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Age-independent Myocardial Infarct quantification by Signal Intensity Percent Infarct Mapping in Swine

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Abstract

Purpose—To test whether signal intensity percent infarct mapping (SI-PIM) accurately determines the size of myocardial infarct (MI) regardless of its age.

Materials and methods—Forty-five swine with reperfused MI underwent 1.5T late gadolinium enhancement (LGE) MRI after bolus injection of 0.2mmol/kg Gd(DTPA) on days 2–62 following MI. Animals were classified into acute, healing, and healed groups by pathology. Infarct volume (IV) and infarct fraction (IF) were determined using binary techniques (including 2–5 standard deviations (SD) above the remote, and full-width at half-maximum) and the SI-PIM method by two readers. Triphenyl-tetrazolium-chloride staining (TTC) was performed as reference. Bias (percent under/overestimation of IV relative to TTC) of each quantification method was calculated. Bland-Altman analysis was done to test the accuracy of the quantification methods, while intraclass correlation coefficient (ICC) analysis was done to assess intra- and interobserver agreement.

Results—Bias of the MRI quantification methods do not depend on the age of the MI. FWHM and SI-PIM gave the best estimate of MI volume determined by the reference TTC (p-values for the FWHM and SI-PIM methods were 0.183, 0.26, 0.95 and 0.073, 0.091, 0.73 in Group 1, Group 2 and Group 3, respectively), while using any of the binary thresholds of 2–4SD above the remote myocardium showed significant overestimation. The 5SD method, however, provided similar IV compared to TTC and was shown to be independent of the size and age of MI. ICC analysis showed excellent inter- and intraobserver agreement between the readers.

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Conclusions—Our results indicate that the SI-PIM method can accurately determine MI volume regardless of the pathological stage of MI. Once tested, it may prove to be useful for the clinic.

Keywords

myocardial infarct; infarct quantification; late gadolinium enhancement; partial volume effect; signal intensity percent infarct mapping

INTRODUCTION

Late gadolinium enhancement (LGE) MR imaging has been accepted as the reference standard for imaging myocardial infarcts (MI) throughout the healing process (1). Since MI size is known to be an important predictor of clinical outcome (2), its accurate quantification is crucial for prognostication. However, currently used methods for image analysis are binary techniques, i.e. each voxel is either classified as dead or live myocardium.

It has been shown that reperfused MIs are patchy rather than confluent (3). In fact, viable regions are admixed with necrotic ones, thus, resulting in an overestimation of MI size due to partial volume effects (4) when MI quantification is carried out using the binary methods of image analysis. Using a binary method, when a given voxel contains a mixture of infarcted and healthy myocytes, the two different LGE signal intensities (SI) characteristic of these two tissue types will be averaged, leading to an intermediate SI value, resulting in an increased number of voxels potentially falsely considered necrotic. Although binary quantification methods are clinically widely accepted, they are substantially dependent on signal-to-noise ratio (SNR) and successful nulling of signal from the remote myocardium (5). It has been shown that voxels with low or intermediate level of the averaged hyperenhancement are detected mainly in the periinfarct zone of the MI (6), a zone which becomes reduced in size or disappears in images obtained 2-6 weeks after MI (7).

As partial volume effects are mainly observed in the periinfarct zone of acute MI, which diminish in size over time (7), one would expect that the accuracy of MI volume quantification by a binary method could strongly depend on the time that elapsed after coronary occlusion and reperfusion. In a study of Matsumoto et al. (8), the median ratio of the size of the periinfarct zone and the size of the entire MI was 37% with interquartile ranges of 19% and 72%. There was an inverse relationship between the relative periinfarct zone and the mean transmural score indicating that smaller subendocardial MIs had larger fraction of periinfarct zone than transmural MIs. This larger periinfarct zone in turn can result in a more prominent partial volume effect and increased number of false fully-necrotic voxels when expressed in relation to the histopathologically determined MI volume.

MI quantification methods currently being used are based on the fact that scar tissue has a SI value above that of the normal myocardium. There is no widely accepted standard for MI volume quantification. Current guidelines recommend the use of a SI threshold of 2 standard deviations (SD) above the average SI in the remote myocardium (9); various other methods, however, are also available (10).

