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INFARCT DENSITY DISTRIBUTION BY MRI IN THE PORCINE MODEL OF ACUTE AND CHRONIC MYOCARDIAL INFARCTION AS A POTENTIAL METHOD TRANSFERABLE TO THE CLINIC

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Abstract

Purpose—To study the feasibility of a myocardial infarct (MI) quantification method (Signal Intensity-based Percent Infarct Mapping, SI-PIM) that is able to evaluate not only the size, but also the density distribution of the MI.

Methods—In 14 male swine, MI was generated by 90 minutes of closed-chest balloon occlusion followed by reperfusion. Seven (n=7) or 56 (n=7) days after reperfusion, Gd-DTPA-bolus and continuous-infusion enhanced Late Gadolinium Enhancement (LGE) MRI, and R1-mapping were carried out and post mortem triphenyl-tetrazolium-chloride (TTC) staining was performed. MI was quantified using binary (2 or 5 standard deviations, SD), SI-PIM and R1-PIM methods. Infarct Fraction (IF), and Infarct-Involved Voxel Fraction (IIVF) were determined by each MRI method. Bias of each method was compared to the TTC technique.

Results—The accuracy of MI quantification did not depend on the method of contrast administration or the age of the MI. IFs obtained by either of the two PIM methods were statistically not different from the IFs derived from the TTC measurements at either MI age. IFs obtained from the binary 2SD method overestimated IF obtained from TTC. IIVF among the three different PIM methods did not vary, but with the binary methods the IIVF gradually decreased with increasing the threshold limit.

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Conclusions—The advantage of SI-PIM over the conventional binary method is the ability to represent not only IF but also the density distribution of the MI. Since the SI-PIM methods are based on a single LGE acquisition, the bolus-data-based SI-PIM method can effortlessly be incorporated into the clinical image post-processing procedure.

Keywords

Myocardial Infarct Quantification; Magnetic Resonance Imaging; Percent Infarct Mapping; Myocardial Infarct Heterogeneity

INTRODUCTION

Determination of viability after myocardial infarction (MI) is crucial for therapeutic decision making. Conventional Signal Intensity (SI)-based Late Gadolinium Enhancement (LGE) MRI is the gold standard for assessment of myocardial viability.[1] Binary-analyzed LGE-MRI, however, often overestimates MI size because the density of MI is heterogeneous within the infarcted myocardium.[2]

Percent Infarct Mapping (PIM) is able to not only assess MI size but also MI density, with a resolution governed by the MRI resolution.[3] PIM was initially developed based on the voxel-by-voxel measurement of myocardial R1.[3] The relatively long time course of the R1 acquisition requires the concentration of the contrast agent (CA) to remain unchanging during this acquisition. The presently available fast tissue-kinetics CAs, however, cannot maintain this necessary steady state. Thus, an R1-map can only be obtained using a continuous infusion protocol.[4,5] In spite of the superior accuracy of the R1-PIM, for the time being the long scanning time, or the relatively high cumulative dose of Gd-CA obtained in the infusion protocol, make this method unsuitable for clinical use.

The drawbacks detailed above motivated us to implement a short time frame PIM protocol that could be used in clinically applicable situations. SI-based PIM (SI-PIM) is such a protocol, which applies the PIM approach to conventional LGE images. This technique calculates PIM using the same percent scale as R1-PIM does. The Percent Infarct (PI) values, however, are based here on the voxel-by-voxel SI values of the LGE images, obtained with a single TI, rather than on voxel-by-voxel R1 values. We have recently studied the performance of the SI-PIM technique in comparison to triphenyl-tetrazolium-chloride (TTC) planimetry.[6,7] A possible shortcoming of the SI-PIM method is that SI enhancement in principle depends on the CA concentration in a non-linear fashion, and may be, in practice, slightly influenced by various imaging factors, such as the pulse sequence, acquisition parameters, and field inhomogeneity. Accordingly the purpose of this study was to evaluate the accuracy of the SI-based PIM method compared to the predecessor R1-based PIM method in two phases of the MI healing process. Since an R1-PIM at present could only be obtained using a continuous CA infusion protocol, we initially investigated whether the CA administration method (bolus vs. infusion) has any effect on the accuracy on MI quantification. Subsequently, we studied the accuracy of the clinically relevant bolus enhanced SI-PIM method compared to the R1-PIM method, and validated the results by the post-mortem gold standard TTC staining. Finally to show the clinical benefit and superiority

of the SI-PIM method over the conventionally used binary thresholding approaches, we compared the SI-PIM analysis to the clinically used MI analytical methods.

