

Measurement of Myocardium at Risk with Cardiovascular MR: Comparison of Techniques for Edema Imaging¹

Elisa J. McAlindon, BMBS
Maria Pufulete, PhD
Jessica M. Harris, PhD
Christopher B. Lawton, BSc
James C. Moon, MD
Nathan Manghat, MD
Mark C. K. Hamilton, FRCR
Peter J. Weale, BA
Chiara Bucciarelli-Ducci, PhD

Purpose:

To determine variability and agreement for detecting myocardial edema with T2-weighted short-tau inversion recovery (STIR), acquisition for cardiac unified T2 edema (ACUT2E), T2 mapping, and early gadolinium enhancement (EGE) after successfully reperfused ST-segment-elevation myocardial infarction (STEMI) and diagnostic accuracy of each sequence to predict infarct-related artery (IRA).

Materials and Methods:

Local ethics committee approved the study, with patient informed written consent. On day 2 after successful primary angioplasty for STEMI, 53 patients were prospectively enrolled; 40 patients (mean age, 60 years) completed study. Two sets of cardiac magnetic resonance (MR) images were obtained on same day 6 hours apart. Basal, midcavity, and apical sections were obtained with each sequence. Interobserver, intraobserver, and interimage variability (1 minus intraclass correlation coefficient) and agreement (Bland-Altman method) were assessed.

Results:

Size of myocardial edema significantly differed. Mean size of myocardium at risk was similar between T2-weighted STIR (18.2 g) and T2 mapping (17.3 g) ($P = .54$). Mean size differed between T2-weighted STIR (18.2 g) and ACUT2E (14.0 g) ($P = .01$) and between T2-weighted STIR (18.2 g) and EGE (14.2 g) ($P = .003$). T2 mapping and EGE had best agreement (interobserver bias: T2-weighted STIR, -0.9 [mean difference] ± 9.6 [standard deviation]; ACUT2E, -2.5 ± 6.9 ; T2 mapping, -3.8 ± 4.7 ; EGE, -5.3 ± 5.9 ; interimage bias: T2-weighted STIR, 1.5 ± 5.8 ; ACUT2E, -0.8 ± 4.9 ; T2 mapping, 3.1 ± 4.0 ; EGE, 1.1 ± 4.9 ; intraobserver bias: T2-weighted STIR, 1.4 ± 5.8 ; ACUT2E, 0.6 ± 4.7 ; T2 mapping, 2.2 ± 3.1 ; EGE, 1.7 ± 2.9). Variability was lowest for T2 mapping (intraobserver, 0.05; interobserver, 0.09; interimage, 0.1) followed by EGE (intraobserver, 0.03; interobserver, 0.14; interimage, 0.14), with improved detection of territory of IRA versus ACUT2E (intraobserver, 0.11; interobserver, 0.22; interimage, 0.12) and T2-weighted STIR (intraobserver, 0.1; interobserver, 0.32; interimage, 0.1).

Conclusion:

Cardiac MR methods to detect and quantify infarct myocardial edema are not interchangeable; T2 mapping is the most reproducible method, followed by EGE, ACUT2E, and T2-weighted STIR.

Clinical trial registration no. NCT01468662

©RSNA, 2014

Online supplemental material is available for this article.

¹From the Bristol Heart Institute (E.J.M., C.B.L., N.M., M.C.K.H., C.B.) and Clinical Trial and Evaluation Unit (M.P., J.M.H.), University of Bristol, Bristol NIHR Cardiovascular Biomedical Research Unit, Level 7 Queens Bldg, Bristol Royal Infirmary, Bristol BS2 8HW, England; Heart Hospital, London, England (J.C.M.); and Siemens Healthcare, Frimley, England (P.J.W.). Received September 1, 2013; revision requested October 15; final revision received February 4, 2014; accepted March 4; final version accepted August 26. Supported by the NIHR Bristol Cardiovascular Biomedical Research Unit in collaboration with University College London Biomedical Research Centre. Address correspondence to C.B. (e-mail: c.bucciarelli-ducci@bristol.ac.uk).

This article presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health.

©RSNA, 2014

The detection and quantification of myocardial edema by using cardiovascular magnetic resonance (MR) imaging (cardiac MR) is transforming the understanding of acute myocardial infarction because the myocardium at risk and myocardial salvage (myocardial edema or myocardium at risk minus infarct size) can now be identified and measured noninvasively (1–3).

In clinical practice, detection of myocardial edema can allow the identification of the infarct-related artery (IRA) and guide management. In the scientific setting, the quantification of myocardial salvage with reperfusion and adjuvant strategies of myocardial infarction can act as surrogate end points in clinical trials (4). Therefore, the precision and the robustness (agreement and variability) of the method used to assess myocardial edema are pivotal.

Advances in Knowledge

- In comparing four sequences to detect edema (T2-weighted short-tau inversion recovery [STIR], T2 mapping, acquisition for cardiac unified T2 edema [ACUT2E], and early gadolinium enhancement [EGE]), T2-weighted STIR and T2 mapping have a similar low interimage variability (1 – intraclass correlation coefficient [ICC] = 0.1 for both).
- In this comparison, T2 mapping has the lowest interobserver variability (1 – ICC = 0.09).
- With this comparison, EGE (1 – ICC = 0.03) and T2 mapping (1 – ICC = 0.05) have a similar low intraobserver variability.
- Overall, among the four sequences tested and taking into account the three variability parameters (intraobserver, interobserver, and interimage), T2 mapping is the most reproducible method for detecting myocardial edema following reperfused ST-segment-elevation myocardial infarction (STEMI).

Currently, the most widely used technique is the T2-weighted short-tau inversion-recovery (STIR) method (5), which also demonstrates prognostic value (6). However, recent technical innovations have introduced alternative methods that may have potential advantages and translate to improved diagnostic precision and robustness. These are T2 mapping (7); acquisition for cardiac unified T2 edema (ACUT2E) (8), a turbo spin-echo steady-state free precession hybrid bright-blood sequence; and imaging early (1–3 minutes) after gadolinium-based contrast agent administration (early gadolinium enhancement [EGE]) (9). However, the experience in using these in the above setting is limited.

