Dynamic Edematous Response of the Human Heart to Myocardial Infarction
Implications for Assessing Myocardial Area at Risk and Salvage

**BACKGROUND:** Clinical protocols aimed to characterize the post–myocardial infarction (MI) heart by cardiac magnetic resonance (CMR) need to be standardized to take account of dynamic biological phenomena evolving early after the index ischemic event. Here, we evaluated the time course of edema reaction in patients with ST-segment–elevation MI by CMR and assessed its implications for myocardium-at-risk (MaR) quantification both in patients and in a large-animal model.

**METHODS:** A total of 16 patients with anterior ST-segment–elevation MI successfully treated by primary angioplasty and 16 matched controls were prospectively recruited. In total, 94 clinical CMR examinations were performed: patients with ST-segment–elevation MI were serially scanned (within the first 3 hours after reperfusion and at 1, 4, 7, and 40 days), and controls were scanned only once. T2 relaxation time in the myocardium (T2 mapping) and the extent of edema on T2-weighted short-tau triple inversion-recovery (ie, CMR-MaR) were evaluated at all time points. In the experimental study, 20 pigs underwent 40-minute ischemia/reperfusion followed by serial CMR examinations at 120 minutes and 1, 4, and 7 days after reperfusion. Reference MaR was assessed by contrast-multidetector computed tomography during the index coronary occlusion. Generalized linear mixed models were used to take account of repeated measurements.

**RESULTS:** In humans, T2 relaxation time in the ischemic myocardium declines significantly from early after reperfusion to 24 hours, and then increases up to day 4, reaching a plateau from which it decreases from day 7. Consequently, edema extent measured by T2-weighted short-tau triple inversion-recovery (CMR-MaR) varied with the timing of the CMR examination. These findings were confirmed in the experimental model by showing that only CMR-MaR values for day 4 and day 7 postreperfusion, coinciding with the deferred edema wave, were similar to values measured by reference contrast-multidetector computed tomography.

**CONCLUSIONS:** Post-MI edema in patients follows a bimodal pattern that affects CMR estimates of MaR. Dynamic changes in post–ST-segment–elevation MI edema highlight the need for standardization of CMR timing to retrospectively delineate MaR and quantify myocardial salvage. According to the present clinical and experimental data, a time window between days 4 and 7 post-MI seems a good compromise solution for standardization. Further studies are needed to study the effect of other factors on these variables.
Clinical Perspective

What Is New?

- This work shows for the first time that myocardial edema in the week after ST-segment-elevation myocardial infarction in humans is a bimodal phenomenon.
- An initial wave of edema appears abruptly at reperfusion, but it is significantly attenuated by 24 hours.
- The initial wave of edema is followed by a second (deferred) healing-related wave of edema several days after reperfusion reaching a plateau ≈4 to 7 days after myocardial infarction.
- This bimodal edematous response has a major impact on retrospective myocardial area at risk and salvage quantification by cardiac magnetic resonance given that measures of edema are greatly influenced by the timing of imaging.

What Are the Clinical Implications?

- Both cardiac magnetic resonance imaging techniques and timing of postinfarction imaging for assessing myocardial area at risk and myocardial salvage should be standardized to take account of the pathophysiology of the bimodal edematous phenomenon.
- The time frame between day 4 and 7 postinfarction seems a good compromise solution according to clinical and experimental data here presented.
- Our results have important implications for the design and interpretation of clinical trials using edema-sensitive cardiac magnetic resonance protocols to quantify myocardium at risk and myocardial salvage as an end point.

N oninvasive tissue characterization by cardiac magnetic resonance (CMR) after myocardial infarction (MI) offers the possibility to evaluate the impact of interventions designed to preserve cardiac function and predict long-term remodeling.1 It has been postulated that an intense edematous reaction confined to the posts ischemic region appears early after MI and persists in stable form for at least 1 week.2,3 On the basis of this assumption, the use of edema-sensitive T2-CMR sequences to delineate the spatial extent of post-MI edema was rapidly incorporated as an index of the original occluded coronary artery perfusion territory (myocardium at risk, MaR).4,5 Quantification of late gadolinium enhancement (LGE) and edema extent (assumed to delineate MaR) in the same imaging session has been extensively used to quantify the amount of salvaged myocardium, a theoretical surrogate of the effect of cardioprotective therapies.6,7 thus reducing the required sample size in trials.8 Consequently, CMR-based myocardial salvage has been and continues to be used as an end point in multiple clinical and experimental studies.9

On the basis of the assumed stable unimodal edematous reaction during the first week after MI, the timing of the end point imaging session in these studies varies considerably. However, recent work in the pig model showed that the post-MI edematous reaction is not stable, and instead follows a bimodal pattern.10 An initial reperfusion-related wave of edema appears abruptly on reperfusion and dissipates at 24 hours. This is followed by a healing-related deferred wave of edema appearing several days after MI, peaking around postreperfusion day 7.11 This coordinated bimodal edema pattern suggests that CMR-quantified MaR may vary according to the day of imaging, but to date this has not been tested in a controlled manner. Some recent studies evaluated MaR extent in patients according to the timing of post-MI imaging, but these were either retrospective analyses12 or did not systematically scan patients at the same time points.13 Consequently, whether this phenomenon occurs in MI patients is unclear.

This study was designed to address these specific 2 questions: (1) is post-MI edematous reaction bimodal in humans, and (2) does the bimodal edematous reaction affect the CMR-based quantification of MaR and myocardial salvage? We designed a longitudinal clinical study in which patients with ST-segment-elevation MI (STEMI) successfully treated by primary angioplasty were prospectively recruited and CMR performed within the first 3 hours postreperfusion and at 24 hours, 4 days, 7 days, and 40 days. The impact of the dynamic edematous response on post-MI CMR measures of MaR, infarct size (IS), and salvaged myocardium was evaluated in the pig model of reperfused MI by performing reference measures of MaR and a comprehensive serial CMR imaging study.

METHODS

Clinical Study

Design

Hemodynamically stable consecutive patients with a first anterior STEMI and undergoing primary percutaneous coronary intervention were prospectively recruited between February 2015 and November 2015 ad hoc for this study. Patients eligible for enrollment were aged ≥18 years, and showed symptoms consistent with STEMI for >90 minutes and ST-segment elevation ≥2 mm in ≥2 contiguous leads in V1 through V5, with an anticipated time from symptom onset to reperfusion of ≤8 hours. Additional mandatory inclusion criteria were evidence of complete occlusion in the proximal or mid portion of the left anterior descending coronary artery (TIMI-0–1 initial flow) and successful primary angioplasty evidenced by appropriate reestablishment of coronary flow in the culprit artery (TIMI-3 flow after angioplasty). Exclusion criteria were Killip class III to IV, persistent systolic blood pressure <100 mmHg, persistent heart rate <50 bpm or >110 bpm, presence of bifascicular or trifascicular block, evidence of second or third-degree atrioventricular block, atrial fibrillation, known history of previous MI, pregnancy, active breastfeeding, and the presence of unstable angina or heart failure.
of metallic objects or devices incompatible with MRI. Patients were managed according to current clinical guidelines.14,15 CMR examinations were performed within 3 hours of reperfusion (hyperacute reperfusion) and at 24 hours, 4 days, 7 days, and 40 days after reperfusion (Figure 1A). Normal T2 relaxation times (baseline) were obtained in 16 healthy age- and sex-matched volunteers. The study was approved by the hospital Ethics Committee, and all patients and volunteers gave written informed consent.

CMR Protocol
CMR examinations were conducted with a Philips 1.5-Tesla Achieva whole-body scanner (Philips Healthcare) equipped with a 16-element phased-array cardiac coil. At all time points, the imaging protocol included a standard segmented cine steady-state free-precession sequence to provide high-quality anatomic references; a T2-weighted short-tau triple inversion-recovery (T2W-STIR) sequence to assess the extent of edema and intramyocardial hemorrhage (IMH); and a T2-gradient-spin-echo mapping sequence to provide precise myocardial T2 relaxation time properties.16 On day 7 and day 40 CMR, LGE imaging was performed to assess infarct size and microvascular obstruction (MVO), using a T1-weighted inversion recovery turbo field echo sequence acquired 10 to 15 minutes after intravenous administration of 0.20 mmol gadobutrol contrast agent per kg body weight.

CMR Analysis
CMR images were analyzed using dedicated software (MR Extended Work Space 2.6, Philips Healthcare; and QMassMR 7.6, Medis) by 2 observers experienced in CMR analysis and blinded to time-point allocation and patient identification. T2 maps were analyzed by placing the region of interest at the transmural ischemic, infarcted (with or without including areas suggestive of IMH), salvage, and transmural remote areas in a midapical ventricular short-axis slice corresponding to the same anatomic level in all acquisitions to track T2 relaxation time changes over time.16,17 The extent of edema, expressed as a percentage of left ventricular (LV) mass (CMR-MaR), was initially identified by using the full width at half-maximum with subsequent manual correction and visual border delineation after tracing the endocardial and epicardial contours of T2W-STIR short-axis images.18 Hypointense areas within the edematous zone, corresponding to IMH, were included within the edematous region.19,20 In addition, IMH area was calculated by manual delineation of the hypointense areas on T2W images19 and expressed as a percentage of LV mass.

