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Dynamic Changes of Edema and Late Gadolinium Enhancement After Acute Myocardial Infarction and Their Relationship to Functional Recovery and Salvage Index

Erica Dall'Armellina, MD; Nina Karia, MBBS; Alistair C. Lindsay, MBChB, DPhil;
Theodoros D. Karamitsos, MD, PhD; Vanessa Ferreira, BSc, MD; Matthew D. Robson, PhD;
Peter Kellman, PhD; Jane M. Francis, DCR(R), DNM; Colin Forfar, MD, PhD; Bernard D. Prendergast, MD;
Adrian P. Banning, MD; Keith M. Channon, MD; Rajesh K. Kharbanda, MBChB, PhD;
Stefan Neubauer, MD, FRCP, FACC, FMedSci; Robin P. Choudhury, DM

Background—Changes in the myocardium in acute ischemia are dynamic and complex, and the characteristics of myocardial tissue on cardiovascular magnetic resonance in the acute setting are not fully defined. We investigated changes in edema and late gadolinium enhancement (LGE) with serial imaging early after acute myocardial infarction, relating these to global and segmental myocardial function at 6 months.

Methods and Results—Cardiovascular magnetic resonance scans were performed on 30 patients with ST-elevation–myocardial infarction treated by primary percutaneous coronary intervention at each of 4 time points: 12 to 48 hours; 5 to 7 days; 14 to 17 days; and 6 months. All patients showed edema at 24 hours. The mean volume of edema (% left ventricle) was 37 ± 16 at 24 hours and 39 ± 17 at 1 week, with a reduction to 24 ± 13 ($P<0.01$) by 2 weeks. Myocardial segments with edema also had increased signal on LGE at 24 hours ($\kappa=0.77$; $P<0.001$). The volume of LGE decreased significantly between 24 hours and 6 months ($27\pm15\%$ versus $22\pm12\%$; $P=0.002$). Of segments showing LGE at 24 hours, 50% showed resolution by 6 months. In segments with such a reduction in LGE, 65% also showed improved wall motion ($P<0.0001$). The area of LGE measured at 6 months correlated more strongly with troponin at 48 hours ($r=0.9$; $P<0.01$) than LGE at 24 hours ($r=0.7$). The difference in LGE between 24 hours and 6 months had profound effects on the calculation of salvage index ($26\pm21\%$ at 24 hours versus $42\pm23\%$ at 6 months; $P=0.02$).

Conclusions—Myocardial edema is maximal and constant over the first week after myocardial infarction, providing a stable window for the retrospective evaluation of area at risk. By contrast, myocardial areas with high signal intensity in LGE images recede over time with corresponding recovery of function, indicating that acutely detected LGE does not necessarily equate with irreversible injury and may severely underestimate salvaged myocardium. (***Circ Cardiovasc Imaging***. 2011;4:228-236.)

Key Words: myocardial salvage ■ myocardial edema ■ late gadolinium enhancement ■ MRI ■ acute coronary syndrome

Cardiac magnetic resonance (CMR) is established as a key noninvasive modality for the evaluation of patients with stable coronary disease. It is the gold standard technique for the assessment of function (cine CMR) and the quantification of scarred myocardium in patients with previous myocardial infarction (MI) (late gadolinium enhancement, [LGE]).[1]

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Recently, the development of T2-weighted (T2W) edema-sensitive sequences has enabled the identification of acutely ischemic myocardium, which is of particular interest in the evaluation of myocardial status in acute MI.[2–5] By comparing the "area at risk," determined by T2W imaging, and the final infarct size, obtained with LGE CMR imaging, myocardial salvage after treatment can be derived and expressed as proportion of myocardial volume initially presumed at risk.[6,7] A number of clinical trials have used this measure, assessed in the acute setting, as a primary end point.[8–10]

However, to capitalize fully on these quantitative CMR techniques requires clear understanding of the dynamic features of each in the context of the rapidly changing patho-
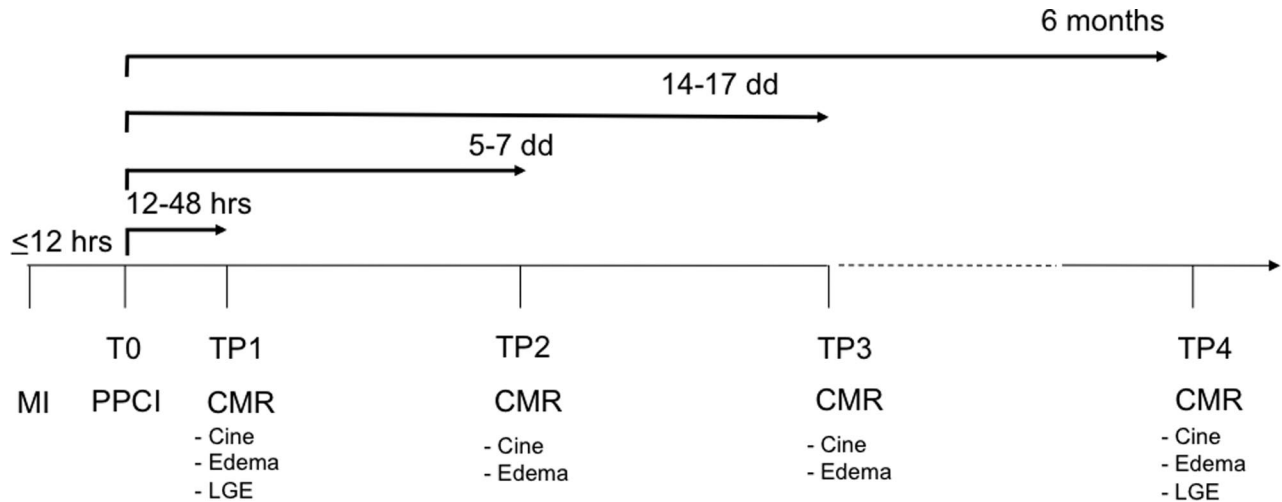
Figure 1. Study protocol. Imaging time points (TP) in relation to the acute MI and primary percutaneous coronary intervention (PPCI). For each TP, the CMR data acquired is given.

logical conditions that pertain in the myocardium after acute ischemic injury and reperfusion.[11] Under these circumstances, there are profound changes in perfusion pressure; small vessel patency and permeability, pH, tissue water content, and cellular composition.[11] Over time, there is resorption of edema, resolution of inflammation and replacement of irreversibly injured myocytes with fibrous tissue.[12] In the acute setting, although it is known that CMR edema imaging may identify both infarct and myocardium at risk and LGE overestimates the infarct zone, acute LGE is still considered a robust prognostic factor, though whether it necessarily always reflects irreversible injury is still debated.[13–15]

Accordingly, we designed a detailed early time course CMR evaluation in patients within 48 hours of technically successful percutaneous coronary intervention (PCI) for acute MI. We quantified (1) myocardial edema at 4 time points after MI (12 to 48 hours; 5 to 7 days; 14 to 17 days, and 6 months) and (2) characteristics of LGE early (12 to 48 hours) and late (6 months) after ischemic injury. We relate each of these parameters to temporally matched measurements of myocardial function at both global and segmental levels.

