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Quantification of Myocardial Viability Distribution with Gd(DTPA) Bolus-Enhanced Signal Intensity-Based Percent Infarct Mapping

Robert Kirschner, MD^{a,e,f}, Akos Varga-Szemes, MD^{a,e,f}, Tamas Simor, MD, PhD^{a,e,f}, Brigitta C. Brott, MD^b, Silvio Litovsky, MD^d, Ada Elgavish, PhD^{c,f}, and Gabriel A. Elgavish, PhD^{a,f,*}

^aDepartment of Biochemistry and Molecular Genetics, University of Alabama at Birmingham, Alabama, USA

^bDivision of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

^cDivision of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

^dDepartment of Anatomical Pathology, University of Alabama at Birmingham, Birmingham, Alabama, USA

^eHeart Institute, Faculty of Medicine, University of Pecs, Hungary, Alabama, USA

^fElgavish Paramagnetics Inc., Birmingham, Alabama, USA

Abstract

Introduction—A substantial, common shortcoming of the currently used semiautomated techniques for the quantification of myocardial infarct with Delayed Enhancement Magnetic Resonance Imaging is the assumption that the whole myocardial slab that corresponds to the hyperenhanced tomographic area is 100% non-viable. This assumption is, however, incorrect. To resolve this conflict, we have recently proposed the signal intensity percent-infarct-mapping method and validated it in an ex-vivo, canine experiment. The purpose of the current study has been the validation of the signal intensity percent-infarct-mapping method in vivo, using a porcine model of reperfused myocardial infarct.

Methods—In swines (n=6) reperfused myocardial infarct was generated occluding for 90 min by an angioplasty balloon either the Left Anterior Descending or the Left Circumflex coronary artery. To obtain DE images, Gd(DTPA) enhanced inversion-recovery fast gradient-echo acquisitions were carried out on day 28 after myocardial infarction. Scanning started 15 minutes after intravenous injection of 0.2 mmol/kg Gd(DTPA). At the end of the MRI session the animal was sacrificed and 2,3,5-triphenyltetrazolium chloride staining was used to validate the existence and to determine the accurate size of the myocardial infarct. Tissue samples were taken and stained with Hematoxylin-Eosin and Masson's trichrome for histological assessment of the infarct and the periinfarct zone. The signal intensity percent-infarct-mapping data were compared with corresponding data from the Delayed Enhancement images analyzed with $SI_{remote}+2SD$ thresholding, and with corresponding triphenyltetrazolium-chloride staining data using Friedman's Repeated Measure Analysis of Variance on Ranks.

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*Corresponding Author: Fax: (205)934-0295. Telephone: (205)934-0294. gabi@uab.edu. .

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Results—The infarct volume determined by the triphenyltetrazolium chloride, $SI_{remote+2SD}$, and signal intensity percent-infarct-mapping methods were 3.04 ml [2.74, 3.45], 13.62 ml [9.06, 18.45], and 4.27 ml [3.45, 6.33], respectively. Median infarct volume determined by $SI_{remote+2SD}$ significantly differed from that determined by triphenyltetrazolium chloride ($p < 0.05$). The Bland-Altman's overall bias was 12.49% of the volume of the left ventricle. Median infarct volume determined by signal intensity percent-infarct-mapping, however, did not differ significantly (NS) from that obtained by triphenyltetrazolium chloride. Signal intensity percent-infarct-mapping yielded only a 1.99% Bland-Altman's overall bias of the left ventricular volume.

Conclusions—This in vivo study in the porcine, reperfused myocardial infarct model demonstrates that signal intensity percent-infarct-mapping is a highly accurate method for the determination of the extent of myocardial infarct. MRI images for signal intensity percent-infarct-mapping are obtained with the pulse sequence of conventional Delayed Enhancement imaging and are acquired within clinically acceptable scanning time. This makes signal intensity percent-infarct-mapping a practical method for clinical implementation.

