JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 1, NO. 3, 2015

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacep.2015.03.012

Gadolinium Augmentation of Myocardial Tissue Heating During Radiofrequency Ablation

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ABSTRACT

OBJECTIVES This study hypothesized that a metal already commonly used in medical procedures, gadolinium (Gd), will augment radiofrequency (RF) thermal injury and affect cardiac ablation lesions.

BACKGROUND Enhancement of RF ablation using metallic particles has been proposed for ablation of tumors.

METHODS A series of ablation lesions were delivered at variable power using an ex vivo model. Tissue temperatures and lesion characteristics were analyzed. Ablation in a porcine in vivo model after direct needle injection of the myocardium with Gd or after systemic administration of Gd encased in heat sensitive liposomes was also performed and compared to control values.

RESULTS Ablation after Gd infiltration of myocardial tissue resulted in significantly larger lesions at both low- and high-power settings. Larger impedance changes were observed during ablation of Gd-treated myocardium. In vivo ablation using a force-sensing irrigated tip catheter resulted in enhanced lesion sizes after Gd injection without a higher incidence of steam pops or perforation. Systemic administration of liposomal Gd with local release by RF heating did not result in larger ablation sizes.

CONCLUSIONS Gd can be used to enhance RF ablation lesions. In both ex vivo studies with a 4-mm ablation catheter under power control and in vivo findings with an irrigated tip catheter, ablation of myocardium infiltrated with Gd resulted in larger lesions, with altered RF electrical and thermal characteristics. More research is needed to refine the potential for Gd facilitation of RF ablation. The use of systemic heat-sensitive liposomes containing Gd with targeted release by RF heating did not affect lesion size. (J Am Coll Cardiol EP 2015;1:177–84) © 2015 by the American College of Cardiology Foundation.

Although radiofrequency (RF) ablation has revolutionized the treatment of cardiac arrhythmias, challenges remain in terms of efficacy and safety. The creation of durable lesions with RF energy for certain arrhythmias remains elusive. Pre-ablation treatment with an RF-facilitating agent may lead to enhanced electrical or thermal conductivity of targeted myocardial tissue and may improve outcomes (1). This strategy of using metals to augment ablation therapy is being actively explored in cancer therapeutics, with the use of gold, carbon, and palladium nanoparticles, among others (2–4). Cho et al. (3) showed that by functionalizing gold nanorods, they were able to locally target bladder cancer cells with thermal ablation. We chose to apply this similar concept for cardiac ablation therapy by considering the use of a metal—gadolinium (Gd)—that is already commonly used clinically in humans.

Chelated Gd is designed as a contrast agent for magnetic resonance imaging but it may have properties favorable for enhancement of RF-induced thermal injury of targeted myocardial tissue, similar to other metals. It is the only chelated metal approved by regulatory agencies for intravenous administration

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Manuscript received January 8, 2015; revised manuscript received February 20, 2015, accepted March 12, 2015.

ABBREVIATIONS AND ACRONYMS

Gd = gadolinium

LV = left ventricle

RF = radiofrequency

and is an attractive candidate for use as an RF-facilitating agent in cardiac ablation.

In this study, we hypothesize that Gd can augment RF ablation and we sought to assess RF characteristics on myocardium after Gd infiltration in both the ex vivo and in vivo settings.

METHODS

EX VIVO MODEL. The experimental protocols have been approved by the Institutional Animal Care and Use Committees of the University of Colorado and University of Chicago. An ex vivo model was used, as previously described in detail elsewhere (5). Briefly, viable bovine myocardium was placed in a circulating saline bath at 37°C above a submersible load cell. The load cell was used to standardize application of energy by measuring force applied to the overlying myocardial tissue. Fluid was circulated in a saline bath at a rate of 5 l/min using a perfusion pump designed for cardiac bypass.

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DELIVERY OF RF ENERGY APPLIED TO INFILTRATED MYOCARDIUM. Using power control mode with a Stockert RF generator (Stockert, Freiburg, Germany) and a standard 4-mm ablation catheter (Celsius, Biosense-Webster, Diamond Bar, California), ablation at low power (20 W) and high power (50 W) was performed on recently excised, viable bovine myocardium. The catheter was mechanically fixed in a long deflectable sheath (Agilis, St. Jude Medical, Sunnyvale California) with precisely 10 g of force applied and with the catheter in a perpendicular position during RF delivery. Excised bovine myocardium specimens were approximately 5 cm × 7 cm in size. Multiple control and experimental lesions were placed on the same specimen; specimens from 10 animals were used. Immediately before RF energy delivery, the myocardium was infiltrated via direct needle injection to a depth of 5 mm, with 1 ml of Gd (Prohance) at a concentration of 279.3 mg/ml. Separate ablation lesions on the same myocardial tissue were produced using 2 types of control values: 1 ml of 0.9% saline injection (saline control), and needle insertion with no injection ("untreated control"). The number of lesions applied per ventricular section depended on the available endocardial surface. No lesions were placed over or in immediate proximity of papillary muscles (5 mm) or within immediate proximity of other lesions. Furthermore, no lesions were placed within 1 cm of section edge.

