JACC: CASE REPORTS VOL. 2, NO. 12, 2020

EDITORIAL COMMENT

A Burning Success

Ganglionated Plexus Ablation for Paroxysmal Atrial Fibrillation*

Reshma Amin, BMBS,[a] Antonio Sorgente, MD, PhD[b,c]

Atrial fibrillation (AF) is the most prevalent cardiac dysrhythmia across the globe, and its invasive management, although widespread, poses a challenge when aiming for long-term freedom from AF. With success rates at approximately 60%, in absence of antiarrhythmic drugs, after a first procedure for paroxysmal AF (pAF) (1), we are yet to find the silver bullet for AF ablation.

In this issue of *JACC: Case Reports*, Kim et al. (2) describe the case of a 58-year-old lady with symptomatic pAF refractory to medical therapy and report the successful ablation of a single ganglionated plexus (GP), triggering ectopy causing AF, resulting in freedom from atrial arrhythmias. This proof-of-concept case describes an innovative potential strategy for ablation in patients with pAF, and we are grateful to the authors for sharing this case with the medical community.

There is a breadth of options for managing pAF and, as described in this case, antiarrhythmic medications, such as flecainide, are often used with a "pill in pocket" strategy. Use of many of the antiarrhythmic medications available is hindered by both side effects and contraindications in certain patient groups, notably those with structural or ischemic heart disease, which both have an increased incidence as people age. As AF disproportionately affects the elderly population, this poses challenges in clinical practice. It is clear that an ablative strategy over antiarrhythmic therapy is the preference for pAF management with regard to improvement in symptoms, maintaining sinus rhythm, and changing its natural history (3).

The history of AF ablation dates back to the 1980s, starting with surgical cut-and-sew techniques resulting in isolation of the atria (4), and as the authors note, it was not until 1998 that the landmark observation associating pulmonary veins to the origin and maintenance of AF was published (5). Subsequent extensive research into AF ablation has resulted in pulmonary vein isolation (PVI) becoming the established recommended procedure in all AF ablations. Following PVI, there are many targets for ablation that have been identified over the years (6): GPs are one of the most attractive among them, both on a pathophysiological and on a procedural standpoint.

Innervation of the heart occurs via the extrinsic (central) and intrinsic cardiac autonomic nervous system. The intrinsic cardiac autonomic nervous system is composed of GPs, which are the point of interest in this case. These GPs comprise afferent and efferent neurons, nerve axons, and ganglia clusters and are located on the epicardial surface of the heart, with the majority embedded in epicardial fat pads (7). The majority of neurons are located on the posterior atrial surface, and the 4 major atrial GPs are anatomically located in close proximity to the pulmonary veins and have projections to atrial tissue (8). These GPs have been found to play a role in the initiation and maintenance of AF (9). When performing wide PVI, the slowing of the RR interval is likely due to the interrupting axons of passage between ganglia.

As described in this case, the location of GPs are identified by delivering high-frequency stimulation (HFS) to the left atrial endocardium with the ablation

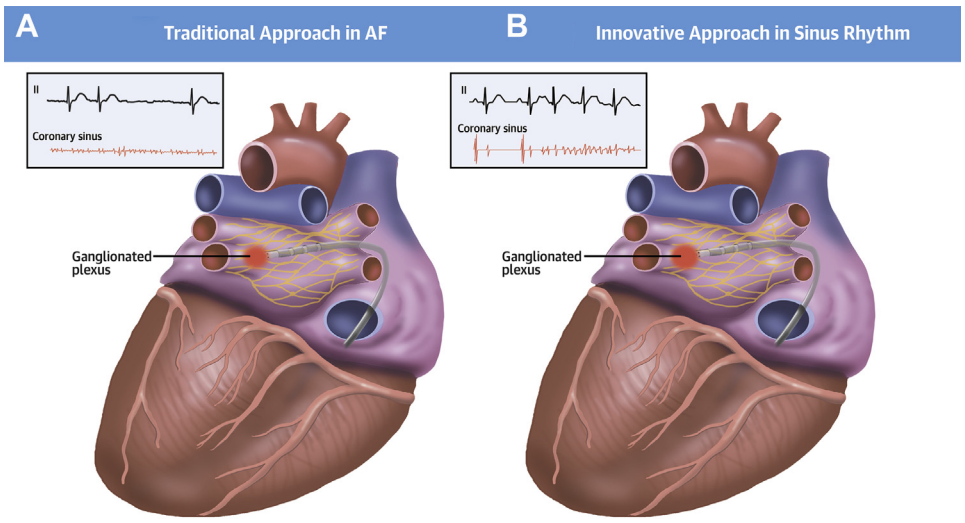
*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

From the [a]Cardiovascular Department, St Thomas' Hospital, London, United Kingdom; [b]Cardiovascular Division, EpiCURA Hospital, Hornu, Belgium; and the [c]Division of Cardiology, Brain and Heart SRL, Brussels, Belgium.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.09.005

CENTRAL ILLUSTRATION **High-Frequency Stimulation of Ganglionated Plexi in Atrial Fibrillation and Sinus Rhythm**



Amin, R. et al. J Am Coll Cardiol Case Rep. 2020;2(12):2010–2.

(A) High-frequency stimulation of a ganglionated plexus when the patient is in atrial fibrillation leading to slowing of the RR interval and **(B)** high-frequency stimulation of a ganglionated plexus in sinus rhythm, which induces an atrial ectopic and leads to atrial fibrillation.

catheter, and while the patient is in AF, this can identify an "atrioventricular dissociating GP," should there be transient complete atrioventricular block or a >50% prolongation in the average RR interval (**Central Illustration A**). The majority of studies identify GP location this method or base GP ablation on known anatomy without prior identification using HFS.

