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Myocardial tissue microstructure with and without stress-induced ischemia assessed by T1 mapping in patients with stable coronary artery disease

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ABSTRACT

Background: Stress-induced myocardial ischemia seems not to be associated with cardiovascular events. However, its effects on myocardial tissue characteristics remain under debate. Thus, we sought to assess whether documented stress-induced ischemia is associated with changes in myocardial microstructure evaluated by magnetic resonance native T1 map and extracellular volume fraction (ECV).

Methods: This is a single-center, analysis of the previously published MASS V Trial. Multivessel patients with a formal indication for myocardial revascularization and with documented stress-induced ischemia were included in this study. Native T1 and ECV values evaluated by cardiac magnetic resonance imaging of ischemic and nonischemic myocardial segments at rest and after stress were compared. Myocardial ischemia was detected by either nuclear scintigraphy or stress magnetic cardiac resonance protocol.

Results: Between May 2012 and March 2014, 326 prospective patients were eligible for isolated CABG or PCI and 219 were included in the MASS V trial. All patients underwent resting cardiac magnetic resonance imaging. Of a total of 840 myocardial segments, 654 were nonischemic segments and 186 were ischemic segments. Native T1 and ECV values of ischemic segments were not significantly different from nonischemic segments, both at rest and after stress induction. In addition, native T1 and ECV values of myocardial segments supplied by vessels with obstructive lesions were similar to those supplied by nonobstructive ones.

Conclusion and relevance: In this study, cardiac magnetic resonance identified similar T1 mapping values between ischemic and nonischemic myocardial segments. This finding suggests integrity and stability of myocardial tissue in the presence of stress-induced ischemia.

1. Introduction

Myocardial ischemia is a complex pathophysiological phenomenon that results from imbalance between oxygen supply and demand.[1,2] Unregulated, prolonged, acute ischemia ultimately causes myocyte edema and conversely irreversible cellular damage, and this can be detected by specific biomarkers release.[2–5] However, transient ischemia commonly presents with no evidence of cellular damage. Thus, myocardial ischemia might engender a wide spectrum of biochemical, structural, and functional myocyte alterations, which depends on the duration, intensity, and time installation of the ischemic insult.[6] In that way, ischemic insult reversibility is directly related to ischemia installation time and cellular membrane integrity. Initial cellular biochemical changes are characterized by Na^+/K^+-ATPase dysfunction, increasing intracellular Na^+ and Cl^-, and myocyte swelling. Also, increased cytosolic Ca^{2+} and mitochondrial impairment leads to progressive membrane permeability and cell disruption.[7] On the other hand, it is not clear whether stress-induced ischemia is related to microstructural tissue changes. Recently, more refined imaging methods have become available to measure the interaction between insult intensity, intracellular oedema, interstitial changes, and ischemia reversibility. T1 mapping, a novel and robust magnetic resonance cardiac technique, which

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quantitatively evaluates the myocardial intra- and extracellular compartments has been recently applied to assess many cardiac diseases.[8–13] It comprises two phases: native T1 map, a precontrast phase that reflects myocyte and the interstitium characteristics, and the extracellular volume fraction (ECV) quantification, which allows the evaluation of diffuse interstitial alterations. From this perspective, T1 mapping might identify possible intracellular and interstitial alterations at rest and during stress ischemia induction in stable coronary artery disease patients (CAD).[14,15]

Therefore, the aim of this study was to evaluate the myocardial characteristics of stable CAD patients with and without stress-induced ischemia identified by myocardial scintigraphy or magnetic resonance and to assess whether ischemia may be associated with changes in native T1 mapping and extracellular volume fraction (ECV) values.

2. Methods

2.1. Study design

The present study is a post-hoc analysis of the Medicine, Angioplasty, or Surgery Study V (MASS-V) Trial. Details of MASS V trial design, protocol, patient selection, and inclusion criteria have been previously published.[16] Briefly, symptomatic patients with stable angina, preserved ejection fraction, with indication of myocardial revascularization, and with angiographically documented proximal multivessel coronary stenosis of >70% by visual assessment were included. Ischemia was documented by stress testing, and angina was evaluated by Canadian Cardiovascular Society (Class II or III) classification. Patients were excluded if they experienced any of previous coronary interventions, recent thromboembolic phenomena, systemic inflammatory disease, or kidney failure (glomerular filtration rate lower than 60 mL/min/1.73m^2). All patients underwent cardiac magnetic resonance (CMR) before revascularization and 7 days after the procedures. For this specific study, preprocedure CMRs were analyzed and patients with documented previous late gadolinium enhancement (LGE) were excluded.

