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Relation of the ischaemic substrate to left ventricular remodelling by cardiac magnetic resonance at 1.5T in rabbits

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Short title: Cardiac Magnetic Resonance at 1.5T in Rabbits

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Abstract

Objectives: Contrast-enhanced cardiac magnetic resonance (CMR) for infarct sizing has been validated in large animals, but studies and follow-up are restricted. We sought to 1) validate CMR for assessment of myocardial area at risk (MAR) and infarct size (IS) in a rabbit model of reperfused myocardial infarction (MI); 2) analyse the relation between ischaemic substrates and subsequent left ventricular (LV) remodelling.

Methods: Experimental reperfused acute MI was induced in 16 rabbits. Ten animals underwent cross-registered cine and contrast-enhanced CMR and histopathology at day 3 for assessment of MAR and IS (group#1). The remaining 6 rabbits had serial CMR for the study of LV remodelling (group#2).

Results: In group#1, mean IS was 12.7±6.4% and 12.7±6.9% of total LV myocardial mass on CMR (late-enhancement technique) and histopathology (P=0.52; r=0.93). No significant difference occurred between CMR and histopathology for the calculation of MAR and IS/MAR ratio (P=0.18 and P=0.17), whereas correlations were strong (r=0.92 and r=0.95). In group#2, mean LV end-diastolic, end-systolic volumes and LV mass were significantly increased at 3 weeks compared with measurements at day 3 (P<0.01). Significant correlations between initial IS and the increase in LV end-diastolic volume (r=0.66) and the increase in LV mass (r=0.48) were observed, as well as correlations between initial MAR and the increase in LV end-diastolic volume (r=0.70) and the increase in LV mass (r=0.37).

Conclusions: Comprehensive CMR provides accurate assessment of IS and MAR in reperfused rabbit MI. Infarct size is closely related to LV remodelling. Through the infarct size/MAR ratio, this approach has great potential for assessing interventions aimed at cardioprotection.

Keywords. Cardiac, magnetic resonance imaging, experimental study, myocardial infarction, left ventricular remodelling.

Introduction

After the onset of a myocardial ischaemic insult, the determination of myocardial viability is of importance for the establishment of prognosis and for therapeutic purposes [1,2]. Contrast-enhanced cardiovascular magnetic resonance (CE-CMR) has emerged as a non-invasive imaging technique for myocardial infarction (MI) and tissue viability and for predicting the probability of recovery of left ventricular (LV) function [3-9]. However, the direct validation of CE-CMR for infarct sizing is not available in humans and the relation of the ischemic insult to LV myocardial remodeling is not fully understood. Measurement of infarct size (IS) by CMR is accurate in large animals [10-12], but these studies are restricted by ethical considerations, whereas in small animals, elevated heart rates and the small size of the heart make CMR challenging. IS by CE-CMR has been feasible in a rabbit model of acute non-reperfused MI, which is not the most common clinical presentation [13]. Furthermore, the myocardial area at risk (MAR) was not evaluated, whereas the distinction between MI and MAR is of importance for preclinical evaluation of therapeutic procedures tailored for cardioprotection [14]. The aims of the study were 1) to validate CMR for the assessment of MAR and IS in a rabbit model of reperfused MI, and 2) to study post-infarct LV remodelling and analyse the relation between ischaemic substrates and subsequent LV remodelling.

Materials and Methods

Experimental study design

All animal experiments were performed in an accredited lab in accordance with the official regulations provided by the French Ministry of Agriculture and with local ethical guidelines. Experiments were approved by the institutional animal care and use committee. We prospectively investigated two groups of rabbits. Group#1 included 10 rabbits with experimentally-induced reperfused acute MI that were studied for assessment of MAR and IS (CMR at day 3 following MI versus histopathology). Group#2 included 6 rabbits with the same experimental protocol of reperfused acute MI that were serially followed at day 3 (CMR#1) and 3 weeks (CMR#2), allowing for the study of post-infarct LV remodelling. Animals were then sacrificed at 3 weeks, immediately after CMR#2.

