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The MOGE(S) classification for cardiomyopathies: current status and future outlook

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Abstract Cardiomyopathies are complex diseases of multifactorial pathogenesis and have a high morbidity and mortality. Over the past decades, several revisions of classifications and definitions of cardiomyopathies have been proposed, primarily focusing on the phenotypic characterization of cardiomyopathies. The MOGE(S) classification system published in 2013 encompasses the classification of rapidly growing knowledge on genetic mutations, acquired causes (i.e., intramyocardial inflammation, viral infections), and further conditions involved in the induction of cardiomyopathies (e.g., storage diseases, toxicity). It is based on five attributes, including morphofunctional characteristics (M), organ involvement (O), genetic or familial inheritance pattern (G), etiological annotation (E), and optional information about the heart failure functional status (S). This review summarizes the development, the cornerstones of the MOGE(S) classification, and the published data on the clinical relevance of the MOGE(S) classification. We furthermore discuss new issues which might be considered for future updates of the MOGE(S) classification of cardiomyopathies.

Keywords Cardiomyopathies · Classification · MOGE(S) · Genetic mutations · Myocarditis · Diagnosis

Abbreviations

ARVC	Arrhythmogenic right ventricular cardiomyopathy
CAM	Cell adhesion molecule(s)
CD	Cluster of differentiation

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CI	Confidence interval
CMR	Cardiac magnetic resonance
DCM	Dilated cardiomyopathy
DCMi	Inflammatory cardiomyopathy
EMB	Endomyocardial biopsy or biopsies
ESC	European Society of Cardiology
GCM	Giant cell myocarditis
HCM	Hypertrophic cardiomyopathy
ISFC	International Society and Federation of Cardiology
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
B19V	Parvovirus B19
RCM	Restrictive cardiomyopathy
SNOMED	Systematized Nomenclature of Medicine Terms
WHF	World Heart Federation
WHO	World Health Organization

Introduction

Cardiomyopathies are diseases of the heart muscle, characterized by myocardial dysfunction in the absence of common secondary cardiovascular causes such as coronary artery disease, hypertension, valvular disease, or congenital heart disease [1, 2]. Though major steps have been made in early diagnosis and treatment, cardiomyopathies still remain diseases with high mortality and morbidity [3–5]. Classification of cardiomyopathies has been traditionally based on the morphofunctional phenotypic characteristics with an aim to assist the clinicians for the diagnosis and family screening. With the expanding knowledge on acquired and genetic causes of cardiomyopathies, it became obvious that etiology should also be taken into consideration, in particular for the differential diagnosis, assessment of prognosis, and identification of subclinical phenotypes. This growing knowledge has led to the development of novel classifications of cardiomyopathies.

Classification systems for cardiomyopathies

In the past 60 years, there have been many revisions of classification systems and definitions of cardiomyopathies due to new results of research. In 1957, Brigden first used the term *cardiomyopathy* and defined it as "uncommon, noncoronary heart muscle disease"[6]. Following this, Goodwin and Oakley categorized cardiomyopathies into congestive dilated (DCM), hypertrophic (HCM) and restrictive (RCM) [7]. Reflecting the incomplete knowledge about the pathogenic mechanisms of the cardiomyopathies in 1980, the World Health Organization (WHO), the International Society and Federation of Cardiology (ISFC), and the World Heart Federation (WHF) defined cardiomyopathies as myocardial diseases of unknown etiology in 1998 [1]. In 1995, the WHO and ISFC adapted the core definition of cardiomyopathies as *diseases of myocardium associated with myocardial dysfunction,* and moreover, arrhythmogenic right ventricular cardiomyopathy (ARVC) and unclassified cardiomyopathies were added [2]. Due to a significant increase in the genetic knowledge of cardiomyopathies, the American Heart Association (AHA) proposed a new classification system based on genetics in 2006 [8]. Subsequently, the European Society of Cardiology (ESC) submitted a similar classification; however, they kept the morphofunctional categories with further division into genetic (familial) and nongenetic (nonfamilial) [9, 10].