For this study, the patients were evaluated using with two different stress-induced techniques. For most of them, myocardial ischemia was assessed with nuclear stress and the ischemia prone tissue was evaluated at rest by CMR. For the others, myocardial tissue as assessed before and during ischemia induction by CMR-stress protocol as explaneid in further details.

2.2. Stress-induced myocardial scintigraphy

Forty five patients were evaluated by a myocardial stress induced scintigraphy with physical (Bruce protocol) or pharmacological exertion. Myocardial segmentation and qualitative and quantitative ischemia assessment were evaluated according to standard international guidelines.[17,18] Myocardial scintigraphies were evaluated in a joint decision by 2 nuclear radiologists who were blinded to the clinical patient information. Based on the results of the scintigraphy, myocardial segments were classified in ischemic and nonischemic segments.

2.3. Cardiac magnetic resonance

All studies were performed with a 1.5 T MRI scanner (Achieva, Philips Healthcare, Amsterdam, Netherlands). Cine and LGE images were obtained as previously described.[19–23] T1-mapping was performed using an ECG-triggered single-shot Modified Look-Locker Inversion recovery (MOLLI) sequence,[24–26] with employment of 3 inversions with 3,3,5 images obtained in the beats following the inversions and 3 heart beat recovery periods between inversions known as “3(3)3(3)5” sampling pattern. The following parameters were used: slice thickness 10 mm, field of view 300x300mm, ACQ matrix (readout x phase-encodings) 152 × 150, flip angle 40, minimum TI 60 ms, inversion-time increment 150 ms. Three MOLLI left ventricle short-axis images (basal, midventricular, and apical) were acquired prior (native T1 rest), and 15 min after (post contrast T1 rest) an intravenous bolus of 0.2mmoL/kg of body weight of gadolinium-based contrast (DotaremVR, Guerbet Aulnay-Sous-Bois, France). The apex (myocardial segment 17) was excluded as proposed by American Heart Association guidelines.[17]

2.4. Stress cardiac magnetic resonance protocol

Additionally, with the same 1.5 T MRI scanner (Achieva, Philips Healthcare, Amsterdam, Netherlands), 20 patients also underwent a MOLLI LV mid-ventricular short-axis slice (6 myocardial segments) 3 min after dipyridamole (0.56 mg/kg) injection prior to gadolinium-based contrast (native T1 stress) and 2 min after (post contrast T1 stress) contrast injection for stress myocardial perfusion (0.1mmoL/kg/min). Based on the results of the perfusion, myocardial segments were classified as ischemic and nonischemic segments. This protocol is summarized in Supplemental **S1 figure**.

2.5. Imaging analysis

All CMR images were analyzed using CVi42 software (Circle Cardiovascular Imaging Inc., Calgary, Canada). End-systolic and end-diastolic LV volumes, LV mass, and LV ejection fraction were measured by standard methods.[27] For quantification of LGE, we adopted a semiautomatic thresholding technique with a signal intensity cutoff value of mean normal myocardium ±5 SD, which had best agreement with the visual analysis, and it seems to have the best correlation with histopathology.[28]

Myocardial T1 evaluation was performed by two CMR experts in T1 mapping analysis by delimitation of a myocardial region of interest (ROI) obtained by drawing endocardial and epicardial contours, avoiding contamination by blood and extra cardiac structures (global analysis). Measurements were executed in basal and midventricular slices, and the values utilized for statistical analyses were a mean of these two slice positions. Measurements of T1 values were also performed only in myocardial regions free of visually detected LGE (remote analysis). Extremely careful measures were taken to limit the effect of occasional segments with thin wall and trabeculation on T1 map analysis, through meticulous adjustments of ROIs.

T1 (longitudinal relaxation time) estimation was performed by an exponential model, using the signal intensity and time after inversion for each image as previously described.[26,29] Changes in the relaxation rate (R1 = 1/T1) are proportional to the post-contrast concentration of gadolinium in tissue. Through the difference of R1 before and after contrast (ΔR1), it is possible to calculate the partition coefficient (λ), a marker of interstitial contrast loading, and then, with contemporaneous hematocrit, the ECV, as follows[28]: $R1 = 1/T1$; $\Delta R1 = R1_{postcontrast} - R1_{precontrast}$; $\lambda = \Delta R1$ myocardium/$\Delta R1$ blood; $ECV = \lambda\ (1 -$ hematocrit).

