REVIEW Cardiac Imaging

Challenges in diagnosis and prognosis of Dilated cardiomyopathy with cardiac MRI

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ABSTRACT

Dilated Cardiomyopathy (DCM) is the final response of the myocardium to several conditions, in most cases related to genetic or inflammatory factors, which lead to progressive left ventricular wall thinning and dilation, myocardial fibrosis, and cardiac dysfunction.
DCM is the third most common cause of heart failure (after ischemia and valvular heart disease) and the most common cardiomyopathy (other types: hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathies). It is end-stage cardiomyopathy, predominantly involving the left ventricle.
Evaluation of the etiology by excluding other causes of LV dilation and dysfunction, may lead to the appropriate therapeutic protocol and contribute to prognosis.
Detection of pre-DCM phenotype may reduce morbidity and mortality.
The aim of surveillance and therapy in each stage of DCM is to prevent remodeling, assess reverse remodeling, and avoid adverse events, especially sudden cardiac death.
Cardiac MRI (CMR) has a major role in diagnosis, prognosis, and selection of therapeutic schema. It is the gold-standard technique to measure chamber dimensions, to assess morphological features, systolic function, and valve disease. Also, tissue characterization may exclude ischemia as well as detect myocardial fibrosis which leads to arrhythmias and heart failure.
In this article, we discuss the predictive value of Cardiac Magnetic Resonance (CMR) for the evaluation of etiology, detection of pre-clinical DCM, assessment of left ventricular dysfunction, cardiac remodeling, and myocardial fibrosis, aspects that give a prognosis of sudden cardiac death and also guidance in the decision for device therapy.

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Introduction

Dilated Cardiomyopathy (DCM) is one of the most common phenotypes in patients diagnosed with heart failure [1,2]. DCM predominantly affects younger adults, especially males [3]. Is the most common diagnosis in patients who are referred for cardiac transplantation.

DCM is characterized as ventricular dilation and depressed myocardial function of the left or both ventricles, in the absence of abnormal loading conditions (hypertension or valvular disease) or coronary artery disease [1,2].

DCM can be divided into genetic and non-genetic [1]:

- Primary-idiopathic DCM. About 20-50% of patients with an initial diagnosis of Idiopathic DCM may be diagnosed as familiar [4-7].
- Secondary DCM has non-genetic etiology, which includes inflammatory or autoimmune myocarditis (refers to 9-10% of DCM), toxins, infiltrative and connective tissue diseases, vasculitis, metabolic or endocrine causes, neuromuscular disease, tachyarrhythmia, peripartum cardiomyopathy [8].

In several studies, DCM is supposed to be the end-stage of the other cardiomyopathies.

The clinical onset of patients with DCM varies from asymptomatic to left heart failure. Right heart failure may be present in advanced cases [9,10]. Patients may present with symptoms of congestive heart failure: progressive dyspnea with exertion, impaired exercise capacity, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema. Other potentially life-threatening symptoms may be ventricular arrhythmias, conduction abnormalities, syncope, thromboembolic events, and sudden cardiac death. Pulmonary vascular redistribution is a common phenotype related to cardiomegaly and DCM. Intracavity thrombus is a common complication of DCM [11].

Histologically, DCM is characterized by a combination of atrophy and hypertrophy of myocytes, with myocyte elongation (myocardial injury and necrosis), which leads to increased chamber size, and myocardial fibrosis [12-14].

DCM has to be differentiated from conditions with phenotypic overlaps, such as ischemic cardiomyopathy, hypertensive heart disease, hypertrophic cardiomyopathy, ARVC, LV non-compaction cardiomyopathy, athlete's heart, and cirrhotic cardiomyopathy [8]. Differential diagnosis can be based on clinical evaluation, laboratory findings, and imaging techniques (echocardiography, nuclear imaging, CT coronary angiography, and CMR).

Role of cmr for the assessment of dcm – diagnostic protocol

Cardiac imaging using MRI is a reliable tool for the early detection of DCM, the evaluation of the etiology, the assessment of the stage of remodeling and myocardial fibrosis, and the selection of patients for ICD implantation or cardiac resynchronization therapy.

- Imaging evaluation relies on the measurement of biventricular volumes and ejection fraction, the thickness of ventricular walls, the detection of LV dilation, valvular function, and detection of LV thrombi usually located in the apex [11].
- Structural study may show loss of normal gradient in systolic wall thickening between LV base and apex [15], as well as enlargement of the LV trabeculae along the lateral LV wall [16].
- Functional studies on MR may demonstrate increased end-systolic and end-diastolic LV volumes, reduced ejection fraction in one or both ventricles, wall motion abnormalities, and diffuse global dysfunction.

