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Differentiating ischemic from healthy myocardium using cardiovascular magnetic resonance dipyridamole rest and stress T1 mapping

Yuan-Ting Chang[1,2,11], Chen-Yen Chien[3,4,5,11], Wei-Ming Huang[1,3], Chung-Lieh Hung[3,4,6,7], Qiang Zhang[8,9], Ricardo A. Gonzales[8], Matthew K. Burrage[8,10], Stefan K. Piechnik[8], Vanessa M. Ferreira[8] & Chun-Ho Yun[1,3,4]✉

Cardiovascular magnetic resonance (CMR) stress T1 mapping using adenosine and regadenoson can differentiate ischemic, infarcted, and healthy myocardium. However, the effect of dipyridamole remains unclear. This study evaluates whether dipyridamole-induced stress T1-mapping can distinguish myocardial tissue types. Twenty-five healthy controls and 20 patients with coronary artery disease (CAD) underwent rest and dipyridamole stress T1-mapping (ShMOLLI), followed by gadolinium-based quantitative perfusion imaging at 1.5T. Native T1 values and stress T1 reactivity (dT1) were assessed across different myocardial tissues. Correlations between dT1 and myocardial blood flow (MBF) were examined. In healthy controls, global rest T1 was 934 ± 26ms, with a stress-induced increase of 6.5 ± 0.6% ($p < 0.0001$). Infarcted myocardium showed elevated resting T1 (1146 ± 71 ms) with an absent stress response (dT1 = -0.9%±1.8%). Ischemic myocardium had mildly elevated rest T1 (965 ± 26 ms; $p < 0.001$) and blunted reactivity (dT1 = 1.3 ± 0.6%) compared to healthy myocardium. Remote myocardium had rest T1 similar to normal tissue (936 ± 19 ms; $p > 0.05$) but reduced stress reactivity (dT1 = 4.5 ± 1.1%; $p < 0.0001$) compared to norm. dT1 strongly correlated with stress MBF ($r = 0.80$) and myocardial perfusion reserve ($r = 0.70$) (both $p < 0.0001$). Dipyridamole-induced stress T1-mapping can differentiate infarcted, ischemic, and healthy myocardium, supporting its use in non-contrast CMR for myocardial tissue characterization.

Keywords Cardiovascular magnetic resonance, Dipyridamole, ShMOLLI, T1 mapping

Cardiovascular magnetic resonance (CMR) is a valuable tool for assessing suspected coronary artery disease (CAD)[1–3]. Patterns of late gadolinium enhancement (LGE) following the injection of gadolinium-based contrast agents (GBCAs) allow for the qualitative characterization of myocardial tissue including myocardial infarction and intramyocardial fibrosis related to cardiomyopathy[4,5]. In addition, previous studies have utilized CMR with GBCAs to detect myocardial ischemia or significant CAD based on changes in qualitative, semi-quantitative analysis or myocardial blood flow (MBF) of perfusion imaging demonstrating high diagnostic accuracy[6–8]. However, the aforementioned methods rely on the use of GBCAs, which may not be feasible in cases involving allergy to contrast agents or impaired renal function. Further, the use of GBCAs increases scan time and

[1]Department of Radiology, Mackay Memorial Hospital, Taipei, Taiwan. [2]Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan. [3]Department of Medicine, Mackay Medical College, New Taipei City, Taiwan. [4]Nursing and Management, Mackay Junior College of Medicine, New Taipei City, Taiwan. [5]Division of Cardiovascular Surgery, Department of Surgery, MacKay Memorial Hospital, Taipei, Taiwan. [6]Division of Cardiology, Departments of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan. [7]Institute of Biomedical Sciences, Mackay Medical College, New Taipei City, Taiwan. [8]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, UK. [9]Li Ka Shing Centre for Health Information and Discovery, Big Data Institute, University of Oxford, Oxford, UK. [10]Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia. [11]Yuan-Ting Chang and Chen-Yen Chien contributed equally to this work. ✉email: med202657@gmail.com

costs, and carries significant carbon footprint[9,10]. In addition, MBF does not reflect capillary recruitment of myocardium inclusive of downstream blood volume distribution[11].

CMR parametric mapping is a novel technique that has been developed recently. It provides a quantitative representation of numerical T1 or T2 relaxation times, expressed in units of time (e.g. milliseconds)[3]. It has several advantages in evaluating CAD. Firstly, parametric T1-mapping is able to leverage the sensitivity of native T1 values to tissue free water content including myocardial water and thus has been associated with myocardial blood volume (MBV) changes at rest and during vasodilatory stress[12]. MBV is thought to be complementary to MBF for the assessment of the status of myocardium including both coronary macro-circulation and capillary recruitment[11,13–15], and thus has a better sensitivity in mirroring the hemodynamics of myocardium at different states[16]. The main strengths of parametric mapping is its quantitative nature with reduced sensitivity to coil profiles, albeit care needs to be taken for the signal arising from BOLD effects and inter-sequence differences[17]. Native T1 mapping does not require the use of GBCAs, and can be used in individuals who are contraindicated to the contrast agents.

Previous studies have demonstrated that stress T1-mapping with adenosine[18] or regadenoson[19] can differentiate between normal, remote, ischemic, and infarcted myocardium. However, most of the study population were located in western countries. Moreover, although regadenoson is preferred over adenosine due to its safety profile and ease of administration,[2] it is not available in some countries around the world, including Taiwan. Dipyridamole, on the other hand, is another widely-used coronary vasodilator, which has been shown to have similar vasodilating efficacy and adverse effects as adenosine,[2] but at a lower cost. In addition, a relatively longer half-life of dipyridamole than adenosine and regadenoson could theoretically produce a steadier vasodilatory effect[20]. Hence, the aim of this study is to (1) investigate resting and dipyridamole-induced stress T1 mapping, (2) compare the results of T1 mapping across normal, remote, ischemic and infarcted myocardium.

