Atrial Fibrillation and the Role of LAA in Pathophysiology and Clinical Outcomes?

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Abstract

Left atrial appendage (LAA) is a source of thromboembolism especially in patients with non valvular atrial fibrillation (AF). It is reasonable to accept LAA as a distinct part of left atrium (LA) with unique anatomical and physiological properties. Advances in imaging modalities increased the knowledge about anatomical and physiological characteristics of LAA. It is important to prevent the AF patients from systemic thromboembolic events, and new pharmacological and non pharmacological management approaches demonstrate encouraging results. Also pulmonary vein isolation which has been accepted as a curative and useful treatment option for the treatment of drug resistant AF has been helpful in understanding the electrophysiological properties of LAA. Accumulating data revealed that LAA continues to be the one of the most important structure of heart during AF because of its distinctive anatomical, mechanical, and electrophysiological properties.

Introduction

Atrial fibrillation (AF) is characterized by presence of chaotic and disorganized electrical activity in atrial myocardium, resulting in deterioration of atrial systolic functions. It is the most common arrhythmia encountered in general population. The prevalence of AF increases with age and reaching approximately 10% in patients over 80 years old. Patients with AF may be asymptomatic or, may experience palpitation, fatigue, dyspnea, exercise intolerance, and/or heart failure. But these symptoms and complications are not responsible for its bad reputation. Ischemic stroke is the most serious complication in patients with non valvular and valvular AF. Ischemic stroke related with AF causes higher mortality rates, long term disability, longer hospitalization, requirement of social support, and great amount of financial cost. Atrial fibrillation is the underlying rhythm abnormality in 15-20% of stroke patients.[1] The annual rate of ischemic stroke in patients with nonvalvular AF varies from 2 to 10% depending on the accompanying risk factors .[2]

Left Atrial Appendage

Disorganized mechanical activity of atrial myocardium during AF promotes blood stasis, enhances coagulation activity and platelet aggregation, and subsequently predisposes thrombus formation in left atrium (LA). Left atrial appendage (LAA) is the most common localization for thrombus formation due to the unique anatomical and physiological properties in patients with non valvular AF.[8] The LAA is a tubular structure with a narrow orifice which connects LAA to LA. Its inferolateral portion is closely related to left ventricle free wall and pericardium. It is generally difficult to visu-

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alize the LAA by transthoracic echocardiography because of its anatomical location. Formerly LAA has been defined as a trivial portion of LA but advanced imaging modalities demonstrated that LAA is a separate structure from LA with distinctive mechanical, hormonal, and structural properties. Earlier studies investigated the anatomical characteristics of LAA by postmortem examination. These studies showed that the greatly varying size and shape of LAA according to the concomitant disease and underlying rhythm abnormality.[9, 10] LAA usually has two or more trabeculated lobes in varying size and shape.[11] Each of these anatomical features have critical role either in its physiological functions or in pathological conditions such as AF, heart failure, valvular heart diseases. Besides the morphological properties, flow dynamics of LAA are also important to understand its clinical significance. Transesophageal echocardiography (TEE) has been used to demonstrate the anatomical properties and flow characteristics of LAA for more than 20 years.[12, 13] TEE examination demonstrated that LAA is not a passively filling and emptying portion of LA. TEE visualizes flow characteristics of LAA perfectly, which are the indicators of LAA contractile functions. Furthermore, TEE is widely used to detect LAA thrombi, with a sensitivity and specificity of approximately 95-100%.[14] The association of decreased LAA flow velocities and thrombus formation has been demonstrated.[13] In addition to TEE, different advanced imaging modalities such as, 3-D TEE, intracardiac echocardiography, multislice computed tomography angiography, magnetic resonance angiography, and multidetector computed tomography are being used to visualize LAA .[15-18] Actually, the efforts to demonstrate the detailed anatomical properties of LAA is because of the development of new sophisticated treatment methods such as percutaneous closure of LAA which prevents thrombus formation in LAA and reduces risk of ischemic stoke in patients with AF .[19] Also, identifying the detailed anatomy of LA and LAA is very critical for successful AF ablation procedures.

