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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Contemporary echocardiographic assessment of atrial appendages in non-valvular atrial fibrillation

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INTRODUCTION

Non-valvular atrial fibrillation (AF) is associated with significant risk of thromboembolic events, such as stroke, transient ischaemic attack (TIA), arterial thrombosis, etc. Atrial contractile dysfunction leads to blood stasis, which creates a favourable milieu for thrombus formation (TF) in atrial appendages and may be associated with increased probability of thromboembolic events [1–7]. During recent years, considerable information has been accumulated regarding the role of atrial appendages in patients with AF. It has been clearly established that left atrial appendage (LAA) is a complex multi- or bilobular structure, which has an elongated, hooked shape and a narrow junction with the left atrium (LA) cavity. In contrast, right atrial appendage (RAA), which has been much less studied, is a broad, triangular structure with a wide junction. Both LAA and RAA, unlike atria with smooth walls, are trabeculated structures because of the pectinate muscles. Due to their structure and location, atrial appendages serve as decompression chambers during ventricular systole as well as in cases when atrial pressure is increased [8–10]. Moreover, LAA and RAA cardiomyocytes contain the greatest density of atrial natriuretic peptide granules found in the atria [8]. The aim of this paper is to review contemporary echocardiographic parameters of the structure and function of atrial appendages in patients with non-valvular AF.

LEFT ATRIAL APPENDAGE

It is well established that approximately 15% of ischaemic stroke events are associated with AF. The risk of stroke increases by five times in patients with non-valvular AF and by 17 times in patients with mitral stenosis [5, 8]. The formation of blood clots in heart cavities (especially LAA) is primarily due to blood stasis, coagulation cascade activation, and endothelial dysfunction [5, 11]. LAA is a typical place for TF in both AF and sinus rhythm (SR) [8, 11–13]. The prevalence of left atrial TF ranged from 8% to 27% in various studies. LAA is a location of 90% of atrial thrombi in non-valvular AF and 60% in patients with rheumatic mitral valve disease [14–16]. Therefore, structural and functional changes of LAA should receive due attention.

Traditional study of LAA structure and function includes two-dimensional (2D) echocardiography (to assess LAA size, morphology, and contractility) and pulsed wave Doppler echocardiography (LAA blood flow) [6, 8, 17]. Recently, new evidence has appeared regarding the use of M-mode and pulsed wave tissue Doppler imaging (TDI) for the study of LAA [2, 18–20]. LAA contractility in both AF and SR can be studied directly through the assessment of fractional area change, ejection fraction, and fractional shortening by means of B- and M-mode echocardiography. Peak LAA ejection and filling velocities are measured by pulsed wave Doppler echocardiography. Peak wall motion velocities are established by pulsed wave TDI, as well as indirectly — by thrombi visualisation and determining spontaneous echo contrast (SEC). Finally, pulmonary venous blood flow is studied by pulsed wave Doppler, using both transthoracic (TTE) and transoesophageal (TEE) echocardiography.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Historically, TEE appeared first for the study of LAA structure and function due to its high resolution and the proximity of the transducer to the structures. Now TEE is still a method of choice for LAA evaluation, thrombus detection, and risk stratification [21–23]. Compared to intraoperative findings, the TEE sensitivity for LAA thrombi detection is 92–100% and its specificity is 98–100% [21, 24]. Two TEE accesses are most useful: upper oesophageal (short axis on horizontal plane at heart base and longitudinal plane at two-chamber position of the left ventricle [LV] and LA) and transgastric [25]. The use of multiplane transducers makes it possible to obtain a number of intermediate LAA views.

During recent years considerable information has been accumulated regarding the assessment of LAA size and fractional area change (which is calculated using the formula: (LAA maximal area − LAA minimal area)/LAA maximal area × 100). It has been shown that increased LAA area or volume, and reduced LAA fractional area change, determined by B-mode 2D echocardiography, is associated with the presence of LAA thrombus in both AF and SR [16, 22, 26, 27]. It should be emphasised that LAA size is increased along with LA enlargement: LAA enlargement was observed in 59% of patients with dilated LA and in only 15% of patients with normal LA size [8]. The probability of LAA TF significantly increases in cases of LAA area > 6 cm^2 and LAA volume > 6 cm^3, as well as LAA fractional area change < 20% [16, 26, 28]. Yet, planimetric assessment of LAA size and contractility has some limitations related to complex LAA three-dimensional (3D) structure (multilobular, trabecular etc.), its translocation during cardiac cycle, and the necessary skills for endocardial delineation. This often causes inaccuracy of linear and volumetric measurements, as well as their insufficient reproducibility. Planimetric measurements of LAA size and function are time-consuming and may not provide additional benefits compared to conventional imaging [17, 29].

