Automated Quantification of Myocardial Infarction from MR Images by Accounting for Partial Volume Effects: Animal, Phantom, and Human Study[1]

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Ethics committees approved human and animal study components; informed written consent was provided (prospective human study [20 men; mean age, 62 years]) or waived (retrospective human study [16 men, four women; mean age, 59 years]). The purpose of this study was to prospectively evaluate a clinically applicable method, accounting for the partial volume effect, to automatically quantify myocardial infarction from delayed contrast material–enhanced magnetic resonance images. Pixels were weighted according to signal intensity to calculate infarct fraction for each pixel. Mean bias ± variability (or standard deviation), expressed as percentage left ventricular myocardium (%LVM), were −0.3 ± 1.3 (animals), −1.2 ± 1.7 (phantoms), and 0.3 ± 2.7 (patients), respectively. Algorithm had lower variability than dichotomous approach (2.7 vs 7.7 %LVM, $P < .01$) and did not differ from interobserver variability for bias ($P = .31$) or variability ($P = .38$). The weighted approach provides automatic quantification of myocardial infarction with higher accuracy and lower variability than a dichotomous algorithm.

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Delayed contrast material–enhanced magnetic resonance (MR) imaging (1) has made MR imaging the method of choice for accurate detection of myocardial infarction (2). Investigators in several studies have validated that delayed gadolinium-enhanced MR images help to closely track the area of irreversible myocardial injury caused by chronic or acute infarction (3–6).

Although partial volume effects have been suggested as a potential source of error in delayed contrast-enhanced MR imaging (3,5,7,8), to our knowledge, no one has incorporated a compensation for partial volume effects in the design of automated methods for quantification of infarct size. Resolution for in vivo delayed contrast-enhanced MR imaging is far from isotropic; typically, it is 1–2 mm in plane and 8–10 mm through plane. The curvature of the left ventricular epicardium is largest in the apical region where one expects the partial volume effect to be the greatest. The infarct itself also may have an irregular shape in the section direction, also contributing to partial volume effects. On a microscopic level, the infarct itself may be a mix of viable myocytes and fibrous or necrotic tissue (9). This factor also may lead to partial volume effects.

Advances in Knowledge

- Partial volume effects on infarct quantification in delayed contrast material–enhanced MR images can be accounted for by weighting infarct volume by using pixel signal intensity values.
- Accounting for partial volume effects reduces the variability from 7.7 to 2.7 percentage left ventricular myocardium in measured infarct size from delayed contrast-enhanced MR images as compared with previously used dichotomous infarct quantification algorithms.
- Infarct size measured by using this automated method did not differ from that with manual delineation performed by three observers.

In the clinical setting, the physician's ability to accurately quantify infarct size is of great importance (10,11). Furthermore, an automated method for quantification of infarct size with high accuracy and low variability is also of importance in scientific studies and clinical trials in which infarct size is used as an outcome parameter to evaluate the performance of treatment strategies (10).

For high-spatial-resolution ex vivo MR imaging with thin sections (0.5 × 0.5 × 0.5 mm), Kim et al (3) suggested the use of a threshold level defined as the mean signal intensity (SI) of a remote region of interest in the myocardium plus 2 standard deviations (SDs) of the SI variation within that region of interest. The partial volume for such thin sections is limited. Subsequent researchers have argued that 2 SDs may not be appropriate in the clinical setting (11–13). This has been followed by automated or semiautomated approaches for quantification of infarct size that have been proposed by several research groups (11,12,14–18). However, all previous methods have been based on a dichotomous classification of each pixel as being either infarcted or not infarcted. Thus, the purpose of our study was to prospectively evaluate a clinically applicable method we developed to take into account the partial volume effect to automatically quantify myocardial infarction from delayed contrast-enhanced MR images.

Materials and Methods

The study was approved by our ethics committees for both human and animal research at Lund University, Lund, Sweden. Informed consent was obtained (prospective study component) or waived (retrospective study component). An example of the partial volume effect (Fig 1) and the proposed method of compensation for this effect (Fig 2) are shown.

Implication for Patient Care

- The algorithm we used was validated both experimentally and clinically and provides an approach to quantify infarct parameters with less variability and without the need for manual adjustment.

