Real-time magnetic resonance imaging-guided cryoablation of the pulmonary veins with acute freeze-zone and chronic lesion assessment

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Aims

The goals of this study were to develop a method that combines cryoablation with real-time magnetic resonance imaging (MRI) guidance for pulmonary vein isolation (PVI) and to further quantify the lesion formation by imaging both acute and chronic cryolesions.

Methods and results

Investigational MRI-compatible cryoablation devices were created by modifying cryoballoons and cryocatheters. These devices were used in canines ($n=8$) and a complete series of lesions (PVI: $n=5$, superior vena cava: $n=4$, focal: $n=13$) were made under real-time MRI guidance. Late gadolinium enhancement (LGE) magnetic resonance imaging was acquired at acute and chronic time points. Late gadolinium enhancement magnetic resonance images show a significant amount of acute tissue injury immediately following cryoablation which subsides over time. In the pulmonary veins, scar covered 100% of the perimeter of the ostium of the veins acutely, which subsided to $95.6 \pm 4.3\%$ after 3 months. Focal point lesions showed significantly larger acute enhancement volumes compared to the volumes estimated from gross pathology measurements ($0.4392 \pm 0.28 \text{ cm}^3$ vs. $0.1657 \pm 0.08 \text{ cm}^3$, $P=0.0043$). Additionally, our results with focal point ablations indicate that freeze-zone formation reached a maximum area after 120 s.

Conclusion

This study reports on the development of an MRI-based cryoablation system and shows that with acute cryolesions there is a large area of reversible injury. Real-time MRI provides the ability to visualize the freeze-zone formation during the freeze cycle and for focal lesions reaches a maximum after 120 s suggesting that for maximizing lesion size 120 s might be the lower limit for dosing duration.

Keywords

Real-time magnetic resonance imaging • Pulmonary vein isolation • Cryoablation • Late gadolinium enhancement magnetic resonance imaging • Cryolesion analysis • Cryoballoon ablation

Introduction

Catheter ablation is routinely used to treat atrial and ventricular arrhythmias. The cornerstone of atrial fibrillation ablation is pulmonary vein isolation (PVI). Cryoablation with a cryoballoon is appealing for this application because with proper placement of the balloon, the isolation can be performed in a single freeze cycle. Compared to traditional point-by-point ablation performed with a radiofrequency (RF) catheter,

cryoballoon ablation can be faster with comparable outcomes.^{1,2} With the traditional implementation of this technique, confirming isolation of the pulmonary vein post-ablation still requires electrophysiological evaluation as it is not possible to visualize ablation related tissue changes.¹

The goals of this study were to develop a method that combines cryoballoon ablation with real-time magnetic resonance imaging (RT-MRI) guidance for PVI as well as to further quantify the freeze-zone for cardiac ablation by imaging both acute and chronic

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What's new?

- This study demonstrates and evaluates the implementation of real-time magnetic resonance imaging (MRI)-guided cryoablation of the pulmonary veins in a canine model.
- Using MRI to visualize the freeze-zone formation in real-time allowed novel insights to the time to max freeze-zone area and potential lesion formation.
- Focal point cryoablations in the ventricular tissue showed maximum freeze-zone area after just 120 s of cryoablation.
- Visualizing the freeze-zone growth in real-time allowed for careful monitoring of the cardiac and non-cardiac anatomy as the tissue was frozen, this could lead to lower rates of complications such as atrio-oesophageal fistula.
- Characterizing the MR images of lesions at acute and chronic time points provides observations of oedema and inflammation that occurs during cryoablation and how it subsides over time to create permanent scar.

cryolesions. It has been proven that RT-MRI provides excellent monitoring of the freeze-zone formation during non-cardiac cryoablations because as the tissue freezes, its MRI signal diminishes, allowing for real-time observation of the freeze-zone.^{3–5} Real-time magnetic resonance imaging also has proven utility when implemented with RF-based ablation systems.^{6,7} Our group was the first to report feasibility of RT-MRI guidance with cardiac cryoablation of right atrium (RA)-superior vena cava (SVC) junction using the cryoballoon.⁵ The main limitation of our previous study was that the cryoballoon lacked the manoeuvrability required to position the cryoballoon at the ostium of the pulmonary vein. In this study, we have investigated an improved cryoablation system that allowed us to place and manoeuvre the MRI-compatible cryoballoon in the left atrium (LA) and perform PVI in a canine model. This new system allowed us to use RT-MRI to follow in real time the freeze-zone formation, which provides information useful in titrating the ablation dose, a topic of active investigation.⁸ We also evaluated the ability of using acute late gadolinium enhancement (LGE) MRI to predict chronic cryolesion formation by comparing these scans with both LGE MRI performed 3 months after the ablation and gross histological examination of the explanted hearts.

