European Heart Journal (2009) **30**, 1440–1449
doi:10.1093/eurheartj/ehp093

Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction

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Received 6 November 2008; revised 12 February 2009; accepted 23 February 2009; online publish-ahead-of-print 3 April 2009

See page 1431 for the editorial comment on this article (doi:10.1093/eurheartj/ehp193)

Aims Myocardial haemorrhage is a common complication following reperfusion of ST-segment-elevation acute myocardial infarction (MI). Although its presence is clearly related to infarct size, at present it is unknown whether post-reperfusion haemorrhage affects left ventricular (LV) remodelling. Magnetic resonance imaging (MRI) can be used to identify MI, myocardial haemorrhage, and microvascular obstruction (MVO), as well as measure LV volumes, function, and mass.

Methods and results Ninety-eight patients (14 females, 84 males, mean age: 57.7 years) with MI reperfused with percutaneous coronary intervention (PCI) were studied within the first week (1W) and at 4 months (4M) after the event. T2-weighted MRI was used to differentiate between haemorrhagic (i.e. hypointense core) and non-haemorrhagic infarcts (i.e. hyperintense core). Microvascular obstruction and infarct size were determined on contrast-enhanced MRI, whereas cine MRI was used to quantify LV volumes, mass, and function. Twenty-four patients (25%) presented with a haemorrhagic MI. In the acute phase, the presence of myocardial haemorrhage was related to larger infarct size and infarct transmurality, lower LV ejection fraction, and lower systolic wall thickening in the infarcted myocardium (all *P*-values <0.001). At 4M, a significant improvement in LV ejection fraction in patients with non-haemorrhagic MI was seen (baseline: $49.3 \pm 7.9\%$ vs. 4M: $52.9 \pm 8.1\%$; $P < 0.01$). Left ventricular ejection fraction did, however, not improve in patients with haemorrhagic MI (baseline: $42.8 \pm 6.5\%$ vs. 4M: $41.9 \pm 8.5\%$; $P = 0.68$). Multivariate analysis showed myocardial haemorrhage to be an independent predictor of adverse LV remodelling at 4M (defined as an increase in LV end-systolic volume). This pattern was independent of the initial infarct size.

Conclusion Myocardial haemorrhage, the presence of which can easily be detected with T2-weighted MRI, is a frequent complication after successful myocardial reperfusion and an independent predictor of adverse LV remodelling regardless of the initial infarct size.

Keywords Myocardial infarction • Remodelling • Magnetic resonance imaging • Haemorrhage

Introduction

Timely restoration of myocardial perfusion is the current standard treatment in patients with ST-segment-elevation acute myocardial infarction (MI).[1,2] However, despite successful recanalization of the culprit vessel, studies in animals and patients have frequently shown the presence of myocardial haemorrhage in the infarct core.[3–6] In contrast to non-reperfused infarcts, reperfusion of ischaemic myocardium with irreversible microvascular damage may cause [intra]myocardial haemorrhage with massive red blood cell extravasation into the extravascular space. This phenomenon is associated with longer duration of coronary artery occlusion, severity of flow depression before reperfusion, and extent of necrosis.[6,7] Myocardial haemorrhage has been

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observed after pharmacological reperfusion and mechanical reperfusion.[4–8] Although a few studies showed lack of functional recovery in haemorrhagic infarcts, at present it is unknown whether myocardial haemorrhage is an independent predictor of left ventricular (LV) remodelling.[7,8]

Several studies both *in vivo* and in cadaver hearts have shown the potential of using T2-weighted magnetic resonance imaging (MRI) to depict myocardial haemorrhage, using the paramagnetic properties of haemoglobin breakdown products.[8–15] Deoxyhaemoglobin in the haemorrhagic myocardium causes shortening of T2-relaxation times, and thus may provide a non-invasive approach to detect and quantify myocardial haemorrhage. In the present study, we examined the relationship between post-reperfusion myocardial haemorrhage and post-infarction LV remodelling with a comprehensive MRI approach. We hypothesized that the presence of myocardial haemorrhage causes more damage to the myocardial ultrastructure, eventually leading to adverse LV remodelling.

Methods

Patient population

Patients with acute ST-elevation MI were prospectively enrolled between May 2005 and December 2007. Patients were included if they were older than 18 years, had cumulative ST-segment elevation of $\geq$6 mm, epicardial reperfusion after primary percutaneous coronary intervention (PCI) within 12 h after symptoms onset, and evidence of significant LV dysfunction (hypokinesia or akinesia, involving more than half of the anterior, septal, lateral, or inferior wall at angiography, or involving three contiguous segments or more at echocardiography). Exclusion criteria included pulmonary oedema, cardiogenic shock, prior coronary artery bypass grafting, previous myocardial infarct, and major co-morbidities limiting life expectancy. We obtained written informed consent from all patients, and the study was approved by the Ethics Review Board of the University Hospital Leuven, Belgium.