Our aims were to establish the longitudinal changes of myocardial edema by CMR and to determine the extent to which edema and LGE, obtained in the acute phase, predicted recovery of global and regional left ventricular (LV) function at 6 months. Clarification of these acute dynamic changes of edema and LGE is crucial to the correct interpretation of CMR data in the acute setting and has important implications for the design and the calculation of sample size of clinical trials with myocardial salvage as end point.

Methods

Patient Population

This prospective study was undertaken in a single tertiary center. The study protocol was approved by the local ethics committee, and all patients gave written informed consent. Patients with first ST-segment elevation–MI (STEMI) were eligible if the onset of symptoms had been <12 hours before PCI and if they had ST-segment elevation of at least 0.1 mV in ≥2 contiguous limb leads or at least 0.2 mV ≥2 contiguous precordial leads. Patients with previous MI,

previous revascularization procedure (coronary artery bypass grafts or PCI), severe heart valve disease, known cardiomyopathy, or hemodynamic instability lasting >12 hours after revascularization were not enrolled. Further exclusion criteria were contraindications to CMR, including implanted pacemakers, defibrillators, or other metallic implanted devices and claustrophobia. Acute clinical management was at the discretion of the responsible physician, with the intention to reflect contemporary practice and guidelines (including use of aspiration catheters; glycoprotein IIb IIIa receptor inhibitors, and high-dose clopidogrel loading). Blood samples were collected for troponin I at the time of admission and every 12 hours after PCI.

Cardiac Magnetic Resonance

Four separate 3-T CMR scans were performed on each patient at the following time points after PCI: 12 to 48 hours (24H); 5 to 7 days (1W); 14 to 17 days (2W); and 6 months (6M). The first and last CMR scans assessed LV function, edema, and LGE. The second and third scans acquired function and edema imaging only (Figure 1). Identical short-axis images at matching slice position with functional images were acquired using T2W and LGE imaging. Edema imaging was performed using a T2 prep-SSFP single-shot sequence with coil signal intensity correction.[3] A spine coil and a phased-array 6-channel flexible surface coil were used. If necessary, shimming and center frequency adjustments were performed before T2W imaging to generate images free from off-resonance artifacts. LGE-CMR was performed with a T1-weighted segmented inversion-recovery gradient echo-phase sensitive-inversion recovery sequence 5 to 10 minutes after the administration of 0.1 mmol/kg contrast agent (Gadodiamide, Omniscan, GE Healthcare, Amersham, UK). The inversion time was meticulously adjusted for optimal nulling of remote normal myocardium. (Refer to the online-only Data Supplement for acquisition parameters for both edema and LGE imaging.)

Postprocessing Analysis

Quantification of LV volumes and wall motion were performed as previously described.[16,17] For objective quantification of edema or LGE, a reference region of interest was placed in remote myocardium. The signal intensity threshold indicating edema/LGE was imposed 2 standard deviations above the mean intensity of the reference region of interest, as previously described.[7] (See online-only Data Supplement.)

Statistical Analyses

Values of continuous variables are expressed as mean (±SD). To investigate differences at multiple time points in LV volumes, ejection fraction, wall motion score index, myocardial volume of edema, and LGE assessed by CMR, ANOVA analyses with adjust-

ment for repeated measurements were performed. The Bonferroni procedure, in which the overall type I error (0.05) is distributed across multiple hypothesis tests, was used for post hoc comparisons. For categorical variables, the Wilcoxon signed-rank test was used to compare regional wall motion abnormalities with segmental scoring of edema and late gadolinium. A χ^2 test and a logistic regression model with a repeated-measures variable for the patient (to adjust for the nonindependence of the data) were used to assess the relationship between the transmural extent of myocardial injury, for example, edema/LGE and improvement in regional function. The relationship between the improvement in wall motion along 6 months and the clinical and CMR characteristics were evaluated using linear regression analyses. The Bland-Altman test for continuous T2W measurements and Cohen κ coefficient for T2W, LGE, and wall motion abnormalities categorical measurements were performed to evaluate interobserver variability for edema assessment and for transmurality grading and wall motion scoring, respectively.

All statistical tests were 2-tailed, and all probability values of <0.05 were considered statistically significant.

Results

Patient characteristics are given in Table 1. All patients presented with ST-segment elevation on the ECG and were treated by primary PCI (except for 2, who were transferred from a different hospital and received thrombolysis and rescue PCI). All PCI took place within 12 hours of chest pain onset, with the mean time from onset of pain to balloon treatment of 253±150 minutes. Of 33 patients enrolled, 2 could not complete the first CMR examination because of claustrophobia, 1 patient was excluded due to urgent reintervention, and 2 did not undergo third scan because of technical difficulties or because of patient refusal (Figure, online-only Data Supplement). The first CMR took place at 29±10 hours from the PCI (24H), the second (1W) at 6±1.4 days after PCI, the third (2W) at 16±2.7 days after PCI, and the fourth (6M) at 6.2±1 month after PCI.

CMR Findings

The total number of successful scans was 112 (30 at 24H and 1W, 28 at 2W, and 24 at 6M), and all were suitable for analysis. In segmental analyses, 8 segments at 24H and 12 at 2W showed resonance artifacts in T2W images and were excluded from analyses at all TP (Table, online-only Data Supplement). Both Bland-Altman (bias=2±10%) for continuous T2W measurements and Cohen κ coefficient ($\kappa=0.8$) for T2W, LGE, and wall motion abnormalities categorical measurements indicated excellent levels of agreement for interobserver variability assessments.

Time Course Assessment of Global LV Function and Myocardial Edema

All patients had positive findings for myocardial injury assessed by T2W imaging at 24H except for 1 patient. In this particular case, the lesion, as assessed by LGE and edema, was confined to the apical segment only. As indicated in the Methods section, the apical slices were excluded to avoid partial volume artifacts.

The mean volume of edema was stable over the first week (37±16% of the LV myocardium at 24H and 39±17% at 1W) with a reduction by 2W (24±13%; $P<0.01$) and near resolution (7±10%; $P<0.001$) by 6M (Figure 2). The ejec-

Table 1.   Patient Characteristics

Variable	Value, mean±SD
Age, y	56±9
Sex, M:F	26:4
Ethnicity, Caucasian: Asian	29:1
Body mass index	29±6
Risk factors, n (%)	
Smoking	16 (53)
Hypertension	11 (37)
Diabetes	3 (10)
Family history	9 (30)
Hyperlipidemia	11 (37)
Troponin I (12 h after PCI), mg/mL	40±16
Pain-to-balloon time, min	253±150
Door-to-balloon time, min, median (interquartiles)	44 (30; 62)
Culprit coronary artery, n (%)	
LAD	15 (50)
LCx	2 (6)
RCA	13 (43)
No. of vessels diseased, n (%)	
1	20 (67)
2	6 (20)
3	4 (13)
TIMI flow before PCI, n (%)	0.6±1
0	21 (70)
1	3 (10)
2	4 (13)
3	2 (6)
TIMI flow after PCI, n (%)	2.5±0.6
0	0
1	2 (6)
2	10 (33)
3	18 (60)
Medications during PCI, n (%)	
GP IIb/IIIa inhibitor	23 (76)
Clopidogrel	30 (100)
Heparin	28 (90)
Aspirin	30 (100)
Concomitant medications on admission, n (%)	
β-blockers	1 (3)
ACE inhibitors	6 (20)
Statins	4 (13)
Medications after infarct	
β-blockers	28 (93)
ACE inhibitors	30 (100)
Statins	30 (100)
Aspirin	30 (100)
Diuretic	3 (10)
Nitrates	8 (27)

