REVIEW

Left atrial appendage morphology and the risk of stroke

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Abstract: In patients with non-valvular atrial fibrillation (AF) the risk of stroke is five times higher than in patients with sinus rhythm. Moreover, stroke is likely to be more severe in the AF patient population. Left atrial appendage (LAA) is the most common source of emboli in AF-related stroke. LAA thrombus is present in 15% of AF patients. Therefore, numerous studies aimed to evaluate the role of LAA structure and function in stroke formation. Higher LAA volume and bigger LAA orifice have been reported to be associated with increased risks of stroke. Moreover, not only the size, but also the shape of the LAA influences thrombus formation. The presence of an obvious bend in the proximal part of the dominant LAA lobe, described as chicken wing LAA morphology has been reported to be protective against stroke. However, other studies are not consistent with this finding and there is no consensus about LAA morphology categories. LAA has reservoir, contractile, electric and endocrine functions, that can provide essential information about the risk of clot formation and embolic events. Decreased LAA flow velocity, reflecting lower LAA contractility has been described to be associated with higher stroke risk. All in all, even if the LAA plays an important role in stroke formation, there are controversial literature data, therefore further studies are needed to evaluate the underlying mechanisms.
Keywords: atrial fibrillation, stroke, thrombus, left atrial appendage, morphology.

Rezumat: La pacienții cu fibrilație atrială non-valvulară (FA) riscul de accident vascular cerebral este de cinci ori mai mare decât la pacienții cu ritm sinusal. Mai mult, accidentul vascular cerebral este probabil mai sever în populația de pacienți cu FA. Apendicele atrial stâng (LAA) este cea mai comună sursă de emboli în accidentul vascular cerebral asociat. Tromboza LAA este prezentă la 15% dintre pacienții cu FA. Prin urmare, numeroase studii au avut ca scop evaluarea rolului structurii și funcției LAA în apariția accidentului vascular cerebral. S-a raportat că un volum LAA mai mare și un orificiu LAA mai mare sunt asociate cu riscuri crescute de apariție a accidentului vascular cerebral. Mai mult, nu numai dimensiunea, ci și forma LAA influențează formarea trombului. S-a raportat că prezența unei benzi în partea proximală a lobului LAA dominant, descrisă ca morfologie a LAA in formă de aripă de pui, este protectoare împotriva accidentului vascular cerebral. Cu toate acestea, alte studii nu sunt în concordanță cu această constatare și nu există un consens cu privire la categoriile de morfologie LAA. LAA are funcție de rezervor, contractilă, electrică și endocrină, care pot oferi informații esențiale despre riscul formării cheagurilor și evenimentelor embolice. Viteza scăzută a fluxului LAA, reflectând contractilitatea LAA mai mică, a fost descrisă ca fiind asociată cu un risc mai mare de accident vascular cerebral. Una peste alta, chiar dacă LAA joacă un rol important în apariția accidentului vascular cerebral, există date controversate în literatură, prin urmare sunt necesare studii suplimentare pentru a evalua mecanismele care stau la baza.
Cuvinte cheie: fibrilație atrială, accident vascular cerebral, tromb, apendicele atrial stâng, morfologie.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia that can increase the risk of stroke, heart failure and hospitalization[1-3]. Around 0.4% to 1% of the general adult population has AF and this rate increases with age, especially over the age of 80, where the prevalence of AF is more than 9%[4]. The number of affected individuals is expected to double or even triple within the next twenty to thirty years[4]. In the developed countries the prevalence is higher than in the developing nations[5]. Moreover, the prevalence is lower in women than in men[5]. The most common risk factors of AF are age, hypertension, valvular and ischemic heart disease, thyroid dysfunction, obesity, diabetes, chronic obstructive pulmonary disease, chronic kidney disease and smoking[6]. Catheter ablation is an effective and safe procedure to treat AF. However, in many cases recurrence occurs. Approximately 20% to 45% of the patients experience a recurrence of AF within 12 months after the catheter ablation[7,8].

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AF can increase the risk of stroke about five times and since the elder population is constantly growing, AF will have an ascendant effect on stroke morbidity and mortality[9]. Moreover, stroke caused by cardioembolic events, mostly by AF is associated with a higher in-hospital mortality and stroke severity than non-AF related stroke[10,11]. In the setting of AF, the left atrial appendage (LAA) is the most common source of emboli[12]. Additionally, according to Di Biase, LAA morphology is related to the risk of stroke[13]. Moreover, the size of the LAA orifice area and the LAA flow velocity also influence the risk of stroke formation[14]. Therefore, it is absolutely necessary to understand the background of the anatomy and function of the LAA in order to understand the pathogenesis of AF-related stroke.

