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Early Gadolinium Enhancement for Determination of Area at Risk

A Pre-Clinical Validation Study

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ABSTRACT

OBJECTIVES The aim of this study was to determine whether early gadolinium enhancement (EGE) by cardiac magnetic resonance (CMR) in a canine model of reperfused myocardial infarction depicts the area at risk (AAR) as determined by microsphere blood flow analysis.

BACKGROUND It remains controversial whether only the irreversibly injured myocardium enhances when CMR is performed in the setting of acute myocardial infarction. Recently, EGE has been proposed as a measure of the AAR in acute myocardial infarction because it correlates well with T2-weighted imaging of the AAR, but this still requires pathological validation.

METHODS Eleven dogs underwent 2 h of coronary artery occlusion and 48 h of reperfusion before imaging at 1.5-T. EGE imaging was performed 3 min after contrast administration with coverage of the entire left ventricle. Late gadolinium enhancement imaging was performed between 10 and 15 min after contrast injection. AAR was defined as myocardium with blood flow <2 SD from remote myocardium determined by microspheres during occlusion. The size of infarction was determined with triphenyltetrazolium chloride.

RESULTS There was no significant difference in the size of enhancement by EGE compared with the size of AAR by microspheres (44.1 ± 15.8% vs. 42.7 ± 9.2%; $p = 0.61$), with good correlation ($r = 0.88$; $p < 0.001$) and good agreement by Bland-Altman analysis (mean bias 1.4 ± 17.4%). There was no difference in the size of enhancement by EGE compared with enhancement on native T1 and T2 maps. The size of EGE was significantly greater than the infarct by triphenyltetrazolium chloride (44.1 ± 15.8% vs. 20.7 ± 14.4%; $p < 0.001$) and late gadolinium enhancement (44.1 ± 15.8% vs. 23.5 ± 12.7%; $p < 0.001$).

CONCLUSIONS At 3 min post-contrast, EGE correlated well with the AAR by microspheres and CMR and was greater than infarct size. Thus, EGE enhances both reversibly and irreversibly injured myocardium. (J Am Coll Cardiol Img 2016;■:■-■) © 2016 by the American College of Cardiology Foundation.

Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) is widely used in the determination of size and extent of myocardial infarction (1); however, it remains controversial whether gadolinium-enhanced CMR only depicts infarcted tissue. Recently, 2 reports presented data in which early gadolinium enhancement (EGE) correlated well with T2-weighted images as a

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ABBREVIATIONS AND ACRONYMS

AAR = area at risk

CMR = cardiac magnetic resonance

ECV = extracellular volume

EGE = early gadolinium enhancement

IQR = interquartile range

LGE = late gadolinium enhancement

PSIR = phase-sensitive inversion recovery

TTC = triphenyltetrazolium chloride

marker of area at risk (AAR) in a clinical setting (2,3). These findings are intriguing and are supported by previous work that found overestimation of infarct size by gadolinium-enhanced imaging (4-6). To further validate the correlation between EGE and AAR, comparison of EGE to a pathological reference standard for the AAR is necessary. Furthermore, the previous studies of the correlations between EGE and T2-weighted AAR assessment were performed on a single slice per patient. How well EGE performs on a whole-heart basis has yet to be determined.

The aim of this study was to examine the relationship between the size of EGE and pathological standards of AAR and infarct size by use of a phase-sensitive inversion recovery (PSIR) sequence that images the entire left ventricle minutes after contrast administration in a canine model of acute myocardial infarction. How well the size of EGE compared with CMR measures of the AAR (quantitative native T1 and T2 maps) was also determined, because these modalities have shown good correlation to the pathological AAR (7).

METHODS

ANIMAL MODEL. Mongrel dogs weighing 15 to 20 kg were studied after approval by the Animal Care and Use Committee of the National Heart, Lung, and Blood Institute of the National Institutes of Health. Animals were pre-treated with amiodarone (6 mg · kg^{-1} · day^{-1}) for 1 week to minimize arrhythmia during ischemia. Anesthesia was induced with a mixture of intramuscular midazolam 0.4 mg/kg and hydromorphone 0.1 mg/kg, followed by intravenous propofol (2 to 6 mg/kg). General anesthesia was maintained during surgery after intubation with 2% to 5% inhaled sevoflurane. Intravenous and arterial lines were established, as well as a permanent left atrial catheter for administration of microspheres. After thoracotomy at the left fifth or sixth intercostal space, the left anterior descending artery was isolated and a snare placed distal to the first diagonal branch. Collateral vessels were not tied off. During occlusion, approximately 5×10^6 fluorescent microspheres (IMT Laboratories, Irvine, California) were administered with simultaneous reference blood sampling from an arterial line. The snare was released after 120 min of occlusion. After surgery, the animals were monitored and treated for pain control and hemodynamic stability by trained animal care personnel for 48 h before CMR. Animals were anesthetized before imaging as described previously. Immediately before CMR, 5×10^6 fluorescent microspheres of a different color were administered to assess the quality of reperfusion. All animals were euthanized on completion of imaging with an overdose of potassium chloride under general anesthesia.

