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Arrhythmic risk stratification in non-ischaemic dilated cardiomyopathy

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Dilated cardiomyopathy is a primary disease of the heart muscle, which affects relatively young patients with a low comorbidity profile. It is characterized by structural and/or functional abnormalities leading to systolic dysfunction of the left ventricle or of both ventricles, often associated with dilatation, in the absence of an ischaemic, valvular, or pressure overload cause sufficient to explain the phenotype. Although the prognosis of the disease has greatly improved over the last few decades, prognostic stratification remains a fundamental objective, especially about the prediction of potentially life-threatening arrhythmic events. An accurate diagnostic work-up and an appropriate aetiopathogenetic characterization affect the patients' outcome and represent the essential basis of an adequate prognostic stratification. It is necessary to adopt a multiparametric approach, especially when the aim is the prediction of arrhythmic risk; it includes an integration of medical history and physical examination with cardiac imaging and genetic testing, in order to obtain a personalized diagnosis and therapeutic strategies. Furthermore, the evaluation should be repeated at every clinical check-up, considering the dynamic trend of the pathology and the arrhythmic risk changes over time. This article aims to illustrate how, starting from an exhaustive aetiological and clinical-instrumental characterization, including all diagnostic methods available at present time, it is possible to obtain a tailored diagnostic evaluation and stratification of the arrhythmic risk as accurate as possible.

Classification and stratification of arrhythmic risk in dilated cardiomyopathy: unsolved points

Cardiomyopathies are diseases in which the heart muscle is structurally and/or functionally abnormal, in the absence of a specific cause sufficient to determine the pathology.

Dilated cardiomyopathy (DCM) is characterized by decreased systolic ventricular function, frequently (but not necessarily) associated with ventricular dilatation and in the absence of pressure or volume overload, coronary artery disease, or valvular disease proportional to systolic dysfunction.[1] Although it encompasses a heterogeneous spectrum of clinical presentations, systolic dysfunction represents the most emblematic sign of DCM. Dilated cardiomyopathy is used as an 'umbrella term', as it represents the final path of different pathogenic processes, in which a key role is provided by the still largely unexplored interaction between genes and environment.

Affected subjects are predominantly males and in their third to fifth decade of life.[2] Given the young age of patients and the consequent low comorbidity profile, the disease outcome is mainly influenced by cardiovascular events, such as heart failure and ventricular arrhythmias. Although prognosis has significantly improved in recent decades, DCM remains one of the leading causes of heart transplantation in Western countries.[3]

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Definitions and classifications of DCM have changed over time, according to the advances in cardiovascular imaging techniques, such as echocardiography and cardiac magnetic resonance (CMR) imaging, as well as in genetics and molecular medicine. Currently, classifications of cardiomyopathies are predominantly, if not exclusively, based on phenotype. However, it appears increasingly evident that cardiomyopathies present heterogeneous clinical manifestations, which can sometimes have overlapping elements among different definitions. In particular, the heterogeneity of pathophysiological mechanisms of DCM explains the lack of uniformity in clinical presentation, functional status, complications, and response to treatment. In this context, the morpho-functional classification 'MOGE(S)' was proposed in 2013: for the first time, the focus was set on the inheritance model on the genotype-phenotype correlation, thus emphasizing the importance of family history and aetiological characterization.[4] Despite 'MOGE(S)' classification worth, due to its complexity, it is rarely used in clinical practice. Therefore, in order to represent the vast and heterogeneous spectrum of DCM, it is essential to develop a less rigid classification of cardiomyopathies, which could be useful to guide the clinician in the management of the pathology.

