Multielectrode Contact Measurement Can Improve Long-Term Outcome of Pulmonary Vein Isolation Using Circular Single-Pulse Electroporation Ablation

Marijn H.A. Groen⍟, PhD; Vincent J.H.M. van Driel⍟, MD, PhD; Kars Neven⍟, MD, PhD; Harry van Wessel, BSc; Jacques M.T. de Bakker, PhD; Pieter A.F. Doevendans⍟, MD, PhD; Fred H.M. Wittkampf⍟, PhD; Peter Loh⍟, MD, PhD; René van Es⍟, PhD

BACKGROUND: Irreversible electroporation (IRE) ablation is generally performed with multielectrode catheters. Electrode-tissue contact is an important predictor for the success of pulmonary vein (PV) isolation; however, contact force is difficult to measure with multielectrode ablation catheters. In a preclinical study, we assessed the feasibility of a multielectrode impedance system (MEIS) as a predictor of long-term success of PV isolation. In addition, we present the first-in-human clinical experience with MEIS.

METHODS: In 10 pigs, one PV was ablated based on impedance (MEIS group), and the other PV was solely based on local electrogram information (EP group). IRE ablations were performed at 200 J. After 3 months, recurrence of conduction was assessed. Subsequently, in 30 patients undergoing PV isolation with IRE, MEIS was evaluated and MEIS contact values were compared to local electrograms.

RESULTS: In the porcine study, 43 IRE applications were delivered in 19 PVs. Acutely, no reconnections were observed in either group. After 3 months, 0 versus 3 ($P=0.21$) PVs showed conduction recurrence in the MEIS and EP groups, respectively. Results from the clinical study showed a significant linear relation was found between mean MEIS value and bipolar dV/dt ($r^2=0.49$, $P<0.001$), with a slope of 20.6 mV/s per Ohm.

CONCLUSIONS: Data from the animal study suggest that MEIS values predict effective IRE applications. For the long-term success of electrical PV isolation with circular IRE applications, no significant difference in efficacy was found between ablation based on the measurement of electrode interface impedance and ablation using the classical EP approach for determining electrode-tissue contact. Experiences of the first clinical use of MEIS were promising and serve as an important basis for future research.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: catheter ■ electric impedence ■ electrode ■ electroporation ■ pulmonary vein

Recently, single-pulse irreversible electroporation (IRE) ablation has been introduced as a novel method for pulmonary vein (PV) isolation (PVI).[1,2] With monopolar single-pulse IRE, a millisecond current pulse is delivered between a multielectrode circular catheter and an indifferent skin patch. Previous studies showed that IRE is capable of creating deep continuous circular lesions.[3,4] Recently, two clinical trials were

Circulation: Arrhythmia and Electrophysiology is available at www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- Irreversible electroporation is a promising alternative to the currently used thermal ablation methods for cardiac ablation.
- It is thought that electrode-tissue contact, or at least proximity, is important for ablation efficacy.

WHAT THE STUDY ADDS

- Contact values as measured by the multielectrode impedance system can improve long-term ablation outcome.
- Experiences of the first clinical use of the contact system were promising and serve as an important basis for future research.

Nonstandard Abbreviations and Acronyms

IPV	inferior pulmonary vein
IRE	irreversible electroporation
LA	left atrium
MEIS	Multielectrode Impedance System
PV	pulmonary vein
RA	right atrium

performed in which single-pulse IRE ablation was used to perform PVI in a total of 30 patients suffering from atrial fibrillation.[2,5]

PVI is most often performed using radiofrequency energy. With radiofrequency ablation, an alternating current lead to resistive heating at the electrode-tissue interface and secondary heat conduction into the surrounding tissue. Multiple studies have shown that electrode-tissue contact, measured using contact force catheters, is an important parameter to predict the efficacy of radiofrequency ablation.[6–8] With IRE ablation, delivered current in combination with the local specific resistance determines the local current density and field strength, which will, in turn, determine the lesion size.[9] Since the electrical resistance of blood is lower than that of cardiac tissue, a large part of the current will travel through the blood rather than into the tissue with a catheter positioned in the left atrium (LA). Therefore, it is believed that electrode-tissue contact, or at least electrode-tissue proximity, is an important factor that influences IRE ablation efficacy.

Measurement of electrode-tissue contact force for each separate electrode of a multielectrode catheter is technically challenging and not yet available. In a previous study, we demonstrated a novel electrical method (multielectrode impedance system [MEIS]) to measure electrode-tissue contact with circular multielectrode catheters.[10] Briefly, with the MEIS system, a small steering current is applied between 2 neighboring electrodes on the catheter, whereas the voltage is measured between each electrode and an indifferent skin patch. By dividing the measured voltage by the steering current at each individual electrode, the local impedance can be calculated. Because the impedance of tissue is higher than that of blood, a higher impedance is measured when the catheter electrodes are in contact with tissue.

The aim of this article is to study the feasibility of determining electrode-tissue contact using the MEIS system as a predictor of long-term success of PV isolation, in a long-term porcine study. In addition, during the first-in-human study using single-pulse IRE ablation, MEIS values were measured throughout the procedure. In this article, the first experience of the clinical use of the MEIS system is presented.

METHODS

Data that support the findings of this study and are not available within the article are available from the corresponding author upon reasonable request.

Multielectrode Impedance System

The MEIS system simultaneously measures and displays individual electrode interface impedance (MEIS value) of all catheter electrodes. To distinguish between good contact and no contact, a reference measurement was performed. Based on fluoroscopy and electrograms, part of the electrodes was gently pushed against the LA endocardial wall (upper limit) while the other electrodes remain free-floating (lower limit).

