

Myocarditis: Whole Heart Involvement Revealed by Cardiac Magnetic Resonance Mapping. A Case-control Study

Tiago Bartzen Pereira,^{1,2} Maurício Balk,³ Gabriela Bartzen Pereira,⁴ Victória Schmidt Ramos,⁵ Luciano Giordani,⁵ Paulo R. Schwartzman,⁵ Luís Beck-da-Silva^{1,2,6}

Programa de Pós-Graduação em Ciências Cardiovasculares, Universidade Federal do Rio Grande do Sul (UFRGS),¹ Porto Alegre, RS – Brazil

Serviço de Cardiologia do Hospital Moinhos de Vento,² Porto Alegre, RS – Brazil

Instituto de Cardiologia de Porto Alegre (ICFUC),³ Porto Alegre, RS – Brazil

Serviço de Medicina Interna, Santa Casa de Misericórdia de Porto Alegre,⁴ Porto Alegre, RS – Brazil

Núcleo de Imagem Cardíaca, Serviço de Radiologia, Hospital Moinhos de Vento,⁵ Porto Alegre, RS – Brazil

Departamento de Medicina Interna da Universidade Federal do Rio Grande do Sul (UFRGS),⁶ Porto Alegre, RS – Brazil

Abstract

Background: Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) only demonstrates regional abnormalities in myocarditis and does not adequately assess diffuse myocardial involvement.

Objectives: To evaluate possible differences in T1 and T2 mapping between ventricular wall segments with and without LGE in patients with myocarditis, compared to control subjects.

Methods: In a case-control design, 22 patients with CMR evidence of myocarditis and 18 controls with normal CMR were assessed. The study included: (1) T1 mapping (shortened modified Look-Locker Inversion recovery); (2) LGE; (3) T2 mapping (steady-state free precession); and (4) the T2 signal intensity of the myocardium divided by that of skeletal muscle (T2 ratio). T1 and T2 mapping of affected (LGE+) and unaffected (LGE-) ventricular segments of cases were compared, as were those of controls versus cases. The level of significance was set at a two-sided alpha level of 0.05.

Results: Comparing only patients with myocarditis, ventricular segments with evidence of late enhancement (LGE+) showed a mean T1 value significantly different from that of unaffected (LGE-) ventricular walls (1057 ± 30 versus 1028 ± 48 ; $p = 0.0001$). Comparing myocarditis versus controls, the mean T1 value of negative LGE segments in cases (myocarditis +) was significantly different from the mean of the corresponding walls in controls (1028 ± 48 versus 996 ± 10 ; $p < 0.0001$). The mean T2 maps of negative LGE walls in cases were not statistically different from those of controls (49 ± 4 versus 49 ± 1 ; $p = 0.9229$).

Conclusions: This case-control study suggests that T1 mapping demonstrates significant involvement of the myocardium of patients with myocarditis, even in the absence of LGE. Specifically, T1 mapping could reveal diffuse myocardial involvement not evidenced by LGE imaging. T2 mapping was noncontributory.

Keywords: Myocarditis, Contrast Media, Magnetic Resonance Imaging.

Introduction

The current incidence of myocarditis is unknown.¹ The epidemiology of this condition is poorly documented, due to the heterogeneity of clinical presentation and challenging diagnosis.

According to the Dallas criteria, myocarditis is defined histologically by the presence of an inflammatory infiltrate in the myocardium, alongside degenerative and/or necrotic

changes in adjacent cardiomyocytes, which differ from the ischemic damage associated with myocardial infarction.² Etiologically, it may be secondary to infectious or noninfectious processes. In developed nations, the leading cause of myocarditis is viral infection, while in developing countries the main causes are rheumatic carditis, Chagas disease, and HIV-related.³

Among several methods available for diagnosis, cardiac magnetic resonance (CMR) is the noninvasive modality best able to characterize the inflamed myocardium, demonstrating edema, necrosis, and fibrosis. The Lake Louise Criteria (LLC) for diagnosis of myocarditis on CMR are based on techniques such as T2-weighted imaging, early gadolinium enhancement, and late gadolinium enhancement (LGE).⁴ However, these CMR sequences have some limitations, such as an inability to identify diffuse fibrosis and the need for paramagnetic contrast. Another

Mailing Address: Luís Beck-da-Silva •

Serviço de Cardiologia – Hospital de Clínicas de Porto Alegre (HCPA) – Rua Ramiro Barcelos, 2350. CEP 90035-003, Porto Alegre, RS – Brazil

E-mail: lbneto@hcpa.edu.br, luibeckdasilva@gmail.com

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CMR method, the T2 ratio, defined as the T2 signal intensity (SI) of the myocardium divided by that of skeletal muscle, has also been losing ground to newer and more objective imaging techniques. These include T1 mapping, contrast-enhanced T1-weighted imaging, characterization of the extracellular volume (ECV) fraction, and T2 mapping, all of which have demonstrated superior diagnostic accuracy compared to the LLC.⁵ Furthermore, T1 and T2 mapping do not require gadolinium contrast,⁶ while contrast-enhanced T1-weighted imaging and ECV mapping do.