LAD indicates left anterior descending; LCx, left circumflex; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; GP, glycoprotein; and ACE, angiotensin-converting enzyme.
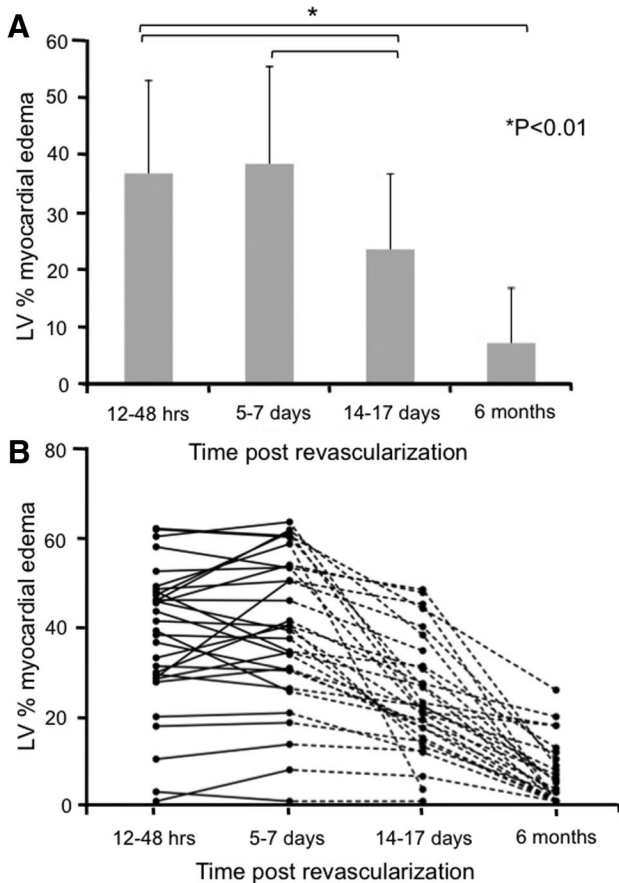
Figure 2. Time course of edema. **A**, Mean percentage of LV volume positive for myocardial edema at each time point. The volume of edema remained stable in the first week after the event with a significant decrease at 15 to 17 days with near resolution by 6 months. **B**, The time course of edema and resolution is given for each patient. There was a large range of LV% volume of edema (0% to 60%). This analysis on an individual level confirms the constancy of edema measured in the first 5 to 7 days, which is suggested in **A**, with marked variation thereafter. Using the objective thresholding methods described in the text, a small number of patients had a substantial volume of apparent residual edema at 6 months.

tion fraction was well conserved (53±9%) at 24H and not significantly different at 6M (59±6%; P=NS) (Table 2).

Time Course Assessment of Edema and LGE on a Segmental Level: Relations to Wall Motion (24H to 2W)

At 24H, 151 of 428 (35%) segments were positive for myocardial edema; 133 of 428 (31%) showed LGE, and 139 of 428 (32%) segments showed abnormal function (Table, online-only Data Supplement). Segments with evidence of injury assessed by T2W or LGE imaging and those with wall motion abnormalities were colocalized (location agreement, κ=0.77; P<0.001), with 120 of 133 (90%) showing all of edema, LGE, and wall motion abnormalities. Similarly, of 277 segments with no edema, 257 (93%) showed normal wall motion, whereas of those with no LGE, 264 (89%) showed no myocardial edema either. Only 31 of 428 (7%) of segments were positive for edema in the absence of LGE.

To assess whether or not the extent of the acute myocardial injury determines regional dysfunction, we examined the relationship between within-segment injury (percentage of segment affected by edema or LGE) and the presence or absence of wall motion impairment in that segment. At 24H, the proportion of segments with wall motion impairment increased in relation to the extent of both myocardial edema (P<0.01; Figure 3A) and LGE (P<0.01; Figure 3B). Of the injured segments (those having either edema or positive for LGE), 75 (17%) had improved motion in the first 2 weeks. This was associated with an improvement in wall motion score index (from 1.52±0.3 at 24H to 1.3±0.3 at 2W, P<0.01) (Table 2).

LGE Volume Reduction Over 6 Months

The volume of LGE decreased significantly between the first time point (27±15% of LV myocardial volume) and the last time point at 6M (22±12%, P=0.002) (Figure 4A). Furthermore, on a patient-by-patient basis, there was considerable variation in the extent of reduction in LGE. The reduction in LGE from acute to 6M was up to 68%, with 46% of patients showing some reduction in LGE at 6M. LGE was also reduced when analyzed at segmental level. Of the 336 segments analyzed at 6M, 108 had been positive for LGE at 24H of which 54 (50%) showed resolution of LGE at 6M (representative examples are shown in Figure 5).

Recovery of Function Accompanies Resolution of LGE

We next examined whether resolution of LGE could be associated with recovery of function in affected segments. Of 336 segments analyzed at 6M, 79 had shown abnormal function at 24H, of which 68 (86%) showed recovery of function at 6M.

Importantly, of those segments that showed an improvement in LGE at 6M 35 of 54 (65%) also showed an improvement in wall motion (P<0.0001) indicating that LGE at 24H did not necessarily signify irreversible myocardial injury.

Conversely, only 8% (6/68) of segments with persistent transmural LGE at 6M had improved function (P<0.01) (Figure 4B). Furthermore, on multivariate analysis the only CMR measure that was predictive of functional recovery was the infarct size determined by LGE CMR (% LV_{score}) at 6M (P=0.015). The importance of CMR assessment of infarct size at 6M is further emphasized by the strong correlation between the infarct size (% LV_{score}) assessed at 6M and troponin I, assessed at 48H (r=0.9; P<0.01), whereas the equivalent relationship with LGE measured at 24H was relatively weak (r=0.7, P<0.01; Figure 6).

Effects of Timing of LGE Measurement on the Calculation of Salvage Index

Calculation of myocardial salvage (index) depends both on (1) the acutely determined area at risk (T2W image) and (2) the final infarct size (LGE). Given the variation in LGE described above, we calculated the effect of its assessment early (24H) versus late (6M) on the estimation of salvage. Depending on the imaging time for LGE, the salvaged myocardium index was substantially different: 26±21% at

Table 2.   CMR Findings

	24 Hours (n=30)	5 to 7 Days (n=30)	14 to 17 Days (n=28)	6 Months (n=23)	P Value	Post Hoc
Ejection fraction, %	53±9	55±10	54±8	59±6	0.9	1.0
End-diastolic volume, mL	144±25	153±33	156±37	158±22	0.2	1.0 (24H vs 1W, 24H vs 2W, 24H vs 6M)
						0.1 (24H vs 2W)
						0.3 (24H, vs 6M)
End-systolic volume, mL	68±22	72±30	73±27	57±24	0.6	1.0 (24H vs 1W, 2W, 6M)
Stroke volume	76±15	82±14	82±16	88±17	0.3	1.0 (24H vs 1W, 24H vs 2W)
						0.7 (24H, vs 6M)
Wall motion score index	1.52±0.3	1.4±0.3	1.35±0.3	1.36±0.3	<0.001	<0.01 (24H vs 1W, 24H vs 2W, 24H vs 6M)
Edema, LV%	37±16	39±17	24±13	6±9	<0.001	0.001 (24H vs 2W)
						0.001 (1W vs 2W)
						0.001 (24H, 2,3 vs 6M)
LGE, LV%	27±15			21±11	0.002	0.002

24H versus 42±23% at 6M ($P=0.02$). Thus, LGE timing critically determines the calculated salvage index.