During the procedure, the degree of electrode-tissue contact between the upper and lower limit per electrode is displayed on the screen of the multielectrode impedance system by color-coding the individual catheter electrodes depending on measured contact (Figure 1).

Porcine Study

Animals

All animal experiments were performed with approval from the Animal Experimental Ethical committee of the University Medical Center Utrecht. In 10 Dalland landrace pigs (60–75 kg), calcium carbasalate (80 mg/d) and clopidogrel (75 mg/d, after a loading dose of 300 mg) therapy was started 3 days before the procedure and continued until euthanasia. Amiodarone therapy was started 1 week before the procedure (600 mg/d) and continued on a 400-mg/d schedule to prevent procedure-related arrhythmias until euthanasia. The animals were intubated and anesthetized according to standard procedures. Transseptal puncture for access to the LA cavity was performed via the right femoral vein. An 8.5F deflectable sheath (Agilis, St. Jude Medical, Minnetonka, MN) was used to facilitate access to PV ostia.

Preablation Procedure

Fluoroscopic angiography of the right PV and inferior PV (IPV) was performed in the anterior-posterior direction and the location of PVs and ostia were marked. Under fluoroscopic guidance, a 7F 20-mm circular decapolar deflectable
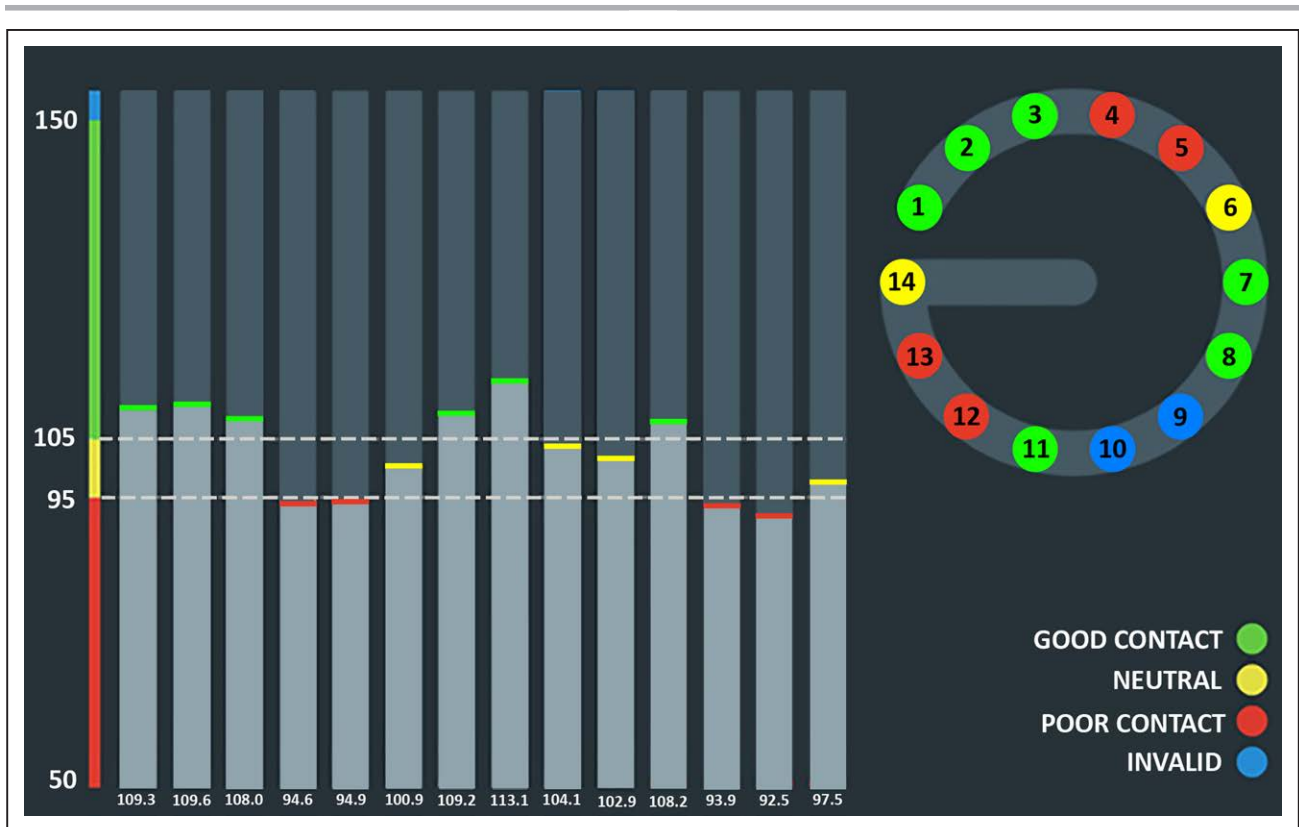
Figure 1. Example of the multielectrode impedance system (MEIS) software as used during the clinical trial.
On the **right** side, an overview of the 14-polar circular catheters is shown. On the **left** side, individual MEIS values per electrode are displayed in a bar graph. The higher (good contact, 105 in this case) and lower (poor contact, 95 in this case) values can be adjusted manually per procedure. Of note: during the animal experiments a decapolar catheter was used and therefore the unused electrodes are displayed as having an impedance of 0.