Experimental model of reperfused acute myocardial infarction

Sixteen male New Zealand rabbits (2–2.5 kg) were anaesthetised, intubated and mechanically ventilated [15,16]. Under deep anaesthesia, a left thoracotomy was performed at the fourth intercostal space and a suture was passed beneath a major branch of the left coronary artery. Acute regional myocardial ischaemia was induced. In all animals, a coronary artery occlusion was performed lasting 30 to 45 minutes, followed by reflow. The chest was then closed in layers. All rabbits underwent CMR 72 h after coronary reflow.

Measurement of risk area and infarct size by histopathology

The 10 rabbits of group#1 were sacrificed at day 3 immediately after CMR, whereas the 6 rabbits of group#2 were sacrificed after CMR#2 at 3 weeks. The ascending aorta was cannulated and perfused (120 mmHg) retrogradely with saline solution followed by Evans blue (5%) after ligation of the previously occluded artery to delineate MAR [16]. The LV

was cut into 6 contiguous 3 mm thick short-axis slices that were matched to CMR locations. These slices were weighed and incubated with 1% triphenyltetrazolium chloride (TTC, Sigma Chemical, Poole, Dorset, UK). Slices were fixed in 10% formaldehyde and then photographed with a digital camera. Using dedicated software (Scion Image, Scion Corporation, Frederick, MD), MAR and IS were determined by planimetry on digital frames: MAR and IS were identified as the non-blue region and as the TTC-unstained zone, respectively (Fig. 1). IS was measured as the TTC unstained region by planimetry on digital photographs taken from the series of 6 LV short axis slices. TTC unstained zones were manually planimetered, as was the whole LV myocardium. Similarly, the MAR was planimetered as the non-blue region on the series of short-axis views of the LV. The MAR was expressed as a percentage of LV weight and IS was expressed as a percentage of LV mass and of area at risk.

Cardiac magnetic resonance protocol

Cardiac magnetic resonance (1.5 T Siemens Symphony®, Erlangen, Germany) was performed in anaesthetised animals (initiated by zolazepam and 20–30 mg/kg IV bolus pentobarbital sodium, and maintained with 2% isoflurane) in the right laterocubital position with electrocardiographic gating and short breath-hold acquisitions (the respirator was switched off). Heart rate was slowed down below 200 beats/min using a combination of inhaled 2% isoflurane and a 5 mg IV bolus of ivabradine (Servier, Courbevoie, France) if necessary. A flexible cardiac phased-array coil was wrapped around the chest for signal acquisition. Six contiguous short-axis locations encompassing LV from base to apex were acquired in the cine steady state free precession (SSFP) sequence (Fig. 1). The first location

at the base was prescribed 3 mm in front of the mitral ring at end-diastole. Typical imaging parameters of cine-CMR were optimised for cardiac imaging in rabbits (170 mm field of view, 256x160 image matrix, 0.7x1.0 mm^2 spatial resolution, 3 mm slice thickness, 2.6 ms repetition time, 1.6 ms echo time, imaging flip angle $\alpha = 45°$, 20 ms temporal resolution, typically 35 s breath-hold time). For infarct imaging, cross-registered inversion-recovery 2D fast gradient-echo images were acquired at end-diastole 10 minutes after 2 ml IV bolus Gadolinium-DOTA injection (Dotarem®, Guerbet, Aulnay, France) (170 mm field of view, 256x160 image matrix, 0.7x1.0 mm^2 spatial resolution, 3 mm slice thickness, 3.1 ms repetition time, 1.6 ms echo time, imaging flip angle $\alpha = 20°$, 220 ms typical inversion time (200-240 ms) (Fig. 1). For this sequence, the optimal inversion time was selected from a look-locker sequence to null the signal of non-infarcted myocardium