LEFT ATRIAL APPENDAGE

The LAA used to be considered as an insignificant part of the heart. It is now recognized to be a structure with important physiological, arrhythmogenic and thrombogenic components. The risk of stroke in patients with non-valvular AF is approximately five-fold higher than in patients with sinus rhythm[9]. LAA thrombus is present in 15% of the patients in AF[15]. In patients with non-valvular AF, 90% of thrombi have a predilection to form within the LAA because of reduced contractility and stasis, in contrast in valvular AF, where this rate is about 56%[12]. It has been proposed that there is a connection between the LAA morphology and the risk of thrombus formation in the LAA[13]. In the presence of LAA dysfunction, there is an increased risk of thromboembolic events and LAA dysfunction has been shown to be a strong predictor of thrombus formation[16,17]. As an outcome of AF, decreased LAA contraction and flow velocity can be observed with TEE which are among the strongest predictors of stroke, but there is limited use of these parameters to predict the risk of ischemic stroke[16,17].

Left atrial appendage structure

The LAA is often a finger-like, long, narrow, tubular, hooked structure originated from the main body of the left atrium (LA)[18]. It is formed at the 4th week of gestation as the remnant of the original embryonic LA. Its size, shape, and relationship with nearby cardiac and extracardiac structures are extremely complex and variable. In most hearts, the LAA lies anteriorly in the atrioventricular sulcus in close relation with the left phrenic nerve, the left superior pulmonary vein and the left circumflex artery. Externally, the LAA is a tubular structure with or without obvious bend and its tip points to the pulmonary artery, the right ventricular outflow tract, and the free wall of the left ventricle[18]. Internally, its orifice opens to the LA main chamber[19]. The shape of the orifice can be classified into several types. The most frequent type is oval shape, besides that it can be foot-like, triangular, water drop-like or round[20,21]. In most appendages, there is a well-defined orifice that continues in the neck region, but there is a wide anatomical variability in the location of the LAA ostia in relation to the venous orifices[22]. Lee et al proposed that the enlargement of the LAA orifice area (>3.5 cm^2) is an independent risk factor of stroke in patients with non-valvular AF, even after adjustment for other risk factors due to the fact that larger LAA promotes slow blood flow, stasis and eventually thrombus formation[14]. The inner surface of the LAA has a single layer of endothelium and reveals complex indentations made by pectinate muscles[23]. The remainder of the wall in between them is paper-thin. At the borders between the inferior and the superior faces, the muscle bundles arrange like feather-type-palm-leaf[24]. In patients with AF, structural remodeling of the LAA with dilation of the chamber and a reduction in the number of pectinate muscles can be seen compared to patients in sinus rhythm[21]. The thicker muscle bundles may give the appearance of an LAA thrombus or intra-arterial mass[25].

According to Veinot et al, the number of LAA lobes ranged from 1 to 4, but the most frequent occurrence is the two-lobe type[25]. An increased number of lobes are associated with the presence of thrombus because of the blood stasis[26]. In the first year after catheter ablation, in patients who maintained sinus rhythm, a clearly visible decrease in LA and LAA volumes can be seen, but the number of lobes remains the same, therefore the number of LAA lobes is not influenced by LAA remodeling during AF[26].

Generally, transesophageal echocardiography (TEE) should be used to get a detailed assessment of the LAA and characterize LAA morphology[27]. With multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI), high-quality images of the LAA can be obtained. In a recent study, Di Base et al categorized LAA morphology into 4 types[13]:

1. **Chicken wing:** An obvious bend presents in the proximal part of the dominant lobe, folding back on itself at some distance from the LAA orifice. This type may have secondary lobes.
2. **Windsock:** The primary structure is one dominant lobe with sufficient length. This type of LAA