Materials and methods

Study population

Twenty-five healthy subjects with no history of cardiovascular disease and no prior cardiovascular symptoms and 20 chronic CAD patients were recruited between December 2021 and December 2023. CAD patients were those with stable angina and referred for invasive coronary intervention or coronary artery bypass surgery (CABG). Exclusion criteria of CAD patients included high-degree atrioventricular block, significant renal function impairment with eGFR < 30 ml/min/1.73m^2, hypotension (systolic blood pressure < 90 mmHg), decompensated congestive heart failure (New York Heart Association functional class III or IV), previous CABG or valvular replacement, implantable cardiac device or other metallic implants and standard contraindications to MRI imaging. Invasive diagnostic coronary angiography was performed at least three weeks before CMR for patients being referred for CABG. For patients referred for invasive coronary intervention, CMR was performed within one month pre-procedure. The study was performed under approval of Institutional Review Board (IRB) of Mackay Memorial Hospital (20MMHIS211e), in accordance with the Declaration of Helsinki. All participants signed a written informed consent form.

Image acquisition

All participants were asked to abstain from beverages with caffeine for 24 h before undergoing CMR study. CMR imaging was performed using a 1.5-Tesla MRI scanner (MAGNETOM Aera, software version VE11C, Siemens Healthcare, Erlangen, Germany) with a phased-array eighteen-channel body matrix coil together with a spine matrix coil. All participants were examined in supine position.

CMR scanning protocol can be found in previously published paper[16], and is demonstrated in Fig. 1. Cine imaging was performed in three long-axis views (HLA, VLA, LVOT) and in short-axis slices covering the entire left ventricle (LV), using retrospectively ECG-gated balanced steady-state free precession (bSSFP) imaging. T1 maps were acquired based on the Shortened Modified Look-Locker Inversion recovery (ShMOLLI) sequence as previously published[16]. The T1 sequence was quality assured using a phantom approach[21]. Quality assessment of ShMOLLI T1 maps using parametric goodness-of-fit (R2) maps were available in-line at time of acquisition.[21–24].

Three short-axis slices (basal, midventricular, and apical) were acquired for both T1 and perfusion mapping at rest and during stress. Dipyridamole infusion (0.56 mg/kg over 4 min)[25] was initiated after the acquisition of the rest T1 map. Two minutes after the end of the dipyridamole infusion which is the traditional protocol of the timing for starting the stress perfusion scan[25]. We have a pilot study for demonstrating the timing of peak and stable vasodilatory response to dipyridamole (based on unpublished work).

Following stress T1 mapping, a stress perfusion scan used a dual sequence approach for subsequent quantitative and qualitative assessments. The details of the myocardial.

perfusion sequence have been previously described[26]. It was performed using gadolinium contrast (0.05 mmol/kg gadobutrol, Gadovist®, Bayer AB, Solna, Sweden) administered intravenously at a rate of 3.5–4 ml/s, followed by a 25 ml saline flush at the same rate. After the stress perfusion scan, aminophylline (100 mg IV over 5–10 s, followed by a 10 ml saline flush) was administered to reverse the pharmacologic stress effect. Eight minutes later, a rest perfusion scan was performed using the same protocol. Subsequently, an additional 0.1 mmol/kg dose of gadolinium was administered, bringing the total contrast dose to 0.2 mmol/kg. Approximately eight minutes afterward, late gadolinium enhancement (LGE) imaging was performed using an inversion-recovery prepared, gated fast gradient-echo sequence (voxel size: 1.5 × 1.7 × 5 mm), acquiring short-axis views covering the entire left ventricle (LV), as well as horizontal long-axis (HLA) and vertical long-axis (VLA) views.

Image analysis

Image analysis was performed using commercially available software (IntelliSpace portal V9.0, Philips, Netherland). Left ventricular systolic and diastolic volume, ejection fraction, and the presence and distribution

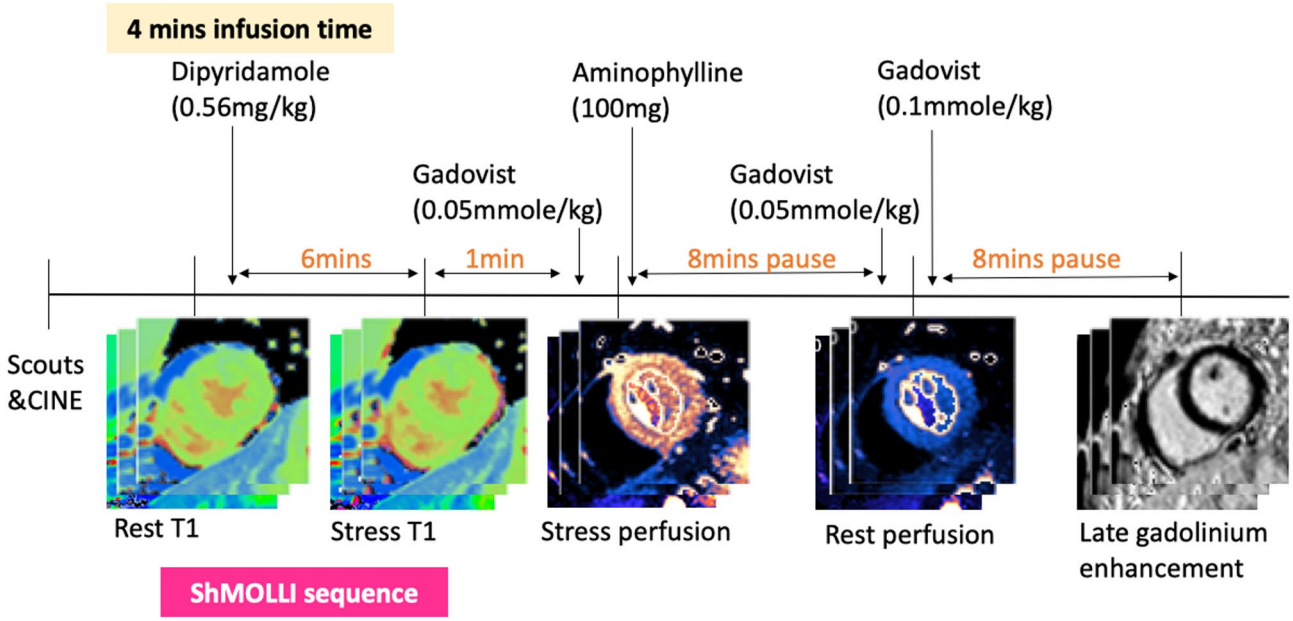

Fig. 1. Pictorial demonstration of the CMR scanning protocol.

