The Left Atrial Appendage, a Small, Blind-Ended Structure*: A Review of Its Echocardiographic Evaluation and Its Clinical Role

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The increasing prevalence of stroke and atrial fibrillation is a stimulus for new therapeutic strategies and also warrants a review of imaging modalities of the most important source of cardiac systemic embolic events: the left atrial appendage (LAA). This blind-ended, complex structure is embryologically distinct from the body of the left atrium and is sometimes regarded as just a minor extension of the atrium. However, it should routinely be analyzed as part of a transesophageal echocardiographic (TEE) examination. A pulsed Doppler TEE analysis of LAA emptying flow should supplement a two-dimensional (2-D) analysis; these examinations have proven to be highly reproducible and to help assess thromboembolic risk. In 2-D imaging, potential thrombus and spontaneous echo contrast should be sought. In addition, LAA plays a hemodynamic role that participates in atrial function and is influenced by various hemodynamic conditions. In view of the embolic risks from a dysfunctional appendage, the LAA is often ligated during cardiac valve surgery. New devices are under evaluation for percutaneous closure of the LAA, and further studies should improve the definition, understanding, and treatment of LAA dysfunction.

Key words: Doppler; left atrial appendage; transesophageal echocardiography

Abbreviations: AF = atrial fibrillation; CHF = congestive heart failure; 2-D = two-dimensional; LA = left atrial; LAA = left atrial appendage; LV = left ventricular; MS = mitral stenosis; SEC = spontaneous echo contrast; SPAF = Stroke Prevention in Atrial Fibrillation; SR = sinus rhythm; TDI = tissue Doppler imaging; TEE = transesophageal echocardiography

The left atrial appendage (LAA) is sometimes regarded as a simple atrial outgrowth. We routinely analyze the LAA during transesophageal echocardiography (TEE), looking for clots, spontaneous echo contrast (SEC), and abnormalities in emptying flow velocities, especially in patients with a cerebrovascular thromboembolic event. It has been demonstrated that >15% of strokes originate from the heart, and from the LAA in particular.1,2 TEE provides an access to this small structure, enabling cardioversion in patients with atrial fibrillation (AF) without 4 weeks of prior anticoagulation.3 The encouraging results of radiofrequency ablation therapy increase the need for good left atrial (LA) and LAA assessment by TEE or intracardiac echocardiography.4,5

In addition, Doppler echocardiographic studies provide us with a better understanding of the determinants of LAA function. This review summarizes the literature and underscores new evidence with regard to the importance of cautious LAA imaging assessment, particularly in patients with an history of AF and/or stroke.

LAA ECHOCARDIOGRAPHIC EXPLORATION

Transesophageal Two-Dimensional Echographic Imaging

The horizontal short-axis view at the base of the heart and the two-chamber longitudinal view of the left cavities can be used to image the LAA. A multiplane probe revolving around the cavity (0 to
180°) improves the assessment of its frequently complex structure. Meticulous LAA cavity evaluation should be sufficient to exclude an abnormal intraluminal echo-density signal. Nevertheless, exclusion of clot might be difficult, and even experts postpone electrical cardioversion because of inability to exclude clot formation. Clots may remain hidden because of the three-dimensional complexity of the LAA, and a false-positive diagnosis of thrombus may stem from false interpretation of a prominent pectinea muscle. An autopsy study demonstrated that 80% of the 500 normal LAAs had multiple lobes and that 54% were bilobular. A thrombus (well-contoured echogenic mass) was described with 100% sensitivity, 99% specificity, and 95% predictive positive value in the study of Manning et al; the prevalence of the LAA thrombus is approximately 15% in AF (48 h). In patients with recent embolic events, the prevalence of thrombi was 14% if the AF began < 3 days before TEE, and 27% if it started > 3 days prior to TEE (Fig 1).

Two-dimensional (2-D) images of the appendage can help diagnose a thrombus but also a SEC. When blood flow velocities are reduced in cardiac chambers and especially in the LAA, “smoke-like” echoes swirling in the cavity may be seen. Currently, SEC is still described qualitatively (Table 1). Although it remains an “eye-ball” judgment, dependent on echo-gain control, backscatter signal information has been tested in an attempt to quantify SEC. Results have been published regarding the atrium and LAA. However, this signal is not characterized on all echo platforms, and its evaluation requires complex and time-consuming postprocessing. With respect to imaging LAA, few studies by MRI and spiral CT scan have been reported on detection of LAA thrombus and SEC. Although TEE is considered the “gold standard” for excluding LAA thrombi, in some patients dense SEC and artifacts may hamper the identification or exclusion of thrombi. New echocardiographic modalities may improve current multiplane 5- to 7.5-MHz TEE evaluation. Tissue Doppler imaging (TDI) has been reported to help pinpoint an abnormal echo-density signal characterized by a different motion phase as compared with the surrounding tissue using 2-D or M-mode TDI. Injection of a

