Left Atrial Appendage: Anatomy, Function, and Importance in Thrombus Formation

Apêndice Atrial Esquerdo: Anatomia, Função e Importância na Formação de Trombos

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Introduction

The left atrial appendage (LAA) is an extension of the left atrium (LA) and has complex anatomical structure and unique pathophysiological properties. The LAA functions as a decompression chamber during left ventricular (LV) systole and under increased left atrial pressure conditions. Despite previously being considered a relatively insignificant portion of the cardiac anatomy, the LAA has been highlighted as an important structure involved in the genesis of thrombus formation and thromboembolic events. With the recent development of percutaneous closure devices, LAA morphology assessments have become increasingly important. This article aims to describe LAA anatomy and morphology, function assessment parameters, thrombus diagnostic challenges, and the main imaging modalities, particularly transesophageal echocardiography.

LAA anatomy

The LAA is a long, thin tubular structure with a narrow base that originates from the LA body (Figure 1).[1] Macroscopically, the LAA is visualized at the left border of the heart between the LV and the pulmonary veins.[2,3] It commonly extends between the anterior and lateral LA walls. Its tip can be variously positioned, most commonly being in the anterosuperior direction and overlapping the left border of the right ventricular outflow tract or the pulmonary trunk and the main branch of the left coronary artery and the circumflex artery, but it can also be in the lateral or posterior direction, reaching the transverse sinus of the pericardium in some patients.[2] Anatomically, the superior portion of the LAA is closely related to the pulmonary artery, while its inferior portion is close to the free LV wall.[4]

The LAA ostium (LAAO) is separated from the left pulmonary vein orifices by the left lateral crest.[5] On the other side, the smooth LA wall separates the LAAO from the mitral annulus.[2] A narrowing that marks the orifice of the appendix is visualized in the transition between the smooth LA endocardium and the wrinkled LAA surface. Morphologically, the LAAO can be elliptical (68.9%), while its long axis is usually oriented obliquely to the mitral annulus in a foot-like (10%), triangular (7.7%), or round (5.7%) shape.[6–8]

The LAA passes through a narrowed region before its body opens up.[2] In this region, one to four lobes can be observed, and a multilobulated LAA (with two or more lobes) was seen in 80% of patients in a relevant study by Veinot JP et al. of 500 postmortem hearts.[9] That study reported the frequency of one, two, three, and four lobes as 20%, 54%, 23%, and 3%, respectively, not corroborating a more recent postmortem study in which two lobes were observed in 64.3% and three lobes in 35.7% of specimens.[8] The quantification of the number of lobes is important because a greater number of lobes is associated with the presence of thrombus regardless of clinical risk and blood stasis.[10,11]

The LAA presents great anatomical diversity. Wang et al.[7] established the classification used to categorize four morphological types, with the "chicken-wing" shape being the most common (48%), followed by the "cactus" (30%), "windsock" (19%), and "cauliflower" (3%) shapes.[12] These categories are related to the risk of clot formation, with the cauliflower shape being apparently more associated with embolic events.[12] This morphology is also associated with lower blood flow velocity,[1] a greater predisposition to blood stasis, while the chicken-wing shape is associated with a lower risk.[13] A Czech study by Stefan et al. related the cauliflower and chicken-wing shapes with a higher risk of silent cerebral ischemia.[14] However, this classification is limited by its subjective and observer-dependent nature as well as the possibility of overlapping morphologies according to viewing angle.[2,15] Other factors also influence the risk of thromboembolic events,[16,17] including a smaller orifice diameter, higher number of trabeculations,[18] and higher number of lobes.[10] Another study[11] highlighted that number and size of lobes and their orifices may be more important factors in risk of thromboembolic events than LAA shape.

Unlike the LA, whose wall is smooth, the internal LAA surface is trabecular, presenting muscle bundles[9] called pectineal muscles that form complex indentations (Figure 1). These muscle bundles resemble feather- or fan-shaped palm leaves.[19] Larger muscle groups can be confused with thrombi or intra-atrial masses.[9] The LAA also presents great size variability by sex (greater in men), age (growing about 0.20 cm^3 per decade),[20] and the presence of atrial fibrillation.