(infarct or non-infarct) of LGE were recorded. Quantitative perfusion maps were available in-line after the perfusion examinations of stress and rest status. The endocardial, subendocardial and epicardial borders were delineated for each basal, mid-ventricular, and apical perfusion map. Average MBF in milliliters per gram per minute was assessed per coronary artery territory according to the 17-segment model modified for coronary dominance and excluding the apical segment[27]. Myocardial perfusion reserve (MPR) was also calculated, defined as the ratio between MBF at stress over rest. Global MBF in milliliters per gram per minute was calculated by averaging MBF across the 3 slices; global MPR was calculated as the ratio between global stress MBF and global rest MBF. All above results were generated automatically in-line.

The analysis of ShMOLLI T1-maps was performed using the software (VE11C, Siemens Healthcare, Erlangen, Germany). Endocardial and epicardial contours were annotated manually on T1 maps. Quality assessment was performed before data analysis, and 8.2% of myocardial segments were excluded due to poor imaging quality, caused by off resonance and motion artifacts. Interobserver analysis of T1 mapping measures were performed by two experienced observers (CHY and WMH). For healthy controls, mean myocardial T1 values were derived from rest and stress T1-maps on a per-slice and per-segment basis according to the American Heart Association (AHA) 16-segment model. Stress T1 reactivity was calculated as: delta T1= (Stress T1- Rest T1)/Rest T1 × 100%.

In patients with CAD, mean T1 values were measured from regions of interest (ROIs) placed in ischemic, infarcted, and remote myocardium, as well as in the left ventricular (LV) blood pool as a reference. ROI placement was guided by first-pass perfusion and LGE imaging, in accordance with previously established methods[19]. Ischemic myocardium was defined as regions demonstrating reversible perfusion defects on stress perfusion imaging without corresponding LGE. Infarcted myocardium was identified by areas of hyperenhancement on LGE images, with ROIs positioned within the infarct core to minimize partial volume effects from the adjacent LV blood pool, using cine images for anatomical guidance[19]. Remote myocardium was defined as myocardial regions contralateral to ischemic territories, without evidence of perfusion defects, wall motion abnormalities, or LGE. ROIs were carefully matched between rest and stress images to ensure consistency. Figure 2 demonstrates an example of the above-mentioned method.

Statistical analysis

Data are reported as mean ± SD for all parametric data based on Shapiro-Wilks tests for normality. For parametric data, paired t-tests are used whenever possible to assess differences between rest and stress in the same individuals; unpaired t-tests are used to assess differences between groups for selected myocardial tissue types and 1-way analysis of variance with post hoc Scheffe's correction to compare the means of multiple groups. Categorical data were compared by using the Fisher's exact test. $P < 0.05$ is considered statistically significant. Inter-observer analysis of T1 mapping measures was performed using the Intraclass Correlation Coefficient (ICC), based on a two-way random-effects model with absolute agreement Statistical analysis and data modelling were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Participants characteristics

In total, 25 healthy participants and 20 participants with CAD were included in our study. Characteristics of the study population are summarized in Table 1. CAD patients were older than healthy volunteers, while no

