Pulmonary Vein Stenosis After Catheter Ablation
Electroporation Versus Radiofrequency

Vincent J.H.M. van Driel, MD*; Kars G.E.J. Neven, MD, PhD*; Harry van Wessel, BSc;
Bastiaan C. du Pré, MD; Aryan Vink, MD, PhD; Pieter A.F.M. Doevendans, MD, PhD;
Fred H.M. Wittkampf, PhD

Background—Radiofrequency ablation inside pulmonary vein (PV) ostia can cause PV stenosis. A novel alternative method of ablation is irreversible electroporation, but the long-term response of PVs to electroporation ablation is unknown.

Methods and Results—In ten 6-month-old pigs (60–75 kg), the response of PVs to circular electroporation and radiofrequency ablation was compared. Ten consecutive, nonarcing, electroporation applications of 200 J were delivered 5 to 10 mm inside 1 of the 2 main PVs, using a custom-deflectable, 18-mm circular decapolar catheter. Inside the other PV, circular radiofrequency ablation was performed using 30 W radiofrequency applications via an irrigated 4-mm ablation catheter. PV angiograms were made before ablation, immediately after ablation, and after 3-month survival. PV diameters and heart size were measured. With electroporation ablation, PV ostial diameter decreased 11±10% directly after ablation, but had increased 19±11% after 3 months. With radiofrequency ablation, PV ostial diameter decreased 23±15% directly after ablation and remained 7±17% smaller after 3 months compared with preablation diameter despite a 21±7% increase in heart size during aging from 6 to 9 months.

Conclusions—In this porcine model, multiple circumferential 200-J electroporation applications inside the PV ostia do not affect PV diameter at 3-month follow-up. Radiofrequency ablation inside PV ostia causes considerable PV stenosis directly after ablation, which persists after 3 months. (Circ Arrhythm Electrophysiol. 2014;7:734-738.)

Key Words: catheter ablation ● complications ● electroporation ● pulmonary veins ● radiofrequency

Circular electroporation ablation is a novel technique for pulmonary vein (PV) isolation. In a previous animal study, feasibility and safety of circular electroporation for the creation of PV lesions were investigated after a 3-week survival period. One to 4 sequential, nonarcing, electroporation applications of 200 J eliminated PV electrograms in most ostia. However, the long-term risk of PV stenosis after electroporation ablation is still unknown.

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From the Departments of Cardiology (V.J.H.M.v.D., K.G.E.J.N., H.v.W., B.C.d.P., P.A.F.M.D., F.H.M.W.) and Pathology (A.V.), University Medical Center, Utrecht, The Netherlands; and Department of Rhythmology, Alfred Krupp Hospital, Essen, Germany (K.G.E.J.N.).
*Drs van Driel and Neven contributed equally to this work.
Correspondence to Vincent J.H.M. van Driel, MD, Division of Heart and Lungs, Department of Cardiology, University Medical Center, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail vjhmvandriel@gmail.com
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The porcine left atrium (LA) has 2 PVs suitable for circular catheter ablation: 1 right or septal PV (RPV) and 1 inferior PV (IPV; Figure 1). The RPV enters the LA in close proximity to the atrial septum and fossa ovalis. Before their entrance into the LA, multiple branches merge into a common RPV tubular segment of ≈10 to 15 mm in length. The IPV has ≈12-mm-long tubular segment, and the RPV has ≈15-mm-long tubular segment after the confluence of a septal and a lateral branch (Figure 1).

First, a coronary sinus catheter was inserted via the right jugular vein as fluoroscopic reference for transseptal access. A quadrupolar catheter was inserted via the right jugular vein into the right ventriculo-apex for backup pacing. Transseptal puncture was performed through the right femoral vein. A deflectable 8F sheath (Agilis; St Jude Medical, Minnetonka, MN) facilitated LA catheterization. A temporary screw-in pacing wire (6416; Medtronic Inc, Minneapolis, MN) was inserted via the right femoral vein and fixated in the atrial septum to serve as positional reference for the NavX 3D Navigation system (St Jude Medical).

