Original Article

Comparison of MOLLI and ShMOLLI Regarding T1 Reactivity, and the Relationship of T1 Reactivity with Conventional Signs of Response During Adenosine Stress Perfusion CMR

Esin Gezmiş[1], Charles Peebles[2], Andrew Flett[3], Ausami Abbas[4], Stephen Harden[4], James Shambrook[4]
[1]Department of Radiology, Baskent University Hospital Izmir Practice and Research Center, İzmir, Turkey
[2]Department of Cardiothoracic Radiology, University Hospital Southampton, Southampton, United Kingdom
[3]Department of Cardiology, University Hospital Southampton, Southampton, United Kingdom
[4]Department of Cardiothoracic Radiology, University Hospital Southampton, Southampton, United Kingdom

Address for Correspondence: Esin Gezmiş, Department of Radiology, Baskent University Hospital Izmir Practice and Research Center, İzmir, Turkey
khnumhetep@gmail.com
+90 232 241 10 47

Received: 28 December 2019
Accepted: 21 April 2020

DOI: 10.4274/balkanmedj.galenos.2020.2019.12.161

Cite this article as: Gezmiş E, Peebles C, Flett A, Abbas A, Harden S, Shambrook J. Comparison of MOLLI and ShMOLLI Regarding T1 Reactivity, and the Relationship of T1 Reactivity with Conventional Signs of Response During Adenosine Stress Perfusion CMR. Balkan Med J

Background: Cardiac Magnetic Resonance (CMR) has proven to be a valuable imaging modality used both to diagnose and to differentiate coronary heart diseases (CHD) from other cardiomyopathies. One of the most important techniques of CMR in assessment of CHD is Adenosine Stress Myocardial First Pass Perfusion Imaging. During this imaging method to make an accurate evaluation, there should be an adequate response to the drug adenosine. The conventional signs of drug response are not always observed, and are often subjective. The methods based on splenic perfusion might possess limitations too. Therefore T1 mapping presents as a novel, quantitative and reliable method. There are several studies analyzing this newly discovered property of different T1 mapping sequences, however most of them are enrolling only one of the techniques.
Aims: We aimed to compare MOLLI and ShMOLLI sequences in terms of T1 reactivity (ΔT1), and to determine the relationship between ΔT1 and conventional stress adequacy assessment methods in Adenosine Stress Perfusion CMR.
Study Design: This is a cross-sectional study and STARD reporting guidelines were used.
Methods: 34 consecutive patients, who were referred for adenosine stress perfusion CMR because of the suspicion of myocardial ischaemia, were prospectively enrolled. 4 patients were disqualified, and 30 patients were included in the final analysis. Mid-ventricular short axis slices of T1 maps using both MOLLI and ShMOLLI were acquired at rest and during peak adenosine stress before gadolinium administration. Then they were divided into 6 segments according to the American Heart Association 17 segments model, and separate measurements were made from each segment. Mean rest and mean stress T1 values of remote, ischaemic, infarcted myocardiums were calculated individually per subject. During adenosine administration patients' heart rates (HR) and blood pressures (BP) are measured and recorded every one minute. Adenosine stress perfusion images were examined for the presence of splenic switch-off.
Results: There was significant difference between rest and stress T1 values of remote myocardium in both MOLLI and ShMOLLI ($p<0.001$). In both MOLLI and ShMOLLI there was no significant correlation between ΔT1 and HR response (MOLLI p=0.30, ShMOLLI p=0.10), BP response (MOLLI p=0.062, ShMOLLI p=0. 0.078), splenic perfusion (MOLLI p=0.35, ShMOLLI p=0.053). There was no statistically significant difference between MOLLI and ShMOLLI regarding ΔT1 of remote (p=0.330), ischaemic (p=0.068), and infarcted (p=0.116) myocardiums.
Conclusion: In summary, we found that ΔT1 is independent of the other stress response signs. MOLLI and ShMOLLI do not differ in terms of ΔT1.
Keywords: Adenosine stress adequacy, CMR, coronary heart disease, MOLLI, ShMOLLI, T1 Mapping

Cardiac Magnetic Resonance (CMR) has proven to be a valuable imaging modality used both to diagnose and to differentiate coronary heart diseases (CHD) from other cardiomyopathies. One of the most important techniques of CMR in assessment of CHD is Adenosine Stress Myocardial First Pass Perfusion Imaging with it's high sensitivity (80-90%) and ability to demonstrate ischaemic but not infarcted areas which are more likely to be viable (1). During this imaging method to make an accurate evaluation, there should be an adequate response to adenosine to avoid false negative findings (2, 3). The increase in heart rate (HR) by 10 bpm and the decrease in systolic blood pressure (SBP) by 10 mmHg are the signs of haemodynamic response. Meanwhile the patient can experience flushing, chest tightness, headache which might also be proof of adequate adenosine stress (4, 5). However those findings are not always observed, and are often subjective. Other recently recommended methods are visual evaluation of splenic perfusion, in which failure of splenic switch-off is an indicator of inadequate pharmacologic stress, and splenic T1 reactivity, which is the difference between rest and stress T1 values of spleen (5, 6). However these might possess limitations too. Therefore an additional quantitative and reliable method may be beneficial. Recent studies showed that T1 values of normal/remote myocardium increase during adenosine stress compared to rest, and also rest/stress T1 mapping can differentiate between normal/remote myocardium and infarcted or ischaemic myocardium without the need for gadolinium contrast (7, 8). The Modified Look-Locker Inversion Recovery (MOLLI) sequence which was created by Messroghli et al. (9) in 2004 and the faster and more robust Shortened Modified Look-Locker Inversion Recovery (ShMOLLI) sequence which was proposed by Oxford group in 2010 are two common mapping techniques for quantification of T1 values of myocardium (10). There are several studies analyzing this newly discovered property of different T1 mapping sequences, however most of them are enrolling only one of the techniques. We aimed to compare MOLLI and ShMOLLI in terms of T1 reactivity, and to determine the relationship between T1 reactivity and conventional stress adequacy assessment methods in Adenosine Stress Perfusion CMR.

