MRI-defined areas of microvascular obstruction (MVO) after acute myocardial infarction represent microvascular destruction and haemorrhage.


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ABSTRACT

Aims and Background
Lack of Gadolinium-contrast wash-in on first-pass perfusion imaging, early gadolinium-enhanced imaging or late gadolinium-enhanced (LGE) cardiovascular magnetic resonance (CMR) imaging after revascularized ST-elevation Myocardial Infarction (STEMI) is commonly referred to as microvascular obstruction (MVO). Additionally, T2 weighted imaging allows for the visualization of infarct-related oedema and intramyocardial haemorrhage (IMH) within the infarction. However, the exact histopathological relation of the contrast-devoid core and IMH is unknown.

Methods
In 8 Yorkshire swine, the circumflex coronary artery was occluded for 75 minutes by balloon catheter. After 7 days, CMR cine imaging, T2 weighted turbospinecho and LGE was performed. CMR images were compared to histological findings after phosphotungstic acid-haematoxylin and anti-CD31/Hematoxylin staining. These findings were compared to CMR findings in 27 consecutive PCI-treated STEMI-patients, using the same scanning protocol.

Results
In the porcine model, the infarct core contained extensive necrosis and erythrocyte extravasation, without intact vasculature and hence, no microvascular obstruction. The surrounding -Gadolinium-enhanced- area contained granulation tissue, leukocyte infiltration and necrosis with morphological intact microvessels containing microthrombi, without erythrocyte extravasation. Areas with IMH (median size 1.92 [0.36-5.25] cm³) and MVO (median size 2.19 [0.40-4.58] cm³) showed close anatomic correlation (ICC=0.85, r=0.85, p=0.03). Of the 27 STEMI-patients, 15 had IMH (median size 6.60 [2.49-9.79] cm³) and 16 had MVO (median size 4.31 [1.05-7.57] cm³). Again, IMH and MVO showed close anatomic correlation (ICC=0.87, r=0.93, p<0.001).

Conclusion
The contrast-devoid core of revascularized STEMI contains extensive erythrocyte extravasation with microvascular damage. Attenuating the reperfusion-induced haemorrhage may be a novel target in future adjunctive STEMI treatment.

Key words: cardiovascular magnetic resonance imaging; microvascular obstruction; intramyocardial haemorrhage; histopathology; reperfusion injury.
INTRODUCTION

Although angioplasty in STEMI restores epicardial coronary flow, the microvascular perfusion may still be inadequate. This can be demonstrated by diminished myocardial blush or decreased epicardial flow after angioplasty, commonly referred to as angiographic no reflow(1,2) and is known to be associated with increased morbidity and mortality(3-6). Animal models of myocardial infarction have shown that 20 minutes after reperfusion, areas of no reflow contain capillaries plugged by erythrocytes, platelets and fibrin thrombi, and swollen intraluminal endothelial protrusions, leading to further obstruction of the capillaries and the formation of microthrombi(1,2,7), which are thought to play an important role in the development of the no reflow phenomenon. Additionally, the hypoxia disrupts the endothelial barrier and damages the microvasculature, facilitating extravasation of blood cells upon reperfusion, causing intramyocardial haemorrhage(5,8).

Contrast-enhanced CMR is a non-invasive technique that allows for the accurate visualization of regions with microvascular damage within the infarcted area. Because of strongly impaired myocardial perfusion, contrast wash-in into these areas is severely impaired. (9,10). As a result, they can be seen as contrast devoid, low signal intensity regions within the high signal intensity infarcted areas. Slow contrast wash-in and low contrast concentration can be demonstrated with a number of CMR techniques: first pass imaging (image acquisition during contrast injection), early gadolinium enhancement (<2-3 minutes after contrast injection) and late gadolinium enhancement (LGE, >5-10 minutes after contrast injection)(11,12). Although LGE is generally slightly less sensitive for the detection of microvascular damage due to slow but on-going contrast wash-in, it was shown to have the greatest clinical significance in predicting functional recovery(11-13). Additionally, pre-contrast T2 weighted CMR imaging allows for the visualization of infarct-related oedema and reperfusion-induced intramyocardial haemorrhage (IMH)(14-17). In haemorrhage, local accumulation of paramagnetic haemoglobin breakdown products leads to shortening of T2 relaxation times, resulting in attenuation of the high signal intensity of infarct-related oedema(14,18-21). The exact clinical relevance of these hypointense zones and their correlation with MVO remains debated. Some studies showed that these phenomena were closely related(14,16,19,21,22), while others claim that, in addition, hypointense zones on T2 weighted images reflect a more severe form of reperfusion injury(23,24) and that its presence is related to an additional increase in infarct size and subsequent increase in morbidity and mortality(25). Although these studies focused on the clinical value of MVO and IMH to predict functional recovery, the exact histopathological relation of these two findings remains debated(20,21,26). We investigated the histological correlate of the CMR findings of IMH and MVO in a porcine model of coronary occlusion-reperfusion and compared this to CMR data performed in STEMI-patients.
METHODS