Discussion

Optimal application and accurate interpretation of CMR in acute myocardial ischemia require that the nature and patterns of change of CMR features are fully defined. We report the first detailed time course study that examines early changes in myocardial function, edema, and LGE in patients treated with primary PCI for STEMI and that relates these early features to late measures of infarct size and functional recovery at global and segmental levels.

The principal findings are that (1) edema was present in virtually all cases; the volume of edema remained unchanged over the first week but decreased significantly by 15 days. (2) A large majority of segments that were positive for edema also showed evidence of LGE, assessed at 24H. (3) In 46% of the patients, LGE present on early scans had diminished in size by 6M, and, in some cases, dramatically. (4) Acute LGE was a weak predictor of functional recovery compared with chronic LGE, as even segments with transmural LGE at 24H, showed an improvement in contractility at 6M. (5) The reduction in LGE at the later time had a profound effect on the calculation of salvage index, which varied by up to ≈60%, depending on the time point used. These findings have important implications for the timing and interpretation of CMR after acute STEMI, including in the estimation of viable versus infarcted tissue and on the design and implementation of clinical trials that use salvage index as an end point.

Acute myocardial ischemia-reperfusion is a dynamic process, involving a complex cascade of intracellular and interstitial changes that affect oxygenation and pH in the myocardium; intravascular pressure; small-vessel permeability and patency; tissue water content, inflammatory cell infiltration; and local hemorrhage.[18] These changes potentially alter both the inherent MR characteristics of the tissue and the delivery, distribution and removal of exogenous contrast agents, compared with the stable setting.[19] Specifically, the kinetics of gadolinium distribution and precise tissue specificity in acute infarction are not fully understood,[13–15] and the potential for accumulation of LGE even in viable myocardium has not been excluded.

Myocardial Edema

Both intracellular edema caused by decoupling of water molecules from proteins[20] and/or tissue accumulation of water leads to a prolongation of T2[21] that appears as transmural bright signal on T2W images.[22] In dogs, myocardial edema has been demonstrated after 30 minutes ischemia.[5] Previous reports have identified persistence of edema signal for at least 12 days after infarction,[3,6] but the timing of maximal myocardial edema and its early evolution had not been defined. This information is important to establish the optimal imaging window for the assessment of salvaged myocardium[6,7] and for estimation of prognosis.[23,24] We demonstrate that edema is maximal and constant during the first week after MI, reducing thereafter. Therefore, the window for retrospective quantification of myocardium "at risk" is up to 7 days, with a risk of underestimation after that time.

Late Gadolinium Enhancement

Late gadolinium enhancement occurs after MI. In the context of established MI and scar formation, the area of myocardial fibrosis is very closely linked to the extent and distribution of LGE.[1,12] Furthermore, the extent of LGE can be used to predict recovery of myocardial function after revascularization,[1,25] with the transmural segmental extent of LGE/scar inversely correlating with the probability of functional recovery. Reduction in LGE has been previously reported from the acute phase to a chronic stage, and attributed to "shrinking of
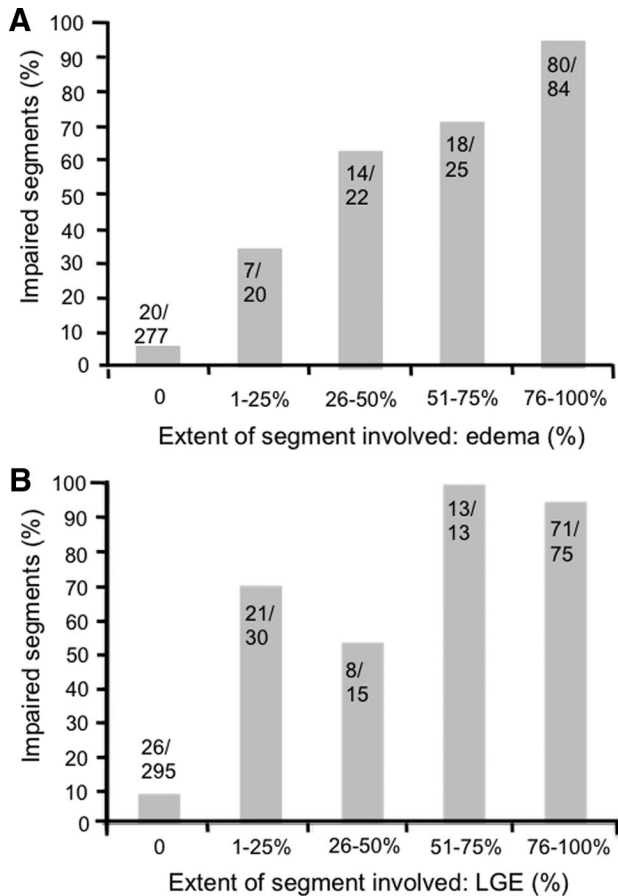
Figure 3. Impaired segments (% affected) as a function of the extent of segment positive for edema (**A**) and LGE (**B**) at 24H. Segments with acute myocardial injury as identified either by presence of LGE and/or edema. For both edema and LGE, the probability of segmental dysfunction increased with the fraction of segment affected. For unaffected segments, as expected, a large majority showed normal function.

Figure 4. A, Myocardial LGE early (12 to 48 hours) versus late (6 months), and **B**, wall motion improvement abnormalities. **A**, The myocardial volume (mean % ±SD) positive for LGE, decreased significantly from 12 to 48 hours to 6 months. The change in extent of LGE is also shown for each patient. Patients with unchanged LGE at 6 months are shown in red; those with decreased LGE in black. Eleven patients of 24 (46%) who underwent CMR at 6 months showed a reduction in LGE volume (of 38±14%). In the remaining 13 patients, no reduction in size of the LGE volume was identified (23±14% versus 23±14%, respectively). **B**, Segments with improved function at 6 months (n=68) broken down by extent of LGE within that segment LGE (none; 1% to 75%=partial thickness and 76% to 100%=full thickness) at both 24H and 6M. Across categories, the extent of LGE, measured at 12 to 48 hours (dark bars) was a poor predictor of functional recovery. Significantly, even segments showing full-thickness LGE were associated with functional recovery. By contrast, LGE extent at 6 months (light bars) was strongly inversely correlated with improved function in that segment.

the scar," together with compensatory hypertrophy of adjacent myocardium.[26,27]