## Left Atrial Appendage and Atrial Fibrillation

The relation of AF with LAA mechanical dysfunc-

Figure 1: Longitudinal two chamber view of left atrium and left ventricle by 2-D transesophageal echocardiography demonstrating the left atrial appendage in a patient without cardiac disease.
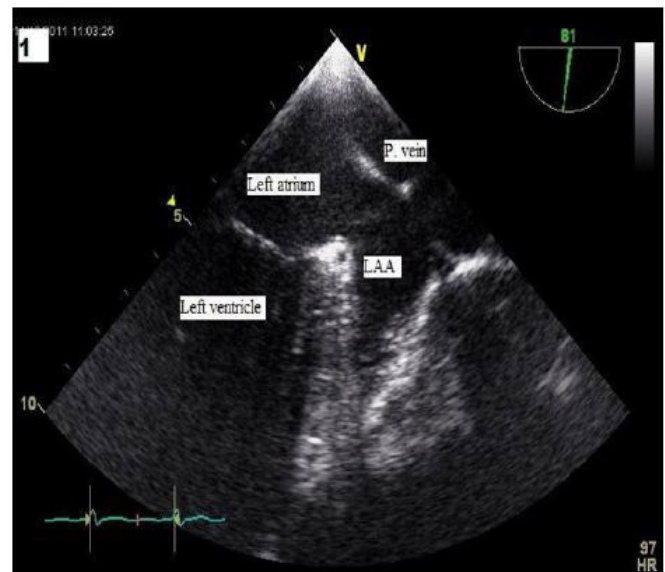
tion has been one of the most popular issues for researchers for a long time. Multiplane TEE examination perfectly demonstrates the detailed flow dynamics and anatomical characteristics of LAA in most cases. LAA is best visualized in horizontal short-axis view at the base of heart and longitudinal two chamber view of LA and left ventricle by 2-D TEE (Figure 1). The 2-D TEE imaging of LAA includes evaluating morphology and measurement of minimum- maximal area and ejection fraction of LAA. Also, it perfectly demonstrates the presence of spontaneous echo contrast (SEC) and thrombus in LAA cavity. Previous analyzes clearly demonstrated the alterations in shape, size, and contraction patterns of LAA during AF. Ernst et al. [9] analyzed the morphological characteristics of LAA of 198 ECG available cases by postmortem examination and found that patients with AF had significantly larger cast volumes of LAA compare to patients with sinus rhythm. Moreover, the orifice diameter of LAA was found to be larger in AF cases. Similar findings were observed in our investigation in which 51 cases with mitral stenosis (29 with sinus rhythm versus 22 with AF) were evaluated. We found that LAA maximal and minimal area were significantly larger in patients with AF compared to patients with sinus rhythm .[20] Relation of SEC and thrombus formation with en-

Figure 2: Outflow and inflow signals recorded during Doppler imaging of left atrial appendage in a patient without cardiac disease. In addition to high amplitude outflow and inflow signals two additional low amplitude inflow and outflow signals are present which can demonstrate the quadriphasic pattern. The velocities of high amplitude outflow and inflow signals are greater than 50cm/s.
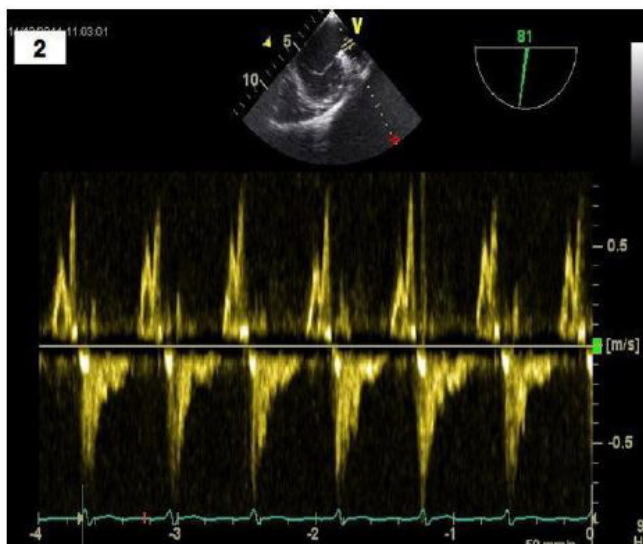

