Transcatheter Myocardial Needle Chemoablation During Real-Time Magnetic Resonance Imaging

A New Approach to Ablation Therapy for Rhythm Disorders

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Background—Radiofrequency ablation for ventricular arrhythmias is limited by inability to visualize tissue destruction, by reversible conduction block resulting from edema surrounding lesions, and by insufficient lesion depth. We hypothesized that transcatheter needle injection of caustic agents doped with gadolinium contrast under real-time magnetic resonance imaging (MRI) could achieve deep, targeted, and irreversible myocardial ablation, which would be immediately visible.

Methods and Results—Under real-time MRI guidance, ethanol or acetic acid was injected into the myocardium of 8 swine using MRI-conspicuous needle catheters. Chemoablation lesions had identical geometry by in vivo and ex vivo MRI and histopathology, both immediately and after 12 (7–17) days. Ethanol caused stellate lesions with patchy areas of normal myocardium, whereas acetic acid caused homogeneous circumscribed lesions of irreversible necrosis. Ischemic cardiomyopathy was created in 10 additional swine by subselective transcoronary ethanol administration into noncontiguous territories. After 12 (8–15) days, real-time MRI–guided chemoablation— with 2 to 5 injections to create a linear lesion—successfully eliminated the isthmus and local abnormal voltage activities.

Conclusions—Real-time MRI–guided chemoablation with acetic acid enabled the intended arrhythmic substrate, whether deep or superficial, to be visualized immediately and ablated irreversibly. In an animal model of ischemic cardiomyopathy, obliteration of a conductive isthmus both anatomically and functionally and abolition of local abnormal voltage activities in areas of heterogeneous scar were feasible. This represents the first report of MRI-guided myocardial chemoablation, an approach that could improve the efficacy of arrhythmic substrate ablation in the thick ventricular myocardium.

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Radiofrequency ablation for rhythm disorders is limited by the inability instantaneously to visualize and monitor ablation lesions and by the mismatch between immediate injury and irreversible conduction block.1 Magnetic resonance imaging (MRI) thermometry only approximates the extent of irreversible lesions.2 Late-gadolinium enhancement (LGE) MRI correlates with histological lesion volume3 but can only be performed once per procedure and is not a surrogate for real-time lesion monitoring during ablation. Furthermore, scar size by LGE several months post ablation is ≤50% smaller than that measured immediately post ablation.4 Not only does the lesion contract during fibrotic healing but LGE immediately and after 12 (7–17) days. Ethanol caused stellate lesions with patchy areas of normal myocardium, whereas acetic acid caused homogeneous circumscribed lesions of irreversible necrosis. Ischemic cardiomyopathy was created in 10 additional swine by subselective transcoronary ethanol administration into noncontiguous territories. After 12 (8–15) days, real-time MRI–guided chemoablation— with 2 to 5 injections to create a linear lesion—successfully eliminated the isthmus and local abnormal voltage activities.

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WHAT IS KNOWN

- Contemporary electrophysiology techniques cannot visualize extent or continuity of radiofrequency energy ablation lesions and struggle to achieve transmural ablation in the ventricular myocardium using endocardial and epicardial electrodes.
- Chemoablation with acetic acid creates more homogenous and well-circumscribed ablation lesions compared with ethanol.
- Unlike radiofrequency energy, endocardial needle chemoablation does not seem to cause an edematous penumbra that may contribute to reversible conduction block and arrhythmia recurrence.

WHAT THE STUDY ADDS

- Magnetic resonance imaging–guided myocardial chemoablation is a completely new approach that overcomes the fundamental limitations of radiofrequency ablation by enabling immediate depiction of irreversible and transmural lesions using endocardial needle catheters.
- Chemoablation with acetic acid creates more homogeneous and well-circumscribed ablation lesions compared with ethanol.
- Unlike radiofrequency energy, endocardial needle chemoablation does not seem to cause an edematous penumbra that may contribute to reversible conduction block and arrhythmia recurrence.

