Journal of Interventional Cardiac Electrophysiology (2023) 66:1961–1963
https://doi.org/10.1007/s10840-023-01572-2

COMMENTARY

Assessing recurrence following pulsed field ablation for atrial fibrillation

Nicholas Y. Tan[1] · **Christopher V. DeSimone**[1]

Received: 16 May 2023 / Accepted: 16 May 2023 / Published online: 29 May 2023

Thermal-based ablation modalities—radiofrequency and cryothermy—are the mainstays of current catheter-based treatment options for atrial fibrillation (AF) [1]. Despite refinements in technology and techniques, the potential for serious complications including pulmonary vein stenosis, phrenic nerve injury, and atrioesophageal fistula still exists. Furthermore, recurrence rates following AF ablation remain suboptimal [2]. Pulsed field ablation (PFA) is an emerging modality that has gained tremendous traction. Delivery of short-pulsed electric fields (PEF) induces loss of cell membrane integrity through the formation of nanopores, this effect can either be transient or irreversible, the latter of which leads to cell death [3]. Extensive pre-clinical studies have demonstrated that cardiomyocytes are more sensitive to PEF effects, hence, surrounding structures are less likely to sustain collateral damage during delivery [4, 5]. Furthermore, it is thought that minimal to no heating occurs at the ablation site, decreasing the likelihood of unintended thermal injury [6]. These findings have prompted a flurry of first in-human studies to assess whether PFA will truly become the "holy grail" for treating AF [7–12].

As with most technological advances, hype is often tempered by reality over time and testing. Early trials of PFA systems showed nearly perfect acute procedural success at isolating the pulmonary veins (PVs) and/or posterior wall (PW). The safety profile appeared excellent, with none of the abovementioned feared complications [9, 11]. However, it soon became clear that AF can recur post-PFA and that previously ablated sites can become reconnected [10, 12]. Thus, as we move beyond the "honeymoon phase" of PFA, it is increasingly important that we refine our knowledge of the mechanisms contributing to these treatment failures.

In this issue of *JICE*, Tancredi Magni et al. focused their attention on 14 patients out of a total of 447 (3.1%) who developed recurrent AF within 1 year of undergoing index PFA catheter ablation. The mean time to recurrence was 4.9 ± 1.9 months; 7 (50.0%) had paroxysmal AF, whereas 6 (42.9%) and 1 (7.1%) had persistent and longstanding persistent AF, respectively. Three patients (21.4%) received concomitant PW isolation (PWI) at the discretion of the operator. Of the 14 patients, 7 (50.0%) had AF recurrence, 5 (35.7%) had both AF and atrial flutter (AFL), and 2 (14.3%) experienced AFL or atrial tachycardia (AT) only. During their redo procedure, 9 (64.3%) had at least 1 PV reconnection, with the posterior-inferior aspect of the right inferior PV (RIPV) being the most common gap observed. Two of the 3 patients who initially received PW isolation had reconnection of the PW. In addition to repeat PV isolation (PVI), most patients underwent additional ablation, including PW (re)isolation, as well as flutter lines along the cavotricuspid isthmus, mitral isthmus, and roof. No complications were noted with the redo cases.

We would like to extend our congratulations to the authors for this important contribution to the literature. Adoption of PFA in the clinical space is anticipated to grow exponentially; hence, electrophysiologists will need to learn how to manage patients with recurrent atrial arrhythmias post-PFA. Although the numbers in this study are small, we are left with important questions and issues to consider as we move forward with this technology.

1) Will pulmonary vein reconnection be common with PFA?