CMR IMAGING. Imaging was performed on a 1.5-T clinical scanner (MAGNETOM Avanto, Siemens Healthcare Sector, Erlangen, Germany) with an 8-channel phased-array coil. Quantitative native T1 mapping was performed with a motion-corrected modified Look-Locker inversion-recovery sequence, with image acquisition 5 s after the first inversion followed by a 3-s pause and 3 s of acquisition after the second inversion, and steady-state free-precession readout. The following typical imaging parameters were used: field of view 280 ×154 mm^2; matrix 192 × 80; slice thickness 6 mm; voxel size 1.9 × 1.5 × 6 mm^3 = 17 μl/voxel; repetition time 2.6 ms; echo time 1.1 ms; and parallel imaging factor 2. Quantitative native T2 mapping was performed with a fast low-angle shot readout sequence and T2 preparations at 5, 40, and 80 ms. Typical parameters were as follows: field of view 280 × 154 mm^2; matrix 192 × 80; slice thickness 6 mm; voxel size 1.9 × 1.5 × 6 mm^3; repetition time 4 ms; echo time 1.6 ms; and parallel imaging factor 2.

EGE imaging was performed 3 min after administration of a 0.2 mmol/kg intravenous bolus of contrast (gadopentetate dimeglumine [Magnevist], Bayer Healthcare Pharmaceuticals, Wayne, New Jersey). To achieve whole-heart coverage at this time point, images were acquired every other heartbeat with an electrocardiography-triggered, breath-held, PSIR single-shot sequence and steady-state free-precession readout. Nine slices were obtained in 18 heartbeats. Typical parameters were as follows: field of view 280 × 154 mm; matrix 192 × 80; voxel size 1.9 × 1.5 × 6 mm^3; 50° flip angle; repetition time 3 ms; echo time 1.5 ms; parallel imaging factor 2; and inversion time 200 ms.

Standard LGE images were acquired >10 min after contrast injection with an electrocardiography-gated, segmented, PSIR fast low-angle shot readout sequence (8) with the following typical parameters: field of view 280 × 156 mm; matrix 256 × 108; voxel size 1.5 × 1.1 × 6 mm^3; 10 μl/voxel; 25° flip angle; repetition time 8.5 ms; echo time 3.3 ms; and parallel imaging factor 2. The inversion time was manually adjusted to null normal myocardium.

PATHOLOGY AND MICROSPHERE ANALYSIS. After explantation, hearts were set in 2% agarose gel, sliced on a commercial meat slicer in 3-mm-thick slices, and

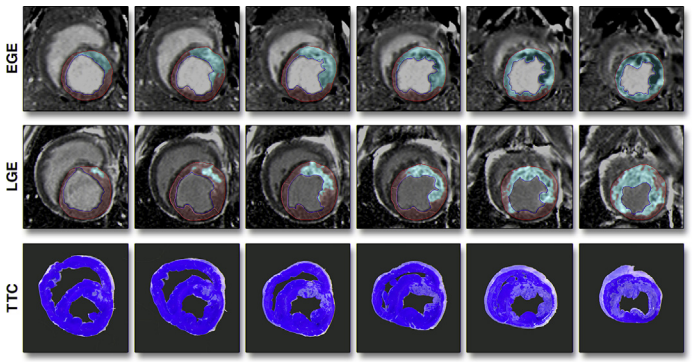
stained with 1% triphenyltetrazolium chloride (TTC) for infarct demarcation and subsequently photographed. TTC images were matched to CMR images by use of landmarks such as papillary muscles and the right ventricular insertion point, blinded to the microsphere blood flow results. For whole-heart coverage, a basal TTC slice and apical TTC slice were matched to corresponding CMR images, and all slices in that range were included in the analysis. The borders of endocardium, epicardium, and nonstained areas were manually delineated to determine infarct size as a percentage of the left ventricle. Additionally, a slice-by-slice comparison of the AAR by microspheres and by EGE was performed. In this comparison, only the slices that could be matched to an image were included. A representative example is depicted in Figure 1.

Two consecutive TTC slices were combined for further transmural sectioning and microsphere analysis to achieve the same slice thickness as the CMR images. The myocardium of the left ventricle was sectioned into transmural radial sectors. Sectors in the infarcted area (defined by TTC) were further sectioned into an endocardial and epicardial section. Having an endocardial section that was clearly TTC positive allowed making measurements within the core of the infarct that were not contaminated by partial volume errors with salvaged myocardium closer to the epicardium. This minimized partial volume effects. A few sectors of normal myocardium were also split into endocardial and epicardial subsections. Each myocardial sector weighed approximately 0.7 g, to ensure a sufficient number of microspheres per sector for reliable analysis. Tissue samples were sent to an external laboratory for myocardial blood flow determination (IMT Laboratories). Myocardial sectors with blood flow <2 SD below blood flow in remote myocardium were defined as AAR. The summed weight of AAR sectors was divided by the total left ventricular mass.

