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ORIGINAL RESEARCH

Changes in Myocardial Native T_1 and T_2 After Exercise Stress

A Noncontrast CMR Pilot Study

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ABSTRACT

OBJECTIVES This study assessed changes in myocardial native T_1 and T_2 values after supine exercise stress in healthy subjects and in patients with suspected ischemia as potential imaging markers of ischemia.

BACKGROUND With emerging data on the long-term retention of gadolinium in the body and brain, there is a need for an alternative noncontrast cardiovascular magnetic resonance (CMR)–based myocardial ischemia assessment.

METHODS Twenty-eight healthy adult subjects and 14 patients with coronary artery disease (CAD) referred for exercise stress and/or rest single-photon emission computed tomography/myocardial perfusion imaging (SPECT/MPI) for evaluation of chest pain were prospectively enrolled. Free-breathing myocardial native T_1 and T_2 mapping were performed before and after supine bicycle exercise stress using a CMR-compatible supine ergometer positioned on the MR table. Differences in $T_{1\ rest}$, $T_{2\ rest}$ and $T_{1\ post\text{-}exercise}$, $T_{2\ post\text{-}exercise}$ values were calculated as T_1 and T_2 reactivity, respectively.

RESULTS The mean exercise intensity was 104 W, with exercise duration of 6 to 12 min. After exercise, native T_1 was increased in healthy subjects ($p < 0.001$). T_1 reactivity, but not T_2 reactivity, correlated with the rate–pressure product as the index of myocardial blood flow during exercise ($r = 0.62$; $p < 0.001$). In patients with CAD, T_1 reactivity was associated with the severity of myocardial perfusion abnormality on SPECT/MPI (normal: 4.9%; quartiles: 3.7% to 6.3%, mild defect: 1.2%, quartiles: 0.08% to 2.5%; moderate defect: 0.45%, quartiles: −0.35% to 1.4%; severe defect: 0.35%, quartiles: −0.44% to 0.8%) and had similar potential as SPECT/MPI to detect significant CAD (>50% diameter stenosis on coronary angiography). The area under the receiver-operating characteristic curve was 0.80 versus 0.72 ($p = 0.40$). The optimum cutoff value of T_1 reactivity for predicting flow-limiting stenosis was 2.5%, with a sensitivity of 83% and a specificity of 92%, a negative predictive value of 96%, a positive predictive value of 71%, and an area under the curve of 0.86.

CONCLUSIONS Free-breathing stress/rest native T_1 mapping, but not T_2 mapping, can detect physiological changes in the myocardium during exercise. Our feasibility study in patients shows the potential of this technique as a method for detecting myocardial ischemia in patients with CAD without using a pharmacological stress agent.
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ABBREVIATIONS AND ACRONYMS

AUC = area under the receiver-operating characteristic

CAD = coronary artery disease

CI = confidence interval

CMR = cardiovascular magnetic resonance

GBCA = gadolinium-based contrast agent

MRPP = maximum rate–pressure product

SPECT/MPI = single-photon emission computed tomography/myocardial perfusion imaging

Cardiovascular magnetic resonance (CMR) myocardial perfusion using a gadolinium-based contrast agent (GBCA) has emerged as a highly sensitive noninvasive imaging technique for evaluation of myocardial ischemia in patients with suspected coronary artery disease (CAD) (1). The noninferiority of CMR was demonstrated in the CE-MARC (Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography for Diagnosis of Coronary Heart Disease) trial, the largest multicenter study that compared CMR perfusion with standard single-photon emission computed tomography/myocardial perfusion imaging (SPECT/MPI) (2). Current CMR perfusion protocols require administration of a GBCA and a stress agent (e.g., dobutamine) or vasodilator (e.g., dipyridamole, adenosine, or regadenoson) (3). However, GBCA drugs are contraindicated in patients with severely reduced renal function, despite the high prevalence of CAD in this patient population (4). Moreover, the prevalence of CAD in patients with end-stage renal disease exceeds 50% and is a major cause of morbidity and mortality (5). Furthermore, over the past few years, there have been emerging data on the long-term retention of GBCA in the brain and other organs, although it has not been directly linked to adverse health effects (6). GBCA retention is related to the number of doses received. Therefore, there is increasing interest in developing noncontrast-based myocardial perfusion imaging techniques.

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There are several techniques for noncontrast-based assessment of myocardial perfusion. Arterial spin labeling has been investigated over the past 2 decades as an alternative technique for CAD assessment (7). Despite its potential, arterial spin labeling has a low signal-to-noise ratio that hampers its clinical adoption (8). Blood oxygen level–dependent imaging has shown potential for assessing myocardial ischemia but has not been used as an alternative to CMR perfusion (9). Yang et al. (10) demonstrated that arterial carbon dioxide has the capability to replace current pharmacological vasodilators. In the presence of blood flow and/or volume changes in the myocardium, myocardial native T_1 and T_2 values can change. Recently, myocardial native T_1 was used to explore changes in myocardial blood volume during vasodilator stress (11–14), which suggested that native T_1 has the potential to detect myocardial ischemia.

Although physiological stress (vs. pharmacological stress) is the preferred stress modality for SPECT/MPI stress testing in patients who can attain adequate levels of exercise, previous CMR studies of myocardial perfusion focused on pharmacological stress (1,2). However, pharmacological stress does not provide data regarding exertional symptoms, hemodynamic responses to exercise, or correlation with electrocardiography and stress imaging findings. Valuable prognostic information concerning exercise duration, chronotropic incompetence, and heart rate recovery are also lacking with pharmacological stress (15). With the availability of CMR-compatible exercise equipment, there is increased interest in CMR perfusion with physiological stress (16). However, technical challenges, such as patient motion and suitable imaging sequences for high heart rate imaging, have made these approaches challenging.

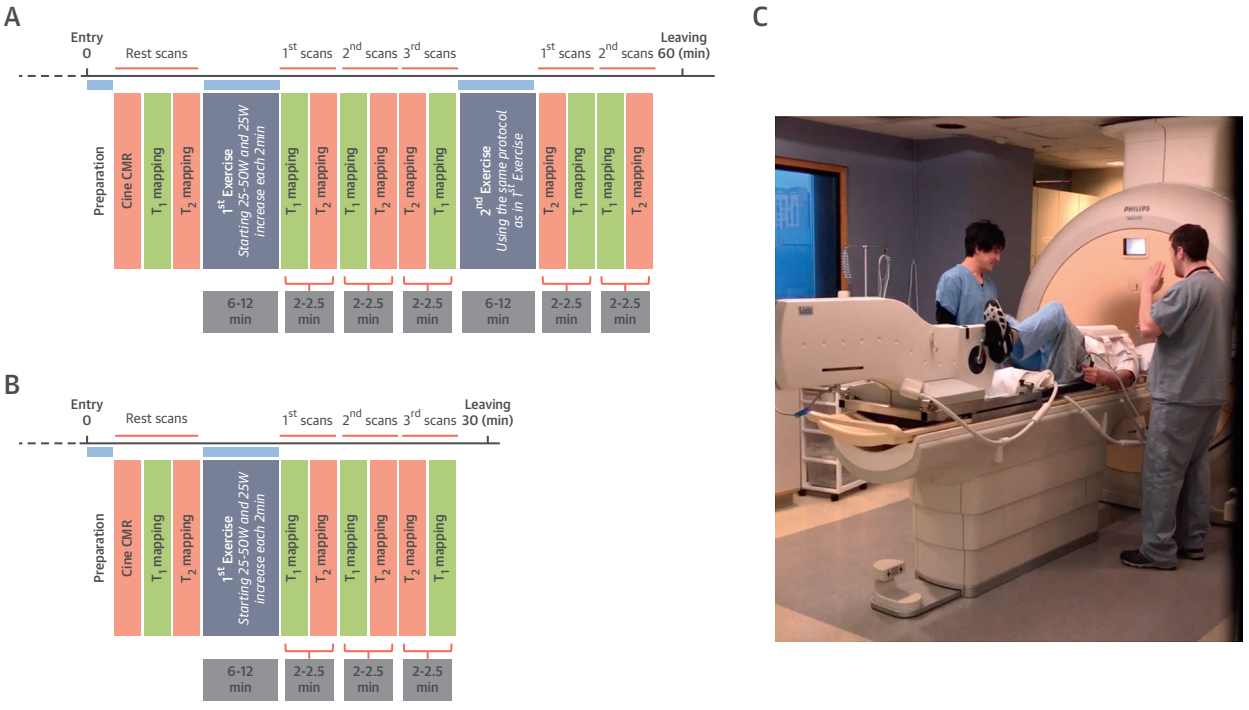
In this study, we sought to assess the feasibility of performing free-breathing stress and/or rest native T_1 and T_2 mapping with an on-table supine bicycle ergometer to detect myocardial physiological changes after exercise. Healthy subjects were imaged to observe temporal changes of myocardial T_1 and T_2 times after exercise. Furthermore, in a proof-of-concept study, we evaluated the usefulness of exercise stress and/or rest native T_1 in a small group of patients with suspected and/or known CAD using the composite reference standard of invasive coronary angiography and exercise stress and/or rest SPECT/MPI.

