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Remote Zone Extracellular Volume and Left Ventricular Remodeling in Survivors of ST-Elevation Myocardial Infarction

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Abstract—The natural history and pathophysiological significance of tissue remodeling in the myocardial remote zone after acute ST-elevation myocardial infarction (STEMI) is incompletely understood. Extracellular volume (ECV) in myocardial regions of interest can now be measured with cardiac magnetic resonance imaging. Patients who sustained an acute STEMI were enrolled in a cohort study (BHF MR-MI [British Heart Foundation Magnetic Resonance Imaging in Acute ST-Segment Elevation Myocardial Infarction study]). Cardiac magnetic resonance was performed at 1.5 Tesla at 2 days and 6 months post STEMI. T1 modified Look-Locker inversion recovery mapping was performed before and 15 minutes after contrast (0.15 mmol/kg gadoterate meglumine) in 140 patients at 2 days post STEMI (mean age: 59 years, 76% male) and in 131 patients at 6 months post STEMI. Remote zone ECV was lower than infarct zone ECV (25.6±2.8% versus 51.4±8.9%; $P<0.001$). In multivariable regression, left ventricular ejection fraction was inversely associated with remote zone ECV ($P<0.001$), and diabetes mellitus was positively associated with remote zone ECV ($P=0.010$). No ST-segment resolution ($P=0.034$) and extent of ischemic area at risk ($P<0.001$) were multivariable associates of the change in remote zone ECV at 6 months (ΔECV). ΔECV was a multivariable associate of the change in left ventricular end-diastolic volume at 6 months (regression coefficient [95% confidence interval]: 1.43 (0.10–2.76); $P=0.036$). ΔECV is implicated in the pathophysiology of left ventricular remodeling post STEMI, but because the effect size is small, ΔECV has limited use as a clinical biomarker of remodeling.

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Key Words: edema ■ extracellular matrix ■ magnetic resonance imaging ■ myocardial infarction ■ myocardium

Early after acute ST-elevation myocardial infarction (STEMI), tissue edema and inflammatory cell recruitment occur as a response to myocyte necrosis and systemic inflammation.[1] The tissue repair response involves remodeling with collagen deposition in both the infarct and remote (noninfarcted myocardium) zones.[1,2] On the basis of recent developments with cardiac magnetic resonance (CMR) imaging, it is now possible to estimate the percentage extracellular volume (ECV) in defined regions of interest.[3,4]

The pathophysiological and clinical significance of remote zone ECV in survivors of acute STEMI is incompletely understood. To date, studies of remote zone ECV have included patients with chronic myocardial infarction (MI) as a small subgroup (n<50).[3,4] Furthermore, these studies are cross-sectional, and the changes that may occur in remote myocardium over time have not been investigated.

Our specific aims were to (1) measure ECV repeatedly in STEMI survivors in a longitudinal cohort study; (2) explore the relationships between remote zone ECV 2 days post STEMI and its absolute change at 6 months from baseline (ΔECV) with clinical characteristics of MI severity; and (3) assess whether remote zone ECV or ΔECV are associated with surrogate left ventricular (LV) outcomes during long-term follow-up.

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Our objective was to assess the pathophysiological significance of remote zone ECV and LV remodeling in patients after an acute STEMI. We hypothesized that ECV in the remote myocardial regions of patients with STEMI would be associated with measures of severity of MI and 6-month LV volumes. To test this hypothesis, we investigated ECV repeatedly during longitudinal follow-up of STEMI survivors and assessed the associations for remote zone ECV and ΔECV with patient characteristics and LV outcomes.

Methods

Design

We enrolled invasively managed patients with acute STEMI[5,6] into a CMR cohort study in a regional cardiac center between January 3, 2012, and November 22, 2012. The study was approved by the National Research Ethics Service (Reference 10-S0703-28) and was publically registered (NCT02072850[7]). Healthy volunteers also underwent CMR. All the participants provided written informed consent. The Methods section in the online-only Data Supplement provides a detailed description of the protocol and methods.

Statistics

For a sample size of 110 subjects, a minimum clinically significant correlation between remote zone ECV at baseline and the within-subject change in LV end-diastolic volume at 6 months from baseline could be detected with 90% power and an α of 0.05.

Continuous variables are described as mean±SD if normally distributed, and median (Q1–Q3) otherwise. Categorical variables are described as n (%). Variables were described overall and by tertiles of remote zone ECV. Patient and angiographic characteristics and CMR findings were compared across ECV tertiles using 1-way ANOVA, Kruskal–Wallis tests, or Fisher tests. Variables were compared between patients and healthy volunteers using *t* tests, Mann–Whitney tests, or Fisher tests. Associations between continuous variables were assessed using Pearson correlation coefficient. ECV was compared between segments using *t* tests. Multivariable linear regression analyses were performed to identify associates of remote zone ECV, ΔECV, and LV outcome. Backward selection was performed, and the remaining variables were included in the multivariable models. Linear regression assumptions were verified using standardized residual plots.

Random effects models were used to compute inter-rater reliability measures (interclass correlation coefficient) for the reliability of remote zone ECV values measured independently by 2 observers in 20 randomly selected patients from the cohort. Root mean square error was calculated. Bland–Altman plots were assessed for interobserver reliability and for agreement between synthetic and conventional ECV measures.

Cox proportional hazards regression was used to explore potential associations between ECV 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, IL).

Results

One hundred and forty patients with STEMI underwent CMR including pre- and postcontrast T1-mapping at 2.3±1.9 days post revascularization. One hundred and thirty-two patients (94%) had 6-month CMR, of whom 131 (94%) had pre- and postcontrast T1-mapping allowing for the measurement of ECV. Clinical case examples are shown in Figure 1. One thousand six hundred and eighty segments at baseline and 1572 at 6 months were included for analysis. The flow diagram for the study is shown in Figure S1 in the online-only Data Supplement.

Patient Characteristics

The characteristics of patients with remote zone ECV measurement at baseline (n=140) are described in Table 1. The mean±SD age was 59±11 years, and 76% were male.

Myocardial ECV in Patients With STEMI and Healthy Volunteers

Fifteen sex-matched healthy volunteers (age: 60±13 years, 73% male) also underwent CMR assessment of ECV. Remote zone ECV was similar in patients with STEMI (25.6±2.8%) and healthy volunteers (25.4±3.2%; *P*=0.797). In healthy volunteers, ECV was associated with myocardial T2-relaxation time (ms; regression coefficient [95% confidence intervals]: 0.90 [0.38–1.41]; *P*=0.002). Further analysis of healthy volunteer ECV is included in Results in the online-only Data Supplement. The results of interobserver agreement of remote zone ECV measurements are shown in Figure S2.

Remote Zone ECV and CMR Findings in Patients With Acute STEMI

The tertiles of remote zone ECV were ≤24.2% (n=46), >24.2 to ≤26.4% (n=47), and >26.4% (n=47). The proportion of men decreased with increasing tertile of ECV (43 [94%] versus 35 [75%] versus 29 [62%]; *P*<0.001), and body mass index (BMI, kg/m^2) reduced with increasing ECV tertile: (30±4 versus 29±5 versus 27±4; *P*=0.018).

Statistically significant CMR findings for patients with baseline ECV (n=140) are summarized in Table 2. The full list of CMR findings are summarized in Table S1. Infarct size was 17±12% of LV mass, and 70 patients (50%) had microvascular obstruction. Remote zone ECV was lower than infarct zone ECV (25.6±2.8% versus 51.4±8.9%; *P*<0.001). The upper tertile of remote zone ECV had values that overlapped with ECV values observed in the infarct zone (Table 2). Remote zone ECV early post MI was positively associated with the extent of myocardial edema (Table 2).

