Left atrial appendage: structure, function, and role in thromboembolism

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Abstract
The left atrial appendage (LAA) is derived from the left wall of the primary atrium, which forms during the fourth week of embryonic development. It has developmental, ultrastructural, and physiological characteristics distinct from the left atrium proper. The LAA lies within the confines of the pericardium in close relation to the free wall of the left ventricle and thus its emptying and filling may be significantly affected by left ventricular function. The physiological properties and anatomical relations of the LAA render it ideally suited to function as a decompression chamber during left ventricular systole and during other periods when left atrial pressure is high. These properties include the position of the LAA high in the body of the left atrium; the increased distensibility of the LAA compared with the left atrium proper; the high concentration of atrial natriuretic factor (ANF) granules contained within the LAA; and the neuronal configuration of the LAA. Thrombus has a predilection to form in the LAA in patients with atrial fibrillation, mitral valve disease (both in atrial fibrillation and in sinus rhythm). Second, the use of transeosophageal echocardiography has made clear imaging of the LAA possible, so that its size, shape, flow patterns, and content can be assessed in health and disease.

The risk of stroke is increased approximately fivefold in non-rheumatic atrial fibrillation and 17-fold in patients with mitral stenosis and atrial fibrillation. About 15% of ischaemic strokes arise as a result of atrial fibrillation. Approximately 90% of atrial thrombi in non-rheumatic atrial fibrillation and 60% of such thrombi in patients with rheumatic mitral valve disease (predominantly stenosis) are seen within the LAA.

Although the incidence of thromboembolism in atrial fibrillation and mitral valve disease can be dramatically reduced with the use of anticoagulants, particularly warfarin, the use of such treatment can be complicated, and is contraindicated in many patients. Alternative forms of treatment are needed for the prophylaxis of thromboembolism in these patients.

In this paper, we will discuss the ultrastructural and physiological function of the LAA and describe the local anatomical and physiological correlates associated with LAA thrombus. Finally, prophylaxis against thromboembolism by obliterating or amputating the LAA will be discussed.

Anatomy
The trabecular LAA is the remnant of the original embryonic left atrium that develops during the third week of gestation. The main smooth walled left atrial cavity develops later and is formed from the outgrowth of the pulmonary veins.

The LAA is a long, tubular, hooked structure which is usually crenellated and has a narrow junction with the venous component of the atrium. In contrast, the right appendage is broad and triangular with a wide junction. Unlike on the right, the junction of the LAA with the atrium proper is not marked either externally or internally by a crest or groove. Both the right and left appendages are trabeculated, with muscle bars largely running parallel to each other giving a comb-like appearance (hence termed pectinate muscles),

In the past, the left atrial appendage (LAA) has been considered to be a relatively insignificant portion of cardiac anatomy. It is now recognised that it is a structure with important pathological associations. First, thrombus has a predilection to form within the LAA in patients with non-valvular atrial fibrillation and to a lesser extent in those with mitral valve disease (both in atrial fibrillation and in sinus rhythm). Second, the use of transeosophageal echocardiography has made clear imaging of the LAA possible, so that its size, shape, flow patterns, and content can be assessed in health and disease.
but these are less pronounced on the left. The extent of the pectinate muscles enables appendages to be designated as morphologically right or left (fig 1), a useful distinction in some cases of complex congenital heart disease.

Comparative anatomy
Until recently, there have been virtually no publications dealing with the comparative anatomy of the LAA. The first such detailed description of the varied morphology of the LAA was provided by Ernst et al, who studied the morphology of the LAA in 220 cases using synthetic resin casts made at necropsy. In 198 cases an antemortem ECG was available (143 in sinus rhythm and 55 in atrial fibrillation). LAA casts varied markedly in volume, from 0.7 ml to 19.2 ml. The size of the orifice of the LAA also varied considerably, with a minimum diameter ranging from 5 to 27 mm, and a maximum diameter from 10 to 40 mm. Likewise, there was great variation in the length of the LAA, which ranged from 16 to 51 mm. In 70% of the cases, the principal axis was markedly bent or spiral, which accounts for some of the differences in shape and size of the LAA in vivo when viewed with transoesophageal echocardiography in different imaging planes.