METHODS

STUDY POPULATION. Twenty-eight healthy adult subjects (age 25 ± 5 years; 6 men) with no history of cardiovascular disease or excessive endurance training were prospectively enrolled. In addition, we studied 14 patients with CAD (age 62 ± 7 years; 12 men) clinically referred for exercise stress and/or rest SPECT/MPI for evaluation of chest pain. Patients underwent exercise stress and/or rest CMR T_1 and T_2 mapping within 60 days of SPECT/MPI with no internal intervention (see the Supplemental Appendix for exclusion criteria). The study protocol was approved by our institutional review board. Written informed consent was obtained from all subjects.

STUDY PROTOCOL. Figure 1A shows the healthy subject protocol. After image localization, subjects underwent rest cine CMR, native T_1 and T_2 mapping, and maximal supine bicycle ergometer exercise followed by 3 successive native T_1 and T_2 mapping scans. To assess reproducibility, healthy subjects also partook in a second exercise followed by 2 successive native T_1 and T_2 mapping scans during the same session. Peak

FIGURE 1 CMR Imaging Protocol



(A) Healthy subject protocol and **(B)** coronary artery disease patient protocol. Native T_1 and T_2 mapping were performed immediately (within 30 s) after physical exercise and acquired 3 times after the first exercise **(A and B)** and twice after the second exercise **(A)**. **(C)** Supine bicycle exercise was performed with a supine bicycle ergometer secured onto the cardiac magnetic resonance (CMR) sliding table such that the subject could exercise without leaving the table.

stress was targeted based on achieving a heart rate of at least 0.85 × (220 − age), with age in years.

Figure 1B shows the CAD patient protocol. Patients with CAD underwent rest cine CMR, native T_1 and T_2 mapping, and maximal exercise followed by 3 successive native T_1 and T_2 mapping scans without additional exercise. Peak stress was targeted based on achieving a similar exercise level to that of the SPECT/MPI stress test.

In both groups, the exercise test was performed with a supine bicycle ergometer (Lode B.V., Groningen, the Netherlands) secured onto the CMR sliding table, such that the subject exercised outside the magnet while on the table (**Figure 1C**), which minimized the time for stress native T_1 and T_2 mapping image acquisition (further details in the Supplemental Appendix). Maximum heart rate–blood pressure product (MRPP) during exercise was calculated as the index of myocardial blood flow during exercise (17).

CMR IMAGE ACQUISITION AND DATA ANALYSIS. All CMR images were acquired on a 1.5-T scanner (Achieva 1.5T, Philips Medical Systems, Best, the Netherlands) equipped with a 32-element cardiac surface coil. The cine image acquisition protocol and data analysis are provided in the Supplemental Appendix. Free-breathing whole heart native T_1 and T_2 mapping were performed using slice-interleaved T_1 and T_2 mapping sequences, which enabled acquisition of 5 slices in the short-axis plane (see the Supplemental Appendix for imaging parameters and data analysis).

For healthy subjects, global native resting T_1 and T_2 times of 16 myocardial segments from 3 slices (basal, midventricular, and apical slice) were measured. T_1 and T_2 relativities to stress were calculated at baseline according to the following formula:

$$\Delta T_1 = \frac{T_{1\,post-exercise} - T_{1\,rest}}{T_{1\,rest}} \times 100(\%)$$

$$\Delta T_2 = \frac{T_{2\,post-exercise} - T_{2\,rest}}{T_{2\,rest}} \times 100(\%)$$

$T_{1,2\ \text{post-exercise}}$ and $T_{1,2\ \text{rest}}$ represent $T_{1,2}$ times shortly after exercise (first scan) and at baseline, respectively. In patients with CAD, individual myocardial segments on native T_1 mapping were assigned to 3 coronary territories (18), and the mean

TABLE 1 Clinical Characteristics

	Healthy Subjects (n = 28)	CAD Patients (n = 14)	p Value
Age (yrs)	25 ± 5	62 ± 7	<0.001
Female	22 (79)	2 (14)	<0.001
Body mass index (kg/m^2)	24.2 ± 3.1	28.7 ± 2.6	<0.001
Coronary risk factor			
Hypertension	0	9 (64)	
Diabetes mellitus	0	2 (14)	
Dyslipidemia	0	12 (86)	
Family history of premature CAD	0	0	
Current smoking	0	4 (29)	
Previous myocardial infarction	0	2 (14)	
Medication			
ACEI/ARB	0	4 (29)	
Beta-blocker	0	11 (79)	
Calcium channel blocker	0	1 (7)	
Long-acting nitrate	0	8 (57)	
Statin	0	14 (100)	
SPECT/MPI			
Myocardial perfusion abnormality	–	11 (79)	
Reversible defect	–	9 (64)	
Fixed defect	–	4 (29)	
Interval between SPECT/MPI and CMR (days)	–	38 ± 20	
Coronary angiography (vessel-based)			
Anatomical CAD (>50%)	–	11/30 (37)	
Anatomical CAD (>70%)	–	5/30 (17)	
Functional CAD (>50%)	–	6/30 (20)	

Values are mean ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; SPECT/MPI = single photon emission computed tomography/myocardial perfusion imaging.

value of all segments for each perfusion territory was used for vessel-based analysis. To evaluate interobserver and intraobserver reproducibility, T_1 reactivity measurements from a random sample of 10 patients with CAD were independently assessed by 2 observers. One observer measured T_1 reactivity twice on 2 separate days with a washout period of at least 2 weeks.

SPECT AND INVASIVE CORONARY X-RAY ANGIOGRAPHY. In all patients with CAD, stress and/or rest SPECT-MPI (using technetium-99m sestamibi) was performed with symptom-limited treadmill exercise stress, according to protocols endorsed by the American Society of Nuclear Cardiology. Results were transferred to a nuclear laboratory for analysis. Using a 16-segment model, 2 experienced observers (board certified in nuclear medicine or nuclear cardiology) scored myocardial segments using a semi-quantitative visual assessment (0: normal; 1: mild reduction in radioisotope; 2: moderate reduction; 3: severe reduction) for rest and stress images, respectively, and reversibility was determined. Any reversible defect was defined as myocardial ischemia, whereas any fixed defect was considered infarcted myocardium. The details of invasive coronary x-ray angiography are provided in the Supplemental Appendix.

STATISTICAL ANALYSIS. Continuous variables of nonrepeated measures were expressed as mean ± SD or median (quartiles) as appropriate and compared using an unpaired Student's *t*-test or a Mann-Whitney *U* nonparametric test if not normally distributed. Categorical variables were reported as counts or percentages and compared using a chi-square test. Repeated-measures data analysis, such as the analyses of serial changes and reproducibility of myocardial native T_1 and T_2 and T_1 reactivity after physical exercise and their relationship to the rate–pressure product, was carried out using linear mixed effects models in which within-subject measurements were modeled using a compound-symmetry, variance-covariance structure. One-way analysis of variance with Bonferroni adjustment was applied to determine significance between multiple comparisons. The Pearson correlation coefficient was calculated to investigate associations between continuous outcome measures. Repeated-measures analysis of covariance using the linear mixed-effects model was conducted to test the equality of regression slopes between normal and remote myocardium. Further details are provided in the Supplemental Appendix.