Multivariable Associations Between Clinical Characteristics and Remote Zone ECV

The multivariable associates of remote zone ECV at baseline are described in Table S2. Male sex (−1.85 [−2.91 to −0.79]; *P*=0001), diabetes mellitus (1.82 [0.43–3.20]; *P*=0.010), BMI (kg/m^2) (−0.12 [−0.22 to −0.02]; *P*=0.018), and LV ejection fraction at baseline (%) (−0.08 [−0.13 to −0.03]; *P*=0.002) were multivariable associates of remote zone ECV. The extent of myocardial edema (% LV mass) was also a multivariable associate of remote zone ECV (0.09 [0.05–0.14]; *P*<0.001).

Remote Zone ECV and CMR Findings at 6 Months

The 6-month CMR findings are described in Table 2 and Table S1. For patients with paired observations, remote zone ECV at baseline and follow-up were similar (25.5±2.9% versus 25.7±2.8%; *P*=0.645). The within-subject ΔECV in the

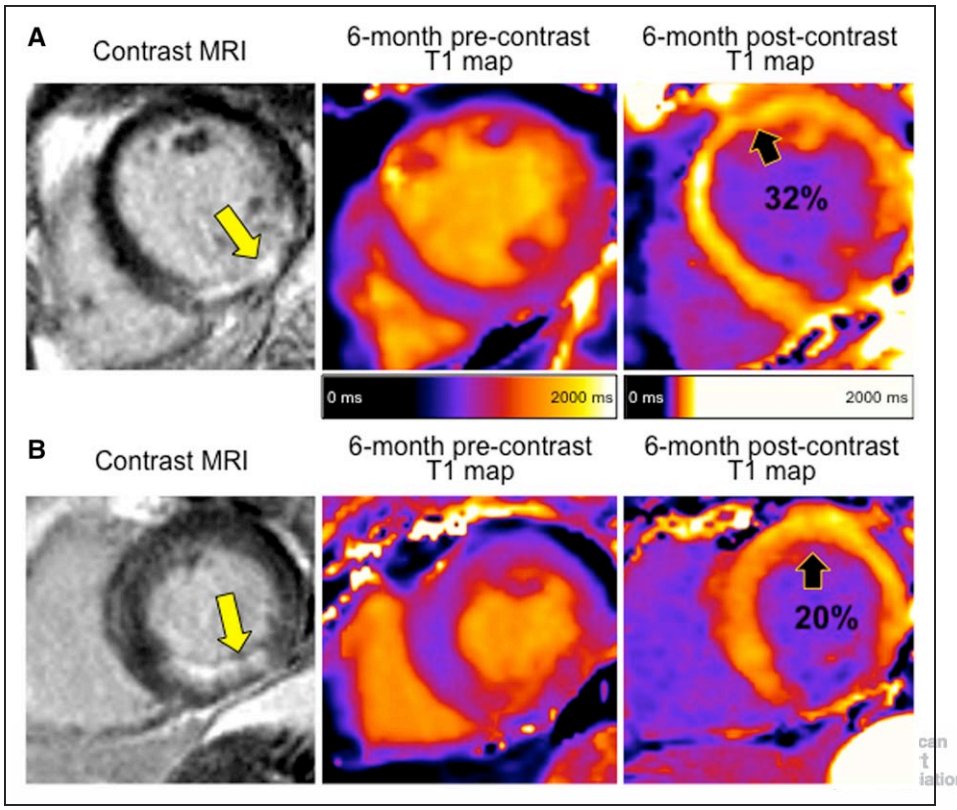

Figure 1. Two patients with similar presentations of acute ST-elevation myocardial infarction (STEMI). Both patients were treated by primary percutaneous coronary intervention and with the same medication. At the end of the procedure, both patients had thrombolysis in myocardial infarction coronary flow grade 3 in the culprit artery. **A**, Increasing remote zone extracellular volume (ECV). Cardiac magnetic resonance (CMR) performed 2 days post STEMI revealed a remote zone ECV of 28%. Remote zone ECV increased by 4% by 6 months to 32%. Left ventricular (LV) end-diastolic volume increased from 116 to 135 mL as measured by the 2-day and 6-month CMR scans. B, Decreasing remote zone ECV: CMR performed 2 days post STEMI revealed a remote zone ECV of 22%. Remote zone ECV decreased by 2% by 6 months to 20%. LV end-diastolic volume decreased from 128 to 102 mL as measured by the 2-day and 6-month CMR scans. MRI indicates magnetic resonance imaging.

remote zone varied markedly (ΔECV 0.1±2.6%). The correlation between remote zone ECV and ΔECV is shown in Figure 2.

At 6 months, LV end-diastolic volume increased on average±SD by 2±25 mL (Table 2) and adverse LV remodeling (an increase in LV end-diastolic volume >20%) developed in 9 patients (7%).

T1- and T2-Relaxation Times and Remote Zone ECV

Remote zone T2 was marginally higher at follow-up (49.9±2.2 ms versus 50.7±2.4 ms; *P*=0.005; mean change 0.7±3.0 ms). ΔECV in the remote zone was not associated with the change in remote zone T2 (0.07 [−0.01 to 0.14]; *P*=0.068). Remote zone T1 did not change over time.

Multivariable Associations Between Clinical Characteristics and the Changes in Remote ECV at 6 Months From Baseline

The multivariable associates of ΔECV in the remote zone are shown in Table S3. A 1-U increase in BMI (−0.14 [−0.23 to −0.04]; *P*=0.005), no ST-segment resolution (1.20 [0.09–2.31]; *P*=0.034), and extent of myocardial edema (0.08 [0.04–0.11]; *P*<0.001) were independently associated with ΔECV.

Remote Zone ECV and LV Remodeling

ΔECV was a multivariable associate of the change in LV end-diastolic volume at 6 months (Table 3); however, this was dependent on size of infarction (% LV mass; Table 3). Baseline remote zone ECV was not associated with LV ejection fraction or volumes at follow-up.

Remote Zone ECV and NT-proBNP

N-terminal pro-brain natriuretic peptide (NT-proBNP) results were available in 82 subjects. The characteristics of these patients were similar to the whole cohort (data not shown).

Remote zone ECV and NT-proBNP were associated at baseline (0.11 on a log scale [0.03–0.19]; *P*=0.007). This relationship remained after adjustment for LV function and volumes. NT-proBNP at baseline was also associated with ΔECV (0.14 [0.05–0.24]; *P*=0.004) after adjustment for baseline remote zone ECV and independently of LV function and volumes.

Remote Zone ECV and Health Outcomes

All-cause death or heart failure hospitalization occurred in 7 patients (5%), including 1 death and 6 heart failure episodes. Three patients (2%) experienced an event post discharge. In a preliminary analysis, remote zone ECV was not associated with all-cause death and heart failure hospitalization (n=7).