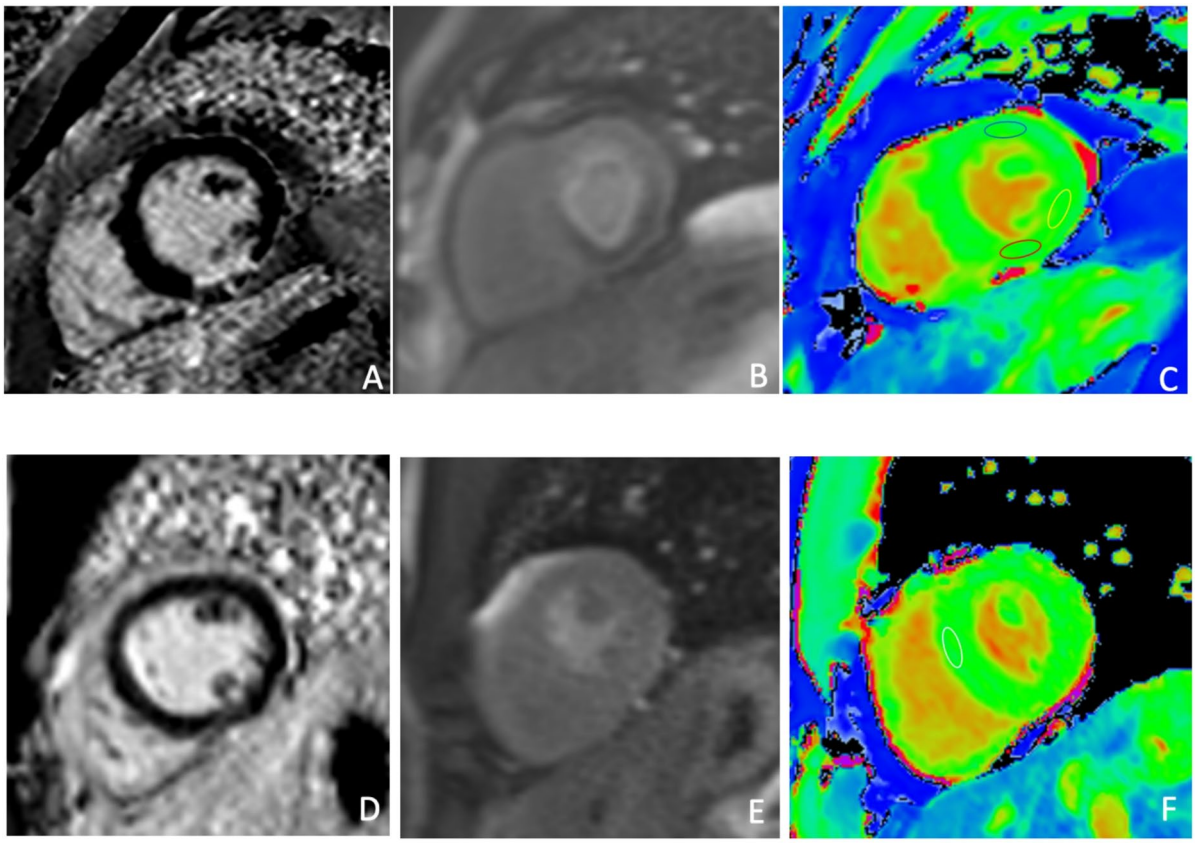

Fig. 2. Example images from a 55-year-old man with significant coronary artery disease of chronic total occlusion of the proximal right coronary artery and 70% stenosis of the proximal left circumflex artery (**A**, **B**, **C**) and a 30-year-old healthy participant (**D**, **E**, **F**). (**A**) Late gadolinium enhancement imaging shows evidence of an inferior myocardial infarction. (**B**) First-pass stress perfusion imaging demonstrates a fixed hypoperfusion defect in the inferior wall corresponding to the area of infarction, as well as inducible hypoperfusion in the lateral wall of the left ventricle. (**C**) Regions of interest were placed in areas of ischemia (yellow circle), infarction (red circle), and the left ventricular (LV) blood pool on T1 maps. ΔT1 was markedly reduced in the lateral wall (1.5%) and within the infarcted myocardium (0.4%). In comparison, the remote myocardium (blue circle) showed a ΔT1 of 4.4%. (**D**), (**E**), (**F**) demonstrates the LGE imaging, stress perfusion imaging, and T1 map of the normal myocardium from a healthy participant, and the ΔT1 of the normal myocardium (white circle) was 6.7%.

significant difference was found in other patient characteristics. All participants exhibited adequate responses to dipyridamole, defined as a rise in heart rate of at least 10 beats per minute (healthy: $n = 17$, CAD: $n = 12$), a fall in systolic blood pressure of more than 10 mmHg (healthy: $n = 2$, CAD: $n = 4$), or both (healthy: $n = 6$, CAD: $n = 4$).

Myocardial rest and stress T1 response to dipyridamole in healthy controls

The global and territorial myocardial resting T1 values of healthy controls were all within the normal range as reported in previous literature[28]. Compared to the resting state, significant rise in stress T1 response was noted in global (rest: 934 ± 26ms, stress: 994 ± 28ms, $p < 0.0001$, dT1: 6.5%±0.6%) (Fig. 3A and B). Similar results were observed in standard short axis slice positions (Basal: rest 926 ± 21ms, stress 986 ± 22ms, $p < 0.0001$, dT1: 6.5%±1.2%; midventricular: rest 936 ± 26ms, stress 997 ± 31ms, $p < 0.0001$, dT1: 6.5%±1.0%; apical: rest 942 ± 35ms, stress 1005 ± 39ms, $p < 0.0001$, dT1: 6.6%±1.2%) (Figure S1A), as well as territorial myocardium supplied by left anterior descending artery (rest: 929 ± 19ms, stress: 989 ± 26ms, $p < 0.0001$, dT1: 6.5%±1.3%), left circumflex artery (rest: 930 ± 29ms, stress: 994 ± 32ms, $p < 0.0001$, dT1: 6.8%±1.1%), and right coronary artery (rest: 940 ± 30ms, stress:1000 ± 29ms, $p < 0.0001$, dT1: 6.3%±1.2%) (Figure S1B). Consistent findings were also shown across AHA segments (Figure S1C).

Myocardial rest and stress T1 response to dipyridamole in patients with CAD

In patients with CAD, significant higher T1 values at rest were observed in infarcted and ischemic myocardium compared to healthy controls (Table 2). In contrast, no significant difference in resting T1 was found when comparing remote myocardium to healthy controls. Significant elevation in dipyridamole-induced stress T1 reactivity compared to resting state was found in remote (rest: 936 ± 19ms, stress: 979 ± 22ms, $p < 0.0001$, dT1: 4.5%±1.1%) and ischemic (rest: 964 ± 26ms, stress: 977 ± 26ms, $p < 0.0001$, dT1: 1.3%±0.6%) myocardium, but

	Healthy subjects ($n=25$)	CAD patients ($n=20$)	p value
Age (yrs)	44.5 ± 16.3	62.5 ± 10.3	< 0.0001
BMI (kg/m^2)	22.4 ± 4.6	26.5 ± 4.4	0.831
Male (%)	11 (44)	13 (65)	0.161
Risk factors (%)			
Hypertension	0	10 (50)	
Diabetes mellitus	0	9 (45)	
Hypercholesterolemia	0	2 (10)	
Family history of CAD	0	3 (15)	
History of CAD	0	11 (55)	
Smoking	0	1 (5)	
Medication (%)			
Aspirin	0	13 (65)	
Beta-blocker	0	8 (40)	
Statin	0	14 (70)	
CMR clinical indices			
LVEF (%)	59.2 ± 4.4	62.1 ± 7.6	0.147
LVEDVI (ml/m2)	61.0 ± 13.4	65.5 ± 17.0	0.266
Number of remote myocardial segments[&]		57	
Number of ischemic myocardial segments[#]		55	
Number of infarcted myocardial segments[#]		14	
Invasive coronary angiography			
1-vessel CAD[$]		7	
2-vessel CAD		4	
3-vessel CAD		9	

Table 1. Characteristics of the study population. [&] no ischemia or infarction. [#] Based on results of first-pass perfusion and late gadolinium enhancement imaging. [$] ≥70% stenosis in a major coronary vessel. CAD: coronary artery disease; CMR: cardiovascular magnetic resonance; LVEF: left ventricular ejection fraction; LVEDVI: indexed left ventricular end-diastolic volume.