METHODS

All patients gave written informed consent to participate in the study and ethical approval was granted by National Research Ethics Service (REC reference 13/YH/0223). The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This is a cross-sectional study and STARD reporting guidelines were used (11).

Patient Population

34 consecutive patients, who were referred for adenosine stress perfusion CMR because of the suspicion of myocardial ischaemia, between December 2016 and February 2017, were prospectively enrolled. 4 patients were disqualified based on exclusion criteria, which were general CMR contraindications, mapping motion artefacts, technical failures, underlying cardiomyopathy and caffeine intake. 30 patients were included in the analysis.

CMR Imaging Protocol

A 1.5T scanner (Magnetom Avanto; Siemens Healthcare, Germany) was used in all patients. Firstly standard cine images and STIR sequences were acquired in three cardiac planes (short axis:SA, 2 Chambers:2Ch, 4 Chambers:4Ch). Then basal, mid-ventricular, apical SA slices of T1 maps using both MOLLI (WIP780B) with 5(3)3 sampling scheme and ShMOLLI were performed at rest (10, 12). As adenosine was administered (140 µg/kg/min, intravenously for ≥3 to 6 min), mid-ventricular SA slices of both MOLLI and ShMOLLI during peak adenosine stress were acquired. In order not to prolong scanning time and patients' exposure to adenosine, which may increase the discomfort and risk of complication, only mid-ventricular SA slices of stress T1 maps were obtained. Mid-ventricular slice was preferred, because there is more myocardium (6 segments), less blood pool contamination and artefact. During each examination the patient' s drug response was assessed by the responsible consultant radiologist, however uptitration of adenosine was not needed in any of the patients based on the findings of symptomatic and haemodynamic responses. Following stress T1 maps, first-pass perfusion imaging was performed, on matching SA slices to rest T1 maps, during peak adenosine stress with an intravenous bolus of gadolinium (0.1 mmol/kg). Late gadolinium enhancement (LGE) imaging was performed 10 min after an additional bolus of gadolinium (0.1 mmol/kg). During adenosine administration patients' HRs and SBPs are measured and recorded every one minute.

Imaging Analysis

It was performed by two cardiothoracic radiologists; one of them accredited consultant and the other one senior clinical fellow, on Siemens Syngo.via VA20 software. Both of them were blinded to the patients' data. The endocardium and epicardium of T1 maps were manually and carefully outlined, avoiding contamination by blood pool and extramyocardial structures. They were divided into 6 segments according to American Heart Association 17 segments model of left ventricle (LV), and separate measurements were made from each segment (Fig1, Fig2, Fig3, Fig4) (12). Mean rest and mean stress T1 values of remote, ischaemic, infarcted myocardiums were calculated

individually per subject. The segments with reversible perfusion defects on first pass stress and rest perfusion images but without LGE were regarded as ischaemic. The segments with subendocardial LGE were defined as infarcted. In ischaemic and infarcted segments, regions of interests (ROIs) were placed to affected portion only, excluding remote myocardium found in the same segment. T1 reactivity to adenosine stress was expressed in absolute terms: $\Delta T1(ms) = T1_{stress} - T1_{rest}$ and as percentages: $\Delta T1(\%) = \Delta T1 \ / \ T1_{rest} \times 100$. $T1_{rest}$ and $T1_{stress}$ represent mean T1 values at rest and during stress, respectively. T1 values of blood pool were also measured in order to exclude partial volume effects. All measurements were firstly made and digitally stored by the senior fellow, then checked by the consultant. Also adenosine stress perfusion images were examined for the presence of splenic switch-off, which is a reduction in attenuation of spleen under adenosine stress compered to rest perfusion images (5).

Statistical Analysis

All analyses were performed on SPSS v21. Shapiro-Wilk test was used for the normality test. Comparisons of rest and stress T1 values of remote myocardium were made with "multivariate Repeated Measures ANOVA"; with HR response, SBP response and splenic switch-off configured as between-subject factors. We calculated ΔT1 of remote, ischaemic and infarcted myocardium separately. The resulting data was analyzed with Wilcoxon Signed Rank Test. Also these differences were assessed with Mann Whitney U test regarding splenic switch-off status. Correlation between ejection fraction (EF) and remote myocardial ΔT1 was tested with Pearson's Correlation Coefficient. Comparison of EF regarding responses was made with paired t test. Comparison of MOLLI and ShMOLLI sequences were made using the data from the patients, who had rest and stress maps of both MOLLI and ShMOLLI. Comparison of MOLLI and ShMOLLI in terms of ΔT1 was made by using "multivariate Repeated Measures ANOVA" for remote myocardium, and "Wilcoxon Signed Rank Test" for ischaemic and infarcted myocardiums. Bland Altman plot was also used for assessment of differences between measurements in remote myocardium (Fig6). $p \leq 0.05$ values were accepted as statistically significant. Post-hoc power analysis was made based on ΔT1 variable with an effect size of 1.25, an alpha level of 0.05, and a sample size of 26, for MOLLI and ShMOLLI groups. The power is 99%

RESULTS

We included 30 patients (23 males and 7 females); mean age was 66.07±11.10. 20 patients had been previously diagnosed with coronary artery disease (CAD). All the patients showed at least one of the conventional response signs. Almost all patients (29/30, 96.7%) experienced symptomatic response. In 25 patients (83.3%) haemodynamic response (HR and/or SBP) was detected. In 17(56.7%) patients splenic switch-off was seen. 15 patients (50%) showed symptomatic response, haemodynamic response (HR and/or SBP), and splenic switch-off. CMR scan results of 5 patients were normal. 14 of the patients with known CAD had infarcted, and 8 of them had ischaemic myocardial segments in CMR (midventricular segments were affected in 8 and 5 of them respectively). Patients' demographics and characteristics are summarized in Table 1 and 2.