electroporation catheter with 2-mm electrodes (Figure 2A) was introduced via an 8.5F deflectable sheath into the LA. Placement of the catheter was anatomically guided by the previously obtained PV angiogram and LA geometry reconstructed with the NavX (St. Jude Medical, Inc.) 3-dimensional electro anatomic mapping system. First, the PV was mapped until the complete loss of local electrograms. Proximal from that location (around the antrum), the ablation position was determined. PV entrance and exit conduction were determined using standard electrophysiological (EP) criteria.
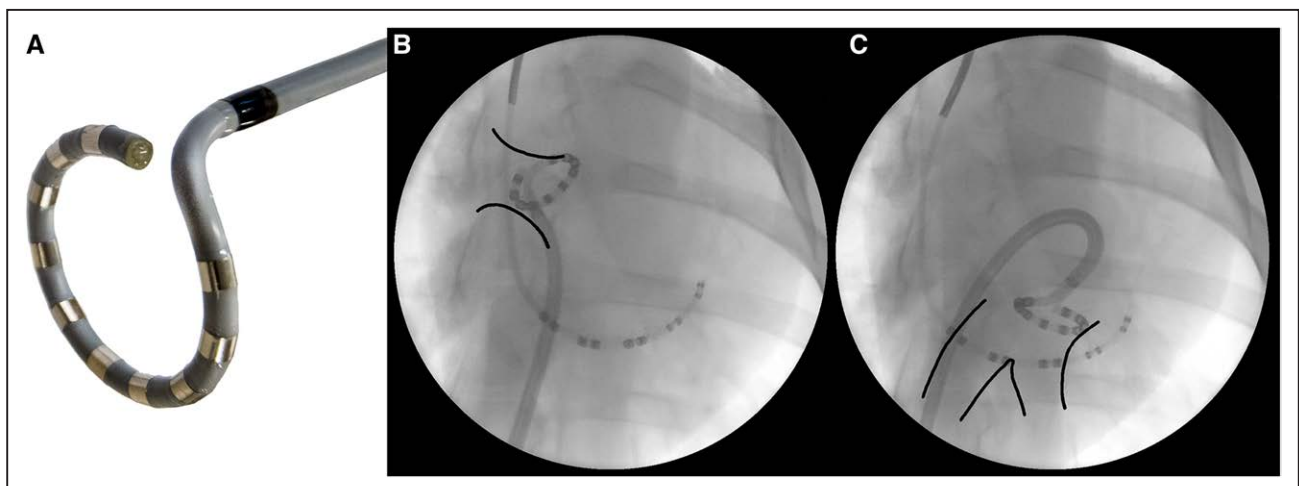

Figure 2. Details of circular catheter and positioning inside the left atrium during the porcine study.
A, The 20-mm circular decapolar catheter that was used to perform the ablations during the preclinical study. **B**, Anterior-posterior fluoroscopic image. The circular catheter is in the right pulmonary vein (RPV). The black lines indicate the marked RPV ostium as obtained using a fluoroscopic contrast agent. **C**, Anterior-posterior fluoroscopic image. The circular catheter is in the inferior pulmonary vein (IPV). The black lines indicate the marked IPV ostium.

Study Design

In the intervention group, in 1 of the 2 PVs, the MEIS values were presented to the operating physician. MEIS values were the sole parameter to decide about additional energy applications. For each vein, maximum electrode MEIS values before successive applications were noted on a 12 hours segmented circle to assist the operating physician in covering the complete venous perimeter with good contact ablations (MEIS group).

In the control group, the applications were delivered based not only on classical EP criteria, like local electrograms that suggested the absence or presence of remaining intact PV sleeve sections, but also on the opinion of the operating physician based on the anatomic 3-dimensional map and fluoroscopy that the complete ostial perimeter was covered during IRE applications (EP group).

Ablation Procedure

The energy (200 J) was delivered using a monophasic external defibrillator (Lifepak 9, Physio-Control, Inc; Redmond, WA). A skin patch (7506, Valleylab, Inc; Boulder, CO) was used as indifferent electrode. Voltage and current waveforms of each energy application were stored on a digital oscilloscope.[1] All catheter positions just before IRE applications were stored fluoroscopically (Figure 2B and 2C) and tagged on the NavX geometry. Electrode interface impedance of all catheter electrodes at 200 Hz were stored continuously.

Follow-Up

Thirty minutes after completing ablation of both veins, bidirectional electrical isolation of both PVs was assessed. The decapolar circular catheter was positioned just distally to the ablation area and the presence of PV potentials was assessed. Bipolar stimulation via all electrode pairs of the circular ablation catheter was applied to detect conducting myocardial sleeve remnants. PV reconnection was presumed if stimulation with 10 mA, 2 ms pacing led to LA capture. Three months after ablation,

the animals were recatheterized and bidirectional electrical isolation of both PVs, and the approximate location of the site of reconnection was assessed as described above. The operators were blinded for the used ablation protocol. Then, all animals were euthanized by exsanguination. The heart was removed and inspected macroscopically.

Data Analysis Porcine Study

Tissue Contact During Ablation

The perimeter of both PV ostia was divided into 12 equal segments (Figure 3). Using the anterior-posterior fluoroscopic images, and NavX to differentiate anterior from posterior positions, 2 observers blinded for study outcome allocated the location of each of the 10 electrodes before each IRE application to a single distinct segment. When multiple IRE applications had been performed in a single PV, the highest recorded electrode impedance per segment was used as the measure of tissue contact. Subsequently, for each of the 12 segments, a MEIS value below the lower reference value was scored as poor; a value above the higher reference value was scored as good.

Reconnections

Sites of reconnection determined during the follow-up procedure were allocated to one of possible four sections (Figure 3). Each of the 4 sections contains 3 electrode segments. Based on the MEIS scores per electrode segment, the contact score per section was determined according to the following protocol. If ≥1 of 3 segments located inside the section was scored as poor, the entire section was scored as poor. In the final analysis, reconnection per section was compared with the contact score per section.