Considering advances in imaging modalities and confirming the need for change in diagnostic criteria, a proposed update to the LLC was published in December 2018.⁵

In view of the limitations of the current criteria for CMR diagnosis of myocarditis and given uncertainties surrounding the putative diagnostic superiority of T1 and T2 mapping, as well as the advantage of not requiring gadolinium contrast, we designed this study to test the hypothesis that T1 and T2 map values would be altered both within the myocardial wall segments affected by late gadolinium enhancement (LGE+) and in seemingly unaffected regions (LGE−). Within this context, the objective of the present case-control study was to compare T1 mapping, T2 mapping, and T2 ratio between affected (LGE+) and non-affected (LGE−) wall segments in patients with myocarditis and controls without myocarditis.

Methods

Study population profile

This retrospective case-control study included 22 cases with acute myocarditis (age 34 ± 16 years; 13% female) and 18 controls (age 42 ± 12 years; 16% female). Study participants underwent CMR at Hospital Moinhos de Vento, located in Porto Alegre, Rio Grande do Sul, Brazil, between January 2017 and June 2019. Analysis of CMR reports was performed consecutively, based on the date of the scans.

The criteria for inclusion of cases were presence of mesocardial and/or subepicardial LGE, which is currently the gold standard method, in addition to European Society of Cardiology criteria for clinically suspected myocarditis.⁷ All cases had (a) symptoms of chest and/or abdominal pain, dyspnea, or palpitations; (b) elevation of cardiac troponin I or T levels > 160 pg/mL; and (c) presence of LGE in the expected anatomical region on CMR.

The criteria for inclusion of controls were (a) symptoms of chest pain, dyspnea, or palpitations; (b) normal/unavailable troponin I or troponin T values; and (c) no evidence of edema, necrosis, fibrosis, or ischemia on CMR.

The ratio of controls to cases was 1:1, and they were matched by age and sex. Exclusion criteria were: CMR demonstrating LGE pattern suggestive of other conditions, such as ischemic cardiomyopathy, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, amyloidosis, aortic stenosis, or pulmonary hypertension; and contraindications to CMR.

In all patients, the workup included LGE (132 case wall segments and 108 control wall segments), T1 mapping

(132 case wall segments and 108 control wall segments), T2 mapping (130 case wall segments and 108 control wall segments), and T2 ratio $\geq 2:1$ (20 affected case wall segments and 21 unaffected case wall segments).

Other variables of interest were: reason for CMR; left ventricular ejection fraction; left ventricular dimensions (atrial, diastolic, and systolic) and volumes (end-diastolic volume, end-systolic volume, and stroke volume); anatomic region of fibrosis (subepicardial or mesocardial; walls: anterior, inferior, inferolateral, anterolateral, or septal; and segments: basal, medial, and apical); comorbidities (ischemic heart disease, stroke, diabetes mellitus, hypertension, ventricular/supraventricular arrhythmia, smoking, renal failure, heart failure, neoplasia); presence of symptoms (dyspnea, chest pain/discomfort, palpitations, abdominal pain); troponin levels; and the endomyocardial biopsy.

Ventricular walls were analyzed according to the presence or absence of LGE. The T1 and T2 maps of the affected (LGE+) walls of cases were compared with the T1 and T2 maps of the contralateral unaffected (LGE−) walls of the same patients. In addition, the T1 and T2 maps of the LGE− walls of cases (patients with myocarditis) were compared with the T1 and T2 maps of the same walls in non-myocarditis controls. The mean T1 and T2 values of the LGE+ walls, the mean T1 and T2 values of the LGE− walls of the patients with myocarditis, and the mean T1 and T2 values of controls were compared. Figure 1 shows image analysis among myocardial walls.

For analysis of T1 and T2 maps, the average values obtained in controls were considered the reference range for normality.