Magnetic resonance imaging protocol

Patients underwent cardiac MRI studies in the first week (1W) and at 4 months (4M) after the initial presentation. All MRI studies were performed on a 1.5 T system (Intera, Philips Medical Systems, Best, The Netherlands; maximum gradient amplitude: 30 mT/m; maximum slew rate: 220 μs rise time) using commercially available cardiac MRI software, electrocardiographic triggering, and cardiac-dedicated five-element phase-array coil. All patients were positioned in supine position. After the determination of the cardiac axes with localizers, the global and regional LV functions were assessed using breath-hold steady-state free-precession cine MRI in the cardiac short axis, vertical and horizontal long axes (*Figure 1*). In the cardiac short-axis direction, the LV was completely encompassed by contiguous 8 mm thick slices. Imaging parameters were as follows: TR: 3.6 ms; TE: 1.8 ms; flip angle: 60°; slice thickness: 8 mm; matrix: 160 × 256; field of view: 300 mm; pixel size: 1.6 mm/1.6 mm; number of phases: 30. Next, T2-weighted MRI was performed in cardiac short-axis direction using a dark-blood T2-weighted short-tau inversion-recovery (STIR) fast-spin echo (FSE) sequence. Imaging parameters were TR: two heart beats; TI: 180 ms; TE: 100 ms; turbo factor: 33; matrix: 160 × 256; field of view: 350 mm; slice thickness: 8 mm. Finally, a breath-hold, T1-weighted, three-dimensional, contrast-enhanced, inversion-recovery gradient-echo sequence was used to depict the presence of microvascular obstruction (MVO) and myocardial infarct. Imaging parameters were as follows: TR: 4.5 ms; TE: 1.3 ms; flip angle: 15°; 20 contiguous slices, slice thickness: 5 mm; matrix: 128 × 256; field of view: 350 mm; pixel size: 1.4 mm/1.4 mm. An intravenous contrast dose of 0.2 mmol/kg gadopentetate dimeglumine was used. Images were obtained in cardiac short axis and in both long axes. The presence and extent of MVO were evaluated on early post-contrast images obtained in the first 5 min after contrast administration, and late post-contrast images (i.e. after 10–25 min) were used to evaluate myocardial infarct extent.[16] The inversion time was individually adapted to suppress the signal of normal myocardial tissue.

Image analysis

All MRI studies were analysed on an off-line workstation (ViewForum, Philips Medical Systems). For the evaluation of global LV function and myocardial mass, endocardial and epicardial borders were manually traced in end-diastolic and end-systolic short-axis slices. End-diastole and end-systole were defined as the largest and smallest LV cavity, respectively, determined at the mid-ventricular short-axis level. Papillary muscles and trabeculations were not included in the myocardium. End-systolic volumes were corrected for longitudinal LV shortening, excluding atrially located short-axis slices at the end-systole from analysis. Summation of delineated slices yielded LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes from which ejection fraction was derived. Myocardial mass was obtained by multiplying myocardial volume by the specific density of myocardial tissue (i.e. 1.05 g/mL). To quantify regional myocardial morphology and function, a three-compartment approach (infarct, adjacent, remote) was obtained by merging cine and post-contrast-enhanced images, as described more extensively elsewhere.[16–18] The location and extent of late myocardial enhancement were used to define the 'infarcted' myocardium on the corresponding short-axis cine MR images. For the entire infarct territory, a single value on end-diastolic, end-systolic wall thickness and systolic wall thickening was calculated. Next, the 'adjacent' peri-infarct territory was defined using an arbitrary angle of 30° on both sides of the infarcted myocardium on all slices showing late myocardial enhancement. In the longitudinal ventricular direction on the first slice of non-enhanced myocardium, the myocardium in immediate contact with the enhanced myocardium was considered adjacent too, whereas the remaining myocardium was considered 'remote'. For both regions, single values were obtained for the aforementioned morphological and functional parameters. T2-weighted STIR FSE images were used to quantify the myocardial area at risk[19,20] and to determine the presence of myocardial haemorrhage in the ischaemic myocardium. In the LV myocardial wall supplied by the infarct-related artery, myocardial tissue with a signal intensity 2 standard deviations (SD) above the mean signal obtained in the remote non-infarcted myocardium was considered area at risk.[20] Increased signal intensity from the blood pool adjacent to the endocardium 'slow flow' was excluded. Myocardial haemorrhage was defined as a hypointense area in the centre of the area at risk having a mean signal intensity 2 SD below the signal intensity of the periphery of the area at risk, having a minimal volume of 1 mL (1 cm^3) (*Figures 2* and *3*).[10,11] For the area at risk calculations, the haemorrhagic area was included in the area at risk. Microvascular obstruction was defined on early-contrast images as a hypointense zone in the infarct-related myocardium. Myocardial infarction was defined on late-contrast images as a hyperintense area. Both were measured by manual tracing of the suspected area in each short-axis slice. Infarct transmurality was calculated as the ratio of mean thickness of enhanced myocardium to mean thickness of the corresponding myocardial wall, multiplied by 100, and expressed in percentage.