In this report, we demonstrate for the first time (1) the feasibility of real-time MRI–guided myocardial chemoablation in swine; (2) MRI characteristics, macroscopic appearance, and histopathology of acute and chronic chemoablation lesions; (3) superior circumscription of myocardial acetic acid chemoablation lesions compared with ethanol lesions; and (4) anatomic and electric interruption of a conductive isthmus in an animal model of ischemic cardiomyopathy.

Methods

The institutional animal care and use committee approved all procedures, which were performed according to contemporary National Institutes of Health guidelines. Eighteen Yorkshire swine with mean body weight 54 (46–57) kg were anesthetized with mechanical ventilation. Chemoablation was performed in a clinical 1.5T MRI catheterization suite, equipped with sound-suppression communication headsets and with video projectors to display hemodynamics and real-time MRI images at the bedside (Figure 1).19 Electroanatomic mapping was performed under x-ray guidance.

Evaluation of Chemoablation Agents

Gadolinium-based contrast agents can release free gadolinium (Gd3+) at low pH. Therefore, we tested whether 50% acetic acid (pH 1.9) caused the release of free gadolinium from 3 different commercially available gadolinium-based contrast agents (gadopentetate, Magnevist, Bayer; gadofosveset, Ablavar, Lantheus; and gadoterate, Dotarem, Guerbet). Details of the assay can be found in the Data Supplement.

We characterized ethanol or acetic acid chemoablation lesions in 8 naive swine. Four were euthanized immediately, and 4 were survived for at least 7 days. Ethanol (70%) and acetic acid (50%) were doped with gadolinium-based contrast agent for MRI conspicuity (2% gadolinium by total volume). Pure ethanol was prediluted to 70% with sterile water because in higher concentrations, gadolinium contrast precipitates. Acetic acid (50%) is the optimal concentration for solid organ tumor ablation.20 Small aliquots (0.1–0.6 mL) of these 2 solutions were injected into the LV myocardium under real-time MRI guidance. Venous blood was collected before and immediately after chemoablation with acetic acid to assess for effect on systemic pH and anion gap.

MRI-Guided Chemoablation

MRI scanning parameters are detailed in the Data Supplement. Injections into the LV myocardium were delivered using a MRI-conditional deflectable sheath (Imricor and Innotom) with a passive marker tip and a custom injection needle catheter incorporating electronics for active visualization. The needle catheter appeared in color on real-time MRI. The sheath was introduced to the LV cavity via transarterial retrograde approach over a Nitinol guidewire (Nitrex) under interactive real-time MRI guidance.19 The needle was navigated to the target myocardium, positioned orthogonally to the endocardial surface (Figure 2) and deployed to a depth of 4 mm (or 50% of the myocardial wall thickness). The chemoablation agent was injected slowly in aliquots of 0.1 to 0.6 mL, and the needle was withdrawn after 30 s. Chemoablation lesions appeared bright in real-time inversion-recovery MRI as the chemoablation agent doped with gadolinium contrast was injected.

Animal Model of Ischemic Cardiomyopathy

Pigs were pretreated with amiodarone, aspirin, and heparin and underwent x-ray–guided left coronary artery branch balloon occlusion. Obtuse marginal and diagonal arteries were selected for ethanol infarction ensuring that at least 1 interposed branch (eg, first diagonal, first obtuse marginal, or ramus intermedius) remained intact to create a simulated VT isthmus between the 2 infarcts. Iopamidol contrast (1–2 mL; 70% ethanol/30%) was infused...
through the balloon guidewire lumen to create infarcts. There was no sustained arrhythmia and no mortality. Animals were survived for 12 (8–15) days before MRI-guided isthmus chemoablation.

**Real-Time MRI–Guided Isthmus Chemoablation**

Gadopentetate (0.2 mmol/kg) was administered intravenously to the ischemic cardiomyopathy animals. Real-time inversion-recovery MRI identified areas of infarction containing gadolinium contrast. In the first 5 animals, we targeted the normal myocardium interposed between infarcted regions with sequential injections to create a contiguous ablation line to test feasibility of conductive isthmus chemoablation under MRI guidance.