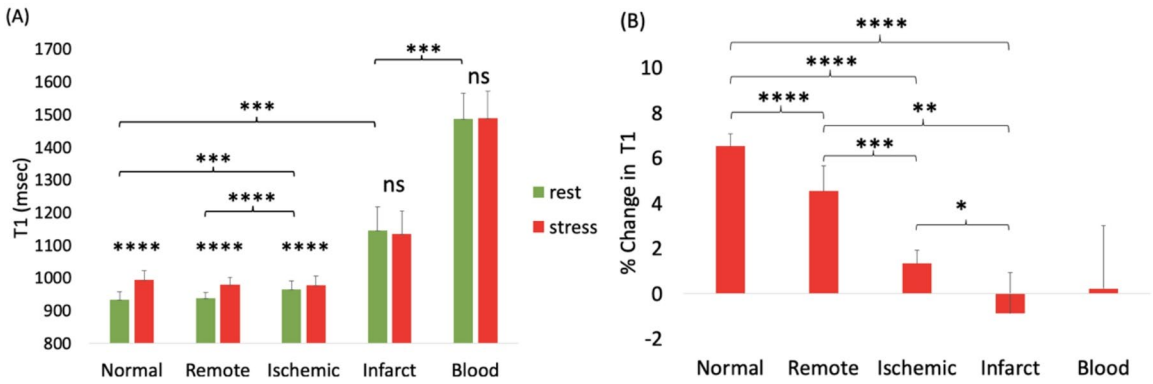

Fig. 3. Dipyridamole stress T1-mapping distinguishes between different myocardial tissues. (**A**) Resting and dipyridamole-induced stress T1 values, in absolute number. (**B**) Dipyridamole-induced percentage change in T1 values. *$p<0.05$; **$p<0.01$; ***$p<0.001$; ****$p<0.0001$; ns = not significant.

not in infarcted (rest: 1145 ± 70ms, stress: 1134 ± 70ms, $p>0.05$, dT1: -0.9%±1.8%) myocardium and blood (rest: 1485 ± 79ms, stress: 1488 ± 83ms, $p>0.05$) (Fig. 3A).

When comparing the change between stress and rest T1 responses (dT1), largest difference was found in normal myocardium, followed by remote, ischemic and infarcted ones. (Fig. 3B). Interobserver ICC was 0.92.

Significant correlations were noted between delta T1 (dT1) and sMBF ($r=0.8$, $p<0.0001$) as well as MPR ($r=0.7$, $p<0.0001$). No significant correlation was found between dT1 and rMBF ($r=0.2$, $p=0.19$) (Fig. 4).

	Healthy Subjects ($n=25$)	CAD patients ($n=20$)			
	Normal	Remote	Ischemic	Infarct	LV blood pool
Rest T1 (ms)	934 ± 26	936 ± 19	965 ± 26	1146 ± 71	1486 ± 79
Stress T1 (ms)	994 ± 28	979 ± 22	978 ± 27	1135 ± 71	1489 ± 83
dT1 (%)	6.5 ± 0.6	4.5 ± 1.1	1.3 ± 0.6	-0.9 ± 1.8	0.2 ± 2.8
Resting MBF	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.4	0.62 ± 0.2	
Stress MBF	3.1 ± 0.7	2.1 ± 0.7	1.5 ± 0.5	0.72 ± 0.4	
MPR	3.8 ± 0.8	2.6 ± 1.0	2.0 ± 0.8	1.1 ± 0.3	

Table 2. Myocardial T1 values and quantitative myocardial perfusion results in healthy subjects and CAD patients. CAD: coronary artery disease; dT1:delta T1; MBF: myocardial blood flow; MPR: myocardial perfusion reserve.

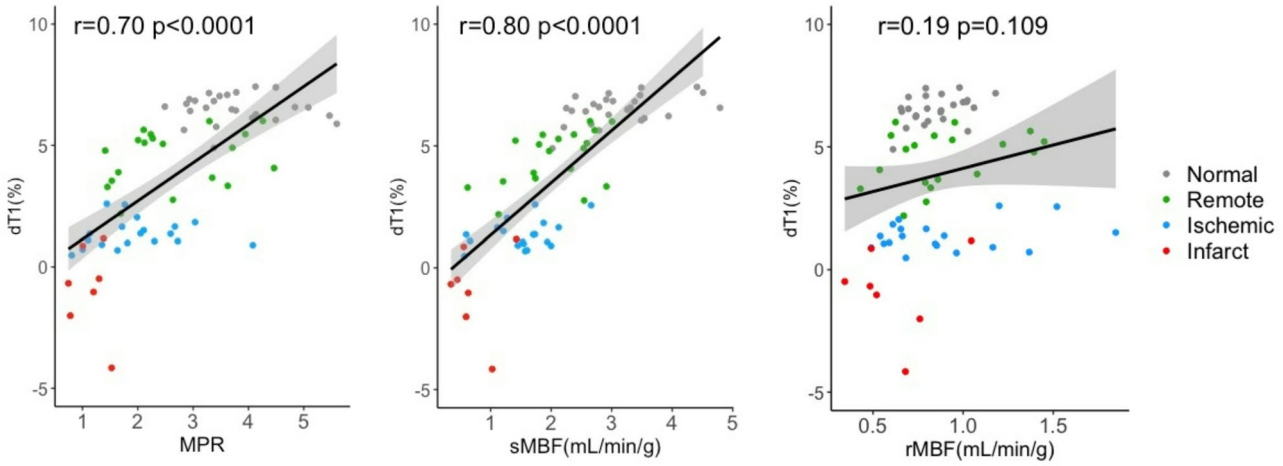

Fig. 4. Correlation between T1 reactivity and MPR, sMBF and rMBF. T1 reactivity is expressed as percentage change in T1 (dT1). Abbreviations: rMBF: myocardial blood flow at rest; sMBF=myocardial blood flow at stress; MPR=myocardial perfusion reserve.