RESULTS

SUBJECT CHARACTERISTICS. Of the 44 consecutive subjects enrolled in the study, 42 subjects completed the protocol. Two patients with CAD did not complete the full exercise due to baseline hypertension and muscle cramps. Baseline clinical characteristics and supine exercise data are summarized in Tables 1 and 2. Healthy subjects were younger, leaner, and more frequently women ($p < 0.001$ for both). The mean exercise intensity was 104 W with a mean exercise duration of 6 to 12 min. There were no differences in workout duration, maximal exercise intensity, or rate–pressure products between both groups. Exercise caused a 29% increase in systolic blood pressure, a 101% increase in heart rate, and a 157% increase in the rate–pressure product compared with resting values (all $p < 0.001$) in all participants. The first scan acquisition was obtained shortly after exercising at an average heart rate of 108 beats/min. After cessation of the first exercise, recovery led to a 23% decrease in systolic blood pressure, a 38% decrease in heart rate, and a 51% decrease in rate–pressure product (all $p < 0.001$ vs. exercise). Heart rate and rate–pressure product remained higher than resting values (both $p < 0.001$) for both groups throughout the study. Cine data are shown in Table 3.

TABLE 2 Supine Exercise Data and Hemodynamics

	Healthy Subjects (n = 28)	CAD Patients (n = 14)	p Value
Workout time (min)	8.5 ± 1.9	8.0 ± 1.6	0.41
Maximal exercise intensity (W)	106 ± 24	100 ± 20	0.41
Resting heat rate (beats/min)	69 ± 10	64 ± 12	0.16
Resting systolic pressure (mm Hg)	110 ± 12	130 ± 9	<0.001
Resting RPP (beats/min × mm Hg)	7,535 ± 1,295	8,272 ± 1,642	0.12
Maximal heart rate during first exercise (beats/min)	141 ± 17	123 ± 12	0.001
Maximal systolic pressure during first exercise (mm Hg)	140 ± 18	169 ± 17	<0.001
Maximal RPP during first exercise (beats/min × mm Hg)	19,594 ± 2,541	20,757 ± 3,411	0.22
Recovery heart rate (shortly before second exercise) (beats/min)	89 ± 14	73 ± 9	0.001
Recovery systolic pressure (shortly before second exercise) (mm Hg)	109 ± 16	125 ± 9	0.009
Recovery RPP (shortly before second exercise) (beats/min × mm Hg)	9,651 ± 2,033	9,241 ± 1,373	0.60
Maximal heart rate during second exercise (beats/min)	146 ± 15	–	
Maximal systolic pressure during second exercise (mm Hg)	134 ± 19	–	
Maximal RPP during second exercise (beats/min × mm Hg)	19,466 ± 2,987	–	

Values are mean ± SD.
CAD = coronary artery disease; RPP = rate–pressure product.

SERIAL CHANGES OF MYOCARDIAL NATIVE T_1 AND T_2 AFTER PHYSICAL EXERCISE AND THEIR RELATIONSHIP TO RATE-PRESSURE PRODUCT. Figure 2 illustrates representative native T_1 and T_2 map images at rest and post-exercise. Figure 3 shows the mean ± SD of T_1 and T_2 changes in the whole myocardium. Statistically significant differences between baseline and each of the time points were obtained using the linear mixed-effects model estimate of fixed effects. Native T_1 was elevated in all healthy subjects immediately after exercise and tended to decrease by the second scan (2.5 to 3.0min after exercise completion), and returned to baseline by the third scan (4.5 to 5.5 min after exercise completion). There were no differences in T_1 reactivity between basal, mid-ventricular, and apical slices (6.6 ± 2.0% vs. 6.2 ± 1.9% vs. 5.9 ± 2.3%; $p = 0.50$). Similarly, there were no statistical differences between intersegmental T_1 reactivity values ($p = 0.79$). This trend was also observed after the second exercise, which indicated that T_1 could be a surrogate marker for detecting myocardial blood flow. In contrast, T_2 gradually increased and was more pronounced after the second scan.

Figure 4 shows the relationship between native T_1 reactivity and MRPP during exercise. T_1 reactivity after the first and second exercises had similar and moderate correlations with the rate–pressure product, respectively ($r = 0.62$, $p < 0.001$ and $r = 0.60$, $p < 0.001$, respectively). Furthermore, when fitting the linear mixed effects model to test the hypothesis of equal slopes from the 2 exercises, we obtained a p value of 0.57, which indicated that the association between T_1 reactivity and MRPP observed in the first exercise was reproducible in the second exercise. However, T_2 reactivity and stress native T_1 time shortly after exercise were not associated with the MRPP.

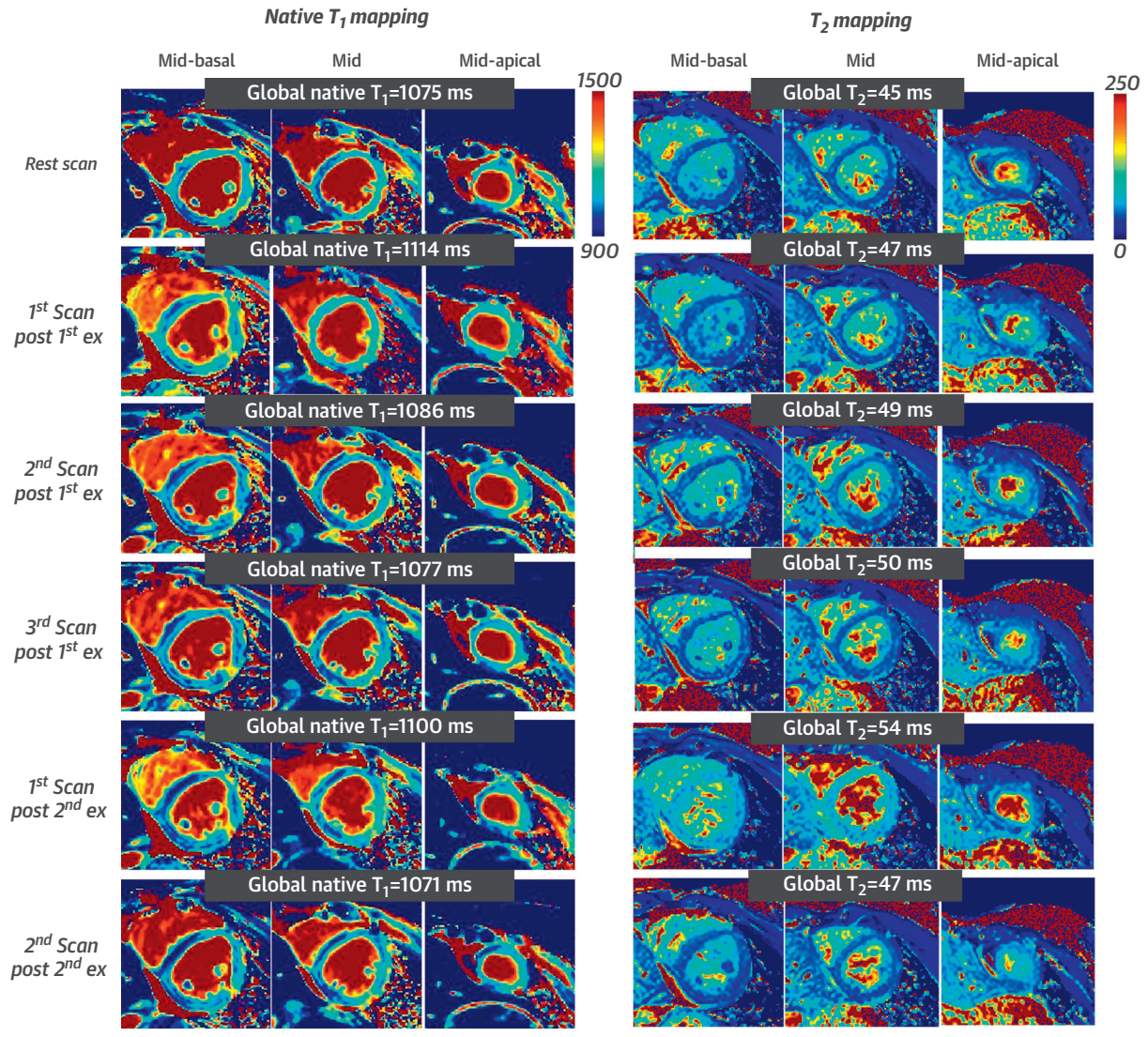
MYOCARDIAL NATIVE T_1 TIME AND REACTIVITY VERSUS SPECT PERFUSION. Among the 14 patients with CAD, SPECT-MPI demonstrated that 50 (22%) of 224 segments had perfusion abnormalities (34 segments had reversible ischemia; 16 had fixed perfusion defects). Of the 19 (45%) vascular territories with perfusion abnormalities, 14 were reversible (11 partially reversible; 5 fixed). In the native T_1 analysis of the whole myocardium, 16 of 224 myocardial segments (7%) were excluded due to poor image quality from cardiac or respiratory motion. Myocardial segments with SPECT-MPI perfusion abnormalities had lower T_1 reactivity values (0.59%; quartiles: −0.17% to 1.5% vs. 4.9%; quartiles: 3.7% to 6.3%; $p < 0.05$) and