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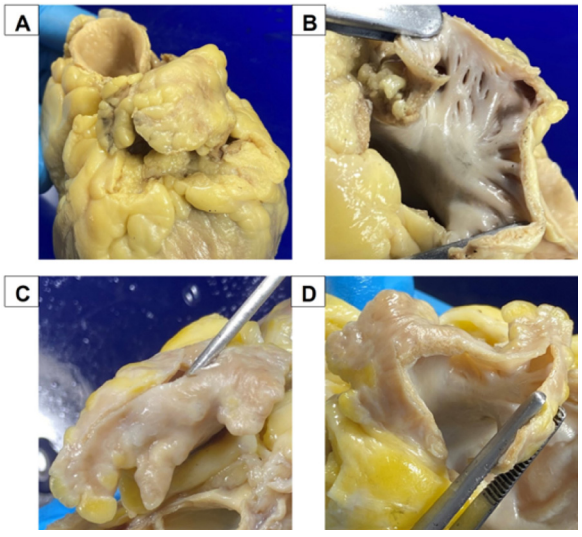


Images acquired in collaboration with anatomopathologist Geraldo Brasileiro Filho.

Figure 1 – *Macroscopical view of the LAA. Images made from explanted hearts showing the external and internal aspect of the LAA. (A) External view of a one-lobe appendage. (B) Internal view of a one-lobe appendage. (C) External view of a multilobed appendage. (A) Internal view of a multilobed appendage.*

LAA dimensions are significantly more voluminous and have larger orifices in patients with atrial fibrillation than in those with sinus rhythm.

LAA function

The LAA has both mechanical and endocrine functions.[21] Its compliance is greater than that of the rest of the atrium; therefore, it can modulate the pressure in the chamber and compensate for volume overloads and pressure increases. In addition, the appendix has the highest concentration of atrial natriuretic peptide (ANP) granules in the LA (about 30%).[4,22,23] Cardiomyocyte distention stimulates ANP secretion; therefore, as it is more compliant and concentrates the largest amount of ANP, the LAA is more sensitive to volume and pressure changes and has greater control of decreased blood pressures and increased heart rate, diuresis, and natriuresis.[4,23,24]

The LAA performs active contraction,[4] and its flow velocity can be quantified by pulsed Doppler. In most patients undergoing transesophageal echocardiography (TEE), this is a four-phase flow (Figure 2).[4,25,26] The first wave corresponds to the outflow caused by appendage contraction at the end of ventricular diastole. The second wave represents the antegrade LAA filling flow during atrial diastole. The third wave has positive and negative components that reflect the mechanical waves at ventricular end systole (in this phase, numerous patterns of low-amplitude positive and negative waves are described).[26] And finally, outflow from the LAA occurs during the rapid ventricular filling phase. The decreased flow velocity in the LAA relates to the presence of spontaneous contrast (SC), sludge, and thrombus.[21,25,27]

LAA function can be assessed by several parameters. LAA filling and emptying velocities by pulsed Doppler express the LAA contractile function. In addition, LAA area, volume, and ejection fraction measurements by different methods reflect LAA function.