In 2013, the WHF proposed a new classification system for cardiomyopathies and described cardiomyopathies as "disorders characterized by morphologically and functionally abnormal myocardium in the absence of any other disease that is sufficient, by itself, to cause the observed phenotype"[11].

The MOGE(S) classification proposed by Arbustini et al. is a phenotype-genotype-based classification system and follows the TNM classification scheme for tumors. It is based on five attributes, including morphofunctional characteristics (M), organ involvement (O), genetic or familial inheritance pattern (G), etiological annotation (E), and optional information about the functional status (S) using the American College of Cardiology/American Heart Association (ACC/AHA) stages A–D and/or the New York Heart Association (NYHA) functional classes I–IV. The phenotypic subtype still provides the basis of this classification system, and also the major clinical decisions are still based on morphological and functional criteria. Nevertheless, the genotype is important for the diagnostic workup, treatment decisions, and follow-up plans.

The incorporation of genetic information in the description of the disease is increasingly becoming a common routine, as it has been shown that different gene mutations may lead to similar phenotypes, whereas mutations in the same gene may lead to different phenotypes. Furthermore, several inherited cardiomyopathies have been lately increasingly recognized and virtually categorized under new terms pointing to the particular genetic etiology (Table 1).

Nomenclature of the MOGE(S) classification system

The nomenclature is based on the terminology applied by internationally accepted systems, such as the SNOMED (Systematized Nomenclature of Medicine Terms) and SNOMED CT (SNOMED Clinical Terms) as well as the ICD (International Classification of Diseases). In order to facilitate the introduction and application of MOGE(S) in the clinical practice, a web-based interface has been developed, which is available for smartphones and portable computers (http://moges.biomeris.com). The available selections for the attributes of the MOGE(S) classification in this application are summarized in Table 2.

Table 1 Terms of cardiomyopathies pointing to the particular genetic etiology

Troponinopathies
Laminopathies
Dystrophinopathies
Desmosomalopathies
Cytoskeletalopathies
Sarcomyopathies
Channelopathies
Cardiodystrophinopathies
Cardiolaminopathies
Zaspopathies
Myotilinopathies
Dystrophinopathies
AlphaB-crystallinopathies
Desminopathies
Caveolinopathies
Calpainopathies
Dysferlinopathies
Sarcoglycanopathies
Merosinopathies
Emerinopathies

The letter *M* characterizes for the *morphofunctional* phenotype: M_D means dilated cardiomyopathy, M_H means HCM, M_A stands for ARVC, M_R stands for RCM, and M_{LVNC} documents LV noncompaction. It is also possible to describe combined phenotypes (e.g., M_{D+H}) as well as red flags, for example, $M_{D(AVB)}$ in case of an atrioventricular block. M_E stands for early involvement and M_0 for an unaffected mutation carrier. Nonspecific phenotypes can be also characterized (M_{NS}). In case that the morphofunctional phenotype information is not available, M_{NA} is documented.

The letter *O* provides information about the *organ involvement* and can be documented as heart only (O_H) or in combination with other organs as, for example, skeletal muscle (O_{H+M}), auditory system (O_{H+A}), or kidney (O_{H+K}) involvement. In addition to the M_0 annotation, healthy mutation carriers are described as O_0. Organ involvements can advert to a systemic disease and lead to a specific genetic testing.

The letter *G* describes the *genetic or familial inheritance pattern* and can be derived from family screenings and pedigree analysis. Autosomal dominant is documented as G_{AD}, autosomal recessive as G_{AR}, and matrilineal as G_M. G_S stands for sporadic and G_N for negative family history. G_{UNDET} characterizes still undetermined inheritance.

The *etiological annotation E* provides the description of the underlying cause. Genetic causes (E_G) can be distinguished from nongenetic etiology, e.g., acquired conditions as virus infection (E_V) or myocarditis (E_M). In case of a genetic cardiomyopathy, the disease gene can be added; in case of a nongenetic disease, the specific infectious agent can be described, for example, in case of HCM, the annotation would be $E_{G\text{-}MYH(p.Arg403Glu)}$. Specifications of myocarditis may be added as identified; e.g., giant cell myocarditis (GCM) may be characterized by $E_{M\text{-}GCM}$, hypereosinophilic myocarditis by $E_{M\text{-}EO}$, and autoimmune myocarditis by $E_{M\text{-}AI}$. Cardiac amyloidosis is denoted E_A and can be further specified as type K ($E_{A\text{-}K}$), type L ($E_{A\text{-}L}$), and type SAA amyloidosis ($E_{A\text{-}SAA}$).

