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The role of cardiac magnetic resonance imaging in the diagnosis and management of myocardial pathology

ABSTRACT OF THE DOCTORAL THESIS

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Contained

LIST OF ABBREVIATIONS

CAVD – arrhythmogenic VS cardiomyopathy

CMP – cardiomiopatii non-ischemice

CMD – dilated cardiomyopathy

HCM – hypertrophic cardiomyopathy

CNDVS – non-dilated cardiomyopathy of the left ventricle

CRTD – cardiac resynchronization therapy

CT – computed tomography

EACVI – European Association of Cardiovascular Imaging

FEVS – left ventricular ejection fraction

LVEF – right ventricular ejection fraction

HVS – left ventricular hypertrophy

ICD – implantable cardiodefibrillator

ICS – Significant Clinical Impact

IM – infarct miocardic

BMI – body mass index

BCI – ischemic coronary artery disease

LGE – late gadolinium enhacement

NYHA – New York Heart Association

CMR – cardiac magnetic resonance imaging

ROC – Receiver Operating Characteristic

SPECT – single-photon emission computed tomography

STIR – short-tau-inversion-recovery

TR – relaxation time

VBVS – left ventricular beat volume

VEC – extracellular volum

VTDS – left ventricular end-diastolic volume

VTDSVS – left vetric telescopic volume

VS – left ventricle

Introduction and Premises

Cardiovascular diseases are the leading cause of mortality worldwide, causing approximately 20.5 million deaths in 2021, with myocardial pathology being the leading cause [1].

Myocardial disorders encompass a broad spectrum of pathophysiological mechanisms that include myocardial ischemia, genetic abnormalities and systemic disorders. Currently, cardiac magnetic resonance imaging (MRI) is the only non-invasive and non-ionizing imaging technique that can accurately differentiate ischemic from non-ischemic pathology of myocardial involvement, based on the typical appearance of post-infarction myocardial scarring [2].

CMR is superior to other cardiac imaging methods, having the unique ability to identify myocardial fibrosis, necrosis or myocardial infiltrate with various substances such as amyloid [3]. Given this special ability to characterize in depth the tissue composition, CMR is a unique imaging method for the diagnosis of various myocardial pathologies and is currently accepted as the "gold standard" imaging method for evaluating cardiac function parameters such as: ventricular volumes, biventricular ejection fractions, left ventricular mass and wall thickness [4,5].

Also, through the new advanced tissue characterization images, it can help identify diffuse interstitial myocardial fibrosis by signal changes occurred on native T1 mapping sequences (in this case, observing the appearance of areas in T1 hypersignal) or by calculating extracellular myocardial volume (ECV) after contrast agent administration. This technique can also identify lysosomal deposits or myocardial infiltration with fat, pathologies that determine the decrease in relaxation time (TR) on T1 mapping images [6]. Myocardial edema can also be highlighted with the help of CMR by the presence of hypersignal areas on STIR (short-tau-inversion-recovery) sequences and on T2 mapping maps [3,7].

All these data were correlated with the results of histopathological examinations from various studies, which supports the importance of this investigation in establishing the etiology and prognosis of the underlying myocardial disease, becoming an essential tool in their evaluation [8,9].

Numerous studies have analyzed the general utility in cardiac pathology of CMD and have reported a change in management in a variable proportion from 16% to 65% following

its performance, either by identifying a new diagnosis or by highlighting cardiac structural changes that have required a new therapeutic approach [10,11].

The present work is structured in two parts: the general part and the special part. The general part will include an overview of the role of CMR in the evaluation of myocardial pathology, which we have briefly divided into non-ischemic cardiomyopathies and ischemic cardiomyopathies, according to the way of separation of myocardial involvement on data obtained from delayed gadolinium uptake (LGE) images. The role of this description is to review the current state of knowledge related to the subject of the doctoral thesis. However, the role of advanced tissue characterization imaging techniques of CMR (T1 mapping and T2 mapping) in the evaluation of various myocardial pathologies will be emphasized.

In the special part, starting from the premise that CMR has an important impact on the diagnosis and management of cardiac pathology, a fact demonstrated in previous studies, we proposed, in the **first study** presented, to evaluate the role of CMR in establishing the diagnosis and management of patients with non-ischemic cardiomyopathies, pathologies that are often at the intersection of the multidisciplinary approach. We also considered the identification of MRI imaging parameters that may have the role of predictors regarding the clinical impact of patients with non-ischemic cardiomyopathies.

Subsequently, in **study two**, we evaluated the relationship between native T1 and T2 times and clinical, demographic, structure and cardiac function parameters in the group of non-ischemic cardiomyopathies previously analyzed. We started from the premise that interstitial fibrosis evidenced by T1 mapping maps and myocardial edema evidenced by T2 mapping maps are associated with cardiac remodeling parameters. This research constitutes a significant contribution to the literature, given that the data obtained have not been previously reported, according to our current knowledge.

In **the third study**, we emphasized the importance of applying the new CMR techniques to tissue characterization, demonstrating their ability to discriminate between the main types of non-ischemic cardiomyopathies, compared to a control group of normal subjects. In this study, non-dilated left ventricular cardiomyopathy (NLDC), a cardiomyopathy introduced in the guidelines in 2023, was also included in the analysis, thus the data in the literature on tissue characterization by T1 and T2 mapping techniques for this pathology being almost non-existent.

The **fourth study** addresses cardiac stress magnetic resonance imaging, from the point of view of practical interest. This study highlights the role of CMR stress among patients with ischemic coronary artery disease or suspected of it, being the first report of its kind in

Romania. This technique is underused in our country due to limited accessibility and expertise.

I chose this topic because I believe, in the current context of the evolution of CMR as a high-class imaging method for both the diagnosis and the follow-up of the evolution of patients with myocardial involvement, that it is important to understand the need for the widest possible adoption of this technique, which allows clinicians to provide health care at the highest standards. We started from the idea that, although we are talking about an imaging method with remarkable capabilities, it has not been widely used in Romania so far due to its expertise and limited accessibility.

Personal contributions

Working hypotheses. Objectives

In the first *three studies* targeting the role of CMR in the evaluation of non-ischemic cardiomyopathies (CMP) we had the following hypotheses and objectives.

Working hypotheses

- CMR can highlight previously undetected diseases in patients diagnosed/suspected with CMP by echocardiography or other cardiac imaging techniques
- In a significant subset of patients with various forms of cardiomyopathy, CMR may lead to a change in their management based on the information disclosed
- This change in diagnosis and/or management correlates with certain cardiac remodeling parameters assessed by CMR
- Native T1 and T2 times, as assessed by advanced tissue characterization techniques, correlate with disease progression in patients with non-ischemic PMC
- The native T1 and T2 times differentiate the main non-ischemic CMPs from normal

Objectives

- Evaluation of the impact of CMR on the diagnosis and management of patients with CMP
- identification of predictors influencing the diagnosis and management of patients with CMP

- analysis of the relationship between native T1 and T2 times with clinical, demographic, as well as cardiac structure and function parameters
- comparative analysis of the impact of T1 and T2 mapping in routine clinical practice on the diagnostic capacity of the main non-ischemic cardiomyopathies, in relation to a control group consisting of normal subjects.