### Table 1—Qualitative Definition of the SEC

<table>
<thead>
<tr>
<th>Score</th>
<th>Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absence of echogenicity</td>
</tr>
<tr>
<td>1+</td>
<td>Mild (minimal echogenicity only transiently detectable with optimal gain settings during the cardiac cycle)</td>
</tr>
<tr>
<td>2+</td>
<td>Mild to moderate (transient SEC without increased gain settings and more dense pattern than 1+)</td>
</tr>
<tr>
<td>3+</td>
<td>Moderate (dense swirling pattern throughout the cardiac cycle)</td>
</tr>
<tr>
<td>4+</td>
<td>Severe (intense echodensity and very slow swirling patterns in the LA appendage, usually with similar density in the main cavity)</td>
</tr>
</tbody>
</table>

*From Fatkin et al.*

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**Figure 1.** Top left, A: Example of a polylobed LAA with severe SEC and the corresponding pulsed Doppler of LAA flows. Top right, B: Second example of polylobed LAA. Bottom left, C: Example of an LAA ligated by the surgeon at the time of plasty of the mitral valve; the ligature is incomplete and there is still flow between the LAA and the LA cavity.
contrast agent may also enhance detection of the complex borders of the LAA\textsuperscript{18,19} (Fig 2). A preliminary study\textsuperscript{18} indicates that color TDI with a contrast agent may improve understanding of LAA structure and function as well as quantify the SEC and subsequent thrombogenic risk.

Three-dimensional echocardiographic imaging should improve the delineation of LAA complexity and thus compensate for current limitations in the measurement of LAA ejection fraction by 2-D planimetry.\textsuperscript{20} Currently, the size of the LAA is considered (not the ejection fraction) in embolic-risk scores such as the Stoke Prevention in Atrial Fibrillation (SPAF) II study\textsuperscript{21} (LAA area > 6 cm\textsuperscript{2} a risk factor for arterial embolic events).

During TEE, SEC and thrombi may also be found in the right atrial appendage. In the study by Bashir et al,\textsuperscript{22} SEC and thrombi were found with 14\% and 1\% prevalence, respectively.

The feasibility and the accuracy of transthoracic Doppler LAA recording have also been reported.\textsuperscript{23} However, data are scant, although it seems possible to measure LAA emptying flow approximately. SEC or thrombi may not be detected (Fig 3). Furthermore, this type of transthoracic examination misses other sources of cardioembolic event (aorta, valves, interatrial septum). The early report from the study by Sallach et al,\textsuperscript{24} assessing the interest of TTE for assessment of cardiac embolic risk, showed that the pulsed TDI findings on the LAA were well correlated with LAA SEC, sludge, or thrombus as assessed by TEE.

**Pulsed Doppler Study of the LAA**

There is no real consensus with regard to the position of the pulsed Doppler index in the LAA. The mouth of the appendage is the most widely reported. It is essential to reduce the gain and to avoid the disturbing spectrum of LAA wall motion, characteristic of low speeds.\textsuperscript{25} The pulsed Doppler examination of the LAA should be done at least twice: in an upper plane at 0° and in the middle plane at approximately 90°. In case of sinus rhythm (SR), four waves can be described (Fig 4, 5):

1. The early diastolic emptying flow: the so-called “e”-wave. After the mitral E-wave, the outflow velocities are often low. The pathophysiology is caused by a combination of passive compression induced by left ventricular (LV) relaxation and a passive suction effect related to opening of the mitral valve and the early diastolic rapid emptying of the left atrium. The importance of this passive e emptying wave is indicated by its preponderance in LAA dysfunction as in the “post-AF stunning period.”\textsuperscript{26}

2. The LAA intrinsic late diastolic contraction: the so-called “a”-wave, positive flow (directed toward the transducer) appears just after the ECG P-wave. This
essential wave occurs simultaneously with the mitral inflow A-wave. There is no correlation between the velocities of these a- and A-waves: a is the largest wave in SR and normal LAA function. Its measurement has been demonstrated to be reproducible and correlated with LAA ejection fraction.

3. LAA filling causes an early systolic negative wave following the a-wave. These waves have been less extensively explored than the emptying waves. Most of the time, their velocities are correlated with those of the emptying wave.