**IS**, expressed as a percentage of LV mass, was defined according to the extent of LGE after manually tracing the endocardial and epicardial contours on T1-weighted inversion recovery turbo field echo short-axis images. Abnormal areas were defined using the full width at half-maximum, with manual correction if needed. Hypointense black areas within the necrotic zone, corresponding to MVO, were included within the necrotic area.19,20 In addition, the size of the MVO area was calculated by manual delineation of
the hypointense areas on LGE images\(^{19}\) and expressed as a percentage of LV mass.

Detailed information about CMR imaging protocol and parameters, and imaging analysis is presented in the online-only Data Supplement Methods.

**Experimental Study**

**Design and MI Procedure**

The study was approved by Institutional and Regional Animal Research Committees.

To study the impact of the dynamic edematous response on post-MI CMR time profile measures of MaR, IS, and salvaged myocardium, a group of 20 pigs underwent closed-chest reperfused MI by the percutaneous catheter–based technique, with 40-minute angioplasty-balloon occlusion of the mid left anterior descending coronary artery, followed by balloon deflation and reestablishment of blood flow\(^{10}\) (Figure 1B). These pigs were euthanized at 120 minutes (n=5), 24 hours (n=5), 4 days (n=5), or 7 days (n=5) after ischemia/reperfusion (I/R). In all pigs, arterial enhanced multidetector computed tomography (MDCT) was performed during the index coronary occlusion, between minute 10 and minute 20 of ischemia, to delineate the reference MaR (hypoperfused region during coronary occlusion).\(^{21}\) Comprehensive CMR scans were performed at every follow-up stage until euthanization (ie, animals euthanized on day 7 underwent baseline, 120 minutes, 24 hours, day4, and day7 CMR examinations).

Full methods can be found in the online-only Data Supplement Appendix.

**Arterial Enhanced MDCT Protocol and Analysis**

All MDCT studies were performed on a 64-slice CT scanner (Brilliance CT 64, Philips Healthcare) after intravenous administration of 60 ml of 400 mg/mL iomeprol (Iomeron 400, Bracco Imaging).\(^{21}\) MDCT images were analyzed using dedicated software (MR Extended Work Space 2.6, Philips Healthcare). MaR and remote areas were visually identified based on contrast enhancement differences, manually delineated, and expressed as a percentage of LV area.

**CMR Protocol and Analysis**

CMR examinations were conducted with a Philips 3-Tesla Achieva Tx whole body scanner (Philips Healthcare) equipped with a 32-element phased-array cardiac coil. The imaging protocol included an steady-state free-precession sequence to provide high-quality anatomic references, and assessment of LV mass and wall thickness; a T2W-TRI sequence to assess the extent of edema and IMH; a T2-gradient-spin-echo mapping sequence\(^ {10,16}\); and a T1-weighted inversion recovery turbo field echo sequence to assess IS and MVO. CMR images were similarly analyzed using dedicated software (MR Extended Work Space 2.6, Philips Healthcare; and QMassMR 7.6, Medis) by 2 observers experienced in CMR analysis and blinded to group allocation.

Detailed information about MDCT and CMR imaging protocol and parameters, and imaging analysis, can be found in the online-only Data Supplement Methods.

**Statistical Analysis**

In the clinical study, the sample size calculation to detect a difference in T2 relaxation time in the ischemic myocardium between examination time points after STEMI was prespecified by using the user-written command nsize (Stata 12.0). A sample size of 16 patients was determined on the basis of our previous experimental results,\(^ {10}\) a 95% confidence level, a statistical power of 80%, a conservative significant mean difference to detect of 15 ms in T2, a SD of 12, and multiple pairwise comparisons between time points.

Normal distribution of each data subset was checked by using graphical methods and a Shapiro-Wilk test. The Leven test was performed to check the homogeneity of variances. For quantitative variables, data are expressed as mean±SD. For categorical variables, data are expressed as frequencies and percentages. To take account of repeated measures, generalized linear mixed models were conducted to analyze the time course of T2 relaxation time, CMR-MaR, IMH, MVO, IS, and salvaged myocardium. Models evaluating the time course of T2 or CMR-MaR were further adjusted by extent of hemorrhage, including the amount of IMH expressed as a percentage of the LV as a covariate, given that this parameter is known to affect T2. Given the hypothesis-driven nature of the study, comparisons among different time points were planned in advance. Nonetheless, \(P\) value was adjusted for multiple comparisons by using the Hochberg method.

All statistical analyses were performed with Stata v12.0 (StataCorp).

**RESULTS**

**Clinical Study**

**General Characteristics of the Population**

Clinical characteristics of the study population are summarized in Table 1. Serial CMR was performed with informed consent in 16 consecutive patients with anterior STEMI fulfilling the inclusion criteria (mean age 58.8±14.5 years, 14 [87.5%] male) and successfully treated by primary percutaneous coronary intervention. A total of 94 CMR examinations were performed: the 16 healthy volunteers were scanned once, and the 16 patients with STEMI were scanned at 2.2±0.5 hours, 24.8±1.8 hours, 3.8±0.4 days, 6.8±0.6 days, and 41.7±4.3 days after reperfusion. In all patients, the first CMR scan was performed within the first 3 hours (90–180 minutes) after primary percutaneous coronary intervention. The timing for the initial CMR scan (around the peak of reperfusion-related wave of edema) was identified before in a dedicated separate group of 5 pigs undergoing serial CMR scans every 20 minutes during the 6 hours following reperfusion (see online-only Data Supplement Methods and Results, and online-only Data Supplement Figures I and II). Evaluable T2-mapping and T2W-TRI data were available in 100% of CMR scans performed. Information on vital status was available for all participants.
Edema Time Course in Patients With STEMI

T2 Relaxation Time
Mean myocardial T2 relaxation times in the 16 healthy volunteers (mean age 59.3±17.7 years, 12 [75%] male) were 53.1±4.1 ms and 51.1±4.5 ms for the midapical anteroseptal and posterolateral LV walls, respectively. In comparison with these values, hyperacute reperfusion in patients with STEMI (≤3 hours) was associated with significantly longer T2 relaxation times in the ischemic area (Figure 2A and 2B). T2 relaxation time in patients with STEMI showed a systematic and significant decrease at 24 hours post-MI. This was followed by a rebound increase, with T2 relaxation times on day 4 postreperfusion reaching values similar to those observed during early reperfusion. Thereafter, T2 relaxation time progressively decreased, with values on day 40 similar to those observed at 24 hours. Similar results were obtained after adjusting T2 for the amount of IMH observed at different time points (online-only Data Supplement Table I). During the first week after MI, T2 relaxation time in the remote myocardium showed a linear trend toward a progressive increase, albeit slight. T2 relaxation times in the ischemic and remote myocardium at different postreperfusion time points are summarized in Table 2. T2 relaxation time was longer in the transmural ischemic myocardium than in the remote myocardium at all time points evaluated. However, the differences observed at 24 hours and 40 days, albeit statistically significant, were of small magnitude and resulted in a wide overlapping of myocardial T2 values within ischemic and remote areas (Figure 2C). Individual trajectories for T2 relaxation time in the ischemic myocardium of STEMI patients are shown in online-only Data Supplement Figure III.

Extent of Edema (CMR-MaR)
The edematous area delineated by T2W-STIR sequences was similar in CMR scans performed at hyperacute reperfusion (≤3 hours) and on day 4 and day 7 (Figure 3). Conversely, the area of edema was significantly smaller at 24 hours postreperfusion. On day 40 post-MI, the area of edema was comparable to that seen at 24 hours. This time-course pattern for edema resembles that observed for T2 relaxation time, and similar results were obtained after adjusting the area of edema for the amount of IMH evaluated by T2W-STIR (online-only Data Supplement Table II). Edematous area at different postreperfusion time points is summarized in Table 2. Individual patient trajectories for area of edema measurements are shown in online-only Data Supplement Figure IV.

Experimental Study

Dynamics of CMR-MaR After Reperfused MI in Comparison With the Reference Standard
CMR-measured MaR values at different times after reperfusion in pigs are summarized in Table 3 and online-only Data Supplement Table III. Mean MaR as assessed by the MDCT reference method was 30.5±5.0% of the LV. Because of the initial swelling of the ischemic myocardium (online-only Data Supplement Table IV), CMR-measured MaR as delineated by T2W-STIR sequence was significantly higher than MaR measured by MDCT at early reperfusion (Figure 4A and 4B). Coinciding with the dissipation of the first edema wave,² MaR was strikingly underestimated by CMR at 24 hours postreperfusion. Conversely, CMR-estimated MaR values for day 4 and day 7 postreperfusion, coinciding with the deferred edema wave,¹⁰ were similar to values measured by MDCT (ie, no overestimation or underestimation). The dynamics of CMR-measured MaR resembled the time course for myocardial T2 relaxation time and water content in the ischemic area.¹⁰

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.8±14.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1±2.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (56.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (56.3)</td>
</tr>
<tr>
<td>Ex-smoker (0–10 y before)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Ischemia duration, min*</td>
<td>185±115</td>
</tr>
<tr>
<td>Killip class at recruitment</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11 (68.7)</td>
</tr>
<tr>
<td>II</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Infarct artery lesion location</td>
<td></td>
</tr>
<tr>
<td>Proximal left anterior descending coronary artery</td>
<td>16 (100.0)</td>
</tr>
<tr>
<td>Mid left anterior descending coronary artery</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Treatment at the time of primary percutaneous intervention</td>
<td>16 (100.0)</td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td>Oral antplatelet</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>8 (50.0)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Thrombus aspiration</td>
<td>9 (56.3)</td>
</tr>
<tr>
<td>Glycoprotein IIb/III during primary percutaneous intervention</td>
<td>9 (56.3)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or n (%).