The diagnostic protocol of CMR must be appropriate in order to detect and assess the stage of DCM:

- *LGE (Late Gadolinium Enhancement) CMR* is the gold standard technique for the identification and quantification of fibrotic deposition on the myocardium. Patients with DCM may present with a lack of pathologic gadolinium enhancement or with a non-ischemic pattern of gadolinium enhancement (mid-wall, subepicardial or patchy distribution) of the LV wall, rarely involving the RV wall [17-19].
- *Cine MRI technique* quantifies cardiac chamber size, LV wall thickening and ventricular mass (as well as the ratio wall thickness /chamber radius) [20-22], left ventricular function and dilatation, stroke volume and ejection fraction, evaluate segmental wall motion abnormalities,

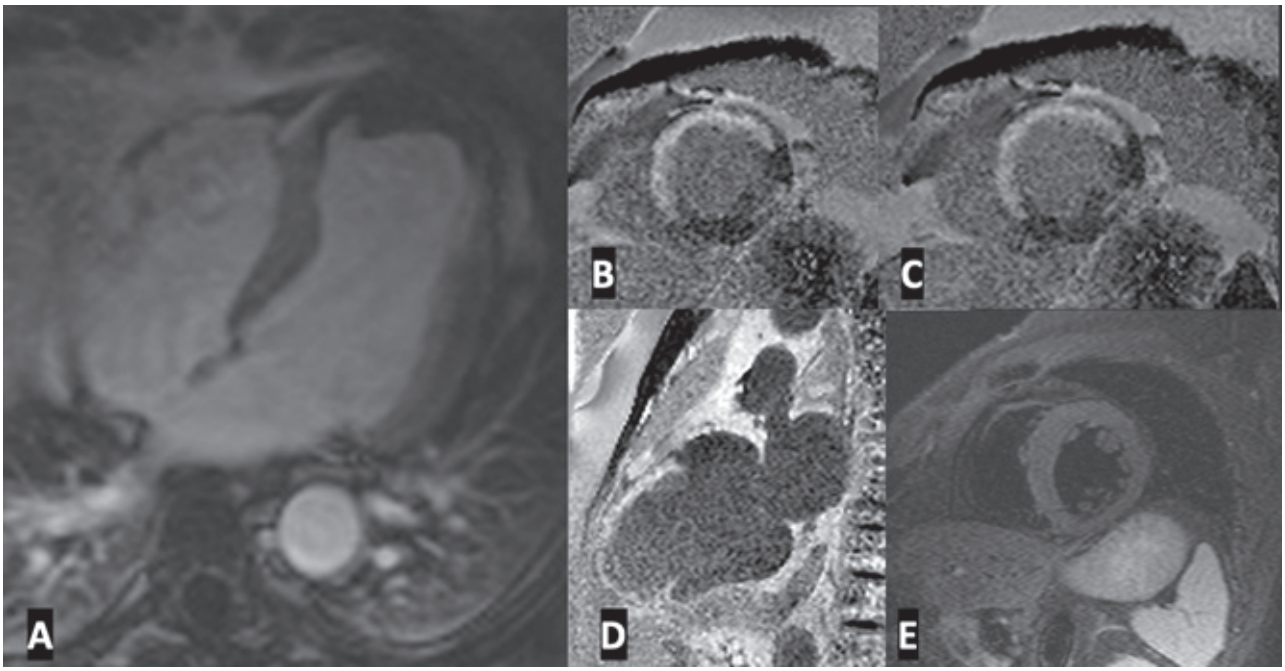

Fig. 1. *Ischemia. 4Chamber(**A**) Cine MRI (SSFP) shows LV dilatation with thrombus at LV apex. PSIR LGE images (**B, C, D**) visualize chronic ischemic scar at anterior and diaphragmatic LV wall following vessel distribution (LAD) and ischemic pattern of enhancement. There isn't edema on the STIR sequence (**E**).*

identify mitral regurgitation and in some cases detect diastolic dysfunction of the right ventricle.