At this juncture, the stratification of arrhythmic risk in patients with DCM is still an unresolved point. Unlike arrhythmogenic cardiomyopathy and hypertrophic cardiomyopathy, DCM does not have real risk scores for major ventricular arrhythmias and sudden death yet. Although DCM does not globally present a high rate of sudden cardiac death, the young age and the few comorbidities of the affected subjects make the assessment of arrhythmic risk a relevant point to define. Recently, implantable defibrillator (ICD) implantation in primary prevention in DCM has undergone a reduction in its degree of recommendation, passing from a Level IB to an IIA; this change mainly comes from the publication of the results of the DANISH trial, a study which did not demonstrate an effective benefit of ICD implantation on global mortality in this group of patients.[5] The subgroup analysis highlighted a potential benefit of ICD implantation in primary prevention in younger patients (age <59 years). The DANISH trial highlights, once again, how aetiological definition and comorbidity profile are fundamental and how stratification of arrhythmic risk cannot naively be focused on ejection fraction (EF) and NYHA (New York Heart Association) class alone; adopting a multiparametric approach is necessary, and it is also useful in competitive risk assessment.

Precision diagnosis: a multiparametric approach for accurate arrhythmic stratification

A precise anamnesis is of fundamental importance in the personalized diagnostic pathway of DCM: it is necessary to investigate the presence of bradyarrhythmia or tachyarrhythmia events or history of sudden cardiac death in the family and properly acknowledge the subject's palpitations episodes or syncope. The physical examination must be accurate and must look for elements that may suggest syndromic phenotypes, such as the presence of neuromuscular pathologies (in this sense, a first evaluation of patients with DCM should always include a creatine phosphokinases dosage), neurosensory pathologies, and mental disability.

When considering the clinical presentation, the first manifestation might be advanced heart failure or even cardiogenic shock in severe forms; rarely, however, the onset is sudden cardiac death or syncope. The latter must be systematically investigated and, when present, it must be accurately characterized. If a potentially cardiogenic origin of the syncope emerges, it represents a very important arrhythmic marker to be taken into account.

First-level exams include the electrocardiogram (ECG) and the echocardiogram, and they must be analysed with a cardiomyopathy-oriented approach. In particular, the ECG is an easily accessible and reproducible tool, capable of providing relevant information for diagnostic and prognostic purposes. Signs of left ventricular hypertrophy, the presence of pseudo-necrosis Q waves, low voltages, fragmentation of QRS complex, Twave inversion, and conduction anomalies such as bundle branch blocks or atrioventricular blocks must be searched. Specific ECG alterations correlate with particular genetic variants: for example, a prolongation of the PR interval is associated with lamin (LMNA), emerin and SCN5A6 gene mutations, as well as the presence of negative Twaves, fragmentation of the QRS complex, and low voltages may indicate the presence of highly arrhythmic genotypes such as those given by variants in the filamin C (FLNC) gene or desmosomal genes (*Figure 1*).[6,7]

In echocardiography, the disease's classic signs are left ventricular dilatation and systolic dysfunction; measurements must be repeated at each check-up, in order to monitor therapeutic efficacy, reverse remodelling, and disease progression. Several findings are useful in prognostic stratification, such as right ventricular function, pulmonary pressures, diastolic filling pattern, and left atrial volume.[8,9] Assessment of global longitudinal strain provides an important input both in arrhythmic risk assessment and in the family members' screening, allowing, in the latter, an early diagnosis, even at the asymptomatic phase.[10]

Cardiac magnetic resonance (CMR) is a second-level examination that, thanks to a precise evaluation of volumes, ventricular systolic function and an accurate tissue characterization, grants additional information for diagnostic, therapeutic, and prognostic purposes. The recently increased accessibility to CMR and the growing amount of literature related to the diagnostic and prognostic importance of this exam in the context of DCM have led to its almost systematic use in the initial classification of the patient. The presence, distribution, and extent of late gadolinium enhancement (LGE), index of tissue fibrosis, contribute to the diagnosis and prognostic stratification of cardiomyopathies. In the setting of DCM, the presence of LGE is reported in ~30% of cases and has now been unequivocally correlated with the risk of malignant ventricular arrhythmias and sudden cardiac death, regardless of systolic function.[11] Additional characteristics of LGE, such as subepicardial distribution, multiple or septal site location, correlate with an increased arrhythmic risk.[12] Similarly, the nearly circumferential distribution of LGE, also known as 'ring-like pattern', is associated with a greater risk of ventricular arrhythmias, probably because they are the expression of particularly

