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Persistence of Infarct Zone T2 Hyperintensity at 6 Months After Acute ST-Segment–Elevation Myocardial Infarction

Incidence, Pathophysiology, and Prognostic Implications

Jaclyn Carberry, BMedSci, MBChB*; David Carrick, MBChB, PhD*; Caroline Haig, PhD; Nadeem Ahmed, BMedSci, MBChB; Ify Mordi, MBChB; Margaret McEntegart, MBChB, PhD; Mark C. Petrie, MBChB, MD; Hany Eteiba, MBChB, MD; Stuart Hood, MBChB, MD; Stuart Watkins, MBChB, MD; Mitchell Lindsay, MBChB MD; Andrew Davie, MBChB, MD; Ahmed Mahrous, MBChB; Ian Ford, PhD; Naveed Sattar, MBChB, PhD; Paul Welsh, PhD; Aleksandra Radjenovic, PhD; Keith G. Oldroyd, MBChB, MD; Colin Berry, MBChB, PhD

Background—The incidence and clinical significance of persistent T2 hyperintensity after acute ST-segment–elevation myocardial infarction (STEMI) is uncertain.

Methods and Results—Patients who sustained an acute STEMI were enrolled in a cohort study (BHF MR-MI: NCT02072850). Two hundred eighty-three STEMI patients (mean age, 59±12 years; 75% male) had cardiac magnetic resonance with T2 mapping performed at 2 days and 6 months post-STEMI. Persisting T2 hyperintensity was defined as infarct T2 >2 SDs from remote T2 at 6 months. Infarct zone T2 was higher than remote zone T2 at 2 days (66.3±6.1 versus 49.7±2.1 ms; $P<0.001$) and 6 months (56.8±4.5 versus 49.7±2.3 ms; $P<0.001$). Remote zone T2 did not change over time (mean change, 0.0±2.7 ms; $P=0.837$), whereas infarct zone T2 decreased (−9.5±6.4 ms; $P<0.001$). At 6 months, T2 hyperintensity persisted in 189 (67%) patients, who were more likely to have Thrombus in Myocardial Infarction flow 0 or 1 in the culprit artery ($P=0.020$), incomplete ST-segment resolution ($P=0.037$), and higher troponin ($P=0.024$). Persistent T2 hyperintensity was associated with NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration (0.57 on a log scale [0.42–0.72]; $P=0.004$) and the likelihood of adverse left ventricular remodeling (>20% change in left ventricular end-diastolic volume; 21.91 [2.75–174.29]; $P=0.004$). Persistent T2 hyperintensity was associated with all-cause death and heart failure, but the result was not significant ($P=0.051$). ΔT2 was associated with all-cause death and heart failure ($P=0.004$) and major adverse cardiac events ($P=0.013$).

Conclusions—Persistent T2 hyperintensity occurs in two thirds of STEMI patients. Persistent T2 hyperintensity was associated with the initial STEMI severity, adverse remodeling, and long-term health outcome.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02072850.

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Key Words: acute coronary syndrome ■ magnetic resonance imaging ■ myocardial infarction ■ myocardium ■ prognosis

In survivors of acute ST-segment–elevation myocardial infarction (STEMI), edema within the infarct zone revealed by T2-weighted cardiac magnetic resonance (CMR) imaging[1,2] is associated with the initial extent of myocardial jeopardy,[3] the size of infarction,[4] and prognosis in the longer term.[5] Edema impairs myocardial contractility by reducing the binding efficiency of actin–myosin filaments leading to reduced force generation in affected cardiomyocytes.[6]

See Editorial by Dharmakumar
See Clinical Perspective

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From the BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences (J.C., D.C., N.A., I.M., M.M., M.C.P., H.E., S.H., S.W., M.L., A.D., A.M., N.S., P.W., A.R., K.G.O., C.B.) and Robertson Centre for Biostatistics (C.H., I.F.), University of Glasgow, Scotland; and West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank (D.C., S.W., C.B.).

*Drs Carberry and Carrick contributed equally to this work.

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Correspondence to Colin Berry, MBChB, PhD, BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, 126 University Pl, University of Glasgow, Glasgow G12 8TA, Scotland, United Kingdom. E-mail colin.berry@glasgow.ac.uk

There is uncertainty about the natural history and clinical significance of persistently high infarct zone T2 values because previous studies were limited by sample size (n=10–62),[7–10] or method of detection,[7,8] for example, T2-weighted short inversion time inversion recovery (STIR) imaging. Contemporary quantitative T2-mapping techniques have better diagnostic accuracy[11] and repeatability[12] compared with T2-weighted STIR imaging.

Our aims were to (1) measure infarct zone T2 (ms) and its changes over time in a longitudinal study of acute STEMI patients; (2) determine the incidence of persistent T2 hyperintensity at 6 months post-STEMI; (3) assess the clinical characteristics and left ventricular (LV) size and function of those patients with persistent T2 hyperintensity and compare them to those patients in whom T2 hyperintensity had resolved; and (4) assess the association of persisting T2 hyperintensity with longer-term health outcome.

We hypothesized that the persistence of myocardial infarct zone T2 hyperintensity would be associated with the initial STEMI severity, and it would be associated with surrogate measures of outcome, including LV volume and NT-proBNP (N-terminal pro-B-type natriuretic peptide), and longer-term health outcome.

Methods

The full methodology has been reported previously (BHF MR-MI [Detection and Significance of Heart Injury in ST Elevation Myocardial Infarction]: NCT02072850) and is detailed in the Methods in the Data Supplement. Patients with acute STEMI were consecutively screened for suitability and those recruited provided written informed consent. The study was approved by the National Research Ethics Service (Reference 10-S0703-28) and was publically registered (NCT02072850). The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.[13]

CMR Image Analyses

Myocardial Edema

CMR images were analyzed on a Siemens workstation. The epicardial and endocardial contours on the last corresponding T2-weighted raw image with an echo time of 55 ms were planimetered and copied to the T2 map.[14] Regions of interest were drawn in the remote and infarct zones to measure the respective signal intensities. T2 hyperintensity was present if the T2 signal in the infarct zone was 2 SDs above the T2 signal in the remote zone.[11,15] Areas of microvascular obstruction or hemorrhage, identified by consulting late gadolinium enhancement and T2* images, respectively, were excluded from the infarct region of interest because this would reduce the signal intensity and may mask the presence of T2 hyperintensity. The remote zone was drawn 180° from infarcted myocardium, midmyocardial, and ≈1 segment in length. Measurement was performed on multiple slices and the average taken.

Infarct Definition and Size

The territory of infarction was delineated using a signal intensity threshold of >5 SD above a remote reference region and expressed as a percentage of total LV mass.[16]

Myocardial Salvage

Myocardial salvage was calculated by subtraction of percent infarct size from percent myocardial edema.[5,17,18] The myocardial salvage index was calculated by dividing the myocardial salvage area by the initial extent of edema.

Adverse Remodeling

Adverse remodeling was defined as an increase in LV end-diastolic volume at 6 months from baseline by ≥20%.[19]

Health Outcomes

We prespecified adverse health outcomes that are pathophysiologically linked with STEMI. The primary composite outcome was major adverse cardiac events (MACE) defined as cardiac death, nonfatal myocardial infarction, or heart failure hospitalization after the 6-month CMR scan. All-cause death or heart failure (heart failure hospitalization or defibrillator implantation) after the 6-month CMR scan was a secondary outcome.

Statistics

The full statistical methods are reported in the Data Supplement. All *P* values were 2-sided. A *P* value >0.05 indicated the absence of a statistically significant effect. Analyses were performed using SPSS version 22 for Windows (SPSS, Inc, Chicago, IL) or R v3.3.0.

Results

Of 343 STEMI patients referred for emergency percutaneous coronary intervention, 283 (87%) patients with paired scans were included in the final analyses. The flow diagram for the study is shown in Figure I in the Data Supplement.

Patient Characteristics

Using T2 mapping, 189 (67%) patients had persistent T2 hyperintensity at 6 months post-STEMI.

Patient characteristics are shown in Table 1. The mean age was 59±11 years, and 75% were male. Patients with persisting T2 hyperintensity were more likely to present with Thrombus in Myocardial Infarction flow 0 or 1 in the culprit artery (Thrombus in Myocardial Infarction flow 0 and 1: 61 [64%] without versus 144 [76%] with persisting T2 hyperintensity; Thrombus in Myocardial Infarction flow 2: 18 [19%] versus 34 [18%]; Thrombus in Myocardial Infarction flow 3: 15 [16%] versus 11 [6%]; *P*=0.020). They were more likely to have partial resolution of the ST-segment postreperfusion (none: 15 [16%] versus 26 [14%]; partial: 25 [27%] versus 79 [42%]; complete: 54 [57%] versus 83 [44%]; *P*=0.037) and had higher troponin levels post-STEMI (1126 [155–3814] versus 2095 [122–5550] ng/L; *P*=0.024). Other clinical characteristics of patients with and without persisting T2 hyperintensity were similar (*P*>0.050).

