International Journal of Cardiology 278 (2019) 153–154

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Second-generation cryo-pulmonary vein isolation for persistent atrial fibrillation: Is it really time to think out of the 'veins'?

Giuseppe Ciconte

Arrhythmia and Electrophysiology Center, IRCCS Policlinico San Donato, Piazza E. Malan 1, 20097 San Donato Milanese, Milano, Italy

ARTICLE INFO

Article history:
Received 26 November 2018
Accepted 30 November 2018
Available online 3 December 2018

Keywords:
Cryoballoon
Persistent atrial fibrillation
Pulmonary vein isolation

In the last two decades, we have witnessed the evolution of radiofrequency catheter ablation (RFCA) from an experimental procedure to a well-established treatment option for many atrial fibrillation (AF) patients. Pulmonary veins (PV) represent one of the main contributing drivers, however, several atrial sites and structural remodeling may play a critical role in the maintenance and perpetuation of the arrhythmia, as long as it progresses to more persistent form [1]. Nevertheless, PV isolation (PVI) gained widespread consensus, whereas commonly applied ablation sets (e.g. lines or CFAEs) beyond PVI seem to provide inconsistent benefit [1].

On these premises, second-generation cryoballoon (CB) ablation has emerged as an effective and practical approach. It gained the overall interest of the electrophysiology community due to its excellent success rate and reproducible results compared to RFCA [2]. Moreover, a favorable clinical outcome seems to be achieved not only in paroxysmal (PAF), but also in persistent AF (PersAF) showing a 60–69% freedom from arrhythmic recurrences at 1-year follow-up [3,4].

Into this area comes the study by Mortsell et al., published in the current issue of the *Journal* [5]. The patient cohort analyzed in this study was derived from a prospective randomized trial that examined the use of one versus two CB applications per vein. The aim of the study was to report the clinical outcome and quality of life (QoL) following Cryo-PVI in patients with PAF ($n = 62$) and PersAF ($n = 77$). All procedures were performed using the 28-mm CB-Adv requiring touch-up in 4% of cases. Overall complication rate (11%), and phrenic nerve palsies (3%) were low. Among patients completing the scheduled 12-month follow-up, symptom status and QoL significantly improved in both groups, whereas the single-procedure success rate was 65% in PersAF and 82% in PAF ($p = 0.03$). Of note, in PersAF group, arrhythmia freedom rate was not significantly different between those receiving a single ($n = 21$) versus double ($n = 29$) cryo-application. Roughly 11% underwent a repeat procedure showing, in almost all patients, at least one PV reconnection. Independent predictors of arrhythmia recurrences were LA volume index and persistent nature of the arrhythmia.

The authors should be commended on executing this trial, most importantly for the main finding of this study reporting that a single cryo-application is equally effective as compared to the routine two-application strategy. Moreover, this analysis certainly adds further evidence in the treatment of PersAF patients with Cryo-PVI. Limitations include the lack of long-term monitoring with event recorders and the definition of AF history. The latter is not different between the two groups and the precise time spent in AF has not been reported. However, these two factors are counterbalanced by the prospective and randomized nature of the study and do not affect, in my opinion, the relevance of the findings. Taken in context, these results suggest that PVI by the means of CB ablation proved to be beneficial in 65% of treated PersAF patients. Noteworthy, these results compare favorably with other groups, also regarding the predictors of arrhythmia recurrences [3].

The mounting evidence that 'less is more' in PersAF gives us the time to speculate upon some still unanswered questions regarding the arrhythmia mechanism and its treatment: Is PVI enough in this patient population? Is it always PV reconnection the recurrence mechanism after ablation? Is CB-ablation the technique of choice in this setting? To date, no definitive conclusions can be drawn, however, as physicians we have to ask to ourselves if there is a chance to further improve success rate. There is substantial evidence that drivers are the leading mechanisms in AF maintenance and can be revealed using various approaches [6–8]. Although the anatomic distribution of drivers may vary according to patients' characteristics, the importance of non-PV regions in AF maintenance have been demonstrated [6–8]. Drivers may be located practically everywhere in both atria, however recent data gathered from randomized and non-randomized studies show how localized ablation may terminate AF, improving the clinical outcome [6–8]. However, the driving mechanisms behind PersAF are poorly known. In this study, repeat PVIs offered little improvement to the index procedure (from 65 to 69%) thus questioning the role of PV reconnection as the only mechanism involved in the recurrences. The higher rate of durable PVI following CB-ablation when compared to

DOI of original article: https://doi.org/10.1016/j.ijcard.2018.10.097.
E-mail address: g.ciconte@gmail.com.

https://doi.org/10.1016/j.ijcard.2018.11.134

other techniques, certainly support the use of such a tool, however limitations of this approach include the fact that recurrences might still occur even with persistent isolation. Moreover, a PV reconnection could be documented also in patients without clinical recurrences, and some experiences report very high rate of successful ablation without even approaching the PVs [9]. Furthermore, CB-Adv determines a considerable electrical debulking of the LA. By targeting the PV antra, a wide circumferential cooling area may also provide collateral benefit by ablating potential local AF contributors (e.g. ganglionic plexi and rotors).