TISSUE TEMPERATURE ANALYSIS. T-type thermocouple wires were inserted horizontally into the myocardium at 3- and 5-mm depths and with the wire stem perpendicular to the ablation surface. Thermocouple analogue inputs were converted to digital signals using LabView software (version 7.0). Temperatures were recorded in a continuous fashion throughout the 60 s of RF application at a rate of 5 Hz. Peak tissue temperature was defined as the maximal temperature reading during RF application. RF applications that generated steam pops were excluded from temperature curve analysis.

IN VIVO EPICARDIAL AND ENDOCARDIAL ABLATION. Yorkshire pigs (n = 4) were anesthetized and intravenous lidocaine (50 to 100 mg) was used intraoperatively for prophylaxis of ventricular arrhythmias. The left ventricle (LV) was accessed using a retrograde aortic approach after femoral arterial access was obtained. Epicardial access was obtained in the same specimen under fluoroscopy using a 17-gauge Pajunk needle (Pajunk Medical Systems, Norcross, Georgia), and a 9-F sheath was placed in the epicardium. An electroanatomic map of the entire endocardium and epicardium was created using the CARTO3 mapping system (Biosense-Webster, Diamond Bar, California).

In 2 pigs, endocardial ablation was performed after direct injection of test substances as follows. Before ablation, 1 ml of either Gd (gadoteridol; ProHance) or 0.9% normal saline was injected to a depth of 5 mm into the myocardium using an endovascular mapping catheter with a retractable needle (Myostar, Biosense-Webster). The site and quality of injections were guided by fluoroscopy, intracardiac echocardiography, and the CARTO electroanatomic mapping system. Observation of premature ventricular complexes at the time of needle deployment and with expected morphology on the basis of site of ventricular contact helped to additionally confirm successful engagement of the needle with tissue. The needle/catheter position was recorded on the electroanatomical map at the time of injection. These markers were used to position the ablation catheter at the sites of injection. Caution was used to annotate catheter positions consistently during the same cardiac and respiratory cycle (end diastole and end expiration) to best verify that ablation was performed at sites of injection. Endocardial ablations were delivered at 50 W for 30 s with the same amount of force as measured by SmartTouch technology on the open irrigated tip RF catheters (Biosense-Webster); ablation lesions were tagged by the electroanatomic mapping system. The LV was divided into quadrants; ablations after Gd or control injections were performed in each

quadrant. After ablation, animals were sacrificed and the hearts were immediately explanted and fixed in formalin. Gross pathology was performed and ablation lesions were analyzed.

LIPOSOMAL Gd PREPARATION AND ADMINISTRATION. Liposomal Gd was prepared using a previously described technique (6). Briefly, lipid components were dissolved in chloroform and evaporated using a Rotovap system and left overnight in a vacuum desiccator. The resulting lipid film was hydrated by a buffer consisting of 300 mM gadoteridol and 100 mM Citrate to yield a final lipid concentration of 50 mg/ml. Liposomes were obtained by extruding the mixture 5 times with a LIPEXTM extruder (Northern Lipids, Burnaby, British Columbia, Canada) at 55°C through 2 stacked Nucleopore polycarbonate membrane filters (Whatman PLC, Maidstone, Kent, United Kingdom) with a pore size of 100 nm. The end product of this process was a mixture of gadoteridol encased within a lipid sphere suspended in saline. The liposomes were 107.7 nm in diameter with a gadoteridol concentration of 100 mM in 50 ml with liposome layer phase change for gadoteridol release of 41.3°C. The liposomal gadoteridol was stored at <4°C, and used within 48 h of preparation.

Pigs who had the liposomal Gd infused (n = 2) were pre-treated with intravenous solu-medrol to prevent an anaphylactic reaction to the liposomes. Because perfusion of the heart occurs from epicardium to endocardium, we determined that the epicardial surface would most consistently contain the greatest concentration of liposomal Gd after systemic administration. The opportunity to observe an effect in terms of augmenting ablation, we reasoned, would be on the epicardial surface. Epicardial lesions were delivered using 50 W for 90 s with the same force as measured by SmartTouch technology using an open irrigated tip catheter. We did not perform coronary angiography to confirm location of coronary arteries but avoided ablation in regions known to contain coronary vessels as well as epicardial fat (e.g., the interventricular and atrioventricular grooves). Avoiding ablation in regions of fat was additionally confirmed by the presence of sharp, near-field ventricular EGMs with consistent impedance measurements. Saline irrigant was suctioned from the epicardium after each ablation. Control lesions were performed on the epicardium before infusion of liposomes in each pig. Then, liposomal Gd was infused at a rate of 1 ml/min for 30 min before ablation. With the liposomal Gd continuing at a rate of 1 ml/min, ablation was performed on the epicardium of each pig. Ablation lesions were tagged by the electroanatomic mapping system. After ablation, animals were sacrificed and the hearts were immediately explanted and fixed in formalin. Specimens were examined visually, and ablation lesion geometry using a digital micrometer without the aid of specific stains or microscopy was performed. The same technique was used for both ex vivo and in vivo lesion analyses.

