

Accepted Manuscript

Title: T₁ Mapping for Assessment of Myocardial Injury and Microvascular Obstruction at One Week Post Myocardial Infarction

Author: Donnie Cameron Nishat Siddiqi Christopher J. Neil Baljit Jagpal Margaret Bruce David M. Higgins Jiabao He Satnam Singh Thomas W. Redpath Michael P. Frenneaux Dana K. Dawson



PII: S0720-048X(15)30128-5
DOI: <http://dx.doi.org/doi:10.1016/j.ejrad.2015.10.008>
Reference: EURR 7274

To appear in: *European Journal of Radiology*

Received date: 26-5-2015
Revised date: 7-8-2015
Accepted date: 11-10-2015

Please cite this article as: Cameron Donnie, Siddiqi Nishat, Neil Christopher J, Jagpal Baljit, Bruce Margaret, Higgins David M, He Jiabao, Singh Satnam, Redpath Thomas W, Frenneaux Michael P, Dawson Dana K. T₁ Mapping for Assessment of Myocardial Injury and Microvascular Obstruction at One Week Post Myocardial Infarction. *European Journal of Radiology* <http://dx.doi.org/10.1016/j.ejrad.2015.10.008>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

T₁ Mapping for Assessment of Myocardial Injury and Microvascular Obstruction at One Week Post Myocardial Infarction

Donnie Cameron, PhD¹, (Corresponding author) d.cameron.09@aberdeen.ac.uk

Nishat Siddiqi, MB ChB¹, n.siddiqi@abdn.ac.uk

Christopher J. Neil, MBBS¹, ctop1@me.com

Baljit Jagpal, MSc¹, b.jagpal@abdn.ac.uk

Margaret Bruce¹, maggie.bruce2@nhs.net

David M. Higgins, PhD², David.Higgins@philips.com

Jiabao He, PhD¹, jiabao.he@abdn.ac.uk

Satnam Singh, MBBS¹, s.singh@abdn.ac.uk

Thomas W. Redpath, PhD¹, t.redpath@abdn.ac.uk

Michael P. Frenneaux, MBBS, PhD¹, m.p.frenneaux@abdn.ac.uk

Dana K. Dawson, DM, DPhil¹, dana.dawson@abdn.ac.uk

Corresponding author contact details: National Institute on Aging/National Institutes of Health, MedStar Harbor Hospital, 3001 South Hanover Street, Baltimore, Maryland 21225, USA. Telephone: +14105588182. Fax: +14103507304.

1. Department of Cardiovascular Medicine, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK.

2. Philips Healthcare, Guildford Business Park, Guildford, Surrey GU2 8XH, UK.

Abstract

Objectives: To compare 3T T₁ mapping to conventional T₂-weighted (T₂W) imaging for delineating myocardial oedema one week after ST-elevation myocardial infarction (STEMI), and to explore the confounding effects of microvascular obstruction (MVO) on each technique.

Methods: T₂W spectral attenuated inversion recovery and native T₁ mapping were applied in 10 healthy volunteers and 62 STEMI patients, and late gadolinium enhancement was included for infarct localisation at 1 week and at 6 months post-STEMI. Segmental T₁ values and T₂W signal intensity ratios were calculated; oedema volumes and salvage indices were determined in patients using image thresholding—a receiver operator characteristic (ROC) derived T₁ threshold, and a 2SD T₂W threshold; and the results were compared between patients with/without MVO (n=35/27).

Results: Native T₁ mapping delineated oedema with significantly better discriminatory power than T₂W—as indicated by ROC analysis (area-under-the-curve, AUC = 0.89 vs 0.83, p=0.009; and sensitivity/specificity= 83/83% vs 73/73%). The optimal ROC threshold derived for T₁ mapping was 1241 ms, which gave significantly larger oedema volumes than 2SD T₂W (p=0.006); with this threshold, patients with and without MVO showed similar oedema volumes, but patients with MVO had significantly poorer salvage indices (p<0.05) than those without. Neither method was significantly affected by MVO, the volume of which was seen to increase exponentially with infarct size.

Conclusions: Native T₁ mapping at 3T can delineate oedema one week post-STEMI, showing larger oedema volumes and better discriminatory power than T₂W imaging, and it is suitable

for quantitative thresholding. Both techniques are robust against MVO-related magnetic susceptibility.

Keywords: acute myocardial infarction; magnetic resonance imaging; myocardium at risk; myocardial oedema; microvascular obstruction; T_1 mapping.

Introduction

Quantitative T_1 mapping has recently emerged as a powerful tool for myocardial tissue characterisation,[1] and previous work has already illustrated its utility for delineating myocardial oedema in acute myocardial infarction (AMI),[2, 3] and acute stress-induced cardiomyopathy patients.[4, 5] We have seen that, in the first 24 hours after acute myocardial injury, native T_1 mapping assessment of oedema appears to be at least as good as that of T_2 -weighted (T_2W) short tau inversion recovery imaging,[3] which is the current standard for oedema assessment with cardiovascular magnetic resonance (CMR). However, it is still unknown whether T_1 mapping's strengths are maintained beyond 24 hours after AMI, as—despite promising initial studies with T_1 -weighted imaging at 1.5T—it has not yet been studied at this time point.[6]

A significant shortcoming of T_2W -based studies to date is that they identify oedema qualitatively, using reference regions in remote myocardium. Such regions are presumed to contain healthy tissue, a questionable assumption in patient populations—where risk factors can lead to subtle myocardial changes.[7] In contrast, native T_1 mapping's primary strength is its quantitative nature, which obviates the need for a reference region and allows for powerful parametric thresholding.[4] Such benefits advocate the use of T_1 mapping for detecting oedematous myocardium; however, this up-and-coming method may yet be confounded by microvascular obstruction (MVO), a phenomenon that is frequently seen after AMI.[8] Indeed, MVO has already been reported to hinder T_2W oedema detection,[9, 10] being associated with paramagnetic species—deoxygenated haemoglobin and elemental iron—that introduce T_2 -shortening susceptibility gradients and decrease signal intensity in the T_2W -detected oedema region.[11, 12] MVO's effects have already been reported in quantitative T_2 mapping studies, where affected regions were indistinguishable from normal myocardium on

T₂ maps.[13] Clearly this phenomenon poses problems for CMR oedema quantification, and its potential repercussions for T₁ mapping warrant immediate investigation.[14]

The primary purpose of this prospective study is to determine how native 3T T₁ mapping and T₂- weighted (T₂W) imaging compare for delineating myocardial oedema, both segmentally and volumetrically, one week after ST-elevation myocardial infarction (STEMI). The volumetric analysis includes an exploration of suitable pixel thresholding approaches for each of the two methods, with comparisons against a typical two-standard-deviation technique. Furthermore, features of MVO are investigated, including its effect on T₁ relaxation times and T₂W signal intensity ratios.