Introduction

Recent progress in management of myocardial salvage post myocardial infarction (MI) increases the number of patients surviving the acute phase of MI. This, however, raises the number of cases of chronic heart failure [1] where myocardial viability assessment is of great importance. Differentiation between viable and infarcted tissue and the quantification of their proportion is necessary for clinical decision making. Clearly viable but hibernated myocardium may exhibit functional recovery following revascularization of the involved coronary artery by either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) [2]. Patients with decisively *nonviable* myocardium, on the other hand, must not be jeopardized needlessly with the high risk procedures of revascularization [3].

During the last decade, delayed contrast enhancement (DE) MRI imaging with standard extracellular contrast agents became the gold standard for assessing the localization, the transmural, and the extent of myocardial infarction [4]. DE MRI is also capable to differentiate stunned myocardium from necrotic tissue in the acute phase [5], and hibernated myocardium from scar tissue in the chronic phase, of myocardial infarction [2]. Correspondence between location, spatial extent, and 3D shape of the hyperenhanced regions on DE images and the irreversibly injured tissue defined by histomorphometry has been demonstrated [5,6].

The quantification of MI size on DE images based on signal intensity (SI) has not been standardized to date. The most popular method is based on the use of a predefined cut-off intensity, above which all voxels of the myocardium are regarded as enhanced. The summation of the volume of all enhanced voxels provides the volume of the infarct. There is no general agreement on the cut-off value, which is defined by most investigators as the mean of SI of the normal myocardial regions plus 2 times its standard deviation (SD) [5,7]. Other authors have used 3 SD [6], 5 SD [8], or 6 SD [2,9-11]. Some researchers employ a user specified threshold [4]. Alternative threshold techniques have also been introduced, e.g., full-width-half-maximum (FWHM) [12,13], or automated infarct-contour-detection methods [14,15].

A substantial common shortcoming of the above mentioned different threshold methods is, that the 5-10 mm thick myocardial slab, corresponding to the enhanced area on the DE image used in everyday practice of cardiovascular MRI, is assumed to be 100% non-viable. This assumption, however, is incorrect. The 3D structure of the infarct could be tortuous, having occasional branches at the border zone [9]. It has been shown that there are areas where the infarct is "patchy": viable regions are mixed with non-viable islets, and vice

versa, viable islets exist in the infarct region [9,16-18]. The image resolution, in particular perpendicular to the plane, limits the representation of these details on the DE MRI images. This leads to partial volume effect in the corresponding voxels, generating SI values above the normal threshold, thus increasing the number of “infarct” voxels, suggesting 100% nonviable tissue unnecessarily, in spite of the partial viability of the involved area.

Taking into account the above mentioned problem, our research group has recently introduced an R1-based infarct-quantification method [19]. It is called percent-infarct-mapping (R1-PIM), as it quantifies infarct density in each voxel individually, yielding a value for each voxel on a percent scale (percent infarct), based on the R1-enhancement induced by the CA. The method has been validated in an in-vivo canine study [19], using an investigational contrast agent [20-26]. R1-PIM, in spite of its accuracy, cannot be implemented at the present time within a clinically acceptable scanning time interval necessary to cover the entire LV, using commercially available sequences.

To implement the same idea with a clinically acceptable scanning time and using a standard extracellular contrast agent, we have recently proposed the signal intensity percent-infarct-mapping (SI-PIM) method [27]. This method is based on the signal intensity of the individual voxels of DE images, but uses the same percent scale as R1-PIM does. The SI-PIM method has been validated in an ex-vivo, canine model of MI [27]. The purpose of the current study has been the validation of SI-PIM in vivo, using a porcine model of reperfused MI.

Materials and Methods

1.1 Surgical procedure

The IACUC of University of Alabama at Birmingham approved the animal protocol in full compliance with the ‘Guidelines for the Care and use for Laboratory Animals’ (NIH). Six male swines (28-32 kg) were used for the study. Food was taken away and 325 mg Aspirin given twelve hours prior to procedure. Pigs were initially anesthetized with an intramuscularly administered telazol (4.4 mg/kg) and xylazine (4.4 mg/kg), intubated, and connected to a Hallowell EMC Model 2000 respirator (Pittsfield, MA, USA) operated with a tidal volume of 400 ml at a rate of 16 BPM. Anesthesia was maintained by continuous Isoflurane (2.5-3 volume %), and repeated Fentanyl (50-100µg I.V. every 30 minutes), administration. 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 left femoral artery was separated surgically and an arterial sheath (6-8 French) was inserted. An I.V. 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 2-3 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.