ABLATION LESION VOLUME MEASUREMENTS. Lesion volumes were acquired by analyzing tissue sections with a digital micrometer. Single lesion volumes were calculated using the equation for an oblate ellipsoid. For each lesion, maximum depth (A), maximum diameter (B), depth at maximum diameter (C), and lesion surface diameter (D) were measured.

$$LesionVolume = \left[0.75\pi\left(\frac{B}{2}\right)^2(A-C)\right] - \left[0.25\pi\left(\frac{D}{2}\right)^2(A-2C)\right]$$

Equation 1: Volume of Oblate Ellipsoid

A = maximum depth, B = maximum diameter, C = depth at maximum diameter and D = lesion surface diameter

These measurements for ablation lesions have been detailed elsewhere (5).

STATISTICAL ANALYSIS. SPSS software was used to perform all calculations. The hierarchal analysis of variance test was used to compare lesion characteristics from ablated Gd treated versus untreated myocardium and saline-injected myocardium.

RESULTS

EFFECT OF Gd INFILTRATION ON ELECTRICAL PROPERTIES OF TARGETED MYOCARDIAL TISSUE AND ON ABLATION LESION GEOMETRY AND VOLUME USING LOW- AND HIGH-POWER RF ENERGY. Using power control and a standard 4-mm ablation catheter at both low and high powers, ablation of Gd-treated myocardium resulted in significantly larger lesions. Ablation at 50 W of Gd-infiltrated myocardium resulted in volumes of 349.6 ± 73.8 ml, compared to 254.1 ± 48.2 ml for tissue pre-treated with saline. Differences in ablation lesion dimensions and volumes, for low- (20 W) and high- (50 W) power RF, are shown in **Tables 1 and 2**, respectively, for untreated controls, saline controls, and Gd-treated myocardium. Ablation of Gd-treated myocardium resulted in significantly wider ablation lesions with increased depth, leading to significantly larger lesion volumes.

Gd-treated myocardium had higher initial and end impedances compared to untreated- and

TABLE 1 Ex Vivo Bovine Myocardial Ablation Lesion Characteristics After Radiofrequency Energy Applied at 20 W for 60 s

	n	Maximum Depth, mm	Maximum Diameter, mm	Surface Diameter, mm	Volume, ml
Group					
No injection/untreated control	30	3.7 ± 0.5	7.6 ± 1.0	6.2 ± 1.0	73.2 ± 23.5
Saline	30	3.9 ± 0.6	7.8 ± 1.4	6.0 ± 1.0	80.5 ± 34.8
Gadolinium	30	4.9 ± 0.4	8.8 ± 0.7	6.3 ± 0.6	133.8 ± 29.9
p values					
Gadolinium vs. untreated control		<0.001	<0.001	0.643	<0.001
Gadolinium vs. saline		<0.001	<0.001	0.097	<0.001
Saline vs. untreated control		0.307	0.437	0.303	0.434

Values are mean ± SD.

saline-control myocardium. Furthermore, impedance reductions during RF ablation, at both low and high powers, were significantly larger for Gd-treated myocardium compared to untreated and saline controls (Figures 1A and 1B).

EFFECT OF Gd INFILTRATION ON MYOCARDIAL TISSUE TEMPERATURE DISPERSION. Using power-control mode with a standard 4-mm ablation catheter, ablation of Gd-treated myocardium showed higher peak temperatures throughout the 60 s of ablation for both 20 W and 50 W of RF energy compared to ablation of saline infiltrated myocardium. Figure 2 displays the mean temperature dispersion at 3- and 5-mm depths in Gd-treated myocardium compared to untreated control and saline infiltration for RF at 20 W (Figure 2A) and 50 W (Figure 2B). The rate of increase for temperatures at 3- and 5-mm depths was greater for Gd-treated myocardium with RF ablation at both 20 W and 50 W.