Materials and Methods

Patients and Healthy Volunteers

Sixty two patients with first acute ST-segment elevation myocardial infarction (STEMI) were consecutively recruited at [REDACTED FOR PEER REVIEW] from September 2011 to April 2013 as part of the [REDACTED FOR PEER REVIEW] clinical trial.[15] All patients had TIMI 0/1 flow at the time of diagnostic angiography and underwent primary percutaneous coronary intervention (PCI) within 12 hours of the onset of chest pain. They were scanned one week after myocardial infarction (MI) and again six months later, provided that no further revascularisation procedures occurred in the interim. Furthermore, to establish the normal range of myocardial T₁ values and T₂W signal intensity ratios, ten age-matched healthy volunteers were recruited: six males, no past medical history, no medication, and median heart rate (range) = 65 (50-75) bpm. All participants gave informed consent, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as

reflected in a priori approval by [REDACTED FOR PEER REVIEW] human research committee.

Cardiac Magnetic Resonance Imaging

CMR was performed using a 3 tesla MRI system (Achieva 3.0T TX, Philips Healthcare, Best, Netherlands) with a six-channel cardiac phased-array coil and radiofrequency shimming. T₂W spectral attenuated inversion recovery (SPAIR) was applied as a short-axis stack, with repetition time (TR)/ echo time (TE) = 1600/80 ms, in-plane resolution 1.8 mm × 2.2 mm, slice thickness/gap = 10/0 mm.[16] A corresponding stack of modified Look-Locker inversion recovery (MOLLI) T₁ mapping images was acquired with: a 3b(3b)3b(3b)5b scheme; balanced steady-state free-precession readout; 35° flip angle; TR/TE = 2.7/1.1 ms; in-plane resolution 1.7 mm × 2.1 mm; slice thickness = 10 mm; sensitivity encoding factor = 2; and cardiac triggering to end diastole. This protocol conformed to the guidelines stipulated in the Society for Cardiovascular Magnetic Resonance T₁ mapping position statement.[17]

For infarct localisation in STEMI patients, short-axis late gadolinium enhancement (LGE) images were acquired using spoiled gradient echo inversion recovery (25° flip angle; TR/TE = 6.1/3.0 ms; in-plane resolution 1.8 mm × 2.2 mm; slice thickness/gap = 8/2 mm) within a 10-20 minute window after contrast administration (0.1 mmol kg⁻¹ gadolinium diethylenetriaminepentacetate, Gadovist; Bayer, Leverkusen, Germany). Infarct size was determined from both the acute scan and the six- month follow-up in order to account for the remodelling process.

Image Analysis

T_1 maps were generated from MOLLI source images using in-house software (IDL, Excelis, Boulder, CO, USA) and controlled for artefacts with the aid of chi-square error maps. They were then prepared for segmental analysis, whereby the multi-slice T_1 data were pooled into basal, mid-cavity, and apical sets, and were segmented according to the American Heart Association 17-segment model,[18] omitting the apical cap and including MVO, where present. Individual T_1 values were calculated for the remaining 16 segments, and a blood pool threshold—measured in normal volunteers as the mean left ventricular blood pool T_1 minus 2SD—was used to exclude pixels contaminated by blood contributions. Consistent with T_1 mapping, T_2 -weighted images were segmented and examined for artefacts, and reference regions of interest (ROIs) were drawn in pectoral muscle for calculation of signal intensity ratios.[19]

Infarcted (LGE+) segments were identified on LGE images by an experienced cardiologist (five years' experience) as regions with signal intensity greater than the mean signal intensity in remote myocardium (diametrically opposite the STEMI area) plus 5SD.[20] Given that early and late gadolinium enhancement show similar sensitivity and specificity for detecting MVO,[10] LGE images were selected for MVO identification. Thus LGE+ segments were subdivided according to whether or not they contained MVO (MVO+ or MVO-, respectively), which was identified as subendocardial or mid-wall hypoenhancement within gadolinium-enhanced myocardium.[21] The total MVO volume was expressed as a percentage of the myocardial volume.

Inter- and Intra-Observer Reproducibility

To compare the inter- and intra-observer reproducibility of T₁ mapping and T₂W-SPAIR, segmental measurements were repeated in five patients and five volunteers and re-measured by a second independent and blinded observer (three years' experience) in those same participants.

T₁ Mapping versus T₂W-SPAIR: Performance for Detecting At-Risk Myocardium

ROC analysis was performed to assess the discriminatory power of T₁ mapping and T₂W-SPAIR in the entire patient cohort, as well in MVO+/MVO- patient subgroups. LGE was considered a surrogate of acute myocardial injury, given that endocardial surface area LGE is accepted as a method for measuring area at risk.[22] Therefore, acute (one week post STEMI) LGE+ segments were used as the oedema-positive test state, as previously described,[3] and normal segments from healthy volunteers were used as the oedema-negative test state. All T₁ map and T₂W-SPAIR segments were categorised as LGE+ or LGE-, and were only included if they were artefact-free in both T₁ maps and T₂W-SPAIR images. ROC thresholds were chosen for equal sensitivity and specificity.

Volume of Myocardium at Risk: T₁ Mapping versus T₂W-SPAIR

For T₂W-SPAIR volumetric analysis, pixels with signal intensities 2SD higher than the mean signal intensity of remote myocardium were considered oedematous,[23] and oedema volume was expressed as a percentage of the total myocardial volume. For T₁ mapping, two methods were used to measure the oedema volume: 1) a 2SD threshold, equivalent to that described for T₂W-SPAIR; 2) a pre-set threshold, where pixels were considered oedematous

if their T_1 values fell between the ROC-derived threshold and the mean blood pool T_1 minus 2SD. The pre-set threshold also included a window to accommodate haemorrhagic T_1 values (500-1025 ms), which would otherwise be excluded from the oedema volume, in order to mitigate any bias in the volume calculation. Infarct size was measured on acute and six-month LGE images using a 5SD threshold, and was used to calculate salvage index as follows: (oedema volume \times infarct size) = oedema volume.

Statistical Analysis

Intra-method comparisons were made in SPSS (IBM, Armonk, NY, USA) using analysis of variance, and significant inter-group differences were verified using two-tailed independent *t*-tests or Mann-Whitney U tests. In ROC analysis, area-under-the-curve (AUC) values were compared according to Hanley and McNeil.[24] Finally, inter- and intra-observer reproducibility were evaluated using Bland-Altman analysis and intra-class correlation coefficients (ICC).

