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Pulsed field ablation lesion Characteristics in Animal Studies

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COI Disclosure

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The authors have no financial conflicts of interest to disclose concerning the presentation

Pulsed Field Ablation (PFA)

- **Pulsed field ablation (PFA)** leads to **cell death by irreversible electroporation.**

- **Myocardial cells have a greater sensitivity to PFA** compared with nerves, arteries, and other collateral structures, making it an attractive energy modality for catheter ablation.

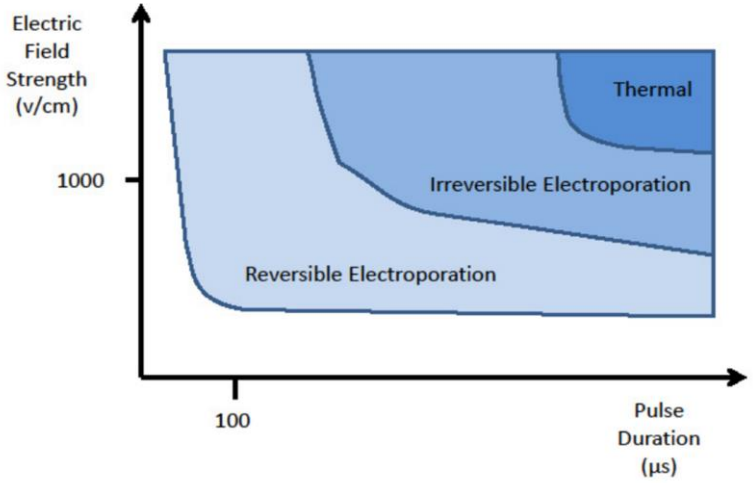
- Prior reports have demonstrated **safety and efficacy for atrial ablation** and have **assessed feasibility of ablation in regions of healthy and myocardial scar in LV**.

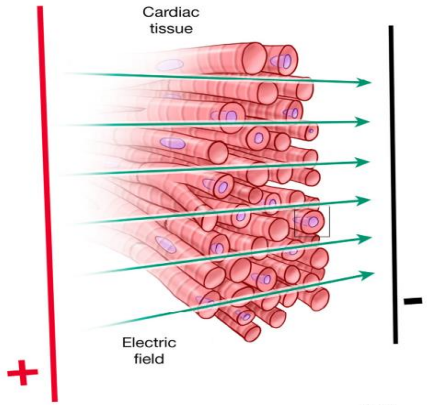
Europace. 2019 Dec;22(3):434-439.
Circ Arrhythm Electrophysiol. 2019 Dec;12(12):e007781.
J Am Coll Cardiol. 2019 Jul 23;74(3):315-326.
J Am Coll Cardiol. 2020 Sep 1;76(9):1068-1080.

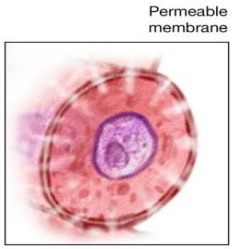
Mechanisms of Cell Death With PFA

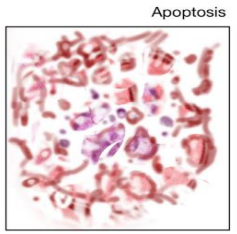
- **Electroporation** is a process in which a <u>cell membranes permeability to ions and molecules is increased</u> when the cell is exposed to **<u>high electric fields.</u>**

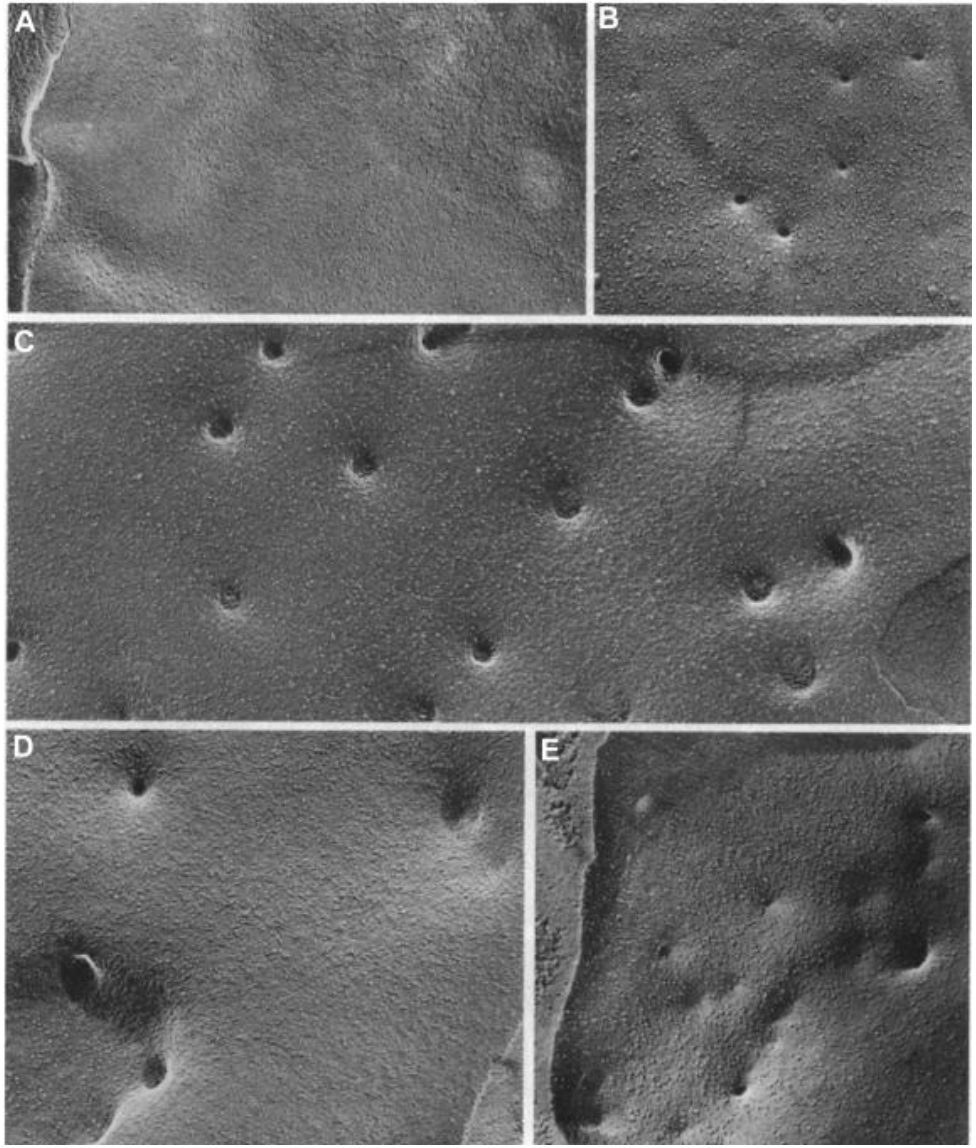
- Usually, in the form of **<u>short Direct Current (DC) pulses</u>**
  → **Cell permeability ↑**
  → **Nanometric pores formation in cell membrane**
  → Hence, the term "**electroporation"**











- **Cell membranes** have a much higher <u>electrical resistance than the extra- and intracellular fluid.</u>
- Both these sections are thus exposed to approximately one-half the voltage gradient across the complete cell and are the most likely sites where **<u>pores will be created</u>**

<u>Micrographs showing the structure of the membranes of red blood cells</u>, frozen at different times (t) after the application of the **<u>electroporating pulse</u>**.
(A) t = 0.5 ms; (B) t = 3 ms; (C) t = 40 ms; (D) t = 5 s; and (E) t = 10 s.
Original magnification: 60,000.

Emerging Technologies for Pulmonary Vein Isolation

F. Daniel Ramirez, Vivek Y. Reddy, Raju Viswanathan, Mélèze Hocini, Pierre Jaïs

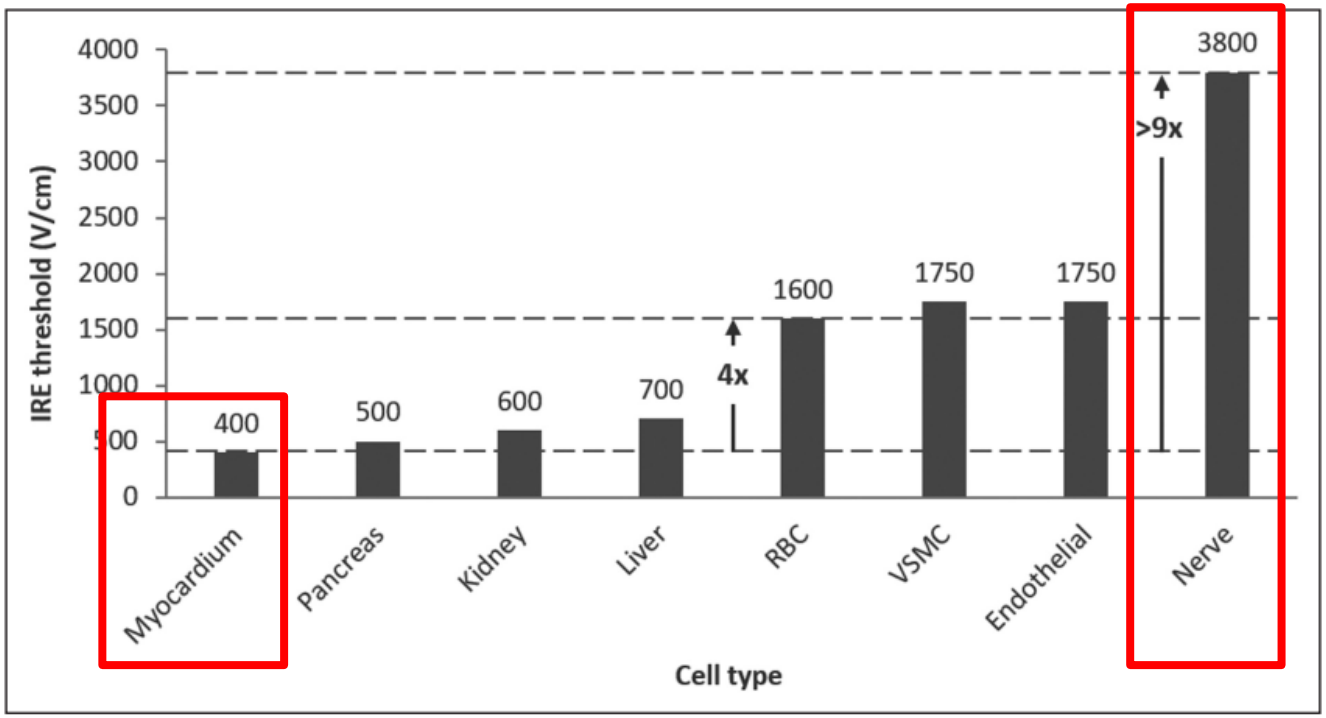


Figure 1. Irreversible electroporation (IRE) thresholds for various cell types.
Data based on threshold values from various sources[36–38,41–45] and from varied delivery parameters and waveforms. RBC indicates red blood cell; and VSMC, vascular smooth muscle cell.

- PFA affects all tissues within a zone exposed to an electric field while still exhibiting tissue selectivity based on the tissue-dependent electric field threshold values required for IRE

Circ Res. 2020 Jun 19;127(1):170-183.

Tissue specificity/selectivity

- **Cells exposed** to an electric field intensity **above their critical threshold** undergo **IRE and die**, whereas **cells exposed** to electric fields **below** their respective **critical thresholds** undergo **reversible electroporation** and survive.

