Isolation of pulmonary veins using a thermoreactive implantable device with external energy transfer: Evaluation in a porcine model

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Abstract

Background: Pulmonary vein isolation (PVI) is a well-established method for the treatment of symptomatic paroxysmal atrial fibrillation, but is only partly successful with a high rate of electrical reconnection. We introduce a novel technique in which PVI is accomplished by noninvasive heating of a dedicated thermoresponse implant inserted into the pulmonary veins (PV), demonstrated in a porcine model.

Methods: A self-expanding nitinol-based implant was positioned in the common inferior PV of 11 pigs, using a fluoroscopy-guided transatrial appendage approach. Ablation was performed through contactless energy transfer from a primary extracorporal coil to a secondary heat ring (HR) embedded in the proximal part of the implant. Electrophysiological conduction was assessed prior to and postablation, and at 3 months. Histological samples were obtained acutely (n = 4) and after 3 months (n = 7).

Results: In total, 13 PV implants were successfully positioned in the inferior PVs of 11 animals. Ablation was performed without injury of adjacent structures. PVI and bidirectional block was electrophysiologically confirmed in all cases immediately at the time of implantation and 3 months later in seven chronic animals in whom testing was repeated. Marked evidence of ablation around the proximal HR was evident at 3 months postprocedure, with scar tissue formation and only mild neointimal proliferation.

Conclusions: Successful PVI can be obtained by external electromagnetic heat transfer to a novel pulmonary vein implant.

KEYWORDS
Ablation, atrial fibrillation, myocardial sleeve, stent

1 INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in human adults. The overall prevalence of AF is estimated between 1.5% and 2% of the general population.1 Furthermore, since AF can also be asymptomatic, the true prevalence of this disease is likely to be underestimated. Because AF is associated with a fivefold increased risk of stroke and a threefold increased incidence of heart failure, the impact of AF on patient well-being and societal health care expenditures is enormous.2,3 In the last two decades, pulmonary vein isolation (PVI) has become the preferred treatment of patients with paroxysmal atrial fibrillation. Current PVI techniques show 1-year success rates of
METHODS

Noninvasive temperature-controlled ablation

Animal model

Implant positioning

Principles of electromagnetic energy transfer

Noninvasive ablation procedure

2.1 Implant

We developed a self-expanding nitinol-based implant that ensures permanent fully circumferential contact with the PV wall. Three different regions are distinguishable: the active heating section or heat ring (HR), the connection part, and the stabilizing support part (Figure 1). As described below, the implant was placed into the proximal segment of the PV via a fluoroscopy-guided transatrial approach.

2.2 Principles of electromagnetic energy transfer (inductive power transmission)

The heating of the implant (and consequently tissue ablation) in the PVs is achieved through contactless transfer of energy from a primary transmitter coil (L1 in Figure 1) to a secondary receiver coil (L2 in Figure 1). The energy delivered to the primary coil originates from a 400-V three-phase mains supply. This supply is transformed by the converter (Easyheat 8310 LI, Ambrell, Scottsville, NY, USA) through the primary coil to generate the required electromagnetic field, which induces a current in the secondary coil. This current, depending on the electrical properties of the coil material, results in heating of the secondary coil (the implant). Using the converter, the amount of electromagnetic energy generated can be adjusted. The coupling factor (the energy transfer efficiency between coils) is approximately 2.1% at an operating frequency of 370 kHz. The coupling factor decreases with the cosine (cos) of the angle between the transmitter and receiver coil. Figure 1 shows the custom-made primary coil.

2.3 Noninvasive temperature-controlled ablation

As the extent of thermal injury is dependent upon the uniformity of contact between the HR and PV tissue, the local temperature achieved, and duration of the ablation, we assessed the temperature achieved through temperature sensors located between the HR and the venous tissue (which approximates the actual vein tissue surface temperature). We used the Opsens OTG-M170 fiberoptic sensor (Opsens, Quebec City, Canada) for temperature measurement. A two-lumen concept was utilized with the temperature sensor able to be freely repositioned to localize the optimal position for temperature feedback (Figure 1). When activating the electromagnet, using a test dose, small temperature increases were sought to determine the optimal position of the temperature sensor with respect to the implant. Using Comsol simulations, we calculated the temperature profile along an axial line between the implant and tissue.