In order to overcome these disadvantages, new echocardiographic methods have been implemented, such as TEE anatomical M-mode (TEE-AM) and 3D-TEE. It was shown that LAA fractional shortening and ejection fraction (calculated by Teichholz method) determined by TEE-AM correlated well with fractional area change in patients with SR [30]. 3D-TEE technology is used in order to further improve reproducibility of parameters, compared to 2D-TEE, better visualise additional lobules of LAA, and to estimate its contractility more accurately [31].

Apart from the assessment of LAA size and function, 2D-TEE is also used for detection and semi-quantitative

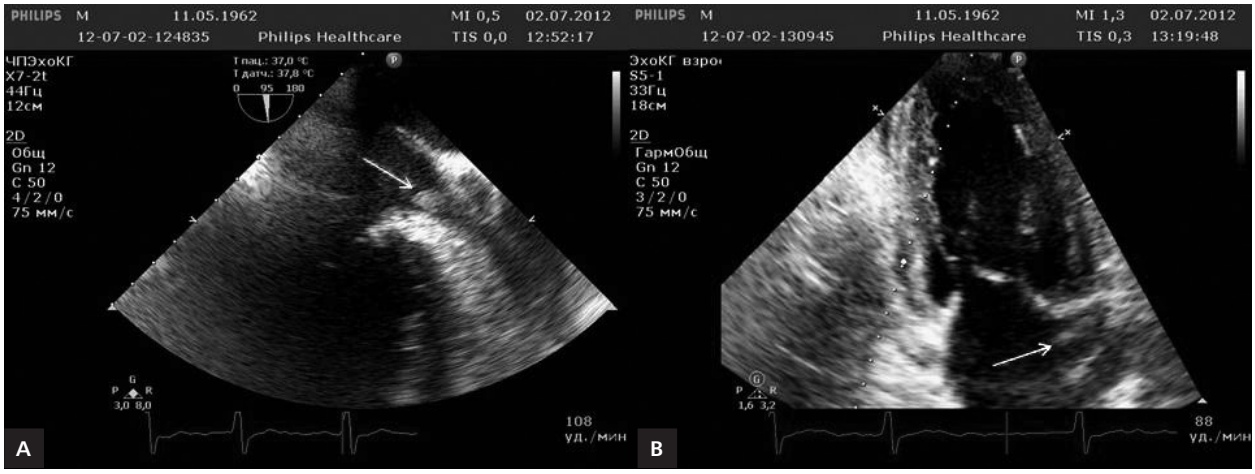

Figure 1. Thrombus in left atrial appendage, visualised by transthoracic (**A**) and transoesophageal echocardiography (**B**)

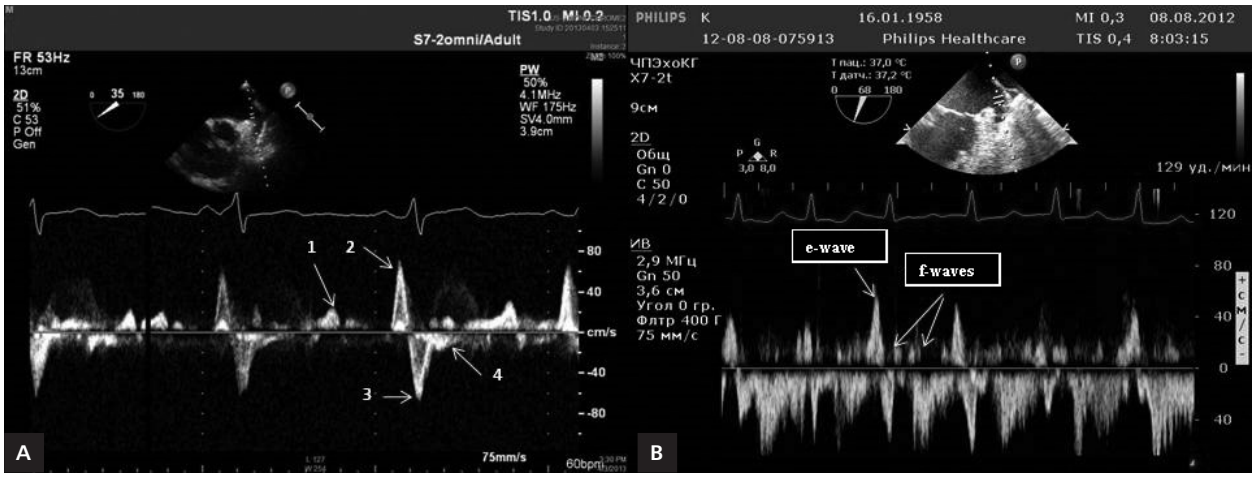

Figure 2. Left atrial appendage blood flow, detected by transoesophageal echocardiography: in the case of sinus rhythm (**A**: four-wave flow) and atrial fibrillation (**B**: two-wave flow)

