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THE ROLE OF CARDIAC MAGNETIC RESONANCE IN PATIENTS WITH DILATED CARDIOMIOPATHY

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Abstract: *Dilated cardiomyopathy (DCM) has an increased risk of heart failure, malignant ventricular arrhythmias, including sudden cardiac death, being the most common cause of heart transplantation. Cardiac magnetic resonance imaging (CMR) is the gold standard technique for assessing left and right ventricular function; the major advantage of CMR is the possibility of tissue characterization, highlighting the replacement of myocardial fibrosis (late gadolinium enhancement - LGE technique) and the interstitial and perivascular reactive fibrosis (mapping techniques - T1 mapping, T2-mapping, T2 * -mapping). Myocardial fibrosis pattern helps to establish the DCM aetiology and has prognostic and therapeutic implications. LGE presence is associated with a weaker therapeutic response and an increased risk of complex ventricular arrhythmias. At the same time, LGE absence associated with the presence of reactive fibrosis quantified by mapping techniques and especially by increasing myocardial extracellular volume, identifies patients with potentially favourable response to optimal drug therapy and cardiac resynchronization therapy.*

INTRODUCTION

Dilated cardiomyopathy (DCM) is characterized by left ventricle (LV) dilation associated with impaired systolic function in the absence of abnormal pre loading or post loading conditions (e.g., uncontrolled hypertension, primary heart valve disease, congenital heart disease) or significant coronary heart disease.(1) In clinical practice, DCM should not be a final diagnosis, but a starting point for further etiopathogenetic investigations.

This explains the complex evaluation of patients with DCM: laboratory tests, electrocardiography (EKG), Holter EKG, cardiopulmonary exercise testing, imaging investigations (echocardiography, cardiac magnetic resonance) and invasive diagnostic techniques (coronary angiography, endomyocardial biopsy).

Given that the most common cause of left ventricular dilation is coronary heart disease, DCM is commonly classified as ischemic or non-ischemic. In this article by non-ischemic DCM we refer only to primary, idiopathic DCM.

CMR has a growing impact on DCM evaluation in terms of aetiology, risk stratification and therapeutic approach (2), being complementary to echocardiography.

CMR is widely accepted as the reference standard for quantifying cardiac chamber size and left and right ventricular ejection fraction. In addition, tissue characterization techniques such as late gadolinium enhancement – LGE and other quantitative parameters such as T1 -mapping, both native and with extracellular volume measurement, T2-mapping and T2- * mapping were validated against the histological examination in a wide range of clinical scenarios.(2)

Many studies have shown important correlations between various changes identified in cardiac MRI and cardiovascular morbidity and mortality. Some parameters are independent predictors of malignant ventricular rhythm disorders, with a risk of sudden cardiac death (SCD), or for non-responder status to cardiac resynchronization therapy.

AIM

The aim of this paper is to highlight the importance of cardiac MRI in patients with DCM in terms of aetiology evaluation, risk stratification, prognosis assessment and establishing the optimal therapeutic conduct based on scientific data.

MATERIALS AND METHODS

PubMed, Science Direct and Medscape search engines were used, using as keywords: non-ischemic and ischemic dilated cardiomyopathy, CMR, LGE, T1-mapping, ventricular arrhythmia, sudden cardiac death.

Published reports, including reviews and original articles, regarding CMR in non-ischemic DCM and ischemic DCM and European and American Societies of Cardiology heart failure and sudden cardiac death Guidelines were evaluated.

The prognostic correlations were followed, according to the ejection fraction, LGE, myocardial extracellular volume highlighted by the mapping techniques. Also, we tried to show the therapeutic implications of the CMR pathological aspects.

RESULTS AND DISCUSSIONS

Data analysis results and discussions will be organized as a comparative presentation between non-ischemic DCM and ischemic DCM. Table no. 1 highlights the changes identified on the CMR cine sequences, table no. 2 shows the changes on the LGE sequences and table no. 3 summarizes the data on the T1 mapping technique of myocardial tissue characterization.

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Table no. 1. CMR cine sequences changes in non-ischemic DCM versus ischemic DCM

