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Classification of cardiomyopathies: bringing order to complexity

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Cardiomyopathy classification remains challenging due to their extraordinary clinical, morphological, and genetic heterogeneity. As diagnostic technologies evolve, so too must the frameworks by which we conceptualize and communicate these diseases. Since the 2008 ESC morphofunctional classification and the genotype–phenotype integrated MOGE(S) system proposed in 2013, substantial advances in imaging and genetics have prompted a revised 2023 ESC phenotype-first model. The five current phenotypes—dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and non-dilated left ventricular cardiomyopathy (NDLVC)—capture major morphological expressions but display extensive overlap, especially among DCM, ARVC, and NDLVC. This overlap underscores the need for dynamic, multiparametric diagnostic pathways and individualized interpretation.

Introduction

Cardiomyopathies are defined as a primary myocardial disorder characterized by structural and functional abnormalities that occur in the absence of coronary artery disease, congenital heart disease, valvular pathology, or abnormal loading conditions sufficient to explain the phenotype. The spectrum of disease encompassed by this definition is vast, with wide variability in clinical presentation, natural history, and prognosis. Therefore, experts in the field have tried to refine it and make it more precise.

The need to classify cardiomyopathies arises from the necessity to organize complex biological information, standardize communication among health professionals and with patients, and promote rigorous scientific investigation. However, any classification inevitably imposes rigid categorical boundaries on diseases that, in reality, exist along phenotypic and genotypic continua. Cardiomyopathies can result from numerous genetic and acquired causes—often interacting in multifactorial ways—making them inherently resistant to simplistic taxonomic structures.

This review traces the evolution of cardiomyopathy classification systems from the early 2000s to the present, examining how advances in diagnostic technology and genetic insight have shaped current

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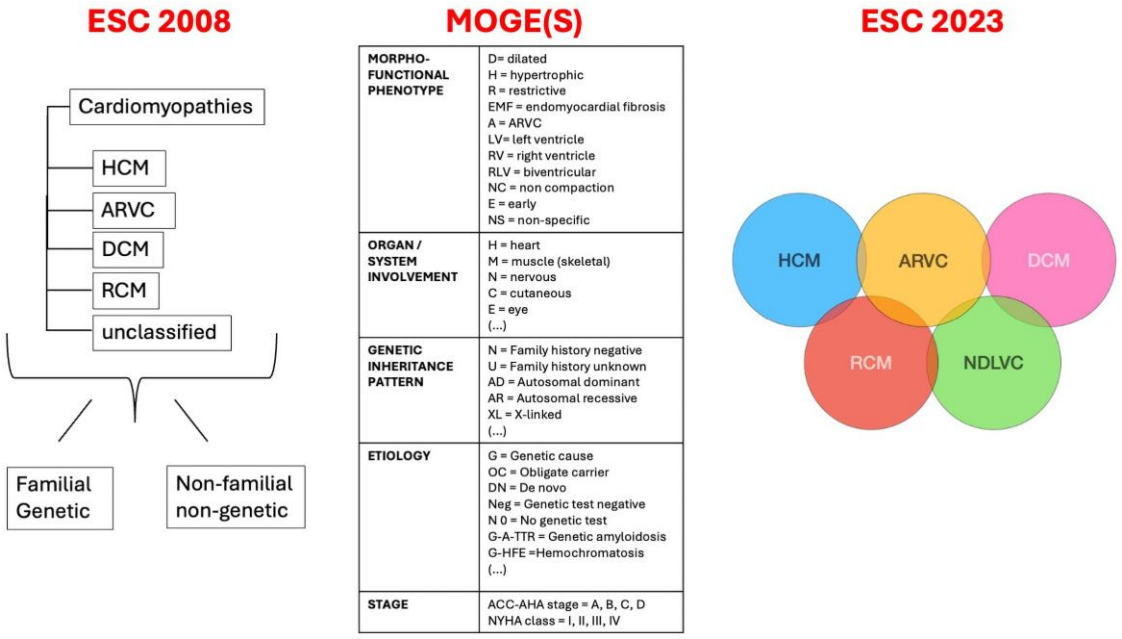

Figure 1 Schematic representation of the main proposed classifications of cardiomyopathies from 2008 to 2023. Modified from Elliott *et al.*,[1] Arbustini *et al.*,[2] Arbelo *et al.*[3]

frameworks and identifying key areas where further refinement is needed (*Figure 1*).