- *CMR tagging technique* detects myocardial contractility and provides information for myocardial stress and strain
- *Feature tracking strain analysis* obtained from cine-imaging is an upcoming tool that is suggested to be valuable to predict survival in DCM. It detects global and means longitudinal strain. Patients with global longitudinal strain may have an excellent prognosis, even with LVEF <35% or with the presence of LGE [23].
- *Native T1 mapping and extracellular volume (ECV)* (pre- and post-contrast T1 mapping) may depict myocardial fibrosis, even in cases without LGE. This might happen because the deposition of collagen increases in the extracellular space. T1 mapping and ECV is considered to be early diagnostic tool, more useful in cases of LMNA mutation [24-26].
- *T2 mapping* detects myocardial edema and active inflammation in cases of myocarditis.
- *T2* relaxation mapping* detects early myocardial iron deposition in order to prevent DCM, but also optimizes the reversal of myocardial iron loading before the onset of LV dysfunction.

Extracardiac assessment of the images may detect abnormalities such as pleural effusion or azygos vein and superior vena cava dilation.

Role of cmr for the evaluation of the etiology of dcm

In order to detect DCM, other conditions of phenotypic overlap have to be excluded:

- LGE-CMR technique has a high accuracy to differentiate coronary artery disease (CAD) from non-CAD-related LV dilatation and dysfunction. Ischemic heart disease shows subendocardial /transmural enhancement in coronary artery perfusion territories (ischemic pattern of gadolinium enhancement) (Fig 1). DCM shows mid-wall, subepicardial or patchy distribution (non-ischemic pattern). However, 13% of patients with LV dysfunction show subendocardial /transmural enhancement without coronary artery disease, which should be considered to be related to CAD [18,27].
- CMR is a reliable tool for differentiating valvular dysfunction related to LV dilatation and dysfunction from DCM, based on the cine MRI technique, by providing information about valvular anatomy and function, as well as the effect of valvular dysfunction on other cardiac structures and function.