In the other 5 animals, we performed electroanatomic mapping of the LV endocardium ± epicardium using a commercial system and catheters under x-ray guidance (NavX and EnSite Velocity; duodecapolar Livewire and FlexAbility, St Jude Medical) before and after chemoablation. Pericardial access for epicardial mapping was

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**Figure 1.** Magnetic resonance imaging (MRI)–guided chemoablation of a conductive isthmus. **A**, Baseline late-gadolinium enhancement (LGE) showing 2 infarcts (green arrows) with isthmus of normal myocardium (black arrow). **B**, Real-time MRI–guided chemoablation. The active visualization injection needle appears in green. **C**, LGE after chemoablation showing infarcts (green arrows) and transmural chemoablation lesion (red arrow). **D**, After 7 days, ex vivo high-resolution MRI confirms transmural chemoablation lesion (red arrow) confluent with both infarcts (green arrows). **E**, Wide-field Masson trichrome stain of a section in the same orientation as (A), (C), and (D). Normal myocardium appears pink, necrotic myocardium appears purple, and fibrotic tissue appears blue. **F**, The operator wears a noise-canceling communications headset. Real-time MRI and hemodynamics are displayed in the room. **G**, Endocardial voltage maps at baseline showing normal amplitude electrograms throughout the conductive isthmus. **H**, Postchemoablation, a band of low (<0.5 mV, white box) voltages interrupts the isthmus. Black lines represent the margins of the original infarcts.
obtained via right atrial appendage exit. Isthmus chemoablation was performed under real-time MRI guidance.

**Ex Vivo MRI and Histology**

After euthanasia, hearts were explanted and suspended in agar for high-resolution MRI. Specimens were fixed in 10% formalin and then sectioned and stained with hematoxylin and eosin or Masson trichrome.

**Statistical Analysis**

Data were analyzed using SPSS (version 19.0; IBM) and are described as mean±SD if normally distributed, otherwise as median (first and third quartiles). Acute and chronic lesion volumes were tested for correlation using Spearman correlation coefficient. Anion gap and pH before and after chemoablation were compared using paired t tests. A P value <0.05 was considered significant.
Results

Chemoablation Lesion Histology

In the 8 naive animals, ethanol lesions exhibited stellate geometry with patchy areas of interposed viable myocardium histologically, whereas acetic acid lesions exhibited greater homogeneity and more circumscribed borders (Figure 3). Acetic acid lesions were 46% larger than ethanol lesions for the same injection volume. On the basis of these findings, we performed chronic experiments only using acetic acid. Acute lesions with either agent had a macroscopic area of discoloration with a hemorrhagic center. Hematoxylin and eosin of acute lesion revealed hypereosinophilia of affected myocardial fibers with mild to moderately pyknotic nuclei and indistinct cross striations, consistent with cellular destruction (Figure 2).

Hematoxylin and eosin of chronic lesions revealed typical features of fibrosis and replacement of normal myocardial.
architecture. Masson trichrome revealed a zone of fibroplasia and fibrosis with collagen stained blue, normal myocardial fibers stained red, and necrotic myocardial fibers stained purple (Figure 2). Chronic acetic acid lesions were well circumscribed with distinct margins abutting normal myocardium.

**Chemoablation Lesion Appearances by MRI**

As gadolinium-doped chemoablation agent was injected into the myocardium, the evolving lesion was visualized in real-time using real-time inversion-recovery MRI (Figure 2). Twelve (7–17) days after chemoablation, lesions enhanced using LGE after systemic gadolinium-contrast administration (Figure 2). The volume of acute acetic acid chemoablation lesions correlated with volume of chronic lesions on LGE (0.78±0.39 versus 0.75±0.34 mL; Spearman correlation coefficient, 0.72; n=34; P<0.001).