TABLE 3 Cine CMR Parameters

	Healthy Volunteers (n = 28)	CAD Patients (n = 14)	p Value
LV end-diastolic volume (ml)	134.5 ± 26.4	159.1 ± 31.0	0.01
LV end-diastolic volume index (ml/m^2)	74.6 ± 11.9	79.9 ± 11.9	0.18
LV end-systolic volume (ml)	51.8 ± 16.1	69.7 ± 25.7	0.008
LV end-systolic volume index (ml/m^2)	60.2 ± 32.9	49.7 ± 25.9	0.27
LV ejection fraction (%)	61.9 ± 5.6	57.4 ± 9.1	0.11
LV mass (g)	80.7 ± 23.5	109.4 ± 34.6	0.003
LV mass index (g/m^2)	45.0 ± 10.7	54.8 ± 15.5	0.02
RV end-diastolic volume (ml)	137.3 ± 35.6	139.9 ± 21.1	0.76
RV end-diastolic volume index (ml/m^2)	75.7 ± 15.1	71.0 ± 12.8	0.33
RV end-systolic volume (ml)	59.1 ± 23.1	55.6 ± 15.1	0.62
RV ejection fraction (%)	59.1 ± 8.0	60.8 ± 5.9	0.51

Values are mean ± SD.
LV = left ventricular; RV = right ventricular; other abbreviations as in Table 1.

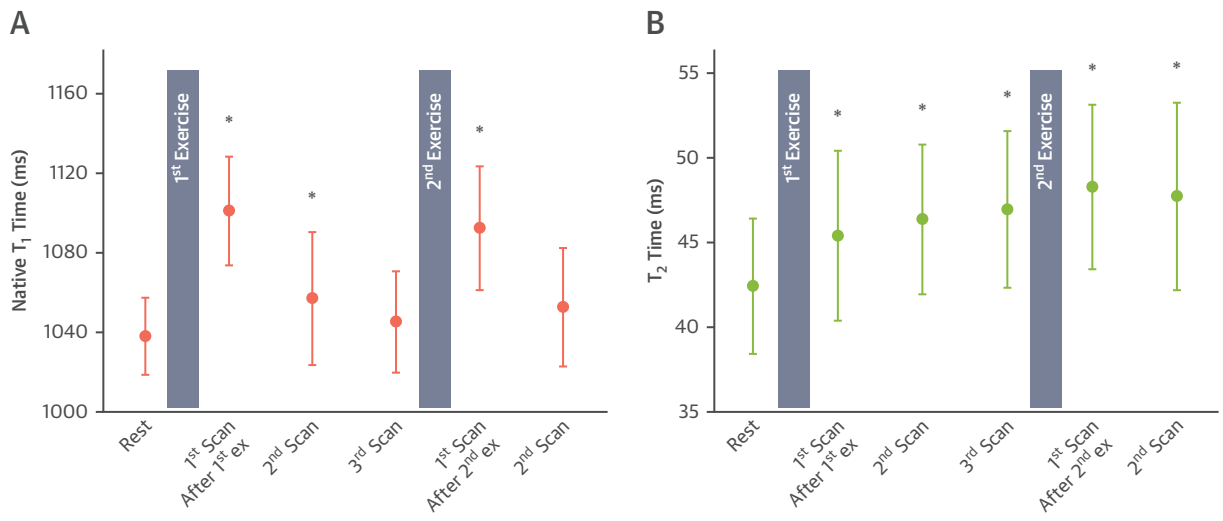
FIGURE 2 **Representative Native T_1 and T_2 Mapping Images of 3 Short-Axis Slices at Rest and After Exercise**



The mean native T_1 in the septal myocardium increased shortly after both first and second exercises, and decreased at the second scan after exercise. T_2 time in the septal myocardium gradually increased and was more pronounced after the second scan.

higher rest native T_1 times (1,090 ms; quartiles: 1,061 to 1,158 ms vs. 1,055 ms; quartiles: 1,030 to 1,078 ms; $p < 0.05$) than myocardial segments with normal SPECT/MPI perfusion. Immediate post-stress native T_1 times were similar in both abnormal and normal myocardium (1,098 ms; quartiles: 1,066 to 1,179 ms vs. 1,103 ms; quartiles: 1,084 to 1,126 ms; $p = 0.80$). T_1 reactivity values (rather than rest and stress T_1 times) were more likely to be associated with severity of myocardial perfusion abnormality on SPECT/MPI (normal: 4.9% [quartiles: 3.7% to 6.3%]; mild defect: 1.2% [quartiles: 0.08% to 2.5%]; moderate defect: 0.45% [quartiles: −0.35% to 1.4%]; severe defect: 0.35% [quartiles: −0.44% to 0.8%]; normal vs. mild defect, $p < 0.001$; mild vs. moderate and severe defect, $p = 0.06$, respectively) (Figures 5A to 5C). Meanwhile, there were no differences in T_1 reactivity between myocardium with reversible and fixed defects. Rest native T_1 was a better surrogate marker for differentiating between myocardium with reversible defects and myocardium with normal perfusion and fixed defects (Figures 5D to 5F). Figure 6 shows representative cases from normal and infarcted myocardium.

FIGURE 3 Serial Changes of Native T_1 and T_2 After Physical Exercise

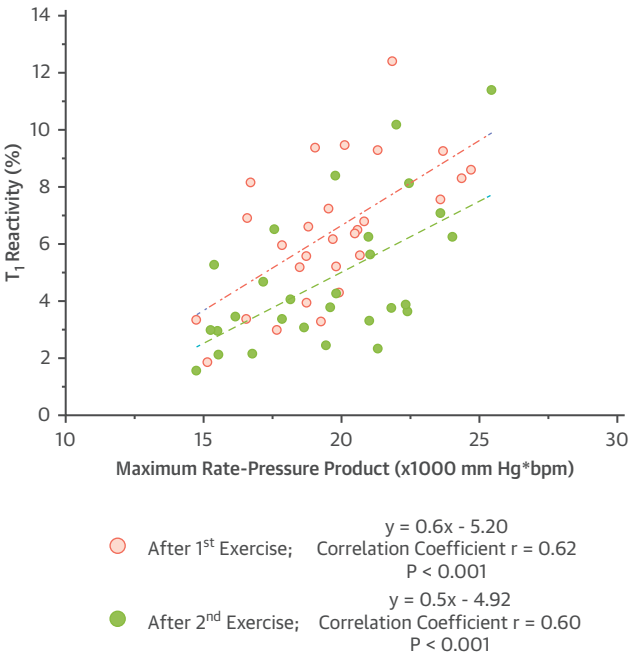


(A) Healthy subject septal native T_1 was significantly elevated immediately after the first (approximately 30 s after exercise completion) and second exercises (approximately 30 s after exercise completion). **(B)** The increase in T_2 was significantly more pronounced after the second scan.