IMAGE ANALYSIS. Image analysis was performed with a custom in-house software program. Endocardial and epicardial borders were manually delineated. Hyperenhancement on EGE images, as well as native T1 and T2 maps, was defined as pixels with signal intensities >2 SD from remote myocardium for semiautomatic quantification. Spurious noncontiguous pixels were excluded. Hypoenhanced pixels within an area of hyperenhancement (regions of microvascular obstruction or hemorrhage) were included as infarcted pixels in the hyperenhanced area.

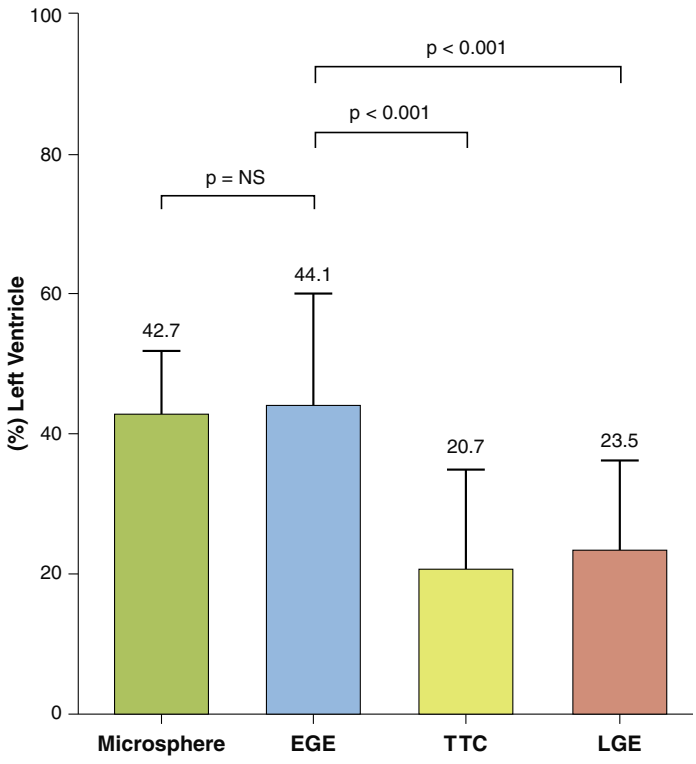
On LGE images, infarct was defined as areas of enhancement based on the feature analysis and combined thresholding computer algorithm, which

FIGURE 1 Slice-by-Slice Comparison From 1 Animal of EGE and LGE Compared With Infarct by Pathology



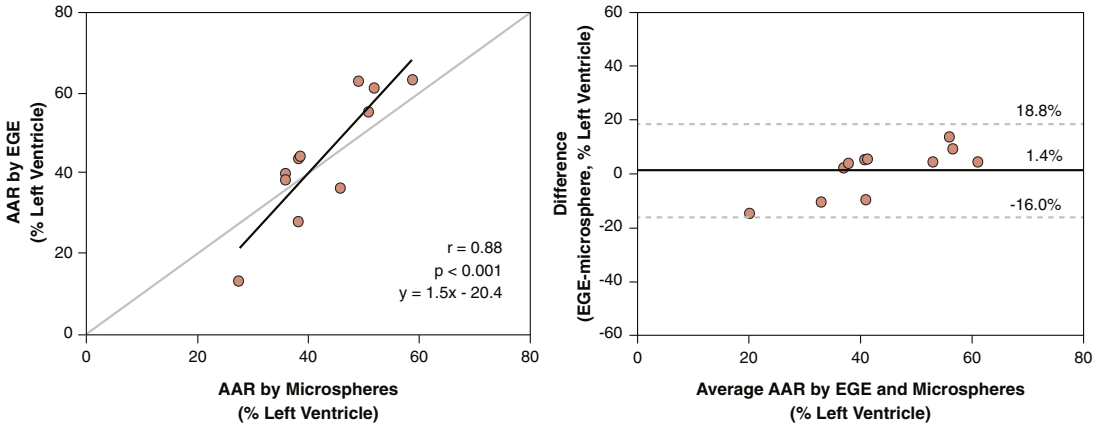
Short-axis stack was aligned from base **(left)** to apex **(right)** for quantification of enhancement. The extent of EGE **(upper row)** exceeded that of LGE **(middle row)** and TTC **(bottom row)** in all slices. EGE = early gadolinium enhancement; LGE = late gadolinium enhancement; TTC = triphenyltetrazolium chloride.

FIGURE 2 Area at Risk and Infarct Measures by Pathology and Cardiac Magnetic Resonance



There was no difference in the size of area at risk by microspheres compared with the size of EGE. EGE was greater than both cardiac magnetic resonance and pathological measures of infarction. Abbreviations as in Figure 1.