Evolution of cardiomyopathy classification

ESC 2008: morphofunctional paradigm

The first European Society of Cardiology (ESC) classification dates back to 2008.[1] It defined five categories: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), and unclassified cardiomyopathies (notably LVNC and Takotsubo syndrome). Each phenotype was subdivided into genetic/familial vs. non-genetic/non-familial, recognizing pathogenic variants or environmental causes when identifiable and leaving the rest under the term 'idiopathic'.

The goal of this approach was to be conceptually practical and suitable for daily clinical practice, being based on the assumption that it is the phenotype that first reaches the cardiologist's attention, but it inevitably underemphasized genetic complexity. In fact, in spite of the new sequencing techniques and discoveries of cardiomyopathy-related genes since the end of the Nineties, genotype remained on the side. Indeed, variant interpretation demands caution due to variable penetrance, variant expressivity, and modifiers of phenotype.

MOGE(S) 2013: towards a genotype–phenotype integrated system

In 2013, stemming from the newly acquired knowledge on the hereditary nature of many cardiomyopathies, and trying to better grasp these diseases' complexity, the MOGE(S) system[2] expanded the taxonomic framework to include:

- M: morpho-functional phenotype (based on the 2008 ESC phenotypes)
- O: organ involvement
- G: genetic inheritance pattern
- E: underlying aetiology
- S: functional status

Although analytically robust and reflective of disease complexity, the system's granularity hindered widespread clinical adoption due to its operational impracticality. For instance, a patient with RCM due to an autosomal dominant desmin variant, with skeletal muscle involvement and atrioventricular conduction block in NYHA class III would have been labelled as $M_{R[AVB]}O_{H+M}G_{AD}E_{G\text{-}Des[p.Gly84Ser]}S_{C\text{-}III}$: somehow intricate.

ESC 2023: updated phenotype-first model

The most recent ESC guidelines consolidate diagnostic and management strategies based on a phenotype-first approach.[3] The updated schema retains DCM, HCM, RCM, and ARVC, while introducing non-dilated left ventricular cardiomyopathy (NDLVC). LVNC and Takotsubo syndrome are no longer classified as cardiomyopathies.

Non-dilated left ventricular cardiomyopathy is a heterogenous entity defined by the presence of myocardial scarring at cardiac magnetic resonance (CMR) and/or by left ventricular systolic dysfunction without dilatation. This new entity reflects the reality that morphological abnormalities typically constitute the initial clinical entry point, with characteristics that at the initial evaluation might not fulfil diagnostic criteria for DCM or

HCM. In NDLVC, the LV is not dilated nor is hypertrophic. This thus includes the previously called arrhythmogenic cardiomyopathy (ACM) that, other than the historically described right ventricular involvement, can also affect the LV, and early manifestations of DCM that do not reach LV dimensions cutoffs (nor carry the same prognosis). This attempt seeks to comprehend left ventricular and biventricular forms of ACM, even if basing their definition on purely morphologic criteria. Nonetheless, the guidelines emphasize that classification should serve only as an initial step towards precision diagnosis, advancing through systematic evaluation of 'red flags', advanced imaging, genetic testing, and clinical context.

Dilated cardiomyopathy

Dilated cardiomyopathy is defined by left ventricular dilatation and systolic dysfunction not attributable to abnormal loading or coronary disease. This definition remained relatively unchanged across the years.[4] The aetiological spectrum remains broad, spanning genetic variants (approximately 30–40%, frequently titin truncating variants), inflammatory and autoimmune triggers, toxic exposures, and reversible conditions such as tachycardia-induced cardiomyopathy. The most common manifestation is heart failure with reduced ejection fraction.

A major clinical challenge of DCM is arrhythmic risk stratification. Risk is predicted mostly by left ventricular ejection fraction, although not entirely: instead, arrhythmogenic potential is influenced by genetic substrate, presence and distribution of myocardial scar, and aetiology.[5] In this regard, a multiparametric evaluation combining genetic analysis and advanced imaging, particularly contrast-enhanced cardiac magnetic resonance (CMR), is essential for accurate risk assessment.[6-8]

Arrhythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is characterized by progressive fibrofatty myocardial replacement that predisposes to ventricular arrhythmias and sudden cardiac death. Historically conceptualized as a right ventricular disorder (ARVC), modern imaging and genetic insights reveal that left-dominant and biventricular involvement are common.