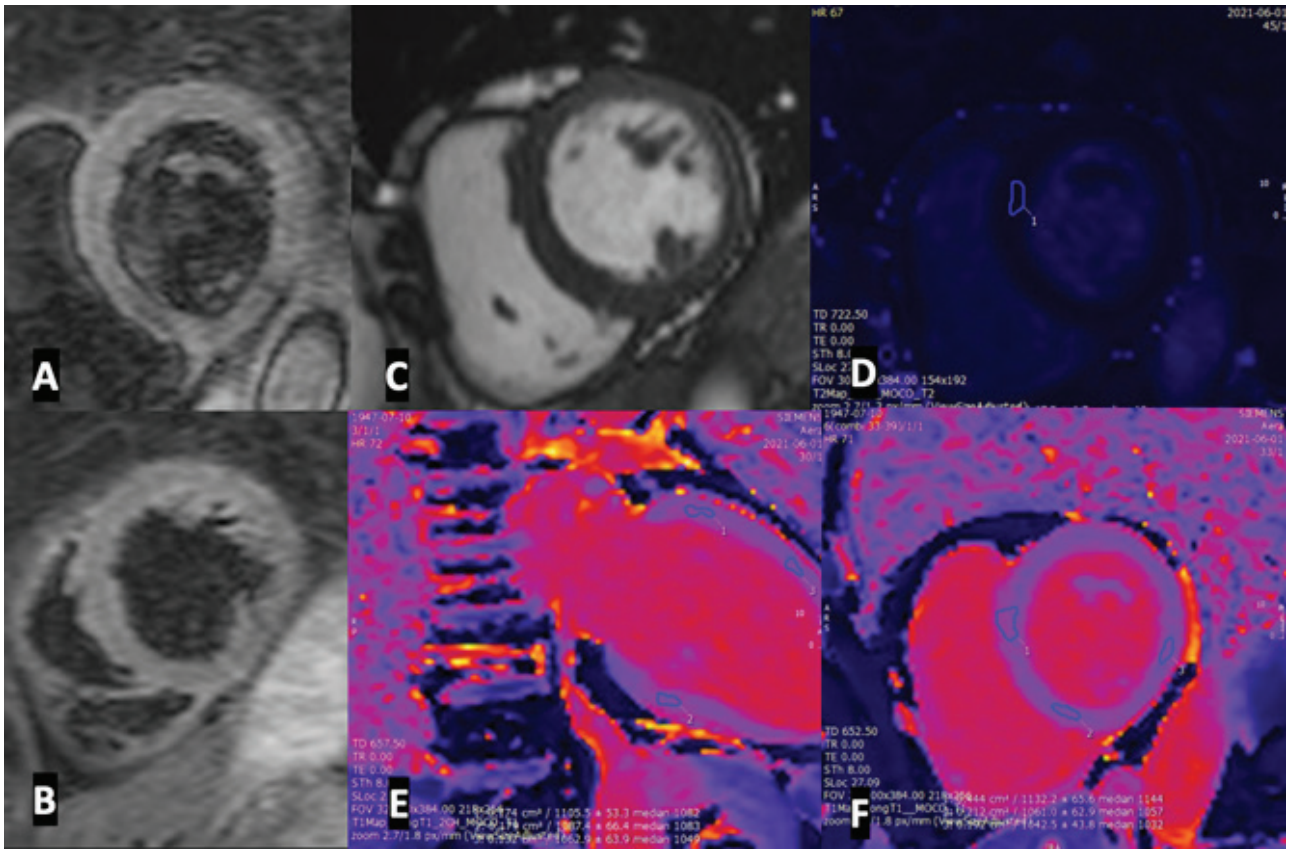

Fig. 2. *73 years old woman who developed DCM after receiving chemotherapy due to operated breast cancer. SA STIR images* ***(A, B)*** *Show subtle edema at the basal intraventricular septum. Short Axis* ***(C)*** *Cine MRI (SSFP) shows LV dilatation (Ejection Fraction 55%). T1 MAPPING* ***(E, F)*** *and T2 MAPPING* ***(D)*** *images visualize increased values indicative of replacement fibrosis and edema.*

Assessing the etiology of DCM:

- CMR provides strong evidence of myocardial inflammation based on Lake Louise criteria [28]: Presence of myocardial edema, with a regional or global increase of signal on T2 or T2 mapping. Presence of inflammatory myocardial injury: increased signal of native T1 mapping or ECV or non-ischemic pattern on LGE series. Pericarditis with effusion or systolic LV dysfunction with wall motion abnormality may present. CMR offers high diagnostic accuracy in acute myocarditis but is less sensitive in chronic inflammation [8]. DCM may be a consequence of long-lasting inflammatory disease of the myocardium, in association with maladaptive post-viral immunocompromised response [29]. Patients recently diagnosed with DCM and identification of myocarditis signs on CMR have a high potential for LV recovery.
- Toxins have been associated with LV dilatation and dysfunction as non-genetic causes of DCM, including regular alcohol consumption [30], anthracycline, amphetamines, and chemotherapeutic agents (Fig 2) or antiretroviral therapy in HIV patients [31].
- Peripartum cardiomyopathy typically develops within 1 month before delivery and 5 months post-delivery. Risk factors are supposed to be preeclampsia, twin gestation, and advanced maternal age. However, hemodynamic stress of pregnancy may trigger an underlying myocardial dysfunction [32].
- Persistent tachyarrhythmia (>100 beats/min) is suspicious of tachycardia-induced cardiomyopathy. In these cases, LV function is supposed to recover within 4 months after the effective rate of rhythm control [8].
- Other causes may be connective tissue diseases, vasculitis, infiltrative diseases (amyloidosis, sarcoidosis, hemochromatosis), neuromuscular diseases, and metabolic and endocrine disorders [33-35].