Porcine model
Approval was obtained from the local Animal Ethics Committee. Eight female Yorkshire swine (median age 83 [68-90] days, median weight 29 [24-35] kg), were treated with 400mg amiodarone 7 days before intervention. At the start of the procedure, 400 mg amiodarone, 5-15 mg metoprolol and 5000 IU heparin were given, followed by induction (ketamine, 10-15 mg/kg, midazolam, 0.5-2 mg/kg and atropine, 0.5 mg IV). Anaesthesia was maintained with sevoflurane (1.2-1.8%), etomidate (15-20 mg), midazolam (0.5 mg/kg/hr), and sufentanyl (6.7 μg/kg/hr). Using a guiding catheter, an over-the-wire balloon was placed in the proximal left circumflex artery and inflated for 75 minutes. Total occlusion was monitored angiographically. After deflation, another bolus of 5000 IU of heparin was given, along with 300 mg acetylsalicylic acid and 300 mg clopidogrel, with daily doses of 80 mg acetylsalicylic acid and 75 mg clopidogrel hereafter. After 7 days, animals were again sedated and intubated (Zolazepam-Tiletamine, 6mg/kg, Virbac, Carros, France and Xylazine, 2 mg/kg). CMR imaging was performed using a clinical 1.5 Tesla scanner (Avanto, Siemens, Erlangen, Germany) with a phased-array cardiac receiver coil. Breath-holds were performed uniformly by pausing the ventilator at the end-expiratory phase.

Patient study
To compare the CMR myocardial tissue characteristics of the porcine model to human CMR myocardial characteristics, 30 consecutive patients between 30 and 75 years old presenting with a first STEMI during the time of the animal study, treated with primary PCI, were asked for participation. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Institutional Review Committee. Main exclusion criteria were hemodynamic instability after PCI, severe comorbidity, and contraindications for CMR. All patients gave written informed consent and underwent CMR between 3-6 days after PCI in a clinical 1.5 Tesla scanner (Avanto, Siemens, Erlangen, Germany), similar to the animal study.

CMR protocol
An identical CMR protocol was used in animals and patients. Cardiac function was assessed with ECG-gated, retrospectively triggered segmented steady-state free precession (SSFP) cine imaging with full short-axis coverage of the left ventricle (LV), starting at the mitral valve annulus and planning contiguous slices through the entire left ventricle. From these images, LV end-diastolic volume, end-systolic volume, stroke volume and ejection fraction were calculated. IMH was visualized using a segmented T2 weighted turbospinecho (T2w) sequence with fat suppression (Short Tau Inversion-Recovery, STIR),
at similar slice positions as the cine images. LGE imaging was performed 10-15 minutes after intravenous administration of a gadolinium-based contrast agent (0.2 mmol/kg Dotarem, Guerbet, Villepinte, France), using a 2-dimensional segmented T1 weighted segmented inversion-recovery gradient echo pulse sequence, again at similar slice positions. Inversion times (TI) were individually adjusted to optimize nulling of unaffected myocardium. Sequence parameters are mentioned in table 1.

