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Recovery of adenosine-sensitive dormant conduction is but one mechanism of pulmonary vein reconnection

Catheter ablation is an established treatment for atrial fibrillation (AF) which can improve symptoms and quality of life [1]. Since the demonstration of the critical role of triggers originating in the pulmonary veins (PVs) in AF [2], PV isolation (PVI) has been the cornerstone of AF ablation. Despite technical advances in catheter ablation, arrhythmia recurrence following ablation remains high, particularly for patients with persistent AF [3]. Additive ablation strategies beyond PVI has been shown to increase procedural complications [4] with no incremental clinical benefit [5], further emphasising the importance of achieving durable PVI. Rapid intravenous adenosine administration at the end of the ablation procedure is often used to differentiate permanent conduction block from dormant conduction [6]. Data on the reconnection rate of PVs without adenosine-sensitive dormant conduction during the index procedure are sparse.

In this issue of the *Journal*, Kottmaier and colleagues report on 67 patients with recurrent paroxysmal AF who underwent two catheter ablation procedures where adenosine was used to unmask dormant conduction [7]. Following confirmation of PVI and a waiting period of 20 minutes, rapid intravenous adenosine was administered in doses sufficient to induce transient third-degree atrioventricular block or sinus arrest. Dormant conduction ablation was guided by a circular mapping catheter placed within each studied PV. Nearly half the patients had at least one PV with dormant conduction, present in about a fifth of the 264 PVs tested. Of the remaining 216 PVs which initially showed no dormant conduction, 58% were demonstrated to have reconnection on repeat procedure. Therefore, PVs exhibiting no re-excitability after adenosine administration during the first PVI procedure are still susceptible to regaining excitability. This suggests that recovery of adenosine-sensitive dormant conduction may represent one, but not the only mechanism of early PV reconnection in AF patients undergoing PVI.

Catheter-based AF ablation aims to create a durable and transmural lesion to electrically isolate the PVs. On the cellular level, energy delivery during catheter ablation depolarizes cardiomyocytes in the targeted tissue within seconds to minutes and the resulting more positive resting membrane potential prevents sodium currents to activate, which clinically manifests in conduction block. Adenosine can induce hyperpolarisation in cardiomyocytes by removing voltage-dependant inward-sodium channel inactivation, allowing restoration in excitability in partially damaged myocytes, thus unmasking dormant conduction [6]. Mechanisms responsible for dormant conduction detected during the PVI ablation procedure typically do not include local inflammation and subsequent scar formation, which occur during the first days and weeks after the ablation procedure and are considered to be important to create a durable and transmural lesion.

The clinical use of adenosine to identify dormant conduction during the PVI procedure has been widely studied with conflicting reported benefits. In the first randomised-controlled trial to test adenosine-guided AF ablation, Macle et al. administered adenosine to 534 paroxysmal AF patients following PVI. They showed, similarly to Kottmaier et al., that dormant conduction was present in about 53% of the patients, who were subsequently randomised to receive consolidative ablation to abolish dormant conduction or no further ablation. The study demonstrated an absolute risk reduction of 27% in arrhythmia recurrence with adenosine-guided ablation compared to controls [8]. On the other hand, the larger "Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate (UNDER-ATP)" trial enrolled 2113 patients, including those with persistent AF (~33%), and randomly assigned patients to adenosine-guided ablation or conventional PVI only. The study found no significant change in arrhythmia-free survival after a follow-up of over 1 year [9]. These divergent results may become less at odds on closer examination. In addition to the differences in the studied population between the two studies, Macle et al. up titrated individual adenosine doses to physiologic response, while in UNDER-ATP, a weight-dependant dosing protocol was followed, which may explain the comparatively lower proportion of patients with dormant conduction seen (27%). The lack of conclusive evidence for the benefit of regular use of adenosine is further highlighted by multiple studies, including meta-analyses, which report seemingly contradictory results [10–12].

The heterogeneous outcomes of these recent clinical studies on adenosine-guided PVI ablation suggest, that adenosine-sensitive dormant conduction does not represent the only mechanism for clinical PVI reconnection and AF recurrence. Potential additional mechanisms include conduction through injured, oedematous tissue that can later recover, particularly in areas where catheter stability is difficult to achieve [13]. Thicker myocardial sleeves extending into the pulmonary veins, particularly at the superior veins [15] can potentially explain the difficulty in achieving transmural ablation and durable PVI. Additionally, the structural remodelling process during durable scar formation involves a complex and temporally dynamic activation of different pro-inflammatory and pro-fibrotic and pro-apoptotic pathways beyond mechanisms

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important for dormant conduction.