assessment of the SEC, and determining the presence, size, and mobility of thrombi in the LAA (Fig. 1). SEC is a surrogate marker of the LAA functional state, visualised by 2D-TEE in 87.5% of patients with AF before electrical cardioversion [32]. It is an independent predictor of LAA TF and risk of thromboembolism in AF patients, regardless of the anticoagulation [17, 33, 34]. SEC phenomenon is explained by formation of the 'rouleaux' (aggregates of red blood cells) and their interaction with plasma proteins (mostly fibrinogen) [11, 35]. To assess the grade of SEC in LAA, the following criteria were proposed: 0 — lack of echogenicity; 1 — minimal movement of echogenic particles in the LAA while increasing sensitivity of the ultrasonic signal without background noise; 2 — slight motion of particles that can be distinguished without amplification, but with a clear picture; 3 — echogenic swirling pattern throughout the cardiac cycle; and 4 — slow swirling-like flow in the LAA of LA cavity [6, 34]. The grade of SEC was significantly related to LA dilation, reduced LAA ejection velocity, systolic fraction of pulmonary vein flow velocity-time integral, and degree of mitral regurgitation [34, 35]. It was also associated with the presence of AF, mitral stenosis, and previous thromboembolic events. Furthermore, SEC evaluation predicted TIA irrespective of age, gender, heart failure, and anticoagulation in the prospective study [5, 35].

BLOOD FLOW PATTERNS AND RISK STRATIFICATION

TEE studies demonstrated that LAA has its own blood flow pattern that may be assessed by pulsed wave Doppler. In healthy SR volunteers four-phase LAA blood flow was described consisting of the following discrete waves (Fig. 2) [6, 17]:

1. Early diastolic positive ejection wave ("e"-wave) with low velocity (mean peak velocity 20–30 cm/s) caused by passive compression of the LAA by the base of LV during diastole and suction effect (caused by mitral valve opening and rapid early diastolic LA emptying).

2. Late diastolic positive ejection wave ("a"-wave) because of LAA walls contraction and appearing just after P-wave on electrocardiography (ECG). "A"-wave velocity (mean peak velocity 50–64 cm/s) correlates with planimetric assessment of LAA ejection fraction.
3. Early systolic negative filling wave, following "a"-wave, caused by active LAA relaxation and elastic recoil. The velocity of this wave strongly correlates with "a"-wave velocity.
4. Systolic reflection waves, which are passive LAA filling and ejection waves, following LAA early systolic filling wave in normal heart rate.

LAA blood flow becomes biphasic in sinus tachycardia. One diastolic ejection wave and a systolic LAA filling wave are observed. In clinical practice, it is also necessary to take into account that the LAA emptying velocity is lower in elderly subjects and in women.

LAA study is especially important immediately after cardioversion. The following findings related to the atrial 'stunning' may be observed: temporary suppression of LA contractile function compared to values before cardioversion, decrease of the LAA filling and emptying velocity, and the appearance or increase of SEC [6, 17]. These findings are extremely important because depression of LA and LAA function, even temporarily, could lead to the formation of blood clots. 'Stunning' may be also observed in the right atrium (RA). Usually atrial contractility is restored within 1–4 weeks after cardioversion, but in some patients this period may be extended, and they need a longer term of anticoagulation [36].

Several types of ejection waves may be observed in AF patients [6, 19]. The first type are low-amplitude high-frequency waves, reflecting active flow in the LAA. They are characterised by high cycle-to-cycle variability and have lower amplitude during LV systole (LAA contraction with mitral valve closed). The second type of waves are observed prior to the QRS complex (early diastole), and there are one or more high-amplitude waves; these waves reflect passive diastolic emptying (wave "e"), which is a key to prevent TF in AF (Fig. 2).

Generally, LAA blood flow velocities are lower in AF than in SR, although they are extremely variable, i.e. with high values on one end of the spectrum (equal to or greater than those in SR) and low values on the other end (absence of flow). This feature displays a wide range of disorders of LAA contractile function in AF — from relatively preserved to complete appendage paralysis.

Three types of blood flow patterns have been described in LAA in patients with AF. In the first type, each ECG wave of AF corresponds to an LAA blood flow wave, registered by pulsed wave Doppler echocardiography. In the second type, the amount of LAA blood flow waves is lower than the number of AF waves on ECG. In the third type, active LAA blood flow is almost absent [37]. Peak LAA ejection velocity decreases from the first to the third type of flow. Patients with the third type of flow have significantly higher prevalence of SEC and TF in LAA, compared to the first and second types [8].

Reduced inflow and outflow in LAA is associated with SEC severity and formation of blood clots in patients with AF or SR [19, 26, 34]. The occurrence of thrombi in LAA correlated with decreased peak ejection velocity (< 25 cm/s) and increased degree of SEC, although anticoagulation might weaken these relations [6, 14, 17, 26, 38]. Repeated TEE investigations in patients with permanent AF showed progressive decrease of LAA emptying velocity and its strong relation to the degree of SEC and other LAA function parameters. SEC grade, established at the first TEE, was preserved during the follow-up period [39].