Results

Patient Demographics

Patient characteristics, risk factors, culprit arteries and CMR characteristics are presented in Table 1. MVO+ patients had significantly larger raw and indexed left ventricular volumes, (end-systolic $p=0.003$, end-diastolic $p=0.03$, indexed end-systolic $p=0.001$, indexed end-diastolic $p=0.01$), reduced left ventricular ejection fractions ($p<0.001$), and higher 12 hour Troponin I levels compared to the MVO- group ($p=0.001$). There was no significant

difference in the time from the onset of chest pain to percutaneous intervention between the MVO- and MVO+ groups.

Imaging Results

Representative images from this study are shown in Figure 1. From a total of 1152 segments, 382 were discarded from T₂W-SPAIR image analysis (5.3 per participant, on average) as a result of coil-sensitivity-related signal dropout, which occurred mainly in infero-lateral segments. A total of 174 T₁ map segments were discarded (2.4 per participant, on average): mostly anterior and infero-lateral segments affected by off-resonance artefact near the coronary veins. The T₁ of normal myocardium in healthy volunteers was seen to be significantly shorter ($p < 0.001$) than the T₁ of the segments most remote from infarction in patients, with mean (SD) T₁ values of 1192 (30) ms versus 1215 (39) ms, respectively. The mean (SD) blood pool T₁ measured in healthy volunteers was 1774 (46) ms, and thus an upper pixel threshold of 1682 ms (mean blood pool T₁ minus 2SD) was chosen to exclude blood pool contamination from myocardial T₁ measurements.

Performance for Detecting At-Risk Myocardium and Effect of MVO

Figure 2 shows ROC analyses, grouped by imaging sequence. For the whole patient group, the AUC for T₁ mapping was significantly greater than that of T₂W-SPAIR (0.89 versus 0.83, $p = 0.009$), and the calculated oedema threshold T₁ was 1241 ms (sensitivity and specificity of 83%). For T₂W-SPAIR, ROC analysis gave a sensitivity and specificity of 73%.

Examining MVO- and MVO+ patient groups: in MVO- patients, T₁ mapping had significantly better discriminatory power than T₂W-SPAIR, with an AUC of 0.93 versus 0.81, ($p = 0.004$); in MVO+ patients, there was no significant difference between the two

techniques, with ROC analysis giving an AUC of 0.88 for T₁ mapping versus an AUC of 0.84 for T₂W-SPAIR, (p=0.11). The oedema threshold T₁ values calculated from these data were 1243 ms (sensitivity and specificity 86%) in the absence of MVO and 1238 ms (sensitivity and specificity 82%) in the presence of MVO. Given the similarity of these values, the 1241 ms threshold derived from the complete dataset was adopted for volumetric analysis.

Volume of Myocardium at Risk: T₁ Mapping versus T₂W-SPAIR

Myocardial oedema volumes and salvage indices derived in all patients using each of the three methods are shown in Table 2. The oedema volume measured with T₁ mapping-ROC was significantly larger than that measured with T₂W-SPAIR 2SD in the entire group (p=0.006) and in the MVO- group (p=0.02), whereas in the MVO+ group no significant difference was seen. With the two T₁ mapping approaches (2SD and ROC) MVO- and MVO+ patients showed similar oedema volumes; however, T₂W-SPAIR showed larger oedema volume measurements in the MVO+ group compared to the MVO- group (p<0.05). Measurements of myocardial salvage index did not differ significantly whether infarct size was measured from acute or follow-up LGE scans. However, with both T₁ mapping thresholds, salvage index was significantly greater in the MVO- group compared to the MVO+ group (p<0.05 for both).

Figure 3 shows examples of oedema highlighted by each of the three threshold methods. The areas delimited by each technique were similar; however, the T₁ mapping ROC threshold highlighted a region of abnormal myocardium extending farther towards the lateral wall than that shown by the T₂W 2SD approach. This region may be curtailed in the T₂W 2SD map as a consequence of subtle signal loss in the source images that is not detectable by

eye. Of the three approaches, the T_1 mapping 2SD gave the most conservative estimate of oedema volume in the example shown.

Microvascular Obstruction Characterisation

Figure 4 demonstrates that, in our study cohort, there is an exponential relationship between MVO extent and infarct size, with a strong, significant positive correlation between the two (Spearman's $\rho = 0.73$, $p \ll 0.001$). Infarcts larger than 35% of the left ventricular myocardium tended to demonstrate large areas of MVO, whereas smaller infarcts tended to contain MVO no more than 5% of the total myocardial volume. Furthermore, three MVO+ patients exhibited the very low T_1 values associated with haemorrhage. In these patients, direct measurement of T_1 in haemorrhagic segments gave a median (range) $T_1 = 785$ (524-1025) ms.

Inter- and Intra-Observer Reproducibility Results

For segmental T_1 mapping and T_2W -SPAIR, inter-observer and intra-observer bias and limits of agreement were similar, with no statistically significant differences. ICCs were 0.91 for T_1 mapping and 0.84 for T_2W -SPAIR.

Discussion

The main findings of this work are as follows: I) 3T native T_1 mapping identifies oedematous myocardium one week post-acute-STEMI and has a better discriminatory performance than T_2W -SPAIR; II) when using an optimised, ROC-derived threshold, T_1 mapping detects significantly larger oedema volumes than 2SD T_2W -SPAIR, whereas with a

2SD threshold, T_1 mapping yields similar oedema volumes to 2SD T_2 W-SPAIR; III) in general, the presence of MVO does not significantly affect the performance of T_1 mapping or T_2 W-SPAIR for identifying oedematous myocardium one week post STEMI; and (IV), typically, MVO is only found in medium-to-large MIs and its extent increases exponentially with infarct size.

Myocardial salvage is an important predictor of mortality in patients with AMI,[25] but to date there is no gold standard for measuring myocardial oedema in vivo in humans. Several oedema imaging methods exist—single-photon emission computed tomography,[26] T_2 W CMR,[19] LGE endocardial surface area,[27] T_1 mapping CMR,[3, 4, 23] and T_2 mapping CMR[13, 23]—but this study represents the first application of T_1 mapping with a quantitative ROC-threshold optimised to a STEMI population. The precedent for such an approach was set by Ferreira et al.[28], in a recent study on myocarditis. This study showed that—with an appropriate T_1 threshold— T_1 mapping detects a significantly larger oedema volume than T_2 W imaging. In the current work we show similar findings in myocardial infarction patients; namely, the extent of oedema identified by our optimised ROC threshold method, one week post-MI, is significantly larger than that measured by T_2 W-SPAIR, except in MVO+ patients where the difference is not statistically significant. This builds on the pre-clinical findings of O h-Ici et al.[29] and Ugander et al.[23], who have already demonstrated that T_1 mapping can identify the area-at-risk, and the region so measured shows excellent correlation with microspheres. In the context of human studies, our work provides an interesting counterpoint to the findings of Dall'Armellina et al.[3] who noted that T_1 mapping and T_2 W-SPAIR detected similar oedema volumes in STEMI patients 24 hours post-MI. The differences may lie in the way oedema was measured; indeed, when we employed the simple

2SD T_1 threshold used by Dall'Armellina et al. at 1.5 T, our findings were consistent with theirs.