The hypothesis of the study was that one of the newer sequences would have reproducibility superior to that of T2-weighted STIR. The purpose of the study was to determine the intraobserver, interobserver, and interimage variability and the agreement for four methods available for detecting myocardial edema (T2-weighted STIR, ACUT2E, T2 mapping, and EGE) in patients after successfully reperfused ST-segment-elevation myocardial infarction (STEMI). In addition, we aimed to determine the diagnostic accuracy of each sequence to predict the IRA.

Materials and Methods

The ACUT2E and T2 mapping sequences were supplied as work-in-progress packages by Siemens Healthcare (Frimley, England). The authors (E.J.M., C.B.) who are not employees

Implication for Patient Care

- In this study, we determined that, of the four sequences tested, the prediction of the infarct-related artery (IRA) territory with T2 mapping and EGE most closely matches the depiction of the IRA territory with angiography following STEMI (98% patients with T2 mapping, 95% patients with EGE).

of Siemens Healthcare (Frimley, England) had control of inclusion of any data and information that might present a conflict of interest for the author (P.J.W.) who is an employee of or a consultant for Siemens Healthcare (Frimley, England).

Patient Population

Consecutive patients with the first myocardial infarction on day 2 after successful primary angioplasty for STEMI were enrolled in the study to minimize referral bias, and these patients reflected clinical practice. Successful primary angioplasty was defined as a final Thrombolysis in Myocardial Infarction, or TIMI, flow grade 3 in the IRA.

Inclusion criteria were (a) patients presenting with STEMI who (b) proceeded with primary percutaneous coronary intervention within 12 hours of pain. Patients were excluded if they had contraindications to MR imaging (two patients), chronic atrial fibrillation (one patient), renal impairment with estimated glomerular filtration rate of less than 30 mL/min/1.73 m², or cardiogenic shock (two patients).

The study was approved by the local ethics committee, and all patients

Published online before print

10.1148/radiol.14131980 Content codes: **CA** **MR**

Radiology 2015; 275:61–70

Abbreviations:

ACUT2E = acquisition for cardiac unified T2 edema
EGE = early gadolinium enhancement
ICC = intraclass correlation coefficient
IRA = infarct-related artery
SD = standard deviation
STEMI = ST-segment-elevation myocardial infarction
STIR = short-tau inversion recovery

Author contributions:

Guarantors of integrity of entire study, E.J.M., C.B.L., C.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, E.J.M., P.J.W., C.B.; clinical studies, E.J.M., C.B.L., J.C.M., N.M., C.B.; statistical analysis, E.J.M., M.P., J.M.H., C.B.; and manuscript editing, E.J.M., M.P., J.C.M., N.M., M.C.K.H., P.J.W., C.B.

Clinical trial registration no. NCT01468662

Conflicts of interest are listed at the end of this article.

gave informed written consent (clinical trial registration no. NCT01468662).

Cardiac MR Protocol

The images were acquired by using a 1.5-T MR imaging system (Magnetom Avanto; Siemens Healthcare, Erlangen, Germany) with a standard 12-channel matrix coil configuration. All images were acquired by the same operator (E.J.M., level 3 Society for Cardiovascular Magnetic Resonance–European Society of Cardiology accredited with more than 3 years of cardiac MR experience).

Two cardiac MR imaging examinations (image set A and image set B) were performed in each patient on the same day, at least 6 hours apart. In five patients, T1 and T2 mapping nonenhanced images were acquired in both image set A and image set B to demonstrate that images in image set B were unaffected by residual contrast agent from image set A.

Each image set consisted of three long-axis (four-, three-, and two-chamber view) and a full stack of short-axis steady-state free precession cine images. This was followed by the acquisition of three short-axis sections (basal, midcavity, and apical) by using T2-weighted STIR, T2 mapping, and ACUT2E sequences. Subsequently, acquisition of the same three short-axis sections (basal, midcavity, and apical) was repeated by using a segmented inversion-recovery gradient-echo sequence 1–3 minutes after the intravenous administration of 0.1 mL/kg of gadobutrol (Gadovist; Bayer Schering Pharma, Berlin-Wedding, Germany) (EGE). Finally, late gadolinium enhancement images were acquired 15–20 minutes after contrast agent injection in the three long-axis and the full stack of short-axis views.

All sequence parameters are illustrated in Table 1, and the corresponding images obtained with the sequences are presented in Figure 1.

To ensure matching of section position among all four sequences, the same acquisition planes were adopted. To maintain the closest anatomic

Table 1

Sequence Parameters				
Parameter	T2-weighted STIR	T2 Mapping	ACUT2E	EGE
Field of view	Variable	Variable	Variable	Variable
Field of view phase (%)	81.3	81.3	81.3	81.3
Repetition time (msec)	700	223.77	233.23	700
Echo time (msec)	74	1.12	1.84	3.17
Flip angle (degrees)	90	70	180	25
Matrix	208 × 256	156 × 192	210 × 256	208 × 256
Bandwidth (Hz/pixel)	235	930	977	140
Echo spacing (msec)	6.74	2.6	3.7	8.2
Trigger pulse	2	4	2	2
Voxel size	2.3 × 1.4 × 8	2.3 × 1.9 × 8	1.4 × 1.4 × 8	1.9 × 1.4 × 8
Coil normalization	Yes	No	Yes	Yes