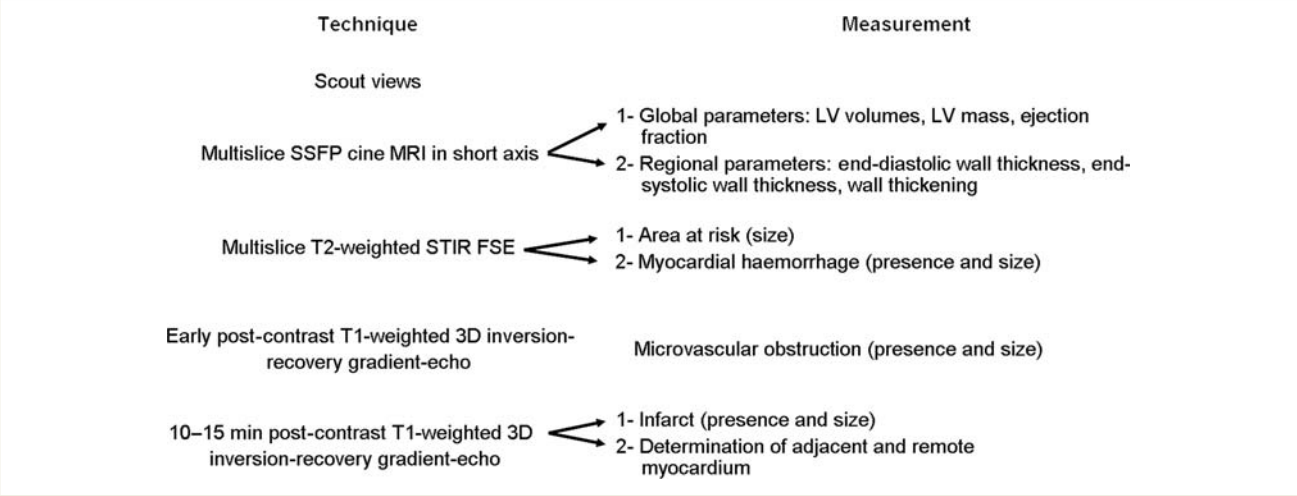

Figure 1 Diagram showing which magnetic resonance imaging techniques were used and which measurements were obtained from each technique.

Statistical analysis

Pre-specified sample-size calculations, based on an expected incidence of myocardial haemorrhage of 20% leading to a difference for the primary endpoint of 8–10% with a common SD of 20%, indicated that 25 patients with myocardial haemorrhage needed to be enrolled to detect a 5% difference with a 5% two-sided significance and 80% power. All quantitative data are expressed as mean ± SD or median and 25th to 75th percentile on the basis of whether they had a normal distribution or not. Comparison between quantitative variables was performed by independent-sample parametric (unpaired Student's *t*-test) or non-parametric (Mann–Whitney) statistical test as appropriate, whereas paired *t*-test was used for comparing results from initial and repeated measurements. Comparison between categorical variables was performed by χ^2 test. Pearson correlation analysis was used to calculate the correlation coefficient between myocardial haemorrhage and infarct size at 1W MRI. Multiple linear regression analysis was performed to determine the independent effect of time to PCI, maximum troponin level, infarct size, size of area at risk, LV mass, infarct location (anterior vs. inferior), and the presence of MVO and myocardial haemorrhage on change in LVESV at 4M. The basic model assumption of normality and constant variance of the residuals were assessed by visual inspection of the residual plots.

All tests were two-sided and performed at the 5% significance level. Because of the exploratory nature of the study, no adjustments for multiple testing were made to the significance level.

Results

Patient characteristics

Of 100 patients who met inclusion criteria, 98 patients with acute MI were studied with cardiac MRI within 1W (median 2 days post-PCI) and at 4M after presentation (*Table 1*). One patient refused to undergo cardiac MRI and one patient did not come back for 4M cardiac MRI study. All the 98 patients had undergone successful revascularization (defined as post-PCI TIMI flow ≥2) with primary PCI within 12 h of symptoms onset (median: 210 min, range: 60–650). The culprit vessel was the left anterior descending, left circumflex, and right coronary artery in 43, 9, and 46 patients, respectively. Myocardial haemorrhage was detected in 24 patients (24%) (*Figure 2*). There was no significant difference in age, time from symptoms onset to revascularization, or history of angina between haemorrhagic and non-haemorrhagic MI patients. However, in the haemorrhagic MI group, there were no women but more smokers, hypertensive and dyslipidaemic patients than in the non-haemorrhagic group. Also, the haemorrhagic infarct group had higher maximal troponin I levels than the non-haemorrhagic group (median: 65.6 μg/L; range: 1.8–282 μg/L vs. 146.0 μg/L, range: 19–619 μg/L; $P < 0.0001$). More patients in the haemorrhagic MI group had pre-PCI TIMI flow 0 or 1 ($P = 0.023$). No differences were found in post-PCI TIMI flow. All patients received glycoprotein IIb/IIIa inhibitors during PCI because this is standard of care at our institution. During 4M follow-up, four patients were re-admitted because of recurrent angina; three of them underwent PCI for restenosis. Four patients were re-admitted for heart failure. No cardiac deaths or re-infarction were noticed during the 4M follow-up period.

Morphological and functional left ventricular and infarct parameters at baseline and at 4 months

Patients with haemorrhagic MI had significantly larger LVEDV, LVESV, LV mass, and lower LV ejection fraction than non-haemorrhagic MI at baseline and at 4M (*Table 2*). Area at risk, infarct size, and the ratio of infarct size to area at risk were significantly larger in the haemorrhagic compared with the non-haemorrhagic group. MVO was present in all patients with haemorrhagic MI and in 39 (53%) of patients with non-haemorrhagic MI. The size of MVO was larger in patients with haemorrhagic MI. Percentage infarct transmurality was significantly higher in the haemorrhagic group both at baseline and at 4M. Myocardial haemorrhage size ranged from 1 to 10 mL (median: 2.8 mL).