Although LGE occurs in context of acute MI, this cannot reflect tissue fibrosis, which takes several weeks to develop. In a dog model, Fieno et al[28] showed that fibrosis increased 11-fold between 3 and 60 days after permanent coronary artery occlusion. Conversely, in a model of acute MI, LGE can be positive within 1 hour of injury.[29] Given the variant tissue composition between acute and chronic states, it cannot be assumed that the presence of LGE necessarily always implies irreversible injury. We found that the overall volume of LGE decreased by 22% between the first time point and 6 months and that on a patient-by-patient basis, there was considerable variation in the extent of reduction in LGE. Importantly, of those myocardial segments showing reduction in LGE at 6 months, 68% also showed an improvement in wall motion ($P<0.0001$). Using a technique based on differential signal intensity threshold analysis, Yan et al[30] identified an peri-infarct "border zone" on the periphery of the LGE area. However, recovery confined to a putative "border zone" is unlikely to account for the observations in the current study because 51% of segments showing improved function had
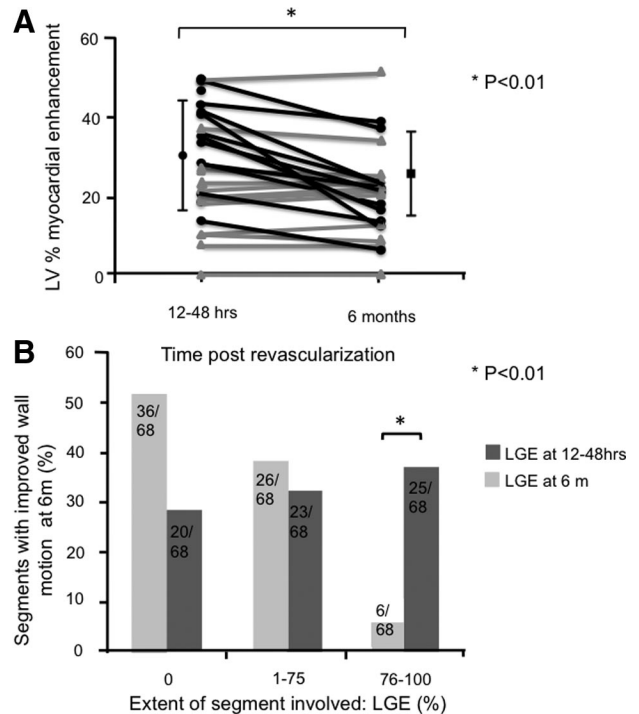
transmural (or near-transmural) LGE extent when imaged <48 hours after primary PCI. These findings indicate that LGE within this time frame does not necessarily reflect irreversible injury. Our findings do not identify the tissue correlate of LGE at early time points but do stress the important possibility of resolution, even of transmural LGE, in association with recovery of myocardial function in that area.

LGE and Recovery of Function

The ability of LGE obtained in the acute setting to predict later functional recovery is contentious.[31–34] Choi et al[32] found that improvement in segmental contractile function between <7 days after infarct and 8 to 12 weeks later was inversely related to the transmural extent of infarction on the first scan. That work differs from the current study in several important respects. Most importantly, the second CMR scan did not include assessment of LGE, making it impossible to
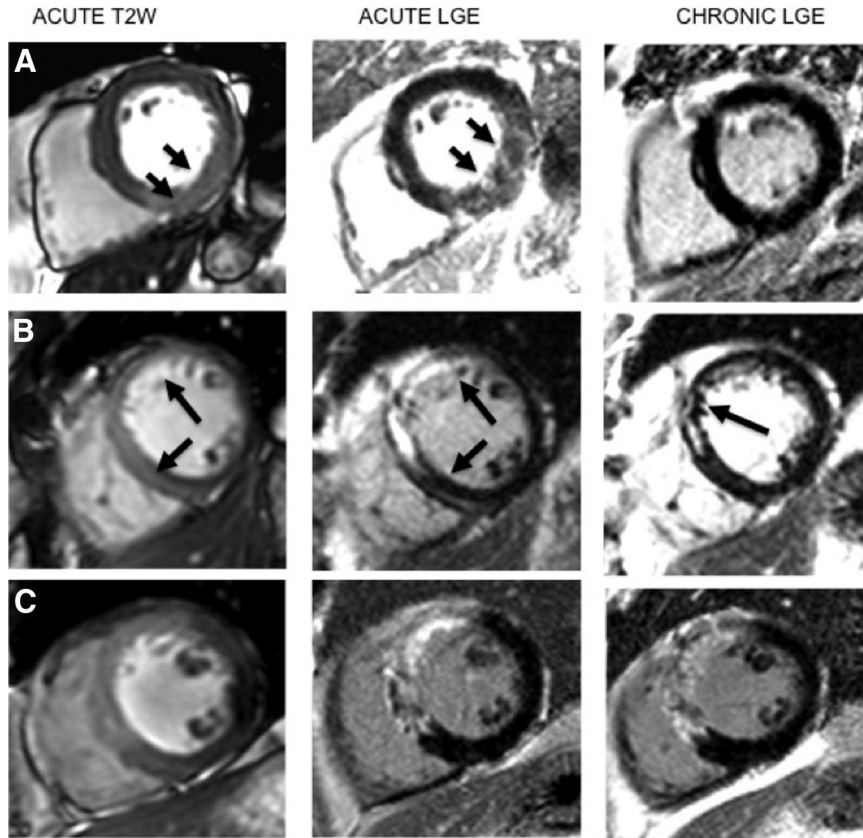
ACUTE T2W   ACUTE LGE   CHRONIC LGE

Figure 5. Representative CMR images. Edema images (left column), acute LGE images (center), and chronic LGE (right column) are displayed. Three separate patients (rows **A** to **C**) representing alternative patterns of acute versus chronic CMR features are shown. **A**, Edema is present in inferior wall; the appearance of LGE is unambiguous as high signal zone that corresponds to the area of edema, but there is no LGE present at 6 months. **B**, T2W image, on the left, shows edema in the anterior wall; the acute LGE shows compact enhancement, which is reduced in size by 6 months. **C**, Edema imaging confirms acute injury. In this example, LGE present early persists without significant alteration to the 6-month time point.

know if LGE had changed between scans. Although early assessment of LGE will, on average, indicate injured tissues, our work demonstrates that LGE early after an event does not always reflect irreversibly injured, nonviable tissue, and even transmural LGE early after acute ischemia can be associated with recovery of function in that segment. In keeping with these findings, Beek et al[33] reported that 25% of segments with transmural hyperenhancement 7 ± 3 days after MI had the potential for functional improvement after 13 weeks.

Our findings of resolving LGE are further consistent with a recent clinical study showing that LGE diminishes within one week of acute MI.[35] The authors speculated that reduction in LGE may have reflected initial LGE in reversibly injured myocardium. By incorporating edema imaging, to demonstrate the extent of the ischemia zone and combining this with (1) early and late phase LGE and (2) functional assessment at a segmental level, the current study demonstrates conclusively that this is indeed the case—and that early LGE does not always lead to late scar. Our findings cannot determine mechanisms of "shrinkage" of the LGE area or whether there is hypertrophy of adjacent viable myocardium in the long term,[36,37] which may contribute to recovery of function at a later stage.