Figure 1

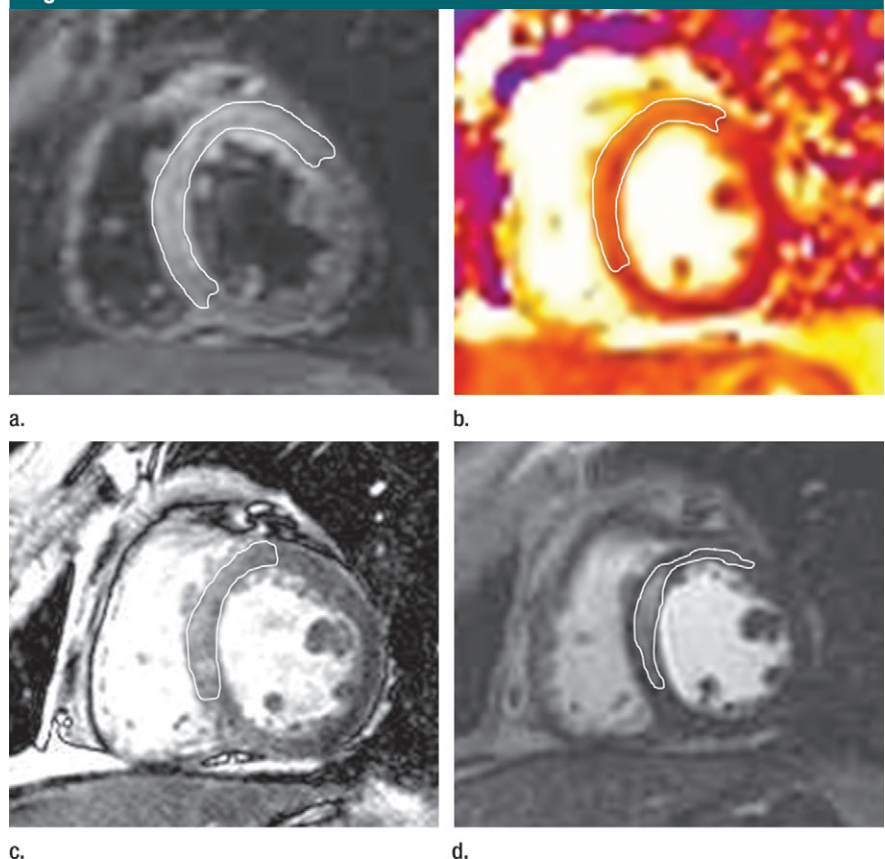


Figure 1: Midcavity short-axis sections show myocardial edema (outlined area) in the left anterior descending artery territory obtained by using (a) T2-weighted STIR, (b) T2 mapping, (c) ACUT2E, and (d) EGE.

position of the three sections between image set A and image set B, the position relative to the mitral valve plane

was measured and copied as a reference for image set B. The same field of view and section thickness were used

for all sequences. Each section was obtained during a breath hold of 10–15 seconds depending on the patient's heart rate.

T2-weighted STIR Sequence

For T2-weighted STIR imaging, a breath-hold black-blood segmented turbo spin-echo technique (10) was adopted, with use of a triple inversion-recovery preparation module to suppress signal from flowing blood, as well as from fat, with surface coil normalization. Typically, parameters were as follows: repetition time, two R-R intervals; echo time, 75 msec; flip angle, 90°; inversion time, 170 msec; section thickness, 8 mm; field of view, 340–400 mm; matrix, 208 × 256; and voxel size, 2.3 × 1.4 × 8 mm. T2-weighted STIR images were acquired during six to eight consecutive breath holds.

ACUT2E Sequence

The ACUT2E sequence is a turbo spin-echo steady-state free precession pulse sequence that does not require a black-blood preparation or a T2 preparation (8). Typical parameters used were as follows: repetition time msec/echo time msec, 233.23/1.84; flip angle, 180°; section thickness, 8 mm; matrix, 210 × 256; and voxel size, 1.4 × 1.4 × 8 mm, with an optimized coil sensitivity correction method.

T2 Mapping Sequence

The T2 mapping sequence (7) consisted of a T2 prepared steady-state free precession sequence that generates three T2-weighted images, each with its own T2 preparation time (0, 24, and 55 msec). These images are acquired in the transient state of single-shot steady-state free precession immediately after the T2 preparation pulse. The signal intensity in each image represents a different echo time along the T2 decay curve. The sequence is performed during seven heartbeats with two R-R intervals to allow for T1 recovery. Typical parameters are as follows: 223.77/1.12; flip angle, 70°; section thickness, 8 mm; field of view, 340–400 mm; matrix,

156 × 192; and voxel size, 2.3 × 1.9 × 8 mm.

EGE Sequence

The EGE images were acquired with an inversion-recovery prepared breath-hold gradient-echo sequence 1–3 minutes after contrast agent injection, in keeping with the literature (9). Typical image parameters were as follows: 700/3.17; matrix, 208 × 256; flip angle, 25°; section thickness, 8.0 mm; and voxel size, 1.9 × 1.4 × 8 mm, with coil normalization. The inversion time was progressively optimized to null normal myocardium (typical values, 200–250 msec).

Image Analysis

All images (three short-axis sections, four sequences, two imaging examinations) were randomized per sequence type and analyzed independently by two observers (E.J.M. and C.B., both of whom were level 3 Society for Cardiovascular Magnetic Resonance–European Society of Cardiology accredited with more than 3 years of cardiac MR experience) who were blinded to clinical and angiographic data. When present, areas of microvascular obstruction and hemorrhage were included within the area contoured for edema. The data set included 480 (40 × 12) images for image set A and 480 images for image set B. For intraobserver variability, observer 1 analyzed image set A and reanalyzed image set A at an interval of 1 month. For interobserver variability, both observer 1 and observer 2 analyzed image set A. For interimage variability, observer 1 analyzed image set A and image set B. Therefore, a total of 1920 images were analyzed. To ensure consensus agreement on the affected territories, the hyperintense zones were first reviewed by two observers with more than 3 years of experience in cardiac MR imaging (E.J.M., C.B.) who were blinded to clinical and angiographic data.