In the *fourth study* that refers to the role of CMR in the evaluation of myocardial ischemia. **The working hypothesis** was that providing preliminary data related to the use and safety of stress CMR in Romania can provide a better understanding of this technique and probably lead to an increase in its addressability and accessibility. **The objectives** of the study were:

- providing data on the clinical indications of this technique
- providing data on information obtained from stress CMR and its impact on patient management
- providing data on the safety and applicability of the imaging method
- characterization of the population at risk for positive stress CMR test

General research methodology

In the studies that analyzed the role of CMR in the evaluation of non-ischemic CMP, the methodology used consisted of the analysis of a batch of patients with non-ischemic CMP, who underwent CMR in two medical units: at the "Professor Doctor Agrippa Ionescu" Emergency Clinical Hospital and the Emerald Medical Center, Bucharest, from January 2021 to March 2022.

The control group consisted of subjects in whom the CMR evaluation was found to be within normal limits, they were selected so as to correspond in age and sex with the analyzed group. This batch was necessary to perform a comparative analysis of tissue characterization times (native T1 and T2) for the various non-ischemic CMPs, compared to normal.

All patients underwent a complete cardiological clinical examination before being evaluated by CMR, and demographic and clinical data were collected at the time of MRI performance.

In the fourth study, the analyzed group consisted of patients who underwent stress CMR in the Emerald Medical Center, Bucharest, between January 2018 and December 2020.

The design of this study was according to a cohort study that included a retrospective analysis of clinical records and CMR reports from the mentioned period.

We performed all CMR studies using a 1.5 Tesla scanner (Siemens, Erlangen, Germany). Our imaging protocol followed current guidelines and recommendations [12], covering all sequences indicated according to the initial clinical suspicion. Gadolinium was administered to all patients for the evaluation of focal myocardial fibrosis by LGE images, obtained 10-15 minutes after contrast agent injection. In those who underwent stress CMR, the administration of the stressor (adenosine, in our case) was done through a separate venous approach. In addition, the T1 and T2 mapping maps were purchased. All CMR examinations were reported by a multidisciplinary team composed of an experienced radiologist and a cardiologist with level 3 accreditation in cardiovascular magnetic resonance imaging by the European Association of Cardiovascular Imaging (EACVI).

The study protocol was approved by the Ethics Committee of the "Prof. Dr. Agrippa Ionescu" Emergency Clinical Hospital. All patients included in the study gave their consent for the evaluation and signed the informed consent.

The statistical analysis of the significant clinical impact was carried out using the R software belonging to the R Foundation for Statistical Computing, R Core Team (2024), Vienna, Austria [13]. Further analysis by disease groups was performed using Python 3.7.4, using the pandas package [14] for database processing and variable selection, division into patient groups, extraction of descriptive statistics. Kolmogorov-Smirnov was performed to verify that the data are normally distributed, and for the parameters that had normal distribution, the verification of the differences between the groups was done using the Student's t-test and for those without normal distribution the Mann-Whitney test was used. Categorical variables were used to construct contingency tables and frequency differences between different groups were checked using the Fisher exact test. The Kolmogorov-Smirnov, t Student, Mann-Whitney, and Fisher exact tests were calculated using the functions implemented in the SciPy package [15]. In order to evaluate the threshold value of the CMR parameters for the optimal separation between normal and sub-groups of pathologies, a linear logistic regression model was used using the sklearn package [16] and the visualization of the results was made using the Receiver Operating Characteristic (ROC) curves.

Study 1. Contributions and considerations on the impact of cardiac magnetic resonance imaging in the diagnosis and management of patients with non-ischemic cardiomyopathies

Methodologies

Between January 2021 and March 2022, 594 patients underwent CMR examinations in our institutions. Of these, 272 were found to meet the criteria for non-ischemic CMP. These patients were then analysed to determine whether the CMR assessment had a clinically significant impact (ICS).

We considered that the CMR had an ICS in the following situations - according to Abbasi's definition [10]:

1) One patient received a **new diagnosis** that was not suspected or confirmed prior to the MRI assessment (e.g., a patient referred for hypertrophic cardiomyopathy, following the MRI suspicion of cardiac amyloidosis was raised).
2) The evaluation of CMR led to a **change in management** translated into:
    a. Indication/contraindication of invasive procedures such as: ICD/CRTD implantation, coronary angiography, myocardial biopsy, electrophysiological study, cardiac surgery.
    b. Change in current medication: initiation of new treatment (e.g., initiation of anticoagulant treatment in patients found with intracavitary thrombus) or discontinuation of initial medication (e.g., stopping treatment with beta-blockers in those initially considered to have hypertrophic cardiomyopathy and discovered with cardiac amyloidosis).
    c. Admission/discharge from the hospital based on the results highlighted at the CMR evaluation (e.g.: hospitalization of the patient discovered with floating thrombus at the VS level).
    d. The indication is to perform other non-invasive imaging investigations to confirm the underlying pathology (e.g.: evaluation of chest CT in those with suspected cardiac sarcoidosis, genetic testing in those with suspected genetic cardiomyopathy).
3) Patients who presented a new diagnosis and management change were quantified only once as having a significant clinical impact.

Results

Characterization of the study population

In the study group, 179 male patients (66%) were predominantly male, and the mean age was 49 years (±14). The majority had more than two cardiovascular risk factors, 152 (56%) of the patients had hypertension, 138 (51%) had hypercholesterolemia, only 8 (3%) had diabetes, 40 (5%) were active smokers, and 10 (4%) had a positive hereditary collateral history for cardiomyopathy.

Regarding the functional status of heart failure of the patients, most of them, 178 (65%) were classified in NYHA functional class II and only three (1%) had resting cardiac symptoms (NYHA functional class IV).

All patients underwent a complete cardiological clinical examination and transthoracic echocardiography before being referred to the evaluation of CMR, 54 (20%) of them were evaluated coronarographically, and in 2 (1%) of them significant coronary lesions were highlighted, they being included in the analyzed group due to the predominant non-ischemic component of myocardial involvement.

The most common referral indications were for the purpose of evaluation:

1) cardiomiopatiei dilatative (CMD)/ non-dilatative de VS (CNDVS)- 45%
2) hypertrophic cardiomyopathy (HCM) / left ventricular hypertrophy (LVH) - 18%
3) suspected cardiac amyloidosis - 5.2%
4) suspicion of arrhythmogenic right ventricular cardiomyopathy (CAVD) - 4%.

Cardiac magnetic resonance imaging parameters

Regarding cardiac function, the end-diastolic LV volume (VTDVS) was 113 (± 47) ml, the LV ejection fraction (LVEF) was 46% (± 15%), reduced compared to normal, which was expected considering the pathology evaluated, and the RV ejection fraction (LVEF) was 55% (±11%) was within normal limits. The presence of LGE was detected in 177 patients (65%). Of these, 164 patients (92.6%) had non-ischemic scarring, while 13 patients (7%) had ischemic scarring and only one patient had a combination of ischemic and non-ischemic scarring. Most patients had a single scar, 91 patients (51.4%), while 38 patients (21.4%) had two scars, 14 patients (7.3%) had three scars, and 34 patients (20%) had more than three scars.