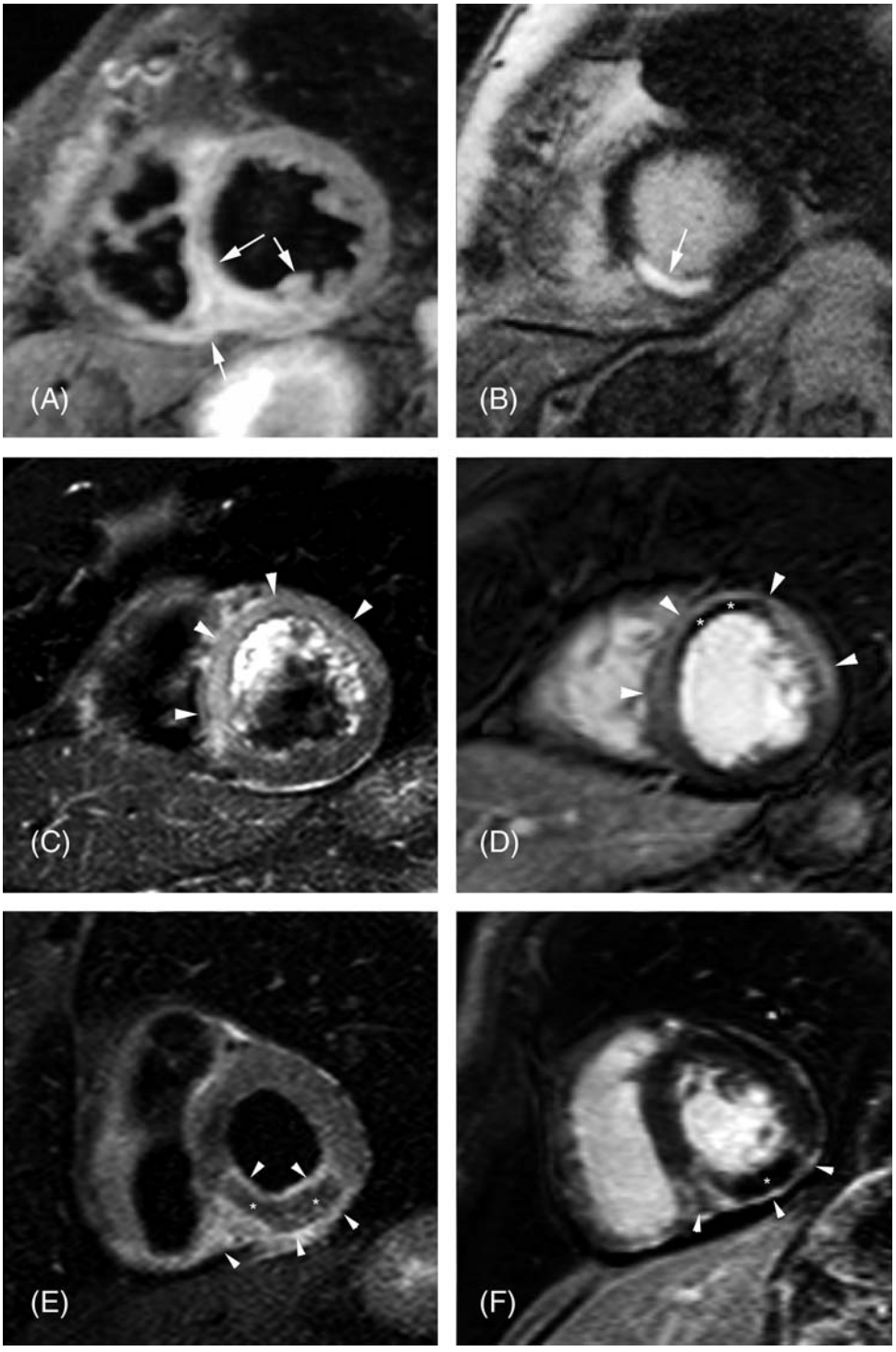

Figure 2 Short-axis T2-weighted (*A*, *C* and *E*) and contrast-enhanced (*B*, *D* and *F*) magnetic resonance images in three patients with acute myocardial infarction. Panels *A* and *B* show matched short-axis views of a patient with an inferoseptal myocardial infarction. High signal intensity on the inferoseptal myocardial segments extending to the inferior right ventricular wall corresponding to the area at risk with myocardial oedema can be seen in panel *A* (arrows). Almost transmural necrosis on the same myocardial segments without evidence of microvascular obstruction (panel *B*, arrows). Panels *C* and *D* show images from a patient with acute anteroseptal myocardial infarction and microvascular obstruction. High signal intensity on the anteroseptal myocardial segments corresponding to myocardial oedema is seen in panel *C* (arrowheads). Early contrast-enhanced images show a hypointense area in the core of the infarct corresponding to microvascular obstruction (panel *D*, asterisks). Panels *E* and *F* show images from a patient with acute inferior myocardial infarction with myocardial haemorrhage and microvascular obstruction. Myocardial haemorrhage is visible as a central hypointense area (panel *E*, asterisks) within the area of myocardial oedema that extends into the right ventricle (panel *E*, arrowheads). Panel *F* shows a large area of transmural necrosis (arrowheads) with a large core of microvascular obstruction (asterisk).