Ethical approval was granted for all study procedures. As the study was purely observational, there were no physical or biological risks. There was also no personal contact or contact via telephone or social media with the participants. Data analysis was confidential, and the participants' names, addresses, and other contact information were not disclosed. In view of the foregoing and of the impossibility of accessing the participants' contact information in medical records, pursuant to National Health Council Resolution 466/2012, the institutional Research Ethics Committee waived the usual informed consent requirement. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were used as a guide for case-control studies.

Cardiovascular magnetic resonance

CMR imaging was performed at 1.5 Tesla in a Siemens Healthcare AERA 45 mT scanner, using an 18-channel coil. Briefly, cine images were obtained in three long-axis sections (four-chamber, three-chamber, two-chamber) and in the short-axis plane, from the base to the apex of the heart. Tissue characterization was performed in a mid-ventricular short-axis view of the left ventricle, with T1 and T2 mapping, turbo spin-echo (TSE) T2-weighted, and short tau inversion recovery (STIR) sequences. LGE images were acquired by sectioning the whole heart, in a manner similar to the cine acquisition along the same axis. For T1 mapping, the shortened modified Look-Locker Inversion recovery (ShMOLLI) acquisition method was used before administration of the contrast agent. LGE images

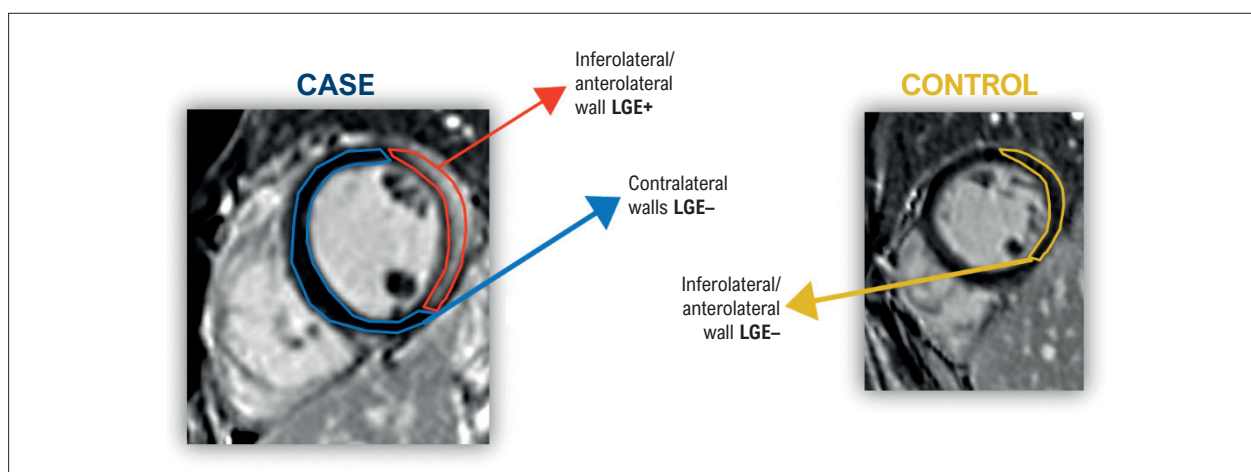


Figure 1 – Image analysis among groups of walls of cases and controls. Designed in MS PowerPoint. LGE: late gadolinium enhancement.

were acquired in the long- and short-axis planes, using a T1-weighted phase-sensitive inversion recovery (PSIR) sequence, 10 minutes after intravenous administration of gadobutrol (Gadovist - Bayer, total 0.20 mmol/kg).

Image analysis

Left ventricular volumes and ejection fraction were analyzed on cine images using Argus software (Siemens Medical Solutions). Short-axis T1 and T2 mapping images, T2 ratio, and LGE were subsequently analyzed. On T2-weighted dark blood images, edema is diagnosed when the T2 ratio is $\geq 2:1$. The ratio was obtained as the T2 SI of the myocardial region of interest (with LGE) divided by the SI of skeletal muscle. T1 and T2 values were obtained from quantitative analysis of all T1 and T2 maps, rather than on visualization of color mapping. When delimiting the endo- and epicardial contours, care was taken to avoid contamination by the ventricular cavity and extra-myocardial structures to minimize the partial volume effect on T1/T2 values of the myocardium. In acute myocarditis, identification of remote myocardium can be challenging, because the inflammatory process is often global; thus, a myocardial region without LGE was chosen to represent the myocardium least affected by the disease process, with care also taken to avoid regions of abnormally low SI. Acute myocardial inflammation was considered when the mean T1 value was > 996 ms and the mean T2 value was > 49 ms. Focal areas of LGE were defined as those with a standard deviation of SI ≥ 2.0 above the mean SI of the remote myocardium. To calculate the extent of myocardial injury detected by tissue characterization techniques, the percentage of abnormal myocardium, as defined above, was determined for each segment and then averaged for that patient.