The method for quantification of infarct described in this study was developed as a team effort in the research group and has been incorporated in a software package freely available for research purposes that can be downloaded at *http://segment.heiberg.se*. One author (E.H.) is a shareholder together with Lund University in a company that sells the software for clinical and commercial use. All other authors had control of any information and data submitted for publication that might present a conflict of interest for that author.

Animal Preparation and MR Imaging

Eight domestic pigs weighing 40–50 kg were fasted overnight with free access to water and were premedicated with azaperone (Stresnil; Leo, Helsingborg, Sweden), 2 mg/kg administered intramuscularly 30 minutes before the procedure. Induction of anesthesia was performed with 5–25 mg/kg of thiopental (Pentothal; Abbott, Stockholm, Sweden). Administration of this anesthetic was complemented with intermittent doses of meprobamat (Mebumal; DAK, Copenhagen, Denmark) and more thiopental, if needed. Ischemia was induced with inflation of an angioplasty balloon

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Abbreviations:
%LVM = percentage left ventricular myocardium
SD = standard deviation
SI = signal intensity

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See Materials and Methods for pertinent disclosures.

in the left anterior descending coronary artery distal to the first diagonal branch for 40 minutes (G.O. and M.G., with 11 and 3 years of experience, respectively). After deflation of the balloon, subsequent angiography was performed to verify restoration of blood flow in the previously occluded artery.

In vivo and ex vivo imaging were performed after a mean of 240 minutes ± 40 (SD) and 300 minutes ± 40, respectively, of reperfusion by using a 1.5-T MR imaging unit (Intera CV; Philips Medical Systems, Best, the Netherlands), hereafter called unit A. An extracellular contrast agent (gadopentetate dimeglumine, Magnevist; Bayer Pharma, Berlin, Germany) was administered intravenously at 0.2 mmol/kg 15 minutes before in vivo imaging and again 15 minutes before explantation. Standard clinical imaging parameters were used for in vivo infarct imaging by using an inversion-recovery gradient-echo sequence. A five-element cardiac synergy coil was used, and imaging parameters were 3.8/1.14/230–290; flip angle, 15°; matrix, 240 × 180; sensitivity encoding factor, one; rectangular field of view, 380 × 280 mm; and resolution after reconstruction, 1.56 × 1.56 × 8 mm.

Ex vivo imaging of the heart was undertaken according to a previously described protocol (3). In brief, the contrast agent was administered at 60 minutes and at 15 minutes prior to removal of the heart. After removal, the heart was immediately rinsed in cold saline. Atria were excised, and the ventricles were filled with balloons containing deuterated water. T1-weighted MR images (20/3.2; flip angle, 70°; field of view, 250 mm; matrix, 512 × 512; and number of signal averages, two) with an isometric resolution of 0.5 mm were acquired by using a quadrature head coil.

Computer Phantom

With a computer phantom, it is possible to generate synthetic images with infarcts of arbitrary size and location at arbitrary resolution and noise level while retaining exact knowledge of infarct volume. The computer phantom is a parametric description of the left and right