Finally, the LA dimension seems to be an accurate predictor of arrhythmia recurrence following ablation by indicating advanced structural remodeling, potentially overcoming the temporal distinction between paroxysmal and persistent. In fact, this indicator is poorly considered. If we look from a different perspective the results reported by Mortsell et al., it may play a relevant role in identifying potential 'PVI-*nonresponders*', destinating those with a significant dilated atrium to a different strategy according to physician preference. Moreover, the CB-Adv has recently shown a certain degree of versatility in targeting extra-PV regions with promising results [10], making this tool even more attractive than previously thought. On the other hand, many PersAF patients without significant LA dilation still benefit from a PVI only strategy.

In conclusion, there are still many uncertainties regarding the most appropriate treatment of PersAF patients. It is a complex arrhythmia, and the future success of catheter ablation in this setting resides into a better knowledge of the underlying arrhythmogenic mechanism to pursue a definite tailored approach. However, there is an overwhelming evidence regarding the safety and efficacy of the Cryo-PVI. Therefore, in the era of evidence-based medicine, the results of this prospective randomized study are welcome, confirming this technique as extremely attractive also in the treatment of PersAF.

Conflict of interest

The author reports no relationships that could be construed as a conflict of interest.

References

[1] H. Calkins, K.H. Kuck, R. Cappato, et al., 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design, Europace 14 (2012) 528–606.

[2] R. Providencia, P. Defaye, P.D. Lambiase, D. Pavin, J.P. Cebron, F. Halimi, F. Anselme, N. Srinivasan, J.P. Albenque, S. Boveda, Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? Europace 19 (2017) 48–57 Jan.

[3] G. Ciconte, L. Ottaviano, C. de Asmundis, G. Baltogiannis, G. Conte, J. Sieira, G. Di Giovanni, Y. Saitoh, G. Irfan, G. Mugnai, C. Storti, A.S. Montenero, G.B. Chierchia, P. Brugada, Pulmonary vein isolation as index procedure for persistent atrial fibrillation: one year clinical outcome after ablation using the second-generation cryoballoon, Heart Rhythm. 12 (2015) 60–66.

[4] S. Boveda, A. Metzner, D.Q. Nguyen, et al., Single procedure outcomes and quality of life improvement 12 months post-cryoballoon ablation in persistent atrial fibrillation: results from the multi-center CRYO4PERSISTENT AF trial, JACC Clin. Electrophysiol. (2018)https://doi.org/10.1016/j.jacep.2018.07.007.

[5] D. Mortsell, H. Malmborg, S. Lonnerholm, V. Jansson, C. Blomstrom-Lundqvist, Clinical outcome of the 2nd generation cryoballoon for pulmonary vein isolation in patients with persistent atrial fibrillation — a sub-study of the randomized trial evaluating single versus dual cryoballoon applications, Int. J. Cardiol. (2018 Oct 29) pii: S0167-5273(18)35500-1.

[6] M. Haissaguerre, M. Hocini, A. Denis, A.J. Shah, Y. Komatsu, S. Yamashita, et al., Driver domains in persistent atrial fibrillation, Circ. Arrhythm. Electrophysiol. 130 (2014) 530–539.

[7] S. Narayan, D. Krummen, K. Shivkumar, P. Clopton, W. Rappel, J. Miller, Treatment of atrial fibrillation by the ablation of localized sources CONFIRM (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial, J. Am. Coll. Cardiol. 60 (7) (2012) 628–636.

[8] C. Pappone, G. Ciconte, G. Vicedomini, J.O. Mangual, W. Li, M. Conti, et al., Clinical outcome of electrophysiologically guided ablation for nonparoxysmal atrial fibrillation using a novel real-time 3-dimensional mapping technique: results from a prospective randomized trial, Circ. Arrhythm. Electrophysiol. 11 (2018), e005904.

[9] J. Seitz, C. Bars, G. Théodore, S. Beurtheret, N. Lellouche, M. Bremondy, A. Ferracci, J. Faure, G. Penaranda, M. Yamazaki, U.M. Avula, L. Curel, S. Siame, O. Berenfeld, A. Pisapia, J. Kalifa, AF ablation guided by spatiotemporal electrogram dispersion without pulmonary vein isolation: a wholly patient-tailored approach, J. Am. Coll. Cardiol. 69 (3) (2017) 303–321 Jan 24.

[10] A. Aryana, J.H. Baker, M.A. Espinosa Ginic, D.K. Pujara, M.R. Bowers, P.G. O'Neill, K.A. Ellenbogen, L. Di Biase, A. d'Avila, A. Natale, Posterior wall isolation using the cryoballoon in conjunction with pulmonary vein ablation is superior to pulmonary vein isolation alone in patients with persistent atrial fibrillation: a multicenter experience, Heart Rhythm. 15 (8) (2018) 1121–1129 Aug.