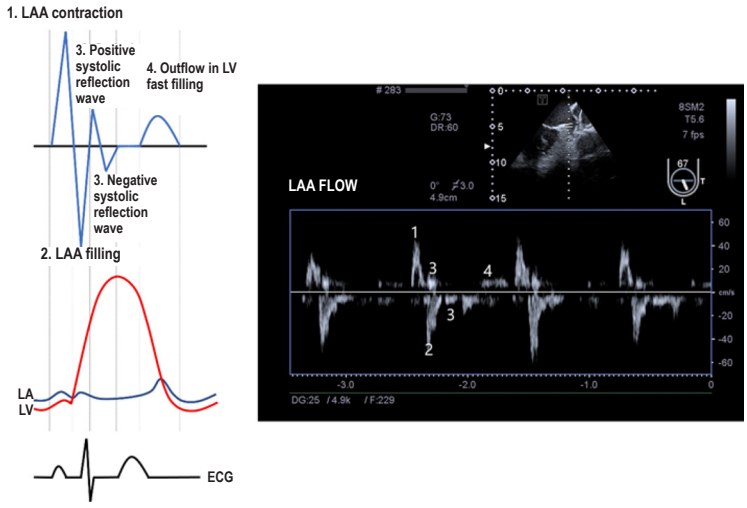
Blood stasis and thrombus formation

LAA contractility changes can lead to thrombus formation and subsequent thromboembolic events[27] regardless of the presence of atrial fibrillation (AF). AF generally presents with decreased LAA contractility, decreased blood flow velocities, and LAA dilation.[28,29] The AF-related remodeling process makes the LAA function a static pocket, resulting in stagnation and thrombosis.

Approximately 75% of patients with cardioembolic episodes are estimated to have emboli arising from the LAA. LAA thrombi are present in up to 14% of patients with acute AF (<3 days).[30] Thrombus formation can develop even in AF patients receiving therapeutic anticoagulation therapy. A previous study showed that 1.6% of patients treated with anticoagulants for 1 month had echocardiographic evidence of a thrombus in the LAA.[31]

Limited data suggest that LV failure and increased LV end-diastolic pressure may also be risk factors for LAA thrombus in the absence of AF. Vigna et al.[36] identified LAA thrombi in eight of 58 patients with dilated cardiomyopathy and sinus rhythm. Consequently, the risk of thrombus formation in the LAA appears to be related to LAA dysfunction resulting from increased filling pressures regardless of cause.

The complex interaction of atrial endothelium, blood constituents, and blood stasis (i.e., the components of Virchow's triad) results in the formation of activated platelet aggregates and leukocytes[32] or fibrinogen-mediated erythrocyte aggregates[33,34] that present as spontaneous dense echocardiographic contrast or "smoke." These aggregates can progress to sludge and, eventually, thrombus.[2,35]



Adapted from Delgado et al.[26] LA: left atrium; LV: left ventricle.

Figure 2 – *Comparison between the flow pattern in the LAA in sinus rhythm, the cardiac cycle, and the electrocardiogram (ECG).*

Imaging methods for assessing the LAA

Transesophageal echocardiography

TEE is the method of choice for studying LAA anatomy and function. Its sensitivity and specificity for detecting LAA thrombi compared to those observed intraoperatively are 92% and 98%, respectively,[2,37,38] with negative and positive predictive values of 100% and 86%, respectively[38]. The absence of a thrombus confirms that it is safe to proceed with cardioversion, with a low rate of thromboembolic events (0–0.8%) in adequately anticoagulated patients.[39,40]

A complete LAA assessment should include LA, LV, and mitral valve imaging associated with a detailed assessment of LAA morphology, contraction, and flow velocities using two- and three-dimensional (3D) echocardiography.[2] LAA assessments can be started using a four-chamber section; however, as it is a lateral structure, the probe must be rotated counterclockwise and flexed to bring it to the center of the screen. Also, using a two-chamber section, the LAA can be zoomed or screen depth can be reduced to increase assessment accuracy.[41] Two-dimensional TEE provides excellent LA and LAA characterization due to the anatomical proximity of these structures to the esophagus. Despite the LAA being a narrow tubular structure with a complex anatomy, thrombi within it can be identified with satisfactory accuracy by TEE. However, assessment sensitivity decreases in cases of small thrombi or those located within a lateral lobe.

Functional Doppler assessment is routinely used to improve LAA analyses (Figure 3). The pulsed Doppler should be placed at 1–2 cm from the LAAO. LAA flow velocity measured by pulsed Doppler is an indicator of risk of thrombus formation (risk increases as velocity decreases).[2] Velocities < 40 cm/s are associated with an increased risk of stroke and the presence of SC,[42] with decreasing velocities of <20 cm/s being associated with thrombi in the LAA and a higher incidence of thromboembolic events.[43–47] Velocities < 40 cm/s require meticulous LAA assessments before cardioversion or interventions involving the LA and LAA.