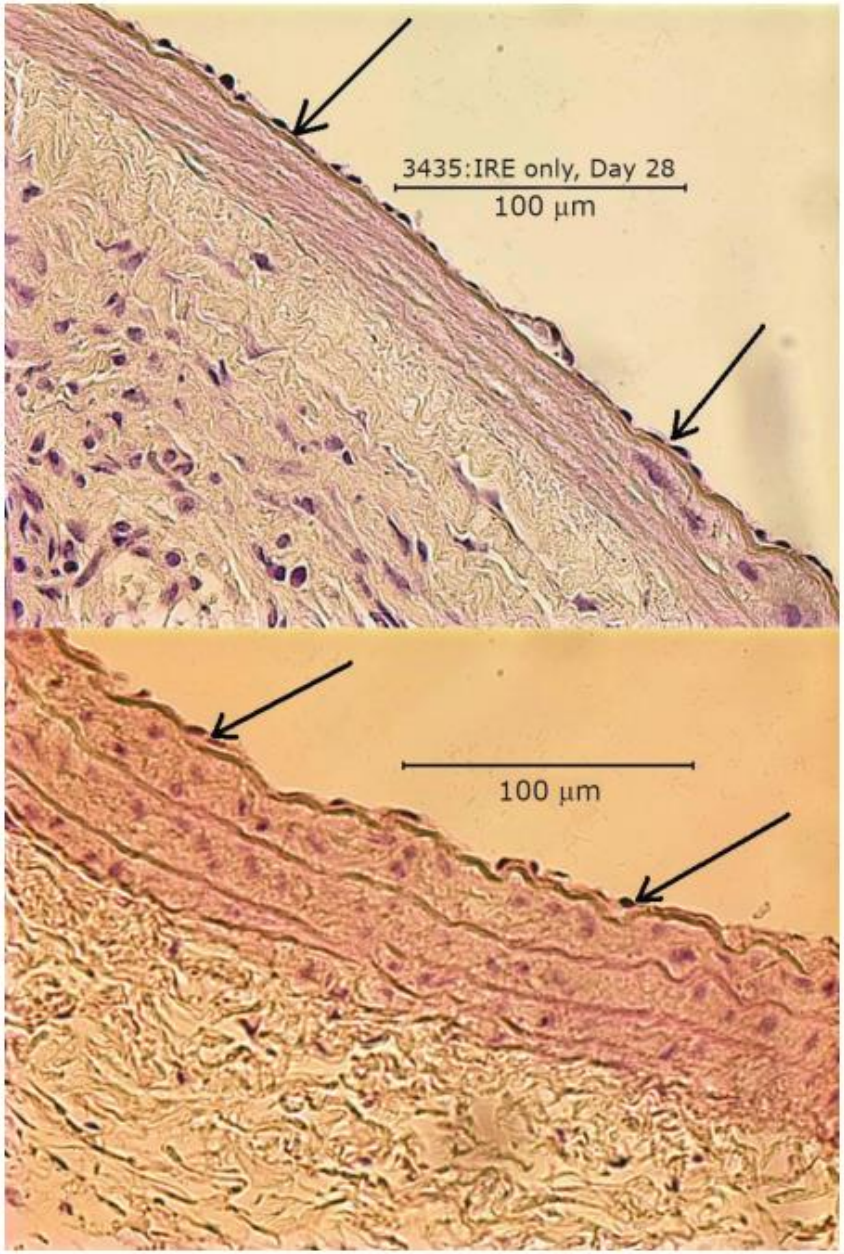
- **Local current density creates an electrical field**, expressed in **volts per centimeter**.

  → **Voltage across each tissue cell** will be proportional to its **diameter measured in the axial direction** of the electrical current.

- **Cell size** may thus be among the **factors that determine tissue specificity of electroporation**

Circ Res. 2020 Jun 19;127(1):170-183.

Blood vessels

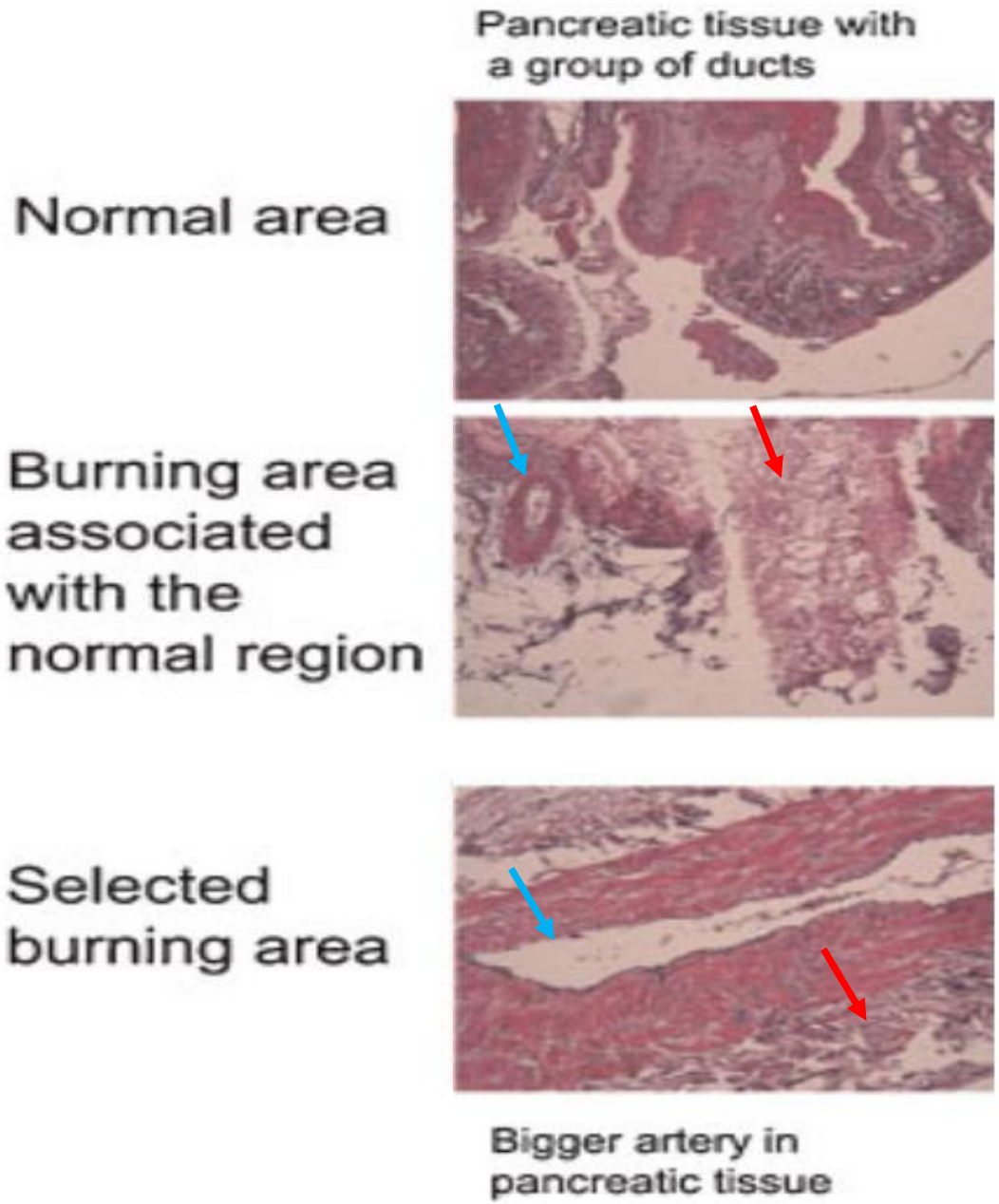


- Motivated by the **anticipated use electroporation for treatment of tumors** near **large blood vessels**, **Carotid artery** has been directly **targeted in rats** using a **bipolar clamp** around the artery.

- Histology, **4 weeks after** the procedure, showed that the **connective matrix of the artery remained intact** with no evidence of aneurysm, thrombus formation, or necrosis.

Technol Cancer Res Treat. 2007 Aug;6(4):307-12.

Blood vessels



- In a **porcine** study, histological analysis 14 days after pancreatic electroporation ablation revealed **patent vascular structures in targeted areas** despite significant destruction of pancreatic tissue.

J Surg Oncol. 2011 Jul 1;104(1):22-8

Electrical Catheter Ablation in the Left and Right Ventricular Wall in Dogs: Relation Between Delivered Energy and Histopathologic Changes

RICHARD N.W. HAUER, MD, WILLEM STRAKS, MD, CORNELIUS BORST, MD,
ETIENNE O. ROBLES DE MEDINA, MD, FACC

Electrical catheter ablation of arrhythmogenic sites is now being used for the treatment of ventricular tachycardias. However, the extent and type of the ablation lesion in relation to energy level are controversial and not well known. In 10 beagles, single cathodal shocks of 30 (4 dogs), 80 (2 dogs) or 250 J (4 dogs) were delivered to the endocardial ventricular wall (5 dogs left ventricular, 5 dogs right ventricular). One week after ablation the dogs were killed for histopathologic examination. In the left ventricular wall, ablation lesion volumes calculated from measured extensions in three perpendicular directions were 0.4 and 0.9 cc at 30 J, 1.9 cc at 80 J and 2.8 and 3.4 cc at 250 J; in the right ventricular wall they were 0.4 and 0.5 cc at 30 J, 1.3 cc at 80 J and 2.5 and 4.2 cc at 250 J. In the right ventricular wall all 30 to 250 J lesions were transmural, whereas in the left ventricular wall only 250 J lesions were transmural. All lesions showed a necrotic area surrounded by granulation tissue with degenerated myofibrils.

Thus, the size of the ablation lesion depends on delivered energy, whereas the pattern of histopathologic change is identical in the 30 to 250 J energy range. These results suggest that with accurate localization of the arrhythmogenic site one low energy shock may be successful with less myocardial damage.

(J Am Coll Cardiol 1986;8:637–43)

Myocardial Lesion Depth With Circular Electroporation Ablation

Fred H.M. Wittkampf, PhD; Vincent J. van Driel, MD; Harry van Wessel, BSc; Kars G.E.J. Neven, MD; Paul F. Gründeman, MD, PhD; Aryan Vink, MD, PhD; Peter Loh, MD, PhD; Pieter A. Doevendans, MD, PhD

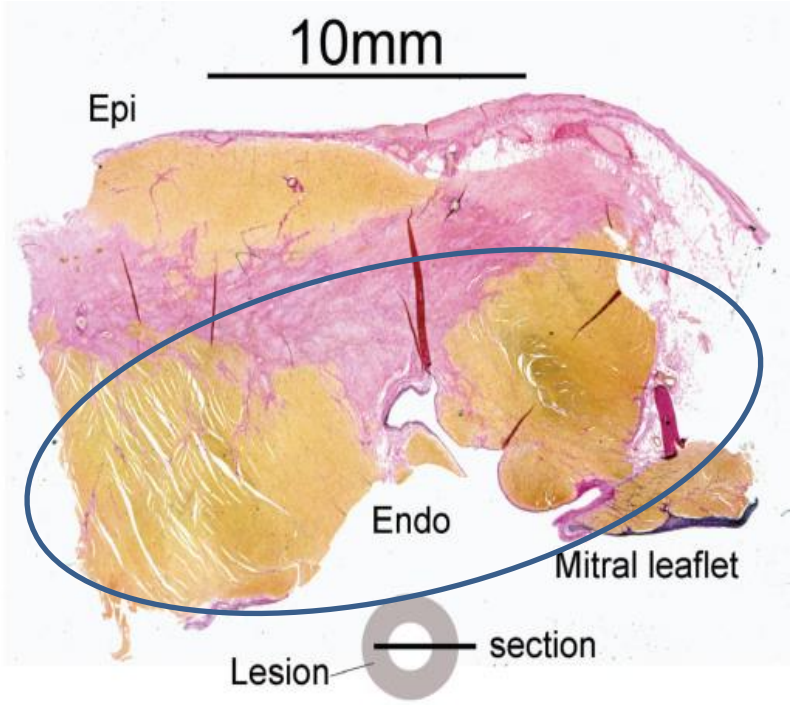


Figure 4. Histological elastic–van Gieson–stained section through the center of a circular lesion created at 200 J with the decapolar device D. The section was taken perpendicular to the epicardial surface and approximately through the middle of the lesion. Left, The lesion apparently continues beyond the end of the section. The lesion extends under a central surviving area. Bottom, The location of the section relative to the circular lesion is sketched.

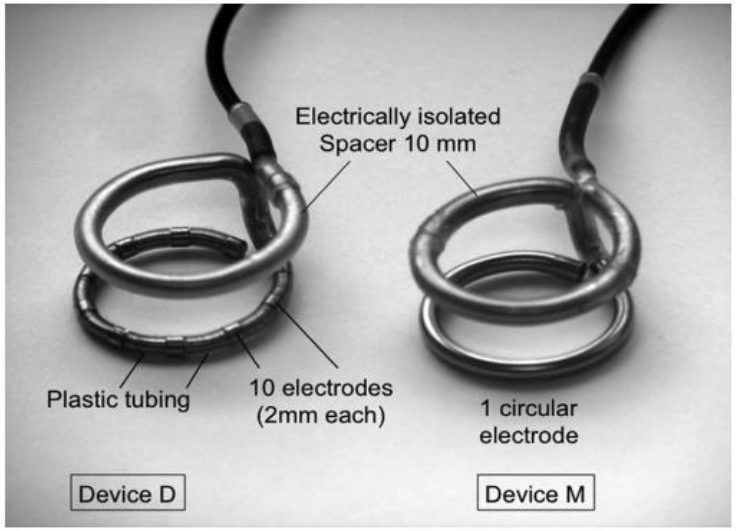


Figure 1. The 2 custom devices used for ablation. Type D has 10 metal 2-mm-long and 7F-diameter contacts mimicking a decapolar circular ablation catheter with all electrodes interconnected. Type M has one 7F circular electrode. Both devices are 20 mm in diameter and have a spacer to ensure at least 10 mm of blood above the ablation area within the pericardial space.