The final diagnosis after evaluation by cardiac magnetic resonance imaging was the most common CMD in 97 (35.%) of the cases, followed by CNDVS in 57 (21%) of the cases and hypertrophic cardiomyopathy in 29 (10.5%) of the cases - see *Figure 1*.

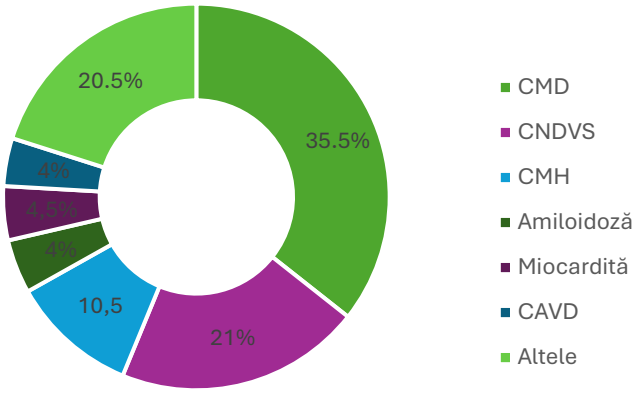

Figure 1 – Final diagnoses following MRI performance:
CMD - dilated cardiomyopathy,
CNDVS - left ventricular non-dilated cardiomyopathy
HCM - hypertrophic cardiomyopathy,
HVS-left ventricular hypertrophy
CAVD - arrhythmogenic cardiomyopathy of the right ventricle

New diagnosis

In **44%** of cases, new diagnoses were discovered based on CMR results. The most common new diagnoses included CNDVS (21% of new diagnoses), CMD (9.6% of new diagnoses), CAVD (6.7% of new diagnoses), myocarditis (5.4% of new diagnoses), SV non-compaction (5% of new diagnoses), SV thrombus (2.4% of new diagnoses), cardiac amyloidosis (2.4% of new diagnoses), cardiac sarcoidosis (1.8% of new diagnoses). Uncommon diagnoses included cardiomyopathy related to muscular dystrophy and chemotherapy-induced cardiomyopathy. It should be noted that in 39 patients who had an apparently normal appearance at the echocardiographic evaluation at CMR, pathological elements were highlighted.

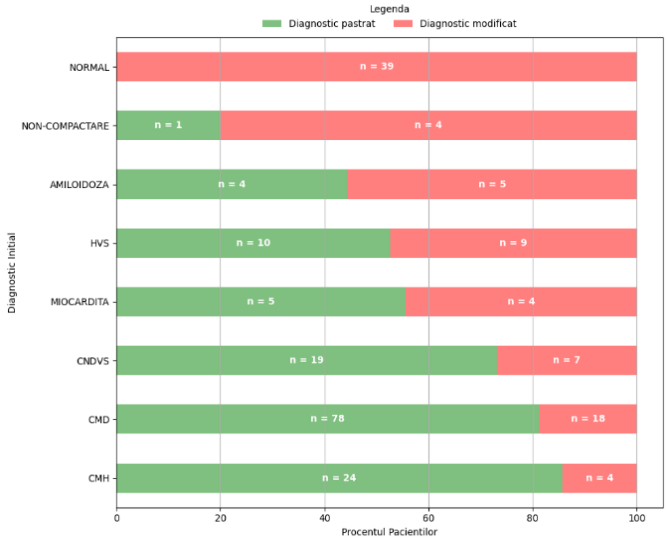

Figure 2. Change of diagnosis after cardiac MRI
CMD- dilated cardiomyopathy
CNDVS- non-dilated cardiomyopathy of the left ventricle
CMH – cardiomiopacity
HVS - left ventricular hypertrophy
CAVD-arrhythmogenic cardiomyopathy of the right ventricle

Change of management

In **47%** of cases, there were changes in patient management, as a result of the findings from the CMR. They directly influenced **the invasive procedures** in 27% of the patients as follows: the decision on ICD/CRTD implantation was influenced in 59 patients (22%), the decision on coronary angiography was modified in 9 patients (3%), the electrophysiological study was recommended in 5 patients (2%). **Therapy modification** was recommended in 40 patients (15%), as follows: initiation of new medication in 38 patients (14%) and discontinuation of cardiac medication in 2 patients (1%). **Hospital admission** was recommended in 2 patients (1%) based on CMR data. And in 10 patients (4%) **other non-invasive investigations** were recommended: e.g. scintigraphy, computed tomography, specific blood tests, such as genetic tests, etc.

Significant clinical impact (SCI)

In about two-thirds of cases, we saw a notable clinical impact, of about 66%, which included a new diagnosis in 44% of cases and a change in management in 47% of cases. A percentage of 25.7% of patients had both a new diagnosis and a change in management. It should be noted that in all patients referred with suspicion of CAVD, an ICS was found after the evaluation of CMR. In contrast, the lowest ICS was observed in the group of patients with initial diagnosis of HCM and CNDVS.

Clinically Significant Impact Analysis

In the univariate analysis, none of the demographic parameters demonstrated an SCI This result was to be expected, given that our study encompasses a wide range of pathologies under the umbrella of cardiomyopathies.

When evaluating the CMR parameters, we found that FEVS, VTDVSi, VTSVSi, FEVD and, in particular, the presence of LGE were predictors of SCI (*Table 1*).

Table 1. Predictors of significant clinical impact

Parameter	All Patients	SCI	Without SCI	p-value*
AGE#	51.5 (22.6-72.0)	52.0 (22.0-72.0)	51.0 (27.5-72.0)	0.763
BSA €	2.00 ±0.30	Select size 1.99 ±0.27	2.01 ±0.31	0.63
SEX				
M	179 (65.8%)	123 (68.0%)	56 (61.5%)	0.3431

Parameter	All Patients	SCI	Without SCI	p-value*
F	93 (34.2%)	58 (32.0%)	35 (38.5%)	
Hypertension	150 (55.1%)	102 (56.4%)	48 (52.7%)	0.6065
Dyslipidemia	139 (51.1%)	96 (53.0%)	43 (47.3%)	0.3721
NYHA Class				
I	29 (11.0%)	19 (11.6%)	(9.9%)	0.8378
II	176 (64.7%)	110 (60.8%)	66 (72.5%)	0.0607
III	34 (12.5%)	27 (14.9%)	7 (7.7%)	0.1193
IV	2 (0.7%)	2 (1.1%)	0 (0.0%)	0.5531
FEVS (%)	46 (15)	50 (12)	44 (16)	<0.001
VTDVSi (ml/m2)	112 (46)	105 (36)	116 (50)	0.039
VTSVSi (ml/m2) €	65 (44)	55 (31)	69 (48)	0.003
VBVSi (ml/m2) €	46 (13)	49 (15)	45 (12)	0.033
VTDVDi (ml/m2) €	84 (27)	84 (24)	84 (28)	0.88
FEVD (%) €	52 (13)	48 (13)	43 (12)	0.002
Early Capture	6 (2.2)	0 (0)	6 (3.4)	0.10
LGE	177 (58)	44 (48)	133 (63)	0.018
T2 (msc) €	49.63 (18.79)	51.70 (31.86)	48.55 (2.97)	0.36
T1 Sept Pre (msc) €	1,031 (55)	1,028 (52)	1,033 (57)	0.50