METHODS

Our protocol was approved by the Institutional Animal Care and Use Committee and complied with the NIH Guidelines for the Care and Use of Laboratory Animals.

Swine Model of Myocardial Infarct

Anesthesia was initiated in male swine ($n=14$, $30.9\pm4.8\text{kg}$) with an intramuscularly administered mixture of telazol (4.4mg/kg) and xylazine (4.4mg/kg). Following intubation, animals were ventilated mechanically (Model 2000, Hallowell EMC, Pittsfield, MA) while maintaining anesthesia by continuous administration of Isoflurane ($2\text{--}3\% \text{V/V}$). Intravenous fentanyl ($50\text{--}100\text{g}$ every 30 min) was used for analgesia. Heart rate, blood oxygen saturation were monitored and ECG was recorded. Heparin (100IU/kg) was administered to maintain the activated clotting time above 300s. The right femoral artery was surgically prepared and cannulated using a 6F arterial sheath (Pinnacle, Terumo Medical Co, Elkton, MD). A 6F coronary guide catheter (RunWay Kimmy Mini, Boston Scientific, Natick, MA) was introduced to cannulate the ostium of the left main, and an initial coronary angiography (Philips BV Pulsera, Best, The Netherlands) was performed. A 2.0-2.5mm angioplasty balloon (Maverick, Boston Scientific, Natick, MA) was introduced over a coronary guide wire into the Left Anterior Descending (LAD) or the Left Circumflex (LCX) coronary arteries. After determining the proper position for occlusion, the balloon catheter was inflated and left in position to produce MI. After 90 minutes of ischemia the balloon was deflated, removed, and coronary angiography was repeated to confirm reperfusion. The femoral artery was decannulated, surgically ligated, and the wound was closed.

Magnetic Resonance Imaging

Animals were randomly assigned to the acute ($n=7$) or chronic ($n=7$) experimental group. Seven (acute MI group) or 56 (chronic MI group) days after reperfusion, MRI studies were carried out using a 1.5T GE Signa Horizon CV/i scanner (GE Healthcare, Milwaukee, WI) equipped with a cardiac phase-array coil. Pigs were anesthetized and ventilated as described above. Imaging was performed during breath-hold at end-inspiration. The timeline of the MRI protocol is shown in Figure 1.

Bolus enhanced LGEMRI—Following pilot scans, a 0.1mmol/kg gadopentetate dimeglumine (Gd-DTPA, Magnevist®, Bayer HealthCare Pharmaceuticals Inc, Wayne NJ) bolus was administered. Short-axis oriented Early Gadolinium Enhancement (EGE) images (6-8 slices covering the entire left ventricle (LV)) were generated two minutes after the administration of the bolus CA to detect myocardial obstruction (MO).[8] LGE images were acquired twelve minutes after bolus administration of the CA to assess viability in accordance with prevailing clinical routine. A segmented, 180° -prepared, inversion recovery (IR), fast-gradient-echo sequence was used (field-of-view (FOV) = 300mm , image-matrix (IM) = 256^2 , slice thickness (ST) = 10mm , flip angle (α) = 25° , echo time (TE) = 3.2ms , repetition time (TR) = 7.2ms , and shot repetition time of three cardiac cycles ($1800\text{--}2400\text{ms}$),

depending on the heart rate)). An inversion time (TI) of 500ms was used for EGE images. The TI was properly adjusted to null the signal in the remote myocardium for LGE images.

Continuous Infusion-aided LGE-MRI and R1-map—The protocol established by Flett et al. was used to generate LGE images and R1 maps during steady state of contrast agent level in the myocardium.[4] Fifteen minutes after the 0.1mmol/kg loading bolus (used to obtain bolus enhanced LGE images, see above), continuous infusion of Gd-DTPA at a rate of 0.001 1mmol/kg/min was started. Using this protocol, steady state contrast can be reached after 30-45 minutes of the loading bolus injection.[4] Based on this time range, a waiting period of 40 min was used in our studies as these required steady-state concentration of the CA during imaging. Forty minutes after the Gd-DTPA bolus (i.e., 25 minutes after the start of the contrast infusion), contrast enhanced R1-mapping was carried out. The same acquisition sequence and parameters were used as in the bolus-enhanced LGE method. Eight TIs were used, ranging from 100 to 1100ms. Image acquisition was timed to the end-diastolic phase for all images to allow pixel-by-pixel analysis. Conventional LGE images were also generated during the steady-state period with the same method as used for bolus-enhanced acquisition.