Casts from patients who had been in atrial fibrillation were more voluminous, had larger orifices and fewer branches, and were broader than casts from patients who had been in sinus rhythm. Similar observations regarding LAA size in patients with atrial fibrillation have been made using transoesophageal echocardiography in different imaging planes.

In 40–70% of patients,15–17 quadriphasic appendage flow have been described in 40–70% of patients.15–17 This pattern is seen less often in patients undergoing transoesophageal echocardiography for clinical indications than in normal volunteers. The cycle begins with a phase of forward flow (out of the appendage) occurring soon after the start of transmural flow in early diastole, followed by a short phase of backward flow (into the appendage). The first forward phase is fixed to the start of early diastole, suggesting a causal relation between left ventricular relaxation and early appendageal emptying.

Physiology
FLOW
The LAA shortens to a greater extent than the rest of the left atrium and has a distinct pattern of contraction. Blood flow within the LAA has been studied with transoesophageal echocardiography, which affords good views of the appendage and its orifice. Doppler measured LAA flow in patients with sinus rhythm was initially described as biphasic, but additional emptying and filling waves resulting in quadriphasic appendage flow have been described in 40–70% of patients. This pattern is seen less often in patients undergoing transoesophageal echocardiography for clinical indications than in normal volunteers. The cycle begins with a phase of forward flow (out of the appendage) occurring soon after the start of transmural flow in early diastole, followed by a short phase of backward flow (into the appendage). The first forward phase is fixed to the start of early diastole, suggesting a causal relation between left ventricular relaxation and early appendageal emptying.

The LAA lies within the fixed, relatively immobile confines of the pericardium. It is closely related in its superior aspect to the pul-
an inflow wave (probably related to appendageal elasticity). Two further waves are seen: an outflow wave (ventricular relaxation), and an inflow wave (probably related to appendageal elasticity). This is followed by flow into the appendage during ventricular systole. Two inflow (below line) and two outflow (above line) phases can be appreciated. During atrial systole (after the P wave) a clear period of flow out of the appendage is seen. This is followed by flow into the appendage during ventricular systole (QRS complex). Two further waves are seen: an outflow wave (ventricular relaxation), and an inflow wave (probably related to appendageal elasticity).

Figure 3 Flow in and out of the appendage during sinus rhythm. A complex quadriphasic pattern can be appreciated. Two inflow (below line) and two outflow waves are present. During atrial systole (after the P wave) a clear period of flow out of the appendage is seen. This is followed by flow into the appendage during ventricular systole (QRS complex). Two further waves are seen: an outflow wave (ventricular relaxation), and an inflow wave (probably related to appendageal elasticity).

monary artery and inferomedially to the free wall of the left ventricle. As the left ventricle dilates during diastole, it fills the intrapericardial space, and it has been suggested that it may contribute to appendageal emptying by compressing the inferomedial wall of the LAA between its free wall and the fixed pericardium. In addition, ventricular filling creates an intracavitary suction effect, influencing emptying and filling of the atrium and consequently the appendage. The extent of emptying and filling of the LAA may be influenced more by changes in left ventricular than LAA function, a finding which could in part help to explain the higher incidence of atrial fibrillation related stroke in patients with left ventricular dysfunction.28 The magnitude of LAA filling and emptying in atrial fibrillation may be inversely related to ventricular rate, a finding that could have implications for optimal rate control in preventing thromboembolism in atrial fibrillation.18,20

The relation of LAA flow to left ventricular filling also raises the question as to whether the appendage actively contracts or whether it functions passively, being compressed by the left ventricle during ventricular diastole and emptied by the negative pressure of ventricular filling. Evidence supports active contraction of the appendage, as it has prominent muscle ridges which, unless they contract, would atrophy. Furthermore, passive emptying and filling of the appendage would not easily explain the quadriphasic appendage flow seen at slower heart rates. In addition a case report of a herniated giant LAA records vigorous contraction during which the “distal tip would flip in an arch of approximately 3 inches with each systole.” Finally, surgeons viewing the LAA at the time of surgery observe active contraction.