Myocardial edema quantitative analyses were performed by manually measuring the area of abnormal signal intensity with a planimeter by

using commercially available semiautomated software (Argus; Siemens Healthcare, Erlangen, Germany) and expressing the measurement in grams (assuming a specific gravity of 1.05 g/mL). For T2-weighted STIR and ACUT2E, the optimal window setting was defined as the sum of the mean myocardial signal intensity of the unaffected area plus 2 standard deviations (SDs) for this area. The level setting was set at the mean signal intensity of the unaffected area (11). For T2 mapping and EGE, the window setting was visually optimized, according to data in previous literature (9,12).

Statistical Analysis

For each of the four sequences, intraobserver, interobserver, and interimage agreement were assessed by using the Bland-Altman 95% limits of agreement method (13) as follows: means and SDs of the differences between repeat measurements and 95% limits of agreement, calculated as $M \pm (1.96 \cdot SD)$, where M is the mean, were calculated. Bland-Altman plots of the difference between the measurements compared with their mean were constructed. Differences in myocardial edema size among all four sequences were assessed between the sequences and the reference standard of T2-weighted STIR by using the paired t test. T1 and T2 values (nonparametric data) were assessed by using the Wilcoxon matched-pairs test. The variability data were graphically displayed, showing the variability attributed to intraobserver, interobserver, and interimage effects as a proportion of total variability for each method ($1 - \text{intraclass correlation coefficient [ICC]}$) (14). The difference between each sequence to detect the IRA was assessed by using an unadjusted Fisher exact test. The difference between the ages of male and female patients was assessed by using an unpaired t test.

Of the 53 patients initially enrolled, 40 completed the protocol successfully (three sections obtained, four sequences performed, and two imaging examinations performed).

Table 2

Baseline Characteristics

Characteristic	Value
Mean age ± SD (y)	60 ± 11
Sex (n = 40)*	
Female	8 (20)
Male	32 (80)
Median age (y)†	
Female	70 (51–80)
Male	57 (38–79)
Time to reperfusion (h)‡	3 (2–5)
Peak troponin T (ng/L)§	3323 (1501–5587)
Time of myocardial infarction to cardiovascular MR (d)‡	2 (1–4)
Time from image set A to image set B (h)‡	7 (7–8)
IRA (n = 40)*	
No. with left circumflex artery	6 (15)
No. with left anterior descending artery	13 (32)
No. with right coronary artery	21 (52)
No. with drug-eluting stent*	25 (62)

* Numbers in parentheses are percentages, and percentages were rounded.

† Numbers in parentheses are ranges.

‡ Data are medians, and numbers in parentheses are interquartile ranges.

§ The reference range is from less than 14 to 10 000. To convert to Système International units in micrograms per liter, multiply by 1.0. Data are the median, and numbers in parentheses are the interquartile range.

Thirteen patients (25%) withdrew following the first imaging examination because of claustrophobia (11 patients), fatigue (one patient), or inability to continue with the second imaging examination (one patient). The median time difference between the two imaging examinations was 7 hours (range, 7–10 hours). Eighty percent of patients were male, and 20% were female. The difference between the ages of the male and female patients was significant ($P = .004$): The mean age for male patients was 57 years (range, 38–79 years), and the mean age for female patients was 70 years (range, 51–80 years). The baseline characteristics of the patients are listed in Table 2.

Table 3

Size of Myocardium at Risk Determined with Each Sequence for Observer 1

Sequence	Mean (g)	Range (g)	P Value vs T2-weighted STIR
T2-weighted STIR	18.2	0–36.1	...
T2 mapping	17.3	4.3–45.9	.54
ACUT2E	14.0	0–36.9	.01
EGE	14.2	1.5–30.5	.003

Results

Size of Myocardial Edema and Myocardium at Risk

The mean size of myocardial edema ranged from 14.0 to 18.2 g (observer 1) among all sequences. T2-weighted STIR was used as the reference standard for myocardial edema mass comparison, as this sequence has the most evidence behind its use and, more important, has prognostic data (6,15,16). T2-weighted STIR produced the largest mass of edema, with a 5% reduction when assessed with T2 mapping, a 23% reduction when assessed with ACUT2E, and a 22% reduction when assessed with EGE (Table 3).

There was a significant difference between T2-weighted STIR (mean, 18.2 g) and ACUT2E (mean, 14.0 g) ($P = .01$) and between T2-weighted STIR (mean, 18.2 g) and EGE (mean, 14.2 g) ($P = .003$). The size of myocardium at risk was similar between T2-weighted STIR (mean, 18.2 g) and T2 mapping (mean, 17.3 g) ($P = .54$). After allowing for multiple testing, the differences between T2-weighted STIR and ACUT2E and T2-weighted STIR and EGE remained significant.

Sequence Agreement

Agreement was assessed by using the Bland-Altman method. Bland-Altman plots for interobserver (Fig E1 [online]), intraobserver (Fig E2 [online]), and interimage (Fig E3 [online]) agreement demonstrated that all sequences had a low bias. However, there is a small but consistent systematic difference between observers for interobserver agreement for all

sequences except T2-weighted STIR (Fig E1 [online]). T2 mapping had consistently tight limits of agreement.

For interobserver agreement, T2-weighted STIR had a bias of -0.9 (mean difference) ± 9.6 (SD), ACUT2E had a bias of -2.5 ± 6.9 , T2 mapping had a bias of -3.8 ± 4.7 , and EGE had a bias of -5.3 ± 5.9 . For interimage agreement, T2-weighted STIR had a bias of 1.5 ± 5.8 , ACUT2E had a bias of -0.8 ± 4.9 , T2 mapping had a bias of 3.1 ± 4.0 , and EGE had a bias of 1.1 ± 4.9 . For intraobserver agreement, T2-weighted STIR had a bias of 1.4 ± 5.8 , ACUT2E had a bias of 0.6 ± 4.7 , T2 mapping had a bias of 2.2 ± 3.1 , and EGE had a bias of 1.7 ± 2.9 .