Mid-ventricular SA slices of MOLLI in 4 patients and of ShMOLLI in 3 patients could not be achieved because of technical failures. In total, 106 mid-ventricular SA slices of T1-maps were acquired (26 MOLLI and 27 ShMOLLI at rest; 26 MOLLI and 27 ShMOLLI under stress) and subsequently divided into 636 segments. 23 segments (3.62%) (7 rest MOLLI, 8 stress MOLLI, 2 rest ShMOLLI, 6 stress ShMOLLI) were excluded due to off-resonance artefacts, partial volume effects, poor T1 fit on the R^2 maps, patient movements or low signal-to-noise. 613 segments were included in the final analysis. 8(26.7%) patients had 12 infarcted myocardial segments in total (In 4 of the infarcted segments LGE thickness was of the order of <50%, whereas 8 of them showed >50% transmurality). 5(%16.7) patients had 6 ischaemic myocardial segments in total.

When we compared rest and stress T1 values of remote myocardium, there was significant difference in both MOLLI and ShMOLLI (Table 3, Fig5, Fig6). There was no significant difference between these sequences regarding ΔT1 of remote myocardium (p=0.33) (Table 5). When we compared ΔT1 between remote and infarcted myocardium, we found significant differences in both MOLLI (p=0.017) and ShMOLLI (p=0.043) (Table 4). However, as we divide the infarcted myocardium into two subgroups based on the thickness, we detected that ΔT1 of <50% thick infarcted myocardium showed no significant difference compared to remote in ShMOLLI (p=0.84) (Table 4). When we compared ΔT1 between remote and ischaemic myocardium, we found no significant differences in both MOLLI (p=0.14) and ShMOLLI (p=0.35) (Table 4). There was no statistically significant difference between MOLLI and ShMOLLI regarding ΔT1 in ischaemic and infarcted myocardiums (Table 5).

We compared ΔT1 of remote myocardium with HR response, SBP response, and splenic switch-off. In MOLLI there was no significant correlation between ΔT1 and HR response (p=0.30), SBP response (p=0.062), splenic switch-off (p=0.35). Similarly there was no significant correlation between ΔT1 and HR response (p=0.10), SBP response (p=0.078), splenic switch-off (p=0.053) in ShMOLLI. There were no statistically significant differences in ΔT1 of remote, ischaemic, infarcted myocardiums between patients with and without splenic switch-off (Table 6). MOLLI and ShMOLLI showed no statistically significant difference in terms of ΔT1 between patients with and without splenic switch-off (Table 7).

There was no significant correlation between ejection fraction (EF) and ΔT1 of remote myocardium in MOLLI (r=0.335; p=0.095), while there was moderate positive correlation in ShMOLLI (r=0.432; p=0.024). When EF was compared between patients with and without HR response, we found no significant difference (p=0.22). We found no significant difference between patients with and without SBP response for the same comparison (p=0.16). On the other hand, patients with splenic switch-off were found to have significantly higher EF values in comparison to patients without splenic switch-off (p=0.020) (Table 8).

DISCUSSION

Mishra et al. (13) proved that HR and SBP correlate poorly with adenosine-induced myocardial hyperemia, and cannot be used to assess the adequacy of stress testing. Splenic markers possess limitations, such as receptor variability, patients having undergone splenectomy, spleen not being visible in perfusion images. Furthermore we actually do not know how well splenic perfusion correlate with the effects of adenosine on myocardium, which is the main region of interest.

There are many recent studies showing the role of T1 mapping in CMR. One of the main factors that T1 relaxation time depends on is water content of the tissue, which is highly affected by blood volume (9, 10, 13, 14, 15). Hence coronary vasodilatation, which increases myocardial blood volume (MBV) is expected to prolong T1, and allow detection of microvascular and MBV changes during ischemia (16-19). Mahmod et al. (20) demonstrated the ability of stress/rest T1 mapping to detect increases in MBV from coronary vasodilatation in patients with severe aortic stenosis and non-obstructive coronary arteries, with complete reversal and normalization after aortic valve replacement. Liu et al. (7) showed that T1 values of normal/remote myocardium increase during adenosine stress compared to rest, and also rest/stress T1 mapping can differentiate between normal/remote myocardium and infarcted or ischaemic myocardium. Another research consisting of rest/stress T1 mapping, which is performed by Kuijpers et al. (8), is about the effect of caffeine intake on myocardial perfusion during adenosine stress MRI. They compared ΔT1 of patients who drank coffee and not. Not only they proved that caffeine inverts the effects of adenosine on myocardium, but also they stated that ΔT1 can be used as a criterion for the validity of the stress induction by adenosine at cardiac MR perfusion studies.

In our study we found that T1 mapping values of remote myocardium increase during stress adequacy as an indicator of coronary hyperemia in both MOLLI and ShMOLLI regardless of whether there are markers of symptomatic response, haemodynamic response, and splenic switch-off. We found that T1 reactivities in patients with splenic switch-off were not different from T1 reactivities in patients without splenic switch-off (Table 6 and 7). Although the number of patients experiencing symptomatic response (29/96.7%) were higher than patients demonstrating T1 reactivity (MOLLI and/or ShMOLLI 28/93.3%) suggesting that it might be a better method, we should keep in mind that symptomatic response is subjective and mainly based on the patients' expressions (Table 2). We had only 1 patient (76 years old, male, no history of CAD or diabetes mellitus), who showed solely symptomatic response. However he was one of the patients with severe LV impairment, and the adenosine dose could not be increased due to the patient's discomfort, which was questionable (the probability of inadequate stress was remarked in his CMR report). We observed that T1 values of two patients with severe LV impairment (EF: 22% and 29%) showed no elevation during stress, although both seemed to have adequate stress based on conventional methods, with both experiencing signs of symptomatic response and one also showing splenic switch-off. Although there was not significant correlation between ΔT1 and EF, and there might be other underlying pathology causing blunted T1, one should be cautious while interpreting stress perfusion CMR keeping in mind that there might not be myocardial hyperemia during adenosine stress. These findings also highlight the suggestion that T1 reactivity could be a better choice to analyze the effect of adenosine on myocardium. To the best of our knowledge the relationship between EF and response to adenosine or ΔT1 have not been investigated briefly and could be researched in larger studies.