Clinical Pilot

Data were obtained in 30 patients who underwent PVI using single-pulse IRE during clinical studies which were approved by the
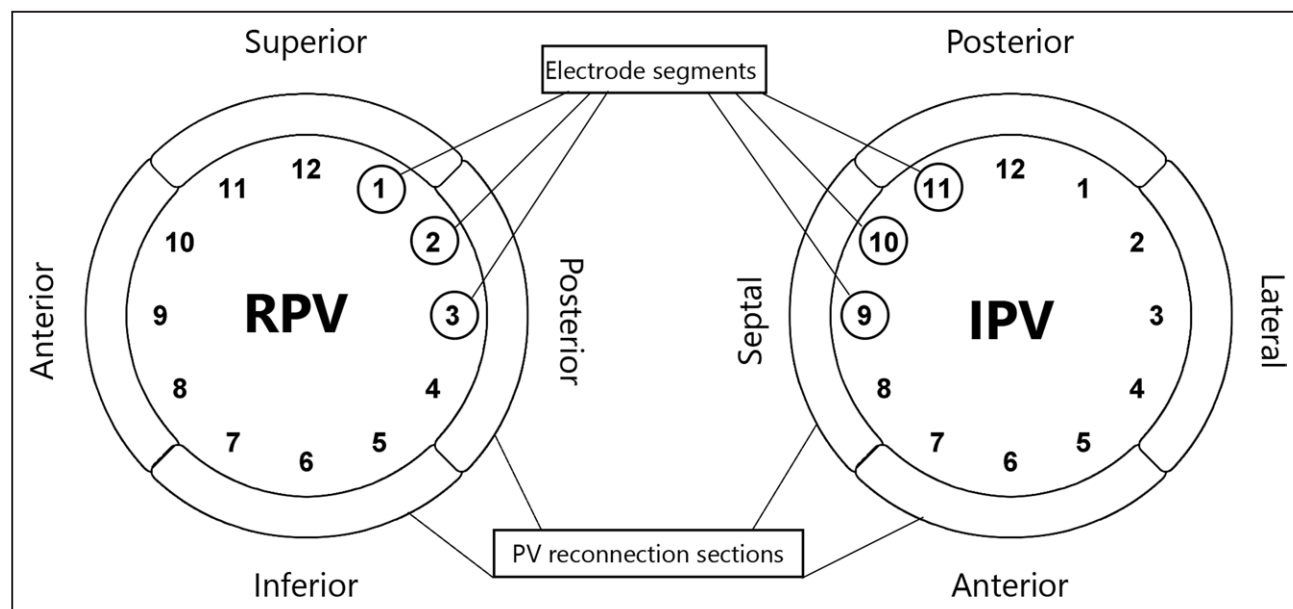

Figure 3. Pulmonary vein (PV) segments used for analysis.
The PVs were subdivided into 12 equal segments. The locations of all electrodes just before the ablation were allocated to one of these segments. During follow-up at 3 months, per PV, the location of reconnection was allocated to any of the 4 PV reconnection sections. IPV indicates inferior PV; and RPV, right PV.

Medical Research Ethics Committee at the University Medical Center Utrecht.[2] During these studies, a custom 14-polar (2.5-mm electrodes, 3.5 mm spacing, with a variable hoop of 16–27 mm) circular IRE catheter was used to deliver IRE applications.[2,5] During the whole procedure, endocardial signals were recorded using a recording system (Prucka Cardiolab EP system, GE Healthcare). At the start of the procedure, the IRE catheter was moved freely in the LA for a period of at least 30 seconds while recording both bipolar electrograms and MEIS signals. MEIS values per electrode were recorded continuously but were not used to guide the ablation procedure.

Data Analysis Clinical Study

Retrospectively, for patients in sinus rhythm, all data recorded during a period of >30 seconds at the start of the procedure was analyzed. Per electrode pair (1–2, 2–3, etc), the maximum bipolar electrogram dV/dt from 300 to 75 ms preceding the R-wave (assumed location of atrial depolarization endocardial electrogram) was determined. In addition, the mean MEIS values per electrode were determined in the same time frame and averaged per electrode pair.

Statistical Analysis

Data are presented as average±SD. For the preclinical study, the average number of IRE applications in right and inferior PVs, the number of applications in both MEIS group and EP group PVs, and average MEIS value representing poor and good contact were compared using a paired t test. Association between locations with a leak and locations with poor contact score was compared using the Fisher exact test. For the clinical evaluation, average MEIS value representing poor and good contact were compared using a paired t test. In addition, a 3-level linear mixed model with random intercept per patient and electrode was fitted, to compare mean MEIS values with bipolar dV/dt amplitude of all electrode pairs. With all tests, a P of <0.05 was statistically significant.

RESULTS

Preclinical Study

A total of 44 IRE applications were delivered to the 20 PVs of 10 animals, without medical complications (Table 1). None of the IRE applications showed signs of arcing on the captured voltage and current waveforms. In one animal, the MEIS failed due to a technical failure, and the procedure in that PV was aborted after one IRE application. Data of this PV was excluded from further analysis. The other PV was ablated according to the protocol for the EP group.

The average impedance values representing poor and good contact were 69±5 Ω and 84±9 Ω (P<0.001), respectively. The mean difference between good and poor contact values within one procedure was 15±4 Ω. In the right PV, 2.3±1.3 and 1.8±0.4 (P=0.53) energy applications were delivered in the MEIS and EP group, respectively (Table 2). In the IPV, 2.6±0.5 and 2.4±0.5 (P=0.58) energy applications were delivered in the MEIS and EP group, respectively.