In the present study, our aim was to test the hypothesis that the accuracy of Signal Intensity Percent Infarct Mapping (SI-PIM) (11), which calculates the infarct percentage of each voxel on a sliding scale of necrotic content, is independent of the size of the MI at the different pathological stages of MI, contrary to binary methods, which are not. We aimed to compare the results to those obtained by binary SI thresholds of 2 to 5 SDs, and the full-width at half-maximum (FWHM) method, as well as to MI size determined by 2,3,5-triphenyl-tetrazolium chloride (TTC) staining.

MATERIALS AND METHODS

Myocardial infarct generation

The animal protocol was approved by the Institutional Animal Care and Use Committee in full compliance with the 'Guidelines for the Care and Use for Laboratory Animals' (NIH). Swine (n=45, between 8-10 weeks of age) weighing 32 ± 9 kg were anesthetized by continuous administration of Isoflurane. Normal body temperature was maintained using a heating pad. To record electrophysiological signs of myocardial ischemia and arrhythmias, ECG electrodes were placed on the chest of the animal. A pulse-oxymeter was placed on the animal's tongue to monitor heart rate and blood oxygen saturation. The right femoral artery was separated surgically and an arterial sheath (6 French) was inserted. An intravenous line was placed into one of the superficial ear veins to administer infusion and drugs. Intravenous heparin (100 IU/kg) was given to maintain the activated clotting time (ACT) above 300 seconds. A 6 French coronary guide catheter was introduced to cannulate the ostium of the left main. A properly sized 2-2.5 mm angioplasty balloon was introduced over a coronary guide catheter under fluoroscopic guidance into the Left Anterior Descending (LAD) or the Left Circumflex (LCx) coronary artery and inflated for 90 minutes to create MI. The balloon was deflated thereafter to restore coronary circulation. Coronary angiography confirmed the onset of reperfusion following balloon deflation. The femoral artery was decannulated, surgically ligated, and the wound was closed.

Magnetic Resonance Imaging

On days 2-62 following MI, animals were re-anesthetized as described above, and MRI studies were performed on a 1.5 T system (Signa-Horizon CV/i, GE Healthcare Milwaukee, WI). A cardiac phased-array coil and ECG gating were employed. Breath-hold was performed at end-inspiration by manual control. Conventional cardiac planes were set and short axis slices covering the entire left ventricle (LV) were obtained using a retrospectively ECG-gated steady-state free-precession sequence. A 180° -prepared, segmented, inversion-recovery fast gradient-echo pulse sequence was used to visualize MI with the following parameters: field of view (FOV), 300 mm; image matrix, 256×256 ; echo time (TE), 3.32 ms; repetition time (TR), two cardiac cycles (1100-1600 ms); bandwidth, 31.25 Hz/pixel; in-plane resolution, 1.36 mm^2 ; slice thickness, 10 mm; and no interslice gap. The inversion time (TI) was optimized to null the signal in normal myocardium (typical TI: 320 ms). LGE images were acquired 15 minutes after intravenous bolus injection of 0.2 mmol/kg Gd(DTPA) (Magnevist, Bayer Healthcare, Whippany, NJ). Euthanasia was performed the day after the MRI experiment.

Experimental groups

According to the pathological appearance, MI can be categorized as acute (6h–7 days; presence of polymorphonuclear leucocyte infiltration), healing (7–28 days; presence of mononuclear cells and fibroblasts) and healed MI (29 days and beyond; presence of acellular scar tissue) (12). Animals were classified into these three groups based on the time elapsed after coronary occlusion and reperfusion (12,13) at the time of the MRI as follows: Group 1 (acute, n=13), Group 2 (healing, n=25) and Group 3 (healed, n=7).

Image post-processing and analysis

All image analyses were carried out by two independent readers (Z.L. with 3 and A.V.S. with 9 years of cardiovascular MRI experience, respectively). MRI dicom images were analyzed with the use of MASS Research Software (Leiden University Medical Center, Leiden, The Netherlands). The endo- and epicardial contours of the LV were traced manually in LGE images. Image histogram was used to find the maximum SI (SI_{max}) and the area containing SI_{max} was circumscribed. In the same slice, a region of interest (ROI) of at least 100 pixels was selected to measure the mean SI of the remote myocardium. Infarct volume (IV) was determined for each individual slice by an automated analysis using the threshold limits of 2–5 SDs above the mean SI of the remote myocardium or applying the FWHM method (14). The sum of IVs represents the total volume of the MI for a particular heart. Infarct fraction (IF) was expressed as the total IV divided by the LV myocardial volume (LVV) and multiplied by 100.

