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Electrical Isolation of the Left Atrial Appendage - A New Frontier in the Treatment for Atrial Fibrillation

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Abstract

Atrial fibrillation is not only the most common clinical arrhythmia, it is also one of the most challenging conditions to treat in day-to-day clinical practice. In particular, the persistent form of this condition is not easily amenable to traditional forms of therapy, whereas, the paroxysmal form is far more responsive to standard modes of treatment. In our relentless quest to find better solutions to overcome persistent atrial fibrillation, arguably the most promising of these currently appears to be electrical isolation of the left atrial appendage. Whilst surgical amputation of the left atrial appendage for stroke prevention has been practiced for more than half a century, only recently has attention gradually been shifting to electrical isolation of the left atrial appendage for the treatment of persistent atrial fibrillation. In this review article, we present compelling pieces of evidence for the use of this strategy, and the various ways in which it can be achieved.

Keywords: Atrial fibrillation • Left atrial appendage • Electrical isolation • Lariat • Atriclip

Introduction

Atrial fibrillation (AF) is not only the most common arrhythmia in humans, but the persistent form of this dysrhythmia is also one of the most challenging conditions to treat in clinical medicine. Whilst paroxysmal AF (PAF) responds very well to pulmonary vein isolation (PVI), persistent AF (PersAF) does not [1,2]. Unlike for PAF, the formation of triggers and substrates outside the pulmonary veins (PVs) is frequently responsible for the pathophysiology and perpetuation of PersAF [3-5]. Mounting evidence suggests that targeting very specific regions within the left atrium (LA), outwith the PVs, during ablation therapy may provide additional benefits to that of PVI alone [6-8].

One of the most promising developments in this field is the concept of electrical isolation of the left atrial appendage (LAA) to reduce the recurrence of atrial dysrhythmias in patients with PersAF. Since the LAA shares embryological origins with the primordial PVs, this may enable it to initiate and perpetuate AF as do the PVs [9,10]. In this review, we shall detail why this vestigial structure is considered to be an important target for the successful treatment of PersAF: we shall provide evidence to support the intimate role of the LAA in PersAF; how the LAA has been managed by surgeons and cardiologists over the years, to now provide us with the opportunity to tackle this substrate in PersAF more effectively; present data on the benefits and risks of performing LAA electrical isolation (LAAEI); and the current interventional options to achieve the goal of LAAEI.

Literature Review

Evidence for the role of the LAA in AF

Four decades ago, Wyndham et al. described the first case of paroxysmal atrial tachycardia (AT) originating from the right atrial appendage [11]. In 1991, De Bakker et al. successfully performed the first known surgical treatment for longstanding AT arising from the LAA, in a symptomatic 32-year-old woman [12]. Following *in vivo* epicardial mapping, they conducted a variety of electrophysiological and histological experiments on the excised LAA to demonstrate spontaneous activity arising from a group of abnormal cells within the apex of the LAA [12]. They followed up the patient for 16 months and found that she remained in sinus rhythm and her exercise tolerance had improved remarkably.

It was not until 2004 that a link between AF and the LAA was first discovered, when Takahashi et al. identified and successfully ablated ectopic foci arising from within the LAA, by electrically isolating the appendage from the rest of the LA, in a patient with PAF [10]. During electrophysiological study, spontaneous AF occurred following ectopic beats from the right superior PV. Ablation to achieve PVI led to prolongation of tachycardia cycle length, with earliest activation within the LAA. Attempts to ablate the foci were unsuccessful in terminating the tachycardia, so electrical isolation of the LAA was undertaken, upon which there was coincident restoration of sinus rhythm. The authors noted that there was a gradual alteration of the activation sequence within the LAA, as opposed to the sudden changes found during PVI, suggesting more dense connections from the LAA to the LA, compared to that of the PVs. They also found that prolonged circumferential ablation for 25 minutes was necessary to achieve electrical isolation of the LAA. Caution was raised for such an approach owing to 1) the

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risk of perforating the LAA by the ablation catheter, 2) lengthy application of radiofrequency energy to achieve isolation, 3) close proximity to the left phrenic nerve, and 4) concern for development of stasis within the LAA and subsequent formation of thrombus. In addition, there is a potential risk of injury to the left circumflex coronary artery, which courses nearby the inferior aspect of the LAA.