In conclusion, recovery of adenosine-sensitive dormant conduction represents one among many mechanisms of PV reconnection and AF recurrence. Therefore, absence of adenosine-sensitive dormant conduction during the index procedure cannot exclude later PV reconnection. Whether other techniques like longer waiting periods [14] or pacing via the distal tip of the ablation catheter along the PVI line to identify viable myocardium and potential gaps [16] improves PVI outcome should be investigated in future studies. While navigating through the optimal techniques to treat AF with catheter ablation, we should not lose sight of the importance of treating AF upstream, where the potential lies to halt the disease progression or even reverse it [17–19]. As for routine adenosine use in catheter ablation, the jury remains out on this contested issue, and further rigorous randomised controlled trials are warranted to help settle the debate.

References

[1] Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014;64(21):2222–31.

[2] Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339(10):659–66.

[3] Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson KC, Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc 2013;2(2). e004549.

[4] Murakawa Y, Yamane T, Goya M, Inoue K, Naito S, Kumagai K, Miyauchi Y, Morita N, Nogami A, Shoda M, Okumura K, Hirao K. Influence of substrate modification in catheter ablation of atrial fibrillation on the incidence of acute complications: analysis of 10 795 procedures in J-CARAF Study 2011-2016. J Arrhythm 2018;34(4):435–40.

[5] Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372(19):1812–22.

[6] Datino T, Macle L, Qi XY, Maguy A, Comtois P, Chartier D, Guerra PG, Arenal A, Fernandez-Aviles F, Nattel S. Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. Circulation 2010;121(8):963–72.

[7] Kottmaier M, Bourier F, Wunscher S, Kornmayer M, Semmler V, Lengauer S, Telishevska M, Koch-Buttner K, Risse E, Brooks S, Hessling G, Deisenhofer I, Reents T. Repeat ablation for paroxysmal atrial fibrillation - does adenosine play a role in predicting pulmonary vein reconnection patterns? Indian Pacing Electrophysiol J 2018;18:203–7.

[8] Macle L, Khairy P, Weerasooriya R, Novak P, Verma A, Willems S, Arentz T, Deisenhofer I, Veenhuyzen G, Scavee C, Jais P, Puererfellner H, Levesque S, Andrade JG, Rivard L, Guerra PG, Dubuc M, Thibault B, Talajic M, Roy D, Nattel S. Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. Lancet (London, England) 2015;386(9994):672–9.

[9] Kobori A, Shizuta S, Inoue K, Kaitani K, Morimoto T, Nakazawa Y, Ozawa T, Kurotobi T, Morishima I, Miura F, Watanabe T, Masuda M, Naito M, Fujimoto H, Nishida T, Furukawa Y, Shirayama T, Tanaka M, Okajima K, Yao T, Egami Y, Satomi K, Noda T, Miyamoto K, Haruna T, Kawaji T, Yoshizawa T, Toyota T, Yahata M, Nakai K, Sugiyama H, Higashi Y, Ito M, Horie M, Kusano KF, Shimizu W, Kamakura S, Kimura T. Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate (UNDER-ATP) trial. Eur Heart J 2015;36(46):3276–87.

[10] McLellan AJA, Kumar S, Smith C, Ling LH, Prabhu S, Kalman JM, Kistler PM. The role of adenosine challenge in catheter ablation for atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol 2017;236:253–61.

[11] Chen YH, Lin H, Xie CL, Hou JW, Li YG. Role of adenosine-guided pulmonary vein isolation in patients undergoing catheter ablation for atrial fibrillation: a meta-analysis. Europace 2017;19(4):552–9.

[12] Letsas KP, Georgopoulos S, Efremidis M, Liu T, Bazoukis G, Vlachos K, Karamichalakis N, Lioni L, Sideris A, Ehrlich JR. Adenosine-guided radiofrequency catheter ablation of atrial fibrillation: a meta-analysis of randomized control trials. J Arrhythm 2017;33(4):247–55.

[13] Rostock T, O'Neill MD, Sanders P, Rotter M, Jais P, Hocini M, Takahashi Y, Sacher F, Jonsson A, Hsu LF, Clementy J, Haissaguerre M. Characterization of conduction recovery across left atrial linear lesions in patients with paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 2006;17(10):1106–11.

[14] Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot N, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14(10):e275–444.

[15] Ho SY, Cabrera JA, Tran VH, Farre J, Anderson RH, Sanchez-Quintana D. Architecture of the pulmonary veins: relevance to radiofrequency ablation. Heart 2001;86(3):265–70.

[16] Schaeffer B, Willems S, Sultan A, Hoffmann BA, Luker J, Schreiber D, Akbulak R, Moser J, Kuklik P, Steven D. Loss of pace capture on the ablation line during pulmonary vein isolation versus "dormant conduction": is adenosine expendable? J Cardiovasc Electrophysiol 2015;26(10):1075–80.

[17] Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, Twomey D, Gallagher C, Hendriks JML, Linz D, McEvoy RD, Abhayaratna WP, Kalman JM, Lau DH, Sanders P. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. Europace 2018. https://doi.org/10.1093/europace/euy117.

[18] Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-Term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015;65(20):2159–69.

[19] Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. Circulation 2017;136(6):583–96.

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