Assessment of CMR image quality

Each myocardial segment of the left ventricle was rigorously assessed for image quality before inclusion in the final analyses. Only segments with minimal or no

artifacts were included. Three controls were rejected due to artifacts. Four controls were excluded due to unavailability of map data.

Statistical analysis

Data were expressed as mean \pm standard deviation or median (confidence interval). A paired Student's t test for continuous distribution with normal distribution was used to compare the walls. For categorical variables, the chi-square or Fisher's exact tests were used. The significance level was set at 5%. Analyses were carried out in the SPSS 21.0 (SPSS, Chicago, IL) and MedCalc 2020 software environments. Due to the unclear prevalence of myocarditis, sample size calculation was not performed. The initial sampling plan provided for 20 cases of myocarditis; 22 cases were found and ultimately included. This number is consistent with the existing literature.⁸

Results

The most common symptom reported as the reason for suspicion of myocarditis and performance of CMR was chest pain (91%). The included patients had few comorbidities. Almost 70% of cases underwent CMR as hospital inpatients, while 95% of controls were scanned in an outpatient setting. Clinical and anatomic profile of myocarditis cases and controls are expressed in Table 1.

T2 ratio

For analysis of the T2 ratio, values $\geq 2:1$ were considered abnormal.

The mean T2 ratio for LGE+ regions in cases were 2.75 ± 1 , which is indicative of myocardial wall edema.

The mean T2 ratio for LGE- regions in patients with myocarditis was 1.50 ± 0.2 , which represents a normal value for these walls.

Accordingly, comparison of the T2 ratio in affected versus unaffected walls showed a statistically significant difference (2.75 ± 1 versus 1.50 ± 0.2 ; $p < 0.0001$).

Table 1 – Clinical and anatomic profile of myocarditis cases and controls

Characteristic	Myocarditis (n=22)	Controls (n=18)
Mean age – years (SD)	34 (16)	42 (12)
Female sex – n (%)	3 (13)	3 (16)
Race - White – n (%)	22 (100)	18 (100)
Reason to perform CMR – n (%)		
Suspected myocarditis	13 (59)	4 (22)
Normal catheterization	6 (27)	3 (17)
Chest pain	1 (5)	11 (61)
Abnormal troponin	2 (9)	0 (0)
Status at the time of CMR – n (%)		
Inpatient	15 (68)	1 (5)
Outpatient	7 (32)	17 (95)
Comorbidities – n (%)		
Hypertension	4 (18)	2 (11)
Diabetes mellitus	0 (0)	0 (0)
Coronary artery disease	0 (0)	0 (0)
Stroke	0 (0)	0 (0)
Heart failure	0 (0)	0 (0)
Smoker	1 (5)	0 (0)
Other medical history – n (%)		
Arrhythmia	0 (0)	0 (0)
Chronic renal disease	0 (0)	0 (0)
Malignancy	0 (0)	1 (5)
Symptoms – n (%)		
Chest pain	20 (91)	15 (83)
Dyspnea	1 (5)	1 (5)
Palpitation	1 (5)	3 (17)
Abdominal pain	3 (14)	0 (0)
Biopsy – n (%)	1 (5)	0 (0)
hsTroponin, pg/ml, * median (IQR)		
First	820 (369 - 76510)	NA
Second	2800 (431 - 14960)	NA
Third	1306 (399 - 40440)	NA
Fourth	2190 (716 - 9140)	NA
LGE topography – n (%)		
Subepicardium	17 (77)	NA
Mesocardium	19 (86)	NA
Anterior	7 (32)	NA
Inferolateral	21 (95)	NA
Anterolateral	15 (68)	NA
Inferior	7 (32)	NA

Inferoseptal	4 (18)	NA
Anteroseptal	4 (18)	NA
Heart dimensions – mean (SD)		
LVEF, %	51 (6)	65 (6)
Left atrium, mm	31 (8)	34 (10)
LVDD, mm	51 (6)	51 (3)
LVSD, mm	37 (6)	32 (4)
Septum, mm	6 (1)	6 (1)
Inferolateral wall, mm	6 (1)	6 (1)
End-diastolic volume, ml	165 (50)	154 (26)
End-systolic volume, ml	82 (32)	52 (14)
Stroke volume, ml	84 (21)	101 (19)
LVEF by group – n (%)		
< 40%	1 (5)	0 (0)
40-50%	5 (22)	0 (0)
> 50%	16 (73)	18 (100)

hsTroponin: high-sensitivity troponin; LGE: late gadolinium enhancement; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; SD: standard deviation; CMR: cardiac magnetic resonance. *NR < 160 pg/mL.