Image Processing

The experimental version of the MASS analytical software (MASS V2013 EXP 13/07/24) was used for image analysis. Endo- and epicardial contours of the LV were traced manually on the short-axis images. Color coding of the images was carried out in Image J (Wayne Rasband, NIH).

Binary LGE Image Processing—Total LV myocardial mass (LVM, g) was calculated from the voxel volume and the specific gravity of the myocardium (1.05g/ml). Mean SI of the remote, plus 2 and 5 times the standard deviation (SD), were used to define the threshold limit for MI. Pixels with SI above the threshold limit were considered infarcted. All infarct-involved voxels were counted, and the total volume of these voxels was calculated (infarct volume, IV, ml) and expressed as a percent of the LVM (infarct fraction, IF, %LVM). The same process was carried out on both the bolus- and the infusion-enhanced LGE images.

SI-PIM Processing—The bolus-enhanced LGE images were obtained conventionally, except that instead of the traditional binary analysis, the PIM method was used for MI quantification. Remote myocardial voxels (mean of the remote + two times the SD) were considered as 0% infarct, and infarct core voxels were chosen as representative of 100% of the maximum infarct. Based on the voxel-by-voxel SI values, a PI scale between 0% and 100% infarct was generated and PI values were then calculated from the SI values for each voxel.[7] IF was calculated by averaging all PI values in a given LV. For comparison's sake, infusion-enhanced LGE images were also processed using the same PIM method.

R1 -PIM Processing—For each myocardial voxel the relaxation rate, R1, was calculated from the SI vs. TI dependence by an automated procedure, applying a non-linear, three-parameter least-squares curve-fitting routine, using the formula:

$$SI = SI_0 \times (1 - A \times e^{(TI \times R1)} + e^{(TR \times R1)})$$

Where SI is the SI at a given TI, SI_0 is the SI at equilibrium, A is a parameter [2] that depends on the accuracy of the 180°-pulse, and TR is the repetition time. The term $e^{(-TR \times R1)}$ accounts for signal saturation if TR is less than five times the T1.[9,10]

The R1-based PI of each voxel was calculated using the formula: [3]

$$PI_v = (R_{1,v} - R_{1,r}) / (R_{1,c} - R_{1,r}) \times 100$$

Where PI_v is the PI of a given voxel v, $R_{1,v}$ is the R1 measured in that voxel, and $R_{1,r}$ and $R_{1,c}$ are the R1 of the remote and of the infarct core, respectively.

Thus the PI value in remote voxels (mean of the remote + two times the SD) was considered as 0% infarction, and the PI of the infarct core voxels was chosen as representative of 100% of the maximum infarction. LVM and IF were also determined.

MO Quantification—MO, the hypoenhanced region within the regions of acute MIs, was manually assigned to the infarct area, i.e. it was considered infarct using the binary methods and 100% infarct using the PIM methods. First the area of the MI was determined as described above. Then the unenhanced MO area contained within was manually traced and measured, and the MI parameters were adjusted accordingly (Figure 2).

Infarct-Involved Voxel Fraction—In addition to the parameters described above, all infarct-involved voxels (which were defined as voxels in which any amount of infarct was detected) were counted, and the volume of these voxels was calculated and expressed as a percent of the LVM (infarct involved voxel fraction, IIVF, %LVM). For the binary quantification methods IIVF involves all voxels with SI above the specific 2SD or 5SD cut off values. For the PIM methods IIVF contains all voxels with non-zero PI values (i.e. all voxels with SI or R1 above the remote mean+2SD, with the latter being considered 0%).

Bias—The calculation of the bias was based on the differences of the IF values determined by each method, each compared to the reference TTC based value. The differences were expressed as the percentage of the volume of the MI measured by the TTC method (%MI).

TTC staining

Immediately following the MRI session, the animal was sacrificed. The heart was excised, rinsed with saline, and bread-sliced based on the orientations of the MRI tomographic slices. The slices were subsequently incubated for 20 min with a buffered 1.5% TTC solution at 37°C.[11] After staining, slices were immersed in 10% formalin for 20min to increase the contrast between healthy and infarcted myocardium. Finally, both surfaces of each slice were digitally scanned. The infarcted area in each TTC slice and the total LV myocardial area of that slice were manually contoured and quantified using Image J. LVM and IF were then determined by surface planimetry.

