Received: 20 February 2024 | Accepted: 29 May 2024

DOI: 10.1002/agm2.12326

Aging Medicine Open Access WILEY

COMMENTARY

Pulse field ablation for atrial fibrillation: Is the curtain about to rise?

Junpeng Liu | **Min Dong** | **Jiefu Yang**

Department of Cardiology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China

Correspondence
Junpeng Liu, Department of Cardiology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, No.1, Da Hua Road, Dongcheng District, Beijing 100 730, China.
Email: ebull2000@163.com

Funding information
The National High Level Hospital Clinical Research Funding, Grant/Award Number: BJ-2023-162 and BJ-2023-107

KEYWORDS
atrial fibrillation, pulse field ablation

1 | BACKGOUND

Catheter ablation has been validated as an effective intervention for atrial fibrillation (AF) patients, significantly reducing recurrence rates, improving prognoses, and enhancing life quality.[1–3] However, conventional methods employing radiofrequency or cryothermal energy suffer from a lack of tissue specificity, potentially leading to complications such as pulmonary vein stenosis, atrioesophageal fistula, and hemidiaphragmatic paralysis.[2,3] Pulsed field ablation (PFA) has recently emerged as a promising alternative, utilizing the microsecond-scale, high-voltage electrical fields to induce irreversible electroporation and cell membrane destabilization, culminating in cellular necrosis.[4,5] Its superior tissue selectivity minimizes damage to non-target tissues during ablation, positioning PFA as an ideal modality for cardiac ablation.

2 | THE EVIDENCE-BASED JOURNEY OF PFA

Preclinical experiments utilizing animal models have underscored the potential of PFA for achieving durable pulmonary vein isolation (PVI),[6,7] highlighting the method's capability to form comprehensive transmural lesions devoid of adverse effects like pulmonary vein ostia stenosis or esophageal damage.[8,9] Notably, PFA's application has shown efficacy in permanently neutralizing the atrial ganglion plexus without compromising atrial myocardium integrity or triggering inflammatory responses and fibrosis.[7–9]

In 2018, Reddy and colleagues[10] pioneered the application of PFA for the clinical management of paroxysmal AF Their groundbreaking work revealed that an average of 3.26 ablations was sufficient to achieve complete PVI with an operation duration of approximately 67 ± 10.5 min. The procedure was characterized by minimal chest and diaphragmatic sensations, yet remarkably, it resulted in no complications. Follow-up studies involving 81 patients undergoing mono-phase and bi-phase PFA demonstrated 100% acute isolation of pulmonary veins, with the procedure taking an average of 92.2 ± 27.4 min and the ablation itself 13.1 ± 7.6 min.[11] Given the pivotal role of pulmonary vein reconnection in ablation recurrence, the stability of PVI post-procedure emerges as crucial. Notably, advancements in PFA waveform technology have significantly increased PVI durability from 18% to a full 100% at the 3-month benchmark. Aside from a single incident of cardiac tamponade related to the operation, no severe complications were reported within the first 120 days post-ablation. At the one-year follow-up mark, the rate of sinus rhythm maintenance impressively stood at 87.4%. These findings collectively affirm the efficacy of PFA in achieving swift and durable PVI, primarily through selective myocardial tissue targeting, while maintaining a commendable safety profile.

Nevertheless, the inherent challenge of high recurrence rates in persistent or permanent AF suggests that PVI through PFA alone might not suffice. Enhanced outcomes may necessitate

adjunctive ablations across other cardiac regions. In an extension of their research, Reddy et al. explored the application of PFA in 25 patients with persistent AF, incorporating ablations of the pulmonary veins alongside the left atrial posterior wall and tricuspid isthmus linear ablations.[12] This comprehensive approach yielded an acute success rate of 100%, with average ablation times for the pulmonary veins and left atrial posterior wall recorded at 22 and 10 min, respectively, and a median total operation time of 125 min (inclusive of a median voltage measurement duration of 28 min). The solitary surgical complication encountered was a groin hematoma. Subsequent 2–3 month follow-ups revealed a notable 96% and 100% electrical isolation persistence in the pulmonary veins and left atrial posterior wall, respectively, marking a significant milestone in demonstrating PFA's efficacy and reliability for managing persistent AF.