Conclusions

- a **significant relationship** between the **magnitude of the application and myocardial lesion depth**.
- In blood-myocardial tissue environment, **continuous 20-mm circular lesions**, deep enough for electric PV isolation, can be created with a **single 200-J application** of a few milliseconds in duration. **Tissue heating does not appear** to play a role in lesion formation

Circ Arrhythm Electrophysiol 2012;5:581–6

Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

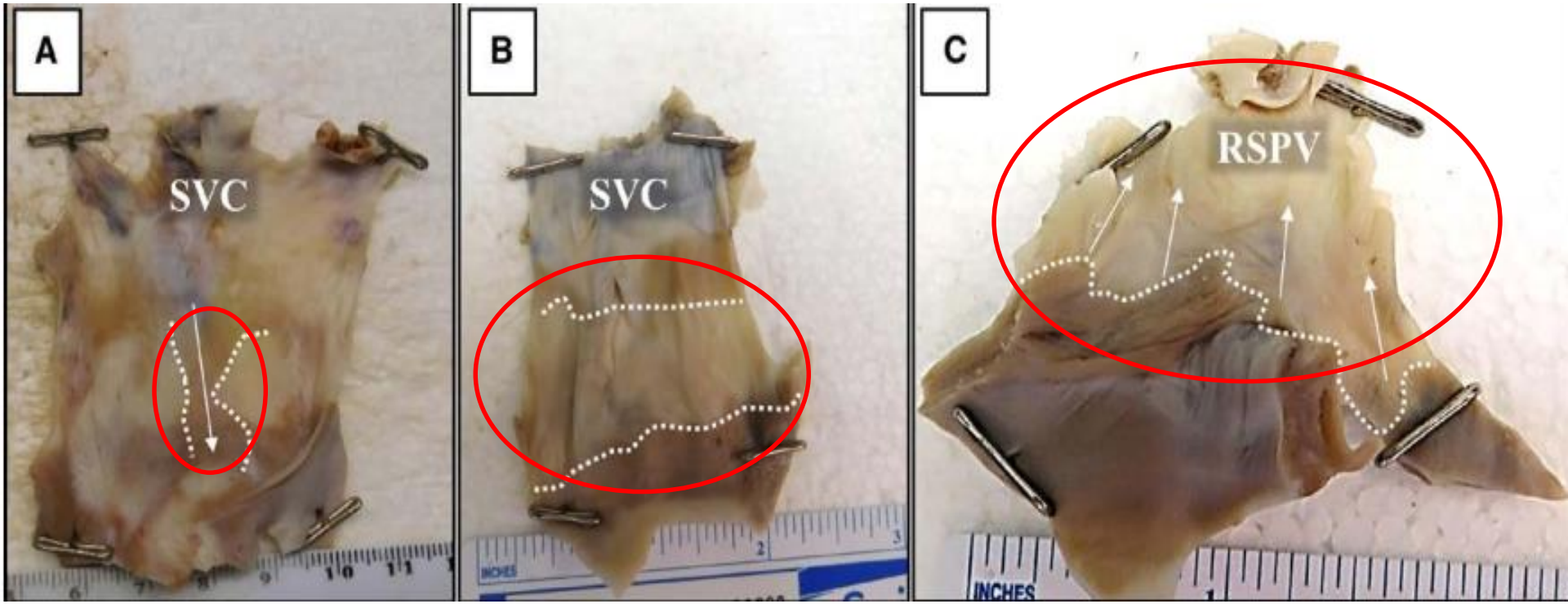
Preclinical Evaluation of Pulsed Field Ablation

Electrophysiological and Histological Assessment of Thoracic Vein Isolation

Figure 1. Multielectrode pulsed field ablation catheter deployed in flower pose.

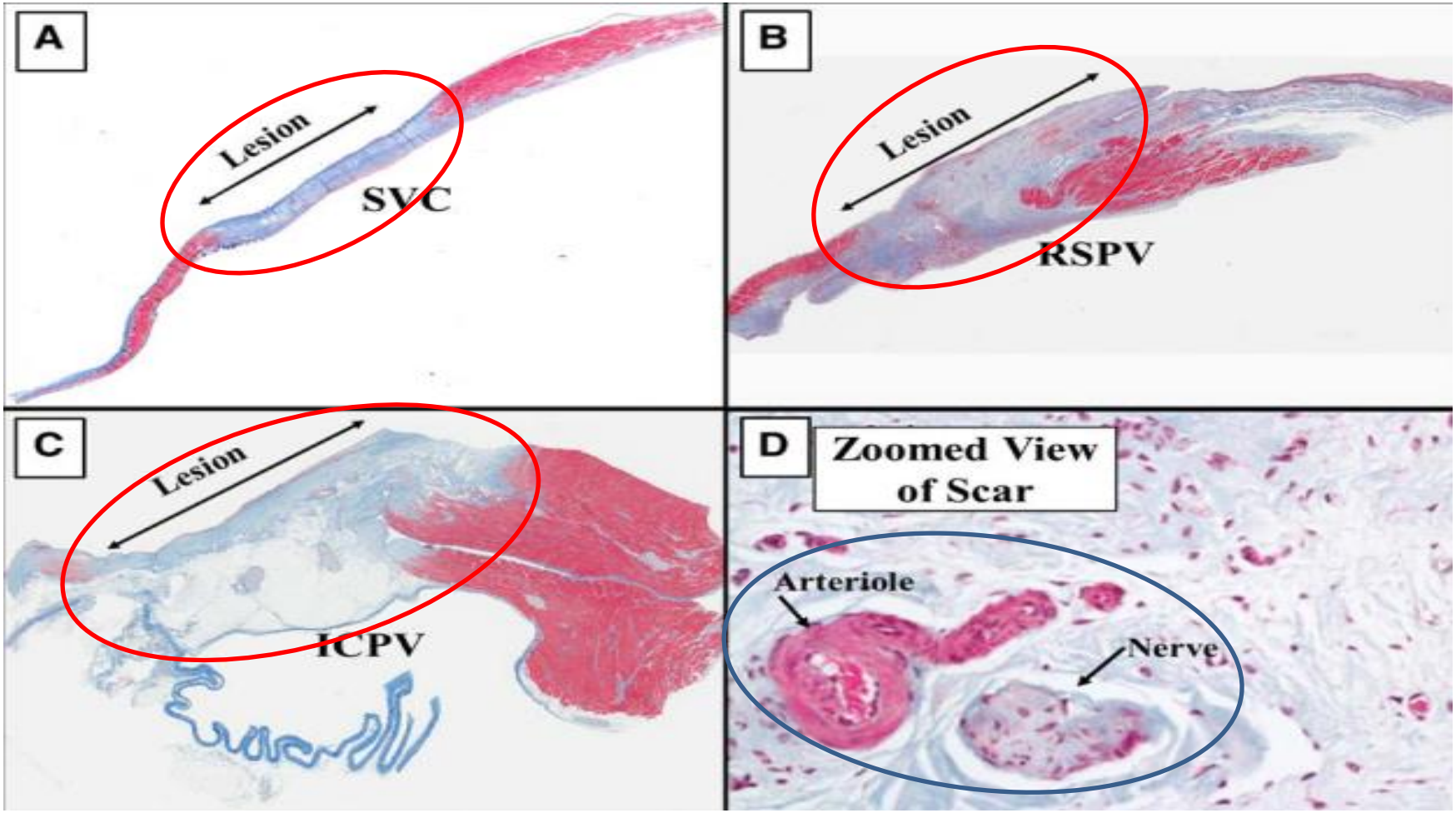
CONCLUSIONS: In this chronic porcine study, PFA-based pulmonary vein and SVC isolation were safe and efficacious with demonstrable sparing of nerves and venous tissue. This preclinical study provided the scientific basis for the first-in-human endocardial PFA studies.

Circ Arrhythm Electrophysiol. 2019;12:e007781



- **Figure 4. Gross appearance** of PFA lesions seen after formalin fixation.
- **A, Monophasic PFA lesion** in the superior vena cava (SVC) with **presence of a visual gap (arrow)**. **B, Biphasic PFA lesion** in the SVC with **contiguous and broad lesion** (between dotted lines). **C, Biphasic PFA lesion** in the right superior pulmonary vein (RSPV) with **contiguous broad lesion** (arrows point in direction of distal pulmonary vein)

Circ Arrhythm Electrophysiol. 2019;12:e007781



- **Figure 5. Masson's trichrome stain** of sections from Biphasic cohort.
- **A, Transmural PFA lesion** in **SVC** (10× magnification). **B, Transmural PFA lesion** in the **RSPV. C, Transmural PFA lesion** in the **inferior common pulmonary vein (ICPV). D, 200× view of fibrotic core of PFA -** SVC lesion ,a **spared arteriole and nerve surrounded by fibrosis**

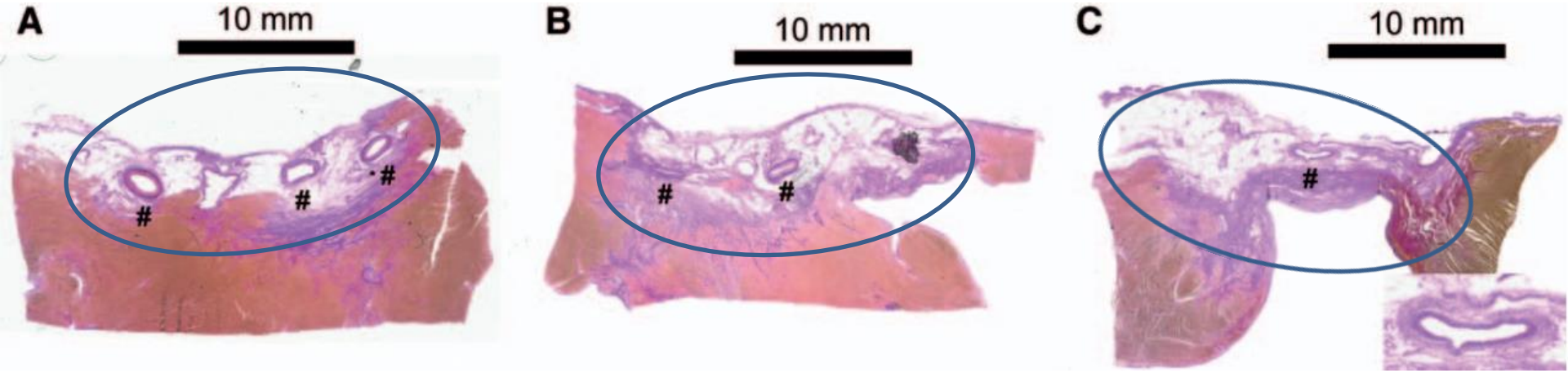
Circ Arrhythm Electrophysiol. 2019;12:e007781

Potential complication of cardiac electroporation

Coronary damage

- **Effect of electroporation ablation** on **coronary arteries** was investigated by **histological analysis of arteries** that happened to be present in electroporation lesions, but also after intentionally targeting main coronary arteries via a **special epicardial circular catheter** in the pericardial space.

- Both studies demonstrated that **coronary arteries remained free of significant damage amid huge transmural myocardial lesions**, up **to 3 months after ablation**



Europace 2013;15:144–9.