The LAA dysfunction is associated with much more frequent thrombus detection [40], while normal LAA function nearly excludes TF. Reduced LAA peak filling and emptying velocities were associated with previous and future systemic embolic events. In patients with AF and LAA ejection velocity less than 20–25 cm/s the risk of thromboembolism is almost three times higher than in those with higher ejection velocity. This parameter was as important for prediction of stroke as it was for high-degree SEC and presence of thrombus inside LAA [17, 34].

In the SPAF III study, higher frequency of LAA dysfunction with decreased peak ejection velocity was observed in patients with high thromboembolic risk [16]. In another study a higher $CHADS_2$ score was associated with more thrombus detection in LAA [14]. LAA thrombosis was diagnosed in one third of patients with $CHADS_2$ score ≥ 4. The LAA velocities could also predict the short-term and long-term success of SR restoration and maintenance in patients with AF. The prospective multicentre study involving 408 patients determined the following independent predictors of successful cardioversion in AF: duration of AF < 2 weeks, average LAA emptying velocity > 31 cm/s, and LA diameter < 47 mm [6]. Another threshold LAA emptying velocity was identified in a study of 186 patients with non-valvular AF [41]. Only LAA emptying velocity > 40 cm/s along with use of preventive antiarrhythmic treatment were the predictors of long-term (over one year) maintenance of SR after cardioversion.

In patients with persistent non-valvular AF blood stasis in LA and LAA is related to blood flow in the pulmonary veins. The systolic wave of flow in the pulmonary veins is associated with LA function and reflects its relaxation. The systolic wave of flow in pulmonary veins in patients with SEC was lower compared to those without SEC [42].

Although TEE is considered a "gold standard" in the study of TF and LAA function, thrombi visualisation may be complicated by a high degree of SEC, hypoechogenicity, and small size of blood clots, as well as multiple artefacts resembling LAA thrombosis [6, 22]. New echocardiographic technologies can improve visualisation and evaluation of LAA function. TDI provides the possibility to assess myocardial wall motion,

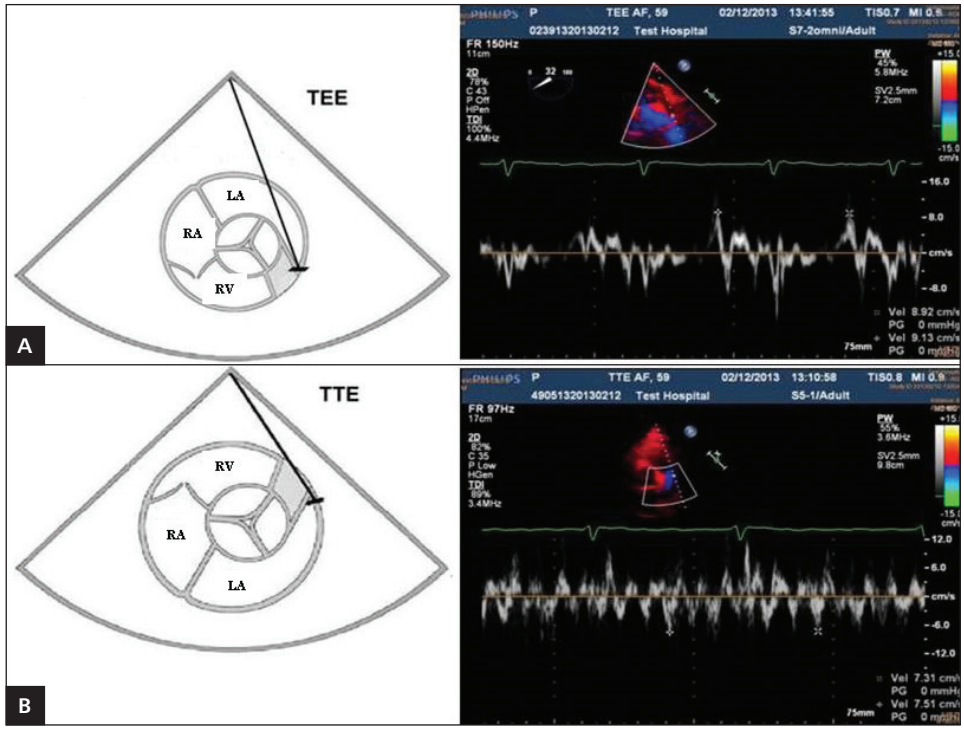

Figure 3. Left atrial appendage apex movement detection by spectral tissue Doppler imaging by transthoracic echocardiography — TEE (**A**) and transoesophageal echocardiography — TEE (**B**); LA — left atrium; RA — right atrium; RV — right ventricle

including LAA (Fig. 3). Furthermore, TEE with TDI is useful for risk stratification and provides additional prognostic information over conventional impulse-wave Doppler parameters [43, 44]. Contrast TDI contributes to better visualisation of LAA, improving our understanding of its structure and function, assessment of SEC, and thromboembolic risk [6, 45].