*Mean time from symptom onset to reperfusion.
Dynamics of CMR-Measured IS, Myocardial Salvage, IMH, and MVO After Reperfused MI

CMR-measured IS and myocardial salvage in pigs are summarized in Table 3 and online-only Data Supplement Table III. A progressive reduction of IS was observed during the first week after I/R (Figure 4C and 4D). Matching the temporal variations in CMR-MaR, CMR-estimated myocardial salvage quantification [(MaR-IS)/MaR, %] also changed dynamically during the first week after I/R (online-only Data Supplement Figure V).

CMR-estimated IMH and MVO are summarized in online-only Data Supplement Table V. IMH was apparent at 24 hours and peaked on day 4 post-I/R; in contrast, MVO was apparent at 120 minutes after reperfusion, peaking on day 1 post-I/R and progressively decreasing thereafter. The dynamics of CMR-estimated...
IMH are consistent with histologically evaluated IMH in the same model previously reported.11

**DISCUSSION**

**First Demonstration of the Postinfarction Bimodal Edema Reaction in the Human Heart**

This is the first comprehensive evaluation of patients with STEMI by serial CMR to include the hyperacute postreperfusion period (the first 3 hours). CMR scans timing was designed as per the protocol of our previous experimental studies, in which we demonstrated the existence of bimodal post-MI edema in pigs.10,11

The main finding of the present clinical study is that, contrary to the accepted view, myocardial edema in the ischemic area after MI in humans is not stable, but rather follows a systematic bimodal pattern. An initial wave of edema appears abruptly very early after reperfusion, but it is significantly attenuated by 24 hours. This is followed by a second (deferred) wave of edema several days after reperfusion reaching a plateau ≈4 to 7 days after MI.

**The Initial Wave of Edema**

To select the optimal timing for the first CMR scan in STEMI patients, we first analyzed the dynamics of the initial wave of edema in a series of 5 pigs; serial CMR scans were performed every 20 minutes until the reperfusion-related edema wave faded. It is interesting to note that this initial wave of edema peaked very early, being significantly attenuated within a few hours after MI: at 180 minutes after reperfusion, the edema had declined by ≈50% from its maximum. In agreement with CMR data, quantification of myocardial water content and histological analysis at 6 hours after MI revealed partial resolution of the massive interstitial edema seen earlier after reperfusion (see online-only Data Supplement Results).11 On the basis of these results in pigs, we decided to perform the first CMR scan in patients within a narrow 3-hour time window after primary percutaneous coronary intervention to be able to detect the noon of the initial wave of edema.

**Implications of the Bimodal Edema Phenomenon for Quantifying MaR and Salvage**

On the basis of an assumed stable edematous reaction lasting for several days after MI and despite recent controversy,30,31 T2-CMR sequences have been widely used to retrospectively quantify the MaR.6,29 In the present clinical study, we show that T2 relaxation time in the ischemic region changes systematically with the post-MI timing of the examination. In parallel, we confirmed significant variation in the extent of the MaR as measured by T2W-STIR. Consistent with the drop in T2 relaxation time at 1 day post-MI, T2W-estimated MaR at this time point was significantly lower than values obtained before and subsequently.

We experimentally confirmed clinical findings by accomplishing a comprehensive CMR serial imaging study in 20 pigs subjected to reperfused MI. Remarkably, we included prereperfusion MDCT imaging as a reference for the assessment of MaR,21 which otherwise we con-
Bimodal Post-STEMI Edema in Humans

Table 2. CMR Data of Patients

<table>
<thead>
<tr>
<th>Reperfusion Time</th>
<th>≤3 h</th>
<th>24 h</th>
<th>4 days</th>
<th>7 days</th>
<th>40 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 transmural ischemic, ms</td>
<td>80.8 (10.9)</td>
<td>65.4 (5.5)</td>
<td>80.5 (11.3)</td>
<td>76.8 (12.1)</td>
<td>65.4 (7.2)</td>
</tr>
<tr>
<td>T2 transmural remote, ms</td>
<td>52.5 (6.7)</td>
<td>57.2 (6.2)</td>
<td>53.7 (6.2)</td>
<td>58.3 (5.9)</td>
<td>52.9 (8.3)</td>
</tr>
<tr>
<td>T2 infarct incl. hypointense core, ms</td>
<td>80.5 (16.4)</td>
<td>63.0 (9.0)</td>
<td>81.5 (15.3)</td>
<td>76.3 (16.6)</td>
<td>65.2 (8.4)</td>
</tr>
<tr>
<td>T2 infarct excl. hypointense core, ms</td>
<td>87.2 (15.1)</td>
<td>65.2 (8.8)</td>
<td>86.0 (16.6)</td>
<td>81.3 (16.9)</td>
<td>66.4 (7.0)</td>
</tr>
<tr>
<td>T2 salvaged, ms</td>
<td>70.2 (9.7)</td>
<td>64.4 (8.3)</td>
<td>78.5 (14.9)</td>
<td>68.9 (9.5)</td>
<td>62.3 (8.2)</td>
</tr>
<tr>
<td>Myocardial area at risk, % of left ventricle</td>
<td>39.9 (13.0)</td>
<td>21.8 (12.2)</td>
<td>42.8 (11.5)</td>
<td>42.9 (13.0)</td>
<td>20.1 (11.5)</td>
</tr>
<tr>
<td>Intramyocardial hemorrhage, % of left ventricle</td>
<td>0.6 (0.5)</td>
<td>1.1 (0.6)</td>
<td>1.7 (1.4)</td>
<td>1.7 (1.8)</td>
<td>0.7 (0.6)</td>
</tr>
<tr>
<td>Infarct size, % of left ventricle</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>30.3 (14.6)</td>
<td>21.9 (11.9)</td>
</tr>
<tr>
<td>Microvascular obstruction, % of left ventricle</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.7 (2.4)</td>
<td>0.9 (0.8)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). T2 maps were analyzed by placing regions of interests at the transmural ischemic, infarcted (with or without including areas suggestive of intramyocardial hemorrhage), salvage, and transmural remote areas in a midapical ventricular short-axis slice corresponding to the same anatomic level in all acquisitions to track T2 relaxation time changes over time. The different myocardial states were initially defined by the localization relative to late gadolinium enhancement. One patient died between day 4 and day 7 cardiac magnetic resonance, and 1 patient was unable to undergo late gadolinium enhancement imaging because of severe renal impairment; therefore, T2 information from the different myocardial states within the ischemic region was obtained from 14 of 16 patients.

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Considered unethical to perform in patients with STEMI. In the experimental study, our results show that, because of the bimodal pattern of post-IR edema formation, the extent of MaR delineated by T2-CMR varies during the first week after IR. Specifically, the edema-sensitive T2W-STIR CMR sequence overestimates MaR in comparison with MDCT at early time points (120 minutes) after reperfusion, which is in agreement with previous reports. This overestimate is mainly driven by swelling of the perfused myocardium. By 24 hours, the scenario is completely altered, with a substantial resorption of edema and normalization of T2 relaxation time, resulting in systematic underestimation of MaR by CMR. This underestimation resulted in biologically implausible negative myocardial salvage data at 24 hours. This finding reinforces the idea that MaR (and consequently salvaged myocardium) cannot reliably be quantified by CMR around this time point. Conversely, on days 4 and 7, CMR-measured MaR was similar to MaR measured by MDCT.

More pronounced dynamic tissue changes were shown in the experimental model. This is a common phenomenon seen in the experimental setting in which many variables are controlled, as opposed to clinical studies. In addition, the more severe ischemic process in the porcine myocardium in the presence of poor collateral circulation, among other reasons, could influence the magnification of this phenomenon. However, the parallel courses of T2 and CMR-MaR fluctuations observed in the clinical and experimental settings strengthen the message of the present study. Thus, our data suggest that between day 4 and day 7 would be a good compromise solution for the delineation of theoretical MaR.