Discussion

In this study, we used dipyridamole as a pharmacological stressor to create resting and stress T1 mapping and demonstrated its potential to distinguish different types of myocardial tissue. To summarize, higher resting T1 values were observed in ischemic and infarcted myocardium compared to normal ones. The percentage change in T1 (dT1) from the resting to stress state was the largest in the normal group, followed in descending order by the remote, ischemic, and infarcted groups. Notably, we found strong and significant correlations between dT1 and both stress myocardial blood flow and myocardial perfusion reserve. This highlights the potential of stress T1 mapping as a non-contrast biomarker for myocardial perfusion assessment.

Dipyridamole stress T1 reactivity in healthy controls

The average global stress T1 reactivity in our healthy participants was 6.5%, which was in concordance with the normal myocardial stress T1 response around 6–7% demonstrated by previous studies[19,29]. In addition, the stress T1 reactivity across basal, mid-ventricular, apical slices, as well as three main vessel territories showed no significant difference in our study. This is different from the previous work by Burrage et al.[19], who using regadenoson as stressor reported a slightly higher response in basal slice. This could be due to interacting results between different pharmacokinetics and the acquisition timing of imaging[19].

Dipyridamole is a potent coronary vasodilator that inhibits adenosine deaminase and phosphodiesterase, requiring a 4-minute infusion and having a half-life of up to 45 min. Aminophylline is typically used for reversal. In contrast, regadenoson is administered as a single 10-second injection with a triphasic half-life (2–4 min, 30 min, and 2 h)[30]. Adenosine has the shortest half-life, less than 10 s. Compared to traditional stress CMR study, the stress T1 protocol included three additional separate T1 mapping scans performed at the baseline, and under stress conditions immediately before Gd administration for the 1st pass perfusion scan (lasting about 40–50 s), both covering the basal, midventricular, and apical slices of LV. Moreover, quality assessment must be performed between each scan and the scans can be repeated if necessary to assure best quality of the data within the relatively long stress response plateau. The stability of the stressor response, and the current setup are substantial improvement over the prior study using adenosine as the stressor[16], where multiple stress T1 exams were before myocardial perfusion, which resulted in a delay and a lower stress MBF than typically observed[27]. It might

be due to the fact that the stress perfusion scan was not conducted at peak stress (which occurs at 4 min after injection). Therefore, dipyridamole, which has a longer half-life compared to adenosine and regadenosone[20], can provide a more stable peak vasodilated state of myocardium (approximately 2 min, based on unpublished work). This could be another advantage of using dipyridamole in CMR with stress T1 protocol. Given that ShMOLLI acquisition takes just 9 heartbeats, which need to be separated by at least 10 s breaks[21], this would allow at least two repeat measures for each slice, with a potential to reduce variability by nearly 30%.

On the other hand, although previous study has shown that regadenoson might have slightly better vasodilatory efficacy[31], dipyridamole has been reported to have fewer adverse events than regadenoson in patients undergoing myocardial perfusion imaging[32]. Our study demonstrated the ability of dipyridamole as a valid stressor in CMR T1 mapping and could potentially be a choice of agent when other options were contraindicated (e.g., allergy) or unavailable (e.g., not marketed in certain countries).

Dipyridamole stress T1 reactivity for the assessment of CAD

Our results of stress T1 reactivity in patients with CAD were consistent with previously published studies, regardless of types of stressor used (i.e., exercise, adenosine, regadenoson)[18,19,29]. The mechanism of delta T1 could be explained by the increased myocardial water content including increased MBV and blood oxygenation changes between rest to stress state[17]. The diminished T1 response to stress in remote and ischemic myocardium, along with the absence of a T1 stress response in infarcted myocardium, reflected compensatory vasodilation at baseline[33], and thus blunted the additional blood recruitment during stress state, with also diminished BOLD effects. This was further evidenced by progressively elevated T1 values at rest in remote, ischemic myocardium, in ascending order. The evidence above suggested that a certain degree of microvascular dysfunction may present in the myocardium of patients with CAD. However the relationship among vasculature, blood flow, blood volume and T1 during stress and rest is still not fully elucidated[12].

Interestingly, we found strong correlations between dT1 and stress MBF as well as MPR, but not resting MBF. This is in consistent with the theory that MBF partially reflects MBV, encompassing both macro- and micro-circulation[11,14], and delta T1 mapping represents change in MBV.

Strength and limitation

Inclusion of healthy participants allows validation of the imaging protocol, comparison of the results with other studies, and more comprehensive characterization of different types of myocardial tissue. Establishment of T1 mapping data in health controls is especially invaluable when considering building the reference for future implication in clinical practice[34]. However, for practical reasons of recruiting cohorts willing to undergo administration of stress and GBCA, the healthy controls were not age, gender-matched with the patients with CAD, and are significantly younger. This may introduce potential confounds as age is known to be associated with reductions in hyperemic flow and MPR[35]. Future studies are needed to better understand the effect of age on myocardial tissue characterization and whether the reference of T1 mapping should be age-specific.

Our study along with other previous work validate the use of T1 maps to distinguish different myocardial tissues, and provide ranges of T1 value in types of myocardium. However, further studies with large numbers of subjects and advanced software analysis are needed to provide not only cutoff values for normal and diseased myocardium, but also quantitative delta T1 maps, in order to avoid the disadvantages of traditional methods that rely on ROI selection and post-contrast images.