4. The systolic reflection waves: if the heart rate is slow enough and if intrinsic LAA function is normal, a variable number of passive LAA inflows and outflows can be observed after the filling wave.

**Effect of Age, Sex, Heart Rate, and LA Function**

If heart rate increases, e-waves and a-waves tend to merge, followed by a slightly higher emptying velocity.

**Assessment of LAA Function in SR Patients: Is It a Surrogate for the Evaluation of Overall LA Function?**

Active (a-wave) and passive (e-wave) emptying LAA flows decrease gradually with age. A decrease of 4.1 cm/s for every decade increase in age has been described for the a-wave. By contrast, body surface area, LA size, LV mass, or a history of hypertension showed no significant association with LAA flow velocities in healthy patients.

In healthy individuals, peak LA emptying velocity (a-wave) is reported to be approximately 50 to 64 cm/s. A higher SR heart rate was shown to increase the LAA a-wave until it reached a critical frequency and a plateau. In clinical practice, it should be borne in mind that women have lower active LAA emptying velocities. Thomas et al reported that the atrium and the LAA compensate for the age-induced changes in LV diastolic properties by increasing active atrial contraction (a-wave). Hondo et al in an animal model and Tabata et al in humans demonstrated an inverse relationship between LA filling pressure and LAA emptying function (inverse correlation between capillary wedge pressure and LAA active emptying a-wave). Because of its compliance, the LAA might act as a beneficial modulator of LA pressure. Details on the influence of LA pressure on LAA function will be discussed in the section on chronic heart failure.

**AF**

Two types of emptying wave can be observed. During systole, a high-frequency, low-amplitude wave, extremely variable from beat to beat, is observed (Fig 4, 5). The frequency of these waves is linked to the electrophysiologic activity of the atrium (ECG f-waves) [Fig 4, 5]. Before the QRS (early diastole), one or several higher velocity waves can be observed. These passive diastolic emptying e-waves certainly play the main role in preventing thrombus formation in AF, when LAA function is depressed (AF or postarrhythmia reduction for instance). The diastolic emptying flow is greater because of valve opening and also because of a “pouch-effect” or suction effect due to LV relaxation. To our knowledge, no study has yet specifically addressed the issue of the impact of LV diastole on LAA function, SEC, or on the risk of thrombus formation. Nevertheless, we believe that it is preferable to measure 5 beats or 10 beats of diastolic LAA emptying waves instead of 5 to 10 consecutive fibrillatory emptying waves (high frequency, low and irregular amplitude, and thus with no real hemodynamic significance), as is often
proposed. Although the amplitude of the fibrillatory f-wave is too small to provoke any mechanical event, it remains the marker of AF cycle length.\textsuperscript{34}

Data from the SPAF study\textsuperscript{1} indicated that LV dysfunction was an independent predictor of thromboembolism and thus influences strong LLA function.\textsuperscript{35,36} The type of atrial arrhythmia significantly influences LAA flows. Even if the average emptying flow is weaker in AF than in SR, LAA emptying velocity has been reported to be greater in atrial flutter than in AF, although it is not normal. A thrombus (1.6%) or a SEC (13%) may be found in patients with atrial flutter, and anticoagulation is indicated.\textsuperscript{37} Grimm et al\textsuperscript{38} attempted to characterize LAA flows and function by Fourier analysis, comparing a flutter group and an AF group with a normal population. They described different frequency spectra for SR, flutter, and AF, with the patterns characteristic of each electrophysiologic status. Typically, AF had a frequency in the 6- to 8-Hz range, whereas flutter had a frequency in the 4-Hz range, and 1 Hz in the normal population. Furthermore, there was a greater subharmonic modulation in AF. In 47 chronic AF patients followed up by TEE for 13 ± 7 months (± SD), these authors found a progressive decrease in LAA emptying flow and a strong correlation between SEC and LAA function as assessed by pulsed Doppler. SEC diagnosed at the first TEE was still observed during the follow-up period.\textsuperscript{39} The database of the Cleveland Clinic Foundation showed a 1.9% prevalence of thrombi in the LA cavity. The incidence of LAA thrombi was 6.6-fold that of LA cavity thrombi. AF was present in most patients with thrombi in the LAA. Anticoagulation during 47 ± 18 days was associated with thrombus resolution in 80.1% of the patients during follow-up TEE, although there was limited additional benefit from further anticoagulation. SEC has been reported as a determinant risk factor for clot independently of the anticoagulation status of patients.\textsuperscript{40,41} SEC is usually found in AF; it was reported in 87.5% of AF patients before electrical cardioversion.\textsuperscript{42}