The most recent diagnostic criteria are from 2010 and only account for the RV form. Progressive advancement in CMR with tissue characterization,[9] though, have shed light on the possible LV and biventricular involvement (with various degree of overlap). Alongside, these insights have been strengthened by the progressive discovery that desmosomal gene variants—traditionally associated with ARVC—are also prevalent in left-dominant and biventricular phenotypes, supporting the concept of a unified arrhythmogenic spectrum.[10] Despite this, the 2023 ESC guidelines did not adopt the ACM terminology, preferring to preserve strictly morphological classifications. This choice was also made to avoid definitions requiring arrhythmia, which may not be present at baseline.

The introduction of NDLVC seeks to unravel this complexity: it encompasses, for example, early-stage DCM, arrhythmogenic left ventricular disease, post-myocarditis scar patterns, and desmoplakin- or lamin-related cardiomyopathy. Nonetheless, the overlap between DCM, NDLVC and ARVC is substantial and it has led to numerous controversies.

Since 2023, numerous studies on NDLVC have been published. It carries a substantial arrhythmic burden: multicentre European data from 13 centres indicate that 15–19% of affected individuals experience major arrhythmic events during a follow-up of 5 years.[11] Pathogenic variants have been reported in 40[12]–50% of cases, though selection bias is possible, especially considered the need for CMR in the diagnosis.

Despite the previously mentioned drawbacks of the term 'arrhythmogenic', from a mechanistic and clinical perspective, right-, left-, and biventricular arrhythmogenic phenotypes likely represent a continuum best described within the broader ACM framework. This will inevitably be separated from DCM, even if there are areas of overlap, but as such, the arrhythmic profile of the disease will not be accounted for by the LVEF alone (*Figure 2*).

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is defined by increased left ventricular wall thickness or mass unexplained by abnormal loading.

An increased LV wall thickness calls for a thorough differential diagnosis that includes sarcomeric HCM and a broad group of phenocopies. It is crucial to distinguish cases in which the myocardial mass increases due to cardiomyocytes hypertrophy and sarcomeric disarray and when it does so due to the intracellular buildup of unmetabolized substances or rather pseudohypertrophy due to increase intercellular space from extracellular material deposition.

Comprehensive evaluation—including ECG, echocardiography, and CMR with tissue characterization—is crucial for distinguishing among these entities. The localization of areas of hypertrophy, its pattern and associated anomalies in atria, valves and subvalvular apparatus need to be addressed. Tissue characterization at CMR can point to interstitial or substitutive fibrosis, lipids, or iron accumulation or infiltration. Assessment of extracardiac findings is essential for diagnosing systemic conditions such as amyloidosis or RASopathies.

Sarcomeric HCM is the most common inherited cardiomyopathy and the first to benefit from targeted molecular therapy via cardiac myosin inhibitors.[13] Phenocopies such as Anderson–Fabry disease, glycogen storage disorders, and transthyretin amyloidosis now have disease-specific therapies,[14,15] further underscoring the importance of precise diagnostic classification.

Management should be based on a precise stratification of the patient based on the most prevalent pathophysiological mechanism (LV outflow