Prior research has firmly established PFA as both a safe and effective modality for AF ablation.[10,11,13] However, these studies, being single-armed, lacked a direct comparison with traditional ablation therapies. At the European Society of Cardiology Annual Meeting in August 2023, the groundbreaking ADVENT study was unveiled.[14] This seminal, multicenter, randomized trial was designed to juxtapose PFA against conventional thermal ablation methods, such as radiofrequency or cryoablation, specifically targeting drug-refractory paroxysmal AF. It set out with two primary endpoints: the efficacy endpoint measured freedom from atrial tachyarrhythmias post a 3-month blanking period, and the safety endpoint focused on acute and chronic device- and procedure-related severe adverse events within the first 7 days post-procedure.

The ADVENT study brought together 65 operators across 30 centers, enrolling symptomatic paroxysmal AF patients resistant to pharmacological treatments. Participants were equally allocated to either the PFA group ($n=305$) or the thermal ablation group ($n=302$), which included 167 patients undergoing radiofrequency ablation and 135 patients undergoing cryoballoon ablation. The patient cohorts were well-matched in baseline characteristics. During the study's blanking period, the use of class I and III antiarrhythmic drugs was permitted, excluding amiodarone. Follow-ups were meticulously conducted via phone and in-clinic visits, with cardiac rhythm assessments performed using a 72-h Holter monitor at 6 and 12 months, complemented by weekly remote monitoring for symptomatology. Remarkably, the immediate success rates of achieving PVI were high across both groups, 99.6% in PFA and 99.8% in the thermal ablation group, underscoring the efficacy of PFA. Notably, PFA was associated with reduced operation, left atrial stay time, and ablation times, though it necessitated longer X-ray fluoroscopy durations. At the one-year mark, the efficacy of PFA stood at 73.3%, closely aligned with the 71.3% noted in the thermal ablation cohort, satisfying the criteria for non-inferiority between the approaches. Safety analysis revealed a comparable profile of major adverse events between groups, further validating PFA's non-inferiority in safety. Additionally, the study provided evidence of PFA's superiority in preserving the pulmonary vein's cross-sectional area, indicating a lower risk of stenosis compared to thermal ablation techniques. In essence, the ADVENT study represents a landmark in clinical research, being the first randomized controlled trial (RCT) to validate the non-inferiority of PFA compared to established thermal ablation methods in treating paroxysmal AF. This affirms PFA's role as a viable, effective, and safer alternative for PVI in this patient population.

The PULSE AF Pivotal Trial, a prospective, global, multi-center, non-randomized controlled, single-arm study, was designed to assess the efficacy and safety of the PulseSelect Pulsed Field Ablation System (Medtronic) in treating both paroxysmal and persistent AF.[15] Detailed in the Circulation journal in March 2023, this expansive study spanned 9 countries and 41 centers, engaging a total of 300 patients—equally divided between paroxysmal and persistent AF cases—over a year-long observation period. This study distinguished itself with rigorously defined endpoints, primarily aiming at a composite measure of acute procedural success, the absence of arrhythmia recurrence, or the need for increased antiarrhythmic medication. After a year of meticulous follow-up, the trial demonstrated that 66.2% of patients with paroxysmal AF and 55.1% of those with persistent AF met the primary effectiveness endpoint. Notably, the freedom from any symptomatic atrial arrhythmia recurrences reached 79.7% and 80.8% across the paroxysmal and persistent AF groups, respectively. The overall rate of major adverse events was remarkably low at 0.7%, with no incidences of esophageal damage, pulmonary vein stenosis, or diaphragmatic nerve injuries reported—positioning this trial's safety outcomes as some of the most favorable among PFA studies to date. The impressive 96% completion rate of the 12-month follow-up in 287 participants provided robust long-term data. These compelling results played a crucial role in securing regulatory approval for the PulseSelect PFA system, marking a significant milestone as it became the first of its kind to be endorsed by the U.S. Food and Drug Administration (FDA) for the treatment of both paroxysmal and persistent AF on December 14, 2023. This approval not only underscores the system's clinical importance but also highlights the potential of PFA technology to transform the therapeutic landscape for AF, offering a safe and effective alternative to conventional ablation therapies.

