The critical isthmus sites of ischemic ventricular tachycardia are in zones of tissue heterogeneity, visualized by magnetic resonance imaging

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BACKGROUND A need exists to develop alternative approaches to VT ablation that provide an improved delineation of the arrhythmicogenic substrate.

OBJECTIVE The aim of this study was to evaluate the hypotheses that: (1) the heterogeneous zone (HZ, a mixture of normal-appearing tissue and scar) in magnetic resonance imaging (MRI) contains the critical isthmus(es) for ventricular tachycardia (VT), (2) successful ablation of VT would include ablation in the HZ, and (3) inadequate ablation of HZ allows for VT recurrence.

METHODS MRI and an electrophysiology study (EP) were performed in a model of chronic myocardial infarction in 17 pigs. In animals that had inducible VT, ablations were done guided by standard EP criteria and blinded to the MRI. After ablation, electroanatomic mapping results were co-registered with MRI.

RESULTS In 8 animals, 22 sustained monomorphic VTs were generated. The HZ was substantially larger in inducible (n = 9) compared with noninducible animals (n = 9) [25% ± 10% vs 13% ± 5% of total scar, respectively, P = .007]. Acutely, all targeted VTs were successfully ablated, and postprocedure analysis showed that at least 1 ablation was in the HZ in each animal. In 5 animals, a second EP and MRI were performed 1 week after ablation. Three animals had inducible VTs, and MRI showed that the HZ had not been completely ablated. In contrast, the 2 animals without inducible VT revealed no remaining HZ.

CONCLUSION These findings show that MRI can define an HZ and determine the location of ablated lesions. The HZ may be a promising ablation target to cure ischemic VTs. Remnants of HZ after ablation may be the substrate for clinical relapses.

KEYWORDS Ischemic ventricular tachycardia; Catheter ablation; MRI

ABBREVIATIONS 3D = three-dimensional; CT = computed tomography; EP = electrophysiology; HZ = heterogeneous zone; LV = left ventricular; MI = myocardial infarction; MRI = magnetic resonance imaging; RF = radiofrequency; VT = ventricular tachycardia

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Introduction

A number of criteria for mapping and ablation of ventricular tachycardia (VT) after myocardial infarction (MI) have been established.1–3 In patients in whom isthmuses of viable myocardium can be identified within scar, interruption of such isthmuses can eliminate VT.4 In a minority of patients, the induction of VT does not cause significant hypotension, and entrainment and activation mapping can be done to identify the critical path of reentry. Success rates have been reported to be approximately 75% after successful mapping procedures.5

Best results are obtained when there is accurate guidance of the ablation catheter using specific mapping criteria.1 An intention-to-treat analysis of patients referred for VT ablation in the setting of healed MI yielded 58% initial success and 71% eventual success with >1 procedure.6 Complications such as perforation and emboli can be as high as 8%, likely due to the sometimes prolonged duration of the procedure,7 and there can still be a greater than 33% recurrence rate.8

In the majority of patients, however, induction of VT leads to severe hypotension, and entrainment and activation mapping during VT is not possible. Voltage mapping during sinus rhythm has been used to identify low-voltage areas (<1.5 mV),8 which are presumed to be areas of a scar (including its
Pace mapping can then be used to reproduce the QRS morphology of a previously recorded clinical VT, and thereby identify an isthmus where the VT exits from the scar. Ablation of an identified isthmus of viable tissue between scar islands can eliminate VT, as well as placing a line of ablations aimed at connecting the area of scar with another anatomic barrier, such as the mitral annulus. Current voltage and pace mapping techniques can be difficult, however, because of ambiguities in correlating maps with anatomy, as well as possible missed critical sites due to the point-by-point endocardial sampling nature of current methods. Thus, a need exists to develop alternative approaches to VT ablation that would provide an improved delineation of the arrhythmogenic substrate.

Magnetic resonance imaging (MRI) can visualize scar and viable tissue, as well as ablation lesions. It has been shown in a swine model of MI that multiple VT morphologies can be induced. In this latter study, MRI demonstrated the presence of scar containing isthmuses of viable myocardium, resulting in a heterogeneous zone (HZ), which may be the critical substrate for the multiple VT morphologies.

The purpose of this study was to use conventional late gadolinium enhancement MRI to (1) help determine the relationship between VT inducibility and the extent of the HZ, and (2) define the location of ablation lesions with respect to the HZ. Conventional electrophysiology (EP)-guided ablation, blinded to MRI, was performed to prevent bias. We tested the hypotheses that: (1) the HZ is the critical substrate for VT, (2) successful ablation of VT would include ablation in the HZ, and (3) inadequate ablation of the HZ may allow for recurrence of VT.