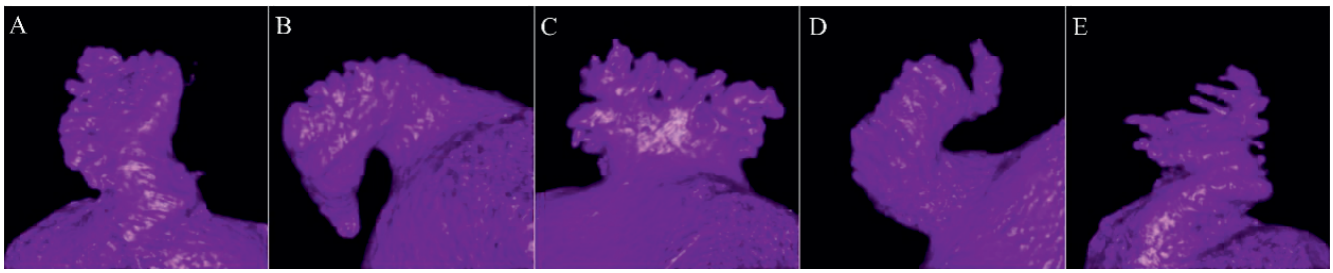

Figure 1. Morphologies of the LAA. The categorization of LAA morphologies according to DiBiease et al. **A:** windsock: the primary structure is one dominant lobe with sufficient length **B:** chicken wing: the dominant lobe has an obvious bend in the proximal part **C:** cauliflower: LAA has limited length and the distal width exceed the proximal width **D:** swan: LAA has a second sharp curve folding the dominant lobe back[13].

may have secondary or even tertiary lobes arising from the dominant lobe from different locations.

3. **Cauliflower:** A short overall length with more complex internal characteristics and a lack of dominant lobe. This type of LAA has variable number of lobes and more irregular shape of the orifice, like oval or round.
4. **Cactus:** The primary structure is one dominant central lobe with secondary lobes inferiorly and superiorly.

The categories of the LAA morphology according to DiBiase et al can be seen in Figure 1.

These results could have a relevant impact on the anticoagulation management of patients with a low-intermediate risk for stroke/TIA.

Nevertheless, this is not the only categorization of LAA morphologies. Rosendael et al also categorized LAA morphologies into four types with MDCT, but with another classification when instead of „cactus", they used „swan" if LAA presented a second sharp curve folding the structure back. Their study demonstrated that MDCT can also provide an exact assessment of the LAA geometry. In their analysis, windsock was the most prevalent morphology of the LAA[28].

The categorization of LAA morphologies according to Rosendael et al. E: cactus: the primary structure is one dominant central lobe with secondary lobes inferiorly and superiorly[28].

Few cases have been reported, that described the congenital absence of the LAA. This extremely rare cardiac anomaly is usually encountered as an incidental finding during routine imaging for other purposes. Due to the very few cases, the physiological consequences of this entity are unknown. Hypothetically, the risk of stroke in patients without LAA should be lower after all the anatomical source of thrombi is absent[29]. The identification of the absence of LAA can be achieved with the use of TEE, MDCT or cardiac MRI[30].

2.2.2. Left atrial appendage function

LAA function has reservoir, contractile, electric and endocrine components, that can provide essential information about the risk of clot formation, embolic events and success of cardioversion[27].

Reservoir and contractile function

LAA volume is normally about 30% of the entire LA volume, thus not just the LA main chamber has a reservoir function during LA pressure, volume overload or left ventricular systole, but the LAA too[19]. Furthermore, LAA is 2.6 times more distensible than the LA main chamber[31]. During early diastole, LAA acts like a conduit for blood passing through to the left ventricle from the left pulmonary veins. In late diastole, LAA

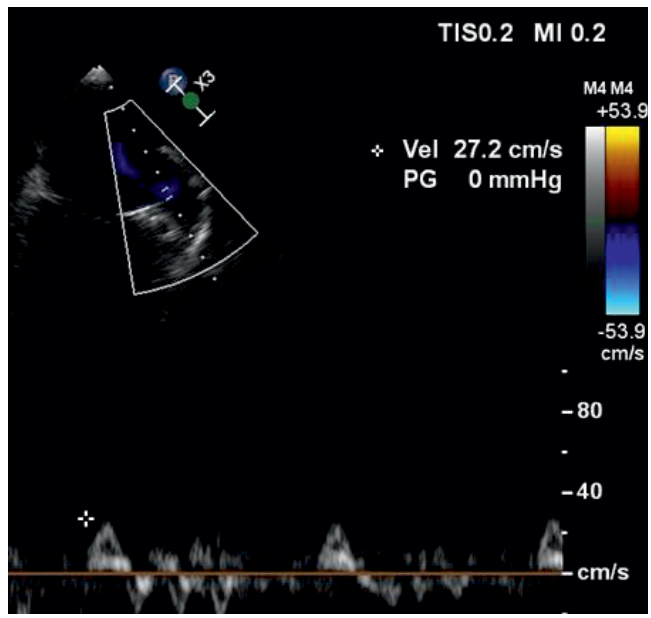

Figure 2. The measurement of LAA flow velocity with pulse wave Doppler. This image represents a decreased LAA flow velocity (27.2 cm/s) in a patient with AF. Courtesy Heart and Vascular Center of Semmelweis University, Budapest, Hungary.

importantly contributes role in increasing the left ventricular filling by functioning as an active contractile chamber[32].

