Acute Infarct Extracellular Volume Mapping to Quantify Myocardial Area at Risk and Chronic Infarct Size on Cardiovascular Magnetic Resonance Imaging

Short Title: Garg, ECV Maps to quantify IS and AAR

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Abstract

Background. Late gadolinium enhancement (LGE) imaging overestimates acute infarct size.

Objective. To investigate if acute ECV-maps can reliably quantify myocardial area at risk (AAR) and final infarct size (IS).

Methods. 50 patients underwent cardiovascular magnetic resonance (CMR) imaging acutely (24hrs-72hrs) and at convalescence (3 months). The CMR protocol included: cines, T2-weighted (T2W) imaging, native T1-maps, 15-minute post-contrast T1-maps and LGE. Optimal AAR and IS ECV thresholds were derived in a validation group of 10 cases (160 segments). 800 segments (16-per-patient) were analysed to quantify AAR/IS by ECV-maps (ECV thresholds for AAR: 33% and IS: 46%), T2W-imaging, T1-maps and acute LGE. Follow-up LGE-imaging was used as the reference standard for final IS and viability assessment.

Results. The AAR derived from ECV maps (threshold of >33) demonstrated good agreement with T2W-imaging derived AAR (Bias=0.18, 95% CI -1.6-1.3) and AAR derived from native T1-maps (Bias=1, 95% CI -0.37-2.4). ECV demonstrated the best linear correlation to final IS at a threshold of >46%, (R=0.96, 95% CI 0.92-0.98; P<0.0001). ECV-maps demonstrated better agreement with final IS than acute IS on LGE (ECV-maps: bias=1.9, 95% CI 0.4-3.4 versus LGE-imaging: bias=10, 95% CI 7.7-12.4). On multiple variable regression analysis, the number of non-viable segments was independently associated with IS by ECV-maps (beta=0.86, P<0.0001).

Conclusion. ECV-maps can reliably quantify AAR and final IS in reperfused AMI. Acute ECV-maps were superior to acute LGE in terms of agreement with final IS. IS quantified by ECV-maps are independently associated with viability at follow-up.

Introduction

Infarct size (IS) and myocardial salvage are important determinants of clinical outcome after myocardial infarction and are most accurately assessed with cardiovascular magnetic resonance (CMR)[1]. The size and extent of myocardial infarction on late gadolinium enhancement (LGE) CMR has prognostic value in the chronic setting[2]. Recent literature however suggests that infarct size on LGE-imaging has limited value in acute myocardial infarction[3] and overestimates actual IS compared to histopathology[4–6]. Separately, T2-weighted (T2W) imaging can be used after acute myocardial infarction to quantify the myocardial area at risk (AAR) and together with LGE extent to compute the myocardial salvage index.

Commonly, IS and AAR are derived with semi-automated thresholding methods, but these methods have important limitations[7]. Semi-automated thresholding is dependent on several factors including: 1) windowing by the operator to decide where the region of interest (ROI) is placed, 2) the variation of signal intensity within the ROI and 3) the size of ROI can also affect the signal intensity variations[8]. The cumulative effect of these factors can significantly influence quantification and intra-/inter-observer variation of the measurements.

Parametric mapping methods, in particular T1 mapping and the derived parameter of extracellular volume (ECV), allow an alternative method for quantification of IS and AAR on an absolute scale (0%-100%). ECV has previously been shown to be increased in the AAR and infarcted myocardium[5,6,9], but thresholding to define cut-offs of ECV to quantify AAR and IS has not been investigated.

The purpose of this study was to: 1) determine ECV thresholds for AAR and IS 2) investigate if acute ECV-maps can be used to quantify the AAR (determined by T2W images during acute setting); 3) determine if acute ECV-maps perform better than LGE-

imaging to predict actual IS at 3 months; 4) investigate the association of acute ECV-maps to viability at 3 months[10].

Methods

Study Population

Patients presenting with acute STEMI were prospectively recruited from a single UK tertiary centre (Study Design: Figure 1). The inclusion criteria were: first-time acute STEMI revascularized by primary percutaneous coronary intervention (PPCI) within 12 hours of onset of chest pain. Acute STEMI was defined as per current European and American guidelines[11]. Exclusion criteria included: previous MI or coronary artery bypass grafting, cardiomyopathy, estimated glomerular filtration rate <30 ml/min/1.73 m2, haemodynamic instability (requiring on-going intravenous therapy or respiratory support) and contraindication to CMR imaging. After PPCI, all patients received standard post-myocardial infarction secondary prevention therapy[12] at the discretion of the treating physician, and were enrolled in a cardiac rehabilitation programme if they were deemed suitable.

Ethics Approval

The study protocol was approved by the National Research Ethics Service (12/YH/0169) and complied with the Declaration of Helsinki and all patients gave written informed consent.

Cardiac catheterization

Coronary angiography and revascularisation were performed in a standard fashion according to current best practice guidelines[12]. TIMI flow grades were assessed visually as described previously after coronary angioplasty[13].

