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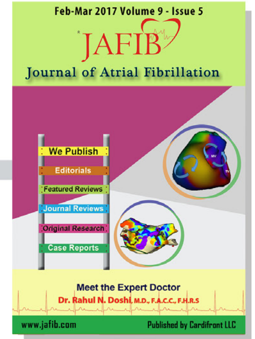

Left Atrial Appendage Characteristics in Patients with Persistent Atrial Fibrillation Undergoing Catheter Ablation (Laapaf Study)

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Abstract

Despite technological and scientific efforts, the recurrence rate of persistent atrial fibrillation (AF) remains high. Several studies have shown that in addition to pulmonary vein (PV) isolation other non-PV triggers, particularly left atrial appendage may be the source of initiation and maintenance of AF. There are few studies showing the role of left atrial appendage (LAA) isolation in order to obtain higher success rate in persistent AF patients. We analyzed the LAA volume, volume index and shape relative to the LA in patients with persistent AF undergoing AF ablation. Fifty-nine consecutive patients with persistent AF who underwent catheter ablation were enrolled. Computerized tomography (CT) was performed in order to assess left atrial and PV anatomy including the LAA. Digital subtraction software (GE Advantage Workstation 4.3) was used to separate the LAA from the LA and calculate: LA volume (LAV), LA volume index (LAV/body surface area), LAA volume (LAAV), LAA volume index (LAA volume/LA volume), and LAA morphology [chicken wing (CW) or non-chicken wing (NCW)]. The mean age was 64.6 ± 9.8 years, 44 % male, and LA diameter 47.6 ± 7.8 mm. Median follow-up (FU) was 13 months. All patients had antral isolation of PVs and ablation of complex fractionation ± linear ablation (roof line/superior coronary sinus/mitral line). Among 59 patients with persistent AF, 26 (44 %) patients were diagnosed with AF recurrences. Mean LAV was 145.0 ± 45.9 ml, LAVI 68.9 ± 20.0 ml/m², LAAV 10.3 ± 4.0 ml, and LAAVI 7.3 ± 2.7 ml/m². LAA shape was non-chicken wing (NCW) in the majority of patients (51 %). LAA parameters were not significantly different between patients with and without AF recurrence (LAAV 11.0 ± 4.3 ml vs. 9.7 ± 3.8 ml, p=0.26; LAAVI 7.5 ± 3.0 ml/m² vs. 7.2 ± 2.5 ml/m², p=0.71; LAA shape of NCW 50 % vs 52 %, p=0.75, respectively). LAV was significantly correlated with the LAAV (r: o.47, p=0.009). The incidence of NCW LAA was significantly higher in patients with previous stroke/TIA (80 % vs. 20 %, p=0.04). The LAA anatomical characteristics (volume/volume index and the shape) were comparable in patients with/out AF recurrence post PVI. It remains to be determined if additional LAA isolation will impact outcomes in patients with persistent AF.

Introduction

Atrial Fibrillation (AF) affects approximately 2.3 million people in North America. [1] Treatment of AF is based on an understanding of the underlying mechanisms. The pulmonary vein isolation is the cornerstone of the catheter ablation of AF. [2] The success rate of catheter ablation is approximately 70% in patients with paroxysmal AF and 50-55% in patients with persistent AF. [1] Long standing persistent (LSP) atrial fibrillation (AF) is the most challenging type of AF to treat with catheter ablation.

Several studies have shown that in addition to pulmonary vein (PVs) isolation other non-PVs areas may be the source of initiation and maintenance of atrial fibrillation in patients. [3] The most common sites are: the superior vena cava, the ligament of Marshall, the coronary sinus, the crista terminalis, the left atrial posterior wall and the left atrial appendage (LAA).

Key Words

Atrial Fibrillation,Cardiac CT,Left atrial appendage,Catheter ablation.