Late gadolinium enhancement

In patients with myocarditis, LGE+ images were often seen in more than one ventricular wall segment. The most affected region was the inferolateral wall (95%), followed by the lateral wall (68%), anterior wall (32%), inferior wall (32%), and septum (18%). Regarding myocardial injury pattern, mesocardial involvement was most common (86%), followed by the subepicardium (77%). The mean fibrosis mass by quantitative analysis was 12 g (9% of the myocardium). The number of segments affected by LGE was 58 of 132 in cases (44%) and 0 of 108 (0%) in controls.

T1 mapping

On analysis of T1 mapping, values ≥ 996 ms were considered abnormal. By this parameter, the number of affected segments was 111 of 132 (84%) in cases. The LGE+ segments of the cases (patients with myocarditis) showed a mean T1 value significantly different from the LGE– segments of the same patients. On between-group comparison, the mean T1 maps of LGE– ventricular walls in the patients with myocarditis were significantly different from the mean of the corresponding walls in controls. The mean T1 values in each group are given in Table 2.

Observing the most frequently abnormal region in our patient population, the inferolateral wall, the mean T1 value of the affected segment in cases was 1068 ± 47 ms, which is significantly different from all unaffected contralateral segments in these same cases. This change remained significant when we compared all unaffected segments of cases to those of controls. Figure 2 shows a representative image of the inferolateral wall.

Table 2 – Between-group comparison by T1 mapping in affected (LGE+) walls of cases versus all other unaffected (LGE–) walls in these cases and the respective unaffected (LGE–) walls of controls

Affected wall (LGE+)	T1 mapping in cases' affected walls (mean ± SD)	p (a)	T1 mapping in all cases' unaffected walls (LGE–) (mean ± SD)	p (b)	T1 mapping of respective wall in controls (mean ± SD)	p (c)
Anterior (n)	1017 ± 41 (7)*	0.3201	1037 ± 44 (15)**	0.0013	981 ± 47 (18)*	0.0859
Inferolateral (n)	1068 ± 47 (21)*	0.0011	1027 ± 49 (71)**	0.0084	994 ± 38 (18)*	<0.0001
Anterolateral (n)	1075 ± 61 (15)*	0.0168	1032 ± 56 (43)**	0.0284	999 ± 40 (18)*	0.0002
Inferior (n)	1079 ± 31 (7)*	0.0037	1018 ± 45 (15)**	0.5783	1010 ± 36 (18)*	0.0002
Inferoseptal (n)	1059 ± 17 (4)*	0.6912	1074 ± 71 (8)**	0.0038	1001 ± 44 (18)*	0.0191
Anteroseptal (n)	1005 ± 69 (4)*	0.1450	1074 ± 71 (8)**	0.0023	993 ± 48 (18)*	0.6776
General Mean (n)	1057 ± 30 (58)**	0.0001	1028 ± 48 (74)**	<0.0001	996 ± 10 (108)**	<0.0001

a: analysis between T1 mapping in cases by affected wall and T1 mapping in all unaffected walls of the same patients; b: analysis between T1 mapping in all case's unaffected walls and T1 mapping of respective wall in controls; c: analysis between T1 mapping in cases by affected wall and T1 mapping of respective wall in controls. LGE+: presence of late gadolinium enhancement; LGE–: absence of late gadolinium enhancement; SD: standard deviation; n*: number of patients; n** number of walls assessed.

T2 mapping

On analysis of T2 mapping, values ≥ 49 ms were considered abnormal. By this parameter, the number of affected segments was 69 of 130 (53%) in cases. The LGE+ segments of the cases showed a mean T2 value significantly different from the LGE– segments of the same patients. The mean T2 values of LGE– segments among cases were not significantly different from the mean T2 values of controls. The mean T2 values in each group are given in Table 3.

Regarding the inferolateral wall, T2 values again showed a significant difference between abnormal myocardial

segments and unaffected walls in the same patients. Figure 3 shows a representative image of the inferolateral wall, and Figure 4 shows the relationship between different imaging methods.

Discussion

The present case-control study demonstrates that T1 mapping allows a more comprehensive, in-depth assessment of supposedly normal myocardium in patients with CMR-proven myocarditis. Comparison of LGE+ versus LGE– segments in cases and of cases versus controls revealed not only a regional inflammatory process, but also diffuse myocardial involvement.