Nonetheless, our results highlight the need for caution in interpreting CMR of the post-MI heart. In the clinical study, 3 of the 16 patients with STEMI showed more limited changes in T2 and extent of edema (see online-only Data Supplement Figures III and IV). Remarkably, these 3 patients were older and showed significantly smaller infarcts and less extent of IMH and MVO, and greater myocardial salvage areas despite having longer intervals between symptom onset to reperfusion (data not shown). We speculate that there might be several factors affecting the dynamics of the bimodal edematous reaction such as the existence of preformed collateral circulation, episodes of spontaneous reperfusion/reocclusion during ischemia duration, or the presence of specific comorbidities. The impossibility of controlling these aspects in the clinical scenario...
myocardial edema\(^{16}\); however, it is unlikely to alter the dynamic pattern of post-MI edema that is attributable to pathophysiological phenomena. The deferred edema wave is related to the post-MI healing process,\(^{11,32}\) and therefore interventions that protect the myocardium could affect the dynamics of edema, and thus bias MaR estimation. This idea is supported by recent suggestions that the extent of edema can be affected by the degree of damage\(^{9}\) or exposure to infarct-limiting interventions.\(^{33–35}\) However, patients in these studies received 1 CMR examination at a single time point, which was not the same for all. Therefore, a dedicated study would be needed to provide evidence to support this hypothesis.

**IMH Is Not the Main Mechanism Underlying Bimodal Post-MI Edema**

In the clinical study, IMH, assessed by T2W-CMR, peaked around day 4 after reperfusion. This finding is in agreement with the present experimental CMR data and histologically validated data from our previous pig study.\(^{11}\) Given that T2 can be affected by hemorrhage, some authors have argued that the bimodal post-MI T2-CMR pattern could be explained entirely by the destructive paramagnetic effects of deoxyhemoglobin, rather than by a real fluctuation of tissue water content.\(^{13,36}\) However, if hemorrhage was the sole explanation for the bimodal T2 pattern, it would be difficult to understand why T2 (both in the pig model\(^ {10}\)) and water content (in the pig model)\(^ {10}\) increased to day 4, coinciding with the maximum extent of hemorrhage.\(^ {11,23}\) In fact, in the clinical study, we observed no significant influence of IMH on T2 relaxation time or area of edema delineation. The finding that infarcted (either with or without IMH areas) and salvaged myocardium displayed the same bimodal pattern strengthens our results. In line with our data, Carrick et al\(^ {13}\) found small differences in T2 (<5 ms) between patients with and without hemorrhage, whereas

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**Figure 3. Time profile of edematous area in patients with ST-segment–elevation myocardial infarction.**

**A.** Time profile of edematous area in patients with ST-segment–elevation myocardial infarction, evaluated by T2W-STIR imaging. Data are means and SD. Cardiac magnetic resonance T2W-STIR scans at ≤3 hours and on day 4 and day 7 revealed a similar edematous area (% left ventricle); in contrast, the edematous area was significantly smaller at 24 hours and on day 40 post-MI. Note the parallel courses of T2 relaxation time fluctuations and the extent of edema by cardiac magnetic resonance. **B.** Representative contiguous short-axis images from a patient with anterior ST-segment–elevation myocardial infarction who underwent serial cardiac magnetic resonance T2W-STIR examinations at 150 minutes, 26 hours, 4 days, 7 days, and 44 days after reperfusion. LV indicates left ventricle; and T2W-STIR, T2-weighted short-tau inversion recovery.

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**Table 3.** Time Profile of CMR-Assessed Myocardium at Risk, Infarct Size, and Myocardial Salvage During the First Week After Reperfused Myocardial Infarction in Pigs

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>120 min After Reperfusion (n=20)</th>
<th>24 h After Reperfusion (n=15)</th>
<th>Day 4 After Reperfusion (n=10)</th>
<th>Day 7 After Reperfusion (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MaR, % of left ventricle</td>
<td>48.1 (6.0)</td>
<td>3.6 (2.8)</td>
<td>30.2 (6.2)</td>
<td>30.1 (2.3)</td>
</tr>
<tr>
<td>Infarct size, % of left ventricle</td>
<td>45.1 (5.3)</td>
<td>35.3 (5.2)</td>
<td>30.2 (4.3)</td>
<td>25.4 (4.0)</td>
</tr>
<tr>
<td>Myocardial salvage, %</td>
<td>4.7 (4.7)</td>
<td>–1285 (858)</td>
<td>–2.5 (20.3)</td>
<td>15.7 (13.3)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). CMR data for each time point correspond to pooled data from all animals undergoing 40 minutes ischemia/reperfusion. n values decrease over time because 5 pigs were euthanized after each CMR examination for histological measurement of water content.\(^ {11}\) The extent of myocardium at risk was assessed by MDCT reference during coronary occlusion in all animals (MDCT-MaR). MDCT-MaR as assessed during the index coronary occlusion was 30.5±5.0%, 29.6±4.7%, 29.1±3.9%, and 28.3±4.3% of left ventricle; for pigs followed up to 120 minutes (n=20), 24 hours (n=15), 4 days (n=10), and 7 days (n=5) after reperfusion. Myocardial salvage as assessed by MDCT/CMR [(MDCT MaR – CMR Infarct Size) / MDCT MaR, %] in each of these groups was –50.6±24.4% at 120 minutes, –20.4±16.9% at 24 hours, –4.8±17.1% at 4 days, and 9.1±19.9% at 7 days after reperfusion, respectively. Note that MDCT was performed in all pigs only once (during the index ischemic event). Online-only Data Supplement Table III shows all individual data from animals euthanized at each time point.

CMR indicates cardiac magnetic resonance; MaR, myocardium at risk; and MDCT, multidetector computed tomography.
Hammer-Hansen et al.\textsuperscript{17} found that T2 relaxation time differed in the infarcted and salvaged myocardium, and both were significantly longer than remote in the postreperfused dog heart. It is interesting to note that the later study followed animals at 4 and 48 hours after MI with results indicating a partial resolution of edema in the first 48 hours after reperfusion.\textsuperscript{17,26} Nevertheless, hemorrhage might exert some influence on T2 relaxation time, as we previously conceded.\textsuperscript{10,11,16,23,24}

**Dynamics of Infarct Size Over the First Week After MI**

Consistent with previous observations,\textsuperscript{3,37,38} our experimental data show a progressive decrease of CMR-based IS. The substantial swelling of the early postreperfused myocardium might explain the large IS detected in our experimental study 120 minutes after MI with results indicating a partial resolution of edema in the first 48 hours after reperfusion.\textsuperscript{17,26} Nevertheless, hemorrhage might exert some influence on T2 relaxation time, as we previously conceded.\textsuperscript{10,11,16,23,24}

**Chronotherapeutic Approaches**

New treatments demonstrating significant promise in preclinical experiments frequently produce no benefits in clinical trials,\textsuperscript{1,39} and the present results hint that timing of intervention might be a key determinant of this mismatch.\textsuperscript{40–43} We believe the discovery of the bimodal nature of post-MI edema will help in the design and new therapies for reducing infarct size and post-MI LV dysfunction.

In summary, we present the first demonstration that myocardial edema after MI is not stable in patients but instead follows a bimodal pattern, confirming recent experimental findings in pigs. The identification of such a pattern has important biological, diagnostic, prognostic, and therapeutic implications, and opens a route to further exploration of factors influencing this phenomenon. Remarkably, this bimodal edematous response after MI has a major impact on CMR-MaR, and consequently, myocardial salvage quantification given that measures of edema are greatly influenced by the timing of post-MI imaging.

**LIMITATIONS**

Only patients with anterior STEMI were recruited to the clinical study. The reasons for this choice include the

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**Figure 4. Temporal evolution of cardiac magnetic resonance-myocardium at risk and infarct size after reperfused myocardial infarction in the pig model.**

Time profile of myocardium at risk evaluated by T2-weighted short-tau inversion recovery imaging (A) and infarct size evaluated by T1-weighted inversion recovery turbo-field echo in pigs subjected to 40 minutes inversion-recovery (C). Arterial enhanced multidetector computed tomography was performed during coronary occlusion in all pigs as a reference standard measure of myocardium at risk. Data are shown as mean±standard error of the mean. B and D, Representative images from a pig that underwent multidetector computed tomography during coronary occlusion followed by serial T2-weighted short-tau inversion recovery (B) and late gadolinium enhancement (D) examinations at 120 minutes, 24 hours, 4 days, and 7 days after reperfusion. LV indicates left ventricle; MaR, myocardium at risk; MDCT, multidetector computed tomography; T1-IR-TFE, T1-weighted inversion recovery turbo-field echo; and T2W-STIR, T2-weighted short-tau inversion recovery.
avoidance of possible magnetic-field nonhomogeneity related to the inferolateral wall. These eligibility criteria closely resemble recommendations for patient selection in clinical trials of cardioprotective interventions. The bimodal edema pattern may occur regardless of MI location; however, caution should be exercised when extrapolating results to other MI locations, especially regarding adequate visualization of the phenomenon by T2W-CMR in lateral MI where signal loss attributable to through-plane cardiac motion might occur. Given that patients were serially scanned, including 1 examination very early after reperfusion, we planned the shortest CMR protocol possible. For this reason we did not include T2* CMR as a diagnostic method for quantifying IMH in vivo. Instead, we assessed both edema and hemorrhage by T2W-STIR imaging, a sequence validated and used for these purposes by many authors.