Despite obvious advantages in assessing LAA, TEE has several limitations. First, TEE is a semi-invasive method, associated with life-threatening complications (laryngospasm, arrhythmias, oesophagus perforation, bleeding) in 1–3% of cases [46]. Second, compared to TTE, it is much more wasteful of resources, requiring expensive equipment and specially trained personnel. Therefore, TEE is not considered suitable for screening purposes.

TRANSTHORACIC ECHOCARDIOGRAPHY

In general, TTE is inferior to TEE in the evaluation of LAA morphology and function [19, 27, 47]. Poor LAA visualisation in more than 20% patients, inability to identify dysfunction, SEC and blood clots are still major obstacles for use of TTE. Furthermore, TTE is less sensitive in identifying other sources of cardioembolic stroke (in aorta, valves, open oval orifice). Despite increased LA size, reduced fractional shortening and increased ratio of transmitral flow velocities were useful predictors of thrombosis in the LAA; these parameters are non-specific and have much lower predictive value than those obtained by TEE [48, 49].

The possible use of TTE for assessment of LAA was evaluated in a study involving 117 patients with previous TIA or stroke [27]. Despite the fact that transthoracic visualisation of LAA was satisfactory in only 75% of patients, the sensitivity and specificity of TTE to diagnose thrombus in LAA was 91% and 100%, respectively (Fig. 1). No thrombi in LAA were found at velocities > 30 cm/s. However, transthoracic evaluation of the flow rates was possible in 69% of cases [27].

New perspectives for the study of LAA appeared due to contemporary TTE techniques to optimise visualisation, i.e. use of second tissue harmonic, TDI, and venous contrasting substances. These substantially improved spatial resolution and image quality [27, 50]. Second tissue harmonic mode allows better visualisation of LAA, providing planimetric assessment of LAA area and fractional area change almost in all patients, as well as pulsed wave Doppler assessment of flow velocity (Fig. 4) [6, 18, 19, 51, 52]. TTE parameters of LAA contractility closely correlated with those measured by TEE. But in the case of TTE the values of LAA area are slightly underestimated, and the values of LAA peak flow velocities are slightly overestimated compared to TEE, which can lead to underestimated LAA thrombosis [19]. However, there is lack of studies comparing both methods.

TDI allows the study of regional myocardial function. Recent data demonstrated the feasibility of using spectral TDI with TTE to detect LAA dysfunction and confirmed the relationship of LAA dysfunction to thrombus in the appendage.

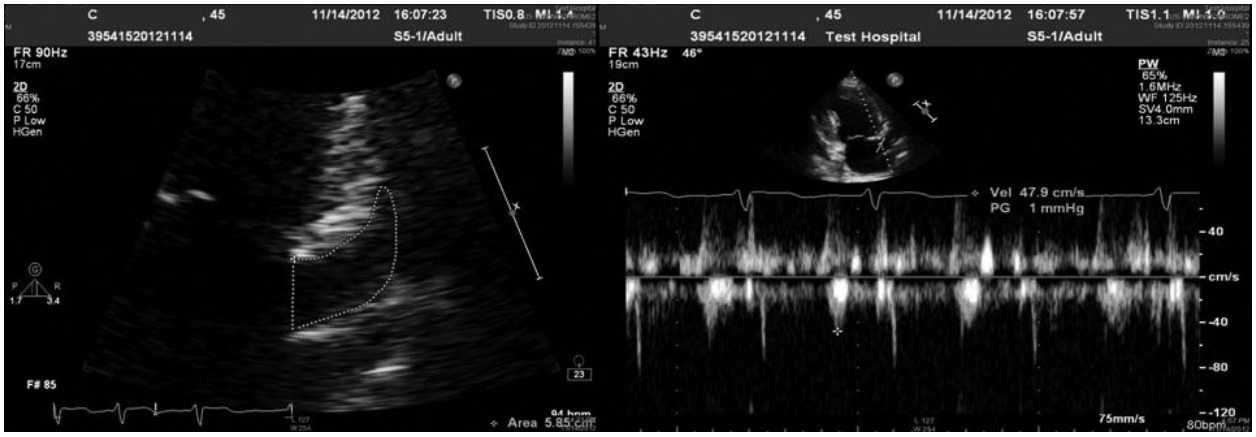

Figure 4. Assessment of left atrial appendage area and blood flow velocity by transthoracic echocardiography

Using spectral TDI, the maximum LAA apex speed velocity is assessed by establishing a sample volume (size 2 mm) on top of the LAA in the left parasternal short-axis position at the level of the aortic valve (Fig. 3) or in the apical two-chamber position. The angle between the axis of LAA and the axis of the ultrasonic beam should be as small as possible [2, 18, 19].