Methods

Equipment

As previously described,⁵ we had developed investigational MRI-compatible cryoablation devices for animal use by removing or replacing all ferromagnetic components from 23 and 28 mm Arctic Front Advance cryoballoons and the Freezor MAX cryocatheter with an 8 mm ablation tip (Medtronic CryoCath, Montreal, Canada). Removal of these components practically eliminated torque force and heating induced by the strong magnetic fields of the MRI scanner and the RF pulses used in MRI sequences but then the catheters lacked manoeuvrability. In this set of catheters, a MRI-compatible steering mechanism was implemented to allow deflection of the balloon segment. The console for the system was placed outside the scanner room and connected to the catheter via custom made nitrous oxide circulation coaxial tubing 8 m in length.

Study protocol

Adult canines ($n = 8$) weighing 27–30 kg, were used as the model for this study under a protocol approved by the institutional animal care and use committee. As in our previous study,⁵ deep sedation was maintained using isoflurane. Right femoral vein access was first obtained and then a 16 Fr MRI-safe fixed-curve sheath (Cook Medical, Bloomington, IN, USA) was inserted so the tip ended in the RA. An intracardiac echocardiogram probe (Siemens Healthcare, Erlangen, Germany) was placed in the RA via an 11 Fr access through the left femoral vein. Trans-septal puncture was performed using a trans-septal needle (St. Jude Medical, St. Paul, MN, USA), and then the sheath was advanced to the LA under guidance by intracardiac echocardiography and fluoroscopy over an MRI-compatible guidewire (MaRVis Interventional, Frenchen, Germany). The animal was then moved to the 3 T MRI scanner (Verio, Siemens Healthcare, Erlangen, Germany) in our joint electrophysiology/MRI lab.

Real-time MRI guidance was used to advance the guidewire and deflated 23 mm cryoballoon to the left and right PV-LA junctions of all of the animals. Once positioned, the cryoballoon was inflated and a 10–15 mL bolus of 10% diluted Gd-BOPTA (Bracco Diagnostic Inc., Princeton, NJ, USA) was injected from the tip of the balloon to confirm PV occlusion. In the case of partial occlusion, the cryoballoon was deflated, repositioned, re-inflated, and occlusion was re-validated. Once complete occlusion was obtained, cryoablation was initiated, and the junction was frozen for either 1 or 2 cycles of 3 min each. During the freeze, real-time MRI was used to monitor the freeze-zone. After thawing, the cryoballoon was deflated and repositioned to the alternative PV-LA junction and the process was repeated. Due to individual anatomy, not all animals received cryoablations in both the left and right PVs. This was specifically avoided in animals with small LA size to prevent overlap of the lesions from the other PV.

While maintaining trans-septal access, the cryoballoon was deflated and removed from the heart and the modified, MRI-compatible Freezor MAX catheter was advanced into the LV. Focal ablations were created in the apex, mid, and basal regions of the LV. Catheter tip-tissue contact was visually verified using RT-MRI, and then a freeze cycle of either 2 or 4 min was performed with simultaneous monitoring of the tissue using RT-MRI. Once the tissue thawed, the catheter was repositioned to the next location. Following each complete lesion set in the LV, the trans-septal sheath was retracted out of the LA, leaving access to the RA. The 28 mm cryoballoon was inserted into the heart and advanced to the RA-SVC junction using real-time MRI guidance. Once in place, the same procedure was followed as for the PVs. We also carried out focal RV ablations as we did in the LV.

After completion of the cryoablations, 3D LGE MRI was acquired to assess the lesions and possible acute collateral damage. The animals were kept at the animal care facility for 3 months until a repeat 3D LGE MRI was acquired to visualize the chronic lesions. For all LGE MRI, the image sequence was acquired around 30 min after injection of contrast (0.1 mmol/kg of Gd-BOPTA). Following the imaging at 3-months post-ablation, the animal was euthanized and the heart was explanted for macroscopic and histological examination.