The letter *S* indicates the *heart failure stage* and is optional. ACC/AHA stage (A to D) and NYHA functional class (I to IV) can be documented, e.g., $S_{A\text{-}I}$ or $S_{C\text{-}II}$.

A web interface is available which enables a quick hierarchical characterization of cardiomyopathies based on the MOGE(S) classification (http://moges.biomeris.com).

The major purpose of the MOGE(S) classification was to integrate diverse information categories provided according to the AHA and ESC classification schemes for cardiomyopathies, by incorporating morphology, function, and involvement of other organs; inheritance and genetic data; and clinical parameters. In this way, the MOGE(S) serves a second role, which is essential for the clinical practice: the individual annotation of the cardiomyopathy in a given patient, genetic proband, family member, or mutation carrier describes the important details of the disease and its etiology, as well as the clinical stage for the specific time point. This enables the clinician to have a precise overview of the disease given by the MOGE(S) annotation, in order not only to categorize patients, but also to be able to follow the progression of the disease or the knowledge of the disease characteristics in a given patient [12].

MOGE(S) classification of specific cardiomyopathies and examples

Hypertrophic cardiomyopathy (HCM) is characterized by a thickening of the left ventricular wall and can be divided into sarcomeric and nonsarcomeric HCM according to the underlying genetic etiology. The sarcomeric HCM is caused by a mutation of structural and regulatory genes of the sarcomere. In 70% of positive genotype, mutations of MYH17 or MYBPC3 are found followed by troponin gene defects.

Dilated cardiomyopathy (DCM) is the most common cardiomyopathy and characterized by LV systolic dysfunction and LV or biventricular dilation. Genetic mutations have been reported in up to about 50% of the investigated DCM patient cohorts by next-generation sequencing. More than 40 genes have been associated to DCM. Lamin A/C is the most common disease gene followed by dystrophin gene defects. An example of a patient with a lamin A/C mutation and atrioventricular block (AVB) would be $M_{D(AVB)}O_HG_{AD}E_{G\text{-}LMNA(p.Arg190Trp)}S_{(C\text{-}II)}$.

Restrictive cardiomyopathy (RCM) is characterized by diastolic dysfunction leading to abnormal ventricular filling with biatrial dilation in the absence of significant LV hypertrophy. The idiopathic RCM is associated with troponinopathies

Table 2 Attributes of the MOGE(S) classification

Morphofunctional	Organ/system involvement	Genetic	Etiology		Stage	
D—dilated	H—heart	N—family history negative	G—genetic etiology	G-OC—obligate carrier	ACC-AHA	A
				G-ONC—obligate noncarrier		B
				G-DN—de novo		C
				G-Neg—genetic test negative		D
				G-N—genetic test not identified		NU—not used
				G-A—genetic amyloidosis		NA—not applicable
H—hypertrophic	M—muscle/skeletal	U—family history unknown	0—no genetic test		NYHA	I
						II
						III
						IV
H(Obs)—hypertrophic obstructive	N—nervous	AD—autosomal dominant	M—myocarditis			
H(noObs)—hypertrophic non obstructive	C—cutaneous	AR—autosomal recessive	V—viral infection			
R—restrictive	E—eye	XLR—X-linked recessive	AI—autoimmune/immune-mediated			
A—ARVC	A—auditory	XLD—X-linked dominant	AI-S—autoimmune/immune-mediated suspected			
NC—LVNC	K—kidney	XL—X-linked	AI-P—autoimmune/immune-mediate proven			
NS—nonspecific phenotype	G—gastrointestinal	M—matrilinear	A—amyloidosis			
NA—information not available	S—skeletal	0	I—infectious, non viral			
E(D)—early diagnosis of dilated	Lu—lung	Undet—inheritance still undetermined	T—toxicity			
E(H)—early diagnosis of hypertrophic	Li—liver	S—phenotypically sporadic	Eo—hypereosinophilic heart disease			
0—unaffected	0—absence of organ/system involvement		A-K—amyloidosis type K			
E(R)—early diagnosis of restrictive			A-L—amyloidosis type L			
E(A)—early diagnosis of ARVC			A-SAA—amyloidosis type SAA			
R EMF—endomyocardial fibrosis			Other			