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Embryologically, the LAA is a remnant of the primordial embryonic left atrium (LA), which explains its trabecular appearance (pectinate muscles). The LAA has an important impact on thromobogenicity of the left atrium; particularly shape of the LAA has utmost importance. [4] The LAA has also been implicated as a significant source of atrial tachycardia and AF. [5] In a study by Di Biase et al, close to 30% of AF triggers in persistent AF were found to be non-pulmonary venous (non-PV), especially LAA, in origin. [3] Successful ablation or isolation of the LAA seems to significantly impact arrhythmia control (reduce AF burden) in these patients. It has been demonstrated that LAA ligation with an epicardial approach (LARIAT device [SentreHEART, Redwood, CA], AtriClip [AtriCure, West Chester, OH], surgical ligation) typically result in both mechanical and electrical isolation because they tend to compress the tissue, resulting in ischemic necrosis of the LAA distal to the site of exclusion [6]-[9]. Most recently, Di Biase et al [10] in a randomized study demonstrated that empirical isolation of the LAA improved long-term freedom from AF in patients with LSP without increasing complications.

Recurrence rate of catheter ablation of persistent AF remains high. It is well known that LA characteristics (dimension, volume, and volume index) are predictors of AF recurrence [11] because it has been established that persistent AF increases predisposition to LA remodeling, however the concept of LAA remodeling has not been adequately investigated. Therefore this study aimed to explore the association between the anatomical and volumetric characteristics of the LAA and AF recurrence after ablation in persistent AF patients.

Methods And Materials

Patient demographics

Consecutive patients from Aug 2014 to April 2016 with longstanding persistent AF who underwent AF ablation were enrolled retrospectively. All patients underwent transthoracic echocardiography (TTE) and cardiac computed tomography (CT) prior to catheter ablation. Longstanding persistent AF was defined according to the HRS/EHRA/ECAS 2012 Consensus Statement as an episode of AF greater than 12 months. [1] Patient demographics and medications at the time of initial ablation were obtained from medical records. Exclusion criteria were defined as follows: patients < 18 years old, paroxysmal and/or permanent AF, patients with LA/LAA thrombus, and unwillingness to participate in the study. Anti-arrhythmic medications (except amiodarone for a minimum of 4 weeks) were discontinued for five half-lives prior to the procedure, and all patients provided written informed consent. This study was approved by the ethics committee of Kingston General Hospital, and Queen's University's Institutional Review Board in Ontario, Canada.

Echocardiography

All patients underwent a standard, full transthoracic echocardiography (TTE) with a Vivid E95 machine (GE Healthcare, USA) according to ASE guidelines. [12] The LA size was assessed at admission by a transthoracic echocardiographic measurement of the short and long-axis views in the parasternal window. LA size was considered severely enlarged when LAD ≥ 50 mm. Nevertheless, TTE biplane method of disks was used to calculate LA volume. LA volume index (LAVI) was calculated by dividing LA volume by the body surface area of patients. Transesophageal echocardiography was performed to exclude any atrial thrombi 24 hours before ablation.

Cardiac computed tomography

All coronary CTA imaging was performed with a 64-MDCT scanner or 320-Toshiba (GE Healthcare, USA) using retrospective gating. ECG-based tube current modulation was used when appropriate. Contrast-enhanced image acquisition was performed during a single breathhold. Imaging parameters included a slice collimation of 64 × 0.625 mm (GE) or 320 x 0.5 mm (Toshiba), gantry rotation time of 350 milliseconds with a tube voltage of 100–120 kV and effective tube current of 550–750 mAs. Intravenous contrast (Omnipaque 350) 50cc, followed by 50cc contrast:saline solution (60:40 ratio) followed by 40cc saline chaser was administered at 5cc/s (GE scanner) or 80cc IV contrast (Omnipaque 350, GE Healthcare,) followed by 40cc saline chaser at 5cc/s.