The LA geometry (including part of the PVs) was reconstructed using the NavX system and a standard deflectable quadrupolar irrigated ablation catheter with a 4-mm distal electrode (Thermocool; Biosense Webster Inc, Diamond Bar, CA). Thereafter, angiography of both PVs was performed using the antero-posterior, 30° right anterio-oblique, and 30° left anterior oblique projections for the IPV, and antero-posterior, 30° cranial, and 30° caudal projections for the RPV. After PV angiography, both PVs were alternately ablated using either electroporation or radiofrequency energy.
Electroporation Ablation

A custom-deflectable, 7F, 18 mm, circular decapolar electroporation catheter containing 2 mm ring electrodes separated by 4 mm spacing was introduced through the deflectable sheath in the right femoral vein (Figure 2). This catheter was deployed in the common tubular segment of 1 of the 2 PVs. Inside the PV, 10 cathodal 200-J shocks were delivered between all electrodes of the electroporation catheter and a large indifferent skin electrode (7506; Valley Laboratory Inc, Boulder, CO) on the shaved lower back. An external, monophasic defibrillator (Lifepak 9; Physio-Control Inc, Redmond, WA) was used for energy delivery.\(^1\,\,^3\,\,^4\) During each application, current and voltage waveforms were recorded on a dual channel oscilloscope (Tektronix TDS 2002B, Beaverton, OR). For each ablation, a different position of the electroporation catheter was chosen to cover the complete tubular segment. Ten applications of 200 J were always delivered even when all PV electrograms had already been eliminated. All electroporation catheter positions were stored with the NavX system. After each application, the circular electroporation catheter was reconnected to the NavX and electrophysiological recording system (Cardiolab; General Electric Healthcare, Waukesha, WI) to check electrode integrity and to visualize the electrode positions on the NavX system.

Radiofrequency Ablation

The other PV was circumferentially ablated approximately in the middle of the common tubular segment using sequential 30 W radiofrequency applications delivered via the 4-mm irrigated ablation catheter and a saline flow rate of 17 mL/min. Maximal electrode temperature was set at 42°C. Intentionally, maximal radiofrequency duration per vein was set at 15 minutes. PV isolation was not the objective or end point for electroporation or radiofrequency ablation.

PV angiography was performed directly after ablating both PVs using the same fluoroscopic settings as the preablation PV angiograms.

Follow-Up

All catheters were removed and the animals were allowed to recover and kept under daily surveillance. After a 3-month survival period, PV angiography was repeated in all animals using the same techniques as described above. Thereafter, the animals were euthanized by exsanguination.
before ablation, directly after ablation, and at 3 months and in all 3 projections. When PV narrowing was obvious at 3 months, PV diameters were always measured at that location. When no narrowing was visible, all measurements were taken in the middle of the common tubular segment. All measurements were taken at the end-systolic phase (maximal PV filling and diameter). Diameters measured in the 3 projections were averaged to obtain 1 value for the PV diameter. The percent change in PV diameter was calculated relative to the preablation diameter. 

As a measure of heart size, the largest transversal heart diameter was measured from the preablation and 3-month angiograms taken in the antero-posterior projection.

### Statistical Analysis

Data are expressed in mean±SD or as mean (95% confidence interval). A P value of 0.05 was used as the level of statistical significance. Special software (SPSS Statistics 20; IBM Inc, Armonk, NY) was used for statistical analysis. A repeated-measures ANOVA of percentage change in diameter was performed to compare the radiofrequency and electroporation ablation measurements between the 3 independent and blinded investigators. The effect of ablation technology on the presence of a (part of the) myocardial sleeve in histological sections, corrected for depth of those sections, was investigated in a binary logistic mixed model. The growth in heart size between the acute and 3-month procedure was investigated with a paired t test.

### Results

None of the electroporation applications resulted in catheter or electrode failure. All shocks resulted in smooth voltage and current waveforms, demonstrating the absence of arcing and barotrauma. The 3-month survival period was uneventful in all animals. Because of technical difficulties, IPV angiography postablation was not performed in 2 animals.

Average radiofrequency application time was 12.3±5.9 minutes. In 2 IPVs (animal #2 and #4), >15 minutes of radiofrequency was necessary to complete the circle because of frequent catheter dislodgement.

### Angiographic Analysis

Repeated-measures ANOVA showed no significant interaction between investigators and methods (P=0.35). With radiofrequency ablation, PV diameters decreased 23±15% directly after ablation and remained 7±17% smaller after 3 months, when compared with preablation diameters. An example of RPV diameter change after radiofrequency ablation is shown in Figure 3. Directly after electroporation ablation, PV diameters decreased 11±10%, but had increased 19±11% after 3 months, when compared with preablation diameters (Figure 4). Repeated-measures ANOVA demonstrated a highly significant difference in long-term (3 months) response between radiofrequency and electroporation ablation (26%; P=0.006; 95% confidence interval, 9.54–42.01; Table). The acute change in PV diameter was not statistically analyzed.

Duringaging of animals from 6 to 9 months, the heart diameter, measured in the anterior-posterior projection, increased 21±7% (P<0.001; Figure 4).