Several animal studies suggest that the LAA is more distensible than the left atrium proper.22–25 In humans, clamping of the LAA during cardiac surgery results in an increase in left atrial pressure and dimension as well as in transmural and pulmonary diastolic flow velocities.26 Because of its increased distensibility, the LAA may augment haemodynamic function by modulating left atrial pressure–volume relations in states of increased left atrial pressure and volume overload.20

**ATRIAL NATRIURETIC FACTOR**

In humans, analysis of ANF content in excised atrial appendages has shown that they contain about 30% of all the cardiac ANF. The cardiocytes of the LAA contain the greatest density of ANF granules found in the left atrium.27 ANF forms the major protein in isolated atrial amyloidosis and it is therefore of interest that this disease has a predilection for the LAA.20

**NEUROPHYSIOLOGY**

The atria and appendages are supplied by a variety of nerves and receptors. Both appendages can be selectively distended by infusing fluid into small balloons located within them without altering the pressures in the right or left atrium or aorta, resulting in an increase in urine flow and sodium excretion. However, crushing the bases of both appendages abolishes or attenuates this effect, suggesting that the response is initiated primarily by stretch sensitive receptors in the atrial appendages. In dogs, this also causes an increase in heart rate (a reflex response with a vagal afferent path and a sympathetic efferent path).20 Therefore it is possible that the LAA maintains left atrial pressure not only through its increased distensibility and its capacity for ANF secretion, but also through stretch sensitive receptors which, when activated, increase heart rate, diuresis, and natriuresis.

**Imaging left atrial appendage thrombus**

From a radiological perspective the LAA forms part of the normal cardiac silhouette on the left cardiac border between the left ventricle and pulmonary outflow tract. Although angiography has been used fairly extensively in the past for the investigation of thrombi in the LAA, this is invasive and is now rarely done. Transthoracic echocardiography does not usually afford views of the LAA; however, transoesophageal echocardiography allows semi-invasive, highly accurate imaging of the LAA and in recent years this has become a valuable tool for the diagnosis of thrombus within the appendage (figs 4 and 5). In a comparison with intraoperative observations, the sensitivity and specificity of transoesophageal echocardiography were 100% and 99%, respectively, with a positive predictive value of 86% and a negative predictive value of 100% for the diagnoses of thrombi within the LAA.22

Current anticoagulation guidelines for cardioversion in patients with atrial fibrillation lasting for more than 48 hours recommend at least three weeks of warfarin treatment before cardioversion and a minimum of four weeks afterwards.23 An alternative approach would be to perform transoesophageal echocardiography and progress to immediate cardioversion without anticoagulation if no thrombi are present.24 This would minimise the duration of atrial
fibrillation before cardioversion and increase the likelihood of success.\textsuperscript{35} It has been shown, however, that this strategy is suboptimal as 2–3% of patients without LAA thrombus on transoesophageal echocardiography before cardioversion still have an embolic event shortly after restoration of sinus rhythm.\textsuperscript{36} This problem may be overcome by a period of anticoagulation after cardioversion, and a large multicentre study (the ACUTE study (assessment of cardioversion using transoesophageal echocardiography)) is under way to evaluate the feasibility, safety, and cost-effectiveness of this approach.

Correlates of left atrial appendage thrombus

The LAA is the site most commonly associated with thrombus formation, particularly in patients with non-valvar atrial fibrillation. The pathogenesis of LAA thrombus has not been fully elucidated, but the predilection for its formation in the LAA is likely to result from stagnation within the long, blind ended trabeculated pouch. Transoesophageal echocardiography on 233 patients with atrial fibrillation of more than 48 hours' duration who were not on chronic anticoagulation revealed that 15% had evidence of left atrial thrombus, and in all but one case this was located in the appendage.\textsuperscript{37} In another series of 272 patients with non-rheumatic atrial fibrillation, the prevalence of thrombi detected at transoesophageal echocardiography was 8% and all were in the appendage.\textsuperscript{38} Less commonly, intra-atrial thrombi also form in patients with atrial flutter and were detected at transoesophageal echocardiography in five of 24 patients with atrial flutter; again, all thrombi were located in the LAA.\textsuperscript{39} Three specific variables of LAA structure and function have been studied with respect to thrombus formation and stroke: size, flow pattern, and flow velocity.