Although T1 mapping has been progressively used as an adjunctive tool in the diagnosis of myocarditis,⁹ the present study was designed to investigate this method as a means of detecting myocardial involvement in areas of the heart that are considered unaffected by myocarditis when evaluated by LGE alone. Comparatively, we found that even seemingly normal myocardial segments in patients with myocarditis could be compromised by inflammation. A mean T1 value of 1028 ± 48 ms in the unaffected walls of the patients with myocarditis proved to be statistically different from that of controls, which confirms the hypothesis that supposedly unaffected segments were in fact not normal. On the other hand, myocardial edema, as assessed by T2 mapping, showed no difference between the LGE– segments of cases and those of controls. The findings of this study are consistent with the existing literature.¹⁰

The proportion of affected segments in cases was 44% when analyzed by LGE alone and 84% when assessed by

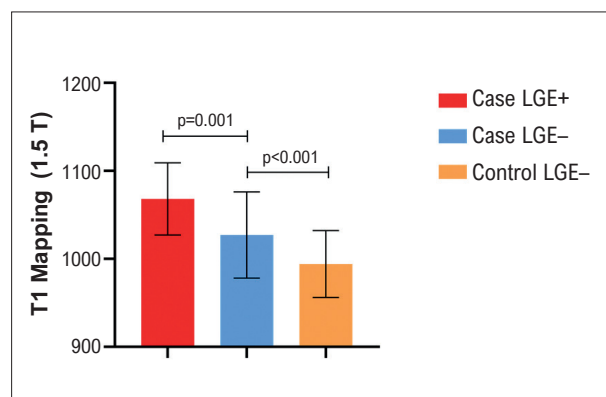


Figure 2 – Inferolateral wall and the intermediate T1 map value of all unaffected walls of cases (blue bar: case LGE–). The T1 values of supposedly normal myocardium actually differed from that of the controls and from that of the affected walls of the same cases. * All $p < 0.05$. Values expressed as means. Designed in GraphPad Prism 9. LGE: late gadolinium enhancement.

Table 3 – Between-group comparison by T2 mapping in affected (LGE+) walls of cases versus all other unaffected (LGE–) walls in these cases and the respective unaffected (LGE–) walls of controls

Wall	T2 mapping in cases' affected walls (LGE+) (mean ± SD)	p (a)	T2 mapping in all cases' unaffected walls (LGE–) (mean ± SD)	p (b)	T2 mapping of respective wall in controls (mean ± SD)	p (c)
Anterior (n)	53 ± 5 (7)*	0.2955	50 ± 5 (15)**	0.7851	49 ± 3 (18)*	0.0803
Inferolateral (n)	52 ± 5 (21)*	0.0062	49 ± 4 (71)**	0.6339	49 ± 4 (18)*	0.0760
Anterolateral (n)	51 ± 5 (15)*	0.2190	49 ± 5 (43)**	0.2245	48 ± 3 (18)*	0.0235
Inferior (n)	49 ± 5 (7)*	0.8068	48 ± 4 (15)**	0.8121	48 ± 4 (18)*	0.6734
Inferoseptal (n)	51 ± 5 (3†)*	0.3317	48 ± 3 (8)**	0.6868	48 ± 3 (18)*	0.1092
Anteroseptal (n)	49 ± 1 (3†)*	0.7519	48 ± 3 (8)**	0.6105	49 ± 3 (18)*	0.9868
General Mean (n)	51 ± 2 (56)**	0.0008	49 ± 4 (74)**	0.9229	49 ± 1 (108)**	<0.0001

a: analysis between T2 mapping in cases by affected wall and T2 mapping in all unaffected walls of the same patients; b: analysis between T2 mapping in all case's unaffected walls and T2 mapping of respective wall in controls; c: analysis between T2 mapping in cases by affected wall and T2 mapping of respective wall in controls. LGE+: presence of late gadolinium enhancement; LGE–: absence of late gadolinium enhancement; SD: standard deviation; n*: number of patients; n** number of walls assessed; †: one wall lost due to image artifact.

T1 mapping. This result was interpreted as demonstrating a significant diffuse involvement of the myocardium, to the extent that almost the entire heart could be considered impaired in our patients with myocarditis.

The contribution of this finding to our knowledge of myocarditis is twofold: a) by enhancing the diagnostic performance of CMR in patients with myocarditis, particularly in borderline or difficult-to-diagnose cases; and b) by introducing a novel concept in the diagnosis of myocarditis which allows objective, numerical, and quantifiable assessment of myocardial involvement, unlike current LGE-based criteria, in which the diagnosis is subjective and operator-dependent. In addition, it should be noted that T1 mapping could obviate the use of gadolinium-based contrast agents, which eliminates the risk of allergic reactions, allows use in patients with renal failure, and reduces cost.