Intra- and inter-observer variability

Image analysis was carried out by two observers (Observer A: A.V.S. with ten years and Observer B: R.K. with 12 years of cardiovascular MRI experience). Intra-observer variability of the different MI quantification methods was calculated from the difference of two repeated analyses performed by Observer A. Inter-observer variability was determined by the difference between MI quantification results obtained by Observers A and B.

Statistical analysis

Statistical analysis was carried out using SigmaPlot v12.5 (Systat Software Inc, San Jose CA). IF values obtained by bolus vs. infusion enhanced LGE imaging were compared using two way repeated measures ANOVA, and the Holm Sidak method was carried out for pairwise comparison. IF values were compared to the reference TTC method applying two way ANOVA combined with the Holm Sidak multi-comparison test. The same test was used to compare the bias of each quantification method in both MI groups. Data with normal distribution were expressed as mean $\pm$ SD. Averages for data that failed the normality test were reported as medians with quartiles. Bland-Altman plots were used to show the accuracy of the SI-PIM method compared to R1-PIM and TTC. Intra- and inter-observer agreement was analyzed using Pearson correlation, and the correlation coefficient (r) was determined. The significance limit was $P<0.05$.

RESULTS

Representative short-axis oriented MRI images as well as corresponding TTC photos, obtained in animals with acute and chronic MIs, are shown in Figure 3.

The mean SI of the remote myocardium in the bolus- and infusion-enhanced LGE images was 8.5 ± 1.4 and 9.3 ± 2.1 , respectively ($P=N.S.$), indicating that the remote myocardium was successfully nulled using either contrast administration protocol. The maximum SI following bolus administration was 55.7 ± 14.6 , while the same parameter during the steady state contrast achieved by infusion was 68.0 ± 21.4 ($P=N.S.$). Mean R1 of the remote myocardium was $1.9\pm0.1s^{-1}$. The R1 maximum in the infarcted region of the myocardium was $6.1\pm0.7s^{-1}$.

The average time needed for R1 acquisition was 27.8 ± 3.2 minutes, thus the average duration of the CA infusion was 67.8 ± 3.2 minutes. The average total dose of Gd-DTPA (0.1mmol/kg bolus + 0.001mmol/kg/min infusion) administered was $0.17\pm0.00\text{mmol/kg}$.

Average LVMs measured by the different methods were in good agreement ($P=N.S.$, Table 1) indicating that all provide equally reliable volumetric data. The IF and IIVF results obtained in acute and chronic MIs by the different methods are shown in Table 2. Intra- and inter-observer agreement of IF obtained by each MI quantification method used in this study is shown in Table 3.

Statistical analysis revealed that the method of contrast administration (bolus vs. infusion) did not affect accuracy. No statistical difference in IFs was observed among the different PIM methods, compared to each other and to the TTC standard, in any of the MI groups. IFs

obtained by the 2SD thresholded binary LGE MRI method, however, were significantly different from each of the other methods ($P<0.05$), particularly the TTC technique, either at acute or at chronic MI age. In contradistinction, results based on 5SD thresholded binary images did not show statistical difference compared to TTC.

The IIVF results by any PIM method, as well as by the 2SD thresholded binary method, showed no significant difference. IIVF was significantly lower, however, by 5SD binary thresholding in both MI age groups compared with all other methods (Table 2). IF equals IIVF by definition when using the binary methods (MRI 2SD and 5SD, and TTC), because by these methods all infarct-involved voxels in which any amount of infarct is detected are considered 100% infarcted, and thus in these cases the percent of infarcted voxels (IIVF) equals the percent of infarct (IF). IIVF by binary 2SD equals IIVF by SI-PIM, since both post-processing algorithms use the same raw image and the same 2SD cut-off (Figure 4). The IFs measured in these same voxels, however, are significantly smaller. The binary 5SD method yielded an IF which was not different statistically from those based on the PIM methods (or even on TTC). It, however, detected MI in a significantly smaller number of voxels than any of the other methods.

