Myocardium at Risk after Acute Infarction in Humans on Magnetic Resonance Imaging: Quantitative Assessment during Follow-up and Validation with SPECT

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ABSTRACT

OBJECTIVES: To validate myocardium at risk on T2 weighted MRI (T2-STIR) over time, compared to perfusion SPECT in patients with ST-elevation myocardial infarction (STEMI), and, to assess the amount of salvaged myocardium after 1 week.

BACKGROUND: To assess reperfusion therapy, it is necessary to determine how much myocardium is salvaged by measuring the final infarct size in relation to the initial myocardium at risk of the left ventricle (LV).

METHODS: Sixteen patients with first-time STEMI received ^{99m}Tc tetrofosmin prior to primary percutaneous coronary intervention. SPECT was performed within 4 hours and T2-STIR MRI within 1 day, 1 week, 6 weeks and 6 months. At 1 week, patients were injected with a gadolinium-based contrast agent for quantification of infarct size.

RESULTS: Myocardium at risk at occlusion on SPECT was 33±10 % of the LV. Myocardium at risk on T2-STIR did not differ from SPECT, at day 1 (29±7 %, p=0.49), or week 1 (31±6 %, p=0.16) but declined at week 6 (10±12 %, p=0.0096 vs. 1 week) and month 6 (4±11 %, p=0.0013 vs. 1 week). The difference between SPECT and T2-STIR at 1 week was -2.3±5.7 %. Both modalities identified myocardium at risk in the same perfusion territory and in concordance with angiography. Final infarct size was 8±7 % and salvage was 75±19 % of myocardium at risk.

CONCLUSIONS: This study demonstrates that T2-STIR performed up to 1 week after reperfusion can accurately determine myocardium at risk as it was before opening of the occluded artery. MR imaging can also quantify salvaged myocardium as myocardium at risk minus final infarct size.

Keywords: Myocardium at risk, SPECT, T2-STIR, MRI, salvaged myocardium

CONDENSED ABSTRACT

This study aimed to validate myocardium at risk on T2-STIR MRI compared to SPECT in patients with first time ST-elevation myocardial infarction, and to assess myocardial salvage. Sixteen patients were injected with ^{99m}Tc-tetrofosmin prior to primary PCI and SPECT images were compared with T2-STIR at 1 day, 1 week, 6 weeks and 6 months. Myocardium at risk did not differ on SPECT and T2-STIR at 1 day or 1 week. T2-STIR performed up to 1 week after reperfusion accurately determines myocardium at risk as it was before opening of the occluded artery.

Abbreviation list

DE = Delayed Enhanced

LVM = Left Ventricular Mass

MI = Myocardial Infarction

MRI = Magnetic Resonance Imaging

PCI = Percutaneous Coronary Intervention

SPECT = Single Photon Emission Computed Tomography

STEMI= ST-elevation Myocardial Infarction

T2- STIR = T2-weighted Short Tau Inversion Recovery

INTRODUCTION

Myocardial infarction (MI) size depends heavily on duration of occlusion, collateral flow, and size of the initial myocardium at risk (1-3). Therefore, ST-elevation MI (STEMI) is treated with reperfusion therapy as soon as possible. The myocardium at risk, defined as the hypoperfused myocardium during acute coronary occlusion, is an important measure, since a variable amount of this area will become infarcted (4). Therefore, to assess the efficacy of reperfusion therapy, it is necessary to determine how much myocardium is salvaged by measuring the final infarct size in relation to the initial myocardium at risk.

MI size has earlier been quantified by single-photon emission computed tomography (SPECT) after injection of a technetium labelled perfusion tracer at rest (5), where MI is indirectly detected as a region with decreased myocardial perfusion. More recently, contrast delayed enhancement (DE) magnetic resonance imaging (MRI) has emerged as the new reference method for infarct localization and quantification (6-8).