Table 1. Characteristics of 140 Patients With STEMI With a CMR Measurement of ECV (%) at Baseline

Characteristics	All Patients, n=140
Age, y	59±11
Male sex, n (%)	107 (76)
BMI, kg/m^2	29±5
Hypertension, n (%)	46 (33)
Current smoking, n (%)	84 (60)
Hypercholesterolemia, n (%)	41 (29)
Diabetes mellitus, n (%)*	16 (11)
Previous angina, n (%)	22 (16)
Previous myocardial infarction, n (%)	10 (7)
Previous PCI, n (%)	8 (6)
Mineralocorticoid receptor antagonist, n (%)	6 (4)
Presenting characteristics	
Heart rate, bpm	78±17
Systolic blood pressure, mm Hg	139±25
Diastolic blood pressure, mm Hg	80±14
Symptom onset to reperfusion, min	247±227
Ventricular fibrillation, n (%)†	8 (6)
Killip class, n (%)	
I	105 (75)
II	31 (22)
III/IV	4 (3)
ECG	
ST-segment resolution post PCI, n (%)	
Complete, ≥70%	64 (46)
Incomplete, 30% to <70%	52 (37)
None, ≤30%	23 (17)
Coronary angiography	
Reperfusion strategy, n (%)	
Primary PCI	132 (94)
Rescue PCI (failed thrombolysis)	5 (4)
Successful thrombolysis	3 (2)
Number of diseased arteries, n (%)‡	
1	78 (56)
2	41 (29)
3	19 (14)
Culprit artery, n (%)	
Left main	2 (1)
Left anterior descending	55 (39)
Left circumflex	26 (19)
Right coronary	59 (42)
Culprit artery TIMI flow grade at initial angiography, n (%)	
0/1	107 (76)
2	21 (15)
3	12 (9)
Culprit artery TIMI flow grade post PCI, n (%)	
0/1	3 (2)
2	5 (4)
3	132 (94)
Blood results on admission	
Troponin I, ng/L	
Median (Q1–Q3)	2718 (1248–6377)
Range	56–28 406
C-reactive protein, mg/L	
Median (Q1–Q3)	3.0 (2.0–6.0)
Range	1.0–125.0
Leucocytes, ×10^9 L	12.4±3.5
Neutrophils, ×10^9 L	9.5±3.3
Monocytes, ×10^9 L	0.8±0.3

Data are given as n (%), mean±SD, or median (Q1–Q3) as appropriate. Killip classification of heart failure post MI: class I, no heart failure; class II, pulmonary rales or crepitations, third heart sound, and elevated jugular venous pressure; class III, acute pulmonary edema; class IV, cardiogenic shock. BMI indicates body mass index; CMR, cardiac magnetic resonance; ECV, extracellular volume; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

*History of diet-controlled or treated diabetes.

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

‡Number of stenoses ≤50% of the reference vessel diameter by visual assessment and if there was left main stem involvement.

Discussion

The main findings are as follows: (1) remote zone ECV 2 days post MI is associated with male sex, BMI, and a history of diabetes mellitus; (2) ΔECV is related to the extent of injury as revealed by myocardial edema; (3) ΔECV was positively associated with changes in LV end-diastolic volume; (4) remote zone ECV and ΔECV were associated with NT-proBNP at baseline. We conclude that in STEMI survivors, an increase in remote zone ECV over time post STEMI is associated with an increase in LV end-diastolic volume, further implicating remote zone interstitial fibrosis in the pathophysiology of adverse LV remodeling.

We recently observed that remote zone tissue characteristics, as revealed by the native myocardial longitudinal relaxation time (T1), were multivariable associates of acute systemic inflammation and subsequent adverse outcomes in the longer term, including LV remodeling and all-cause death or heart failure.[8] The results from the current study extend these findings in several ways. First, ECV early post MI is inversely associated with the change in ECV over time. Our results indicate that remote zone ECV is likely

Table 2. CMR Findings at Baseline (n=140) and at 6 Months (n=131) in Patients With STEMI Grouped by Tertiles of Remote Zone ECV (%) at Baseline

Characteristics*	All patients n=140	STEMI Patient Tertiles, Remote Zone ECV at Baseline ≤24.2% n=46	>24.2 to ≤26.4% n=47	>26.4% n=47	*P* Value
CMR findings 2 days post MI (n=140)					
LV ejection fraction, %	56±9	57±8	56±9	54±10	0.182
Edema and infarct characteristics					
Myocardial edema, % LV mass	31±11	29±12	30±11	35±9	0.033
Myocardial salvage, % LV mass	19±8	18±7	18±8	22±9	0.025
Myocardial native T1 and T2 values					
T1 remote (all subjects), ms	961±24	953±20	963±26	967±23	0.010
T2 remote, ms	49.9±2.1	48.9±1.9	50.1±2.3	50.7±1.9	<0.001
Myocardial ECV values					
ECV remote (all subjects), %	25.6±2.8	22.5±1.3	25.4±0.6	28.7±1.7	<0.001
Men	25.2±1.8	22.6±1.3	25.4±0.6	28.8±1.8	<0.001
Women	26.9±2.5	22.1±1.1	25.4±0.7	28.7±1.5	<0.001
Myocardial ECV values at 6 mo					
ECV remote at 6 mo (all subjects), %	25.7±2.8	24.3±2.4	25.3±2.3	27.6±2.5	<0.001
Men	25.4±2.7	24.3±2.4	25.2±2.4	27.1±2.5	<0.001
Women	26.9±2.7	24.2±1.0	25.4±2.3	28.3±2.4	0.002

Data are given as n (%) or mean±SD as appropriate. Myocardial edema was measured with T2-mapping. CMR indicates cardiac magnetic resonance; ECV, extracellular volume; LV, left ventricle; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; T1, longitudinal relaxation time; and T2, transverse relaxation time.

**P* values were obtained from 1-way ANOVA, Kruskal–Wallis test, or Fisher test.

to remain persistently elevated in patients with a large MI, implying replacement fibrosis and LV remodeling. The absence of an association between remote zone ΔECV and changes in remote zone T2 (ms) over time implies that the persistent elevation in ECV is not explained by edema, indicating that extracellular matrix remodeling and fibrosis is a plausible alternative explanation. Second, the changes over time in remote zone T2 (<1 ms) were biologically insignificant, and remote zone T1 (ms) was unchanged, indicating that the changes in ECV are much more likely because of progressive interstitial fibrosis than interstitial edema. In our previous work, remote zone native T1 was not associated with NT-proBNP,[8] which is in contrast to the positive association between remote zone ECV and NT-proBNP. These results may be explained by the fact that ECV is a more specific biomarker of the extracellular space, whereas native T1 reflects both intracellular and extracellular compartments. Finally, for the first time, we have reported changes in remote zone ECV over time post MI and the associations with clinical characteristics and LV remodeling. In agreement with previous observations,[8] the absence of an association between remote zone ECV and the number of stenosed arteries suggest that ischemia is not a factor in remote zone remodeling. In linear regression analyses, λ had similar associations as ECV (data not shown), implying these variables are closely associated.

In this study, remote zone ECV exhibited a sex variation. This is in keeping with studies of remote zone ECV in patients with cardiovascular disease[3,4] and healthy subjects.[9,10] Sado et al[10] also found height to be related to ECV, which agrees with our finding of the link between BMI and ECV. In contrast to findings by Ugander et al,[3] we observed that remote zone ECV overlapped with the lower limits of infarct zone ECV. The possible explanations for this result include (1) large sample of an unselected real-world STEMI population in our study compared with a smaller sample (n=36) of patients studied by Ugander et al; (2) time between MI and CMR, which was not specified by Ugander et al and may have resulted in higher remote zone ECV in our study because of global edema and inflammatory cell influx, although the overlap persisted at 6-month follow-up.