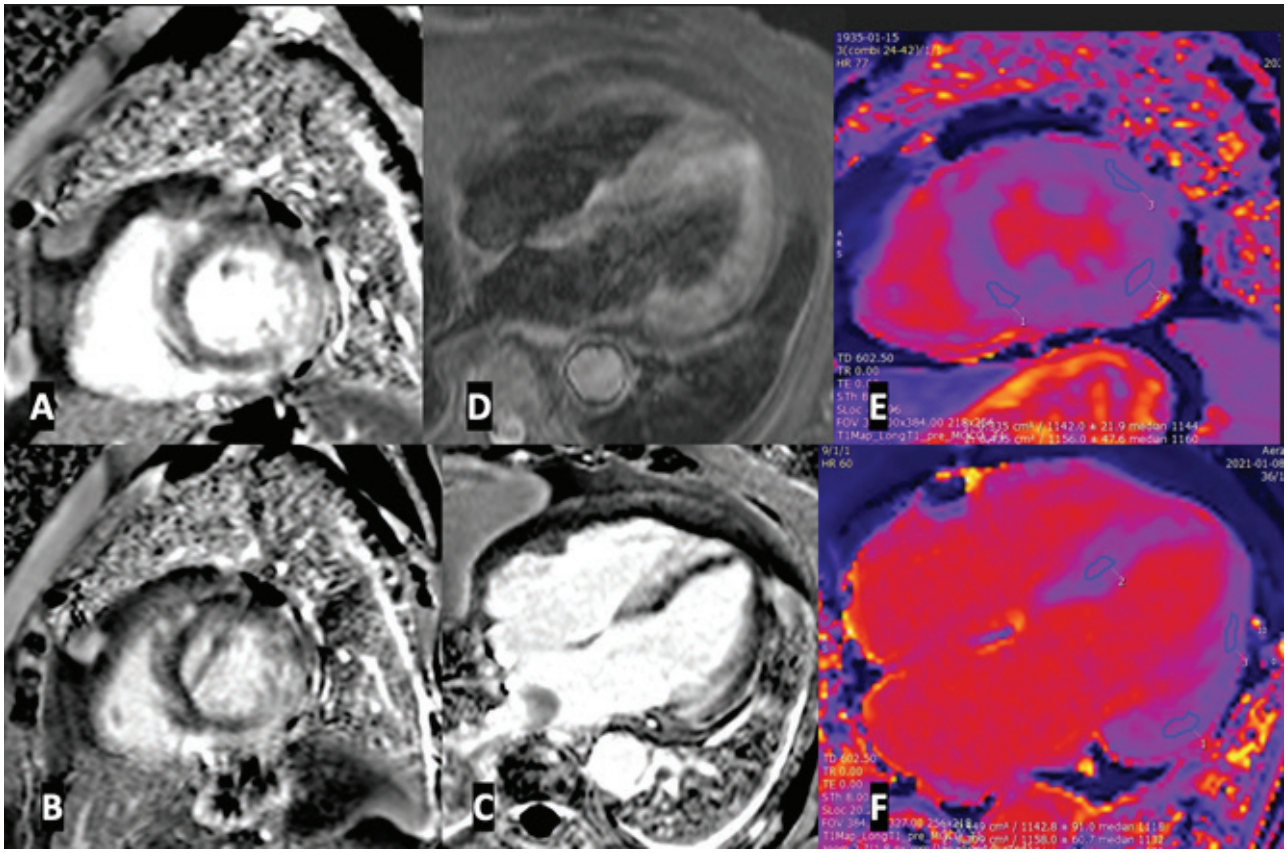

Fig. 3. *Amyloidosis. 85-year-old female with shortens of breath and slightly reduced Ejection fraction (EF 45%).LGE Short Axis* ***(A, B)*** *and 4Chamber* ***(C)*** *images display a mixed enhancement pattern (ischemic, nonischemic). There is no edema on STIR* ***(D)****. T1 MAPPING* ***(E, F)*** *visualizes increased T1 values with subsequent increased ECV (0,35) characteristic of this pathology.*

In the absence of any detectable cause, DCM will be classified as idiopathic.

- Idiopathic DCM is considered familiar (genetic) when more than one first-degree relative has been diagnosed with DCM [7] or with the presence of an unexplained sudden cardiac death before the age of 35 years of a relative of a DCM patient [36]. Approximately 40% of the genetic causes have been attributed to rare variants in over 60 genes [37,38]. The most frequently involved genes codify for cytoskeleton or sarcomere proteins [32]. In some patients with genetic DCM, some phenotypes may suggest a particular gene defect: cardiac conduction abnormalities may be related to LMNA or SCN5A mutations, while elevated serum creatine kinase or muscle weakness with muscle dystrophy or LMNA mutation [39]. DMC related to LMNA mutation has been associated with poor prognosis, due to conduction system disease, malignant ventricular arrhythmias, and sudden cardiac death.

Role of cmr for the detection of the pre-clinical dcm

Early detection of DCM may prevent heart failure symptoms and increase life expectancy.

Familiar screening for DCM concerns first-degree relatives of DCM patients. Relatives without detected etiology should undergo ECG and echocardiography every 2-5 years until the age of 50-60. If a gene mutation is present, relatives who carry the mutation should undergo clinical surveillance every 1-3 years [33,40].

CMR may have a supplementary role in detecting latent disease, by using Cine images, Feature tracking strain analysis, T1 mapping, and T2* mapping:

- Left ventricular enlargement may be detected in 15-25% of relatives of patients with idiopathic or familial DCM, even without systolic dysfunction [41,42].
- Reduced myocardial strain and strain rate may be detected in relatives of patients with idiopathic or familial DCM with mutation carries, despite normal LV size and LVEF [43].
- Reduced global longitudinal strain may be detected in