Attributes of cardiomyopathies available in the MOGE(S) classification

entailing a high arrhythmogenic risk and desminopathies with a high risk for AVB. An example of a patient with a desmin mutation could be $M_{R(AVB)}O_{H+M}G_{AD}E_{G\text{-}Des(p.Gly84Ser)}S_{C\text{-}III}$.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is primarily characterized by ventricular arrhythmias and secondarily by a fibrolipomatous degeneration of the myocardium, primarily of the right ventricle. In 40% of the cases, a positive family history can be ascertained, with mutations in desmosomal genes, as well as in DCM-related genes. An example of a patient with epsilon waves and a desmoglein mutation may be characterized as follows: $M_{A(\varepsilon)}O_HG_{AD}E_{G\text{-}DSG2(p.Glu1020AlafsX18)}$ $S_{A\text{-}I}$. The introduction of MOGE(S) was criticized especially because of the difficulty to describe all attributes of ARVC [10, 13]. ARVC is characterized by a complex clinical phenotype, often involving both or only the left ventricle, and the diagnosis involves a number of criteria that would seem difficult to include in a MOGE(S) notation. It was therefore proposed that, owing to its flexibility, the MOGE(S) system could be expanded to accommodate a description of the major and minor criteria leading to the diagnosis in the individual patient, e.g., for a patient with a plakophilin mutation having three major and one minor criteria: $M_{A(M3+m1)}O_HG_{AD}E_{G\text{-}PKP2(p.Lys672ArgfsX12)}S_{A\text{-}I}$ [14, 15].

Clinical application of the MOGE(S) classification

In oncology, TNM classification is used on a daily routine in clinical practice, in order to provide clinical and other information regarding the stage of the cancer. TNM classification is a universally used tool and serves as a common "language" to communicate information for the patient's malignancy status and prognosis between physicians. Similar was the background idea driving the development of MOGE(S) classification. More specifically, the combination of morphofunctional characteristics (M), with the second descriptor which is the organ involvement (O), could provide very useful clinical information on patients' cardiomyopathy. The addition of genetic inheritance (G) and etiology (E) has an additive value to further characterize the cardiomyopathy for a specific patient and its family members.

Whether this classification system is applicable and of prognostic relevance is examined in a study by Hazebroek et al. including 213 patients with DCM in Maastricht [16]. A full diagnostic workup including endomyocardial biopsy (EMB) and genetic evaluation (family history and gene sequencing) was performed. According to these results, DCM was divided into seven causes: (1) genetic or familial, (2) virus-positive inflammation, (3) virus-positive inflammatory-negative, (4) virus-negative inflammatory, (5) virus-negative inflammatory negative with a proven systemic disease, (6) arrhythmogenic, and (7) toxic. Genetic or familial DCM was diagnosed in 33% of the patients of whom 8% had a pathogenic mutation. Any possible cause was found in 73% of the patients; multiple causes were present in 23%. Genetic or familial DCM only had prognostic significance in combination with additional etiologic-environmental factors such as significant viral load, rhythm disturbances, immune-mediated factors, or toxic triggers. Left ventricular reverse remodeling was significantly higher in nongenetic or nonfamilial DCM than in patients with genetic or familial DCM. The primary endpoint was the heart transplantation-free survival without life-threatening ventricular arrhythmias and was reached in 13% of the cases. Extracardiac organ involvement was diagnosed in 16% as well as NYHA functional class ≥3 associated with a significant worse outcome. The authors developed a scoring system assigning one point for each MOGE(S) attribute (organ involvement (O), gene-environment interaction (G + E), and NYHA functional class (S)) and proved it as a strong predictor of significant adverse outcome. This finding shows the prognostic relevance of each attribute and its interactions. Nevertheless, Hazebroek et al. commented that it is not possible to document multiple causes of etiology and that patients with comorbidities are excluded from this classification system (for example, hypertension or CAD). They claimed a more detailed specification of extracardiac organ involvement due to possible indistinct involvement. In addition, they concluded that genetic testing should also be done in patients with negative family history.