Conclusion

This study demonstrates the validity and benefits of using dipyridamole as a stressor in non-GBCA-based CMR study, documenting the ability of T1 parametric mapping to differentiate different types of myocardial tissue.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to IRB restrictions but are available from the corresponding author on reasonable request.

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References

1. Ricci, F. et al. Diagnostic and Prognostic Value of Stress Cardiovascular Magnetic Resonance Imaging in Patients With Known or Suspected Coronary Artery Disease: A Systematic Review and Meta-analysis. *JAMA Cardiol.* **8** (7), 662–673. https://doi.org/10.1001/jamacardio.2023.1290 (2023).
2. Vinco, G. et al. Stress Cardiovascular Magnetic Resonance Imaging for the Detection of Coronary Artery Disease. *Rev. Cardiovasc. Med.* **24** (9), 254. https://doi.org/10.31083/j.rcm2409254 (2023).
3. Ferreira, V. M. & Piechnik, S. K. CMR Parametric Mapping as a Tool for Myocardial Tissue Characterization. *Korean Circ. J.* **50** (8), 658–676. https://doi.org/10.4070/kcj.2020.0157 (2020).
4. Mavrogeni, S. I. et al. Cardiovascular magnetic resonance for the evaluation of patients with cardiovascular disease: An overview of current indications, limitations, and procedures. *Hell J. Cardiol.* **70**, 53–64. https://doi.org/10.1016/j.hjc.2023.01.003 (2023).
5. Pontone, G. et al. Appropriate use criteria for cardiovascular magnetic resonance imaging (CMR): SIC-SIRM position paper part 1 (ischemic and congenital heart diseases, cardio-oncology, cardiac masses and heart transplant). *Radiol. Med.* **126** (3), 365–379. https://doi.org/10.1007/s11547-020-01332-6 (2021).
6. Yun, C-H. et al. Qualitative and semi-quantitative evaluation of myocardium perfusion with 3 T stress cardiac MRI. *BMC Cardiovasc. Disord.* **15**, 164. https://doi.org/10.1186/s12872-015-0159-1 (2015).
7. Kwong, R. Y. et al. Cardiac Magnetic Resonance Stress Perfusion Imaging for Evaluation of Patients With Chest Pain. *J. Am. Coll. Cardiol.* **74** (14), 1741–1755. https://doi.org/10.1016/j.jacc.2019.07.074 (2019).