FIGURE 3 Per-Animal Comparison of EGE and AAR by Microspheres

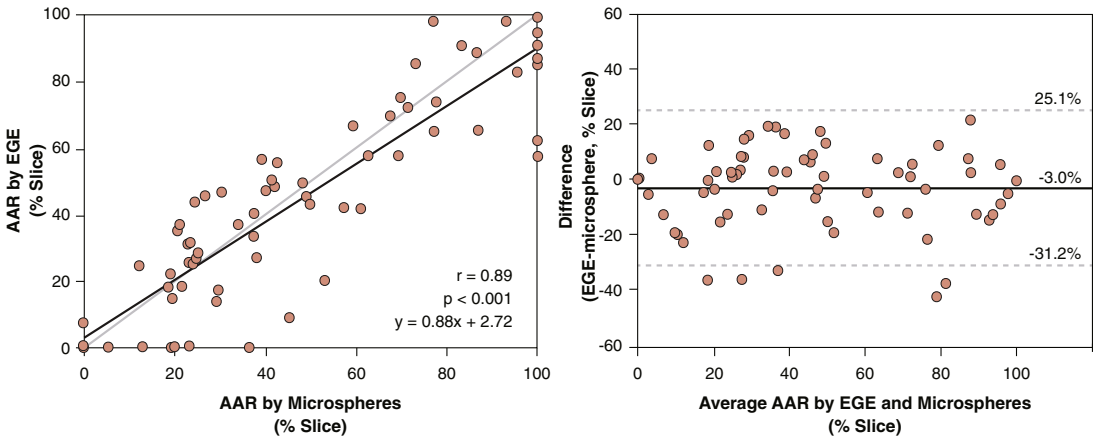


The size of enhancement on EGE images correlated very well to the size of AAR by microsphere analysis (scatterplot) **(left)**, with minimal systematic bias on the Bland-Altman plot **(right)**. **Dotted lines** represent line of identity in scatterplot and mean ± 2 SD in Bland-Altman plot. AAR = area at risk; other abbreviation as in Figure 1.

was validated previously by pathology (9). Enhancement on CMR images was presented as a percentage of the entire left ventricular myocardium. Whole-heart coverage was used to minimize partial volume effects, potential misregistration, and ex vivo shrinking of the myocardium for comparisons to pathological infarct sizing by TTC.

STATISTICAL ANALYSIS. Statistical analysis was performed with MedCalc version 12.7.7 (Ostend, Belgium). Normally distributed data are presented as mean ± SD, and non-normally distributed data are presented with medians and interquartile ranges (IQR). After confirmation of normality, paired Student *t* tests were performed to compare means. The Wilcoxon signed rank test was used for nonparametric data. Correlations were assessed by Pearson correlation coefficient (r) for normally distributed data and Spearman rank correlation in other cases. Limits of agreement were performed with Bland-Altman analysis and are presented as mean difference ± 2 SD.

FIGURE 4 Slice-by-Slice Comparison of EGE and AAR by Microspheres



On a per-slice basis, the correlation between EGE and pathological AAR (microsphere analysis) was very good (scatterplot) **(left)**. The bias by Bland-Altman **(right)** was only 3%. Data represent 68 slices from 11 animals. Abbreviations as in Figures 1 and 3.

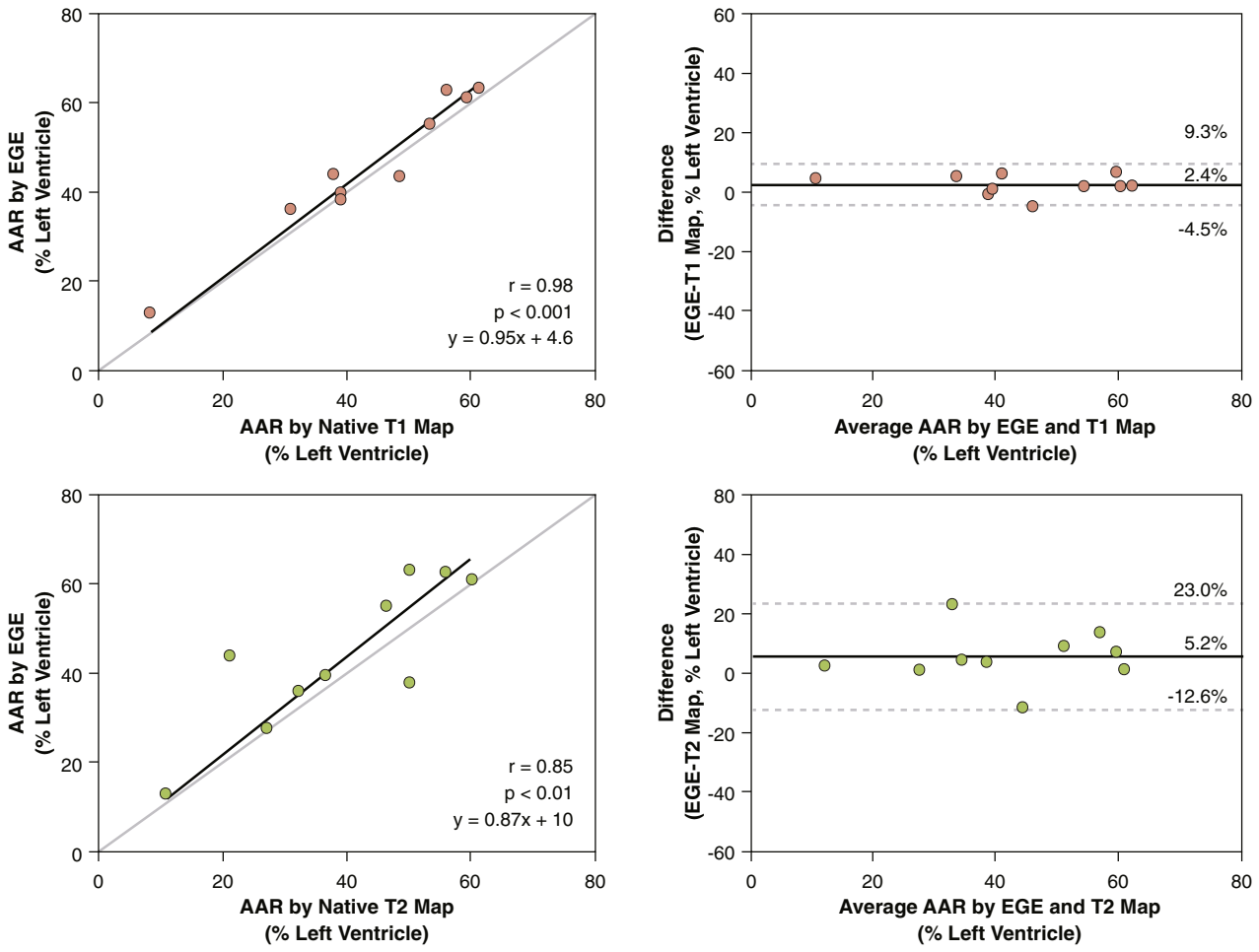
On the basis of an a priori sample size calculation, a minimum of 10 experiments were required to detect a correlation of 0.9 between AAR by EGE and microspheres with a power of 0.9 and alpha of 0.01.