Agarwal et al. tried to evaluate the clinical applicability of MOGE(S) nomenclature in patients with HCM [17]. One main objective of this study was to characterize phenotypically and genetically patients with HCM by using the new classification. After clinical and genetic evaluation in the trial, 181 HCM phenotype-positive probands participated. Gene testing was performed in 125 subjects with HCM phenotype. Slightly more than 50% of the study populations were male subjects (54.7%), and 176 patients were symptomatic, mainly suffering from dyspnea. A significant percentage (24.3%) of the participants was at NYHA class III/IV, while all participants underwent the routine clinical evaluation for HCM patients and were under the guideline-based medical treatment. Study participants were divided into two MOGE(S) categories: $M_HO_HG_{AD}E_{G-}$ were gene-negative HCM subjects and $M_HO_HG_{AD}E_{G+}$ were gene-positive HCM subjects. Overall, 57 patients were gene-positive and 67 were gene-negative, while data were not available for 1 patient. Gene-positive patients ($M_HO_HG_{AD}E_{G+}$) were younger at the time of the initial setting of HCM diagnosis and more likely to be female and have a family history of HCM or sudden cardiac death, as well as more likely to have ventricular tachycardia. There were no significant differences in other clinical or imaging characteristics between the two groups. According to authors' opinion, the MOGE(S) classification should be slightly modified in order to include information regarding the presence or absence of obstruction and the location of hypertrophy, given the role of these data on the clinical course of the disease. For this reason, it has been proposed that HCM should be further categorized in (obs-neg) HCM, meaning patients with nonobstructive HCM, (obs) HCM, meaning patients with obstructive HCM, and (obs-NA) HCM, if this information is unknown. Though study population was limited in order to gain further, more solid data with clinical and prognostic significance, Agarwal et al. found the MOGE(S) classification system helpful in better characterizing subjects with HCM in clinical setting [17].

Diagnostic techniques facilitating the MOGE(S) classification

The classification of cardiomyopathies according to the MOGE(S) system is still based on the morphology and function of the ventricular myocardium. This requires the indispensable contribution of imaging diagnostic methods, in order to achieve the precise diagnosis. Echocardiography is traditionally the first diagnostic step after patient and family history, physical examination, and electrocardiography and is of paramount importance for the morphological diagnosis of most cardiomyopathy patients [18]. If the phenotype is not unequivocally recognizable by echocardiography, due, e.g.,

to preclinical stadium, incomplete penetrance, mixed forms of myocardial alterations, or simply due to technical difficulties for the acquisition of all diagnostic views, further imaging modalities are required to add relevant morphological information [19]. Especially cardiac magnetic resonance (MRI) is the gold standard for providing high-quality diagnostic images, and moreover, the tissue characterization identifies myocardial fibrosis (late gadolinium enhancement (LGE)), inflammation in clinically suspected myocarditis, edema, or fibrofatty replacement [20]. Finally, the issue of risk stratification by CMR gained an important role for risk stratification in various cardiomyopathies [21–24].

A multimodality imaging strategy can be sometimes necessary, as is the case of sarcoidosis, where positron emission tomography can have a vital impact in the diagnostic efficacy [25]. Invasive heart catheterization may add significant information in diagnosing RCM or accurately measuring the left ventricular gradient in obstructive HCM, whereas the invasive coronary angiography to rule out significant coronary artery disease has been to some extent replaced by CT angiography in patients with lower probability of coronary artery disease.