<table>
<thead>
<tr>
<th>Table 1: CMR parameters of sequences in the porcine model and patient study.</th>
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<tbody>
<tr>
<td><strong>Sequence - Parameter</strong></td>
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<tr>
<td><strong>Steady-state free precession (SSFP) cine imaging</strong></td>
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<tr>
<td>Spatial resolution (frequency encoding dir.)</td>
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<td>Spatial resolution (phase encoding dir.)</td>
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<td>Percentage phase field of view</td>
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<tr>
<td>Temporal resolution</td>
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<td><strong>Short Tau Inversion-Recovery (STIR)</strong></td>
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<td>Spatial resolution (frequency encoding dir.)</td>
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<td>Field-of-view matrix</td>
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<td>Percentage phase field of view</td>
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<td>Time of repetition (TR)</td>
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<td>Echo Time (TE)</td>
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<td>Inversion time (TI)</td>
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<td><strong>T1 weighted inversion-recovery gradient echo (LGE)</strong></td>
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<td>Spatial resolution (frequency encoding dir.)</td>
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<td>Spatial resolution (phase encoding dir.)</td>
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<td>Echo Time (TE)</td>
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<td>Inversion time (TI)</td>
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CMR analysis

Volumes and function were calculated on the end-diastolic and end-systolic phase of the cine images. Infarct size was calculated on LGE images by using the full-width at half-maximum method and is expressed in grams (27). MVO was identified in LGE images as hypointense recesses within the hyperenhanced myocardium (Figure 1, panel 1/3). The area at risk (AAR) size was calculated from the T2w-images (28). Myocardial tissue with signal intensity of >2 SD from the unaffected myocardium was incorporated. The AAR is expressed in grams. IMH was identified on T2w-images as hypointense areas within the hyperintense signal of infarct-related oedema (Figure 1, panel 2/4). The size of the areas of IMH and MVO was calculated by manual delineation of the hypointense areas on T2w-images (for IMH) and the LGE images (for MVO), respectively, and was expressed in cm². The total volume of IMH and MVO in cm³ was calculated by multiplying the area size with [slice thickness + slice gap]. The volumes were converted to grams of tissue by correcting for the myocardial tissue density (i.e. 1.05 g/cm³). To standardize the CMR

Figure 1: Late Gadolinium Enhancement (LGE) images (top row) compared to weighted turbospinecho (T2w) images (bottom row) in one animal (1 and 2) and one PCI-treated STEMI patient (54-year old male with anterior wall infarction). CMR was performed 5 days after PCI. LGE imaging (3) shows MVO (arrow), consistent with the hypointense area of haemorrhage on T2w-image (4). IMH and MVO are very comparable in size and location and show a close relationship.
parameters, the amounts of IMH and MVO were expressed as a percentage of the total infarcted area. The AAR and total infarct size were expressed as percentage of the LV mass. Delineation of IMH and MVO was performed by consensus of 2 experienced readers (LR, AB). Analysis of MVO and IMH series was performed independently from and blinded to the results of the other techniques. After measurement, the calculated areas of IMH and MVO were compared for size.

**Histopathological analysis**

After CMR imaging, the animals were sacrificed and hearts were transversally cut into short axis slabs (thickness 0.3–1.5 cm). The slabs were photographed for macroscopic assessment of infarct presence and location, and fixated in formaldehyde solution. The macroscopically infarcted area and its surrounding border zone were dissected, embedded in paraffin and subsequently cut into slices of 4 μm. Slices were stained with phosphotungstic acid-haematoxylin (PTAH) to detect the presence and extent of vital and necrotic cardiomyocytes, granulation tissue and fibrosis(29). Two zones were identified in the PTAH slices for tissue analysis. The infarct core was defined as the area containing haemorrhage and positive staining for necrosis, without granulation tissue. The infarct border was defined as the surrounding area containing necrosis and granulation tissue (figure 2, panel 1).

An immunohistochemical stain for CD31, using a mouse anti-pig CD31 antibody (1:80 MCA1746G, Bioconnect, Huissen, the Netherlands) and Envision (Dako REAL™Envision, Dako, Glostrup, Denmark) was performed to assess the presence of endothelium and microthrombi in the two defined regions(30). In both the infarct core and the aforementioned border zone, four adjacent sections [magnification 100x, area 31 × 10^3 μm^2] were selected at random per animal. In each section, the number of (micro)vessels and thrombi was counted. From the section size and the average number of vessels and thrombi per section, the number of vessels and thrombi per mm^2 was estimated for the infarct core and the border zone.

For comparison of the histopathological images and the CMR images, the histopathological slices were matched with the CMR images by consensus of 4 experienced readers (LR, MJ, NR, AB), using various anatomical landmarks and the slice position in relationship to the mitral valve annulus and the apex.