**Figure 4.** Representation of LAA pulsed Doppler ECG recording in SR (left, A) and AF (right, B). The mitral inflow recorded in pulsed Doppler, the LV outflow tract flow, and the pulmonary vein flows are also presented on these two diagrams to illustrate their timing. e = passive LAA emptying flow; a = active LAA emptying flow; f = passive LAA emptying flow in AF; E = early diastolic mitral inflow; A = late-diastolic mitral inflow; S = systolic pulmonary venous flow; D = diastolic pulmonary venous flow; Arev = active reversal wave recorded in the pulmonary vein corresponding to the active contraction of the atrium.
Analysis/Overview of Different Pathologic Conditions

Congestive Heart Failure

In patients with heart failure, the LAA has a significant role as it contributes to left ventricular filling and AF is prevalent in this population. In chronic congestive heart failure (CHF), there is a negative correlation between LAA emptying velocity (and LAA ejection fraction) and LV end-diastolic pressure. An LAA active emptying velocity predicted LV end-diastolic pressure with a sensitivity of 72.7%, a specificity of 92.9%, and positive and negative predictive values of 88.9% and 81.3%, respectively.43,44

LAA distension rather than the increase in LA pressure appeared to be the predominant cause of the elevation of circulating atrial natriuretic peptide, which is regarded as a marker of CHF severity with prognostic significance.45 In a dog model of heart failure, infusion of phenylephrine (inotropic stimulation) had no impact on LAA function.44 Conversely, volume infusion decreased the early to late emptying ratio via an increase in peak late emptying velocity (a-wave; the active one) and a decrease in peak early emptying velocity (e-wave, the passive one). In view of the Starling law, these observations point to the importance of a reservoir function of the LAA in pathologic conditions such as CHF.47 In a multivariate model, the early emptying velocity was strongly correlated with the time constant of LV relaxation and the LV end-systolic dimension, whereas late emptying velocity was strongly correlated with maximum rate of rise of LV pressure and fractional shortening.46,47

Thus, being more compliant than the left atrium, the LAA tends to modulate LA pressure in heart failure but remains strongly dependent on ventricular function.48 The study by Cleland et al49 was designed to find out whether antithrombotic therapy was as effective and safe as warfarin in CHF patients, and failed to demonstrate any advantage of one treatment over the other. The disappointing results of the study by Cleland et al49 might encourage new strategies, using echocardiography to assess the thrombotic risk before prescribing warfarin or an antiaggregant treatment for patients in SR suffering from systolic heart failure. Although systematic TEE would be too aggressive, a transthoracic approach might be envisaged, especially if the preliminary results of the study by Sallach et al24 are confirmed.

Mitral Stenosis

Mitral stenosis (MS) causes a substantial increase in preload and so enlarges the atrium and the LAA. We thought it of interest to examine LAA behavior in this extreme hemodynamic condition.50 A comparison of LAA function in mitral regurgitation and MS populations with the same degree of LA dilation revealed that MS resulted in a significantly greater LAA dysfunction irrespective of LV function. Passive and active flows are frequently unrecordable before mitral commissurotomy but reappear immediately after valve opening and so after LA pressure decrease.51 TEE examinations early after balloon mitral valvulotomy have demonstrated recovery of LAA function within 48 to 72 h after the procedure; however, less impressive results were observed after mitral valve replacement.52

LA function is difficult to assess noninvasively, and several studies29,37,50 have evaluated LAA function as a surrogate. In patients with MS, it seems to be sufficient. However, LAA contraction velocities poorly correlate with multiple LA variables and should not therefore be used as surrogates for global LA function.24 LA and LAA are two distinct histologic structures, and thus might have quite different behaviors.53 Further studies using the TDI properties may help characterize LAA dysfunction, especially in patients with mitral valve disease.54

There are few data regarding mitral regurgitation. Experience and literature data accredit the general opinion that mitral regurgitation increases LA pres-
sure and thus dilates the LAA, but also tends to wash out the whole LA and LAA cavities in proportion to the extent of the regurgitation. Thus, the risk of thrombus formation is low in significant mitral regurgitation. Guidelines do not exclude mitral regurgitation patient with AF from patients who need warfarin.