2.4 Animal model

The porcine model was used for catheterization of the PVs. The breed chosen was a mixture between Landrace and Large white, and the animals were between 3 and 4 months of age, weighing between 60 and 65 kg. This age and size of the pigs was chosen so that they would fit inside the transmitter coil with an inner diameter of 30 cm. Eleven animals were used. All animals were orally preloaded with oral aspirin 300 mg and clopidogrel 300 mg at least 24 hours preprocedure, and were continued on aspirin 75 mg and clopidogrel 75 mg daily until termination of the trial.

2.5 Procedure

2.5.1 Experimental setting

Under general anesthesia, a left thoracic incision in lateral position was made and direct puncture of the left atrial appendage was performed. A sheath was placed over a guidewire. A second guidewire was placed through the sheath. The sheath was taken out of the left atrium and put in place again, but only over one of the two guidewires, thus providing direct sheath access to the left atrium (for placement of the temperature control system) and a guidewire for delivery of the implant. A guiding catheter was brought into the left atrium, and contrast dye was injected to visualize the antrum and PV ostia. Both guidewires were positioned distally into the common inferior vein. These images were stored and used as a guide. The outline of the PVs was drawn on the monitor, also as a guide. The PV diameter was then measured angiographically using a validated online quantitative system (Siemens, Munich, Germany), and the appropriate size of the implant was chosen. Implants were chosen to be ≥10% larger in diameter than the angiographic measurement.

2.5.2 Implant positioning

The implant was introduced into the PV and positioned at the atrio-pulmonary junction, specifically in the antrum of the PV ostium (at the transition between the ostium and left atrium, and the nonmuscular parts of the PV). Positioning and deploying of the implant was performed using angiography. After the implantation of the device, the transmitter coil was positioned in exactly the same plane as the heating segment of the implant.

2.5.3 Noninvasive ablation

Correct temperature probe positioning was performed using an ablation test dose. When the correct position was confirmed, the temperature probe was fixed, and the calculated ablation power was delivered over 3 minutes. The power needed was calculated using a proprietary algorithm, which incorporates the size of the implant, the measured expansion, and the calculated deviation from the perfect alignment of device and ablation coil in the same plane. The temperature probe was removed after 2 minutes, to also ensure ablation of the small space where the temperature probe was positioned between the implant and the PV wall.
2.5.4 | Verification

After the ablation, the position of the implant was again checked using angiography, to ensure the device had remained in the same position. Prior to and following the ablation, a 10-pole steerable diagnostic electrophysiologic (EP) catheter (Viacath, Biotronik, Berlin, Germany) was introduced into the PVs. Distal pacing was performed to check for exit block.

After removal of all catheters, four animals were sacrificed immediately, and seven at 3 months. The animals that survived were again catheterized at 3 months, and conduction block patency checked. Heart and lungs were carefully inspected macroscopically, and specimens of the PVs were histologically evaluated.

3 | RESULTS

3.1 | Animal characteristics

In total, 11 pigs were treated. In all animals, the antrum of the inferior PV was chosen as the ablation target. No major peri procedural complications occurred. A single implant was placed in 10 animals while two implants were placed in one animal. The sequence of the two implants being placed into the two PVs (i.e., left and right) from upper left to lower right is shown in Figure 2.

