

Novel concepts in atrial fibrillation ablation—breaking the trade-off between efficacy and safety

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Abstract

Despite substantial technological and procedural advances that have improved the efficacy and safety of AF ablation in recent years, the long-term durability of ablation lesions is still not satisfactory. There also remains concern regarding rare but potentially life-threatening procedure-related complications like cardiac tamponade and atriopharyngeal fistulae. Current ablation strategies are aiming to optimize the trade-off between efficacy and safety, where more extensive ablation appears to inevitably increase the risk of collateral injury. However, new forms of energy application may have the potential to resolve this quandary. The emerging concept of high power-short duration radiofrequency ablation features a more favorable lesion geometry that appears ideally suited to create contiguous lesions in the thin-walled atrium. Moreover, novel non-thermal ablation methods based on electroporation appear to provide a unique selectivity for cardiomyocytes and to spare surrounding tissues composed of other cell types. Both, high power-short duration and electroporation ablation might have the potential to break the trade-off between effective lesions and collateral damage and to substantially improve risk-benefit ratios in AF ablation. In addition, both approaches lead to considerable reductions in ablation times. However, their putative benefits regarding efficacy, efficiency, and safety remain to be proven in randomized controlled trials.

KEYWORDS

atrial fibrillation, catheter ablation, electroporation, high power-short duration ablation, pulsed-field ablation

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common clinically relevant arrhythmia and associated with substantial morbidity and mortality, inferring a high socioeconomical burden.¹ The currently estimated prevalence of AF in adults in Europe is between 2% and 4%, and a 2.3-fold rise is expected over the next 40 years.¹ Ablation therapy in terms of

pulmonary vein isolation (PVI) is a cornerstone of AF treatment, and accumulating data indicates that it may be superior to medical therapy.^{2,3} Technological advances have substantially improved the efficacy and safety of AF ablation. Besides improved clinical outcome in terms of AF burden, this is evidenced by increasing rates of redo-procedures where persistent isolation of all pulmonary veins is encountered.⁴⁻¹⁰ However, despite these advances, in almost 40 percent

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of the redo-procedures at least one pulmonary vein is still found to be reconnected, which reflects non-durable ablation lesions that appear to be one of the primary mechanisms of AF recurrence.⁶ On the other hand, severe complications such as cardiac tamponade or esophageal injury still occur. According to the current paradigm more extensive ablation, required to improve lesion durability, inevitably increases the risk of collateral injury. Thus, current ablation strategies are aiming to optimally balance safety with efficacy. This review will focus on two novel concepts of energy applications, high power-short duration (HPSD) radiofrequency (RF) ablation and electroporation-based ablation, that may have the potential to break the trade-off between the lesion extent and durability and procedural risk, and to improve the risk-benefit ratio of AF ablation.

The concept of HPSD ablation aims to minimize conductive heating and increase resistive heating to deliver targeted energy to the atrial wall, while reducing the risk of collateral tissue damage.¹¹ On the other hand, novel methods of electroporation-based ablation, which in contrast to radiofrequency, cryotherapy, and laser ablation is a non-thermal ablative mechanism, appear to preferentially ablate myocardial tissue and to spare non-myocardial tissue such as blood vessels or nerve fibers. Against this background, these two emerging concepts have the unique potential to reduce the risk of collateral tissue damage without compromising myocardial ablative efficacy.

2 | HIGH POWER-SHORT DURATION RADIOFREQUENCY ABLATION

2.1 | Rationale and basic principles

RF ablation results in two consecutive phases of tissue heating. In the first phase, direct resistive heating occurs immediately upon RF application as a result of electric current flow and local tissue resistance. In the proximity of the catheter electrode, where the current density is sufficiently high, this will result in temperatures $\geq 50.0^{\circ}\text{C}$ leading to immediate tissue denaturation and cell death.¹² As current density decreases rapidly with distance to the electrode, the area of resistive heating is spatially very limited and does typically not cover the full atrial transmurally when conventional power settings are applied. However, this direct and locally restricted resistive heating creates a temperature gradient along which thermal conduction and

subsequent heating of adjacent and deeper tissue layers occur with a temporal delay until an equilibrium is reached. This progressive heat transfer is relatively slow, which explains why RF application times of 30–60 seconds may be required to accomplish transmural lesions. Moreover, depending on the distance to the heat source this second phase of conductive heating may result in local temperatures $< 50^{\circ}$ and thus reversible injury with edema formation.^{12,13}

The heat generated by resistive heating is proportional to the product of local tissue resistance and the square of the current flow. The variables that determine current flow and thus resistive heating in RF ablation are the applied power and the total circuit impedance. While conductive heating is secondary to the temperature gradient created by resistive heating and thus also dependent on the applied power, its main determinant is the duration of an RF application. Hence, with RF applications of high power and short duration, resistive heating is predominating over conductive heating (Figure 1). The rationale of this concept is to achieve homogeneous and irreversible lesions through immediate resistive heating of the full transmurally, while limiting delayed thermal conduction that may result in less predictable, more heterogeneous lesions and could inadvertently affect adjacent tissues and organs.^{12,13}