Extrapolation of the experimental results to the clinical setting should be done with caution. Nonetheless, the pig is one of the most clinically translatable large-animal models for the study of reperfused MI. The similar edema and hemorrhage time courses in the pig and the patient cohort highlight the great translational value of the pig model, especially considering the difficulty of performing a comprehensive CMR study that includes serial examinations within the first hours after reperfusion and reference techniques for the assessment of the MaR. The fact that myocardial edema and LGE follow a disparate dynamic pattern after ischemia/reperfusion highlights the complexity of measuring myocardial salvage in real practice. Thus, acutely detected LGE does not necessarily equate to irreversible injury and may contribute to severely distorted estimates of salvaged myocardium when comparing against a prereperfusion standard to assess MaR. Other reasons might contribute to inaccurate estimations. Among them, it has been previously demonstrated that damage after ischemia/reperfusion may extend beyond the boundaries of the hypoperfused region during coronary occlusion; that MaR might slightly shrink in MDCT performed during coronary occlusion because of a lack of perfusion in animal models with poor collateral circulation; and that residual edema in salvaged myocardium might contribute to the overestimation of infarct size early after reperfusion.

Last, it is fair to acknowledge that although previous studies have validated the use of MDCT to measure MaR there is probably no perfect method for such purpose, because there is no consensus on a standardized method for the identification of MaR on T2W-CMR imaging. Underestimation of the maximum intensity at time points exhibiting shorter myocardial T2, ie, 24 hours and day 40, could potentially bias results in the case of the full width at half-maximum method. However, we believe the region of interest selection as initial thresholding for the full width at half-maximum method did not have a significant impact on our results for several reasons. First, the blinded analysis included manual correction and visual border delineation after initial thresholding. Second, the hemorrhagic area was larger at day 4 and day 7 coinciding with the largest edematous area delineated. Third, the demonstration of a similar bimodal edema pattern by the use of a quantitative and more objective method, ie, T2 mapping, both in the human and pig myocardium strongly supports our findings here reported.

CONCLUSIONS

Contrary to the accepted view, the post-MI edematous reaction in patients is not stable, but follows a bimodal pattern. The initial edema wave appears early on reperfusion and dissipates by 24 hours. The deferred edema wave emerges thereafter and reaches a plateau lasting from approximately day 4 to day 7 postreperfusion. Consequently, the MaR as measured by T2W-CMR changes dynamically according to timing of the CMR examination. Timing of CMR after MI for assessing MaR and salvaged myocardium needs to be standardized. According to the data presented, a time frame between day 4 and day 7 after reperfusion seems a good compromise solution although some other factors might affect these variables.

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DISCLOSURES

Dr Sánchez-González is a Philips Healthcare employee. The other authors declare no conflict of interest.

AFFILIATIONS


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Dynamic Edematous Response of the Human Heart to Myocardial Infarction: Implications for Assessing Myocardial Area at Risk and Salvage


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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Clinical study

Design

Hemodynamically stable consecutive patients with a first anterior ST-segment-elevation acute myocardial infarction (STEMI) and undergoing primary percutaneous coronary intervention (PCI) were prospectively recruited between February 2015 and November 2015. Patients eligible for enrollment were aged 18 years or older, and showed symptoms consistent with STEMI for >90 minutes and ST-segment elevation ≥2 mm in ≥2 contiguous leads in V1 through V5, with an anticipated time of symptom onset to reperfusion of ≤8 hours. Additional compulsory inclusion criteria were evidence of complete occlusion in the proximal or mid portion of the LAD coronary artery (TIMI 0-1 initial flow) and successful primary angioplasty evidenced by appropriate reestablishment of coronary flow in the culprit artery (TIMI-3 flow after angioplasty). Exclusion criteria were Killip class III to IV, persistent systolic blood pressure <100 mmHg, persistent heart rate <50 bpm or >110 bpm, presence of bifascicular or trifascicular block, evidence of second- or third-degree atrioventricular block, atrial fibrillation, known history of previous MI, pregnancy, active breastfeeding, and the presence of metallic objects or devices incompatible with MR imaging. Patients were managed according to current clinical guidelines.1, 2 CMR exams were performed within 3 hours of reperfusion (hyperacute reperfusion) and at 24 hours, 4 days, 7 days, and 40 days after reperfusion. Baseline myocardial T2 relaxation time was measured in 16 healthy age- and sex-matched volunteers. The study was approved by the hospital Ethics Committee, and patients and volunteers gave written informed consent.

CMR protocol
CMR examinations were conducted with a Philips 1.5-Tesla Achieva whole-body scanner (Philips Healthcare, Best, the Netherlands) equipped with a 16-element phased-array cardiac coil. At all time-points, the imaging protocol included a standard segmented cine steady-state free-precession (SSFP) sequence to provide high-quality anatomical references; a T2-weighted short-tau triple inversion-recovery (T2W-STIR) sequence to assess the extent of edema and intramyocardial hemorrhage (IMH); and a T2-gradient-spin-echo mapping (T2-GraSE map) sequence to provide precise myocardial T2 relaxation time properties. On day-7 and day-40 CMR, late gadolinium enhancement (LGE) imaging was performed to assess infarct size (IS) and microvascular obstruction (MVO), using a T1-weighted inversion recovery turbo field echo (T1-IR-TFE) sequence acquired 10 to 15 minutes after intravenous administration of 0.20 mmol gadobutrol contrast agent per kg body weight (Gadovist, Bayer HealthCare Pharmaceuticals). All sequences were acquired during expiration breath-hold mode.

The imaging parameters for the SSFP sequence were a FOV of 342 x 342 mm, a slice thickness of 8 mm with no gap, TR 3.0 ms, TE 1.5 ms, flip angle 60°, cardiac phases 30, voxel size 2.0 x 2.0 mm², and 1 NEX. The imaging parameters for the T2W-STIR sequence were FOV 320 x 320, slice thickness 10 mm, TR 2 heartbeats, TE 85 ms, voxel size 1.9 x 2.4 mm², delay 160 ms, end-diastolic acquisition, echo-train length 28, and 2 NEX. The imaging parameters for the T2-GraSE mapping were FOV 320 x 320 with an acquisition voxel size of 2.0 x 2.5 mm² and slice thickness 8 mm, TR 2 heartbeats, and eight echo times ranging from 23 to 194 ms, EPI factor 7. No registration algorithm was used before T2 maps estimation; however, the presence of motion artifacts between different TE for every analyzed T2 map was specifically checked. To minimize motion artefact, the breath-hold per slice in the T2-GraSE sequence was less than 10 seconds to enable proper patient breath-hold during the acquisition at every time point, including the within 3 hours post-reperfusion exam. The imaging parameters for T1-IR-TFE were as follows: FOV 265 x 265, slice thickness 10 mm with no gap, TR 8.1 ms, TE 4.0 ms, flip angle 20°, voxel size 1.8 x 2.1 mm², inversion time 250 to 350 (optimized to null normal myocardium), TFE factor 18, averages 1.
SSFP, T2W-STIR and T1-IR-TFE sequences were performed to acquire 8-11 contiguous short axis slices covering the heart from the base to the apex, whereas T2-maps were analyzed in a mid-apical ventricular short axis slice corresponding to the same anatomical level in all acquisitions, in order to track T2 relaxation time changes over time.

**CMR analysis**

CMR images were analyzed using dedicated softwares (MR Extended Work Space 2.6, Philips Healthcare, The Netherlands; and QMassMR 7.6, Medis, Leiden, The Netherlands) by two observers experienced in CMR analysis and blinded to time-point allocation and patient identification.

T2-maps were automatically generated on the acquisition scanner by fitting the signal intensity of all echo times to a monoexponential decay curve at each pixel with a maximum likelihood expectation maximization algorithm. The different myocardial states were initially defined by the localization relative to LGE defined infarction. Regions of interest (ROI) were manually drawn at the transmural ischemic, infarcted (with or without including areas suggestive of IMH), salvage and transmural remote areas; and then copied to the corresponding areas of the individual T2 maps. Care was taken to include the entire wall thickness and were individually adjusted by hand to avoid the ventricular cavities or image artefacts.

The extent of edema, expressed as a percentage of LV mass (CMR-MaR), was defined after manually tracing the endocardial and epicardial contours of T2W-STIR short-axis images. Abnormal areas were initially identified using the full-width at half-maximum (FWHM) method. Given that the solely use of FWHM may be prompt to patchy inaccurate estimations, extensive manual correction and visual border delineation were performed. Extreme care was taken to avoid including any artificially high signal intensity due to inadequately suppressed slow flow within the cavity space. Hypointense areas within the edematous zone, corresponding to IMH, were included within the edematous region. Additionally, the size of IMH area was calculated by manual delineation of the hypointense areas on T2W-images and expressed as a percentage of
LV mass. Manual delineation of clear hypointense areas was permitted in the absence of
discernible hyperintense myocardium.