RESULTS

Eleven animals underwent successful coronary artery occlusion and reperfusion before CMR (Figure 1). Microsphere data were available for all animals (n = 11) at occlusion. On average, the left ventricle of each animal was sliced into 91 sectors (range 66 to 131 sectors). Microsphere data were only available for 9 animals 48 h after reperfusion because of inadequate reference blood flow sampling. During vessel occlusion, blood flow in the AAR was significantly lower than in remote myocardium, 0.177 ± 0.043 ml/min/g versus 0.579 ± 0.17 ml/min/g ($p < 0.001$). In the ischemic core, the myocardial blood flow during occlusion was 9.4% (IQR: 6.2% to 8.7%) of the blood flow in remote myocardium. The myocardial sectors identified as infarcted by TTC during slicing had significantly lower blood flow than the epicardial sectors that were part of the AAR (0.067 ml/min/g [IQR: 0.034 to 0.17 ml/min/g] vs. 0.16 ml/min/g [IQR: 0.097 to 0.28 ml/min/g]; $p < 0.001$). The transmural gradient in the subdivided remote myocardial sectors was not statistically significant (remote endocardium 0.60 ± 0.20 ml/min/g vs. remote epicardium 0.57 ± 0.17 ml/min/g; $p = 0.25$).

At the time of CMR, there was no difference in blood flow in the AAR compared with remote

FIGURE 5 Comparison of EGE and CMR Measures of AAR



The size of enhancement by EGE also correlated very well to the size of the AAR by both cardiac magnetic resonance measures of AAR. Data for comparisons were available from 10 animals. **Dotted lines** represent line of identity in scatterplot and mean ± 2 SD in Bland-Altman plot **(right)**. Abbreviations as in Figures 1 and 3.

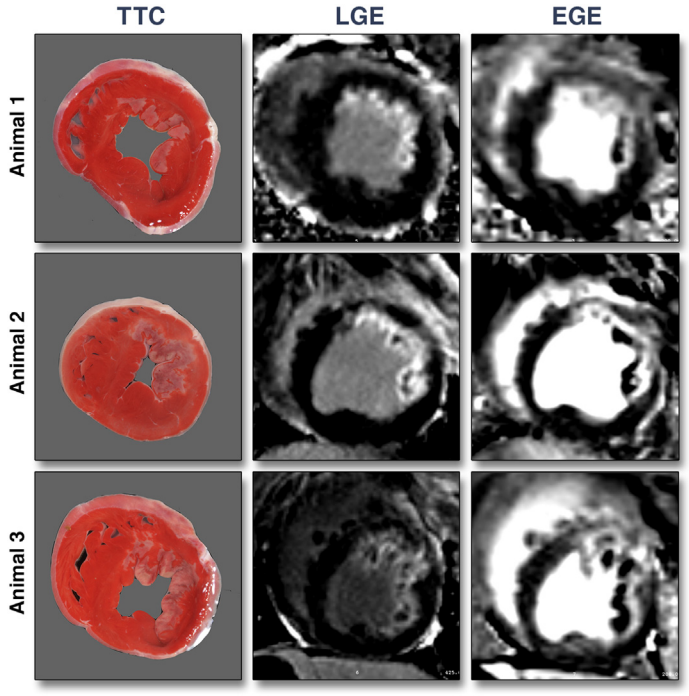
(0.34 ± 0.21 ml/min/g vs. 0.31 ± 0.18 ml/min/g; p = 0.17) or in the ischemic core compared with remote (0.29 ± 0.20 ml/min/g vs. 0.31 ± 0.18 ml/min/g; p = 0.58), which indicates successful reperfusion. The size of the AAR by microspheres was greater than the size of infarct by TTC in all animals (42.7 ± 9.2% vs. 20.7 ± 14.4%; p < 0.001), which indicates significant salvage.

