Viewpoint

Clinical Reasoning and Classification of Cardiomyopathies

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Definition

Cardiomyopathies (CMPs) are a group of diseases with multiple etiologies and heterogeneous phenotypes, ranging from microscopic changes in cardiomyocytes in asymptomatic patients to cases of fulminant heart failure with fluid retention, and perfusion and heart rhythm changes. A CMP was initially defined as a heart muscle disease caused by genetic defects, myocyte injury or myocardial infiltration, and characterized by structural and functional abnormalities in the absence of congenital disease, valvular disease or hypertension.[1] The initial approach of patients with CMP consists of clinical evaluation and complementary imaging techniques and genetic testing, in search of diagnostic evidence and the need for specific tests (Figure 1).[1,2]

Classification of CMPs

The classification of CMP is used to standardize the nomenclature, by grouping disorders that share morphological characteristics or biochemical and genetic abnormalities.[1]

In 1957, Brigden was the first author to use the term CMP to describe patients with idiopathic (noncoronary) CMP, many of them with familial disease.[3] The CMPs were initially classified based on dominant pathophysiology, structural changes and, if possible, on etiological and pathogenic factors, into three phenotypes – hypertrophic, dilated, and restrictive CMP. As shown in Figure 2, with the development of complementary methods and genetic studies, new classifications have been proposed, but still with vulnerable and inconclusive issues.[4,5]

In 1980, with the publication of the report of the World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC),[6] CMP was defined as a heart muscle disease of unknown cause. Myocardial disorders caused by systemic or pulmonary arterial disease, heart valve diseases, coronary and congenital diseases were excluded. In this report, the CMPs were classified as dilated, hypertrophic and restrictive, on the basis of structural and hemodynamic phenotypes.

Keywords

Cardiomyopathies; Hypertrophy; Genetics.

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In 1996, a new WHO/ISFC classification was proposed.[7] CMPs were defined as diseases of the myocardium associated with cardiac dysfunction and classified by the dominant pathophysiology and by etiological and pathogenetic factors. In addition, arrhythmogenic right ventricular CMP was added to dilated, hypertrophic, and restrictive CMPs. Unclassified CMPs were also included, *i.e.*, those cases that do not fit into any group, such as fibroelastosis and mitochondrial involvement. In the "specific CMPs" group were included heart muscle diseases that are associated with specific cardiac or systemic disorders, which were previously defined as specific heart muscle diseases – ischemic, valvular, hypertensive, inflammatory, and peripartal CMPs, general system disease, muscular dystrophies, and neuromuscular disorders.

In 1990, β-myosin heavy chain gene mutation was reported in patients with hypertrophic CMP and in dilated CMP years later.[8] Then, two further classifications were proposed, reflecting advances in genetics and complementary methods in CMP.[3,4]

In the classification of CMPs offered by the American Heart Association in 2006, the diseases were defined as "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation, due to a variety of etiologies that frequently are genetic. CMPs are either confined to the heart or are part of generalized systemic disorders". Within this definition, CMPs are associated with failed cardiac function, that may be either mechanical (diastolic or systolic), or a primary electrical disease. Also, ion channelopathies are defined as distinct entities (long QT syndrome and Brugada syndrome), as primary electrical diseases, without histological abnormalities, responsible for the arrhythmic substrate.[4,8]

This classification tries to cover new methods of diagnostic molecular biology, for the characterization of genetic mutations and, at cellular level, of protein expression. The American classification divides CMPs into two large groups: primary CMPs, comprising those confined to heart muscle (subdivide into genetic, mixed, and acquired);[4] and secondary CMPs, that show myocardial involvement as part of a systemic disorder, previously known as specific CMPs. Myocardial dysfunction secondary to or associated with coronary artery disease, hypertension, valvular heart disease, or congenital heart disease were not classified as CMP.

The 2008 European statement (Figure 3) defines CMP as a heart muscle disorder in which the heart muscle is structurally and functionally abnormal, in the absence of specific causes. Structural and morphological changes of CMP subtypes –