Myocardial Edema Variability

Variability was determined as 1 minus the ICC for assessing myocardial edema and is shown in Figure 2. Compared with any other technique and by taking into account interobserver, intraobserver, and interimage variability, T2 mapping had the lowest variability overall. However, EGE had the lowest intraobserver variability. For T2 mapping, 1 minus ICC was 0.05 for intraobserver variability; that for interobserver variability was 0.09, and that for interimage variability was 0.1. For EGE, 1 minus ICC was 0.03 for intraobserver variability; that for interobserver variability was 0.14; and that for interimage variability was 0.14. For ACUT2E, 1 minus ICC was 0.11 for intraobserver variability; that for interobserver variability was 0.22; and that for interimage variability was 0.12. For T2-weighted STIR, 1 minus ICC was 0.1 for intraobserver variability; that for interobserver variability was 0.32; and that for interimage variability was 0.1.

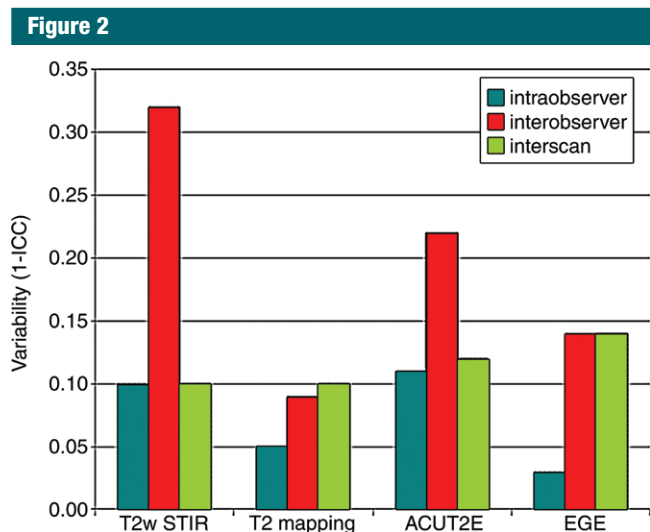


Figure 2: Intraobserver, interobserver, and interimage (*interscan*) variability of the sequences. Overall, variability was the lowest for T2 mapping and the highest for T2 weighted (*T2w*) STIR, ACUT2E. Variability was calculated as 1 minus ICC.

allow for contrast agent elimination, T1 and T2 mapping sequences were used to generate T1 and T2 values of the edematous myocardium and remote myocardium. With use of T1 mapping, there was no significant difference between the T1 readings for remote myocardium (image set A, 1141 msec; image set B, 1100 msec; $P = .81$) and edematous myocardium (image set A, 964 msec, image set B, 924 msec; $P = .19$) between image set A and image set B (Fig 3). Similarly, there was no significant difference between T2 values for the edematous area (image set A, 71 msec; image set B, 71 msec; $P = .72$) or remote myocardium (image set A, 54 msec; image set B, 53 msec; $P = .09$) between image set A and image set B.

Detection of IRA Territory

For the purposes of analysis, IRAs were assigned to a territory according to standardized myocardial segmentation (17): the anteroseptum and anterior wall were assigned to the left anterior descending artery territory, the lateral wall was assigned to the left circumflex artery territory, and the inferior wall and inferoseptum were assigned to the right coronary artery territory (17). Many patients had a large amount of myocardial salvage (minimal late gadolinium enhancement) from early intervention.

In using myocardial edema for the identification of IRA, the edema segments with T2 mapping closely matched IRA determined by using angiography (98% of patients [39 of 40]) compared with EGE (95% of patients [38 of 40]), ACUT2E (88% of patients [35 of 40]), and, last, T2-weighted STIR (82% of patients [33 of 40]). However, this result was not significant at a .05 cutoff ($P = .1$). A case example in a patient is illustrated in Figure 4.

Image Quality

Image quality was subjectively visually graded as 1 or 2 (grade 1, good; grade 2, suboptimal or nondiagnostic). Images were suboptimal or nondiagnostic if there was artifact or signal loss that interfered with the ability of the observers to interpret the image. The overall image quality was good for all sequences. However,

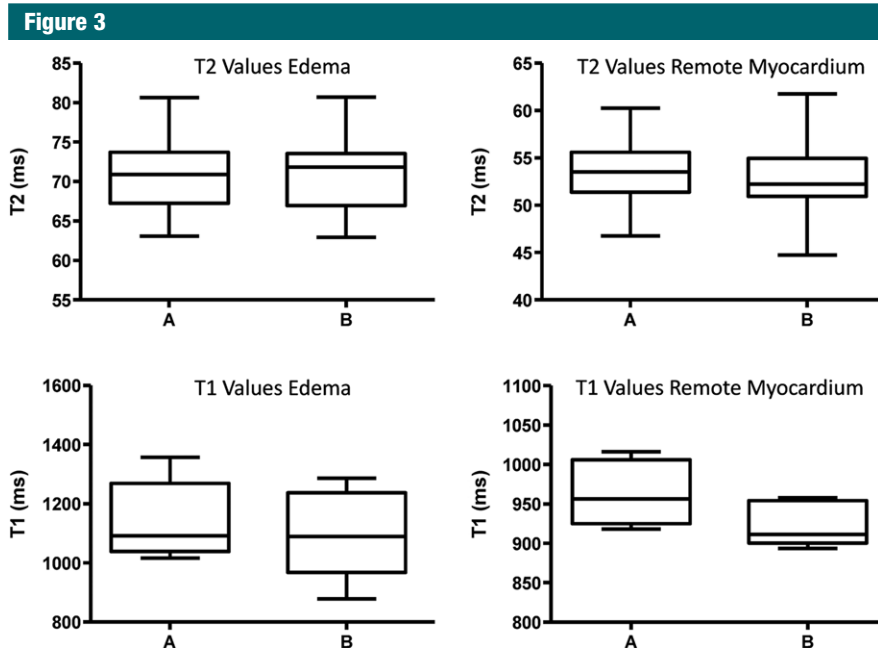


Figure 3: Box plots of nonenhanced T1 and T2 values in image set A (A) and image set B (B). Central line = median value, box = interquartile range, and whiskers = minimum to maximum values. There is no difference in nonenhanced T1 and T2 values between image set A and image set B, suggesting no influence on image set B of the contrast agent administered during acquisition of image set A.