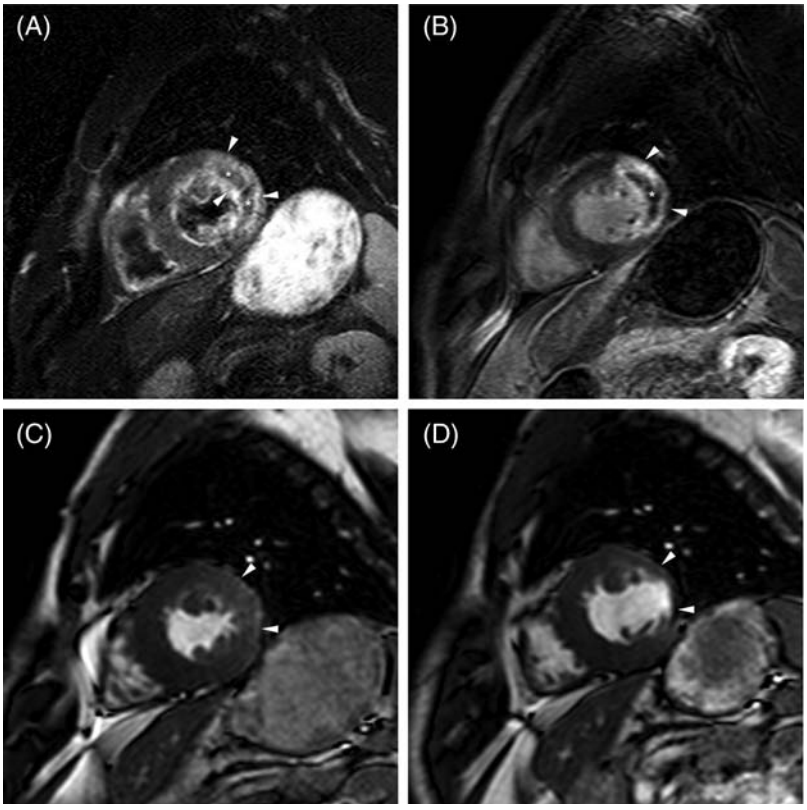

Figure 3 Extensive lateral haemorrhagic infarction in a 48-year-old man. Short-axis T2-weighted magnetic resonance imaging (*A*), contrast-enhanced magnetic resonance imaging at 1 week (*B*), and cine magnetic resonance imaging (end-systolic time frame) at 1 week (*C*) and at 4 months (*D*). T2-weighted magnetic resonance imaging (*A*) shows the area of increased signal intensity in the left ventricular lateral wall (arrowheads), and the presence of a large hypointense core (asterisk) corresponding to an area of myocardial haemorrhage. Contrast-enhanced magnetic resonance imaging at 1 week (*B*) shows complete transmural enhancement of the left ventricular lateral wall (arrowheads) with central area of microvascular obstruction (asterisk). On cine magnetic resonance imaging (*C* and *D*), important thinning of the left ventricular lateral wall between baseline and 4 months can be well appreciated. Important impact on left ventricular ejection fraction (30% at 1 week) without functional recovery at 4 months (31%), and obvious increase in left ventricular end-systolic volume, 116 mL at 1 week to 157 mL at 4 months.

The presence of myocardial haemorrhage correlated with infarct size at baseline ($r = 0.53$; $P < 0.001$).

When comparing data between baseline and 4M, there was a significant improvement in LV ejection fraction in patients with non-haemorrhagic MI (baseline: 49.3 $\pm$ 7.9% vs. 4M: 52.9 $\pm$ 8.1%; $P < 0.01$). Left ventricular ejection fraction did, however, not improve in patients with haemorrhagic MI (baseline: 42.8 $\pm$ 6.5% vs. 4M: 41.9 $\pm$ 8.5%; $P = 0.68$) (*Figure 3*). As parameters of LV remodelling, a significant increase in LVEDV and LVESV was noted in patients with haemorrhagic MI. These parameters did not change significantly between baseline and at 4M in patients with non-haemorrhagic MI. Left ventricular mass and infarct size decreased significantly in both groups between baseline and 4M.

Parameters of regional left ventricular function at baseline and at 4 months

In the haemorrhagic infarct group, systolic wall thickening was significantly lower in the infarct and adjacent myocardium than in the non-haemorrhagic group at baseline (*Tables 3* and *4*). At 4M, a significant improvement was found in the non-haemorrhagic group but not in the haemorrhagic group. At baseline, haemorrhagic MI patients showed a significantly larger end-diastolic wall thickness in the infarcted and adjacent areas, but also a significantly larger degree of wall thinning at 4M follow-up (*Figure 3*). In addition, patients with haemorrhagic MI showed a significant thinning of the remote myocardium.

Predictors of left ventricular remodelling

Multiple regression analysis showed that the presence of myocardial haemorrhage and infarct size at baseline were the strongest independent predictors of adverse LV remodelling at 4M (*Table 5*). Also, maximum troponin I levels, size of MVO, and area at risk were associated with more adverse LV TI: 180 ms remodelling, LV mass, increased degree of infarct transmurality, time to PCI, and infarct location did not influence LVESV. *Figure 4* shows the relationship between haemorrhage and change in LVESV at 4M according to infarct size quartiles. For all

Table 1 Patient characteristics

	Non-haemorrhagic MI ($n = 74$)	Haemorrhagic MI ($n = 24$)	*P*-value
Age (years)	60.0 ± 11.6	57.7 ± 10.7	0.384
Male/female	60/14	24/0	0.017
Diabetes mellitus [*n* (%)]	7 (9)	3 (12)	0.591
Current smoker [*n* (%)]	33 (45)	16 (66)	0.019
Hypertension [*n* (%)]	19 (26)	8 (33)	0.034
Hyperlipidaemia [*n* (%)]	38 (51)	16 (66)	0.021
Number of risk factors [median (IQR)]	2 (1–3)	2 (1–3)	0.530
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2	0.561
Systolic blood pressure at admission (mmHg)	131.4 ± 23.1	129.5 ± 27.1	0.834
Diastolic blood pressure at admission (mmHg)	73.7 ± 16.6	77.8 ± 15.4	0.393
Time to PCI (min) [median (IQR)]	259 (162–485)	279 (168–492)	0.564
TIMI flow before PCI [*n* (%)]			
Grade 0 or I	49 (66)	21 (88)	0.023
Grade II	15 (20)	2 (8)	
Grade III	10 (14)	1 (4)	
TIMI flow post-PCI [*n* (%)]			
Grade II	9 (12)	3 (12)	
Grade III	65 (88)	21 (88)	
Peak troponin I (μg/L) [median (IQR)]	64.0 (30–99)	149.0 (91–312)	<0.001
Peak CK-MB (U/L) [median (IQR)]	184 (92–259)	327 (254–461)	<0.001
Medication at discharge [*n* (%)]			
Aspirin	73 (98)	24 (100)	
Clopidogrel	73 (98)	23 (96)	
Beta-blockers	70 (95)	22 (92)	
Angiotensin-converting enzyme-inhibitors	72 (96)	23 (96)	
Statins [*n* (%)]	70 (95)	23 (96)	

IQR, inter-quartiles.

infarct size quartiles, the presence of myocardial haemorrhage was associated with larger LVESV.