Our findings are evidence of associations between tissue characteristics in the myocardial remote zone and LV remodeling post STEMI.[3,4,8] Although the effect size of the changes in ECV limits clinical use, the result is nonetheless important from the perspective of the pathophysiology and mechanisms of LV remodeling. On the contrary, we also observed that the size of infarction was a similar predictor of LV remodeling than remote zone ECV. Whether drugs that inhibit LV remodeling, for example, mineralocorticoid receptor antagonists, might have differential effects in patients according to their baseline ECV status (within the infarct and/or remote zones)

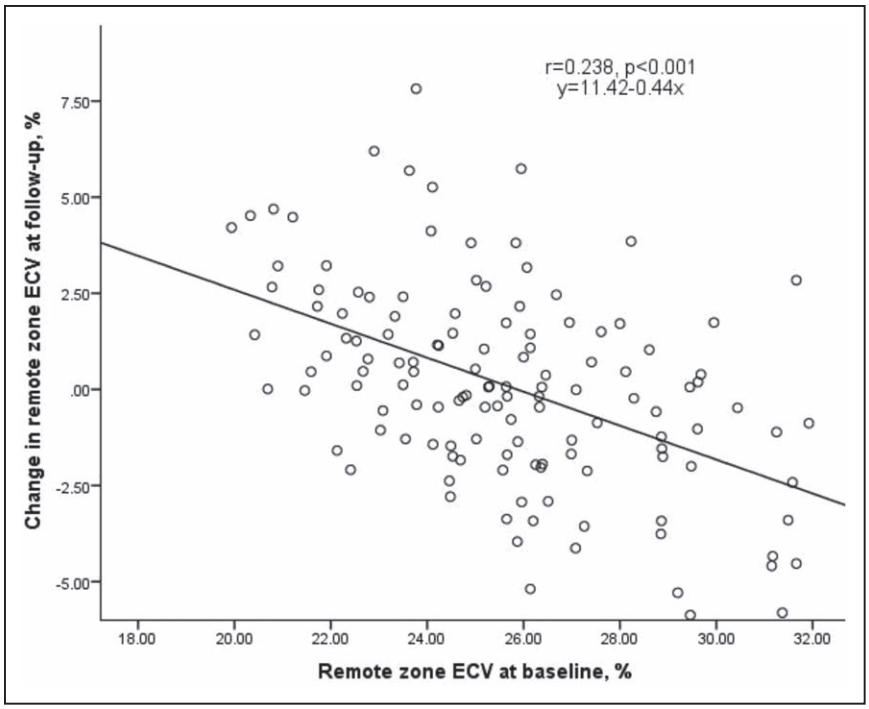

Figure 2. Remote zone extracellular volume (ECV) at baseline versus change in remote zone ECV at follow-up.

merits further research. Wong et al[11] observed that patients treated with renin-aldosterone-angiotensin system blockade had lower ECV.

Limitations

Postcontrast T1 maps were not acquired in all patients because of time constraints in our busy clinical service. CMR was performed at a single time point early post MI; therefore, we lack results on the temporal evolution of ECV post reperfusion. Angiotensin-converting enzyme inhibitors were prescribed in almost all patients with STEMI in our cohort (98%), and mineralocorticoid receptor antagonists were prescribed in the minority (4%); therefore, it was not possible to assess for associations between these therapies and ECV post MI. The relationship between remote zone ECV and health outcomes in STEMI survivors merits further study in a larger population. We have undertaken the largest longitudinal study of remote zone ECV in patients after an acute STEMI. Nonetheless, the results do not provide evidence of causality.

Conclusions

In STEMI survivors, remote zone ECV is associated with sex, BMI, and a history of diabetes mellitus. Remote zone ECV at baseline and ΔECV are associated with the severity of MI including NT-proBNP. Only ΔECV was associated with LV remodeling, as revealed by CMR. ΔECV is implicated in the pathophysiology of LV remodeling post STEMI, but because the effect size is small, ΔECV has limited use as a clinical biomarker of remodeling.

Perspectives

Our findings provide further evidence of the pathophysiological importance of remote zone tissue characteristics and LV remodeling in survivors of acute STEMI. Future research is warranted into the association between remote zone ECV and longer-term health outcomes. Remote zone ECV is implicated in the pathophysiology of LV remodeling.

Table 3. Multivariable Associates of the Change in Left Ventricular End-Diastolic Volume (ml) at 6 Months Post STEMI in 131 Patients

Multivariable Associations	Coefficient (95% CI)	*P* Value
ECV and clinical associates of remodeling		
Change in remote zone ECV, %	1.43 (0.10 to 2.76)	0.036
Baseline remote zone ECV, %	0.86 (−0.41 to 2.13)	0.184
LV end-diastolic volume at baseline, ml	−0.28 (−0.38 to −0.17)	<0.001
Male sex	15.40 (7.31 to 23.49)	<0.001
Diabetes mellitus	−10.34 (−19.71 to −0.97)	0.031
Previous angina	−11.97 (−21.39 to −2.54)	0.013
Killip class IV	200.76 (165.40 to 236.12)	<0.001
No ST-segment resolution	15.17 (6.69 to 23.64)	0.001
TIMI coronary flow grade 3 pre PCI	−13.24 (−25.07 to −1.41)	0.029
TIMI coronary flow grade 2 post PCI	−27.92 (−53.86 to −1.99)	0.035

The coefficient (95% CIs) indicates the magnitude and direction of the difference in change in LV end-diastolic volume (ml) for the patient characteristic (binary or continuous). When infarct size was included in the model, the change in remote zone ECV was no longer an associate of the change in LV end-diastolic volume.

CI indicates confidence interval; ECV, extracellular volume; LV, left ventricle; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; and TIMI, thrombus in myocardial infarction.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Extracellular volume (ECV) measured by cardiac magnetic resonance imaging has been measured in regions of interest repeatedly over time (2 days and 6 months) in a reasonably large cohort of patients after acute ST-elevation myocardial infarction (MI).
- ECV in the remote zone is associated with patient characteristics and the severity of MI.
- The change in remote zone ECV is associated with left ventricular remodeling.
- Remote zone ECV and the change in remote zone ECV are associated with NT-proBNP, a biochemical marker of MI severity.

What Is Relevant?

- The change in remote zone ECV is implicated in the pathophysiology of LV remodeling post ST-elevation MI, but because the effect size is small, it has limited use as a clinical biomarker.

Summary

Remote zone ECV and the change in remote zone ECV over time are linked with clinical markers of MI severity as evidenced by reperfusion injury and myocardial edema. The change in remote zone ECV is linked with left ventricular remodeling during longer-term follow-up.

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Remote Zone Extracellular Volume and Left Ventricular Remodeling in Survivors of ST-Elevation Myocardial Infarction

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Short Title: Remote zone extracellular volume post-STEMI

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Supplemental Methods

Setting and study populations

ST-elevation myocardial infarction patients

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 percutaneous coronary intervention (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.

Healthy volunteers

The purpose of including healthy volunteers was to collect normative reference data for myocardial extracellular volume (ECV) in individuals without prior cardiovascular disease or therapy and who were reasonably representative of the population of individuals from whom the ST-elevation myocardial infarction (STEMI) patients were drawn. Second, the reference ECV values were required to be measured on the same CMR scanner and with the same protocol that was used for the STEMI patients including during the same time-period.

Healthy volunteers were invited to participate by placing adverts in public buildings (e.g. hospital, University) and through personal contacts of the researchers. Matching and selection of the healthy volunteers was done by the researchers in order to reflect the age and gender distribution of the STEMI patients. The healthy volunteers were resident in the same catchment area as the STEMI population. Age- and gender-matched healthy volunteers who had a normal electrocardiogram (ECG) and no prior history of cardiovascular disease or therapy underwent CMR during the same time period. The absence of late gadolinium enhancement (myocardial fibrosis or scar) was determined qualitatively by visual assessment, and the absence of late gadolinium enhancement was a requirement for inclusion of the volunteer in this analysis.

The rationale for including healthy volunteers in this study is as follows. First, ECV values may vary between CMR scanners and so a local reference range for ECV is recommended in CMR guidelines [1, 2]. Second, ECV may vary spatially in the heart and therefore, since the focus of our study was to assess ECV in myocardium remote from the infarct zone, we aimed to collect ECV values in different segments of the heart in order to compare the remote zone ECV values from STEMI patients with reference spatially matched remote zone ECV values in age- and gender-matched healthy volunteers. Myocardial ECV values were regionally segmented in regions-of-interest and summarized according to the American Heart Association (AHA) model [3].

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 (Little Chalfont, UK).