Interimage T1 and T2 Readings

To demonstrate that there was no residual effect on T1 or T2 values on image set B from the gadolinium-based contrast

agent delivered during acquisition of image set A, that is, that the more than 6-hour delay chosen between the two imaging examinations was appropriate to

Figure 4

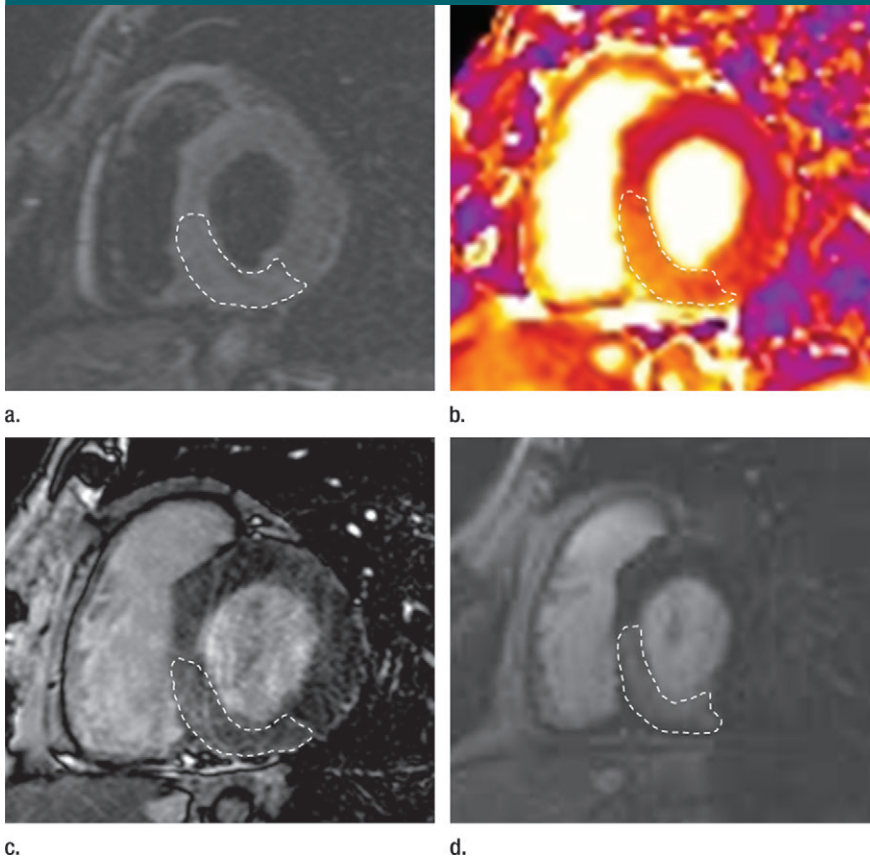


Figure 4: Case example. Basal short-axis sections obtained in a 63-year-old man with a right coronary artery territory acute myocardial infarction by using (a) T2-weighted STIR, (b) T2 mapping, (c) ACUT2E, and (d) EGE. Myocardial edema (outlined area) is well demarcated on T2 mapping and EGE images, while the borders are less clear on T2-weighted STIR and ACUT2E images, with implication in the precision of contouring.

it was reported by the two observers (100% agreement) as suboptimal in 5% of cases for the T2-weighted STIR images and in 3% of cases for the ACUT2E images. Both the T2 mapping and EGE images provided good and interpretable image quality in 100% of patients.

Discussion

Comparison of the four edema detection methods (T2-weighted STIR, ACUT2E, T2 mapping, EGE) after infarction and their variability has not previously been well established in the literature. Our most important finding was that T2 mapping has a low variability and good agreement over other methods for edema detection, with improved qualitative

detection of myocardium at risk when compared with the IRA detected at angiography. This study has shown for the first time the interstudy reproducibility of these four techniques. As the reproducibility squared determines power calculations, using the more reproducible technique, the number needed in trials is smaller. This may have important implications for clinical trials in which myocardium at risk or myocardial salvage is used as a surrogate end point, given the effect of this outcome precision and assessment on trial design and results.

Opportunities and Limitations of T2-weighted STIR

Currently, T2-weighted STIR is the most commonly used method to assess

the presence and extent of myocardial edema both in clinical practice (18) and in clinical trials and outcome studies (19,20). In clinical practice, T2-weighted STIR has been proven to be useful in differentiating acute from chronic infarcts (21,22), as well as acute from chronic phase of inflammatory myocardial disease (23), providing valuable clinical information that can guide treatment. In the setting of clinical trials, T2-weighted STIR has been consistently used to measure myocardium at risk and myocardial salvage (4,20) following different reperfusion strategies. Although T2-weighted STIR is validated (2,24) and established in clinical practice, it has many limitations, and researchers in recent studies have developed newer methods that may be more reproducible (7,8,25). However, while researchers in previous studies investigated the head-to-head comparison of two sequences, in our study, we compared four sequences.

From the literature (26,27), the main limitations of T2-weighted STIR include the following: (a) not very sharp images (relatively low signal-to-noise ratio and relatively small contrast-to-noise ratio between normal and affected myocardium); (b) images with false-negative findings that could be avoided with surface coil intensity correction, which we used in this study; (c) images with false-positive findings, caused by incomplete dark blood preparation, that can lead to bright rim blood artifact adjacent to the endocardium; and (d) artifacts and incomplete images (susceptibility to through-plane cardiac motion with potential myocardial signal loss). These limitations can lead to inaccuracy in the assessment and measurement of myocardial edema or salvage, and this is a particularly important issue when considering using myocardial edema as a surrogate end point in clinical trials (4). In fact, in this setting, it is pivotal to have a parameter that is robustly measurable and reproducible. In our study, T2-weighted STIR images were suboptimal in 5% of the patients ($n = 2$), and this result was caused by artifacts due to ectopic beats in one patient and signal loss due

to through-plane motion in the other patient.