3.2 | Implants

Figure 2 shows an example of angiographic measurements prior to the implantation. Table 1 shows the procedural data. All implants were successfully positioned. In pig number 7, two implants in two different PVs were implanted. In pig number 11, one implant dislocated from the PV due to undersizing of the device, which embolized to the left atrium. Therefore, this animal was sacrificed immediately. Average duration of the procedure was $81 \pm 22$ minutes including surgery, catheterization, implant delivery, and ablation. The implantation and ablation process took $17 \pm 6$ minutes. After device implantation, the ablation coil was positioned over the animals. The coil was positioned such that the ablation coil and the implant were in the same plane. Deviations of the plane were fed into the algorithm described above and power/current delivered was adjusted accordingly. Temperature measurements were performed following a fixed protocol. Table 2 shows the current provided to the ablation coil and the temperatures reached during the procedures. The average temperature increase generated in the vessel wall was $8.9 \pm 6.8 ^\circ C$. Duration of ablation was $200 \pm 201$ seconds.
**FIGURE 2** Panel 1: Implantation sequence with two consecutive implants being placed into both pulmonary veins ostia (left and right) from upper left to lower right. Panel 2: Angiographic measurements of the antrum of the inferior pulmonary vein complex. (A) The reference measurement taken with the injection sheath (7 French) taken as actual reference. (B) The actual measurements and (C) the corresponding sites where the measurements were taken [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Procedural data of the 11 treated pigs

<table>
<thead>
<tr>
<th>Pig number</th>
<th>Age (months)</th>
<th>Size (kg)</th>
<th>Common PV size (diameter, mm)</th>
<th>Implant size (mm)</th>
<th>Successful placement of implant</th>
<th>Total procedural time (min)</th>
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<td>3</td>
<td>60</td>
<td>14</td>
<td>25</td>
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<td>80</td>
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<td>62</td>
<td>18</td>
<td>25</td>
<td>Yes</td>
<td>75</td>
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<td>60</td>
<td>21</td>
<td>30</td>
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<td>55</td>
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<td>70</td>
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<tr>
<td>11 (**)</td>
<td>3</td>
<td>61</td>
<td>23.5 (average of 20 (distal) and 27 (proximal))</td>
<td>30</td>
<td>Yes (**)</td>
<td>60</td>
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Note: *In pig number 7, two implants were positioned into two different pulmonary veins.
**First implant in this animal dislocated from the PV into the left atrium. PV = pulmonary vein.
TABLE 2  Temperature and data during testing and ablation

<table>
<thead>
<tr>
<th>Pig number</th>
<th>Core body temperature (°C)</th>
<th>VWT pre (°C)</th>
<th>Positioning test dose current (amp)</th>
<th>VWT Peak (°C)</th>
<th>Δ °C</th>
<th>Max Current (amp)</th>
<th>Duration of ablation (sec)</th>
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<td>1</td>
<td>33.4</td>
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<td>2</td>
<td>33.8</td>
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<td>150.4</td>
<td>40</td>
<td>6.2</td>
<td>302.4</td>
<td>180</td>
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<td>3</td>
<td>34.3</td>
<td>35.7</td>
<td>165.9</td>
<td>40</td>
<td>5.7</td>
<td>275.1</td>
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<td>33.5</td>
<td>35.2</td>
<td>243.6</td>
<td>38</td>
<td>4.5</td>
<td>390.0</td>
<td>180</td>
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<tr>
<td>5</td>
<td>35.9</td>
<td>Dislocated temp sensor</td>
<td>NA</td>
<td>NA</td>
<td>396.0</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>35.1</td>
<td>36.0</td>
<td>207.9</td>
<td>39.0</td>
<td>3.9</td>
<td>401.1</td>
<td>180</td>
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<tr>
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<td>36.5</td>
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<tr>
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<td>36.0</td>
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<td>201.6</td>
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<td>35.0</td>
<td>133.3</td>
<td>40</td>
<td>6.3</td>
<td>354.1</td>
<td>180</td>
</tr>
</tbody>
</table>

Note: Core body temperature = anal measurement of pig body temperature. VWT pre = vessel wall temperature prior to ablation; VWT-peak = peak temperature during ablation; Δ °C = Temperature increase.