Short-axis cine-MR images were analysed for the assessment of LV volumes and mass (Argus® software, Siemens, Erlangen, Germany). The dysfunctional myocardium was assessed visually from the 6 short-axis locations as the planimetry of the surface of severely hypokinetic and/or akinetic myocardium, and then expressed as a percentage of the total LV mass for the estimation of MAR. Delayed-enhanced myocardium was planimetered on the series of cross-registered inversion-recovery short-axis images for precise delineation of myocardial infarction (Fig. 1). IS was measured by CMR using the late-enhancement technique 10 minutes after gadolinium injection. Delayed-enhanced myocardium was planimetered on the series of cross-registered inversion-recovery short-axis images for precise delineation of myocardial infarction. Infarct size was expressed as the percentage of total myocardial mass and as a percentage of MAR. CMR was compared with cross-registered histopathology with the same number of short-axis locations and same slice

thickness. When available, specific anatomical landmarks were used to check for correct cross-registration (distance from mitral ring, papillary muscles, RV-LV attachment points). CMR and histopathology were assessed by two independent observers.

Statistical analysis

Continuous variables are presented as mean ± SD and ranges, unless otherwise specified. Categorical data are presented as absolute values and percentages. Continuous and categorical variables were compared with use of the Chi-squared test, paired t tests, unpaired t tests or Fisher's exact test, as appropriate. Linear regression analysis was used to compare CMR and histopathology for the assessment of the MAR and IS, and for reproducibility measurements. Agreements between CMR and histopathology were evaluated using Bland-Altman plots. We analysed the data using the Stata® statistical software package, version 8.0 (Stata Corp, College Station, TX). All tests were two-tailed and a P value < 0.05 was considered statistically significant.

Results

CMR was interpretable in all rabbits and there was no mortality during the study period. Mean heart rate during CMR was 178 ± 11 beats/min (range, 165-200). On histopathology, mean LV weight was 4.7 ± 0.8 g in group#1 at day 3 and 6.0 ± 0.8 g in group#2, 3 weeks after MI.

Infarct size and myocardial area at risk by CMR

In group#1, there was no significant difference between CMR and histopathology for the assessment of IS. Mean IS expressed as the percentage of LV mass was 12.7 ± 6.4% and 12.7 ± 6.9% for CMR and histopathology (range 1-24%), respectively ($P = 0.52$), with strong correlations between the 2 series of measurements (Fig. 2A). Mean MAR represented 29.9 ± 10.9% and 32.5 ± 13.7% of the total LV mass for CMR and histopathology, respectively ($P = 0.18$) and the 2 series were highly correlated (Fig 2B). IS expressed as the percentage of MAR was 40.8 ± 19.2% and 36.7 ± 16.1% for CMR and histopathology, respectively ($P = 0.17$), with strong correlations (Fig. 2C). The limits of agreement for IS, expressed as a percentage of LV mass and as a percentage of the MAR, were good between CMR and histopathology, with 95% confidence intervals of -3.8 to +4.8% and -9.4 to +10.7%, respectively. The limits of agreement for the MAR were in the range of -13.3 to +7.9% with a 95% confidence interval (Fig 2).

In group#1, intra- and interobserver reproducibility for CMR measurements of IS ($y = 0.99x-0.09$, $r = 0.98$, standardised error (SE) = 0.06; and $y = 0.95x+0.58$, $r = 0.94$, SE = 0.13, respectively, all $P < 0.001$) and MAR ($y = 1.03x-0.41$, $r = 0.97$, SE = 0.10; and $y = 1.05x+0.17$, $r = 0.93$, SE = 0.14, respectively, all $P < 0.001$) were good.

Post-infarct left ventricular remodelling

In group#2, there were good agreement and correlations for the determination of IS between CMR and histopathology (10 ± 3% versus 9 ± 3% of total LV mass, $P = 0.17$; $r = 0.85$, $P < 0.0001$). Mean LV end-diastolic and end-systolic volumes and mean LV mass were significantly increased at 3 weeks compared with measurements at day 3 (Table 1).