Myocardium at risk can be measured on SPECT by injection of a technetium based tracer before opening of the occluded vessel and is currently the most widely practised technique to determine myocardium at risk (9-11). However, drawbacks in the use of SPECT to estimate myocardium at risk are the availability of a technetium based tracer, the need for injection of the isotope in the acute setting of coronary occlusion and scanning with a gamma camera after completion of primary percutaneous coronary intervention (PCI), which could interfere with patient care in the acute setting. These factors have limited the applicability of SPECT in measurement of myocardium at risk. Therefore, new clinical methods to quantify myocardium at risk need to be developed.

T2-weighted MRI (T2-STIR) highlights myocardial edema (12) present after myocardial infarction (13) without the need of tracer administration. Moreover, MRI with T2-STIR allows the detection of the ischemic zone several days after the occluded coronary artery is

opened (14,15). Therefore, MRI with T2-STIR can potentially be used for quantification of myocardium at risk. Previous studies have shown the use of T2-STIR imaging for acute infarction in both reperfused and non reperfused infarcts (12,14-17) and validated T2-STIR for myocardium at risk in animals (14). There are, however, no validation studies in humans for the quantification of myocardium at risk using T2-STIR MR imaging. Hence, the purpose of this study was to validate the measurement of the myocardium at risk on T2-STIR over time, in comparison with SPECT in humans with acute myocardial infarction, and to assess the amount of salvaged myocardium after 1 week.

METHODS

Study population and design

The study was approved by the local ethics committee and all patients gave their written informed consent. Sixteen patients (age; 64 ± 12, 14 males) with no history of myocardial infarction, presenting with acute STEMI due to an occluded coronary artery, were included in the study. All patients were treated by primary percutaneous coronary intervention (PCI) with coronary stents, resulting in TIMI grade 3 flow in the opened artery and received GPIIb/IIIa inhibitor.

Prior to primary PCI, ^{99m}Tc tetrofosmin was administered intravenously and myocardial perfusion SPECT was performed 3-4 hours after primary PCI for determination of myocardium at risk. MRI with T2-STIR was undertaken 1 week after revascularization. In one patient adequate T2-STIR images at 1 week were not obtained. To determine the time evolution of the increase in T2-STIR signal, early imaging was performed at 1 day in 8 patients and within 2 days in two patients (hereafter described as day 1), and 9 patients underwent MRI follow up at 6 weeks and 6 months. For comparison, all patients received delayed enhancement MR imaging with administration of gadolinium at 1 week. The culprit vessel was identified on angiography by two observers in consensus.

Myocardial perfusion SPECT

Patients were injected with 500-700 MBq ^{99m}Tc tetrofosmin (Amersham Health, Buckinghamshire, UK), depending on bodyweight. Myocardial perfusion ECG-gated SPECT was performed according to the standard clinical protocol at rest, using a dual head camera. Nine patients were imaged using an ADAC Vertex camera (Milpitas, California, USA), seven patients with a cardiac dedicated GE Ventri camera (GE Healthcare, Buckinghamshire, UK). The patients were placed in supine position and imaged in steps of 5.6 degrees using a 64 x 64 matrix with a pixel size of 5.02 mm for the ADAC camera and a pixel size of 6.4 mm for the

GE Ventri camera. Image acquisition time was approximately 15 minutes, but was extended to 25 minutes when imaging was performed after three hours. Short- and long-axis images, covering the left ventricle were reconstructed. Myocardium at risk was determined using an in-house developed segmentation software (Segment v1.702; http://segment.heiberg.se) (18). The automatic segmentation finds the centreline through the left ventricular wall and identifies the endo- and epicardium based on an individually estimated wall thickness and signal intensity values within the image. Manual adjustment of the automatic delineation was sometimes required in the left ventricular outflow region.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed on either of two 1.5T systems: Magnetom Vision (Siemens, Erlangen, Germany) with a CP body array coil, or Philips Intera CV (Philips, Best, the Netherlands) with a cardiac synergy coil. All subjects were placed in supine position and images were acquired at end-expiratory breath hold with ECG-gating. Initial scout images were acquired to locate the heart and a T2-weighted double inversion blood suppressed turbo spin echo sequence (T2-STIR) was employed to depict myocardium at risk. T2-STIR images were acquired in the short-axis view, covering the left ventricle from the base to apex. Image parameters for T2-STIR were: echo time, 43 ms (Siemens), or 100 ms (Philips); repetition time, 2 heart beats; number of averages, 2; inversion time 180 ms; image resolution, 1.5 x 1.5 mm; slice thickness, 10 mm (Siemens) or 8 mm with a slice gap of 2 mm (Philips). When acquiring images with the cardiac synergy coil parallel imaging with SENSE=1 was used to minimize signal inhomogeneities due to differences in coil sensitivity.