Salvage Index

The difference between volume of myocardium at risk and of that eventually infarcted gives a measure of myocardial salvage that can be indexed to the area at risk to provide the salvage index.[6] In clinical trials, this indexed measure should reduce the interpatient variability associated with measures of absolute infarct size, with a consequent reduction in sample size[38] needed to assess therapies intended to reduce infarct size.[9]

Figure 6. Relationship between the extent of LGE and troponin I at 48 hours. The correlation between the LV% of LGE (%LV$_{score}$) assessed at 6 months and troponin I assessed at 48 hours ($r=0.9$; $P<0.01$) is shown in comparison to the equivalent relationship with LGE measured at 12 to 48 hours ($r=0.7$, $P<0.01$).

Our data suggest that, given the tendency to reduction in LGE over time, studies incorporating imaging time points as early as 12 hours[23] will markedly overestimate the area of irreversible injury in some patients. Based on our findings,
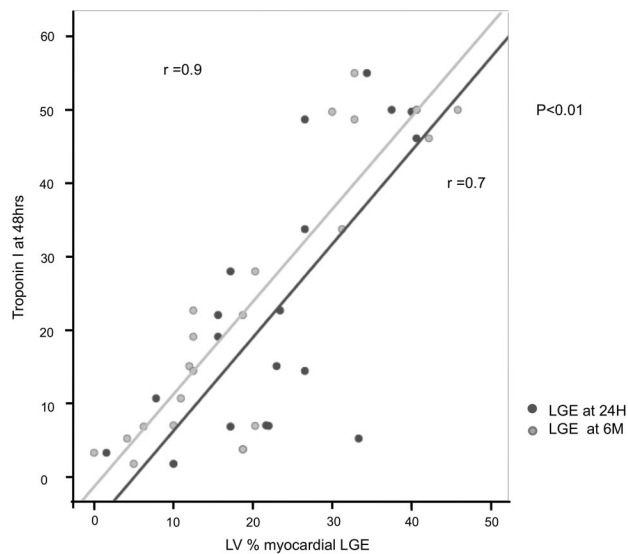
the magnitude of the underestimate of salvage that could be introduced in assessment <48 hours after MI (versus 6 months) is 38±14%, with important implications for trial design and implementation.

Study Limitations

Our data suggest almost complete resolution of edema at 6 months. However, in a small number of cases, persistently increased T2 signal intensity was identified at 6 months. From experimental studies, resolution of myocardial edema occurs within 2 months of acute MI.[39] Although accumulation of lipid may occur in the very early phases after acute MI,[40] this would not contribute significantly to T2 relaxation properties. A further possibility may relate to the threshold for edema quantification. Although efforts were made to impose a recognized and objective segmentation protocol, it is possible that an alternative segmentation strategy or the measurement of absolute myocardial relaxivity values may provide additional benefit. The use of new CMR techniques as T2 mapping should provide a better understanding of tissue composition both in acute stage and chromic stage; however, further research will be needed to validate these techniques. The patients in this study were subject to an intensive sequence of MR scans, including 3 CMR scans within 15 days of acute MI. For reasons of safety, gadolinium was not given at each time point but was reserved for the first and last. For this reason, we were unable to define the precise time course of resolution of LGE. Although LGE resolution was associated with improved myocardial segmental function, we did not undertake any additional evaluation of myocardial viability, specifically no comparative study using positron emission tomography, nor, in this clinical study, were histological samples available to define precisely the tissue correlates during each MR time point. Finally, the patients included in the study were mostly white and men and therefore further investigation will be needed in order to establish potential application of these data to those of other race and sex.

Conclusions

Edema of the myocardium occurs in almost all cases of STEMI and primary PCI. It is maximal and constant over the first week after MI, providing a stable window for the retrospective evaluation of area at risk. By contrast, LGE, although present early in acute MI, recedes over time, and acutely detected LGE does not necessarily equate with irreversible injury. These findings have important implications for the interpretation of CMR early after acute MI and the design of clinical research studies using CMR-derived infarction or salvage index as end points.

References

1. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343:1445–1453.
2. Aletras AH, Tilak GS, Natanzon A, Hsu L-Y, Gonzalez FM, Hoyt RF, Jr., Arai AE. 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;113:1865–1870.
3. Kellman P, Aletras AH, Mancini C, McVeigh ER, Arai AE. T2-prepared SSFP improves diagnostic confidence in edema imaging in acute myocardial infarction compared to turbo spin echo. *Magn Reson Med*. 2007;57:891–897.
4. Cury RC, Shash K, Nagurney JT, Rosito G, Shapiro MD, Nomura CH, Abbara S, Bamberg F, Ferencik M, Schmidt EJ, Brown DF, Hoffmann U, Brady TJ. Cardiac magnetic resonance with T2-weighted imaging improves detection of patients with acute coronary syndrome in the emergency department. *Circulation*. 2008;118:837–844.
5. Abdel-Aty H, Cocker M, Meek C, Tyberg JV, Friedrich MG. Edema as a very early marker for acute myocardial ischemia: a cardiovascular magnetic resonance study. *J Am Coll Cardiol*. 2009;53:1194–1201.
6. Friedrich MG, Abdel-Aty H, Taylor A, Schulz-Menger J, Messroghli D, Dietz R. The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2008;51:1581–1587.
7. Berry C, Kellman P, Mancini C, Chen MY, Bandettini WP, Lowrey T, Hsu LY, Aletras AH, Arai AE. Magnetic resonance imaging delineates the ischemic area-at-risk and myocardial salvage in patients with acute myocardial infarction. *Circ Cardiovasc Imaging*. 2010;3:527–535.
8. Francone M, Bucciarelli-Ducci C, Carbone I, Canali E, Scardala R, Calabrese FA, Sardella G, Mancone M, Catalano C, Fedele F, Passariello R, Bogaert J, Agati L. 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;54:2145–2153.
9. Larose E, Tizon-Marcos H, Rodès-Cabau J, Rinfret S, Dèry J-P, Nguyen CM, Gleeton O, Boudreault J-R, Roy L, Noîl B, Proulx G, Rouleau J, Barbeau G, Larochellière RD, Bertrand OF. Improving myocardial salvage in late presentation acute ST-elevation myocardial infarction with proximal embolic protection. *Catheter Cardiovasc Interv*. 2010;76:461–470.
10. Ortiz-Pèrez JT, Lee DC, Meyers SN, Davidson CJ, Bonow RO, Wu E. Determinants of myocardial salvage during acute myocardial infarction: evaluation with a combined angiographic and CMR myocardial salvage index. *J Am Coll Cardiol Cardiovasc Imaging*. 2010;3:491–500.
11. Buja LM. Myocardial ischemia and reperfusion injury. *Cardiovasc Pathol*. 2005;14:170–175.
12. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen E-L, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. 1999;100:1992–2002.
13. de Roos A, Doornbos J, van der Wall E, van Voorthuisen A. MR imaging of acute myocardial infarction: value of Gd-DTPA. *Am J Roentgenol*. 1988;150:531–534.
14. Saeed M, Bremerich J, Wendland MF, Wyttenbach R, Weinmann HJ, Higgins CB. Reperfused myocardial infarction as seen with use of necrosis-specific versus standard extracellular MR contrast media in rats. *Radiology*. 1999;213:247–257.
15. Klein C, Schmal TR, Nekolla SG, Schnackenburg B, Fleck E, Nagel E. Mechanism of late gadolinium enhancement in patients with acute myocardial infarction. *J Cardiovasc Magn Reson*. 2007;9:653–658.
16. Karamitsos TD, Hudsmith LE, Selvanayagam JB, Neubauer S, Francis JM. Operator induced variability in left ventricular measurements with cardiovascular magnetic resonance is improved after training. *J Cardiovasc Magn Reson*. 2007;9:777–783.

