shift from a phenotypic to an etiological classification, as well as the inclusion of ion channel diseases among cardiomyopathies, although proposed to guide future research rather
than to be employed in the clinical arena, sparked a passionate transatlantic debate, culminating in a thorough reworking of the original 1995 classification by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial diseases, in 2008 [8]. Intrinsically faithful to the concept of classifying cardiomyopathies based on phenotype, the 2008 classification aimed to provide a simple operational framework for the medical community, which might have a direct impact in diagnosing and managing these complex diseases. Each of the time-honoured categories dilated, hypertrophic, restrictive and arrhythmogenic right ventricular were maintained, divided into familial and non-familial to replace the pre-genetic era concept of “unknown etiology”. Furthermore, only two new entities were included into the unclassified group, while the confusing “hypertensive”, “valvular” and “ischemic” categories were removed.

CURRENT CLASSIFICATION OF CARDIOMYOPATHIES (ESC WORKING GROUP ON MYOCARDIAL AND PERICARDIAL DISEASES)

The panel felt the proposed classification should be useful for everyday clinical practice. The very definition of cardiomyopathies was changed, from “myocardial diseases of unknown cause”, to “myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular or congenital heart disease sufficient to cause the observed myocardial abnormality” [8]. Ion channel diseases were excluded, despite their genetic nature, in view of their lack of a structural cardiac phenotype affecting the heart muscle.

Because cardiomyopathies are diagnosed based on clinical examination and imaging, the four classical morphological subgroups of “hypertrophic, dilated, restrictive, arrhythmogenic” were maintained, with a fifth subgroup of “unclassified”, comprising the recently described “LV non-compaction” and “Takotsubo cardiomyopathy” [Fig. 2].

Each category was subdivided in a familial and non-familial subset, with the latter including all known causes that might be responsible for that phenotype. A list of potential genetic and non-genetic causes is provided for each subgroup of cardiomyopathies [Tables 1–5]. The precise
identification of the disease etiology has obvious clinical implications, by virtue of its direct impact to totally different management. For example, amyloidosis, Anderson Fabry diseases and glycogen storage diseases may be diagnosed as hypertrophic cardiomyopathy (HCM); yet their treatment varies widely. Of note, the inclusion of amyloidosis in this classification was widely debated [9]. Substantial doubts also regarded takotsubo, a disease that is generally transient, has no proven inherited cause, and appear related to regional myocardial hypoperfusion rather than to heart muscle abnormalities. Ultimately, both were included as this was felt to be conceptually useful in clinical practice.

Finally, a stepwise approach was proposed for diagnostic work-up. Step one is the identification of cardiomyopathies on the basis of the presenting morphologic features. Following diagnosis in the proband, a comprehensive family screening by ECG and echocardiography should be offered to first-degree relatives, in order to assess whether there is a familiar transmission. The third step
Table 3. Restrictive cardiomyopathy.

| Category | Description |
|----------|-------------|
| **FAMILIAL, unknown gene** |  |
| **Sarcomeric protein mutations:** Troponin I (RCM +/− HCM), Essential myosin light chain |  |
| **Familial Amyloidosis** | Transthyretin (RCM + neuropathy) |
| | Apolipoprotein (RCM + nephropathy) |
| **Desminopathy** |  |
| **Pseudoxanthoma elasticum** |  |
| **Haemochromatosis** |  |
| **Anderson-Fabry disease** |  |
| **Glycogen storage disease** |  |
| **Endomyocardial fibrosis (Familial)** | (Fusion FIP1-like-1 / PDGFRA genes) |
| **NON FAMILIAL** |  |
| **Amyloid (AL/prealbumin)** |  |
| **Scleroderma** |  |
| **Endomyocardial fibrosis** | Hypereosinophilic syndrome, Idiopathic chromosomal cause |
| **Drugs:** serotonin, methysergide, ergotamine, mercurial agents, busulfan, anthracyclines |  |
| **Carcinoid heart disease, Metastatic cancers, Radiation** |  |

Table 4. Arrhythmogenic right ventricular cardiomyopathy.

| Category | Description |
|----------|-------------|
| **FAMILIAL, unknown gene** |  |
| **Intercalated disc protein mutations:** |  |
| | Plakoglobin, Desmoplakin |
| | Plakophilin 2, Desmoglein 2 |
| | Desmocollin 2 |
| **Cardiac ryanodine receptor** (RyR2) |  |
| **Transforming growth factor-β3** (TGFβ3) |  |
| **NON FAMILIAL** | Inflammation? |