RELATIONSHIP BETWEEN MYOCARDIAL T_1 REACTIVITY AND MRPP IN THE WHOLE POPULATION. Figure 7 shows the analysis using the linear mixed-effects model of T_1 reactivity plotted against the MRPP obtained from the normal myocardium of healthy subjects and the remote, ischemic, and infarcted myocardium of patients with CAD in a vessel-based analysis. In normal and remote myocardium, the T_1 reactivity moderately and positively correlates with the MRPP (normal myocardium group: $r = 0.62$, $p < 0.001$; remote myocardium group: $r = 0.51$, $p = 0.01$). However, the line for the remote myocardium group lies significantly below that of the normal myocardium group ($p = 0.014$), indicating that the remote myocardium in patients with CAD has lower T_1 reactivity for an equivalent MRPP. In contrast, there is no correlation between T_1 reactivity and MRPP, and T_1 reactivity remains lower, despite the increases in MRPP in the ischemic or infarcted myocardium. Even after adjusting for MRPP, differences in T_1 reactivity among normal, remote, ischemic, and infarcted myocardium remained statistically significant ($p = 0.003$).

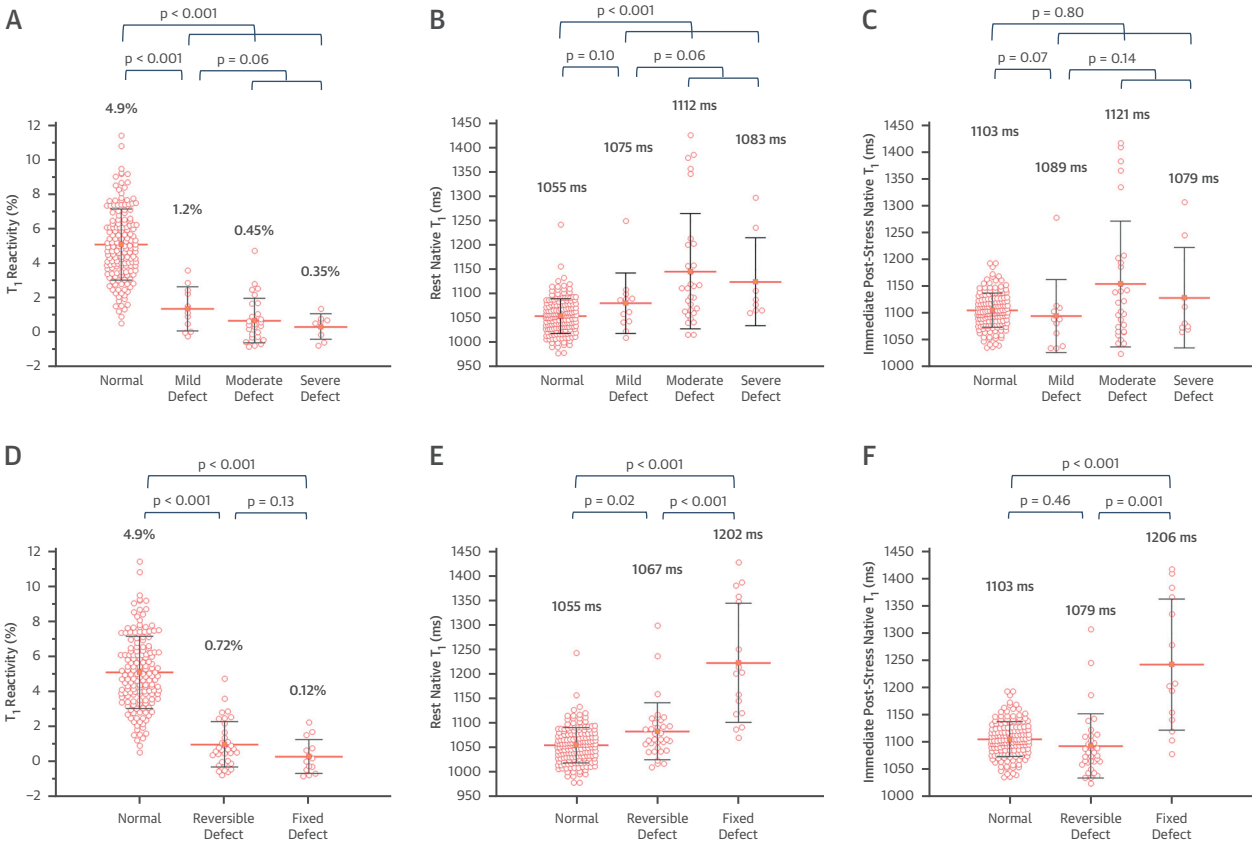
DIAGNOSTIC PERFORMANCE OF STRESS/REST MYOCARDIAL T_1 MAPPING. Figure 8 shows representative cases with varying severities of myocardial ischemia. The accuracy of stress and/or rest T_1 mapping for detecting significant coronary artery stenosis (>50%) on coronary angiography provided a

FIGURE 4 Correlation Between T_1 Reactivity and MRPP



T_1 reactivity after the first exercise and second exercise similarly and moderately correlated with the rate–pressure product. Testing of the equality of the2 slopes from the linear mixed-effects model yielded a p value of 0.57, which indicated good reproducibility of the association between maximum rate–pressure product (MRPP) and T_1 reactivity. bpm = beats per minute.

FIGURE 5 Relationship Between Regional Native T_1 Parameters and Myocardial Perfusion Abnormality on SPECT/MPI



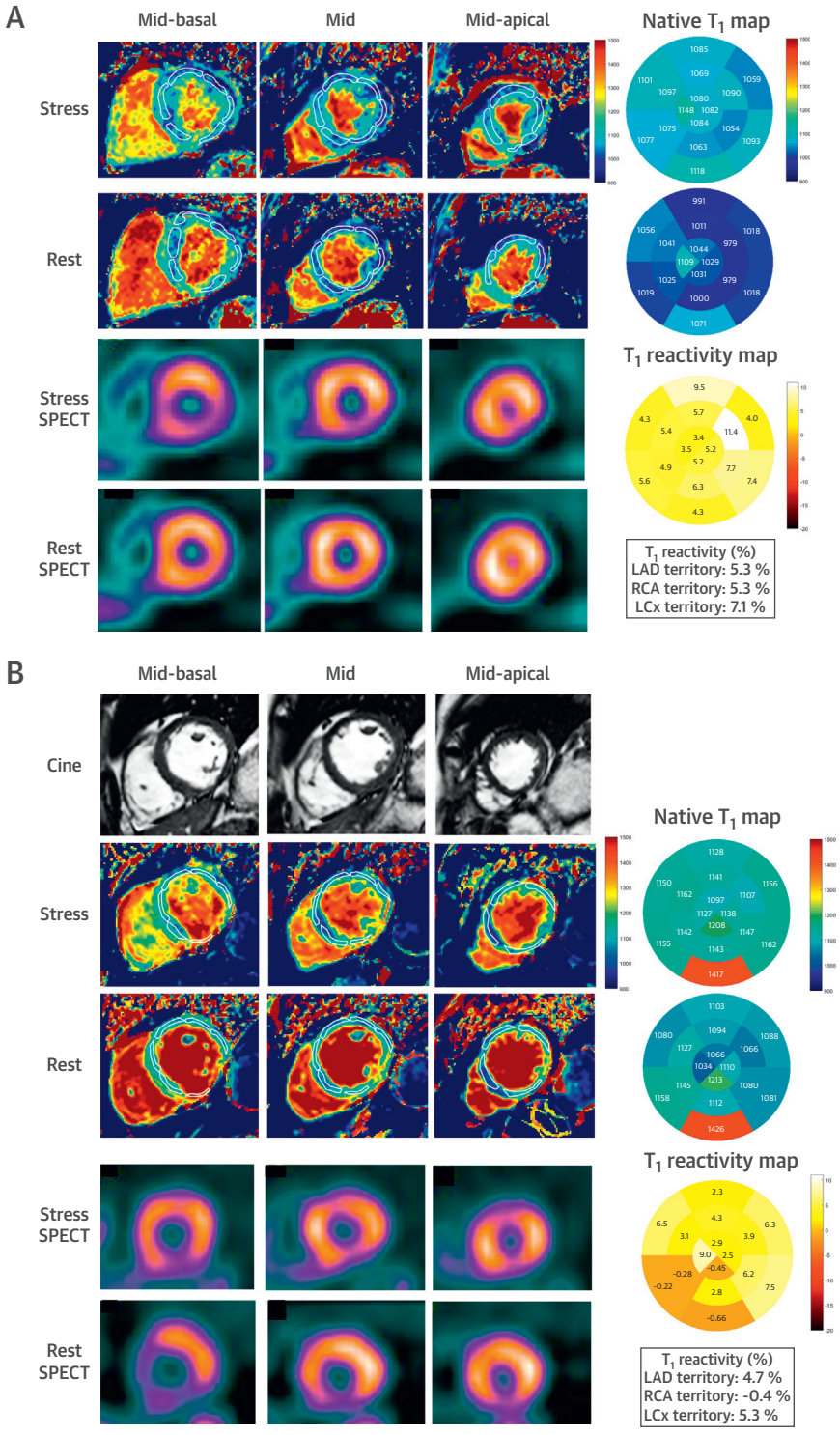
(A to C) Regional T_1 reactivity was most likely correlated with severity of myocardial perfusion abnormality on single-photon emission computed tomography/myocardial perfusion imaging (SPECT/MPI) (normal: 4.9% [quartiles: 3.7% to 6.3%]; mild defect: 1.2% [quartiles: 0.08% to 2.5%]; moderate defect: 0.45% [quartiles: −0.35% to 1.4%], severe defect: 0.35% [quartiles: −0.44% to 0.8%]; normal vs. mild defect; $p < 0.001$; mild vs. moderate and severe defect; $p = 0.06$, respectively). **(D to F)** Meanwhile, rest native T_1 time was the best surrogate marker for differentiating between myocardium with reversible defects and myocardium with normal perfusion and fixed defects.