Modern technology has enabled genetic testing to be increasingly performed for the diagnostic assessment of cardiomyopathies. Knowing the gene mutation responsible for the disease in a specific family can aid the genetic diagnosis of family members in whom the disease is not yet clinically evident and—most importantly—can relieve those who do not have the mutation. Beyond this ideal scenario, everyday clinical experience has uncovered several difficulties, such as the need to clarify the role or the pathogenetic mechanism of not formerly known or studied mutations in the context of a suspected or diagnosed cardiomyopathy. On the other hand, a genetic confirmation of special conditions producing cardiomyopathy phenocopies, such as Anderson-Fabry disease, is essential for the initiation of specific etiologic treatment.

Endomyocardial biopsy (EMB) can be decisive for the diagnosis of myocarditis, in particular for the differential diagnosis of DCM. Several EMB samples per patient (typically >4) are subjected to the contemporary multimodal diagnostic workup including the following three major fields:

1. Histology for the detection of active or borderline myocarditis (Dallas criteria) [26]: This approach does not have prognostic and therapeutic impact [27–29]. For rare, specific diseases (e.g., GCM, eosinophilic myocarditis, cardiac amyloidosis), histological assessment is indispensable. Although rare, and still with an incompletely understood pathogenesis, giant cell myocarditis (GCM) and eosinophilic myocarditis have class I level of evidence for immunosuppressive treatment, which has led to an improved overall outcome [30–33].
2. Immunohistology for the detection, quantification, and phenotypic characterization of infiltrates, and of the endothelial, interstitial, and sarcolemmal expression of several cell adhesion molecules (CAM): The sensitivity and specificity of the immunohistological approach is beyond the high sampling interobserver variability and sampling error being associated with the histological Dallas criteria, which might have contributed to the neutral results of the US Myocarditis Treatment Trial [28]. Two monocentric randomized controlled trials have shown significant benefits in DCM patients with immunohistologically confirmed inflammatory cardiomyopathy (DCMi) [34, 35]. Noticeably, in one these trials, the immunohistological diagnosis of DCMi was based on CAM expression alone, without quantifying infiltrates [34], which might be reasonable since endothelial CAM induction is a prerequisite transendothelial migration of infiltrates [36, 37]. The precision of quantification of immunohistological stainings benefits from digital image analysis systems compared with the mere visual assessment [38, 39].
3. PCR for the detection of various viruses which have been associated with the pathogenesis of myocarditis and DCM: The pathogenic link for enteroviruses (EV) is confirmed by meta-analysis and for the adverse prognostic impact [40, 41], and animal models are established for the EV-induced myocarditis and post-myocarditis DCM/DCMi. There is considerable discrepancy regarding Parvovirus B19 (B19V), which has a known "bioportfolio" phenomenon (lifelong DNA persistence in various tissues without biological relevance) [42, 43]. These profound differences of viral pathways may also be responsible for the differential clinical outcomes under antiviral interferon treatment [44, 45].

Clinical implications of the MOGE(S) classification

Utilizing the MOGE(S) system in everyday clinical practice may appear difficult and complex in the beginning. Nonetheless, if it is systematically applied to describe the disease at patient's discharge, it will have advantages for the further clinical management of the patient and his/her family. It enables the clinician to have a complete image of the disease in the particular patient and see the information gaps in terms of the history, genetics, and etiology. It can therefore act as a tinder that urges clinicians to fill in the gaps in personal and family history of the patient, thus enabling the identification of a familial pattern of inheritance. On the other hand, new upcoming medical information, for example, genetic mutations or specific organ involvements in relatives, can be also noted in the MOGE(S) description, enabling a quick overview of the genetic etiology or raised suspicion for a specific diagnosis in the family. Further implications are derived from the

description of the functional status (S) of the patient, which can enable the clinician to follow a possible clinical deterioration or assess the effect of treatment in serial investigations.

Future outlook

A classification encompassing all cardiomyopathies has always been a difficult task, as it should comprise holistically the known important morphological, etiological, and clinical parameters. One source of complexity may be derived from overlaps of different cardiomyopathies or variable phenotypic presentations in patients diagnosed with the same disease, due, e.g., to individual degrees of penetrance, varying time courses of the disease when diagnosed in the respective time frame of its natural history, and highly variable effects of acquired conditions affecting the course of cardiomyopathies.