SI-PIM Processing

The previously introduced R1-PIM algorithm (11) has been redesigned to be able to process analysis based on SI, instead of R1. This algorithm requires the same remote myocardial ROI as used for binary quantification. SI values less or equal than the mean + 2 SDs of remote myocardium are denoted as 0% infarcted, while the core of the infarct (10 maximally enhanced pixels) is assigned as 100% infarcted. Based on the voxel-by-voxel SI values, a percent infarct (PI) scale between 0 and 100 % infarct content is generated and PI values are then calculated from the SI values for each voxel. Thus the infarct content of each voxel is now represented by a specific PI value.

SI-PIM was generated from the LGE image set. To each myocardial voxel a PI value was assigned by applying the PIM algorithm (11). IVs were determined as sum of the partial volumes of voxels. IF was assessed by taking the average of the PI values in the entire LV.

Microvascular Obstruction

Areas of microvascular obstruction were denoted by definition as being 100% infarcted and were automatically added to the binary and SI-PIM based IVs by the MASS software used for LGE image analysis.

TTC-staining and calculations

Hearts were excised following successful euthanasia, rinsed with saline, and sliced into 5 mm thick sections based on the orientations of the MRI tomographic slices. The sections

were then incubated with a buffered (pH 7.4) 1.5% 2,3,5-triphenyl-tetrazolium chloride (TTC) solution at a temperature of 37°C for 20 min, as described by Fishbein et al. (15). Both surfaces of each slice were digitally scanned at a 300 dots per inch image resolution using a Lexmark X1270 (Lexmark International Inc, Lexington KY) image scanner.

The existence and size of MIs were validated by assessing the TTC images. Digitized images were analyzed using ImageJ. Image analysis was carried out independently by two observers (Z.L. with 3 and A.V.S. with 9 years of experience, respectively). The MI area and the LV myocardial area on both sides of each TTC slice were manually determined by planimetry. Multiplying the total slice surface and the infarcted area by half of the TTC slice thickness provided the volume of myocardium and of infarct for every slice, respectively. The volume data (IV and LVV) were summarized for the entire image set.

Bias

Bias in quantification of IV by the distinct post-processing techniques was calculated as follows:

$$Bias = (IV_{MRI} - IV_{TTC}) / IV_{TTC} \times 100$$

where IV_{MRI} is the IV determined based on either the binary or the SI-PIM method. IV_{TTC} refers to the IV calculated from TTC-stained slices.

Based on the equation above, negative values indicate an underestimation, whereas bias with a positive value can be interpreted as an overestimation of IV compared to TTC staining.

Statistical analysis

Statistical analyses were carried out using SigmaPlot v11 (Systat Software Inc, San Jose, CA). Normality and equality of variances were tested on the IV and IF data. If data passed the normality test, they were analyzed with an all pairwise multiple comparison procedure (Holm-Sidak method) and were expressed as mean $\pm$ SD. When data were not normally distributed, they were analyzed using the non-parametric Kruskal-Wallis One Way ANOVA test and results were reported as median (with quartiles in brackets). If significant differences were found between groups, an all pairwise multiple comparison procedure (Tukey test) was carried out. Pearson product moment correlation was used to examine the relationship between bias and the size of MI determined from TTC-staining. Multiple regression analysis was performed to examine if the bias depended on the age and size of MI using all of the animals without any grouping. Bland-Altman analysis was done to test the accuracy of the MR quantification methods compared to TTC. Intra- and interobserver agreement between the two readers was tested by intraclass correlation coefficient (ICC). ICC was interpreted as follows: < 0.4, poor; 0.4 to 0.75, fair, to good; and > 0.75 excellent. The study was designed to achieve the desired power of 0.75. A p-value smaller than 0.05 was considered significant.

RESULTS

Figure 1 shows a representative image set (raw, binary, SI-PIM) of MI obtained in one animal from each of the acute, healing, and healed MI group of swine, respectively.