Figure 1

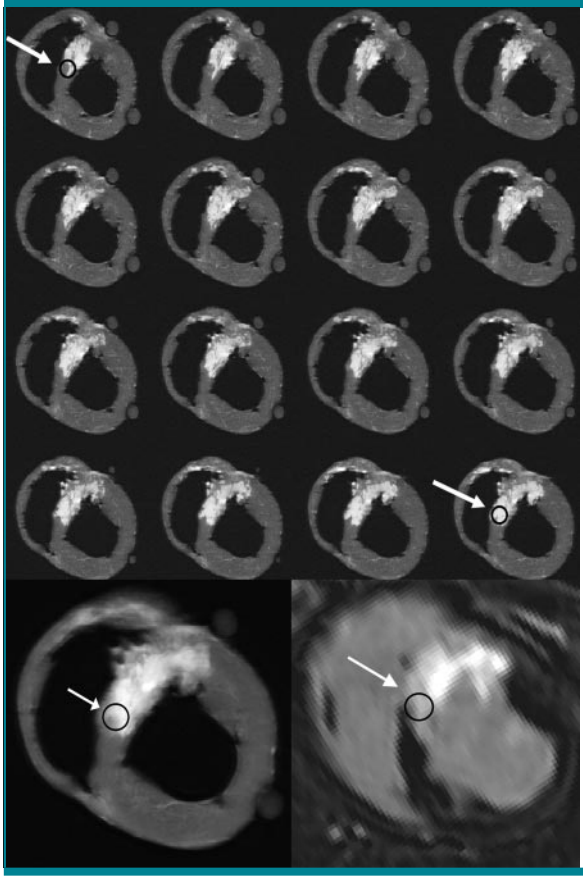

Figure 1: Top four rows: T1-weighted short-axis ex vivo MR images (repetition time msec/echo time msec, 20/3.2; flip angle, 70°; number of signal averages, two; isotropic resolution, 0.5 mm) in an image stack of 16 consecutive thin 0.5-mm-thick ex vivo sections. Sections are arranged from base to apex starting at upper left and advancing left to right, then top to bottom. Arrow with circle shows a region that is not completely infarcted in top row and almost completely infarcted in bottom row. Bottom left: Image shows average of 16 thin ex vivo sections corresponding to one 8-mm-thick section. Bottom right: In vivo inversion-recovery MR image (repetition time msec/echo time msec/inversion time msec, 3.8/1.1/230–290; flip angle, 15°; resolution, 1.56 × 1.56 × 8 mm) shows good agreement with averaged ex vivo image. Note partial volume effect seen as the relatively intermediate SI on bottom right image where arrow with circle shows same region as for the corresponding ex vivo images.

Figure 2

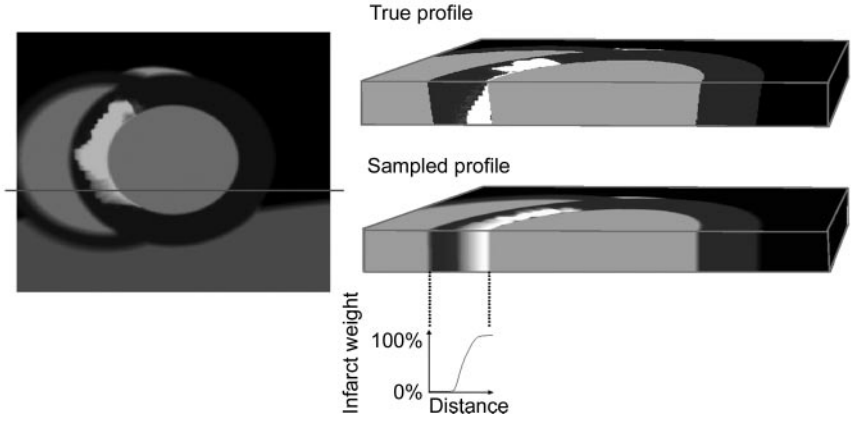

Figure 2: Depiction of partial volume weighting of an infarction in an image from a computer-generated phantom. Left: Short-axis view of 8-mm-thick section with partial volume effects. Top right: True profile along the marked horizontal line in the short-axis image. Middle right: Sampled thick section with partial volume effects. Bottom right: Resulting infarct weight by using the weighted approach.

ventricles. It also includes epicardial fat in the apical part of the ventricle and fat in the septal groove. For this study, 40 phantoms were used.

To achieve realistic models of location and shape of infarcts, the images in patients in our study (as discussed later) were used to model location of infarcts and to estimate image SI (Appendix E1 [*radiology.rsnajnls.org/cgi/content/full/2461062164/DC1*]).

The computer phantom was modeled at a high resolution of $0.1 \times 0.1 \times 0.1$ mm. Each voxel at this high resolution was treated as either infarcted or not infarcted. In the case of an infarct, the complete voxel was treated as a region where the cellular structure had broken down, causing increased extracellular space and, consequently, hyperenhancement (4). The high-resolution computer phantoms were downsampled by using a virtual MR imaging unit. This virtual imaging procedure included noise and partial volume effects. When the computer phantom was developed, care was taken to produce images similar to those acquired in a clinical situation (Fig 3).