Infarct quantification was performed on DE-MRI 30 ± 9 minutes after intravenous administration of 0.2 mmol/kg extracellular gadolinium-based contrast agent (gadoteric acid, Gd-DOTA; Guerbet, Gothia Medical AB, Billdal, Sweden). DE-MRI with an inversion-recovery turbo fast low-angle shot sequence (Siemens; slice thickness, 10 mm; field of view,

380 mm; matrix, 126 x 256; flip angle, 25º; repetition time, 100 ms; echo time, 4.8 ms) or a inversion-recovery balanced turbo field echo sequence (Philips; slice thickness, 8 mm; field of view, 340 mm; repetition time, 3.14 ms; echo time, 1.58 ms) was performed, covering the left ventricle.

The MR images were analyzed using the same software as for the SPECT images (Segment v1.702; http://segment.heiberg.se) (19). Observers were blinded to patient data and time of acquisition after infarction. The myocardium in each LV short-axis slice was manually segmented by tracing the endocardial and epicardial borders. Regions of myocardium at risk and MI were identified as hyperenhanced regions, within the T2-STIR images and DE-MRI images, respectively. The myocardium at risk region was delineated manually by independent and blinded observers and the infarcted region was delineated automatically as previously described with manual adjustment when needed (19). Myocardium at risk size and MI size were defined as the total amount of myocardium at risk /MI in all short-axis slices and expressed as percentage of Left Ventricle Mass (LVM).

Statistical methods

Continuous variables are presented as mean ± SD. Pearson's correlation was used to determine the relationship between T2-STIR and SPECT. Two-tailed paired t-test was used to detect differences in myocardium at risk between techniques, differences in myocardium at risk on T2-STIR at different time points and the final infarct size compared to myocardium at risk on T2-STIR. A p-value below 0.05 was considered significant. Agreement between methods was expressed as mean difference ± SD and the limits of agreement was shown in a Bland-Altman graph as mean difference ± 2SD.

RESULTS

Myocardium at risk

Table 1 shows the patient characteristics for all 16 patients included in this study. Figure 1 shows multislice images from base to apex from T2-STIR at week 1, SPECT at day 1 and DE-MRI at week 1 from one patient. Myocardium at risk presented as a perfusion defect on SPECT and hyperenhanced regions on T2-STIR. In all patients, T2-STIR and SPECT identified myocardium at risk in the same perfusion territory and in concordance with angiography. The resulting infarction on DE-MRI was present in the same region in all patients.

Myocardium at risk on SPECT was 33 ± 10 % of the LV and on T2-STIR at day 1 29 ± 7 % ($p = 0.49$ compared to SPECT). Myocardium at risk on week 1 was 31 ± 6 % ($p = 0.16$ compared to SPECT) (Table 2). Myocardium at risk on T2-STIR at day 1 and week 1 did not differ ($p=1.00$). Over time, myocardium at risk declined to 10 ± 12 % at week 6 ($p = 0.0096$ vs. T2-STIR at 1 week and $p = 0.0026$ vs. SPECT) and 4 ± 11 % at month 6 ($p = 0.0013$ vs. T2-STIR at 1 week and $p = 0.001$ vs. SPECT). In patient 5 the observers were unable to designate the culprit vessel within the T2-STIR images at day 1, however, at week 1 the myocardium at risk could be identified. Figure 2A shows the relationship between myocardium at risk demonstrated on T2-STIR at week 1 and SPECT ($r^2 = 0.70$, $p<0.001$). There was no statistical significant difference between myocardium at risk on T2-STIR compared to SPECT on Bland-Altman analysis (-2.3 ± 5.7, $p=0.16$) (Figure 2B).