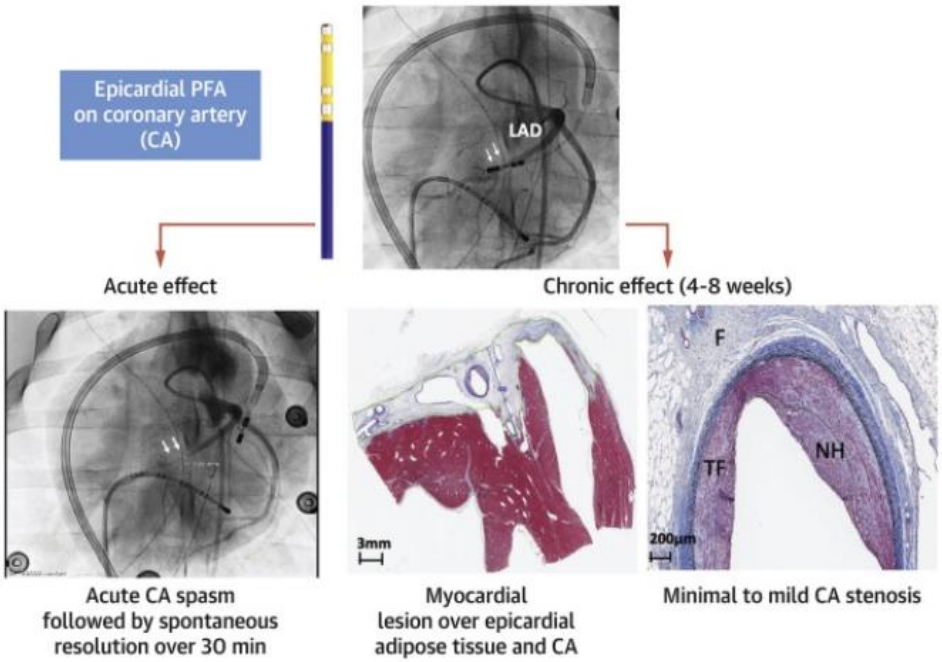
Circ Arrhythm Electrophysiol 2014;7:728–33

Circ Arrhythm Electrophysiol 2014;7:913–9

Coronary damage

Effect of Epicardial Pulsed Field Ablation Directly on Coronary Arteries

Satoshi Higuchi, MD,[a] Sung Il Im, MD,[a] Carol Stillson, BS,[a] Eric D. Buck, MS,[b] Samantha Jerrell, BS,[b] Christopher W. Schneider, MENG,[b] Molly Speltz, DVM,[c] Edward P. Gerstenfeld, MD[a]



- intracoronary PFA resulted both in significant coronary spasm and fixed coronary stenosis.
- Epicardial PEF, delivered at lower energy, resulted in reversible spasm but no fixed coronary stenosis.

Conclusion

In swine model, epicardial PFA directly on CA allowed the creation of myocardial lesions but led to **CA response characterized by acute moderate spasm** and **chronic mild stenosis via neointimal hyperplasia**.

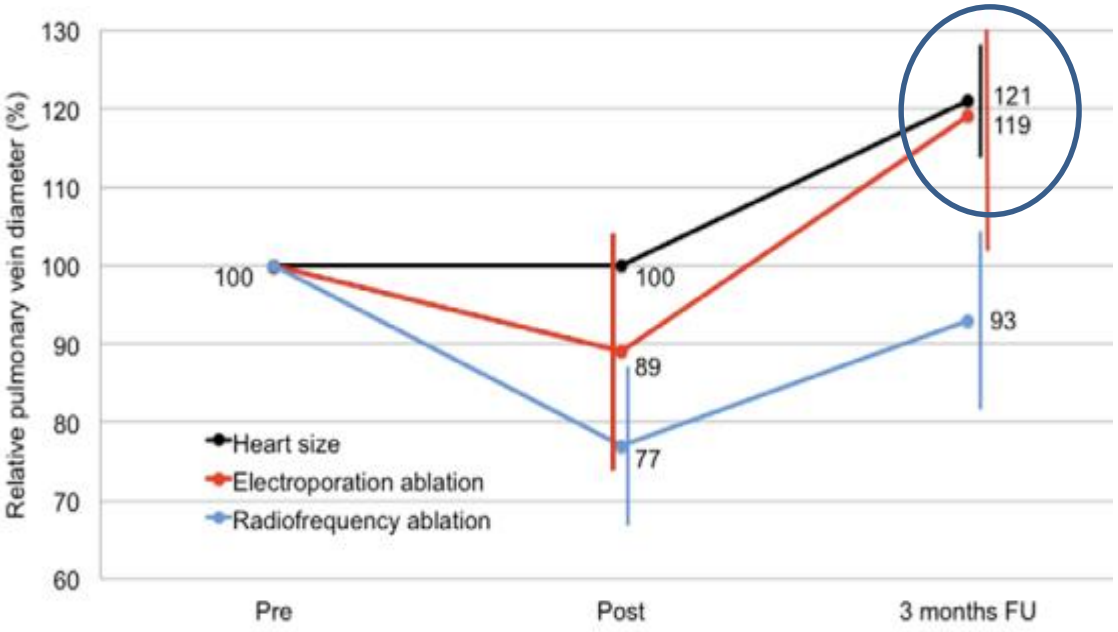
JACC Clin Electrophysiol. 2022 Dec;8(12):1486-1496

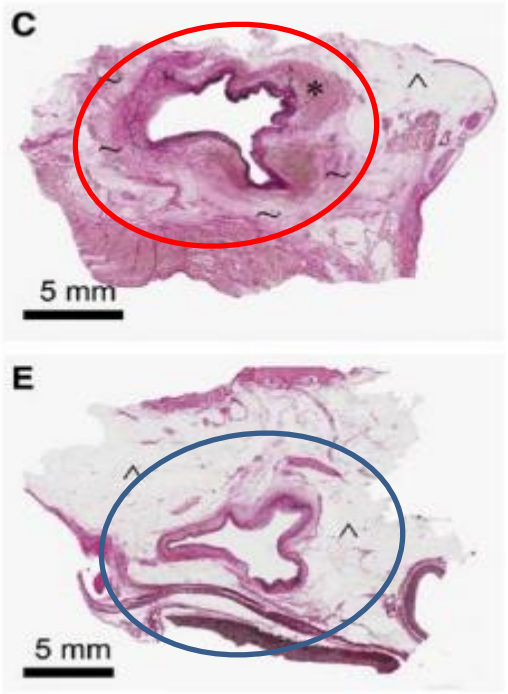
Circ Arrhythm Electrophysiol. 2022 Oct;15(10):e010668.

PV stenosis

- In **PV ablated with electroporation**, **angiographic narrowing was absent after 3 months' follow-up**, in contrast to PV in which RF ablation had been performed.

- **Electroporation-ablated PV only showed minor intimal proliferation**, whereas PV treated with RF had intimal proliferation, necrotic myocardium, proliferation of the elastic lamina, and large amounts of scar tissue surrounding the myocardial sleeve.



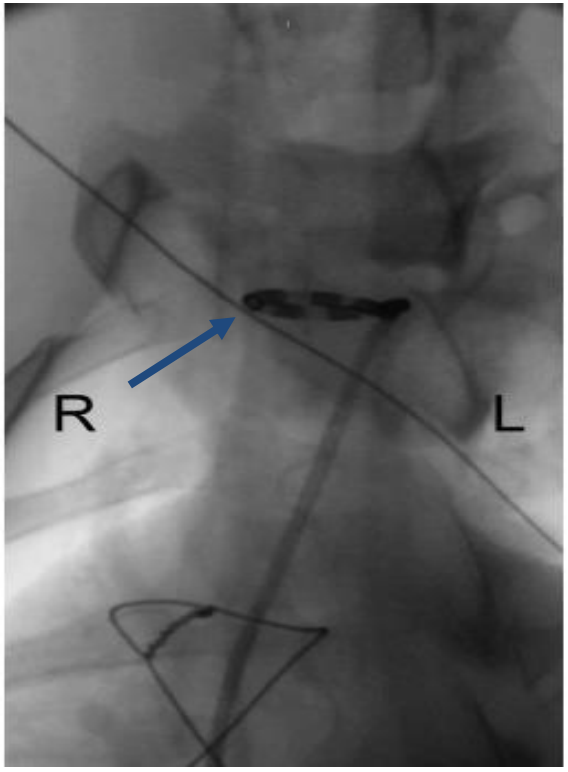


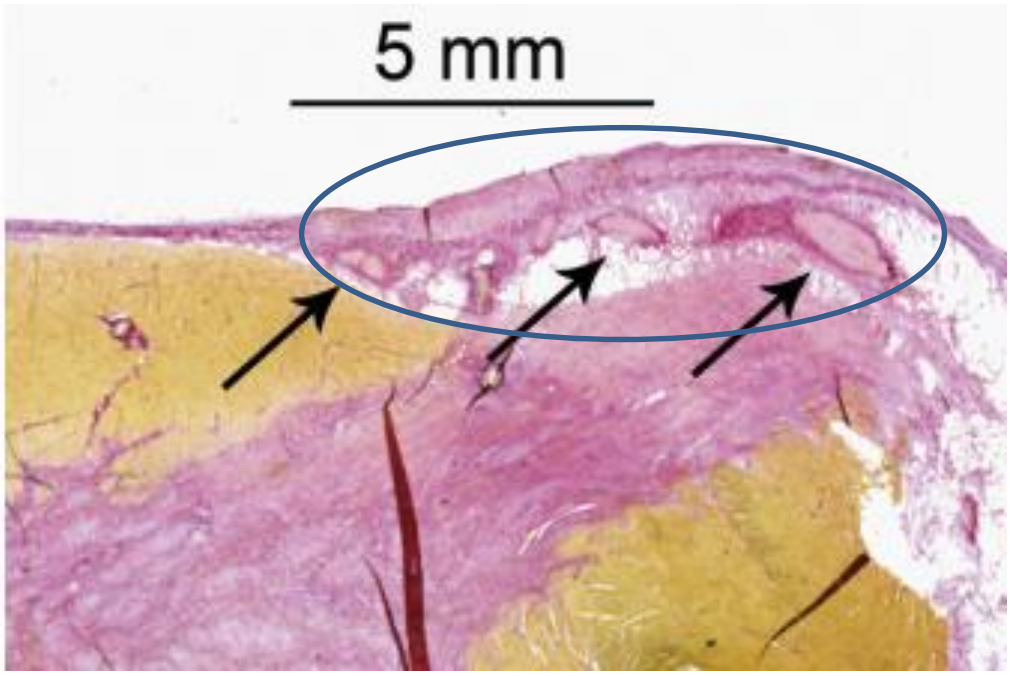
Circ Arrhythm Electrophysiol. 2014 Aug;7(4):734-8.

Phrenic nerve injury

- Given unknown effect of the different application mode and current density, **Right phrenic nerve was targeted using a circular 200 J application** with good tissue contact inside SVC.

- Sometimes, **phrenic nerve was transiently affected**, but normal function was demonstrated **by capture-pacing from SVC 30 min and 3 months after the application.**



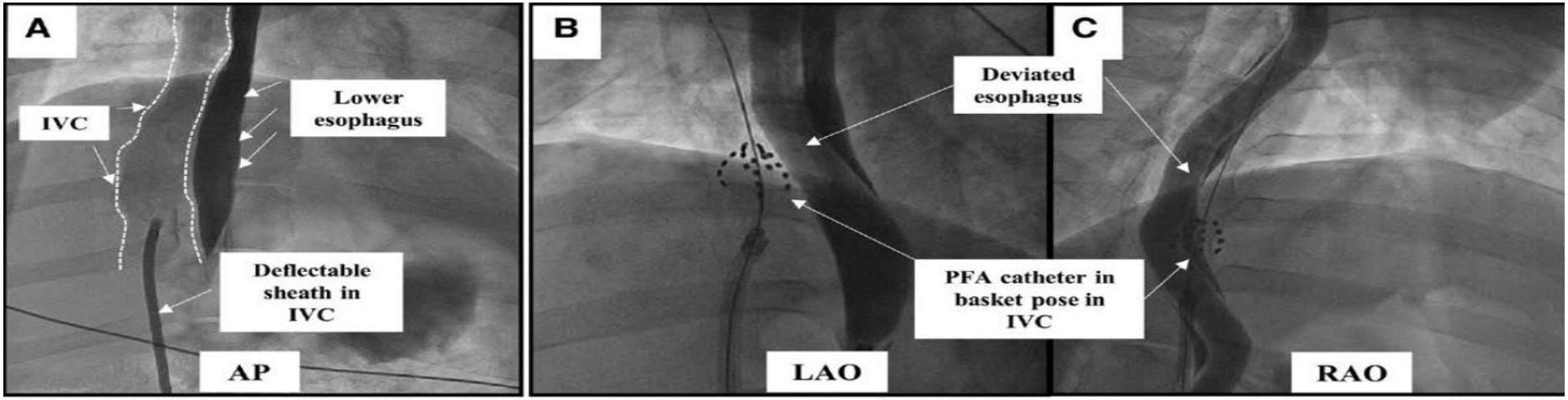


Heart Rhythm. 2015 Aug;12(8):1838-44.