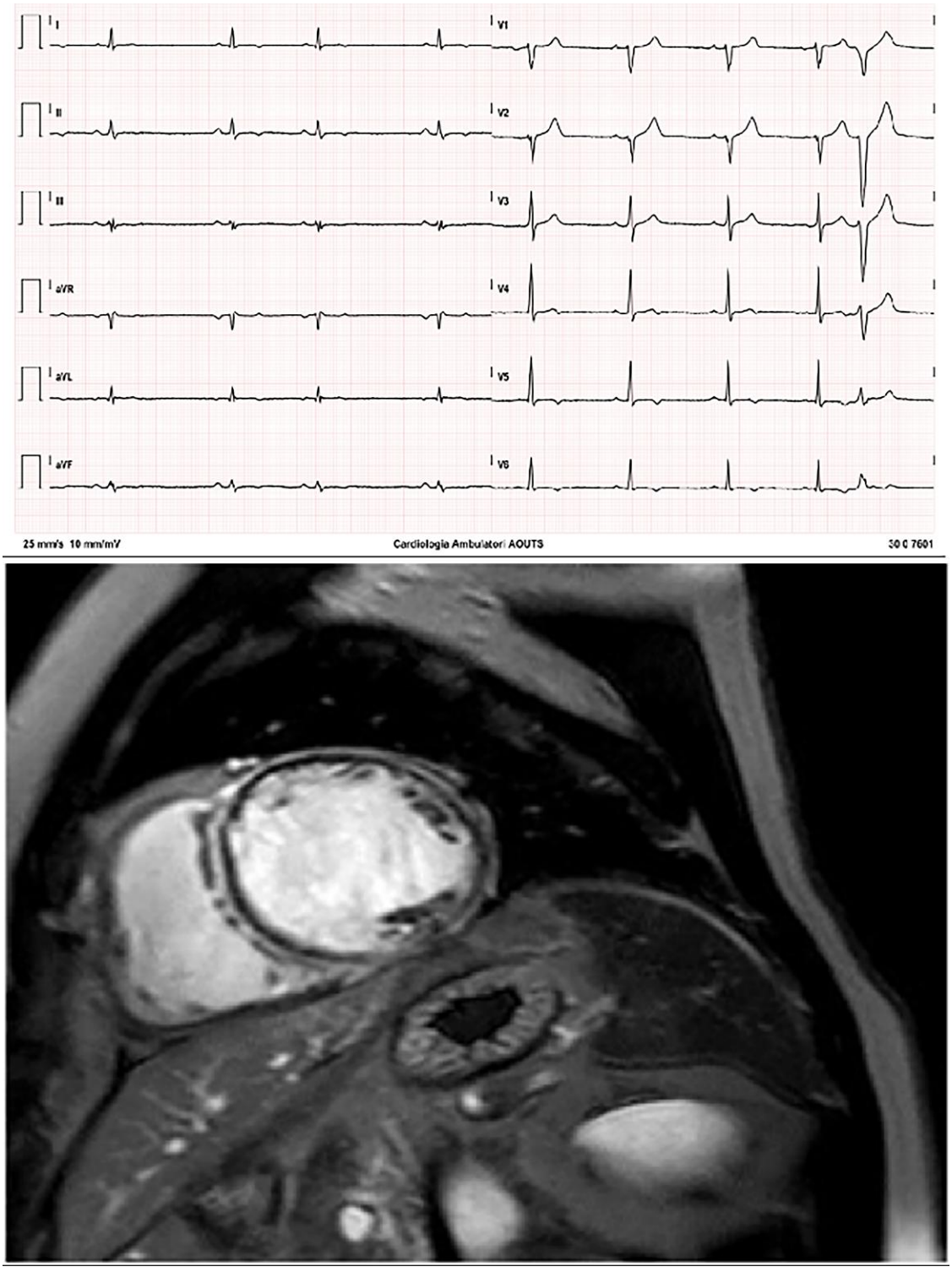

Figure 1 Multiparametric characterization of a patient with dilated cardiomyopathy, left ventricular ejection fraction of 43%, New York Heart Association Class I, but at high arrhythmic risk: the electrocardiogram shows negative T waves in the lateral and inferior leads and low voltages in the peripheral leads. Cardiac magnetic resonance shows the presence of late gadolinium enhancement in subepicardial and intramyocardial areas, with a circumferential pattern ('ring-like' pattern). The patient is a carrier of a pathogenetic variant of filamin C.