Table 5. Unclassified cardiomyopathies.

| Category | Description |
|----------|-------------|
| **FAMILIAL, unknown gene** |  |
| **Left ventricular non-compaction:** |  |
| Barth Syndrome |  |
| Lamin A/C |  |
| ZASP |  |
| α-dystrobrevin |  |
| **NON FAMILIAL** | Takotsubo cardiomyopathy |

consists in the search for the specific cause of the disease, with the help of genetic analysis, metabolic and biochemical laboratory tests, additional imaging and, in selected instances, myocardial biopsy.

**ROLE OF GENETIC TESTING**

Many cardiomyopathies are believed to derive from the interaction between one or more genetic mutations, often unidentified modifier genes and environmental factors [10]. When genetic analysis is performed in candidate genes, the probability of identifying the pathogenic gene mutation is in the range of 40–60%, for patients with HCM, with approximately 5% of complex mutations [11,12]. Results for dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM) and isolated LV non-compaction are considerably less rewarding [10], although the advent of next generation, genome-wide techniques may increase the yield substantially, as recent data on titin in DCM suggests [13].

In the meantime, however, cross-talk between geneticists and clinicians has developed slowly, with modalities of interaction and degree of mutual comprehension that vary wildly in various settings. In many institutions, particularly in the US, a geneticist is not available on-site, and genetic testing is often performed remotely via private companies [14]. In addition, clinicians often question the clinical utility of genetic testing in cardiomyopathy patients and their families. The apparent lack of practical benefit, in the face of considerable costs, has long hindered large-scale diffusion of genetic testing, and still accounts for understandable (but not always justifiable) resistance by the clinician. An indisputable benefit of systematic genetic testing lies in the cross-fertilization between
cardiologists and geneticists. The former, generally show limited expertise and propensity at investigating the hereditary nature of cardiac diseases, and at identifying complex, syndromic phenotypes associated with cardiomyopathies (e.g. Noonan’s, Leopard’s, mitochondrial disease and Anderson Fabry) [15–18]. Standard protocols for genetic testing routinely include pre-test counselling by a multidisciplinary team involving clinical geneticists [15]. This is a valuable moment for reciprocal education among professionals, ultimately benefitting a wide spectrum of patients with rare conditions.

**HYPERTROPHIC CARDIOMYOPATHY**

HCM is a genetic disease characterized by unexplained LV hypertrophy, associated with non-dilated ventricular chambers, in the absence of another cardiac or systemic disease capable of producing that degree of hypertrophy [Fig. 3]. HCM is diagnosed by a maximal LV wall thickness greater than 15 mm, based on echocardiography (ECHO) or cardiac magnetic resonance (CMR) [19]. This value is lowered to 13–14 mm, when family members are screened. In children, a wall thickness greater than 2 standard deviations (SD) for age, sex or body size is considered diagnostic.

![Figure 3. Hypertrophic cardiomyopathy. Echocardiographic and cardiac magnetic resonance images from a 17-year old female patient with HCM. Parasternal long and short axis views show severe LV thickness values (max LV wall thickness 31 mm), with redundant mitral leaflets (panels A, B and D) and small cavity size. Apical 4 chambers view shows massive hypertrophy of the septum and the antero-lateral wall (panels C and E). Image of late gadolinium enhancement showing limited and nontransmural area of fibrosis of the IVS (panel F: black arrow). Abbreviations: LV = left ventricle, RV = right ventricle IVS = inter-ventricular septum.](image)

The distribution of hypertrophy is usually asymmetric and sometimes confined to one or two LV segments. As a consequence, LV mass (measured by CMR) can be within the normal range. LV outflow tract obstruction is an important feature of HCM, and may be demonstrated in up to 70% patients [20]. Overall, the clinical course of patients with HCM is relatively benign, with an annual mortality rate of about 1%. Contrary to prior perceptions, the risk of sudden cardiac death is relatively low [21], although still a major concern in young individuals and athletes. Furthermore, about half of patients show some degree of disease progression and functional limitation, with a small subset of about 5% developing the so-called end-stage HCM. Family screenings, following the introduction of genetic testing has led to the identification of genotype-positive phenotype-negative individuals, a novel category within the HCM spectrum, characterized by absence of LV hypertrophy, assessed by ECG and ECHO [19].