MR Imaging in Patients

The patient participants in our study have previously been described (18). In short, 20 patients had acute first-time ST-elevation myocardial infarction (all men; mean age, 62 years ± 11; age range, 41–84 years; mean time between infarct and MR imaging, 8 days ± 1; time range, 6–10 days) and were prospectively enrolled in our study. Another group of 20 patients were retrospectively included and had been clinically referred for viability assessment (16 men, four women; mean age, 59 years ± 14; age range, 23–78 years; mean time between infarct and MR imaging, 4.7 years ± 5.3; time range, 0.5–17 years). No patient was excluded on the basis of poor image quality. For both patient groups, half of the patients were imaged with a 1.5-T MR unit (Vision Magnetom; Siemens Medical Solutions, Erlangen, Germany), hereafter called unit B, and the other half were imaged with unit A, as described previously. Imaging was performed in the short-axis plane during end-expiratory apnea. Delayed contrast-enhanced MR imaging of the infarction was performed in late diastole by using a segmented inversion-recovery turbo fast low-angle shot sequence (1) in either a multibreath-hold two-dimensional (unit B) or a single–breath-hold three-dimensional (unit A) fashion. Image resolution was $1.6 \times 1.6 \times 8$ mm with a gap of 2 mm (unit B) or $1.56 \times 1.56 \times 8$ mm with no gap (unit A). Imaging parameters were 3.8/1.1/230–290, flip angle of 25°, field of view of 400 mm, and matrix of 240×180 for unit A or 250/3.4/150–210, flip angle of 15°, field of view of 410 mm, and matrix of 256×192 for unit B.

Figure 3

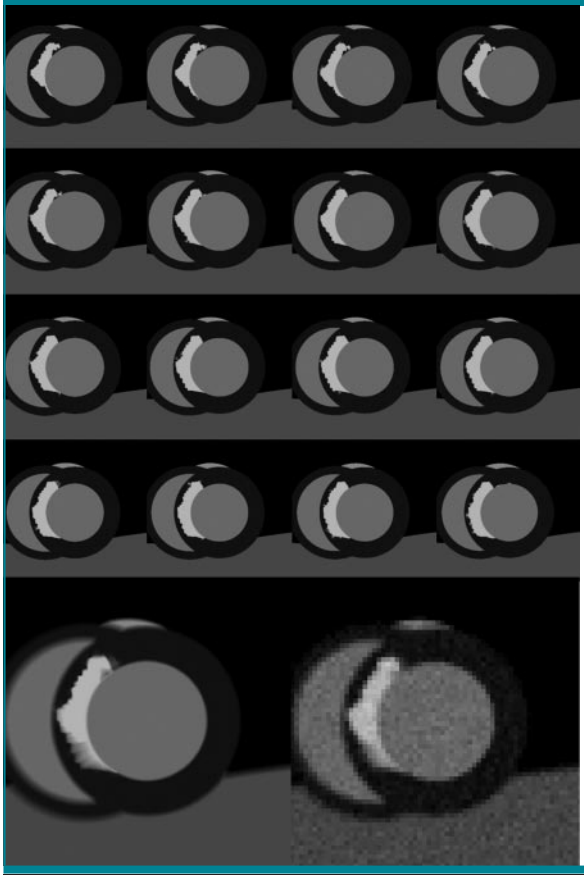

Figure 3: Short-axis computer phantom images. Top four rows: Sections are arranged from base to apex starting at upper left and advancing left to right, then top to bottom. Top row shows thin sections (spatial resolution, $0.5 \times 0.5 \times 0.5$ mm). Bottom left: Averaged section corresponding to the image stack with 8-mm section thickness. Bottom right: Corresponding 8-mm section from the virtual MR image, including imaging noise and downsampling to clinically achievable resolution of $1.56 \times 1.56 \times 8$ mm.

Image Analysis

The myocardium of the high-spatial-resolution ex vivo images of the infarct was manually delineated (H.E., with 4 years of experience). The infarct was automatically quantified by using threshold-level analysis that was based on mean remote myocardial image SI plus a fixed number of SDs. The number of SDs was identified by using the k-means algorithm (19), by which we calculated a threshold level that, as well as possible, separated two normally distributed populations (ie, infarction and noninfarction). Manual corrections of infarct delineation were allowed in regions with microvascular obstruction (H.E.).