In a comprehensive comparative cohort study conducted by Urbanek and colleagues, 400 patients (56.5% male, with 60.8% presenting paroxysmal AF and an average age of 70 years) were evenly divided into two groups for treatment with either cryoablation or PFA.[16] The cryoablation group underwent procedures using Medtronic's 28 mm second-generation cryoballoon (Arctic Front Advance), while the PFA group was treated with Boston Scientific's 31 mm or 35 mm Farawave pulse ablation catheter. Remarkably, the study demonstrated a 100% immediate PVI success rate for PFA patients and a 98% success rate for those undergoing cryoablation. Significantly, PFA procedures boasted a median operation time of 34.5 min, notably shorter than the 50 min recorded for cryoablation, with the fluoroscopy duration being comparable between the two. The overall complication rate was lower in the PFA group at 3.0%, compared to 6.5% in the cryoablation group, attributed primarily to the higher incidence of phrenic nerve paralysis associated with cryoablation. Following a

year of follow-up, the success rates, defined by the absence of atrial arrhythmia recurrence, were closely matched between the two methods: 83.1% for cryoablation and 80.3% for PFA in patients with paroxysmal AF, and 71% for cryoablation versus 66.8% for PFA in those with persistent AF, indicating no significant differences in efficacy. This study substantiates the non-inferiority of PFA to cryoablation concerning treatment effectiveness, with PFA demonstrating a particular safety advantage in reducing the risk of phrenic nerve paralysis. In a significant development following this research, Boston Scientific's FARAPULSE, a PFA product, was granted FDA approval in January 2024, marking a pivotal moment as the first PFA system to receive such accreditation, further supported by its prior CE certification in January 2021. This endorsement underscores the growing recognition of PFA's role in the safe and effective treatment of AF, heralding a new era in ablation therapy.

On December 27, 2023, a significant milestone was achieved in the field of cardiac ablation therapy when the China National Medical Products Administration (NMPA) granted market access approval to the LEAD-PFA cardiac PFA apparatus and the PulsedFA PFA catheter, both innovations by Sichuan Jinjiang Electronics.[17] This marked a historic moment as these products became the first PFA tools authorized for market distribution in China. This approval is part of a broader trend, as multiple PFA products are currently under active development within the country, including the LotosPFA ablation catheter by Northcore Medical, the CardioPulsePFA ablation catheter from Deno Electrophysiology, Xuanyu Medical's PFA system, and the nsPFA system by Maiwei Medical. The concurrent issuance of medical device registration certificates by both the NMPA and the FDA to various PFA products underscores the global entrance into a new era for the management of arrhythmias through PFA This burgeoning interest in PFA technologies signals a potential shift in the therapeutic landscape, promising more options for the safe and effective treatment of cardiac arrhythmias.

Despite these advancements, it is imperative to acknowledge that PFA technology remains in its nascent stages. There are vast territories within this field yet to be explored and understood. The journey ahead requires a concerted effort to delve deeper into the unknowns, with an emphasis on rigorous clinical research to solidify the evidence base regarding the effectiveness and safety of PFA therapies.

3 | THE CHALLENGES OF PFA

The foundational principle of PFA lies in electroporation, a process that distinguishes itself as a nonthermal approach utilizing electric fields to precisely target and disrupt tissue structures.[4,5] By applying a high-voltage electric field, alterations occur within the cellular membranes, manifesting as nano-scale holes or pores. These modifications compromise cellular integrity and viability, a mechanism central to the effectiveness of PFA. This technique, known as irreversible electroporation, is intricately dependent on specific PFA parameters and the configuration of electrodes used.[18] Despite its potential, the development and standardization of PFA face challenges due to existing patent issues. This has prevented the establishment of a universally accepted standard for PFA application, resulting in considerable variability in its clinical application. Such heterogeneity introduces disparities in clinical outcomes and safety profiles across different PFA implementations. Consequently, while PFA represents a significant advancement in the therapeutic landscape, its widespread endorsement and application are curtailed, necessitating rigorous, targeted research to validate its efficacy and safety in diverse clinical scenarios.

Regarding therapeutic outcomes, PFA has not demonstrated clear superiority over conventional ablation therapies. A notable potential benefit of PFA lies in the reduced time needed to achieve electrical isolation of the pulmonary veins. However, the necessity for general anesthesia in PFA procedures means that the overall duration of the operation may not be significantly reduced and could potentially extend longer than traditional methods. Nevertheless, as advancements in PFA technology continue and as techniques for anesthesia are streamlined, it is anticipated that the operational time will decrease. This evolution in practice holds the promise of enhancing PFA's efficiency and patient experience in the future.