LA thrombus is defined as an echogenic mass in the LAA or LA distinct from the LA endocardium or pectineal muscles (Figure 4).[38] Several differential diagnoses and thrombi misinterpretations should be considered, including acoustic shadowing of the ligament of Marshall, pectineal muscles, or non-differentiation of sludge and dense spontaneous echogenic contrast.[2,48]

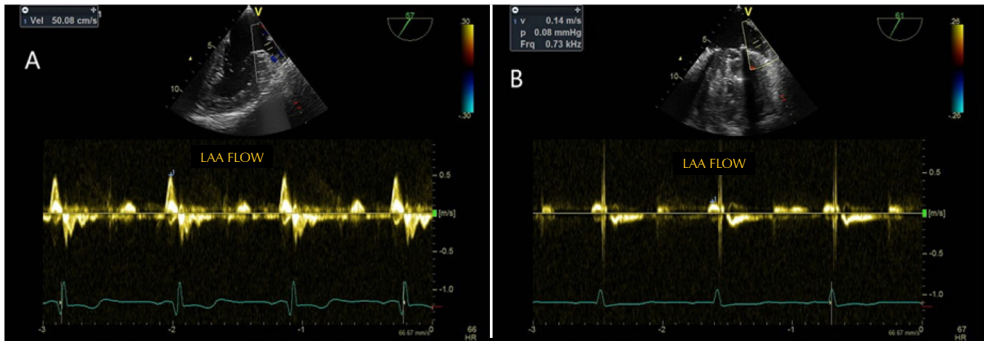
In cases in which the LAA images are suboptimal, ultrasound contrast agents help improve LAA visualization. The use of contrast eliminates many artifacts and usually demonstrates complete LAA opacification or filling defects.[49,50]

LAA echocardiographic imaging is operator-dependent and, therefore, has a learning curve. Interobserver variability is an important limitation of this investigation since interobserver disagreement rates can reach 22% in the diagnosis of thrombus.

Challenges in diagnosing LAA thrombus

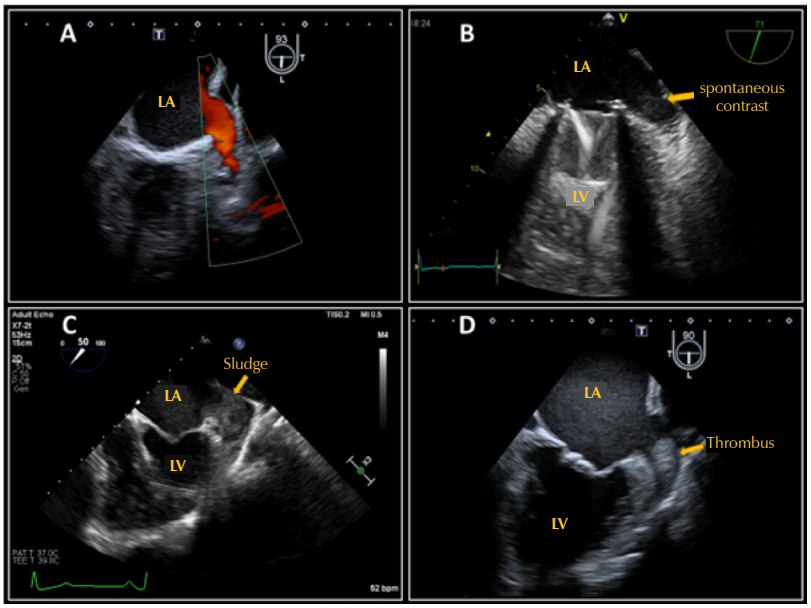
Echocardiographic evaluation of the LAA requires careful analysis by the echocardiographer. In some situations, LAA imaging misinterpretations can lead to hasty decisions. Exuberant pectineal musculature or appendage lobes can be interpreted as thrombi, thereby resulting in the use of unnecessary anticoagulant therapy (Figure 5). Thrombus misdiagnosis also leads to suspended percutaneous procedures, such as LAA, patent foramen ovale, and atrial septal defect occlusion, MitraClip implantation, AF ablation, and mitral valvuloplasty with a balloon catheter. Such procedures involve manipulation of catheters inside the atria and, consequently, increase the risk of embolization.