**Ischemic Cardiomyopathy Isthmus Chemoablation**

All 10 animals developed cardiomyopathy (LV end-diastolic volume index, 136±17 mL/m²; end-systolic volume index, 83±13 mL/m²; ejection fraction, 39%±5%). After systemic gadolinium contrast administration, infarcts were distinguishable from normal myocardium by LGE or real-time inversion-recovery MRI. Successful transcatheter chemoablation of the isthmus between infarcts was defined as the presence of a confluent chemoablation lesion spanning the gap between infarcts and was achieved in all 10 animals with 2 to 5 separate injections (Figure 1). We mapped LV endocardial ± epicardial voltages before and after MRI-guided chemoablation in 5 of these animals. Voltage maps confirmed that a functional ablation line through the isthmus of normal myocardium was successfully created in all 5 animals (Figures 1 and 4; Figure I in the Data Supplement). Voltages over infarcts were low (0.5–1.5 mV), but voltages over chemoablation lesions were even lower (<0.5 mV) with clearly defined borders (Figure 5). Local abnormal voltage activities with fragmented slow conduction were abolished with chemoablation (Figure 6).

**Safety Considerations**

Chemoablation did not cause conduction abnormality or sustained tachyarrhythmia in the early postablation period. No intramyocardial hematoma, myocardial perforation or rupture, pericardial effusion, pericarditis, or tamponade occurred. Linear gadolinium-based contrast agents (Magnevist and Ablavar) released free gadolinium in 50% acetic acid solution (pH 1.9) within minutes but did not in 70% ethanol (pH 7). A macrocyclic gadolinium-based contrast agent (gadoterate) did not release any free gadolinium after 60 minutes of incubation in 50% acetic acid (Table I in the Data Supplement). Chemoablation with acetic acid did not alter serum pH (preprocedure...
versus postprocedure, 7.52±0.17 versus 7.57±0.15; *P*=0.34) or anion gap (15.8±3.5 versus 15.1±3.3, *P*=0.24; normal range in swine, 10–25 mEq/L).

**Discussion**

In this study, we demonstrate for the first time the feasibility of real-time MRI-guided transcatheter myocardial chemoablation. We show that gadolinium doping of chemoablative agents provides immediate visualization of lesion extent and continuity. Chemoablation lesions correlate with irreversible myocardial injury as evidenced by chronic LGE and histological necrosis. Acetic acid creates homogeneous and well-circumscribed lesions compared with irregularly contoured ethanol lesions. In an animal model of ischemic cardiomyopathy, we demonstrate successful substrate-guided chemoablation of a conductive isthmus between 2 infarcts, with functional ablation confirmed by endocardial and epicardial voltage mapping, and abolition of local abnormal voltage activities in the scar border zones.

**Substrate-Guided Ablation**

Conventional electroanatomic mapping relies on surface voltage and activation maps to locate arrhythmia substrate, which can be challenging in the thick-walled LV. In contrast, LGE could afford direct visualization of culprit-diseased myocardium for targeted anatomic substrate-guided ablation. Areas of LGE correspond to areas of low endocardial voltage in patients with ischemic cardiomyopathy. Heterogeneous zones, which are a complex mixture of scar and viable myocardium, exhibit abnormal potentials more frequently than dense scar or normal myocardium and commonly represent the arrhythmic substrate in patients with scar-related VT. MRI-based computational simulation with identification of heterogeneous zones can accurately determine ablation targets and may be used to predict the risk of VT for an individual patient. These may enable entirely substrate-guided ablation in the future. MRI-guided chemoablation could also be used to ablate different structures, for example, the interventricular septum in patients with LV outflow tract obstruction.

**Endocardial Versus Epicardial Ablation**

Endocardial radiofrequency ablation fails to eliminate LV epicardial arrhythmia substrate in many patients. Consequently, epicardial ablation is often required. Subxiphoid access to the naive pericardium and epicardial ablation can cause serious complications, including tamponade, abdominal hemorrhage, and coronary artery occlusion. Pericardial adhesions and epicardial fat can prevent effective ablation or mislead the
operator to believe that effective ablation has been achieved. In contrast, transcatheter needle chemoablation achieves full-thickness ablation from the endocardial surface, avoiding the need for epicardial access. Needle catheters have also been used to deliver radiofrequency energy deeper into the myocardium.