Magnetic resonance imaging protocol

Real-time MRI guidance and 3D LGE MRI scans were performed using similar protocols as previously described.⁵ Briefly, the typical scan parameters were as follows:

RT-MRI: 2D turbo-FLASH pulse sequence with in-plane resolution = 1.8×2.4 mm, slice thickness = 4 mm, repetition time (TR) = 3.5 ms, echo time (TE) = 1.5 ms, and flip angle = 12° . During the navigation phase of the study, the sequence ran unsynchronized at 4 Hz. To validate occlusion and visualize the freeze-zone formation during ablation, the pulse

sequence was ECG-gated, resulting in temporal resolution of 1 image per heartbeat. For the occlusion validation with contrast, we used a saturation recovery preparation with inversion time (TI) of 200 ms.

3D LGE: respiratory navigated, ECG triggered, inversion recovery prepared 3D turbo-FLASH pulse sequence with spatial resolution $1.25 \times 1.25 \times 2.5$ mm, TR/TE = 3.1/1.4 ms, flip angle = 14° , and TI = 250–330 ms.

Lesion validation

It has been previously demonstrated that frozen tissues appear as signal voids in real-time MRI.^{9,10} It is important to note that this void region comprises the cryoballoon, the region of frozen tissue, and ice on the cryoballoon. The growth in the signal void region was quantified using an automated method by importing the gated RT-MRI images in Matlab. A region of interest around the balloon or the focal lesion was defined and then image sequence was processed to define the contiguous area with no signal. In the 3D LGE MRIs, lesions appear as enhancement of signal, which we quantified by a manual threshold-based segmentation of the lesions at both the acute and chronic time points. The PV and SVC scars were then reconstructed in 3D space and analysed by orienting the view plane so that it was perpendicular to the lumen of the vein. The scar region was then projected onto this plane perpendicular to the ostium of the vein. The perimeter of the vein lumen was defined semi-automatically by using dilation and erosion morphological operations to connect regions of gap in the scar. We used this perimeter to mask off a line around the lumen and calculated the percent circumferential scar by dividing the number of scar pixels on the perimeter by the total number of pixels making up the perimeter of the vein.

The focal ablations were characterized in a similar manner. Each lesion was segmented, and its volume measured from images acquired at the acute and chronic time points. Acute scans showed two concentric injury domains, one a region of enhancement indicating tissue injury and the other an inner dark region indicating microvascular obstruction (MVO). In contrast, chronic scans showed only a bright region of enhancement indicating permanent scar. For the analysis, the acute enhancement volume includes the MVO volume.

In each animal, we explanted the heart and performed qualitative visual inspection of the SVC and PVs to confirm our MRI-based characterization. The ventricles of the fixed hearts were then sliced into 2 mm sections to find all of the ventricular focal lesions. These lesions were then measured manually to obtain values for the penetration into the ventricular wall and the diameter of the lesion, from which we estimated equivalent spherical lesion volumes. Additionally, regions of interest were collected for histological studies including sectioning and staining the tissue with Masson's trichrome.

Results

In this study, we successfully performed and documented real-time MRI-guided cardiac cryoablation procedures in canines ($n = 8$). The average time from the beginning of the procedure on the fluoroscopy side to the end of the PV isolation in the MRI was 211.3 ± 24 min. The average time from when the animal was moved to the MRI to the end of PV isolation was 59.7 ± 22.7 min. One animal yielded poor acute images due to ectopy, while another had significant tachycardia including what appeared to wide complex tachycardia immediately post-ablation again resulting in poor quality image; the result was good quality acute and chronic (3-month post-ablation) images in six animals. A further source of complication was the lack of safety features on the investigation cryoballoon, which resulted in technical

obstacles during two of the procedures (e.g. inner catheter leaks which rendered the device unusable for the rest of the study) as well as difficulty manoeuvring the balloon in the small left atria of dogs with a non-steerable sheath. Furthermore, in multiple animals the small left atria posed a risk of overlapping lesions when targeting both the left and right PVs. The resulting yield from all these challenges in lesions was five in the PVs and four in the SVCs. As for the focal ventricular lesions, we obtained and compared quantitative volumes at acute and chronic time points from 13 lesions. From this set of focal lesions, three of the RT-MRI sequences acquired during the cryoablation showed movement of the cryocatheter out of the imaging plane during the cryoablation, leading to inaccurate measurements. This yielded only 10 quality RT-MRI sequences allowing for the analysis of the freeze-zone growth of lesions performed for either 2 ($n = 5$) or 4 ($n = 5$) min.

