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EDITOR'S FORUM

To "*isolate*" or "not to *isolate*," the left atrial appendage, "that is the question"

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The left atrial appendage (LAA) has a trabecular shape, various morphologies, and derives from the embryonic left atrium as an outgrowth of the pulmonary veins (PV). The LAA plays a role in volume homeostasis secreting ANP and in autonomic innervation due to the presence of ganglia along the groove between the left superior PV and the LAA [1–9].

PVs isolation is the cornerstone of ablation of atrial fibrillation (AF) [10, 11]. Despite a permanent PVs isolation, patients may experience AF recurrences due to the presence of non-PV triggers responsible of AF [12, 13]. The relevance of non-PV triggers ablation in addition to PV isolation is extremely important for the treatment of persistent and long-standing persistent AF [12]. The most common and reported non-PV trigger sites are the superior vena cava, the coronary sinus, the atrial septum, and the ligament of Marshall. Recently, the LAA has been reported as an unrecognized trigger site of AF in all subtype of AF and especially in patients with non-paroxysmal AF [14]. For many years, electrophysiologists have concentrated their effort to achieve durable PVs isolation, considering PVs reconnection the only cause of ablation failure. There is now evidence that despite isolated PVs patients may experience AF recurrence. In 2010, we reported a series of 266 patients undergoing redo AF ablation procedures with demonstrated silent PVs. In 27 % of these patients, a firing from the LAA was documented, and in 8 % of the patients, the LAA was the only site responsible for AF. In our series, we also showed that focal ablation of the LAA was not as efficacious as complete electrical isolation to achieve freedom from AF at follow-up [14]. After our initial report, many case reports and series have shown the relevance of the LAA for triggering and the maintenance of AF [15–18]. Hocini et al. [19] reported patients with localized re-entrant arrhythmias originating within the LAA after failed standard AF ablation and supported the hypothesis of LAA as a main trigger for the maintenance of AF. Chan et al. [20] also suggested that LAA isolation may be caused by disruption of Bachmann's bundle, which runs along the LA anterior wall and surrounds the LAA. Recently, the LAALA registry has shown a lower AF burden by mechanically inducing electrical isolation with the LARIAT closure device [21]. The aMAZE trial [22] will enroll patient with persistent AF undergoing LARIAT LAA closure and mechanical electrical isolation and then PV isolation with radiofrequency. Although other non-PV triggers such as the coronary sinus and posterior wall will not be ablated, which might jeopardize the results, the study will probably support the relevance of the LAA as an AF trigger.

In this issue of the journal, Hwan-Cheol Park [23] et al. from Korea present a series of 846 consecutive patients undergoing PVI plus extensive left atrial wall ablation guided by