On day 28 following MI, animals were re-anesthetized as described above, and MRI studies performed. After the MRI session, animals were sacrificed using 100 mg/kg sodium pentobarbital and potassium chloride solution. The euthanasia was monitored by ECG and auscultation above the thorax. 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, similarly as described by Fishbein et al. Both surfaces of the slices were digitally scanned with a Lexmark X1270 (Lexmark International Inc, Lexington KY) image scanner. The slices were fixed in 10% formalin, embedded in paraffin. The entire slices were sectioned at 5 µm thickness. Hematoxylin-eosin and Masson's trichrome staining was performed.

1.2 Magnetic Resonance Imaging

MRI studies were performed 4 weeks following MI on a 1.5-T system (Signa-Horizon CV/i, GE Healthcare Milwaukee, WI). A cardiac phased-array coil and ECG gating were employed. Conventional cardiac angulation planes were set and short axis slices covering the entire left ventricle (LV) were obtained using breath-hold real-time and steady-state free-precession sequences. Breath-hold was performed at end-expiration by manual control. A 180°-prepared, segmented, inversion-recovery fast gradient-echo pulse was used with: Field of View (FOV) 30 cm, Echo Time (TE) 3.32 ms, Repetition Time (TR) two cardiac cycles (1100-1600 ms), slice thickness 10 mm. The Inversion Time (TI) was optimized to null the signal in normal myocardium. DE images were scanned 15 minutes after intravenous injection of 0.2 mmol/kg Gd(DTPA) (Magnevist, Schering).

1.3 Image Post-Processing and Analysis

1.3.1 Manual Input—MRI Dicom images were imported as image sequences with the use of ImageJ (Wayne Rasband, NIH). The endo- and epicardial contours of the LV muscle were traced manually and this circumscribed area was further analyzed. Large regions of interest (ROI), remote from the infarct (SI_{remote}) were selected in DE-MRI images to measure baseline $\pm$ SD of SI. All other analyses were automated to eliminate observer bias.

1.3.2 DE-MRI Analysis—The voxel-by-voxel SI histogram of each DE-MRI image set, segmented in the above manner, was generated with ImageJ, and these histograms were used for further analysis. Voxels enhanced over the $SI_{remote} + 2SD$ threshold were counted as 100 % infarcted. Infarct Volume (IV) was determined as sum of the volume of those voxels having SI values above this threshold. The volume of a single voxel was calculated using the following formula:

$$V = ST \cdot \frac{FOV^2}{RES^2}$$

where V= Voxel (mm³), ST= Slice thickness (mm), FOV= Field of view, RES= image resolution. LV was determined as the sum of the volume of voxels circumscribed by the endocardial and epicardial border.

1.3.3 Generation of Signal-Intensity Percent-Infarct-Map (SI-PIM)—SI-PIM (See an example in Figure 1) was generated from the DE-MRI image set using the above detailed segmented image matrix. For each myocardial voxel a percent-infarct (PI) value was assigned, applying the PIM algorithm [19], calculating the amount of infarcted tissue per voxel. SI values less than, or equal to the mean SI of healthy (remote) myocardium were denoted as 0% infarcted, while the center of the infarct (10 maximally enhanced pixels) was assigned as 100% infarcted. PI values were shown on color scales in the image matrix provided the color SI-PIM (Figure 1.). IV was determined as sum of the PI values of the individual voxels.

1.3.4 TTC Calculations—The existence of infarcts was validated by assessing the TTC images. Digital images were analyzed using ImageJ. The infarct area and the LV area on both sides of each TTC slice were manually determined by planimetry method. Multiplying the area data by half of the TTC slice thickness provided the volume of myocardium and of infarct for every slice. The volume data (infarct volume and LV volume) were summarized for the entire image set.