The evaluation of segmental contractility, LGE areas, and T1-mapping was performed using the segmentation proposed by the American Heart Association.[17]

2.6. Statistical analysis

Quantitative variables are presented as means and standard deviations (SD) or as medians and interquartile ranges (IQR). Qualitative variables are presented as relative frequencies. Categorical variables were compared using the chi-square test, Fisher exact test, or the likelihood ratio. Quantitative variables were assessed for distribution using the Shapiro–Wilk test. Those with symmetrical distribution were compared using the Student *t*-test, and those with asymmetrical distribution were compared using the Wilcoxon test. Given that there was an interdependence between variables (myocardial segments) and a non-parametrical distribution, with distinct number of ischemic and non-ischemic segments in each group, we performed a linear mixed model

test to compare native T1 and ECV values of ischemic and nonischemic myocardial segments at rest and after stress-induced ischemia using lme4 R package using the command lmer and *P* values were obtained by Satterhwaite's model. Also, the same model with a random intercept was also constructed to quantify native T1 mapping and ECV values of myocardial segments supplied by obstructive coronaries (obstructions greater than or equal to 90% of the lumen vessel) and compare them to myocardial segments supplied by nonobstructive vessels using the same R package. An additional analysis of ischemia degree classified in "Severe/Moderate" when there were >4 myocardial segments with at least moderate ischemia or belonging to two different coronary territories, "Discrete" and "Absent" was performed using Kruskal-Wallis test. The analyses were performed using the statistical package R (version 3.6.2, 12-12-2020; www.R-project.org), and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline clinical characteristics

Between May 2012 and March 2014, 326 prospective patients were eligible for isolated CABG or PCI, and 219 were included in the MASS V trial. The sample selection of this study is illustrated in Fig. 1. For this specific analysis,162 patients were evaluated with preprocedure T1 mapping CMR. Of these, myocardial ischemia was assessed by myocardial scintigraphy in 45 patients and by stress-perfusion CMR in 20 patients. Of a total of 840 myocardial segments, there were 654 nonischemic segments and 186 ischemic segments.

The baseline characteristics of the population are presented in Table 1. The mean (SD) population age was 62 (9) years and 45 (69%) were men. Arterial systemic hypertension and type 2 diabetes mellitus were present in 56 (87%) and 36 (55%) individuals, respectively. Mean baseline LDL levels (SD) were 88.8 (33.0) mg/dL.

Table 1
Baseline characteristics of the study population.

Characteristics	Population (*N* = 65)
Demographic profile	
Age, mean (SD), y	62 (9)
Male, No. (%)	45 (69)
Medical history	
Current or past smoker, No. (%)	18 (29)
Hypertension, No. (%)	56 (87)
Diabetes mellitus, No. (%)	36 (55)
Ejection fraction, mean (SD), %	63 (9.5)
Laboratorial findings	
Creatinine, mean (SD), mg/dL	1.01 (0.21)
LDL, mean (SD), mg/dL	88.8 (33.0)
Angiographic findings	
Double-vessel disease, No. (%)	24 (37)
Triple-vessel disease, No. (%)	41 (63)
Syntax score, (SD)	20.4 (7.44)

Abbreviations: LDL, low-density lipoprotein; SD, standard deviation.

3.2. T1 mapping results at rest of nonischemic and ischemic myocardial segments

Native T1 and ECV results of ischemic and nonischemic myocardial results are shown in Table 2 and illustrated in Fig. 2. No statistical

Table 2
Rest T1 mapping results of nonstress CMR population.

Characteristics	Nonischemic segments (*N* = 584)	Ischemic segments (*N* = 136)	*P* value[a]
Native T1 map, (95%CI), ms	1017.06 (983.70–1042.03)	1012.84 (983.70–1042.0)	0.53
ECV (95%CI)	28.72 (26.91–30.51)	28.30 (25.63–31.07)	0.42

Abbreviations: ECV, extracellular volume fraction; ms, milliseconds, CMR, cardiac magnetic resonance.
[a] Obtained by linear mixed models.