In the realm of safety, preclinical studies have highlighted the potential of PFA to minimize risks of pulmonary vein stenosis, atrioesophageal fistula, and hemidiaphragmatic paralysis.[7–9] However, when juxtaposed with traditional ablation methods in clinical settings, the body of evidence supporting PFA's safety advantages remains inconclusive. This gap is attributed to the limited scale of existing studies, underscoring a need for more extensive research. Additionally, the established efficacy of traditional ablation techniques in mitigating complications further complicates direct comparisons. Concerns have also emerged regarding the increased incidence of pericardial tamponade and stroke associated with PFA, possibly linked to the operational proficiency with PFA equipment and the experience level of practitioners. It is anticipated that ongoing advancements in PFA technology and procedural techniques, alongside the growing expertise of operators, will contribute to a reduction in these complications. Moreover, attention must be directed towards PFA-induced coronary artery injuries, categorized mainly into direct injuries and coronary spasms. Although direct application of PFA has not been shown to cause significant arterial narrowing or intimal hyperplasia, the potential for injury from excessive PFA exposure warrants further investigation.[19] Notably, instances of PFA-induced coronary spasms have been documented, with Reddy et al. observing that such spasms were not induced during procedures away from coronary arteries but occurred during ablations close to these vessels, such as cavotricuspid isthmus ablation.[20] Interestingly, these spasms could be mitigated with intracoronary nitroglycerin, either as a preventive measure or a treatment.

The effects of PFA on cardiac implants, including stents and pacing leads, remain to be fully elucidated, signaling an area ripe for

future research. As we continue to refine PFA applications and accumulate data, a clearer understanding of its safety profile, especially concerning coronary artery injury and interactions with cardiac devices, will emerge, paving the way for broader clinical adoption and optimized patient care.

While current research, including the ADVENT study featuring participants with an average age of 62, incorporates elderly patients, the efficacy and safety of PFA within this demographic remain uncertain. Given its potential safety benefits, PFA stands out as a promising choice for catheter ablation in elderly patients with AF. Nonetheless, the adoption of PFA for this patient group should proceed cautiously, pending the accumulation of more comprehensive evidence. This cautious approach is vital to ensuring that the deployment of this technology is both prudent and tailored to meet the specific needs and risks associated with treating AF in the elderly.

4 | CONCLUSION

PFA represents an innovative, non-thermal approach to cardiac ablation, utilizing pulsed electric fields to address heart diseases. This emerging method is a promising advancement, likely to stimulate further research into its broader applications. Particularly, it holds potential as a preferred treatment option for elderly patients with AF, who might benefit significantly from its safety profile. Despite this promise, the path to PFA becoming a mainstream alternative to the established ablation techniques, such as radiofrequency and cryoablation, is strewn with hurdles. These include the need for technical enhancements, the accumulation of robust clinical evidence, and overcoming various operational challenges. As such, while PFA is a bright spot on the horizon of cardiac care, realizing its full potential will require concerted efforts in development, research, and clinical validation.

AUTHOR CONTRIBUTIONS

Dr. Junpeng Liu and Dr. Min Dong did the literature search. Dr. Junpeng Liu wrote the manuscript draft. Dr. Jiefu Yang critically revised the manuscript draft.

ACKNOWLEDGMENTS

We extend our sincere gratitude to ChatGPT for its invaluable assistance in refining the manuscript. The support provided in polishing the language and enhancing the clarity of our discussions.

FUNDING INFORMATION

This work was supported by The National High Level Hospital Clinical Research Funding (BJ-2023-162 and BJ-2023-107).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Junpeng Liu https://orcid.org/0000-0003-4036-563X