CMR Findings

During the Index Hospitalization

CMR findings are summarized in Table 2 and Table I in the Data Supplement. Exemplar clinical cases are included in Figure 1. At 2 days, the T2 signal in the infarct zone was higher than in the remote zone (66.3±6.1 versus 49.7±2.1 ms; *P*<0.001).

Patients with persisting T2 hyperintensity had higher LV volumes, more extensive infarcts, and lower myocardial salvage indexes (Table 2). They were more likely to have microvascular obstruction, a larger extent of microvascular obstruction, and T2 signal and extracellular volume in the infarct zone were significantly higher than in those without persisting T2 hyperintensity (Table 2). There was an association between the extent of microvascular obstruction and the extent of myocardial edema at 2 days (0.21% [0.17%–0.25%]; *P*<0.001) and a trend to association in the extent of myocardial edema at 2 days post-STEMI and the persistence of T2 hyperintensity (Table 2). There was no difference in T1 or T2 core signal between patients with and without persisting T2 hyperintensity (Table I in the Data Supplement).

Table 1. Characteristics of 283 Patients With Acute STEMI

Characteristics	All Patients; n=283
Age, y	59±11
Male, n (%)	211 (75)
BMI, kg/m^2	29±5
Hypertension, n (%)	94 (33)
Current smoking, n (%)	167 (59)
Hypercholesterolemia, n (%)	80 (28)
Diabetes mellitus*, n (%)	32 (11)
Previous angina, n (%)	34 (12)
Previous myocardial infarction, n (%)	14 (5)
Previous PCI, n (%)	11 (4)
Medical therapy	
Aspirin, n (%)	282 (99)
Clopidogrel, n (%)	281 (99)
β-blocker, n (%)	269 (95)
ACE-I or ARB, n (%)	279 (99)
Statin, n (%)	283 (100)
Presenting characteristics	
Heart rate, bpm	77±17
Systolic blood pressure, mm Hg	135±24
Diastolic blood pressure, mm Hg	79±14
Symptom onset to reperfusion, min	248±207
Ventricular fibrillation†, n (%)	17 (6)
Killip class‡, n (%)	
I	209 (74)
II	56 (20)
III/IV	18 (6)
ECG	
ST-segment resolution post-PCI, n (%)	
Complete, ≥70%	137 (49)
Incomplete, 30% to <70%	104 (37)
None, ≤30%	41 (15)
Coronary angiography	
Reperfusion strategy, n (%)	
Primary PCI	265 (94)
Rescue PCI (failed thrombolysis)	12 (4)
Successful thrombolysis	6 (2)
No. of diseased arteries§, n (%)	
1	152 (54)
2	87 (31)
3	38 (13)
Left main	6 (2)
Culprit artery, n (%)	
Left anterior descending	105 (37)
Left circumflex	49 (17)
Right coronary	129 (46)
Culprit artery TIMI flow grade at initial angiography, n (%)	
0/1	205 (72)
2	52 (18)
3	26 (9)
Culprit artery TIMI flow grade post-PCI, n (%)	
0/1	4 (1)
2	9 (3)
3	270 (95)
Blood results on admission	
C-reactive protein, mg/L, median (Q1, Q3), range	3.0 (2.0, 7.0), 0–125.0
NT-proBNP, pg/mL, median (Q1, Q3), range	767 (334, 1633), 29–19521
Troponin I, ng/L, median (Q1, Q3), range	1710 (141, 5229), 0–28406

Data are given as n (%), mean±SD, or median (Q1, Q3) as appropriate. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

*History of diet-controlled or treated diabetes mellitus.

†Successfully electrically cardioverted ventricular fibrillation at presentation or during PCI.

‡Killip classification of heart failure post-STEMI: class I—no heart failure, class II—pulmonary rales or crepitations, third heart sound, and elevated jugular venous pressure, class III—acute pulmonary edema, and class IV—cardiogenic shock.

§No. of stenoses ≤50% of the reference vessel diameter by visual assessment and if there was left main stem involvement.

The results of interobserver agreement of infarct zone T2 measurements are shown in Figure II in the Data Supplement.

At 6 Months

T2 remained higher in the infarct zone compared with the remote zone at 6 months (56.8±4.5 versus 49.7±2.3 ms; $P<0.001$). Remote zone T2 did not change between day 2 and 6 months (mean change, 0.0±2.7 ms; $P=0.837$), whereas infarct zone T2 decreased (−9.5±6.4 ms; $P<0.001$; Figure 2). Patients with persistent T2 hyperintensity had a smaller reduction in infarct zone T2 (−8.8±6.6 versus −10.9±6.0 ms; $P=0.010$). The change in infarct zone T2 was associated with the extent of microvascular obstruction at 2 days (0.20% [0.08%–0.33%]; $P=0.002$).

At 6 months, those with persisting T2 hyperintensity had lower LV ejection fractions and larger LV volumes. Infarct size remained larger in those with persisting T2 hyperintensity, and infarct zone CMR parameters were higher (T1, T2, and extracellular volume; Table 2). Remote zone T2 signal was lower in those with persisting T2 hyperintensity, whereas remote zone T1 signal was the same (Table 2; Table I in the Data Supplement).

Table 2. CMR Findings in 283 Patients Grouped According to the Presence or Absence of Persistent T2 Hyperintensity Revealed by T2 Mapping at 6 Months Post-STEMI

Characteristics	All Patients; n=283	No Persistent T2 Hyperintensity; n=94 (33%)	Persistent T2 Hyperintensity; n=189 (67%)	*P* Value*
CMR findings 2 days post-STEMI				
LV end-diastolic volume, mL				
Men	161±31	155±30	164±31	0.036
Women	124±25	130±23	121±25	0.172
LV end-systolic volume, mL				
Men	74±26	69±25	78±26	0.014
Women	54±18	57±18	52±17	0.225
LV mass, g				
Men	144±33	137±29	148±34	0.028
Women	97±21	101±17	95±23	0.216
Edema and infarct characteristics				
Myocardial edema, % LV mass	32±12	30±13	33±11	0.050
Infarct size, % LV mass	18±13	13±13	20±13	<0.001
Myocardial salvage, % LV mass	19±9	21±10	18±8	0.033
Myocardial salvage index, % LV mass	63±24	73±24	58±23	<0.001
Late microvascular obstruction present, n (%)	138 (49)	33 (35)	105 (56)	0.002
Late microvascular obstruction, % LV mass	2.6±4.6	1.5±3.6	3.1±4.9	0.004
Myocardial T1, T2, and ECV values				
T1 hypointense core present, n (%)	137 (48)	33 (35)	104 (55)	0.002
T2 infarct, ms	66.3±6.1	64.4±5.7	67.3±6.1	<0.001
T2 hypointense core present, n (%)	165 (58)	41 (44)	124 (66)	0.001
ECV infarct, %	56.0±11.7	52.8±12.9	57.7±10.7	0.024
CMR findings at 6 mo				
LV ejection fraction at 6 mo, %	62±9	65±8	61±10	<0.001
LV end-diastolic volume at 6 mo, mL				
Men	169±42	151±31	177±45	<0.001
Women	127±30	125±22	128±34	0.627
LV end-systolic volume at 6 mo, mL				
Men	68±35	54±19	74±38	<0.001
Women	46±18	45±18	47±18	0.550
Adverse remodeling, n (%)	32 (12)	1 (1)	31 (17)	<0.001
Infarct characteristics at 6 mo				
Infarct size at 6 mo, % LV mass	13±10	9±9	15±10	<0.001
Myocardial T1, T2 and ECV values at 6 mo				
T1 infarct at 6 mo, ms	1058±66	1035±59	1068±67	<0.001
T2 remote at 6 mo, ms	49.7±2.3	50.3±2.5	49.4±2.1	0.001
T2 infarct at 6 mo, ms	56.8±4.5	53.5±3.4	58.5±4.0	<0.001
ECV infarct at 6 mo, %	51.6±11.1	47.5±11.0	53.7±10.5	<0.001

Data are given as n (%) or mean±SD as appropriate. Only variables with a significant difference between groups are reported. The full table is reported in the Data Supplement. CMR indicates cardiac magnetic resonance; ECV, extracellular volume; LV, left ventricle; STEMI, ST-segment–elevation myocardial infarction; T1, longitudinal relaxation time; and T2, transverse relaxation time.