Percutaneous coronary intervention

Consecutive admissions with acute STEMI referred for emergency percutaneous coronary intervention (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 [4, 5]. 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 [4, 5]. 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 [4, 5]. 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) [4, 5], as clinically appropriate. In patients with multivessel coronary disease, multivessel PCI was not recommended, in line with clinical guidelines [4, 5]. 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 [4, 5]. Thrombus in Myocardial Infarction (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 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 [2]. 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) [6-8] that incorporates an automatic registration algorithm based on a previously described approach [9]. The MOLLI T1 cardiac-gated acquisition involved three inversion-recovery prepared look locker experiments combined within one protocol (3 (3) 3 (3) 5) [7]. 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 T2 relaxation time directly reflects tissue water content and mobility [10,11]. 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 [10, 11]. 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 LV were acquired 10-15 minutes after intravenous injection of 0.15 mmol/kg of gadoterate meglumine (Gd^{2+}-DOTA, Dotarem, Guebert S.A.) using segmented phase-sensitive inversion recovery (PSIR) turbo fast low-

angle shot [12]. Microvascular obstruction (MVO) was defined as a dark zone on early delayed enhancement imaging 1, 3, 5 and 7 minutes post-contrast injection and within an area of late gadolinium enhancement at 10-15 minutes. 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 mm^3. Inversion times were individually adjusted to optimize nulling of apparently normal myocardium (typical values, 200 to 300 ms).

Healthy volunteers underwent the same imaging protocol, with the exception that those <45 years did not receive gadolinium.

MR image analyses

The images were analyzed 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.). Left ventricular (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 with computer-assisted planimetry on the best spatially matched raw T1 image and copied onto color-coded spatially co-registered maps. Care was taken to have adequate margins of separation from tissue interfaces, such as myocardium and blood, to prevent partial volume averaging [1, 2, 13]. Regions-of-interest (ROIs) were drawn in 1) remote myocardium, placed 180^o from infarct zone; 2) infarct zone, including the entire area of injury; 3) LV blood pool. ROIs were copied between the pre- and post-contrast T1 maps with manual correction to maintain margins of separation from tissue interfaces. ECV was calculated as a ratio of corresponding T1 values measured pre- and post- contrast in each of the ROIs. No registration between T1 maps was therefore required for accurate calculation of ECV values. ECV was calculated using Eq. (1), where Lambda (λ)=$\Delta R1_{myocardium}/\Delta R1_{blood,}$ $\Delta R1=R1_{post\text{-}contrast}-R1_{pre\text{-}contrast}$, R1=1/T1 [14, 15]. Hematocrit (HCT) was measured at the time of scanning.

$$ECV = (1 - HCT) \times \lambda \quad (1)$$

ECV analysis in the healthy volunteer cohort was calculated for 6 equal segments (anterior, anterolateral, inferolateral, inferior, inferoseptal, anteroseptal) of the mid-ventricular T1 maps according to the 17-segment model of the American Heart Association (AHA) [3]. Per-segment values were averaged to give a global ECV for each case. To expand the healthy volunteer cohort, synthetic HCT was calculated using the equation HCT = 0.88-($T1_{blood}$/3240) [16].

Infarct definition and size

The presence of acute infarction was established based on abnormalities in cine wall motion, rest first-pass myocardial perfusion, and delayed-enhancement imaging. In addition, supporting changes on the ECG and coronary angiogram were also required. Acute infarction was considered present only if late gadolinium enhancement was confirmed on both the axial

and long axis acquisitions. 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 MVO were included within the infarct area and the area of MVO was assessed separately and also expressed as a percentage of total LV mass.

Microvascular obstruction

MVO was defined as a dark zone on early gadolinium enhancement imaging 1, 3, 5 and 7 minutes post-contrast injection that remained present within an area of late gadolinium enhancement at 10-15 minutes. The late time-point was used to delineate MVO [1]. Identification of MVO was performed independently by I.M. and N.A. MVO area was assessed separately and expressed as a percentage of LV mass.

Myocardial edema

The extent of myocardial edema was defined as LV myocardium with pixel values (T1/T2) >2 SD from remote myocardium [17-18]. In order to assess myocardial edema the epicardial and endocardial contours on the last corresponding T2-weighted raw image with an echo time of 55 ms were planimetered [19]. Contours were then copied to the map and corrected when necessary by consulting the SSFP cine images.

Myocardial salvage

Myocardial salvage was calculated by subtraction of percent infarct size from percent myocardial edema (a retrospective estimate of the initial ischemic area-at-risk) [20-22]. The myocardial salvage index was calculated by dividing the myocardial salvage area by the initial extent of edema (% LV mass).

Adverse remodeling

Adverse remodeling was defined as an increase in LV end-diastolic volume ≥ 20% at 6 months from baseline [23].

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 analyzed by the University of Glasgow ECG Core Laboratory which is certified to ISO 9001: 2008 standards as a UKAS Accredited Organization.

The extent of ST-segment resolution on the ECG assessed 60 minutes after reperfusion compared to the baseline ECG before reperfusion [4] was expressed as complete (≥70%), incomplete (30% to < 70%) or none (≤30%).

Biochemical assessment 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 [24].

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

Supplemental Results

The flow diagram for the study is shown in Supplemental Fig. S1.

Remote zone ECV inter-observer reliability

Remote ECV in a subgroup of 20 randomly chosen patients was independently measured by two observers. The ICC for reliability of remote zone ECV was 0.92 (95% confidence interval (CI): 0.79, 0.97); $p<0.001$). The mean absolute difference between measures was 0.48%, and the root-mean-square error was 1.01. Bland-Altman plots showed no evidence of bias (Supplemental Fig. S2). The coefficient of variation for values of remote zone ECV at baseline in STEMI patients (n=140) was 13.36.

Remote zone ECV in healthy volunteers

Twenty-eight healthy volunteers (mean±SD 60±11 years, 16 (57%) male) with no history of cardiovascular disease or treatment had CMR scans including post-contrast T1-mapping with MOLLI. Volunteers were scanned using the same 1.5 Tesla MRI scanner (Siemens AVANTO) as the STEMI patients. Twenty patients had available HCT measures on the day of scanning. For these patients, synthetic ECV and conventional ECV were highly correlated (R^2=0.82, p<0.001). The correlation was similar for synthetic and conventional remote ECV in STEMI patients (R^2=0.68, p<0.001). SD of differences for healthy volunteers was 1.3%. The Bland-Altman plot showed no evidence of bias (Supplemental Fig. S3). Regression coefficients between synthetic and conventional ECV measurements were similar. We proceeded to calculate synthetic HCT and ECV for the remaining healthy volunteers, giving a total of n=28 healthy volunteers.

At the mid ventricular level, remote zone synthetic ECV was similar in STEMI patients and healthy volunteers for a sex-matched grouped (n=21, age 58±12 years, 76% male) (24.2±2.7% vs. 24.1±2.6%; p=0.959). In all healthy volunteers (n=28), remote zone ECV was higher in females than in males (25.6±2.4% vs. 23.0±1.7%; p=0.002). Overall, remote zone ECV was negatively associated with age (-0.09 (-0.16, -0.01); p=0.027), however the association was sex-dependent (women: -0.16 (-0.27, -0.04); p=0.015; men: -0.03 (-0.11, 0.06); p=0.498). There was a trend to interaction between age and sex when assessed using linear regression (p=0.052). ECV was higher in septal segments in females (anteroseptal: 25.8±3.0% vs. 22.9±1.9%; p=0.004; inferoseptal: 25.9±2.9% vs. 22.6±1.8%; p=0.001), whereas no differences were observed for other segments (anterior: 24.1±3.4% vs. 22.0±1.9%; p=0.077; anterolateral: 23.9±3.7% vs. 23.0±1.8%; p=0.457; inferolateral: 25.7±3.6% vs. 24.5±2.2%; p=0.309; inferior: 25.3±3.8% vs. 23.8±2.6%; p=0.283).

The coefficients of variation for remote zone ECV in the mid-ventricular level with regions-of-interest within myocardial regions were: anterior CoV = 12.54; anterolateral CoV = 12.09; anteroseptal CoV = 11.53; inferior CoV = 13.26; inferolateral CoV = 11.55; inferoseptal CoV = 11.83.