The median SI of the remote myocardium in Groups 1, 2, and 3 were 7.96 [7.46, 9.42], 8.37 [7.66, 8.75] and 8.08 [7.10, 8.71] respectively. The mean of the maximum SI in MI areas was 49.83 ± 7.88 , 46.28 ± 15.03 and 53.86 ± 17.88 in the same groups, respectively. LVV calculated from the MRI images and those obtained by TTC-staining were 64.84 ± 14.81 ml and 67.91 ± 14.57 ml, respectively ($p=0.325$). The infarct age range was 6h-7 days in the acute (median 4 [3, 5.5] days), 7-28 days in the healing (median 13 [10.5, 25.5] days), and 29 days and beyond in the healed phase (median 55 [53, 60] days), respectively. IV and IF values in Groups 1, 2, and 3 are compiled in Tables 1 and 2.

The correlation between IV_{TTC} and the bias of each of the MRI quantification methods applied in this study were tested. Also tested was the relationship between the age of the MI and the bias of each method in all animals without any grouping (Table 3). Bias of the binary methods using 2 to 4 SDs as a threshold above the SI of the remote myocardium showed significant negative correlation with IV_{TTC} , but there was no significant relationship when using the 5 SD threshold. Statistical analysis revealed significant negative correlation between the bias of SI-PIM and the volume of MI determined by TTC-staining, as well as between IV_{FWHM} and IV_{TTC} . There was no significant correlation between the age of the MI and any of the MRI quantification methods. (Table 3).

In each group, all pairwise multiple comparisons revealed that the IVs quantified by the SI-PIM method did not differ from the IVs determined from the TTC stained myocardial slices (Table 1 and Figure 2). In each group, IV_{FWHM} and IV_{5SD} also gave a good estimate of IV_{TTC} . IV_{2SD} and IV_{3SD} provided marked overestimation of IV_{TTC} . IV_{4SD} differed significantly from IV_{TTC} in Group 1, but there was not a significant difference in Groups 2 and 3.

IF measured with SI-PIM did not differ significantly from the IF obtained from TTC-staining (Table 2 and Figure 2). IF_{FWHM} provided a good estimate of IF_{TTC} . In Group 1, IFs determined with the binary methods using 2-5 SDs differed significantly from IF_{TTC} . In Group 2, there was significant difference between IF_{TTC} and IFs determined with thresholds of 2-4 SDs, but using 5SD as the cut-off provided good estimate of the TTC-derived IF. In the healed phase of MI, 4 and 5 SDs provided an IF similar to IF_{TTC} , while IF_{2SD} and IF_{3SD} did not.

ICC analysis showed excellent intra-and interobserver agreement of IV and IF obtained by the different MI quantification methods (Table 4).

Bland-Altman plots revealed good agreement between the SI-PIM and the TTC as well as between the FWHM and TTC results with the mean of difference at -1.3 and -0.7 , respectively. Narrow limits of agreement indicate that the methods yield similar results (Figure 3). Contrary to this, wide 95% limits of agreement can be seen with high means of

differences when applying the 2-5 SD SI thresholds and comparing the results to the reference TTC method.

DISCUSSION

In the present study, we showed that MI size measured with the SI-PIM method did not differ significantly from that determined with the gold standard TTC-staining. A slight underestimation by SI-PIM could be seen at the different pathological stages of MI. The bias of this method did not correlate with the age of MI, meaning that SI-PIM provided a good estimate of the histopathologically determined MI extent, independently of the pathological stage of the MI. Among the binary methods, MI size calculated with the FWHM method did not differ significantly from the TTC-derived values. Although the bias of this method did not depend on the age of the MI, it has a significant negative correlation with IV_{TTC} . The 5 SD method provided a good estimate of IV_{TTC} in each phase of the MI and the bias of this method did not depend on the size or age of the MI. Using 2 SD as a SI threshold - which is at present widely used in everyday clinical practice - significantly overestimated the IV compared to that which was determined from the corresponding TTC-stained myocardial slices. The bias of applying the SI threshold of 2SD above the remote myocardium showed a negative correlation with IV_{TTC} , suggesting that a smaller MI volume would result in a larger overestimation when using 2SD as a SI cut-off value for MI quantification.