Pulsed Field Ablation Versus Radiofrequency Ablation

Esophageal Injury in a Novel Porcine Model

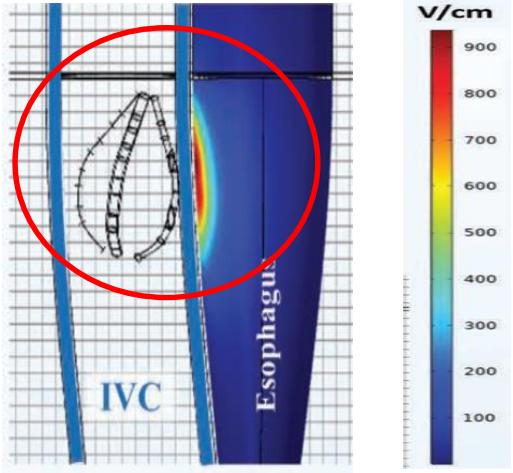
Jacob S. Koruth, MD; Kenji Kuroki, MD; Iwanari Kawamura, MD; Richard Brose, MS; Raju Viswanathan, PhD; Eric D. Buck, MS; Elina Donskoy, MD, PhD; Petr Neuzil, MD, PhD; Srinivas R. Dukkipati, MD; Vivek Y. Reddy, MD



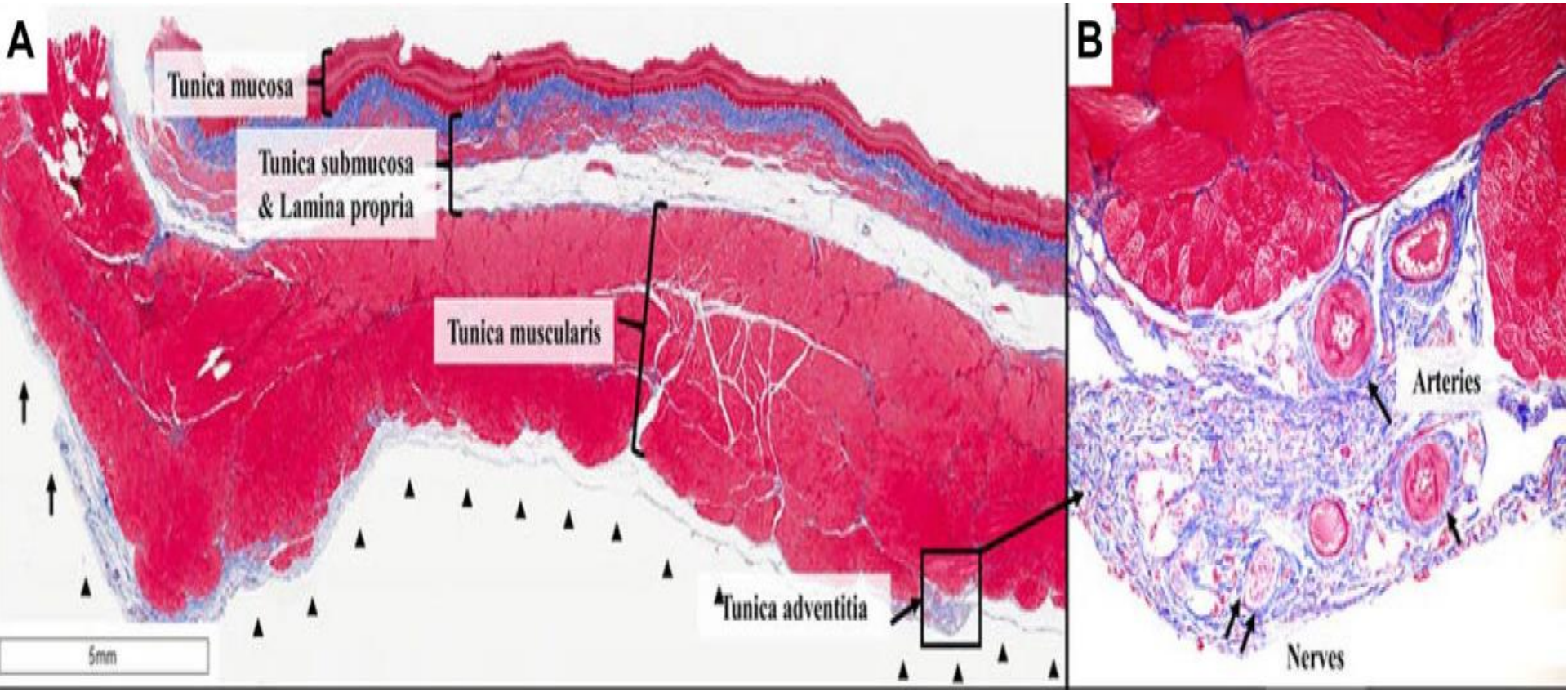
Fluoroscopic view of the esophageal injury mode: pulsed field ablation (PFA) cohort.

WHAT THE STUDY ADDS?

- A novel preclinical model was created to nonsurgically assess the response to esophageal injury. This was accomplished by delivering the energy source from within the inferior vena cava, against the esophagus (which was purposefully mechanically deviated toward the inferior vena cava).
- Biphasic pulsed field ablation induced no chronic histopathologic esophageal changes, whereas radiofrequency catheter ablation demonstrated a spectrum of esophageal lesions including esophageal ulcers, abscess, and fistula.



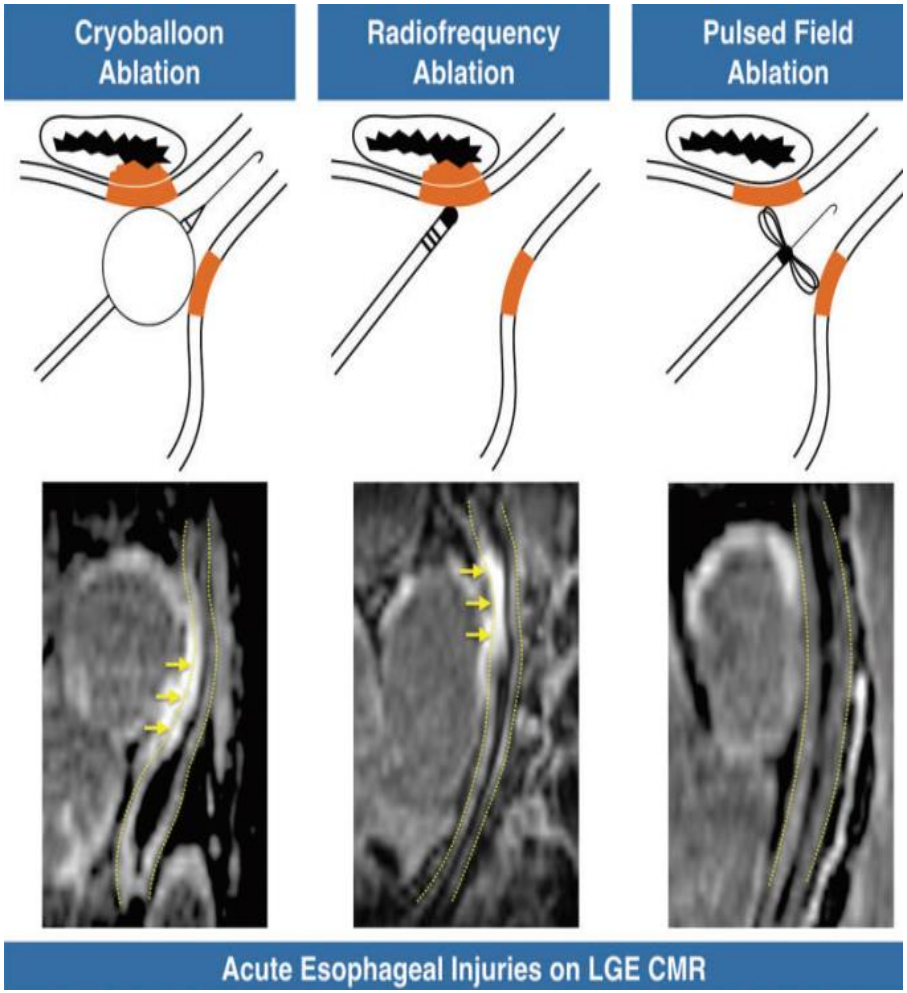
Circ Arrhythm Electrophysiol 2020; 13: e00803



- **<u>Esophageal histology after application of PFA</u>**.
- A) all 4 layers of esophageal wall are shown after application of PFA. These layers are **<u>all normal along the entire circumference of the esophagus</u>**
- B) **<u>magnified view of tunica adventitia</u>** is shown which depicts **<u>normal vessels</u>** and **<u>nerve fascicles without any fibrosis or inflammation</u>**.

Circ Arrhythm Electrophysiol 2020; 13: e00803

Pulsed field ablation selectively spares the oesophagus during pulmonary vein isolation for atrial fibrillation



Conclusions

- **PFA** used to isolate the PVs in patients with paroxysmal AF create transmural myocardial lesions
- Crucially, **PFA does not induce any signs of esophageal injury** while these are commonly observed after thermal ablation.

Europace 2021 Sep 8;23(9):1391-1399

Preclinical assessment of the feasibility, safety and lesion durability of a novel 'single-shot' pulsed field ablation catheter for pulmonary vein isolation

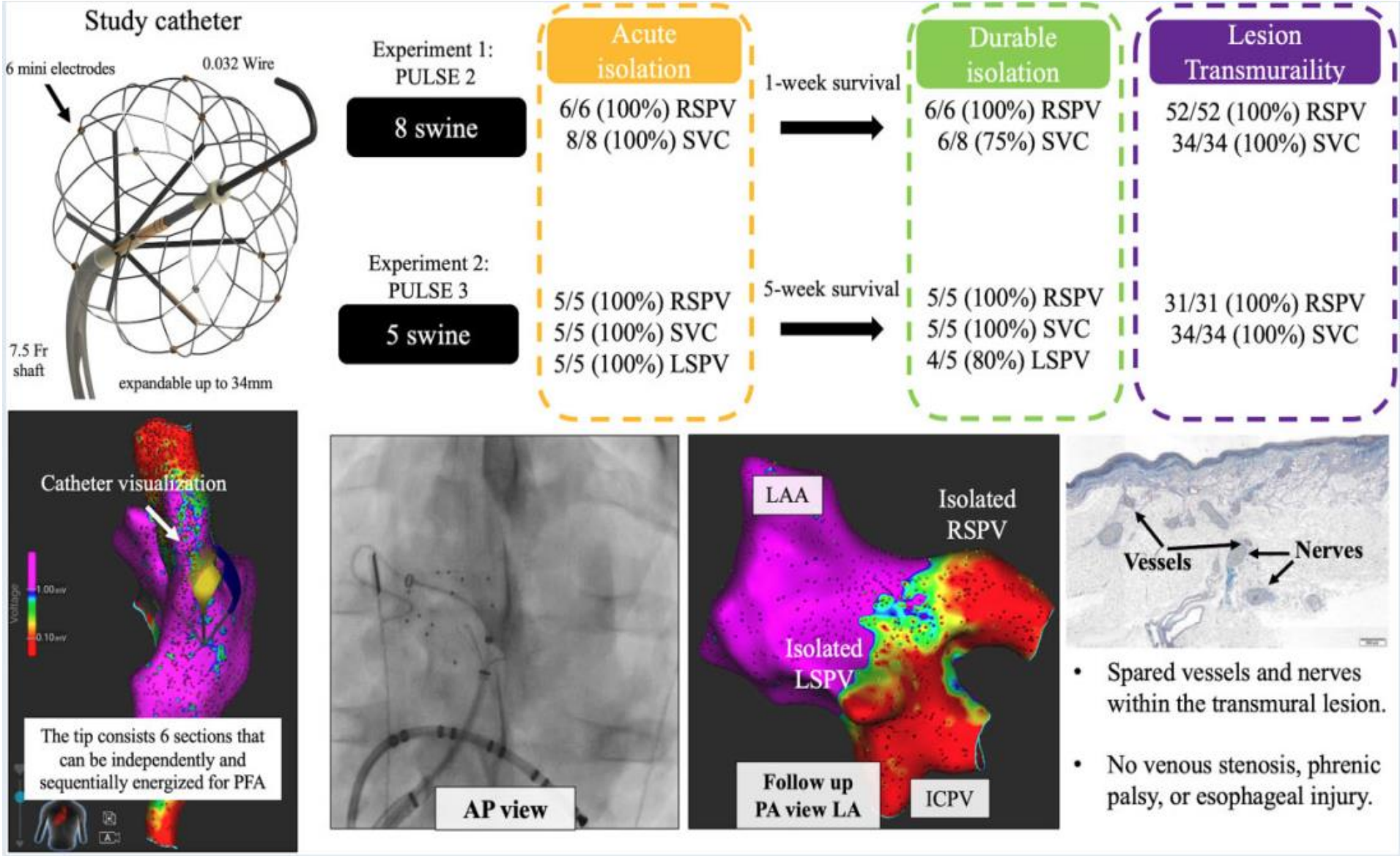
Jacob Koruth [1]*, Iwanari Kawamura [1], Srinivas R. Dukkipati[1], Petr Neuzil [2], and Vivek Y. Reddy [1]

Aims Single-shot pulmonary vein isolation can improve procedural efficiency. To assess the capability of a novel, expandable lattice-shaped catheter to rapidly isolate thoracic veins using pulsed field ablation (PFA) in healthy swine.