In these animals, IS expressed as total infarct mass, slightly increased over time between day 3 and 3 weeks (0.6 ± 0.1 g versus 0.7 ± 0.2 g, $P = 0.05$). When expressed as percentage of the LV mass, IS decreased significantly over time (15.2 ± 5.0% versus 11.8 ± 3.1%, $P = 0.02$). Significant correlations were observed between initial IS by CMR at day 3 and the increase in LV end-diastolic volume ($r = 0.66$, $P < 0.001$), and between initial IS by CMR and the increase in LV mass ($r = 0.48$, $P < 0.001$). Although less pronounced, this relation was also observed between initial IS on CE-CMR and the subsequent increase in LV end-systolic volume ($r = 0.27$, $P < 0.05$). Interestingly, correlations were also observed between initial MAR by CMR at day 3 and the increase in LV end-diastolic volume ($r = 0.70$, $P < 0.01$), and between initial MAR by CMR at day 3 and the increase in LV mass ($r = 0.37$, $P < 0.05$).

Discussion

The main results of the present study are: 1) comprehensive CMR provides accurate assessment of IS and MAR in a rabbit model of reperfused myocardial infarction; 2) the determination of IS is accurate at the 3-week follow-up with the extravascular contrast agent used; 3) this animal model seems promising for the longitudinal study of LV remodelling; 4) the accurate assessment of the IS/MAR ratio could allow the longitudinal evaluation of targeted strategies aimed at cardioprotection.

Barkhausen et al. [13] have demonstrated the accuracy of the standard Gadolinium-based extracellular contrast agent to assess IS in a rabbit model of non-reperfused acute MI. The present report offers the advantage of studying myocardial distribution of Gd-DOTA at the acute phase and at the 3-week follow-up in an experimental model of brief coronary artery occlusion followed by reflow, which is the most common clinical presentation. The time for coronary occlusion has been selected on the basis of previous experimental studies which provided a wide range of infarct size and a clear delineation between myocardial infarct and the area at risk (15,16). Compared with histopathology, there was no overestimation of IS in the present model. It is likely that differences between histopathology and CE-CMR in IS can, at least in part, be explained by partial volume effects [12]. In the current report, partial volume effect might be significantly decreased because of the use of thin slices [13]. Also, hyperenhancement in the peri-infarction zone seen with Gadolinium chelates has been mainly reported within the first 24h following induction of acute MI [17]. In our study, the first CMR was performed 3 days after induction of MI, which may concur to explain the lack of IS overestimation, and which

mimics the usual clinical scenario after the onset of acute coronary syndrome. In addition, comprehensive cross-registered evaluation of dyskinetic myocardium on cine-CMR was used to assess MAR. In comparison with the Evans Blue staining, the current study shows that the size of the MAR can be determined using this visual approach, although the lack of direct imaging of the myocardial areat at risk was a clear limitation. Thus, the infarct size/MAR ratio can be assessed with this comprehensive approach. In the experimental setting, this ratio represents the crucial quantitative index for the evaluation of novel therapies aimed at cardioprotection such as pharmacological approaches, cell therapy or post-conditioning techniques [15].

During coronary occlusion, the visual control of the epicardial surface along with the prompt release of the snare for coronary reflow enabled a wide range of IS to be obtained, i.e. from 1 to 24% of the LV mass. In addition, the robustness of the model allows for a 3-week follow-up of the animals after induction of MI, which enabled the study of post-infarct LV remodelling. Therefore, the present experimental study permits a non-invasive analysis of the relationship between the size of the initial ischaemic damage and subsequent LV remodelling, showing good correlations between the size of induced MI and the subsequent increase in LV mass and volumes. As suggested by others [18], the current data support the concept that the presence and extent of dysfunctional viable myocardium may represent a determinant of subsequent LV remodelling. In vivo serial CMR imaging was restricted in larger animals such as dogs or pigs [3,10-12,19,20]. Among the various advantages of the current rabbit model, one can point out the possibility of studying several animals in one imaging session, with easier applicability and at lower costs. The possibility of serial non-invasive imaging is crucial for the analysis of LV remodelling but also for

longitudinal assessment in the same animals of targeted interventions designed to impact on the infarct size/MAR ratio.