Our findings confirmed the results of previous studies about differentiating infarcted myocardium from remote using ΔT1 (7, 8). Meanwhile no statistically significant difference was detected between ΔT1 of ischaemic and remote myocardium, which contradicts them. The number of ischaemic segments was low in our study. Moreover the thicknesses of all these perfusion deficits were <50%. Although ROIs were carefully placed, we suspect that the interference from remote myocardium found in the same segments might not have been overcome. Additionally when we look at the percentage values of ΔT1, especially in MOLLI, we could detect a slight difference (Table 4), which might have become statistically significant should there have been more and thicker ischaemic segments. The specificity and sensitivity of ΔT1 in differentiating <50% thick perfusion deficits from remote, should be investigated in larger studies.

In literature there are a few studies comparing T1 mapping sequences, however all of them are about native T1 mapping, and most of them studied on phantoms or healthy volunteers. Roujal et al. (21) compared the accuracy, precision, reproducibility of four T1 mapping sequences (MOLLI, ShMOLLI, SASHA, SAPPHIRE) by using both a phantom and 7 healthy volunteers, and reported that precision of MOLLI was more than ShMOLLI, whereas their reproducibility was similar. Another study by Child et al. (22), which is about the bioequivalence of MOLLI, ShMOLLI, SASHA in myocardial characterization of diffuse myocardial fibrosis, proved that they differ in their bioequivalence for discrimination between health and disease as well as associations with diffuse myocardial fibrosis. Teixeira et al. (23) compared MOLLI, ShMOLLI, SASHA for native T1 mapping at 3T, and concluded that MOLLI had the smallest overall variability while SASHA the best accuracy. Piechnik et al. (10) studied the difference between rest T1 values of MOLLI and ShMOLLI using both phantom and in-vivo materials. They revealed that ShMOLLI rest T1s were shorter than MOLLI T1s by 10 ± 16 ms at 1.5T, and ShMOLLI showed a 15% larger T1 difference between infarcted and unaffected myocardium. Similar to Piechnik et al.' s findings, we observed that both rest and stress ShMOLLI T1s were shorter than MOLLI T1s except rest and stress ShMOLLI T1s of <50% thick infarcted myocardium. Moreover the percentage values of ΔT1 in ShMOLLI were higher in all kind of myocardial tissues except >50% thick infarcted myocardium. However the difference between rest T1 values of infarcted and remote myocardiums were larger in MOLLI compared to ShMOLLI (MOLLI 5.32% and ShMOLLI 4.93%) (Table 5). We did not see statistically significant difference between T1 reactivity of <50% thick infarcted myocardium and remote myocardium in ShMOLLI (p=0.84), whereas in MOLLI the difference was statistically significant (p=0.028) (Table 4). Additionally we noticed that the distinction between ΔT1 values of affected myocardiums and ΔT1 values of remote myocardium were more evident in MOLLI compared to ShMOLLI (Table 5). Even though there was no statistically significant difference between MOLLI and ShMOLLI and the result about <50% thick infarct in ShMOLLI might have been due to the intertwined remote myocardium, if researched and confirmed in larger studies, ΔT1 MOLLI might prove to be better in distinguishing the affected tissues from remote. Because of artefacts we had to exclude 23 segments, of which only 8 were ShMOLLI. This is also in agreement with the published data claiming that ShMOLLI has a smaller noise penalty than MOLLI (10).

In conclusion, T1 reactivity is independent of systemic, haemodynamic, splenic switch-off responses. ΔT1 can be used as an additional tool to estimate stress adequacy, as they are robust, reproducible, objective findings specific to myocardium. MOLLI and ShMOLLI mapping sequences do not differ in terms of T1 reactivity.

STUDY LIMITATIONS:
Our study population and the number patients with ischaemic and/or infarcted myocardiums were small. We did not have a control group consisting of healthy volunteers to assess the normal T1 reactivity.

ACKNOWLEDGEMETS:
Not applicable.

REFERENCES

1. Coelho Filho OR, Rickers C, Kwong RY, Jerosch-Herold M. MR myocardial perfusion imaging. Radiology 2013; 266(3):701-15.
2. Hamon M, Fau G, Née G, Ehtisham J, Morello R, Hamon M. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. J Cardiovasc Magn Reson 2010; 12(1):29.