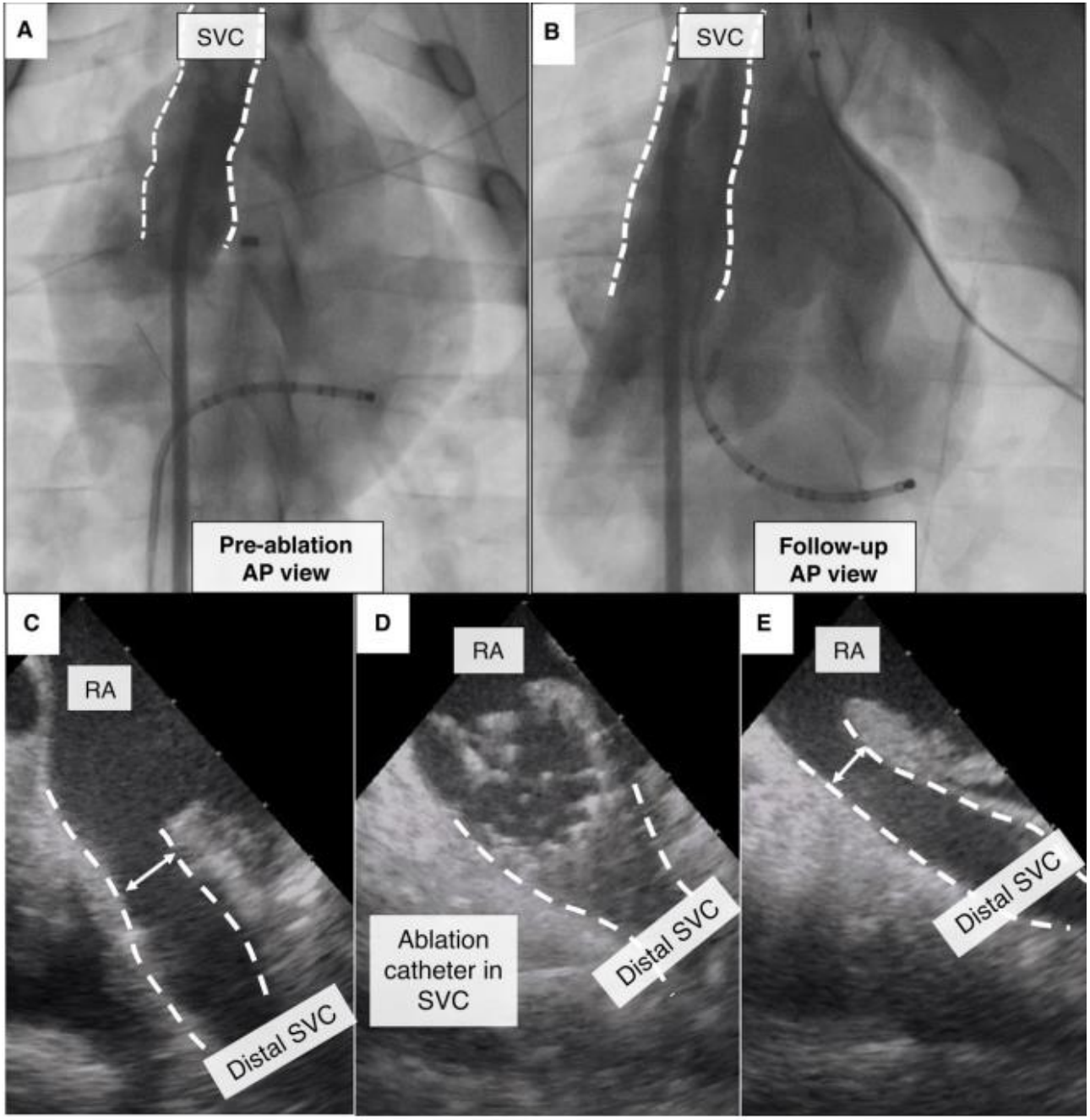
Methods and results The study catheter (SpherePVI; Affera Inc) was used to isolate thoracic veins in two cohorts of swine survived for 1 and 5 weeks. In Experiment 1, an initial dose (PULSE2) was used to isolate the superior vena cava (SVC) and the right superior pulmonary vein (RSPV) in six swine and the SVC only in two swine. In Experiment 2, a final dose (PULSE3) was used for SVC, RSPV, and left superior pulmonary vein (LSPV) in five swine. Baseline and follow-up maps, ostial diameters, and phrenic nerve were assessed. Pulsed field ablation was delivered atop the oesophagus in three swine. All tissues were submitted for pathology. In Experiment 1, all 14/14 veins were isolated acutely with durable isolation demonstrated in 6/6 RSPVs and 6/8 SVC. Both reconnections occurred when only one application/vein was used. Fifty-two and 32 sections from the RSPVs and SVC revealed transmural lesions in 100% with a mean depth of 4.0 ± 2.0 mm. In Experiment 2, 15/15 veins were isolated acutely with 14/15 veins (5/5 SVC, 5/5 RSPV, and 4/5 LSPV) durably isolated. Right superior pulmonary vein (31) and SVC (34) sections had 100% transmural, circumferential ablation with minimal inflammation. Viable vessels and nerves were noted without evidence of venous stenosis, phrenic palsy, or oesophageal injury.

Conclusion This novel expandable lattice PFA catheter can achieve durable isolation with transmurality and safety.

Europace. 2023 Apr 15;25(4):1369-1378.



Europace. 2023 Apr 15;25(4):1369-1378.



Europace. 2023 Apr 15;25(4):1369-1378.

Endocardial ventricular pulsed field ablation: a proof-of-concept preclinical evaluation

Jacob S. Koruth [1]*, Kenji Kuroki[1], Jin Iwasawa[1], Raju Viswanathan[2], Richard Brose[2], Eric D. Buck[2], Elina Donskoy[3], Srinivas R. Dukkipati[1], and Vivek Y. Reddy[1]

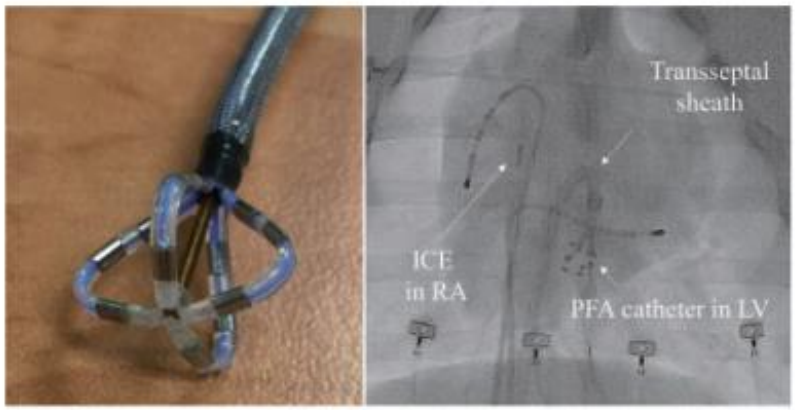
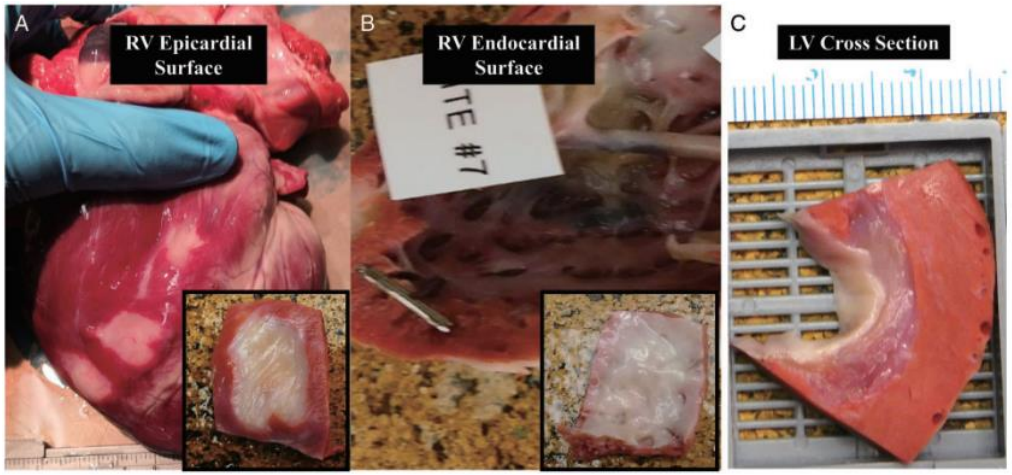


Figure 1 (Left panel) Distal aspect of the ablation catheter in deployed position. (Right panel) Fluoroscopic view demonstrating pacing catheters placed in the right ventricle and coronary sinus along with ICE positioned in the RA. A deflectable transseptal sheath is in position with the ablation catheter positioned in the LV. ICE, intracardiac echocardiography; LV, left ventricle; PFA, pulsed field ablation; RA, right atrium.



- In this initial study of an exploratory dose, we demonstrate that **endocardial focal PFA can be delivered using a prototype catheter**.
- **Myocardium-specific lesions were rapidly and safely created, with dimensions that are relevant for ablation of ventricular tachycardia** in the clinical setting.

Europace. 2020 Mar 1;22(3):434-439.

Pulsed Field Ablation of Left Ventricular Myocardium in a Swine Infarct Model

Sung Il Im, MD, PhD,[a] Satoshi Higuchi, MD, PhD,[a] Adam Lee, MBBS, MMed (Clin Epi),[a] Carol Stillson, RVT,[a]
Eric Buck, MS,[b] Blake Morrow, MS,[b] Kit Schenider, MEng,[b] Molly Speltz, DVM,[c] Edward P. Gerstenfeld, MD[a]