For the images in animals, one observer (E.H.) outlined the endo- and epicardial surfaces of the in vivo images. The reference infarct volume was taken from a manual delineation of the high-spatial-resolution ex vivo images, as described previously. For the images in patients, three experienced readers (H.E., H.A., and a nonauthor, with 4, 11, and 4 years of cardiac MR imaging experience, respectively) who were blinded to each other's results manually delineated the in-

farct volume. Their mean infarct volume was taken as the consensus infarct volume. All observers used the same delineation of endo- and epicardium (H.E.). Our study began by applying the same basic algorithm for delineating infarct as previously described (18). The algorithm can be summarized as follows:

1. The mean SI and SD were calculated in five sectors in each section. The midmural half of the sector with the lowest mean SI was considered remote myocardium.

2. A section-specific threshold level was calculated by adding together the mean of the remote sector and a fixed number of SDs from the mean SI in the remote region.

3. A fast-level set algorithm (20) was applied, and the speed term was set to a value calculated by subtracting the section-specific threshold level from the SI.

4. Isolated regions that were smaller than 1.5 cm^3 were removed unless they either constituted more than 1.0 percentage left ventricular myocardial (%LVM) volume or were the largest infarction in the image volume.

However, one important modification was made to the originally proposed algorithm (18). The total infarct volume was not calculated by summing dichotomously classified pixels. Instead, the infarct volume was calculated by weighting each pixel according to its SI. The weight was set to be linearly proportional to the pixel SI. Parameters that could be adjusted in the weighted algorithm were as follows: *(a)* the number of SDs from the mean SI in remote myocardium to be included in the region of infarction; *(b)* the weight assigned to the darkest pixel of the delineated infarct area, which thereby defines the minimum detectable infarct fraction; and *(c)* the SI at which the pixels were assigned a weight of 100%.

To identify optimal values for parameters *a* and *b* just mentioned, a range of values was systematically and iteratively tested. The SD from remote myocardium ranged from 0 to 6 SDs, and minimal weight ranged from 0% to 100%. Different values for parameter *c* were also evaluated. Bias and variability for the animals were determined for each combination of SD and minimal weight. To evaluate our nondichotomous approach versus a dichotomous approach, we set parameter *b* to be 100% and evaluated performance of the algorithm when we again varied the SD from remote myocardium from 0 to 6 SDs.

Figure 4

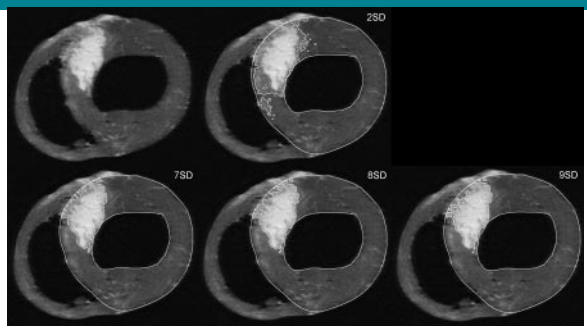

Figure 4: Top left: High-spatial-resolution ex vivo short-axis T1 weighted MR image (20/3.2; flip angle, 70°; number of signal averages, two; isotropic resolution, 0.5 mm). Top right: Result of infarct quantification based on 2 SDs from remote myocardium. Bottom left to right: Infarct delineation with threshold levels of 7, 8, and 9 SDs from remote myocardium, respectively. The differences in infarct size as measured by 7–9 SDs from remote myocardium were small.

Microvascular Obstruction

Microvascular obstruction may cause regions of low SI in the core of a region of infarction. This can typically occur in the acute infarct phase. Hsu et al (5) suggested a technique to fill these "holes" in the infarct by means of morphologic image operations. In our study, we used a related but simplified approach. The blood pool is added to the binary image of the infarct. The resulting image is then filled with a flood fill algorithm. Areas in the infarct that are not reached with the flood fill algorithm are classified as infarct, blood pool, or holes. After removal of the blood pool again, the resulting binary image was of the infarct region plus the filled holes. The infarct weight for the filled holes was set to be 100%.