By 2010, Di Base et al. conducted seminal work to assess in more detail the role of the LAA in AF, by way of a large multi-centre international trial [13]. Of the nine hundred and eighty-seven patients undergoing redo AF ablation therapy, two hundred and sixty-six (27%) were found to have firing from the LAA, with eighty-six (8.7%) found to have LAA as the only source of AF; 18% had a history of PAF and the remaining had PersAF. Of the 266 patients with LAA firing, 43 had no LAA ablation performed (group 1), 56 had focal ablation of the LAA (group 2), and 167 had LAAEI (group 3). In the latter group, LAAEI was achieved by segmental lesions in 70% and with circumferential ablation in 30%. At a mean follow-up of 12 ± 3 months, AF recurrence in groups 1, 2 and 3, were 74%, 68% and 15%, respectively (log-rank p<0.001). The following year, Hocini et al. showed that the LAA is an important source for localised re-entrant ATs in patients undergoing ablation for stepwise PersAF [14]. By targeting ablations at points of long fractionated or mid-diastolic electrograms inside the LAA, they successfully terminated the ATs in each of the fifteen cases.

LAAEI using radiofrequency ablation

During the last decade, several studies have been published in the field of LAAEI using radiofrequency catheter ablation. In the prospective randomised BELIEF trial, 171 patients with longstanding PersAF were assigned to either LAAEI plus LA extensive ablation (group 1) or extensive LA ablation alone (group 2) [15]. LAAEI was achieved in all patients by catheter ablation. At 12 months follow-up and after a single procedure, 56% of patients in group 1 and 28% in group 2 were free of recurrent atrial dysrhythmias (p=0.001; after adjusting for certain parameters p=0.004). At 24 months and after repeat procedures (1.3 on average), 76% in group 1 and 56% in group 2 remained free of atrial dysrhythmias (p=0.003).

Panikker et al. performed LA ablation plus LAAEI and LAA occlusion (using Watchman, Boston Scientific, MA, USA) in patients with PersAF [16]. The study patients (n=20) were compared to a matched control group (n=40) that had LA ablation but did not undergo LAAEI or LAA occlusion. The authors demonstrated that in the LAAEI/occlusion group there was a significant improvement in freedom from AF at 12 months, whilst off anti-arrhythmic agents, when compared to the control group (95% versus 63%, respectively (p=0.036)); whereas freedom from atrial dysrhythmias showed a tend towards improvement, this did not reach statistical significance (60% versus 40%, respectively (p=0.17)). Their work also produced the first-in-human safety, feasibility, and efficacy study in the field of concomitant LAAEI and occlusion in patients undergoing catheter ablation for longstanding PersAF. In a single-arm study, Fassini et al. also assessed the feasibility of PVI (using cryoballoon) and concomitant LAA occlusion (using Amplatz Cardiac Plug, St. Jude Medical, MN, USA or Watchman, Boston Scientific, MA, USA); although, the main focus of this study was on the outcomes of device-related leaks and thrombo-embolic features [17].

Three meta-analyses on LAAEI in AF were published in 2018, two of which were published in early 2018 [18-20]. One was conducted by Romero et al. to assess the cohort of patients with PersAF undergoing catheter ablation plus LAAEI by radiofrequency ablation (RFA), cryoablation or implantation of the Lariat device [18]. Seven studies, which included control arms, with a total of 930 patients that received follow-up for at least 1 year were included in this meta-analysis. They found that at 12 months of follow-up, there was a significant benefit with LAAEI in freedom from all-arrhythmia recurrence compared to standard ablation alone; 75.5% vs. 43.9%, respectively (p<0.0001). When comparing PersAF with longstanding PersAF, there was no difference in recurrence of atrial arrhythmias (p=0.49). Interestingly, there was no significant difference in the rate of ischaemic stroke between the groups at follow-up, particularly when advice for oral anticoagulation was adhered to (LAAEI 0.4% vs. control 2.1% (p=0.13)).