**Statistical analysis**

Categorical data are presented as frequencies (percentage) and continuous data as mean±SD or median with [IQR]. Log transformation was applied for the area size of IMH and/or MVO to achieve normal distribution for parametric testing. To determine the level of agreement between continuous variables (i.e. MVO size, IMH size and
Chapter 3

Figure 2: Histology of the porcine model (1) shows that the infarct core zone (red frame) is surrounded by a perfused border zone (green frame). The core zone corresponds on late Gadolinium Enhanced (LGE) images (2) with the area known as MVO. Microscopy reveals extensive haemorrhage on PTAH-staining (3, 200x magn.) with a complete loss of the vascular integrity on anti-CD31-staining (4). The border zone corresponds with the enhanced area on LGE (2); this area contains myocyte necrosis, leukocyte influx, and granulation tissue on PTAH (5), with intact vessels on anti-CD31-staining (6, 200x magn., of which some are plugged by microthrombi (arrow)).
general infarct size parameters), intraclass correlation coefficients (ICC, single measures, absolute agreement) were calculated and Bland-Altman plots were made. ICC values of >0.80 were considered very good agreement between the variables. To compare two continuous variables, a Wilcoxon’s signed ranks test or Mann-Whitney U test was used, due to the small number of subjects. All P-values are two-sided and statistical significance was set at p<0.05. Statistical analysis was done with the Statistical Package for Social Sciences software (IBM SPSS Statistics 20 for Windows).

RESULTS

Close correlation of IMH and MVO in the porcine model
The mean infarct size measured on LGE was 7.8±2.5 g. Of the 8 animals, 6 animals showed both IMH and lack of contrast wash-in (MVO); no cases of IMH without areas lacking contrast wash-in or vice-versa were seen. The other two animals did not show either IMH or a lack of contrast wash-in in the infarct core. One animal did not have a substantial infarction (no systolic functional impairment, no contrast enhancement on LGE images, and no haemorrhage on histopathological analysis). The other animal did suffer a substantial infarction, but microscopic analysis of the infarct core showed that the haemorrhagic area was very small (670 x 364 μm) in size.

In the porcine model, no significant relationship was found between the infarcted area (as % of the LV) and the total MVO size for each animal (Spearman’s Rho=0.47, p=0.23). To investigate whether the relationship may exist on a per-slice basis, the correlation analysis was repeated in the 6 animals with MVO for each slice. A total number of 48 slices contained LGE. Within this set, 38 slices contained MVO within the enhanced area. The median amount of LGE enhanced myocardium was 15 [9-22] % of the total slice and the median size of the MVO area was 5 [4-8] % of the slice. On a per-slice basis, a significant relationship was now seen between the percentage of LGE and the percentage of MVO (Spearman’s Rho=0.51, p=0.001). However, after correcting for a cluster effect by means of a Spearman’s Rho with repeated measures, a Rho of 0.22 with a p-value of 0.32 was found.

There was an excellent anatomical correlation between the localization and extent of MVO and IMH (figure 1). Also, the total amounts of IMH (median size 1.92 [0.36-5.25] cm³) and MVO (median size 2.19 [0.40-5.58] cm³) correlated very well (ICC 0.85, r=0.85, p=0.03, figure 3, panel a).
**Histological characterization**

Haemorrhage was found in 7 out of 8 animals by macroscopic histopathological analysis in the centre of the infarction (figure 2, panel 1). The individual infarct size characteristics are mentioned in table 2a. PTAH staining showed extensive necrosis, cellular debris and large areas of extravasation of erythrocytes in the areas defined as infarct core (figure 2, panel 3). Anti-CD-31 staining of the infarct core revealed an almost complete disruption of vessels (median 0, range 0-2 vessels per animal) and no microthrombi in any section at all, indicating that in these areas, microvessels are no longer present (figure 2, panel 4).