So far, there are a lack of studies examining the diagnostic and prognostic value of TTE using spectral TDI in the evaluation of LAA and risk of TF. The LAA apex velocity parameters are closely related to traditional parameters of LAA function, such as ejection velocity, and can be determined by TTE in most patients, even at suboptimal visualisation [19, 53, 54]. Besides, significant reduction of the LAA apex movement, the velocity is associated with a higher degree of SEC and more frequent detection of LAA thrombosis by TEE [2, 18, 19, 54]. Therefore, the reduced LAA apex movement velocity might be a potential noninvasive marker of LAA dysfunction and predictor of TF.

The assessment of LAA by TTE is also possible in M-mode providing the possibility to measure medial wall thickening and identify the so-called dip-wave (M-wave). This wave is visualised after synchronised ECG P-wave in the case of preserved SR, and has a repetitive nature and permanent amplitude. Conversely, in AF patients M-wave has a notched appearance with varying amplitude (Fig. 5). Reduction of its amplitude or disappearance is considered to be a marker of LAA dysfunction. Visualisation of LAA by TTE with use of M-mode second harmonic tissue was possible in 96% of patients [20]. Measurement of the medial wall thickening was technically feasible in 98% of cases with SR, and 94% in AF or atrial flutter. Further, thickening of the LAA medial wall more than 0.25 cm was a sign of normal function. Compared to the LAA ejection velocity obtained by TTE with pulsed-wave Doppler, thickening of the LAA medial wall in M-mode was identified in most of the patients (96% vs. 89%), and was characterised by a higher diagnostic accuracy (95% vs. 90%), sensitivity (98% vs. 92%), and specificity (94% vs. 89%).

Finally, TEE should not be superseded as a "gold standard" for evaluation of the LAA, in particular for the detection of blood clots. Nonetheless, the available evidence suggests TTE may be sufficient for assessment of LAA in low-risk patients. In addition, surrogate risk markers, particularly LAA wall movement velocities and M-waves, can help to identify a group of patients at low risk even in the case of poor LAA visualisation. In this context, use of TTE is promising, particularly for risk stratification of thromboembolic events in patients with AF, including prior to radiofrequency catheter ablation and cardioversion. Moreover, early use of TTE allows the determination of patients in which further TEE will be necessary [6, 19].

RIGHT ATRIAL APPENDAGE

Information on the structure and function of the RAA in patients with AF of different aetiology is scarce. This is probably due to the location of the RAA, leading to inability or difficulties of its visualisation not only during TTE but also noted in 1.3–16% of TEE studies [55]. In the course of TEE, the RAA is visualised from upper transoesophageal accesses in bicaval view (in the longitudinal view of the RA) in a continuum of angles from 90° to 140° [25].

Although the LAA is a major source of thromboembolism in non-valvular AF, this arrhythmia is associated with damage to both atria. It is no wonder that thrombi can form also in the RA, and especially in its appendage (Fig. 6) [55, 56]. There are serious reasons to assume that dysfunction of RAA in AF may cause thrombi formation in the right heart.

Use of TEE in patients with persistent AF demonstrated the presence of SEC and possible thrombi formation in the RAA. In various studies, the incidence of SEC and thrombi in the RA and its appendage in patients with AF ranged between 1–7.5% and 10–57% [56–59]. Although systemic thromboembolism risk is mostly studied, pulmonary embolism is also possible in patients with AF. Its prevalence in patients with non-valvular AF amounted to as much as 19% in a sample