Table 1. Details of Animal Procedures

Animal#	Vein	Shocks	Group	Position of reconnection
1	RPV	4	MEIS	…
	IPV	2	EP	…
2	RPV	2	EP	Anterior
	IPV	3	MEIS	…
3	RPV	2	MEIS	…
	IPV	3	EP	…
4	RPV	1	EP	Anterior
	IPV	3	MEIS	…
5	RPV	1	MEIS	…
	IPV	2	EP	…
6	RPV	2	EP	…
	IPV	3	MEIS	…
7	RPV	1	MEIS	Excluded
	IPV	2	EP	Lateral
8	RPV	2	EP	…
	IPV	2	MEIS	…
9	RPV	2	MEIS	…
	IPV	3	EP	…
10	RPV	2	EP	…
	IPV	2	MEIS	…

EP indicates group in which the ablation was performed based on EP criteria; IPV, inferior pulmonary vein; MEIS, group in which the ablations were performed based on electrical contact information; and RPV, right pulmonary vein.

PV Reconnections

No acute reconnection after a 30-minute waiting period was observed in either group. After 3 months, PV reconnection was found in 3 sections within the EP group: 2 in the right PV and 1 in the IPV. In the right PV, both reconnections were in the anterior segment. In the IPV, the reconnection was in the anterior lateral segment. No reconnections were found in the MEIS group. There was a nonsignificant difference (P=0.21) in the number of PV reconnections between the two groups. In the EP group, there was no significant difference in the number of IRE applications between the PVs with and without the presence of PV reconnection: 1.7±0.6 and 2.3±0.5 (P=0.12), respectively. Overall, PV reconnections were identified in 2 out of 11 (18%) reconnection sections with a poor contact score. PV reconnections were identified in 1 out of 65 (2%) reconnection sections with a good contact score. The sections with PV reconnections showed a nonsignificant association with poor contact scores (P=0.05).

Clinical Pilot

The average MEIS values representing poor and good contact were 90±7 Ω and 99±7 Ω, respectively (P<0.05). The mean difference between good and poor contact values within one procedure was 9±1.9

Table 2. Number of IRE Applications per Pulmonary Vein

	RPV	IPV	P value
MEIS group	2.3±1.3	2.6±0.5	0.63
EP group	1.8±0.4	2.4±0.5	0.10
P value	0.54	0.58	

EP indicates group in which the ablation was performed based on EP criteria; IPV, inferior pulmonary vein; IRE, irreversible electroporation; MEIS, group in which the ablations were performed based on electrical contact information; and RPV, right pulmonary vein.

ohm. Although MEIS values were not considered for optimal catheter position, the MEIS values corresponded with the operator's interpretation of electrode-tissue contact based on fluoroscopic images, endocardial signals, and location of the catheter in the NavX model.

Comparison between MEIS and local electrograms were performed in 19 out of 30 patients that were in sinus rhythm at the start of the procedure. For the comparison between bipolar dV/dt amplitude and MEIS values, a total of 30 316 heartbeats (123±62 per patient, on 13 electrode pairs) were used (Figure 4). A significant linear relation was found between mean MEIS value and bipolar dV/dt (r^2=0.49, P<0.001), with a slope of 20.6 mV/s per Ohm.

DISCUSSION

In the preclinical study, circular IRE was used to isolate both PVs in 10 animals using either a classical EP approach or a novel multielectrode interface impedance measurement to determine the necessity for additional IRE applications. The acute success rate after a 30-minute observation period was 100% for both approaches. After 3 months follow-up, three PVs with recurrent conduction were found in the 10 PVs of the classical approach (EP group), whereas all PVs that were ablated based on electrical contact information (MEIS group) did not show recurrent conduction. During the clinical pilot, first impression was that the MEIS values correlated well with the operator's interpretation of electrode-tissue contact. Mean MEIS values are significantly related to the amplitude of the bipolar electrograms.