TABLE 3  Results of sensing and pacing from a distal focus in the pulmonary vein before and after implantation and heating of the device

<table>
<thead>
<tr>
<th>Pig number</th>
<th>Signals recorded</th>
<th>Conduction of paced signals preablation</th>
<th>Conduction of paced signals postablation</th>
<th>Long-term persistence of conduction block (3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>+</td>
<td>-</td>
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<tr>
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<td>5</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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</tbody>
</table>

3.3  Electrophysiological testing

Prior to ablation, PV signals were detected distally from the HR in all animals, demonstrating intact conduction. After ablation, the same location was checked for entry and exit block. Bidirectional block was confirmed from the 11 tested PVs in 10 animals. EP characteristics are shown in Table 3.

3.4  Acute tissue injury evaluation

Four animals were sacrificed immediately, and seven were kept alive for 3 months. In the animals that were sacrificed immediately, the ablation zone was evaluated after removal of the implants for gross anatomical changes. A typical ablation zone is shown in Figure 3. No damage to the surrounding structures was observed in any of the four acute animals, nor in the seven chronic ones.

3.5  Histology

Histological data of the seven animals at 3 months postprocedure showed marked evidence of ablation around the proximal HR with loss of tissue architecture and scar tissue formation. There was no inflammation or necrosis adjacent to the mid and distal section of the implant. A mild degree (0.4 ± 0.7 mm) of neointimal proliferation was noted (Figure 3). Figure 3 demonstrates the Mallory-Azan-stained ablated myocardial sleeve tissue, in which ingrown fibrous connective tissue, due to the ablation procedure, is indicated by blue staining.

4  DISCUSSION

In this report, we have shown for the first time that complete PVI using an externally applied energy source is safe and feasible via a novel catheter-delivered implant. In this experiment, 11 animals received nitinol self-expanding implants into the antrum of the inferior PV without periprocedural complications. In all animals, the current test allowed establishing an optimal temperature-sensing zone, after which a full ablation current was applied. All treated PVs were electrically isolated without vascular necrosis or other evidence of damage to adjacent structures. No PV electrical reconnections occurred 3 months postablation in seven studied animals.

4.1  Ablation target

In contrast to current ablation modalities, this new approach targets the PVs via a permanent implant. PVI is achieved by uniform heating of the implant's proximal ring. Preliminary histological results show only
minimal intimal proliferation, suggesting that PV stenosis as a potential complication may be infrequent. As a result of expansion of the vein during implant deployment, a slight increase in PV size was seen, despite scar formation on the HR 3 months postablation.

Precise positioning of the HR potentially enables exact ostial isolation of the PVs in a safe manner. Current (antral) ablation techniques are often challenged by considerable differences in tissue thickness (posterior wall vs left atrial appendage ridge). If the perivenous myocardial tissue around the PVs itself can be targeted, application of a short uniform circumferential heating protocol should be sufficient to achieve PVI, as observed herein.

4.2 Potential advantage of a permanent implant

Currently, AF recurrence following PVI is thought to be mainly due to gap formation in the ablation zones or tissue recovery. Contributing factors are both patient related (PV anatomy, individual scar formation) and technique related (radiofrequency vs cryoablation, operator skill, etc.). In the present study, we sought to evaluate the PV reconnection rate in the presence of permanent implants, positioned slightly more to the ostial side of the traditional RF ablation zone. Theoretically, the chronic presence of the device would facilitate repeated electromagnetic heating should AF recur.