**P* values were obtained from 2-sample *t* test, Mann–Whitney test or Fisher exact test.

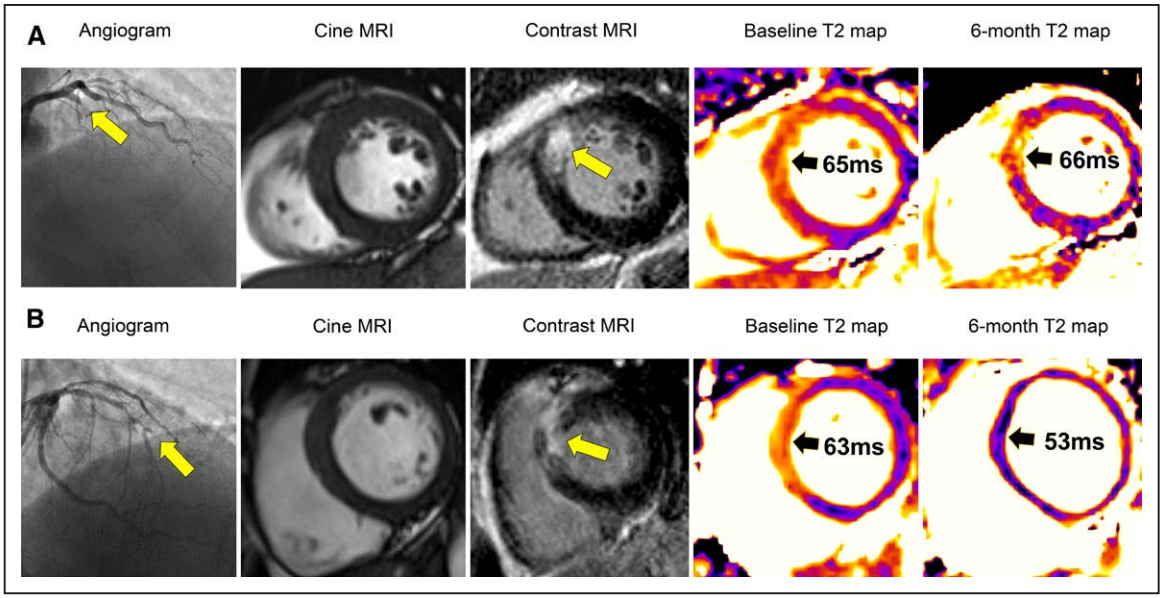

Figure 1. Two patients with a similar presentation of acute anterior ST-segment–elevation myocardial infarction. Both patients were treated by percutaneous coronary intervention and with the same antithrombotic drugs. At the end of the procedure, both patients had Thrombus in Myocardial Infarction (TIMI) coronary flow grade 3 in the culprit left anterior descending artery. **A**, A patient with persistent infarct zone T2 hyperintensity: cardiac magnetic resonance (CMR) imaging was performed 2 days post-revascularization. T2 mapping revealed an infarct zone T2 value of 65 ms. CMR performed at 6 mo revealed a persistently high infarct zone T2 value of 66 ms in a matched myocardial slice position to baseline. Left ventricular (LV) end-diastolic volume increased from 143 to 175 mL at 6 mo representing adverse remodeling. This patient was readmitted with heart failure after the 6-mo CMR scan. **B**, A patient without persistent infarct zone T2 hyperintensity: CMR was performed 2 days post-revascularization. T2 mapping revealed an infarct zone T2 value of 63 ms. CMR performed at 6 mo revealed a lower infarct zone T2 value of 53 ms. LV end-diastolic volume decreased from 120 to 118 mL at 6 mo. This patient had an uncomplicated clinical course. MRI indicates magnetic resonance imaging.

The higher the initial infarct zone T2 signal, the larger the decrease in infarct zone T2 signal by 6 months (Figure 3).

Persistent T2 Hyperintensity and LV Remodeling

Adverse remodeling occurred in 32 (12%) patients (Table 2). In a binary logistic regression analysis, persistent T2 hyperintensity was a multivariable associate of adverse remodeling (Table 3). When the change in infarct zone T2 (1 ms change and 10 ms change) was included in place of persistent T2 hyperintensity at 6 months, this was also associated with adverse remodeling (Table 3). When the change in infarct zone extracellular volume was included in the multivariable models, persistent T2 hyperintensity and change in infarct zone T2 were not associated with the change in LV end-diastolic volume.

Persistent T2 Hyperintensity and LV Function at 6 Months

At 2 days, LV ejection fraction was similar between patients with and without persisting T2 hyperintensity, whereas 6-month ejection fraction was lower in those with persisting T2 hyperintensity (Table 2). The mean change in LV ejection fraction was 6.7±7.8%. Patients with persisting T2 hyperintensity had a numerically lower increase in LV ejection fraction without statistical significance (6.1±7.8% versus 7.9±7.7%).

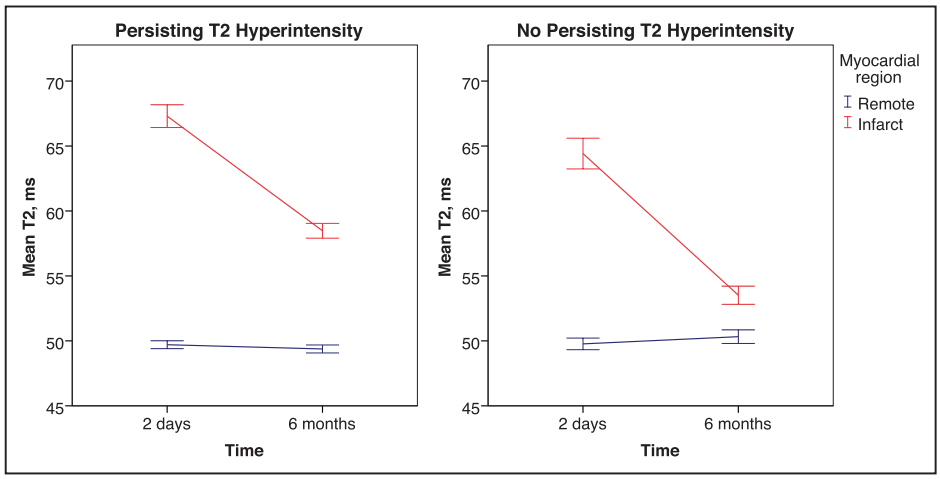

Figure 2. Change in T2 signal in patients with ST-segment–elevation myocardial infarction with or without persisting infarct zone T2 hyperintensity at 6 mo. Infarct zone T2 decreases in the majority of patients but to a lesser degree in patients with persisting edema.

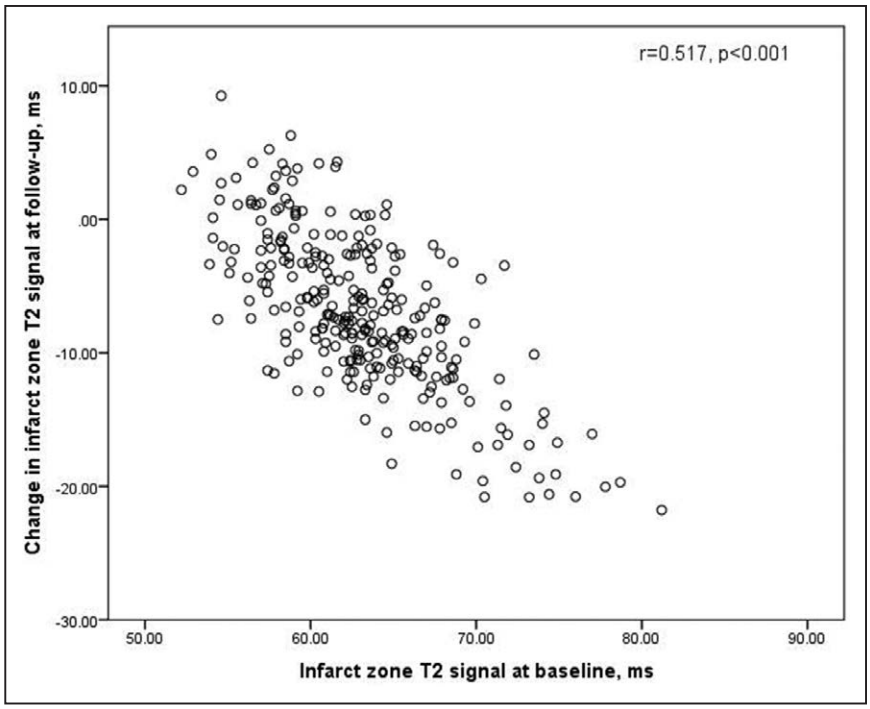

Figure 3. Change in infarct zone T2 vs infarct zone T2 at baseline. Infarct zone T2 at baseline was negatively associated with the change in infarct zone T2 at 6 mo.

The change in LV ejection fraction was associated with both persisting T2 hyperintensity and the change in infarct zone T2 (Table II in the Data Supplement).