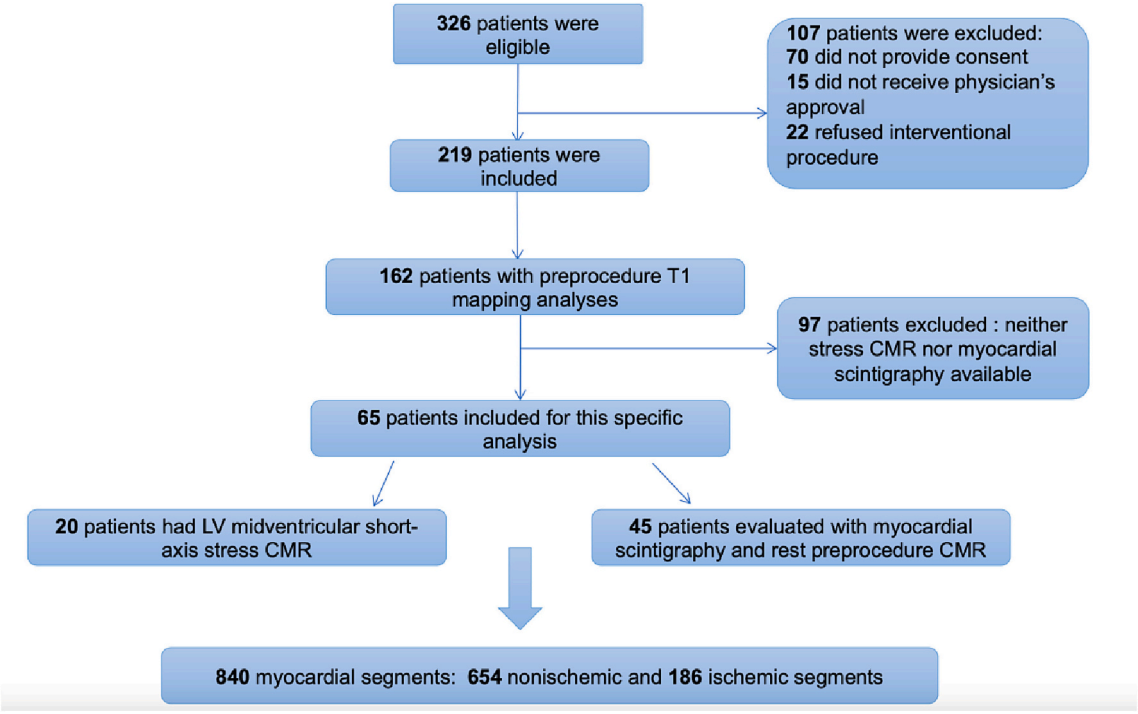

Fig. 1. Patients' enrollment flowchart.
Abbreviations: LV, left ventricle; CMR, cardiac magnetic resonance.