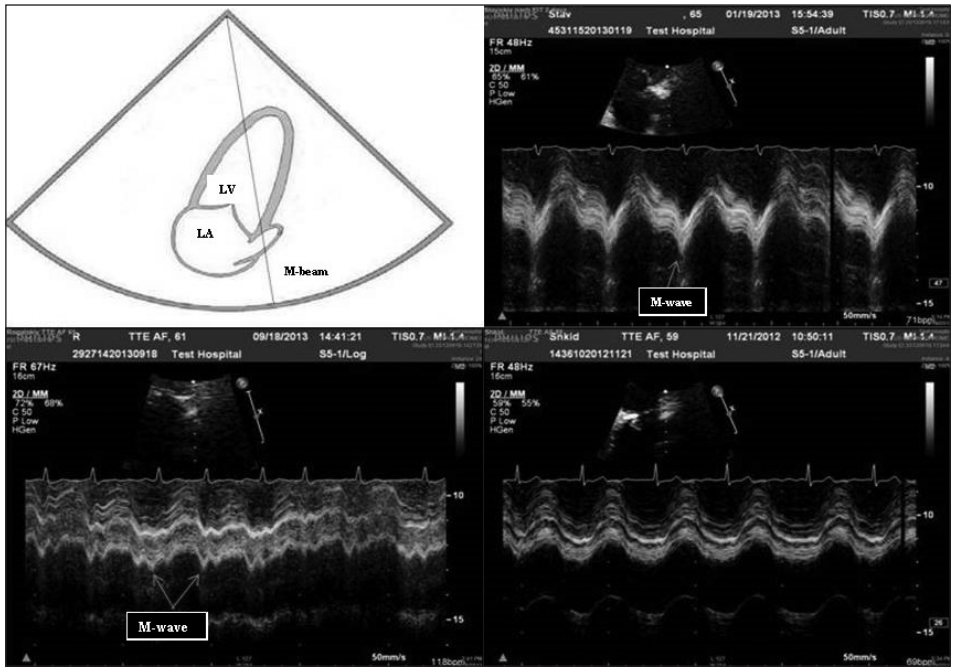

Figure 5. M-wave detection: M-wave presence in the case of sinus rhythm (upper right) and atrial fibrillation (AF) (lower left); M-wave absence in AF (lower right) in left atrial appendage dysfunction; LA — left atrium; LV — left ventricle

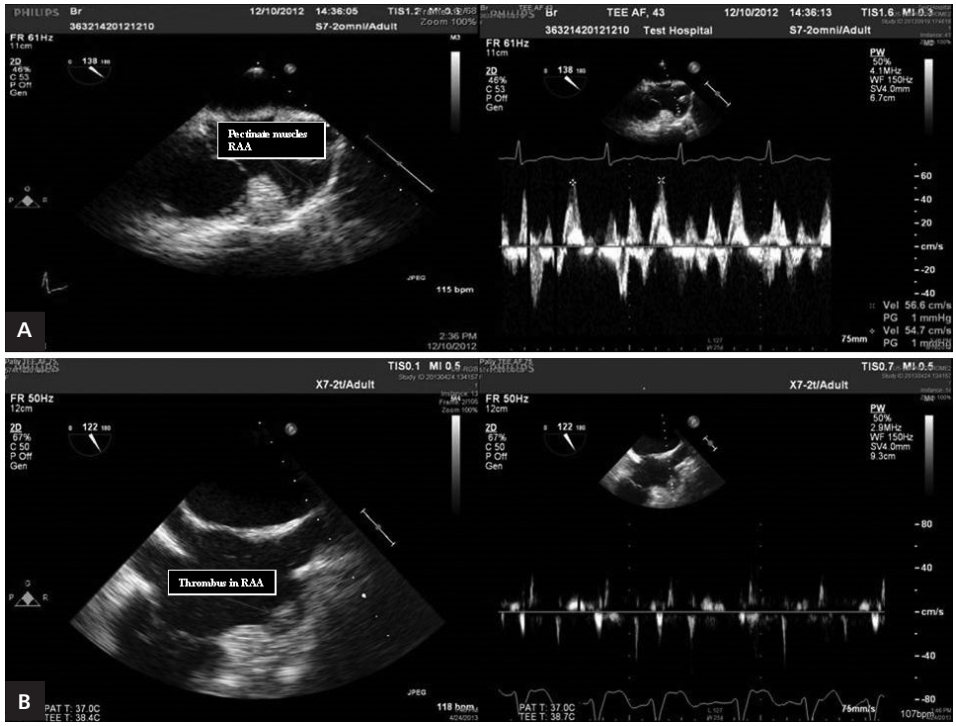

Figure 6. **A**. Right atrial appendage (RAA) without signs of thrombus formation (pectinate muscles are visualised) and normal ejection flow velocity (EFV); **B**. RAA thrombus and reduced EFV

of 102 patients with permanent form of AF [4]. In another research project, right atrial thrombi were observed in 3.1% of 23,796 autopsies, and the prevalence of pulmonary embolism was 42.6% [3].

Different frequencies of TF in atrial appendages are partly explained by anatomical and physiological features. The anatomical measurements of the RAA are relatively independent of the scanned area, unlike those of te LAA [60]. The width of