17. Dall'Armellina E, Morgan TM, Mandapaka S, Ntim W, Carr JJ, Hamilton CA, Hoyle J, Clark H, Clark P, Link KM, Case D, Hundley WG. Prediction of cardiac events in patients with reduced left ventricular ejection fraction with dobutamine cardiovascular magnetic resonance assessment of wall motion score index. *J Am Coll Cardiol*. 2008;52: 279–286.

18. van Gaal WJ, Banning AP. Percutaneous coronary intervention and the no-reflow phenomenon. *Expert Rev Cardiovasc Ther*. 2007;5:715–731.

19. Lima JAC, Judd RM, Bazille A, Schulman SP, Atalar E, Zerhouni EA. Regional heterogeneity of human myocardial infarcts demonstrated by contrast-enhanced MRI: potential mechanisms. *Circulation*. 1995;92: 1117–1125.

20. Kuntz ID Jr, Brassfield TS, Law GD, Purcell GV. Hydration of macromolecules. *Science*. 1969;163:1329–1331.

21. Friedrich MG. Myocardial edema: a new clinical entity? *Nat Rev Cardiol*. 2010;7:292–296.

22. Karolle BL, Carlson RE, Aisen AM, Buda AJ. Transmural distribution of myocardial edema by NMR relaxometry following myocardial ischemia and reperfusion. *Am Heart J*. 1991;122:655–664.

23. Larose E, Rodès-Cabau J, Pibarot P, Rinfret S, Proulx G, Nguyen CM, Dèry J-P, Gleeton O, Roy L, Noîl B, Barbeau G, Rouleau J, Boudreault J-R, Amyot M, De Larochellière R, Bertrand OF. Predicting late myocardial recovery and outcomes in the early hours of ST-segment elevation myocardial infarction: traditional measures compared with microvascular obstruction, salvaged myocardium, and necrosis characteristics by cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2010;55:2459–2469.

24. Raman SV, Simonetti OP, Winner Iii MW, Dickerson JA, He X, Mazzaferri EL Jr, Ambrosio G. 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;55:2480–2488.

25. Selvanayagam JB, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, Neubauer S. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation*. 2004;110:1535–1541.

26. Ingkanisorn WP, Rhoads KL, Aletras AH, Kellman P, Arai AE. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. *J Am Coll Cardiol*. 2004;43:2253–2259.

27. Ichikawa Y, Sakuma H, Suzawa N, Kitagawa K, Makino K, Hirano T, Takeda K. Late gadolinium-enhanced magnetic resonance imaging in acute and chronic myocardial infarction: improved prediction of regional myocardial contraction in the chronic state by measuring thickness of nonenhanced myocardium. *J Am Coll Cardiol*. 2005;45:901–909.

28. Fieno DS, Hillenbrand HB, Rehwald WG, Harris KR, Decker RS, Parker MA, Klocke FJ, Kim RJ, Judd RM. Infarct resorption, compensatory hypertrophy, and differing patterns of ventricular remodeling following myocardial infarctions of varying size. *J Am Coll Cardiol*. 2004;43: 2124–2131.

29. Schulz-Menger J, Gross M, Messroghli D, Uhlich F, Dietz R, Friedrich MG. Cardiovascular magnetic resonance of acute myocardial infarction at a very early stage. *J Am Coll Cardiol*. 2003;42:513–518.

30. Yan AT, Shayne AJ, Brown KA, Gupta SN, Chan CW, Luu TM, Di Carli MF, Reynolds HG, Stevenson WG, Kwong RY. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation*. 2006;114:32–39.

31. Gerber BL, Garot J, Bluemke DA, Wu KC, Lima JA. Accuracy of contrast-enhanced magnetic resonance imaging in predicting improvement of regional myocardial function in patients after acute myocardial infarction. *Circulation*. 2002;106:1083–1089.

32. 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;104:1101–1107.

33. Beek AM, Kuhl HP, Bondarenko O, Twisk JWR, Hofman MBM, van Dockum WG, Visser CA, van Rossum AC. Delayed contrast-enhanced magnetic resonance imaging for the prediction of regional functional improvement after acute myocardial infarction. *J Am Coll Cardiol*. 2003; 42:895–901.

34. Rogers WJ Jr, Kramer CM, Geskin G, Hu YL, Theobald TM, Vido DA, Petruolo S, Reichek N. Early contrast-enhanced MRI predicts late functional recovery after reperfused myocardial infarction. *Circulation*. 1999; 99:744–750.

35. Engblom H. Rapid initial reduction of hyperenhanced myocardium after reperfused first myocardial infarction suggests recovery of the peri-infarction zone: one-year follow-up by MRI. *Circ Cardiovasc Imaging*. 2009;2:47–55.

36. Rehwald WG, Fieno DS, Chen E-L, Kim RJ, Judd RM. Myocardial magnetic resonance imaging contrast agent concentrations after reversible and irreversible ischemic injury. *Circulation*. 2002;105:224–229.

37. Holmes JW, Yamashita H, Waldman LK, Covell JW. Scar remodeling and transmural deformation after infarction in the pig. *Circulation*. 1994; 90:411–420.

38. Klocke FJ. Cardiac magnetic resonance measurements of area at risk and infarct size in ischemic syndromes. *J Am Coll Cardiol*. 2010;55: 2489–2490.

39. Reimer KA, Jennings RB. The changing anatomic reference base of evolving myocardial infarction: underestimation of myocardial collateral blood flow and overestimation of experimental anatomic infarct size due to tissue edema, hemorrhage and acute inflammation. *Circulation*. 1979; 60:866–876.

40. Bilheimer DW, Buja LM, Parkey RW, Bonte FJ, Willerson JT. Fatty acid accumulation and abnormal lipid deposition in peripheral and border zones of experimental myocardial infarcts. *J Nucl Med*. 1978;19:276–283.

CLINICAL PERSPECTIVE

Late gadolinium enhancement (LGE) and edema imaging are used to assess acute myocardial injury, area at risk, and salvaged myocardium after reperfusion. LGE is currently considered the gold standard for myocardial infarct visualization both in acute and chronic myocardial infarction and an accurate predictor of recovery of wall motion after revascularization. The present study shows that cardiac magnetic resonance features of acute myocardial infarction are dynamic and change for both LGE and edema. After revascularization, edema is shown to peak within the first week after reperfusion. LGE performed in the first 24 hours does not necessarily indicate irreversible injury; our results show that 51% of the segments with transmural LGE at 24 hours after reperfusion recovered function at 6 months. A detailed knowledge of the early dynamic changes of both LGE and edema imaging is crucial in assessing final infarct size and myocardium salvage, especially when designing clinical trials using cardiac magnetic resonance.