IS, expressed as a percentage of LV mass, was defined according the extent of late gadolinium
enhancement after manually tracing the endocardial and epicardial contours on T1-IR-TFE short
axis images. Abnormal areas were defined using the FWHM, with manual correction if needed.
Hypointense black areas within the necrotic zone, corresponding to MVO, were included within
the necrotic area.\textsuperscript{9,10} Additionally, the size of the MVO area was calculated by manual delineation
of the hypointense areas on LGE images\textsuperscript{9} and expressed as a percentage of LV mass.

\textit{Experimental study}

\textit{Design}

The study was approved by Institutional and Regional Animal Research Committees. Myocardial
infarction was induced in 5 castrated male Large-White pigs weighing 30 to 40 kg to identify the
optimal time-window for the first post-reperfusion CMR scan in the clinical study. Reperfused
MI was generated by the percutaneous catheter-based technique, with 40min angioplasty-balloon
occlusion of the mid-LAD coronary followed by balloon deflation and reestablishment of blood
flow.\textsuperscript{11} CMR exams including CINE, T2W-STIR and T2-mapping were performed immediately
before MI induction and at 20 minute intervals post-reperfusion to 6 hours, when LGE sequence
was performed. Immediately after, animals were sacrificed and myocardial tissue samples from
ischemic and remote areas were rapidly collected for histology and evaluation of water content.
In a second set of experiments, a total of 20 pigs underwent reperfused acute myocardial infarction
induced experimentally by closed-chest 40-minute left anterior descending coronary artery
ischemia/reperfusion (I/R). These pigs were sacrificed at 120 minutes (n=5), 24 hours (n=5), 4
days (n=5), and 7 days (n=5) after reperfusion. CMR scans including CINE, T2W-STIR, T2-
mapping, and LGE sequences were performed at every follow-up stage until sacrifice. Thus,
animals sacrificed on day 7 underwent baseline, 120 min, 24 hours, day 4, and day 7 CMR exams.
In all pigs, arterial enhanced multidetector computed tomography (MDCT) was performed during
the index coronary occlusion, between minute 10 and minute 20 of ischemia, to delineate the reference MaR (hypoperfused region during coronary occlusion).12

**Myocardial infarction procedure**

The MI protocol has been detailed elsewhere.11 Anesthesia was induced by intramuscular injection of ketamine (20 mg/kg), xylazine (2 mg/kg), and midazolam (0.5 mg/kg), and maintained by continuous intravenous infusion of ketamine (2 mg/kg/h), xylazine (0.2 mg/kg/h) and midazolam (0.2 mg/kg/h). Animals were intubated and mechanically ventilated with oxygen (fraction of inspired O2: 28%). Central venous and arterial lines were inserted and a single bolus of unfractioned heparin (300 IU/kg) was administered at the onset of instrumentation. The LAD coronary artery, immediately distal to the origin of the first diagonal branch, was occluded for 40 minutes with an angioplasty balloon introduced via the percutaneous femoral route using the Seldinger technique. Balloon location and maintenance of inflation were monitored angiographically. After balloon deflation, a coronary angiogram was recorded to confirm patency of the coronary artery. Continuous infusion of amiodarone (300 mg/h) was maintained during the procedure in all pigs to prevent malignant ventricular arrhythmias. In cases of ventricular fibrillation, a biphasic defibrillator was used to deliver non-synchronized shocks.

**Arterial enhanced MDCT protocol**

Arterial enhanced multidetector computed tomography (MDCT) was performed during coronary occlusion in all pigs, between minute 10 and minute 20 of ischemia, to delineate the reference MaR (hypoperfused region during coronary occlusion).12 All MDCT studies were performed on a 64-slice CT-scanner (Brilliance CT 64, Philips Healthcare, Cleveland, Ohio). The pigs were positioned supine, and all scans were performed in the cranio-caudal direction during free-breathing. Arterial phase MDCT was performed after intravenous administration of 60 ml iomeprol 400 mgI/ml (Iomeron 400, Bracco Imaging, Milano, Italy) at a flow rate of 3 ml/s followed by a 20-ml saline chaser bolus at the same flow rate. The scan delay was determined
using a bolus tracking technique. Data acquisition started 15 seconds after a threshold of 180 Hounsfield Units was reached in a region of interest placed in the descending aorta. MDCT examinations were acquired using retrospective cardiac triggered at the 75% of the cardiac cycle with 64 x 0.625 mm collimation and a pitch of 0.2, 120 kV tube voltage, 800 mA tube current and tube rotation time of 400 ms. Image reconstruction was performed with a 512x512 matrix size over a 273x273mm² FOV and 0.45mm slice thickness by using high resolution filter (Xres Sharp).

**Arterial enhanced MDCT analysis**

MDCT images were analyzed using dedicated software (MR Extended Work Space 2.6, Philips Healthcare, Best, The Netherlands). Short axes orientation were obtained from volumetric CT images by multi-planar reconstruction using equivalent anatomical coordinates used for T2W-STIR planning acquisition. In order to have equivalent LV sections, MDCT studies had to be reconstructed in slices equivalent in thickness and level to the CMR ones. Thus, T2W-STIR and multi-planar reconstructed (MPR) short axis CT images were co-registered in 13 to 15 short-axis LV slices by one observer. To ensure CT as independent reference for MaR, endocardial and epicardial borders from MPR CT short-axis images were manually traced by a different observer blinded to the co-registration information; and MaR and remote areas were visually identified based on contrast enhancement differences, manually delineated, and expressed as a percentage of LV area.

**CMR protocol**

Baseline CMR scans were performed immediately before myocardial infarction and scans were subsequently repeated at all post-infarction follow-up times until sacrifice. CMR examinations were conducted with a Philips 3-Tesla Achieva Tx whole body scanner (Philips Healthcare, Best, the Netherlands) equipped with a 32-element phased-array cardiac coil. The imaging protocol included a standard segmented cine SSFP sequence to provide high quality anatomical references,
and assessment of LV mass and wall thickness; a T2W-STIR sequence to assess the extent of edema and IMH; a T2-GraSE mapping sequence to provide precise myocardial T2 relaxation time properties; and a LGE sequence to assess IS and MVO. To avoid interference with T2 measures at immediate reperfusion, gadolinium contrast was not administered at baseline CMR scans.

All sequences were acquired in free-breathing mode. The imaging parameters for the SSFP sequence were FOV 280 x 280 mm, slice thickness 6 mm with no gap, TR 2.8 ms, TE 1.4 ms, flip angle 45°, cardiac phases 30, voxel size 1.8 x 1.8 mm, and 3 NEX. The imaging parameters for the T2W-STIR sequence were FOV 300 x 300, slice thickness 6 mm, TR 2 heartbeats, TE 80 ms, voxel size 1.4 x 1.9 mm², delay 210 ms, end-diastolic acquisition, echo-train length 18, and 2 NEX. The imaging parameters for the T2-GraSE mapping were FOV 300 x 300 with an acquisition voxel size of 1.8 x 2.0 mm² and a slice thickness 8 mm, TR 2 heartbeats, and eight echo times ranging from 6.7 to 53.6ms, EPI factor 3. LGE imaging was performed 10 to 15 min after intravenous administration of 0.20 mmol of gadopentetate dimeglumine contrast agent per kg of body weight using a T1-IR-TFE sequence with the following parameters: FOV 280 × 280 mm, voxel size 1.6 × 1.6 mm, end-diastolic acquisition, thickness 6 mm with no gap, TR 5.6 ms, TE 2.8 ms, inversion delay time optimized to null normal myocardium, and 2 NEX.

SSFP, T2W-STIR, and T1-IR-TFE sequences were performed to acquire 13 to 15 contiguous short-axis slices covering the heart from the base to the apex, whereas T2-maps were analyzed in a mid-apical ventricular short axis slice corresponding to the same anatomical level in all acquisitions in order to track T2 relaxation time changes over time. In the experiments to identify the optimal time-window for the first post-reperfusion CMR scan in the clinical study, SSFP and T2W-STIR sequences were performed to acquire only 3 short axis slices (mid-basal, mid, and mid-apical) given that shorter time acquisitions were needed to image at 20 minute intervals.

CMR analysis

CMR images were analyzed using dedicated softwares (MR Extended Work Space 2.6, Philips Healthcare, The Netherlands; and QMassMR 7.6, Medis, Leiden, The Netherlands) by two
observers experienced in CMR analysis. LV mass, myocardial T2 relaxation time, and extent of edema, necrosis, IMH and MVO were determined.