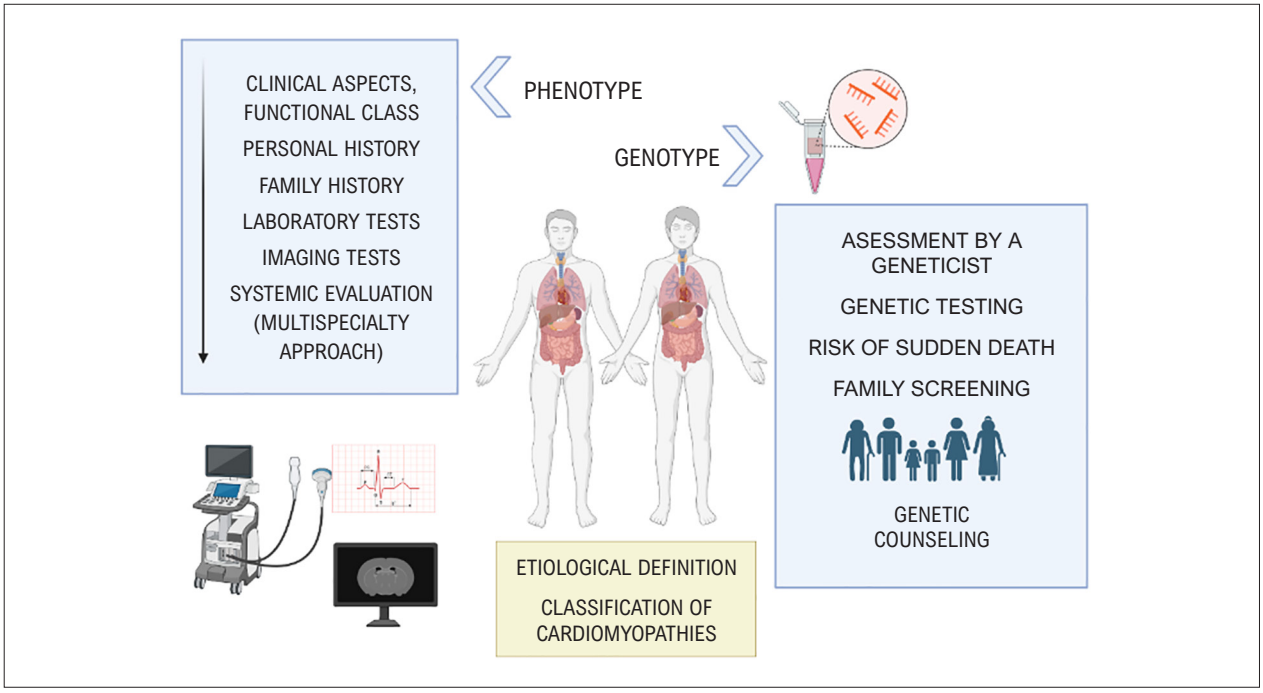

Figure 1 – *Clinical reasoning: clinical, laboratory and imaging data in cardiomyopathy classification.*

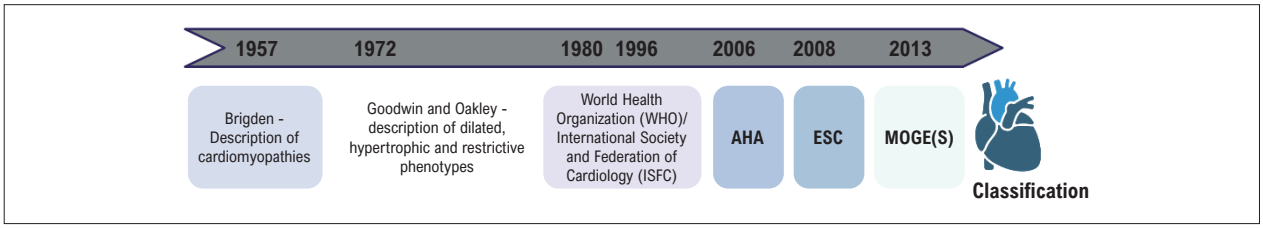

Figure 2 – *Historical timeline of classification of cardiomyopathies.*

dilated, hypertrophic, restrictive and arrhythmogenic right ventricular CMP – were maintained and defined as familial (genetic) and non-familial (non-genetic).[3] Familial refers to the occurrence, in more than one family member, of either the same disease or a phenotype that could be caused by the same genetic mutation. Non-familial CMPs are clinically defined by the presence of CMP in one family member and the absence of disease in the others other family members. They are subdivided into idiopathic (without an identifiable cause) and acquired CMPs in which ventricular dysfunction is a complication of the disorder rather than an intrinsic feature of the disease. In addition, there is an attempt to identify diagnostic labels and tailored treatments. In contrast, differently from the American Heart Association, the European Society of Cardiology deems inadequate and of limited clinical usefulness the inclusion of channelopathies as a distinct clinical entity.[4,10]

Therefore, despite differences between current American and European recommendations, both classify cardiac muscle diseases based on their morphological and functional changes.[3,4] The identification of genetic determinants in the etiology of CMPs allowed their sub-classification into familial and non-familial forms in the European position statement, while in the American classification the categories are "genetic", "mixed" and "acquired".