Real-time MRI provided two main sources of benefit to the ablation procedure: precise positioning and visualization of the catheter within the anatomy of the heart and assessment of freeze-zone formation during the ablation. *Figure 1* shows a sequence of 2D four chamber MRI images of the heart at various z-depths centred on the cryoballoon catheter. *Figure 1A*, at $z = 19$ mm, shows that the LA, LV, aorta, and RV are all clearly visible. Moving deeper into the tissue revealed the RA and at $z = 7.6$ mm (*Figure 1B*), the edge of the inflated cryoballoon was clearly visible. At $z = 0$ mm (*Figure 1C*) the fully inflated cross section of the cryoballoon and catheter was visible, and at $z = -11.3$ mm (*Figure 1D*), the other edge of the cryoballoon appeared in relation to the anatomy of the four chambers of the heart. This figure shows a consistent finding that MRI was clearly superior to conventional fluoroscopy in the level of anatomical detail obtained. We used this detail to track the location of the cryoballoon in 3D space and manoeuvre it to the RSPV (*Figure 1C*). Once positioned at the ostium of the vein (*Figure 2A*), real-time MRI visualized the heart as contrast was injected (*Figure 2B*) and occlusion of the PV was confirmed. See the [Supplementary material online](#) for a highly resolved (2 Hz) video of contrast injection. Once positioning of the cryoballoon and vein occlusion were confirmed, cryoablation was initiated. *Figure 3* shows axial views of the heart before and during cryoablation. At 10 s before ablation ($t = -10$ s in *Figure 3A*), the deflated cryoballoon is clearly visible in the centre of the red circle. At $t = 0$ s (*Figure 3B*), the flow of nitrous oxide was initiated and the cryoballoon was fully inflated, the start of cryoablation. As the tissue froze, the MRI signal became weaker, indicated by the growth of the black region, which provided real-time visualization of the potential damage done to the tissue. At $t = 180$ s (*Figure 3C*) the signal void region reached its maximum diameter, as documented by the graph in *Figure 3D*. This time corresponded with the duration of the flow of nitrous oxide for the lesion visualized in *Figure 3*. See [Supplementary material online](#) for another example of the growth in the black region and video of the cryoablation.

Real-time MRI was also able to document focal point ablations created with the modified Freezor Max catheter; these ablations were performed for either 2 or 4 min. We were able to monitor the growth of the freeze-zone in real time, as shown in *Figure 4*, starting with panel A, which shows the Freezor Max catheter in position before ablation. After 120 s, there was visible growth of the freeze-zone to around three times the initial area (*Figure 4B*), as shown in the plot

Figure 1 Real-time MRI showing the anatomy of heart (A). Imaging plane along the four chamber view of the heart. The inflated balloon catheter is centred at $z = 0$ mm (C). Important landmarks and structures of the heart have been labelled in red. The lateral edges of the cryoballoon are visible in planes $z = 7.6$ mm (B) and $z = -11.3$ (D) mm and highlighted by blue arrowheads. Scale bar is 1 cm. The balloon is in the left atrium. LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; RA, right atrium; RSPV, right superior pulmonary vein; RV, right ventricle.

Figure 2 Real-time MRI validation of PV occlusion. (A) Placement of the catheter and cryoballoon before injection of contrast. (B) Contrast injected from the distal tip of the balloon and confirms occlusion of the RSPV by the inflated cryoballoon. Scale bar is 1 cm. See [Supplementary material online](#) for the full video of contrast injection. MRI, magnetic resonance imaging; PV, pulmonary vein; RSPV, right superior pulmonary vein.

of the freeze-zone area normalized to the initial area of the catheter tip in *Figure 4C*. Lesions of 4-min duration showed similar results, with growth to around three times the catheter size (*Figure 4D–F*). *Figure 4G* shows a summary graph of the lesion areas for the freeze-zones of the 2 ($n = 5$) and 4 ($n = 5$) min focal ablations.