2.2 | Lesion geometry

As a consequence of the increasing ratio of resistive to conductive heating, HPSD ablation results in shallower, less invasive lesions with a wider diameter (Figure 1). These lesions are typically better demarcated with the border zones of reversible injury being smaller compared to conventional RF ablation. As temperature dispersion in the tissue is more uniform with resistive heating, HPSD may also improve transmural homogeneity and lesion-to-lesion consistency. In line with these theoretical considerations and experimental observations *ex vivo*, preclinical studies using porcine models are suggestive of more uniform and contiguous ablation lines compared with conventional RF ablation.^{13,14}

2.3 | Clinical data

As the term of HPSD ablation is not well-defined, clinical data is very heterogeneous reporting on a wide spectrum of power and duration

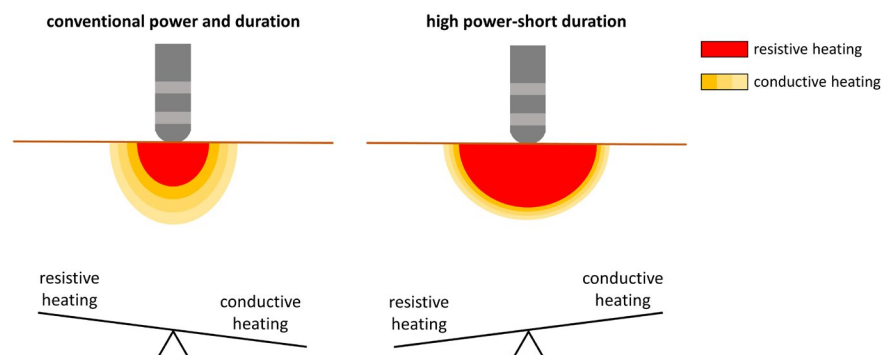


FIGURE 1 Resistive versus conductive heating in radiofrequency ablation (adapted from Leshem *et al. J Am Coll Cardiol EP* 2018;4:467–79)¹³

settings ranging from 45 W over 15 seconds to 90 W over 4 seconds. The feasibility and relative safety of PVI have been demonstrated along the full spectrum.

Winkle et al reported on successful PVI with very low complication rates in 13,974 HPSD ablations performed in 4 experienced centers applying RF powers of 45–50 W over 2–15 seconds.¹⁵ However, higher power settings have been investigated as well. Interestingly, Kottmaier et al found significantly less arrhythmia recurrence during 1-year follow-up in 97 patients undergoing HPSD ablation with 70 W over 5–7 seconds compared to a historical control group of 100 patients undergoing conventional RF ablation (83.1% vs. 65.1% freedom of arrhythmia).¹⁶ Again, no serious procedure-related complications occurred in either group.

In the POWER FAST PILOT study, PVI was accomplished in 100% of the PVs in 48 patients by application of either 50 W ablation index- or LSI-guided (18 patients), or 60 W over 7–10 seconds (30 patients).¹⁷ The safety profile was good compared to a historical control group, with no pericardial effusion. Postprocedural esophageal endoscopy performed in all patients found less esophageal lesions in the HPSD groups. It is noteworthy that audible steam pops occurred in 8% of the patients treated by HPSD ablation.

Two recent trials also investigated ablation index-guided approaches of HPSD ablation. The FAFA AI High Power Study applied 50W, targeting ablation index values of 550 at the anterior wall and 400 at the posterior wall.¹⁸ Complete PVI was achieved in all 50 patients with very high first-pass isolation rates (92%) and absence of major complications such as death, stroke, tamponade, or atrio-esophageal fistula. Postablation esophageal endoscopy performed in all patients revealed only one patient (2%) with a minimal lesion. Steam pops were perceived by the operators in 8%, interestingly all of them during left anterior ablation with ablation index values >550. Another approach of ablation index-guided HPSD ablation was reported in the POWER AF study that randomized a total of 100 patients with paroxysmal AF to ablation following the CLOSE protocol with 45 W versus 35 W power.¹⁹ There were no significant differences between the groups regarding any of the outcome measures. Of note, first-pass isolation was achieved in 96% of the pulmonary veins with 45 W. Moreover, no acute procedural complications nor steam pops were observed in any of the groups. An intraesophageal temperature rise >38.5°C, which by protocol triggered an endoscopic evaluation, occurred in 40% of the high power group and in 52% of the control group, with one esophageal lesion evidenced by endoscopy in each group. In the case of high power ablation, this was an esophageal perforation that necessitated positioning of a covered stent. Retrospective analysis revealed that both lesions occurred following excessive RF applications with ablation index values of 460–480 and inadvertent application of contact forces up to 50 g in the proximity of the esophagus.