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CFAEs, cavo tricuspid isthmus bidirectional block and a clear pre- and post-LAA angiogram in sinus rhythm during right ventricular pacing. Of these, 89 patients (14 paroxysmal AF and 75 non-paroxysmal) met all the pre-identified inclusion criteria. These 89 patients were divided into three groups according to the LAA delay or LAA electrical isolation during ablation. Group 1 was composed by 24 patients where no LAA delay or electrical isolation was present; group 2, where LAA delay without electrical isolation was present ($n = 47$), and group 3 was composed by patient with LAA electrical isolation ($n = 18$). The LAA potential injury was evaluated by the ejection fraction of the LA and of the LAA measured by LA angiograms. No statistical differences in the patient demographic and procedural characteristic among groups were noted. Interestingly, at the 21 months follow-up, only 3 patients (17 %) in group 3 (LAA electrical isolation) had recurrence when compared to 11 (23 %) in group 2 (LAA delay but no isolation), and 12 (50 %) in group 1 (no LAA delay or isolation) ($P = 0.028$). In multivariate analysis, only diabetes mellitus and LAA potential delay were independent predictors of AF recurrence ($P = 0.021$, $P = 0.008$, respectively). Although this data shows that LAA delay is associated with decreased recurrence, one must recognize that LAA isolation and LAA delay share common physiology; hence, as the authors appropriately addressed in the discussion, the insufficient number of patients in the LAA isolation group may be the reason for non-significance in terms of recurrence (47 vs. 18 patients, respectively). Of note, despite the immediate post-ablation LA angiography showing severely decreased LAA contractility in the LAA isolation cases compared to the other patients, the values of LA ejection fraction (EF) did not statistically differ among groups. The changes from LAA EF1 (pre-ablation) to LAA EF2 (post-ablation) in each of the three groups were significantly reduced ($P < 0.001$ for groups 1, 2, 3, respectively). At the post-ablation transesophageal echocardiogram (TEE), 16 patients in group 3 (LAA isolation) underwent TEE 1 month after ablation to evaluate LAA systolic function, detect thrombus formation, LAA flow velocity, and transmitral E/A ratio. Only one of the 16 patients lacked any detectable emptying velocity of the LAA. LAA contractility was well preserved or mildly decreased in eight patients (50 %), and the remaining patients had poor contractility. No spontaneous echo contrast or thrombus was observed in the LA or LAA. The authors data [23] are consistent with our 2010 [14] series and demonstrate the relevance and efficacy of LAA isolation to achieve freedom from AF at follow-up without increasing the thromboembolic risk. The BELIEF randomized trial [NCT01362738] has been recently presented at the late breaking trial of the ESC 2015 [24] and clearly showed that the empirical electrical isolation of the LAA improves the ablation outcome at follow-up of long standing persistent (LSP) AF patients without increasing complications. There is common "BELIEF" that LAA does not play a role in the initiation and maintenance of AF and that LAA isolation could be dangerous. However, this was not shown in the trial. Additionally, more recently, we presented at HRS 2016 data from 1854 consecutive AF patients (84 % non-paroxysmal AF) receiving LAA isolation along with PV isolation [25, 26]. TEE at 6 months post-ablation follow-up showed impaired LAA mechanics in 58 % of the patients. The overall thromboembolic event rate was 0.08 and 2.26 % in on and off oral anticoagulation (OAC) populations, respectively ($P < 0.001$). Of the 14 patients with stroke, 12 (85.7 %) had sub-therapeutic INR or discontinued their OACs for >5 days. These results provide more evidence that LAA isolation is not associated with higher risk of thromboembolic events even in the presence of impaired LAA function as long as optimal anticoagulation is maintained. For many years, several treatment strategies have "made sense" in the electrophysiology field before we could realize they were actually wrong. D-sotalol post-myocardial infarction, cardiac pacing for the treatment of vasovagal syncope, class IC antiarrhythmic drug to suppress PVCs, ventricular stimulation for hyperthrophic cardiomyopathy, and amiodarone use to reduce mortality in patients with left ventricular dysfunction represent all examples of negative evidence based medicine, but "common belief" for clinicians. In the field of catheter ablation for AF, for a long period of time, many assumed that only the PV triggering AF had to be isolated. Only years after, clinical experience as the guidelines and the consensus documents have agreed that all PVs should be "empirically" isolated in patients undergoing ablation for AF to increase success rate at follow-up. The final results of the BELIEF randomized [24] trial will probably answer the question of whether or not the LAA should be always empirically isolated in patients with LSP AF to improve clinical outcomes. The current paper by Hwan-Cheol Park et al. [23] clearly shows the efficacy of LAA isolation. Furthermore, the notion that Cox-Maze III surgery data have demonstrated a 90 % success rate at maintaining sinus rhythm and a low incidence of thromboembolic events with successful LAA exclusion/excision over long-term follow-up is of interest [27]. The present study reinforces the relevance of the LAA as an important structure to be isolated irrespective of the firing in persistent and LSP AF.

The main criticism against LAA electrical isolation is its potential added thromboembolic risk. Our results, including data from the BELIEF trial [14, 24–26], and the current paper by Hwan-Cheol Park et al. [23] demonstrate that around 50 % of patients have a flow velocity within normal range after LAA isolation and that with proper AC no added stroke risk exists. Importantly, many of the patients requiring LAA electrical isolation need long-term AC due to their CHADS-VASc score >2 irrespective of the LAA electrical status. In patients with abnormal flow velocity, long-term AC or LAA closure device can be considered.

In conclusion, we believe this is the price to pay to maintain sinus rhythm. The question about love in Shakespeare's play Hamlet translates into LAA electrical isolation: to be isolated or not to be isolated it is an easy answer in this author's opinion.

Compliance with ethical standards

Conflicts of interest Dr. Di Biase is a consultant for Biosense Webster, Stereotaxis, and St. Jude Medical, and has received speaker honoraria/travel from Boston Scientific, Medtronic, Janssen, EPiEP, Biotronik, and Pfizer. Dr Natale received speaker honorariums from Boston Scientific, Biosense Webster, St. Jude Medical, Biotronik, and Medtronic, and is a consultant for Biosense Webster St. Jude Medical and Janssen.

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