4.3 Externally delivered ablative energy

For the first time, we have demonstrated a method wherein the energy required for ablation is delivered from an external source to an indwelling implant, in contrast to current clinical strategies where radiofrequency or cryoablative energy is delivered locally from an indwelling catheter. The potential advantages of this new technique are multiple and include:

1. The amount of energy delivered can be tailored individually, depending on patient characteristics, size, and orientation of the implants.
2. The adjustment and calculation of the magnetic field results in focused heating of the implant without damaging surrounding structures.
3. A short ablation time (≤200 seconds) is needed for effective lesion formation.
4. Ablation may be performed offline. In case of recurrence, repeat ablation could be performed in an ambulatory setting.
5. Since the ablation target is located more distally in comparison to conventional techniques, formation of atrioesophageal fistulas is less likely to occur.\(^\text{10}\)

### 4.4 Limitations

This article describes the feasibility of a new technique with the potential to disrupt the way PVI procedures are performed. Especially the potential to simplify the procedure minimizing the use of complex mapping and ablation techniques are appealing. However, there are several limitations that deserve to be highlighted:

1. Separate energy delivery is needed for each implant, since setting of the magnetic field and positioning of the external coil need to be adjusted to each implant’s position and orientation. This could be completed in one procedure, however, as each ablation session is short.
2. Although the ablation itself is not invasive, positioning of multiple devices is. Nevertheless, shorter procedure times are possible than for current techniques.
3. This technique may not be sufficient for patients with persistent or long-standing persistent AF, since the underlying mechanism of AF may not be confined to the PVs.\(^\text{11}\)
4. Although all seven chronic animals were in apparent good health before sacrifice, we did not actively investigate the possibility of phrenic nerve injury.
5. AF ablation is not limited to PVI but this poses a limitation for this technology as no additional ablation lines can be applied with this technique.
6. In our study, we cannot conclude whether the stent implantation or ablation procedure was associated with thrombus formation. Therefore, prior to human trial initiation, further investigations using brain magnetic resonance imaging are needed to assess the risk of thromboembolization and potential brain injury.

### 4.5 Future developments

Several improvements in this technology are under investigation and need to be implemented in future studies. First, in this study, the PVs were approached through the transatrial approach. This will need to be adapted to a transseptal approach.\(^\text{12}\) Second, we implanted one single device per animal, while in humans up to four implants will be needed to achieve full PVI. However, in contrast to arterial stents that contain a considerable amount of metal to achieve sufficient radial support (and provoke substantial vascular responses), the present implants target expansion of venous structures. Therefore, these implants imply a much lower metallic burden and radial force and neointimal hyperplasia has been minimal.

In our experiment, the temperature sensor was placed adjacent to the implant, and was removed during the procedure. This may prove to be impractical when implants need to be placed into several PVs during the same procedure (as the temperature probe needs to be positioned through a separate guiding catheter for each PV). Other means for assessing the amount of energy delivered locally to the implant (and the temperature generated) are currently being developed. Flexible microelectronics could be added to the implant, allowing real-time in situ temperature feedback during ablation, electrical signal recognition, and even detection and monitoring of acute and chronic intracardiac electrocardiographic signals (to derive a 12-lead electrocardiogram), to monitor for AF recurrence, etc. Position and orientation of the implant with respect to the transmitter coil is of high importance. Currently, it is difficult to find the optimal position of the transmitter coil for efficient and homogenous heating of the implant. Three-dimensional (3D) mapping or other visualization techniques should improve or overcome this limitation.

The entire procedure took on average 81 minutes, including positioning of the ablation coil around the animal, which proved cumbersome and often required 30–40 minutes. Significantly shorter procedure times are expected in the future. However, complete electrical isolation would require an implant in each PV. In our study, conduction block acutely and at 3 months was demonstrated via pacing on both sides of the ablation ring. Long-term validation is needed using a 3D electromagnetic mapping system to confirm a closed circumferential ablation line as well as bidirectional block.

### 5 CONCLUSIONS

In the present study, we have demonstrated that implantation of a self-expanding nitinol-based device in the PVs is safe and feasible, and that energy can be delivered to the implant in a noninvasive, controlled manner, achieving bidirectional conduction block without complications. Compared to contemporary techniques to achieve AF ablation, this device may provide advantages including ease of use, consistency of effect, and repeatability, if necessary. Further device iterations and technique modifications are ongoing to improve the utility of this novel approach.

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### REFERENCES


