Research Article

Is Transesophageal Echocardiogram Mandatory for Patients Undergoing Ablation for Right Atrial Flutter with Uninterrupted Anticoagulants? A Prospective Single Registry

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Abstract

Background: Limited data exist regarding the prevalence of left atrial appendage (LAA) thrombi and spontaneous echocardiographic contrast (SEC) in patients with atrial flutter (AFL).

Objectives: Our prospective single-center observational study sought to evaluate the prevalence of LAA thrombi in patients referred for AFL ablation, compared to those requiring atrial fibrillation (AFib) ablation during the same time period, as well as to determine the predictive factors of LAA thrombi in terms of arrhythmia etiology.

Methods and Results: From July 2019 to August 2020, 321 consecutive patients who were referred for either AFib ablation (n= 229) or AFL ablation (n= 92) were included in the study, with a thrombus detected by transesophageal echocardiography (TEE) in 3.22% (12/321). Prior to ablation under anticoagulants, the percentage of thrombi was similar between patients referred for AFL ablation and those

referred for AFib ablation (5.4% [n= 5/92] vs. 3.1% [n= 7/229]; p= 0.3). In the overall population, patients with LAA thrombi had a higher CHA^2DS^2-VASc score (3 ± 2 vs. 2 ± 1.5; p= 0.048) and a higher presence of valvular prothesis (25% vs. 4.9%; p =0.003), with relevant left atrial remodeling more often observed, such as demonstrated by a higher left atrium (LA) volume (57 ± 19 vs. 46 ± 17 ml/m²; p= 0.04), a lower LAA velocity (0.41 ± 0.3 vs. 0.55 ± 0.2; p =0.04) and a more severe LAA echo contrast (83.3% vs. 3.2%; p <0.0001). In the subset of patients with right AFL, patients with LAA thrombi had a higher CHA^2DS^2-VASc score (4.4 ± 1 vs. 2.5 ± 1.5; p= 0.008), had more often hypertension (100% vs. 53%; p= 0.04) and more often diabetes mellitus (60% vs. 18.4%; p= 0.03), and a more severe LAA echo contrast (80% vs. 5.7%; p <0.0001). Predictive factors of atrial thrombi evaluated by crude odds ratios were the presence of valvular prosthesis (OR =6.53; [1.60, 26.65]; p =0.009), the CHA^2DS^2-VASc score (OR =1.41 [0.99, 2.01]; p =0.05), the LAA velocity (cm/s) (OR =0.03; [0.001, 0.79]; p =0.04) and presence of severe LAA contrast (OR =188 ; [35.32, 1002.02] ; <0.0001) rather than the atrial arrhythmia itself.

Conclusions: Patients referred for ablation with right AFL have a similar risk of LAA thrombi, compared to those with AFib. The risk of LAA thrombi is better related to the presence of valvular prosthesis, CHA^2DS^2-VASc score and LA remodelling than the atrial arrhythmia itself. Accordingly, TEE should be recommended before right AFL ablation, especially in case of a valvular prosthesis, high CHA^2DS^2-VASc score or LA alteration.

Keywords: Atrial fibrillation; right atrial flutter; left atrial appendage; thrombus; transesophageal echocardiography