3. Kidambi A, Sourbron S, Maredia N, Motwani M, Brown JM, Nixon J et al. Factors associated with false-negative cardiovascular magnetic resonance perfusion studies: A Clinical evaluation of magnetic resonance imaging in coronary artery disease (CE-MARC) substudy. J Magn Reson Imaging 2016 Mar; 43(3):566-73.
4. Ogilby JD, Iskandrian AS, Untereker WJ, Heo J, Nguyen TN, Mercuro J. Effect of intravenous adenosine infusion on myocardial perfusion and function. Hemodynamic/angiographic and scintigraphic study. Circulation 1992; 86(3):887-95.
5. Manisty C, Ripley DP, Herrey AS, Captur G, Wong TC, Petersen SE et al. Splenic Switch-off: A Tool to Assess Stress Adequacy in Adenosine Perfusion Cardiac MR Imaging. Radiology 2015; 276(3):732-40.
6. Liu A, Wijesurendra RS, Ariga R, Mahmod M, Levelt E, Greiser A et al. Splenic T1-mapping: a novel quantitative method for assessing adenosine stress adequacy for cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2017;19(1):1.
7. Liu A, Wijesurendra RS, Francis JM, Robson MD, Neubauer S, Piechnik SK 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 Jan; 9(1):27-36.
8. Kuijpers D, Prakken NH, Vliegenthart R, van Dijkman PR, van der Harst P, Oudkerk M. Caffeine intake inverts the effect of adenosine on myocardial perfusion during stress as measured by T1 mapping. Int J Cardiovasc Imaging 2016;32(10):1545-53.
9. Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified Look Locker inversion recovery (MOLLI) for high resolution T1 mapping of the heart. Magn Reson Med 2004;52(1):141-6.
10. Piechnik SK, Ferreira VM, Dall'Armellina E, Cochlin LE, Greiser A, Neubauer S et al. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3T within a 9 heartbeat breathhold. J Cardiovasc Magn Reson 2010; 19(12):69.
11. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L et al. For the STARD Group. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies.
12. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK et al. Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart. Circulation 2002;105:539-542.
13. Mishra RK, Dorbala S, Logsetty G, Hassan A, Heinonen T, Schelbert HR et al; RAMPART investigators. Quantitative relation between hemodynamic changes during intravenous adenosine infusion and the magnitude of coronary hyperemia: implications for myocardial perfusion imaging. J Am Coll Cardiol Img 2005; 45(4):553-8.
14. Nagel E, Narula J. Evolution and revolution in CMR imaging. J Am Coll Cardiol Img 2013; 6(7):837-8.
15. Piechnik SK, Ferreira VM, Lewandowski AJ, Ntusi NAB, Banerjee R, Holloway C et al. Normal variation of magnetic resonance T1 relaxation times in the human population at 1.5 T using ShMOLLI. J Cardiovasc Magn Reson 2013; 15:13.
16. McCommis KS, Goldstein TA, Abendschein DR, Misselwitz B, Pilgram T, Gropler RJ et al. Roles of myocardial blood volume and flow in coronary artery disease: an experimental MRI study at rest and during hyperemia. Eur Radiol 2010; 20:2005-12.
17. McCommis KS, Goldstein TA, Zhang H, Misselwitz B, Gropler RJ, Zheng J. Quantification of myocardial blood volume during dipyridamole and dobutamine stress: a perfusion CMR study. J Cardiovasc Magn Reson 2007; 9:785-92.
18. McCommis KS, Zhang H, Goldstein TA, Misselwitz B, Abendschein DR, Gropler RJ et al. Myocardial blood volume is associated with myocardial oxygen consumption: an experimental study with cardiac magnetic resonance in a canine model. J Am Coll Cardiol Img 2009; 2:1313-20.
19. Wacker CM, Bauer WR. Myocardial microcirculation in humans–new approaches using MRI. Herz 2003; 28:74-81.
20. Mahmod M, Piechnik SK, Levelt E, Ferreira VM, Francis JM, Lewis A 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.
21. Roujol S, Weingärtner S, Foppa M, Chow K, Kawaji K, Ngo LH et al. Accuracy, precision, and reproducibility of four T1 mapping sequences: a head-to-head comparison of MOLLI, ShMOLLI, SASHA, and SAPPHIRE. Radiology 2014;272(3):683-9.
22. Child N, Suna G, Dabir D, Yap ML, Rogers T, Kathirgamanathan M et al. Comparison of MOLLI, shMOLLLI, and SASHA in discrimination between health and disease and relationship with histologically derived collagen volume fraction. Eur Heart J Cardiovasc Imaging. 2018;19(7):768-76.
23. Teixeira T, Hafyane T, Stikov N, Akdeniz C, Greiser A, Friedrich MG. Comparison of different cardiovascular magnetic resonance sequences for native myocardial T1 mapping at 3T. J Cardiovasc Magn Reson 2016;18(1):65.

TABLES

Table 1. Demographics and Characteristics of Patients	
Age	66.07 ± 11.10
Gender	
Male	*23 (76.7%)*
Female	*7 (23.3%)*
Diabetes Mellitus	5 (16.7%)
Previous CAD Diagnosis	20 (66.7%)
Only CAG	*8 (26.%)*
PCI	*7 (23.3%)*
CABG	*3 (10%)*
PCI + CABG	*2 (6.7%)*
No History of CAD Diagnosis	10 (33.3%)
Symptoms	*8 (26.7%)*
LV systolic function impairment	*1 (3.3%)*
Aortic dissection repair	*1 (3.3%)*
LV Ejection Fraction (%)	54.10 ± 12.72
Heart Rate (beats/min)	
Baseline	*69.53 ± 14.08*
Peak	*84.50 ± 16.82*
Systolic Blood Pressure (mmHg)	
Baseline	*139.83 ± 19.31*
Peak	*134.83 ± 20.57*
Diastolic Blood Pressure (mmHg)	
Baseline	76.60 ± 14.49
Peak	71.83 ± 13.58
Normal CMR	5 (17%)
Previous CAD Diagnosis	*1 (3.3%)*
No history of CAD Diagnosis	*4 (13.3%)*
Data given as mean ± standard deviation or frequency (percentage).	