Supplemental Material

Supplemental Methods

CMR

CMR examinations were performed on a 3 Tesla MR scanner (Trio, Siemens Healthcare, Erlangen, Germany). After piloting, steady-state free precession (SSFP) cine images using retrospective gating (TE / TR = 1.4 / 3.2 ms; flip angle = 50°; pixel size: 1.6 x 1.6 mm; slice thickness: 8 mm) were acquired. The short axis stack was acquired parallel to the atrio-ventricular groove in 1 cm increments (slice thickness 8 mm, inter-slice gap 2 mm). Identical short axis images at matching slice position with cine images were acquired using T2W and LGE imaging.

Edema imaging was performed using a T2 prep-SSFP single shot sequence[1] (TE / TR = 1 / 4.1 ms; effective TE = 60 ms; flip angle = 90°; pixel size: 2.1 x 2.8 mm; slice thickness: 8 mm).

LGE-CMR was performed with a T1-weighted segmented inversion-recovery gradient echo-phase sensitive-inversion recovery (GRE_PSIR) sequence (echo time 2.5 ms, voxel size 1.8 x 1.4 x 8 mm, flip angle 20°) 5 to 10 minutes after the administration of 0.1 mmol / kg contrast agent (Gadodiamide, Omniscan[TM], GE Healthcare, Amersham, UK).

Image co-registration and post-processing analysis

Cine, edema and LGE images were acquired parallel to the AV groove and were radially aligned to the position of the papillary muscles. CMR image sets acquired at different time points were analyzed in random order by observers blinded to the origin of the image.

Quantification of LV volumes and damaged myocardium

Left ventricular volumes and ejection fractions were calculated from the short axis images as previously described.[2] Injured fractions (injured myocardium volume / slice volume) in each short axis slice both for LGE and T2W images were quantified using computer assisted planimetry in MATLAB version 7.3.0.267 (Natick, USA) by a single experienced operator (ED). Apical slices were not included in LGE and T2W analysis due to partial volume effects.

For objective quantification of edema or LGE, a reference region of interest (ROI) was placed in remote myocardium. The signal intensity threshold indicating edema/LGE was imposed 2 standard deviations above the mean intensity of the reference ROI, as previously described.[3] Microvascular obstruction (MVO) / hemorrhage was defined as the low intensity core within an area of LGE or edema. Both MVO and haemorrhage were included in the measurement of the areas of infarction or edema.

A second reader blinded to the results of the first and to the results of PCI and CMR imaging, analysed edema images to assess interobserver variability on 20 randomly selected patients.

The index of myocardial salvage was calculated as difference in area between edema and late gadolinium divided by the area of edema. Our standardised methods for analysing and calculating LGE, along with reproducibility, have been reported previously.[4, 5]

Semi-quantitative assessment of regional function, edema and late gadolinium

Myocardial anatomical segmentation was according to the American Heart Association 17 segment model (excluding segment 17, true apex).[6] Semi-quantitative assessments of wall motion abnormalities, myocardial edema and LGE were undertaken by an experienced observer (E.D.) using Argus software (Version 2002B, Siemens Medical Solutions). For regional function, segments were graded: 1 = normal; 2 = hypokinetic; 3 = akinetic or 4 = dyskinetic. Change in regional contraction was defined as a difference of $\geq$ 1 functional grade between time points. Wall motion score index (WMSI) was defined as the sum of segmental scores divided by the number of segments scored, as previously published.[7]

The extent of LGE within each segment was estimated visually and categorized according to the percentage hyperenhanced area of each segment:[8] 0 = no LGE; 1 = 1 - 25% LGE; 2 = 26 - 50% LGE; 3 = 51 - 75% LGE and 4 = > 75%. Similarly, the extent of edema per segment was also assessed visually and categorized for each segment according to an equivalent scoring system. A second blinded reader scored the images for LGE / edema and wall motion in 20 patients. The infarct size score (% LVscore) was also calculated based on the scoring system as previously shown[9] (sum of all the scores throughout the LV (range 0 to 4) / total number of segments x 4).

Supplemental Table

	Segments edema + n (%)	Segments LGE + n (%)	Segments WMA + n (%)	Total segments analyzed per each modality
Time point 1	151 (35%)	133 (31%)	139 (32%)	428
Time point 2	157 (37%)	N/A	107 (25%)	428
Time point 3	152 (36%)	N/A	95 (22%)	428
Time point 4	25 (6%)	100 (29%)	94 (23%)	336

Supplemental Figure Legend

Figure. Patient flow.

Disposition of patients with STEMI recruited to this study, indicating numbers at each follow-up

CMR examination up to six months and reasons for loss from study.

References

1.	Kellman P, Aletras AH, Mancini C, McVeigh ER, Arai AE. T2-prepared ssfp improves diagnostic confidence in edema imaging in acute myocardial infarction compared to turbo spin echo. *Magn Reson Med*. 2007;57:891-897

2.	Karamitsos TD, Hudsmith LE, Selvanayagam JB, Neubauer S, Francis JM. Operator induced variability in left ventricular measurements with cardiovascular magnetic resonance is improved after training. *J Cardiovasc Magn Reson*. 2007;9:777-783

3.	Berry C, Kellman P, Mancini C, Chen MY, Bandettini WP, Lowrey T, Hsu LY, Aletras AH, Arai AE. Magnetic resonance imaging delineates the ischemic area-at-risk and myocardial salvage in patients with acute myocardial infarction. *Circ Cardiovasc Imaging*. 2010;3:527-535

4.	Hudsmith LE, Steffen EP, Damian JT, Jane MF, Adrian SHC, Kieran C, Joseph BS, Matthew DR, Stefan N. Determination of cardiac volumes and mass with flash and ssfp cine sequences at 1.5 vs. 3 tesla: A validation study. *Journal of Magnetic Resonance Imaging*. 2006;24:312-318

5.	Porto I, Selvanayagam JB, Van Gaal WJ, Prati F, Cheng A, Channon K, Neubauer S, Banning AP. Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: Insights from delayed-enhancement magnetic resonance imaging, thrombolysis in myocardial infarction myocardial perfusion grade analysis, and intravascular ultrasound. *Circulation*. 2006;114:662-669

6.	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;105:539-542

7. Dall'Armellina E, Morgan TM, Mandapaka S, Ntim W, Carr JJ, Hamilton CA, Hoyle J, Clark H, Clark P, Link KM, Case D, Hundley WG. Prediction of cardiac events in patients with reduced left ventricular ejection fraction with dobutamine cardiovascular magnetic resonance assessment of wall motion score index. *Journal of the American College of Cardiology*. 2008;52:279-286

8. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343:1445-1453

9. 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;104:1101-1107

T0	**33 STEMI post PCI**

2 claustrophobia
1 urgent PCI (chest pain recurrence)

T1 = 24 hours	**CMR = 30 STEMI**

2 LGE incomplete
(technical failure)

T2 = 5-7 days	**CMR = 30 STEMI**

1 pt not available
1 pt scanner technical failure

T3 = 14-17 days	**CMR = 28 STEMI**

1 urgent CABG
3 refused
1 low GFR-no LGE

T4 = 6 months	**CMR = 24 STEMI**