ANALYSIS OF LESIONS CREATED AFTER IN VIVO ENDOCARDIAL INFILTRATION USING DIRECT INJECTION BEFORE DELIVERY OF RF ENERGY. Six ablation lesions were applied in each pig (n = 2) that underwent endocardial ablation after direct injection of test substances (Figure 3). The mean force applied during the delivery of RF was 13.3 + 3.0 g at the Gd-injected sites (n = 6) and 13.7 + 5.0 g at the saline-injected sites (n = 6, p = 0.89). In vivo ablation after endocardial Gd injection (Figure 4A) resulted in significantly larger lesions compared to ablation of saline-treated myocardium (Figure 4B) (592 ml vs. 102 ml; p < 0.001). Nearly transmural lesions in the LV were achieved at 50 W with open irrigated ablations on Gd-infiltrated myocardium. There was no evidence of cardiac perforation or steam pops at sites of injection.

TABLE 2 Ex Vivo Bovine Myocardial Ablation Lesion Characteristics After Radiofrequency Energy Applied at 50 W for 60 s

	n	Maximum Depth, mm	Maximum Diameter, mm	Surface Diameter, mm	Volume, ml
Group					
No injection/Untreated control	30	6.3 ± 0.7	10.6 ± 0.9	8.0 ± 1.1	244.5 ± 64.1
Saline	30	6.4 ± 0.7	11.0 ± 1.0	8.2 ± 1.3	254.1 ± 48.2
Gadolinium	30	7.1 ± 0.5	11.7 ± 1.0	8.6 ± 0.9	349.6 ± 73.8
p value					
Gadolinium vs. untreated control		<0.001	<0.001	0.044	<0.001
Gadolinium vs. saline		<0.001	0.005	0.196	<0.001
Saline vs. untreated control		0.580	0.197	0.607	0.515

Values are mean ± SD.

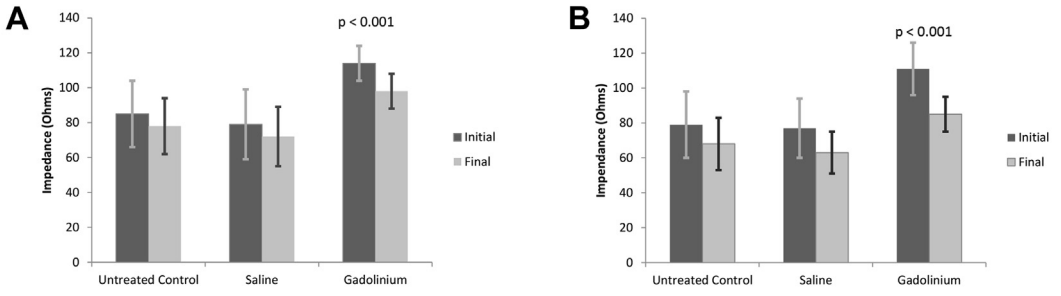
ANALYSIS OF LESIONS PRODUCED AFTER SYSTEMIC ADMINISTRATION OF Gd ENCASED WITHIN HEAT SENSITIVE LIPOSOMES. Epicardial ablation lesions were applied with a force of 16.5 + 3.6 g in the setting of liposomal Gd administration (N = 12), compared to 18.9 + 4.5 g in the control group (N = 12, p = 0.09). Epicardial ablation of the LV after infusion of liposomal Gd created larger lesions compared to control epicardial ablation before infusion of the liposomes, but the difference was not statistically significant (242 ± 67 ml for liposomal Gd vs. 207 ± 79 ml for control ablations; p = 0.4).

DISCUSSION

STUDY RESULTS. The findings from this study have shown enhanced thermal injury with RF ablation of myocardium treated with Gd. After controlling for power, time, and catheter pressure, the delivery of RF energy resulted in greater lesion volumes in myocardium previously infiltrated with Gd using both ex vivo and in vivo models. An attempt at using systemic administration of Gd to enhance epicardial RF ablation lesions was not more efficacious than standard ablation; this was likely due to a limited ability to achieve sufficiently high concentrations of the Gd after being released from liposomes as well as likely due to the limited amount of Gd-containing liposomes that reached the epicardial surface.

POTENTIAL MECHANISMS AND PRIOR INVESTIGATIONS INTO FACILITATED ABLATION. We have previously shown that RF ablation can be significantly enhanced in myocardium that has been pretreated with a facilitating agent such as carbon nanotubes and metallic nanoparticles (1). Gd was studied as a potential RF facilitating agent because it is one of the few metals already approved for human use. After ex vivo studies showed the effectiveness of Gd-infiltrated RF ablation, we pursued in vivo methods of delivering Gd to myocardial tissues to facilitate RF ablation. One approach was via direct injection using

FIGURE 1 Mean Starting and Ending Impedance Measurements in Untreated Controls, Saline-Infiltrated Controls, and Gd-Treated Myocardial Tissue Before and After Ablation



20W	Initial Imp	Final Imp	Imp Drop
Untreated Control	85±19	78±16	7±5
Saline	79±20	72±17	7±6
Gadolinium	114±10	98±10	16±8
Gadolinium vs. Untreated Control p-value			p<0.001
Gadolinium vs. Saline p-value			p<0.001