Ruling out LAA thrombi using TEE may enable early and safe cardioversion without the need for prolonged



AAE: apêndice atrial esquerdo.

Figure 3 – *TEE demonstrating in (A) the normal velocity (50 cm/s) flow in the LAA of a patient in sinus rhythm, with an LA of normal dimensions and without the presence of SC. In (B), the reduced velocity (14 cm/s) flow in the LAA of a patient in the postoperative period of mitral valve replacement (mechanical prosthesis), in sinus rhythm, with dilated LA and presence of SC in the LAA.*



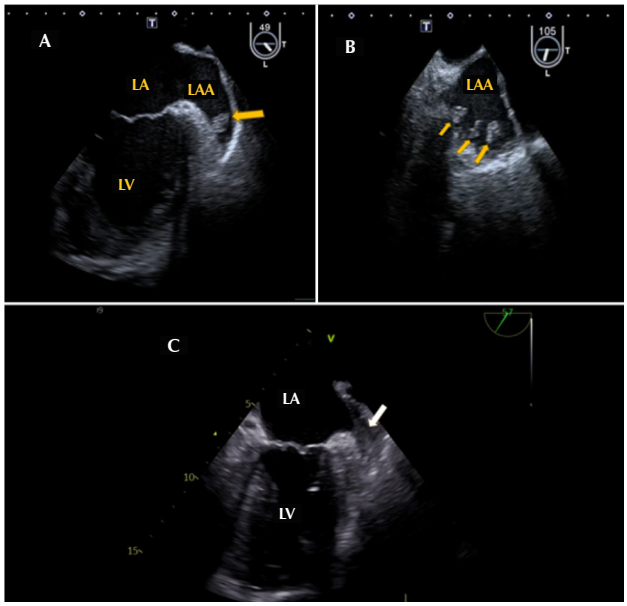
LV: left ventricle. LA: left atrium.

Figure 4 – *TEE showing the LAA filled in by color Doppler in image A. Images B and C show the presence of SC (B) and sludge (C) inside the LAA, respectively. In image D, the arrow indicates a thrombus in the LAA and the presence of SC in the LA.*

previous anticoagulation.[38,51] Thrombi within the LAA must be differentiated from the pectineal muscles, reverberation artifact originating from the coumadin ridge, septa between multiple lobes,[52] SC, and sludge.

Thrombi are often located at the distal end of the LAA, almost always confined to its lumen and adherent to its walls. They have independent movement and echogenicity patterns as well as uniform consistency and textures that differ from those of the LAA wall. Their morphology varies, but they are generally rounded (Figure 4). They are often associated with the presence of SC within the LA.

Reverberation artifacts are also found within the LAA, being located at a position twice the distance from the transducer to the coumadin ridge. Its mobility totally depends on the coumadin crest movement. Its morphology is compatible with that of the object or structure that causes the artifact and is not related to the presence of SC in the LA. Reducing gain and using other imaging planes are strategies that the echocardiographer can use to avoid artifact formation. On the other hand, the stepped appearance and the position at a doubled distance reinforce the presence of a reverberation artifact inside the LAA. The echocardiographer should be



LV: left ventricle; LA: left atrium; LAA: left atrial appendage.

Figure 5 – *Mid-esophageal slice TEE at 50º showing a mass within the LAA that can be easily interpreted as a thrombus (arrow) (A). Image of the same patient at 105º, clarifying that the mass is probably the three LAA lobes (B). Image C shows a reverberation artifact (arrow) produced by the coumadin ridge and visualized inside the LAA.*

aware of the presence of a prominent coumadin ridge, which can also be misdiagnosed as a thrombus.