A multicenter observational study showed that T1 and ECV values were strong predictors of poor prognosis in non-ischemic dilated cardiomyopathy.¹¹ Nevertheless, it remains unknown whether this altered myocardium is in itself a predictor of cardiovascular events in myocarditis and other cardiovascular diseases, due to a lack of studies with sufficient follow-up.

The diffuse T1 abnormalities in seemingly unaffected myocardial segments described in our study may have a major prognostic impact in the long term. Taylor et al note that diffuse fibrosis has been identified as an etiological factor in diastolic dysfunction, heart failure, and sudden death.¹²

Regarding T2 mapping, some studies have shown that this method might be able to locate areas involved in

myocarditis with better sensitivity than conventional T2-weighted images alone. In 1.5-Tesla CMR, a cutoff value of > 59 ms demonstrated 94% sensitivity and 97% specificity for identification of affected myocardium.¹³ Using a mean of > 49 ms, our study confirmed a statistically significant difference between cases with affected LGE+ walls and controls (Table 3).

The mean T2 ratio in LGE+ segments was 2.75 ± 1 , which is an abnormal value, whereas, in segments without late gadolinium enhancement (LGE–), this ratio was normal. While T1 mapping was able to demonstrate

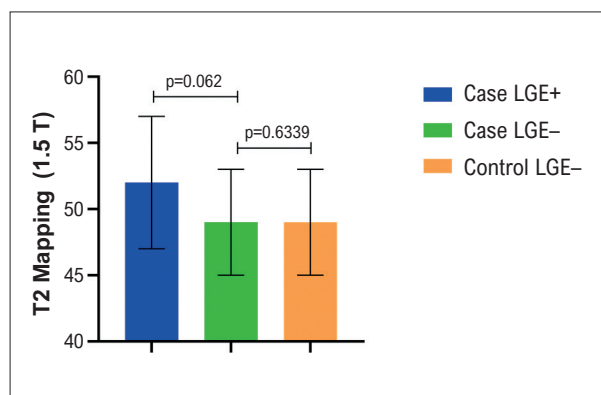


Figure 3 – Analysis of the inferolateral wall by T2 mapping showed significant difference between LGE+ walls of cases (blue bar) and LGE– walls of the same cases (green bar). No significant difference was found compared to LGE– walls of controls (yellow bar). Values expressed as means. Designed in GraphPad Prism 9. LGE: late gadolinium enhancement.