Persistent T2 Hyperintensity and NT-proBNP

Blood samples were collected in the participants who were enrolled during office hours (n=123 patients at baseline and n=98 patients at follow-up). The characteristics of these patients were similar to the whole cohort (data not shown). Persistent T2 hyperintensity was associated with NT-proBNP at 6 months (0.57 on a log scale [0.42–0.72]; *P*=0.004), but not at baseline.

Persistent T2 Hyperintensity and Health Outcomes

Health outcome data were available in 283 (100%) patients. The median duration of follow-up was 1330 days (minimum–maximum postdischarge censor duration 794–1622 days). All-cause death or heart failure occurred in 19 (7%) patients, including 7 noncardiovascular deaths, 4 cardiovascular deaths, 1 stroke death, 1 undetermined cause of death, and 6 heart failure episodes. Sixteen (6%) patients experienced a MACE after the CMR scan at 6 months, including 6 heart failure episodes (Killip class 3 or 4 heart failure or defibrillator implantation), 4 cardiovascular deaths, 4 admissions with non-STEMI, and 2 admissions with STEMI.

Persisting T2 hyperintensity (binary, yes or no) was associated with the occurrence of all-cause death or heart failure (hazard ratio, 4.31; 95% confidence interval, 1.00–18.67; *P*=0.051); however, the association was not statistically significant. Persisting T2 hyperintensity was not associated with MACE (Figure III in the Data Supplement).

The change in infarct zone T2 (1 ms change) was associated with all-cause death or heart failure (hazard ratio, 1.15; 95% confidence interval, 1.05–1.27; *P*=0.004) and with MACE (hazard ratio, 1.14; 95% confidence interval, 1.03, 1.27; *P*=0.013). Similar results were observed when considering a 10 ms change in infarct zone T2 (all-cause death or heart failure hazard ratio, 3.77; 95% confidence interval, 1.58–8.97; *P*=0.003: MACE hazard ratio, 3.60; 95% confidence interval, 1.42–9.15; *P*=0.007).

Discussion

We present a natural history study of the changes in infarct zone T2 over time and prognostic significance over 4 years in a large unselected cohort of STEMI patients.

The main findings are as follows: (1) T2 hyperintensity persisted in approximately two thirds of patients at 6 months post-STEMI; (2) infarct zone T2 decreased in the long term

Table 3. Binary Logistic Regression Analysis for Associations With Adverse Remodeling at 6 Months Post-STEMI in 283 Patients

Multivariable Associations	Odds Ratio (95% CI)	*P* Value
Patient characteristics, angiographic data, and persistent infarct zone T2 hyperintensity		
Persistent T2 hyperintensity	21.91 (2.75–174.29)	0.004
Patient characteristics, angiographic data, and change in infarct zone T2 (1 ms change)		
Change in infarct zone T2, 1 ms	1.22 (1.10–1.35)	<0.001
Baseline infarct zone T2, ms	1.20 (1.08–1.35)	0.001
Patient characteristics, angiographic data, and change in infarct zone T2 (10 ms change)		
Change in infarct zone T2, 10 ms	3.45 (1.53–7.77)	0.003
Baseline infarct zone T2, ms	1.13 (1.02– 1.24)	0.015

Only statistically significant variables are reported. All variables included in the model are described in the Data Supplement. The odds ratio (95% CIs) indicates odds of adverse remodeling at 6 mo given exposure to the independent variable. CI indicates confidence intervals; STEMI, ST-segment–elevation myocardial infarction; and T2, transverse relaxation time.

in most patients, and the decrease was larger in patients with higher infarct zone T2 at baseline; (3) persisting T2 hyperintensity was associated with electrocardiographic, angiographic, CMR, and biochemical markers of STEMI severity including the initial size of infarction, presence of microvascular obstruction, the myocardial salvage index, peak troponin, and NT-proBNP; (4) persistent T2 hyperintensity and the change in infarct zone T2 were associated with adverse remodeling and worsening LV function; and (5) the change in infarct zone T2 was associated with adverse health outcomes. T2 hyperintensity in the infarct zone that persists at 6 months post-STEMI is an adverse prognostic sign and presents a mechanistic explanation for worsening LV volumes and function.

Direct comparison with previous studies[7–10] is qualified by differences in sample size and imaging methods. These previous studies have defined persisting T2 hyperintensity as edema; however, strong evidence that elevated infarct zone T2 at 6 months post-STEMI represents edema is lacking. Histological studies validating T2 signal as a representation of edema have been focused on the acute phase post-STEMI.[20–22] Infarct zone edema as a cause of persisting T2 hyperintensity at 6 months cannot be excluded; however, other causes of increased myocardial mobile water content such as myocardial fat should be considered.

The incidence of persistent T2 hyperintensity in the present study was high (two thirds of patients) in comparison to some[9,10] but not all prior recent studies.[7,8] In those studies, the numbers of participants with paired data were limited (n=10–62)[7–10] implying imprecision.

Ripa et al[7] found that myocardial T2 hyperintensity (defined as edema) persisted in 51 of 54 (94%) STEMI patients using T2 STIR imaging. The average number of affected segments per patient decreased by 4.5 segments at 6 months. Persistent edema was not associated with LV ejection fraction.

Nilsson et al[8] identified a prevalence of high T2 at 6 months which was comparable with our result (60%); however, this analysis was performed on a small sample, using T2 STIR imaging, and clinical and prognostic information was limited. Dark blood STIR edema imaging is a qualitative technique[11] with reduced diagnostic accuracy, when compared with quantitative T2 mapping.[12] The authors speculate that T2 hyperintensity may represent edema or an alternative process, such as hemoglobin breakdown products or increased unbound water.[8]

Dall'Armellina et al[9] used bright blood T2-weighted CMR (n=23 [77%] with paired data). They found that 35% of myocardial segments had evidence of edema acutely, and the proportion of edematous segments reduced to 6%, with a small number of cases having infarct zone edema at 6 months. They found that a reduction in edema was associated with an improvement in wall motion score index.

Zia et al[10] used T2 mapping and found that infarct zone T2 signal equalizes with remote zone T2 signal at 6 months suggesting complete recovery of myocardial edema. There are some reasons why the results of this article may be so different to those we present. The sample size was limited (n=62 compared with our n=283).[10] The methodology refers to infarct segment rather than zone.[10] If infarct T2 signal has been measured across an entire myocardial segment, then that segment may also contain unaffected myocardium (and hypointense core) and therefore bias the results by averaging the signal across 2 myocardial states.

Our study is the first and largest to use contemporary, quantitative methods to identify the incidence and clinical significance of persistent T2 hyperintensity in a cohort of near-consecutive patients with acute STEMI. Our study presents new insights. The adverse clinical significance of persistent T2 hyperintensity was underscored by its associations with the initial STEMI severity and LV remodeling, and the validity of our observations is enhanced given that the T2 maps were of diagnostic quality in nearly all patients.

We saw that there was a larger extent of acute microvascular obstruction in those with persisting T2 hyperintensity, and there was also an association between the extent of microvascular obstruction and the extent of myocardial edema acutely. The relationship between microvascular obstruction and myocardial edema may provide a mechanistic explanation into the persistence of T2 hyperintensity, specifically because evidence has shown myocardial hemorrhage, which is related to microvascular obstruction, leads to iron driven inflammation.[23,24] We also observed worsening LV ejection fractions in patients with persisting T2 hyperintensity, which is in keeping with previous reports of edema and attenuated strain.[25]

Previous research from this cohort suggests that there is a significant difference in remote zone T2 between the 2 time points,[26,27] which may be explained by the larger sample size in the present study (n=30 in Carrick et al[26] and n=131 in Carberry et al[27]). Persisting T2 hyperintensity may reflect the natural history of infarct healing[3] and inflammation,[28] and potentially, latency of edema within the infarct zone to dissipate, especially if water content is substantially increased acutely. Nonetheless, we observed that persistent T2 hyperintensity has adverse prognostic implications based on its association with LV remodeling and health outcome. The reason why the change in infarct zone T2 was associated with MACE and persisting T2 hyperintensity was not explained by the nature of the data. Dichotomizing a continuous variable can reduce statistical power. In addition, our results may simply reflect the fact that the absolute change in T2 signal in the infarct zone is more predictive of MACE than the presence or absence of T2 hyperintensity. Because the analysis was limited by the event rate, further research is warranted.

Limitations

Because of the length of the imaging protocol, we restricted other imaging methods, such as for myocardial fat. The survival analysis was limited by the absolute number of heart failure and all-cause death events (n=19) and MACE events (n=16), so these results should be interpreted carefully and taken as hypothesis generating.