larged LAA is clearly demonstrated by TEE in patients with AF .[21] However; the relation of thromboembolic risk with enlarged LAA is thought to be a more sophisticated issue. Analyzing the characteristics of flow dynamics of LAA is one of the most critical point to estimate the thromboembolic risk either in patients with AF or in patients with sinus rhythm .[22, 23] Transesophageal echocardiography provides us to evaluate the flow dynamics of LAA. Doppler measurement of LAA shows a typical biphasic pattern including outflow and inflow signal in healthy subjects (Figure 2).[24] In some healthy people TEE Doppler examination demonstrates quadriphasic flow pattern which includes two additional low amplitude flow signals (Figure 2) .[25] The first high amplitude outflow Doppler signal occurs during LAA contraction. It is well correlated with mitral late diastolic A wave .[25] This outflow signal has been well correlated with LAA contractile function and clinical outcomes .[13] The high amplitude inflow signal follows outflow signal which correlates with LAA filling. However it is not clearly understood, the underlying mechanism of inflow signal is thought to occur due to combination of active relaxation and passive elastic recoil of LAA .[25] The

velocity of inflow signal is commonly in correlation with outflow signal. Generally the outflow and inflow LAA velocities are higher than 50 cm/sec in patients without cardiac disease .[20,25-27] The Doppler imaging of LAA may demonstrate an irregular saw tooth pattern or no identifiable flow signal during AF (Figure 3). The reduction in LAA flow velocities were related to the presence of SEC, thrombus formation, and a history of systemic embolism in patients with non-valvular AF .[13, 26] It has been thought that LAA becomes a passively filling and emptying structure during AF .[28] Absence of effective and organized contraction can cause dilatation of LAA alike with LA. The contiguity of LAA with left ventricle free wall seems to be important for its emptying function especially in patients with AF .[29] During ventricular diastole inferomediale portion of LAA is compressed between ventricle and pericardium which may ease emptying of appendage. Also ventricular suction effect during diastole may influence the emptying of LAA. Akosah KO et al.[29] analyzed the influence of heart rate on contractile function of LAA in AF. They found that the magnitude of LAA emptying is strongly and inversely influenced by ventricular rate during AF. The ventricular response rate during AF seems to affect the LAA contractile function; however the association of ventricular rate with clinical outcome is still uncertain. The flow velocities are commonly lower in AF compare with sinus rhythm (Figure 3).[28] A flow velocity value of 25 cm/sec has been accepted as a cutoff value to estimate the contractile function of LAA[26] and a flow velocity lower than cutoff value has been thought as a sign of impaired LAA contractile function and increased thromboembolic risk.[30] Nevertheless, LAA inflow and outflow velocity values greatly vary case by case according to the clinical and echocardiographic characteristics of patients with AF. Doppler imaging of LAA can demonstrate irregular flow signals in varying velocities during AF (Figure 3). But, in some cases no identifiable flow signal can be measured by Doppler imaging.[24] Patients without identifiable flow signal have a higher risk for SEC and thrombus formation, and thromboembolic events. Numerous factors and clinical conditions affect the flow magnitude and contractile
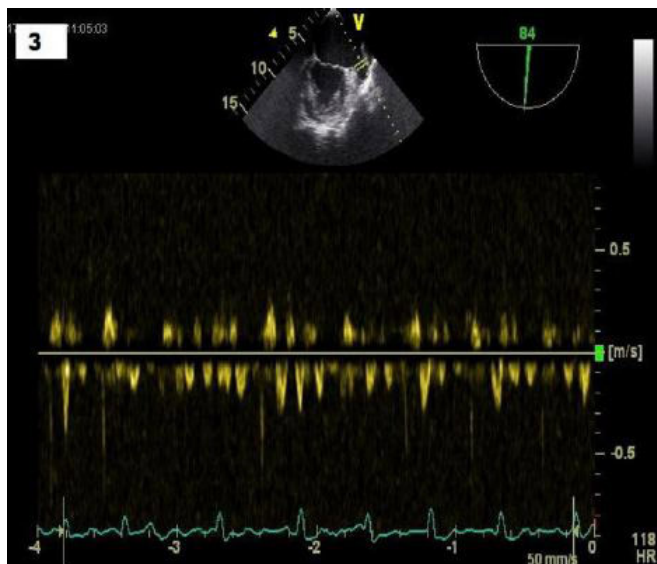
function of LAA in AF. For instance, no identifiable inflow and outflow flow signals are commonly observed in patients with mitral stenosis in AF because chronic pressure overload heavily depresses the LAA contractile function in such cases. So generally the LAA contractile function is more depressed in patients with mitral stenosis compared to patients without mitral stenosis. But the most important determinant factor for magnitude of LAA flow velocities is the duration of AF. Atrial fibrillation is characterized by a progressive remodeling process of atrial myocardium. However it is not clear yet, tachycardia induced cardiomyopathy, cytosolic calcium alterations, atrial hibernation, and atrial fibrosis have been thought to be underlying mechanisms.[31] Also, duration of AF is closely related with duration of recovery of LAA contractile function after cardioversion. [21, 32] Some authors use the term 'Atrial stunning' to describe both LAA contractile dysfunction during persistent or chronic AF and transient further impairment of LAA contractile function after successful cardioversion. Although the underlying mechanisms seem to be same in both situations, atrial stunning better defines the cardioversion associated transient depression of LAA contractile function in patients with AF.[31] Observations showed that the depression of LAA contractile function is