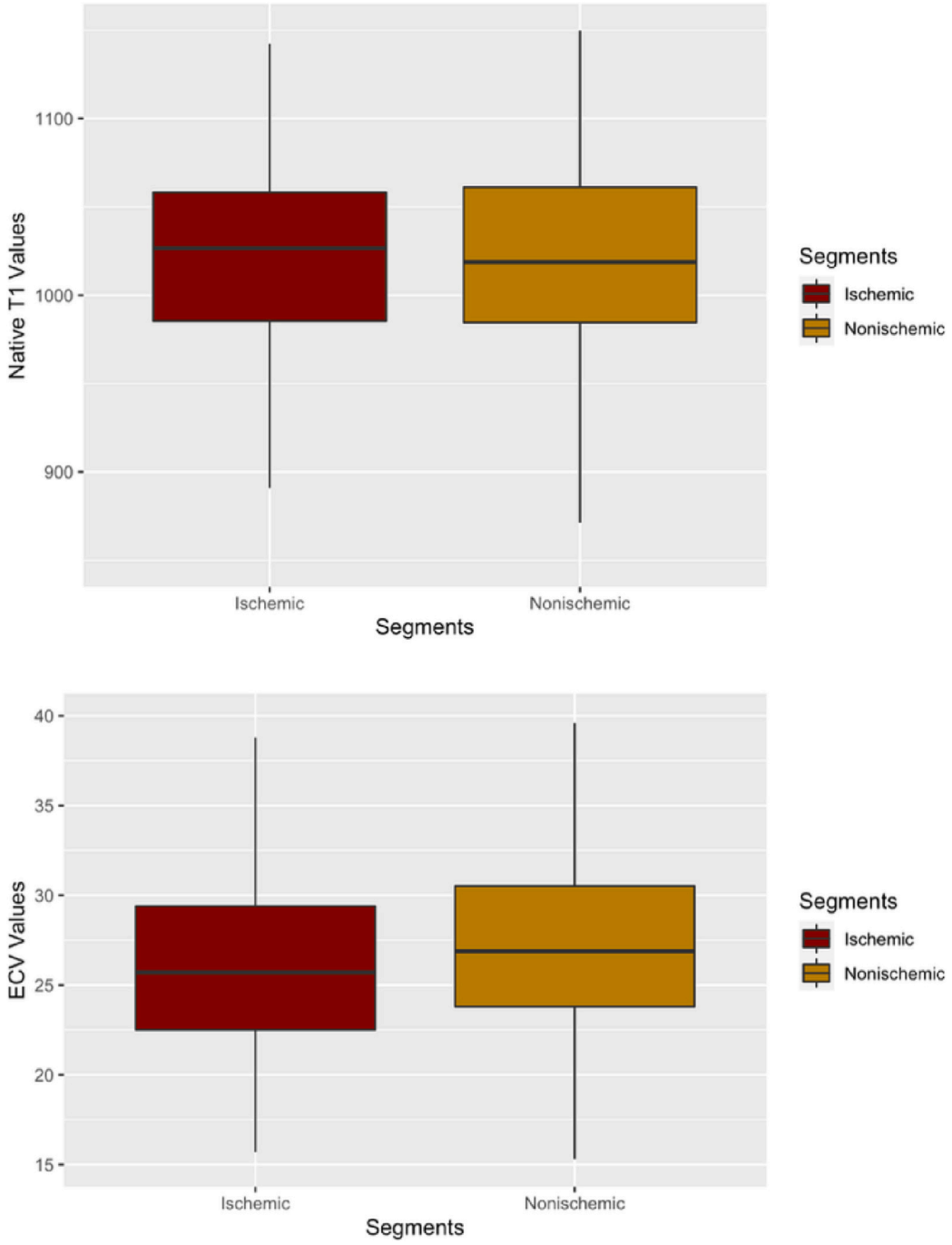

Fig. 2. Native T1 and ECV mean values of ischemic and nonischemic segments at rest.

differences were observed between native T1 and ECV values of non-ischemic (NIS) and ischemic (IS) myocardial segments.

3.3. T1 mapping results of stress CMR protocol group

Native T1 and ECV results of stress IS and NIS myocardial results are depicted in Table 3 and illustrated in Fig. 3. The results show that the presence of ischemia was not associated with significant differences in T1 mapping components in relation to the segments with no ischemia.

T1 mapping component values of predipyridamole and post-dipyridamole of these groups are shown in Table 4. No statistical differences were observed between predipyridamole and postdipyridamole native T1 values of NIS and IS myocardial segments, respectively.

Table 3
Effect of stress-induced ischemia on T1 mapping components in patients who underwent stress-CMR.

Characteristics	Nonischemic segments ($N = 70$)	Ischemic segments ($N = 50$)	P value[a]
Native T1 map, (95%CI) ms	1023.05 (974.42–1067.37)	1038.49 (932.82–1135.56)	0.39
ECV (95%CI)	29.47 (27.06–32.11)	30.93 (25.01–36.97)	0.46

Abbreviations: ECV, extracellular volume fraction; ms, milliseconds, CMR, cardiac magnetic resonance.
[a] Obtained by linear mixed models.