**Time Period After Atrial Arrhythmia Reduction: “Stunning” Time**

The recent review of Khan provides an overview of the basic and clinical considerations concerning atrial stunning. There is a decrease in active LAA emptying immediately after conversion of AF or atrial flutter to SR. This is the LA and LAA “stunning” phenomenon, a transient impairment of atrial mechanical function. This decrease in functional status of the LAA resembles the LAA SEC and thrombus formation following cardioversion (Fig 6, 7). The degree of LAA stunning and its duration are particularly unpredictable and are poorly understood. This stunning phenomenon appears to be partially influenced by the method of cardioversion. Although pharmacologic conversion and radiofrequency ablation are reported to provide less sustained LAA stunning, the extent of stunning does not differ significantly between high-energy external electrical and internal low-energy shock cardioversion. A study using a new technology combining TEE and esophageal probe for low-energy bi-phasic cardioversion observed similar LAA stunning. In a dog model, an exclusively passive LAA emptying flow with a slow progressive recovery of the active a-wave just after electrical cardioversion was observed. It has also been suggested that surgical or transvenous interventional radiofrequency ablation procedures for AF or atrial flutter provide a quicker recovery of LA function than previous treatments. Yamada et al demonstrated the potential interest of vitamin C, while Sanders et al found that atrial pacing or isoproterenol infusion could attenuate the stunning phenomenon following reduction of short-duration AF, although this was not confirmed in the long-duration AF population. This might indicate that the stunning phenomenon is a functional and reversible remodeling for short-term atrial arrhythmia but is due to a structural remodeling for long-duration AF. The duration of LAA stunning therefore remains variable and rather unpredictable. It requires further study.

**Prediction of Cardioversion Success Rate in Conversion of AF to SR**

LAA emptying velocities > 20 cm/s are associated with a statistically superior rate of immediate success of restoration to SR. An international, prospective, multicenter study including 408 patients found by multivariate logistic regression analysis that three parameters were independent predictors of the success of cardioversion: (1) a duration of AF < 2 weeks; (2) a mean LAA flow velocity > 31 cm/s; and (3) a LA diameter < 47 mm.

**Surgical and/or Percutaneous LAA Closure**

LAA ligation is a routine procedure in the surgical treatment of the mitral valve. The objective is to...
reduce the incidence of LAA thromboembolic events. However, the surgical closure might not be as safe as expected (Fig 1).\textsuperscript{71} In 36\% of the cases, exclusion of the LAA was incomplete. Moreover, 50\% of these patients had a SEC and a partially excluded LAA thrombus, and thromboembolic events were observed in 22\% of cases over a mean study period of 64 months (no control group reported).\textsuperscript{71} This important observation will need to be confirmed. The reservoir function of the LAA has also been demonstrated, and this observation was supported by the significantly higher concentration of atrial natriuretic factor (atrial natriuretic peptide) in the appendage than in the rest of the atrium.\textsuperscript{45} However, the clinical hemodynamic or rhythmic impact of LAA ligation remains unknown. Tabata et al\textsuperscript{73} demonstrated a significant decrease in LA reservoir function after LAA clamping in 15 patients, but the clinical consequence of LAA suppression on the outcome of the patients was not mentioned. In a population of 205 patients with mitral valve prostheses, Garcia-Fernandez et al\textsuperscript{73} demonstrated the clinical value of LAA surgical ligation in patients with a high risk of late thromboembolism. A recent publication by Hanna et al\textsuperscript{74} reported the safety and feasibility (technique of the device implantation very close to the one use to close interatrial communication) of the device with no significant effect on the structure and function of the pulmonary vein and left atrium.\textsuperscript{74}

In common with the monocentric study of Mügge et al,\textsuperscript{75} the SPAF III study\textsuperscript{76} demonstrated a strong correlation between clot, SEC, and LAA emptying flow velocities < 20 cm/s or 25 cm/s. However, SEC was noted in 30\% of patients with LAA emptying flows < 20 cm/s and even in 5\% of those with LAA emptying flows > 30 cm/s. Moreover, there was 17\% incidence of thrombus in patients with LAA flows < 20 cm/s, and a clot was still found in 6\% of patients with LAA flows > 30 cm/s. The predictive value of LAA emptying flow velocities < 20 cm/s has also been demonstrated for cerebrovascular embolic risk. In the SPAF III study,\textsuperscript{1} there was a 2.6-fold increase in risk for this type of depressed LAA function.

**CONCLUSION**

LAA function studies during routine TEE and perhaps also during transthoracic echocardiography provides insight into the hemodynamic state of the heart and thromboembolic risk. The presence of a thrombus should be excluded, and a SEC must be characterized. New methods such as TDI and contrast agent injection are emerging. Pulsed Doppler assessment of LAA function might be helpful to adapt the anticoagulation therapy. It is now established that TEE imaging is a safe way of proceeding to AF conversion without prolonged anticoagulation. Further studies should help adapt postcardioversion therapy to the echographic findings and would undoubtedly improve our understanding of LAA physiology.

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