### Histological Analysis

Because of various reasons, unrelated to the degree of PV stenosis, 3 hearts were not available for histological analysis of PV sleeves. Of the remaining hearts, 1 IPV had accidentally been cut off during heart explantation. Consequently, only 7 RPVs and 6 IPVs could histologically be analyzed for the

### Table. Data of the 10 Animals

<table>
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<tr>
<th>Animal</th>
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<th>Ablation Method</th>
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<th>3 mo, mm</th>
<th>Change, %</th>
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<td>20.4</td>
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</table>

Pulmonary vein (PV) diameters before ablation and after 3-mo survival were measured by angiography. The percentage change in diameter is listed. At 3 mo, the average change in PV diameter was −7±17% with radiofrequency (RF) ablation and +19±11% with circular electroporation (CE) ablation. IPV indicates inferior PV; and RPV, right PV.
lesions.4 Median sleeve coverage in these PVs was 0% at all 3 sleeve, only minor intimal hyperplasia was present, comparable at 4, 8, and 12 mm distance from the PV antrum, respectively. Ablation, the median sleeve coverage was 40%, 13%, and 0%.

Of these 13 PVs, 7 had been treated with radiofrequency and 6 with electroporation. The 3 control PVs from 2 untreated pigs revealed complete sleeve coverage and normal vessel wall. The PV treated with RF shows a partially undamaged myocardial sleeve, intimal proliferation, necrotic myocardium, and proliferation of the elastic lamina. In addition, the vein is surrounded by scar tissue. The PV treated with electroporation shows a completely ablated myocardial sleeve surrounded by healthy connective tissue. The differences in luminal area or shape of the pulmonary vein (PV) in A versus C and E is the result from minor differences in fixation technique.

Discussion

In this porcine animal model, electroporation and radiofrequency ablation were purposely delivered inside the PVs to provoke stenosis. In the absence of previous porcine studies about PV stenosis or narrowing in response to radiofrequency ablation, we alternated circular radiofrequency and electroporation ablation between the 2 suitable PVs, thereby using the animals as their own control. Despite a significant growth of the animals and heart size (21±7%) during aging from 6 to 9 months, PVs that had been ablated with radiofrequency reduced in diameter, whereas those ablated with electroporation grew in size (−7±17% versus +19±11%; P=0.006).

Given the large myocardial lesions obtained with circular 200-J electroporation ablation in previous studies, histological analysis of the PVs was not part of the original study protocol.1,3 This analysis was later added to the protocol to be absolutely sure about the effectiveness of electroporation ablation. However, 3 hearts were no longer available. Data of the histological sections of 13 PVs from the remaining 7 hearts suggest that the absence of PV stenosis with electroporation ablation is not because of ineffective applications.

With focal trigger ablation and ostial PV isolation using radiofrequency energy in humans as originally described by Haïssaguerre et al,8 PV stenosis did occur in a relatively large number of patients (≤27%).6–8 With segmental PV isolation, PV stenosis still did occur in ≤2% of patients.10 Wide area circumferential ablation of the PV antrum has significantly reduced this incidence, but still is associated with a 0.4% risk of PV narrowing.11

Results of the present study suggest that PV stenosis may not be an issue with circular electroporation ablation at the settings used in the present study, even when it is (accidentally) performed inside PVs.

Electric PV isolation was not the end point of our radiofrequency and electroporation applications. The shift from ostial to antral radiofrequency ablation has reduced the incidence of PV stenosis after PV isolation with radiofrequency energy.12 This suggests that not PV isolation but the depth of the application inside the PV relates to the risk of PV stenosis.

PV stenosis is a well-known complication for thermal ablation.5–12 With 10 circular 200-J applications inside the PVs, we tried hard to provoke such a response. Although difficult to compare, total energy delivered with electroporation was 2,000 J, whereas 10 minutes of radiofrequency at 30 W results in a total energy delivery of 18,000 J. With this in mind, our histological data suggest that electroporation is far more effective in ablating the myocardial sleeve.

The histological analysis of PVs treated with radiofrequency versus electroporation showed that radiofrequency-treated PV sections had more unaffected myocardial sleeve as compared with electroporation-ablated PV sections. This suggests that, at least, not more myocardial sleeve was ablated with radiofrequency than with electroporation. Next, similar to the article of Taylor et al,3 we analyzed the presence of pathological changes associated with PV stenosis. We found that PVs treated with radiofrequency had intimal proliferation, necrotic myocardium, proliferation of the elastic lamina, and large amounts of scar tissue surrounding the myocardial sleeve, whereas electroporation-ablated PVs only showed minor intimal proliferation, comparable with our previous report.6