Cardiovascular Magnetic Resonance Imaging

All patients had CMR imaging at either 1.5 Tesla (Ingenia, Philips, Best, Netherlands) or 3.0 Tesla (Achieva TX, Philips, Best, Netherlands) within 72-hours (median 48-hours) of their index presentation and were invited to attend for a further CMR study at 3-months follow-up. A dedicated cardiac phased array receiver coil was used (1.5T: 24-channel; 3T: 32-channel).

Image Acquisition and Analysis

In-depth details on CMR acquisition methods and T1-analysis and quality assurance checks are included in the online 'Supplemental Material'.

Extracellular volume mapping analysis

ECV-maps were generated for the 3 slices (base, mid and apex) from pre-/post-contrast T1-maps and haematocrit using standard techniques[14]. The endo- and epi-cardial contours were outlined to define myocardium (Figure 2). Similar to the T2W and the LGE-imaging, the IS and AAR estimation included any hypo-intense core (MVO with/without IMH).

Validation of ECV thresholds

Validation of ECV threshold is detailed in the online 'Supplemental Material'.

Follow-up scans

Follow-up scans were planned at 3-months following the index event. Patients were scanned at 3-months at the same field strength as the baseline scan. IS was estimated using the most validated method to estimate chronic infarct size: the FWHM method[15]. Segmental infarction using a 16-segment model[16] was assessed from LGE images and a greater than 75% volume of infarction per-segment was considered transmural and the segment classified as 'non-viable'[17]. The number of non-viable segments was recorded for each patient. Adverse LV remodeling was defined as an increase in LV end-systolic volume of $\geq 15\%$ at follow-up[18].

Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics 21.0. Continuous variables are expressed as mean ± SD. Normality of quantitative data was established using the Shapiro-Wilk test. Demographic comparisons were performed with an independent samples t-test (continuous variables) and by Chi-Square test (categorical variables). A repeated-measures analysis of variance (ANOVA) was performed on demographic and different field strength CMR. Paired sample T-test was used for validation of ECV thresholding to the reference methods. Scanner field strength was a covariate in all linear correlation analysis to the reference method. Agreement between the different tests for IS and AAR are expressed as bias according to the Bland-Altman analysis[19] and intra-class correlation coefficient (ICC). For paired comparison of the IS, non-parametric Wilcoxon test (paired samples) was used. Univariate analysis was performed for each variable separately. Step-wise multivariate linear regression was used for parameters with statistical significance from one-way analysis ($p<0.1$). All statistical tests were 2-tailed; p values <0.05 were considered significant.

Results

Patient characteristics

Seventy patients were considered for inclusion, of which 50 had baseline and follow up CMR (Figure 1). Patient demographics are presented in Table 1.

Validation of ECV thresholds

Validation results are presented in the online 'Table 2'. For the quantification of acute AAR, all ECV thresholds (32%, 33% and 34%) were very similar when compared to the reference method of T2W imaging. However, ECV threshold of 33% demonstrated the least absolute error and coefficient of variability (CoV). For the quantification of final IS, ECV thresholds of 46% demonstrate the least absolute error of 10.1% when

compared to the final IS on follow-up LGE imaging. Therefore, ECV thresholds of 33% and 46% were used in the prospective analysis to quantify AAR and IS respectively.

Myocardial area at risk (AAR) characteristics

AAR characteristics are listed in Table 3. The AAR estimated by T2W-imaging was not significantly different to the AAR estimated from ECV-maps at a threshold of 33% (47.4±18% versus 47.2±17.4%, P>0.5) and demonstrated excellent linear correlation to it (R=0.95, 95% CI 0.90-0.98; P<0.0001) (Figure 3). AAR derived using ECV-maps also demonstrated excellent linear correlation to AAR derived from quantitative T1-Maps (R=0.96, 95% CI 0.93-0.98; P<0.0001). The AAR derived from ECV-maps demonstrated good agreement with T2W-imaging derived AAR (Bias=0.18, 95% CI -1.6-1.3; ICC=0.97, 95% CI 0.92-0.97) and AAR derived from native T1-maps (Bias=1, 95% CI -0.37-2.4) (Figure 3). Using Annona statistics, there was no significant association between AAR methods (T2W-imaging, P=0.77; 33% ECV thresholding method, P=0.64) and number of days to CMR study.

Myocardial salvage index (MSI)

MSI based on T2W-imaging and T1-mapping demonstrated poor correlation with follow-up LV EF (R=0.07, P=0.6; R=0.06, P=0.6) (Figure 4). MSI based on ECV-map demonstrated modest correlation to follow-up LV function (R=0.52, P<0.001).