Late gadolinium enhancement magnetic resonance imaging was also able to provide documentation of both acute and chronic lesions following cryoablation. Immediately after the procedure, the animal underwent LGE MRI imaging to obtain a 3D MRI of the acute lesions. Chronic lesion results followed after 3 months of recovery. Both image

Figure 3 Real-time MRI of PV isolation. (A) Position of the deflated balloon catheter (centre of red circle) can be seen at $t = -10$ s. (B) Growth of signal void region corresponding to cryoballoon and frozen tissues can be monitored from $t = 0$ s. The balloon diameter is 2.29 cm. (C) The time point where the freeze-zone is at its maximal diameter, $t = 180$ s. The balloon diameter is 2.5 cm. (D) Graph showing the area of the freeze-zone. Scale bars represent 5 cm. See [Supplementary material online](#) for an image and video of another example of cryoablation. MRI, magnetic resonance imaging; PV, pulmonary vein.

Figure 4 Real-time MRI monitoring Freezor Max focal ablations. (A) Short-axis view of the heart with the Freezor Max catheter (arrow) in position at the start of ablation. (B) Short-axis view of the heart showing the freeze-zone in (A) after 120 s of cryoablation. (C) Growth of ablation in A–B over time and normalized to the area at $t = 0$ s. (D) Four chamber view of the heart with the Freezor Max catheter in position at the start of ablation. (E) Four chamber view of the heart showing the freeze-zone in (D) after 240 s of cryoablation. (F) Growth of ablation in D–E over time and normalized to the area at $t = 0$ s. (G) Mean and standard deviation of the average normalized growth of 2 min ablations ($n = 5$, red xs) vs. 4 min ablations ($n = 5$, turquoise squares). Scale bars in RT-MR images represent 5 cm. LV, left ventricle; MRI, magnetic resonance imaging; PV, pulmonary vein; RV, right ventricle.

sets were acquired at a spatial resolution of $1.25 \times 1.25 \times 2.5$ mm. *Figure 5A* and *B* show a comparison from axial views of the heart for the acute and chronic lesion from the same animal, highlighting the LSPV lesion, identified by the arrows. In the acute LGE MRI, a much larger area of enhancement was visible than in the chronic LGE MRI, likely the effect of oedema and inflammation immediately after the cryoablation, which subsides over time. After 3 months, only the permanent scar was, is

visible, confirmed by gross pathology. The black arrows in *Figure 5C* point to the scar formed around the PVs. While clinical MRI lacks the spatial resolution to visualize the transmural extent of ablation lesions, we were able to ensure from histology that the cryoablations we created were, indeed, transmural in extent (*Figure 4E*).

Thresholding and segmenting the 3D LGE MRIs allowed us to reconstruct the 3D shape of the scar. *Figure 6* shows reconstructions

Figure 5 Representative LGE images of the same LA lesion at acute (A) and 3-month chronic (B) time points after cryoablation. White arrows point to LSPV scar enhancement. (C) Gross pathology of the LA after the heart was fixed. Visible scar surrounding both the right and left PVs (black arrows). (D) Gross pathology of the transmural cross section of the LA wall from the fixed heart near the LSPV. Red arrowhead points to endocardium, red arrow points to epicardium. (E) Histology of the same region shown in D. Red arrowhead and arrows point to the same locations in E and D. White scale bars in MRIs and gross pathology represent 1 cm, black scale bar in histology represents 1 mm. LA, left atrium; LAA, left atrial appendage; LSPV, left superior pulmonary vein; LV, left ventricle; LGE, late gadolinium enhancement; PV, pulmonary vein; RA, right atrium; RSPV, right superior pulmonary vein; RV, right ventricle.

from both the acute (Figure 6A) and chronic (Figure 6B) LGE MRI scans presented in Figure 5. Figure 6C and D show additional (orthogonal) LGE MRI images of the same lesion shown in Figure 5A and B. These reconstructions are oriented in a manner that the lumen of the LSPV is perpendicular to the view plane to visualize the full perimeter of the ostium. This form of visualization confirms that the acute lesion showed a much larger area of enhancement compared to the chronic result. This orientation allowed us to calculate the extent of isolation achieved around the perimeter of the vein for both SVC and PV lesions, as shown by the graph in Figure 6C. We found that in all ablations, the acutely acquired images showed 100% circumferential enhancement around the ostium, whereas after 3 months, values were reduced to $98.7 \pm 1.9\%$ for the SVCs ($n = 4$) and $95.6 \pm 4.3\%$ for the PVs ($n = 5$). When examining the explanted hearts, we indeed saw visible scars encircling the PVs and the SVCs (Figure 5C). While our results indicate that MRI imaging can provide evidence of

circumferential scarring, the resolution limits the ability to identify small gaps that may provide functional connections and thus undermine ablation success.