** Welch Two Sample t-test; Pearson's Chi-squared test, # For age the median value (CI 5-95%) is presented, € as the mean value + SD, the rest of the values are presented as number (percentage). VS - left ventricle, RV - right ventricle, VTD - tele-diastolic volume. VTS – tele-systolic volume, VB- beat volume, EF – ejection fraction, LGE-delayed Gadolinium uptake*

Predictors that had a p-value of less than 0.10 were introduced into a multiple univariate binomial logistic regression; and the analysis showed that, regardless of the presence of LGE, a 1-unit increase in VTSVSi is associated with a 1% increase in the chances of ICS. Also, regardless of the VTSVSi value, the presence of LGE was associated with an increase in the chances of ICS (OR 1.75). (*Table 2*).

Table 2. Univariate and multivariate analysis of ICS predictors

	Univariate Logistics Analysis			Multivariate Logistics Analysis-VIF1		
	HR	95% IC	p	HR	95% IC	p
FEVS	0.97	0.95 - 0.99	0.002			
VTDVSi	1,01	1.00-1.01	0.067			
VTSVSi	1.01	1.00 -1.02	0.012	1.01	1.005-1.02	**0.021**
VBVSi	0.98	0.96-1.00)	0.026			
FEVD	0.97	0.95 - 0.99	0.002			
LGE	1.84	1.11 to 3.07	0.019	1.72	1.03 -2.89	**0.038**

VS – left ventricle, RV – right ventricle, VTD – end-diastolic volume. VTS – telesystolic volume, VB – beat volume, EF – ejection fraction, LGE – Gadoliunium late capture

Discussions

Our study aimed to evaluate the clinically significant impact of CMR in the diagnosis and management of patients with cardiomyopathies. We observed a change between baseline and post-CMR diagnosis in 44% of cases, with a significant clinical impact in 66% of patients. These findings are consistent with previously published data related to the impact of CMR in the assessment of cardiac pathology [11,17-21].

The CMR capacity for tissue characterization makes this investigation a unique tool in evaluating the etiology of cardiomyopathies, but not only, the presence of focal and interstitial fibrosis, as well as myocardial edema are negative prognostic factors illustrated in many studies [8,22-26]. Considering the crucial role of the LGE in diagnostic discrimination, it would be reasonable to emphasize that its presence and appearance have an important impact in establishing the final diagnosis but also in the therapeutic management, a fact also demonstrated in our study [27].

Also, indexed VTSVS and biventricular systolic function were shown to be predictors of clinical impact, in our study, these findings can be attributed to the fact that a large proportion of patients had CMD, and the most significant impact on patient management was observed in decisions related to ICD/CRTD implantation.

Clinical implications

CMR plays a crucial role in the evaluation of patients with PMC, as early intervention on the cause of the underlying pathology (e.g., immunosuppression in cardiac sarcoidosis, iron chelators in hemochromatosis) or implantation of ICDs can improve the prognosis associated with these diseases [28,19]. Based on the data from our study, we recommend that CMR be considered in all patients with suspected non-ischemic PMC, in addition to other specific tests. However, larger multicentre studies are needed to assess the results and cost-effectiveness of this investigation.

Limitations of the study

This study has several limitations that influence the interpretation of its results. Most importantly, it is a retrospective study. We also had no data on treatment and clinical outcomes after CMR assessment. We accept that the evaluation of pre- and post-CMR diagnostic changes constitutes an imperfect surrogate for estimating changes in patient management. Despite this, CMR's unique ability to detect new or alternative etiologies of myocardial disease sets it apart from other imaging modalities.

Study 2. The impact of advanced tissue characterization techniques by cardiac magnetic resonance imaging in the evaluation of cardiac remodeling in patients with non-ischemic cardiomyopathies.

Methodologies

Of the 272 patients with non-ischemic cardiomyopathies previously studied, we excluded 20 patients, 17 did not have optimal advanced tissue characterization images or were not purchased, 2 patients with Fabry and one patient with hemochromatosis, because the T1 time in them is low.

T1 time was assessed at the level of the middle interventricular septum (see *Figure 3A*), excluding focal fibrosis areas

Time 2 was analyzed at the level of the mean interventricular septum or the mean between it and the areas with hypersignal (*Figure 3B*), on the T2 mapping map.

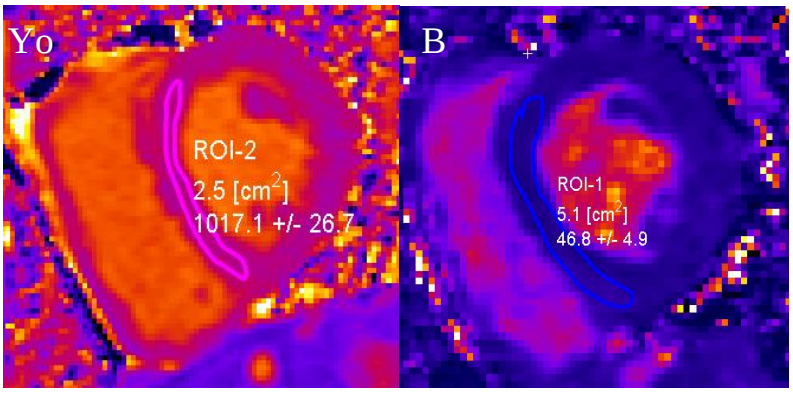

Figure 3. A) T1 mapping-time analysis T1 by placing a region of interest (ROI) at the level of the interventricular septum B)T2 mapping-time analysis T2 by placing an ROI at the level of the interventricular septum.

Results

At the analysis of demographic and clinical correlations, we identified a weak correlation of native T1 and T2 times in relation to age, which aligns with the information in the literature. Regarding gender differences, the native T1 time was higher in women, while the T2 time remained unchanged by gender.

The native T1 time was significantly higher in symptomatic patients compared to asymptomatic patients, and showed a correlation with symptomatology, so patients in NYHA functional class 3 had the highest values (in those in NYHA functional class IV, these images were not purchased, in order to shorten the duration of acquisition). In contrast, T2 time did not show a significant correlation with NYHA functional class, showing similar values between symptomatic and asymptomatic patients.

Related to the parameters of cardiac structure and function, the native T1 time was inversely correlated with FEVS (r=-0.2576, p=0.0001) and FEVD (r=-0.13, p=0.0465). In addition, a directly proportional correlation was observed with the indexed volumes of the SV (VTDVSi, r=0.296, p<0.0001 and VTSVSi, r=0.3378, p<0.0001) and with the indexed mass of the SV (r=0.2183, p=0.0126).