Similarly, the ECV values were also similar, when pre- and

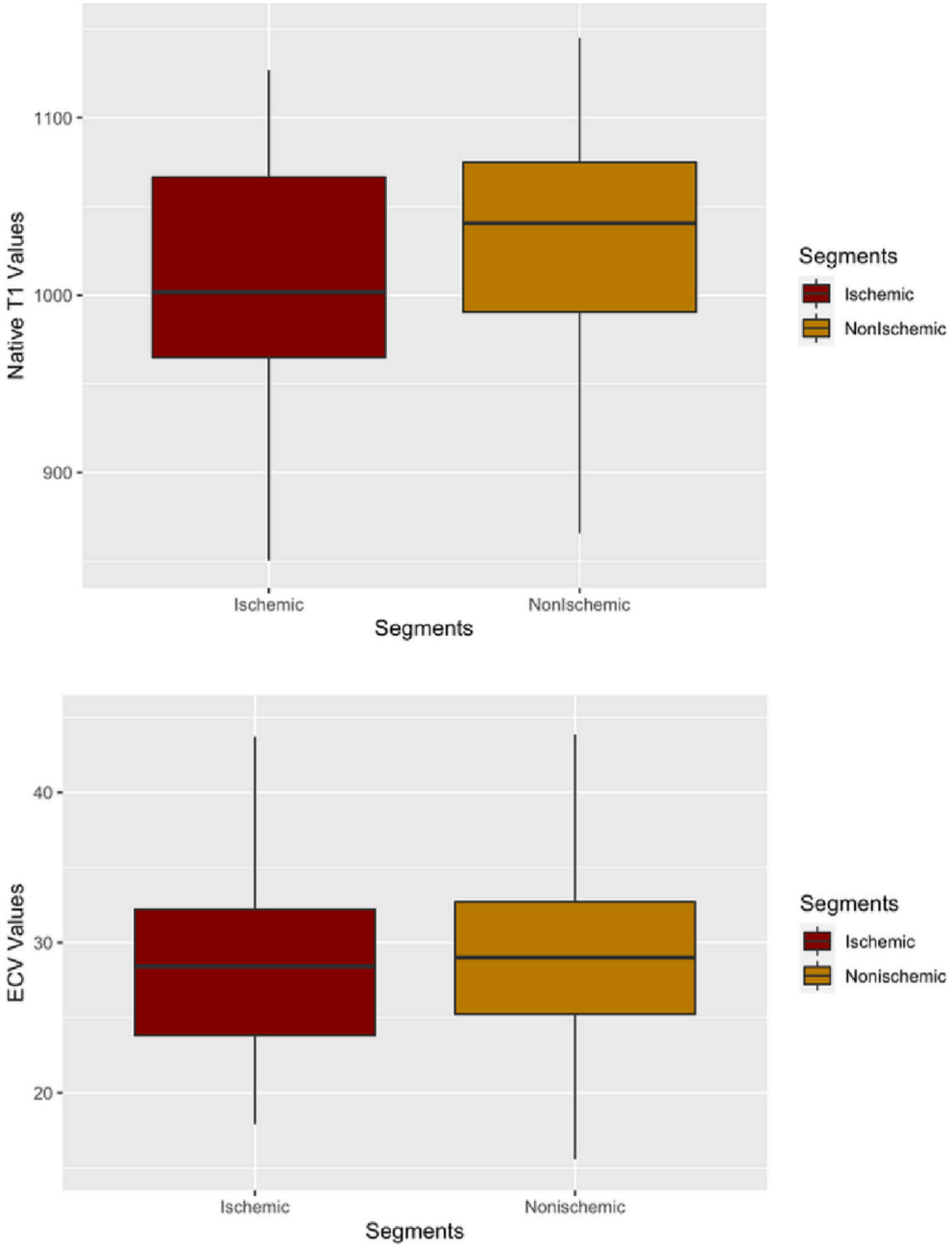

Fig. 3. Native T1 and ECV mean values of ischemic and nonischemic segments evaluated by Stress Magnetic Resonance Protocol.

Table 4
T1 mapping values before and after stress with dipyridamole in patients who underwent stress-CMR.

Characteristics	Nonischemic segments at rest (N = 70)	Ischemic segments at rest (*N* = 50)	*P* value[a]	Non-ischemic segments after stress (N = 70)	Ischemic segments after stress (N = 50)	*P* value[a]
Native T1 map, mean, (SD), ms	1030.20 (113.8)	1043.40 (154.3)	0.78	1040.50 (101.0)	1030.50 (114.5)	0.25
ECV, mean, (SD)	29.19 (5.8)	30.20 (6.7)	0.65	31.34 (7.5)	29.30 (7.9)	0.18

Abbreviations: ECV, extracellular volume fraction; ms, milliseconds; MRI, cardiac magnetic resonance imaging.
[a] Obtained by paired Wilcoxon test.

postdipyridamole NIS and IS were compared.