The time course of the evolution of MI has been well-studied by means of LGE MRI. Gd-DTPA and the necrosis-avid gadophrin-2 showed different sizes of LGE areas when administered a day after coronary occlusion and reperfusion (16,17). After injection, gadophrin-2 specifically binds to the necrotic component of myocardium, while Gd-DTPA freely distributes in the extracellular space which contains dead myocytes and edematous tissue in the acute phase of MI, suggesting a periinfarct zone around the necrotic area. A moderate periinfarct zone can be seen on the day of the coronary occlusion in gadolinium-enhanced spin-echo MRI images, a zone which is reduced in size or disappears in images obtained 2-6 weeks after MI (7). The area of enhanced myocardium is larger than the area of MI detected by histochemical morphometry when images are obtained several hours after coronary occlusion (7). The peripheral zone contains a mixture of necrotic and viable but possibly edematous myocytes in the acute phase of MI (7). In the chronic setting, collagen fibers are densely packed and replace the necrotic myocytes thus reducing the volume of the periinfarct zone.

Partial volume effect, observed mainly in the periinfarct zone, is a major confounding factor when quantifying MI volume in LGE images. There have been several attempts to overcome the shortcomings of the binary methods but all those, per definition, classified myocardial pixels as either being fully infarcted or not infarcted at all. Heiberg et al. (18) emphasized the importance of using a quantification process that would account for the partial volume effect. In their automated algorithm that had a low variability, myocardial pixels were weighted according to SI so that myocardial fraction was calculated for each pixel individually. They found the lowest bias and variability by using 4.7 SD as SI threshold that is close to the 5 SD cut-off value Bondarenko et al. mentioned in their study (19). In our study, in each group, the MI volume measured with SI-PIM was slightly smaller than

measured by TTC-staining. This can be understood on the basis of the different tissue substrate probed by the MRI vs. the histology technique. While SI-PIM reflects the MI content of each volume element of tissue, the histology measurements on TTC stained slices are made on the two surfaces of each slice, without including any appreciable depth. This would mean that using the TTC method, the amount of infarcted tissue is tacitly assumed to be homogeneous throughout the whole depth of the slice, necessarily resulting in an overestimation of MI volume as compared to SI-PIM which is based on the PI content of each voxel individually. Also, the thermal-conditioning step during TTC-staining may change the configuration of the necrotic tissue by dehydrating the myocardium possibly leading to an inaccurate delineation of the true MI zone (14).

We found a significant overestimation of MI size that has already been proven by previous studies (20,21) when using 2-4 SDs as a cut-off value for binary analysis. However, 5 SD provided a good estimate of MI size independently of the age and size of the MI. The selection of the ROI in the remote myocardial area has great influence on the accuracy of IV quantification in the binary analysis. On the other hand, SI-PIM uses the maximum SI of the infarct core (10 pixels), which is generated automatically, thus it is less affected by any observer bias. The SI-PIM quantification is not based on an average voxel SI resulting from the component SIs of partly necrotic and partly viable areas in a voxel, but determines the MI content of each voxel on a percent scale (22). Varga-Szemes et al. highlighted that there can always be found a specific threshold value that, when used, would make the binary method provide an IF equal to the one obtained from TTC (23). However, it needs to be emphasized that binary methods quantify all myocardial voxels as being viable or nonviable. Thus, even if providing an IF equal to the reference TTC value, the infarct-involved area might be mischaracterized. Infarct density is usually the highest in the core of the MI, while toward the periphery there are viable cells mixed with dead myocytes, the area that is the most affected by the partial volume effect (18). SI-PIM can reliably detect this periinfarct zone by measuring the infarct content of each voxel individually. On the other hand, binary methods using a higher threshold are more prone to “miss” this region (18). Using a high SI cut-off value would result in loss of useful data, and thus mischaracterization of real MI volume and morphology, especially in the periinfarct zone, which has a great clinical importance by serving as the source of malignant ventricular arrhythmias post MI (24). According to our data, the accuracy of SI-PIM to measure MI size depends on the size of MI. It needs to be emphasized, however, that TTC-staining can distort the ‘real’ MI territory possibly causing this ambiguous result. Our results indicate that bias in measuring MI size by the SI-PIM method is independent of the age of the MI. This suggests that this voxel-by-voxel MI quantification method is capable to determine MI size independently of the time elapsed after coronary occlusion and reperfusion.