In our patient cohort, we observed that remote myocardial segments—diametrically opposite the infarction—had significantly increased native T_1 values compared to segments in age-matched healthy volunteers. There are two possible explanations for this important finding. First, in AMI the entire myocardium may suffer mild inflammation. Indeed, this hypothesis was put forward by other investigators who showed that ultra-small superparamagnetic particles of iron oxide are retained in segments very remote from the infarct.[27] Second, the T_1 may have been abnormal in these patients prior to myocardial infarction, due to discrete microscopic fibrosis caused by comorbidities such as diabetes, hypertension or hypercholesterolemia.[30, 31] In order to establish which hypothesis is correct, our findings would have to be validated through histology. Given that our proposed ROC-derived threshold is free from any assumptions regarding remote myocardium, we believe it is more appropriate than T_2W imaging for delimiting myocardial oedema in vivo.

More than half of the patients included in this study exhibited MVO—demonstrating differentially worse cardiac remodelling and significantly higher levels of cardiac biomarkers than those that did not. They also showed comparable oedema volumes but lower salvage indices than MVO- patients, confirming the significance of MVO as an adverse prognostic marker in STEMI.[32] We included MVO in our T_1 mapping and T_2W SPAIR ROIs to establish its effect on the discriminatory power of these techniques. In patients with MVO, we observed that both methods are subtly—not significantly—influenced by haemorrhage, with some haemorrhagic pixels showing T_1 values similar to those of normal myocardium, and much lower in some extreme examples, which also showed reduced T_2W signal intensity

ratios. Despite this, T_1 mapping was superior to T_2W -SPAIR for detecting oedema, both overall and in the subgroup of patients without MVO. T_1 mapping was also less prone to artefact than T_2W -SPAIR, and its ICC was larger—though not significantly so.

Study Limitations

Due to time constraints, T_2^* mapping was not applied in this work, thus haemorrhage and MVO were both identified using LGE images alone. Furthermore, improvements have been made to the MOLLI T_1 mapping pulse sequence since the beginning of the study, resulting in higher signal-to-noise, reduced artefact, shorter breath-holds and minimal T_1 heart-rate dependence—further increasing clinical utility. Our fixed T_1 threshold value may differ slightly for other T_1 mapping sequences, but this is to be expected due to different manufacturer setups, hardware and other factors. Further studies are required to determine appropriate T_1 mapping ROC thresholds on other platforms.

Given that this is a clinical study, histology would not have been a viable means of validating our technique; however, we and others have previously shown that T_1 mapping reflects oedema in other acute pathologies in man.[4, 5] Human studies such as this are very important, as the immediate post-infarct stage represents a dynamic post-reperfusion healing process that differs between man and animal models.

In conclusion, T_1 mapping at 3T robustly detects myocardial oedema one week post-AMI. Compared to standard T_2W imaging, it shows superior discriminatory power and similar reproducibility, it can be applied with a receiver operator characteristic threshold—rendering it independent of assumptions about the remote myocardium—and it describes

larger volumes of oedema. Neither T_1 mapping nor T_2W imaging were significantly affected by microvascular obstruction.

Conflict of Interest

David M. Higgins is an employee of Philips Healthcare. All other authors have no further conflicts of interest to declare.

Acknowledgements

This study was supported by a Medical Research Council UK grant (grant number G0800901), as a sub-study of Nitrites in Acute Myocardial Infarction. Thanks are due to Roger Staff, for invaluable advice regarding receiver operator characteristic analysis.

References

- [1] D. R. Messroghli, A. Radjenovic, S. Kozerke, D. M. Higgins, M. U. Sivananthan, J. P. Ridgway. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T_1 mapping of the heart, *Magnetic Resonance in Medicine* 2004; 52; 141–6. doi:10.1002/mrm.20110.
- [2] E. Dall'Armellina, T. D. Karamitsos, S. Neubauer, R. P. Choudhury. CMR for characterization of the myocardium in acute coronary syndromes, *Nature Reviews Cardiology* 2010; 7; 624–36. doi:10.1038/nrcardio.2010.140.
- [3] E. Dall'Armellina, S. K. Piechnik, V. M. Ferreira, Q. L. Si, M. D. Robson, J. M. Francis, et al. Cardiovascular magnetic resonance by non contrast T_1 -mapping allows assessment of

severity of injury in acute myocardial infarction, *J Cardiovasc Magn Reson* 2012; 14; 15.

doi:10.1186/1532-429X-14-15.

[4] V. M. Ferreira, S. K. Piechnik, E. Dall'Armellina, T. D. Karamitsos, J. M. Francis, R. P. Choudhury, 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* 2012; 14; 42. doi: 10.1186/1532-429X-14-42.

[5] D. K. Dawson, C. J. Neil, A. Henning, D. Cameron, B. Jagpal, M. Bruce et al. Tako-Tsubo cardiomyopathy: A heart stressed out of energy? *JACC: Cardiovascular Imaging*. doi:10.1016/j.jcmg.2014.10.004.

[6] J. W. Goldfarb, S. Arnold, J. Han. Recent myocardial infarction: Assessment with unenhanced T₁-weighted MR imaging, *Radiology* 2007; 245; 245–50. doi:10.1148/radiol.2451061590.

[7] W. Chan, S. J. Duffy, D. A. White, X.M. Gao, X.J. Du, A. H. Ellims, et al. Acute left ventricular remodeling following myocardial infarction: Coupling of regional healing with remote extracellular matrix expansion, *JACC: Cardiovascular Imaging* 2012; 5; 884–93. doi:10.1016/j.jcmg.2012.03.015.

[8] R. A. Kloner, C. E. Ganote, R. B. Jennings. The no-reflow phenomenon after temporary coronary occlusion in the dog, *Journal of Clinical Investigation* 1974; 54; 1496. doi:10.1172/JCI107898.

[9] I. Eitel, S. Desch, G. Fuernau, L. Hildebrand, M. Gutberlet, G. Schuler, H. Thiele, Prognostic significance and determinants of myocardial salvage assessed by cardiovascular

magnetic resonance in acute reperfused myocardial infarction, *Journal of the American College of Cardiology* 2010; 55; 2470–9. doi:10.1016/j.jacc.2010.01.049.