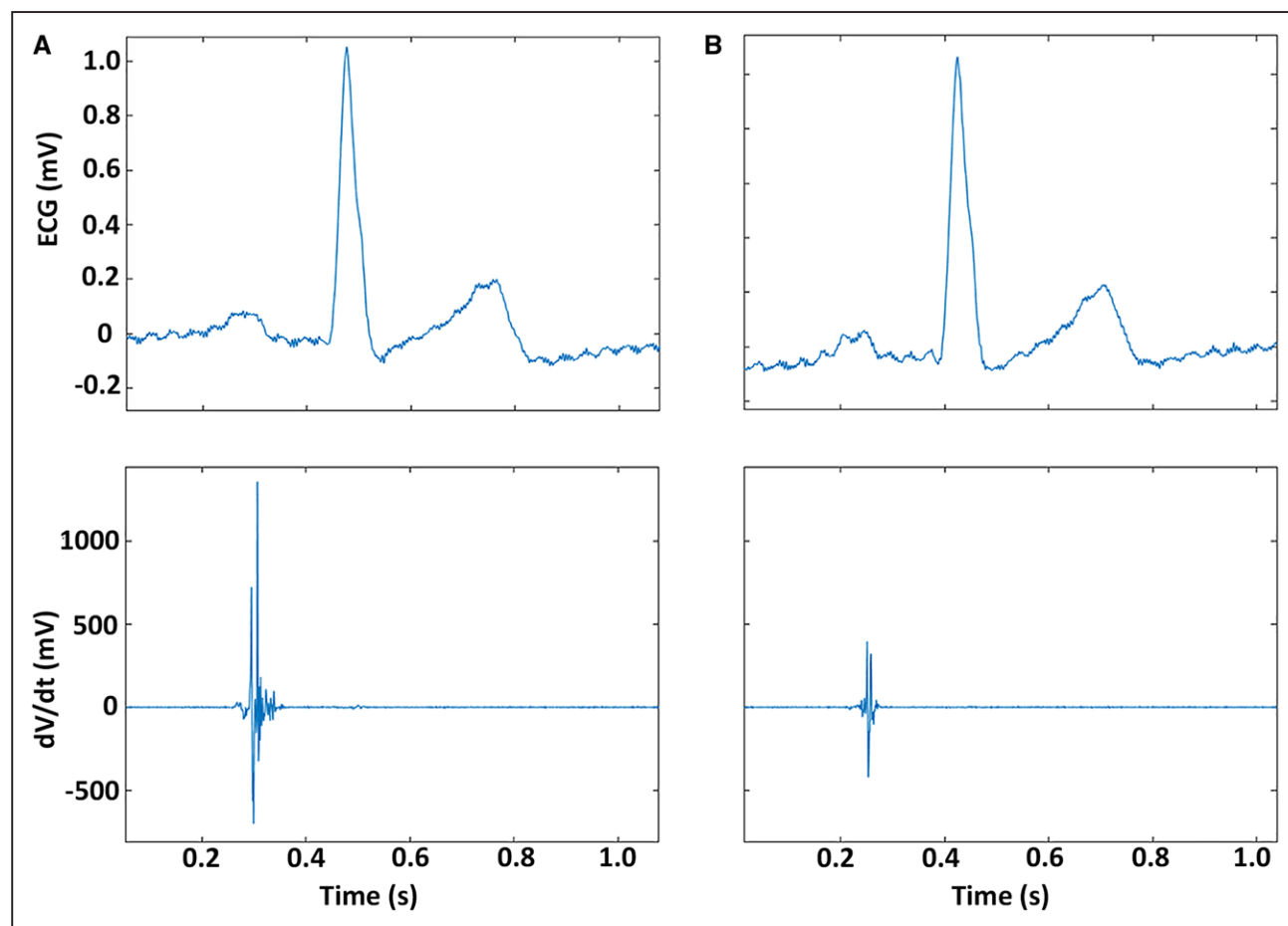There are other methods available to measure impedance, for example, ablation impedance as measured

Figure 4. Example of bipolar signals compared to multielectrode impedance system (MEIS) values.
Top figures show the surface ECG, whereas the **bottom** figures show the accompanying bipolar electrograms. **A**, Example of a high MEIS score and (**B**) a low MEIS score.

by radiofrequency generators, electrical coupling index as described by Piorkowski et al,[11] or local impedance measured with the Rhythmia MiFi ablation catheter.[12] The first 2 methods measure global impedance between the electrode and 1 or 2 skin patches, which is significantly influenced by remote (high impedance) structures. Therefore, these methods are not accurate enough to determine electrode-tissue contact. With both MEIS and the Rhythmia MiFi ablation catheter local impedances are measured, which are not influenced by remote structures such as the lungs or PVs. However, these measurements can currently not be used to distinguish between atrial wall or PV wall. Although the Rhythmia MiFi catheter is capable of measuring contact at a single electrode, the MEIS can be used to determine contact values simultaneously at multiple electrodes.

Reconnection Score

In the porcine study, we observed a strong trend toward association between contact scores per section during ablation and reconnection at follow-up at the same section. The low incidence and small number of animals cause this trend to be nonsignificant.

At 3 months follow-up, 16 out of 19 (84%) of the ablated PVs showed complete electrical isolation. In clinical studies, in which complete circumferential PV isolation was accomplished during the index procedure using thermal ablation, at a repeat EP study after 2 or 3 months, PV reconnection was observed in 62% to 70% of the patients.[7,13,14] The clinical studies were not designed to study long-term efficacy. Pulsed-field ablation is comparable to single-pulse IRE ablation, based on electroporation instead of thermal damage.[15,16] In the first clinical trials using pulsed-field ablation to perform PVI in 81 patients, after 3 months, a reconnection rate of 82% with their initial protocol down to 0% with their optimized protocol was reported.[15]

A model with 4 sections to allocate the sites of PV reconnection was used to compensate for inaccuracies due to (1) possible differences in animal position between the 2 procedures; (2) changes in LA geometry and PV diameter as a result of growth of the pig[17]; (3) the use of bipolar stimulation to detect PV reconnection; (4) the fact that LA capture by stimulation at a site distal to the ablation line does not unequivocally prove the presence of an intact myocardial sleeve at exactly that location.

The absence of any reconnection within the 30-minute observation period during the porcine study suggests that such observation period may be too short with circular IRE ablation and thus not relevant. This is further emphasized by the absence of reconnection after the 30-minute waiting period in 119 out of 120 PVs in the clinical study.[2,5]

Comparison With Electrograms

For the clinical data, a comparison between the MEIS values and endocardial electrograms was performed. Because the electrode-tissue contact fluctuates upon the contraction of the heart, the average MEIS value over 300 to 75 ms before the R-wave and thus during contraction of the atria, was used.

Analysis of the clinical data showed a linear relationship between bipolar dV/dt amplitude and mean MEIS value per electrode pair. Electrogram morphology represents both local and remote activation and can thus provide information about electrode-tissue proximity.[18] A higher bipolar dV/dt is associated with higher proximity between the electrode and the tissue, suggesting that a higher MEIS value is also associated with a higher electrode-tissue proximity. Although this measure is indicative of distance, there are some limitations regarding the use of electrograms. First, electrogram information can only be used while the patient is in sinus rhythm. Additionally, after delivery of a single IRE application, stunning of the local myocardium will occur, making it impossible to use electrogram information. Moreover, no cutoff values are known to distinguish between real electrode-tissue contact and (close) proximity. Future studies should be conducted to determine the cutoff MEIS value for (no) electrode-tissue contact.