arrhythmogenic genotypes.[13] Finally, in those cases in which LGE is not diriment in the diagnostic process, it is advisable to use specific techniques for the evaluation of diffuse fibrosis, such as T1 mapping and calculation of the extracellular volume, as well as strain analysis ('tissue tracking'). In general, we should aim to evaluate as quantitatively as possible the extent, distribution, localization, and dispersion of fibrosis.

Among invasive tests, endomyocardial biopsy in selected patients is the only tool that allows a differential diagnosis in the context of inflammatory cardiomyopathies (myocarditis, sarcoidosis) and accumulation or infiltrative diseases (phenocopies). Furthermore, the endomyocardial biopsy represents a decision-making turning point in the therapeutic management of high-risk myocarditis and contributes to the diagnostic process of the so-called 'hot phases', which are the clinical presentation of some forms of arrhythmogenic cardiomyopathy.

Tools so far described, considered within a 'red flag' approach, must guide the clinician in the diagnosis and aetiological characterization of the patient. To date, the term 'Idiopathic' dilated cardiomyopathy indicates an increasingly smaller group of patients, as there is a better characterization of the pathology, that allows highlighting the possible presence of known potentially reversible and curable triggers, represented by tachyarrhythmias, labile arterial hypertension, alcohol abuse, some chemotherapy treatments, and inflammatory forms.[14] Furthermore, the aetiological classification has relevant prognostic implications: for example, tachyarrhythmia-induced cardiomyopathy may be reversible after the elimination of the arrhythmic burden and, therefore, it is associated with a benign prognosis. In contrast, chemotherapy-induced forms have the lowest survival rates, though mainly driven by non-cardiovascular and rarely arrhythmic events.[15]

The contribution of genetics -> genetic testing contribution

Genetic testing is giving an increasingly important contribution to the accuracy of DCM diagnosis and classification, up to the point of being recommended by recent guidelines and consensus documents.[16] Genetic testing primarily provides diagnostic and prognostic aetiological information in the stratification of arrhythmic risk in affected probands; secondly, it allows early identification of mutation carriers among family members.

In DCMs, a pathogenic variant is identified in up to 55% of cases previously defined as idiopathic.[16] More than 50 genes involved in the pathogenesis of DCM have been identified: they encode proteins of the sarcomere, cytoskeleton, sarcolemma, nuclear membrane, ion channels, and intercellular junctions.

The presence of pathogenic variants affecting lamin (LMNA), FLNC, RBM20 (RNA Binding Motif Protein 20), SCN5A, and phospholamban (PLN) genes gives peculiar 'arrhythmogenic' characteristics to the cardiomyopathy. In this sense, in the consensus document drawn up in 2019 related to arrhythmogenic cardiomyopathy, it is underlined that, in the presence of mutations affecting LMNA, FLNC, and PLN, it is reasonable to evaluate ICD implantation in primary prevention also when EF is lower than 45%.[17] Furthermore, in recent European Society of Cardiology (ESC) guidelines regarding the management of ventricular arrhythmias and the prevention of sudden cardiac death, an ICD implant in primary prevention in subjects affected by DCM is to be considered in patients with an EF lower than 50% and at least two additional elements, including the history of syncope, the presence of LGE, the induction of ventricular tachycardia on the electrophysiological study, and the finding of a pathogenic variant affecting LMNA, FLNC, PLN, RBM20.[16] Additionally, pathogenic variants of FLNC and desmosomal genes, especially desmoplakin (DSP), may clinically manifest both as DCM and as arrhythmogenic cardiomyopathy, highlighting the overlap between the two forms and reiterating the need for an implementation of the classifications of cardiomyopathies. As demonstrated by the study of Gigli *et al.*,[18] in some genotypic settings, patients present a greater arrhythmic risk; therefore, ICD implantation should be the result of a balanced integration of EF with family history, symptoms, arrhythmic expressivity, presence of the right dysfunction, and fibrosis.