[10] C. Berry, P. Kellman, C. Mancini, M. Y. Chen, W. P. Bandettini, T. Lowrey, et al. Magnetic resonance imaging delineates the ischemic area at risk and myocardial salvage in patients with acute myocardial infarction, *Circulation: Cardiovascular Imaging* 2010; 3; 527–35. doi:10.1161/CIRCIMAGING.109.900761.

[11] D. P. O'Regan, B. Ariff, C. Neuwirth, Y. Tan, G. Durighel, S. A. Cook. Assessment of severe reperfusion injury with T_2^* cardiac MRI in patients with acute myocardial infarction, *Heart* 2010; 96; 1885–91. doi:10.1136/hrt.2010.200634.

[12] A. N. Mather, T. A. Fairbairn, S. G. Ball, J. P. Greenwood, S. Plein. Reperfusion haemorrhage as determined by cardiovascular MRI is a predictor of adverse left ventricular remodelling and markers of late arrhythmic risk, *Heart* 2011; 97; 453–9. doi:10.1136/hrt.2010.202028.

[13] D. Verhaert, P. Thavendiranathan, S. Giri, G. Mihai, S. Rajagopalan, O. P. Simonetti, et al. Direct T_2 quantification of myocardial edema in acute ischemic injury, *JACC: Cardiovascular Imaging* 2011; 4; 269–78. doi:10.1016/j.jcmg.2010.09.023.

[14] S. F. Pedersen, S. A. Thrysoe, M. P. Robich, W. P. Paaske, S. Ringgaard, H. E. Botker, et al. Assessment of intramyocardial hemorrhage by T_1 -weighted cardiovascular magnetic resonance in reperfused acute myocardial infarction, *J Cardiovasc Magn Reson* 2012; 14; 59. doi:10.1186/1532-429X-14-59.

[15] Author redacted for peer review.

- [16] M. S. Cocker, S. M. Shea, O. Strohm, J. Green, H. Abdel-Aty, M. G. Friedrich. A new approach towards improved visualization of myocardial edema using T₂-weighted imaging: A cardiovascular magnetic resonance (CMR) study, *J Magn Reson Imaging* 2011; 34; 286–92. doi:10.1002/jmri.22622.
- [17] J. C. Moon, D. R. Messroghli, P. Kellman, S. K. Piechnik, M. D. Robson, M. Ugander, 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* 2013; 15; 92. doi:10.1186/1532-429X-15-92.
- [18] M. D. Cerqueira, N. J. Weissman, V. Dilsizian, A. K. Jacobs, S. Kaul, W. K. Laskey, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart, *Circulation* 2002; 105; 539–42. doi:10.1161/hc0402.102975.
- [19] H. Abdel-Aty, A. Zagrosek, J. Schulz-Menger, A. J. Taylor, D. Messroghli, A. Kumar, et al. Delayed enhancement and T₂-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction, *Circulation* 2004; 109; 2411–6. doi:10.1161/01.CIR.0000127428.10985.
- [20] M. O. Versteysen, S. C. Bekkers, M. W. Smulders, B. Winkens, C. Muhl, M. H. Winkens, et al. Performance of angiographic, electrocardiographic and MRI methods to assess the area at risk in acute myocardial infarction, *Heart* 2012; 98; 109–15. doi:10.1136/heartjnl-2011-300185.
- [21] J. J. Sandstede, M. Beer, C. Lipke, T. Pabst, W. Kenn, K. Harre, et al. Time course of contrast enhancement patterns after Gd-BOPTA in correlation to myocardial infarction and

viability: A feasibility study, *J Magn Reson Imaging* 2001; 14; 789–94.

doi:10.1002/jmri.10007.

[22] M. G. Friedrich, Tissue characterization of acute myocardial infarction and myocarditis by cardiac magnetic resonance, *JACC: Cardiovascular Imaging* 2008; 1; 652–62.

doi:10.1016/j.jcmg.2008.07.011.

[23] M. Ugander, P. S. Bagi, A. J. Oki, B. Chen, L.Y. Hsu, A. H. Aletras, et al. Myocardial edema as detected by pre-contrast T₁ and T₂ CMR delineates area at risk associated with acute myocardial infarction, *JACC: Cardiovascular Imaging* 2012; 5; 596–603.

doi:10.1016/j.jcmg.2012.01.016.

[24] J. A. Hanley, B. J. McNeil. The meaning and use of the area under a receiver operating characteristic (ROC) curve, *Radiology* 1982; 143; 29–36. doi:

10.1148/radiology.143.1.7063747.

[25] G. Ndrepepa, J. Mehilli, M. Schwaiger, H. Schühlen, S. Nekolla, S. Martinoff, et al. Prognostic value of myocardial salvage achieved by reperfusion therapy in patients with acute myocardial infarction, *Journal of Nuclear Medicine* 2004; 45; 725–9.

[26] J. T. Frans, R. J. Gibbons, M. S. Verani, D. S. Kayden, P. Pellikka, T. Behrenbeck, et al. Serial quantitative planar technetium-99m isonitrile imaging in acute myocardial infarction: Efficacy for noninvasive assessment of thrombolytic therapy, *Journal of the American College of Cardiology* 1989; 14; 861–73.

[27] S. R. Alam, A. S. Shah, J. Richards, N. N. Lang, G. Barnes, N. Joshi, et al. Ultrasmall superparamagnetic particles of iron oxide in patients with acute myocardial infarction: Early

clinical experience, *Circulation: Cardiovascular Imaging* 2012; 5; 559–65.

doi:10.1161/CIRCIMAGING.112.974907.

[28] V. M. Ferreira, S.K. Piechnik, E. Dall'Armellina, T.D. Karamitsos, J.M. Francis, N. Ntusi, et al. Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents, *J Cardiovasc Magn Reson* 2014; 16; 3. doi: 10.1186/1532-429X-16-36.

[29] D. O h-Ici, S. Jeuthe, F. Berger, T. Dietrich, T. Kuehne, S. Kozerke, et al. T1 mapping allows the study of the development of oedema in a small animal model of Ischemia-Reperfusion, *J Cardiovasc Magn Reson*, 2014; 16, 16. doi:10.1186/1532-429X-16-S1-P16.

[30] C.Y. Liu, Y.C. Liu, C. Wu, A. Armstrong, G. J. Volpe, R. J. Van der Geest, et al. Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic resonance contrast-enhanced T₁ mapping: MESA (Multi-Ethnic Study of Atherosclerosis), *Journal of the American College of Cardiology* 2013; 62; 1280–7. doi:10.1016/j.jacc.2013.05.078.