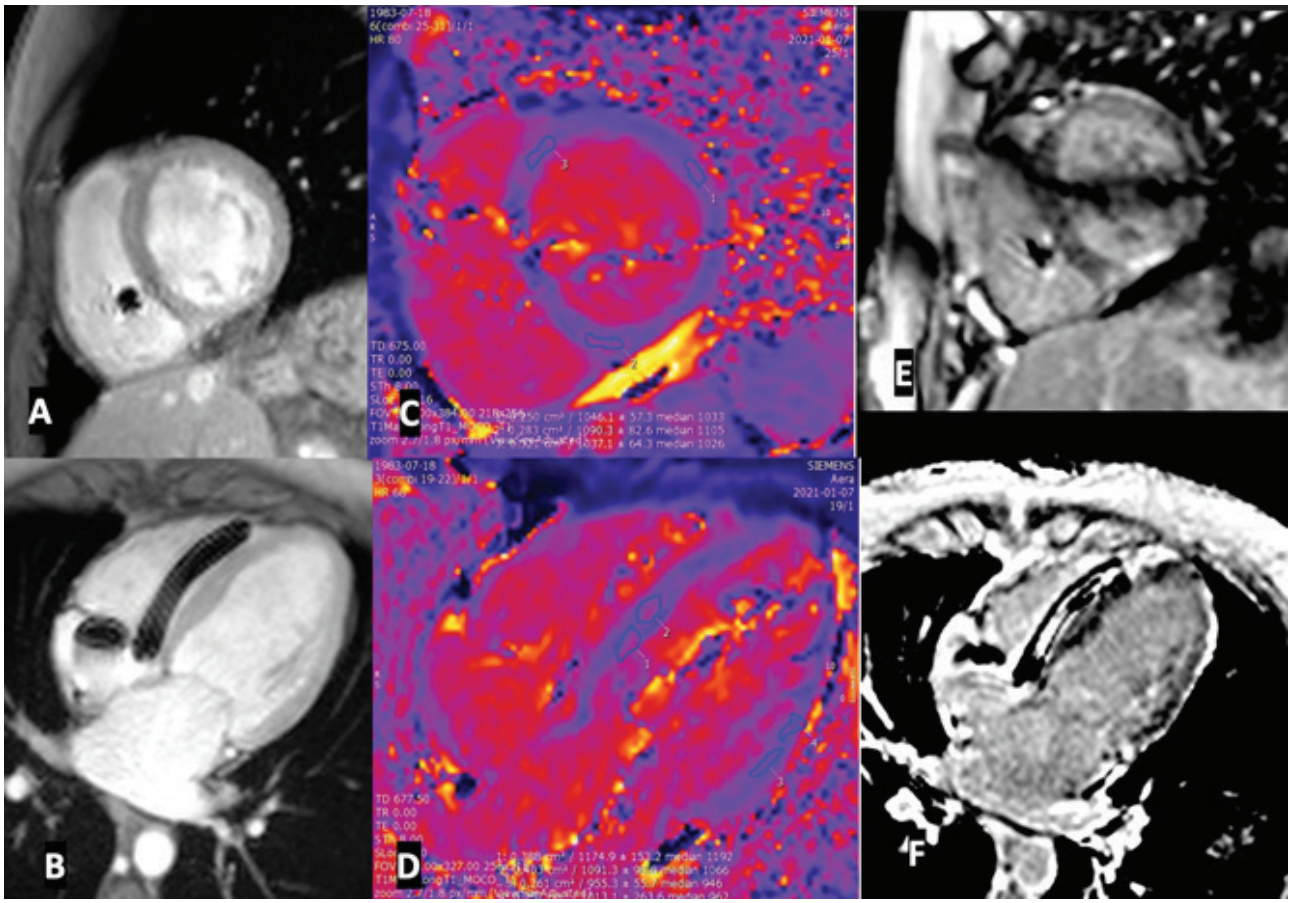

Fig. 4. *Female 37 years old with LMNA-related dilated cardiomyopathy and implanted pacemaker. Short Axis (**A**) and 4Chamber(**B**) Cine MRI (SSFP) show LV dilatation (LV Ejection Fraction 37%,RV EF 32%). T1 mapping SA and 4CH (**C and D**) visualizes increased T1 values indicative of fibrosis mainly at the IVS. SA and 4CH LGE (**E and F**) show areas of enhancement with a non-ischemic pattern.*

patients receiving potentially cardiotoxic chemotherapy, which may lead to LV dysfunction [44].

- High myocardial ECV fraction may be assessed in patients with mutation carries, even in the absence of clinical symptoms or LGE [24-26].
- Iron overload of the myocardium may be assessed in transfusion-dependent patients, which leads to LV dysfunction and heart failure. Iron chelation therapy may reverse myocardial iron overload before the onset of LV dysfunction [8].