Sarcomeric gene mutations, often private, are the most frequent cause of HCM, accounting for approximately 30–65% of probands in different cohorts [22]. In the remaining subset the genetic substrate is unknown. Furthermore, a small proportion of patients with the HCM phenotype are affected by cardiofacial syndromes (e.g. Noonan, LEOPARD, Costello), neuromuscular diseases (e.g. Frederick’s ataxia), mitochondrial diseases [23], metabolic disorders of lysosomal storage
diseases (i.e. Fabry, Pompe, Danon) [24]. These rare conditions sometimes exhibit an X-linked rather than the autosomal pattern of inheritance, usually observed in HCM [Table 1].

DILATED CARDIOMYOPATHY
DCM is characterized by LV dilatation and global systolic dysfunction (EF < 50%), in the absence of coronary artery disease or other identifiable causes (such as systemic hypertension, valve disease, drugs, inflammatory heart diseases) capable of causing that magnitude of impairment [Table 2]. In familial DCM, screening of first-degree relatives will identify the disease in up to 50% [10]. As for many other cardiomyopathies, the prevalence of DCM is underestimated, because many patients may have a subclinical form of the disease which may be difficult to diagnose for the lack of symptoms. Familial and sporadic forms of DCM have similar morphological manifestation and clinical course [Fig. 4]. They are progressive diseases, with a prognosis that, although improved in the last decades, is usually poor due to heart failure, atrial and ventricular arrhythmias, stroke and sudden death [25]. In patients with refractory heart failure, heart transplant represent the final option.

RESTRICTIVE CARDIOMYOPATHY
RCM is defined by the presence of a restrictive LV physiology, with normal or more often reduced diastolic/systolic volumes, normal wall thickness and systolic function, marked diastolic flow
Impairment and biaatrial dilatation. RCM are rather uncommon, although their prevalence is still unknown. Either Amyloid Light-chain (AL) amyloidosis or amyloidosis due to transthyretin gene mutations with heart involvement, often cause RCM [Table 3] [9]. A striking subtype of disease with restrictive physiology, endomyocardial fibrosis, endemic in areas of the African continent, has an unknown etiology and very poor prognosis [29]. Moreover a “restrictive phenotype” may be part of the clinical spectrum of end-stage HCM [30], and may occasionally originate as a primary, non-HCM-related phenotype from sarcomere gene mutations (generally in the thin filament protein coding genes). RCM is usually associated with severe functional limitation, mainly related to the extreme diastolic dysfunction, with reduced diastolic filling and stroke volume, and a poor prognosis [31].

**ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY**

ARVC is characterized by fibrofatty replacement of the right ventricular myocardium and ventricular arrhythmias [32]. In the most common right-dominant form, structural changes may be absent or confined to a localized region of the right ventricle (inflow and outflow tract, right ventricular apex, known as the ‘triangle of dysplasia’) at an early stage [Fig. 5]. Progression to more diffuse right ventricular disease and LV involvement (typically affecting the posterior lateral wall), associated with ventricular systolic dysfunction, is common at later stages [33]. Ventricular arrhythmias are the clinical hallmark of the disease, but atrial fibrillation may also occur. The diagnosis of ARVC is often challenging for the cardiologist, in particular during the early ‘concealed phase’, when individuals are still asymptomatic. Predominant LV disease has also been recognized. New diagnostic criteria with higher sensitivity and specificity have recently been published [32,34]. ARVC is generally a familial disease with autosomal dominant inheritance but it may be recessive when associated with woolly hair and palmopalmar hyperkeratosis (eg, Naxos disease, Carvajal syndrome). Mutations in desmosomal and non-desmosomal genes have been identified, but interpretation of their pathogenicity is often challenging in the affected individual [Table 4].

![Figure 5. Arrhythmogenic right ventricular cardiomyopathy. 38 year old female with diagnosis of ARVC, resuscitated from out-of-hospital cardiac arrest. She has family history of ARVC (mother) and sudden death (brother, 28 year old). CMR images show clearly wall aneurysms within the so-called “triangle of dysplasia” (panel A–C, white arrows: evident systolic bulging in infundibular, apical, and subtricuspid regions of the RV). Abbreviations: LV = left ventricle, RV = right ventricle.](image)