Conclusions

Infarct zone T2 hyperintensity persisted at 6 months in approximately two thirds of STEMI patients. Persistent T2 hyperintensity was prognostically important because it was associated with markers of STEMI severity and adverse LV

remodeling. The change in infarct zone T2 signal as a continuous variable was associated with health outcome. Whether T2 hyperintensity at 6 months represents edema or another process is uncertain and merits further discussion and study. Further studies are warranted to assess whether or not infarct zone T2 may track the response to therapy in STEMI patients and thus represent a therapeutic target for use in clinical trials.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In survivors of acute ST-segment–elevation myocardial infarction, edema within the infarct zone is associated with the initial extent of myocardial jeopardy, the size of infarction, and prognosis. Edema impairs myocardial contractility by reducing the binding efficiency of actin–myosin filaments leading to reduced force generation in affected cardiomyocytes. There is uncertainty about the natural history and clinical significance of the persistence of T2 hyperintensity because previous studies were limited by sample size or method of detection. We present a natural history study of the change in infarct zone T2 signal over time and prognostic significance over 4 years in a large unselected cohort of ST-segment–elevation myocardial infarction patients and using contemporary, quantitative T2-mapping techniques. Infarct zone T2 hyperintensity was present at 6 months in approximately two thirds of ST-segment–elevation myocardial infarction patients. Persistent T2 hyperintensity was prognostically important because it was associated with markers of MI severity and adverse left ventricular remodeling. Whether T2 hyperintensity at 6 months represents edema or another process is uncertain and merits further discussion and study. The change in infarct zone T2 signal as a continuous variable was associated with health outcome. Further studies are warranted to assess whether or not infarct zone T2 may track the response to therapy in ST-segment–elevation myocardial infarction patients and thus represent a therapeutic target for use in clinical trials.

Circulation
Cardiovascular Imaging

Persistence of Infarct Zone T2 Hyperintensity at 6 Months After Acute ST-Segment–Elevation Myocardial Infarction: Incidence, Pathophysiology, and Prognostic Implications

Jaclyn Carberry, David Carrick, Caroline Haig, Nadeem Ahmed, Ify Mordi, Margaret McEntegart, Mark C. Petrie, Hany Eteiba, Stuart Hood, Stuart Watkins, Mitchell Lindsay, Andrew Davie, Ahmed Mahrous, Ian Ford, Naveed Sattar, Paul Welsh, Aleksandra Radjenovic, Keith G. Oldroyd and Colin Berry

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SUPPLEMENTAL MATERIAL

Persistence of infarct zone T2 hyperintensity at 6 months after acute ST-elevation myocardial infarction: incidence, pathophysiology and prognostic implications

ClinicalTrials.gov registration NCT02072850

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Supplementary Methods

Setting and study populations

ST-elevation myocardial infarction patients

We performed a longitudinal cohort study in a regional cardiac center between 11 May 2011 and 22 November 2012. Patients with acute ST-elevation myocardial infarction (STEMI) were consecutively screened for suitability and those recruited provided written informed consent. Inclusion criteria were an indication for primary percutaneous coronary intervention (PCI) or thrombolysis for STEMI[1]. Exclusion criteria were contraindications to contrast-enhanced cardiac magnetic resonance (CMR) imaging. For the purposes of this analysis, STEMI patients who experienced a recurrent MI or had an additional PCI following the index procedure were not included since these events could influence myocardial T2 (ms) during the intervening period. STEMI management followed current guidelines[1,2]. The study was approved by the National Research Ethics Service (Reference 10-S0703-28) and was publically registered (NCT02072850). The flow diagram for the study is shown in Supplementary Figure 1.

Screening, enrolment, and data collection were prospectively performed by cardiologists in the cardiac catheterization laboratories of the Golden Jubilee National Hospital, Glasgow, United Kingdom. This hospital is a regional referral center for primary and rescue PCI. The hospital provides clinical services for a population of 2.2 million. A screening log was recorded, including patients who did not participate in the cohort study.

Coronary angiogram acquisition and analyses

Coronary angiograms were acquired during usual care with cardiac catheter laboratory X-ray (Innova®) and IT equipment (Centricity®) made by GE Healthcare.

Percutaneous coronary intervention

Consecutive admissions with acute STEMI referred for emergency PCI were screened for the inclusion and exclusion criteria. During ambulance transfer to the hospital, the patients received 300 mg of aspirin, 600 mg of clopidogrel and 5000 IU of unfractionated heparin[1,2]. The initial primary PCI procedure was performed using radial artery access. A conventional approach to primary PCI was adopted in line with usual care in our hospital[1,2]. Conventional bare metal and drug eluting stents were used in line with guideline recommendations and clinical judgment. The standard transcatheter approach for reperfusion involves minimal intervention with aspiration thrombectomy only or minimal balloon angioplasty (e.g. a compliant balloon sized according to the reference vessel diameter and inflated at 4-6 atmospheres 1-2 times). During PCI, glycoprotein IIbIIIa inhibitor therapy was initiated with high dose tirofiban (25 μg/kg/bolus) followed by an intravenous infusion of 0.15 μg/kg/min for 12 hours, according to clinical judgment and indications for bail-out therapy[1,2]. No reflow was treated according to contemporary standards of care with intra-coronary nitrate (i.e. 200 μg) and adenosine (i.e. 30 – 60 μg)[1,2], as clinically appropriate. In patients with multivessel coronary disease, multivessel PCI was not recommended, in line with clinical guidelines[1,2]. The subsequent management of these patients was symptom-guided.

Angiographic analysis

The coronary anatomy and disease characteristics of study participants were described based on the clinical reports of the attending cardiologist.

Outcome definitions

Coronary blood flow can be described based on the visual assessment of coronary blood flow revealed by contrast injection into the coronary arteries[1,2]. TIMI Coronary Flow Grade 0 is no

flow, 1 is minimal flow past obstruction, 2 is slow (but complete) filling and slow clearance, and 3 is normal flow and clearance.

CMR acquisition

CMR imaging was performed on a Siemens MAGNETOM Avanto (Erlangen, Germany) 1.5-Tesla scanner with a 12-element phased array cardiac surface coil.

Myocardial native longitudinal relaxation time (T1) reflects tissue water content and cellularity[3]. T1-mapping was performed pre- and 15 minutes post-gadolinium contrast administration. T1 maps were acquired in 3 short-axial slices (basal, mid and apical), using a modified look-locker inversion-recovery (MOLLI) investigational prototype sequence (Work-in-Progress (WIP) method 448, Siemens Healthcare)[4–6] that incorporates an automatic registration algorithm based on a previously described approach[7]. The MOLLI T1 cardiac-gated acquisition involved three inversion-recovery prepared look locker experiments combined within one protocol (3 (3) 3 (3) 5)[5]. The CMR parameters were: bandwidth ~1090 Hz/pixel; flip angle 35°; echo time (TE) 1.1 ms; T1 of first experiment 100 ms; TI increment 80 ms; matrix 192 x 124 pixels; spatial resolution 2.2 x 1.8 x 8.0 mm; slice thickness 8 mm; scan time 17 heartbeats.

Myocardial transverse relaxation time (T2) directly reflects tissue water content and mobility[8,9]. T2-mapping (WIP method 447, Siemens Healthcare) was acquired in contiguous short axis slices covering the whole ventricle, using an investigational prototype T2-prepared (T2P) TrueFisp sequence[8,9]. The CMR parameters were: bandwidth ~947 Hz/pixel; flip angle 70°; T2 preparations: 0 ms, 24 ms, and 55 ms respectively; matrix 160 x 105 pixels; spatial resolution 2.6 x 2.1 x 8.0 mm; slice thickness 8 mm.

Late gadolinium enhancement images covering the entire left ventricle (LV) were acquired 10-15 minutes after intravenous injection of 0.15 mmol/kg of gadoterate meglumine (Gd2+-

DOTA, Dotarem, Guebert S.A.) using segmented phase-sensitive inversion recovery (PSIR) turbo fast low-angle shot[10]. Typical imaging parameters were: bandwidth ~130 Hz/pixel, flip angle 25°, TE 3.36 ms, matrix 192 x 256 pixels, echo spacing 8.7ms and trigger pulse 2. The voxel size was 1.8 x 1.3 x 8 mm3. Inversion times were individually adjusted to optimize nulling of apparently normal myocardium (typical values, 200 to 300 ms).

CMR image analyses

The images were analysed on a Siemens work-station by observers with at least 3 years CMR experience (N.A., D.C., I.M, S.R.). All of the images were reviewed by experienced CMR cardiologists (C.B., N.T.). LV dimensions, volumes and ejection fraction were quantified using computer assisted planimetry (syngo MR®, Siemens Healthcare, Erlangen, Germany). All scan acquisitions were spatially co-registered.

ECV measurement

LV contours were delineated on the best spatially matched raw T1 image and copied onto color-coded spatially co-registered maps. Regions of interest were drawn in infarcted myocardium surrounding core, remote myocardium and LV blood pool. Hematocrit (HCT) was measured at the time of scanning. Extracellular volume (ECV) was calculated as a ratio of corresponding T1 values measured pre- and post- contrast in each of the regions of interest. ECV was calculated using ECV = (1-HCT) × λ, where Lambda (λ)=ΔR1myocardium/ΔR1blood, ΔR1=R1post-contrast-R1pre-contrast and R1=1/T1[11,12].