We were also able to image the effects of focal lesions made by the Freezor MAX catheter. Figure 7 shows an example of acute and chronic LGE MRI scans of the same focal lesion. In the acute LGE scan (Figure 7A), we see a large region of enhancement correlating to tissue inflammation and oedema (blue arrow) surrounding a darker region known as the region of MVO (green arrow).¹¹ Images acquired 3 months post-lesion (Figure 7B) show no such MVO, rather a chronic enhancement correlating to the permanent scar as measured in histology (Figure 7C). Over 13 different focal lesions, we found that the volume of the acute enhancement was significantly larger than the acute MVO volume ($P = 0.0013$), the chronic enhancement ($P = 0.003$), and the estimated histology volume ($P = 0.0043$). While both the chronic lesion volume and estimated gross histology volume

Figure 6 3D reconstructions of the LA lesion shown in Figure 4. View is oriented so we are looking parallel the longitudinal axis of the LSPV lumen from inside of the LA. White Xs mark the lumen of the LSPV. (A) The segmented scar from the acute LGE scan; (B) the same scar from the 3 month follow-up, chronic scan. Scale bars represent 5 mm. A slice of acute and chronic LGE MRI for these lesions is shown in Figure 5A and B, respectively. (C and D) Another orthogonal slice for the same acute and chronic lesions, respectively. (E) Summary data comparing the percent circumferential scar in SVCs ($n = 4$) and PVs ($n = 5$) at both acute and chronic time points. LA, left atrium; LGE, late gadolinium enhancement; LSPV, left superior pulmonary vein; MRI, magnetic resonance imaging; PV, pulmonary vein; SVC, superior vena cava.

Figure 7 (A) Acute LGE MRI showing an RV lesion highlighting the enhanced area (turquoise) and the MVO area (red). (B) LGE MRI showing the same lesion at a chronic time point (green). (C) Gross histology of the same lesion after explanation. Scale bars represent 1 cm. The graphs show summary data ($n = 13$) of the volumes and depths of the acute enhancement region, acute MVO region, and the chronic enhancement region. Brackets indicate significance of $P < 0.05$. LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; MVO, microvascular obstruction; RV, right ventricle.

were significantly larger than the acute MVO volume ($P = 0.0091$ and $P = 0.036$, respectively). We did not find any significant difference in the volumes estimated from the gross histology and the chronic enhancement in MRI. This result indicates that neither acute enhancement nor acute MVO is a reliable method of predicting the size of the resulting scar; however, if both acute values are known, it is possible to predict chronic scar volume using the acute volumes as limits. We saw a similar correlation with the depth of the ablation into the ventricular wall.

Discussion

This study reports on the evaluation of a real-time MRI-based cryoablation system applied to left atrial ablation and demonstrates the advantages provided by MRI. Real-time MRI provides the ability to visualize the freeze-zone formation during the freeze cycle. This information allows for a direct measure of the effective cooling and ice formation and provides real-time feedback on vessel occlusion, potential lesion formation, and potential collateral damage. If the

occlusion of the vessel is not sufficient, flow of warm blood around the catheter would affect the size and symmetry of the freeze-zone, providing real-time information that can be used to determine whether or not to abort the ablation. The tissue around the catheter also becomes void of MRI signal as it freezes,⁹ thus providing a means to estimate potential lesion during the freeze cycle. For point lesions, the extent of the freeze-zone reached a maximum in about 2 min, suggesting that longer duration may not improve yield. Histology of lesion size following 2-min ablations supported this hypothesis. This is in agreement with a recently published paper exploring the difference in lesion size when varying the freeze time of cryoablation.¹²

In the past, the recommended dosage for cryoablation has been 2 freeze cycles of 4 min each; more recent studies have sought to titrate the time needed for ablation to minimize collateral damage that comes with longer freeze cycles.^{8,13,14} The data presented here show that for PVI, 1 freeze cycle of 3 min is sufficient to create permanent scar. Similarly, with focal lesions, 1 freeze cycle of 2 min created chronic lesions.

An additional advantage of monitoring the freeze-zone using real-time MRI is that it allows the physician to abort the ablation immediately if any concerns for collateral damage or lack of effective lesion delivery arise. Further studies will be needed to clarify the relationship between ice formation, total ablation time, temperature, and resulting lesion volume. Real-time MRI has unmatched potential to provide the information needed to titrate cryoablation time.