Infarct Size (IS) characteristics

Baseline infarct characteristics are listed in Table 3 and did not differ between the two field strengths. IS estimated from LGE images at the acute scan using the 5SD method overestimated final IS at the follow-up scan (P<0.0001). IS estimated from acute ECV-maps using a 46% threshold did not differ significantly from LGE-defined IS at follow-up (P>0.05). The IS on acute ECV-maps demonstrated excellent linear correlation (R=0.96, 95% CI 0.92-0.98; P<0.0001) to the IS at follow-up. IS estimated by acute

LGE-imaging (FWHM) also correlated with final infarct size but with a lower r value than ECV maps (R=0.87, 95% CI 0.8-0.9, P<0.01) (Figure 3). Moreover, the ECV-maps demonstrated superior agreement to final IS (Bias=1.9, 95% CI 0.4-3.4, ICC=0.91, 95% CI 0.84-0.95) when compared to the acute IS by LGE-imaging (Bias=10, 95% CI 7.7-12.4, ICC=0.80, 95% CI 0.68-0.88). Acute IS estimated by the 5-standard deviation method on LGE-imaging demonstrated the lowest linear correlation to IS at follow-up (0.76, 95% CI 0.61-0.86) with worst agreement (Bias=11, 95% CI 7.7-14). Using Annona statistics, there was no significant association between acute infarct size by all methods (LGE-imaging, P=0.33; ECV methods, P=0.69) and number of days to CMR study.

Per segment viability characteristics

Of the 800 segments 32(4%) were non-viable on follow-up LGE images. On per patient based analysis, 14(28%) patients demonstrated loss of viability in at least one segment. There were no statistically significant differences in the area under the curve (AUC) on receiver operator characterises curve (ROC) analysis for either ECV-maps IS or LGE-imaging IS to predict viability (AUC=0.94, 95% CI 0.88–1 versus AUC=0.93, 95% CI 0.86-1; P=0.82). The number of non-viable segments per patient correlated with IS by ECV (r=0.70, P<0.0001) and LGE-imaging (r=0.64, P<0.0001) and demonstrated a linear trend of rise of these parameters (P<0.0001, Figure 5).

Adverse LV remodeling

Adverse LV remodeling occurred in 8(16%) patients. The IS based on acute ECV-maps was significantly different in patients with/without adverse LV remodeling (17±13% versus 30±13%, P=0.01). Differences in IS based on LGE were not statistically significant (26±14% versus 37±14%, P>0.05) (Figure 6). Acute ECV-maps demonstrated slightly higher, not statistically significant AUC than LGE-imaging for

predicting adverse LV remodeling at follow-up (AUC=0.77, 95% CI 0.6-0.9 versus AUC= 0.71, 95% CI 0.5-0.9, P=0.12).

Regression analysis

Regression analysis is presented in Table 4. On multivariable linear regression analysis, acute IS by ECV-maps was independently associated with follow-up IS (beta 0.92; P<0.0001) and not acute IS by LGE-imaging (p=0.89). Moreover, the number of non-viable segments was independently associated with acute IS by ECV-maps (beta=0.70, P<0.0001) and not with IS by LGE-imaging.

Discussion

The present study demonstrates that acute ECV-maps offer a robust and reliable alternative to acute T2w-imaging and T1-maps to quantify the AAR (at an ECV threshold of 33%) and to acute LGE-imaging to quantify the final IS at follow-up (at an ECV threshold of 46%). Secondly, ECV-maps are superior to acute LGE-imaging in terms of agreement with final IS. Thirdly, IS quantified by ECV maps is strongly associated with the number of non-viable segments at 3-months follow-up and IS by ECV-maps is significantly higher in patients with adverse LV remodeling. Fourthly, MSI derived from ECV-maps better predicts LV function on follow-up than MSI derived from T2w-imaging and T1-maps.

Multi-parametric tissue characterisation

In a previous pilot study, we demonstrated that the signal intensity on LGE-imaging cannot be used to quantify the extent of extracellular matrix expansion[20]. Native (non-contrast) T1-maps are sensitive, among others, to myocardial oedema, protein deposition and changes in lipid/iron content[14]; native T1 maps do not directly inform us however about the intra-/extra- cellular composition of the myocardium. Moreover, even though quantification of native T1 is highly reproducible, it varies between field

strengths, vendor platforms and mapping sequences[21]. ECV is a measure of extracellular matrix expansion, which is related to mechanical, electrical and vasomotor dysfunction[14]. Hence, ECV-maps add incremental diagnostic value to quantify global/focal myocardial fibrosis, which is mainly a process in the extracellular matrix. Furthermore, ECV values are independent of the field strength of the CMR scanners[22].