Chemoablation is not dependent on catheter tip contact force and is not subject to steam pop and coagulum embolization although these problems seem less common with modern irrigated radiofrequency ablation catheters. Because chemoablation does not seem to create an edematous penumbra, it is unlikely to cause reversible conduction block as does radiofrequency ablation.

**Choice of Chemoablation Agent**

Bio enzymatic myocardial ablation has been reported through topical epicardial application of collagenase-soaked sponges that homogenized patchy scar, but the result is not instantaneous and it is not clear whether transmural penetration of the enzyme is achievable. We tested ethanol and acetic acid, the 2 most commonly used agents for tumor chemoablation in other organs. On the basis of our bench top and preclinical experiments, we favored acetic acid for the following reasons: (1) it has been used safely in humans; (2) it achieved tissue necrosis with smaller injectate volumes compared with ethanol, reducing the risk of extravasation; (3) lesions within the myocardium were more homogenous, well circumscribed, and without patchy interposed viable tissue, an observation that corroborates previous reports using ethanol in the heart and other organs; and (4) we did not observe a change in serum pH or anion gap with acetic acid in swine. We confirmed in a bench top assay that a macrocyclic gadolinium-based contrast agent, unlike linear agents, does not release free gadolinium in swine. On the basis of our bench top and preclinical experiments, we favored acetic acid for the following reasons: (1) it has been used safely in humans; (2) it achieved tissue necrosis with smaller injectate volumes compared with ethanol, reducing the risk of extravasation; (3) lesions within the myocardium were more homogenous, well circumscribed, and without patchy interposed viable tissue, an observation that corroborates previous reports using ethanol in the heart and other organs; and (4) we did not observe a change in serum pH or anion gap with acetic acid in swine. We confirmed in a bench top assay that a macrocyclic gadolinium-based contrast agent, unlike linear agents, does not release free gadolinium after incubation in 50% acetic acid. On the basis of the dissociation half-lives (T_{1/2}) at low pH of the available macrocyclic contrast agents, we recommend gadoterate (T_{1/2} 26.4 hours at pH 1) be the contrast of choice for chemoablation using acetic acid.

**Real-Time MRI–Guided Catheter Navigation**

Coregistration of previously acquired computed tomography or MRI 3-dimensional volumes or electroanatomic maps can be used to enhance catheter positioning. But coregistration is subject to errors from respiration and cardiac motion, does not permit real-time monitoring of lesions, and cannot accommodate for geometric changes imparted by catheters and guidewires.

For device visualization in MRI, we relied on passive markers on the deflectable sheath and active visualization of the needle catheter to navigate and target chemoablation. Using real-time MRI, needle position was confirmed on orthogonal short- and long-axis planes through the LV. Future integration of needle catheters with MRI-conditional electroanatomic mapping systems may simplify this task.

**Chemoablation Lesion Imaging**

Correlation between lesion volumes by MRI and macroscopic volumes of injury has been evaluated for radiofrequency catheter ablation. LGE best approximates macroscopic volumes of injury, but T2-weighted MRI overestimates and underestimates acute and chronic lesion volumes, respectively. Although LGE may enable identification of radiofrequency lesions, it can only be performed once per procedure because of limitations in total gadolinium dose and cannot accurately distinguish true necrotic core from edematous penumbra. Insufficient or incomplete radiofrequency ablation likely explains current high recurrence rates after VT ablation.

Small volumes of gadolinium-containing solution can be visualized in real time as they are injected into the myocardium using needle catheters. In this study, the volume of lesions immediately post ablation correlated with the volume of LGE chronically. Extent of LGE correlates closely with volume of necrosis. Chemoablation lesions that enhance on LGE correspond to areas of myocardial necrosis and fibrosis histologically. Radiofrequency lesion size can shrink by ≤50% chronically compared with immediately post ablation. This phenomenon is likely caused by the reversible radiofrequency-induced edematous penumbra around the true necrotic core, which may impair the efficacy of repeated radiofrequency delivery. We did not observe this phenomenon with acetic acid lesions.