The pectineal muscles, in turn, are confined to the body of the LAA. Their mobility follows LAA movement, and they have identical echogenicity to that of the LAA wall. They are not related to the presence of SC.

SC, also known as smoke, is a swirling mist of varying density that reflects the low blood flow velocity (Figure 4).[53] It can be classified into four groups (1 to 4) by intensity, location, and presence of a vortex (movement) as proposed by Fatkin et al.[42] (Table 1). However, SC quantification in clinical practice is difficult and depends on image quality, gain settings, and operator experience.

SC is reportedly noted in up to 60% of patients with AF.[54] Aspirin and warfarin therapy does not appear to affect the presence of SC in the LA.[55] Although patients with dense SC visualized in the LAA have a stroke rate of 18.2% per year if not treated with warfarin and a risk of stroke of 4.5% per year despite dose-adjusted warfarin, the presence of an LAA thrombus triples the overall rate of stroke.[40]

Sludge, a dynamic fluid of gelatinous echogenicity with no well-defined mass, is present throughout the cardiac cycle.[48] It is often difficult to differentiate between sludge and thrombus. Sludge represents a stage after SC prior to thrombus formation that may have prognostic significance.[56]

Other imaging methods for assessing LAA

Transthoracic echocardiography

Transthoracic echocardiography (TTE) has a limited capacity to identify or exclude thrombi in the LA and LAA, with a reported sensitivity of 40–60%, mainly due to poor visualization of the LAA, where most atrial thrombi are located (Figure 6). In this sense, the use of harmonic images and the administration of ultrasound contrast agents can increase its ability to detect intracavitary thrombi.[37,38,48]

Contrast echocardiography

Since the late 1990s, ultrasound contrast agents have been administered to improve the visualization of endocardial borders, including an improved LAA assessment. Recent studies of LA and LAA enhanced interrogation techniques reported statistically significant improvements in dimensional measurements and emptying characteristics. In cases of suboptimal LAA images, contrast agents help improve LAA visualization, eliminate artifacts, and reveal body filling defects.[2,57]

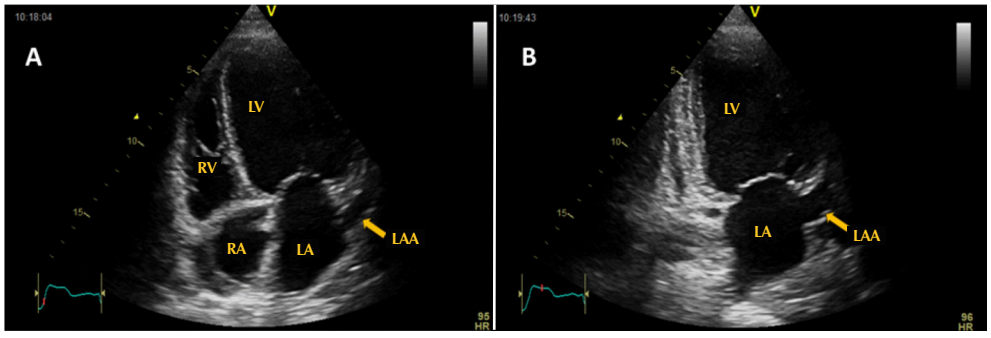
Contrast agents improve the delineation of cardiac chamber endocardial borders, but their use has not been implemented in clinical routine to detect or exclude thrombi. Several reasons explain this circumstance, such as the use of predictive markers of thrombus formation such as pulsed Doppler of LAA blood flow and SC assessments; the low prevalence of thrombus in the LAA (5–13% in patients with AF but without therapeutic anticoagulation); and the even lower risk of an embolic event. In addition, the use of ultrasound contrast increases the time required to perform the test as well as its cost.[48,58]

The ability of the contrast agent to completely opacify the LAA even in the presence of artifacts during native imaging minimizes the false identification of thrombi and allows the delineation of atrial thrombi, reducing the amount of inconclusive TEE and improving the echocardiographer's degree of interpretive

Table 1 - Classification of spontaneous contrast as proposed by Fatkin et al.