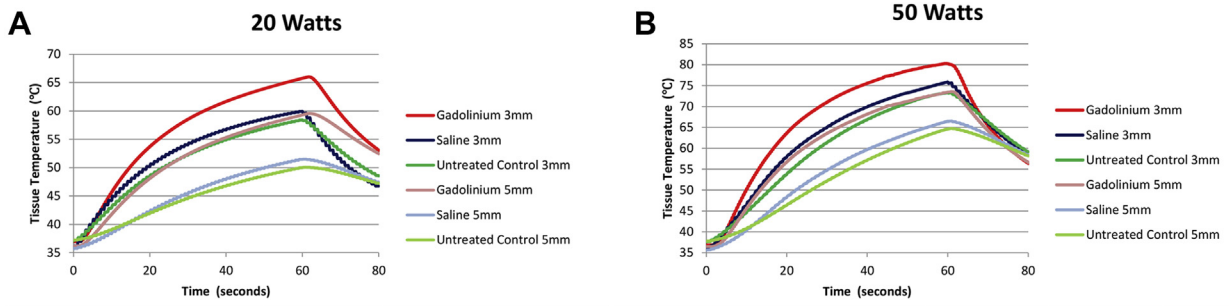
50W	Initial Imp	Final Imp	Imp Drop
Untreated Control	79±19	68±15	12±6
Saline	77±17	63±12	14±8
Gadolinium	111±15	85±10	27±10
Gadolinium vs. Untreated Control p-value			p<0.001
Gadolinium vs. Saline p-value			p<0.001

Compared to the saline infiltrated myocardium, gadolinium (Gd)-infiltrated myocardial tissue had a higher starting and ending impedance with a larger impedance reduction observed with ablation, at both low **(A)** and high **(B)** powers.

an endovascular catheter with a retractable needle. Another approach was appropriated from the field of cancer therapeutics, where investigators have been using liposomal preparations of chemotherapeutic agents to deliver toxic medications at a much higher local concentration to an area of heated tissue (7-10). Our experiments sought to replicate this phenomenon by encapsulating Gd as a direct biophysical facilitating agent and administering it during the delivery of RF energy in myocardium.

PRACTICAL CONSIDERATIONS FOR THE CLINICAL USE OF Gd AS AN ABLATION FACILITATING AGENT. The local myocardial concentration of Gd must be sufficiently high to conduct RF energy for one to observe a facilitated ablation effect. In our in vivo model, only direct injection of undiluted Gd was able to

FIGURE 2 Mean Temperature Dispersion at 3- and 5-mm Depths in Gd Treated Myocardium Compared to Untreated Controls and Saline Controls at 20 W and at 50 W

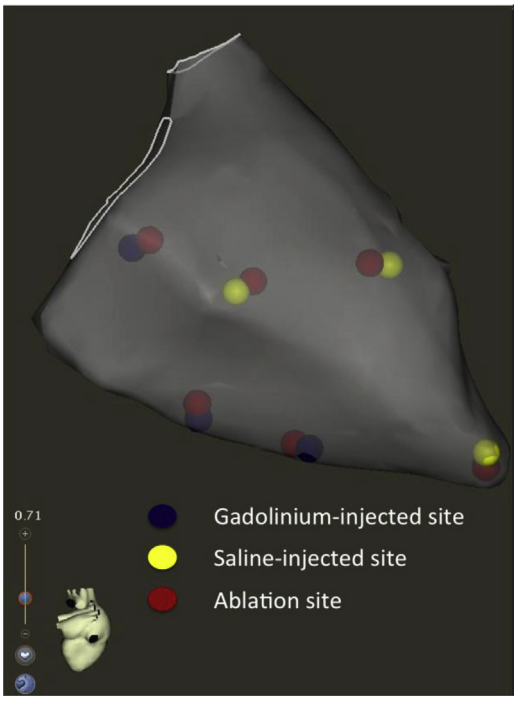


Time (s)	0	10	20	30	40	50	60
Gadolinium 3mm	36.9±0.7	45.8±2.7	53.8±3.7	58.6±3.9	61.7±4.0	63.9±4.1	65.8±4.1
Saline 3mm	35.8±0.7	44.2±3.2	50.2±4.2	54.0±4.7	56.7±5.0	58.5±5.2	59.9±5.3
Untreated Control 3mm	37.1±0.8	42.9±2.5	48.4±3.4	52.2±3.6	54.9±3.7	56.9±3.9	58.4±4.0
Gado vs. Saline 3mm p-value		p = 0.163	p = 0.020	p = 0.008	p = 0.005	p = 0.004	p = 0.002
Gado vs. Untreated Control 3mm p-value		p = 0.006	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Saline vs. Untreated Control 3mm p-value		p = 0.223	p = 0.219	p = 0.242	p = 0.277	p = 0.327	p = 0.382
Gadolinium 5mm	36.2±0.9	41.9±2.0	48.1±2.9	52.4±3.0	55.3±2.8	57.5±2.7	59.3±2.5
Saline 5mm	35.6±1.0	38.4±1.6	42.2±2.8	45.4±3.5	47.9±4.0	49.9±4.2	51.5±4.4
Untreated Control 5mm	37.2±0.8	39.0±1.2	41.9±2.3	44.5±2.9	46.7±3.1	48.5±3.2	50.0±3.2
Gado vs. Saline 5mm p-value		p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Gado vs. Untreated Control 5mm p-value		p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Saline vs. Untreated Control 5mm p-value		p = 0.243	p = 0.775	p = 0.481	p = 0.373	p = 0.329	p = 0.310