Because of elevated heart rates and short diastolic times, T2-weighted black blood spin echo CMR imaging could not be performed and represents a limitation. It is known that the T2-enhanced area corresponds to the location of ischaemic injury but overestimates IS [19,20]. T2 changes are indicative of the presence of oedema rather than the area of damaged myocardium itself [21-23]. More importantly, these non-contrast-enhanced imaging techniques have limited signal-to-noise and contrast-to-noise ratios and most authors found it difficult to precisely distinguish infarcted from non-infarcted myocardium. Increased T2 signal has low specificity for the detection of myocardial necrosis, and T2 alterations are less consistent especially for the detection of chronic myocardial infarction [21]. The current experiments were performed on a 1.5T MR clinical system. To our knowledge, there are no available data on segmented T2-weighted imaging after induced infarction at higher magnetic fields in rabbits. Finally, the delineation between myocardial infarction and the area at risk is clearly dependent on the amount of collaterals, which is highly variable in different animal species and in humans.

Conclusion

Comprehensive CMR provides accurate assessment of IS and MAR in a rabbit model. The determination of IS is accurate at the 3-week-follow up with the extravascular contrast agent used. Serial imaging demonstrated a close relationship between initial IS, the extent of initially dysfunctional myocardium, and subsequent LV remodelling. Through the accurate assessment of the infarct size/MAR ratio and the use of serial non-invasive

imaging, this approach has accurate potential for the longitudinal evaluation of targeted interventions aimed at cardioprotection.

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Figure Legends

Figure 1. A. Still frames extracted from the steady-state free precession cine-CMR at the mid LV level during end-diastole (upper left) and end-systole (upper right), along with matched delayed CE-CMR (bottom left) and corresponding histopathology (bottom right) in an animal for which experimental coronary occlusion led to a small MAR (16% of total LV mass, 30% of LV mass in this short-axis location) and limited MI (6% of total LV mass, 14% of LV mass in this short-axis location). The MAR was assessed by the extent of severely dyskinetic myocardium on cine CMR (arrows) and the Evans blue unstained tissue on histopathology, whereas infarction appeared as the enhanced region on delayed contrast CMR (arrows) and unstained (non-red) region on TTC stain (arrows). **B.** CMR data acquired at the LV apical level in another animal with an extensive MAR (38% of total LV mass, 82% of LV mass in this slice location, arrows) and large infarct (17% of total LV mass, 76% of LV mass in this slice location) on CE-CMR (arrows) and corresponding TTC stain (arrows). **C.** CMR data acquired at the LV apical level in another animal with mild MAR (24% of total LV mass, 48% of LV mass in this short-axis location) and mild MI (11% of total LV mass, 20% of LV mass in this short-axis location). LV: left ventricular, MAR: myocardial area at risk, MI: myocardial infarction, CE-CMR: contrast-enhanced cardiac magnetic resonance.