PTAH staining of the border zone showed cellular necrosis and debris, granulation tissue, and granulocytes and monocytes infiltrating the tissue. In this area, almost no extravasation of erythrocytes was seen (figure 2, panel 5). Anti-CD31 staining of the border zone showed a median of 35 [27-44] vessels per animal and 13 [7-17] vessels per section (p=0.02). A median of 10 [7-18] microthrombi were found in the microvasculature per animal and 3 [1-6] microthrombi per section (figure 2, panel 6). The amount of vessels and microthrombi was significantly higher in the border zone compared to the infarct core (infarct core versus border zone compared with Wilcoxon’s signed-rank test; vessels: p=0.02. thrombi: p=0.02. Table 2a, figure 4). Representative images of histology findings are shown in figure 2.

**General characteristics of the patient study**

In 26 STEMI-patients, CMR data sets were available; one patient did not fit in the scanner and 2 patients withdrew consent for CMR after inclusion. Patients had CMR examination 5±2 days after primary PCI. All patients had clinical characteristics of a STEMI (rise in serum cardiac enzyme levels, impaired regional systolic function and contrast enhancement on MRI images. Patients had a mean indexed LV end-diastolic volume of 92±17 ml, indexed LV end-systolic volume of 46±15 ml, LV ejection fraction
of 51±6%, indexed myocardial mass of 59±13 g and infarct percentage of 15±13% of the LV. The general characteristics and the infarct parameters are provided in table 2b.

**CMR tissue characteristics in patients**

In 2 patients, T2w- images were of insufficient quality for analysis. Of the 25 patients with evaluable T2w-images, 15 patients (60%) showed IMH (median amount 6.60 [2.49-9.79] cm³). In 1 patient, a small hypointense region was seen within the hyperintense area of infarct-related oedema, without any signs of MVO on LGE images.
All patients showed regional contrast enhancement on LGE images. Sixteen patients (59%) had MVO (median amount 4.31 [1.05-7.57] cm$^3$) on LGE images. Patients with MVO had larger infarctions (MVO+: 28±17 g; MVO-: 6±5 g, p=0.05) and lower LVEF (MVO+: 48±6%; MVO-: 55±4%, p=0.005) than patients without MVO. In the patient group, a strong correlation between the total amount of MVO (median 2 [1-4] % of the LV) and the total infarct size (median 21 [11-30] % of the LV) was seen, with a Spearman’s Rho of 0.74 (p=0.001). Fourteen patients had both IMH and MVO. When both present, the amounts of IMH and MVO correlated well (ICC 0.87, r=0.93, p<0.001; figure 4, panel b). Visual assessment confirmed that areas of MVO on LGE images and areas of IMH on T2w-images show a very close anatomic relationship (figure 1).

<table>
<thead>
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<th>Parameter</th>
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<td>Age (years)</td>
<td>56 ± 13 years</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>21 (78%)</td>
</tr>
<tr>
<td>Indexed LV end-diastolic volume (ml/m$^2$)</td>
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</tr>
<tr>
<td>Indexed LV end-systolic volume (ml/m$^2$)</td>
<td>46 ± 15 ml/m$^2$</td>
</tr>
<tr>
<td>Indexed LV stroke volume (ml/m$^2$)</td>
<td>46 ± 6 ml/m$^2$</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>51 ± 6 %</td>
</tr>
<tr>
<td>Indexed LV mass (g/m$^2$)</td>
<td>59 ± 13 g/m$^2$</td>
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</table>

**Baseline characteristics of the patient group (n=27).**

LV=Left Ventricle, LGE=Late Gadolinium Enhancement, AAR=Area at Risk, IMH=Intramyocardial Haemorrhage, MVO=Microvascular obstruction. Amounts calculated when present in the subject. Values are mentioned as mean±SD, median with [interquartile range] or absolute number (with percentage).
DISCUSSION

Using an in vivo porcine model of reperfused STEMI, we found that all LGE-defined areas of MVO show haemorrhage on (1) T2w-images, (2) macroscopic histological assessment and (3) microscopic histological assessment, and that areas of MVO and IMH show close anatomical correlation. Histological assessment of these areas show severe disruption of endothelial cells and absence of capillaries and microthrombi, suggesting that the commonly used term ‘microvascular obstruction’ for the lack of contrast wash-in on LGE images might not be completely appropriate. Instead, the area containing contrast enhancement, surrounding the infarct core, showed signs of morphological intact microvasculature with microthrombi and is therefore the ‘true’ anatomical area of microvascular obstruction in the animal model.