Data from the pivotal IMPULSE, PEFCAT, and PULSED AF trials have shown that PV reconnection continues to be a major reason for AF recurrence following PFA [10, 12]. The present study, which took place post-regulatory approval,

This comment refers to the article available at https://doi.org/10.1007/s10840-023-01559-z

✉ Christopher V. DeSimone
desimone.christopher@mayo.edu

[1] Department of Cardiovascular Medicine, Mayo Clinic, 200 1St Street SW, Rochester, MN 55905, USA

provides further substantiation of their findings. There are multiple potential reasons for PV reconnection, including limited operator experience with new technology, inaccurate intraprocedural assessment of lesion durability, inadequate energy delivery, and intrinsic anatomic or tissue factors affecting ablation effectiveness [6]. With regard to the latter, it is interesting that the posterior-inferior aspect of the RIPV was the most common site for reconnection noted by the authors. Although this may certainly be simply due to chance, limited catheter reach and/or contact to that region coupled by variations in anatomy may in part account for the gaps seen in this cohort. Since PVI remains the cornerstone of AF catheter ablation, decreasing the rate of PV reconnection with PFA will be of paramount importance if we want to improve outcomes.

2) How do we address targets for ablation beyond the pulmonary veins?

Apart from PV reconnection, a significant fraction of the study cohort experienced AT or AFL, most of which were *de novo*. While there is little data to support performing empiric flutter lines to reduce atrial arrhythmia recurrence, one may make the argument that PFA is an ideal ablation modality for such given its safety profile. However, our group and others have found that PFA within or near coronary arteries can lead to effects ranging from vasospasm to overt stenosis in animal models [13, 14]. Indeed, there have been emerging case reports of coronary vasospasm during mitral and cavotricuspid isthmus ablations as well [15, 16]. Although the clinical significance of PFA-associated coronary vasospasm remains undetermined, it does raise doubts whether PFA, at least in its current form, is the answer for flutter ablations in the vicinity of coronary arteries.

The PW is a known trigger for AF particularly given its shared embryologic origin with the PVs [17]. There is preliminary data suggesting reasonable acute success rates at PWI [9]. In the present study, however, 2 of the 3 patients who received PWI experienced reconnections, highlighting the need for improvement in this regard. Perhaps this is related to suboptimal catheter-tissue contact given the current catheter design and/or movement which occurs during pulse delivery that leads to inadequate catheter force and stability. Other known triggers for AF such as the superior vena cava and atrial appendages were not addressed in this study, and therefore bear further investigation.

3) How does pulsed field ablation affect cardiac autonomic ganglia and ablation outcomes?

There is progressive awareness that the autonomic nervous system plays a substantive role in modulating the onset and maintenance of cardiac arrhythmias including AF [18]. To this end, the utility of cardiac ganglia (radiofrequency) ablation as an alternative or in addition to PVI has been explored in several studies, albeit with mixed results [19, 20]. Although open-chest application of PFA can successfully ablate cardiac ganglia in animal studies [21], no significant autonomic effects have been elicited with endocardial PFA from early human trials [22]. Whether this is a function of relative tissue resistance to PFA or technological limitations (or both) remains to be seen. If cardiac ganglia are spared by endocardial PFA delivery, other approaches or PFA delivery protocols would be ripe for investigation to include ganglia destruction.

4) Why do we not have a uniform recipe for PFA delivery?

At the heart of it all, our foray into the vast frontier of PFA has only just begun. There are a multitude of parameters that factor into each ablation—voltage, pulse width, waveform, electrode shape/size, to name just a few [6]. Patient-related factors and anatomy are also likely to play an important role. The ideal configuration for any given arrhythmia is a big unknown, particularly for something as complex as AF. In fact, there may never be only one. Even so, studies such as the present work are a crucial step in our never-ending pursuit of simply being. It is likely that each catheter design and delivery protocol requires its own special delivery protocol. However, publication of the exact protocol parameters would be most welcome and would benefit the entire field as we push forward in understanding PFA. Publication of these protocols would help determine the best parameters to use, and most importantly, illustrate those that are suboptimal. Only through struggle and continued learning from bench and clinical PFA delivery, along with a collaborative approach to defining optimal delivery protocols, we will reach our collective goal toward improved efficacy and safety of AF ablation.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42:373–498.