LAA contractile function can be characterized by the LAA flow velocity which can be measured with pulse-wave Doppler on TEE (Figure 2).

During sinus rhythm, a characteristic quadriphasic flow pattern can be seen[33]:

- Early diastolic emptying velocity: a first passive contraction during the early phase of the ventricular diastole. This phase includes the opening of the mitral valve followed by a fall in the LAA pressure and the distension of the left ventricle causing external compression of the LAA. The normal early diastolic emptying velocity ranges between 20–40 cm/s[34-36].
- Late diastolic emptying velocity: the late diastolic emptying velocity is caused by an active contraction of the LAA during atrial systole. It has been reported to significantly increase thromboembolic risk 14. The normal late diastolic emptying velocity ranges between 50–60 cm/s[34-36]. Lee et al proposed that a decreased LAA flow velocity (<37 cm/s) and enlarged LAA orifice area (>3.5 cm^2) are associated with a greater risk of stroke[14]. Therefore, the evaluation of the LAA contraction flow could be an important part in the assessment of stroke risk.
- LAA filling: this is a retrograde and negative wave that is a consequence of the LAA relaxation. The normal LAA filling velocity ranges between 40–50 cm/s[34-36].
- Systolic reflection waves: low inflow and outflow waves during ventricular systole[34-36].

During tachycardia, LAA emptying velocity shows an increased flow. Early and late diastolic emptying velocities decrease with age and women tend to have lower emptying velocities than men[37].

During AF, variable amplitude and irregularity of emptying and filling can be seen with lower velocities[16,17]. It can be characterized by a saw-tooth emptying pattern or no visible active emptying pattern. On TEE, turbid LAA emptying peak flow velocity, LAA fractional area change and decreased LAA velocities can be observed. The listed abnormalities of the LAA function, especially when no visibly active emptying can be seen, are associated with increased risk of thrombus formation due to the blood stasis in the LA and LAA[16,17].

Endocrine function

The LAA functions as an endocrine organ too. It contains stretch sensitive receptors that respond to changes in atrial pressure by natriuretic peptide secretion. LAA produces approximately 30% of all cardiac atrial natriuretic peptides (ANP)[38]. An animal study proposed that LAA has a significant role in normal cardiac function. When increased pressure in the LAA occurs, diuresis, natriuresis and increased heart rate can be observed[39]. Thus, LAA plays an important role in the maintenance of normal fluid hemostasis.

Thrombogenic features of the LAA

As mentioned before, LAA is the most prevalent source of thrombi in non-valvular AF. The pathogenesis of thrombus formation in AF is multifactorial. The three factors that are thought to contribute to thrombosis were described by Virchow: (1) endothelial or endocardial damage or dysfunction and related structural changes; (2) hemodynamic changes, such as blood stasis or turbulence; (3) increased coagulability[40]. In AF, there is a prothrombotic or hypercoagulable state caused by abnormal changes in blood flow, atrial wall, and blood components. Abnormal changes in coagulation and hemostasis such as increased turnover of fibrin or abnormal concentrations of prothrombotic factors have been described in AF[41,42]. Increased amount of D-dimer found to be a predictor of subsequent thromboembolic events in patients with AF. Indeed, D-dimer can be useful in identifying low-risk patients, whereby a low amount of D-dimer predicts a low risk of stroke[43,44]. An increased rate of von Willebrand factor (vWF) is a mark of endothelial damage and dysfunction[45]. Tissue factor and vWF are increased in patients with AF who have a history of cardiogenic thromboembolism[46]. Changes in the atrial tissue, such as inflammation and fibrosis can also lead to a prothrombotic state in AF. There is a clear influence of increased levels of inflammatory markers in the pathogenesis of AF, thus inflammation can also be the consequence of the prothrombotic state during AF[47]. CTA can estimate the presence of LAA thrombi and by performing an affirmative delayed phase the determination of pseudothrombus and thrombus can be achieved. CTA images of pseudothrombus and thrombus are represented in Figure 3.