Prognostic factors for adverse events in dcm: The assessment of (the stage of) remodeling

In DCM, the extent of LV dilation and contractile impairment has a predictive value of adverse outcomes. Adverse remodeling in DCM includes LV wall thinning and dilation, functional mitral regurgitation, myocardial fibrosis, enlargement of other chambers, and dyssynchronous vertical contraction.

Left Ventricular (LV) remodeling

CMR is the gold standard for left ventricular assessment, avoiding geometric assumptions of the LV chamber. Cine MRI technique quantifies the telodiastolic measurements of the LV (structural and functional): LV size, LV volume, wall thickening, ventricular mass, as well as the ratio of wall thickness /chamber radius. The functional study is excellent to assess ventricular function and dilatation and identifying stroke volume and ejection fraction [8]. LV ejection fraction (LVEF) <45% at presentation is an independent prognostic factors for adverse events [45]. Feature tracking strain analysis represents a promising tool for the assessment of LV systolic function.

Functional Mitral Regurgitation (FMR)

Increasing LV size and sphericity as well as annular dilation, lead to tethering of the mitral valve leaflets, defective leaflet coaptation, and functional regurgitation, which leads to increased morbidity and mortality [46]. Velocity-encoded CMR is a useful modality for evaluating FMR. Medical therapy, cardiac resynchronization therapy, and surgical annuloplasty reduce FMR severity and therefore improve LV remodeling and improve survival [47-49].

Myocardial Fibrosis

One-third of the patients with advanced DCM develop myocyte injury or necrosis [50], which leads to replacement fibrosis typically in the mid-wall of the myocardium. This process is involved in the genesis of re-entry circuits which may lead to focal ventricular re-entrant arrhythmia and sudden cardiac death [51,52]. The presence of myocardial fibrosis may decrease the likelihood of LV reverse remodeling in response to pharmacological therapy and cardiac resynchronization therapy (CRT) [53-55]. Cardiac ventricles in DCM with replacement of viable myocardium with a reparative scar, are less likely to recover. Myocardial scar has an independent prognostic value for sudden cardiac death [56-59]. LGE-CMR is the gold-standard technique to identify myocardial fibrosis, so is likely to guide the selection of patients for device therapy. T1 mapping may detect myocardial fibrosis even in the absence of LGE and consequently has a valuable contribution to early DCM diagnosis. Also, ECV is a valuable biomarker of interstitial fibrosis because ECV fraction has been associated with the degree of fibrosis (Fig 3) [60].

Left Atrium (LA) remodeling

Left atrial dilation may be observed as a consequence of diastolic dysfunction, functional mitral regurgitation, atrial fibrillation, and LV cavity enlargement. The Cine MRI technique has great accuracy for measurements of LA size and LA volume. LA volume is an index that provides prognostic information in DCM [61]. LA remodeling may predict adverse outcomes in DCM.

Right Ventricle (RV) remodeling

Right ventricular dilation may be a result of secondary pulmonary hypertension or primary myocardial disease. The Cine MRI technique has great accuracy for the assessment of tricuspid regurgitation and for measurements of RV volumes and RV ejection fraction. RV systolic dysfunction is defined by RVEF <45%. RV remodeling may predict adverse outcomes in DCM. RV volume and RV ejection fraction are the indexes which provide prognostic information in DCM [62,63].

Contractile Dysfunction and Ventricular Dyssynchrony

QRS interval prolongation (>150ms) with association with left bundle branch block (LBBB) morphology, are the criteria for ventricular dyssynchrony in patients with DCM. Patients with ventricular dyssynchrony due to LBBB, present LV-free walls longest delay activation time and they benefit from resynchronization of ventricular contraction with cardiac resynchronization therapy (CRT), which improves LV remodeling [64]. Myocardial motion and deformation may be assessed by CMR tagging [65] or short-axis cine imaging [66], which shows hypokinetic or dyskinetic wall motion or ventricular dyssynchrony.

Staging the LV remodeling [8]

- *Latent DCM*, which refers to patients at risk, is characterized by early LV phenotype and/or pathogenic gene mutation, and altered biomarkers. In this stage, remodeling can be retarded with the neurohormonal blockade, and molecular/gene therapy and needs imaging and biomarker surveillance.
- *Established DCM* is characterized by increased LV volume and decreased LVEF, limited or no replacement fibrosis and/or functional mitral regurgitation, LV dyssynchrony, and active myocarditis. In this stage, remodeling is reversible using neurohormonal blockade, cardiac resynchronization, mitral valve interventions, molecular/gene therapy, and immunosuppressive /antiviral treatment.
- *Advanced DCM* is characterized by the severe increase of LV volume and severe decrease of LVEF, extensive replacement fibrosis, wall thickening, and/or right ventricular remodeling. In this stage, DCM does not respond to conventional therapies and needs stem cell therapy or cardiac transplantation.