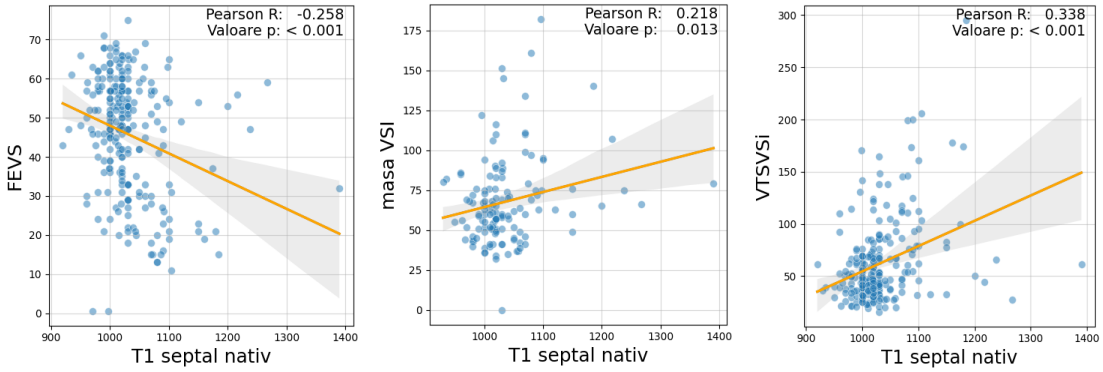

Figure 4 Linear regression analysis and Pearson correlation coefficients for the relationship between native T1 time and FEVS, indexed VS mass, and indexed VTSVS

Importantly, however, the native T1 time, considered an indirect marker for the evaluation of interstitial fibrosis, did not demonstrate a correlation with the presence of focal fibrosis, the values of the native T1 time being similar between those with or without LGE (r=0.0623, p=0.3353). On the other hand, a correlation was found between the native T1 time and the number of focal scars (r=0.3218, p<0.0001). The native T1 time was also correlated with the post-contrast septal T1 time and ECV (this being calculated only in 67 of the patients), normal data considering that they are the parameters derived from it.

In the analysis of the correlation with the parameters of cardiac structure and function, the native T2 time demonstrated a correlation with the presence of focal fibrosis (r=0.1697, p=0.0068) and its quantity (r=0.2949, p<0.0001). It was also correlated with indexed VS

mass (r=0.266, p=0.0024) and also had a weak correlation with VTSVSi (r=0.1291, p=0.0402). Another important, and intuitive, correlation was between the T2 time and the native T1 time, both being the parameters influenced by the amount of water in the myocardium.

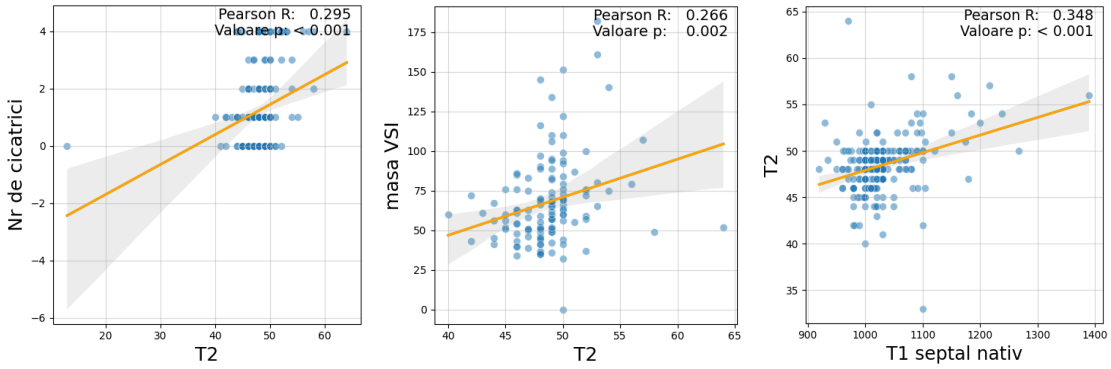

Figure 5. Linear Regression Analysis and Pearson Correlation Coefficients for the Relationship Between T2 Time and Amount of Myocardial Fibrosis, Indexed VS Mass, and Number of Focal Scars

Discussions

Correlations between native T1 time and cardiac structure and function parameters

In this study, we identified several important findings. First, it is the largest cohort evaluated to date by non-ischemic PMCs in which the relationship between native T1 and T2 times with cardiac structure and function parameters as well as with clinical, demographic data has been evaluated.

The significant correlation between native T1 time and VS volume and mass underscores the role of this parameter in the evaluation of structural remodeling of the heart. And the inverse correlation observed between the native T1 time and FEVS highlights the negative impact of interstitial myocardial fibrosis, quantified by T1 time, on the contractile function of the VS. This relationship suggests that as time T1 increases, the VS ability to contract efficiently decreases. Puntmann et al. [30] demonstrated that patients with CMD had significantly higher native T1 times compared to normal ones, and these values correlated with ventricular volumes and inversely proportional to LVEFs. In another study involving patients with AL amyloidosis, T1 time as well as ECV correlated with SV mass and cardiac systolic and diastolic function [31]. At the same time, T1 time was associated with VS remodeling regression in patients with CMD [32].

Myocardial fibrosis is a common feature in cardiovascular pathologies, playing a crucial role in the deterioration of cardiac function, thus the link between T1 time and the amount of focal fibrosis is evident. Multiple studies suggest that T1 time may serve as an indirect indicator of interstitial and focal fibrosis [33-34].

Thus, these findings emphasize the importance of T1 time as a biomarker for assessing myocardial remodeling and disease progression.

Correlations between T2 time and cardiac structure and function parameters.

T2 time, although used in the evaluation of myocardial edema and inflammation, in our study was significantly correlated with VS mass and focal fibrosis. This suggests that an increased T2 time could indicate not only the presence of inflammation, but also an increased risk of disease progression manifested by the onset of focal fibrosis, especially in patients with a higher SV mass. These data raise the question of whether this time only quantifies myocardial edema or can it also be considered a marker of progress of the various myocardial pathologies analyzed in our study. Also, T2 correlated with the native T1 relaxation time, which is logical, because the T2 time increases in myocardial edema, and the amount of water at the myocardial level also modifies the longitudinal T1 relaxation time, causing it to increase.

Limitations of the study

First of all, it is a study with a relatively small cohort, although, to our knowledge, this is the largest cohort studied in this field on a varied batch of non-ischemic cardiomyopathies. However, larger studies are needed to confirm our findings and identify any potential prognostic benefits.

Clinical implications

Given these results, the native T1 and T2 times prove to be valuable parameters in the evaluation of patients with non-ischemic cardiomyopathies. Future research directions could include investigating the impact of treatment on T1 time and the evolution of cardiac function, as well as studying changes in T2 time according to disease stages and evaluating its role in monitoring the condition of patients with PMC.