In order to allow for safe application of very high power an ablation catheter with a novel thermocouple technology has been introduced that enables valid monitoring of the temperature at the interface of the catheter tip and endocardial tissue in real-time despite irrigation

(QDOT MICRO™ Catheter; Biosense Webster, Inc).²⁰ In the very high power mode the associated RF generator modulates power up to 90 W to maintain target temperatures of 60°C. In the QDOT FAST study, temperature-controlled ablation using this catheter has proven to be safe with a power as high as 90 W applied over 4 seconds.²¹ PVI was achieved in all 52 patients, however, additional ablations using a standard ablation mode (50 W) with the same catheter were deemed necessary by the investigator in 21% of the patients. While no procedural complications occurred, there was one subclinical cerebral thromboembolism evidenced by MRI and one esophageal ulcer bleeding observed in esophageal endoscopy. Unfortunately, the incidence of steam pops that this system aims to prevent, has not been reported.

Not surprisingly, HPSD ablation consistently resulted in a reduction of RF and procedure times throughout all studies. This was obviously most pronounced when very high power was applied. In the study by Kottmaier et al (70 W, 5–7 seconds) mean RF time (12.4 vs. 35.6 min) and procedural time (89.5 min vs. 111.15 min) were significantly shorter in the HPSD group compared to the historical control group.¹⁶ In the QDOT fast trial (90 W, 4 seconds) RF application time was even shorter (mean 8.1 min) resulting in a mean procedure time of 105 minutes (including 20 min waiting time).²¹

In line with their preclinical data indicating enhanced lesion contiguity and transmural, Yavin et al demonstrated improved long-term lesion durability with HPSD ablation.¹⁴ While they found first-pass isolation rates to be similar in HPSD (90%) compared to conventional ablation (83%), pulmonary vein reconnection in patients who required a redo procedure was observed much more frequently after conventional ablation (52.2% vs. 16.6%; $P = .03$).

2.4 | Limitations and safety

Randomized controlled trials are warranted to demonstrate whether the potential advantages of HPSD ablation approaches indeed translate into clinical benefit beyond shorter procedure times and to define relative safety compared to established approaches. Even though in clinical data generated so far there is no signal for an excess in any complication like cardiac tamponade or stroke, the potential risk of steam pop and thrombus formation with high power RF applications remains a concern. Moreover, despite a theoretically more favorable lesion geometry, serious esophageal injury did still occur in clinical trials investigating HPSD ablation,¹⁹ and according to a recent report, the incidence of esophageal lesions may be substantially higher than suggested by some of the above-mentioned trials.²² This may reflect the narrower safety margin when applying RF at high or very high power, where only slightly superoptimal RF application times can already constitute a substantial overshoot resulting in serious complications.¹³ Moreover, ablation with contact forces >20 g was recently identified as an independent predictor of esophageal thermal injury in ablation index-guided HPSD-ablation.²³ Against this background, avoidance of excessive contact force and RF application, particularly at the posterior wall in the proximity of the esophagus, appears to be even more critical in HPSD ablation.^{13,19} In that respect, it is also

noteworthy that the amount of energy delivered is determined by current flow rather than the applied power and is therefore dependent on total impedance. Thus, there can be substantial variability in lesion size based on differences in total impedance, despite identical power settings. This may be particularly relevant in high power applications associated with a pronounced decrease in local impedance that could result in excessive energy delivery. In this context, current-controlled ablation may be an option to improve safety.²⁴

Whether real-time temperature measurement at the catheter-tissue interface using novel thermocouple technologies does indeed reliably reflect tissue temperatures and can thus guide energy delivery through an automated feedback system to reduce the risk of steam pops, thrombus formation, and collateral injury remains to be determined.²⁰

One of the potential advantages of HPSD ablation is the shorter period of time over which the catheter has to be maintained in a stable position. However, the other side of the coin is that with RF application times of as little as 4 seconds, catheter stability appears to be even more critical, as a brief loss of catheter position or tissue contact may already constitute a relevant proportion of the total RF application and thus lead to an incomplete lesion.

3 | ELECTROPORATION

3.1 | Rationale and Basic principles

In contrast to all currently established ablation methods, electroporation constitutes a non-thermal mechanism where the application of an electrical voltage gradient between tissue-spanning electrodes establishes a high voltage electric field, which will lead to a transcellular current flow and the formation of nanoscale pores in the cell membrane lipid bilayers (Figure 2). If the transcellular electrical field is above a tissue-specific threshold, the resulting pore formation will be permanent and eventually culminate in cell death.^{25,26}

Electroporation can be accomplished by the application of direct current (DC), alternating current or pulsed DC, and in fact the DC ablations performed in the 1980s may have been based on the mechanism of electroporation without electrophysiologists being aware of it at the time. Most systems currently under investigation in clinical trials for AF ablation and PVI employ so-called pulsed-field ablation (PFA) with sub-second trains of high voltage biphasic DC pulses in the millisecond range delivered in a bipolar manner by multipolar catheters in terms of single-shot devices.^{25,26} However, very recently, technical feasibility and safety of PVI has also been demonstrated for single pulse electroporation ablation, where a single monophasic capacitive discharge was applied through a circular multielectrode catheter.²⁷ Monophasic pulses typically cause substantial muscular activation compared to biphasic waveforms and thus may require general anesthesia. How different application forms of electroporation, including single pulse electroporation versus PFA with distinct waveforms, affect lesion characteristics and safety properties remains to be defined.