3.4. T1 mapping results in relation to ischemia degree

Native T1 and ECV results of myocardial segments according to ischemic burden are depicted in Table 5 and illustrated in Fig. 4. The results show that even higher ischemic degree was not associated with significant differences in Native T1 and ECV values compared to mild and absent ischemia.

Table 5
Native T1 and ECV values in relation to ischemia degree.

Characteristics	Severe/ moderate ($N = 137$)	Discrete ($N = 49$)	Absent ($N = 654$)	P value[a]
Native T1 map, (95%CI) ms	1031.7 (972.6–1072.2)	1017.0 (974.4–1055.8)	1021.1 (978.5–1066.0)	0.81
ECV (95%CI)	28.12 (26.4–31.6)	28.9 (25.9–33.4)	29.1 (27.8–32.5)	0.46

Abbreviations: ECV, extracellular volume fraction; ms, milliseconds.
[a] Obtained by Kruskal-Wallis test.

3.5. T1 mapping results of myocardial segments supplied by nonobstructive and obstructive coronaries

The results of native T1 and ECV of myocardial segments supplied by nonobstructive versus obstructive vessels are shown in Supplemental Table 1 and Supplemental Fig. 2. Confirming the previous results, no differences were observed in any of the T1 mapping component values of both groups.

T1 mapping components of a normal population assessed by the same equipment at our cardiology center was previously described[30] with similar values compared to this study.

4. Discussion

A detailed assessment of myocardial tissue characteristics of ischemic and nonischemic segments in patients with stable CAD was performed by native T1 analysis at rest and after stress induction. The results showed similarities between these groups. In this perspective, stress-induced ischemia, regardless of ischemia degree, seems not to alter myocardial structure. Besides, ECV values also did not change in ischemic segments when compared with nonischemic ones. It is already known that ECV elevations might be interpreted as consequence of the loss of membrane permeability control and extracellular matrix expansion. Also, abnormal ECV values resulting from interstitial expansion with a protein component is robustly established.[31,32] Thus, ECV findings also highlight microstructural integrity in this population.