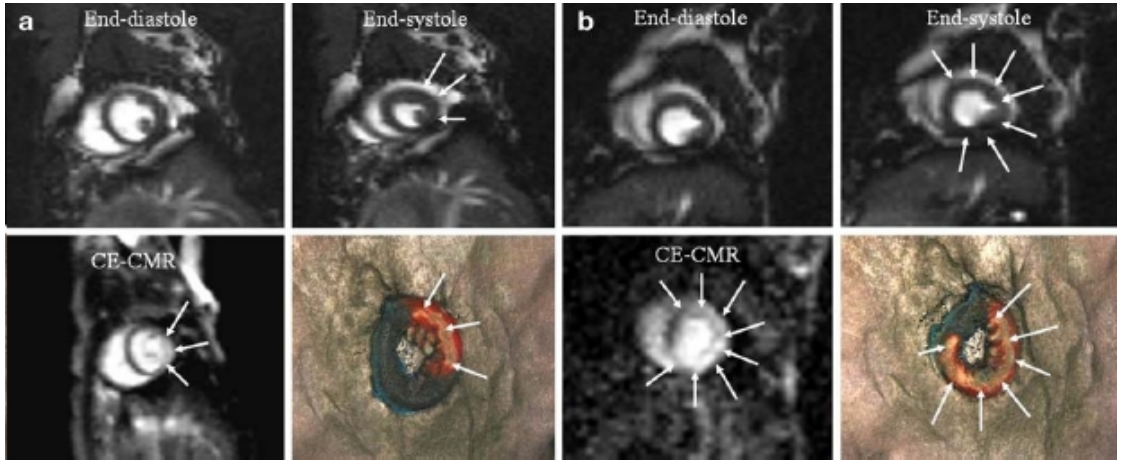
Figure 2. Linear regression (*left*) and Bland-Altman plots (*right*) for comparisons of infarct size (IS) (upper panel **[A]**), myocardial area at risk (MAR) (mid panel **[B]**), and IS/MAR ratio (lower panel **[C]**) as assessed by CMR and histopathology.

Table 1. Left ventricular alterations after reperfused myocardial infarction assessed by CMR in group#2

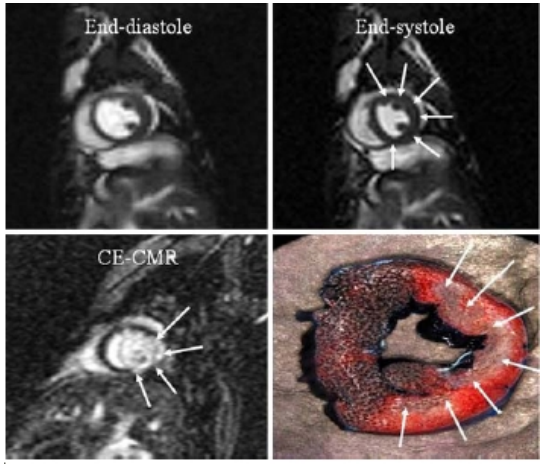
	CMR#1	CMR#2	P Value
Left ventricular end-diastolic volume (ml)	3.7 ± 0.5	4.7 ± 0.4	0.0006
Left ventricular end-systolic volume (ml)	2.7 ± 0.6	3.4 ± 0.4	0.01
Left ventricular mass (g)	4.72 ± 0.55	5.22 ± 0.46	0.01