Discussion

Our study shows that myocardial haemorrhage, defined on T2-weighted MRI, occurs in one-fourth of patients with reperfused MI. In the acute phase, the presence of myocardial haemorrhage is associated with larger infarct size and transmurality, larger LV volumes and lower LV ejection fraction, and more impaired contractility in the infarcted and peri-infarct territory. At 4M follow-up, haemorrhagic infarcts show pronounced increase in end-diastolic and end-systolic LV volumes with lack of functional recovery (globally and regionally in the infarcted area), and significant wall thinning in the infarcted, adjacent, and remote areas. The presence of myocardial haemorrhage is an independent predictor of adverse LV remodelling defined as an increase in LVESV at 4M follow-up.

T2-weighted STIR MRI allows the non-invasive detection of myocardial oedema and haemorrhage. T2-weighted sequences are sensitive to water-bound protons and haemoglobin breakdown products. On T2-weighted images, a hyperintense signal intensity indicates tissue oedema. Previous studies have identified this as the spatial extent of the area of myocardium at risk.[19,20] On T2-weighted images, a hypointense signal intensity in the core of the infarct territory indicates the presence of haemorrhage. We used T2-weighted images to detect and quantify myocardial haemorrhage; this approach has been validated both *ex* and *in vivo*.[9–15] Our data agree with these previous findings showing that myocardial haemorrhage can be seen as a distinct hypointense area within the larger area of myocardial oedema in patients with acute MI. It is important to acknowledge that T2-weighted STIR MRI suffers from relatively low contrast resolution, so small areas of myocardial haemorrhage may be missed with this technique. Others have used post-contrast T1 inversion recovery gradient-echo sequence to detect myocardial haemorrhage, which is visible because of haemoglobin-induced susceptibility artefacts as a hyperintense signal within the hypointense area of MVO.[13–15] The accuracy of the latter approach may be hampered by the heterogeneity in the spatial distribution of contrast agent within the infarct.

Myocardial haemorrhage is considered to be a sign of severe microvascular injury.[21] Histologically, it is characterized by vascular cell damage, with leakage of red blood cells from injured vessels affecting mainly the mid-myocardial layer.[6] In the current study,

Table 2 Changes in left ventricular morphological and functional parameters and infarct characteristics in patients with non-haemorrhagic and haemorrhagic myocardial infarct

	Non-haemorrhagic MI ($n = 74$)	Haemorrhagic MI ($n = 24$)	*P*-value
LVEDV (mL)			
Baseline	156.2 ± 31.1	185.4 ± 33.2	<0.001
4M	160.4 ± 36.1	205.6 ± 37.5	<0.001
Difference	4.3 ± 29.1	20.2 ± 27.7	0.01
P-value baseline vs. 4M	0.46	0.005	
LVESV (mL)			
Baseline	79.2 ± 21.1	106.9 ± 23.2	<0.001
4M	75.4 ± 24.2	120.7 ± 29.4	<0.001
Difference	−3.7 ± 19.5	13.9 ± 18.6	<0.001
P-value baseline vs. 4M	0.31	0.01	
LVEF (%)			
Baseline	49.3 ± 7.9	42.8 ± 6.5	<0.001
4M	52.9 ± 8.1	41.9 ± 8.5	<0.001
Difference	3.6 ± 7.1	−0.9 ± 4.9	0.005
P-value baseline vs. 4M	0.01	0.68	
LV mass (g)			
Baseline	117.8 ± 28.1	147.8 ± 33.4	<0.001
4M	107.9 ± 29.4	119.1 ± 23.2	0.09
Difference	−9.9 ± 19.0	−28.7 ± 25.6	0.005
P-value baseline vs. 4M	0.03	0.001	
Area at risk (g)	36.4 ± 20.5	60.7 ± 25.0	<0.001
Infarct size			
Baseline	18.5 ± 12.5	43.1 ± 21.9	<0.001
4M	9.9 ± 7.6	22.3 ± 8.7	<0.001
Difference	−8.7 ± 8.0	−21.7 ± 16.2	<0.001
P-value baseline vs. 4M	0.001	0.001	
Infarct size/area at risk (%)	51.4 ± 21.9	73.9 ± 21.9	<0.001
MVO (g)	6.0 ± 4.6	18.9 ± 16.8	<0.001
Infarct transmurality (%)			
Baseline	75.3 ± 21.1	97.1 ± 4.2	<0.001
4M	65.7 ± 22.6	93.2 ± 10.7	<0.001
Difference	−9.7 ± 13.7	−5.7 ± 1.0	0.01
P-value baseline vs. 4M	0.001	0.07	
Infarct size/LV mass (%)			
Baseline	15.8 ± 11.2	28.9 ± 12.2	<0.001
4M	9.2 ± 7.3	19.2 ± 8.4	<0.001
Difference	−6.6 ± 6.8	−9.7 ± 7.5	0.02
P-value baseline vs. 4M	0.001	0.001	