The other significant improvement this technique provides is that with real-time MRI, the location of the cryoballoon within the heart is visualized, improving the ability to know precisely where ablation is performed, while being aware of the surrounding cardiac and non-cardiac structures. With this added information, it might be possible to minimize collateral damage and reduce the occurrence of atrio-oesophageal fistula, which continues to be a major complication of atrial ablation procedures.¹⁵ Furthermore, with cryoablation, validating the catheter tip-tissue contact before performing the ablation is extremely important for creating effective lesions.¹⁶ Gaps in the formed lesion can result in a lack of electrical isolation and a recurrence of AF. With fluoroscopy, vessel occlusion information is obtained solely through contrast injection; however, with the MRI-based system we can visualize multiple planes of the heart and verify the apposition of the balloon to the vessel wall in addition to the conventional method of contrast injection. Thus RT-MRI provides an advantage of being able to validate vessel occlusion in real time with and without contrast, providing a much higher level of confidence that the resulting lesion will provide electrical isolation of the pulmonary vein.

Prior reports have suggested that in RF ablations, up to a third of the area targeted for ablation might not result in chronic lesions and this affects clinical outcomes.^{17,18} The ability to detect lesion formation in an acute setting is enhanced by having the subject in the MRI environment during the ablation.¹⁹ In this study, we compared the lesion visualized using LGE MRI at both an acute and chronic time point. We found that the LGE MRI at the acute time point shows a significantly different visualization of the tissue volume affected by the cryoablation compared to what is acquired 3 months later. In the acute LGE MRI, we see two distinct regions of the scar: the first is the enhancement volume and the second is the MVO region.¹¹ These two volumes were significantly different than the chronic and gross histological volumes. The presence of MVO regions has been

reported in radio-frequency cardiac ablations but not for cardiac cryoablations.²⁰ The MVO region enhancement is a diffusive process, and so its volume can be highly dependent on the time delay between contrast injection and image acquisition. Prior, atrial RF studies have also shown that MVO regions correlate well with scar formation.¹¹ With RF ablation, we know there is oedema and inflammation that occurs during and immediately after the ablation.²⁰ Based on the acute images presented here, even with cryoablation we see that there is a larger area of acute injury as compared to chronic lesions. Thus, it is important to consider how this injury will subside and what the resulting permanent scar will be. The MVO region was a closer approximation to the volume and depth of the permanent scar than the acute area of enhancement even though the acute MVO volume was significantly smaller than the chronic lesion size. The MVO region analysed here was in images acquired approximately 30 min after contrast injection. Given that the MVO region enhancement is a diffusive process, images acquired with a shorter delay after contrast injection will likely provide a more accurate representation of chronic scar volume but that will require further studies.¹¹

A fully functional clinically acceptable MRI-guided cryoablation system will still need further development. For this application, active-tracking capability by means of active generation of MRI signal would be an improvement over current capabilities of interpreting ambiguous voids in the images using passive tracking of catheters. Active tracking has been used in radiofrequency ablation carried out in real-time MRI but even with radiofrequency real-time MRI ablation the passive tracking catheters preceded the active tracking catheter development.^{7,19} Additional tools, for instance, an MRI-compatible lasso catheter for further testing electrical isolation created by the ablation would also improve effectiveness of the procedure. Furthermore, many of the standard safety mechanisms were removed from the cryo-devices used in this study in order to reduce heating and undesired device motion that would arise from the MRI environment. Magnetic resonance imaging-compatible versions of these safety features would need to be implemented before this system could be used clinically. Finally, while some deflection was possible with this cryoballoon, the addition of an MRI-compatible steerable sheath would enhance placement and control of the device. This study is the first to demonstrate the advantages of real-time MRI for cryoablation of the pulmonary veins.

Conclusion

This study reports on the development of an MRI-based cryoablation system including left atrial ablation and demonstrates the advantages provided by MRI. Real-time MRI provides the ability to verify position of the cryoballoon in relation to the anatomy of the heart and surrounding structures as well as to visualize the freeze-zone formation during the freeze cycle. This system was tested in a canine model and resulted in multiple successful PVIs as well as RA-SVC isolations and focal ventricular ablations.

Supplementary material

Supplementary material is available at *Europace* online.

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