LV endocardial borders were automatically traced with manual adjustment in each cine image. In the tracing convention used, the papillary muscles were included as part of the LV cavity volume. LV epicardial borders were also traced on the end-diastolic images to measure end-diastolic wall thickness, with LV mass computed as the end-diastolic myocardial volume (ie, the difference between the epicardial and endocardial volumes) multiplied by myocardial density (1.05 g/mL). Values of LV mass normalized to body surface area were calculated with the modified Brody’s formula.13

T2-maps were automatically generated on the acquisition scanner by fitting the signal intensity of all echo times to a monoexponential decay curve at each pixel with a maximum likelihood expectation maximization algorithm. T2 relaxation maps were quantitatively analyzed by placing a wide transmural ROI at the ischemic and remote areas of the corresponding slice in all studies. Hypointense areas suggestive of IMH or MVO were included in the ROI for T2 quantification purposes.3, 11, 14

The extent of edema, expressed as a percentage of LV mass (CMR-MaR), was defined after manually tracing the endocardial and epicardial contours of T2W-STIR short-axis images. Abnormal areas were initially identified using the FWHM method.5, 6 Given that the solely use of FWHM may be prompt to inaccurate patchy estimations,7, 8 extensive manual correction and visual border delineation were performed. Areas corresponding to slow-flow artifacts were carefully excluded from edematous area. Hypointense areas within the edematous zone, corresponding to IMH, were included within the edematous region.9, 10 Additionally, the size of the area of IMH was calculated by manual delineation of the hypointense areas on T2W-images,9 and expressed as a percentage of LV mass. Manual delineation of clear hypointense areas was permitted in the absence of discernible hyperintense myocardium.

IS, expressed as a percentage of LV mass, was defined according the extent of late gadolinium enhancement after manually tracing the endocardial and epicardial contours on T1-IR-TFE short
axis images. Abnormal areas were defined using the FWHM, with manual correction if needed. Hypointense black areas within the necrotic zone, corresponding to MVO, were included within the necrotic area.\textsuperscript{9,10} Additionally, the size of the area MVO was calculated by manual delineation of the hypointense areas on LGE images,\textsuperscript{9} and expressed as a percentage of LV mass.

\textit{Quantification of myocardial water content}

Paired myocardial samples were collected within minutes of euthanasia from the ischemic myocardium of all pigs. Tissue samples were immediately blotted to remove surface moisture and introduced into laboratory crystal containers previously weighed on a high-precision scale. The containers were weighed before and after drying for 48 hours at 100°C in a desiccating oven. Tissue water content was calculated as follows: water content (%) = \( \frac{(\text{wet weight} - \text{dry weight})}{\text{wet weight}} \times 100 \). An empty container was weighed before and after desiccation as an additional calibration control.

\textit{Histological and immunohistochemical analysis}

Myocardial samples were collected within minutes of euthanasia from the ischemic (anteroseptal) and remote (posterolateral) mid-apical ventricular wall. Tissue samples were fixed in 10\% neutral buffered formalin for 48 hours and processed by dehydrating the tissue in increasing concentrations of ethanol. Samples were then cleared in xylene, embedded in paraffin wax and cut into 4 micron sections.

For histopathological analysis, sections were stained with hematoxylin and eosin (H&E) and Masson’s Trichrome. Necrotic tissue was identified by the presence of typical signs of coagulative necrosis, including marginal contraction bands, fading, and eventually loss of nuclei and striation in cardiomyocytes.

For immunohistochemical analysis, sections were deparafﬁnized and antigens were unmasked using heat induced epitope retrieval (HIER) with citrate buffer at pH6. Before incubation with
primary antibodies, endogenous peroxidase was blocked by incubation with H_2O_2 for 5 minutes, and endogenous antigens were blocked with fetal bovine serum (FBS) for 20 minutes. Neutrophils were detected with mouse monoclonal anti-PM1 primary antibody (BMA biomedicals; T-3503) as previously described. The secondary antibody was HRP-conjugated goat anti-mouse (Dako; P0447). Bound antibody was revealed by staining with diaminobenzidine, and nuclei were counterstained with hematoxylin. All immunohistochemical procedures were performed using an automated autostainer (Autostainer Plus®, Dako). For analysis, images were digitalized with a scanner (Nanozoomer-RS C110730®, Hamamatsu) and examined with image analysis software (Tissuemorph®, Visiopharm) by an experienced veterinary pathologist blinded to experimental procedure.
SUPPLEMENTAL RESULTS

*Dynamics of the initial wave of edema*

Five male pigs (mean body weight 36.4±2.9 kg) underwent CMR exam before MI induction (baseline) and at 20 min intervals after reperfusion for 6 hours (19 CMR exams per pig). Mean myocardial T2 relaxation time before MI induction was 44.3±1.6 ms and 43.0±1.3 ms for the mid-apical anteroseptal and posterolateral left ventricular walls, respectively. In the ischemic area, reperfusion was associated with an immediate sharp increase in T2 relaxation time above baseline values, reaching a peak at 40 minutes after reperfusion (*Supplemental Figure 1*). Thereafter, a progressive decrease in T2 was observed, with T2 relaxation time at 6 hours closer to the values obtained in baseline CMR scans. In the remote myocardium, T2 relaxation time showed no significant trend or differences at different times post reperfusion. Tissue water content in the formerly ischemic myocardium at 6 hours after reperfusion was 82.7 ± 1.0%. Histological analysis of such myocardial tissue at 6 hours after reperfusion revealed typical features of early acute transmural necrosis (*Supplemental Figure 2*).
SUPPLEMENTAL TABLES

**Supplemental Table 1.** Point estimates and differences in T2 relaxation time in the transmural ischemic myocardium relative to the value obtained in the hyperacute CMR exam (≤3 hour reperfusion), with adjustment for the extent of intramyocardial hemorrhage.

<table>
<thead>
<tr>
<th>Reperfusion time</th>
<th>≤3 hours</th>
<th>24 hours</th>
<th>4 days</th>
<th>7 days</th>
<th>40 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 transmural ischemic, ms</td>
<td>80.8 (76.1, 85.4)</td>
<td>65.4 (60.8, 70.0)</td>
<td>80.5 (75.9, 85.1)</td>
<td>76.8 (72.1, 81.6)</td>
<td>65.4 (60.7, 70.2)</td>
</tr>
<tr>
<td>Δ T2 transmural ischemic, ms</td>
<td>-15.3 (-21.3, -9.4)</td>
<td>-0.3 (-6.2, 5.7)</td>
<td>-3.9 (-10.0, 2.2)</td>
<td>-15.3 (-21.3, -9.2)</td>
<td></td>
</tr>
<tr>
<td>Δ T2 transmural ischemic (*), ms</td>
<td>-14.7 (-20.7, -8.7)</td>
<td>1.0 (-5.3, 7.3)</td>
<td>-2.7 (-9.1, 3.7)</td>
<td>-15.1 (-21.1, -9.1)</td>
<td></td>
</tr>
</tbody>
</table>

To take account of repeated measures, a generalized linear mixed model was conducted to analyze the time course of T2 relaxation time. The model was further adjusted by extent of hemorrhage, including the amount of intramyocardial hemorrhage (IMH) expressed as a percentage of the left ventricle as a covariate.

Data are presented as point estimates (95% confidence interval), or mean difference (95% confidence interval) in T2 relaxation time (Δ T2) in the transmural ischemic myocardium relative to the first CMR examination, performed within 3 hours after reperfusion. The table shows nonadjusted differences and (*) differences adjusted for the amount of IMH (% of left ventricle).

Globally, T2 relaxation time in the transmural ischemic area decreased 1.1 ms (95% CI, -3.1 to 1.0, \( p = 0.297 \)) for every 1% absolute increase in IMH (expresses as a percentage of the left ventricle).
**Supplemental Table 2.** Point estimates and differences in edematous area relative to the value obtained in the hyperacute CMR exam (≤3 hour reperfusion), with adjustment for the extent intramyocardial hemorrhage.

<table>
<thead>
<tr>
<th></th>
<th>Reperfusion time</th>
<th>≤ 3 hours</th>
<th>24 hours</th>
<th>4 days</th>
<th>7 days</th>
<th>40 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Area of edema, % of LV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>39.9</td>
<td>21.8</td>
<td>42.8</td>
<td>43.0</td>
<td>20.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(34.1, 45.7)</td>
<td>(16.1, 27.6)</td>
<td>(37.0, 48.6)</td>
<td>(37.1, 48.9)</td>
<td>(14.3, 26.2)</td>
</tr>
<tr>
<td><strong>Δ Area of edema, % of LV</strong></td>
<td></td>
<td>-18.0</td>
<td>2.9</td>
<td>3.1</td>
<td>-19.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-24.2, -11.9)</td>
<td>(-3.2, 9.1)</td>
<td>(-3.2, 9.4)</td>
<td>(-25.9, -13.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Δ Area of edema (*), % of LV</strong></td>
<td></td>
<td>-19.0</td>
<td>1.0</td>
<td>1.2</td>
<td>-19.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-25.3, -12.7)</td>
<td>(-5.7, 7.7)</td>
<td>(-5.6, 8.0)</td>
<td>(-26.1, -13.6)</td>
<td></td>
</tr>
</tbody>
</table>

To take account of repeated measures, a generalized linear mixed model was conducted to analyze the time course of edematous area as measured by T2W-STIR. The model was further adjusted by extent of hemorrhage, including the amount of intramyocardial hemorrhage (IMH) expressed as a percentage of the left ventricle as a covariate.