In this regard, it seems important to define the level of impairment of the left and/or right ventricular systolic (and diastolic) function at first diagnosis of the cardiomyopathy and to reassess these therapeutically and prognostically important issues in follow-up analyses. This might be carried out according to the known zones of left ventricular ejection fraction (LVEF) impairment for heart failure, adopted to the underlying cardiomyopathy. For the case of myocarditis, it would be thus differentiated between MCrEF (myocarditis with reduced LVEF), MCmrEF (myocarditis with mid-range LVEF), and MCpEF (myocarditis with preserved LVEF) [46]. This differentiation has obvious clinical consequences for the class of evidence of disease-modifying heart failure medication [47] and for the indication evidence for EMB diagnostics for the case of myocarditis [31, 48].

A further issue which has not been addressed precisely thus far is the classification of cardiomyopathies after successful etiological treatment. This issue affects, e.g., GCM, which may heal after immunosuppressive treatment (class I indication) [30, 32, 33]. Such patients under successful immunosuppression may not have a persisting GCM in follow-up EMB, would thus fulfill the status of healed GCM [49] (Fig. 1). It appears therefore feasible to introduce a further characterization in the existing MOGE(S) classification, to encompass the course of these patients, e.g., $E_{M\text{-}GCM\text{-}IS\text{-}HEALED}$. Comparable situations are conceivable for healed autoimmune myocarditis after immunosuppression [34, 35] (proposal: $E_{M\text{-}AI\text{-}IS\text{-}HEALED}$) and for viral elimination after effective interferon (IFN) antiviral treatment and clinical improvement [50] (proposal: $E_{V\text{-}IFN\text{-}HEALED}$).

Based on the morphofunctional description of the distinct cardiomyopathies, a classification aims for the diagnostic identification of patients, while the continuously expanding knowledge on the genetic etiology has led to the development of characteristic new terms describing groups of cardiomyopathies based on the underlying genetic defect. Apart from the identified patients, the use of pedigrees and family screening could identify phenotypically negative family members with a probable positive genotype leading to early treatment and initiation of clinical follow-up. The system is flexible and can be