Electroporation

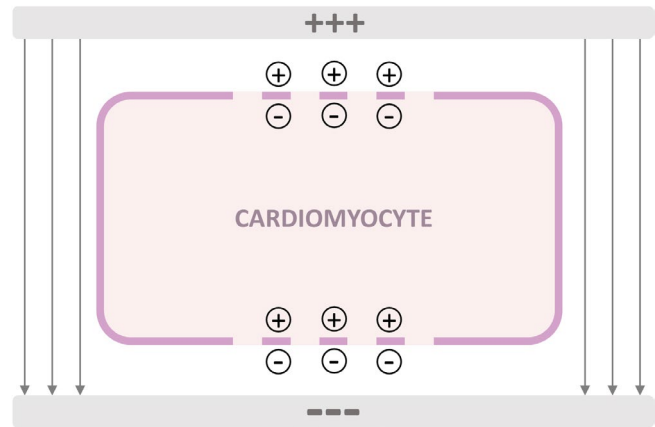


FIGURE 2 Electroporation and formation of permanent pores resulting in irreversible cell death.

3.2 | Lesion characteristics

In general, compared to radiofrequency ablation lesions, electroporation lesions appear more demarcated and of wider diameter at similar depth (as with HPSD ablation). Unlike RF lesions, electroporation lesions do not show coagulation necrosis or hemorrhage. Moreover, electroporation spares intralesional vessels and nerves and does not cause epicardial fat tissue inflammation. Early replacement fibrosis of the treated tissue equally occurs after both RF and electroporation ablation, but the post-ablation fibrotic remodeling of the atrial wall was shown to be more homogeneous with electroporation, without islets of surviving cardiomyocytes or residual sequesters of necrotic cardiomyocytes. In particular, myocardial sparing around intralesional arteries or trabeculae because of convective cooling by arterial or intracavitary blood flow, as in RF ablation, has not been observed with electroporation.^{25,28}

3.3 | Ablation time

In contrast to thermal ablation forms, that require catheter stabilization over seconds (RF) or even minutes (Cryo), electroporation has been shown to create transmural lesions in less than one second.

3.4 | Tissue specificity

Perhaps the greatest potential advantage of electroporation-based ablation approaches is its relative selectivity for cardiomyocytes. The current density threshold for the formation of permanent pores and thus cell death appears to be relatively low in cardiomyocytes, while cell types at risk of collateral damage display higher thresholds. In particular, in preclinical studies electroporation of tumors that are vascularized and/or adjacent to blood vessels has left vascular structures intact. Of note, even when directly targeting the carotid

TABLE 1 Trials on PVI with high power-short duration ablation

Trial	Patients (n)	Trial design	Ablation settings & targets	Follow-up	Key findings for HPSD
Winkle et al. [15]	13, 974; parox. or pers. AF	Retrospective, observational, single-arm multicenter,	<ul style="list-style-type: none"> • 45-50 W, • 2-15 sec 	n.a.	<ul style="list-style-type: none"> • Very low complications rates • relatively low procedure and RF times
Kottmaier et al. [16]	97; parox. AF	Prospective, single-center, historical control	<ul style="list-style-type: none"> • 70 W • 5 s post., 7 s ant. Historical control: 30-40 W, 20-40 s	12 months	<ul style="list-style-type: none"> • Less arrhythmia recurrence after 1 year compared to historical control • Comparable safety • Shorter RF and procedural times
Castrejón Castrejón et al. [17]	48; parox. or pers. AF	Prospective, single-center, historical control, esophageal endoscopy in all patients	<ul style="list-style-type: none"> • 18 Pts: 50 W, LSI ≥ 5 or AI ≥ 350 • 30 Pts: 60 W, 7-10 s Historical control: 30 W, 30 s	No follow-up data provided	<ul style="list-style-type: none"> • Steam pops in 8% • Lower incidence and severity of esophageal lesions • Higher first-pass isolation rate • Shorter RF but not procedure time
Chen et al. [18]	50; parox. or pers. AF	Prospective, single-arm, single-center, esophageal endoscopy in all patients	<ul style="list-style-type: none"> • 50 W • AI targets: 550 ant., 400 post. 	6 months	<ul style="list-style-type: none"> • No major complications • Only 2% (1 patient) with esophageal lesion (minimal) • Steam pops in 8%
Wielandts et al. [19]	96; parox. AF	Randomized, single-center	<ul style="list-style-type: none"> • HPSD group: 45 W • Control group: 35 WAI-guided ablation (CLOSE-protocol) 	6 months	<ul style="list-style-type: none"> • Shorter procedure and RF times • Similar freedom of AF at 6 m • 1 ulcerative esophageal perforation in HPSD group • No acute procedural complications • No steam pops
Reddy et al. [21]	52; parox. AF	Prospective, multicenter, single-arm, MRI screening for silent cerebral lesions	<ul style="list-style-type: none"> • max. 90 W • temperature-controlled • 4 s 	3 months	<ul style="list-style-type: none"> • No serious adverse events • 1 asymptomatic cerebral thromboembolism • 6 patients with silent cerebral lesions • 1 esophageal ulcer bleeding
Yavin et al. [14]	112; parox. or pers. AF (18 with invasive re-mapping at redo)	Prospective, single-center, historical control group, assessment of lesion durability in redo procedures	<ul style="list-style-type: none"> • 45-50 W • 8-15 s Historical control: 20-40 W, 20-30 s	1.2 years (median)	<ul style="list-style-type: none"> • Higher first-pass isolation rate • Lower incidence of PV reconnection at invasive re-mapping during redo • Shorter RF time
Piringer et al. [22]	31; parox. or pers. AF	Prospective, single-center, single-arm, esophageal endoscopy in all patients	<ul style="list-style-type: none"> • 50 W • AI target post. 350 	106 d (mean)	<ul style="list-style-type: none"> • Esophageal lesions in 16% • (2 erosions, 3 ulcers)