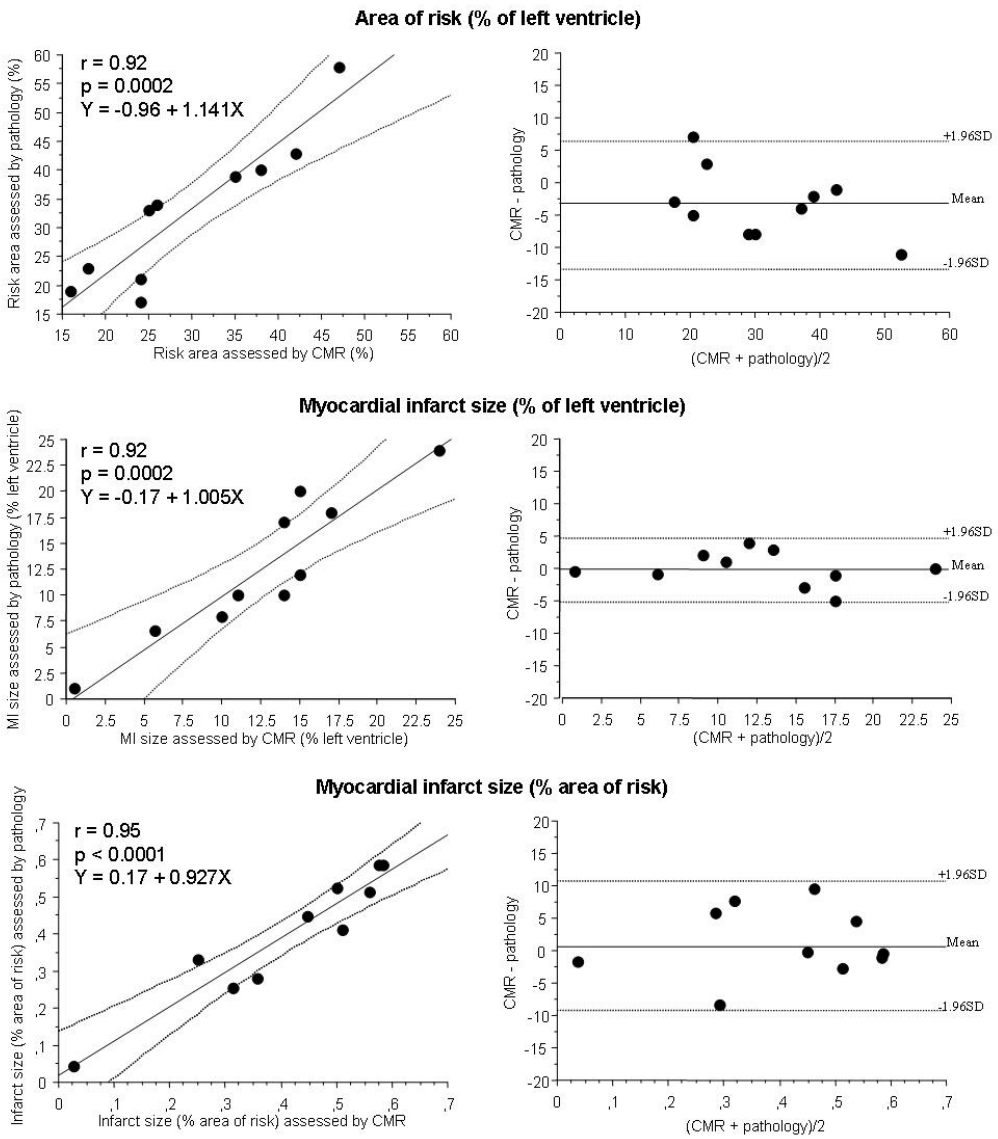
CMR#1 = cardiac magnetic resonance at day 3; CMR#2 = CMR 3 weeks later

A


a
End-diastole
End-systole
b
End-diastole
End-systole
CE-CMR
CE-CMR

B


End-diastole
End-systole
CE-CMR


Area of risk (% of left ventricle)
r = 0.92
p = 0.0002
Y = -0.96 + 1.141X
Risk area assessed by pathology (%)
Risk area assessed by CMR (%)
CMR - pathology
(CMR + pathology)/2
+1.96SD
Mean
-1.96SD
Myocardial infarct size (% of left ventricle)
r = 0.92
p = 0.0002
Y = -0.17 + 1.005X
MI size assessed by pathology (% left ventricle)
MI size assessed by CMR (% left ventricle)
CMR - pathology
(CMR + pathology)/2
+1.96SD
Mean
-1.96SD
Myocardial infarct size (% area of risk)
r = 0.95
p < 0.0001
Y = 0.17 + 0.927X
Infarct size (% area of risk) assessed by pathology
Infarct size (% area of risk) assessed by CMR
CMR - pathology
(CMR + pathology)/2
+1.96SD
Mean
-1.96SD