REFERENCES

1. Michaud GF, Stevenson WG. Atrial Fibrillation. *New Engl J Med*. 2021;384(4):353-361. doi:10.1056/NEJMcp2023658
2. Parameswaran R, Al-Kaisey AM, Kalman JM. Catheter ablation for atrial fibrillation: current indications and evolving technologies. *Nat Rev Cardiol*. 2021;18(3):210-225. doi:10.1038/s41569-020-00451-x
3. Cappato R, Ali H. Surveys and registries on catheter ablation of atrial fibrillation: fifteen years of history. *Circ-Arrhythmia Elec*. 2021;14(1):e008073. doi:10.1161/CIRCEP.120.008073
4. Batista NT, Polajzer T, Miklavcic D. Cell death due to electroporation–a review. *Bioelectrochemistry*. 2021;141:107871. doi:10.1016/j.bioelechem.2021.107871
5. Kotnik T, Rems L, Tarek M, Miklavcic D. Membrane electroporation and Electropermeabilization: mechanisms and models. *Annu Rev Biophys*. 2019;48:63-91. doi:10.1146/annurev-biophys-052118-115,451
6. Stewart MT, Haines DE, Verma A, et al. Intracardiac pulsed field ablation: proof of feasibility in a chronic porcine model. *Heart Rhythm*. 2019;16(5):754-764. doi:10.1016/j.hrthm.2018.10.030
7. Wittkampf FH, van Driel VJ, van Wessel H, et al. Feasibility of electroporation for the creation of pulmonary vein ostial lesions. *J Cardiovasc Electrophysiol*. 2011;22(3):302-309. doi:10.1111/j.1540-8167.2010.01863.x
8. Koruth J, Kuroki K, Iwasawa J, et al. Preclinical evaluation of pulsed field ablation: electrophysiological and histological assessment of thoracic vein isolation. *Circ-Arrhythmia Elec*. 2019;12(12):e007781. doi:10.1161/CIRCEP.119.007781
9. Yavin H, Shapira-Daniels A, Barkagan M, et al. Pulsed field ablation using a lattice electrode for focal energy delivery: biophysical characterization, lesion durability, and safety evaluation. *Circ-Arrhythmia Elec*. 2020;13(6):e008580. doi:10.1161/CIRCEP.120.008580
10. Reddy VY, Koruth J, Jais P, et al. Ablation of atrial fibrillation with pulsed electric fields: an ultra-rapid, tissue-selective modality for cardiac ablation. *JACC-Clin Electrophy*. 2018;4(8):987-995. doi:10.1016/j.jacep.2018.04.005
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(3):315-326. doi:10.1016/j.jacc.2019.04.021
12. Reddy VY, Anic A, Koruth J, et al. Pulsed field ablation in patients with persistent atrial fibrillation. *J Am Coll Cardiol*. 2020;76(9):1068-1080. doi:10.1016/j.jacc.2020.07.007
13. Ekanem E, Reddy VY, Schmidt B, et al. Multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation (MANIFEST-PF). *Europace*. 2022;24(8):1256-1266. doi:10.1093/europace/euac050
14. Reddy VY, Gerstenfeld EP, Natale A, et al. Pulsed field or conventional thermal ablation for paroxysmal atrial fibrillation. *New Engl J Med*. 2023;389(18):1660-1671. doi:10.1056/NEJMoa2307291
15. Verma A, Haines DE, Boersma LV, et al. Pulsed field ablation for the treatment of atrial fibrillation: PULSED AF pivotal trial. *Circulation*. 2023;147(19):1422-1432. doi:10.1161/CIRCULATIONAHA.123.063988
16. Urbanek L, Bordignon S, Schaack D, et al. Pulsed field versus Cryoballoon pulmonary vein isolation for atrial fibrillation: efficacy, safety, and long-term follow-up in a 400-patient cohort. *Circ-Arrhythmia Elec*. 2023;16(7):389-398. doi:10.1161/CIRCEP.123.011920
17. Guo F, Wang J, Deng Q, et al. Effects of pulsed field ablation on autonomic nervous system in paroxysmal atrial fibrillation: a pilot study. *Heart Rhythm*. 2023;20(3):329-338. doi:10.1016/j.hrthm.2022.11.013
18. Tabaja C, Younis A, Hussein AA, et al. Catheter-Based electroporation: a novel technique for catheter ablation of cardiac arrhythmias. *JACC-Clin Electrophy*. 2023;9(9):2008-2023. doi:10.1016/j.jacep.2023.03.014

19. du Pre BC, van Driel VJ, van Wessel H, et al. Minimal coronary artery damage by myocardial electroporation ablation. *Europace*. 2013;15(1):144-149. doi:10.1093/europace/eus171
20. Reddy VY, Petru J, Funasako M, et al. Coronary arterial spasm during pulsed field ablation to treat atrial fibrillation. *Circulation*. 2022;146(24):1808-1819. doi:10.1161/CIRCULATIONAHA.122.061497

How to cite this article: Liu J, Dong M, Yang J. Pulse field ablation for atrial fibrillation: Is the curtain about to rise? *Aging Med*. 2024;7:287-291. doi:10.1002/agm2.12326