Infarct definition and size

The territory of infarction was delineated using a signal intensity threshold of >5 standard deviations (SD) above a remote reference region and expressed as a percentage of total LV mass[13]. Infarct regions with evidence of microvascular obstruction were included within the

infarct area and the area of microvascular obstruction was assessed separately and also expressed as a percentage of total LV mass.

Reference ranges

Reference ranges used in the laboratory were 105 – 215 g for LV mass in men, 70 – 170 g for LV mass in women, 77 – 195 ml for LV end-diastolic volume in men, 52 – 141 ml for LV end-diastolic volume in women, 19 – 72 ml for LV end-systolic volume in men and 13 – 51 ml for LV end-systolic volume in women.

Electrocardiogram

A 12 lead ECG was obtained before coronary reperfusion and 60 minutes afterwards with Mac-Lab® technology (GE Healthcare) in the catheter laboratory and a MAC 5500 HD recorder (GE Healthcare) in the Coronary Care Unit. The ECGs were acquired by trained cardiology staff. The ECGs were de-identified and transferred to the local ECG management system. The ECGs were then analysed by the University of Glasgow ECG Core Laboratory which is certified to ISO 9001: 2008 standards as a UKAS Accredited Organisation.

The extent of ST-segment resolution on the ECG assessed 60 minutes after reperfusion compared to the baseline ECG before reperfusion[1] was expressed as complete (≥70%), incomplete (>30% to < 70%) or none (≤30%).

Biochemical measurement of infarct size

Troponin T was measured (Elecsys Troponin T, Roche) as a biochemical measure of infarct size. The high sensitive assay reaches a level of detection of 5 pg/ml and achieves less than 10%variation at 14 pg/ml corresponding to the 99th percentile of a reference population. A blood sample was routinely obtained 12 – 24 hours after hospital admission, and again between 0700 - 0900 hours during the first two days of the index hospitalization.

Biochemical measurement of LV remodeling

Serial systemic blood sample were obtained immediately after reperfusion in the cardiac catheterization laboratory, and subsequently between 0600 - 0700 hrs each day during the initial in-patient stay in the Coronary Care Unit.

NT-proBNP, a biochemical measure of LV wall stress, was measured in a research laboratory using an electrochemiluminescence method (e411, Roche) and the manufacturers calibrators and quality control material. The limit of detection is 5 pg/ml. Long-term coefficient of variations of low and high controls are typically <5%, and were all within the manufacturers range.

Research Management

The study was conducted in line with Guidelines for Good Clinical Practice (GCP) in Clinical Trials[14].

Trial management included a Trial Management Group, and an independent Clinical Trials Unit. Day to day study activity was coordinated by the Trial Management Group who was responsible to the Sponsor which was responsible for overall governance and that the trial was conducted according to GCP standards.

Health outcomes

We prespecified adverse health outcomes that are pathophysiologically linked with STEMI. The primary composite outcome was major adverse cardiac events (MACE) defined as cardiac death, non-fatal myocardial infarction or heart failure hospitalization following the 6-month CMR scan. All-cause death or heart failure (heart failure hospitalization or defibrillator implantation) following the 6-month CMR scan was a secondary outcome.

Research staff screened for events from enrolment by checking the medical records and by contacting patients and their primary and secondary care physicians as appropriate. Each serious adverse event was reviewed by a cardiologist who was independent of the research team and blinded to all of the clinical and CMR data. The serious adverse events were defined according to standard guidelines[15].

Statistics

Continuous variables are described as mean±SD, if normally distributed, and median (Q1, Q3) otherwise. Categorical variables are described as n (%). Variables are described overall and by presence or absence of persistent T2 hyperintensity. Patient and angiographic characteristics and CMR findings were compared between groups with presence or absence of persistent T2 hyperintensity using independent sample t-tests or Mann-Whitney tests, as appropriate. Binary logistic regression was used to identify associates of persistent T2 hyperintensity. Multivariable linear regression analyses using the enter method were performed to identify associates of the change in infarct zone T2 and LV parameters. Linear regression assumptions were verified using standardized residual plots.

Random effects models were used to compute inter-rater reliability measures (inter-class correlation coefficient (ICC)) for the reliability of infarct zone T2 values measured independently by 2 observers in 20 randomly selected patients from the cohort.

Cox proportional hazards regression was used to explore potential associations between persisting T2 hyperintensity and health outcome. The proportional hazards assumption was verified using log-minus-log plots. For these plots, continuous variables were categorized as above and below the median.

All p-values were 2-sided. A p-value >0.05 indicated the absence of a statistically significant effect. The natural log was used in transformations of variables. Analyses were performed using SPSS version 22 for Windows (SPSS, Inc., Chicago, Illinois), or R v3.3.0.

Supplementary Results

CMR findings

The full list of CMR findings are summarized in Supplementary Table 1.

The association between change in LV ejection fraction and persisting T2 hyperintensity and the change in infarct zone T2 is shown in Supplementary Table 2.

Infarct zone T2 inter-observer reliability

Infarct zone T2 in a subgroup of 20 randomly chosen patients was independently measured by two observers. The intra-class correlation coefficient for reliability of infarct zone T2 was 0.92 (95% confidence interval (CI): 0.75, 0.97); $p<0.001$. Bland-Altman plots (Supplementary Figure 2) showed no evidence of bias. The coefficient of variation for infarct zone T2 was 7.4%.

Persistent T2 hyperintensity and extracellular volume

Infarct zone ECV was measured in 127 patients at baseline and 124 patients at follow-up (n=124 paired measurements). The characteristics of these patients were similar to the whole cohort (data not shown). Infarct zone ECV and T2 were associated at baseline (0.14 (0.04, 0.24); p=0.007) which likely reflects the early increase in infarct zone extracellular water content. Additionally, infarct zone ECV at 6 months was higher in patients with persisting T2 hyperintensity (Table 2). There was an association between the change in infarct zone ECV at 6 months compared to baseline and the change in T2 in the infarct zone (0.15 (0.05, 0.24); p=0.002; n=124). The directions of change in infarct zone T2 and infarct zone ECV were independent (Chi square; p=0.420). In the majority of patients, infarct zone T2 decreased

over time, which means those who had a smaller decrease in infarct zone T2 had a larger increase in infarct zone ECV.

Since ECV may also reflect extracellular collagen volume fraction[16], progressive extracellular fibrosis within the infarct zone may lead to an increase in ECV in the chronic phase post-STEMI. After adjustment for infarct zone ECV, infarct zone T2 was no longer a multivariable associate of LV remodeling. Accepting some loss of statistical power in this subset analysis, the potential explanations for this result may include 1) progressive infarct zone fibrosis is associated with persistent T2 hyperintensity at 6 months; 2) extracellular rather than intracellular edema is prominent in pathological remodeling post-MI and; 3) measurement error, since hematocrit, which is required to calculate ECV, may not be uniformly distributed in systemic blood and injured capillaries may allow varying amounts of formed blood elements to occupy the microvascular compartment.

Associates with adverse remodeling at 6 months

The clinical characteristics that were included in the multivariable model with adverse remodeling at 6 months were BMI (p=0.589), age (p=0.502), male sex (p=0.812), previous MI (p=0.708), previous PCI (p=0.347), diabetes mellitus (p=0.432), previous angina (p=0.879), hypertension (p=0.437), hypercholesterolemia (p=0.879), cigarette smoking (p=0.117), no ST-segment resolution vs. complete or partial ST-segment resolution (reference category) (p=0.882), TIMI coronary flow grade 0/1 pre-PCI vs. TIMI coronary flow grade 2/3 pre-PCI (reference category) (p=0.280), TIMI coronary flow grade 0/1/2 post-PCI vs. TIMI coronary flow grade 3 post-PCI (reference category) (p=0.295) systolic blood pressure at initial angiography per 10mmHg (p=0.419), heart rate (p=0.818), symptom onset to reperfusion time (p=0.258), percentage stenosis of culprit artery (p=0.274).

The multivariable predictors are described in Table 3 in the main paper.

Persistent T2 hyperintensity and health outcomes

Kaplan-Meier plots for the association between persisting T2 hyperintesity and all-cause death or heart failure and major adverse cardiac events are shown in Supplementary Figure 3.