EGE FOR AAR ASSESSMENT BY MICROSPHERE ANALYSIS. There was no significant difference in the size of enhancement on EGE images compared with the size of perfusion defect by microspheres (44.1 ± 15.8% vs. 42.7 ± 9.2%; p = 0.61) (Figure 2). The size of EGE correlated well to the size of the AAR by microspheres (r = 0.88; p < 0.001) (Figure 3). Bland-Altman analysis revealed good agreement, with a mean bias of 1.4 ± 17.4% of the entire left ventricle (Figure 3). In a per slice comparison, the size of enhancement on EGE also correlated well with the microsphere AAR (r = 0.89; p < 0.001) (Figure 4).

EGE FOR AAR ASSESSMENT BY QUANTITATIVE MAPS. Compared with CMR measures of AAR (native T1 and T2 map data were available in 10 studies), there was no significant difference in the size of enhancement by EGE compared with the size of enhancement on native T1 maps (45.8 ± 15.6% vs. 43.4 ± 16.1%; p = 0.06). The correlation between EGE and T1 maps was excellent (r = 0.98; p < 0.001), with a mean bias of 2.4 ± 6.9%. Similarly, there was no significant difference between the enhancement by EGE and native T2 maps (44.2 ± 16.7% vs. 39.0 ± 16.2%; p = 0.11). There was good correlation (r = 0.85; p < 0.01) between EGE and enhancement on T2 maps, with a slight overestimation by Bland-Altman analysis (5.2 ± 17.8%). The comparison of the size of EGE to the size of AAR defined by CMR measures is presented in Figure 5. The size of the AAR by both types of quantitative maps did not show any difference compared with the size of the AAR by microsphere analysis: 43.4 ± 16.1% versus 43.2 ± 9.6% (p = 0.95) for T1 maps versus microspheres and 39.0 ± 16.2% versus 43.2 ± 9.6% (p = 0.27) for T2 maps versus microspheres.

EGE AND MEASURES OF INFARCTION. Three representative studies are depicted in Figure 6 in which the EGE exceeded the infarction by LGE and TTC. In all animals, the size of enhancement by EGE was greater than the size of infarction by TTC (Figures 1 and 7). The size of EGE was significantly greater than the infarct by TTC (44.1 ± 15.8% vs. 20.7 ± 14.4%; p < 0.001). This was also the case for the size of enhancement by EGE compared with that of LGE (44.1 ± 15.8% vs. 23.5 ± 12.7%; p < 0.001). In addition, LGE showed excellent correlation to infarct size by TTC (r = 0.95; p < 0.001) and only very small systematic bias (Figure 8). Example T1, EGE, LGE, and TTC images are shown in Figure 9.

FIGURE 6 Midventricular EGE, LGE, and TTC Slices From 3 Representative Animals

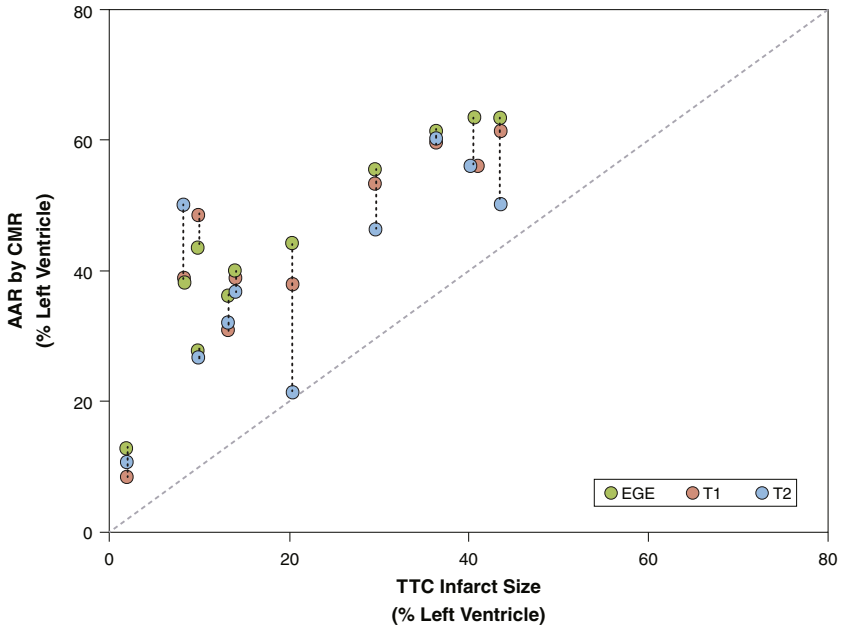


The transmural extent of EGE was clearly greater than the infarction by TTC or LGE. Abbreviations as in Figure 1.