sensitivity of 64% (7 of 11 vascular territories) and a specificity of 89% (17 of 19 vascular territories) with an area under the receiver-operating characteristic (AUC) of 0.80 (95% confidence interval [CI]: 0.62 to 0.93) for per-vessel level. In contrast, SPECT/MPI exhibited a sensitivity of 55% (6 of 11 vascular territories) and a specificity of 89% (17 of 19 vascular territories) with an AUC of 0.72 (95% CI: 0.53 to 0.87) (DeLong test; $p = 0.40$). Stress and/or rest T_1 mapping tended to be better than SPECT/MPI even when the angiographic cutoff value was adjusted to ≥70% (AUC for stress and/or rest T_1 mapping: 0.84; 95% CI: 0.66 to 0.95 vs. AUC for SPECT/MPI: 0.70; 95% CI: 0.51 to 0.85; $p = 0.28$) (per-patient analysis in the Supplemental Appendix). Because the cutoff T_1 reactivity value of 2.5% determined by receiver-operating characteristic curve analysis for predicting flow-limiting stenosis (defined as >50% stenosis by coronary angiography causing a reversible perfusion defect by SPECT/MPI), stress and/or rest T_1 mapping provided the following values for sensitivity, specificity, negative predictive value, and positive predictive value: 83% (5 of 6 vascular territories), 92% (22 of 24 vascular territories), 96% (22 of 23 vascular territories), and 71% (5 of 7 vascular territories), respectively, on a per-vessel basis with an AUC of 0.86 (95% CI: 0.60 to 0.96) (**Central Illustration**). The intraclass correlation coefficients for interobserver and intraobserver measurements of T_1 reactivity were 0.88 (95% CI: 0.61 to 0.97) and 0.93 (95% CI: 0.76 to 0.98), respectively.

DISCUSSION

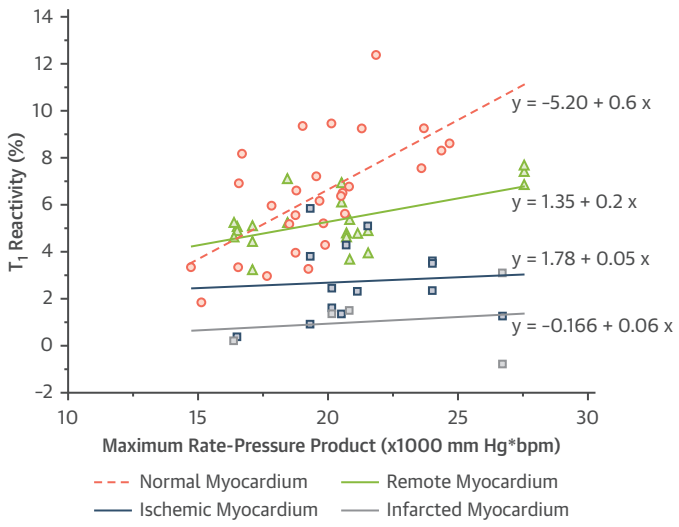
In this study, we assessed the feasibility of exercise stress and/or rest native T_1 and T_2 mapping for

FIGURE 6 **Representative Cases**



(A) A 60-year-old male with atypical chest pain, T_1 reactivity in the normal range, and normal perfusion on SPECT. **(B)** A 61-year-old male with previous inferior myocardial infarction and inferior fixed defects on SPECT. Rest and/or stress native T_1 map shows higher native T_1 time in the basal inferior wall, and the T_1 reactivity map demonstrates severely reduced T_1 reactivity in the right coronary artery (RCA) territory. LAD = left anterior descending; LCx = left circumflex; other abbreviation as in Figure 5.

FIGURE 7 Correlation of T_1 Reactivity and Rate–Pressure Product



T_1 reactivity moderately and positively correlates with the MRPP in normal and remote myocardium (normal myocardium group; $r = 0.62$, $p < 0.001$ and remote myocardium group; $r = 0.51$, $p = 0.01$). The line for the remote myocardium group lies significantly below that of the normal myocardium group ($p = 0.003$). Abbreviations as in Figure 4.

detecting abnormal myocardial blood flow after exercise. We demonstrated that: 1) changes in native T_1, but not T_2, could be a surrogate marker for detecting myocardial blood flow during exercise; and 2) T_1 reactivity was associated with severity of myocardial perfusion abnormality on SPECT/MPI. More importantly, combined assessment of resting native T_1 and T_1 reactivity had the potential to differentiate ischemic myocardium from infarcted myocardium.