The Bland-Altman plots indicated excellent correlation between the SI-PIM and the R1-PIM results (Figure 5). Comparing the PIM methods to the reference TTC, the mean of differences was less than 2% in the acute group, and less than 1% in the chronic group. The 95% limits of agreement, however, were wide in each case when we compared the PIM MRI methods to the TTC reference. The mean of differences reached 4% using binary 5SD and more than 8% using binary 2SD (Table 2). The inaccuracy of the binary 2SD method resulted in a significant overestimation of IF. Comparing the results obtained by the bolus- vs. infusion-enhanced methods confirmed that the IFs measured were statistically independent from the method used for contrast administration.

The bias shown by the Bland-Altman analysis was normalized to the MI volume measured by the TTC method, instead of normalizing to LVM, and expressed as %MI. The statistical analysis of the bias revealed that the accuracy of the methods was independent from the age of the MI (Figure 6).

DISCUSSION

In this study, we demonstrated that the method of CA administration (bolus vs. continuous infusion) has no significant influence on the accuracy of the MI quantification, thus the methods used here were comparable to each other. Our findings are supported by the publication of White et al, who compared bolus vs. infusion equilibrium techniques in different patient populations and found that T1 mapping is feasible even with the bolus enhancement technique in patients with lower than 0.4 extracellular volume fraction.[12] The SI-PIM method is proven here to be as accurate a way to quantify MI as the infusion-aided R1-PIM method.

Intra- and inter-observer studies of IF determined by each method showed good agreement indicating satisfying reproducibility (Table 3). As the MRI quantification methods used here

are semi-automated, we did not expect significant variability in IF data either between observers, or between repeated measurements. The most sensitive part of the quantification process is contour drawing. Contouring not only determines the actual LVM (which is used in IF calculation), but it can affect the size of the MI area especially on the edges of the endocardium, where the blood signal is often difficult to discriminate from the enhanced myocardium. The selection of the remote myocardium can also influence the quantification process if the image quality is inconsistent throughout the LV and/or the myocardium is not successfully nulled. In such cases, the determination of the remote mean SI highly depends on the location and size of the region of interest (ROI) drawn. As the SI and SD measured in the ROI determines the threshold used for the delineation of the MI region, it may have a significant effect on MI quantification. In case of the PIM methods, an additional parameter, the maximum SI (or R1) of the MI, is used to generate the percent scale. As the maximum SI is measured automatically by averaging five pixels with the highest SI (or R1), any possible observer bias is eliminated. The intra- and inter-observer agreements show a less strong correlation in the case of the TTC analyses, which can be explained by the fact, that the TTC image analysis requires the most manual input, as all contours, including the contour to delineate the MI, are drawn manually.

We show that LGE imaging using the conventional binary 2SD analysis overestimates MI size, compared to TTC, in agreement with the literature.[13,14] The reason for this overestimation of MI size is partly because in binary LGE images all enhanced voxels are counted as 100% infarcted, i.e. images are analyzed as binary maps. Thus any voxel is considered either infarcted or viable, but voxels with a mixture of viable and infarcted myocardium are misquantified. Since studies had shown that the 2SD threshold value for LGE-MRI might be inappropriate, novel techniques were developed enhancing the apparent accuracy of the LGE method.[13-16] These techniques employ a specific cut-off value but still classify each voxel as viable or nonviable, in binary manner.

The SI-PIM image which demonstrates the patchiness of the MI, and the corresponding graph (Figure 7) clearly show that the PI varies within a wide range between the epi- and endocardium and that the lowest PI is observed in the infarct border zone. The binary method when used with a 2SD threshold by definition generates exactly the same IIVF as all PIM methods as they also use a 2SD threshold, but it severely overestimates IF. The higher threshold, 5SD, while it provides statistically the same IF as the PIM and TTC methods, by ignoring, however, a large number of partially infarcted voxels, ends up with a significantly smaller IIVF, i.e. the volume into which the 5SD binary method locates the MI is significantly smaller (Table 2). Theoretically, a specific threshold that provides an IF that equals the IF determined by TTC can be always found, but at a price. While the IF would be equal to the gold standard value, the extent of the specific area of infarct would be distorted. Because infarct density is typically the highest at the core of the infarct, while gradually diminishing towards the peripheral areas of the MI, voxels in the peri-infarct zone (PIZ) are the most severely affected by MRI partial volume effects and by the binary bias, and consequently are mostly in danger of being mischaracterized when a high threshold is applied.[7,17,18] In a comparison of results from LGE-MRI to those from delayed enhancement multi-detector computed tomography (DE-MDCT), DE-MDCT provided more detailed characterization of the PIZ, because MDCT is much less susceptible to partial

volume effects than MRI due to the higher resolution of the former.[2] Since PIZ may serve as the bed of post-infarct ventricular arrhythmias, and the heterogeneity of PIZ predicts post-infarct mortality, the characterization of PIZ has high clinical importance.[19,20] Thus its mischaracterization by high-SD MRI analysis is clearly undesirable.