1. Introduction

Stroke is a potential complication of atrial fibrillation (AFib), which is a serious condition. However, its incidence is low (approximately 1%) [1, 2]. To prevent this risk, preprocedural transesophageal echocardiography (TEE) is the standard method to assess left atrial appendage (LAA), which is the primary site of embolism (>90%) [2]. Several articles have emphasized the low risk of both stroke and atrial thrombus (AT) formation under uninterrupted vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) before atrial fibrillation (AFib) ablation [3-6]. Moreover, a meta-analysis confirmed the efficacy and safety of uninterrupted DOACs in 11,686 patients, revealing no difference in stroke occurrence following AFib ablation (0.28% vs. 0.19%), with a similar incidence of major bleeding (1.1% vs. 1.6%) [6]. Although the incidence of thromboembolism appears low, stroke is clearly a devastating complication that must be prevented. In a recent study, our group found that the prevalence of TEE-detected thrombi in patients referred for AFib ablation was similar under DOACs (2.1%) and VKAs (2.6%), and that TEE is recommended to eliminate a left AT, in spite of the anticoagulants used for invasive strategy [7]. In this clinical setting, typical right atrial flutter (AFL) is related to AFib, as both have been shown to coexist in the same patients: AFib may trigger AFL, and AFib is common after AFL ablation [8-12]. Typical AFL may also frequently occur in patients treated for AFib with class IC drugs or amiodarone, but recommendations for TEE use before AFL ablation are still unclear. Data concerning the embolic risk of AFL have usually been derived from patients with concomitant AFib, which makes individualized risk stratification difficult. LAA “stunning” and thrombi seem to be less common in AFL patients than in AFib patients, even though only little data exist on this topic [13-

15]. Although the thrombo-embolic risk of AFL appears to be lower than that of AFib, it may still be relevant [15-16]. This, together with its common association with AFib, justifies thrombo-prophylaxis, and anticoagulation has thus been recommended [17, 18]. These recommendations extend to the acute setting for cardioversion when AFL lasts for >48 hours. However, it should be noted that there is a lack of prospective, dedicated studies, particularly concerning DOACs. Furthermore, the value of the CHA^2DS^2-VASc score in preventing ischemic stroke in AFL patients has not yet been established, while the threshold for the initiation of anticoagulation is likely lower than that for patients with AFib [19, 20]. In the literature, there is a lack of studies analyzing the prevalence of thrombi in patients referred for AFL ablation or cardioversion by means of TEE, and there is a lack of predictive factors of LAA thrombi in apparently pure AFL (21-24). TEE is not commonly and systematically used to detect AT before AFL ablation [21-26]. This highlights a need to evaluate the heightened risk for systemic embolism, both in patients with initial episodes of AFL and in those with AFib, whose anticoagulation has been deemed adequate. This approach strategy has been extrapolated from guidelines for AFib and from retrospective studies [2, 18]. Moreover, limited data exist regarding the prevalence or clinical associations of AT and spontaneous echocardiographic contrast (SEC) in AFL patients. Both AT and SEC are believed to be risk factors for systemic embolization [27, 28].

The primary objective of our prospective single-center observational study was to evaluate the prevalence of LAA thrombi in patients referred for AFL ablation, compared to patients requiring AFib ablation during the same time period. We also sought to determine the predictive factors of LAA thrombi in the entire population, in terms of arrhythmia etiology.

2. Methods

2.1 Study population: Between July 2019 and August 2020, all patients referred for either AFL ablation or AFib ablation were screened. In the absence of contraindications, patients were invited to participate in the study and submitted their written informed consent prior to entry. The study was approved by the Institutional Committee on Human Research at the authors' institution. This work was not supported by any extramural funding. The authors were solely responsible for the study's design, execution, and analyses, as well as for drafting the paper, and its final editorial content. During the period of inclusion, all consecutive patients with drug-refractory AFib who were scheduled to undergo transcatheter AFib ablation and AFL patients who were scheduled to undergo cavotricuspid isthmus ablation had a pre-ablation cardiac TEE. Only patients without an AFib history were included in the group of right AFLs. Patients were excluded because they refused to participate (n =14), and TEE was impossible to perform (n =5).

2.2 Per-procedural anticoagulation regimen: All of the referred patients were on anticoagulants (including DOACs and VKAs) for at least two months prior to the AFib ablation and for at least one month prior to right AFL ablation, as per practitioner preference. Apixaban was prescribed at doses of 2.5/5mg twice a day, dabigatran 110/150mg twice a day, and rivaroxaban at 15–20mg once a day, based on creatinine clearance. Patients on VKAs before the procedure had to achieve 3–4 weeks of therapeutic international normalized ratio (INR), with warfarin monitored weekly in the 3–4 weeks preceding ablation. Patients were invited to take DOACs and

VKAs the day before the procedure without any discontinuation. Anticoagulants were resumed systematically in the evening of the procedure.