With circular multielectrode catheters, it may be difficult to achieve good electrode-to-tissue contact for all electrodes around the PV antrum perimeter. Therefore, multiple energy applications are usually required to achieve complete circumferential PV isolation with current thermal circular ablation techniques.[19] In the porcine study, per PV an average of 2.3 IRE applications were needed using a fixed diameter 20-mm circular multielectrode catheter. The size of the IPV antrum is often >20 mm, thus requiring more IRE applications for circumferential coverage.[17] In the clinical study, a larger multielectrode circular catheter with a variable hoop of 16 to 27 mm was used, thereby optimizing IRE catheter placement. In the clinical studies, multiple IRE pulses (a mean of 2.4±0.3 per PV during the first study, and a mean of 2.9±0.7 per PV during the second study) were delivered per PV to assure circumferential coverage.[2,5] The availability of real-time contact information will facilitate optimal catheter positioning. In addition, use of the MEIS system together with a 3-dimensional navigation system may enable systematic targeting of specific segments of the PV perimeter to ensure complete circumferential coverage during the ablation procedure. In the future, the electrode-tissue contact values should be implemented within the 3-dimensional navigation systems, to allow for automatic analysis of circular good contact lesions.

Limitations

In the porcine study, adenosine was not administered to check for acute PV reconnection. Prior studies have shown that adenosine can unmask sites of possible PV

reconnection after radiofrequency ablation.[20,21] In the clinical study, in only 1 out of 120 PVs reconnection was found upon adenosine testing after 30 minutes, suggesting that this period is too short to reveal dormant PV connection.

In the porcine study, no histology analysis was performed after the follow-up period. With the used method, it is very challenging, if not impossible to relate the precise ablation locations with histology. Therefore, no direct comparison can be made between reconnection site and viable myocardium upon histology.

The catheters used in both studies differ in number of electrodes and more importantly in electrode size (2 mm versus 2.5 mm for the porcine and clinical catheter, respectively).

The clinical study was not designed to study long-term efficacy of IRE ablation, moreover, the MEIS values were not used to guide ablation position and number of IRE pulses. Therefore, no comparison was made between MEIS values during ablation and reconnection upon repeated PVI. Although no hard conclusions can be drawn, these results warrant further research and are indicative of the future implementation of the MEIS system during (single-pulse) IRE ablation.

Clinical Perspective

The significance of electrode-tissue contact is well known for radiofrequency ablation; however, due to its novelty, not much is known about the importance of electrode-tissue contact for IRE ablation. IRE ablation can be achieved by multiple energy modalities, for example, a single-pulse direct current, pulsed field, or alternating current. Moreover, the energy can be delivered in a monopolar fashion between the catheter and a skin patch or through bipolar delivery on neighboring electrodes. All these factors will influence the electric field, and therefore the influence of electrode-tissue contact might be different for these different methods. Furthermore, in a recent in vitro study, it was shown that electroporation is much more effective with tissue contact, or at least tissue proximity.[22]

The demonstrated technique enables the real-time visualization of electrode interface impedance for each individual electrode of a circular multielectrode catheter and facilitates direct feedback to the physician for optimal catheter positioning in the PV antrum. With this method, procedure time can be reduced while procedural efficacy can be increased. The first impression of the clinical use of the MEIS system was affirmative of this clinical perspective. However, further clinical studies are required to demonstrate the benefit of contact information for long-term efficacy of circular PV isolation with single-pulse IRE.

Conclusions

Data of this study suggest that MEIS values predict effective IRE applications. The low chronic reconnection rate suggests that circular single-pulse IRE ablation is an adequate technique for electrical PV isolation. First clinical results are promising but more clinical studies are needed to determine the added value of MEIS measurements compared to standard procedures used to evaluate electrode-tissue contact.

REFERENCES

1. Wittkampf FH, van Driel VJ, van Wessel H, Vink A, Hof IE, Gründeman PF, Hauer RN, Loh P. Feasibility of electroporation for the creation of pulmonary vein ostial lesions. *J Cardiovasc Electrophysiol.* 2011;22:302–309. doi: 10.1111/j.1540-8167.2010.01863.x

2. Loh P, van Es R, Groen MHA, Neven K, Kassenberg W, Wittkampf FHM, Doevendans PA. Pulmonary vein isolation with single pulse irreversible electroporation: a first in human study in 10 patients with atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2020;13:e008192. doi: 10.1161/CIRCEP.119.008192

3. Wittkampf FH, van Driel VJ, van Wessel H, Neven KG, Gründeman PF, Vink A, Loh P, Doevendans PA. Myocardial lesion depth with circular electroporation ablation. *Circ Arrhythm Electrophysiol.* 2012;5:581–586. doi: 10.1161/CIRCEP.111.970079

4. Neven K, van Driel V, van Wessel H, van Es R, Doevendans PA, Wittkampf F. Myocardial lesion size after epicardial electroporation catheter ablation after subxiphoid puncture. *Circ Arrhythm Electrophysiol.* 2014;7:728–733. doi: 10.1161/CIRCEP.114.001659

5. Loh P, Groen M, Taha K, Wittkampf F, Doevendans P, Van Es R. Pulmonary vein isolation by irreversible electroporation: an efficacy and safety study in 20 patients with atrial fibrillation. *EP Eur.* 2021;23:euab116-095. doi: 10.1161/CIRCEP.119.008192

6. Wittkampf FH, Nakagawa H. RF catheter ablation: Lessons on lesions. *Pacing Clin Electrophysiol.* 2006;29:1285–1297. doi: 10.1111/j.1540-8159.2006.00533.x