DISCUSSION

This study demonstrates that AAR can be determined by EGE, because there is a good correlation between the size of EGE by CMR and the size of the AAR as determined by microspheres, the pathological reference standard. There was also a very good correlation between the size of hyperenhancement by EGE and other CMR measures of AAR in this study (native T1 and T2 maps). Furthermore, the size of gadolinium enhancement 3 min after contrast administration was clearly greater than the pathological standard of infarct size in this canine model of reperfused acute myocardial infarction. LGE correlates much more closely with infarct size. Also, the method presented here can image EGE of the entire left ventricle in approximately 18 heartbeats. The combination of EGE and LGE enabled evaluation of AAR and infarct size for the whole heart, as Matsumoto et al. (2) suggested previously. An independent pathological standard of microspheres and TTC confirmed this finding.

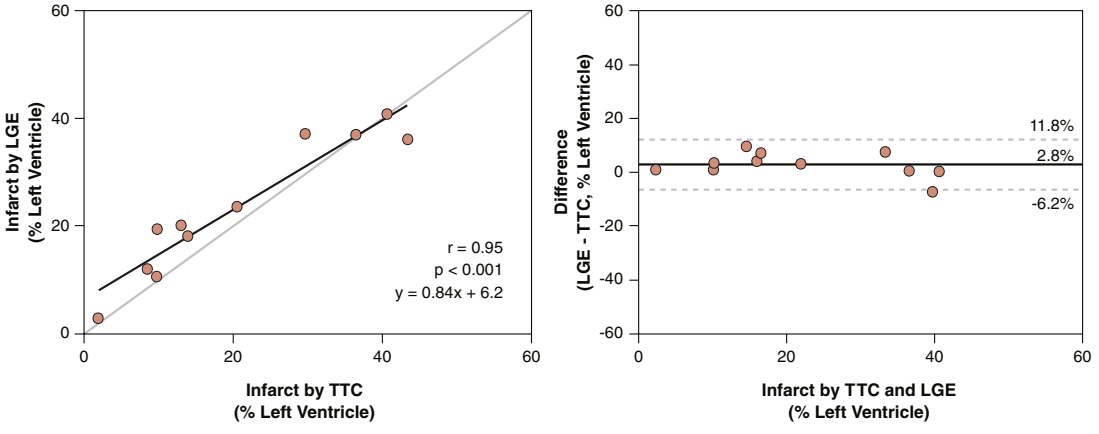
FIGURE 7 Comparison of AAR by CMR (Native T1, Native 2 and EGE) and Infarct Size by Pathology



In all animals, the size of enhancement by CMR was greater than the size of infarct by TTC. **Dotted lines** link CMR data from the same animal. Native T1 data were only available for 10 dogs, and native T2 data were only available for 10 other dogs. The **diagonal line** indicates the line of identity. CMR = cardiac magnetic resonance; other abbreviations as in Figure 1.

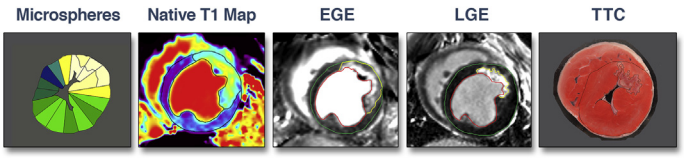
Although the correlation between AAR by T2-weighted imaging and EGE has been demonstrated in recent clinical studies (2,3), previous pre-clinical studies have also reported a close correlation between gadolinium enhancement and AAR by pathological standards (6,10). The findings in this study support the hypothesis of possible overestimation of infarct size by gadolinium enhancement in acute myocardial infarction, which has been reported by numerous authors throughout the years

FIGURE 8 Infarct Size Comparisons



The size of infarction by LGE showed excellent correlation to infarct size by pathology and minimal bias in the Bland-Altman plot **(right)**. **Dotted lines** represent line of identity in scatterplot **(left)** and mean ± 2 SD in Bland-Altman plot. Abbreviations as in Figure 1.

FIGURE 9 Pathology and CMR Images of the Same Midventricular Short-Axis Slice



The AAR determined by abnormal microsphere blood flow during occlusion was not significantly different from the size of hyperenhancement on native T1 maps, native T2 maps, or EGE. The size of enhancement by EGE 3 min after contrast administration was significantly greater than the size of enhancement by LGE and the pathological infarct size determined by TTC. Abbreviations as in Figures 1 and 7.