LAA SIZE

There has been controversy over whether the size of the LAA determines thromboembolic risk.\textsuperscript{40–42} However, LAA size determined at surgery has been related to the occurrence of embolic events\textsuperscript{41} and studies with transoesophageal echocardiography have shown that thrombus and subsequent thromboembolic events are clearly related to LAA size. An enlarged left atrium on transoesophageal echocardiography is associated with an enlarged LAA in 59% of patients; conversely, a normal sized left atrium is associated with an enlarged LAA in 15% of patients. Spontaneous echo contrast, or smoke-like echo, has been defined as an amorphous, swirling, light grey haze inside the cardiac chambers, great vessels, and veins. It arises in conditions of stasis, has been attributed to rouleaux formation, and is strongly associated with LAA thrombus formation. LAA size is larger in patients with spontaneous echo contrast and thrombus formation in the LAA than in those without these features (52.1 (9.0) mm v 39.6 (11.0) mm, mean (SD)). LAA area has been shown to be larger in patients who have evidence of LAA thrombus, whether they are in atrial fibrillation or in sinus rhythm.\textsuperscript{43} In patients with recent onset atrial fibrillation, LAA thrombus is associated with a large LAA area,\textsuperscript{44} and in chronic atrial fibrillation it has also been shown, using intravenous albumin as a contrast agent, that LAA area is significantly larger in patients with thrombus than in those without.\textsuperscript{45}

LAA FUNCTION AND FLOW PATTERNS

Doppler transoesophageal echocardiography has been used extensively in recent years to determine the velocity and pattern of blood flow at the orifice of the appendage (fig 6). Reduced or absent LAA inflow and outflow velocities and low LAA ejection fractions are associated with LAA spontaneous echo contrast and thrombus formation in patients in sinus rhythm and in those in atrial fibrillation,\textsuperscript{46–48} and low peak LAA filling and emptying velocities have been found to be related to a history of systemic embolism.\textsuperscript{37}
Thrombus formation in this patient would be relatively low. The maximum inflow velocity is approaching 0.4 m/s, a relatively high velocity. Thus, the risk of thromboembolic events. In this example, a well-defined flow pattern is present and the flow has been related to the formation of thrombi and the development of subsequent thromboembolic events. In this case, a well-defined flow pattern is present and the flow has been related to the formation of thrombi and to the development of subsequent thromboembolic events.

Figure 6: Left atrial appendage flow during atrial fibrillation, as determined by pulsed Doppler transoesophageal echocardiography. Both the velocity and the pattern of flow have been related to the formation of thrombi and to the development of subsequent thromboembolic events. In this example, a well-defined flow pattern is present and the flow has been related to the formation of thrombi and to the development of subsequent thromboembolic events.

LAA flow patterns have been classified into three types according to the appearance on Doppler transoesophageal echocardiography:

Type I—patients in sinus rhythm with a regular pattern of filling and emptying;
Type II—patients in atrial fibrillation with an active “sawtooth” pattern;
Type III—patients in atrial fibrillation with no identifiable flow waves.

Patients with the type III pattern have a significantly higher incidence of LAA spontaneous echo contrast and thrombus than those with the type II or I pattern. LAA flow patterns have been related to the appearance of fibrillatory waves on the ECG. Patients with coarse fibrillatory waves had lower peak LAA emptying velocity and ejection fraction and a higher incidence of LAA spontaneous echo contrast and thrombus than those with fine fibrillatory waves. The cause of LAA dysfunction in patients with atrial fibrillation has not been fully elucidated. It is likely to be related in part to a myopathic process which results in atrial fibrillation or which occurs as a result of the atrial fibrillation itself (an atrial fibrillation induced myopathy). LAA function in patients with atrial flutter is reported to be associated with a regular pattern of LAA emptying and significantly higher peak emptying velocities than in patients with atrial fibrillation, in keeping with the lower incidence of thromboembolism in atrial flutter.