Time (s)	0	10	20	30	40	50	60
Gadolinium 3mm	36.8±0.6	50.3±4.7	63.7±6.5	71.1±6.4	75.6±5.9	78.5±5.6	80.2±4.9
Saline 3mm	35.7±1.2	46.4±5.9	57.9±7.1	65.0±6.4	69.9±5.9	73.3±5.4	75.9±5.0
Untreated Control 3mm	37.5±1.1	44.6±2.6	53.8±3.8	61.3±3.7	66.8±3.6	70.8±3.4	73.3±3.4
Gado vs. Saline 3mm p-value		p = 0.056	**p = 0.027**	**p = 0.014**	**p = 0.013**	**p = 0.014**	**p = 0.023**
Gado vs. Untreated Control 3mm p-value		**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**
Saline vs. Untreated Control 3mm p-value		p = 0.302	p = 0.060	p = 0.069	p = 0.097	p = 0.144	p = 0.117
Gadolinium 5mm	36.5±0.7	45.7±4.3	56.8±7.1	63.6±7.8	68.2±7.7	71.2±7.1	73.4±6.5
Saline 5mm	35.5±1.3	40.3±2.6	48.2±4.9	54.7±5.4	59.7±5.1	63.5±4.7	66.5±4.5
Untreated Control 5mm	37.7±1.1	40.8±1.3	46.4±2.5	52.1±3.0	57.1±3.2	61.3±3.4	64.6±3.4
Gado vs. Saline 5mm p-value		**p < 0.001**	**p < 0.001**	**p = 0.001**	**p = 0.001**	**p = 0.002**	**p = 0.002**
Gado vs. Untreated Control 5mm p-value		**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**
Saline vs. Untreated Control 5mm p-value		p = 0.527	p = 0.197	p = 0.125	p = 0.119	p = 0.159	p = 0.218

(A) 20 W; **(B)** 50 W. Mean temperatures (± SD) are provided for each group at 10-s intervals. p values for comparisons between each group are provided below the mean temperatures.

FIGURE 3 Electroanatomic Map of the LV Endocardium After In Vivo Ablation in Posteroanterior Projection

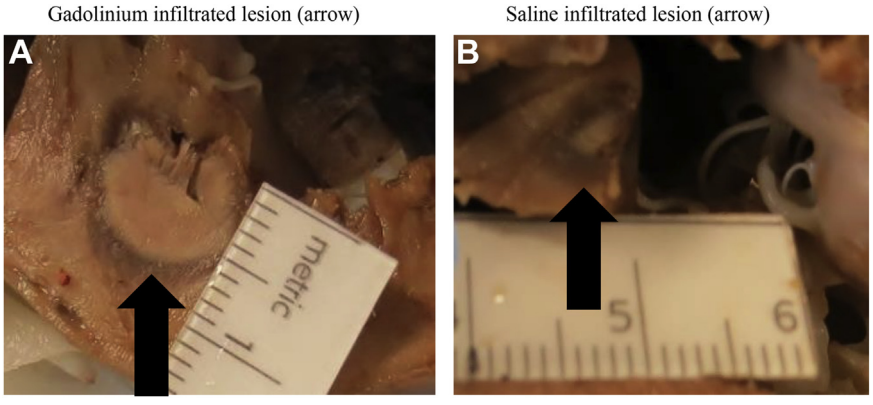


Before ablation, saline **(yellow dots)** or Gd **(blue dots)** was injected at the sites annotated on the map. The ablation catheter was then positioned at these sites for delivery of radiofrequency ablation **(red dots)**. Gd = gadolinium; LV = left ventricular.

achieve sufficiently high enough concentrations of Gd to have altered ablation lesion characteristics; these effects resulted in significantly larger lesions compared to standard ablation. An effort to administer Gd in a liposomal formulation, designed to deliver Gd in the presence of temperatures $> 45^{\circ}$C, did not produce significantly altered ablation lesions compared to standard ablation. However, improved understanding of the liposomal pharmacokinetics may allow for higher Gd concentration delivery in the future. Furthermore, endocardial ablation at the time of liposomal infusion, instead of epicardial ablation, will be considered in future studies.