ECV-mapping in acute and chronic myocardial infarction

Previous studies have explored ECV in both acute and chronic myocardial infarction[5,6,9,23]. In a porcine model of acute myocardial infarction, Jablonowski et al demonstrated that LGE-imaging overestimated infarct size by 23% as compared to histopathological findings, and that this overestimation is due to higher ECV in the peri-infarct region, or the border-zone between necrosed and oedematous myocardium (Figure 7)[6]. They reported that the ECV in this border-zone was significantly different to the ECV in the remainder of the AAR region (48.3±4.4% vs. 32.4±3.2%; P<0.01). The border-zone ECV in the present clinical study (38.6±2.4%) was lower than in this previous study even though we ran validation tests to define the ECV thresholds informed by their biopsy findings. This can potentially be explained by the fact that pigs were imaged far more acutely than our patient cohort (6hrs versus >24hrs). ECV in the border-zone drops very rapidly in the first few days post-acute myocardial infarction as oedema regresses[6]. In a more recent study, Hammer-Hansen and colleagues[5] demonstrated that the extent of gadolinium enhancement in acute myocardial infarction patients is modulated by the extracellular space and the contrast kinetics in the injured myocardium and consequently contributes to the over-estimation of IS by LGE-imaging. Another pertinent finding was that the ECV of the infarcted myocardium, computed using the different post-contrast T1-maps at different time points, ranging from 5-20 minutes after the contrast injection, remained similar. This

may explain why ECV is more reliable to quantify the IS acutely versus the LGE-imaging, which heavily depends on timing of the acquisition post-contrast delivery.

Ugander et al explored the utility of ECV in chronic infarct patients and demonstrated significantly higher ECV (51±8%) in the infarct zone[9]. Another key finding of their study was that remote myocardial ECV, where there was no hyper-enhancement on LGE-imaging, increased concurrently with a decrease in ejection fraction (r=-0.50, P=0.02), suggesting that ECV provides insights into sub-clinical myocardial pathology. This study raises the possibility that the pattern of ECV in the infarcted and remote myocardium changes from the acute to the chronic setting.

More recently, in a study which recruited 131 acute STEMI patients, Carberry et al[24] confirmed that remote zone ECV (assessed by ROI) is inversely related to ejection fraction (P<0.001) and delta-ECV of the remote zone was associated left ventricle volume at follow-up. Bulluck et al[25] investigated the utility of automated segmental ECV in acute myocardial infarction and additionally demonstrated that patients with higher remote myocardial ECV on acute presentation were more likely to have adverse remodeling of their left ventricle. Moreover, recent evidence from our group suggests that the actual expansion in the extracellular matrix of the infarct core quantified by ECV-maps predicts functional recovery better than any other imaging parameter[26]. Therefore, post-acute myocardial infarction, ECV-maps have been shown to measure the extent of damage within the infarct zone, while AAR and remote-zone predict the likelihood of functional recovery and adverse left ventricular remodeling.

The present study adds to this existing evidence and shows that acute ECV-maps offer a new quantitative thresholding tool to quantify both AAR/ IS reliably and accurately.

Limitations

The present study has limitations. The sample size in the present study is not large, nevertheless is comparable to published research studies in this patient population and also inter-/intra-observer variations are very low for multi-parametric CMR. Of the 70 patients identified at initial recruitment, 50 patients were recruited, possibly introducing a selection bias (Figure 1). A key limitation of T1-mapping for clinical application is the error due to partial volume contamination from blood. MOLLI sequences used in the present study, have been shown to be precise and reproducible[27]. They are widely available and are relatively mature. However, magnetization transfer significantly affects inversion recovery sequences. Despite this, the estimate of apparent inversion recovery time is a sensitive measure, which is established to characterise myocardial tissue and discriminate disease. Additionally, different T1-mapping schemes were used to derive ECV on 1.5T and 3T systems. To address this in the study, we investigated all correlations between the reference method and ECV thresholds while controlling for scanner type. Finally, the differences in the LV coverage between all the reference methods and ECV-maps may introduce some bias. Irrespective of the scanner type and sequences used, the results demonstrated reliability of using ECV thresholding method over standard LGE.

Conclusion

This study demonstrates that ECV-maps in patients with acute reperfused STEMI permit reliable quantification of AAR, MSI and final IS at follow-up. Furthermore, acute IS by ECV-maps is independently associated with the number of non-viable infarcted segments at follow-up. Acute IS by ECV-maps is significantly higher in patients who go on to develop adverse LV remodeling. Only ECV-maps derived MSI were associated to final LV function. Therefore, acute ECV-maps offer enhanced early

tissue characterisation, quantification and clinically relevant prognostic information over standard LGE-imaging.

References

1. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SDS, Fogel MA, Friedrich MGM, Kim RRJ, von Knobelsdorff-Brenkenhoff F, Kramer CCM, Pennell DJD, Plein S, Nagel E, Douglas P, Hendel R, Cummings J, Dent J, Hodgson J, Hoffmann U, Horn R, Hundley W, Kahn C, Martin G, Masoudi F, Peterson E, Rosenthal G, Solomon H, Stillman A, Teague S, Thomas J, Tilkemeier P, Weigold WG, Hundley W, Bluemke DA, Bogaert J, Friedrich MGM, Higgins C, Lawson M, McConnell M, Raman S, Rossum A van, Flamm SDS, Kramer CCM, Nagel E, Neubauer S, Pennell DJD, Sechtem U, Higgins C, Manning W, Pohost G, Rademakers F, Rossum A van, Shaw L, Yucel E, Hendel R, Patel M, Kramer CCM, Poon M, Carr J, Gerstad N, Gillam L, Hodgson J, Kim RRJ, Lesser J, Martin E, Messer J, Redberg R, Rubin G, Rumsfeld J, Taylor AA, Weigold WG, Woodard P, Brindis R, Douglas P, Peterson E, Wolk M, Allen J, Hundley W, Bluemke DA, Finn J, Flamm SDS, Fogel MA, Friedrich MGM, Ho V, Jerosch-Herold M, Kramer CCM, Manning W, Patel M, Pohost G, Stillman A, White R, Woodard P, Kramer CCM, Barkhausen J, Flamm SDS, Kim RRJ, Nagel E, Cerqueira M, Weissman N, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing. *J Cardiovasc Magn Reson*. 2013;15:35.