8. Arai, A. E. et al. Gadobutrol-Enhanced Cardiac Magnetic Resonance Imaging for Detection of Coronary Artery Disease. *J. Am. Coll. Cardiol.* **76** (13), 1536–1547. https://doi.org/10.1016/j.jacc.2020.07.060 (2020).
9. Chaban, Y. V. et al. Environmental Sustainability and MRI: Challenges, Opportunities, and a Call for Action. *J. Magn. Reson. Imaging.* **59** (4), 1149–1167. https://doi.org/10.1002/jmri.28994 (2024).
10. Picano, E., Mangia, C., D'Andrea, A. & Climate Change Carbon Dioxide Emissions, and Medical Imaging Contribution. *J. Clin. Med.* **12** (1). https://doi.org/10.3390/jcm12010215 (2022).
11. McCommis, K. S. et al. Myocardial blood volume is associated with myocardial oxygen consumption: an experimental study with cardiac magnetic resonance in a canine model. *JACC Cardiovasc. Imaging.* **2** (11), 1313–1320. https://doi.org/10.1016/j.jcmg.2009.07.010 (2009).
12. Nickander, J. et al. The relative contributions of myocardial perfusion, blood volume and extracellular volume to native T1 and native T2 at rest and during adenosine stress in normal physiology. *J. Cardiovasc. Magn. Reson. Off J. Soc. Cardiovasc. Magn. Reson.* **21** (1), 73. https://doi.org/10.1186/s12968-019-0585-9 (2019).
13. Nickander, J. et al. Stress native T1 and native T2 mapping compared to myocardial perfusion reserve in long-term follow-up of severe Covid-19. *Sci. Rep.* **13** (1), 4159. https://doi.org/10.1038/s41598-023-30989-y (2023).
14. McCommis, K. S. et al. Roles of myocardial blood volume and flow in coronary artery disease: an experimental MRI study at rest and during hyperemia. *Eur. Radiol.* **20** (8), 2005–2012. https://doi.org/10.1007/s00330-010-1740-8 (2010).
15. McCommis, K. S. et al. Quantification of myocardial blood volume during dipyridamole and doubtamine stress: a perfusion CMR study. *J. Cardiovasc. Magn. Reson. Off J. Soc. Cardiovasc. Magn. Reson.* **9** (5), 785–792. https://doi.org/10.1080/10976640701545206 (2007).
16. Burrage, M. K. et al. Cardiac stress T1-mapping response and extracellular volume stability of MOLLI-based T1-mapping methods. *Sci. Rep.* **11** (1), 13568. https://doi.org/10.1038/s41598-021-92923-4 (2021).
17. Piechnik, S. K., Neubauer, S. & Ferreira, V. M. State-of-the-art review: stress T1 mapping-technical considerations, pitfalls and emerging clinical applications. *MAGMA* **31** (1), 131–141. https://doi.org/10.1007/s10334-017-0649-5 (2018).
18. Yimcharoen, S., Zhang, S., Kaolawanich, Y., Tanapibunpon, P. & Krittayaphong, R. Clinical assessment of adenosine stress and rest cardiac magnetic resonance T1 mapping for detecting ischemic and infarcted myocardium. *Sci. Rep.* **10** (1), 14727. https://doi.org/10.1038/s41598-020-71722-3 (2020).
19. Burrage, M. K. et al. Cardiovascular magnetic resonance stress and rest T1-mapping using regadenoson for detection of ischemic heart disease compared to healthy controls. *Int. J. Cardiol.* **333**, 239–245. https://doi.org/10.1016/j.ijcard.2021.03.010 (2021).
20. Pagnanelli, R. A. & Camposano, H. L. Pharmacologic Stress Testing with MyocardialPerfusion Imaging. *J. Nucl. Med. Technol.* **45** (4), 249–252. https://doi.org/10.2967/jnmt.117.199208 (2017).
21. Zhang, Q. et al. Quality assurance of quantitative cardiac T1-mapping in multicenter clinical trials - A T1 phantom program from the hypertrophic cardiomyopathy registry (HCMR) study. *Int. J. Cardiol.* **330**, 251–258. https://doi.org/10.1016/j.ijcard.2021.01.026 (2021).
22. Piechnik, S. K. et al. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within a 9 heartbeat breathhold. *J. Cardiovasc. Magn. Reson. Off J. Soc. Cardiovasc. Magn. Reson.* **12** (1), 69. https://doi.org/10.1186/1532-429X-12-69 (2010).
23. Carapella, V. et al. Standardized image post-processing of cardiovascular magnetic resonance T1-mapping reduces variability and improves accuracy and consistency in myocardial tissue characterization. *Int. J. Cardiol.* **298**, 128–134. https://doi.org/10.1016/j.ijcard.2019.08.058 (2020).
24. Ferreira, V. M. et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. *J. Cardiovasc. Magn. Reson. Off J. Soc. Cardiovasc. Magn. Reson.* **14** (1), 42. https://doi.org/10.1186/1532-429X-14-42 (2012).
25. Henzlova, M. J., Duvall, W. L., Einstein, A. J., Travin, M. I. & Verberne, H. J. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. *J. Nucl. Cardiol. Off Publ Am. Soc. Nucl. Cardiol.* **23** (3), 606–639. https://doi.org/10.1007/s12350-015-0387-x (2016).
26. Kellman, P. et al. Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. *J. Cardiovasc. Magn. Reson. Off J. Soc. Cardiovasc. Magn. Reson.* **19** (1), 43. https://doi.org/10.1186/s12968-017-0355-5 (2017).
27. Kotecha, T. et al. Automated Pixel-Wise Quantitative Myocardial Perfusion Mapping by CMR to Detect Obstructive Coronary Artery Disease and Coronary Microvascular Dysfunction: Validation Against Invasive Coronary Physiology. *JACC Cardiovasc. Imaging.* **12** (10), 1958–1969. https://doi.org/10.1016/j.jcmg.2018.12.022 (2019).
28. Piechnik, S. K. et al. Normal variation of magnetic resonance T1 relaxation times in the human population at 1.5 T using ShMOLLI. *J. Cardiovasc. Magn. Reson. Off J. Soc. Cardiovasc. Magn. Reson.* **15** (1), 13. https://doi.org/10.1186/1532-429X-15-13 (2013).
29. Nakamori, S. et al. Changes in Myocardial Native T(1) and T(2) After Exercise Stress: A Noncontrast CMR Pilot Study. *JACC Cardiovasc. Imaging.* **13** (3), 667–680. https://doi.org/10.1016/j.jcmg.2019.05.019 (2020).
30. Lieu, H. D. et al. Regadenoson, a selective A2A adenosine receptor agonist, causes dose-dependent increases in coronary blood flow velocity in humans. *J. Nucl. Cardiol. Off Publ Am. Soc. Nucl. Cardiol.* **14** (4), 514–520. https://doi.org/10.1016/j.nuclcard.2007.02.016 (2007).
31. Vasu, S. et al. Regadenoson and adenosine are equivalent vasodilators and are superior than dipyridamole- a study of first pass quantitative perfusion cardiovascular magnetic resonance. *J. Cardiovasc. Magn. Reson. Off J. Soc. Cardiovasc. Magn. Reson.* **15** (1), 85. https://doi.org/10.1186/1532-429X-15-85 (2013).
32. Amer, K. A., Hurren, J. R., Edwin, S. B. & Cohen, G. Regadenoson versus Dipyridamole: A Comparison of the Frequency of Adverse Events in Patients Undergoing Myocardial Perfusion Imaging. *Pharmacotherapy* **37** (6), 657–661. https://doi.org/10.1002/phar.1940 (2017).
33. Mahmod, M. 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. Off J. Soc. Cardiovasc. Magn. Reson.* **16** (1), 92. https://doi.org/10.1186/s12968-014-0092-y (2014).
34. Moon, J. C. et al. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J. Cardiovasc. Magn. Reson. Off J. Soc. Cardiovasc. Magn. Reson.* **15** (1), 92. https://doi.org/10.1186/1532-429X-15-92 (2013).
35. Uren, N. G. et al. Effect of aging on myocardial perfusion reserve. *J. Nucl. Med.* **36** (11), 2032–2036 (1995).

Author contributions

YTC: Writing – Original Draft Preparation; Writing – Review & Editing; Visualization. CYC: Investigation. WMH: Data Curation. CLH: Investigation. QZ: Methodology; Writing – Review & Editing. RAG: Methodology; Writing – Review & Editing. MKB: Writing – Review & Editing. SKP: Methodology; Writing – Review & Editing. VMF: Conceptualization; Methodology; Writing – Review & Editing. CHY: Conceptualization; Funding Acquisition; Investigation (primary); Supervision; Methodology; Writing – Review & Editing.

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Declarations

Competing interests
Dr Piechnik has patent authorship rights for U.S. patent 9285446 B2 (systems and methods for Shortened Look Locker Inversion Recovery [Sh-MOLLI] cardiac gated mapping of T1), granted March 15, 2016; The patent is managed by Oxford University Innovations. Other authors declare no conflict of interest.

Additional information
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Correspondence and requests for materials should be addressed to C.-H.Y.