[31] W. Chan, S. J. Duffy, D. A. White, X.M. Gao, X.J. Du, A. H. Ellims, et al. Acute left ventricular remodeling following myocardial infarction: Coupling of regional healing with remote extracellular matrix expansion, *JACC: Cardiovascular Imaging* 2012; 5; 884–93. doi:10.1016/j.jcmg.2012.03.015.

[32] K. C. Wu, E. A. Zerhouni, R. M. Judd, C. H. Lugo-Olivieri, L. A. Barouch, S. P. Schulman, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction, *Circulation* 1998; 97; 765–72. doi:10.1161/01.CIR.97.8.765.

Figure Captions

Figure 1: Representative short-axis CMR images—from a patient with no microvascular obstruction (MVO)(A-D), a small amount of MVO (E-H) and a large, confluent area of MVO (I-L). The top row shows an inferior myocardial infarction (infarct size 3% of total myocardium), middle and bottom rows are anteroseptal myocardial infarctions (infarct sizes 33% and 57% respectively). T₂-weighted spectral attenuated inversion recovery turbo spin echo (T₂W-SPAIR TSE) images were acquired with repetition time (TR) = 1600 ms and echo time (TE) = 80 ms. Acute late gadolinium enhancement (LGE) images were acquired with a 25° flip angle, TR/TE = 6.1/3.0 ms, and an inversion time chosen to optimise myocardial nulling. T₁ maps and chi-square maps were generated from T₁ mapping source images, which were acquired with a 3b(3b)3b(3b)5b sampling scheme, 35° flip angle, and TR/TE = 2.7/1.1

ms. The T_1 map colour scale was chosen to highlight myocardium.

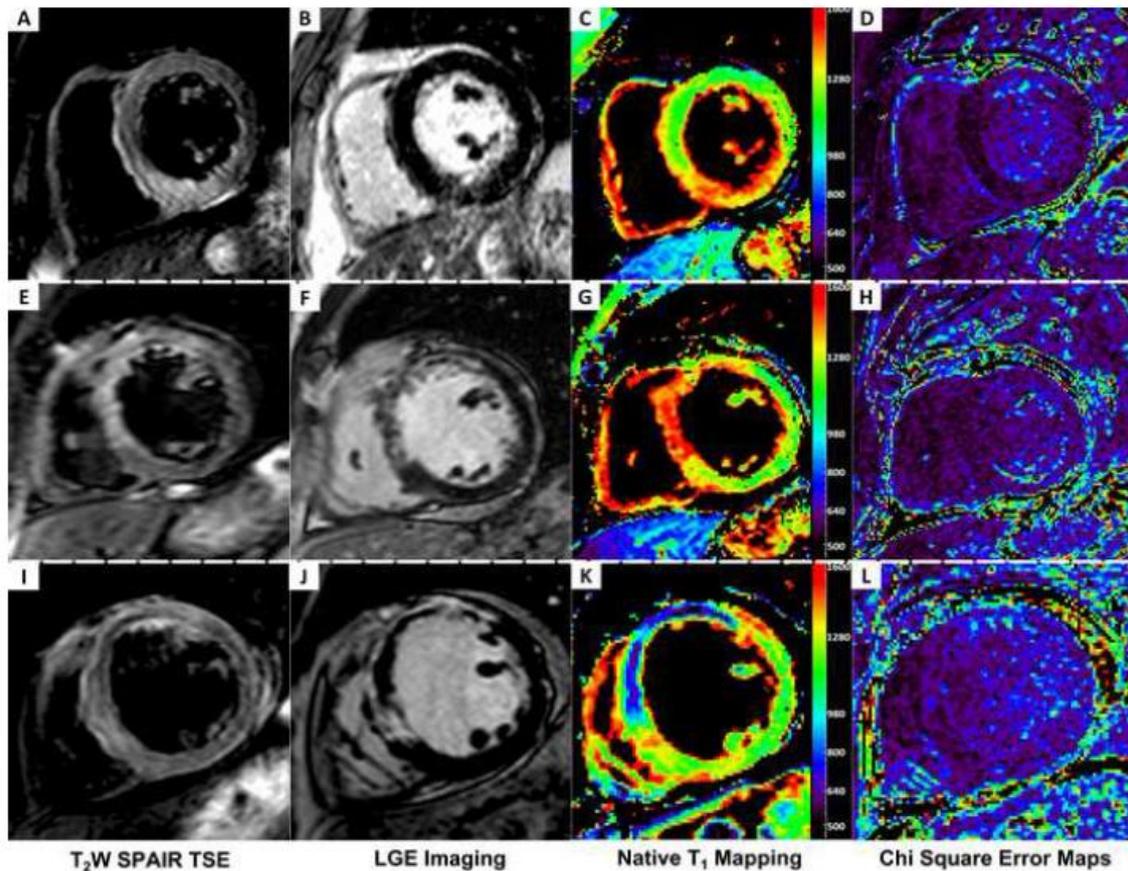


Figure 2: Receiver operator characteristic (ROC) curves—demonstrating the discriminatory power of T_1 mapping (A) and T_2 -weighted spectral attenuated inversion recovery (T_2 W-SPAIR)(B) for identifying myocardial oedema. Each of the plots are subdivided into microvascular obstruction (MVO)+ and MVO- patient groups. No statistically significant differences were seen between the MVO+/- groups with either method, but T_1 mapping gave a significantly larger area-under-the-curve (AUC) than T_2 W-SPAIR.