A genome-based classification is still structurally complex, since some gene mutations affecting the sarcomere may lead to different phenotypes, such as dilated CMP and hypertrophic CMP. Troponin I mutation can lead to anatomical changes similar to those seen in the restrictive and hypertrophic forms, and desmosomal gene mutations are associated with arrhythmogenic right ventricular dysplasia, but can also lead to dilated CMP phenotype, making classification difficult. For this reason, a classification based on morphological, clinical, and genetic features is important.[1]

A descriptive nosological classification encompassing these individual attributes and allowing a common platform for collaborative research efforts was published in 2013.[11] This new classification system, named MOGE(S), was endorsed by the World Heart Federation, and inspired from the TNM staging of tumors. This nosology is based on morphofunctional abnormalities (M), extension of organ involvement (O), genetic

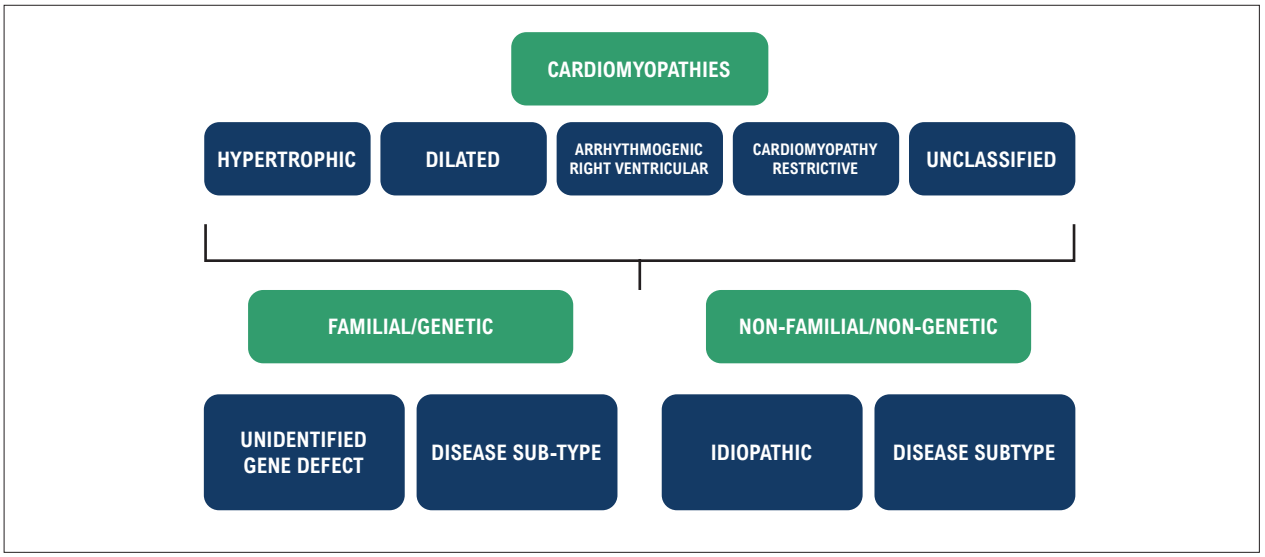

Figure 3 – *2008 European Society of Cardiology classification of cardiomyopathies.*

inheritance (G), (E) details of molecular genetic defect or etiology (E), and degree of heart failure or stage of exertion intolerance (S) (Figure 4). In this classification, CMP is defined as a morphological or functional disorder of abnormal myocardium in the absence of any other disease that cause the observed phenotype. Conventional phenotypes of CMP subtypes (e.g., dilated, hypertrophic, restrictive) are the basis of this classification, and establishes whether the disease is systemic or if the involvement of the heart is part of the systemic disease. The combination of M and O can suggest diagnostic clues, and the inclusion of investigation for the family history and the pattern of inheritance (G) add valuable information for complete characterization of the CMP.[11] The purpose is to achieve a precise classification that tries to relate the etiology with clinical phenotypes, and by inference, with treatment and prognosis.[11,12]

One of the advantages of this new classification lies in the inclusion of individuals at early stages of the disease that do not show clear phenotypic alterations. In family members with known mutation but still no disease manifestation, the preclinical diagnosis can be made by the genetic study. This classification could also be useful for sports recommendations in cases that are in the "gray area" to receive a definitive recommendation.[11] The inclusion of a graded risk for sudden death, in conjunction with heart failure status. The usefulness of the MOGE (S) scheme to prevent the outcome would be reinforced by the inclusion of risk factors for sudden death from arrhythmia in CMP patients.