1.4 Histological Evaluation

Short axis LV slice specimens were processed on an extended time processing schedule using a VIP 1000 (Sakura Finetek, USA) tissue processor, including extended times in paraffin infiltration. Afterwards, samples were embedded in paraffin wax in large embedding molds (5×7 cm). The large paraffin blocks were cut with a Leica 2265 automated microtome, and the specimens were mounted on large size plus slides (Brain Research Laboratory, Boston MA). The sections were deparaffinized in xylene and then stained with Hematoxylin-Eosin and Masson's Trichrome, and coverslipped with large coverslips (Brain Research Laboratory, Boston MA).

The short axis LV slices stained with Hematoxylin-Eosin and Masson's trichrome were assessed by a pathologist. The analysis of correspondence between SI-PIM and histology was assisted by quantitative computerized morphometry using an Olympus BX51 microscope with motorized stage and version 9.0 of Bioquant Osteo 2009 software (Bioquant Analysis Corporation, Nashville, TN). This enabled the integration of the histological details of the whole short axis LV slice in one digital image montage.

1.5 Statistical Analysis

Statistical analysis was carried out using SigmaStat 2.03 (SPSS Inc., Chicago, IL). Normal distribution of data and equality of variances were tested on the infarct volume data set. The data failed the equality of variances test and therefore the results are reported as median with 25th and 75th percentiles shown in brackets, rather than as mean±SD. Friedman's Repeated Measure Analysis of Variance on Ranks was used to check the null hypothesis whether the median IV values determined by SI_{remote+2SD}, SI-PIM or TTC are not statistically different. An overall significance ($P < 0.05$) was established for rejecting the null hypothesis that the three groups were not different. Accordingly, pairwise differences between the groups were revealed by using Tukey's method of multiple comparisons. The null hypothesis was rejected with $P < 0.05$.

Bland-Altman analysis was also used, to assess the level of agreement among the IV parameters determined by the different methods. A range of agreement was defined as mean bias $\pm$ 1.96 SD.

Results

All infarcts were clearly visible in Gd(DTPA)-enhanced DE images of all six pigs. No microvascular obstruction in the form of large unenhanced regions in the center of the infarcts was detected. The existence and localization of the infarcts were confirmed by TTC histomorphometry.

The infarct volume (IV) determined by TTC, SI_{remote+2SD}, and SI-PIM methods were 3.04 ml [2.74, 3.45], 13.62 ml [9.06, 18.45], and 4.27 ml [3.45, 6.33], respectively. Tukey's method of multiple comparisons showed that median IV determined by SI_{remote+2SD} significantly differed from IV determined by TTC ($p < 0.05$). The Bland-Altman's analysis of the data (see the corresponding plot on Figure 2) revealed a remarkable overall bias of the

IV by $SI_{remote+2SD}$ method vs. TTC histomorphometry. Although all the difference values were between the mean ± 1.96 SD interval, the mean of differences was 10.68 ml indicating a notable (12.49 % of the LV volume) overestimation of the real infarct size.

Median IV determined by SI-PIM, however, did not differ significantly (NS) from that obtained by TTC histomorphometry using Tukey's method of multiple comparisons. The Bland-Altman's analysis (see Figure 3) of the IV obtained by SI-PIM method and the IV determined by TTC histomorphometry showed close agreement. SI-PIM yielded a 1.99 % overall bias of the LV volume indicating that the overestimation of infarct size was not remarkable using this method. Histological evaluation of the samples showed calcification in the scar, mostly in the center but some close to the edge. Both edges of the scar were similar to the center of the scar in terms of cellularity, i.e. they were not more cellular than the center of the scar. Most cells in the scar were spindle shaped with few mononuclear inflammatory cells. The blood vessels in the scar showed thick, muscular walls, increased extracellular matrix, and small lumen. Although the scars were quite homogeneous, focal "tongues" of myocytes were embedded in the scar, usually no further than 200 microns from the border zone. Although the demarcation was quite sharp between infarcted and non-infarcted tissue, the border zone appeared irregular. The infarct-involved segments were markedly thinned. While the endocardial side of the segment was usually free of scar for about 300-400 microns, on the epicardial side less than 100 microns were spared.

The analysis of correspondence between SI-PIM and histology revealed that SI-PIM was able to visualize the mixing of infarcted and viable tissue in vivo as demonstrated in Figure 4.