Cardiac MRI cine sequences – structural and functional cardiac information, being complementary to echocardiographic examination		
	Non-ischemic DCM	**Ischemic DCM**
1. Cavity dimensions	➔ Dilated LV (3) (reference range EDV 56-96 ml/m^2,ESV 14-34 ml/m^2) (4) ➔ Dilated or normal size right ventricle (RV) (3) reference range EDV 48-112 ml/m^2, ESV 12-52 ml/m^2) (4) ➔ Dilated or normal size left atrium (LA) and right atrium (RA) (3) (reference range LA volume 27-53 mL/m^2, RA volume (18-90 mL/m^2) (4)	
2. LV, RV mass	➔ Normal LV, RV parietal thickness (3) ➔ Increased LV mass (eccentric LV hypertrophy) (3) (reference range 41-81g/m^2) (4)	➔ Low/normal/increased LV, RV parietal thickness (3) ➔ Increased LV mass (eccentric LV hypertrophy) (3) (reference range 41-81g/m^2) (4) or normal LV mass
3. Kinetics disorder	➔ Moderately or severe global LV hypokinesia (3) ➔ Interventricular septum (IVS) dyskinesia (frequently associated with branch block and related with myocardial fibrosis degree) (3)	➔ Regional hypokinesia corresponding to a coronary territory (3) ➔ LV regional akinesia/ regional dyskinesia/ aneurysm (3)
4. LV, RV systolic function	➔ Reduced LV ejection fraction (EF) (3) (reference range 57-77%) (4) ➔ Reduced or normal RV ejection fraction (3) (reference range 51-71%) (4) ➔ Normal or low stroke volume/ normal or low cardiac output (3)	
5. Valvulopathy	➔ Functional mitral and tricuspid regurgitation (mitral and tricuspid ring dilation and LV, RV geometry change) (3)	➔ Functional mitral regurgitation (ischaemic mechanism ± mitral ring dilation ± degenerative component) (3) ➔ Functional tricuspid regurgitation (3)

Table no. 2. Localised myocardial fibrosis (scars) evaluation by LGE technique –non-ischemic DCM versus ischemic DCM

Late gadolinium enhancement (LGE) sequences – localised fibrosis (repair and replacement fibrosis)		
	Non-ischemic DCM	**Ischemic DCM**
1. Intracavitary thrombus	LGE – CMR can easily differentiate thrombus from surrounding myocardium, due to the absence of contrast uptake in the avascular thrombus – thrombus appears homogenously black (5). Their presence requires association of anticoagulant treatment for a period of 6 months; subsequently imaging re-evaluation is required to determine whether or not further anticoagulant treatment is needed.	
2. LGE location	In LV and RV walls ➔ Linear or focal LGE present in 30% of patients – typical pattern: mid-wall enhancement most common in IVS middle portion (2) (Figure 1) ➔ 70% of patients do not have LGE (2)	In LV and RV walls ➔ Subendocardial LGE with varying degree of transmurality in one or more territories of coronary perfusion (correlated with kinetic disorder) (2) (Figure 2) ➔ LGE is present in all patients
3. Myocardial viability tests	Not recommended: no additional information.	➔ LGE over 50% of parietal thickness - low chance of recovery after revascularisation (5) ➔ LGE less than 50% of parietal thickness - intermediate or good chance of recovery after revascularisation (5) Stress test with dobutamine or vasodilators agents (adenosine, regadenosone, dipyridamole) bring additional diagnostic information on myocardial viability (5)
4. Correlation with LVEF	The correlation between myocardial scar and LVEF is not as apparent as in ischemic heart disease, the underlying mechanism of functional impairment being much more heterogeneous (6,7)	LGE size and degree of transmurality correlate with low LVEF (1)
5. Correlation with complex ventricular arrhythmia	➔ Ventricular tachycardia (VT) has a heterogeneous substrate such as inflammation, fibro-fatty replacement, interstitial fibrosis and scars (the re-entry phenomenon being the main mechanism of production).(8,9) ➔ SCD also occurs in patients with only moderately low LVEF (> 35%) (10-11), and the presence of mid-wall LGE has identified a subgroup of patients at high risk of SCD (1) ➔ LGE could be useful for determining the timing of defibrillator implantation: DCM without LGE - delaying defibrillator implantation, with LVEF reassessment after at least 3 months of optimal medical therapy, because the chance of reverse remodelling is substantial and the risk of arrhythmias is low. DCM with extended LGE - defibrillator implant before discharge due to increased risk of MSC (12)	➔ Ventricular tachycardia originates in the subendocardial scar or in the aneurysm formed secondary to myocardial infarction.(1) ➔ Clear correlation between LGE size and severely reduced LVEF (<35%) and the risk of complex ventricular arrhythmias.(6,7)
According to the current SCd guideline, all patients with LVEF <35% should receive optimal medical therapy ≥3 months before prophylactic implantation of the defibrillator is considered.(13) Primary prevention trials of SCD in patients with heart failure have shown that when a defibrillator was implanted based on low LVEF, mortality was reduced more effectively in patients with ischemic heart disease versus DCM.(14-16) One possible explanation for this prognostic difference is that in ischemic heart disease the reduction in EF is more strongly correlated with the extension of the myocardial scar, consequently increasing the substrate for ventricular arrhythmias compared to DCM.(17,18) The DANISH trial demonstrated a similar aspect: patients with non-ischemic DCM had limited benefit from defibrillator implantation when the implantation decision was based only on low EF according to current guidelines.(13,19,20)		
6. Ventricular arrhythmias ablation therapy	Transcateter ablation has been shown to be ineffective in patients with predominantly intramural scars (mid-wall).(3)	Endo- versus epicardial scar location was important to determine the optimal ablation approach.(3)
7. Cardiac resynchronization therapy response	➔ Patients without LGE had a significant better evolution after resynchronization therapy compared to those with LGE or those who performed this therapy non-LGE-guided.(21) ➔ LGE guided implantation of the biventricular pacemaker has been associated with a significant improvement in the identification of patients with the highest chance of benefiting from this therapy.(21)	