Around the same time, Friedman et al. also published a meta-analysis [19]. In this paper, seven studies with a total of 1,037 patients were observed for a minimum mean of 12 months post intervention. Each study contained a control arm and follow-ups included assessments for AF as well as AT. There were significantly fewer recurrent atria tachyarrhythmias in patients who received LAAEI than those who did not (or 0.375, p=0.02). Since these findings included two surgical studies with LAA excision, the authors performed a subgroup analysis in the other five studies with percutaneous LAAEI (n=623) and found even lower recurrence rates (or 0.223, p<0.001); of note, in one of these studies (n=138) the Lariat device was used for LAAEI, not ablation.

Later in 2018, AlTurki et al. presented their meta-analysis [20]. They identified five studies that included a control arm, total 781 patients who underwent PVI ± LAAEI for PersAF, with follow-up for 12-15 months. Four of the studies employed RFA, and one used cryoballoon, for LAAEI. There was marked reduction in recurrence of AF in the LAAEI group compared to the PVI alone group (p<0.00001); this study did not assess outcomes for all atrial dysrhythmias.

Cryoballoon therapy for LAAEI

A large single-centre, propensity-score matched study was undertaken by Yorgun et al. to investigate the efficacy and safety of cryoballoon therapy for LAAEI in patients with PersAF [21]. In under 1 year, the team at this high-volume centre performed 100 cases of cryoballoon PVI plus LAAEI (group 2) and matched these to 100 cases of cryoballoon PVI alone (group 1). In six patients, additional to the 100 in group 2, LAAEI was not possible and these were not included as part of the analysis. All patients completed follow-up for 1 year, which included trans-oesophageal echocardiography to assess the mechanical function of, and any thrombus formation in, the LAA. At 12 months, 67% patients in group 1 and 86% patients in group 2 were free from atrial dysrhythmias (p=0.001) following the index procedure and excluding the 3-month blanking period. Within the whole study population of 200 patients, they found that some factors were associated with a greater likelihood of recurrent atrial dysrhythmias; these were, a larger LA diameter (p<0.001), hypertension (p=0.022), cardioversion resistant AF pre-ablation (p<0.001), and early recurrence of AF within the 3-month blanking period (p<0.001); some factors that were associated with a trend toward greater recurrence of AF, but did not quite reach statistical significance, included diabetes mellitus (p=0.054), higher LAA flow velocities (p=0.057) and heart failure (p=0.092). Collateral damage during cryoballoon therapy to the LAA may occur to adjacent structures, such as the left phrenic nerve and left circumflex coronary artery. The latter courses in close proximity to the ostium of the LAA and cryoballoon therapy may give rise to spasm of this vessel and that may be asymptomatic but is completely resolved with administration of intracoronary nitrate [21,22].

Endo-epicardial closure to achieve LAAEI - the lariat device

The Lariat suture device (SentreHEART, Redwood City, CA, USA) is unique in its approach insofar that it aims to snare and ligate the appendage using combined endo-epicardial access. Opposite polarity magnet-tipped guidewires are opposed across the LAA, via transseptal-endocardial and percutaneous-epicardial routes, to achieve end-to-end alignment of the wires. A pre-tied Teflon coated braided polyester suture, in the shape of a lasso, is advanced over the epicardial guidewire, onto the LAA and carefully positioned around the base of this structure. Next, an over-the-wire endocardial balloon is inflated within the body of the LAA and gently retracted toward the neck to facilitate accurate positioning of the epicardial suture around the neck of the LAA. The suture is deployed, and the endocardial balloon is deflated and removed together with the guidewire. Finally, the suture is tightened, resulting in both LAA occlusion and electrical isolation

(see data below for possible mechanisms); once the pre-tied ligature is snipped, the epicardial system is withdrawn from the body.