maximal immediately after cardioversion.[31, 33] Depressed LAA functions begin to recovery within a few days following successful cardioversion. This period well correlates with the clinical outcomes because the most of thromboembolic events occur in first 3 days after cardioversion .[34] The correlation between AF duration and the time course of recovery of LA and LAA dysfunction has been demonstrated .[21, 32, 35] Recovery of LAA contractile dysfunction can be delayed for weeks after successful cardioversion according to the duration of AF. Accumulating data clearly revealed that duration of AF is the main determinant of magnitude and time course of recovery of LAA contractile dysfunction. As a result of growing evidences, anticoagulation therapy after successful cardioversion for 4 weeks is recommended for patients with AF duration of greater than 48 hours .[36]

Non pharmacological Therapeutic options in Preventing Systemic Thromboembolism

There is no debate on the pivotal role of LAA in thromboembolic events during AF. The success of anticoagulation therapy in preventing thromboembolic events is well established in AF .[37] However, drug to drug interactions, bleeding side effect, and difficulties in monitoring the efficacy of therapy limits the success of anticoagulant regimen. Alternative preventive methods are needed in patients unable to use anticoagulant therapy. The obliteration LAA has been thought as a reasonable option for a long time. The methods of surgical LAA obliteration are exclusion or excision of LAA. The technique of exclusion method is ligation of LAA with epicardial or more commonly endocardial sutures .[38] The surgical excision of LAA is commonly performed by stapled excision or removal and oversews .[38] The success rate of complete closure of LAA was found 45 % with suturing and 77 % with stapling in LAAOS (Left Atrial Appendage Occlusion Study: Results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke) trial .[39] Ligation alone of LAA exclusion is seems to be an inferior method compared with excision by stapling and removal .[38] The choice of the surgical method depends on the type of operation, patient charac-