MI size is a significant predictor of functional recovery after MI (25) as well as the determinant of the occurrence of post MI malignant ventricular arrhythmias (26,27) which in turn is a negative prognostic factor. Patients with large MI are more likely to develop cardiac decompensation and congestive heart failure than those with smaller MI (28). Along with the clinical setting, accurate MI determination is also a key factor in clinical trials and scientific studies when MI size is an outcome parameter (29).

We acknowledge some limitations to our study. First, the swine model of reperfused MI may not fully reflect human cases. Also, the existing pathology gold standard for MI quantification is by no means perfect. While data from TTC-staining are accepted as an accurate method for obtaining MI volume, they do not reflect true MI size due to the reasons stated in the Discussion. The delineation of the endocardial and epicardial contours in LGE images may also result in inaccuracy. Apical MIs in the short axis plane may be difficult to visualize by LGE, possibly leading to inaccurate quantification of MI in such cases.

Despite some limitations, being able to accurately quantify MI volume makes the SI-PIM method a promising tool for MI quantification in scientific experiments and it may have the potential, once tested, to become useful for clinical practice.

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Figure 1.

In vivo short axis inversion recovery MR images and post-processed SI-PIM with the corresponding TTC-stained slice from the acute, healing and healed phase in a reperfused MI swine model. Endocardial (red) and epicardial (green) contours were traced manually. The binary method was applied using the threshold limit of 2 SDs above the mean SI of the remote myocardium. The MI area demarcated by the 2SD binary method equals the MI area highlighted by the SI-PIM approach since both techniques employ a 2 SD cut-off to define the normal myocardium. The central hypoenhanced area, which reflects microvascular obstruction, was traced manually (pink) and added to the MI. From top to bottom shown are raw LGE images from the three groups (A, E, I), their binary parametric, daughter images (B, F, J) that were used to calculate MI size. Shown are the corresponding SI-PIM parametric, daughter images (C, G, K) which are based on the percent infarct content of each voxel individually. Percent infarct values are shown on a color scale. TTC photos (D, H, L) validate the localization and size of MI.

Figure 2.

The IVs and IF values calculated by the binary (2SD, 3SD, 4SD, 5SD, FWHM), SI-PIM, and TTC methods in Group 1 (A, B), Group 2 (C, D), and Group 3 (E, F), are shown. Data passed the normality test are shown using a bar chart indicating mean + SD. Data not normally distributed are shown with box plots displaying the median values with corresponding quartiles. * indicates significant difference compared to the reference TTC-staining.

Figure 3.

Bland-Altman analysis of IV obtained by the different MI quantification methods compared to TTC analysis are shown. Dashed lines show the 95% limits of agreement (± 1.96 SD) and the solid line shows the mean of differences.

Table 1

IVs calculated with the binary methods or SI-PIM, and those obtained with TTC-staining. Data are presented as median values with the quartiles in brackets if the data failed the normality test and they were reported as mean $\pm$ SD if they were distributed normally.

Method	Group 1		Group 2		Group 3	
	IV (ml)	p [*]	IV (ml)	p [*]	IV (ml)	p [*]
2SD	10.12 [7.53, 12.03]	0.007	5.97 [4.69, 8.91]	0.003	6.21 $\pm$ 1.94	0.001
3SD	9.03 [6.81, 11.53]	0.024	5.06 [3.84, 8.51]	0.03	5.26 $\pm$ 1.97	0.008
4SD	8.66 [6.27, 10.91]	0.046	4.62 [3.28, 8.19]	0.157	4.64 $\pm$ 2.32	0.089
5SD	8.37 [5.36, 10.58]	0.124	4.16 [2.59, 7.49]	0.522	4.29 $\pm$ 2.33	0.08
FWHM	5.01 [3.74; 5.85]	0.183	3.11 [1.9; 4.41]	0.26	2.83 $\pm$ 1.4	0.95
SI-PIM	4.6 [3.57, 5.37]	0.073	2.43 [1.76, 4.03]	0.091	2.57 $\pm$ 0.99	0.73
TTC	6.09 [4.48, 9.08]	N/A	3.87 [2.12, 6.31]	N/A	2.78 $\pm$ 1.29	N/A

IV, infarct volume; SD, standard deviation; FWHM, full-width at half-maximum; SI-PIM, signal intensity percent infarct mapping; TTC, triphenyl-tetrazolium-chloride; N/A, not applicable

* when compared to the reference TTC

Table 2

IFs calculated with the binary methods or SI-PIM, and those obtained with TTC-staining. Data are presented as median values with the quartiles in brackets if the data failed the normality test and they were reported as mean $\pm$ SD if they were distributed normally.