2. Kuck KH, Albenque JP, Chun KJ, et al. Repeat ablation for atrial fibrillation recurrence post cryoballoon or radiofrequency ablation in the FIRE AND ICE Trial. Circ Arrhythm Electrophysiol. 2019;12:e007247.
3. Maor E, Sugrue A, Witt C, et al. Pulsed electric fields for cardiac ablation and beyond: a state-of-the-art review. Heart Rhythm. 2019;16:1112–20.
4. Stewart MT, Haines DE, Miklavcic D, et al. Safety and chronic lesion characterization of pulsed field ablation in a Porcine model. J Cardiovasc Electrophysiol. 2021;32:958–69.
5. Witt CM, Sugrue A, Padmanabhan D, Vaidya V, Gruba S, Rohl J, et al. Intrapulmonary vein ablation without stenosis: a novel balloon-based direct current electroporation approach. J Am Heart Assoc 2018;7(14):e009575. https://doi.org/10.1161/JAHA.118.009575.
6. Sugrue A, Maor E, Del-Carpio Munoz F, Killu AM, Asirvatham SJ. Cardiac ablation with pulsed electric fields: principles and biophysics. Europace. 2022;24:1213–22.
7. Cochet H, Nakatani Y, Sridi-Cheniti S, et al. Pulsed field ablation selectively spares the oesophagus during pulmonary vein isolation for atrial fibrillation. Europace. 2021;23:1391–9.
8. Loh P, van Es R, Groen MHA, 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.
9. Reddy VY, Anic A, Koruth J, et al. Pulsed field ablation in patients with persistent atrial fibrillation. J Am Coll Cardiol. 2020;76:1068–80.
10. Reddy VY, Dukkipati SR, Neuzil P, 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.
11. Reddy VY, Neuzil P, Koruth JS, et al. Pulsed field ablation for pulmonary vein isolation in atrial fibrillation. J Am Coll Cardiol. 2019;74:315–26.
12. Verma A, Haines DE, Boersma LV, et al. Pulsed Field ablation for the treatment of atrial fibrillation: PULSED AF Pivotal Trial. Circulation. 2023;147:1422–32.
13. Higuchi S, Im SI, Stillson C, et al. Effect of epicardial pulsed field ablation directly on coronary arteries. JACC Clin Electrophysiol. 2022;8:1486–96.
14. Ladejobi A, Christopoulos G, Tan N, et al. Effects of pulsed electric fields on the coronary arteries in swine. Circ Arrhythm Electrophysiol. 2022;15:e010668.
15. Gunawardene MA, Schaeffer BN, Jularic M, et al. Coronary spasm during pulsed field ablation of the mitral isthmus line. JACC Clin Electrophysiol. 2021;7:1618–20.
16. Reddy VY, Petru J, Funasako M, et al. Coronary arterial spasm during pulsed field ablation to treat atrial fibrillation. Circulation. 2022;146:1808–19.
17. Kistler PM, Chieng D, Sugumar H, et al. Effect of catheter ablation using pulmonary vein isolation with vs without posterior left atrial wall isolation on atrial arrhythmia recurrence in patients with persistent atrial fibrillation: the CAPLA Randomized Clinical Trial. JAMA. 2023;329:127–35.
18. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res. 2014;114:1500–15.
19. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J Am Coll Cardiol. 2013;62:2318–25.
20. Kim MY, Coyle C, Tomlinson DR, et al. Ectopy-triggering ganglionated plexuses ablation to prevent atrial fibrillation: GANGLIA-AF study. Heart Rhythm. 2022;19:516–24.
21. Padmanabhan D, Naksuk N, Killu AK, et al. Electroporation of epicardial autonomic ganglia: safety and efficacy in medium-term canine models. J Cardiovasc Electrophysiol. 2019;30:607–15.
22. Musikantow DR, Neuzil P, Petru J, et al. Pulsed field ablation to treat atrial fibrillation: autonomic nervous system effects. JACC Clin Electrophysiol. 2023;9:481–93.