Figure 4: a) The PLAATO system (ev3, Inc, Plymouth, Minnesota) b) Amplatzer cardiac plug (AGA Medical Corpo-Corporation, Plymouth, Minnesota, USA) c) The WATCHMAN (Atritech Inc., Plymouth, Minnesota, USA) device d) LARIAT Suture Delivery Device (SentreHEART Inc, Palo Alto, CA)
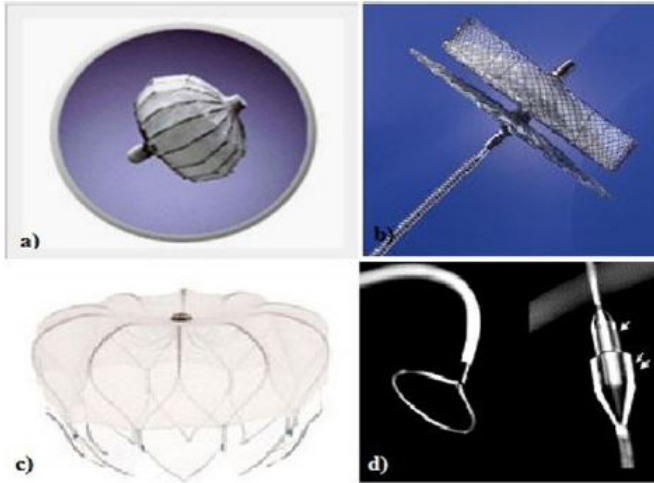
teristics, and the experience of operator. Former reports indicate that the surgical obliteration of LAA decreases the stroke risk approximately % 50. However there is no large randomized trial focusing on the effect of surgical LAA occlusion on stroke rates. In addition to surgical obliteration, percutaneous or transpericardial approaches are under development. In recent years a number of percutaneous transcatheter delivery systems have demonstrated encouraging results in selected patients .[19, 40, 41] The PLAATO system (ev3, Inc, Plymouth, Minnesota) was the first developed percutaneous occluder system for LAA occlusion. It consists of a self-expandable nitinol cage covered with a non-thrombogenic expanded polytetrafluoroethylene (ePTFE) membrane (Figure 4a). The size of device ranges 15mm to 32mm. The 5 years results of PLAATO study (Percutaneous left atrial appendage transcatheter occlusion) showed that the annualized stroke/transient ischemic attack rate was 3.8 % in device group in which the anticipated annualized stroke risk was 6.6 % according to the CHADS$_2$ risk score .[41] Despite the encouraging results the device was withdrawn because of commercial problems. The Amplatzer cardiac plug (AGA Medical Corpo-Corporation, Plymouth, Minnesota, USA) is another device designed for closure of LAA. The system is a transcatheter self-expanding device consisting of a cylinder and a disk connected by a central waist (Figure 4b). The device is retriev-

able and re-deployable. Park et al. analyzed 143 patients who have undergone transcatheter LAA occlusion with the Amplatzer cardiac plug. The procedural success rate was 96 % and with a serious complication rate of 7 % .[42] The WATCHMAN (Atritech Inc., Plymouth, Minnesota, USA) device is the only transcatheter LAA occlusion system evaluated with a randomized clinical trial. The WATCHMAN device is a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the atrial facing surface of the device. The device is preloaded within a delivery catheter (Figure 4c). The device is available in 5 sizes to accommodate the unique anatomy of each patient's LAA. The Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) trial compared the closure of LAA (WATCHAN device) with long-term warfarin therapy. [19] 707 patients were randomized in a device-to-control ratio of 2:1. Patients with device continued warfarin for 45 days after the procedure then with clopidogrel and aspirin alone for 6 months and then aspirin alone for chronic therapy. The trial showed that closure of the LAA with WATCHMAN device was found to be non inferior to warfarin for all-cause of stroke and mortality and hemorrhagic stroke was lower in the device group, meeting superiority criteria .[19] Implantation of WATCHMAN device carries a procedural risk. Serious procedural complications occurred in 12.5 % of device group in PROTECT AF. Pericardial effusion requiring drainage was 5 % and acute stroke due to air or thromboemboli was 1.1 %. Also 2.2 % of device implantations required surgical interventions because of post implantation sepsis, device embolization, and cardiac tamponade. Trans-septal puncture related complications such as pericardial effusion/tamponade or air/thromboembolism were higher in less experienced laboratories which indicates the learning curve of trans–septal puncture technique. In addition to percutaneous approaches, LARIAT Suture Delivery Device (SentreHEART Inc, Palo Alto, CA) uses a combination of transpericardial and trans-septal approach (Figure 4d). The system was approved in Europe and by FDA in 2009 (Food and Drug Administration).