The LAA volumes were calculated using GE Advantage Workstation 4.3. Volume rendered (VR) images of the left atrium were populated automatically by the software. The left atrial ridge was used as a consistent landmark to identify the LAA ostium. The remainder of the ostium was estimated by visual inspection using a combination of VR and multiplanar 2D images. The remainder of the left atrial volume was cropped leaving only the LAA volume (Figure). LA and LAA volumes were indexed for body surface area calculated using the Du Bois formula [13]. The morphology of the LAA was also assessed. CW was defined as LAA with an obvious bend in the proximal and middle part of the dominant lobe, or the LAA folding back on itself at some distance from the perceived LAA orifice. Non-CW (cauliflower, cactus, and wind sock) was defined as LAA without any bends. [14]

Periprocedural Anticoagulation

Patients were anticoagulated with warfarin and the procedure was performed without interruption of therapy, with an INR level between 2 and 3. Patients on any new oral anticoagulants (NOAC) were instructed to withhold the doses for 48 hours prior to the procedure. After transeptal access to the LA, intravenous unfractionated heparin was administered at 20-minute intervals to attain a target-activated clotting time of 300-350 seconds.

Table 1: Demographic and procedural data of patients with persistent AF

Number of patients	59
Age, years	64.6 ± 9.8
Gender, male	26
BMI, kg/m²	32.0 ± 5.8
DM, n (%)	12 (20)
HTN, n (%)	41 (69)
CAD, n (%)	11 (19)
CVA-TIA, n (%)	10 (17)
SA, n (%)	20 (34)
CHA_2DS_2VasC	2.3 ± 1.2
AAD, n (%)	19 (32)
EF, %	53.3 ± 11.3
LAD, mm	47.6 ± 7.8
PT, min	293 ± 79
FT, min	21.3 ± 8.3
Recurrence, n (%)	26 (44)
FU, months*	13 (4 and 67)

BMI, body-mass index; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CVA-TIA, cerebrovascular accident-transient ischemic attack; SA, sleep apnea; AAD, anti-arrhythmic drugs; EF, ejection fraction; LAD, left atrial diameter; PT, procedure time; FT, fluoroscopy time; FU, follow-up.
* median (min, max)

Electrophysiology study and Ablation

Patients were brought to the Electrophysiology lab fasting, and the procedure was conducted under conscious sedation with intravenous fentanyl and midazolam. Venous access was gained from the femoral veins. Standard intra-cardiac catheters were introduced through right femoral vein as appropriate for the procedure: (1) Decapolar coronary sinus catheter (IBI Inquiry, St. Jude Medical, St. Paul, MN, USA), (2) duodecapolar halo-type catheter (Supreme, St. Jude Medical, St. Paul, MN, USA) positioned in the right atrium, (3) mapping and ablation catheter (Tacticath™ Quartz, St. Jude Medical, St. Paul, MN, USA) delivered through a 9 Fr femoral sheath (St. Jude Medical, Minneapolis, MN) (4) long steerable sheath (Agilis, St. Jude Medical, Minneapolis, MN) was used in cases for better stability, or longer reach to the TV annulus, and (5) quadripolar catheter (Supreme, St. Jude Medical, St. Paul, MN, USA) placed at the right ventricular (RV) apex. Intracardiac echocardiography (ICE) (ViewFlex XTRA, St.Jude Medical) was used to guide transseptal punctures in certain cases. Following this, a spiral multipolar PV catheter (AFocus II, St. Jude Medical, St. Paul) and CF-sensed catheter (TactiCath Quartz, St.Jude Medical St Paul, MN) were used to perform the ablation. Before mapping, the CF enabled catheter, TactiCath™ Quartz was calibrated either outside the body, or while freely floating in the mid right atrium to set the baseline value of contact force at zero grams. Afterwards, a 3-D reconstruction of the LA and pulmonary veins was created with the use of EnSite Velocity™ system (St. Jude Medical, St. Paul, USA)