Statistical Analysis

Continuous data are presented as the mean ± SD. Infarct size is presented as %LVM. Bias was defined as the mean difference in infarct volume between the algorithm and the reference infarct volume for each of the image types (images of animals, phantoms, and patients). Variability was calculated as the SD of the differences in infarct size. Bias and variability are expressed as %LVM. The *t* test was used to test whether the difference in bias between manual observers and the automated method was significantly different from zero. The *F* test was used to determine the difference in variability between methods or observers. A retrospective numeric power analysis was performed to determine the power with which one could detect a difference in variability between dichotomous and nondichotomous algorithms for quantification of infarcts. A difference with a *P* value of less than .05 was considered significant. Statistical analysis was performed by using software (Matlab, version 7.3.1, release 14; MathWorks, Natick, Mass).

Results

Ex Vivo MR Imaging

The k-means algorithm identified the threshold level for infarction on the ex vivo images to be 8.1 ± 0.4 SDs from remote myocardium. The difference between taking 9 SDs and 7 SDs from remote myocardium was, on average, 1.9 cm^3 or 1.9%LVM. The threshold level was, therefore, set to be 8 SDs from remote myocardium (Fig 4).

SI Level

The SI level at which the pixels were assigned a weight of 100% was not critical to the bias or variability of the algorithm. Changing this level from the 85th to the 95th percentile of the SI values within the infarct caused a change in variability of the algorithm that was less than 0.2 %LVM. This level was therefore set to be at the 90th percentile of the SI values within the infarct.

Bias and Variability

The optimal combination of bias and variability for animal data was found at a minimum weight of 10% and 1.8 SDs from remote myocardium (Fig 5). With the use of this optimal combination, the algorithm was applied (Fig 6). The bias of the automated method in animals was shown to be −0.3 %LVM, and the variability was 1.3 %LVM. These values corresponded to a bias of -0.8 cm^3 and a variability of 3 cm^3 for infarct volume. The bias of the computer phantoms was −1.2 %LVM or 1.5 cm^3, and the variability was 1.7 %LVM or 1.9 cm^3 when compared with the known reference infarct size. The variability for images in both animals and computer phantoms was not larger than the interobserver variability for those in the patients (P = .97 and P = .11, respectively). The bias compared with that of the consensus-determined infarct size in 40 patients was 0.3 %LVM or 0.8 cm^3; the variability was 2.7 %LVM or 4.5 cm^3, as compared with the variability among the three observers, which was 2.6 %LVM, as previously reported (18). The bias for the interobserver variability was zero by construction. Both the bias and variability of the algorithm did not differ compared with the consensus-determined delineation of the three observers (bias: 0.3 vs 0 %LVM, P = .31; variability: 2.7 vs 2.6 %LVM, P = .38). However, the bias among the three observers differed significantly (P = .01), as previously reported (18).

Dichotomous Threshold Level

A dichotomous threshold level, with use of a minimum weight of 100%, yielded an optimum of 4.7 SDs from remote myocardium. This factor resulted in a bias of 0.1 %LVM and a variability of 7.7 %LVM for the animal data. The lowest possible variability, with use of a dichotomous threshold level, was 4.6 %LVM for the phantom data and 4.4 %LVM for the patient data. The weighted algorithm had lower variability compared with that of the dichotomous approach for animals, phantoms, and patients ($P < .01$ for all). Retrospective power analysis showed that a decrease in variability from 7.7 to 2.7 %LVM could be detected in 40 patients with a power of 0.99.

Discussion

Our study findings show that weighting of infarcted pixels results in compensation for the partial volume effect on myocardial infarction from delayed contrast-enhanced MR images. Our method is completely automated after delineation of the endo- and epicardial contours. Furthermore, this approach has a variability that is much lower than that for a dichotomous approach and is not different from the interobserver variability of manual delineations of infarction.