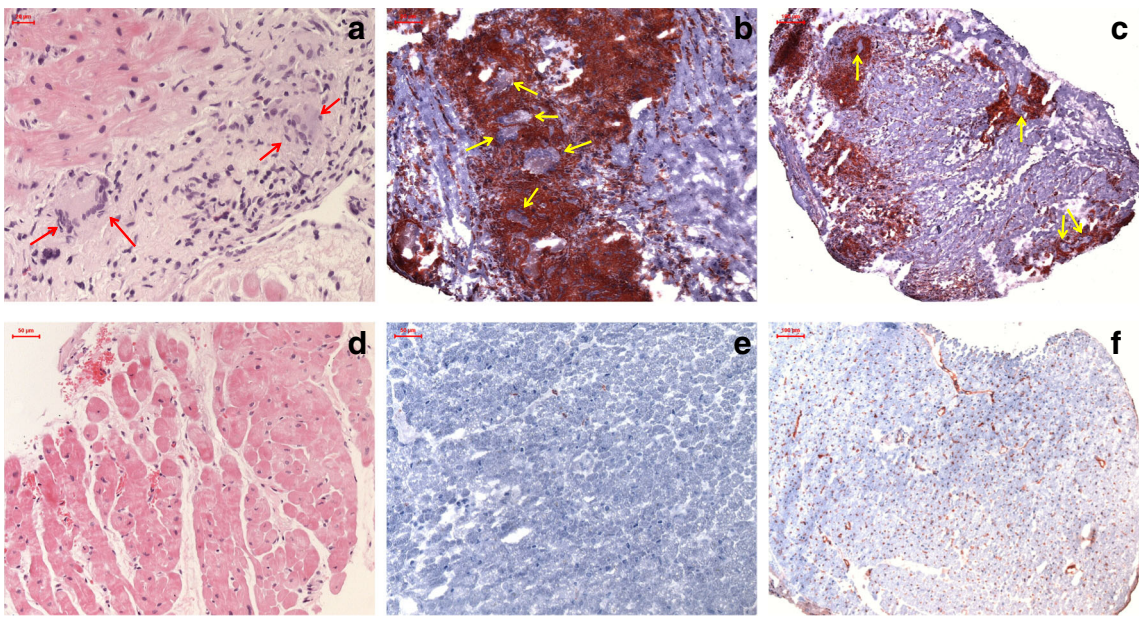

Fig. 1 Histological and immunohistological findings of EMBs at the initial EMBs (**a**–**c**) and after immunosuppression (**d**–**f**). **a** Histology (H&E staining) demonstrated focal lymphocytic infiltration and multinucleated giant cells (*arrows*; ×400). **b** Immunohistological staining of focal CD11a/LFA-1$^+$ lymphocytes with giant cells (*arrows*; ×200). **c** Focal ICAM-1 abundance pronounced in areas adjacent to giant cells (*arrows*; ×100). **d** Histology in the follow-up EMBs after immunosuppression, devoid of any giant cells (×200). **e** Normal LFA-1$^+$ infiltration in the follow-up EMBs after immunosuppression (×200). **f** Baseline ICAM-1 expression in the follow-up EMBs after immunosuppression (×100). Reproduced with permission from [49]

expanded accordingly to cover still unrecognized or unthought-of characteristics that could improve the understanding of cardiomyopathies and the interaction between physicians and facilitate registering of patients and research on cardiomyopathies.

However, it is important to consider that there is some skepticism regarding the applicability of this nosological system. For instance, it seems that there is a disagreement about the validity of MOGE(S) when applying to patients with ARVC. It has been stated that the clinical phenotype of this cardiomyopathy may be very complex, so that it could not be adequately reflected when using MOGE(S) classification alone [10, 13]. Moreover, it has become evident that subjects or relatives with cardiomyopathies in early stages could represent a "gray" zone, as clinical phenotypes are nonspecific, which would evidently lead to misclassification of this group of subjects.

Another point of criticism refers to the absence of classification of clinically important cardiomyopathies, such as tachycardia-induced cardiomyopathy and peripartum cardiomyopathy [51]. The authors of MOGE(S) have, however, improved the classification attributes for tropical endomyocardial fibrosis ($M_{R\text{-}EMF}$), the cause of 20% of heart failure in endemic areas in Africa [52].

A further field of development is the differentiation of biologically relevant viral infections of the myocardium, versus the bioportfolio phenomenon applicable especially to B19V (lifelong DNA persistence in various tissues without biological relevance) [42, 43]. The currently applied MOGE(S) classification does not comprise the known various aspects of the term "viral infection," which is often understood as the amplification of viral genomes by PCR from EMB. Several further aspects might be implemented in the update of a forthcoming MOGE(S) classification, enabling also a differentiation of "active viral infections" versus "persistence of latent viral genomes" [42]; the implementation of viral copies [24, 53], of the genotype of viruses [54], of the pattern of the antiviral immune response, which is important for the differentiation between acute, active, and latent B19V infections in noncardiac diseases [55, 56], and of the presence of viremia [57]; and the intramyocardial expression of viral proteins, which indicate viral protein synthesis in the target organ [58, 59].

Conclusions

A classification of cardiomyopathies is of great importance and still remains a challenge for the clinical routine of cardiologists and cardiovascular surgeons. The MOGE(S) nomenclature is a new classification system for cardiomyopathies that has proven to add an additional layer of much needed detailed complexity, enabling a standardized denomination of the cardiomyopathies and of the underlying pathogenesis and results of the clinical diagnostic workup. This approach might ultimately lead to improved diagnosis and treatment outcomes of cardiomyopathy patients, as well as of their family members. More studies, especially large-scale multicenter studies, are needed to further confirm the clinical utility and applicability of this new classification system, as well as its prognostic significance. However, further novel diagnostic aspects have arisen in the meantime, which might be implemented in future updates of the MOGE(S) classification.

Compliance with ethical standards

Declaration of ethics The manuscript does not contain clinical studies or patient data.

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