**Isthmus Ablation**

Clinical usefulness of this technique depends on the ability to target specific tissues that can support VT. We demonstrate that real-time MRI permits precise targeting of chemoablation in an animal model of ischemic cardiomyopathy with an isthmus of normal myocardium between 2 areas of infarction. We demonstrate the ability to create a linear chemoablation lesion using multiple small injections confluent with the 2 infarcts, resulting in electroanatomic mapping–confirmed disruption of the conductive isthmus.

**Limitations**

This was a preclinical feasibility study, and we did not directly compare chemo- versus radiofrequency ablation. However, the limitations of radiofrequency ablation in the thick-walled LV are well recognized. Procedure success rates remain low, despite the advent of irrigation-tip catheters to enable longer ablations, needle-tip electrodes to facilitate deeper delivery of radiofrequency energy or contact force-sensing catheters to improve delivery of radiofrequency energy to the myocardium, almost certainly due to incomplete ablation. Porcine models of hemodynamically stable VT are difficult to create, and for this reason, we did not test the ability of chemoablation to terminate arrhythmia. However, chemoablation did abolish late and fractionated electrograms within and around infarcted areas, suggesting that critical substrate was eliminated. Recent data suggest that elimination of late potentials is at least as strong a predictor of freedom from VT in patients as noninducibility. We did not test chemoablation within areas of dense or patchy scar. Further studies are needed to determine optimal injection volume, number of injections, and distance from scar or grey zone to achieve arrhythmia termination while minimizing effect on ventricular function.
Equipping an MRI suite for interventional procedures requires additional infrastructure, including communication headsets, video projectors, and hemodynamic monitoring systems. MRI injection catheters are not yet commercially available.

Many patients with VT have implantable cardioverter defibrillators that usually would disqualify them from undergoing MRI. MRI-conditional defibrillators may permit MRI-guided chemoablation although implanted devices and leads can still cause imaging artifacts that obscure target tissue and ablation lesions. These artifacts may be overcome with newer MRI pulse sequences.

Conclusions
This is the first report of real-time MRI-guided transcatheter myocardial chemoablation. MRI enables instantaneous visualization of arrhythmic substrate and real-time monitoring of irreversible ablation lesions. Acetic acid creates more homogenous and well-circumscribed ablation lesions compared with ethanol. Unlike radiofrequency energy, endocardial needle chemoablation achieves fully transmural and irreversible ablation lesions, without edematous penumbra that may contribute to reversible conduction block and arrhythmia recurrence. We demonstrate feasibility of conductive isthmus ablation with ablation of local abnormal voltage activities in an animal model of ischemic cardiomyopathy. MRI-guided chemoablation could improve procedural success of VT ablation.

Acknowledgments
We thank Robert S. Balaban for thoughtful comments, Joni Taylor and Katherine Lucas of the National Heart, Lung, and Blood Institute Animal Surgery and Resources Core, and Stephanie French for technical help; St Jude Medical for electroanatomic mapping; and Innomet and Imricor for MRI-conditional deflectable sheaths.

Sources of Funding
This work was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health (Z01-HL005062).

Disclosures
National Institutes of Health and Siemens have a collaborative research and development agreement. S. Mahapatra and S. Kim are employees of St Jude Medical. The other authors report no conflicts.

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_Circ Arrhythm Electrophysiol._ 2016;9:
doi: 10.1161/CIRCEP.115.003926

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/9/4/e003926

Data Supplement (unedited) at:
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Figure S1: Mapping density before and after chemoablation in an animal model of ischemic cardiomyopathy.
Corresponding maps for Figure 4 showing mapping density for (A) baseline endocardial voltage map, (B) baseline epicardial voltage map, (C) post-chemoablation endocardial voltage map, and (D) post-chemoablation epicardial voltage map.

**MRI parameters**

**Steady-state free precession (SSFP) cine imaging:** Repetition time (TR)/echo time (TE) 3.1/1.3ms; flip angle 57°; bandwidth 930Hz/pixel; field of view (FOV) 300mmx300mm; matrix 256x256pixels; slice thickness 8mm.