In previous studies of algorithms for automated quantification of infarcts (5,11,15), researchers have reported similar results for bias, but to our knowledge, no investigators have systematically and quantitatively reported the variability of their algorithm. Variability is important because it provides an estimate of the limits of possible errors, and in some cases, a small variability is more important than a low bias. It should be noted that even though the area of the region of infarction differs between the automated and the manual delineations, the bias between the algorithm infarct volume and reference infarct volume is small. Delineation with the use of a minimal weight of 100% is equivalent to a dichotomous approach to infarct delineation. This gives a much higher combination of bias and variability for all possible SDs from remote myocardium. Thus, the weighted approach is less variable than any nonweighted approach. We found the lowest bias and variability for a dichotomous approach when we used a value of 4.7 SDs from remote myocardium, and this finding corresponds

Figure 5

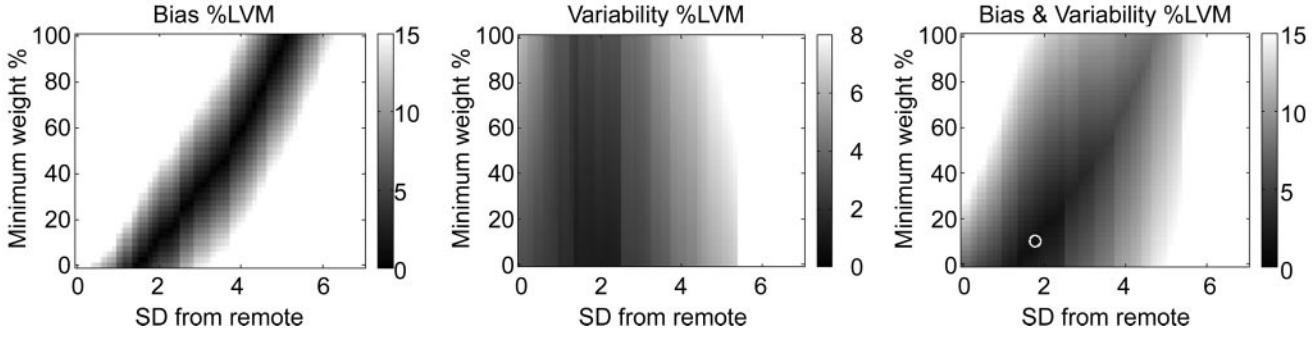

Figure 5: Images show influence of the number of SDs from remote myocardium and minimum weight on bias and variability. Left: Bias. Middle: Variability. Right: Sum of bias and variability. Values greater than maximum of given gray scale have been truncated for visualization purposes. Values compare results from in vivo MR infarct size by using the proposed algorithm with ex vivo MR infarct size in eight pigs. Circle = optimum value that yielded smallest bias and variability.