Methods

Full experimental details are available in the Online Supplementary Material. MI preparation

Twenty-five domestic swine were studied with an occlusion of their mid-left anterior descending coronary artery.

Experimental protocol

At least 4 weeks after MI induction, the animals underwent in vivo MRI in a 3.0-T scanner (Achieva, Philips Medical Systems, Best, the Netherlands) for assessment of cardiac function and visualization of the HZ. Additionally, a computed tomography (CT) scan was done for merging the left ventricular (LV) endocardial surface and aorta with a three-dimensional (3D) electroanatomic mapping system (CARTO, Biosense Webster, Inc; Diamond Bar, California). One day after the MRI, an EP study was done to determine inducibility or noninducibility of sustained VT, followed by an ablation procedure in inducible pigs guided by CARTO.

The pigs were allowed to survive the VT ablation procedure for 7 to 9 days. They then underwent (1) an EP study that again tested for inducibility of VT, and (2) an in vivo and ex vivo MRI to visualize the HZ.

Electrophysiological evaluation and identification of VT circuits

After detailed voltage mapping during sinus rhythm (Fig. 1A), pace mapping was performed in both ventricles. VT exit sites were defined by pace mapping to be sites where the QRS morphology matched the most leads of the 12-lead VT electrocardiogram (Fig. 1B).

Irrigated radiofrequency (RF) energy was delivered at 30 W for 60 seconds. In only 1 animal, a nonirrigated-tip ablation was performed. Ablations were done at the location of the best pace map for each VT morphology. The operators performing the ablations were blinded to the MRI
results. The end point of RF application was noninducibility of any VT. Targeted, single RF applications were made, as opposed to linear lesions.

**MRI protocol and data analysis**

Late gadolinium-enhanced images were used for infarct characterization. Endocardial and epicardial contours were traced manually. The core of the infarct was defined as the volume of myocardium that was $\geq 3$ SD signal intensity greater than the mean signal intensity of the remote (noninfarcted) myocardium, and the HZ was defined as the volume of myocardium that was 2 to 3 SD signal intensity greater than the mean signal intensity of the remote myocardium, both as described previously.  

**Relation between electroanatomic-mapped ablation success sites and MRI**

Using anatomical landmarks (mitral annulus plane, LV apex, and aortic root), an offline registration process was performed between the MRI and the CT image using custom software developed in our laboratory. Subsequently, the CARTO-CT-merged maps were used to allow each CARTO map point to be located in a corresponding MRI slice. The location of any ablation site could thus be evaluated in relation to its proximity to scar or HZ visualized on MRI.

**Results**

Three animals died during infarct induction, and 5 in the postinfarct period. The remaining 17 animals underwent VT induction 55 ± 18 days after MI. Detailed electroanatomic voltage maps were constructed and contained a mean of (± SD) 207 ± 32 sampled points for the LV.

No VT could be induced in 9 pigs, and in 8 pigs sustained monomorphic VT was reproducibly induced. At the time of VT induction, LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction showed no differences between inducible and noninducible animals (Table 1).

**MRI visualization of scar and the HZ**

All pigs had evidence of scar tissue on contrast-enhanced MRI (Fig. 2). The mean infarct core was 4,827 ± 1,897 mm$^3$, and the mean infarct HZ was 1,089 ± 688 mm$^3$ (Fig. 2, Table 1).

For the different preparations of MI in the nonreperfused group (coil and alcohol injection), HZ was only in trend larger in pigs that were inducible than in pigs that were not inducible (25% ± 10% vs 13% ± 5%, $P = .007$). High-resolution MRI (Fig. 3) confirmed that the MRI-intensity-based determination of infarct core and HZ did, in fact, correspond to actual scar and tissue heterogeneity, respectively, with much greater tissue heterogeneity in inducible animals than noninducible animals (Fig. 2). As opposed to

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**Table 1** Characteristics of inducible and noninducible animals