2.3 Echocardiography before AFL or AFib ablation:

Conventional transthoracic echocardiography and TEE were systematically performed 24–72 hours before the ablation procedure using a commercially available system (Vivid E9 or E95, GE Healthcare, France). TEE studies were performed in our central echo laboratory by two experienced echocardiographers (RP and AS), who were unaware of the patient's clinical status and outcome. All patients with a suspicion of LAA thrombi were reevaluated separately by both operators. In discrepancy cases, a third expert was consulted (KI). Left atrium (LA) volume, right atrium surface, LVEF, LV diastolic function and RV function were quantified using transthoracic echocardiography and LAA surface and contractility as well as LAA velocities were quantified using TEE. Upon the TEE, special attention was paid to assessing the presence or absence of LA thrombi and SEC [22-28]. A thrombus was considered present if a mass detected in the appendage or body of the atrium appeared to be distinct from the underlying endocardium, was not caused by pectinate muscles, and was detected on more than one imaging plane [22-24]. The degree of SEC was independently characterized as absent, mild, moderate, or severe [27, 28]. The delay between these echocardiography studies and the scheduled AFib ablation procedure was ≤3 days.

2.4 Thrombus-related patient outcome data:

An observational evaluation of patients with TEE thrombi was elaborated to report the percentage of TEE thrombi prior to AFib ablation and the percentage of thrombi under DOACs and VKAs.

2.5 Statistical analysis:

All clinical variables were assessed at the time of hospitalization and prior to the AFib ablation and AFL procedures. The characteristics of the study population were described according to either the presence of TEE LAA thrombus or the presence of TEE LAA thrombus and/or severe SEC. Continuous variables were expressed as means ± SD. Categorical variables were expressed as percentages. Comparisons of means between groups were performed using the Student's t-test. When the assumption of homogeneity of variances between groups was not met (verified with the Levene test), the P value of the corrected Student's t-test with unequal variances assumption was presented. Comparisons of proportions between groups were performed using the Pearson's Chi-squared test or Fisher's exact test, as appropriate. The presence of TEE thrombus or TEE thrombus and/or severe SEC were both considered as binary outcome variables. The relationships between potential predictors and risk of TEE thrombus, and TEE thrombus and/or severe SEC were assessed using binary logistic regression. All the covariables that were found significant in the unadjusted models were included in a stepwise multivariate logistic regression to assess the effect of the combination of variables on the outcomes. In the multivariate models, the missing values of the variables left atrial volume (n =48), right atrial surface (n =56) and LAA velocity (n =21) were handled with imputation using linear interpolation method. Results are presented as crude and adjusted odds ratios (OR), 95% confidence interval (95% CI) and P value. All tests were two-tailed, with a P value of less than 0.05 considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) statistical software Version 19.0 for Windows

(SPSS Inc., Chicago, IL) or STATA (version 13; Stata Corp, College Station, TX).