The evolution of myocardial edema in a patient with LAD occlusion is shown in Figure 3, SPECT is shown for comparison. The size of the affected region is similar at day 1 and week 1 on T2-STIR, but can not be detected at week 6 in this patient. Figure 4 displays the ratio between T2-STIR and SPECT at the different acquisition times, day 1 (0.97 ± 0.20), week 1 (0.97 ± 0.18), week 6 (0.35 ± 0.40) and month 6 (0.11 ± 0.27).

Myocardial salvage

The mean infarct size at week 1 was 8 ± 7 % LV (range 0 – 19), significantly smaller than myocardium at risk ($p<0.001$) (Table 2). Myocardial salvage, calculated as the difference of T2-STIR and DE-MRI at week 1 was on average 75 ± 19 % (range 41 – 100 %). One patient did not have any infarcted myocardium on DE-MRI after the acute revascularization meaning that all myocardium was salvaged by primary PCI, salvage in this patient was therefore 100%. This patient underwent revascularization within one hour after pain onset. In patient 1 infarct size by DE-MRI was compared to T2-STIR at day 1 in absence of T2-STIR data at week 1. The amount of salvaged myocardium is exemplified in one patient in Figure 5. Note that the salvage occurs in the subepicardial layers of the myocardium.

DISCUSSION

This study is the first to validate the quantification of myocardium at risk on T2-STIR over time in comparison to SPECT, in patients with STEMI. The main finding is that T2-STIR accurately identifies and quantifies myocardium at risk up to 1 week after opening of the occluded coronary artery. Thus, the success of reperfusion therapy can be assessed on MRI within one image session utilizing the combination of DE and T2-STIR to measure final infarct size and myocardium at risk, respectively, and thereby measuring myocardial salvage.

Myocardium at Risk

Earlier studies (12,14-17,20) have demonstrated the use of T2-weighted imaging for acute infarction, in both reperfused and non reperfused infarcts. The current study showed that T2-STIR accurately assessed myocardium at risk in reperfused infarcts in patients using SPECT at the time of coronary occlusion as the reference method. In agreement with studies on humans (21,22) and animals (12,14,23), the area with high T2 signal exceeded that of irreversible injury in acute MI. Pathology studies in humans have shown complete resorption of edema after AMI within 5 weeks (13) and Aletras et al (14) showed that edema was still present at the 2 month follow-up MRI in a canine model. No evidence of edema was found on T2-STIR in 7 of the 9 patients at 6 months after the acute coronary occlusion in the present study. One may hypothesize that these 2 patients may have had residual or recurring ischemia within the same myocardial region.

Myocardial ischemia increases cellular and extracellular osmolarity, alters plasma membrane permeability, causes cell swelling and interstitial edema (24). Quantification of interstitial edema has been demonstrated in experimental studies of myocardium at risk after reperfusion by light microscopy, autoradiography and contrast-enhanced IR echo planar MR imaging (25). Once reperfusion is established, an inflammatory reaction within the perfusion bed of the culprit vessel takes place, which significantly increases tissue edema. Myocardial

edema is therefore a consistent feature of acute ischemia (26) which can be demonstrated on T2-STIR (12) although the myocardium is reperfused (14,15). The results of the present study showed that the amount of edema present after 1 week was similar to the amount of edema at 1 day after reperfusion.

Advantages of T2-STIR over SPECT in assessing myocardium at risk are: 1) no need of tracer administration, 2) no complicated imaging interfering with patient care in the acute setting, 3) no radiation dose and 4) higher spatial resolution. Although quantification of myocardium at risk by T2-STIR at day 1 and week 1 did not show any significant difference, image quality was in favour to T2-STIR week 1.