2. Di Bella G, Siciliano V, Aquaro GD, Molinaro S, Lombardi M, Carerj S, Landi P, Rovai D, Pingitore A. Scar extent, left ventricular end-diastolic volume, and wall motion abnormalities identify high-risk patients with previous myocardial infarction: a multiparametric approach for prognostic stratification. *Eur Heart J*. 2013;34:104–11.

3. El Aidi H, Adams A, Moons KGM, Den Ruijter HM, Mali WPTM, Doevendans PA, Nagel E, Schalla S, Bots ML, Leiner T. Cardiac magnetic resonance imaging findings and the risk of cardiovascular events in patients with recent myocardial infarction or suspected or known coronary artery disease: a systematic review of prognostic studies. *J Am Coll Cardiol*. 2014;63:1031–45.

4. Saeed M, Lund G, Wendland MF, Bremerich J, Weinmann H, Higgins CB. Magnetic resonance characterization of the peri-infarction zone of reperfused myocardial infarction with necrosis-specific and extracellular nonspecific contrast media. *Circulation*. 2001;103:871–6.

5.   Hammer-Hansen S, Bandettini WP, Hsu L-Y, Leung SW, Shanbhag S, Mancini C, Greve AM, Køber L, Thune JJ, Kellman P, Arai AE. Mechanisms for overestimating acute myocardial infarct size with gadolinium-enhanced cardiovascular magnetic resonance imaging in humans: a quantitative and kinetic study. *Eur Heart J Cardiovasc Imaging*. 2016;17:76–84.

6.   Jablonowski R, Engblom H, Kanski M, Nordlund D, Koul S, van der Pals J, Englund E, Heiberg E, Erlinge D, Carlsson M, Arheden H. Contrast-Enhanced CMR Overestimates Early Myocardial Infarct Size: Mechanistic Insights Using ECV Measurements on Day 1 and Day 7. *JACC Cardiovasc Imaging*. 2015;8:1379–89.

7.   McAlindon E, Pufulete M, Lawton C, Angelini GD, Bucciarelli-Ducci C. Quantification of infarct size and myocardium at risk: evaluation of different techniques and its implications. *Eur Heart J Cardiovasc Imaging*. 2015;16:738–46.

8.   Kwong RY, Farzaneh-Far A. Measuring myocardial scar by CMR. *JACC Cardiovasc Imaging*. 2011;4:157–60.

9.   Ugander M, Oki AJ, Hsu L-Y, Kellman P, Greiser A, Aletras AH, Sibley CT, Chen MY, Bandettini WP, Arai AE. Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. *Eur Heart J*. 2012;33:1268–1278.

10. Tarantini G, Razzolini R, Cacciavillani L, Bilato C, Sarais C, Corbetti F, Marra MP, Napodano M, Ramondo A, Iliceto S. Influence of transmurality, infarct size, and severe microvascular obstruction on left ventricular remodeling and function after primary coronary angioplasty. *Am J Cardiol*. 2006;98:1033–40.

11. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Apple FS, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker R V, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon J-L, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P,

McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60:1581–98.

12. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–619.

13. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med*. 1985;312:932–6.

14. Moon JC, Messroghli DR, Kellman P, Piechnik SK, Robson MD, Ugander M, Gatehouse PD, Arai AE, Friedrich MG, Neubauer S, Schulz-Menger J, Schelbert EB. 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.

15. Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, Muthurangu V, Moon JC. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging*. 2011;4:150–6.

16. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–42.

17. Choi KM, Kim RJ, Gubernikoff G, Vargas JD, Parker M, Judd RM. Transmural extent of acute myocardial infarction predicts long-term improvement in contractile function. *Circulation*. 2001;104:1101–7.

18. Masci PG, Ganame J, Strata E, Desmet W, Aquaro GD, Dymarkowski S, Valenti V, Janssens S, Lombardi M, Van de Werf F, L'Abbate A, Bogaert J. Myocardial Salvage by CMR Correlates With LV Remodeling and Early ST-Segment Resolution in Acute Myocardial Infarction. *JACC Cardiovasc Imaging*. 2010;3:45–51.

19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet (London, England)*. 1986;1:307–10.