Liposomal Gd has been used as an adjunctive imaging agent for oncological applications. In many of these studies (7,9-11), liver tumors were targeted, but these represent a much different environment compared to cardiac tissue. It is likely that, although the liposomes were releasing Gd after reaching target temperatures, the transit time of the liposomes through the area of heated tissue was not of sufficient duration to allow for an accumulation of the required amounts of the Gd to augment RF heating. Other methods of Gd delivery such as intracoronary or coronary venous injection should be considered but were not tested in this study. In addition, it may be possible to slow intramyocardial liposomal transit time by intentionally reducing cardiac output or by impeding coronary venous drainage. Other potential limitations to the administration of a systemic agent designed to facilitate ablation include unpredictable perfusion characteristics of myocardial scar (which is

FIGURE 4 In Vivo Ablation of the Left Ventricle After Endocardial Gd Injection Resulted in Significantly Larger Lesions Compared to Lesions From Ablation of Saline-Treated Myocardium



(A) Gd injection; **(B)** saline treated. The dark ring surrounding lesions in each **panel** represents border-zone erythema of the necrotic lesion. Gd = gadolinium.

oftentimes the target site), as well as the potential toxicities of such an agent.

USE OF CARDIAC MAGNETIC RESONANCE IMAGING GUIDANCE WITH CATHETER ABLATION PROCEDURES. The most common use for Gd is as a contrast agent in cardiac imaging. Cardiac magnetic resonance imaging has been studied as an adjunctive imaging modality in catheter-based procedures and as a tool for assessing myocardial lesions sizes (12–14). We did not evaluate the potential role of direct injection of Gd for use as an adjunctive imaging agent but instead have shown that the Gd itself would improve efficacy of RF ablation.

OTHER AGENTS OF POSSIBLE VALUE IN ENHANCING THE EFFECTS OF RF HEATING. There have been other metals studied for enhancing RF energy delivery into targeted tissue. Gold nanoparticles have been used to enhance radiofrequency heating of liver tissue in a rat model, achieving tumor destruction with 35 W (15). The conduction of RF energy and conversion of RF energy to heat depends on a number of physical factors specific to a metal type and therefore it is unknown what metals may be viable candidates for RF facilitating agents in cardiac ablation. In addition, the toxicity of the metallic agent is of greatest importance when considering its use for cardiac ablation. We chose to study Gd in a commonly used formulation intended for imaging to limit the potential toxicity of this agent should it ever be considered clinically. Iron Oxide Nanoparticles (Feridex) have also been used safely in imaging; therefore, this agent may also be a feasible RF-facilitating agent (16). Local or systemic administration of nontoxic metallic agents could improve RF ablation outcomes if safe delivery of these agents to targeted myocardium can be achieved. However, further study in animal models will be required before any consideration of this concept in humans.

STUDY LIMITATIONS. We attempted to control for variations in RF ablation caused by external variables such as circulation rate, passive catheter cooling, and catheter contact by standardizing these variables, using force-sensing technology, and applying repetitive RF ablations. Nevertheless, the variable conditions that may exist would be nondifferential among the individual experiments and is unlikely to explain our results. Additionally, despite efforts to ensure that needle positioning and deployment were stable in the in vivo experiments, we did not have a means to guarantee the accuracy of Gd infiltration within tissue. We also cannot guarantee that ablation lesions were delivered at exactly the same sites that injection occurred, although great care was made to ensure consistency with annotation of catheter positions on the electroanatomic map. However, these limitations would have, if anything, biased our results towards no effect.

In the assessment of the effect of liposomal Gd infusion, we only performed epicardial and not endocardial ablation, as we believed that the epicardium represented a more consistent surface to target for ablation and allow for comparison of relatively few lesions created during the infusion and circulation of the liposomal Gd. Subsequent study comparing endocardial and epicardial ablation lesions after infusion of liposomal Gd in the same specimen would be worthwhile to understand optimal delivery. However, this was outside the scope of the present study.

This study used bovine myocardium in an ex vivo model to approximate RF ablation characteristics produced during indicated procedures performed in patients with cardiac arrhythmias. We further tested these findings in an in vivo setting but only studied the effects of Gd-enhanced ablations on normal myocardium. In addition, no arrhythmias were targeted and therefore the efficacy of this strategy in arrhythmia treatment requires further investigation. Finally, the impact of lesion changes with time were not allowed or assessed in the in vivo experiments; lesion maturity may be affected by the presence of gadoteridol and therefore this effect may have impacted the clinical relevance of our findings. Hence, although our results are intriguing and have implications for clinically relevant ablation strategies, further studies are needed.