Myocardial Salvage

The clinical usefulness of the present study is mainly that the size of myocardium at risk and MI, and therefore myocardial salvage, can be assessed at the same image session within 1 week after acute coronary occlusion, without interfering with patient care in the acute setting. In acute infarcts, the necrotic region is surrounded by a region of reversible injury, characterized by edema, and consists of myocardial tissue which has not undergone irreversible injury. This region is referred to as the salvageable myocardium at risk, and the region of irreversible injury, if left untreated, will expand in the first hours after acute myocardial infarction in accordance with the wavefront phenomena described by Reimer et al (27). To assess reperfusion therapy, it is necessary to determine how much myocardium is salvaged by measuring final infarct size in relation to the initial myocardium at risk. DE-MRI has the ability to quantify final infarct size (6,7) and as shown in this study T2-STIR accurately quantifies myocardium at risk. Therefore, MRI has the ability to calculate salvaged myocardium within the same imaging acquisition session (21). This can be used to evaluate new drugs and therapeutic procedures aimed at reducing infarct size without interfering with patient care in the acute setting. Indeed, Ibanez et al. (28) recently showed that metoprolol

administered before revascularization increased myocardial salvage in a pig model where myocardium at risk and final infarct size were assessed with T2-STIR and DE MR imaging. The results of the current study in patients with primary PCI showed that 75 % (range 41 – 100 %) of the initial myocardium on average was salvaged. Hence, this line of research can be applied in patient populations providing a salvageable index for each patient undergoing primary PCI after AMI and would potentially increase the knowledge on infarct-related tissue injury.

Limitations

The present study was performed on a limited number of patients, all presenting with first-time STEMI and undergoing successful reperfusion. Thus, how this would translate to other populations, for example unsuccessful revascularization, patients treated with trombolytic therapy or patients with previous myocardial infarctions, is not known (15). Only two women were included in this study and more data on females are therefore needed. However, T2-STIR images from the two females showed similar enhancement as the 14 male patients and there is no a priori reason to expect a gender difference in edema formation after AMI. Quantification of myocardium at risk by SPECT has previously been performed using sestamibi-tracers. In the present study, tetrofosmin was used, however, sestamibi and tetrofosmin are used interchangeably in patient studies (29). Image quality can be a limitation in assessing myocardium at risk by T2-STIR and the image quality of the present study did not allow for automated segmentation. New sequences, however, are continuously developed to overcome this problem (30,31). Images were acquired using a body array coil with the Siemens scanner and a cardiac surface coil with the Philips scanner. It has been suggested that a body coil has a more homogenous reception whereas the surface coil has an inherent signal intensity gradient (21). However, image reconstruction with parallel imaging techniques uses differences in coil sensitivity and therefore compensate inhomogenous reception. Thus the

images obtained with the surface coil in the present study was acquired using a parallel imaging factor (SENSE factor) of 1 to minimize this effect.

Conclusions

This is the first study to validate T2-STIR for quantification of myocardium at risk against an independent method (SPECT) in patients with acute myocardial infarction after reperfusion therapy. The results demonstrate that T2-STIR performed up to one week after reperfusion can accurately determine myocardium at risk as it was before opening of the occluded artery. The result of reperfusion therapy can therefore be assessed clinically by calculating myocardial salvage as the difference between myocardium at risk and final infarct size using MR imaging.

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FIGURE LEGENDS

Figure 1: Myocardium at risk by SPECT and T2-STIR MR imaging and final infarct size by DE-MR imaging in one typical patient.

Short-axis slices at the same ventricular level of SPECT day 1, T2-STIR week 1 and DE-MRI week 1, in a patient with reperfused right coronary occlusion resulting in an inferior infarct. The epicardium is traced in green, the endocardium is traced in red and the affected region is traced in yellow. Note the similarity in size of the affected region between perfusion defect size during coronary occlusion by SPECT and T2-STIR MR imaging one week later, showing that T2-STIR at week 1 can be used to quantify MaR.

Figure 2: Agreement between T2-STIR and SPECT.