The size and mobility of the thrombus are also determinants of thromboembolic risk. Thrombus dimensions of more than 1.5 cm and thromboli that are pedunculated and mobile are associated with increased risk of thromboembolism.

Patients with atrial fibrillation who are successfully cardioverted with drugs or dc shock show depressed left atrial mechanical function for a variable period following restoration of sinus rhythm. Similar findings have been reported in studies on LAA function.

LAA spontaneous echo contrast develops de novo, and inflow and outflow velocities in the appendage decrease after successful cardioversion of atrial fibrillation. These findings are important, as depressed LAA function may result in thrombus formation. The findings of decreased atrial mechanical function after cardioversion is sometimes referred to as “stunning”; however, this term is a misnomer as it implies that the dc shock itself results in damage to the atrium and appendage with consequent depressed function and stasis. This is unlikely to be the case as studies on patients have shown that the phenomenon occurs after both pharmacological and spontaneous cardioversion of atrial fibrillation, and shocks have not been shown to cause atrial mechanical dysfunction in patients cardioverted for ventricular tachycardia. Decreased atrial mechanical function after cardioversion may occur as a result of an atrial fibrillation induced atrial appendage myopathy as the depression of function is related to the duration of the previous atrial fibrillation.

LAA thrombus in patients in sinus rhythm
Five per cent of patients in sinus rhythm with a history of stroke, transient ischaemic attack, or systemic embolisation and no significant carotid stenosis have LAA thrombi. Significant left ventricular dysfunction in sinus rhythm is associated with left atrial thrombus formation, and about 15% of patients with severe dilated cardiomyopathy in sinus rhythm have identifiable atrial thrombi, the majority of which are located within the LAA. These and other data suggest that the atrial appendage may be a source of embolic material even in the absence of atrial fibrillation.

Hæmatological and endocardial correlates of LAA thrombus
Thrombi are not fixed structures but are continuously forming and resolving. Hence, left atrial thrombus is associated with raised peripheral blood concentrations of fibrinopeptide A, reflecting thrombin-mediated fibrin formation, and D dimer, a degradation product of fibrinogen. The observation that warfarin treatment results in disappearance of LAA thrombi when patients are re-examined with transoesophageal echocardiography after four weeks of therapy further suggests that the presence of thrombus is the result of a dynamic process of clot formation and lysis. The relative role of platelets and endothelium in the pathophysiology of LAA thrombus formation is not known.

Obliteration of the left atrial appendage for the prophylaxis of thromboembolism
Randomised trials have shown that anticoagulation with warfarin results in a significant reduction in stroke rate and mortality in patients with atrial fibrillation. The effects of aspirin are far more modest. It should be noted that in these trials anticoagulated patients were highly selected (in three of the North American warfarin/placebo trials, only about 10% were...
ultimately randomised). In those assigned to warfarin, withdrawals occur at rates of up to 38% a year. In warfarin treated patients, approximately 50% of the strokes occurred in individuals who had inadvertent therapeutic lapses, or who required temporary or permanent cessation of therapy, a finding that parallels experience in patients with valvar prostheses.

More than 50% of the atrial fibrillation population are aged 75 or older and it has been estimated that 20% or more have a contraindication to warfarin treatment. There is not only underprescribing of warfarin in patients who are eligible, but also a high incidence of contraindications in patients who are at risk of thromboembolism. Thus, although warfarin is effective in reducing the incidence of stroke, in practice it is often difficult to treat patients continuously and effectively in the recommended manner.