Univariable associates with the change in LV end-diastolic volume at 6 months in all patients

Characteristics also included in the model include age (p=0.437), BMI (p=0.437), cigarette smoking (p=0.394), history of hypertension (p=0.846), hypercholesterolemia (0.958), previous PCI (p=0.150), previous MI (p=0.057), heart rate (p=0.183), systolic blood pressure at initial angiography (p=0.848), symptoms to reperfusion time (p=0.210), sustained ventricular arrhythmia (p=0.956), TIMI coronary flow grade 2 pre-PCI vs. TIMI coronary flow grade 0/1 pre-PCI (reference category) (p=0.465), rescue PCI vs. primary PCI (reference category) (p=0.525), incomplete ST-segment resolution vs. complete ST-segment resolution (reference category) (p=0.474), TIMI coronary flow grade 3 post-PCI vs. TIMI coronary flow grade 0/1 post-PCI (reference category) (p=0.191), Killip class II vs. Killip class I (reference category) (p=0.239), Killip class III vs. Killip class I (reference category) (p=0.110).

The multivariable predictors of the change in LV end-diastolic in all patients are described in Table 3 of the main paper.

Remote zone ECV and health outcomes in the longer term

Health outcome data was available in 140 (100%) patients. The median duration of follow-up was 724 days (minimum-maximum post-discharge censor duration 598- 923 days). Twelve (9%) patients experienced a major adverse cardiac event (MACE), including 6 recurrent MI hospitalizations and 6 heart failure episodes (hospitalization with Killip Class 3 or 4 heart failure or defibrillator implantation). Seven (5%) patients experienced a MACE post-discharge. Remote zone ECV was not associated with MACE (n=12). All-cause death or heart failure hospitalization occurred in 7 (5%) patients, including 1 death and 6 heart failure episodes. Three (2%) patients experienced an event post-discharge. Remote zone ECV was not associated with all cause death and heart failure hospitalization (n=7) (hazard ratio (95% confidence interval) 1.08 (0.73, 1.59)).

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Supplemental Tables

Supplemental Table S1. CMR findings at baseline (n=140) and at 6 months (n=131) in STEMI patients grouped by tertiles of remote zone ECV (%) at baseline.

Characteristics*		STEMI patient tertiles, remote zone ECV at baseline			P-value
	All patients	≤24.2%	>24.2 to ≤26.4%	>26.4%	
	n=140	n=46	n=47	n=47	
CMR findings 2 days post-MI (n=140)					
LV ejection fraction, %	56±9	57±8	56±9	54±10	0.182
LV end-diastolic volume, ml					
Men	162±34	158±41	162±31	167±23	0.532
Women	125±24	121±22	133±26	120±23	0.389
LV end-systolic volume, ml					
Men	75±26	70±30	76±26	81±21	0.213
Women	53±16	56±14	53±16	53±18	0.955
LV mass, g					

Men	146±37	147±42	146±31	144±36	0.753
Women	101±22	107±31	105±23	97±20	0.699
Edema and infarct characteristics					
Myocardial edema, % LV mass	31±11	29±12	30±11	35±9	0.033
Infarct size, % LV mass	17±12	17±12	16±12	18±12	0.606
Myocardial salvage, % LV mass	19±8	18±7	18±8	22±9	0.025
Myocardial salvage index, % LV mass	63±23	61±20	63±22	65±25	0.585
Late microvascular obstruction present, n (%)	70 (50)	26 (57)	20 (43)	24 (51)	0.412
Late microvascular obstruction, % LV mass	2.3±4.5	1.9±4.5	2.4±4.7	2.5±4.3	0.804
Myocardial native T1 and T2 values					
T1 remote (all subjects, ms)	961±24	953±20	963±26	967±23	0.010
Men	959±24	952±20	963±27	966±25	0.025
Women	967±21	969±17	965±25	969±20	0.866
T1 infarct, ms	1100±51	1103±53	1103±51	1096±48	0.737
T1 hypointense core present, n (%)	74 (53)	24 (52)	23 (49)	27 (57)	0.704
T1 hypointense infarct core, ms	1004±63	1001±61	1007±68	1005±64	0.939
T2 remote, ms	49.9±2.1	48.9±1.9	50.1±2.3	50.7±1.9	<0.001

Myocardial ECV values					
ECV remote (all subjects), %	25.6±2.8	22.5±1.3	25.4±0.6	28.7±1.7	<0.001
Men	25.2±1.8	22.6±1.3	25.4±0.6	28.8±1.8	<0.001
Women	26.9±2.5	22.1±1.1	25.4±0.7	28.7±1.5	<0.001
ECV infarct, %	51.4±8.9	50.4±10.1	51.0±7.5	52.9±9.0	0.363
ECV hypointense infarct core, %	43.2±12.1	40.4±9.7	44.2±13.5	44.9±12.9	0.390
ECV infarct zone out-with the infarct core, %	55.8±11.6	53.6±11.5	55.7±11.3	58.2±11.9	0.155
CMR findings 6 months post-MI (n=131)					
LV ejection fraction at 6 months, %	63±9	63±9	63±9	63±10	0.988
LV end-diastolic volume at 6 months, ml					
Men	165±43	164±56	164±36	168±30	0.456
Women	123±18	109±14	130±16	121±18	0.157
LV end-systolic volume at 6 months, ml					
Men	65±36	64±46	64±30	67±25	0.376
Women	43±17	40±21	46±14	42±18	0.585
Myocardial ECV values at 6 months					
ECV remote at 6 months (all subjects), %	25.7±2.8	24.3±2.4	25.3±2.3	27.6±2.5	<0.001

Men	25.4±2.7	24.3±2.4	25.2±2.4	27.1±2.5	<0.001
Women	26.9±2.7	24.2±1.0	25.4±2.3	28.3±2.4	0.002
ECV infarct at 6 months, %	51.4±10.3	51.9±10.1	49.6±10.2	52.6±10.7	0.368

Footnote: Abbreviations: ECV = extracellular volume, LV = left ventricle, T1 = longitudinal relaxation time, T2 = transverse relaxation time. Myocardial edema was measured with T2-mapping.
Data are given as n (%) or mean±SD, as appropriate. *P-values were obtained from one-way ANOVA, Kruskal-Wallis test, or Fischer's test. 6 month ECV values were available in 131 patients.

Supplemental Table S2. Multivariable association of patient characteristics at initial presentation with baseline remote zone ECV assessed by CMR 2 days after reperfusion (n=140).

Multivariable associations	coefficient (95% CI)	P-value
Patient characteristics, angiographic data and LV ejection fraction		
Male sex	-1.85 (-2.91, -0.79)	0.001
BMI, kg/m^2	-0.12 (-0.22, -0.02)	0.018
Diabetes mellitus	1.82 (0.43, 3.20)	0.010
LV ejection fraction, %	-0.08 (-0.13, -0.03)	0.002
Patient characteristics, angiographic data and myocardial edema		
Male sex	-1.61 (-2.63, -0.60)	0.002
BMI, kg/m^2	-0.14 (-0.24, -0.04)	0.006
Diabetes mellitus	1.85 (0.49, 3.21)	0.008
History of MI	1.90 (0.19, 3.62)	0.030
Myocardial edema, % LV mass	0.09 (0.05, 0.14)	<0.001
Patient characteristics, angiographic data and remote zone T2		
Male sex	-1.41 (-2.47, -0.35)	0.010
Diabetes mellitus	1.53 (0.14, 2.93)	0.032
T2 remote, ms	0.35 (0.14, 0.57)	0.001
Patient characteristics, angiographic data and remote zone T1		
Male sex	-1.22 (-2.28, -0.16)	0.024
BMI, kg/m^2	-0.13 (-0.23, -0.03)	0.010
Diabetes mellitus	1.70 (0.32, 3.07)	0.016
T1 remote, ms	0.04 (0.02, 0.06)	<0.001

Footnote: Abbreviations: BMI = body mass index, CI = confidence interval, LV = left ventricle, MI = myocardial infarction, T1 = longitudinal relaxation time, T2 = transverse relaxation time.