20. Garg P, Kidambi A, Ripley DP, Dobson LE, Swoboda PP, Musa TA, McDiarmid AK, Erhayiem B, Greenwood JP, Plein S. Is signal intensity of late gadolinium enhancement a substitute for extracellular volume mapping in acute myocardial infarction? *J Cardiovasc Magn Reson*. 2015;17:P156.

21. Dabir D, Child N, Kalra A, Rogers T, Gebker R, Jabbour A, Plein S, Yu C-Y, Otton J, Kidambi A, McDiarmid A, Broadbent D, Higgins DM, Schnackenburg B, Foote L, Cummins C, Nagel E, Puntmann VO. Reference values for healthy human myocardium using a T1 mapping methodology: results from the International T1 Multicenter cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson*. 2014;16:69.

22. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson*. 2016;18:89.

23. White SK, Sado DM, Fontana M, Banypersad SM, Maestrini V, Flett AS, Piechnik SK, Robson MD, Hausenloy DJ, Sheikh AM, Hawkins PN, Moon JC. T1 mapping for myocardial extracellular volume measurement by CMR: bolus only versus primed infusion technique. *JACC Cardiovasc Imaging*. 2013;6:955–62.

24. Carberry J, Carrick D, Haig C, Rauhalammi SM, Ahmed N, Mordi I, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay M, Davie A, Mahrous A, Ford I, Sattar N, Welsh P, Radjenovic A, Oldroyd KG, Berry C. Remote Zone Extracellular Volume and Left Ventricular Remodeling in Survivors of ST-Elevation Myocardial Infarction. *Hypertens (Dallas, Tex 1979)*. 2016;68:385–91.

25. Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuva AN, Treibel TA, Fontana M, Gonzalez-Lopez E, Reant P, Ramlall M, Hamarneh A, Sirker A, Herrey AS, Manisty C, Yellon DM, Kellman P, Moon JC, Hausenloy DJ.

Automated Extracellular Volume Fraction Mapping Provides Insights Into the Pathophysiology of Left Ventricular Remodeling Post-Reperfused ST-Elevation Myocardial Infarction. *J Am Heart Assoc*. 2016;5:e003555.

26. Kidambi A, Motwani M, Uddin A, Ripley DP, McDiarmid AK, Swoboda PP, Broadbent DA, Musa T Al, Erhayiem B, Leader J, Croisille P, Clarysse P, Greenwood JP, Plein S. Myocardial Extracellular Volume Estimation by CMR Predicts Functional Recovery Following Acute MI. *JACC Cardiovasc Imaging*. 2016;

27. Kellman P, Hansen MS, Moon J, Messroghli D, Kellman P, Piechnik S, Robson M, Ugander M, Gatehouse P, Arai A, Friedrich M, Neubauer S, Schulz-Menger J, Schelbert E, Wong T, Piehler K, Meier C, Testa S, Klock A, Aneizi A, Shakesprere J, Kellman P, Shroff S, Schwartzman D, Mulukutla S, Simon M, Schelbert E, Wong T, Piehler K, Kang I, Kadakkal A, Kellman P, Schwartzman D, Mulukutla S, Simon M, Shroff S, Kuller L, Schelbert E, Pennell D, Sechtem U, Higgins C, Hunold P, Schlosser T, Vogt F, Sado D, Flett A, Moon J, Mewton N, Liu C, Croisille P, Bluemke D, Lima J, Gai N, Turkbey E, Nazarian S, Lee J, Liu S, Nacif M, Ugander M, Kawel N, Sibley C, Kellman P, Arai A, Bluemke D, Arheden H, Saeed M, Higgins C, Jerosch-Herold M, Sheridan D, Kushner J, Flett A, Hayward M, Ashworth M, Kehr E, Sono M, Chugh S, Jerosch-Herold M, Broberg C, Chugh S, Conklin C, Sahn D, Jerosch-Herold M, Schelbert E, Testa S, Meier C, Ugander M, Oki A, Hsu L-Y, Kellman P, Wilson J, Xue H, Bandettini W, Shanbhag S, Druey K, Ugander M, Arai A, Puntmann V, Voigt T, et al. T1-mapping in the heart: accuracy and precision. *J Cardiovasc Magn Reson*. 2014;16:2.

Table 1. Clinical and angiographic characteristics

	All patients (n=50)	1.5 Tesla (n=32)	3 Tesla (n=18)	p-value
Age, yrs	59±11	61±12	57±11	0.27
Male	42	26	16	0.49
BMI, kg/m2	28±4	28±4	28±3	0.44
Smoker	30	18	12	0.48
Hypertension	8	6	2	0.49
Hyperlipidaemia	17	10	7	0.59
Diabetes Mellitus	6	4	2	0.89
Family History of Coronary Heart Disease	21	14	7	0.74
Presenting Characteristics				
Systolic Blood Pressure, mmHg	135±31	138±35	130±21	0.41
Heart rate, beats/min	73±15	76±14	68±14	0.06
Time from onset of CP to reperfusion, min	228(155-392)	234(144-383)	222(185-407)	0.68
Heart Failure Killip Class †				
I	46	30	16	0.55
II	3	2	1	0.92
III or IV	1	0	1	0.19