LAA obliteration as an alternative means of stroke prophylaxis is attractive, as over 90% of thrombi associated with non-rheumatic atrial fibrillation occur predominantly within the LAA. Data from the placebo arm of the European atrial fibrillation trial suggest that in patients who have had a previous stroke and have contraindications to warfarin treatment, the annual stroke rate is 12% a year. It is estimated that if obliteration reduces the incidence of stroke by 50% to 75%, this high stroke rate could be reduced to 3–6% a year. This is similar to findings reported in the North American symptomatic carotid endarterectomy trial. There are thus two possible situations in which amputation or obliteration of the LAA may be considered: first, as an additional procedure during cardiac surgery in patients in whom warfarin is required but is contraindicated; and second, as an isolated closed chest (for example thoracoscopic) procedure.

In 1952 Bailey et al suggested that the LAA could be amputated at mitral valvotomy as a means of prophylaxis of thromboembolism. A few years later Belcher and Somerville added support for this strategy and advocated surgical obliteration of LAA when it was large. It was suggested that this procedure could offer approximately 50% protection against the risk of stroke even in patients with mitral valve disease.

Amputation of the LAA remains controversial, although excision or ligation of the right atrial appendage is frequently performed during insertion or withdrawal of cannulae during coronary artery bypass grafting. A recent review suggested that surgeons use the technique of LAA obliteration sporadically. Some obliterate the appendage during mitral valve replacement and repair, while others use it only as part of the maze or corridor procedures for the surgical treatment of atrial fibrillation. Various techniques for the intraoperative amputation of the LAA have been described, including the use of an automatic surgical stapler.

LAA obliteration may result in adverse haemodynamic and physiological effects. Various animal models have been used to examine the effects of amputation of the atrial appendages on natriuresis and diuresis in response to volume loading. In the monkey, bilateral appendectomy greatly attenuates the rise in plasma ANF and attenuates natriuresis after acute volume expansion. Atrial appendectomy also results in a reduction in stroke volume, which may be explained by a reduction in atrial “kick.” Bilateral atrial appendectomy in conscious dogs eliminates ANF release and blunts renal excretion of sodium and water after a large acute volume load. Similar findings have been reported in human subjects. It may be possible to diminish the hormonal effects of LAA obliteration by preserving the right atrial appendage.

In addition to the effects on ANF secretion, amputation of the LAA may also have undesirable effects on atrial compliance. Removal of the appendage in open chested dogs causes a decrease in atrial compliance associated with altered left ventricular filling and atrial systolic function, and in patients undergoing cardiac surgery, the mean left atrial pressure and dimension and transmural and pulmonary diastolic flow velocities rose after LAA clamping.

Thus before the routine use of LAA obliteration during cardiac surgery can be advocated or novel treatments such thoracoscopic LAA obliteration proposed, the haemodynamic and hormonal effects of such a manoeuvre must be carefully evaluated.

Conclusions

The LAA has unique developmental, anatomical, and physiological properties. These properties render it ideal to act as a reservoir in conditions of volume overload, and to effect the adaptive responses necessary for the reduction of circulating blood volume. The LAA is the major site of thrombus formation in non-valvar atrial fibrillation and to a lesser extent in mitral valve disease. Although the exact pathogenesis of this complication has not been fully elucidated, it is likely that stasis of blood flow within the LAA plays a major role, but much is unknown. In particular, the role of the endothelium of the LAA and the haematomatological mechanisms of LAA thrombus formation have not been adequately studied.

The most effective current prophylaxis of stroke in atrial fibrillation is warfarin. Warfarin is contraindicated in many patients, particularly in the elderly in whom the risk of stroke is highest. Alternative treatments are needed, and obliteration of the LAA is one such option. However, this is technically challenging and may result in unfavourable haemodynamic and hormonal effects, which could be particularly important in patients with left ventricular failure and valvar heart disease. Direct or thoracoscopic obliteration are possibilities, but technical aspects of the thoracoscopic procedure must be developed before it can be offered as an alternative. The technique will not prevent all episodes of thromboembolism, particularly in patients with mitral valve disease, in whom
the appendage is the sole location of thrombus in only 60% of patients.

Future research will explore alternative treatments for thromboprophylaxis in atrial fibrillation and will determine whether LAO obliteration results in effective prophylaxis against thromboembolism in humans, and whether clinically significant adverse effects result from such a procedure.

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Primary References