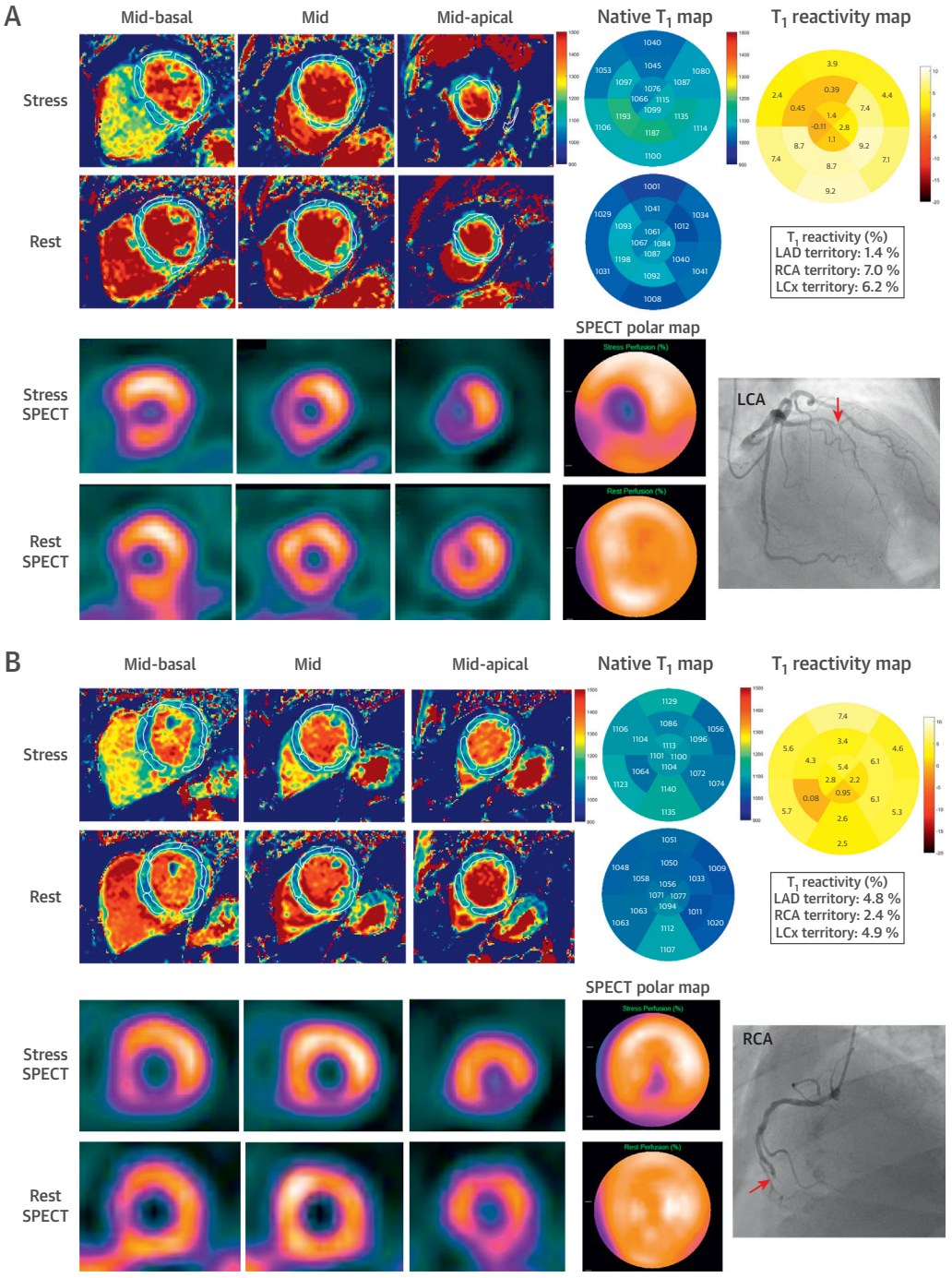
The results from our study were consistent with recent reports by Liu et al. (13,14) who showed pre- and/or post-native T_1 increases in myocardial blood flow during vasodilator adenosine stress and predicted myocardial ischemia in patients with CAD. Because exercise stress provided additional information that was unobtainable from pharmacological stress, such as hemodynamic response and symptoms during exercise, exercise stress was preferable for cardiac stress testing in patients unwilling or unable to tolerate pharmacological stress. Despite the importance of exercise stress cardiac testing, the clinical usefulness of exercise-stress CMR was limited by difficult image acquisition during high heart rates and rapid and/or deep breathing. The introduction of free-breathing native T_1 mapping enabled T_1 measurements of the whole heart within 90 s. Pharmacological or exercise stress could lead to differences in the cutoff T_1 reactivity value for detecting flow-limiting coronary artery stenosis.

Currently, SPECT/MPI is a commonly used stress test that is well validated. A negative result provides reassuring prognostic information (19). We found that segments with myocardial perfusion abnormality on SPECT/MPI had lower T_1 reactivity, and more importantly, integration of native T_1 at rest allowed differentiation between reversible and fixed perfusion defects. In addition, in this pilot study, exercise stress and/or rest T_1 mapping seemed to be similar to SPECT/MPI in its ability to detect significant CAD. Exercise stress and/or rest T_1 mapping could overcome the limitations of soft tissue attenuation and low spatial resolution of SPECT/MPI (20). A multicenter perfusion CMR study showed a sensitivity of 85% and a specificity of 67% with an AUC of 0.86 for detecting significant CAD on coronary x-ray angiography (1). Similarly, the large CE-MARC CMR study demonstrated that the AUC of comprehensive CMR (left ventricular function, myocardial perfusion, late gadolinium enhancement, coronary artery imaging) was 0.84 (2). These AUC values were slightly higher than that of our exercise stress and/or rest native T_1 mapping. The present study demonstrated that exercise stress and/or rest native T_1 mapping could be an effective alternative to radionuclide MPI for detection of flow-limiting coronary stenosis without GBCA or ionizing radiation. Considering the pathological and prognostic aspects of myocardial tissue characterization such as myocardial scar and/or diffuse fibrosis and edema (21–23) in the rest native T_1 mapping, exercise stress and/or rest T_1 mapping might have the potential to improve patient outcomes.

There was a substantial difference in the regression analysis of T_1 reactivity in relation to MRPP between normal myocardium in healthy young subjects and remote myocardium in patients with CAD. The difference might be partly explained by impaired microvascular dilatation during exercise in the remote myocardium. The MRPP was the index that best correlated with myocardial oxygen consumption (17). Alternatively, a reduction in oxygen supply might decrease contractility in patients with CAD, and, in turn, further reduce oxygen cost and exercise tolerance (24). The difference in the T_1 reactivity versus MRPP relationship was not due to a difference in blood catecholamine levels, because this factor would have resulted in changes in the opposite direction.

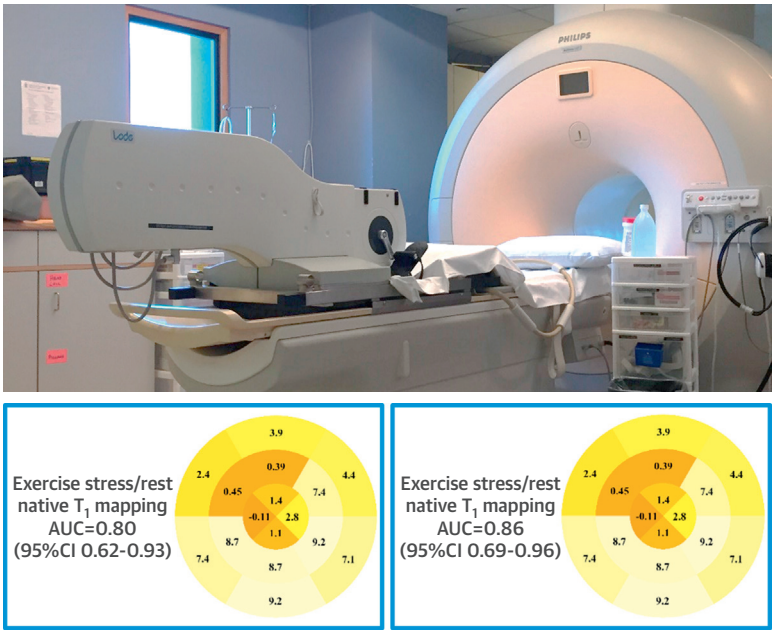
Myocardial T_2 is theoretically more sensitive to changes in myocardial water content secondary to increased myocardial blood flow during stress.

FIGURE 8 **Representative Cases**



(A) A 66-year-old female with angina on effort and single-vessel disease. T_1 reactivity map demonstrates a lower T_1 reactivity in the mid-anteroseptal and apex walls. The mid-LAD reveals severe stenosis by coronary angiography **(arrow)**. Stress SPECT/MPI shows moderate to severe perfusion defects in the LAD territory, confirming flow-limiting stenosis. T_1 reactivity in the LAD territory was severely reduced to 1.39% in this case. **(B)** A 53-year-old male with angina on effort, ventricular arrhythmia, and single-vessel disease. Coronary angiography reveals single-vessel disease with RCA total occlusion **(arrow)** with rich collaterals from left coronary artery. Stress SPECT/MPI shows mild to moderate perfusion defects, suggesting flow-limiting lesions. T_1 reactivity map demonstrates lower T_1 reactivity in the corresponding myocardial segments, and T_1 reactivity in the RCA territory moderately decreased to 2.35%. Abbreviations as in Figures 5 and 6.