AF ablation was performed with a standard wide area circular ablation (WACA) approach. No traditional lines were routinely performed. Primary end point was considered as entry and exit block in all PVs. RF was delivered using a 4 mm externally irrigated-tip ablation catheter at a flow of 17-25 ml/min with a power range from 25 to 30 W (TactiCath Quartz, St.Jude Medical St Paul, MN). For each lesion, CF of at least 10 grams, and lesion duration of at least 40 seconds were targeted. In sites with low CF such as LA/LAA ridge, FTI > 400 gs was targeted. The PV isolation was considered complete when the circular catheters no longer recorded any PV potentials. Acute reconnection was assessed in both groups at the end of the procedure. It was defined when the LA-PV conduction spontaneously re-appeared after a waiting period of 20 minutes following the completion of the PV isolation, or when PV dormant conduction was evoked by an intravenous adenosine infusion. The patients were kept overnight, and discharged the following day.

Table 2: Cardiac CT parameters

LAV, ml	145.0 ± 45.9
LAVI, ml/mm²	68.9 ± 20.0
LAAV, ml	10.3 ± 4.0
LAAVI, ml/mm²	7.3 ± 2.7
LAA shape, NCW (%)	30 (51)

LAV, left atrial volume; LAVI, left atrial volume index, LAAV, left atrial appendage volume; LAAVI, left atrial appendage volume index, NCW, non-chicken wing

Follow up

Post ablation, all patients received anticoagulation for at least 3 months. They were maintained on anticoagulation according to the CHA_2DS_2VASc score. Patients were evaluated by 24-h ECG Holter monitoring at 3 months, 6 months, and yearly thereafter. Recurrence was defined as an episode of any atrial arrhythmia lasting more than 30 seconds and occurring at least 3 months after ablation (post-blanking period). [1]

Statistics

Data was collected in an Excel file and imported into IBM SPSS (Version 21 for Windows, Armonk, New York, 2015) for statistical analysis. Data was initially described using means, standard deviations and medians for continuous data, and frequencies and percentages for categorical data. Continuous data was also graphed to assess its underlying distribution. The association between LAA parameters and AF recurrence was assessed using independent samples t-tests, with the Mann-Whitney U test in the event of non-normal distributions. A p -value less than 0.05 was considered significant.

Results

Fifty-nine consecutive patients with persistent AF undergoing catheter ablation for AF were included in this study. Demographics and procedure details are depicted in [Table 1]. Mean left atrial diameter (LAD) was 47.6 ± 7.8 mm. During a median follow-up of 13 months (range 4 and 67 months) after a single ablation procedure, 33 patients (56 %) maintained sinus rhythm [Table 1].

Analysis of the cardiac tomography (CT) parameters is depicted in [Table 2]. LAA shape was non-chicken wing in majority of patients (51 %).

As depicted in [Table 3], age, comorbidities, LVEF, and procedure details were comparable in patients with AF recurrence, and to those without. Patients with AF recurrences had a larger LA size than those without recurrences (50.1 ± 8.3 mm vs. 45.8 ± 6.9 mm, p=0.05) [Table 3].

CT findings of patients with and without AF recurrence are listed in [Table 4]. LA volume, LA volume index, and LAA volume tended to be higher in patients with AF recurrence, however this difference did not reach statistical significance. LAA volume index and the shape of the appendage were comparable in both groups [Table 4]. Patients with history of cerebrovascular accident (CVA)/transient ischemic attack (TIA) had significantly higher frequency of non-chicken wing LAA morphology (NCW of 80 % vs. CW of 20 %, p=0.04).

Procedural Outcome

Acute procedural success was achieved in all 59 (100 %) patients, and all patients were in sinus rhythm at the end of the procedure. AF terminated to SR or organized atrial tachycardia in 23 patients. Sinus rhythm was achieved by electrical cardioversion in the remaining patients.

Follow up

During a follow-up of 13 months (range 4 and 67 months) after a single ablation procedure, there were 26 patients (44 %) with AF recurrences. Of those 26 patients, 12 patients underwent another catheter ablation, 6 patients required electrical cardioversion, and the remaining 8 patients were followed up with antiarrhythmic treatment.