Note: PVI, pulmonary vein isolation; HPSD, high power-short duration ablation; RF, radiofrequency; post., posterior wall; ant., anterior wall; AI, ablation index; LSI, lesion size index; parox. AF, paroxysmal atrial fibrillation; pers. AF, persistent atrial fibrillation.

artery in a rat model, electroporation did not affect long-term vascular integrity.²⁹ Analogously, nervous tissue appears to have relative resistance to electroporation; even though data are less clear, pre-clinical studies suggest only minimal damage upon direct high power application and full regeneration over time, respectively.³⁰

What's more, full power electroporation purposely targeting the adventitia of the esophagus in a porcine model did not result in any mucosal or submucosal lesions.³¹ Beyond the differences in tissue-specific thresholds, in contrast to thermal ablation, PFA also appears to spare the extracellular matrix, preventing disruption of tissue planes that may result in complications like atri-esophageal fistula.

In line with these experimental data, preclinical studies on cardiac catheter ablation consistently found myocardial electroporation lesions to spare vascular tissue including coronary arteries, nervous tissue including the phrenic nerve, and the esophagus even when intentionally ablating in their immediate proximity.³²⁻³⁵ These favorable properties have recently been confirmed in pre-clinical studies comparing atrial PFA with conventional radiofrequency ablation.^{32,35}

The exact reasons for the distinct current density thresholds inferring this relative selectivity for cardiomyocytes are yet to be defined. However, as cardiomyocytes are relatively large compared to other cell types, equal local electrical fields (voltage per distance)

TABLE 2 Trials on PVI with electroporation-based ablation

Trial	Patients (n)	Trial design	Electroporation modality	Follow-up	Key findings
Reddy et al. [36]	22; parox. AF	Prospective, single-arm, 2 centers	<ul style="list-style-type: none"> PFA (bipolar) 900 to 2,500 V 	1 month	<ul style="list-style-type: none"> 100% acute PVI No complications
Reddy et al. [37] & Reddy et al. [38]	121; parox. AF	Prospective, single-arm, 2 centers multiple ablation protocols, invasive remapping at 3 months	<ul style="list-style-type: none"> 4 different PFA protocols (bipolar) Monophasic, 900-1000 V (n = 15); biphasic, 1800-2000 V (n = 106) 4-10 pulses per application 	12 months	<ul style="list-style-type: none"> 100% acute PVI 65% durable PVI at 3 months (between 18% and 84%, depending on PFA protocol) 79% freedom of arrhythmia at 12 months 2 cardiac tamponades, 1 TIA; otherwise no serious complications
Reddy et al. [39]	25; pers. AF	Prospective, single-arm, 2 centers, PVI +PWI, invasive remapping at 2-3 months	<ul style="list-style-type: none"> PFA (bipolar) Biphasic 1800-2000 V 	202 days (median)	<ul style="list-style-type: none"> 100% acute PVI Durable PVI at 3 months in 96% of PVs 1 cardiac tamponade (4%), otherwise no serious complications Endoscopy in 21/25, no esophageal lesions
Loh et al. [27]	10	Prospective, single-arm, single-center	<ul style="list-style-type: none"> Monopolar single-pulse electroporation 6 ms, 200 J 	14 days	<ul style="list-style-type: none"> 100% acute PVI No periprocedural complications 1 cerebrovascular event 14 d after ablation

Note: PV, pulmonary vein; PVI, pulmonary vein isolation; PFA, pulsed-field ablation; PWI, posterior wall isolation; parox. AF, paroxysmal atrial fibrillation; pers. AF, persistent atrial fibrillation; TIA, transient ischemic attack.

will result in higher transcellular voltage gradients, which may be one factor explaining their susceptibility to electroporation. Taken together, the relative selectivity of electroporation for cardiomyocytes clearly bears the potential to reduce the risk of collateral damage during catheter ablation and to prevent complications like coronary injury, phrenic nerve palsy or atrioesophageal fistula.