The coefficient (95% confidence intervals) indicates the magnitude and direction of the difference in remote zone ECV(%) for the patient characteristic (binary or continuous).

The clinical characteristics that were univariably associated with remote zone ECV at baseline that were also included in the model were age (p=0.406), current smoker (p=0.483), hypertension (p=0.114), hypercholesterolemia (p=0.348), previous angina (p=0.335), previous MI (p=0.217), previous PCI (p=0.884), symptom onset to reperfusion time (p=0.637), systolic blood pressure at initial angiography (p=0.508), heart rate (p=0.589), TIMI coronary flow grade 2 at initial angiography vs. TIMI coronary flow grade 0/1 at initial angiography (reference category) (p=0.530), TIMI coronary flow grade 3 at initial angiography vs. TIMI coronary flow grade 0/1 at initial angiography (reference category) (p=0.342), TIMI coronary flow grade 2 post-PCI vs. TIMI coronary flow grade 0/1 post-PCI (reference category) (p=0.810), TIMI coronary flow grade 3 post-PCI vs. TIMI coronary flow grade 0/1 post-PCI (reference category) (p=0.777), no ST-segment resolution vs. complete ST-segment resolution (reference category) (p=0.528), incomplete ST-segment resolution vs. complete ST-segment resolution (reference category) (p=0.562), Killip class III vs. Killip class I (reference category) (p=0.738), Killip class IV vs. Killip class I (reference category) (p=0.529).

Supplemental Table S3. Multivariable regression analysis of clinical characteristics and ΔECV (n=131).

Multivariable associations	coefficient (95% CI)	P-value
Patient characteristics and angiographic data		
Baseline remote zone ECV, %	-0.48 (-0.62, -0.34)	<0.001
BMI, kg/m^2	-0.14 (-0.23, -0.04)	0.005
No ST-segment resolution	1.20 (0.09, 2.31)	0.034
Patient characteristics, angiographic data and myocardial edema		
Baseline remote zone ECV, %	-0.62 (-0.76, -0.48)	<0.001
Age, years	0.03 (0.00, 0.07)	0.044
BMI, kg/m^2	-0.13 (-0.22, -0.04)	0.004
Myocardial edema, % of LV mass	0.08 (0.04, 0.11)	<0.001

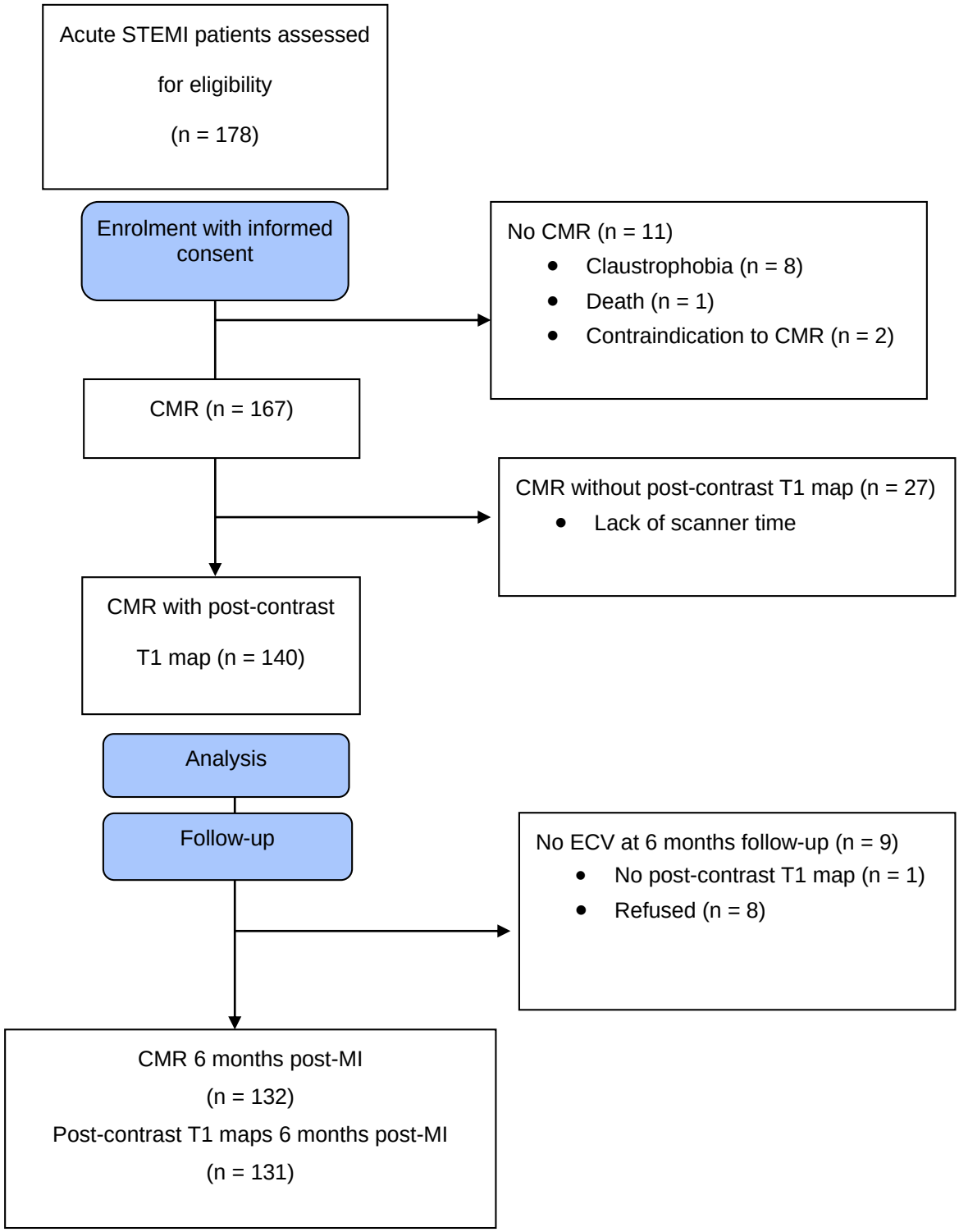
Footnote: Abbreviations: BMI = body mass index, CI = confidence interval, ECV = extracellular volume, LV = left ventricle.

The coefficient (95% confidence intervals) indicates the magnitude and direction of the difference in ΔECV(%) for the patient characteristic (binary or continuous). Lambda = $\Delta R1_{myocardium}/\Delta R1_{blood}$.

Characteristics also included in the model were age (p=0.275), gender (p=0.482), diabetes mellitus (p=0.184), current smoker (p=0.216), hypertension (p=0.767), hypercholesterolemia (p=0.899), previous angina (p=0.646), previous MI (p=0.754), previous PCI (p=0.310), symptom onset to reperfusion time (p=0.260), systolic blood pressure at initial angiography (p=0.626), heart rate (p=0.296), rescue PCI vs. primary PCI (reference category) (p=0.529), TIMI coronary flow grade 2 at initial angiography vs. TIMI coronary flow grade 0/1 at initial angiography (reference category) (p=0.855), TIMI coronary flow grade 3 at initial angiography vs. TIMI coronary flow grade 0/1 at initial angiography (reference category) (p=0.217), sustained ventricular arrhythmia (p=0.240), TIMI coronary flow grade 2 post-PCI vs. TIMI coronary flow grade 0/1 post-PCI (reference category) (p=0.145), TIMI coronary flow grade 3 post-PCI vs. TIMI coronary flow grade 0/1 post-PCI (reference category) (p=0.344), incomplete ST-segment resolution vs. complete ST-segment resolution (reference category) (p=0.355), Killip class II vs. Killip class ((reference category) (p=0.520), Killip class III vs. Killip class I (reference category) (p=0.380), Killip class IV vs. Killip class I (reference category) (p=0.789).