However, the MOGE(S) classification system does not include some MCP groups, such as tachycardia-induced CMP, endocrine CMPs and paripartum CMP. Finally, the complexity of the MOGE(S) system could hamper its use in clinical practice. Besides, key information, such as the molecular genetic diagnosis, is only available in a few centers and countries in the world. The authors of the MOGE nomenclature have also developed an application, accessible at http://moges.biomeris.com, that may be handy in clinical practice to complement the descriptive classification of CMPs.[11,12]

Since most CMPs have a familial origin, genetic testing has been crucial in the clinical context as several new genes and mutations have been detected in the different etiologies of CMPs. Several genetic diseases have been identified; the penetrance of the genetic mutation is variable, and phenotypic manifestations are age dependent. Most genetic CMPs are autosomal dominant traits, with a minority of autosomal recessive, X-linked recessive or dominant (rare).[9,11]

Recently, the role of the atrium in cardiac dynamics and in systemic and pulmonary circulation has been highlighted, and the concept of atrial CMP has emerged. Atrial CMP would be defined as structural, architectural, contractile, or electrophysiological changes that may produce relevant clinical manifestations.[13] This concept, however, has not been incorporated into the societies of cardiology and deserve to be addressed in future classifications.

Conclusion

The classification of CMPs is challenging; although classification systems have evolved, there is not a definite classification yet. As Goodwin said, "since any classification is necessarily incomplete and acts as a bridge between complete ignorance and total understanding, further modification and changes are likely to occur as knowledge advances. In clinical practice, due to its simplicity and ease of use, the European classification has been used in most centers. On the other hand, the MOGE classification is more complex and comprehensive, allowing better characterization of CMPs, especially regarding their forms and etiologies. Atrial CMPs still have gaps in their classification.

Author Contributions

Conception and design of the research, Acquisition of data and Critical revision of the manuscript for important intellectual content: Madrini Junior V, Mesquita ET, Avila DX, Fernandes F; Analysis and interpretation of the data and Writing of the manuscript: Madrini Junior V, Avila DX.

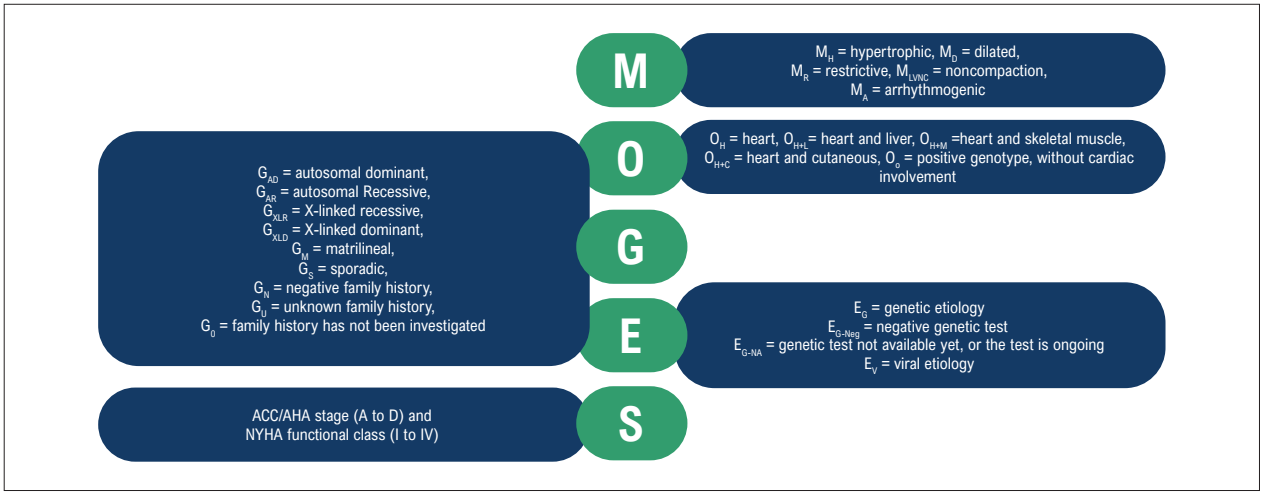

Figure 4 – *The MOGE(S) classification.*

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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