3.5 | Clinical trials

The first in-human report of electroporation for endocardial AF ablation was published in 2018 using a custom pentaspline PFA catheter (Farawave, Farapulse inc.).³⁶ In fact, to date most clinical experience has been established with this catheter, which can be used either in a basket or a flower configuration, allowing for ostial and antral ablations, respectively. In three consecutive non-randomized trials including a total of 121 patients with paroxysmal AF, safety and efficacy of PFA could be demonstrated with this system.^{37,38} Freedom from any atrial arrhythmia was reported as 78.5% at one year. Of note, the durability of PVI steadily improved over the trials from 18% with monophasic PFA to 84% with optimized biphasic waveforms at 3 months post-ablation. While PVI was achieved in as little as three minutes ablation time, in the last trial of the series total procedure times were still in the range of conventional ablation approaches. With only three major complications (2 cardiac tamponades, 1 cerebrovascular event) the procedure appears to be relatively safe. Of note, in a subgroup of 29

patients endoscopy did not find any esophageal lesions at a median of 3 days post-ablation.

In another study, the same group investigated the safety and efficacy of their approach in 25 patients with persistent AF.³⁹ In addition to PVI they demonstrated that posterior wall isolation and ablation of the cavotricuspid isthmus, the latter using a focal PFA catheter, might be feasible too. Invasive re-mapping at three months confirmed durable PVI in more than 90% of the PVs. Again, esophagogastroduodenoscopy, which was performed in 21 of the 25 patients, showed no signs of esophageal injury despite PVI and PWI with extensive ablation at the posterior wall. Also, no phrenic nerve palsy or pulmonary vein stenosis was reported in any of the trials.

Very recently, first in human experience has demonstrated the feasibility of PVI with monopolar single pulse electroporation in 10 patients. In this study PVI was performed by delivering nonarcing, nonbarotraumatic 6 ms, 200 J direct current applications via a custom nondeflectable 14-polar circular electroporation catheter with a variable diameter (16–27 mm). All 40 pulmonary veins were successfully isolated with a mean of 2.4 electroporation applications per pulmonary vein, without procedural complications.²⁷

3.6 | Limitations

Despite the potential for very rapid ablation, reported mean procedure times were still in the range of conventional ablation approaches (97 and 148 minute, respectively) with rather high fluoroscopy times

(mean 14 and 29 minutes, respectively), depending on the system used.^{27,38} This could of course reflect a certain learning curve of the new method and novel catheter systems, and procedure and fluoroscopy times should be expected to improve.

Even though the sample size is not sufficient for a definite safety estimate, cardiac tamponade may be a concern, as it occurred in 3 out of 146 patients treated with the Farapulse PFA system.³⁷⁻³⁹ Thus, the specific risk of cardiac tamponade for this approach remains to be determined in comparison with established approaches of thermal ablation.

Another finding that has to be further investigated are transient ST-segment elevations (resolution within a mean of 13 seconds), which have been observed in 9 out of 10 patients after monopolar single pulse electroporation, particularly in the inferior ECG leads.²⁷ These ST-segment elevations are likely to represent an electrical phenomenon specific to this modality, and their clinical relevance remains to be determined.

One clinical cerebrovascular event with MRI correlate occurred each in the pilot study with the monopolar single pulse electroporation system (10 patients) as well as in a cohort of 121 patients treated with the Farapulse system.^{27,38} This is particularly noteworthy, as the formation of gaseous microemboli is typically detected by intracardiac ultrasound immediately upon electroporation-based ablation.^{40,41} However, although these concerns had already been articulated by the investigators in the respective pilot studies, none of the subsequent clinical studies systematically evaluated cerebral complications by means of cerebral MRI, thus safety data remains incomplete in this respect.

4 | CONCLUSION

With their unique properties both HPSD and electroporation ablation have the potential to break the trade-off between effective lesions and collateral damage and to improve risk-benefit ratios in AF ablation. In addition, both approaches may lead to considerable reductions in ablation times and thus advance procedural efficiency. While HPSD ablation has already been established in routine clinical practice, electroporation ablation is still to be considered an experimental treatment reserved for clinical trials. Without any doubt, both hold great promise for the future of AF ablation but need to be further validated regarding long-term effectiveness and safety. In particular, randomized controlled trials are lacking.

CONFLICT OF INTEREST

Dr Till Althoff declares no Conflict of Interests for this article.

Dr Lluís Mont has received honoraria as a lecturer and consultant and has received research grants from Abbott, Biosense Webster, Boston Scientific and Medtronic. He is a shareholder of ADAS-3D.