CENTRAL ILLUSTRATION **Diagnostic Performance**



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Diagnostic performance of exercise stress and/or rest T_1 mapping for significant coronary artery stenosis (>50%) on coronary angiography (CA) and flow-limiting stenosis defined as >50% stenosis by CA causing a reversible perfusion defect by single-photon emission computed tomography/myocardial perfusion imaging (SPECT/MPI). AUC = area under the receiver-operating curve; CAD = coronary artery disease; CI = confidence interval.

However, the current T_2 mapping technique might not have the necessary sensitivity needed to detect changes in myocardial T_2 associated with a change in blood flow during stress. The serial changes of T_2 time after exercise might also be explained by T_2 mapping detection of subclinical myocardial edema after intense exercise. We observed an approximate 10% variation in myocardial T_2 among healthy volunteers. Another potential source for this variation could be attributed to the imaging and physiological confounders of myocardial T_2 mapping, including sensitivity to field inhomogeneities. T_1 might have some advantages related to T_2 and/or blood oxygen level–dependent sensitivities and magnetization transfer effects (25). Further studies are warranted to assess this rigorously.

STUDY LIMITATIONS. First, the present study was a single-center and small proof-of-concept study with a small sample size. Neither myocardial blood flow nor perfusion was directly measured. However, it was known that MRPP was well correlated with myocardial blood flow and myocardial oxygen consumption during exercise. It would be ideal for healthy subjects to partake in a second exercise followed by native T_1 and T_2 mapping scans on 2 separate days to assess reproducibility of T_1 reactivity. We assessed 3 middle slices covering the left ventricle to report the degree of T_1 reactivity heterogeneity in healthy control subjects. However, T_1 reactivity might not be as homogeneous across the left ventricle as in the middle 3 slices when the true basal, mid-ventricular, and apical slices were analyzed. Exercise stress and/or rest native T_1 mapping was not validated against perfusion CMR and late gadolinium enhancement CMR. Reliable measurement of native T_1 in a thin-wall area might be challenging. However, the present study demonstrated that it might be applicable to infarcted myocardium characterized by a thin myocardial wall. The study was too small to assess diagnostic accuracy of the proposed exercise stress and/or rest T_1 mapping protocol.

CONCLUSIONS

Exercise changes in myocardial native T_1 are evident, with T_1 reactivity associated with severity of myocardial perfusion abnormality on SPECT/MPI. This might have the potential to assess flow-limiting coronary artery stenosis in patients with suspected CAD without the need for GBCA, ionizing radiation, or pharmacological stress agents. Although myocardial T_2 gradually increased after exercise, it was not associated with MRPP. T_2 mapping might not be able to assess increased myocardial blood flow during exercise. Larger studies are warranted to confirm the usefulness of exercise stress and/or rest native T_1 mapping as an alternative to the currently common methods of noninvasive assessment of myocardial perfusion.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Exercise stress and/or rest T_1 mapping can detect physiological changes in blood volume and/or flow in the myocardium during exercise. T_1 reactivity correlates with the severity of myocardial perfusion abnormality on SPECT/MPI and has the potential to assess flow-limiting coronary artery stenosis in patients with CAD without the need for gadolinium contrast or pharmacological stress agents.

TRANSLATIONAL OUTLOOK: In a proof-of-concept study, we evaluated the feasibility of exercise stress and/or rest T_1 mapping at excluding flow-limiting coronary stenosis in patients with suspected CAD using the composite reference standard of invasive coronary angiography and exercise stress and/or rest SPECT/MPI. Larger studies are warranted to confirm the diagnostic accuracy of exercise stress and/or rest T_1 mapping as an alternative to current common methods for assessing myocardial perfusion noninvasively.

REFERENCES

1. Schwitter J, Wacker CM, van-Rossum AC, et al. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. Eur Heart J 2008;29:480–9.

2. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet 2012;379:453–60.

3. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J Am Soc Nephrol 2006;17:2359–62.

4. Hage FG, Smalheiser S, Zoghbi GJ, et al. Predictors of survival in patients with end-stage renal disease evaluated for kidney transplantation. Am J Cardiol 2007;100:1020–5.

5. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014;270:834–41.

6. Hu HH, Pokorney A, Towbin RB, Miller JH. Increased signal intensities in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evidence in children undergoing multiple gadolinium MRI exams. Pediatr Radiol 2016;46:1590–8.

7. Wacker CM, Fidler F, Dueren C, et al. Quantitative assessment of myocardial perfusion with a spin-labeling technique: preliminary results in patients with coronary artery disease. J Magn Reson Imaging 2003;18:555–60.

8. Zun Z, Wong EC, Nayak KS. Assessment of myocardial blood flow (MBF) in humans using arterial spin labeling (ASL): feasibility and noise analysis. Magn Reson Med 2009;62:975–83.

9. Walcher T, Manzke R, Hombach V, Rottbauer W, Wöhrle J, Bernhardt P. Myocardial perfusion reserve assessed by T2-prepared steady-state free precession blood oxygen level-dependent magnetic resonance imaging in comparison to fractional flow reserve. Circ Cardiovasc Imaging 2012;5:580–6.

10. Yang HJ, Dey D, Sykes J, et al. Arterial CO2 as a potent coronary vasodilator: a preclinical PET/MR validation study with implications for cardiac stress testing. J Nucl Med 2017;58:953–60.

11. Mahmod M, Piechnik SK, Levelt E, et al. Adenosine stress native T1 mapping in severe aortic stenosis: evidence for a role of the intravascular compartment on myocardial T1 values. J Cardiovasc Magn Reson 2014;16:92.

12. Nakamori S. Changes in myocardial native T1 and T2 after physical exercise: a feasibility study. Paper presented at: SCMR 20th Annual Scientific Sessions; February 3, 2017; Washington, DC.

13. Liu A, Wijesurendra RS, Francis JM, et al. Adenosine stress and rest T1 mapping can differentiate between ischemic, infarcted, remote, and normal myocardium without the need for gadolinium contrast agents. J Am Coll Cardiol Img 2016;9:27–36.

14. Liu A, Wijesurendra RS, Liu JM, et al. Gadolinium-free cardiac MR stress T1-mapping to distinguish epicardial from microvascular coronary disease. J Am Coll Cardiol 2018;71:957–68.

15. Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. Circulation 2006;114:2070–82.

16. Foster EL, Arnold JW, Jekic M, et al. MR-compatible treadmill for exercise stress cardiac magnetic resonance imaging. Magn Reson Med 2012;67:880–9.

17. Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 1978;57:549–56.

18. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–42.

19. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004;11:171–85.

20. Manglos SH, Thomas FD, Gagne GM, Hellwig BJ. Phantom study of breast tissue attenuation in myocardial imaging. J Nucl Med 1993;34:992–6.

21. Ugander M, Bagi PS, Oki AJ, et al. Myocardial edema as detected by pre-contrast T1 and T2 CMR delineates area at risk associated with acute myocardial infarction. J Am Coll Cardiol Img 2012;5:596–603.

22. Nakamori S, Alakbarli J, Bellm S, et al. Native T1 value in the remote myocardium is

independently associated with left ventricular dysfunction in patients with prior myocardial infarction. J Magn Reson Imaging 2017;46:1073–81.

23. Puntmann VO, Carr-White G, Jabbour A, et al. Native T1 and ECV of noninfarcted myocardium and outcome in patients with coronary artery disease. J Am Coll Cardiol 2018;71:766–78.

24. Holmberg S, Serzysko W, Varnauskas E. Coronary circulation during heavy exercise in control subjects and patients with coronary heart disease. Acta Med Scand 1971;190:465–80.

25. Thulborn KR, Waterton JC, Matthews PM, Radda GK. Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochim Biophys Acta 1982;714:265–70.

KEY WORDS cardiovascular magnetic resonance, exercise stress, flow-limiting coronary artery stenosis, T_1/T_2 mapping

APPENDIX For an expanded Methods section, please see the online version of this paper.