Ventricular fibrillation at presentation	3	2	1	0.92
Angiographic Characteristics				
Number of diseased arteries⌀				
1	31	18	13	0.27
2	10	8	2	0.25
3	8	5	3	0.93
Left Main Stem	1	1	0	0.46
Culprit Vessel				
Left anterior descending	29	21	8	0.15
Left circumflex	4	3	1	0.64
Right coronary	17	8	9	0.08
TIMI coronary flow pre-PCI				
0-1	44	28	16	0.59
2-3	6	4	2	
TIMI coronary flow post-PCI				
0-1	1	1	0	0.29
2-3	49	31	18	
Laboratory results				
Red blood cells, grams/litre	146(136-151)	144(135-150)	149(142-155)	0.15

White blood cell, x10^9/litre	11(10-13)	11(10-13)	11(10.4-12.5)	0.40
Creatine kinase, U/l	1538(826-2440)	1627(906-2485)	987(553-2120)	0.57
Troponin I, >40,000	37	27	10	0.04
Estimated glomerular filtration rate, ml/min/1.73m^2	90(77-90)	90(78-90)	83(80-87)	0.99

Values are mean±SD, n (%), median (IQR). † Killip classification of heart failure after acute myocardial infarction: class I=no heart failure; class II=pulmonary rales or crepitations, a third heart sound, and elevated jugular venous pressure; class III=acute pulmonary edema; and class IV=cardiogenic shock.

∅ Multi-vessel coronary artery disease was defined according to the number of stenoses of at least 50% of the reference vessel diameter by visual assessment and whether or not there was left main stem involvement.

Abbreviations: BMI, body mass index; CMR, cardiac magnetic resonance; ECV, extracellular volume; IQR, interquartile range; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Table 2. Validation of ECV thresholding informed by the histo-pathological biopsy data from[6].

	ECV cut-off	Acute ECV AAR		T2-W (AAR)		Paired differences				CoV	Absolute Error (%)	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**95% CI**	**P** [∞]		**Median**	**95% CI**
AAR	32	38.7	20.4	37.6	15.1	-1.1	7.2	-6.2 to 4.0	0.64	12.8	12.0%	2.2 to 28.5
	33	35.9	19.7	37.6	15.1	1.7	6.8	-3.2 to 6.5	0.45*	12.8*	11.5%*	3.8 to 28.5
	34	33.3	19.0	37.6	15.1	4.3	6.5	-0.3 to 8.9	0.06	15.0	11.6%	4.8 to 35.9
		Acute ECV IS		**LGE IS (Day 90)**								
IS	44	15.8	12.6	12.9	9.8	-2.9	4.0	-5.7 to -0.1	0.05	23.6	30.4%	20.7 to 74.4
	45	14.7	12.0	12.9	9.8	-1.7	3.8	-4.4 to 0.9	0.18	20.4	17.0%	12.6 to 74.1
	46	13.2	11.2	12.9	9.8	-0.2	2.9	-2.3 to 1.8	0.80*	15.0*	10.1%*	5.1 to 70.7
	47	12.2	10.4	12.9	9.8	0.8	2.5	-1.0 to 2.5	0.36	14.0	19.8%	3.8 to 56.5
	48	11.2	9.8	12.9	9.8	1.8	2.3	0.1 to 3.4	0.04	16.5	25.5%	8.1 to 41.5
	49	10.1	9.1	12.9	9.8	2.9	2.4	1.1 to 4.6	0.00	22.6	25.9%	9.3 to 49.2
	50	9.1	8.5	12.9	9.8	3.8	2.7	1.8 to 5.7	0.00	29.6	34.6%	9.4 to 56.7
	51	8.2	7.9	12.9	9.8	4.8	3.2	2.6 to 7.0	0.00	37.8	43.4%	19.2 to 64.4
	52	7.3	7.3	12.9	9.8	5.7	3.6	3.2 to 8.3	0.00	46.5	49.9%	28.6 to 72.5

[∞] P-values for paired sample T-Test for each thresholding technique.

* Values on which decision to choose the AAR and IS ECV thresholding values.

Abbreviations:AAR=area at risk; CoV=coefficient of variability (%); CI=confidence interval; ECV=extracellular volume; IS=infarct size; LGE=late gadolinium enhancement.

Table 3. Baseline infarct characteristics.