**Three-dimensional radial SSFP non-contrast whole heart:** TR/TE 3.1/1.5ms; flip angle 115°; bandwidth, 898Hz/pixel; FOV 220x220mm; voxel size 1.1x1.1x1.1mm; base resolution 192; radial views 12360.

**Realtime MRI:** TR/TE 2.9/1.4ms; flip angle 45°; bandwidth 1000Hz/pixel; matrix 192x108; FOV 300x300mm; GRAPPA Factor 2-4) or gradient echo (TR/TE 4.2/1.9ms; flip angle 15°; bandwidth 500Hz/pixel; matrix 192x144; FOV 300x300mm; GRAPPA Factor 2-4. A real-time inversion recovery sequence could be toggled on to highlight gadolinium enhancement of injection sites, relative to normal myocardium and areas of prior infarction. A non-selective inversion pre-pulse was performed before every bSSFP image acquisition with an interactive inversion time (TI). The next inversion pulse immediately followed the image acquisition, with no additional time for signal recovery. Typical imaging parameters were TI 417ms, TR/TE 2.54/1.27ms, flip angle 45°, FOV 300mm, slice thickness 6 mm, matrix 128x128, GRAPPA factor 2 and frame rate 2 frames/second. The real-time MRI user interface (Interactive Front End, Siemens) enabled control of slice plane and thickness, and toggling between rapid imaging for catheter navigation and high contrast real-time inversion-recovery MRI during injection.

**Ex-Vivo 3D Hi-Res Isotropic T1-W SPGR:** TR/TE 10/5.4ms; flip angle 20°; bandwidth 210Hz/pixel;
matrix 320x320; FOV 180x180mm; voxel size 0.6x0.6x0.6mm; slab thickness 72mm; 120 slices per slab.

**LGE PSIR segm FLASH 724**: TR/TE 8.2/3.2ms; flip angle 25°; bandwidth 140Hz/pixel; matrix 256x144; FOV 360x270mm; slice thickness 8mm.

**MRI analysis**: Images were analyzed using QMass MR (Medis). Acutely, infarct and lesion could be differentiated by relative signal intensity on phase sensitive inversions recovery LGE (3 and 10 standard deviations above mean respectively). Chronically, lesion signal intensity was similar to infarct (3 standard deviations above mean).

**Free gadolinium (Gd³⁺) assay**

The amount of Gd³⁺ was quantified using Arsenazo III, which binds to gadolinium ions to form a complex that can be quantified with a colorimetric assay(1). The amount of free gadolinium was quantified by using Arsenazo III. Arsenazo III binds to gadolinium ions to form a complex, which can be quantified with a colorimetric assay. Standards at concentrations of 0 – 50 μg/ml Gd³⁺ were prepared with gadolinium (III) chloride hexahydrate (Alfa Aesar) prepared in 50% acetic acid (Mallinckrodt Baker). An ultraviolet-visible spectrophotometer (Shimadzu) was used to read absorbance values at 652 nm to form a linear calibration curve. Samples of MRI contrast agents (Magnevist 500mM Gd, Ablavar 250mM Gd, and Dotarem 500mM Gd) were prepared in 50% acetic acid (pH 1.9) at concentrations of 2% and 5% Gd³⁺, and samples were incubated for 15 minutes before absorbance values at 652 nm were recorded. For Dotarem, values were also recorded after 30 minutes and 60 minutes of incubation time.

**Tables**

<table>
<thead>
<tr>
<th>Gadolinium-based contrast agent</th>
<th>Concentration in 50% acetic acid</th>
<th>Incubation time (minutes)</th>
<th>Free Gd³⁺ concentration (mg/ml)</th>
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<tbody>
<tr>
<td>Gadofosveset</td>
<td>2%</td>
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<td>23</td>
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<td>5%</td>
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</table>

**Table S1:** Concentration of free Gd\(^{3+}\) in 50% acetic acid solution with 2% or 5% gadolinium-based contrast agent. LOD: limit of detection.

**References**