Figure 5. Elastic van Gieson stained sections of a control pulmonary vein (PV; A and B), a PV treated with radiofrequency (RF) ablation (C and D), and a PV treated with 10 circular electroporation applications (E and F). B, D, and F, Magnifications of A, C, and E, respectively. The control PV shows complete sleeve coverage and normal vessel wall. The PV treated with RF shows a partially undamaged myocardial sleeve, intimal proliferation, necrotic myocardium, and proliferation of the elastic lamina. In addition, the vein is surrounded by scar tissue. The PV treated with electroporation shows a completely ablated myocardial sleeve surrounded by healthy connective tissue. The differences in luminal area or shape of the pulmonary vein (PV) in A versus C and E is the result from minor differences in fixation technique. *Undamaged myocardial sleeve; †healthy connective tissue; ºscar tissue surrounding the PV; %ablated myocardial sleeve; §intimal hyperplasia; #proliferation of elastic lamina.

presence of a myocardial sleeve 3 months after ablation. In total, 37 of 39 histological sections made from these 13 PVs were eligible for analysis. Of these 13 PVs, 7 had been treated with radiofrequency and 6 with electroporation. The 3 control PVs from 2 untreated pigs revealed complete sleeve coverage and normal vessel wall of the vein (Figure 5A and 5B). In the histological sections of the PVs treated with radiofrequency, scar tissue surrounded the PV (Figure 5C). In addition, intimal proliferation, necrotic myocardium, and proliferation of the elastic lamina were found (Figure 5D), comparable with previous findings of Taylor et al.3 Three months after ablation, the median sleeve coverage was 40%, 13%, and 0% at 4, 8, and 12 mm distance from the PV antrum, respectively.

Conversely, the PVs treated with IRE ablation are surrounded by healthy connective tissue. Apart from the ablated myocardial sleeve, only minor intimal hyperplasia was present, comparable with our findings with coronary arteries inside electroporation lesions.5 Median sleeve coverage in these PVs was 0% at all 3 depths. With radiofrequency, the myocardial sleeve was totally absent in 9 of 20 sections, whereas with electroporation, the myocardial sleeve was absent in 14 of 17 sections (P=0.01; odds ratio, 16.96; 95% confidence interval, 2.0–142.7).
Despite the higher amount of successfully ablated myocardial sleeve, histological changes associated with PV stenosis seem to be less present in the electroporation-ablated PVs. These findings also correspond with our previous results, which showed that myocardial tissue is more prone to electroporation damage as compared with other structures, such as connective tissue. This demonstrates that scarring of connective tissue surrounding the PV is the explanation for PV stenosis after radiofrequency ablation.

Acute narrowing after radiofrequency application may relate to heat. Clinically, radiofrequency ablations will never or only rarely be performed inside the common tubular segment of PVs, and therefore, acute PV stenosis in humans may have only infrequently been reported. With electroporation ablation, holes in the cell membrane may cause acute depolarization and contraction as suggested by coronary spasm that we observed directly after epicardial applications on these arteries in other still unpublished studies. However, this resolved spontaneously <30 minutes.

Limitations

Differences in anatomy and architecture between human and porcine LAs and PVs are a serious limitation for this study. To the best of our knowledge, a porcine model has never been used to study the effects of ablation on PV diameter. Therefore, the animals were used as their own control by alternating electroporation and radiofrequency energy between the 2 PVs.

The fundamental cause of PV narrowing is still unknown, and therefore, one cannot be sure that a porcine model using young animals is valid for the elderly human population.

In this study, we used quantitative PV angiography to assess the degree of PV stenosis. Although quantitative PV angiography is a widespread and commonly used method to assess the degree of luminal stenosis, PV angiography using computed tomography may have been more accurate, but this technology was not available in our animal facility.

Conclusions

In this porcine model, multiple circular 200-J electroporation ablations inside PVs did not affect PV diameter at 3-month follow-up. Conversely, radiofrequency ablation inside PVs caused considerable PV stenosis, because of scarring of connective tissue surrounding the PV.

Acknowledgments

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Disclosures

F.H.M. Wittkampf is a consultant for St Jude Medical, Atrial Fibrillation division. Both F.H.M. Wittkampf and H. van Wessel are coinventors of circular electroporation. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

Despite the use of advanced 3-dimensional mapping systems, pulmonary vein (PV) stenosis remains one of the potential complications of PV isolation using radiofrequency ablation. Circular electroporation ablation is a novel technique for PV isolation. It has been proven that one 6-ms, 200-J electroporation application can isolate a PV. However, the long-term risk of PV stenosis after electroporation ablation is still unknown. In this porcine model, multiple circular 200-J electroporation ablations inside PVs did not affect PV diameter at 3-month follow-up. Conversely, radiofrequency ablation inside PVs caused considerable PV stenosis, because of scarring of connective tissue surrounding the PV. The clinical implementation of circular electroporation ablation as a novel, effective, and very fast technique for PV isolation could, therefore, be performed safely, without the risk of PV stenosis.
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