	All patients (n=50)	1.5 Tesla (n=32)	3 Tesla (n=18)	p-value
LVEDVi, ml/m2	81±17.7	82±14.7	79.4±22.6	0.65
LVESVi, ml/m2	44±12.6	45.5±14.5	41.3±8.1	0.27
LVMi, grams	58±12.8	59.4±13.8	55.3±10.8	0.27
Ejection Fraction, %	44.6±10	45±11.1	44±7.6	0.72
MVO size, volume in %	4±4.8	4.9±5.4	2.3±3	0.06
Border-zone ECV, %	38.6±2.4	38.2±2.3	39.4±2.5	0.11
AAR Volumes by different techniques				
AAR (T2W), volume (%)	47.4±18	47.3±19.2	47.5±16.2	0.96
AAR (T1-Maps), volume (%)	46.2±17	45.4±18	47.5±16	0.67
ECV >33%, volume (%)	47.2±17.4	46.8±18.7	47.9±15.5	0.82
Infarct Volumes by different techniques				
Acute LGE IS (FWHM), volume (%)	27.5±14.5	28.8±15.7	25.2±12.2	0.41
Acute LGE IS (5SD), volume (%)	28.3±16.7	28.1±17	28.6±16.5	0.92
Acute ECV >46%, volume (%)	19.4±13.4	20.4±13.7	17.6±13	0.49
Follow-up LGE IS (FWHM), volume (%)	17.4±11.4	18.3±11.4	16±11	0.51

n=50. Values are mean±SD. LV measurements are indexed to body surface area (BSA), infarct volumes are unindexed. LVEDVi=left ventricular end diastolic volume (indexed), LVESVi=left ventricular end systolic volume (indexed), LVMi=left ventricular mass (indexed).

Table 4. Predictors of follow-up IS and per-patient number of non-viable segments in uni-/multi-variable regression analysis.

	Follow-up IS					Number of non-viable segments				
MV Variable	B	SE	UV	B	MV	B	SE	UV	B	MB
Age	-0.1	0.14	0.53			0.002	0.02	0.92		
Gender	1.8	4	0.69			0.58	0.49	0.24		
Current Smoker	-7	3	0.03			-0.8	0.3	0.04	-0.08	0.50
Hypertension	-0.1	4	0.98			0.28	0.49	0.57		
Hypercholesterolemia	-1.4	3	0.69			-0.17	0.38	0.66		
Diabetes	-3.8	5	0.44			-0.35	0.55	0.53		
Family history of CAD	-2.4	3	0.47			-0.53	0.36	0.15		
Systolic BP	-0.05	0.05	0.29			0	0.06	0.96		
Heart Rate	0.1	0.1	0.22			-0.01	0.01	0.76		
TIMI flow pre-PCI			<0.01		0.37	-0.38	0.24	0.12		
TIMI flow post-PCI			0.96			0.03	0.5	0.95		
Door to Balloon time	-0.01	0.01	0.20			0	0.001	0.53		
LVEDV	0.11	0.04	0.01		0.98	0.002	0.005	0.74		
LVESV	0.22	0.05	<0.01		0.91	0.01	0.006	0.04	-0.18	0.16
LV Mass	0.07	0.05	0.16			0.001	0.006	0.89		
Ejection Fraction	-0.67	0.14	<0.01		0.37	-0.05	0.01	<0.01	0.05	0.68
MVO	13	3	<0.01		0.71	1	0.3	<0.01	-0.04	0.75
Acute IS (LGE FWHM)	0.65	0.06	<0.01		0.89	0.06	0.01	<0.01	0.1	0.68
Acute IS (ECV >46%)	0.79	0.05	<0.01	0.9	<0.01	0.07	0.01	<0.01	0.70	**<0.01**

Abbreviations: B=beta, SE=standard error, MV=multivariate, UV = univariate.

Figures

Figure 1. Study Design.

Figure 2. AAR quantification: **Case 1**: Anterior AMI by T2W-imaging (applying FWHM thresholding), native T1-maps (applying 2SD thresholding) and ECV-maps (applying greater than 33% threshold). The AAR quantified by all three methods is comparable. **Case 2**: IS quantification (non-transmural infarction): Demonstrates, acute IS by LGE-imaging appears to be transmural whereas acute ECV-maps demonstrate less transmurality (red-zone is above 46%) and follow-up LGE-imaging confirms viability in the inferior segments (<50% transmural). **Case 3**: IS quantification (near transmural infarction): Demonstrates near transmural infarct acutely on LGE-imaging and ECV-maps and also on follow-up LGE-imaging.

Figure 3. Comparison of established quantification methods and ECV-maps.

Figure 4. Scatter-plot of MSI estimated by all methods against LV function at follow-up.

Figure 5. Panel A: Dot and line diagram comparing paired IS by acute ECV-maps and LGE-imaging to actual (follow-up) IS on LGE-imaging (FWHM). Panel B: Bar chart demonstrating trend of increase in IS with increase in number of non-viable segments. The trends for both, acute ECV-maps and LGE-imaging are statistically significant.

Figure 6. Box-and-whiskers plot of IS by both methods in patients with/without adverse LV remodeling.

Figure 7. Short-axis illustration of the LV demonstrating acute infarct size is overestimated using acute LGE-imaging. On ECV-maps, it is possible to differentiate three zones in the territory of AMI: the AAR, the border-zone (zone with extensive peri-infract oedema and possible islets of cell injury, which recovers over-time) and the

actual infarcted zone (necrosed myocardial tissue, which does not recover on follow-up).