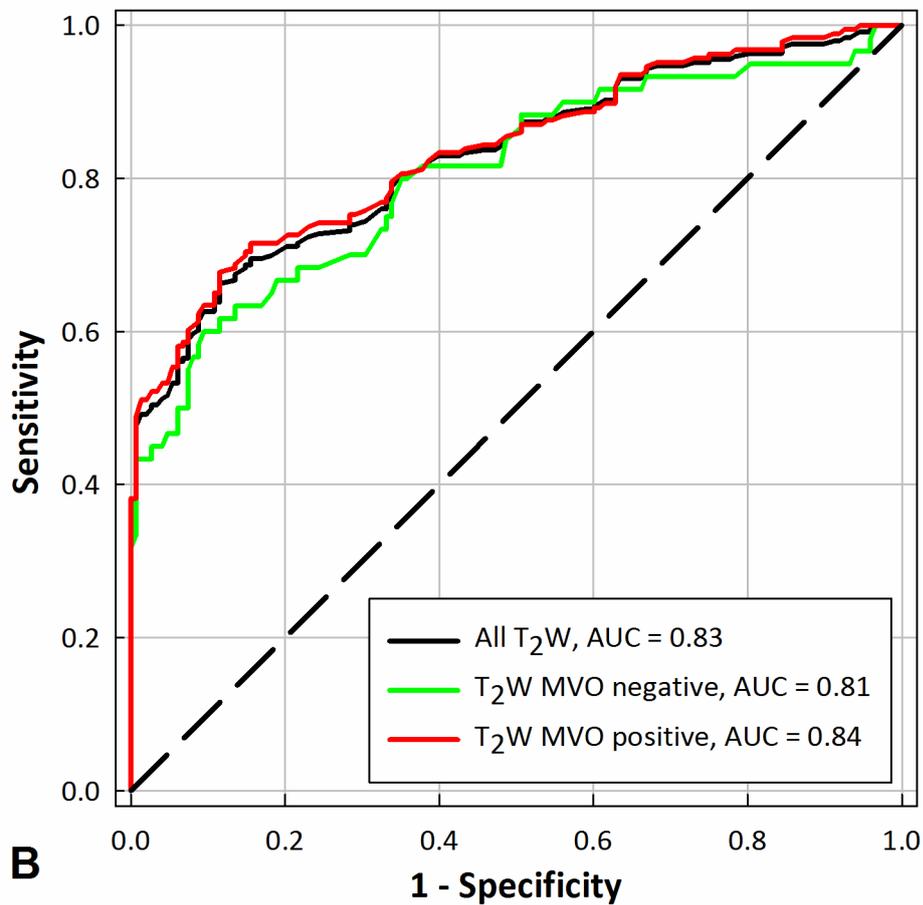
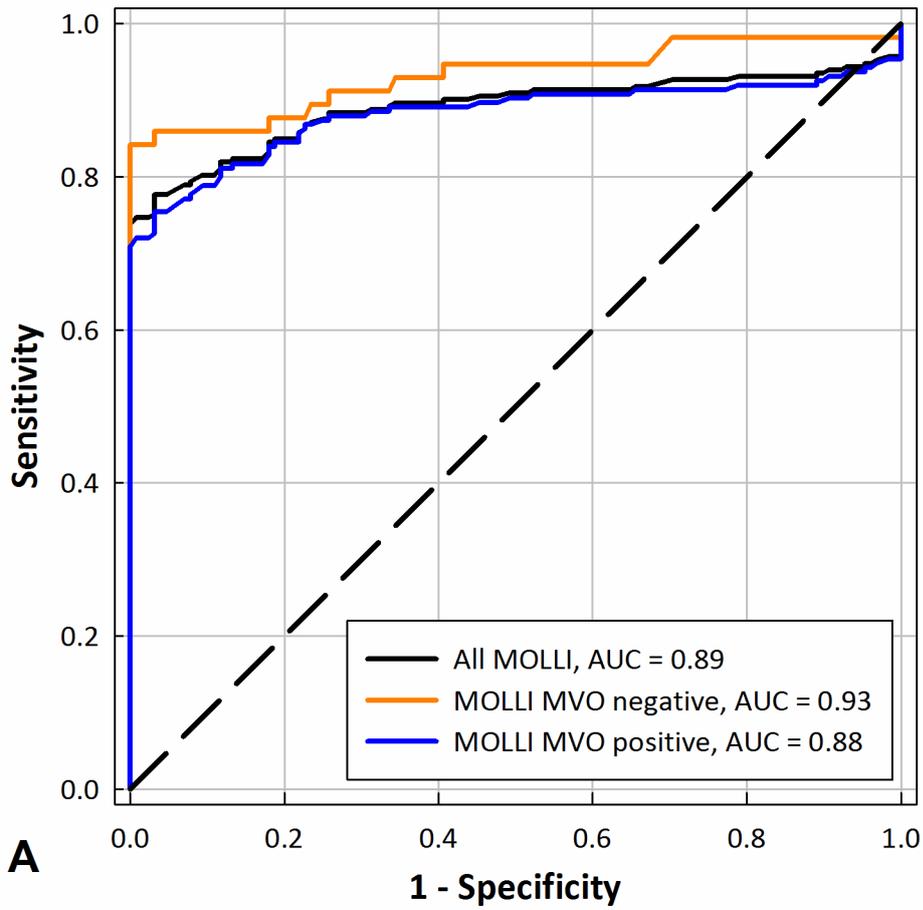


Figure 3: Basal short-axis images with visual thresholds—(A) a T₂-weighted spectral attenuated inversion recovery (T₂W-SPAIR) image with a 2SD threshold, (B) a T₁ map with a 2SD threshold, (C) a T₁ map with a receiver operator characteristic (ROC)-derived threshold. Highlighted regions (delimiting elevated signal intensity or T₁ values) are visible in the inferior part of the myocardium, corresponding to late gadolinium enhancement. Green and red lines denote epicardial and endocardial borders, respectively.

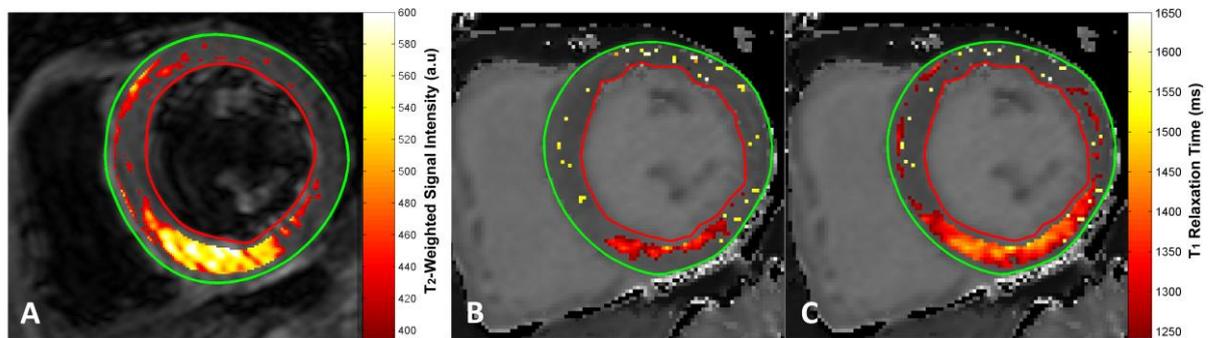


Figure 4: Plot showing the extent of microvascular obstruction (MVO) versus infarct size, as measured by late gadolinium enhancement (LGE) imaging - both are measured as a percentage of the total myocardium. Very large volumes of MVO (>5%) can be seen in larger infarcts (>35% of total myocardium). An exponential regression line indicates the tendency for MVO size to increase with infarct size.