<table>
<thead>
<tr>
<th></th>
<th>Inducible (n = 8)</th>
<th>Noninducible (n = 9)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>38 ± 5</td>
<td>42 ± 7</td>
<td>.2</td>
</tr>
<tr>
<td>LV mass ED (g)</td>
<td>43 ± 7</td>
<td>40 ± 7</td>
<td>.5</td>
</tr>
<tr>
<td>LV mass ES (g)</td>
<td>56 ± 6</td>
<td>56 ± 4</td>
<td>.9</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>2.3 ± 0.3</td>
<td>2.3 ± 0.4</td>
<td>.7</td>
</tr>
<tr>
<td>Weight of animal at infarct (kg)</td>
<td>29 ± 6</td>
<td>30 ± 7</td>
<td>.9</td>
</tr>
<tr>
<td>Total infarct size (percent total LV volume)</td>
<td>14 ± 4</td>
<td>12 ± 4</td>
<td>.22</td>
</tr>
<tr>
<td>Heterogeneous zone (percent total infarct volume)</td>
<td>25 ± 10</td>
<td>13 ± 5</td>
<td>.007</td>
</tr>
<tr>
<td>Infarct (mm$^3$)</td>
<td>5,424 ± 1,702</td>
<td>4,750 ± 2,367</td>
<td>.52</td>
</tr>
<tr>
<td>Heterogeneous zone (mm$^3$)</td>
<td>1,618 ± 657</td>
<td>619 ± 205</td>
<td>.001</td>
</tr>
<tr>
<td>Lesion volume (mm$^3$)</td>
<td>2,154 ± 802</td>
<td>NA</td>
<td>NA</td>
</tr>
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ED = enddiastolic; ES = endsystolic; LV = left ventricular.

the HZ, however, there was no relation between inducibility and the percentage of total infarct size for inducible and noninducible animals (14% ± 4% vs 12% ± 4%, $P = .22$).

**Electrophysiological studies and ablations**

Sustained monomorphic VT was reproducibly induced in 8 of 17 animals. In these animals, a total of 22 VTs were induced with a mean cycle length of 232 ± 48 ms. All VTs in each animal had nearly the same cycle length, except for 1 animal (Table 2, suppl material). Because the majority of VTs [20 of 22 or 91%] were hemodynamically unstable, pace mapping was used to guide ablation for all animals. Pace mapping was performed in each animal at an average of 46 ± 16 different sites along the border zone between the normal and the low-voltage area identified by electroanatomical mapping (Fig. 1). In 2 animals during RF application, the induced VT cycle length became prolonged and then the VT terminated.

All 21 of the VTs where ablation was attempted (7 animals) were rendered noninducible by ablation. In 1 other animal with 1 VT, there were technical problems with the ablation generator, and the animal died 1 week later of pneumonia before any ablation could be attempted. In that latter animal, however, high-quality pace mapping and imaging were performed.

**Correlation of the HZ and successful ablation sites**

RF lesions were applied in a total of 13 areas. In some animals, the best pace maps for individual VTs were at locations that were in very close proximity. For example, in 1 animal, 5 different VT were successfully ablated in 3 areas, which were in close spatial proximity to each other (Fig. 1). The average volume of ablation was 2,154 ± 802 mm$^3$, which is consistent with lesion volumes previously reported.  

RF energy was applied for 60 seconds (30 W) between 1 and 5 times at each ablation area. Maps of anatomic relationships between the CARTO-CT merge marked ablation
areas, and the MRI-visualized HZ and scar showed that 10 of 13 the ablation areas were touching part of the HZ (Fig. 4). At least 1 ablation area was in the HZ in every animal. Three ablations areas were not located in the HZ: in 2 cases, success was not tested acutely after each RF application, but at the end of the procedure, after application of further ablations. In 1 case, continued inducibility was demonstrated after application of ablations and the off-line analysis revealed healthy myocardium surrounding the ablation lesions, thus demonstrating the ineffectiveness of that ablation area. In some cases, acute ablation did not cover the entire HZ, and there were gaps between the ablations, whereas in other cases the acute ablation did cover the entire HZ (Fig. 5).

Chronic effect of ablation

One animal had to be killed immediately, and a second animal 5 days after the ablation procedure, due to noncardiac medical issues. The remaining 5 animals underwent an EP evaluation with programmed stimulation 7 days after ablation. In 2 animals, no VT could be induced. In these animals, MRI showed that the HZ had been almost completely ablated (Fig. 5). In these 5 animals, the ejection fraction before and after ablation was not significantly different (41 ± 7 vs 35 ± 5, \( P = .16 \)), although there was a trend toward a decrease of the ejection fraction.

In 3 animals that had a total of 9 VTs before ablation, 5 different VTs were induced at the 1 week postablation study. Three VTs did not match the morphology of previously induced VTs, and 2 VTs were significantly slower than the VT ablated in the index procedure, but showed the same morphology. In these animals with inducible VT 1 week postablation, MRI confirmed that the HZ had not been completely ablated (Fig. 6). The HZ in these animals preablation was 1850 ± 680 mm³, and postablation the HZ was 1,720 ± 540 mm³.