Table no. 3 Diffuse myocardial fibrosis evaluation by T1 mapping – non-ischemic DCM versus ischemic DCM

Native and post contrast T1-mapping - measurement of T1 relaxation time and extracellular volume (ECV)	
➔ Native T1 values are influenced by: magnetic field strength (higher T1 values on 3T compared to 1.5T), sequence used (MOLLI or ShMOLLI), cardiac cycle phase (diastole or systole) and measurement region (22) ➔ Increased native T1 time is determined by: oedema (acute myocardial infarction or inflammation), increase of interstitial space (fibrosis – chronic myocardial infarction, cardiomyopathy, amyloid deposition) (23) ➔ Decreased native T1 time is determined by: lipid overload (Anderson Fabry disease, lipomatous metaplasia in chronic myocardial infarction), iron overload (hemochromatosis) ➔ T1 post contrast mapping is used to calculate ECV according to the formula: ECV= (1-hematocrit) * [(1 / post contrast T1 myocardial - 1 / native T1 myocardial)] / (1 / post contrast T1 blood-1 / native T1 blood) ECV is a marker of myocardial tissue remodelling, with normal values in healthy patients in a 1.5T magnetic field being 25.3 ± 3.5% (24)	
Non-ischemic DCM	**Ischemic DCM**
Native T1 has high values and correlates with ventricular walls thickness (23)	Native T1 is elevated in acute myocardial infarction regardless of its form,

	STEMI or non-STEMI. The distinction between acute versus chronic myocardial infarction is difficult to make: the T1 time has higher values in the acute phase compared to the chronic phase, but at present no cut-off values are validated for differentiation (23)
➔ ECV is elevated and reflects high amounts of myocardial collagen (25) (figure no.1) ➔ ECV can serve as a non-invasive imaging biomarker to monitor therapy response (drugs or cardiac resynchronization) and to help in risk stratifying in different stages of the disease (25)	***Acute myocardial infarction*:** increased native T1 and increased ECV (58.5 ± 7.6%). Peculiarity: pseudonormalization of T1 time occurs in case of microvascular obstruction located in the center of the infarcted area or shortening of T1 time in case of intramyocardial haemorrhage, due to methemoglobin accumulation (23) (figure no. 2)
ECV has values similar to those of patients with hypertrophic cardiomyopathy (28 ± 4% - 1.5T) (23)	***Chronic myocardial infarction***: native T1 time is increased (fibrous scar) but has lower and less extensive values compared to the acute phase. Particularity: the central portion of the infarcted area with very low T1 values (230-350 ms at 1.5T) highlights lipomatous metaplasia in chronic myocardial infarction, which plays an important role in the occurrence of post-myocardial infarction arrhythmias. (26,27) (figure no. 2)

Figure no. 1 (23) Representative examples in short axis views for non-ischemic CMD: A – mid-wall LGE in IVS; C - without LGE, B - increased values of native T1 time in the IVS (1000-1200ms); D - increased ECV values (red areas represent ECV> 30%) (D)

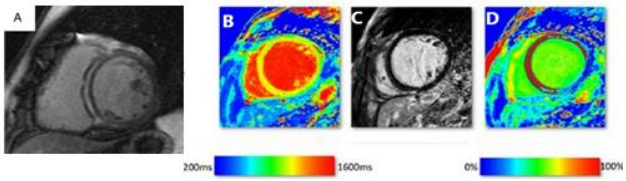
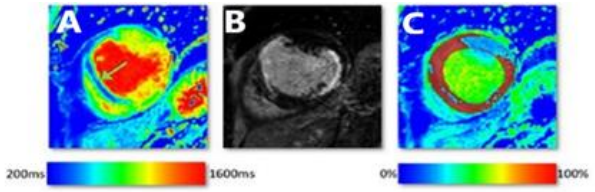


Figure no. 2 (23) CMR tissue characterization in a patient with anteroseptal chronic myocardial infarction: area with low native T1 values (A) in the IVS (green arrow) corresponding to lipomatous metaplasia from chronic myocardial infarction. Acute myocardial infarction in the lateral wall (B) with an area of periinfarct oedema visualized on the native T1 sequence. C - Red areas correspond to VEC > 30%.



CONCLUSIONS

In conclusion, CMR is a very useful imaging technique for patient's evaluation with ischemic and non-ischemic DCM, having a major role in the quantifying cardiac function, but especially in myocardium tissue characterization.

All this information is particularly useful in clinical practice, because it allows patients risk-stratification according to myocardial damage. This way, a more individualized therapeutic decision can be made, with therapies prioritisation according to patient's risk: optimal drug therapy associated or not with cardiac resynchronization therapy and complex ventricular arrhythmias therapy (radiofrequency ablation and / or cardio defibrillator implantation as primary prophylaxis of SCD).

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