When the myocardial tissue becomes hypoxic due to a coronary artery occlusion, the hypoxia disrupts the endothelial barrier and damages the microvasculature, facilitating extravasation of blood cells upon reperfusion(8). Therefore, reperfusion after ischemia is a prerequisite for the presence of IMH(31;32). It seems that haemorrhage and destruction of the vascular integrity are closely related. Although it is most likely that haemorrhage is preceded by destruction of the vascular integrity, it is possible that activation of inflammation and coagulation leads to thrombosis, endothelial activation and subsequent consumption of coagulation factors. The consequent vessel injury by this thrombus formation may aggravate the haemorrhage. As the border of the infarcted area can still receive

Figure 4: On anti-CD31 stained slices, the number of arterial vessels in the core of the infarct zone was strongly reduced as compared to the border zone, using Wilcoxon’s signed rank test (p=0.02).
and produce coagulation factors, this may explain why thrombus formation was found in the border zone. Histopathology of animals with a reperfused myocardial infarction showed haemorrhage as early as 30 minutes to 3 hours after reperfusion, favouring the theory that reperfusion injury is associated with early loss of vascular integrity and subsequent haemorrhage(8;33;34).

It should be noted that vessel injury and subsequent haemorrhage are only one component of reperfusion injury to the heart. Several other processes are considered to contribute, such as leukocyte activation and plugging, vasoconstriction, embolization of thrombotic debris, activation of inflammatory pathways and cellular oedema(5;35).

Studies already stated that regions lacking contrast wash-in -referred to as MVO- can occur without signs of IMH on T2 weighted images(21;25). More recent studies have suggested that these two findings are closely correlated[14;23;24;34;36;37]. Most likely, visible IMH on T2w-images is a reflection of a larger infarction. A certain amount of haemorrhage is needed before the paramagnetic effects are significant enough to cause signal loss on T2w-images. This is in concordance with earlier findings that total infarct size and severity of haemorrhage are closely interdependent(38). A recent study already showed that IMH and MVO show anatomic correlation, but a causal relationship was not established(21). Our findings support these conclusions, but also demonstrate that at one week after reperfused STEMI, MVO and IMH are two CMR manifestations of the same pathophysiologic correlate, reflecting extensive coagulation necrosis with severe disruption of endothelial coherence and erythrocyte extravasation. The pathophysiology of the porcine occlusion-reperfusion model lacks the atherothrombotic component of the coronary occlusion in human acute myocardial infarction. However, the close relation of IMH and MVO in both animals and patients, and the development of MVO in the absence of an atherothrombotic occlusion in the animals suggest an important role for haemorrhage in the occurrence of MRI-defined MVO and its associated adverse ventricular remodelling.

In one patient, a small hypointense region was seen on T2w-images, without MVO on LGE. This may be caused by passive diffusion of contrast agent into the small infarct core, obscuring the presence of MVO on the LGE images. This may also explain why the average size of the IMH area was slightly larger than the average size of the MVO area. Other studies have already demonstrated slow but ongoing contrast wash-in into areas with microvascular injury(11;39). STIR does have some limitations in depicting small amounts of IMH(15), often due to partial volume averaging; oedema-related signal increase combined with haemorrhage-related signal decrease within one voxel leads to an intermediate signal intensity. Since haemorrhage and microvascular destruction are predictors of adverse ventricular remodelling coinciding with an increase in morbidity and mortality(11;12;25;36), assessment of the presence and extent of haemorrhage and
microvascular destruction may be a more appropriate surrogate endpoint for therapeutic strategies than the gross infarct size or the myocardial salvage (index) in future studies.

CONCLUSION

The infarct core on histology, the area of IMH on T2w-images and the area of MVO on LGE show close correlation in size and location. This infarct core contains disrupted microvasculature and large extravasated deposits of erythrocytes, while ‘genuine’ microvascular obstruction is found in the infarct border. Although its clinical significance remains to be established, our results suggest an important role for haemorrhage in the development of myocardial reperfusion injury. We therefore advocate the use of the term ‘microvascular destruction’ or ‘intramyocardial haemorrhage’ for the area with impaired contrast wash-in on LGE images. This implies that future strategies aimed at preserving the vascular integrity(33) may improve the outcome in revascularized STEMI-patients by reducing myocardial haemorrhage.

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CONFLICT OF INTEREST

None declared.
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