Using R1-PIM, the patchiness of the infarct is accurately taken into account. Using the PIM method, voxels do not need to be categorized into viable and non-viable groups. Per voxel PI is calculated for each myocardial voxel based on the observed R1 whose enhancement by the CA is in linear proportion with CA concentration in each voxel. The CA concentration in the tissue is, in turn, proportional to infarct content. The varying PI among the voxels thus faithfully reflects infarct patchiness.[3]

The main drawback of R1-PIM is the relatively long scanning time necessary for acquiring a multi-T1 R1 map. Since 2004, several attempts have been made to implement a fast T1 mapping MRI sequence. The Modified Look-Locker IR sequence (MOLLI) has been introduced by Messroghli et al.[21] The MOLLI sequence was optimized for integration into the clinical imaging protocols.[22,23] Using the traditional MOLLI sequence, a T1 map of a single heart slice can be acquired during a single breath-hold, thus a whole heart T1 mapping can be performed in 4-5 minutes depending on the number of slices planned. Another advancement of the past years is the short-MOLLI (shMOLLI) sequence, which further shortens the necessary scanning time.[24] Although these techniques are promising and highly desired, they are not available commercially.

In the absence of a practical clinical use of fast R1 mapping that would allow the use of R1-PIM analysis, implementation of the PIM approach using single T1 LGE images seems to be a solution relevant to the clinic. This approach is promising for the accurate quantification and characterization of MI. In this work we have shown that SI-PIM demonstrates an accuracy similar to that of R1-PIM. Although both R1-PIM and SI-PIM show results that are statistically comparable to the gold standard TTC values, the average IF values measured by PIM are usually slightly below those found by TTC. Bland-Altman plots also indicate that the agreement between the PIM methods and the TTC technique is ambiguous. The agreement is substantially better in the chronic phase of the MI, a fact that is likely due to the shrunken scar, which is much more homogeneous than the acute MI. The major reason for the somewhat weak agreement between PIM and TTC results is the binary nature of the TTC method itself. This binary nature is the result of the TTC method's practical restriction to surface reading only. Thus each voxel is represented only by its 2D, surface pixel counterpart. This means that all of the PIM methods provide less than 100% infarct in the majority of voxels, while the TTC method considers most of these voxels as infarcted (i.e. 100% infarct) as they present themselves as such on the surface. On the other hand, there are voxels where the PIM methods detect infarct deep in a voxel, which cannot be seen on the surface of the TTC slice. Therefore, an improved in vitro gold standard technique would be one that allows in-depth analysis with high through-plane resolution of microscopic histology.[4] Such an improved in vitro standard could show the advantage of the PIM method in an enhanced fashion.

A concern about SI is, that it is more sensitive than R1 to field inhomogeneity and acquisition parameters, and it also highly depends on the pulse sequence used.[3] Moreover, in distinction from the R1 enhancement, the SI enhancement, caused from the Gd-induced shortening of the T1, does not depend exactly linearly on the CA concentration in the myocardial voxel observed.[3] Although these limitations may in theory affect SI based quantification approaches, the practical accuracy of SI-PIM demonstrated here is comparable to that of the R1-PIM. SI-PIM performs with the same accuracy in the acute and chronic phases of MI. Additionally, SI-PIM has advantages over the R1-PIM method, as it can be generated with a single TI, IR, fast-gradient echo sequence within a clinically practical scanning time, and it only requires an added short post-processing of the same LGE images that are generally acquired in a routine LGE protocol. Clinical validation, however, is still necessary to make the SI-PIM method applicable as a clinical tool for the characterization of not only the extent but also the density distribution of MI, both of which are necessary for a reliable diagnostic use of LGE MRI.

In conclusion, we have proven that SI-PIM provides the same accurate evaluation of MI as R1-PIM does. The SI-PIM method performs with the same accuracy independently of the age of the MI. The advantage of SI-PIM over the conventional binary methods is the ability to represent not only IF but also the density-distribution of the infarct. Since the SI-PIM method is based on a single LGE acquisition, it can effortlessly be implemented in the clinical image post-processing procedure.