Table 2. Adenosine Drug Responses of Patients						
Patient	Symptomatic Response	Haemodynamic Response		Splenic Switch Off	Remote Myocardium ΔT1 Response MOLLI	Remote Myocardium ΔT1 Response ShMOLLI
		HR	SBPR			
1	+	-	-	-	N/A	+
2	+	-	+	+	+	+
3	+	-	-	-	+	+
4	+	+	+	-	+	+
5	+	+	-	+	N/A	+
6	+	+	-	+	N/A	+
7	+	+	+	+	+	+
8	+	+	+	+	+	N/A
9	+	-	-	-	+	N/A
10	-	+	-	+	+	+
11	+	+	+	+	+	+
12	+	+	-	+	+	+
13	+	+	+	+	+	+
14	+	+	-	-	+	+
15	+	+	-	+	+	+
16	+	+	-	+	+	+
17*	+	-	-	-	-	-
18*	+	-	-	+	-	-
19	+	+	+	-	+	+
20	+	+	+	+	+	+
21	+	+	-	-	+	+
22	+	+	+	-	+	N/A
23	+	+	-	+	N/A	+
24	+	+	-	+	+	+
25	+	+	-	-	+	+
26	+	+	+	-	+	+
27	+	+	+	+	+	+
28	+	+	-	-	+	+
29	+	+	-	-	+	+
30	+	+	-	+	+	+
TOTAL (+)	29 (96.7%)	24 (80%)	11 (36.7%)	17(56.7%)	24 (80%)	25 (83.3%)
		25 (83.3%)			28 (93.3%)	
HR: Heart rate response. SBPR: Systolic blood pressure response. N/A: Not available *(could not be obtained because of technical failures and artefacts).* *: Patients with severe left ventricular impairment.						

Table 3. Comparison of T1 values of Remote Myocardium				
	n	Rest	Stress	p
MOLLI	26	980.12 ± 35.74	1020.77 ± 51.25	<0.001
ShMOLLI	27	926.93 ± 32.46	975.41 ± 44.67	<0.001
Data given as mean ± standard deviation.				

Table 4. Comparison of T1 Values of Remote, Ischaemic and Infarcted Myocardiums In MOLLI and ShMOLLI

	MOLLI				ShMOLLI			
TISSUES	Mean Rest T1 (ms) (Nb of patients / Nb of segments)	Mean Stress T1 (ms) (Nb of patients / Nb of segments)	ΔT1 (ms) %	P Value (ΔT1 compared to remote)	Mean Rest T1 (ms) (Nb of patients / Nb of segments)	Mean Stress T1 (ms) (Nb of patients / Nb of segments)	ΔT1 (ms) %	P V (ΔT con to r
Remote	980.12 ± 35.74 (26 / 134)	1020.77 ± 51.25 (26 / 133)	40.65 ± 32.58 4.14 ± 3.35 %	N/A	926.23 ± 32.46 (27 / 144)	975.41 ± 44.67 (27 / 137)	49.18 ± 36.72 5.26 ± 3.94 %	N/A
Ischaemic	959.50 ± 61.93 (4 / 5)	963.75 ± 48.55 (4 / 5)	4.25 ± 30.51 0.54 ± 3.11 %	0.14	918.20 ± 93.78 (5 / 6)	966.80 ± 78.04 (5 / 6)	48.60 ± 33.03 5.53 ± 4.12 %	0.3
Infarcted	1030.25 ± 65.26 (8 / 10)	1027.13 ± 59.82 (8 / 10)	-3.13 ± 22.34 -0,25 ± 2.23 %	0.017	969.71 ± 53.97 (7 / 10)	990.71 ± 42.13 (7 / 10)	21.00 ± 26.20 2.25 ± 2.81 %	0.0
< 50% Infarcted	983.00 ± 49.21 (4 / 4)	983.25 ± 48.27 (4 / 4)	0.25 ± 31.83 0.07 ± 3.22 %	0.028	932.67 ± 20.21 (3 / 3)	977.33 ± 27.79 (3 / 3)	44.67 ± 20.55 4.79 ± 2.24 %	0.8
> 50% Infarcted	1077.50 ± 39.53 (4 / 6)	1071.00 ± 29.74 (4 / 6)	-6.50 ± 11.03 -0.58 ± 0.97 %	0.009	997.50 ± 56.13 (4 / 7)	1000.75 ± 52.17 (4 / 7)	3.25 ± 10.53 0.35 ± 1.09 %	0.0

Negative values show decrease in T1 values during adenosine stress. Data given as mean ± standard deviation. N/A: not available.

Table 5. Comparison of MOLLI and ShMOLLI sequences in terms of T1 reactivity of Remote, Ischaemic and Infarcted Myocardiums In Patients with complete sets of rest and stress maps of both MOLLI and ShMOLLI

	MOLLI			ShMOLLI			
TISSUES (Nb of patients / Nb of segments)	Mean Rest T1 (ms)	Mean Stress T1 (ms)	ΔT1 (ms) %	Mean Rest T1 (ms)	Mean Stress T1 (ms)	ΔT1 (ms) %	ΔT1 MOLLI vs ΔT1 ShMOLLI P value
Remote (23 / 123)	981.43 ± 36.41	1022.39 ± 52.14	40.96 ± 34.23 4.17 ± 3.52 %	931.22 ± 32.50	975.65 ± 47.94	44.43 ± 37.18 4.78 ± 3.93 %	0.330
Ischaemic (4 / 5)	959.50 ± 61.93	963.75 ± 48.55	4.25 ± 30.51 0.54 ± 3.11 %	869.50 ± 92.67	943.50 ± 67.09	47.00 ± 37.92 5.54 ± 4.76 %	0.068
Infarcted (6 / 8)	1033.67 ± 76.10	1037.33 ± 62.07	3.67 ± 16.02 0.44 ± 1.56 %	977.17 ± 55.03	999.33 ± 38.81	22.17 ± 28.50 2.38 ± 3.06 %	0.116
< 50% Infarcted (3 / 3)	976.33 ± 58.01	992.33 ± 54.78	16.00 ± 5.57 1.66 ± 0.66 %	932.67 ± 20.21	977.33 ± 27.79	44.67 ± 20.55 4.79 ± 2.24 %	0.109
> 50% Infarcted (3 / 5)	1091.00 ± 35.37	1082.33 ± 23.59	-8.67 ± 12.42 -0.77 ± 1.10 %	1021.67 ± 34.96	1021.33 ± 39.25	-0.33 ± 9.45 -0.04 ± 0.94 %	0.593

Negative values show decrease in T1 values during adenosine stress. Data given as mean ± standard deviation.