CONCLUSIONS

The treatment of myocardium with Gd results in a greater degree of RF-induced thermal injury. Gd infiltration into cardiac tissues enhances RF ablation and results in higher temperature dispersions, greater impedance changes, and larger lesion volumes with RF. This was shown using direct injection of Gd into myocardial tissues in both ex vivo and in vivo models. Further studies are required to develop a systemic delivery system for potential RF facilitating agents and to study the impact of facilitated ablation on arrhythmia management.

ACKNOWLEDGMENTS The authors thank Drs. Brad Wood, Ayele Negussie, Andrew Mikhail, and Yarmolenko Pavel for providing liposomal Gd and expertise in its potential use in our experiments.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: RF ablation can sometimes be limited by inadequate lesion durability and failure to reach mid-myocardial circuits despite the use of high power. We sought to potentiate the thermal destruction of myocardial tissue by augmenting RF current using chelated Gd. We chose this metal because it is routinely used safely in magnetic resonance imaging. We found that the pre-treatment of myocardial tissue with Gd resulted in larger ablation lesions.

TRANSLATIONAL OUTLOOK: There are potential clinical applications of our findings if we are able to find a reliable and safe way to deliver Gd to targeted tissue to address some limitations of RF ablation. However, further research is needed before we can consider this strategy in humans.

REFERENCES

1. Nguyen DT, Barham W, Zheng L, et al. Carbon nanotube facilitation of myocardial ablation with radiofrequency energy. J Cardiovasc Electrophysiol 2014;25:1385–90.

2. Gannon CJ, Cherukuri P, Yakobson BI, et al. Carbon nanotube-enhanced thermal destruction of cancer cells in a noninvasive radiofrequency field. Cancer 2007;110:2654–65.

3. Cho SK, Emoto K, Su LJ, Yang X, Flaig TW, Park W. Functionalized gold nanorods for thermal ablation treatment of bladder cancer. J Biomed Nanotechnol 2014;10:1267–76.

4. Xiao JW, Fan SX, Wang F, Sun LD, Zheng XY, Yan CH. Porous pd nanoparticles with high photothermal conversion efficiency for efficient ablation of cancer cells. Nanoscale 2014;6:4345–51.

5. Olson MD, Phreaner N, Schuller JL, et al. Effect of catheter movement and contact during application of radiofrequency energy on ablation lesion characteristics. J Interv Card Electrophysiol 2013;38:123–9.

6. Negussie AH, Yarmolenko PS, Partanen A, et al. Formulation and characterisation of magnetic resonance imageable thermally sensitive liposomes for use with magnetic resonance-guided high intensity focused ultrasound. Int J Hyperthermia 2011;27:140–55.

7. Gabizon A, Peretz T, Sulkes A, et al. Systemic administration of doxorubicin-containing liposomes in cancer patients: A phase 1 study. Eur J Cancer Clin Oncol 1989;25:1795–803.

8. Gaber MH, Wu NZ, Hong K, Huang SK, Dewhirst MW, Papahadjopoulos D. Thermosensitive liposomes: extravasation and release of contents in tumor microvascular networks. Int J Radiat Oncol Biol Phys 1996;36:1177–87.

9. Needham D, Anyarambhatla G, Kong G, Dewhirst MW. A new temperature-sensitive liposome for use with mild hyperthermia: characterization and testing in a human tumor xenograft model. Cancer Res 2000;60:1197–201.

10. Ahmed M, Goldberg SN. Combination radiofrequency thermal ablation and adjuvant iv liposomal doxorubicin increases tissue coagulation and intratumoural drug accumulation. Int J Hyperthermia 2004;20:781–802.

11. Goldberg SN, Kamel IR, Kruskal JB, et al. Radiofrequency ablation of hepatic tumors: increased tumor destruction with adjuvant liposomal doxorubicin therapy. AJR Am J Roentgenol 2002;179:93–101.

12. Lardo AC, McVeigh ER, Jumrussirikul P, et al. Visualization and temporal/spatial characterization of cardiac radiofrequency ablation lesions using magnetic resonance imaging. Circulation 2000;102:698–705.

13. Dickfeld T, Kato R, Zviman M, et al. Characterization of radiofrequency ablation lesions with gadolinium-enhanced cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2006;47:370–8.

14. McGann CJ, Kholmovski EG, Oakes RS, et al. New magnetic resonance imaging-based method for defining the extent of left atrial wall injury after the ablation of atrial fibrillation. J Am Coll Cardiol 2008;52:1263–71.

15. Cardinal J, Klune JR, Chory E, et al. Noninvasive radiofrequency ablation of cancer targeted by gold nanoparticles. Surgery 2008;144:125–32.

16. Cherukuri P, Glazer ES, Curley SA. Targeted hyperthermia using metal nanoparticles. Adv Drug Deliv Rev 2010;62:339–45.

KEY WORDS ablation biophysics, facilitated ablation, gadolinium, liposomes, radiofrequency ablation