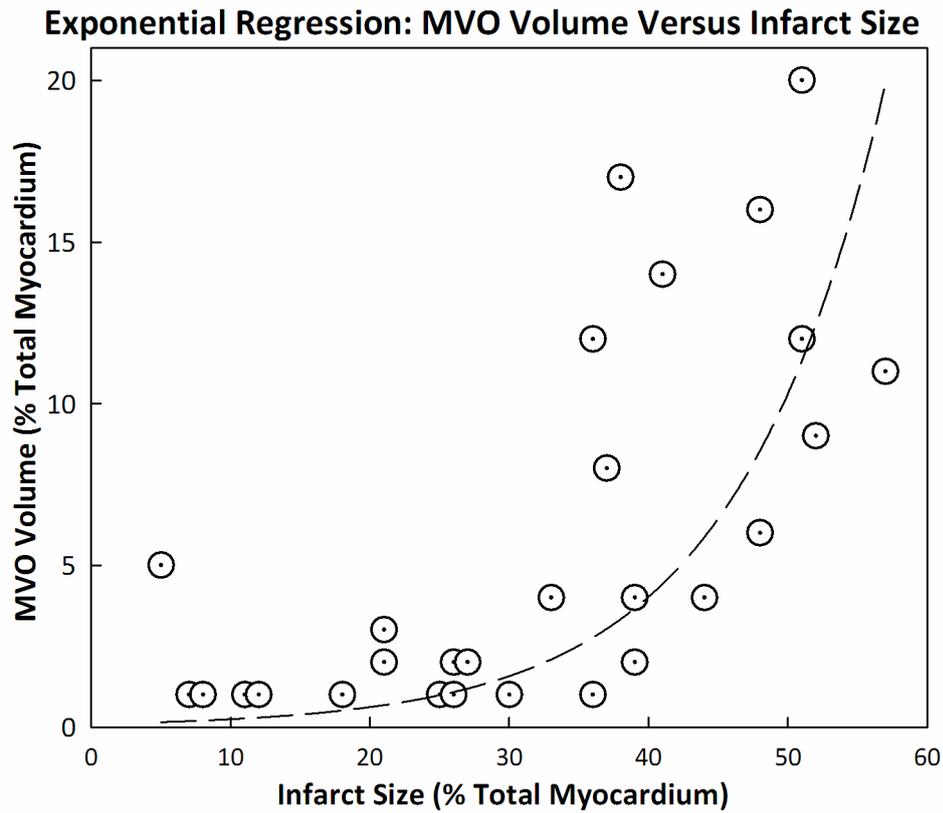


Table 1. General and CMR Patient Characteristics

	All Patients (n=62)	MVO- (n=27)	MVO+ (n=35)
Age [Median (range) yrs]	59 (29-88)	60 (46-83)	58 (29-88)

Male gender [%]	46 (74%)	18 (67%)	28 (80%)
BSA [Median (range) m ²]	1.96 (1.48-2.35)	1.95 (1.48-2.22)	1.99 (1.53-2.35)
Heart Rate [Median (range) bpm]	65 (50-85)	62 (53-70)*	68 (50-85)*
Risk Factors [n (%)]			
-Diabetes Mellitus	5 (8%)	1 (4%)	4 (11%)
-Smoking	24 (39%)	10 (37%)	14 (40%)
-Hypertension	11 (18%)	3 (11%)	8 (23%)
-Hypercholesterolemia	27 (24%)	8 (30%)	9 (26%)
-Prior Angina	1 (2%)	1 (4%)	0 (0%)
Troponin I (12 Hr) [Median (range) ng/ml]	64 (2-461)	43 (2-155)*	97 (16-461)*
Time Onset C/P to PCI [Median (range) hrs]	2.7 (0.8-12.0)	3.3 (0.8-12.0)	4.1 (1.1-8.2)
Time PCI to CMR [Days]	7	7	7
Culprit Artery			
-LAD	25 (40%)	4 (15%)	21 (60%)
-LCX	3 (5%)	0 (0%)	3 (9%)
-RCA	34 (55%)	23 (85 %)	11 (31%)
LVEDV [Mean (SD) ml]	164 (37)	146 (30)*	179 (37)*
LVESV [Mean (SD) ml]	84 (33)	65 (21)*	100 (32)*
EF [Mean (SD) %]	50 (10)	57 (7)*	45 (9)*
LVM [Mean (SD) ml]	147 (45)	130 (42)	161 (44)
Indexed LVEDV [Mean (SD) ml]	84 (17)	76 (11)*	90 (18)*
Indexed LVESV [Mean (SD) ml]	43 (16)	33 (9)*	51 (16)*
LVM Index [Mean (SD) g/m ²]	75 (20)	67 (18)	81 (19)

Table 1. Patient characteristics - * denotes a statistically significant difference between MVO+ and MVO- groups ($p < 0.05$), with specific p-values shown in the text. BSA = body surface area, C/P = chest-pain, CMR = cardiovascular magnetic resonance, EF = ejection fraction, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVM = left ventricular mass, PCI = percutaneous coronary intervention, RCA.

Table 2. Myocardium at Risk and Salvage Index	All Patients	MVO-	MVO+
Oedema Volume (%)			
-T ₂ W-SPAIR 2SD	40 (16)	28 (11)†	48 (13)†
-T ₁ Mapping 2SD	37 (9)	37 (12)	38 (7)*
-T ₁ Mapping ROC	55 (7)*	57 (7)*	53 (8)
Salvage Index			
-1 Week: T ₂ W-SPAIR 2SD	0.66 (0.23)	0.75 (0.17)	0.59 (0.25)
-1 Week: T ₁ Mapping 2SD	0.59 (0.35)	0.84 (0.09)†	0.42 (0.36)†
-1 Week: T ₁ Mapping ROC	0.73 (0.22)	0.89 (0.08)*†	0.63 (0.22)†
-6 Months: T ₂ W-SPAIR 2SD	0.56 (0.25)	0.69 (0.29)	0.51 (0.22)
-6 Months: T ₁ Mapping 2SD	0.51 (0.30)	0.76 (0.19)†	0.39 (0.30)†
-6 Months: T ₁ Mapping ROC	0.67 (0.21)	0.85 (0.12)*†	0.59 (0.21)†

Table 2. Myocardial oedema volume and salvage index measured using T₂W-SPAIR and T₁ mapping - Data are presented as mean (SD). * denotes a statistically significant difference between T₁ mapping with a two standard deviation (2SD) or receiver operator characteristic (ROC) threshold and T₂-weighted spectral attenuated inversion recovery (T₂W-SPAIR); † denotes a statistically significant difference between microvascular-obstruction-positive (MVO+) and microvascular-obstruction-negative (MVO-) groups (p values in the text). No significant difference was seen between salvage index measurements made using infarct size at one week and infarct size at six months.