Radiology

Figure 6

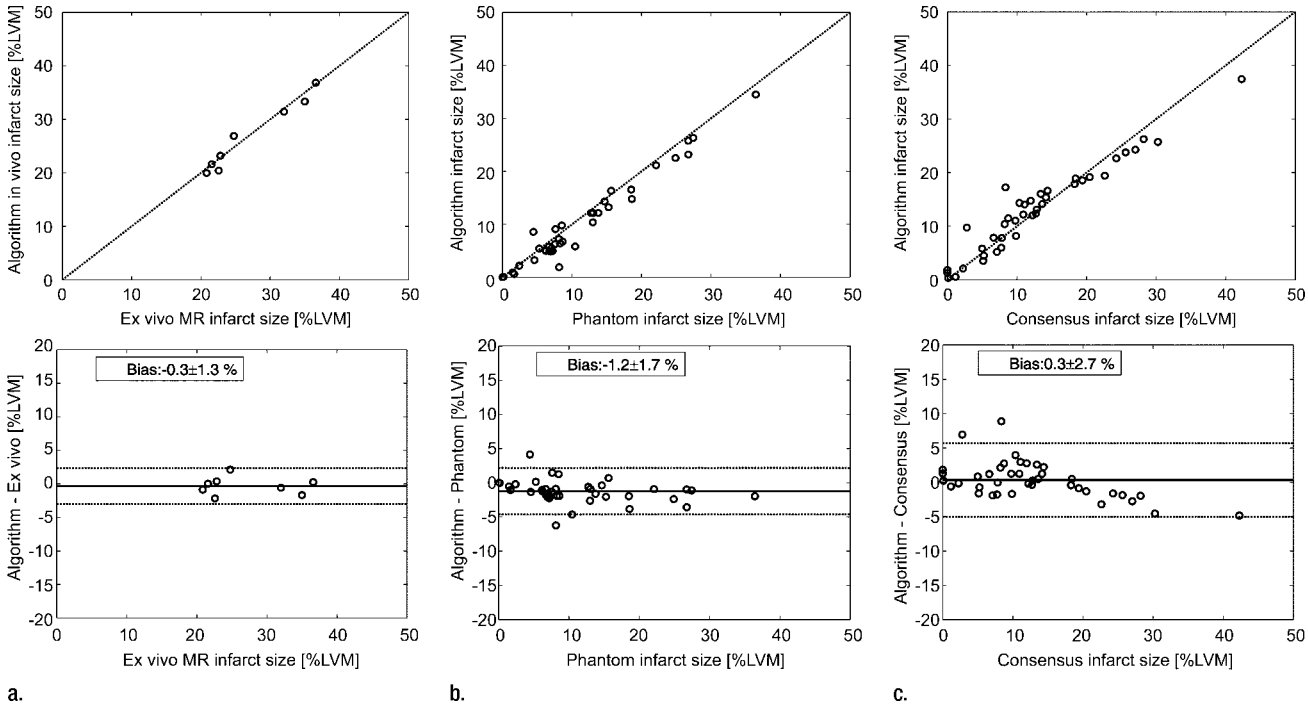

Figure 6: Graphs show results for performance of algorithm. Top: Results comparing algorithm with reference infarct size. Dotted line is line of identity. Bottom: Difference calculated by subtracting result with algorithm from reference infarct volume. **(a)** Animal data. **(b)** Computer phantom data. **(c)** Patient data. Consensus infarct size denotes the mean of manual measurements from three observers.

closely to 5 SDs, as proposed by Bondarenko et al (11).

Infarct transmurality is an important parameter for prediction of functional recovery after myocardial infarction (21,22). However, infarct transmurality is a measure that is sensitive to errors in delineation since the myocardium at clinically achievable image resolutions is typically not more than 8 pixels thick. The algorithm we used enables the calculation of a weighted transmurality measure that has potential to be less sensitive to errors in delineation of the infarcted area. Future studies are needed to assess how such a measure influences the prediction of functional recovery.

The optimum number of SDs identified by the optimization process (1.8 SD) is close to what Kim et al (3) proposed for thin-section ex vivo MR imaging. This finding indicates that a value of approximately 2 SDs is an appropriate number of SDs from remote myocardium to use for thick sections but only if compensation for partial volume effects is performed by weighting. The large difference in the number of SDs from remote myocardium used in the current ex vivo images compared with what Kim et al reported (3) may be explained by differences in signal-to-noise ratio, size of remote myocardial region of interest, or gadolinium-based contrast agent dose, or all three.

Inhomogeneous coil sensitivity may affect any algorithm in which pixel SI values are used to quantify volume. For parallel imaging, differences in coil sensitivity are used, and images reconstructed by using such techniques have effectively compensated for inhomogeneous coil sensitivity. Although we did not use parallel imaging when we imaged the patients, we were able to show results that were superior to those with a dichotomous approach and that did not differ from results with manual delineation.

A possible limitation with our study is that the reference infarct volume for the images in animals was taken from high-spatial-resolution ex vivo MR images. However, researchers in previous studies have shown that delayed gadolinium-enhanced MR imaging helps to closely track the area of irreversible myocardial injury caused by chronic or acute infarction (3–6,23). Furthermore, our approach includes assessment of the voxels in the ex vivo and phantom reference images as either homogeneously infarcted or not infarcted. This approach does not differentiate between a voxel with a low infarct fraction and either a homogeneous or a partitioned mixture of myocytes and ruptured cells or fibrocytes. However, the relatively high resolution of our reference images appears sufficient enough to account for most of the partial volume effect. Also, the physiologic significance of different partitioning of partially injured myocardium and its effects on healing are not yet known.

In conclusion, the proposed weighted algorithm for quantification of myocar-

dial infarction from delayed contrast-enhanced MR images has a variability that is much lower than that for dichotomous approaches and is not different from the interobserver variability of manual delineations of infarction.

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