7. Neuzil P, Reddy VY, Kautzner J, Petru J, Wichterle D, Shah D, Lambert H, Yulzari A, Wissner E, Kuck KH. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. *Circ Arrhythm Electrophysiol.* 2013;6:327–333. doi: 10.1161/CIRCEP.113.000374

8. Andrade JG, Monir G, Pollak SJ, Khairy P, Dubuc M, Roy D, Talajic M, Deyell M, Rivard L, Thibault B, et al. Pulmonary vein isolation using "contact force" ablation: The effect on dormant conduction and long-term freedom from recurrent atrial fibrillation—A prospective study. *Hear Rhythm.* 2014;11:1919–1924. doi: 10.1016/j.hrthm.2014.07.033

9. Wittkampf FHM, van Es R, Neven K. Electroporation and its Relevance for Cardiac Catheter Ablation. *JACC Clin Electrophysiol*. 2018;4:977–986. doi: 10.1016/j.jacep.2018.06.005

10. van Es R, Hauck J, van Driel VJHM, Neven K, van Wessel H, A Doevendans P, Wittkampf FHM. Novel method for electrode-tissue contact measurement with multi-electrode catheters. *Europace*. 2018;20:149–156. doi: 10.1093/europace/euw388

11. Piorkowski C, Sih H, Sommer P, Miller SP, Gaspar T, Teplitsky L, Hindricks G. First in human validation of impedance-based catheter tip-to-tissue contact assessment in the left atrium. *J Cardiovasc Electrophysiol*. 2009;20:1366–1373. doi: 10.1111/j.1540-8167.2009.01552.x

12. Sulkin MS, Laughner JI, Hilbert S, Kapa S, Kosiuk J, Younan P, Romero I, Shuros A, Hamann JJ, Hindricks G, et al. Novel measure of local impedance predicts catheter-tissue contact and lesion formation. *Circ Arrhythm Electrophysiol*. 2018;11:e005831. doi: 10.1161/CIRCEP.117.005831

13. Das M, Wynn GJ, Morgan M, Lodge B, Waktare JE, Todd DM, Hall MC, Snowdon RL, Modi S, Gupta D. Recurrence of atrial tachyarrhythmia during the second month of the blanking period is associated with more extensive pulmonary vein reconnection at repeat electrophysiology study. *Circ Arrhythm Electrophysiol*. 2015;8:846–852. doi: 10.1161/CIRCEP.115.003095

14. Kuck KH, Hoffmann BA, Ernst S, Wegscheider K, Treszl A, Metzner A, Eckardt L, Lewalter T, Breithardt G, Willems S; Gap-AF–AFNET 1 Investigators*. Impact of complete versus incomplete circumferential lines around the pulmonary veins during catheter ablation of paroxysmal atrial fibrillation: results from the gap-atrial fibrillation-german atrial fibrillation competence network 1 trial. *Circ Arrhythm Electrophysiol*. 2016;9:e003337. doi: 10.1161/CIRCEP.115.003337

15. Reddy VY, Neuzil P, Koruth JS, Petru J, Funosako M, Cochet H, Sediva L, Chovanec M, Dukkipati SR, Jais P. Pulsed field ablation for pulmonary vein isolation in atrial fibrillation. *J Am Coll Cardiol*. 2019;74:315–326. doi: 10.1016/j.jacc.2019.04.021

16. Reddy VY, Anic A, Koruth J, Petru J, Funasako M, Minami K, Breskovic T, Sikiric I, Dukkipati SR, Kawamura I, et al. Pulsed field ablation in patients with persistent atrial fibrillation. *J Am Coll Cardiol*. 2020;76:1068–1080. doi: 10.1016/j.jacc.2020.07.007

17. Van Driel VJHM, Neven KGEJ, Van Wessel H, Du Pré BC, Vink A, Doevendans PAFM, Wittkampf FHM. Pulmonary vein stenosis after catheter ablation electroporation versus radiofrequency. *Circ Arrhythmia Electrophysiol*. 2014;7:734–738. doi: 10.1161/CIRCEP.113.001111

18. de Bakker JM. Electrogram recording and analyzing techniques to optimize selection of target sites for ablation of cardiac arrhythmias. *Pacing Clin Electrophysiol*. 2019;42:1503–1516. doi: 10.1111/pace.13817

19. Laish-Farkash A, Khalameizer V, Fishman E, Cohen O, Yosefy C, Cohen I, Katz A. Safety, efficacy, and clinical applicability of pulmonary vein isolation with circular multi-electrode ablation systems: PVAC® vs. nMARQ™ for atrial fibrillation ablation. *Europace*. 2016;18:807–814. doi: 10.1093/europace/euv258

20. Tritto M, De Ponti R, Salerno-Uriarte JA, Spadacini G, Marazzi R, Moretti P, Lanzotti M. Adenosine restores atrio-venous conduction after apparently successful ostial isolation of the pulmonary veins. *Eur Heart J*. 2004;25:2155–2163. doi: 10.1016/j.ehj.2004.08.023

21. Datino T, Macle L, Qi XY, Maguy A, Comtois P, Chartier D, Guerra PG, Arenal A, Fernández-Avilés F, Nattel S. Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. *Circulation*. 2010;121:963–972. doi: 10.1161/CIRCULATIONAHA.109.893107

22. Hunter DW, Kostecki G, Fish JM, Jensen JA, Tandri H. In vitro cell selectivity of reversible and irreversible electroporation in cardiac tissue. *Circ Arrhythmia Electrophysiol*. 2021;14:440–448. doi: 10.1161/CIRCEP.120.008817