FIGURE 1 PFA and RFA Catheters and Gross Infarct in a Porcine Infarct Model

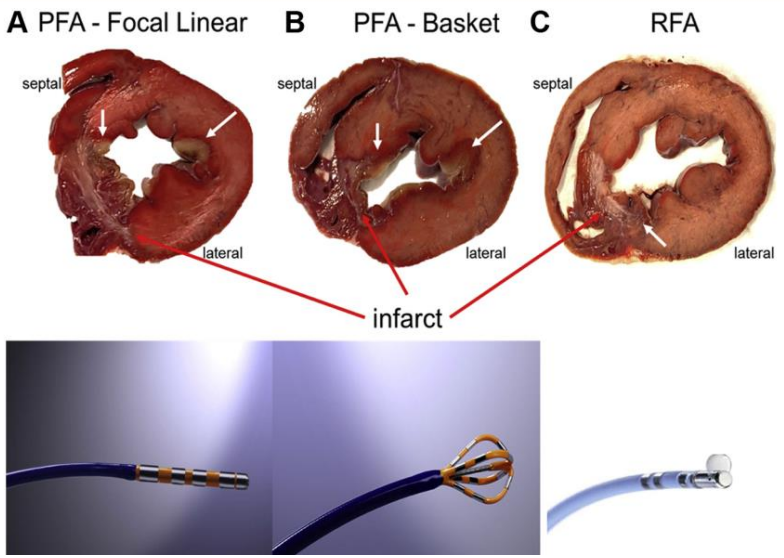
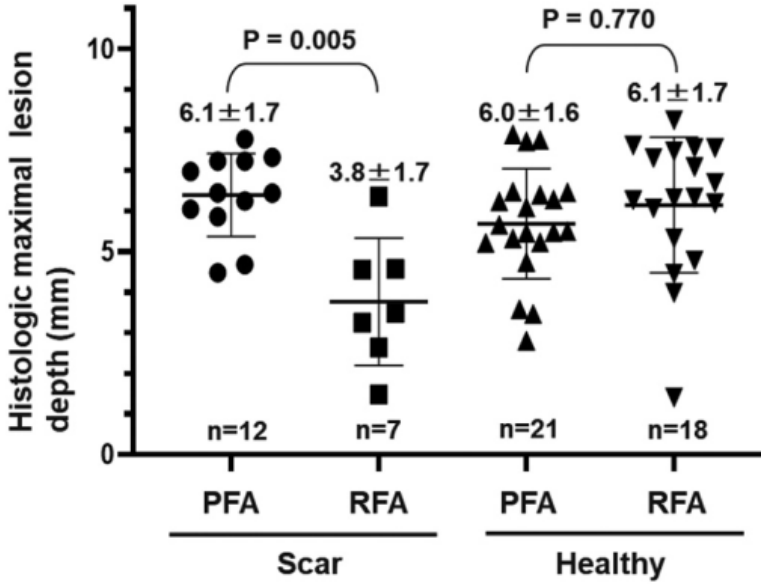


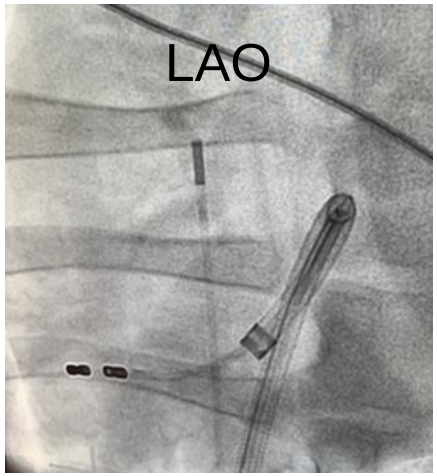
FIGURE 6 Histologic Maximal Lesion Depth Comparison

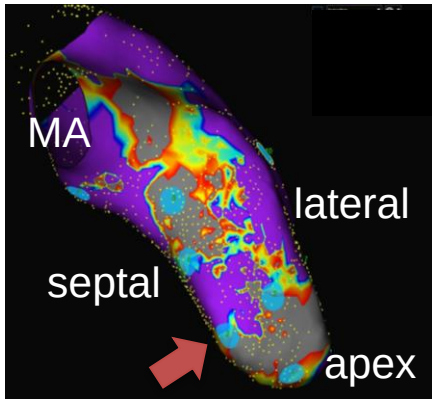


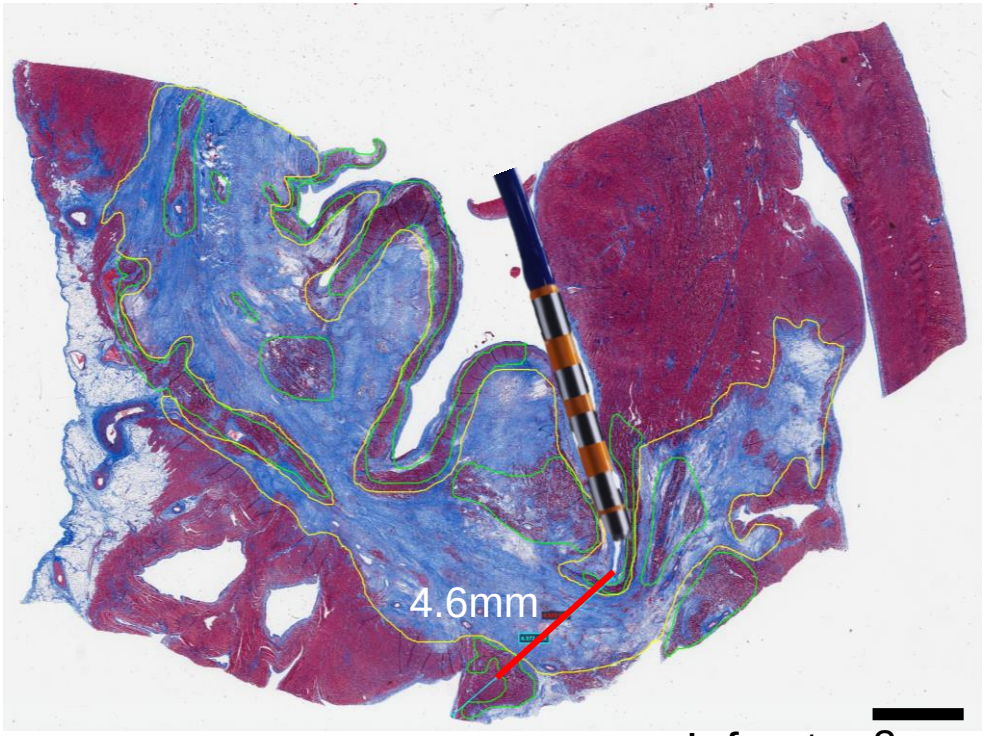
CONCLUSIONS PFA allows rapid, safe, and effective ablation of surviving islands of myocardium within and around infarcted LV substrate. This technology holds promise for treating infarct-related ventricular tachycardia in humans.