3. Results

3.1 Population characteristics (Table 1)

From July 2019 to August 2020, 321 consecutive patients who were referred for AFib ablation (n=229) and AFL ablation (n=92) were included in the study (Table 1). Prior to ablation, 22 patients were on VKAs (warfarin [n=9], acenocoumarol [n=7], and fluindione [n=6]) and 291 were on DOACs (apixaban [n=157], rivaroxaban [n=118], and dabigatran [n=16). The remaining patients were on other agents (n=8). At baseline, differences were observed between both groups (AFib vs. AFL). Patients with AFL were older (71 ± 12 vs. 64 ± 11; p<0.001), had more hypertension (55.4 vs. 40.6%; p=0.02), more diabetes mellitus (20.7% vs. 12.2%; p=0.05), more ischemic cardiomyopathy (21.7% vs. 11.8%; p=0.02) and the LVEF was lower (54 ± 12 vs. 57 ± 10; p=0.007). Accordingly the CHA^2DS^2-VASc score was higher (2.6 ± 1.6 vs 1.9 ± 1.5; p =0.0003) and the LAA contrast was more present (9.8% vs. 3.9%; p=0.04). Patients with pure right AFL and LAA thrombi had a higher CHA^2DS^2-VASc score (4.4 ± 1 vs. 2.5 ± 1.5; p=0.008), had more often hypertension (100% vs. 53%; p=0.04) and more often diabetes mellitus (60% vs. 18.4%; p=0.03), and a more severe LAA echo contrast (80% vs. 5.7%; p <0.0001), despite the same LA or RA dimensions.

3.2 Population characteristics according to the presence of LAA thrombus (Table 2)

A thrombus was detected using TEE in 3.22% (12/321). The percentage of pre-ablation thrombus under anticoagulants was similar in patients referred for AFL ablation, compared to those referred for AFib ablation (5.4% [n=5/92] vs. 3.1% [n=7/229]; p= 0.3). Patients with LAA thrombi had a higher CHA^2DS^2-VASc score (3 ± 2 vs. 2 ± 1.5; p=0.048) and a higher presence of valvular prothesis (25% vs. 4.9%; p=0.003), with relevant left atrial remodeling more often observed, such as demonstrated by a higher left atrium (LA) volume (57 ± 19 vs. 46 ± 17 ml/m^2; p=0.04), lower LAA velocity (0.41 ± 0.3 vs. 0.55 ± 0.2; p =0.04) and a more severe LAA echo contrast (83.3% vs. 3.2%; p <0.0001).

3.3 Factors affecting the risk of LAA thrombi in the entire population (Crude odds ratios) (Table 3)

In the entire population the significant predictive factors of atrial thrombi evaluated by crude odds ratios were the presence of valvular prosthesis (OR =6.53; [1.60, 26.65] ; p =0.009), the CHA^2DS^2-VASc score (OR =1.41 [0.99, 2.01]; p =0.05), left atrial volume (OR 1.03 [1.01, 1.06]; p= 0,041), the LAA velocity (cm/s) (OR =0.03; [0.001, 0.79]; p =0.04) and presence of severe LAA contrast (OR =188 ; [35.32, 1002.02] ; <0.0001). When the predictor variables were modelled together, only the presence of severe LAA contrast remained significantly associated with LAA thrombi (adjusted OR =188 (35; 1002), p<0.0001), while valvular prosthesis p =0.57), LAA velocity (p=0.85), left atrial volume (p =0.76) did not contribute significantly to the model.

3.4 Population characteristics according to the presence of LAA thrombus and/or severe LAA echo contrast (Table 4)

Patients with LAA thrombi and/or severe LAA echo contrast (n =20, 6.2%) were older (73.2 ± 10 vs. 65.5 ± 12; p= 0.004), had more often hypertension (70% vs. 43.2%; p=0.02), diabetes mellitus (30% vs. 13.6%; p=0.04), and prior valvular prothesis (20% vs. 4.7%; p <0.004), as well as a higher CHA^2DS^2-VASc score (3.2 ± 2 vs. 2.1 ± 1.5; p= 0.002) and a bigger LA volume (55 ± 17 vs. 46 ± 17 ml/m^2; 0.04). There was a tendency toward a lower LVEF (53 ± 15 vs. 57

± 171 p=0.09). LAA velocities were significantly altered in patients with LAA thrombi and/or severe LAA contrast (0.35 ± 0.2 vs. 0.56 ± 0.2 cm/s; p= 0.0003).