Pre-clinical studies in animals and early studies in humans showed that the device could be deployed successfully, with very high rates (around 95%) of complete LAA closure [23-26]. The first multicentre study to assess the efficacy and safety of this device was conducted retrospectively by Price et al. on 154 patients [27]. They demonstrated a high level of closure success (94%, residual leak <5 mm) with the Lariat, but the overall success of the procedure (86%) was limited by complications such as bleeding. Sievert et al. reviewed 139 patients and reported a 99% acute closure rate with the Lariat device [28]. In this early study, the periprocedural complication rate was 11.5%, which included 2 cardiac perforations and 1 death due to a pulmonary embolus. The largest study to date, involving 712 patients, to assess the efficacy and safety of the Lariat device was reported by Lakkireddy et al. in 2016 [29]. The device was successfully deployed in 95.5% of cases - with complete closure in 98.1% and only a trace leak (<2 mm) in 1.9%. Cardiac perforation necessitating open heart surgery occurred in 1.4%, while another 2% were successfully managed without surgery. Importantly, the incidence of such acute complications was significantly reduced following the use of micro-puncture needles rather than large bore needles (2.2% vs. 10.1%, p<0.0001) and delayed complications, such as severe pericarditis, was reduced with the use of colchicine (p<0.01). The benefit of using colchicine has also been demonstrated by Gunda et al. [30]. Additional data on complication rates have been reported by other groups [31-33]. As part of a systematic review by Chaterjee et al. published in 2015, the authors included a specific analysis of adverse events from real-world practice using the FDA MAUDE database [31]. Very recently, Tilz et al. reported on the collective European experience [32]. In their series of 141 patients, successful deployment of the Lariat device was achieved in 97.8%. Major procedure related complications were reported in 2.8% and minor complications in 13.5% (the latter included 2 pericardial effusions requiring pericardiocentesis). There were 2 patients (1.8%) that developed a transient ischemic attack at 4 and 7-months follow-up, despite no leak observed on TOE.

Although the originally intended design of the Lariat system was primarily to reduce the risk of stroke, subsequent trial data has shown the device may also electrically isolate the LAA. Having said that, the data on clinical outcomes in this field is limited and there is a need for further randomised studies, to be undertaken [34]. The earliest clinical study to assess the acute consequences of Lariat suture device on electrical activity in the LAA was conducted by Han et al. on 68 patients [35]. Upon deployment of the Lariat device, they demonstrated marked reductions of unipolar voltage from 1.1 ± 0.53 mV to 0.3 ± 0.38 mV (p<0.001) and bipolar voltage from 4.7 ± 2.83 mV to 0.6 ± 0.27 mV (p<0.001), in 94% of cases; ischemic necrosis distal to the site of ligation was hypothesized to be the underlying mechanism for these changes. Recently, Parikh et al. have shown that the Lariat device is more efficacious than one-time endocardial radiofrequency ablation at producing LAAEI (96.7% vs. 52.8%, respectively; p<0.01) [36].

In 2015, Lakkireddy et al. presented data from a prospective, observational study, with a matched control group, the LAALA-AF registry [37]. In a total of 138 patients, freedom from AT or AF at 1 year, off antiarrhythmic therapy and after the index procedure, was significantly higher in the Lariat group when compared to the ablation-only group (65% vs. 39%, p=0.002). Afzal et al. studied 50 patients with pre-existing cardiac implantable devices and AF (PAF or PersAF), by performing LAA closure alone (utilising the Lariat device) and without LA ablation [38]. They discovered that AF burden was significantly reduced at 3 months (42% ± 34%, p<0.0001) and 12 months (59% ± 26%, p<0.001) when compared to baseline (76% ± 33%). The greatest benefit at 12 months appeared to be in those with known AF triggers in the LAA (p<0.0001). Of further interest, they found that those with PAF had a reduced burden at 3 months, but not at 12 months. This study clearly highlighted the value of selective LAAEI in reducing arrhythmia burden in PersAF.

The benefit and safety profile in decreasing the recurrence of AF with Lariat placement following AF ablation is under current research in the multicentre randomized aMAZE trial (LAA Ligation Adjunctive to PVI for Persistent or Longstanding Persistent Atrial Fibrillation, NCT02513797).

Surgical LAA amputation

Cardiac surgeons have long been proponents of concomitant LAA amputation, with the rationale of preventing postoperative stroke in patients undergoing mitral valve surgery [39]. This technique then formed part of the maze and 'corridor' procedures that were performed to treat non-rheumatic atrial fibrillation by surgical means [40]. In parallel, LAA amputation gained popularity as an adjunct to other types of cardiac surgery [41-43].