The color rectangles on Figure 4 depict 3 typical areas of the infarct. Arrows with the same color as the corresponding rectangle point to the histology section which shows the depicted area with 12.5 $\times$ and 100 $\times$ magnification. The yellow rectangle (Fig. 4B) depicts the border zone between the antero septal scar (blue on Masson's trichrome histology) and adjacent normal myocardium (red brown). The demarcation between the two tissue types is distinct, the border, however, is quite irregular in shape (Fig 4C). An interdigitation of normal myocardial tissue and scar tissue is seen (Fig. 4D). The pixels' false color in the corresponding area on the SI-PIM (Fig. 4A) is blue and purple, indicating PI values between 30 and 50%. Thus, SI-PIM shows the mixing of viable and scar tissue at the anterior border zone. The green rectangle (Fig. 4B) depicts an area in the posterior border zone. The histological finding is similar to that of the anterior border zone (Figs. 4G and 4H). SI-PIM (Fig. 4A) also indicates mixing of viable and scar tissue, as the pixels' PI values, similarly to the anterior border zone, are between 30 and 50%. The red rectangle (Fig. 4B) depicts an area in the center of the infarct. No surviving myocytes are seen within the scar (Figs. 4E and 4F). In the corresponding area on the SI-PIM (Fig. 4A), the pixels are shown in yellow color corresponding to PI values close to 100%. Thus, SI-PIM indicates well the center of the infarct, as expected.

Discussion

The present in vivo study in the porcine, reperfused MI model demonstrates that SI-PIM is a highly accurate method for the determination of the extent of MI. By determining PI values in the LV myocardium, we have focused on the assessing of hyperenhanced SI distribution in the infarct and periinfarct regions. We have validated the accuracy of infarct size determination by SI-PIM with the gold standard method of histomorphometry by TTC. The SI-PIM method determined the size of the infarct size far more accurately than the $SI_{remote+2SD}$ method did.

The identification of viable myocardium is important for the prediction whether a patient will have regional function improvement [2,10], increased LV ejection fraction [28], or improved survival [3], after revascularization. Patients with coronary artery disease (CAD) and severe LV dysfunction are at higher risk for perioperative complications associated with CABG [3]. Accordingly, the identification of those patients who may benefit from revascularization is of great importance.

Although DE-MRI with standard extracellular CAs has been widely used for assessing myocardial viability following MI, the tissue characterization potential of the technique has not been exploited in full. To date, image analysis has generally been based on a binary approach: voxels with SI above the threshold have been denoted as necrotic and all other LV voxels have been considered as healthy myocardium. Such analysis implies that the whole myocardial slab that corresponds to the hyperenhanced area in the DE-MRI image is 100% non-viable. This assumption is, however, histologically incorrect, as our results demonstrate.

Some studies have shown [9,16-18] that scar morphology is often complex in the different stages of infarct healing, and it would be inappropriate to simply categorize them to transmural or non-transmural infarcts. A more accurate information on the morphological structure of the infarct is important not only for the accurate assessment of myocardial viability, but because of its clinical consequences.

In a canine study, Wetstein et al. classified two-week old reperfused and non-reperfused myocardial infarcts on histopathological basis into heterogeneous and homogeneous infarct groups [16]. The heterogeneous infarcts consisted of surviving foci of myocardial fibers admixed everywhere with granulation and fibrous tissue, showing a complex of interdigitating areas. Although within the center of homogeneous infarcts were no surviving fibers, slight interdigitation of myocardial fibers within the granulation or fibrous tissue was also seen in the peripheral zone in some cases. 67% of the reperfused MIs were heterogeneous, while only 17% of the non-reperfused infarcts were in the study by Wetstein et al. [16]. They established that the presence of a variable epicardial rim was the best predictor for the inducibility of sustained ventricular tachycardia.

Ashikaga and al. [9] presented in a swine study, that 12 weeks following reperfused myocardial infarct, the scar exhibits variable wall thickness, with occasional branching of the infarct structure at the periphery. There were areas where viable regions were mixed with non-viable islets, and, vice versa, viable islets existed in the infarct region. They demonstrated that infarct tissue heterogeneity was associated with the formation of reentry circuits responsible for the development of sustained ventricular tachycardias.