3.5 Predictive factors associated with LAA thrombus and/or severe LAA echo contrast evaluated by Crude odds ratio (Table 5) and by adjusted odds ratio (Table 6)

In the entire population the significant predictive factors of atrial thrombi and/or severe LAA contrast (prothrombotic state) evaluated by crude odds ratios were the age (OR=1.08; [1.02, 1.13]; p=0.004), hypertension (OR=3.07; [1.15, 8.20]; p=0.03), diabetes mellitus (OR=2.72; [0.99, 7.47]; p=0.05) presence of valvular prosthesis (OR=5.13; [1.51, 17.36]; p=0.009), the CHA^2DS^2-VASc score (OR=1.52 [1.15, 2.02]; p=0.003), left atrial volume (OR=1.03 [1.01, 1.05]; p=0.041) and LAA velocity (OR=0.03 [0.001, 0.06]; p<0.0001). By the adjusted odds ratio model, only the presence of valvular prothesis (OR=4.2; [1.04, 16.93; p =0.04), and LAA velocity (OR=0.62 [0.45, 0.85]; p =0.003) remained significantly and independently associated with the risk of thrombi.

Variable	Study population (n=321)	AFib (n=229)	AFL (n=92)	P
Age - mean±SD	66±12	64±11	71±12	<.0001
Gender - n (% female)	87 (27.1%)	68 (29.7%)	19 (20.7%)	0.1
Hypertension - n (%)	144 (40.6%)	93 (40.6%)	51 (55.4%)	0.02
Diabetes mellitus - n (%)	47 (14.6%)	28 (12.2%)	19 (20.7%)	0.05
High blood cholesterol - n (%)	83 (25.9%)	54 (23.6%)	29 (31.5%)	0.14
Body mass index – (kg/m^2)- mean±SD	27±5	27±4	28±5	0.4
Ischemic cardiomyopathy - n (%)	47 (14.6%)	27 (11.8%)	20 (21.7%)	0.02
CABG - n (%)	12 (3.7%)	6 (2.6%)	6 (6.5%)	0.1
Stroke - n (%)	15 (4.7%)	10 (4.4%)	5 (5.4%)	0.7
Valvular prothesis- n (%)	18 (5.6%)	11 (4.8%)	7 (7.6%)	0.3
CHA^2DS^2-VASc score- mean±SD	2.1±1.6	1.9±1.5	2.6±1.6	0.0003
LVEF (%) - mean±SD	56±11	57±10	54±12	0.007
Left atrial volume (ml/m^2)- mean±SD	47±17	47±19	46±12	0.5
Right atrial surface (cm^2)- mean±SD	23±6	23±7	24±6	0.1
LAA thrombi - n (%)	12 (3.7%)	7 (3.1%)	5 (5.4%)	0.3
Severe LAA contrast - n (%)	18 (5.6%)	9 (3.9%)	9 (9.8%)	0.04

Table:1 Population Characteristics.

Values are expressed as mean±SD or number (%); AFib, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; LAA, left atrial appendage.

Variable	Atrial Thrombi (n=12)	No Atrial Thrombus (n=309)	p
Age - mean±SD	71 .4±11	66±12	0.1
Gender - n (% female)	3 (25%)	84 (27.2%)	0.9
Hypertension - n (%)	8 (67%)	136 (44%)	0.1
Diabetes mellitus - n (%)	4 (33%)	43 (14%)	0.06
High blood cholesterol - n (%)	3 (25%)	80 (26%)	0.9
Body mass index – (kg/m²) - mean±SD	28.6±5	27.5±5	0.4
Ischemic cardiomyopathy - n (%)	3 (25%)	44 (14%)	0.3
CABG - n (%)	1 (8.3%)	11 (3.6%)	0.4
Stroke - n (%)	1 (8.3%)	14 (4.5%)	0.5
Valvular prothesis - n (%)	3 (25%)	15 (4.9%)	0.003
CHA^2DS^2-VASc score - mean±SD	3±2	2±1.5	0.048
Arrhythmia aetiology- n (%) AFL	5 (42%)	87 (28%)	0.3
AFib	7 (58%)	222 (72%)	55
LVEF (%) - mean±SD (n=273)	52±16	57±11	0.3
Left atrial volume (ml/m²) - mean±SD	57±19	46±17	0.04
LAA velocity (cm/s) - mean±SD (n=300)	0.41±0.3	0.55±0.2	0.04
Right atrial surface (cm²) - mean±SD (n=265)	21±3	23±7	0.4
Severe LAA contrast - n (%)	10 (83.3%)	8 (3.2%)	<.0001

Table 2: Patients with Thrombus versus patients without.