Grade	SEC	Description
0	None	Absence of echogenicity
1+	Mild	Minimal echogenicity located in the LAA or sparsely distributed in the LA main cavity that may be only transiently detectable during the cardiac cycle
2+	Mild to moderate	Swirling pattern denser than 1+ but similarly distributed, detectable without increased gain settings
3+	Moderate	Moderate and dense swirl in the LAA usually associated with lower intensity in the main cavity; may fluctuate in intensity but is constantly detectable throughout the cardiac cycle
4+	Intense	Intense echogenicity and very slow swirl patterns in the LAA, often with similar density in the main cavity
Sludge	Intense	Prethrombotic state can be defined as gelatinous echogenicity without a well-defined mass; present throughout the cardiac cycle

SEC, spontaneous echogenic contrast.



LV: left ventricle; RV: right ventricle; LA: left atrium; RA: right atrium; LAA: left atrial appendage.

Figure 6 – *TTE showing the LAA in apical four-chamber (A) and two-chamber view (B).*

confidence. However, in cases in which non-contrast images are diagnostic and in the absence of SC evidence, the use of contrast fails to improve diagnostic confidence.[50,57]

Three-dimensional echocardiography

The development of 3D TEE improves the ability to assess the LAA, allowing a selective perspective of its anatomy and better discrimination between artifacts, masses, and thrombi (Figure 7). The 3D method allows a more comprehensive assessment of multiple LAA lobes, which can be located in different planes, as well as a more accurate estimate of its geometry, size, and function with better distinction between pectineal muscles and thrombi.[26]

Data remain limited regarding the sensitivity and specificity of 3D TEE for thrombus detection in the LAA. However, with recent advances in percutaneous device therapy for LAA closure, 3D TEE has become important for planning and guiding interventions.[2]

Intracardiac echocardiography

Intracardiac echocardiography (ICE) is an alternative imaging method when TEE is unavailable or inconclusive. ICE can provide multiple views and detailed LAA images to enable the reliable diagnosis of the presence of thrombus.[3]

Although it is less sensitive than TEE for thrombus detection, it can be a complementary method, especially when TEE findings require further assessment. However, as an invasive procedure, its use in daily practice is limited, being primarily reserved for the cardiac catheterization laboratory during planned interventional procedures.[2]

Computed tomography

Computed tomography (CT) can identify LAA thrombi with good sensitivity and moderate specificity. Recent studies have concluded that LA and LAA thrombus analysis with isolated multislice CT is probably sufficient and non-inferior to TEE in patients with paroxysmal AF and normal systolic function.[7] However, CT is not currently recommended for identifying thrombi in the LA and LAA (Figure 8).[11–13,43]

CT generates 3D volumetric data of the heart, which can be reconstructed across different cardiac planes and phases to provide an accurate assessment of LAA anatomy with high spatial and temporal resolution and quantitative assessment.[2,3] However, CT is not highly specific for the presence of a thrombus and, therefore, the high rate of false-positive results, together with the use of radiation and iodine-based contrast media, are the main limitations for its widespread use.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMRI) is the main imaging method for evaluating cardiac masses.[2] Several imaging techniques provide relevant information about the

histological components and vascularization of the masses that, together with clinical data, can help distinguish between benign and malignant neoplastic masses, non-neoplastic masses (thrombi and cysts), or other structures.[26]

Intracavitary thrombus is the most common non-neoplastic mass, and its appearance on CMRI depends on the time of their formation. In more acute cases, in which the thrombus has a large amount of oxyhemoglobin, the thrombi tend to appear with increased signaling on T1- and T2-weighted sequences. Subacute cases present hypersignaling on T1 and low signal intensity on T2 due to the paramagnetic effects of methemoglobin. In chronic cases, the thrombus is water-depleted and cellular debris is replaced by fibrous tissue, thus leading to low signaling on T1 and T2.

The paramagnetic contrast agent has an important role in aiding tissue differentiation between thrombi and tumors. First-pass perfusion imaging allows a clear distinction between the thrombus and the adjacent myocardium since the thrombus is an avascular structure and classically does not absorb the contrast medium. In addition, late gadolinium enhancement can quantify atrial fibrosis, which is independently associated with the presence of thrombus in the LAA and SC and may be an additional risk stratification method.