In our study, the evaluation of the histological samples taken from porcine hearts 4 weeks after onset of reperfused MI revealed mixing of viable and nonviable tissue at border zones similarly to the above mentioned studies.

Accordingly, these studies demonstrate that the infarcted region cannot be treated simply as a uniform tissue bed, irrespectively of the stage of the infarct and the species. The image resolution limits the representation of the details of the complex structure of the myocardial scar, especially in the in vivo DE-MRI images. This leads to partial volume effect in the corresponding voxels, generating SI values above the threshold in such voxels, suggesting 100% nonviable tissue, in spite of the partial viability of the involved area.

Contrary to the binary approach, SI-PIM quantifies infarct density in each voxel individually, yielding a value for each voxel on a percent scale, based on the extent of SI enhancement induced by the CA. Our present study shows that the SI-PIM method yields an accurate determination of infarct size in vivo. Recently, we have shown in an ex vivo canine

study [27] that the accuracy of the SI-PIM method approaches that of the R1-based PIM method. SI-PIM has the notable advantage, however, that it is obtained with the pulse sequence of conventional DE imaging within a clinically acceptable scanning time, so SI-PIM could become a practical method for clinical implementation. Our present study demonstrates that SI-PIM clearly indicates, in vivo, the mixing of viable and nonviable tissues in the border zones. SI-PIM can help the cardiologist in the assessment of the often complex structure of the infarct scar by in vivo visualization of infarct inhomogeneity on a color percent scale.

In summary, this in vivo study in the porcine, reperfused, MI model demonstrates that SI-PIM is a highly accurate method for the determination of the extent and distribution of myocardial infarct. SI-PIM can help the cardiologist in the assessment of the often complex structure of the infarct scar by in vivo visualization of infarct inhomogeneity on a color percent scale. As SI-PIM is obtained with the pulse sequence of conventional DE imaging, it is acquired within a clinically acceptable scanning time. These features make SI-PIM a practical method for clinical implementation.

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Figure 1. In vivo DE MRI image and post-processed maps from a pig heart

Top row: Five chamber long axis images show MI in the LAD area. From left to right, shown are DE raw image, $SI_{remote+2SD}$ thresholded DE image, and the voxel-by-voxel calculated SI-PIM. Percent Infarct values are shown on a color scale (bottom row, right column).

Middle row: A short axis image from the same heart. The methods used are as above.

Bottom row: The corresponding TTC-stained LV section (left), and the histology slide with Masson's trichrome staining (right).

Figure 2. Bland-Altman's plot of SI_{remote+2SD} versus TTC

A Bland-Altman's plot between the IV obtained by the DE method using a normal+2SD threshold versus IV determined by TTC. Although all the difference values are within the mean $\pm$ 1.96 SD interval, the mean of differences is 10.68 ml, indicating a significant (12.49 % of the LV volume) overestimation of the real infarct size as determined by TTC.

Figure 3. Bland-Altman's plot of SI-PIM versus TTC

A Bland-Altman's plot of the IV obtained by the SI-PIM method versus the IV determined by TTC. This plot shows a close agreement between these two methods. The mean of differences shows that the overestimation of infarct size is not significant using SI-PIM (1.99% of the LV volume) as compared to the gold standard of TTC staining. In addition, none of the difference values are outside of the mean $\pm$ 1.96 SD interval. This interval is notably narrower than that on the previous plot (Figure 2).

Figure 4. Demonstration of SI-PIM's ability to visualize the mixing of infarcted and viable tissue

A. In vivo short axis SI-PIM of the same porcine transversal LV slice seen in Figure 1. middle row, right column. B. Corresponding histology of the entire slice with Masson's trichrome staining (1.5 $\times$). C. The border zone between the antero-septal scar (blue) and adjacent normal myocardium (red brown) (Masson's trichrome, 12.5 $\times$). D. The same area as in C. with higher magnification (Masson's trichrome, 100 $\times$). E The center of the infarct (Masson's trichrome, 12.5 $\times$). F The same area as E with higher magnification (Masson's trichrome, 100 $\times$). G The posterior border zone (Masson's trichrome, 12.5 $\times$). H The same area as G with higher magnification (Masson's trichrome, 100 $\times$).