Values are expressed as mean±SD or number (%); AFib, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; LAA, left atrial appendage.

Variable	Atrial Thrombi n (%)	Crude odds ratio	95% CI	P value
Age	_	1.05	0.99, 1.12	0.1
Gender (female/male as reference)	3 (3.4%) / 9 (3.8%)	0.89	0.24, 0.89	0.87
Hypertension (presence/absence)	8 (5.6%) / 4 (2.3%)	2.54	0.75, 8.63	0.13
Diabetes mellitus (presence/absence)	4 (8.5%) / 8 (2.9%)	3.09	0.89, 10.72	0.08
High blood cholesterol (presence/absence)	3 (3.6%) / 9 (3.8%)	0.95	0.25, 3.61	0.95
Body mass index – (kg/m²)	_	1.06	0.94, 1.19	0.37

Ischemic cardiomyopathy (presence/absence)	3 (6.4%) / 9 (3.3%)	2.01	0.52, 7.71	0.31
CABG (presence/absence)	1 (8.3%) / 11 (3.6%)	2.46	0.29, 20.80	0.41
Stroke (presence/absence)	1 (6.7%) / 11 (3.6%)	1.92	0.23, 15.90	0.55
Valvular prothesis (presence/absence)	3 (16.7%) / 9 (3%)	6.53	1.60, 26.65	0.009
CHA^2DS^2-VASc score	_	1.41	0.99, 2.01	0.05
Arrhythmia aetiology- n (%) AFL (Afib as reference)	5 (5.4%) / 7 (3.1%)	1.82	0.56, 5.90	0.32
LVEF	_	0.97	0.93, 1.01	0.14
Left atrial volume (ml/m^2)	_	1.03	1.01, 1.06	0.041
LAA velocity (cm/s)	_	0.03	0.001, 0.79	0.036
Right atrial surface (cm^2)	_	0.94	0.83, 1.07	0.37
Severe LAA contrast (Severe/non severe as reference)	10 (55.6%) / 2 (0.7%)	188.13*	35.32, 1002.02	<0.0001

Table.3: Crude odd ratios for effects of factors on the risk of LAA thrombi in the entire population.

Values are expressed as mean±SD or number (%); AFib, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; LAA, left atrial appendage* When all the variables associated with the risk of LAA thrombi were modelled together, only severe LAA contrast remained significant ($p<0.0001$), valvular prothesis ($p=0.57$), LAA velocity ($p=0.85$), and Left atrial volume ($p=0.76$) did not remain significant.

Variable	**Atrial Thrombi**	**No Atrial Thrombus**	**p**
	(n=20)	**(n=301)**	
Age - mean±SD	73.2±10	65.5±12	0.004
Gender - n (% female)	5 (25%)	82 (27.2%)	0.8
Hypertension - n (%)	14 (70%)	130 (43.2%)	0.02
Diabetes mellitus - n (%)	6 (30%)	41 (13.6%)	0.04
High blood cholesterol - n (%)	6 (30%)	77 (26%)	0.7
Body mass index – (kg/m^2) - mean±SD	28.5±4	27.4±5	0.3
Ischemic cardiomyopathy - n (%)	5 (25%)	42 (14%)	0.2