However, CMRI has been evaluated in a limited number of studies, and its sensitivity and specificity for identifying LAA thrombus are similar to those of CT with high agreement with those of TEE. Thus, despite the evident advantages of CMRI, limitations remain to its widespread use in clinical practice, and it is not the recommended imaging modality for assessing thrombi in the LA or LAA.

Conclusions

The LAA, a complex structure with variable anatomy, constitutes the most common site of thrombus formation in the context of non-valvular AF. LAA function plays an important role in blood flow stasis and the risk of thrombus formation with subsequent thromboembolic events. TEE is the imaging modality of choice in LAA assessments, with high accuracy for detecting thrombi. Current and emerging transcatheter therapies, especially the implantation of LAA occlusion and exclusion devices, have further highlighted the importance of understanding LAA anatomy and function in clinical practice.

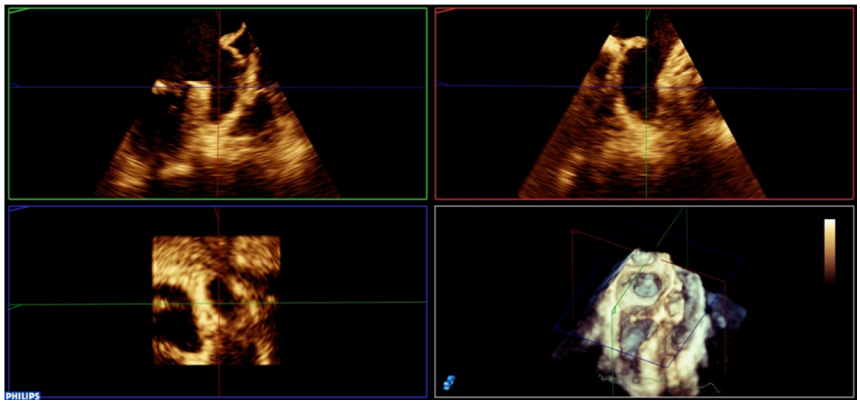
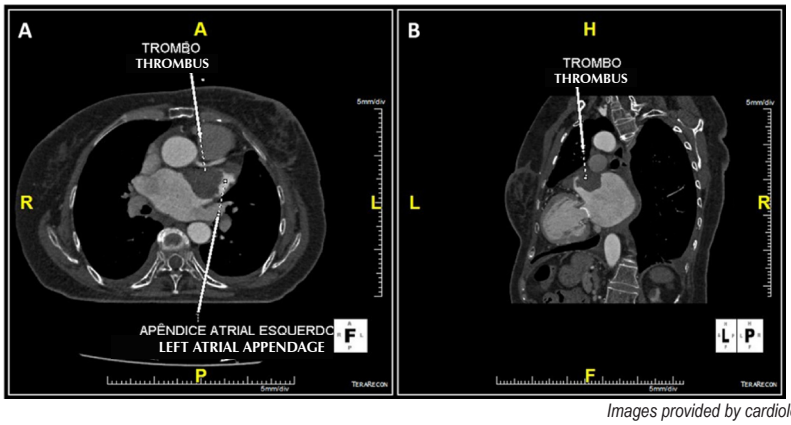


Figure 7 – *Three-dimensional TEE showing the LAA in several projections and allowing contractile function assessment.*



Images provided by cardiologist Victor Pimentel de Matos.

Figure 8 – *CT angiography image showing a thrombus in the LAA and LA.*

Authors' contributions

Research conception and design: Silva TM e Oliveira GB; data collection: Silva TM, Andrade BA; Furlan BB e Barros TLS; data analysis and interpretation: Oliveira GB e Nunes MCP; manuscript writing: Silva TM, Andrade BA; Furlan BB e Barros TLS; critical review of the manuscript for important content: Nunes MCP.

Conflict of interest

The authors have declared that they have no conflict of interest.

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