Discussion

In our cohort, although LAAV tended to be higher in patients with AF recurrence compared to those without AF recurrence, however this did not reach statistical significance. Also the other LAA parameters (LAAVI and LAA shape) were comparable between groups. The prevalence of NCW LAA was significantly higher in patients with CVA/TIA.

Despite successful and permanent PV isolation, patients may experience AF recurrences due to non-PV triggers responsible for initiation of AF [3], [15]. The most common and reported non-PV triggers are the superior vena cava, the coronary sinus, atrial septum, ligament of Marshall, and left atrial appendage. Several predictors of AF relapse after ablation procedures have been suggested, including age and comorbidities, type of AF, episode duration, electrocardiographic parameters, biomarker levels. Much attention

Table 3: Comparison of patients with and without recurrence of AF

	Recurrence (n=26)	Non-recurrence (n=33)	p value
Age, years	63.8 ± 8.7	65.2 ± 10.8	0.60
Gender,male	15	11	0.07
BMI, kg/m²	32.3 ± 5.7	31.9 ± 5.9	0.80
DM, n (%)	6 (23)	6 (18)	0.89
HTN, n (%)	20 (76)	21 (64)	0.54
CAD, n (%)	4 (15)	7 (21)	0.52
CVA-TIA, n (%)	6 (23)	4 (12)	0.48
OSA, n (%)	10 (38)	10 (30)	0.43
CHA_2DS_2VASc	2.4 ± 1.2	2.2 ± 1.2	0.73
AAD, n (%)	7 (27)	12 (21)	0.49
EF, %	53.6 ± 12.1	52.9 ± 10.8	0.87
LA, mm	50.1 ± 8.3	45.8 ± 6.9	0.05
PT, min	292.7 ± 88.6	292.9 ± 73.2	0.99
FT, min	21.0 ± 6.6	21.6 ± 9.9	0.86
FU, months	21.3 ± 17.0	16.7 ± 12.9	0.25

was paid to LA size and function as well. However the role of LAA has not been investigated thoroughly.

Recently, the LAA has been reported as an unrecognized and overlooked trigger site of AF especially in persistent AF patients [16]. Yamada and colleagues [5] demonstrated first case of atria tachycardia originating from the LAA. Di Biase and colleagues [16] have reported a series of 266 patients undergoing redo AF ablation procedures with demonstrated silent PVs in 27 % of these patients. This group of patients had a driving trigger from the LAA and that was the only site responsible for AF recurrence. After this report, many case series have shown the relevance and importance of the LAA for triggering and maintenance of AF. [5], [7], [17], [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 the LAA as a main trigger for the maintenance of AF.

Table 4: Comparison of cardiac CT parameters in patients with and without AF recurrence

	Recurrence (n=26)	Non-recurrence (n=33)	p value
LAV, ml	153.6 ± 54.0	139.1 ± 39.3	0.26
LAVI, ml/mm²	74.4 ± 22.4	65.2 ± 17.8	0.11
LAAV, ml	11.0 ± 4.3	9.7 ± 3.8	0.26
LAAVI, ml/mm²	7.5 ± 3.0	7.2 ± 2.5	0.71
LAA shape, NCW (%)	13 (50)	17 (52)	0.75