The novel approach proposed by Kim et al. (2) is to look for GPs also in sinus rhythm. The authors propose to perform synchronized HFS in the left atrium in sinus rhythm in order to identify specifically a particular type of GP, called ectopy-triggering GP (ET-GP) (**Central Illustration B**). HFS on these locations triggers short-cycle atrial ectopics and subsequently AF. The authors demonstrated that ablation on this site resulted in restoration of sinus rhythm during ablation and freedom from atrial arrhythmias at midterm follow-up.

GP ablation for the treatment of AF is not a novel technique: it has long been a controversial topic and is not recommended in current established guidance (10); however, this case describes the first ablation in humans, solely targeting the GP triggering AF, resulting in long-term freedom from AF, for which the authors must be applauded. The limitation of this technique stands in a potential lower reliability compared with PVI because localization of this particular type of GP could be cumbersome and time-consuming or not doable in patients in whom sinus rhythm cannot be restored with electrical or pharmacological cardioversion.

Furthermore, it is still debatable if GP ablation should be performed with or without PVI. Indeed, on the one hand, there is evidence that ablation of GPs in conjunction with traditional PVI confers a higher success rate when treating pAF (74% success, compared with 56% in PVI alone, in freedom from AF at 12 months) (11). On the other hand, when GPs were ablated without PVI, on an anatomical basis, this led to only 48% of success rate (11).

To confirm that when it rains it pours, there are data from canine studies suggesting that there could be not only no benefit in reduction of AF burden, but also proarrhythmic sequelae to GP ablation potentially secondary to reduction in the atrial effective refractory period in the long term, although all data are again based on anatomical ablation of GPs (12–14). On the clinical side, more recently the AFACT (Ganglionated Plexus Ablation in Advance Atrial Fibrillation) study showed no additional benefit to epicardial GP ablation when undergoing

thoracoscopic ablation for advanced AF and indeed resulted in a higher proportion of adverse events (15). A theory behind the limitation of long-term success of GP ablation lies in the diverse effects of ablation on atrial tissue and nervous tissue. Localized ablation performed on atrial tissue results in the creation of infarction and scar; however, neural tissue can exhibit plasticity whereby, should cell bodies be preserved (which may occur after GP ablation), nerve sprouts can emerge from each parent axon, leading to regeneration. In this case, the limited ablation of only 1 ET-GP as opposed to widespread GP ablation may prevent the previously mentioned potential adverse consequences.

When considering an ablative strategy for patient with pAF, this case highlights that there may well be a focal ET-GP trigger to target in certain patients. More data are needed to demonstrate if this approach may prevent the need for further widespread ablation and if it may reduce procedure time, adverse events, and the need of redo procedures. Anyway, this patient-centered approach to ablation with such success should be encouraged and warrants further consideration.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Reshma Amin, Cardiovascular Department, St. Thomas' Hospital, Westminster Bridge Road, London, United Kingdom SE1 7EH. E-mail: reshma.amin2@nhs.net.

REFERENCES

1. Takigawa M, Takahashi A, Kuwahara T, et al. Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol 2014;7:267–73.

2. Kim M-Y, Lim PB, Coyle C, Sandler B, Koa-Wing M, Kanagaratnam P. A single ectopy-triggering ganglionated plexus ablation without pulmonary vein isolation prevents atrial fibrillation. J Am Coll Cardiol Case Rep 2020;2:2004–9.

3. Jaïs P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation. Circulation 2008;118:2498–505.

4. Defauw JJ, Guiraudon GM, van Hemel NM, Vermeulen FE, Kingma JH, de Bakker JM. Surgical therapy of paroxysmal atrial fibrillation with the "corridor" operation. Ann Thorac Surg 1992;53:564–71.

5. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.

6. O'Neill MD, Jaïs P, Takahashi Y, et al. The stepwise ablation approach for chronic atrial fibrillation—evidence for a cumulative effect. J Interv Card Electrophysiol 2006;16:153–67.

7. Armour JA, Murphy DA, Yuan B-X, MacDonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec 1997;247:289–98.

8. Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. Anat Rec 2000;259:353–82.

9. Nakagawa H, Scherlag BJ, Patterson E, Ikeda A, Lockwood D, Jackman WJ. Pathophysiologic basis of autonomic ganglionated plexus ablation in patients with atrial fibrillation. Heart Rhythm 2009;6:S26–34.

10. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275–444.

11. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation. J Am Coll Cardiol 2013;62:2318–25.

12. Mao J, Yin X, Zhang Y, et al. Ablation of epicardial ganglionated plexi increases atrial vulnerability to arrhythmias in dogs. Circ Arrhythm Electrophysiol 2014;7:711–7.

13. Oh S, Zhang Y, Bibevski S, Marrouche NF, Natale A, Mazgalev TN. Vagal denervation and atrial fibrillation inducibility: epicardial fat pad ablation does not have long-term effects. Heart Rhythm 2006;3:701–8.

14. Wang X, Zhang M, Zhang Y, et al. Long-term effects of ganglionated plexi ablation on electrophysiological characteristics and neuron remodeling in target atrial tissues in a canine model. Circ Arrhythm Electrophysiol 2015;8:1276–83.

15. Driessen AHG, Berger W, Krul SPJ, et al. Ganglion plexus ablation in advanced atrial fibrillation. J Am Coll Cardiol 2016;68:1155–65.

KEY WORDS ablation, atrial fibrillation, electrophysiology