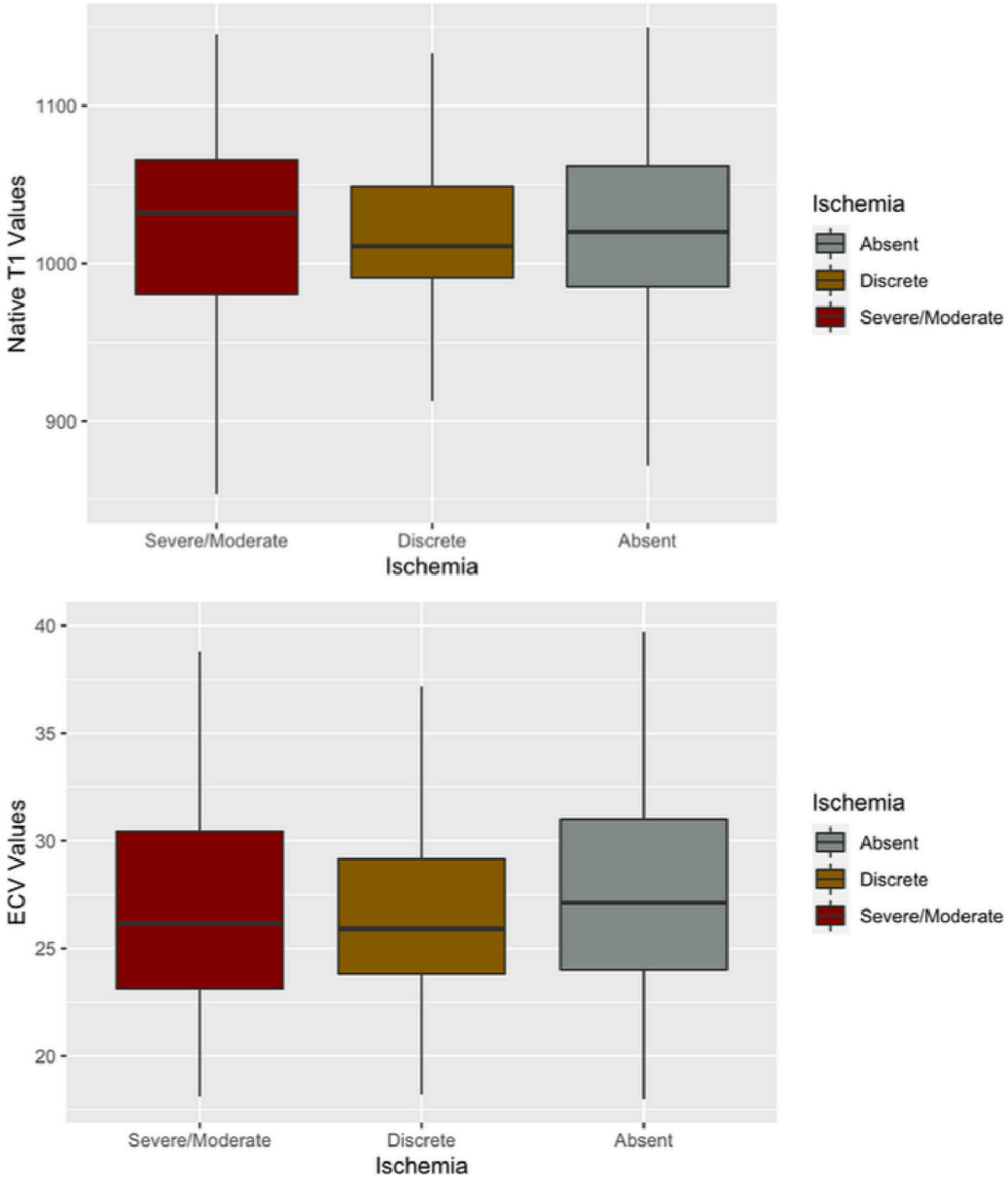

Fig. 4. Native T1 and ECV mean values in relation to ischemia degree.

Moreover, T1 mapping components of myocardial segments supplied by coronary arteries with severe obstructive lesions, (defined as ischemic) compared with the segments supplied by vessels without obstructions, also proved to be similar. All these data allow us to consider that short ischemic insults, even in the presence of electrocardiographic changes, are not capable of causing permanent disturbances in the cell and, therefore, not contributing to the extravasation of cell components into the interstitium without the consequent alteration of the ECV.

All these findings are in line with the established concept that ischemic insults, when intense and lasting, can rupture the cell membrane, leak intracellular material into the interstitium, increasing native T1 and ECV, releasing biomarkers of necrosis, causing the appearance of a new Q wave on the ECG, and late enhancement in CMR.

Moreover, a study carried out at our center[33] with multivessel CAD patients and preserved ejection fraction, revealed the stability of ventricular function after 10 years of follow-up, despite the presence of documented stress-induced ischemia. Furthermore, when the ventricular function of patients with myocardial ischemia was compared with the function of patients in similar conditions but without stress-induced ischemia, they showed no differences. Thus, the findings of this present study using a sophisticated imaging technique corroborates the long-term stability of ventricular function observed in this 10-year follow-up study, even in the presence of stress-induced ischemia over the long term.[34]

Although the comparison of micro and macroscopic parameters has limitations, the stability of chronic myocardial ischemia, in the absence of coronary events, may contribute to the mechanistic knowledge of stress-induced ischemia. In this same direction, the ISCHEMIA Trial,[35] which assessed patients with chronic and stable ischemic heart disease, did not find an association between the magnitude of documented myocardial ischemia and the occurrence of cardiovascular events.

The main message of our study confirms the hypothesis that transient, brief, stress-induced episodes of ischemia do not sufficiently and permanently alter the biochemical and cellular processes of the membrane, and, therefore, the myocyte integrity remains preserved to the point when a vulnerable plaque leads to a dysregulated ischemic insult and rupture of cellular membrane.

The strength of our study lies in the assessment of ischemic and nonischemic myocardial segments with a new and robust CMR technique, in a population with chronic multivessel obstructive CAD, with the evaluation of T1 mapping components at rest and after the induction of ischemia. On the other hand, this study has limitations: This is a unicentric study, with a small sample size, and that may be biased due to the study design and stress-CMR that was not performed in all patients. Besides, it was not possible to consider T1 mapping trend values of maximal/minimum subendocardial ischemic areas in our analysis model.

5. Conclusion

In this study, T1 mapping identified the stability and integrity of the myocardial tissue in the presence of stress-induced ischemia in patients with stable multivessel coronary artery disease.

Declaration of competing interest

All authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinimag.2023.06.004.

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