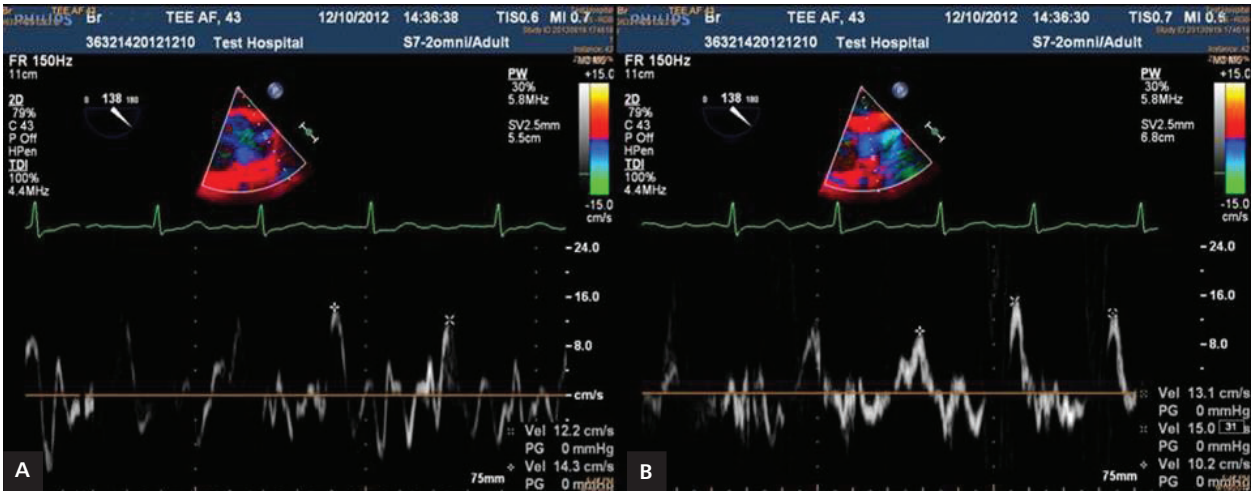

Figure 7. Assessment of movement velocity of lateral (**A**) and medial (**B**) right atrial appendage wall by means of transoesophageal echocardiography spectral tissue Doppler imaging

the RAA was larger than that of the LAA, but the LAA area was greater than that of the RAA. In addition, enlargement of the LAA was found in patients with AF, but significant remodelling of the RAA was not always observed. No statistically significant differences in the area of the RAA and the ratio of the width of appendage/area of the RAA in patients with AF and SR were found. While both appendages fibrillated, and their ejection velocities decreased similarly, the thrombus in the RAA was an infrequent finding. The authors of the research suggested that the reason for this could be a wider appendage and larger ratio of width of the RAA to its area. Other authors reported that non-valvular AF resulted in significant morphological and functional changes of the RAA compared to patients with SR, with increased area and decreased fractional area change and blood flow velocity into RAA, which can be measured by pulsed wave Doppler (Fig. 6) [60, 61].

The study by de Divitiis et al. [59] revealed higher values of the area of the RA and a maximum area of the RAA and lower fractional area change and emptying velocities of the RAA in patients with AF compared to SR. Similar changes were also found in patients with thrombosis of the RAA compared to its absence. SEC in the RAA was found in 57% of patients with AF. All patients with thrombus in the RAA (7% of patients) had SEC of grade 3–4. In contrast, high-grade SEC was found only in 11% of patients without thrombus. SEC grade in the RAA was the only independent predictor of thrombus in the RAA. Enlargement and dysfunction of the RA and RAA were related to enlargement of the right ventricle, deterioration of its systolic function, and increased pulmonary artery pressure. Therefore, the increase and dysfunction of RA and right ventricle may be a prerequisite for the increase and breach of the function of the RAA. In addition, significant correlation between the size and function of the atria and their appendages was noted, indicating parallel development of the dysfunction.

The lower frequency of TF in the RAA may also be due to the influence of other important factors, including the special structure of the RAA wall, its pectineal muscles, and the possibility of latent migration of thrombi from the RAA, which stipulates their less frequent detection.

There is little data regarding the RAA in patients with non-valvular AF using contemporary technologies. For example, the diagnostic and prognostic indicators of velocities of medial and lateral walls of the RAA were studied using pulsed wave TDI [58, 61, 62]. For this purpose, the images of the RAA by TEE were obtained and the sample volume (size: 2 mm) of corresponding walls of RAA was determined by activating pulsed wave TDI (Fig. 7).

According to Sahin et al. [58], blood flow velocity in the atrial appendages and the velocity of the wall movement in appendages in subjects with SR were significantly higher than those in patients with AF. All patients with RAA thrombus demonstrated RAA fractional area change less than 20%, RAA blood flow velocity less than 25 cm/s, and velocity of RAA wall movement less than 6 cm/s. The authors suppose that the velocity of RAA wall movement may help to diagnose RAA dysfunction, but it has no advantage over the traditional parameters of RAA function, such as fractional area change and blood flow velocity. Our study performed in patients with non-valvular AF showed that the most informative markers of RAA dysfunction were a decrease in the velocity of its wall movement and blood flow velocity [62]. Indication of the movement of RAA walls was also most closely associated with LAA thrombosis.

The available data indicate that AF is associated with dysfunction of both atria and their appendages, contributing to thrombus formation, and changes in RAA function are related to the dysfunction of the LAA [58, 62]. Thus, detection of the severe LAA dysfunction is an argument for careful study of the

RAA, which may provide additional clinical and prognostic information in patients with AF.

CONCLUSIONS

In conclusion, echocardiographic study of atrial appendages using contemporary imaging technologies enables the determination of their structure and function, making it possible to detect early signs of TF. Recent echocardiographic imaging advances, such as second tissue harmonics, TDI, and use of venous contrasting agents, allow a detailed study of the morphology and function of atrial appendages using both TEE and TTE. As a result, this may improve thromboembolic risk stratification in patients with non-valvular AF.

Conflict of interest: *none declared*

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