CABG - n (%)	1 (5%)	11 (3.7%)	0.8
Stroke - n (%)	2 (10%)	13 (4.3%)	0.2
Valvular prothesis - n (%)	4 (20%)	14 (4.7%)	0.004
CHA^2DS^2-VASc score - mean±SD	3.2±2	2.1±2	0.002
Arrhythmia aetiology - n (%) AFL	10 (50%)	82 (27%)	0.3
AFib	10 (50%)	219 (73%)	
LVEF (%) - mean±SD	53±15	57±11	0.09
Left atrial volume (ml/m^2) - mean±SD	55±17	46±17	0.04
LAA velocity (cm/s) - mean±SD	0.35±0.2	0.56±0.2	0.0003
Right atrial surface (cm^2) - mean±SD	22±3	23±7	0.2

Table 4: Patients with Thrombus and/or severe LA contrast versus patients without.

Values are expressed as mean±SD or number (%); AFib, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; LAA, left atrial appendage.

4. Discussion

4.1 Major findings

Our prospective cohort study revealed that the prevalence of LAA thrombi detected by TEE was similar between patients referred for AFL ablation and those referred for AFib ablation, despite the use of DOACs in the majority of cases (≈91%). Rather than the arrhythmia etiology, the factors that were more predictive of LAA thrombi were related to the presence of vavular prosthesis, the CHA^2DS^2-VASc score and LA remodeling, with the latter evaluated using anatomical and functional parameters. Accordingly, LA dilatation and severe LAA contrast were more common in the subset of patients with LAA thrombi and lower LAA velocities.

4.2 LA mechanical alteration in patients with AFL

An evident limitation in the literature on AFL is the definition of arrhythmia. In many studies, a patient is defined as having AFL if this rhythm is noted during the intervention or observation period *(e.g.*, at the time of echocardiographic study or cardioversion). However, many patients exhibit alternating periods of AFib and AFL, making it difficult to evaluate the risk of thrombus formation in pure AFL [9, 11, 12]. In our study, we attempted to only select patients with pure apparent AFL without a history of AFib. In general, both mitral valve M-mode and transmitral Doppler studies demonstrated some organized atrial mechanical function with sustained AFL. Based on physiological alterations, AFL may theoretically be responsible for a much lower risk of thromboembolism. One study, for example, performed TEE immediately before and after cardioversion in 19 AFL patients and 44 AFib patients, which revealed the following findings [14]. Prior to cardioversion, patients with AFL displayed greater LAA flow velocities and shear rates than those with AFib. After cardioversion, appendage flow velocities and shear rates decreased in both patient groups, but the impaired LAA function was less pronounced in patients with AFL [14]. New or increased SEC, which is a marker of blood stasis, was significantly less frequent in patients with AFL (21% vs. 50% for AFib) [14]. The left atrium is akinetic in AFib, and there is an atrial contraction in AFL, which

potentially leads to less stasis of blood and less prevalence of thrombi. However, this hypothesis has not yet been demonstrated, particularly in the area of DOAC use. Moreover, a transient reduction in atrial mechanical activity, called atrial "stunning," is common after successful cardioversion or AFL radiofrequency therapy [14, 23, 24]. Yet, in general, atrial stunning appears to be less pronounced in AFL than in AFib, which probably explains the lower embolic risk after cardioversion in AFL [14, 23, 24].