Data are presented as point estimates (95% confidence interval), or mean difference (95% confidence interval) in edematous area (Δ Area of edema) relative to the first CMR examination, performed within 3 hours after reperfusion. The table shows nonadjusted differences and (*) differences adjusted for the amount of IMH (% of left ventricle). Globally, the area of edema increased 1.7% of the left ventricle (95% CI, -0.6 to 4.0, p = 0.154) for every 1% absolute increase in IMH (expresses as a percentage of the left ventricle).
**Supplemental Table 3.** Time course of myocardium at risk, infarct size, and myocardial salvage as assessed by cardiac magnetic resonance during the first week after reperfused myocardial infarction in pigs.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CMR measure</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R-120min</td>
</tr>
<tr>
<td>Sacrificed at 120 min</td>
<td>MaR, % of LV</td>
<td>51.6 (6.2)</td>
</tr>
<tr>
<td></td>
<td>Infarct size, % of LV</td>
<td>47.2 (2.9)</td>
</tr>
<tr>
<td></td>
<td>Myocardial salvage, %</td>
<td>3.7 (3.4)</td>
</tr>
<tr>
<td>Sacrificed at 24 hours</td>
<td>MaR, % of LV</td>
<td>47.7 (5.7)</td>
</tr>
<tr>
<td></td>
<td>Infarct size, % of LV</td>
<td>46.8 (5.6)</td>
</tr>
<tr>
<td></td>
<td>Myocardial salvage, %</td>
<td>1.9 (1.7)</td>
</tr>
<tr>
<td>Sacrificed at 4 days</td>
<td>MaR, % of LV</td>
<td>50.0 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Infarct size, % of LV</td>
<td>47.6 (3.6)</td>
</tr>
<tr>
<td></td>
<td>Myocardial salvage, %</td>
<td>4.6 (4.6)</td>
</tr>
<tr>
<td>Sacrificed at 7 days</td>
<td>MaR, % of LV</td>
<td>42.9 (5.7)</td>
</tr>
<tr>
<td></td>
<td>Infarct size, % of LV</td>
<td>39.2 (3.8)</td>
</tr>
<tr>
<td></td>
<td>Myocardial salvage, %</td>
<td>8.3 (6.4)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation). Mean myocardium at risk assessed by MDCT reference standard for pigs was 33.7±5.8 % of the LV for those sacrificed at 120 minutes, 30.7±6.2 % for 24 hours, 29.8±3.9 % for day 4, and 28.3±4.3 % for day 7.

CMR: cardiac magnetic resonance; MaR: myocardium at risk; LV: left ventricle; I/R: ischemia/reperfusion; R: reperfusion.
Supplemental Table 4  Time profile of left ventricular mass and wall thickness ratio as assessed by cardiac magnetic resonance during the first week after reperfused myocardial infarction in pigs.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CMR measure</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Sacrificed at</td>
<td>LV mass, g/m²</td>
<td>75.8 (7.9)</td>
</tr>
<tr>
<td>120 min</td>
<td>Wall thickness ratio, ischemic/remote</td>
<td>1.07 (0.04)</td>
</tr>
<tr>
<td>Sacrificed at</td>
<td>LV mass, g/m²</td>
<td>79.6 (9.3)</td>
</tr>
<tr>
<td>24 hours</td>
<td>Wall thickness ratio, ischemic/remote</td>
<td>1.08 (0.07)</td>
</tr>
<tr>
<td>Sacrificed at</td>
<td>LV mass, g/m²</td>
<td>72.5 (3.1)</td>
</tr>
<tr>
<td>4 days</td>
<td>Wall thickness ratio, ischemic/remote</td>
<td>1.07 (0.04)</td>
</tr>
<tr>
<td>Sacrificed at</td>
<td>LV mass, g/m²</td>
<td>64.0 (7.4)</td>
</tr>
<tr>
<td>7 days</td>
<td>Wall thickness ratio, ischemic/remote</td>
<td>1.06 (0.18)</td>
</tr>
<tr>
<td>Pooled</td>
<td>LV mass, g/m²</td>
<td>73.0 (9.0)</td>
</tr>
<tr>
<td></td>
<td>Wall thickness ratio, ischemic/remote</td>
<td>1.07 (0.09)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation). No significant statistical differences were found between time-points except for R-120 min CMR, when LV mass and end-diastolic wall thickness ratio (MaR/remote) were significantly higher than at the other time-points due to the intense swelling of the ischemic myocardium at early reperfusion.

CMR: cardiac magnetic resonance; R: reperfusion; LV: left ventricle.
**Supplementary Table 5.** Time course of intramyocardial hemorrhage (IMH) and microvascular obstruction (MVO) assessed by cardiac magnetic resonance during the first week after reperfused myocardial infarction in pigs.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CMR measure</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-120min</td>
<td>R-24hours</td>
</tr>
<tr>
<td>Sacrificed at 120 min</td>
<td>IMH, % of LV</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>MVO, % of LV</td>
<td>4.7 (4.8)</td>
</tr>
<tr>
<td>Sacrificed at 24 hours</td>
<td>IMH, % of LV</td>
<td>0.5 (0.9)</td>
</tr>
<tr>
<td></td>
<td>MVO, % of LV</td>
<td>3.8 (3.6)</td>
</tr>
<tr>
<td>Sacrificed at 4 days</td>
<td>IMH, % of LV</td>
<td>0.2 (0.5)</td>
</tr>
<tr>
<td></td>
<td>MVO, % of LV</td>
<td>1.5 (1.3)</td>
</tr>
<tr>
<td>Sacrificed at 7 days</td>
<td>IMH, % of LV</td>
<td>0.2 (0.5)</td>
</tr>
<tr>
<td></td>
<td>MVO, % of LV</td>
<td>5.1 (4.5)</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td>IMH, % of LV</td>
<td><strong>0.2 (0.5)</strong></td>
</tr>
<tr>
<td></td>
<td>MVO, % of LV</td>
<td><strong>3.7 (3.7)</strong></td>
</tr>
</tbody>
</table>

Values are mean (standard deviation).

CMR: cardiac magnetic resonance; I/R: ischemia/reperfusion; IMH: intramyocardial hemorrhage; MVO: microvascular obstruction; LV: left ventricle.
SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

Supplemental Figure 1. Dynamics of the initial wave of edema

(A) Time course of T2 relaxation time (ms) in the ischemic and remote myocardium during the first 6 hours after ischemia/reperfusion in the pig model. Data are means and standard deviation. Cardiac magnetic resonance (CMR) scans were performed immediately before induction of myocardial infarction and at 20 minute intervals after reperfusion up to 6 hours, when pigs were sacrificed.

(B) Representative images from an animal that underwent 40min-I/R and serial CMR T2W-STIR and T2-mapping exams to study the precise dynamics of the first edema wave. Due to space restrictions, the representative images shown were taken at 40 minute intervals. All T2 maps were scaled between 30 and 120 ms.

CMR: cardiac magnetic resonance; R: reperfusion; STIR: Short-tau inversion recovery; ms: milliseconds.
Supplemental Figure 2. Histological analysis of porcine myocardium 6 hours after ischemia/reperfusion

Representative histological images of ischemic myocardium (top) and remote myocardium (bottom) 6 hours after 40-minute ischemia and reperfusion (I/R) in the pig model. Images show staining with hematoxylin and eosin (H/E), anti-PM1 antibody (PMN), and Masson’s trichrome. Neutrophils were quantified and interstitial hemorrhage was graded from 0 (absence) to 5 (very severe). The remote area showed no relevant pathological findings at this time-point. In contrast, ischemic myocardium exhibited typical features of acute transmural myocardial infarction, with extensive coagulative necrosis, contraction bands, loss of nuclei and striation in cardiomyocytes, wavy fibers, and cell edema. Interstitial edema in the ischemic area at 6 hours post-I/R was significantly lower than at 120 min after ischemia onset, consistent with partial resolution of the initial wave of edema. Massive tissue infiltration by neutrophils (473±190 cells per mm² in the lesion area) was observed at 6 hours post-I/R, which was at least as high as that observed at 24 hours post-I/R. Mild interstitial hemorrhage was detected (median score of 1; interquartile range, 0-1). Scale bars, 100μM.
Supplemental Figure 3. Individual patient T2 relaxation time trajectories in the ischemic myocardium

Line-plots showing changes in individual T2 relaxation times in the ischemic myocardium of anterior STEMI patients after reperfusion by primary PCI. Cardiac magnetic resonance was scheduled within the first 3 hours and at 24 hours, 4 days, 7 days, and 40 days after reperfusion. T2 values at all time-points were obtained from T2-GraSE mapping sequences.³
Supplemental Figure 4. Individual patient trajectories for area of edema

Line-plots showing changes in individual area of edema measurements of anterior STEMI patients after reperfusion by primary PCI. Colors identify the same individuals as in Supplemental Figure 3. Cardiac magnetic resonance was scheduled within the first 3 hours and at 24 hours, 4 days, 7 days, and 40 days after reperfusion. Edematous area at all time points was determined from T2W-STIR sequences.
Supplemental Figure 5. Temporal evolution of myocardial salvage assessed by cardiac magnetic resonance after reperfused myocardial infarction in pigs.

Data are means ± standard error of the mean.

MaR: myocardium at risk.
SUPPLEMENTAL REFERENCES