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REFERENCES

- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2020;42:373-498.
- Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med*. 2021;384:305-15.
- Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA Randomized Clinical Trial. *JAMA*. 2019;321:1261-74.
- Chinitz LA, Melby DP, Marchlinski FE, Delaughter C, Fishel RS, Monir G, et al. Safety and efficiency of porous-tip contact-force catheter for drug-refractory symptomatic paroxysmal atrial fibrillation ablation: results from the SMART SF trial. *Europace*. 2018;20:f392-f400.
- Das M, Loveday JJ, Wynn GJ, Gomes S, Saeed Y, Bonnett LJ, et al. Ablation index, a novel marker of ablation lesion quality: prediction of pulmonary vein reconnection at repeat electrophysiology study and regional differences in target values. *Europace*. 2017;19:775-83.
- De Pooter J, Strisciuglio T, El Haddad M, Wolf M, Philips T, Vandekerckhove Y, et al. Pulmonary vein reconnection no longer occurs in the majority of patients after a single pulmonary vein isolation procedure. *JACC Clin Electrophysiol*. 2019;5:295-305.
- Duytschaever M, De Pooter J, Demolder A, El Haddad M, Philips T, Strisciuglio T, et al. Long-term impact of catheter ablation on arrhythmia burden in low-risk patients with paroxysmal atrial fibrillation: the CLOSE to CURE study. *Heart Rhythm*. 2020;17:535-43.
- Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. *J Am Coll Cardiol*. 2014;64:647-56.
- Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque J-P, Kautzner J, et al. Randomized, controlled trial of the safety and effectiveness of a contact force-sensing irrigated catheter for ablation of paroxysmal atrial fibrillation: results of the taticath contact force ablation catheter study for Atrial Fibrillation (TOCCASTAR) Study. *Circulation*. 2015;132:907-15.
- Taghji P, El Haddad M, Philips T, Wolf M, Knecht S, Vandekerckhove Y, et al. Evaluation of a strategy aiming to enclose the pulmonary veins with contiguous and optimized radiofrequency lesions in paroxysmal atrial fibrillation: a pilot study. *JACC Clin Electrophysiol*. 2018;4:99-108.
- Ali-Ahmed F, Goyal V, Patel M, Orelaru F, Haines DE, Wong WS. High-power, low-flow, short-ablation duration-the key to avoid collateral injury? *J Interv Card Electrophysiol*. 2019;55:9-16.
- Qiu J, Wang Y, Wang DW, Hu M, Chen G. Update on high-power short-duration ablation for pulmonary vein isolation. *J Cardiovasc Electrophysiol*. 2020;31:2499-508.
- Leshem E, Zilberman I, Tschabrunn CM, Barkagan M, Contreras-Valdes FM, Govari A, et al. High-power and short-duration ablation for pulmonary vein isolation: biophysical characterization. *JACC Clin Electrophysiol*. 2018;4:467-79.
- Yavin HD, Leshem E, Shapira-Daniels A, Sroubek J, Barkagan M, Haffajee CI, et al. Impact of high-power short-duration radiofrequency ablation on long-term lesion durability for atrial fibrillation ablation. *JACC Clin Electrophysiol*. 2020;6:973-85.
- Winkle RA, Mohanty S, Patrawala RA, Mead RH, Kong MH, Engel G, et al. Low complication rates using high power (45-50 W) for short duration for atrial fibrillation ablations. *Heart Rhythm*. 2019;16:165-9.