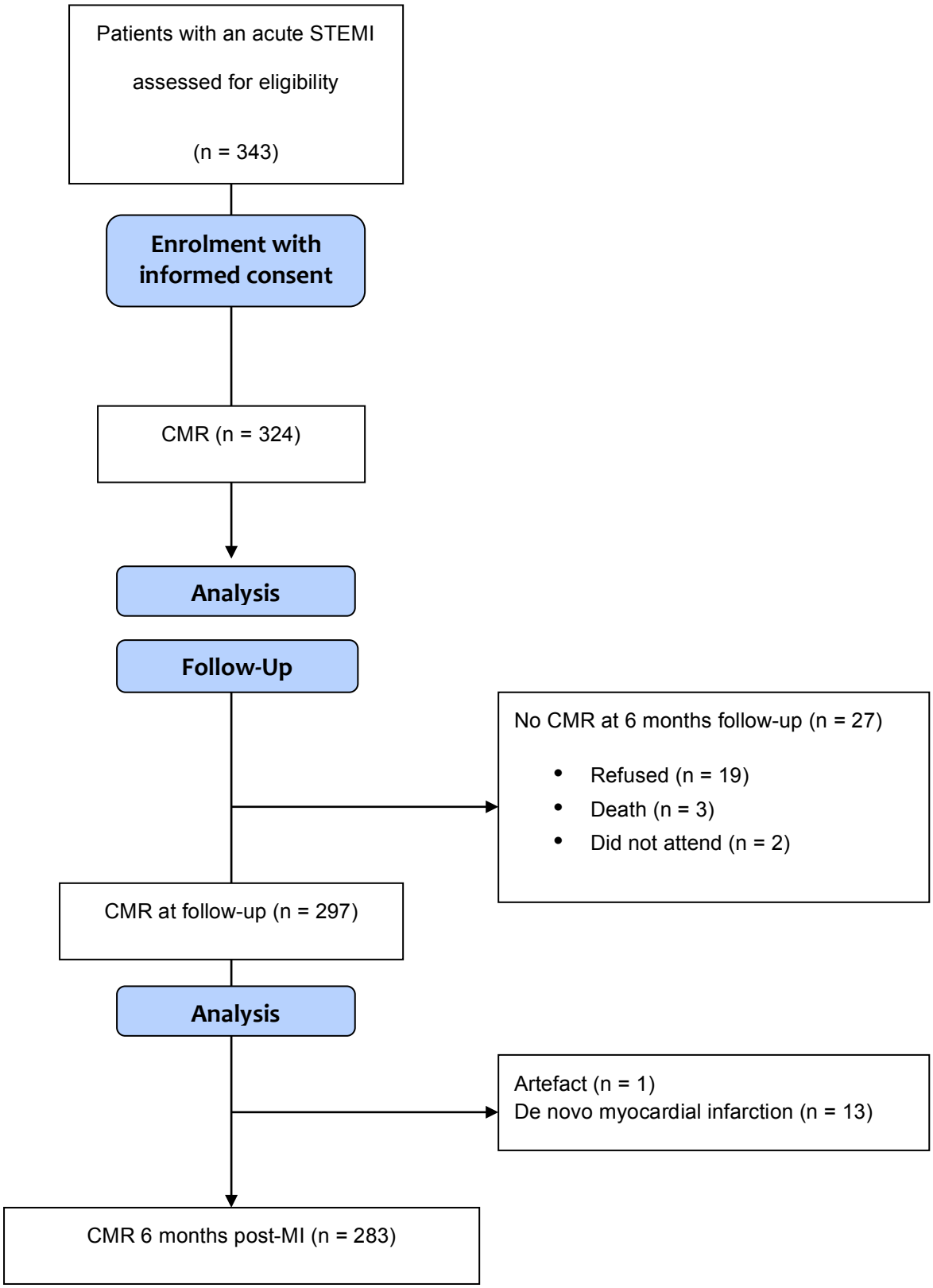
Supplementary Figures

Supplementary Figure 1. CONSORT flow diagram.

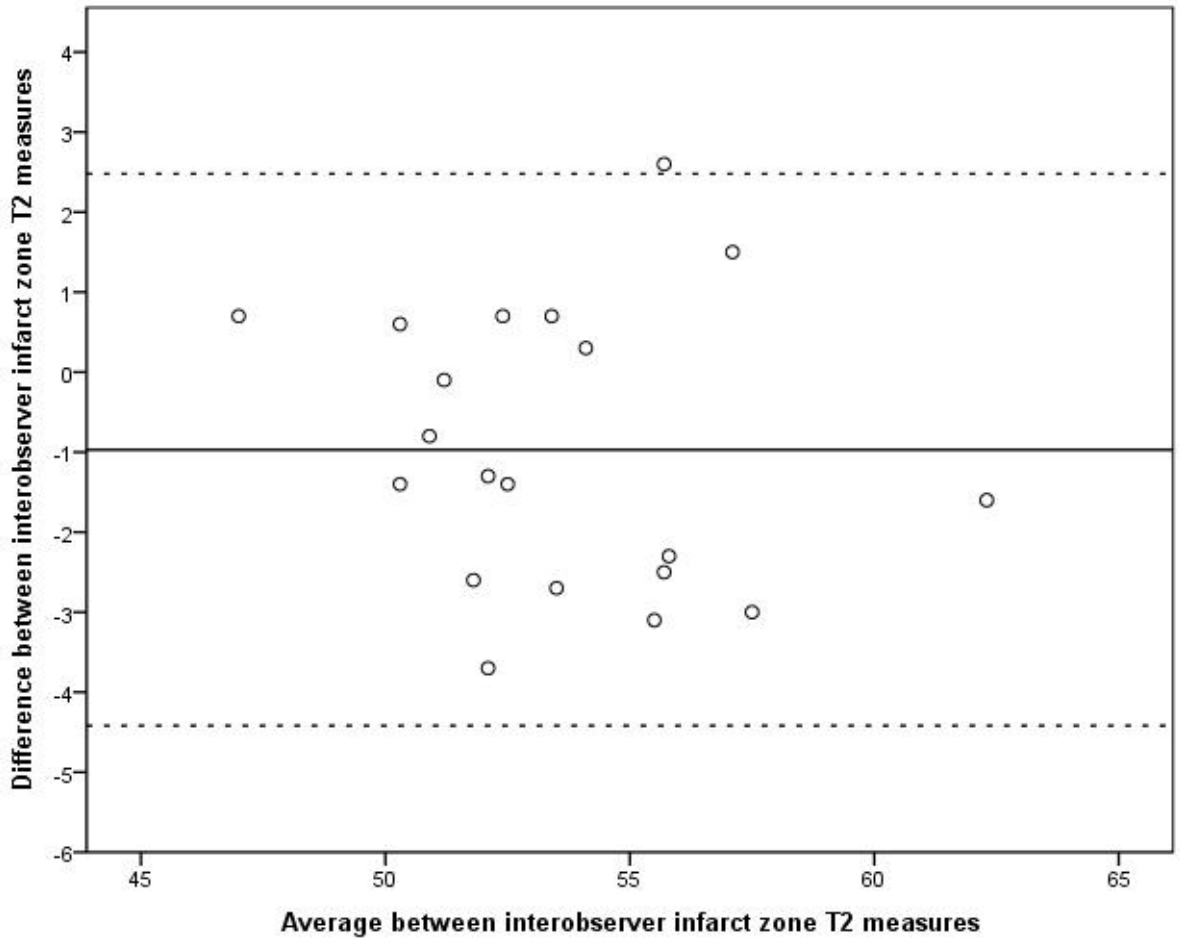
Supplementary Figure 2. Bland-Altman plot for inter-observer variability in infarct zone T2 measurement.

Supplementary Figure 3. Kaplan-Meier plots for the association between persisting T2 hyperintesity and A) all-cause death or heart failure (Log rank = 0.115) and B) major adverse cardiac events (Log rank = 0.212).