Discussion

The main findings of this study are that: (1) contrast-enhanced MRI can define the HZ and can determine the location of ablated lesions with respect to the HZ, (2) successful ablation sites after an induced MI were in the area with tissue heterogeneity assessed by contrast-enhanced MRI, and (3) incomplete ablation of the HZ allows for recurrence of VT. In addition to recurrence of preablation VT morphologies with incomplete ablation of the HZ, changes of the VT morphology and/or cycle length can occur, likely due to changing the HZ, which changes the substrate of the VT. These findings are consistent, therefore, with the HZ being the critical substrate for VT.
The majority of patients with cardiac arrest have underlying structural heart disease. In the context of coronary artery disease, VT and VF are the most common presenting arrhythmias, accounting for up to 70% of cardiac arrests. In patients with previous MI, scar tissue may serve as a substrate for VT, most likely through areas of slow conduction due to intermingling of viable myocytes and fibrous tissue, leading to reentrant tachycardia.

Contrast-enhanced MRI is a valuable technique that allows for accurate delineation of scar tissue in patients with coronary artery disease. Yan et al demonstrated using in vivo MRI examinations with an 8-mm slice thickness that infarct tissue heterogeneity characterized by contrast-enhanced MRI is a powerful predictor of mortality in patients after MI. Subsequently, Schmidt et al showed that infarct tissue heterogeneity on contrast-enhanced MRI was the only significant predictor of inducibility of sustained monomorphic VT during programmed ventricular stimulation or device testing.

A recent study by Ashigaka et al evaluated the relation between 3D scar geometry assessed with contrast-enhanced MRI.

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**Figure 3**

A: Three-dimensional high-resolution image of a noninducible animal (ex vivo MRI). The scar is colorized in red, and the viable tissue is colorized in gray. There are very few islands of viable tissue in the scar. A2: Two-dimensional cross section through the scar (white) showing sharp edges. A3: Colorized image of B2 with scar shown in red and viable tissue shown in gray. B: High-resolution 3-dimensional image of an inducible animal (ex-vivo MRI). The scar is colorized in red, and the viable tissue is colorized in gray. There are numerous fingers and islands of viable tissue in the scar (arrows). B2: Two-dimensional cross section through the scar (white) showing complex, irregular edges with substantial viable tissue intermingled with the scar. B3: Colorized image of A2 with scar shown in red and viable tissue shown in gray. MRI = magnetic resonance imaging.

**Figure 4**

Anatomic relationships between the CARTO-CT-merge marked success site, and the MRI-visualized heterogeneous zone and scar. The CARTO-CT merged image with tagged ablation sites (A) was registered with the MRI (1 slice shown in B). The scar and heterogeneous zones (B, arrows) was then segmented (C, scar in blue, heterogeneous zone in yellow per Figure 2). The resulting image (D) is the fused composite of A, B and C. Offline matching between the CT image and MRI was done first using anatomical landmarks (mitral annulus plane, LV apex, and aortic root). The CARTO-CT-merged maps were then used to allow each CARTO map point to be located (via the CT) in a corresponding MRI slice. The success site for this ablation is shown in red, and is touching part of the heterogeneous zone. CT = computed tomography; LV = left ventricular; MRI = magnetic resonance imaging.
MRI, and VT reentry circuits in a swine model with chronic MI. MRI revealed scar with spatially complex structures containing a mixture of viable myocardium and scar tissue, with complex isthmuses of viable myocardium that serve as substrate for multiple VTs. In that study, a high-resolution post-mortem MRI was used to determine the heterogeneous structures in the peri-infarct zone.

This study supports the notion that tissue heterogeneity can be the underlying substrate for multiple morphologically distinct monomorphic VTs arising from the same region of the heart. The observation that patients with a prior infarction frequently have more than 1 morphology is well known. These morphologically distinct VTs can occur because of (1) a single reentry circuit used in 1 or in the opposite direction, or (2) the existence of a common intra-scar bridge of surviving myocardium connecting with different branches that have separate exits at the other side of the scar, or (3) the existence of more than 1 intra-scar bridge. In every case, the critical isthmus may be in a defined area with tissue heterogeneity. In this study, a number of tachycardias with multiple morphologies could be abolished successfully by ablation around a single location. In our study, nearly all VTs in each animal had nearly the same cycle length, suggesting that there was a single late conduction zone in otherwise healthy myocardium.