Table 6. Comparison of ΔT1 of Remote, Ischaemic, Infarcted Myocardiums with Splenic Switch-off in MOLLI and ShMOLLI

	MOLLI ΔT1 (ms) %			ShMOLLI ΔT1 (ms) %		
TISSUES	SPLENIC SWITCH OFF (+) (Nb of patients / Nb of segments)	SPLENIC SWITCH OFF (-) (Nb of patients / Nb of segments)	P Value	SPLENIC SWITCH OFF (+) (Nb of patients / Nb of segments)	SPLENIC SWITCH OFF (-) (Nb of patients / Nb of segments)	P Value
Remote	43.43 ± 36.31 4.46 ± 3.80 % (14 / 76)	37.42 ± 28.86 3.77 ± 2.84 % (12 / 63)	0.74	49.06 ± 36.38 5.36 ± 3.95 % (16 / 88)	47.64 ± 38.98 5.11 ± 4.11 % (11 / 56)	0.61
Ischaemic	19.00 ± 26.87 2.04 ± 2.89 % (2 / 2)	-10.50 ± 34.65 -0.97 ± 3.40 % (2 / 3)	0.67	70.00 ± 20.22 7.98 ± 3.22 (3 / 3)	16.50 ± 10.61 1.83 ± 1.34 % (2 /3)	0.20
Infarcted	3.50 ± 19.91 0.45 ± 1.93 % (4 / 6)	-9.75 ± 25.53 -0.96 ± 2.56 % (4 / 4)	0.34	23.67 ± 20.03 2.50 ± 2.12 (3 / 5)	19.00 ± 33.06 2.07 ± 3.57 % (4 / 5)	0.86
< 50% Infarcted	18.50 ± 4.95 1.92 ± 0.67 % (2 / 2)	-18.00 ± 41.01 -1.78 ± 4.11 % (2 / 2)	0.33	34.00 ± 12.73 3.61 ± 1.26 % (2 / 2)	66.00 ± N.A 7.17 ± N.A (1 / 1)	0.67
> 50% Infarcted	-11.50 ± 16.26 -1.02 ± 1.44 % (2 / 4)	-1.50 ± 0.71 -0.14 ± 0.06 % (2 / 2)	1.00	-23.00 ± N.A 0.28 ± N.A (1 / 3)	3.33 ± 12.90 0.37 ± 1.34 % (3 / 4)	1.00

Negative values show decrease in T1 values during adenosine stress. Data given as mean ± standard deviation. N/A: not available.

Table 7. Comparison MOLLI and ShMOLLI in terms of ΔT1 of Remote, Ischaemic, Infarcted Myocardiums in patients with and without Splenic Switch-off *

SPLENIC SWITCH OFF (+)				SPLENIC SWITCH OFF (-)			
TISSUES (Nb of patients / Nb of segments)	MOLLI ΔT1 (ms) %	ShMOLLI ΔT1 (ms) %	P Value	TISSUES (Nb of patients / Nb of segments)	MOLLI ΔT1 (ms) %	ShMOLLI ΔT1 (ms) %	P Value
Remote (13 / 71)	42.23 ± 37.50 4.35 ± 3.94 %	42.69 ± 35.61 4.61 ± 3.78 %	0.86	Remote (10 / 52)	39.30 ± 31.36 3.93 ± 3.10 %	46.70 ± 40.96 5.00 ± 4.31	0.24
Ischaemic (2 / 2)	19.00 ± 26.87 2.04 ± 2.89 %	77.50 ± 21.92 9.25 ± 3.34 %	0.18	Ischaemic (2 / 3)	-10.50 ± 34.65 -0.97 ± 3.40 %	16.50 ± 10.61 1.83 ± 1.34 %	0.18
Infarcted (3 / 5)	4.67 ± 24.21 0.60 ± 2.33 %	23.67 ± 20.03 2.50 ± 2.12 %	0.11	Infarcted (3 / 3)	2.67 ± 7.23 0.28 ± 0.73 %	20.67 ± 40.28 2.25 ± 4.35 %	0.59
< 50% Infarcted (2 / 2)	18.50 ± 4.95 1.92 ± 0.67 %	34.00 ± 12.73 3.61 ± 1.26	0.18	< %50 Infarcted (1 / 1)	11.00 ± N/A 1.13 ± N/A %	66.00 ± N/A 7.17 ± N/A %	N/A

		%					
> 50% Infarcted (1 / 3)	-23.00 ± N/A -2.04 ± N/A %	3.00 ± N/A 0.28 ± N/A %	N/A	> %50 Infarcted (2 / 2)	-1.50 ± 0.71 -0.14 ± 0.06 %	-2.00 ± 12.73 -0.20 ± 1.27 %	0.66
**Patients who had rest and stress T1 maps of both MOLLI and ShMOLLI. Negative values show decrease in T1 values during adenosine stress. Data given as mean ± standard deviation. N/A: not available.*							

Table 8. Comparison of Ejection Fraction (EF) Regarding Responses

	n	EF (%)	p
Heart Rate Response			
Absent	6	45.00 ± 19.75	0.223
Present	24	56.38 ± 9.60	
Blood Pressure Response			
Absent	19	51.58 ± 13.74	0.157
Present	11	58.45 ± 9.83	
Splenic Switch-Off			
Absent	13	48.08 ± 13.39	0.020*
Present	17	58.71 ± 10.33	
*Data given as mean ± standard deviation. *: statistically significant ($p < 0.05$)*			