**UNCLASSIFIED CARDIOMYOPATHIES**

Isolated LV non-compaction (LVNC) is characterized by prominent LV trabeculae and deep inter-trabecular recesses, that can be associated with LV dilatation and systolic dysfunction [Fig. 6]. LVNC is familial, with 25% of asymptomatic first-degree relatives having some echocardiographic abnormalities [Table 5]. Of note, this rather mysterious disease shows substantial phenotypic overlap with other cardiomyopathies (in particular HCM and DCM, which often exhibit limited areas of non-compaction in the left ventricle), as well as a common genetic substrate [8]. Furthermore, LVNC may be associated with congenital cardiac disorders (such as Ebstein’s anomaly or complex cyanotic...
Figure 6. Unclassified cardiomyopathy. Isolated left ventricular non-compaction in a 45 year-old male, with mild systolic dysfunction (EF 48%), ventricular arrhythmias and normal LV diameters. Multiple trabeculations and recesses are evident, particularly in the apex and the free wall of the LV (panels A and C: apical 4 chambers view; panels B and D: apical 3 chambers view). CMR confirmed the diagnosis (panels E–F). Abbreviations: LV = left ventricle, RV = right ventricle IVS = inter-ventricular septum.

heart disease) and some neuromuscular diseases. Therefore, it is still debated whether isolated LVNC should be considered a separate clinical and genetic entity, or a morphological trait shared by many distinct cardiomyopathies. As a result of the difficult comprehension of this clinical entity, the real prevalence of LVNC and its outcome remain largely unknown.

Takotsubo cardiomyopathy, also known as LV apical ballooning or stress-induced cardiomyopathy, is characterized by transient regional systolic dysfunction involving the apex and/or mid-ventricle in the absence of obstructive coronary artery disease on angiogram [8]. The condition is reported all over the world, and most reported cases occur in post-menopausal women following physical or psychological stress, but it has been described also in patients with intracranial haemorrhage or other acute cerebral accidents (so-called “neurogenic myocardial stunning”). Typically, takotsubo cardiomyopathy has a sudden onset, with chest pain, diffuse T-wave inversion and mild cardiac enzyme elevation. Symptoms are often preceded by emotional or physical stress. If the patient survives the acute phase of disease, the prognosis is almost invariably favourable, with a normalization of LV function over a period of days to weeks; recurrence is possible, but rare.

LIMITATIONS OF CURRENT CLASSIFICATIONS AND NOVEL PERSPECTIVES

As more families with cardiomyopathies are genotyped, and new diseases are being described, the paradigm "one gene, one disease" appears no longer sustainable. The same mutation can be expressed at a different age and give rise to hugely different phenotypes within the same family, due to environmental factors and modifier genes. Different phenotype patterns may originate from the same genetic substrates, in a spectrum encompassing HCM, DCM, RCM and LVNC (all associated with sarcomere genes), or ARVC/DCM (associated with desmosomal genes).
Furthermore, the recent introduction of next generation sequencing has started what promises to be a revolution in molecular diagnostics, allowing rapid and affordable testing of hundreds of genes, or even whole genomes. As an example, a wide range of truncating gene mutations encoding Titin, a very large cytoskeleton gene which could not be assessed by traditional sequencing techniques, has recently been discovered to represent a prevalent cause of familial DCM, up to 25% [13].

In the near future, the list of causative genes will therefore likely require an update. This should ideally become an ongoing process, under the auspices of the ESC Working Group on Myocardial and Pericardial Diseases and AHA experts. The focus for researchers will necessarily shift from analyzing single mutations in candidate genes, to interpreting the hundreds of variants of unknown significance in putative causative as well as modifier genes, requiring entirely new skills and significant interaction with biophysicists and computer scientists. At present, and in the foreseeable future, however, clinical classifications of cardiomyopathies based on clinical presentation and morphological criteria represent an important tool for clinicians involved with these complex diseases. While calling for constant improvement and update in the light of advances provided by imaging genetics and basic science, individual patient phenotypes continue to represent the core of any classification in clinical medicine, something that has not changed with time.

LIST OF ABBREVIATIONS:
ESC: European Society of Cardiology
AHA: American Heart Association
ECHO: echocardiography
CMR: Cardiac magnetic resonance
LV: left ventricular
EF: ejection fraction
HCM: hypertrophic cardiomyopathy
DCM: dilated cardiomyopathy
RCM: restrictive cardiomyopathy
ARVC: arrhythmogenic right ventricular cardiomyopathy
LVNC: left ventricular non compaction

COMPETING INTERESTS
The authors have no competing interests.

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