The actual impact of these gene variants in the development of the disease is currently not completely and analytically understood: the same genetic mutation can cause different clinical phenotypes, confirming the possibility of overlap between DCM and other forms (hypertrophic, restrictive, arrhythmogenic, or of ion channels diseases). Furthermore, it is now known that some secondary DCMs, such as tachyarrhythmias, chemotherapy, peripartum, and post-inflammatory induced forms can have a pathological genetic background, mainly represented by titin mutations, thus paving the way for future studies on genotype–environment correlation, on the relevance of the impact of a 'second hit' and the weight of the polygenic risk scores in DCM.

Dynamic assessment of DCM

The arrhythmic risk assessment carried out by the clinician must not only be multiparametric but also dynamic over time. The extent of left ventricular reverse remodelling in response to medical therapy is an important prognostic factor. In ∼40% of DCMs, reverse remodelling can be seen over time thanks to optimized medical therapy: in ∼15% of patients, a normalization of the pump function can be achieved and maintained over time, but it requires punctual therapeutic compliance.[3] Therefore, a correct diagnostic approach is of fundamental importance, but also a personalized follow-up is required, to allow the physician to appreciate the effectiveness of the prescribed therapies or, vice versa, to identify early signs of disease progression. The best timing for ICD implantation in primary prevention still remains a subject of debate. An adequate selection of the patient allows both to avoid an invasive act, not free from complications, and to intercept major arrhythmic events, even early ones. In this sense, patients presenting with severe left ventricular dilatation, left bundle branch block, extensive LGE at CMR, and inability to introduce or adequately titrate medical therapy represent ideal candidates for early implantation, even before the third month after treatment start.[19] Conversely, early improvements in left ventricular and atrial dimensions, right ventricular function, and mitral regurgitation may predict subsequent improvement in left ventricular systolic function even after three to six months of therapy, thus suggesting a possible deferment of the ICD implantation.

Conclusions and future perspectives

Sudden cardiac death accounts for up to 35% of all deaths in DCM.[16] Although sudden cardiac death has a lower

incidence than other forms of cardiomyopathy, the heterogeneity of DCM makes assessing arrhythmia risk a complex process, which must necessarily be tailored to the patient.

In the classic DCM phenotype setting, there are currently no specific arrhythmic risk scores, except for laminopathy-induced DCMs, in which the relative risk of the onset of threatening ventricular arrhythmias at 5 years was evaluated with a multivariate score that includes male gender, the presence of non-missense mutation, non-sustained ventricular tachycardia, and atrioventricular block.[20] There are some elements capable of identifying a profile of greater arrhythmic risk, such as a severe left ventricular dilatation present at baseline, a lengthening of the QRS complex, a long duration of symptoms, a family history of sudden cardiac death, cardiogenic syncope, arrhythmic manifestations at Holter ECG, and extensive fibrosis in CMR imaging.

From these considerations, the need to have more updated and less rigid classifications arises; they should take into account, for example, the possibility of overlap between DCM and arrhythmogenic cardiomyopathy. Integrating each element, from medical history, from first- and second-level exams, including CMR and genetic testing is essential, to obtain a complete and exhaustive picture of the DCM patient arrhythmic risk. Evaluating advanced imaging, such as three-dimensional echocardiography and CMR mapping techniques, and polygenic risk scores, is essential. In this process, the possible contribution of artificial intelligence and machine learning techniques will be investigated and developed in the near future, with the ultimate goal of continuing to improve patients' stratification and outcome.

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