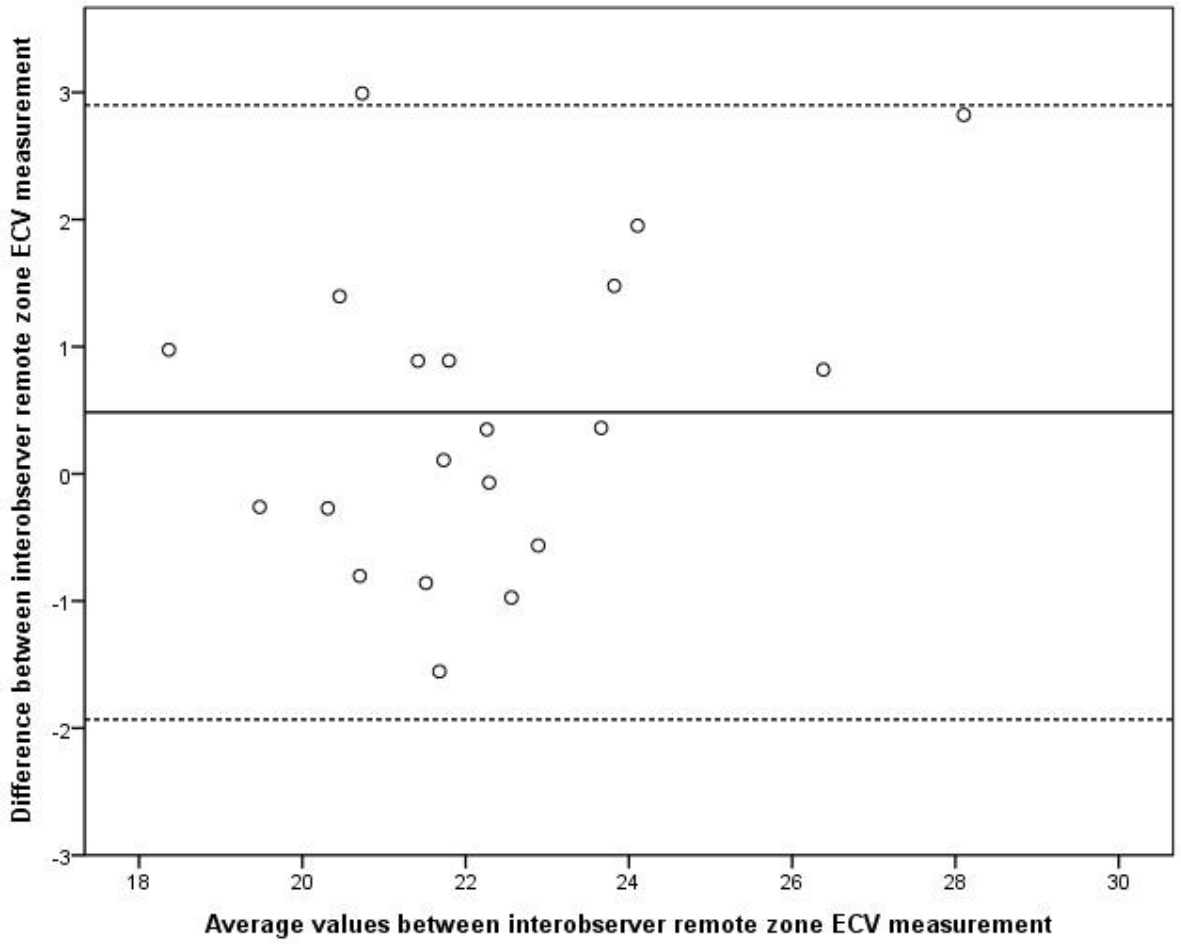
Supplemental Figures

Supplemental Figure S1.



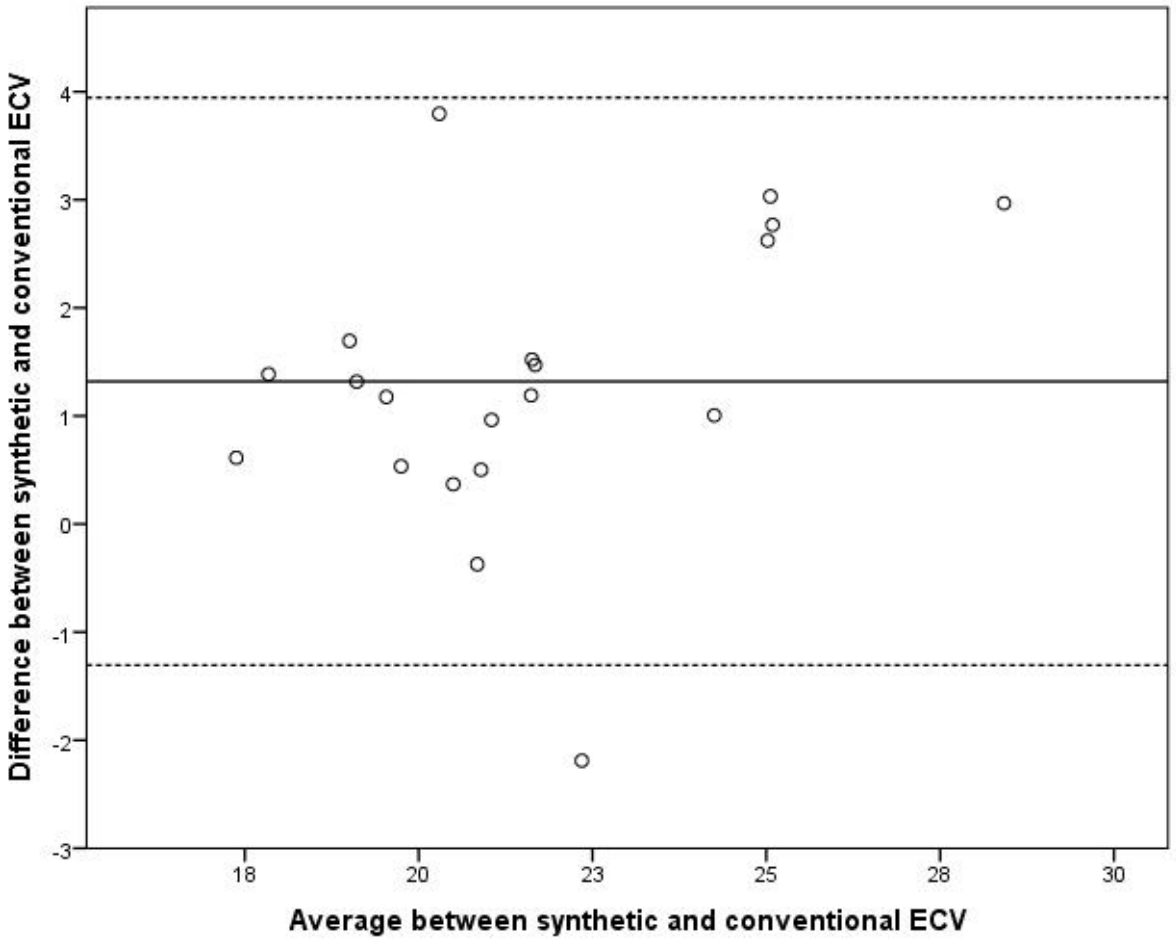
CONSORT flow diagram.

Supplemental Figure S2.



Bland-Altman plot for inter-observer variability in remote zone ECV measurement.

Supplemental Figure S3.



Bland-Altman plot for agreement between conventionally measured ECV and synthetic ECV in 20 healthy volunteers.