The surgical techniques involve closure at the base, with or without amputation of the remaining LAA. Closure is achieved by either hand-sewn suturing, the application of staples, or deploying a single clip around the base of the LAA. The open-chest Cox-Maze IV approach employs amputation and full cut-and-sew of the LAA, using pledgeted, bi-layer sutures. Application of staples alone may occasionally give rise small pouches or bleeding, so this may be reinforced with hand-sewn sutures. Of note, sutures or staples may erode through the LAA wall allowing it to reopen [44]. Over the last decade, the FDA-approved AtriClip (Atricure, Inc., West Chester, OH, United States) has gained much popularity as the alternative option in this field; it appears to be safe, quick and easy to deploy, and highly efficacious (see section below).

Although the traditional rationale of concomitant surgical LAA amputation was to prevent LAA thrombus formation and subsequent development of stroke, there is mounting interest as to whether or not this may also reduce the burden of AF [45]. However, at present, there is insufficient trial data to support this technique as the main purpose for amputation in routine clinical practice.

Atriclip for LAAEI

The AtriClip (Atricure, Inc., West Chester, OH, United States) is the most widely used LAA exclusion device. It is composed of a self-closing implantable clip, that may be applied via minimally invasive epicardial access from a pre-loaded and re-adjustable deployment tool. The clip is made of 2 parallel rigid titanium tubes, linked at both ends by nitinol springs, and covered with a woven polyester fabric. The design enables steady pressure to be applied at the base of the appendage, resulting in rapid electrical isolation and gradual atrophy of the LAA. The efficacy of the device relates to its ability to sustain a high occlusion pressure that is smoothly distributed along the entire base of the LAA when compared to suture ligation or stapling. Furthermore, the AtriClip system is versatile and allows for repeated attempts to reposition and redeploy the clip in a well-controlled manner that minimise's the risk for atrial wall damage, bleeding, and injury to the circumflex artery [46].

Aside from use in open-chest surgery as a concomitant intervention, the AtriClip may also be applied as a standalone intervention on a beating heart using video assisted thoracoscopic surgery (VATS). Although viewed as a 'surgical approach', this is minimally invasive and may be performed in a short procedure of under one hour [47]. Placement of the device using this approach allows for direct visualization of the LAA and adjacent structures that, in the presence of adjunctive intraoperative trans-oesophageal echocardiography for guidance, permits more consistent and complete LAA exclusion. With either the open-chest or minimally invasive approach, there is no contact of the device with intracardiac blood, and in contrast to percutaneous devices, anticoagulation may be discontinued immediately, if required. An advantage over other types of closure devices is it appears to be suitable for most, if not all, types of LAA morphology and ostial size [48].

The device initially gained a CE mark in 2009 during an initial study showing feasibility and safety in 34 patients undergoing cardiac surgery, with no device related complications and 100% occlusion sustained at 3 months on CT scanning [49]. Since then, several different generations have been

added including the AtriClip PRO, PRO2, PRO V, FLEX and FLEX V. The latest models (PRO2, PRO V and FLEX V) have several benefits over the original models, including ambidextrous use, locking and trigger-style clip closing mechanism, handle-based active articulation levers, 12mm port compatibility, and suture-less deployment. The use of active articulation was noted to be a significant advance, with an increase in exclusion rates to >90% in a study by Bulava et al. [50].

Strong short-term evidence for the efficacious open-chest application of the AtriClip came from the EXCLUDE trial in 2011, which led to the device being granted FDA approval [51]. A longer-term dataset published in 2014 by Emmert et al. showed good long-term stability of the device, without any dislodgement, out to 36 months [52]. Subsequently, many studies have been conducted to show the high levels of success and safety in deploying the AtriClip device, including a recent systematic review of 11 studies by Toale et al. [53]. At present, there is a current lack of adequately powered, prospective, randomised studies to accurately assess the reduction in risk of stroke with the use of the AtriClip; however, there is very encouraging evidence from smaller-scale or non-randomised studies, a large registry study, and a systematic review [42,53-56].