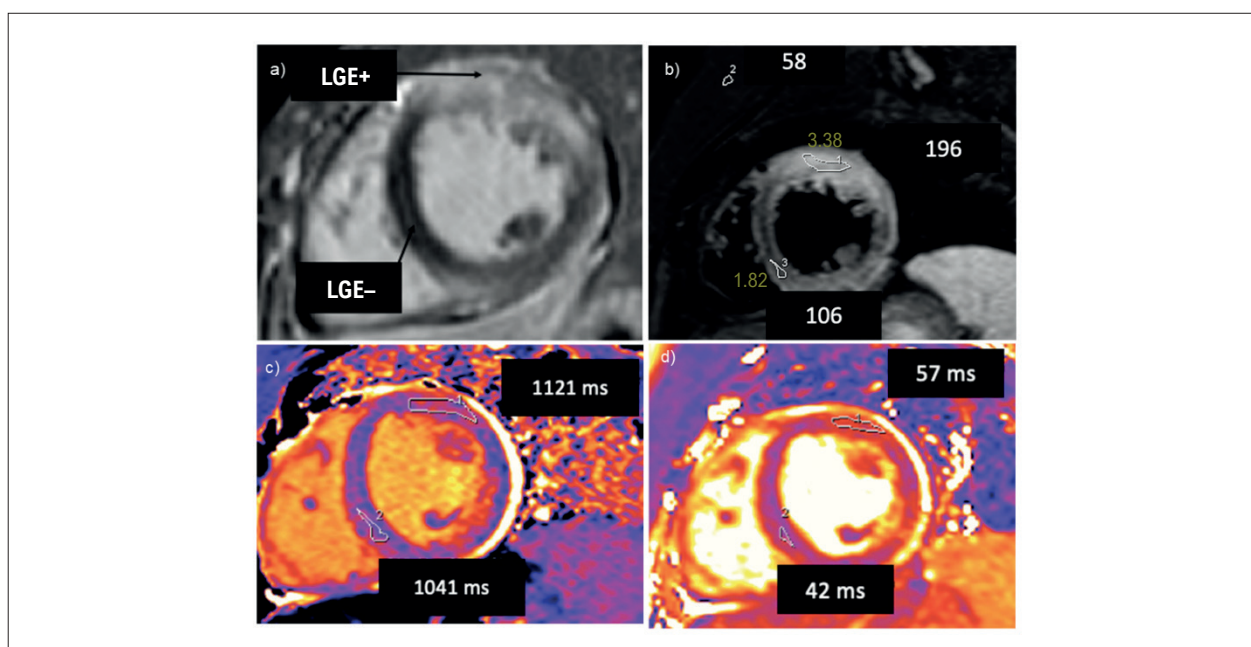


Figure 4 – Relationship between different imaging methods: a) LGE+ in anterolateral wall and LGE– in septum; b) T2 ratio (3.38) shows edema in anterolateral wall and normal value (1.82) in septum; c) Affected T1 map in anterolateral wall (1121 ms) and in the septum (1041 ms); d) Affected T2 map in anterolateral wall (57 ms) and normal in the septum (42 ms). Designed in MS PowerPoint. LGE: late gadolinium enhancement.

that, in addition to a regional inflammatory process, myocarditis is characterized by widespread, diffuse myocardial involvement, the T2 ratio was consistent with the presence or absence of LGE and did not reflect this diffuse inflammation. T2 ratio failed to detect the alterations suggestive of diffuse involvement detected by T1 mapping.

A systematic review assessed the prevalence of abnormal CMR findings in recovered COVID-19 patients. Almost 47% of recovered patients exhibited one or more abnormal CMR findings, which included elevated native T1 or T2 values.¹⁴ Another review that assessed data of 199 patients with the same profile showed that the most common imaging findings were abnormalities in T1 (73%) and T2 mapping (63%) and edema on T2/STIR sequences (51%). LGE was observed in only 43% of cases. Similar to our previous pandemic data with non-COVID-19 patients, this study revealed that new quantitative mapping techniques are essential to detect diffuse myocardial inflammation also associated with COVID-19.¹⁵

Therefore, T1 mapping was the only CMR technique capable of identifying diffuse changes in myocardial tissue, demonstrating abnormalities even in apparently normal ventricular walls.

Considering that the reference values of maps are determined by the value of the controls, and these are related to the characteristics of the patients at the study center and the magnetic resonance imaging device used, we believe that the work has internal validity.

Study limitations

Patients included in this study were selected at the time of CMR and not necessarily at the time of diagnosis with myocarditis. This may have slightly reduced the diagnostic accuracy of CMR, considering that the diffuse changes in the myocardial tissue could be in a healing curve after a few days, and T1 map values may be lower than in the acute phase. However, as our main objective was to compare myocardial segments in the same patients, this limitation may actually have enhanced, rather than jeopardized our analysis.

Although a T1 map has its own normality value according to the center in which it is evaluated, by way of comparison, our mean T1 map was slightly higher than reported in previous studies.^{8,16} This may have reduced the odds of finding significant differences between cases and controls. However, even considering this unexpected finding, we were able to detect a significant difference between the T1 values of controls and the LGE– segments of cases. We thus believe this was a conservative bias. This limitation may also have decreased the statistical significance of the analysis of T2 map values between groups.

Other limitations include the small sample size, the retrospective design, and the absence of endomyocardial biopsy to confirm the imaging findings.

Conclusion

This study suggests that, in patients with myocarditis, even ventricular wall segments with no LGE are abnormal on T1 mapping. The abnormal T1 map values found in

LGE— were intermediate between those of LGE+ walls in cases and those of LGE— walls in controls. Specifically, T1 mapping revealed a diffuse myocardial involvement not evidenced by LGE imaging. This method should be used to demonstrate whole heart involvement in the diagnosis of myocarditis.

Author Contributions

Conception and design of the research and Writing of the manuscript: Pereira TB, Schwartzman PR, Beck-da-Silva L; Acquisition of data: Pereira TB, Balk M, Pereira GB, Ramos SR, Giordani L, Schwartzman PR; Analysis and interpretation of the data: Pereira TB, Balk M, Pereira GB, Ramos SR, Giordani L, Schwartzman PR, Beck-da-Silva L; Statistical analysis: Pereira TB, Beck-da-Silva L; Critical revision of the manuscript for important intellectual content: Schwartzman PR, Beck-da-Silva L.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Moinhos de Vento under the protocol number 3.796.462. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.



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