Study 3. The impact of advanced tissue characterization techniques by cardiac magnetic resonance in the diagnosis of the main non-ischemic cardiomyopathies

Methodologies

From the 272 patients with CMP, we selected the main pathologies analyzed from our group as follows: 97 patients with CMD, 57 patients with CNDVS, 29 patients with CMH, 13 patients with myocarditis and 12 patients with cardiac amyloidosis, which we compared with a control group. The aim was to highlight the diagnostic power of the native T1septal and T2 times in differentiating these diseases from normal. The control group consisted of 50 subjects similar in age and sex to the analyzed group.

Results

The control group was similar in terms of age (48± 9 years) with the main pathologies analyzed: CMD (51 ±13 years), CNDVS (48±14 years), CMH (53±12 years) and cardiac amyloidosis (49 ±13 years). In contrast, the population in the myocarditis group was significantly younger (36±9 years, p=0.0034).

As expected, the VTDVSi was significantly higher among patients with CMD (147.15±50.1ml, p<0.0001) and slightly increased in those with amyloidosis (103.17 ±25.3ml, p=0.0009) compared to VTDVSi in the control group (78.5 ±13.9 ml), the rest of the sub-groups analyzed had VTDVSi values within normal limits. On the other hand, VTSVSi was higher both in patients with CMD (99.99 ±47.55ml, p<0.0001) and cardiac amyloidosis (59.6±24.83ml, p=0.0001), as well as in those with CNDVS (43.13±11.5ml, p<0.0001) and MHC (42.72±22.45ml, p=0.0038), compared to VTSVSi from the control group (30.48±7ml).

Compared to the systolic function VS estimated by FEVS, it was significantly reduced in patients with CMD (33.3±11.6%, p<0.0001) and slightly decreased in those with cardiac amyloidosis (44.8±14.8%, p=0.001), CNDVS (50.4±8.2%, p<0.0001) and CMH (56.06±9.4%, p=0.0042) compared to FEVs in the control group (61.28±5%). And the mean LVEF was significantly lower in the group of patients with CMD (51.39±11.5%, p<0..0001), CNDVS (50.4±8.2%, p<0.0001), amyloidosis (55.3±14.6%, p=0.042) and higher in the group with CMH (65±8%, p=0.0122) compared to the mean LVEF in the control group (60.9±6%).

The indexed SV mass was increased in the group of patients with HCM (84.69 ±37.3g/m2, p<0.001), cardiac amyloidosis (80.1±30.2g/m2, p=0.0004), CMD (77.07 ±3.1g/m2, p<0.001), CNDVS (58.2±2.4g/m2, p=0.0002) and myocarditis (56±8g/m2, p=0.013), compared to the indexed SV mass in the group of normal subjects (43±16.6 g/m2).

The native T1 time compared to that of the control group (1007 ±26.19 msc) was significantly higher among patients with cardiac amyloidosis T1 (1169 ±109.83 msc p<0.0001), CMD (1033 ±45.91 msc, p<0.0001) and CMH (T1 1031±36.16 msc, p=0.003). On the other hand, among patients with CNDVS (T1 1010.15±35.4 msc, p=0.6787) and myocarditis (T1 1010.79 ±35.16 msc, p=0.711), the mean was not significantly higher than the mean in the control group.

On the other hand**, the T2 time** was significantly higher in all 5 groups analyzed: cardiac amyloidosis (52.0±2.661msc, p<0.0001), myocarditis (50.92±5.07msc, p=0.0021), CMD (48.4±3.47msc, p=0.0004), CMH (48.7±2.51msc, p=0.0018) and CNDVS (48.0±2.5msc, p=0.0061) compared to the T2 time in the control group (46.66 ±2.63msc).

Subsequently, in order to be able to comparatively analyze the diagnostic accuracy of the native T1 and T2 myocardial times, in the sub-groups of pathologies analyzed, the ROC analysis was performed and the threshold values for each pathology analyzed were calculated (*Table 3*).

Table 3. ROC analysis of native T1 and T2 times in the studied batch

Disease	Biomarker	Threshold	Youden_j	Sensib. (%)	Specif. (%)
CMD	T2	48	0.348	70.24	64.58
	T1 native	1020	0.405	62.5	78
CNDVS	T2	47	0.28	69.64	58.33
	T1 native	1030	0.125	24.53	88
CMH	T2	48	0,362	77,78	58,43
	T1 native	1010	0,5	82,14	67,82
Amyloidosis	T2	50	0,782	91,67	86,52
	T1 native	1030	0,897	100	89,66
Myocarditis	T2	51	0,462	46,25	100
	T1 native	1020	0,328	50,00	82,76

CMD – dilated cardiomyopathy, CNDVS – non-dilated cardiomyopathy of the left ventricle, CMH – hypertrophic cardiomyopathy.

Discussions

In patients with cardiac amyloidosis, as expected, T1 time values are significantly increased compared to normal values, with a sensitivity of 100% and a specificity of 89.6%, which is supported by previous studies. Interestingly, the T2 time was also greatly increased compared to normal. This result, highlighted in our study, supports the hypothesis that myocardial edema is a significant factor in the evolution of the disease, suggesting that cardiac amyloidosis is not exclusively an infiltrative condition caused by amyloid deposition in the interstitial space [35,36].

Currently, there is little information on T2 time in the context of cardiac amyloidosis [37,38], suggesting that further large-cohort studies are needed to better explore these findings and understand the causes of myocardial edema in these patients.

In our study, we also highlighted that T1 time is significantly increased among patients with CMD and HCM, data that correspond to previous studies [30,40], but T2 time also had a good power to discriminate these pathologies from normal.

On the other hand, T1 mapping in our study had lower efficiency in identifying abnormalities in conditions such as myocarditis. One explanation would be that in some cases of myocarditis only certain segments of the myocardium are affected, so the evaluation of the native T1 time only at the level of the septum is insufficient [6,41]. Of course, another explanation would be the small batch of myocarditis patients analyzed, in order to support this finding.

In fact, in patients with CNDVS we also found that the native T1 time values did not show significant differences from normal This observation was unexpected considering that patients with VS dysfunction, but without dilation, have a long-term prognosis similar to that of patients with CMD [42], suggesting that we should expect a different native T1 time from that of the control population. It is possible that these cases represent early forms of CMD, with the appearance of VS dysfunction before changes in the myocardial interstitial compartment. Another explanation could be the fact that patients with normal systolic function, but with focal fibrosis observed on LGE images, were also included in the cohort with CNDVS, these being usually patients with arrhythmic genetic cardiomyopathies, in which myocardial tissue is often replaced with adipose tissue, which causes a decrease in T1 time values. It should be noted that, although the T1 time was normal, in patients with CNDVS the T2 time was increased compared to normal, supporting the idea of an inflammatory etiology among these patients.

It is important to emphasize that in the groups studied, T2 time was increased in all sub-groups of pathologies analyzed, even in those in which the native septal T1 time was not, which suggests that myocardial edema could represent one of the main mechanisms of cardiac remodeling in the different pathologies analyzed.

Limitations of the study

One limitation is the small number of patients with myocarditis and cardiac amyloidosis to support our findings. And regarding the data on CNDVS, given that this cardiomyopathy is newly introduced in the guidelines and we do not have data in the literature on its tissue characterization by T1 and T2 mapping techniques, we believe that larger studies are needed to confirm these data.