Epicardial mechanical and electrical exclusion of LAA has shown promising results in decreasing the burden of AF and this was more pronounced in patients with persistent AF. [9], [20]-[22] LAA exclusion using a suture or a clip causes an acute infarct of the tissue and results in a significant voltage reduction. A recent article by Han et al. [9] showed that snare closure of the LAA using the LARIAT device produces an acute reduction in LAA voltage and inhibits capture of the LA during LAA pacing. Recently, the LAALA-AF (Left Atrial Appendage Ligation and Ablation for persistent Atrial Fibrillation) registry has shown a lower AF burden by mechanical inducing electrical isolation with the LARIAT closure device. [23] Ligation of the LAA possibly can remove the reentrant and triggered arrhythmias that arise from the structure. Typically there is a 10 % to 40 % reduction in LA volume and surface area after LAA exclusion, which essentially decreases the available LA substrate for AF propagation and perpetuation. [20] Chan et al. [24] also suggested the LAA isolation may be caused by disruption of Bachman's bundle, which runs along the LA anterior wall and surrounds the LAA. BELIEF randomized study has been recently published and showed that empirical electrical isolation of the LAA improved the ablation outcome at follow up of long-standing persistent AF patients. [10]

The main criticism against LAA electrical isolation is its potential thromboembolic risk. Recent studies showed that around 50 % of patients have flow velocity within normal range after LAA isolation and with proper anticoagulation. [10], [25]

Nedios et al. reported that normal maximal LAA volume in end-systole was 6.5 ± 1.9 ml. [26] In addition MRI and CT studies showed that LAA volume is increased in persistent AF patients compared those with paroxysmal AF. [27]-[29] In our study, LAA parameters (volume and volume index) were comparable in patients with and without AF recurrence. However, mean LAAV was 10.3 ± 4.0 ml in a study cohort. Nevertheless LAAV tended to be higher in patients with AF recurrence. It has previously been demonstrated that LAA volume index (LAAVI) larger than 5.6 ml/m² indicates LAA enlargement. [30] In our study population, mean LAAVI was 7.3 ± 2.7 ml/m² indicated enlarged LAA.

In addition to the LAA volumetric measurements the shape of the LAA has also been investigated in our study. Previously, Gerede et al. [31] demonstrated that a low LAA velocity (<30 cm/s) was an independent predictor of AF recurrence after cryoballoon ablation. Kanda et al. also demonstrated that low LAA flow velocity was associated with AF recurrence after initial RF ablation of persistent AF [32]. There are 2 different LAA morphologies: CW and NCW (cauliflower, cactus, and wind sock). Patients with persistent AF have a higher prevalence of non-CW morphology LAA than did those in the paroxysmal AF group. [33] Non-CW morphology LAA patients have larger LAA size and volume. In our study, the prevalence of NCW LAA was comparable in patients with and without AF recurrence. However, the prevalence of NCW LAA was significantly higher in patients with previous stroke and/or TIA. Our results are in accordance with these previous findings showing that patients with NCW LAA morphology are more likely to develop thromboembolism than patients with CW LAA morphology. [4] The possible explanation is LAA volume is higher in patients with NCW LAA and LAA volume is negatively correlated with LAA flow velocity, suggesting that larger LAAV may lead to blood stasis. [34], [35]

Limitations

Several limitations to this study warrant mention. First, this is a single-center, retrospective study, and bias is inherent to this type of design. Hence, large-scale, prospective studies are required. Second, there is no landmark for CT measurement, which divides the LA and pulmonary veins. Third, the lack of LAA flow velocity is one of the limitations in this study. Fourth, electrical signals and activation of the LAA has not been investigated in our study. Finally, in all AF studies, conventional approaches to documenting asymptomatic recurrences are prone to underestimate the overall recurrence rate during follow up.

Conclusions

Anatomical and volumetric characteristics of the LAA were comparable in patients with AF recurrence compared to those without AF recurrence, however this result does not diminish the role of the LAA in patients with persistent AF because electrical activation of the LAA is still a matter of importance.

Conflict Of Interests

All authors declare that, the manuscript, as submitted or its essence in another version, is not under consideration for publication elsewhere, and it will not be submitted elsewhere until a final decision is made by the editors of Journal of Atrial Fibrillation. The authors have no commercial associations or sources of support that might pose a conflict of interest. All authors have made substantive contributions to the study, and all authors endorse the data and conclusions. Nevertheless, confirmation of informed patient consent for publication was obtained.

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