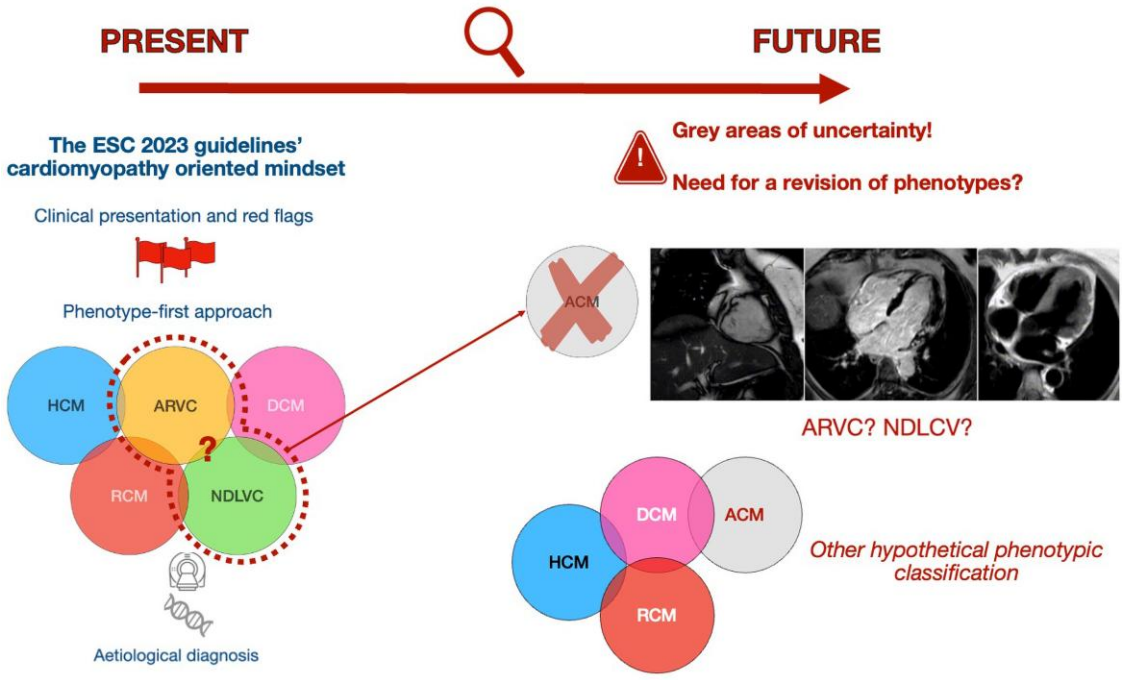

Figure 2 Evolution of the diagnostic approach to cardiomyopathies. On the left, the approach proposed by the European Society of Cardiology 2023 guidelines on cardiomyopathies is illustrated, which starts from clinical red flags to identify the phenotype and uses genetic testing and magnetic resonance imaging to arrive at an etiological diagnosis. On the right, the controversies on the phenotypes defined in the guidelines are shown through cardiac magnetic resonance images of an individual with desmoplakin cardiomyopathy. These images highlight the overlapping zones and grey areas between arrhythmogenic right ventricular cardiomyopathy and non-dilated left ventricular cardiomyopathy, previously included under the umbrella term of arrhythmogenic cardiomyopathy. Reproduced with permission of the authors. ACM, arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy.

tract obstruction, diastolic dysfunction, microvascular ischaemia) and arrhythmic risk.

Restrictive cardiomyopathy

Restrictive cardiomyopathy is defined by both physiological and morphological characteristics, requiring restrictive ventricular physiology but also absence of ventricular dilatation. Although rare, its prognosis is often poor, and the phenotype frequently overlaps with hypertrophic or infiltrative cardiomyopathies. Cardiac amyloid cardiomyopathy is a good example of this overlap, where amyloid deposition not only causes a hypertrophic phenotype but also restrictive filling.

In RCM, the diagnostic process demands precision and detailed analysis. Systemic diseases are common causes, and extracardiac manifestations need to be thoroughly searched. RCM prognosis is often poor and requires cardiac transplantation; therefore, endomyocardial biopsy retains diagnostic value in selected cases.[16]

Future directions

From this brief outline, the importance of a reasoned diagnostic approach to cardiomyopathies emerges, in which the cardiologist is required to bring together different pieces of information to arrive at appropriate diagnoses and, consequently, at careful disease management shared with the patient.

Although genotype-based models have enhanced disease understanding and can predict disease prognosis better than phenotype alone,[17] pathogenic variants remain unidentified in 60–70% of cardiomyopathies. Genetic architecture is further complicated by multilocus interactions, epigenetic regulation, non-coding regions, variable penetrance, and environmental modifiers. For these reasons, a genotype-based classification is likely premature. Nevertheless, phenotypic categories will withstand differently the test of time: DCM, HCM, and RCM with all their differential diagnoses remain rather robust categories, whereas ARVC and NDLVC display fluid boundaries and extensive overlap. Conceptually, many of these phenotypes may be better unified under the arrhythmogenic cardiomyopathy spectrum.

Single descriptors—such as dilation, hypokinesia, scar, or arrhythmogenicity—are inadequate for capturing disease complexity or guiding individualized management. Precision diagnosis requires a multiparametric, patient-specific approach integrating clinical, imaging, and genetic information.

Conclusions

Classification systems provide a valuable but inherently limited framework for understanding cardiomyopathies.

Effective diagnosis demands a comprehensive, rigorous, and individualized approach that transcends categorical labels. Clinicians must understand both the utility and limitations of existing classifications to apply them appropriately and to guide precise diagnostic, risk stratification, and therapeutic strategies for patients and their families.

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Data availability

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Disclaimer

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