Method	Group 1		Group 2		Group 3	
	IF (%)	p [*]	IF (%)	p [*]	IF (%)	p [*]
2SD	18.08 $\pm$ 5.63	<0.001	11.23 [6.46, 15.45]	<0.001	8.76 $\pm$ 3.67	0.008
3SD	17.02 $\pm$ 5.53	0.002	8.95 [5.73, 14.68]	0.006	7.7 $\pm$ 3.89	0.037
4SD	15.94 $\pm$ 5.47	0.008	6.74 [4.67, 13.15]	0.041	6.94 $\pm$ 4.1	0.096
5SD	14.83 $\pm$ 5.57	0.027	5.83 [3.89, 11.67]	0.256	6.47 $\pm$ 4.02	0.07
FWHM	9 $\pm$ 2.57	0.322	4.65 [3.87; 7.45]	0.726	4.12 $\pm$ 2.52	0.85
SI-PIM	8.28 $\pm$ 3.11	0.218	4.11 [2.72, 7.01]	0.135	3.65 $\pm$ 1.82	0.405
TTC	10.67 $\pm$ 4.9	N/A	5.57 [3.18, 8.51]	N/A	3.89 $\pm$ 1.82	N/A

IF, infarct fraction; SD, standard deviation; FWHM, full-width at half-maximum; SI-PIM, signal intensity percent infarct mapping; TTC, triphenyl-tetrazolium-chloride; N/A, not applicable

* when compared to the reference TTC

Table 3

Relationship between the bias of the MRI quantification methods and the size of MI as well as between the bias and the age of the MI without any group consideration. Bias values indicate the over- or underestimation of MI size by the binary or the SI-PIM method compared to the reference TTC-staining. Data are presented as median values with the quartiles in brackets.

Method	Bias in IV	Correlation with IV _{TTC}	Correlation with age of MI
2SD	64.71 [39.95; 127.22]	$r = -0.51$ $p < 0.01$	$r = 0.28$ $p = 0.07$
3SD	45.81 [25.90; 95.21]	$r = -0.41$ $p < 0.01$	$r = 0.22$ $p = 0.14$
4SD	36.79 [14.97; 74.6]	$r = -0.35$ $p = 0.02$	$r = 0.2$ $p = 0.2$
5SD	25.87 [0.66; 60.09]	$r = -0.28$ $p = 0.07$	$r = 0.2$ $p = 0.19$
FWHM	-16.48 [-25.32; 14.04]	$r = -0.335$ $p = 0.03$	$r = -0.08$ $p = 0.61$
SI-PIM	-27.79 [-36.36; -8.81]	$r = -0.38$ $p = 0.01$	$r = 0.15$ $p = 0.31$

IV, infarct volume; MI, myocardial infarct; SD, standard deviation; FWHM, full-width at half-maximum; SI-PIM, signal intensity percent infarct mapping; TTC, triphenyl-tetrazolium-chloride

Table 4

Interobserver and intraobserver agreement in IV and IF measurements by the different quantification methods

Method	Interobserver ICC		Intraobserver ICC	
	IV	IF	IV	IF
2SD	0.849	0.789	0.897	0.862
3SD	0.861	0.794	0.887	0.816
4SD	0.812	0.805	0.901	0.849
5SD	0.823	0.817	0.891	0.887
FWHM	0.914	0.859	0.943	0.919
SI-PIM	0.897	0.851	0.926	0.908

IV, infarct volume; IF, infarct fraction; ICC, intraclass correlation coefficient; SD, standard deviation; FWHM, full-width at half-maximum; SI-PIM, signal intensity percent infarct mapping