Opportunities and Limitations of ACUT2E

A bright-blood turbo spin-echo steady-state free precession hybrid (ACUT2E) sequence has been developed and tested in comparison with T2-weighted STIR and has been found to have lower inter- and intraobserver variability on a single image set following STEMI (25). ACUT2E overcomes artifacts such as posterior wall signal loss due to cardiac motion and bright-blood subendocardial rims due to stagnant blood.

In keeping with our results (identification of IRA), the results in previous studies have suggested that bright-blood imaging has a higher diagnostic accuracy than does T2-weighted STIR. Payne et al (25) demonstrated an increased diagnostic accuracy of the bright-blood ACUT2E sequence compared with T2-weighted STIR. In our study, although the diagnostic accuracy (detection of IRA) of ACUT2E was better than that of T2-weighted STIR, it was significantly worse than that of both T2 mapping and EGE and presented a high intraobserver and interimage variability. This is most likely due to lower contrast-to-noise ratio, resulting in blurring of the contours between normal and abnormal myocardium.

Opportunities and Limitations of EGE

The researchers in a recent study have proposed that performing imaging 2 minutes following gadolinium-based contrast agent administration (EGE) could delineate myocardial edema rather than the infarcted tissue (9). The basis for this is the alterations in gadolinium-based contrast agent kinetics following acute myocardial infarction (28). This study (9) showed a good correlation with myocardial edema detected by using T2-weighted STIR. The administration of contrast agent can improve image quality by sharpening the contours between normal and abnormal myocardium. This explains the low intra- and interobserver variability. However, our results also show that this sequence had the highest interimage variability. This can be explained by the intricacies

of gadolinium-based contrast agent kinetics and the fact that imaging took place between 1 and 3 minutes after contrast agent injection. The optimal timing to acquisition of EGE images following STEMI has not yet been completely validated (29). From our study, it also appeared that the size of myocardial edema was significantly smaller, as measured with this method, when compared with that of the other three sequences. This difference, again, can be explained with the dynamic contrast agent kinetics intrinsic to this sequence (30). Given the limited evidence, further work is needed to validate this technique in clinical practice.

Opportunities and Limitations of T2 Mapping

A T2 mapping sequence (7) has been proposed. Direct estimation of myocardial T2 value can be extrapolated from these images (12), compared with the other T2 sequences, and it provides potentially attractive quantitative parameters to be used in studies. In a previous validation study, this T2 mapping sequence appeared to be superior to T2-weighted STIR (12). A T2 mapping sequence overcomes some of the limitations of T2-weighted STIR. Our study results confirm what was previously observed by Verhaert et al (12) that T2 mapping is a robust quantitative method for assessing myocardial edema following STEMI compared with T2-weighted STIR. To our knowledge, there have been no head-to-head comparisons between T2 mapping and bright-blood sequences. In our study, this was the only sequence with consistently low variability for all interobserver, intraobserver, and interimage readings. Both T2 mapping and EGE consistently provide interpretable images and good image quality when compared with T2-weighted STIR and ACUT2E. T2 mapping and EGE were also the most reliable methods to help correctly identify the IRA.

Despite the observers having significantly more experience with T2-weighted STIR than with ACUT2E, T2 mapping, and EGE, the interobserver variability was lower in the latter three

sequences compared with T2-weighted STIR. T2 mapping has the lowest interobserver variability, and therefore, may be potentially less user dependent with a smaller learning curve.

Study Limitations

Given the clinical nature of the study, an intrinsic limitation is the lack of histologic validation. Despite T2-weighted STIR having the limitations described above, T2-weighted STIR was used as the current reference standard for myocardial edema mass comparison, as this sequence has the most evidence behind its use and, more important, has prognostic data (6,15,16). In absolute terms, the reference standard to use would have been histologic examination, but in the setting of a human clinical study, as ours, this option would not have been possible. A more complete validation of these sequences could have been performed with animal studies, but this option was outside the purpose of the current study. However, human studies are important despite this lack of histologic findings, as it has been shown that infarct evolution differs according to species for time to reperfusion following myocardial infarction (31). Currently, although there are proposed semiautomatic methods for T2-weighted STIR analysis (32), a standardized method for analyzing for T2-weighted STIR, T2 mapping, and ACUT2E images is not available (33). Also, the 5-SD or full width at half maximum methods (14) proposed for contrast material-enhanced images (ie, late myocardial enhancement) are not validated and do not necessarily apply to the EGE method. T1 mapping may have the potential to detect edema (34) but it has not yet been substantially studied in reperfused infarction.

Conclusion

The results of this study demonstrate that T2 mapping is the most reproducible method for assessing myocardial edema following reperfused STEMI, with the lowest variability. The results of this study should be taken into consideration when designing trials in which myocardial edema or myocardial salvage is used as an end point.

Acknowledgments: We thank the patients who took part in this study and the staff of the Primary Angioplasty Service and Cardiac MR Imaging Service, Bristol Heart Institute (Bristol, England), who enabled this research to happen.

Disclosures of Conflicts of Interest: E.J.M. Activities related to the present article: was paid for travel expenses for 2013 SCMR meeting to present the abstract by University Hospitals Bristol NHS Trust. Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships. M.P. disclosed no relevant relationships. J.M.H. disclosed no relevant relationships. C.B.L. disclosed no relevant relationships. J.C.M. disclosed no relevant relationships. N.M. disclosed no relevant relationships. M.C.K.H. disclosed no relevant relationships. P.J.W. disclosed no relevant relationships. C.B. disclosed no relevant relationships.