In our study, up to 5 VTs could be successfully ablated by placing lesions in 1 to 3 areas. Using the nonirrigated-tip catheter, the ablation lesions were small and nontransmural. In contrast, applications of 30 W RF energy, each for 60 seconds, with the irrigated-tip catheter obtained overall lesion volumes up to 3,162 mm³, which is consistent with lesion volumes recently reported. These volumes were larger than those of the HZ (Table 1), and could, therefore, be sufficiently large to ablate the entire HZ. Because the average ablated tissue volume was greater than that of the HZ (Table 1), substantial amounts of tissue outside of the HZ were ablated.

To the best of our knowledge, this is the first study showing that successful ablation sites for sustained VTs include areas of the HZ determined by MRI. Furthermore, this study strongly suggests that complementary MRI scar information may help to enhance success and shorten current VT ablation proce-
dures. It has already been shown that electroanatomical mapping focused on intracardiac electrogram characteristics was unable to predict transmural scar depth. Most importantly, 3D electroanatomic mapping, compared with MRI, provides only a rough delineation of infarct areas. Mismatch typically occurred in regions where achievement of catheter stability and good wall contact were technically challenging, as well as with nontransmural infarction. As a consequence, acquisition of incorrect electrogram signals resulted in an erroneous definition of scar contours. Thus, integration of accurate scar information by contrast-enhanced MRI could help to identify not only the infarct zone itself, but furthermore, the heterogeneous areas in the peri-infarct zone. Thesuccess rate. Concerns regarding decreases in myocardial function after ablation have not been confirmed in this study, which demonstrated that the ejection fraction 1 week after ablation was not significantly lower than before ablation. It is likely that the HZ is not of significance for ventricular function, and therefore, ablation of the HZ does not decrease the ejection fraction. In addition, extensive ablation of VT in patients, which likely consists of ablation inside and outside the HZ, has shown that there is not a significant decrease in ventricular function postablation.

Study limitations
The method we used for detection of VT exit sites with pace mapping has several limitations. The activation wave front from a site of origin that lies within a region of scar reaches the endocardial surface by conduction through preferential fibers. When pacing is performed, capture of the myocardium surrounding the catheter tip may result in a QRS complex that reflects local capture and that is different from the native QRS complex of the VT. As the porcine hearts are smaller relative to human hearts, and therefore the ablation lesions are relatively larger (Figs. 4 and 5), the spatial distribution may be

![Figure 6](image-url) In vivo and ex vivo (high-resolution) MRI in animals that were inducible (A) and not inducible (B) 1 week after ablation. Upper row: Preablation; semiautomatic algorithm for detection of HZ. Red = scar; green = HZ. Second row: One week postablation; in vivo MRI shows that substantial remnants of the HZ were still present in inducible animals (A) but minimal HZ was present in noninducible animals (B). Third row: Postablation; semiautomatic algorithm for detection of HZ. Red = scar, green = HZ. Lower row: Postablation; corresponding ex vivo MRI confirmed that remnants of tissue heterogeneity were present in inducible animals (A), compared with noninducible animals (B). HZ = heterogeneous zone; MRI = magnetic resonance imaging.
small enough that ablations guided by good pace mapping lead to noninducibility, which may not carry over exactly to humans. Finally, the complexity of this swine infarction model makes studying larger numbers of swine problematic. Due to double integration (CT-CARTO and CT-MRI images), it is possible to have more errors in image integration, which have an influence on image precision.

Study implications

Our findings raise several important issues that may have profound therapeutic implications and deserve further investigation. First, image-guided methods may help to identify and ablate the substrate initiating and maintaining VT in patients after an ischemic coronary event. An image-guided ablation procedure may become significantly shorter and more sensitive for the substrate itself and hence would increase the success rate and reduce recurrences. Furthermore, this type of technique may be especially helpful in patients with hemodynamically unstable VTs. It is becoming more acceptable to image patients who have an ICD or pacemaker with an acceptable risk/benefit ratio under controlled conditions, providing the opportunity to use this ablation technique in the near future also in patients with an implanted device.

Second, the existence of viable myocytes in a large peri-infarct zone may raise the interesting hypothesis that devascularization could be beneficial by reducing arrhythmogenic triggers, without loss of significant contractile function. Third, a better identification of high-risk patients for implantable cardioverter-defibrillator therapy may be warranted by identification of a large amount of HZ by MRI, owing to the potential for multiple reentry circuits in the peri-infarct zone, even if LV function is relatively well preserved.

Conclusion

These findings show that contrast-enhanced MRI can determine the location of ablated lesions with respect to the HZ, and support the hypothesis that tissue heterogeneity serves as the critical slow conduction substrate for VT. The HZ detected by MRI may be a promising ablation target to cure ischemic VTs. In addition, remnants of HZ after ablation may be the substrate for clinical relapses of VT.

Appendix

Supplementary data


References