Results from the recently completed ATLAS study (https://clinicaltrials.gov/ct2/show/NCT02701062) are eagerly awaited. This multicentre, prospective, randomised trial was conducted to assess the impact of LAA closure on the development of AF following open chest cardiac surgery. 562 patients undergoing open chest cardiac surgery, but with no previous history of AF, were recruited to undergo AtriClip closure, or not, in a 2:1 randomised fashion. Patients who developed post-operative AF were followed up for 1 year to see if the potential 'protective' strategy of empirical LAA closure may be beneficial in reducing the risk of stroke. Depending on the outcomes, this study may have implications on guidelines for patients undergoing cardiac surgery in the future.

Since the AtriClip is highly efficacious in LAA closure, and also likely to reduce the risk of stroke, the next intriguing question is whether or not it may produce LAAEI; in turn, this may improve outcomes from recurrent dysrhythmias in patients with persistent AF. The first glimpse at this was back in 2011, when Benussi et al. demonstrated the ability of this device to induce LAAEI. A 15-year old boy with incessant drug and ablation-refractory atrial tachycardia, arising from the distal portion of the LAA, finally received an AtriClip device. As soon as the clip was deployed the atrial tachycardia terminated and they were then able to confirm LAAEI by electrical stimulation studies [57].

Lately, the AtriClip has been employed as part of hybrid AF ablations - initially with the aim of mitigating cardiac thromboembolic risk, but subsequently also as a potential tool for electrical isolation of the LAA. Traditionally, these hybrid ablation procedures have utilised a VATS approach and have shown great promise in treating more advanced persistent or long-standing PersAF where outcomes from traditional catheter ablation are less than optimal. In such cases, the AtriClip is deployed when approaching the heart from the left-sided VATS. This technique has been shown to be feasible and effective in several small VATS hybrid AF ablation studies [50,58-60].

There is now growing evidence for the successful use of the AtriClip in Convergent hybrid AF ablations. Indeed, in the paper by Tonks et al., the results support the theory that LAAEI plays a significant role in freedom from atrial dysrhythmias following hybrid ablation therapy [61]. In their small but informative study, of 13 patients who had concomitant placement of the AtriClip, none of them had recurrence of AF by 12 months (excluding the blanking period). Within these small, non-randomized studies it is not feasible to decipher the precise extent to which LAA exclusion contributes to the improved outcomes.

Discussion and Conclusion

There are two main forms of AF, namely PAF and PersAF, and each is quite different in the underlying pathophysiology mechanisms as well as responsiveness to therapies. Traditional forms of treatment for PAF, such as PVI, are much less effective for PersAF, particularly in longstanding PersAF. Hence, for several years the search for better forms of treatment in PersAF has shifted beyond the role of the PVs alone; one of the most promising candidates in this field is LAAEI.

The means to achieve LAAEI have been evolving over the last decade. Radiofrequency catheter, or cryoballoon, ablation are challenging techniques to ensure complete electrical isolation of the LAA, without resulting in collateral damage to this organ or nearby structures. Furthermore, the electrically inactive LAA acts as a greater source for thrombus formation in the absence of strict lifelong oral anticoagulation or without the application of a closure device.

The Lariat suture device offers the combination of LAAEI and LAA closure all at once. Complications rates related to the procedure and subsequent recovery from inserting a Lariat device require further inspection. Surgical amputation has long been practiced in general cardiac surgery, but this usually requires open chest access; in addition, research is necessary to assess the outcomes specifically for PersAF. The AtriClip device is easy to deploy, either during concomitant open chest surgery or as a stand-alone minimally invasive procedure. It too offers the combined benefit of LAAEI and LAA closure and is becoming an increasingly popular adjunct to the minimally invasive Convergent hybrid AF ablation technique. Whilst there is much excitement in this area, studies are required to assess the outcomes in preventing recurrent AF.

Conflicts of Interest

Dr. R. A. Kaba is a consultant for Daiichi Sankyo, Bayer, Atricure and Biotronik. Mr. A. Momin is a consultant for Atricure.

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