DISCUSSION

The LAA is a frequent site of thrombus formation in AF, since this common cardiac arrhythmia cause a

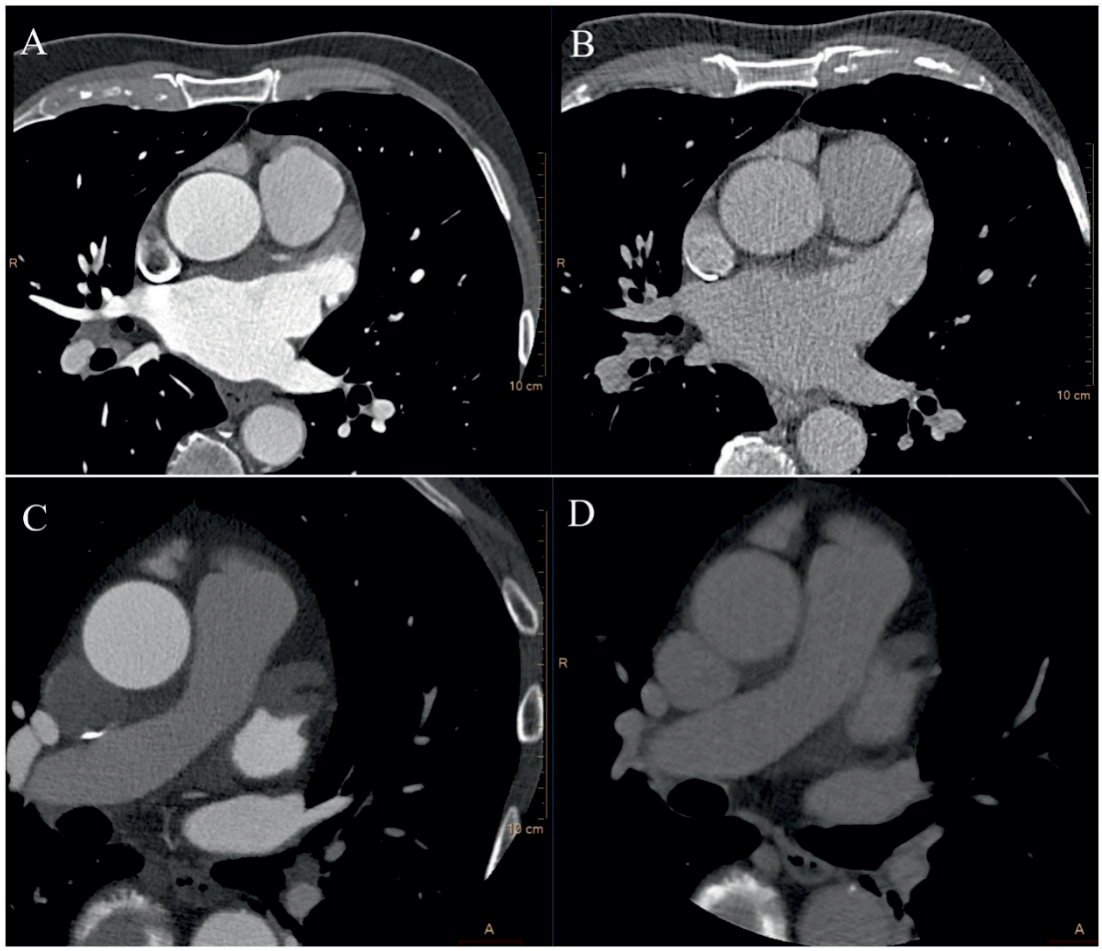

Figure 3. Differentiation between pseudothrombus (A-B) versus genuine thrombus (C-D). **A:** filling defect in the LAA. **B:** an affirmative delayed phase showing an empty LAA. This phenomenon is due to poor filling of the LAA with contrast secondary to venous stasis and/or left atrial dysfunction. **C:** a filling defect in the LAA. **D:** low attenuation filling defect in the delayed phase scan confirming the presence of LAA thrombus (Courtesy Heart and Vascular Center of Semmelweis University, Budapest, Hungary).

prothrombotic or hypercoagulable state by reducing the contractility of the appendage wall, causing abnormal blood stasis and dilation of the LAA chamber[40]. These listed complications of AF promote thrombus formation, thus systemic embolism can occur. The size and shape of the LAA and its orifice is extremely complex and variable. Previous studies have conflicting results regarding the association between LAA morphologies and the risk of stroke/TIA. Di Biase et al. categorize LAA shapes into four types: windsock, cauliflower, chicken wing and cactus[13]. They suggested that chicken wing morphology is protective against ischemic stroke, while non-chicken wing shapes might be associated with an increased risk of stroke. However, other studies demonstrated that patients with a history of stroke are more likely to have cauliflower morphology[48,49]. This can be explained by the multilobular aspect of the cauliflower shape.

The shape and size of the LAA orifice is highly variable. In a recent study, Lee et al have reported that the enlargement of the LAA orifice area and decreased LAA flow velocity are associated with an increased risk of stroke[14].

Conflict of interest: none declared.

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