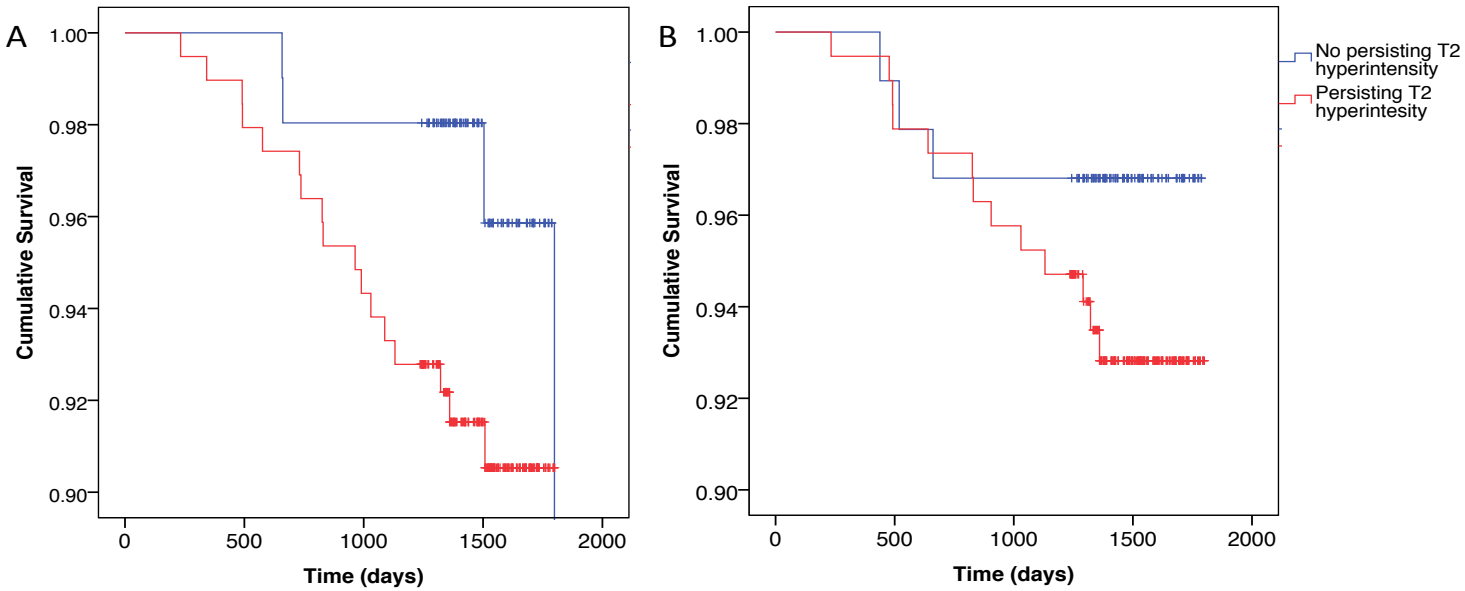
Supplementary Figure 1.



Supplementary Figure 2



Supplementary Figure 3



Supplementary Tables

Supplementary Table 1. CMR findings in 283 patients grouped according to the presence or absence of persistent T2 hyperintensity revealed by T2-mapping at 6 months post-STEMI.

Characteristics	All patients	No persistent T2 hyperintensity	Persistent T2 hyperintensity	P-value*
	n=283	n=94 (33%)	n=189 (67%)	
CMR findings 2 days post-MI				
LV ejection fraction, %	55±10	57±10	55±10	0.071
LV end-diastolic volume, ml				
Men	161±31	155±30	164±31	0.036
Women	124±25	130±23	121±25	0.172
LV end-systolic volume, ml				

Men	74±26	69±25	78±26	0.014
Women	54±18	57±18	52±17	0.225
LV mass, g				
Men	144±33	137±29	148±34	0.028
Women	97±21	101±17	95±23	0.216
Edema and infarct characteristics				
Myocardial edema, % LV mass	32±12	30±13	33±11	0.050
Infarct size, % LV mass	18±13	13±13	20±13	<0.001
Myocardial salvage, % LV mass	19±9	21±10	18±8	0.033
Myocardial salvage index, % LV mass	63±24	73±24	58±23	<0.001
Late microvascular obstruction present, n (%)	138 (49)	33 (35)	105 (56)	0.002

Late microvascular obstruction, % LV mass	2.6±4.6	1.5±3.6	3.1±4.9	0.004
Myocardial T1 and T2 values				
T1 remote, ms	960±26	958±25	961±26	0.354
T1 infarct, ms	1097±52	1093±49	1099±53	0.338
T1 hypointense core present, n (%)	137 (48)	33 (35)	104 (55)	0.002
T1 hypointense infarct core, ms	996±60	999±56	995±61	0.702
T2 remote, ms	49.7±2.1	49.8±2.2	49.7±2.1	0.811
T2 infarct, ms	66.3±6.1	64.4±5.7	67.3±6.1	<0.001
T2 hypointense core present, n (%)	165 (58)	41 (44)	124 (66)	0.001
T2 hypointense infarct core, ms	54.1±4.8	53.9±5.1	54.2±4.7	0.698
Myocardial ECV values at baseline				

ECV remote (all subjects), %	25.6±2.9	25.6±2.8	25.6±3.0	0.995
Men	25.2±2.9	25.0±2.7	25.3±2.9	0.612
Women	27.0±2.6	27.1±2.4	26.8±2.8	0.763
ECV infarct, %	56.0±11.7	52.8±12.9	57.7±10.7	0.024
ECV hypointense infarct core, %	43.2±12.6	44.8±15.1	42.5±11.7	0.537
CMR findings at 6 months				
LV ejection fraction at 6 months, %	62±9	65±8	61±10	<0.001
LV end-diastolic volume at 6 months, ml				
Men	169±42	151±31	177±45	<0.001
Women	127±30	125±22	128±34	0.627
LV end-systolic volume at 6 months, ml				

Men	68±35	54±19	74±38	<0.001
Women	46±18	45±18	47±18	0.550
Adverse remodeling, n (%)	32 (12)	1 (1)	31 (17)	<0.001
Infarct characteristics at 6 months				
Infarct size at 6 months, % LV mass	13±10	9±9	15±10	<0.001
Myocardial T1 and T2 values at 6 months				
T1 remote at 6 months, ms	957±29	957±28	958±29	0.713
T1 infarct at 6 months, ms	1058±66	1035±59	1068±67	<0.001
T2 remote at 6 months, ms	49.7±2.3	50.3±2.5	49.4±2.1	0.001
T2 infarct at 6 months, ms	56.8±4.5	53.5±3.4	58.5±4.0	<0.001
Myocardial ECV values at 6 months				

ECV remote at 6 months (all subjects), %	25.6±2.7	25.5±2.6	25.7±2.8	0.519
Men	25.3±2.7	25.0±2.6	25.4±2.7	0.288
Women	26.8±2.5	26.9±2.1	26.8±2.9	0.917
ECV infarct at 6 months, %	51.6±11.1	47.5±11.0	53.7±10.5	<0.001

Footnote: Abbreviations: CMR = cardiac magnetic resonance, ECV = extracellular volume, LV = left ventricle, T1 = longitudinal relaxation time, T2 = transverse relaxation time. Data are given as n (%) or mean±SD as appropriate. *P-values were obtained from two-sample t-test, Mann Whitney test or Fisher's test.

Supplementary Table 2. Linear regression analysis for associations with the change in LV ejection fraction at 6 months post-STEMI.

Multivariable associations	coefficient (95% CI)	p value
Patient characteristics, angiographic data and persistent T2 hyperintensity		
Persistent T2 hyperintensity	-2.53 (-4.39, -0.68)	0.008
Previous MI	6.29 (1.75, 10.83)	0.007
LV ejection fraction at baseline, %	-0.38 (-0.48, -0.29)	<0.001
Patient characteristics, angiographic data and change in infarct zone T2 (1 ms change)		
Change in infarct zone T2, 1 ms	-0.45 (-0.65, -0.26)	<0.001
Percentage stenosis of culprit artery, %	-0.14 (-0.24, -0.04)	0.007
Previous MI	5.47 (1.07, 9.86)	0.015
Hypertension	2.24 (0.31, 4.17)	0.023
Baseline infarct zone T2, ms	-0.52 (-0.73, -0.31)	<0.001
LV ejection fraction at baseline, %	-0.39 (-0.49, -0.30)	<0.001
Patient characteristics, angiographic data and change in infarct zone T2 (10 ms change)		
Change in infarct zone T2, 10 ms	-2.37 (-4.00, -0.75)	0.004
Percentage stenosis of culprit artery, %	-0.16 (-0.26, -0.05)	0.003
Previous MI	5.65 (1.14, 10.16)	0.014
Baseline infarct zone T2, ms	-0.36 (-0.55, -0.16)	<0.001
LV ejection fraction at baseline, %	-0.39 (-0.48, -0.29)	<0.001

Footnote: Abbreviations: CI = confidence intervals, LV = left ventricle, MI = myocardial infarction, T2 = transverse relaxation time. The coefficient (95% confidence intervals) indicates the magnitude and direction of the difference in change in LV ejection fraction (%) for the patient characteristic (binary or continuous).

The clinical characteristics that were included in the multivariable model with adverse remodeling at 6 months were BMI (p=0.574), age (p=0.354), male sex (p=0.460), previous PCI (p=0.808), diabetes mellitus (p=0.671), previous angina (p=0.402), hypertension (p=0.076), hypercholesterolemia (p=0.468), cigarette smoking (p=0.246), no ST-segment resolution vs. complete or partial ST-segment resolution (reference category) (p=0.746), TIMI coronary flow grade 0/1 pre-PCI vs. TIMI coronary flow grade 2/3 pre-PCI (reference category) (p=0.764), TIMI coronary flow grade 0/1/2 post-PCI vs. TIMI coronary flow grade 3 post-PCI (reference category) (p=0.529) systolic blood pressure at initial angiography per 10mmHg (p=0.578), heart rate (p=0.782), symptom onset to reperfusion time (p=0.617).

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