Panel A: T2-STIR at week 1 versus perfusion defect during coronary occlusion by SPECT (r^2 = 0.70, $p<0.001$) with the line of identity. Panel B: Bland-Altman graph showing the difference between myocardium at risk quantified on T2-STIR (week 1) and SPECT vs. the reference method SPECT. The difference between T2-STIR and SPECT was -2.3 ± 5.7 %. Solid line = mean of T2-STIR – SPECT and dotted lines are ±2 SD.

Figure 3: T2-STIR over time in one typical patient

Mid-ventricular short-axis slices of automatically delineated perfusion defect during coronary occlusion by SPECT and blinded manual delineation of T2-STIR over time, in the same patient with a left anterior descending occlusion. The epicardium is traced in green, the endocardium is traced in red. The myocardium at risk is delineated in yellow. Note that the signal of the affected region on T2-STIR imaging is similar at day 1 and week 1, but disappears at week 6.

Figure 4: T2-STIR over time in all patients in relation to perfusion defect at occlusion by SPECT imaging

Ratio between T2-STIR and SPECT, at day 1, week 1, week 6 and month 6 were 0.97 ± 0.20; 0.97 ± 0.18; 0.35 ± 0.40; and 0.11 ± 0.27, respectively, showing that the T2-STIR signal at day 1 and week 1 agree with perfusion defect at occlusion by SPECT imaging. Presence of edema at 6 months was found in 2 out of 9 patients.

Figure 5: Myocardial salvage by MR imaging

Mid-ventricular short-axis slices in a patient with an LCx occlusion. The epicardium is traced in green, the endocardium is traced in red. Left: T2-STIR image showing the myocardium at risk (white arrows). Middle: Delayed enhanced MRI showing myocardial infarction (MI) (white arrows). Right: T2-STIR image with inclusion of infarcted region showing the amount of salvaged myocardium (blue area).

TABLES

Table 1: Patient Characteristics

Male	14	88%
Age (y)	64 ± 12	(36 – 83)
Body Mass Index	27 ± 3	(24 – 33)
Occluded artery by angiography		
LAD*	7	44%
RCA†	8	50%
LCX‡	1	6%

Values are presented as n (%) or as mean ± SD (range). * left anterior descending artery (LAD), † right coronary artery (RCA), ‡ left circumflex

Table 2: Percentage myocardium at risk and percentage infarcted and salvaged myocardium

Patients	SPECT	T2-STIR			DE	Salvaged myocardium*
			week 1	week 6	month 6	week 1	
	%	day 1 (%)	(%)	(%)	(%)	(%)	(%)
1	28	25	-	16	0	8	68.0 †
2	38	-	36	-	-	16	55.6
3	37	40	36	0	0	2	94.4
4	24	27	27	27	0	16	40.7
5	26	NA	24	13	5	7	70.8
6	38	30	36	0	0	19	47.2
7	28	-	23	-	-	1	95.7
8	39	25	26	30	32	10	61.5
9	34	34	34	0	-	2	94.1
10	39	39	31	-	0	0	100.0
11	20	18	25	5	-	2	92.0
12	20	27	25	-	-	1	96.0
13	46	-	42	-	-	19	54.8
14	31	-	29	0	0	6	79.3
15	25	-	30	-	0	10	66.7
16	56	-	43	-	-	7	83.7
Mean±SD	33 ± 10	29 ± 7	31 ± 6	10 ± 12	4 ± 11	8 ± 7	75 ± 19
vs.SPECT		p=0.49	p=0.16	p=0.0026	p=0.001		

* Salvaged myocardium: Percent of myocardium salvaged in comparison with T2-STIR week 1. † Salvaged myocardium in comparison with T2-STIR day 1. -: no imaging performed. NA: unable to appoint occluded vessel.