References

- Pennell D. Myocardial salvage: retrospection, resolution, and radio waves. *Circulation* 2006;113(15):1821–1823.
- Aletras AH, Tilak GS, Natanzon A, et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation* 2006;113(15):1865–1870.
- Arai AE, Leung S, Kellman P. Controversies in cardiovascular MR imaging: reasons why imaging myocardial T2 has clinical and pathophysiologic value in acute myocardial infarction. *Radiology* 2012;265(1):23–32.
- Desch S, Eitel I, de Waha S, et al. Cardiac magnetic resonance imaging parameters as surrogate endpoints in clinical trials of acute myocardial infarction. *Trials* 2011; 12:204.
- Simonetti OP, Finn JP, White RD, Laub G, Henry DA. “Black blood” T2-weighted inversion-recovery MR imaging of the heart. *Radiology* 1996;199(1):49–57.
- Eitel I, Desch S, de Waha S, et al. Long-term prognostic value of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *Heart* 2011;97(24):2038–2045.
- Giri S, Chung YC, Merchant A, et al. T2 quantification for improved detection of myocardial edema. *J Cardiovasc Magn Reson* 2009; 11:56.
- Aletras AH, Kellman P, Derbyshire JA, Arai AE. ACUTE T2E-TSE-SSFP: a hybrid method for T2-weighted imaging of edema in the heart. *Magn Reson Med* 2008;59(2):229–235.
- Matsumoto H, Matsuda T, Miyamoto K, Shimada T, Mikuri M, Hiraoka Y. Peri-infarct zone on early contrast-enhanced CMR imaging in patients with acute myocardial infarction. *JACC Cardiovasc Imaging* 2011;4(6): 610–618.
- Kitabata H, Imanishi T, Kubo T, et al. Coronary microvascular resistance index immediately after primary percutaneous coronary intervention as a predictor of the transmural extent of infarction in patients with ST-segment elevation anterior acute myocardial infarction. *JACC Cardiovasc Imaging* 2009; 2(3):263–272.
- Payne AR, Casey M, McClure J, et al. Bright-blood T2-weighted MRI has higher diagnostic accuracy than dark-blood short tau inversion recovery MRI for detection of acute myocardial infarction and for assessment of the ischemic area at risk and myocardial salvage. *Circ Cardiovasc Imaging* 2011;4(3): 210–219.
- Verhaert D, Thavendiranathan P, Giri S, et al. Direct T2 quantification of myocardial edema in acute ischemic injury. *JACC Cardiovasc Imaging* 2011;4(3):269–278.
- Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999;8(2):135–160.
- Flett AS, Hasleton J, Cook C, et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2011;4(2):150–156.
- Eitel I, Desch S, Fuernau G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *J Am Coll Cardiol* 2010; 55(22):2470–2479.
- Raman SV, Simonetti OP, Winner MW 3rd, et al. Cardiac magnetic resonance with edema imaging identifies myocardium at risk and predicts worse outcome in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 2010;55(22): 2480–2488.
- Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105(4):539–542.
- Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. *J Am Coll Cardiol* 2009;53(17):1475–1487.
- Thiele H, Schindler K, Friedenberger J, et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST-elevation myocardial infarction trial. *Circulation* 2008;118(1): 49–57.
- Francone M, Bucciarelli-Ducci C, Carbone I, et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol* 2009;54(23): 2145–2153.
- Abdel-Aty H, Schulz-Menger J. Cardiovascular magnetic resonance T2-weighted imaging of myocardial edema in acute myocardial infarction. *Recent Patents Cardiovasc Drug Discov* 2007;2(1):63–68.
- Abdel-Aty H, Tillmanns C. The use of cardiovascular magnetic resonance in acute myocardial infarction. *Curr Cardiol Rep* 2010;12(1): 76–81.
- Friedrich MG. Tissue characterization of acute myocardial infarction and myocarditis by cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2008;1(5):652–662.
- Beyers RJ, Smith RS, Xu Y, et al. T2-weighted MRI of post-infarct myocardial edema in mice. *Magn Reson Med* 2012;67(1):201–209.
- Payne AR, Berry C, Kellman P, et al. Bright-blood T2-weighted MRI has high diagnostic accuracy for myocardial hemorrhage in myocardial infarction: a preclinical validation study in swine. *Circ Cardiovasc Imaging* 2011;4(6):738–745.
- Eitel I, Friedrich MG. T2-weighted cardiovascular magnetic resonance in acute cardiac disease. *J Cardiovasc Magn Reson* 2011;13:13.
- Croisille P, Kim HW, Kim RJ. Controversies in cardiovascular MR imaging: T2-weighted imaging should not be used to delineate the area at risk in ischemic myocardial injury. *Radiology* 2012;265(1):12–22.
- Oshinski JN, Yang Z, Jones JR, Mata JF, French BA. Imaging time after Gd-DTPA injection is critical in using delayed enhancement to determine infarct size accurately with magnetic resonance imaging. *Circulation* 2001;104(23):2838–2842.
- Arai AE. Magnetic resonance imaging for area at risk, myocardial infarction, and myocardial salvage. *J Cardiovasc Pharmacol Ther* 2011;16(3-4):313–320.

30. Kim RJ, Chen EL, Lima JA, Judd RM. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. *Circulation* 1996; 94(12):3318–3326.
31. Hedström E, Engblom H, Frogner F, et al. Infarct evolution in man studied in patients with first-time coronary occlusion in comparison to different species: implications for assessment of myocardial salvage. *J Cardiovasc Magn Reson* 2009;11:38.
32. Sjögren J, Ubachs JF, Engblom H, Carlsson M, Arheden H, Heiberg E. Semi-automatic segmentation of myocardium at risk in T2-weighted cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2012;14:10.
33. Schulz-Menger J, Bluemke DA, Bremerich J, 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.
34. Ferreira VM, Piechnik SK, Dall'Armellina E, 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.