Prognostic factor for long-term outcome in dcm: The assessment of lv reverse remodeling

LV reverse remodeling (LVRR) is characterized by a decrease in LV end-diastolic volume and an increase in LVEF. Is a key therapeutic goal in the established stage of DCM, because is a strong independent predictor of long-term outcomes [53,67].

One-third of patients with DCM have partial or complete

functional recovery with 3 months of optical medical treatment, which renders ICD implantation unnecessary [67-69]. Nearly 40% of patients diagnosed with DCM, experience LV reverse remodeling.

LGE-CMR can identify patients with high reverse remodeling potential. Patients without mid-wall LGE are more likely to experience LVRR, compared to those with LGE, and consequently, absence of LGE is supposed to be a strong predictor of LVRR [53,70,71].

Depending on the etiology of DCM, reversible causes such as alcohol-related, peripartum, or acute inflammatory cardiomyopathy, increase the likelihood of functional recovery.

Prediction of risk of sudden cardiac death with therapy devices: Icd implantation and cardiac resynchronization therapy

Implantation of an ICD (implantable cardioverter-defibrillator) reduces the incidence of sudden cardiac death and thus mortality [72], while CRT (cardiac resynchronization therapy) reduces mortality and hospitalization by improving cardiac function, in patients with LVEF <35%.

Considering the ICD or CRT placement-related complications, it is crucial to identify patients with a high risk of sudden cardiac death who are likely to respond to these therapies.

LGE-CMR may predict arrhythmias and sudden cardiac death in DCM, by detecting myocardial fibrosis. The absence of mid-wall LGE is supposed to identify patients with DCM at low risk of sudden cardiac death, even when LVEF is <35% [70,73].

Indications for ICD implantation include life expectancy and quality of life, as well as primary and secondary prevention [68,69]: 1) Symptoms NYHA classes II and III (mild shortness of breath, angina, slight limitation during activity /marked limitation in activity), LVEF <35% despite at least 3 months of optical medical therapy. 2) History of ventricular arrhythmia with hemodynamic compromise.

DCM patients with LVEF <35% and LGE, may benefit from ICD implantation [74].

Even if LV scars generate focal arrhythmias, ICD implantation does not necessarily offer survival benefits [75].

In LMNA carries, non-sustained ventricular tachycardia, male gender, LVEF <45% at presentation and non-missense mutation are independent predictors of malignant ventricular arrhythmias and thus sudden cardiac death, and consequently the threshold for ICD implantation should be lower (Fig 4) [68].

Patients with QRS interval prolongation (>150ms) and left bundle branch block, benefit from CRT.

Patients with borderline QRS interval (130-150ms) or non-LBBB, are in the study if they benefit from CRT.

Patients without QRS prolongation (<130ms) have no benefit from CRT, whereas imaging detects mechanical dyssynchrony [76].

The clinical response of CRT depends on the optimal lead position and viable myocardium to be depolarized. LGE-CMR may guide the lead placement away from areas of fibrosis.

RV lead near a scar may be associated with impacted LVRR [77].

LV lead near a scar may be associated with poor LV resynchronization and QRS prolongation.

LV lead over a scar may be associated with a higher risk of adverse events than LV lead over viable myocardium [78].

Conclusion

CMR with specific multiple techniques plays an important role in the prognosis of DCM, even in the stage of diagnosis, or in the stage of surveillance.

LVEF is supposed to be an independent prognostic factor for adverse events (mortality, future hospitalization, and sudden cardiac death): LVEF <45% has a poor prognostic value.

Myocardial fibrosis is also supposed to be an independent prognostic factor for adverse events: the presence of myocardial fibrosis detected by LGE-CMR has a poor prognosis.

Characterization of Remodeling, ECV, LV Reverse Remodeling (LVRR), and Feature Tracking Strain Analysis is supposed to be predictive factors for the outcome of DCM:

Poor prognostic factors for the outcome of DCM may be: high ECV fraction, RV systolic dysfunction, increased LV volume and mass as well as the increased extent of LV dilation and contractile impairment (LV remodeling), increased LA volume (LA remodeling), increased RV volume and decreased RV ejection fraction (RV remodeling) and Functional Mitral Regurgitation.

Prognostic factors for the long-term outcome may be LVRR and global longitudinal strain as detected by Feature Tracking Strain Analysis. **R**

Conflicts of interest

The authors declare no conflicts of interest.

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