FIGURE LEGENDS

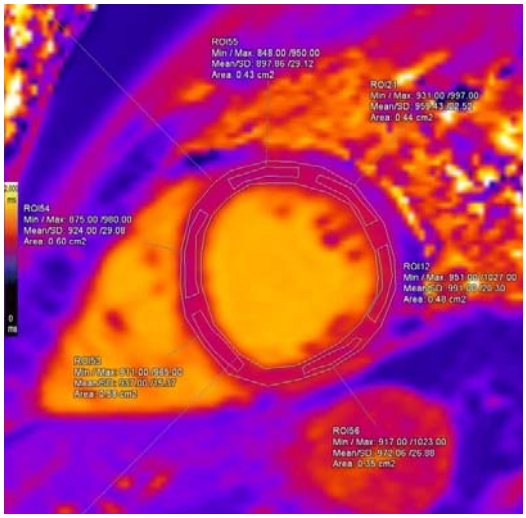

FIG. 1. T1 value measurements in rest MOLLI T1 map

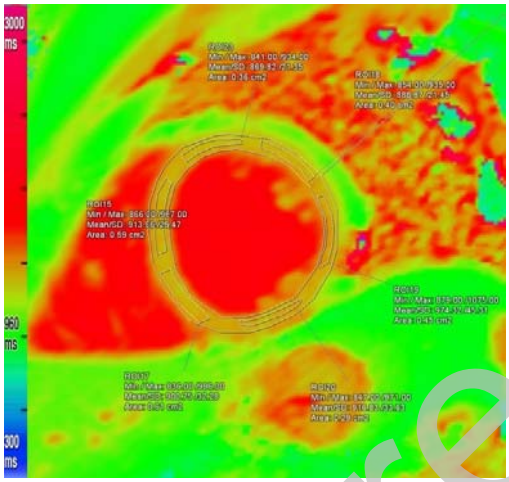

FIG. 2. T1 value measurements in rest ShMOLLI T1 map

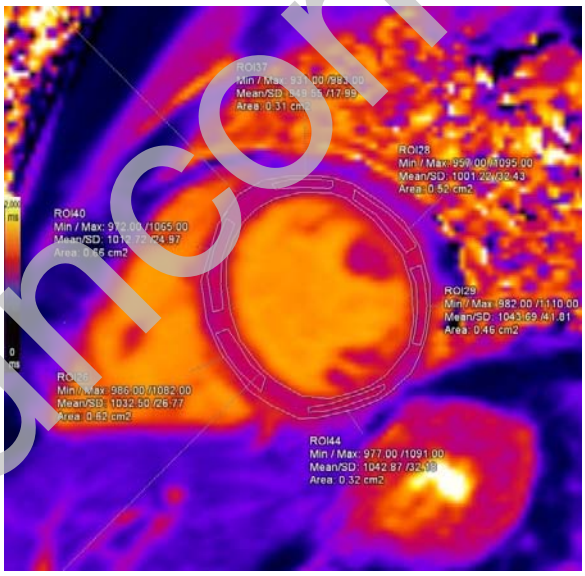

FIG. 3. T1 value measurements in stress MOLLI T1 map

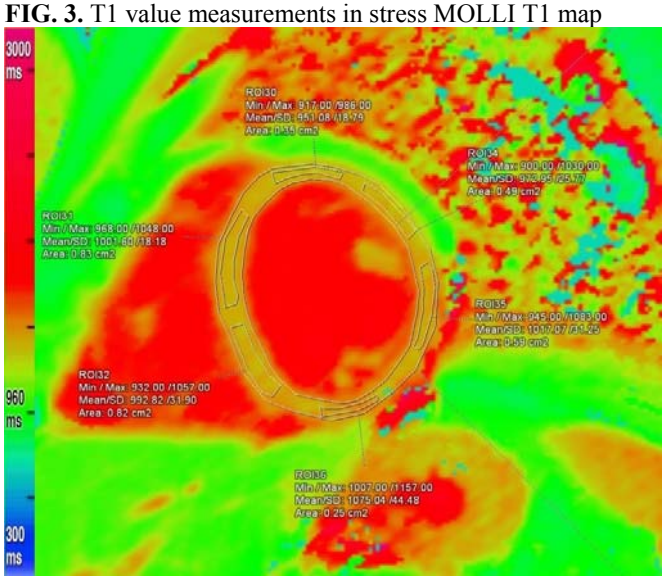

FIG. 4. T1 value measurements in stress ShMOLLI T1 map

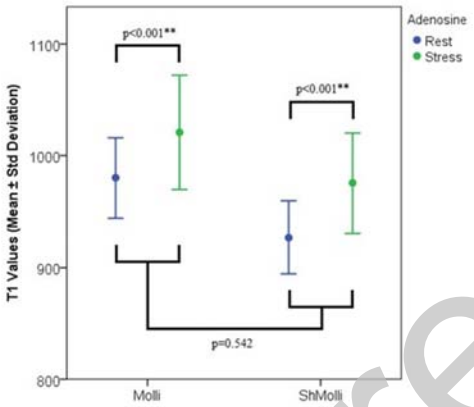

FIG. 5. T1 values of Remote Myocardial Segments at rest and stress in MOLLI and ShMOLLI sequences

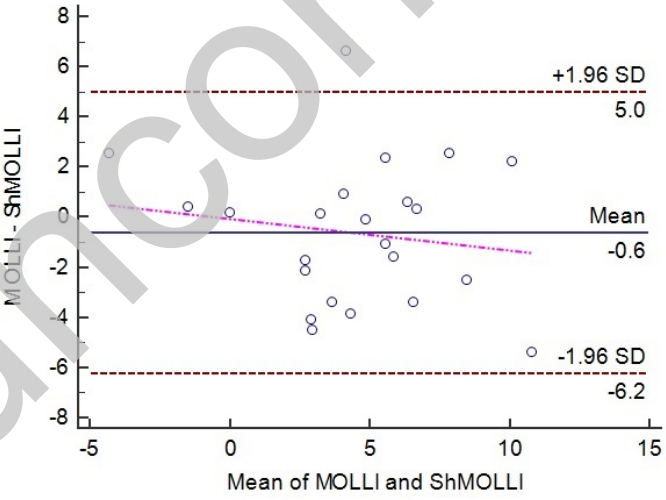

FIG. 6. Bland Altman Plot for T1 values of remote myocardium