Figure 1

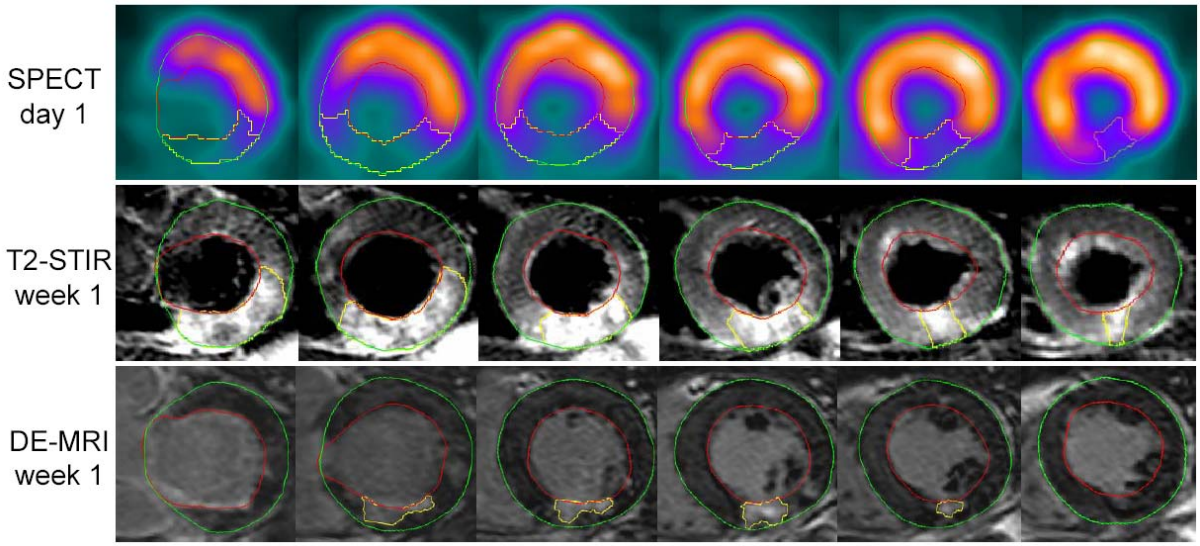


Figure 2

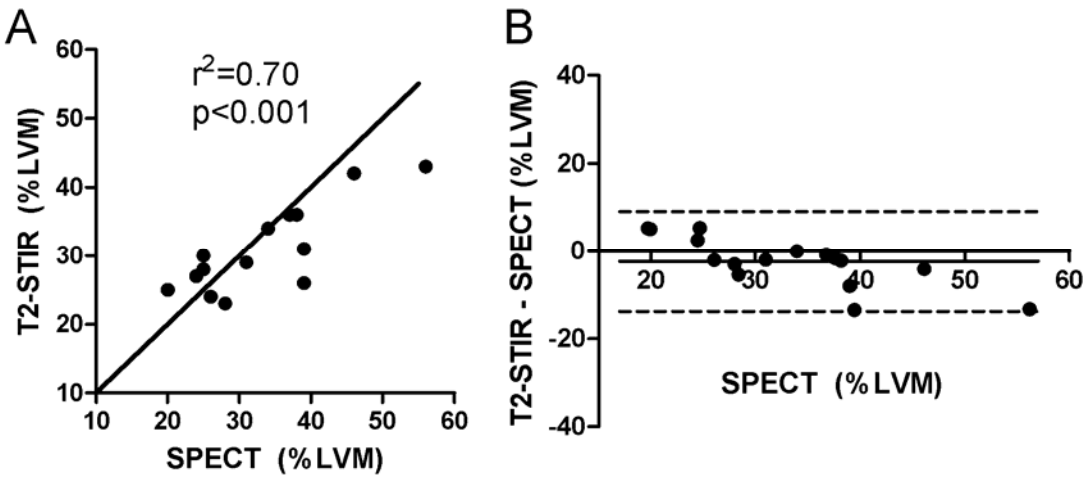

A
r²=0.70
p<0.001
T2-STIR (%LVM)
SPECT (%LVM)
B
T2-STIR - SPECT (%LVM)
SPECT (%LVM)

Figure 3.