Study Limitations

The presented data were obtained at the time points of seven and 56 days after reperfusion, thus our results are, in principle, not necessarily applicable for yet untested other ages of MI, especially not for hyper-acute and early acute stages, when the most rapid tissue changes occur. The animal model of MI used in this study may not be fully comparable with human MI, as the nature of the occlusion is quite different (e.g., sudden occlusion, controlled level of occlusion, controlled MI size, programmed revascularization, and continuous anesthesia, etc.). Although, the number of animals in our study was small, as usually the case in large mammal studies, the number of animals does meet the minimum required to reach the necessary statistical power. Further limitation is the R1 mapping technique used in our study. As the scanning of the whole LV, using the single-TI IR acquisitions, takes 25-30 minutes (one TI per slice per breath-hold, thus, e.g., eight TIs and eight slices need 64 breath-holds), such a technique cannot be applicable in human routine MRI studies. In addition, the long scanning time can be challenging in terms of image co-registration. In animal studies, the breath-holds are controlled by a ventilator, i.e. the deepness of the breaths equal during the acquisitions. In conscious humans, the level of the diaphragm is hard to control. Further challenge is the significant change of the heart rate during the MRI scans, which becomes an increasing problem with increasing scan time. These shortcomings can negatively influence the image co-registration causing misalignment and false T1 values mostly at the endocardial and epicardial edges.

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Fig. 1.
The timeline of the MRI protocol.

Fig. 2.

Short axis oriented IR EGE images are shown. The presence of MO surrounded by the rim of the MI is apparent in the raw image (**a**). The endo- (red) and epicardial (green) contours were manually traced, then the enhanced myocardial area was determined (2SD binary threshold is used, **b**). The area of MO (dark area completely surrounded by enhanced myocardium) was then manually traced and assigned as infarct (**c**).

Fig. 3.

Representative image sets obtained from the acute (**Panel I**) and the chronic MI (**Panel II**) experimental groups are shown. Endo- and epicardial borders are shown as red and green contours, respectively. Bolus (**a, j**) and infusion (**d, m**) enhanced raw LGE images, as well as infusion enhanced R1 images (**g, p**) were used to quantify MI. Corresponding color-coded SI-PIM images in Panel I (**b, e**) and Panel II (**k, n**) processed from bolus (**a, j**) and continuous infusion (**d, m**) enhanced LGE images, respectively, represent the density distribution of the MI, showing gradually decreasing PIs from the center to the peripheral zone of the infarct. PI in each voxel is shown on a color scale. Corresponding binary-analyzed images in Panel I (**c, f**) and Panel II (**l, o**) show the infarct area as superimposed color layers. Note, that in **c, f, l**, and **o** all enhanced voxels are counted as 100% infarcted due to the binary method. Corresponding R1 maps (**g, p**), and R1-PIM (**h, q**) are also shown. Corresponding TTC photos (**i, r**) confirm the localization and post-mortem size of the MI.

Fig. 4.

IF and IIVF data obtained from the chronic experimental group are shown as bar graphs.

Results are shown only from the infusion enhanced method, since we have proven that the accuracy is independent of the method of CA administration.

Fig. 5.

Bland-Altman analyses of IF obtained by SI-PIM, R1-PIM, and TTC are shown (acute group left panel, chronic group right panel). Dashed lines show the 95% limits of agreement ($\pm 1.96SD$) and the solid line shows the mean of differences (i.e. bias). The plots of SI-PIM versus R1-PIM in the acute and chronic groups (top row) show excellent agreement, with the mean of differences at 0.16 and -0.13%, respectively. Narrow agreement limits can be observed indicating that the methods are essentially equivalent. Bland-Altman plots of IF by SI-PIM and R1-PIM compared to TTC (middle and bottom row) show a bias of -1.45 and -1.61% in the acute group, respectively, while the bias in the chronic group was -0.59 and

-0.46%, respectively. Although the means of differences show non-significant bias, the wide agreement limits indicate ambiguous agreement.

Fig. 6.