16. Kottmaier M, Popa M, Bourier F, Reents T, Cifuentes J, Semmler V, et al. Safety and outcome of very high-power short-duration ablation using 70 W for pulmonary vein isolation in patients with paroxysmal atrial fibrillation. *Europace*. 2020;22:388–93.
17. Castrejón-Castrejón S, Martínez Cossiani M, Ortega Molina M, Escobar C, Froilán Torres C, Gonzalo Bada N, et al. Feasibility and safety of pulmonary vein isolation by high-power short-duration radiofrequency application: short-term results of the POWER-FAST PILOT study. *J Interv Card Electrophysiol*. 2020;57:57–65.
18. Chen S, Schmidt B, Bordignon S, Urbanek L, Tohoku S, Bologna F, et al. Ablation index-guided 50 W ablation for pulmonary vein isolation in patients with atrial fibrillation: Procedural data, lesion analysis, and initial results from the FAFA AI High Power Study. *J Cardiovasc Electrophysiol*. 2019;30:2724–31.
19. Wielandts J-Y, Kyriakopoulou M, Almorad A, Hilfiker G, Strisciuglio T, Philips T, et al. Prospective randomized evaluation of high power during CLOSE-guided pulmonary vein isolation: the POWER-AF Study. *Circ Arrhythm Electrophysiol*. 2021;14:e009112.
20. Rozen G, Ptaszek L, Zilberman I, Cordaro K, Heist EK, Beeckler C, et al. Prediction of radiofrequency ablation lesion formation using a novel temperature sensing technology incorporated in a force sensing catheter. *Heart Rhythm*. 2017;14:248–54.
21. Reddy VY, Grimaldi M, De Potter T, Vijgen JM, Bulava A, Duytschaever MF, et al. Pulmonary vein isolation with very high power, short duration, temperature-controlled lesions: the QDOT-FAST trial. *JACC Clin Electrophysiol*. 2019;5:778–86.
22. Piringer R, Deneke T, Foldyna B, Sonne K, Nentwich K, Ene E, et al. Incidence of ablation-induced esophageal injury associated with high-power short duration temperature-controlled pulmonary vein isolation using a specialized open-irrigated ablation catheter: a retrospective single-center study. *J Cardiovasc Electrophysiol*. 2021;32:695–703.
23. Kaneshiro T, Amami K, Hijioaka N, Nodera M, Yamada S, Yokokawa T, et al. Significance of contact force on esophageal thermal injury during relative high-power short-duration ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2021;14. <https://doi.org/10.1161/circep.121.009897>
24. Barkagan M, Rottmann M, Leshem E, Shen C, Buxton AE, Anter E. Effect of baseline impedance on ablation lesion dimensions: a multimodality concept validation from physics to clinical experience. *Circ Arrhythm Electrophysiol*. 2018;11:e006690.
25. Bradley CJ, Haines DE. Pulsed field ablation for pulmonary vein isolation in the treatment of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2020;31:2136–47.
26. Wittkamp FHM, van Es R, Neven K. Electroporation and its Relevance for Cardiac Catheter Ablation. *JACC Clin Electrophysiol*. 2018;4:977–86.
27. Loh P, van Es R, Groen MHA, Neven K, Kassenberg W, Wittkamp FHM, et al. 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.
28. Stewart MT, Haines DE, Verma A, Kirchhof N, Barka N, Grassl E, et al. Intracardiac pulsed field ablation: proof of feasibility in a chronic porcine model. *Heart Rhythm*. 2019;16:754–64.
29. Maor E, Ivorra A, Leor J, Rubinsky B. The effect of irreversible electroporation on blood vessels. *Technol Cancer Res Treat*. 2007;6:307–12.
30. Onik G, Mikus P, Rubinsky B. Irreversible electroporation: implications for prostate ablation. *Technol Cancer Res Treat*. 2007;6:295–300.
31. Neven K, van Es R, van Driel V, van Wessel H, Fidler H, Vink A, et al. Acute and long-term effects of full-power electroporation ablation directly on the porcine esophagus. *Circ Arrhythm Electrophysiol*. 2017;10:e004672.
32. Koruth JS, Kuroki K, Kawamura I, Brose R, Viswanathan R, Buck ED, et al. Pulsed field ablation versus radiofrequency ablation: esophageal injury in a novel porcine model. *Circ Arrhythm Electrophysiol*. 2020;13:e008303.
33. Koruth JS, Kuroki K, Kawamura I, Stoffregen WC, Dukkupati SR, Neuzil P, et al. Focal pulsed field ablation for pulmonary vein isolation and linear atrial lesions: a preclinical assessment of safety and durability. *Circ Arrhythm Electrophysiol*. 2020;13:e008716.
34. van Driel VJ, Neven K, van Wessel H, Vink A, Doevendans PA, Wittkamp FH. Low vulnerability of the right phrenic nerve to electroporation ablation. *Heart Rhythm*. 2015;12:1838–44.
35. Yavin H, Brem E, Zilberman I, Shapira-Daniels A, Datta K, Govari A, et al. A Circular Multielectrode Pulsed-Field Ablation Catheter "Lasso PFA": Lesion Characteristics, Durability and Effect on Neighboring Structures. *Circ Arrhythm Electrophysiol*. 2021.
36. Reddy VY, Koruth J, Jais P, Petru J, Timko F, Skalsky I, et al. Ablation of atrial fibrillation with pulsed electric fields: an ultra-rapid, tissue-selective modality for cardiac ablation. *JACC Clin Electrophysiol*. 2018;4:987–95.
37. Reddy VY, Neuzil P, Koruth JS, Petru J, Funosako M, Cochet H, et al. Pulsed field ablation for pulmonary vein isolation in atrial fibrillation. *J Am Coll Cardiol*. 2019;74:315–26.
38. Reddy VY, Dukkupati SR, Neuzil P, Anic A, Petru J, Funasako M, et al. Pulsed field ablation of paroxysmal atrial fibrillation: 1-year outcomes of IMPULSE, PEFCAT, and PEFCAT II. *JACC Clin Electrophysiol*. 2021;7:614–27.
39. Reddy VY, Anic A, Koruth J, Petru J, Funasako M, Minami K, et al. Pulsed field ablation in patients with persistent atrial fibrillation. *J Am Coll Cardiol*. 2020;76:1068–80.
40. Groen MHA, van Es R, van Klarenbosch BR, Stehouwer M, Loh P, Doevendans PA, et al. In vivo analysis of the origin and characteristics of gaseous microemboli during catheter-mediated irreversible electroporation. *Europace*. 2021;23:139–46. <https://doi.org/10.1093/europace/euaa243>
41. van Es R, Groen MHA, Stehouwer M, Doevendans PA, Wittkamp FHM, Neven K. In vitro analysis of the origin and characteristics of gaseous microemboli during catheter electroporation ablation. *J Cardiovasc Electrophysiol*. 2019;30:2071–9.

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