The measurement of T1 and T2 times at the level of the interventricular septum is accepted as an appropriate surrogate for the entire myocardium, but we consider that both sequences require further optimization depending on the pathology evaluated.

Clinical implications

In unconstrained settings, at least one T1 and T2 mapping image is recommended for each CMR protocol for the assessment of suspected cardiomyopathy, due to the minimal additional time required for acquisition [6]. In those with myocarditis and CNDVS, where the changes in the interstitial space are more subtle, in order to be able to objectify them, we recommend an evaluation of the entire myocardium and not just at the level of the interventricular septum, as in our case. On the other hand, in patients with significant structural damage to the heart, manifested by larger ventricular volumes and/or increased myocardial mass, associated with cardiac dysfunction, we consider that the evaluation of the native T1 and T2 times at the level of the septum is sufficient, having a high power of discrimination compared to normal.

STUDY 4. Contributions and considerations regarding cardiac stress perfusion magnetic resonance imaging performed for the first time in a center in Romania

Results

Study population

Between January 2018 and December 2020, 1036 CMR exams were conducted at the Emerald center. Of these, there were 121 examinations of stress CMR in 120 patients (mean age 57 ± 11 years, 79.1% male); one patient underwent stress CMR twice, 1 year apart. Complete data on cardiovascular risk factors were available for 75 patients, and many of them had more than 1 risk factor (mean number of aggregate risk factors=2).

Fifty-one patients (42.5%) had a history of MI while 77 patients (64.16%) were coronarographically assessed prior to the stress CMR test. Invasive evaluation showed normal coronary arteries in 6 patients (7.79%), unicoronary lesion in 23 patients (29.87%), bicoronary lesions in 22 patients (28.57%) and tricoronary lesions in 26 patients (33.76%). Forty-seven patients (39.16%) had a history of coronary artery bypass grafting, 40 (33.3%) with percutaneous intervention, and 7 (5.83%) with coronary artery bypass grafting (5.83%).

Prior non-invasive testing for coronary artery disease was performed in 28 patients (23.33%) prior to stress CMR. The most commonly used non-invasive test was the ECG stress test (20 patients, 16.66%), while some of the patients were assessed by coronary CT angiography, SPECT or stress echocardiography, with a minority of patients being assessed with 2 different non-invasive imaging modalities prior to the CMR stress test.

Clinical indications for cardiac stress magnetic resonance imaging

The clinical indications for stress infusion CMR have been classified into 5 main categories, as follows:

1. Detection of ischemia in patients with a history of myocardial infarction or previous coronary revascularization, 51 patients (42.5%).
2. Detection of the functional significance of intermediate coronary lesions, 37 patients (30.83%).
3. Detection of ischemia in patients with risk factors or atypical chest pain, 36 patients (30%).
4. Detection of ventricular arrhythmia substrate, 5 patients (4.16%).

5. Evaluation of the etiology of dilated cardiomyopathy, 4 patients (3.33%).

General findings of cardiac magnetic resonance imaging

During CMR, 113 patients (94%) were in stable sinus rhythm, while 7 patients (6%) were in atrial fibrillation. Eight patients (6.66%) had extrasystoles during image acquisition. The artifacts were present in 4 examinations (3.33%). In 2 patients the artifacts resulted from ventricular extrasystoles, in 1 patient from motion artifacts, and in 1 patient they were caused by the presence of ICD. Patients with atrial fibrillation had optimal infusion images, without artifacts leading to difficult interpretation. In 34 patients (28.33%), extracardiac findings were reported

The final diagnosis of cardiac magnetic resonance imaging

The most common final diagnosis of CMR was ischaemic cardiomyopathy (51 patients, 42.5%), non-ischemic cardiomyopathy was diagnosed in 8 patients (6.66%), and myocardial ischemia without other structural changes was diagnosed in 3 patients (2.5%). A completely normal CMR assessment was found in 24 patients (20%), while 34 patients (28.33%) had other cardiac abnormalities. In 19 patients (15.83%), CMR contributed to a **major change in diagnosis**, such as: diagnosis of unknown previous myocardial infarction, intraventricular thrombus or myocarditis.

Cardiac Stress MRI Results (Table 4)

Vasodilator stress was adequate in 113 patients (94.16%), while the others did not meet the clinical criteria for maximal vasodilation. It should be noted that in one patient, the clinical criteria of adequate stress were not met, even though the images highlighted the phenomenon of splenic switch-off. In this patient, the test was considered equivocal. During the adenosine infusion, patients experienced the characteristic symptoms but did not experience serious side effects (transient atrioventricular block, myocardial infarction or bronchospasm was not present). A positive stress test was observed in 21 patients (17.5%).

Patients who had a positive stress CMR test were more frequently male, 20 (95.24%, **p=0.0418**) and had a more frequent history of myocardial infarction in the past, 14 patients (66.67%) of those with a positive test compared to 35 patients (36.46%) with a negative test (p=0.0146). Regarding the presence of cardiovascular risk factors and their number, there was no statistically significant difference between the 2 groups.

Most patients positive for stress CMR were referred because they had a history of BCI. Only three of the patients (8.33%) with no history of coronary artery disease had an abnormal stress test.

Table 4 . Characteristics of patients according to the result of stress MRI

		Ischemia Miocardica		P-value
	All patients	**Negative**	**Positive**	
Number	120	96 (71,4%)	21 (18,5%)	
Sex				
M	94 (78,3%)	71 (73,9%)	20 (95,2%)	**0,0418***
F	25 (20,8%)	24 (25,0%)	1 (4.8%)	
Age*	57.21 ± 11.4	56.34 ± 11.3		0,1076
IMC*	28.16 ± 3.6	28.13 ± 3.53		0,4385
IN				
Also	51 (42,50%)	35 (36,46%)	14 (66,67%)	**0,0146 ***
Right away	69 (57,50%)	61 (63,54%)	7 (33,33%)	
Hypertension	53 (70.67%)	64 (67,4%)	17 (83,4%)	0,489
Dyslipidemia	57 (76%)	72(75,4%)	18(84,5%)	0,718
Diabetes	19 (25.33%)	47(49,13%)	11(54,5%)	0,144
Smokers	33 (44%)	48 (44%)	11 (54%)	1
VTDVSi (ml/m2)*	92.68 ± 29.1	86.16 ±29	92.32±29	0,984
VTSVSi (ml/m2)*	41.6±21	41.38 ±19	41.55 ±27.4	0,981
VSi Time (g/m2)*	56.74 ± 15.2	55.8 ±16.7	69.71 ±8.9	**0,004 ***
FEST(%)*	56.87 ± 13.5	61.05 ±13	57.30 ±12	0,817
T1 nativ(msc)*	982.60 ± 151	987.1 ±123	993.3 ±139	0,366
T 2 (msc)*	46.06 ± 2.56	47.0 ±4.4	46.63 ±2.2	0,7055

** are reported as mean ± standard deviation, the rest as number and percentages. VS – left ventricle, RV – right ventricle, VTD – end-diastolic volume. VTS – the telescopic volumeFE – the ejection fraction*

Regarding cardiac function and structure, there were no notable changes between the two groups, only a higher indexed SV mass was noted in the group of patients with a positive stress test (**p=0.004**).