(4,5,11). The use of PSIR sequences mitigates the difficulties associated with choosing correct TI times, reducing the bias that might be caused by imaging parameters and addressing technical variables that might have contributed to the disparate findings. Overestimation of infarct size by gadolinium enhancement was recently confirmed in a porcine study by Jablonowski et al. (12) using a PSIR sequence.

Contrast-enhanced cine steady-state free-precession images have also been reported to correspond to the AAR determined by SPECT and by T2-weighted imaging in patients (13,14). Although this technique relies on both the T1 and T2 properties of the myocardium, it has been proposed that part of the bright signal could be a result of the T1-shortening properties of gadolinium in the salvaged myocardium and not just in the infarct. Additionally, clinical studies have found functional recovery in areas of myocardium that display gadolinium enhancement, as well as reduction in the extent of enhancement in the following weeks to months, which also indicates that irreversibly injured myocardium shows dynamic gadolinium enhancement (15–18).

Arheden et al. (19) demonstrated in rats that the distributional volume of gadolinium contrast was greater in myocardium that had undergone 20 min of ischemia but did not display infarction by TTC compared with normal myocardium, although it was less than that of infarcted myocardium (19). Recently published data also showed that the salvaged myocardium in a porcine model of ischemia and reperfusion had an increased extracellular volume (ECV) compared with normal myocardium both 1 day and 7 days after ischemia (12). This provides a basis for the understanding of accumulation of gadolinium, an extracellular contrast agent, not only in the irreversibly damaged myocardium but also in reversibly damaged myocardium. The expansion of the extracellular space and interstitial edema as a response to ischemia in reversibly injured myocardium, in addition to intracellular edema, has been reported previously in pathoanatomic studies (19–21). Expansion of the ECV in reversibly injured myocardium might be a result of several features of ischemic injury: shifts in electrolytes from the intracellular to the extracellular space, increased microvascular permeability resulting in protein leakage from the intravascular compartment, and structural alterations in the extracellular matrix (21–25). Conversely, the greater ECV in irreversibly injured myocardium is also caused by loss of membrane integrity in the injured cells and passive diffusion of gadolinium into the intracellular space (26), which is why this ECV is greater than in the normal and reversibly injured myocardium. Klein et al. (27) showed different wash-in/washout kinetics in infarcted and remote myocardium in a clinical study. Differences in contrast kinetics must also be important in reversibly damaged myocardium, because enhancement of the salvaged myocardium is not as pronounced in LGE acquisitions. The findings in this study therefore support the current literature and add important new insight into the concept that gadolinium not only depicts irreversibly injured myocardium but also transiently enhances reversibly injured myocardium.

Although the use of EGE for determination of myocardial AAR is exciting and easily interleaved in the clinical work flow, more work is necessary to unveil its clinical usefulness. It remains to be determined how long after a myocardial infarction this technique can reliably be applied. In a canine model, a substantial decrease of T2 values in the salvaged myocardium (and thus edema) was evident within the first 48 h after infarction (28), and a recent porcine study suggests a bimodal pattern of edema within the first days of reperfusion (29). These might be species-specific effects, because the size of AAR by T2-weighted imaging in clinical studies has been shown to be stable within the first 7 days (30). Furthermore, the optimal timing for EGE image acquisition after contrast administration requires further elucidation. In patients imaged up to 5 days after acute myocardial infarction, Matsumoto et al. (3) found the optimal timing for demarcation of EGE to be 2 min after contrast administration compared with T2-weighted enhancement as an indicator of the AAR.

STUDY LIMITATIONS. A canine model of reperfused infarction could exhibit different contrast kinetics compared with humans. Animals were imaged only once after 48 h of reperfusion. Studying EGE after various durations of reperfusion is necessary to

understand the dynamic processes involved in the regression of edema and the effect this has on the accuracy of EGE in quantifying the AAR. The AAR by EGE (or other CMR measures) might have a higher signal intensity than the remote in animals scanned after only a few hours of reperfusion and thus a higher contrast-to-noise ratio than after 2 days, assuming that some of the initial expansion of the ECV resolves by 2 days of reperfusion. Additionally, this study was performed in a tightly controlled setting with healthy animals. The influence of factors such as pre-conditioning, various amounts of collateral flow, adequacy of reperfusion, and differences in contrast elimination could have an influence on these findings in the clinical setting.

CONCLUSIONS

EGE correlates well with the size of the AAR and thus enhances both reversibly and irreversibly injured myocardium. LGE accurately images myocardial infarction in the same animals.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Andrew E. Arai, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room B1D416, MSC 1061, 10 Center Drive, Bethesda, Maryland 20892-1061. E-mail: araia@nih.gov.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In acute reperfused infarcted myocardium, gadolinium enhancement of the myocardium in the first minutes after contrast administration is a novel CMR measure of the AAR that correlates well with established CMR measures and a histopathologically defined size of the AAR.

TRANSLATIONAL OUTLOOK: This study demonstrates gadolinium enhancement of both reversibly and irreversibly damaged myocardium in acute myocardial infarction. Further study of the optimal timing of early gadolinium enhancement after contrast administration for AAR determination in clinical studies is warranted.

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