All values are mean ± standard deviation.

patients with myocardial haemorrhage had lower pre-PCI TIMI flow, larger infarct size, and higher peak troponin values. Although experimental and clinical data have shown the presence of myocardial haemorrhage to be related to a longer time to reperfusion as well as extensive and progressive myocardial and microvascular damages,[4–7] in the current patient group there was no significant difference in time from symptoms onset to revascularization between haemorrhagic and non-haemorrhagic MI patients. This suggests that ischaemia duration is not the only determinant of infarct and haemorrhage size. It may be argued that a severe and prolonged initial ischaemic insult may lead to myocardial haemorrhage, which represents a late event in the course of MI occurring at a time of irreversible myocardial damage. Interestingly, myocardial haemorrhage is not seen in non-reperfused infarcts, hence

Table 3 Regional systolic wall function in infarcted, adjacent, and remote myocardia in patients with haemorrhagic and non-haemorrhagic myocardial infarct

	Non-haemorrhagic MI ($n = 74$)	Haemorrhagic MI ($n = 24$)	*P*-value
Systolic wall thickening in infarcted area (%)			
Baseline	22.5 ± 15.3	9.4 ± 8.4	<0.001
4M	29.2 ± 19.4	10.0 ± 7.2	<0.001
Difference	6.7 ± 9.7	0.6 ± 4.5	0.01
P-value baseline vs. 4M	0.001	0.72	
Systolic wall thickening in adjacent area (%)			
Baseline	33.7 ± 15.4	24.6 ± 11.5	0.015
4M	40.2 ± 18.5	31.6 ± 13.6	0.154
Difference	6.5 ± 8.4	7.0 ± 10.1	0.726
P-value baseline vs. 4M	0.001	0.51	
Systolic wall thickening in remote area (%)			
Baseline	50.7 ± 17.6	55.8 ± 28.4	0.317
4M	51.9 ± 17.7	56.7 ± 23.4	0.339
Difference	1.2 ± 8.4	0.9 ± 14.3	0.872
P-value baseline vs. 4M	0.83	0.71	

All values are mean ± standard deviation.

Table 4 Regional end-diastolic wall thickness in infarcted, adjacent, and remote myocardia in patients with haemorrhagic and non-haemorrhagic myocardial infarct

	Non-haemorrhagic MI ($n = 74$)	Haemorrhagic MI ($n = 24$)	*P*-value
End-diastolic wall thickness in infarcted area (mm)			
Baseline	7.9 ± 1.5	8.8 ± 2.1	0.037
4M	6.8 ± 1.2	6.0 ± 1.1	0.028
Difference	−1.1 ± 0.6	−2.8 ± 1.1	0.001
P-value baseline vs. 4M	0.001	0.001	
End-diastolic wall thickness in adjacent area (mm)			
Baseline	7.7 ± 1.2	8.6 ± 2.0	0.019
4M	7.1 ± 1.3	7.0 ± 1.2	0.753
Difference	−0.6 ± 0.6	−0.4 ± 0.3	0.167
P-value baseline vs. 4M	0.001	0.001	
End-diastolic wall thickness in remote area (mm)			
Baseline	7.1 ± 1.2	7.6 ± 1.9	0.106
4M	6.9 ± 1.1	6.7 ± 1.0	0.541
Difference	−0.2 ± 0.1	−0.9 ± 0.4	0.035
P-value baseline vs. 4M	0.34	0.01	

All values are mean ± standard deviation.

Table 5 Results of multiple linear regression of left ventricular remodelling

Predictors of endpoint	95% CI	R^2	*F*-value	*P*-value
Haemorrhagic MI	0.15–0.31	0.17	20.19	<0.001
Infarct size at baseline	20.84–27.73	0.16	18.11	0.001
MVO	5.03–9.31	0.12	13.13	0.001
Maximum troponin I	91.91–142.60	0.10	10.75	0.001
Size of area at risk	37.02–46.51	0.09	9.12	0.003
LV mass at baseline	118.62–131.44	0.02	2.31	0.132
Per cent MI transmurality	78.64–87.20	0.03	3.39	0.068
Infarct location	0.37–0.58	<0.01	0.41	0.892
Time to PCI	241.18–305.63	<0.01	0.02	0.874

MI, myocardial infarct; PCI, percutaneous coronary intervention; LV, left ventricular; CI, confidence interval; MVO, microvascular obstruction.

restoration of flow through the occluded vessel appears to be a prerequisite for haemorrhagic infarct.[7] In addition, experimental data showed that myocardial haemorrhage expands gradually after reperfusion, suggesting the coronary microvascular damage may progress for several hours after the restoration of coronary flow.[22] This had led to the assumption that myocardial haemorrhage is part of the ischaemia–reperfusion injury phenomenon. Whether haemorrhage is simply a marker or a contributor to ischaemia–reperfusion injury remains a matter of debate.[23] Studies looking at the relationship between temporal changes in myocardial perfusion, viability, and myocardial haemorrhage might help clarify this issue.