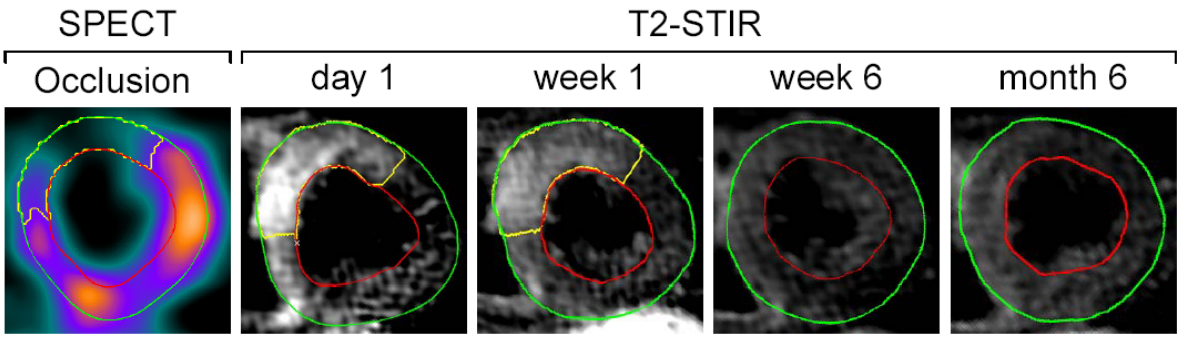


Figure 4

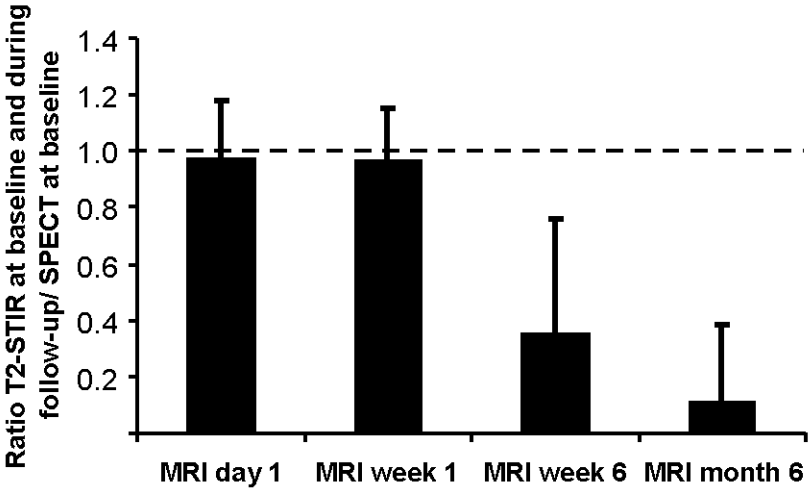
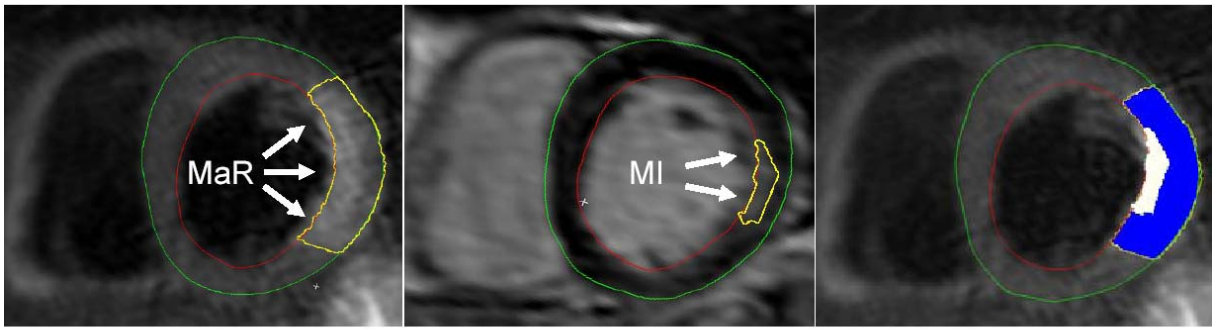

Ratio T2-STIR at baseline and during follow-up/ SPECT at baseline
1.4
1.2
1.0
0.8
0.6
0.4
0.2
MRI day 1
MRI week 1
MRI week 6
MRI month 6

Figure 5



MRI T2-STIR DE-MRI Salvaged myocardium