JACC Clin Electrophysiol. 2022 Jun;8(6):722-731

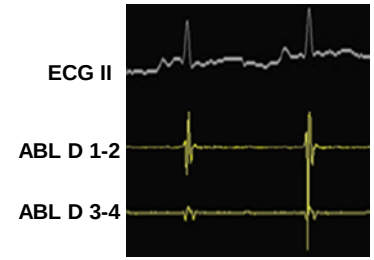
Focal linear - Apical-septal Infarct





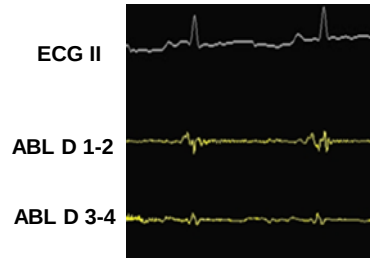


Pre



Pre ablation Voltage (mV) 1.0 mV

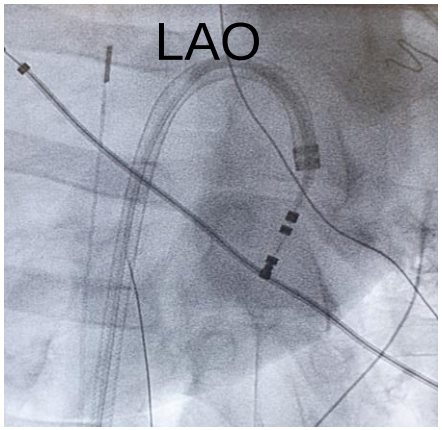
Post

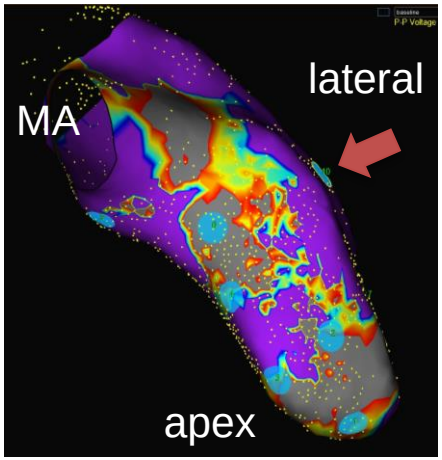


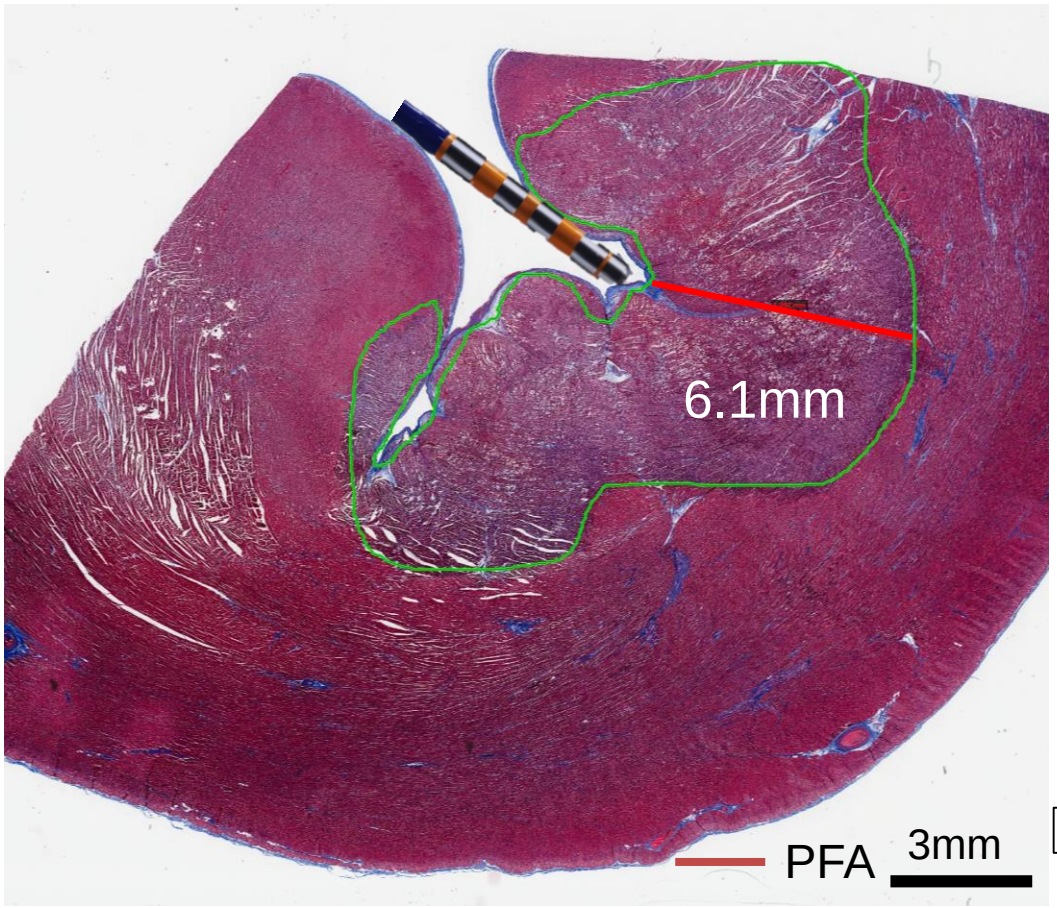
Post ablation Voltage (mV) 0.3 mV

JACC Clin Electrophysiol. 2022 Jun;8(6):722-731

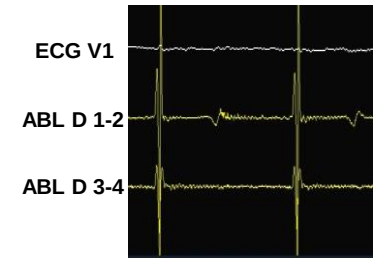
Focal linear – Healthy Myocardium





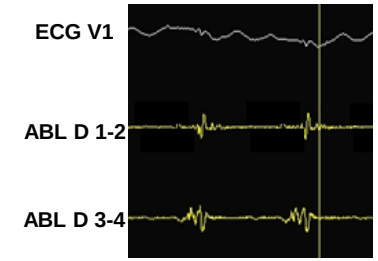


Pre



Pre ablation Voltage (mV) 4.6 mV

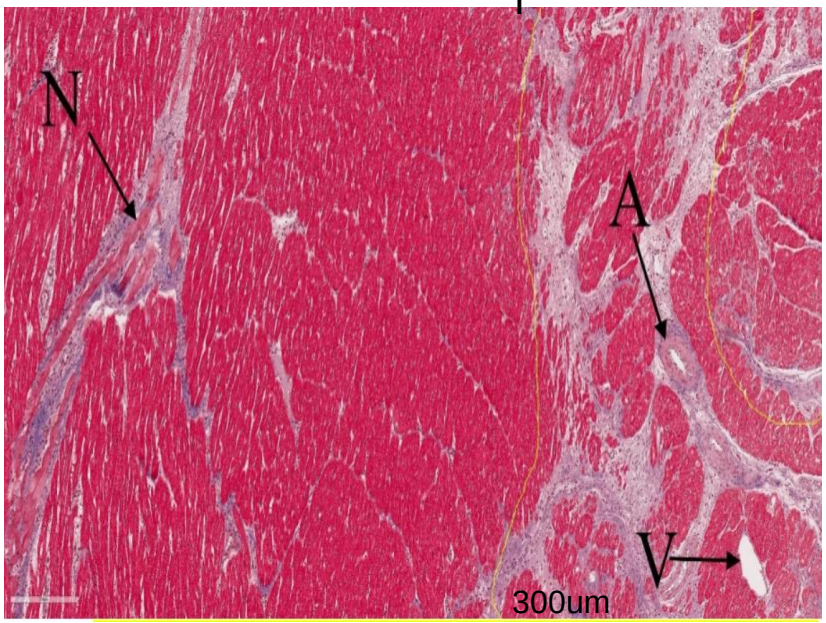
Post



Post ablation Voltage (mV) 0.6 mV

JACC Clin Electrophysiol. 2022 Jun;8(6):722-731

PFA Spares Nerve, Artery and Vein

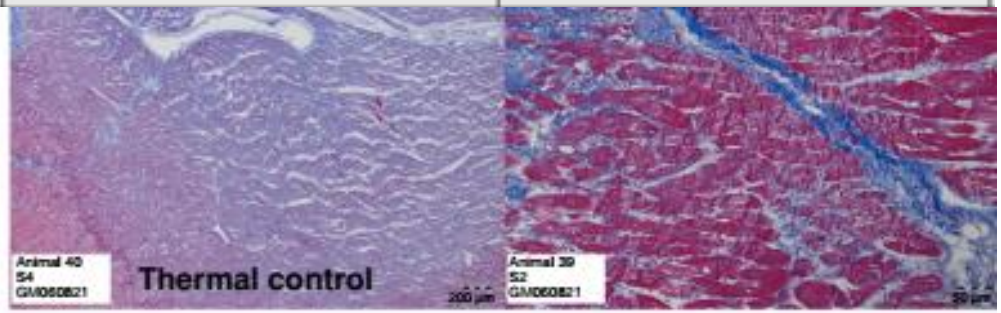


N=nerve
A=artery
V=vein

JACC Clin Electrophysiol. 2022 Jun;8(6):722-731

In vivo pulsed-field ablation in healthy vs. chronically infarcted ventricular myocardium: biophysical and histologic characterization

Model	Coagulative necrosis (% of sections)	Contraction band necrosis (% of sections)
PFA (n = 25 sections)	16	100
Thermal ablation (n = 4 sections)	75	100



What's new?

- Pulsed-field ablation (PFA) was able to generate effective lesions in and around a ventricular scar in a swine myocardial infarction (MI) model, with lesions that were only slightly smaller than those made in normal myocardium.
- Histology confirmed the penetration of PFA effects into surviving myocytes within the MI scar, and occasionally beyond it, to the epicardial scar border as well.
- Contact force and the degree of R-wave amplitude reduction did not predict lesion formation or lesion size.

Europace. 2023 Apr 15;25(4):1503-1509.

RESEARCH ARTICLE

Feasibility of selective cardiac ventricular electroporation

Alan Sugrue[1], Vaibhav R. Vaidya[1], Christopher Livia[2], Deepak Padmanabhan[1], Anas Abudan[1], Ameesh Isath[1], Tyra Witt[2], Christopher V. DeSimone[1], Paul Stalboerger[2], Suraj Kapa[1], Samuel J. Asirvatham[1,3], Christopher J. McLeod[1]*

Table 3. Histopathological analysis from acute animals.

Animal	Myocardial damage		Subendocardial Ablation (average percentage) *	Purkinje damage
	Contraction Necrosis	Endocardial hemorrhage		
1	None	None	No (0%)	No
2	Minimal	Mild	Yes (1.0%)	Yes
3	None	Minimal	Yes (5.0%)	Yes
4	None	Minimal	Yes (1.0%)	Yes
5	Minimal	Minimal	Yes (1.0%)	Yes

Table 4. Histopathological analysis from the chronic animals.

Animal	Myocardial damage		Subendocardial Ablation (average percentage)*	Purkinje damage
	Endocardial fibrosis	Myocardial fibrosis		
1	Minimal	Minimal	Yes (11.7%)	No
2	None	None	No	No
3	Minimal	Minimal	Yes (15.0%)	No
4	Minimal	Minimal	Yes (24.0%)	No
5	Minimal	Minimal	Yes (17.5%)	No
6	Minimal	Minimal	Yes (11.7%)	No

PLoS One . 2020 Feb 21;15(2):e0229214.

Conclusion

PEF can be safely delivered to the endocardium of the ventricle and at our pulsing protocol we have observed a dose-dependent cell-specific effect on ventricular myocardium. Specifically with the energy we delivered, we observed a PEF effect on electrical conduction on all left ventricular Purkinje fibers with limited damage to the underlying myocardium in canine studies. Further study and electric field modification are necessary to study reversible and irreversible effects on these fibers, as well as implications for cardiac conduction, mechanical function and especially ventricular arrhythmia initiation and propagation.

PLoS One . 2020 Feb 21;15(2):e0229214.

https://doi.org/10.1093/europace/euac179

Selective sparing of Purkinje fibres with pulsed-field myocardial ablation

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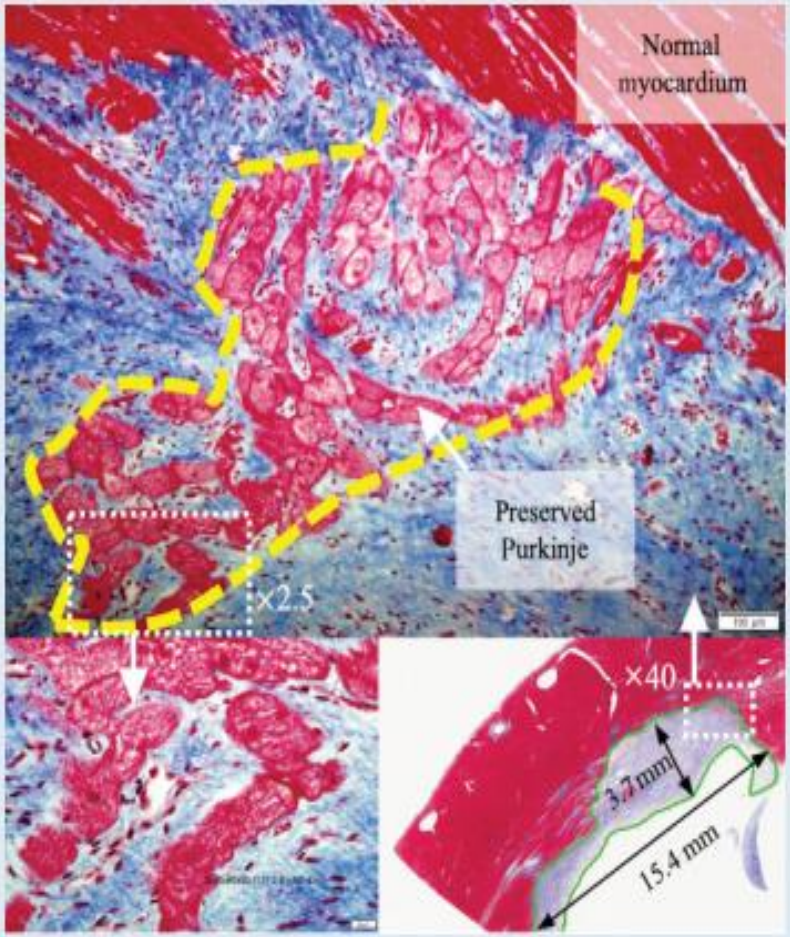
The effect of pulsed fields on the conduction system has not been well characterized. Selected lesions ($n = 26$) from four swine ventricles were submitted as part of a dosing study after bipolar, biphasic ablation using a multielectrode catheter (Faraflex, Farapulse Inc.) that delivers, microsecond pulses (2.2 kV) —four applications/site were applied. Histology after 4 weeks revealed a single image of viable Purkinje fibres (PjF), despite the ablation of adjacent cardiomyocytes as evidenced by fibrosis surrounding the PjF (*Panel*). The sparing of PjF seen, although a solitary finding, in this study may suggest a lower susceptibility than cardiomyocytes and requires further confirmatory studies.

This study was supported by a research grant from Farapulse Inc.

Conflict of interest: V.Y.R. hold stock options in Farapulse, Inc. J.S.K. serves as a consultant to Farapulse. The other authors report no conflicts.



RESEARCH LETTER

Troponin release after pulmonary vein isolation using pulsed field ablation compared to radiofrequency and cryoballoon ablation

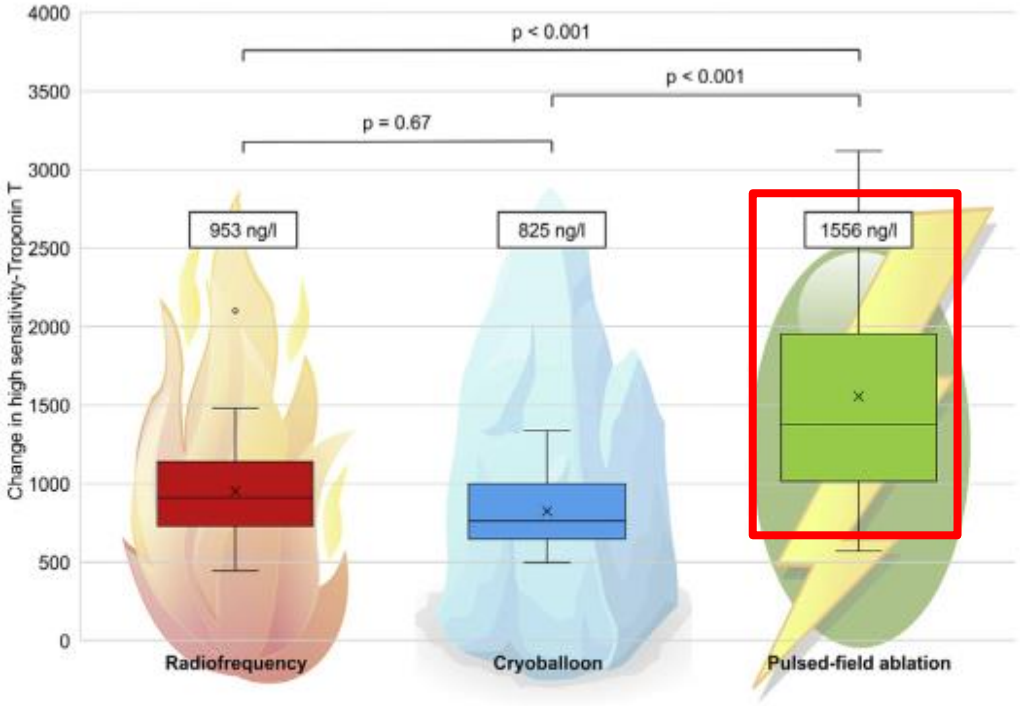


Figure 1 Change in high-sensitivity troponin T stratified by ablation modality. *Boxes* contain interquartile range; *horizontal lines* the median; *crosses* and *numbers* the mean; and *whiskers* the most extreme values within 1.5* interquartile range and further values as individual points.

- Respective ablation times

1) RF: 1328±316 secs 2) Cryo: 1097±325 secs
3) PFA: 84±29 secs

- Prospectively **60 patients** undergoing their **first PVI (20/ablation modality)** measured **hsTnT levels** 1day before and the morning after the procedure.

- Alternatively, **larger increase in biomarkers may indicate more comprehensive ablation** inside PV antrum by the basket shape of PFA catheter compared to linear, antral ablation by thermal energies.

Conclusion

- we found a **significantly higher increase of hsTnT** as a **surrogate for myocardial injury** after PFA compared to RF and Cryo

Heart Rhythm 2022;19:1471–1472.

Summary (PFA)

- PFA of viable and infarcted myocardium in both atrium & ventricle is feasible
- PFA waveforms quickly and safely produced lesion depths up to >5mm
- In myocardial infarct, lesion depths were greater with PFA compared to RFA
- Nerve/artery/vein spared with PFA, except reversible coronary spasm
- Electroporation is a promising energy source for rapid ablation of atrial & ventricular myocardium to treat arrhythmia

Thank You for Your Attention!!