Myocardial scars were detected on LGE sequences in 63 patients (52.5%). Of these, 49 patients (40.83%) had ischemic scars, while 14 patients (11.66%) had non-ischemic scars. Most patients had a single scar (49 patients, 77.77%), while 11 patients (17.46%) had 2 scars and 3 patients (4.76%) had 3 scars. Notably, only 1 patient experienced a combination of

ischemic and non-ischemic scarring. Also, the advanced tissue characterization times native T1 and T2 were not different between the two groups.

Discussions

To our knowledge, this is the first report of a retrospective cohort of patients who underwent stress infusion CMR in Romania [43].

Twenty-one patients (18.58%) in the cohort had an abnormal stress infusion cardiac magnetic resonance imaging test. Most of these patients have already been diagnosed with coronary artery disease. A recent study reported a prevalence of positive stress examinations of 33% in patients with known or suspected coronary artery disease [44] This discrepancy may be due to the fact that we included in the study stress examinations that were performed for other indications, such as detection of arrhythmic substrate or the etiology of dilated cardiomyopathy in patients with a low probability of coronary artery disease.

From the group of patients, 49 patients (40.83%) had ischemic scars, and the concomitant information on viability contributed to the best decision for subsequent myocardial revascularization. In this context, cardiac magnetic resonance imaging is the preferred imaging modality when concomitant information on myocardial ischemia and viability is required [45].

Clinical implications

Non-invasive imaging is increasingly used in our country for the diagnosis of coronary heart disease, coronary CT angiography, stress echocardiography and SPECT being more available than CMR. Given the low availability of MRI scanners, high costs and lack of properly trained personnel, stress CMR is currently rarely performed in Romania, unlike in high-income countries, and this study can be considered a reference point for the future development of this technique in our country.

Stress infusion CMR is generally considered safe, even when performed early after an acute myocardial infarction [46-48]. None of the patients in the cohort experienced serious adverse effects during the adenosine infusion. Patients experienced the usual adenosine-related symptoms, but the symptomatology was not severe enough to discontinue the scan. One patient developed atrial fibrillation during the examination, but immediately returned to sinus rhythm after the examination was completed.

Limitations of the study.

There are several limitations of this study, which inevitably influence the interpretation of the results. Most importantly, this is a retrospective study, conducted in a single center. As the availability of cardiac stress magnetic resonance imaging will increase in our country, a national registry could be compiled and will provide updated information on the performance of this technique throughout the country. There was no follow-up of patients over time, so we could not assess disease progression and the long-term impact of myocardial changes seen through stress CMR.

Final conclusions and personal contributions

Our studies have highlighted the relevance and diagnostic and prognostic impact of cardiac magnetic resonance imaging in the evaluation of myocardial pathology of both non-ischemic and ischemic causes.

To our knowledge, it is the first study that evaluated the clinically significant impact of CMR in the evaluation of non-ischemic cardiomyopathies, with subsequent emphasis on the times of advanced tissue characterization native T1 and T2 in their characterization, as well as their relationship with cardiac structure and function.

Also, the study related to the role of cardiac magnetic resonance imaging in the evaluation of myocardial ischemia represents the first report related to its use in Romania.

a) Conclusions related to the role of cardiac magnetic resonance imaging in the evaluation of non-ischemic cardiomyopathies:

STUDY 1

- We found a change in the initial diagnosis in 44% of the patients with non-ischemic cardiomyopathies evaluated by CMR, and in 47% of them there was a change in management based on the data obtained by CMR.

- Global CMR demonstrated a significant clinical impact in approximately 66% of the non-ischemic cardiomyopathies cases studied, which underlines the importance of this technique in routine clinical practice.

- The presence of LGE, FEVS, FEVD, VTDVi and VTSVSi proved to be predictors of clinical impact among patients with non-ischemic cardiomyopathies analyzed, and VTSVSi and the presence of LGE proved to be independent predictors. These data highlight the importance of these parameters in assessing the complexity and severity of patients with non-ischemic cardiomyopathies.

STUDY 2

- As for the native T1 time, it demonstrated a significant correlation with cardiac function and structure parameters, such as: FEVS, FEVD, indexed VS volumes and indexed VS mass. Also, the native T1 time correlated with the amount of focal fibrosis, but there was no direct correlation with the presence of focal fibrosis.

- Another significant correlation of native T1 time was also with the NYHA functional class of classification of heart failure symptomatology. These resulting data suggest that

native T1 time could be used as a valuable biomarker for stratifying symptomatology and assessing disease severity in patients with non-ischemic cardiomyopathies

- On the other hand, T2 time serving as a marker of myocardial edema showed significant correlations with the presence and amount of focal fibrosis. These data suggest that T2 time is not only a marker of myocardial inflammation, but probably reflects deeper pathological processes, still unelucidated.

- We also observed a significant correlation between the two evaluated times, native T1 and T2, normal data, given that both parameters are sensitive to the amount of water in the myocardium.

STUDY 3

- At a general level, native T1 mapping can clearly differentiate cardiac amyloidosis, dilated cardiomyopathy and hypertrophic cardiomyopathy from normal, data already demonstrated; However, the distinction between non-dilated cardiomyopathy and left ventricular cardiomyopathy and myocarditis from normal was reduced in our study.

- On the other hand, T2 mapping demonstrated a superior power to differentiate all groups of myocardial pathologies analyzed, supporting the hypothesis of a persistent inflammatory process in myocytes, involved in the various forms of myocardial remodeling.

- These data emphasize the importance of monitoring both T1 and T2 times in providing a complete assessment of myocardial pathologies.

b) Conclusions related to the role of cardiac magnetic resonance imaging in the evaluation of myocardial ischemia

STUDY 4

- This is the first report on the use of stress CMR in Romania. Although the technique is not yet widely available in our country, our study has shown that it is feasible and has a very good safety profile.

- Stress CMR not only provides information about the presence of myocardial ischemia, but also about cardiac structure and function, including the presence of interstitial and focal fibrosis. These data are crucial for an accurate diagnosis and risk stratification of patients with ischemic coronary artery disease.

- In the analyzed group, over 95% of the patients with a positive test were men, most of them with a history of myocardial infarction in the past, and, related to cardiovascular risk factors, there were no statistically significant differences between those with a positive test versus a negative test.
- Our experience can encourage other institutions in the country to implement this technique in the routine evaluation of patients with ischemic coronary artery disease, or suspicion, offering not only direct benefits for the patient, but also improving the overall management of ischemic coronary artery disease in Romania.

Final Conclusion

In conclusion, our studies confirm the essential role of cardiac MRI in the evaluation of patients with myocardial pathology and emphasize the importance of integrating this advanced technique into routine clinical practice. This not only improves diagnostic accuracy, but also contributes to improving patients' prognosis through therapeutic interventions better adapted to their needs.

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