Patients should receive aspirin (81-325 mg) after the transcatheter LAA closure. Clopidogrel is advised at least for 4 to 6 weeks after the procedure .[43] Today percutaneous transcatheter occlusion of LAA is accepted as an alternative therapeutic option in patients in whom anticoagulation therapy carries high risk or contraindicated.

Left Atrial Appendage as a Triggering Focus For Atrial Fibrillation

Developments in transcatheter AF ablation procedures have provided us to understand the detailed electrophysiological mechanisms which are responsible for initiating of AF. Pulmonary vein isolation has been used for transcatheter ablation of AF since the pulmonary veins were defined as an important source of AF .[44] Successful AF ablation can reverse the progressive dilatation and remodeling of LAA. Chang SH et al. [45] evaluated the changes of LAA morphology after AF ablation by magnetic resonance imaging. The report showed that progressive alterations in LAA morphology could be reversed after successful AF ablation without recurrence. Also they showed that LA and LAA continued dilating in patients with recurrent AF after catheter ablation which might show the role of LAA dilatation in the perpetuation of persistent AF. Could LAA have a potential role in AF initiation in addition to defined arrhythmic sources such as pulmonary veins, superior vena cava, coronary sinus, crista terminalis? Unfortunately, there is limited data evaluating this relation .[46-49] Biase LD et al. [46] evaluated 987 non-paroxysmal and paroxysmal AF patients underwent redo catheter ablation and they showed that LAA was responsible for arrhythmias in 27% of patients. Interestingly LAA was found to be the only source of arrhythmia in 8.7% of patients. Catheter ablation of LAA is not a completely safe procedure. Left atrial appendage has a thin wall and electrical isolation carries a potential risk for perforation of LAA. Biase LD et al. reported a rate of 1.8 % for pericardial effusions requiring pericardiocentesis during procedure. Isolation of LAA may cause LAA mechanical dysfunction which is related with clot formation and subsequent thromboemboli. Continuing warfarin therapy is advised at least for 6 months after the successful LAA isolation procedure .[46] Transesophageal echocardiographic evaluation of LAA flow velocities after 6 months of procedure and ceasing warfarin therapy only in cases with adequate LAA flow velocities and LAA contraction is reasonable. The knowledge about the potential role of LAA as a triggering focus for AF initiation is still insufficient. There is no consensus of whether ablation around LAA should be routinely performed in addition to pulmonary vein isolation for AF. Also more data is needed to define the technical aspects of LAA ablation/isolation and patients who may benefit from procedure. Nevertheless, it should be kept in mind that LAA may be the source of AF especially in patients undergone repeated AF ablation with recurrences.

Conclusions

Alteration in LAA functions during AF has always been the most popular concern for researchers and clinicians. Transesophageal echocardiography and new sophisticated imaging modalities revealed the detailed anatomical and physiological characteristics of LAA. Growing amount of data demonstrated the pivotal role of LAA in systemic thromboemboli during AF. However, advances in transcatheter AF ablation procedures showed that the electrophysiological role of LAA in the initiation and recurrence of AF has not been fully understood yet.

Disclosures

No disclosures relevant to this article were made by the author.

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