The differences between IF obtained by each of the MRI methods vs. the reference TTC are shown here. As we have shown, the binary 2SD method significantly overestimated MI size, while no statistical difference was observed among the other methods compared to the TTC technique. As shown here, the bias values of the binary 5SD, SI-PIM and R1-PIM methods are close to the line of origin (dashed line), where the bias is zero. The overestimation of IF by the LGE 5SD method, and the slight underestimation of IF by the SI-PIM and R1-PIM methods, however, did not reach significance.

Fig. 7.

The transmural distribution of the density of the MI is shown in an acute MI. The infarct area is enlarged in both the SI-PIM (a) and the binary (b) LGE images. A single radial transmural cord was defined (white line) and the voxel-by-voxel distribution of the PI values along the cord was plotted (c). As typical, the PI is highest at the center of the infarct and gradually decreases towards the peripheral zones (c, **black line**). The arbitrary threshold binary methods (b), however, show each voxel as either infarcted (PI=100%) or non-infarcted (PI=0%). In the specific cord shown, the use of the conventional threshold level (2SD, blue) yields a transmural infarct with 100% nonviable tissue in all voxels along the cord, while the higher threshold level (5SD, orange) highlights only the non-transmural core of the infarct. The area between the blue and black lines (c, **solid blue** and **striped areas**) shows the overestimation of the 2SD method compared to the SI-PIM method. The plot of 5SD thresholding shows the same overestimation at the center of the infarct as the 2SD thresholding (**striped area**), but also demonstrates a severe underestimation at the peripheral zones by treating them as 100% viable (**solid orange areas**).

Table 1

LVM (n= 14, median and [quartiles]) values obtained by the different imaging methods

Methods	LVM (g)
LGE bolus	78.1 [75.1; 80.7]
LGE infusion	75.0 [71.5; 80.3]
R1-PIM	74.5 [70.6; 79.4]
TTC	81.8 [77.1; 88.2]

Table 2

IF and IIVF obtained by the different methods

MI group	Method	IF by bolus (%LVM)	IF by infusion (%LVM)	<i>P</i> [*]	IIVF by bolus (%LVM)	IIVF by infusion (%LVM)	<i>P</i> [*]
Acute	Binary 2SD	16.3±4.9 [§]	18.7±8.7 [§]	N.S.	16.3±4.9	18.7±8.7	N.S.
	Binary 5SD	11.1±5.4	14.2±6.7	N.S.	11.1±5.4	14.2±6.7	N.S.
	SI-PIM	8.3±2.9	8.8±3.3	N.S.	16.3±4.9	18.7±8.7	N.S.
	R1-PIM		8.2±2.7			18.9±8.3	
Chronic	Binary 2SD	9.1±3.1 [§]	10.2±3.4 [§]	N.S.	9.1±3.1	10.2±3.4	N.S.
	Binary 5SD	6.2±2.4	6.2±2.7	N.S.	6.2±2.4	6.2±2.7	N.S.
	SI-PIM	4.5±1.6	4.5±1.8	N.S.	9.1±3.1	10.2±3.4	N.S.
	R1-PIM		4.6±1.9			10.2±3.1	

IFs (and IIVFs) determined by TTC in the acute and the chronic experimental groups were 9.8±2.9 and 5.1±1.8%LVM, respectively.

^{*} Compared between bolus versus infusion contrast administration.

[§] Significantly (*P*<0.05) different from each of the other quantification techniques and from the reference TTC method.

Note, that by definition IF equals IIVF using the binary techniques (LGE 2SD and 5SD, and TTC), because all infarct-involved voxels in which any amount of infarct is detected are considered 100% infarcted by the binary methods. Also note, that IIVF by binary (with 2SD) equals to IIVF by SI-PIM, because IIVF is defined in a binary manner and the 2SD threshold is shared in common by the two methods in this case.

Table 3

Intra- and inter-observer agreement of the different MI quantification methods (n= 14)

Methods	Intra-observer		Inter-observer	
	Mean difference in IF (%LVM)	r	Mean difference in IF (%LVM)	r
Binary 2SD bolus	-0.39	0.96	0.90	0.96
Binary 2SD infusion	0.36	0.95	0.99	0.98
Binary 5 SD bolus	-0.37	0.92	0.94	0.91
Binary 5SD infusion	0.46	0.97	0.96	0.96
SI-PIM bolus	-0.40	0.96	0.87	0.93
SI-PIM infusion	0.29	0.91	0.80	0.92
R1-PIM	-0.29	0.98	-0.45	0.93
TTC	-0.44	0.88	-1.13	0.75

r, Pearson correlation coefficient