In agreement with previous studies, we found a significant association between the presence of myocardial haemorrhage and the extent of MVO.[8,15] In our study, myocardial haemorrhage was always associated with MVO, and the extent of MVO was significantly larger in the haemorrhage group. Although it may be criticized that we are basically looking at the same phenomenon with different MRI techniques, it can be hypothesized that myocardial haemorrhage and MVO represent distinct events of different importance occurring during the reperfusion (injury) phenomenon. Of note, 15 out of 39 patients with MVO did not show myocardial haemorrhage (*Figure 2C* and *D*). Whether severe ischaemia–reperfusion injury with extravasation of red blood cells to the interstitial compartment and haemorrhage leads to swelling of the myocardial wall and compression on the microvasculature, creating or worsening microvascular damage, or whether MVO leads to endothelial damage and subsequent leakage of blood cells to the interstitium remains to be determined.[23,24]

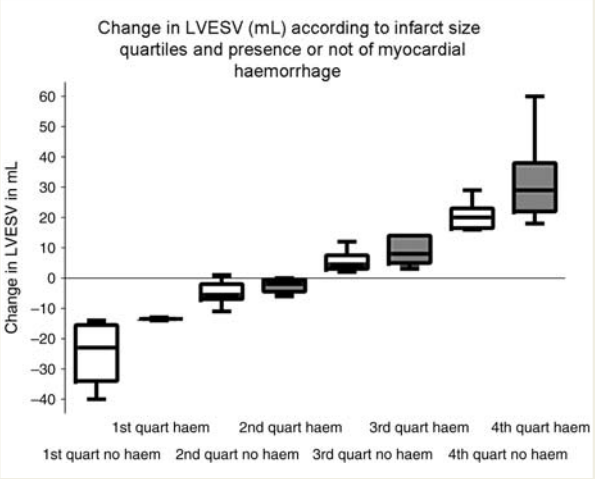

Figure 4 Box-and-whisker plot of the change in left ventricular end-systolic volume at 4 months after myocardial infarct for the different quartiles of infarct size at baseline and for the presence of myocardial haemorrhage or not. For all quartiles of infarct size, a larger increase in left ventricular end-systolic volume is seen in patients with myocardial haemorrhage.

An interesting finding is the increased LV mass and wall thickness in the infarct and adjacent myocardium at baseline MRI in the haemorrhagic infarct group, suggesting more extensive myocardial oedema in this group. Post-reperfusion myocardial oedema is caused by capillary leakage as well as cell swelling,[25] and may contribute to the death of cardiomyocytes, which otherwise would have survived the ischaemic insult. Increased tissue turgor causes capillary compression and will lead to further flow reduction and ischaemia not only in the infarct core but also in the surrounding myocardium,[26] thus involving segments that were initially not compromised. This might be an important trigger for adverse LV remodelling.

At 4M follow-up, the divergence both morphologically and functionally between haemorrhagic and non-haemorrhagic infarcts is obvious. Haemorrhagic infarcts showed adverse remodelling as indicated by increase in LVESV and LVEDV and lack of improvement in LV ejection fraction. Patients with haemorrhagic MI showed a larger reduction in LV mass than patients with non-haemorrhagic MI (−29 vs. −10 g) despite a larger increase in LVEDV (20 vs. 4 mL). This can be explained by the significant wall thinning in all myocardial segments seen in patients with haemorrhagic MI. The more extensive wall thinning in the infarcted myocardium in the haemorrhagic infarct group can be explained by the greater infarct transmurality at baseline and resorption of myocardial oedema,[27,28] unfavourably contributing to increased wall stress in the non-infarcted myocardium. Probably, the wall thinning in the adjacent and remote myocardia in the haemorrhagic infarcts reflects adverse remodelling of the non-infarcted myocardium.

Clinical implications

Because myocardial haemorrhage predicts adverse LV remodelling, treatment strategies aimed to reduce microvascular and endothelial damages and LV dilatation might be useful to improve these patients' long-term prognosis.[23] Studies looking at the effect of agents that enhance mitochondrial or endothelial function such as nitric oxide donors, calcium channel blockers, or adenosine are warranted.[24] Cardiac MRI provides a comprehensive non-invasive characterization of MI because it provides information on LV volumes, global and regional systolic functions, as well as quantification of infarct size and detection of area at risk, MVO, and myocardial haemorrhage. For these reasons, cardiac MRI appears as the ideal tool to evaluate the effect of these novel therapeutic approaches.

Study limitations

A main limitation of our study is the lack of pathological correlation whereby the true presence of myocardial haemorrhage could be proved. However, the accuracy of T2-weighted MRI in the diagnosis of myocardial haemorrhage has been documented in experimental *ex-* and *in vivo* studies. Moreover, it is unlikely that other substances or tissue changes such as fibrosis or calcifications could cause the hypointense signal in the infarcted area because none of the patients in this study had a history or evidence of prior infarction. Care should be taken when extrapolating current results to patients receiving thrombolytic therapy. Previous data have, however, shown that myocardial haemorrhage is present after thrombolysis as well.[7] Because T2-weighted MRI has limited signal-to-noise ratio, it is sometimes difficult to visualize the area of myocardial haemorrhage accurately. This may lead to underestimating of the true area of myocardial haemorrhage or even misclassifying some haemorrhagic MIs. Improvements in sequence design or imaging at higher magnetic fields strength with higher contrast resolution like 3T are being investigated and might lead to higher accuracy in, and possibly incidence of, the detection of myocardial haemorrhage.[29]

Conclusions

Myocardial haemorrhage, whose presence can easily be detected using T2-weighted MRI, is a frequent complication after successful mechanical reperfusion of acute MI. Its presence is associated with larger infarct size, increased ventricular volumes, and lack of functional recovery. Moreover, since myocardial haemorrhage is an independent predictor of adverse LV remodelling regardless the initial infarct size, depiction of myocardial haemorrhage using T2-weighted MRI is warranted.

Acknowledgements

We want to thank Belmans for her advice on the Statistical analysis section.

Funding

This study was partially funded by FWO grant G.0613.09.

Conflict of interest: none declared.

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