4.3 Prevalence of AT in AFL

Conversely, TEE evidence of AT has been documented in a number of reports of patients with AFL [22, 24-26]. Thrombi prevalence varies largely in the literature, depending on the study type, publication time, and anticoagulant used [22]. For example, Schmidt et al. detected LA thrombi in two cases (1%) in a series of 202 consecutive AFL patients referred for an electrophysiological study [22]. This prevalence was lower than another older study that reported a prevalence of 11% out of 47 patients who were not on anticoagulation [24]. Other small studies have reported quite different results. Gaibazzi et al. found a 14% prevalence of LA thrombus (3% in patients without concomitant AFib) and 32% prevalence of SEC [29]. Black et al. detected a similar incidence of LA thrombus using TEE in patients with AFL (14%) and a 43% risk of SEC, but they only included seven (non-anticoagulated) patients in their analysis [30]. Irani et al. reported an 11% prevalence of LA thrombus (40% of thrombi in the LA body, rather than the LA appendage) and a 32% prevalence of SEC in patients with AFL [31]. Grönefeld et al. reported a 6.5% prevalence of LA thrombus and a 22.6% prevalence of SEC before planned radiofrequency catheter ablation of AFL [32]. This elevated prevalence was attributed, to a great extent, to the coexistence of AFib, which was associated with a 12-fold increased relative risk, compared to the existence of AFL alone [32]. The Flutter Atriale Società Ialiana di Ecografia Cardiovascolare (FLASIEC) conducted a prospective multicenter study analysis involving 124 patients with pure AFL, which revealed that the prevalence of thrombi was lower than in initial studies (1.6%), whereas SEC was present in 13% of cases [21]. More recent studies have confirmed that thrombus prevalence detected by TEE varies from 0% to 4.5%, but these studies were generally retrospective in nature or included only a low patient number [15, 21, 26]. In a meta-analysis based on 52 available articles [33], the authors reported prevalence of thrombus material ranging from 0% to 38% and a prevalence of SEC from 21% to 28% [33]. A particularly powerful study was published by Parikh et al., in which, despite its retrospective study design, TEE LLA thrombi and/or SEC were reported in 5.3% and 25.9% of patients, respectively [26]. Using CHA^2DS^2-VASc, LA thrombus was found in 1.7% of the low- to intermediate-risk group and 6.5% of the high-risk group (p=0.053) [26]. SEC was found in 11.8% of the low- to intermediate-risk group, versus 30.9% of the high-risk group (p= 0.004) [26]. In our study, we retrieved very similar findings, with a prevalence of 5.4% of thrombi in pure AFL patients. Furthermore, as reported by Parikh et al., thrombi were related to the CHA^2DS^2-VASc score but in addition we found a strong association with LAA remodeling (low LAA velocities and severe LAA echo contrast) and as expected the presence of valvular prothesis. Similarly, when we analyzed the risk of both thrombi and severe LAA contrast in association, we found that the presence of valvular prosthesis and LAA velocities alteration were independent predictive factors in reference of AFib.

4.4 Embolic risk in right AFL

There appears to be an increased risk for clinical thromboembolism in patients with chronic AFL [13, 34-36]. In a systematic review that was based on limited data, long-term embolic risk in patients with sustained AFL was estimated to be approximately 3% per year [13]. As an example, one study evaluated 100 patients who were referred to an electrophysiology laboratory for cardioversion of AFL, which had been present for least six months. Of these, 13 patients had a thromboembolic event, and this was attributable to AFL in six patients [36]. The embolism occurred during AFL or after cardioversion, with none of these patients receiving adequate anticoagulation. There were no embolic events in patients on adequate anticoagulation therapy. Similar results were noted in a series of 191 patients who were referred for cardioversion or AFL ablation [35]. During a follow-up of 26 months, an embolic event occurred in nine patients (5%), only one of whom was receiving therapeutic warfarin anticoagulation. In three of these patients, the embolic event was related to cardioversion. Using multivariate analysis, only a history of hypertension was an independent predictor of embolic risk. One problem with interpreting these data, as previously mentioned, is that many patients with chronic AFL (34% in the preceding report) [35] also had a history of AFib. In a review of the Medicare database, the risk of stroke was significantly increased in patients with AFL (relative risk of 1.41, compared to a control group). In these patients, the relative risk was 1.56 in patients who subsequently had an episode of AFib (which is similar to the risk with AFib alone), while the stroke risk for those with isolated AFL differed significantly from that of the control population (relative risk of 1.11) [34]. Risk factors for embolization, in addition to AFib, include rheumatic heart disease, depressed left ventricular systolic function, a history of thromboembolism, and atypical AFL.

4.5 Clinical implications

Our prospective study comparing AFib patients and pure AFL patients referred for ablation in our center demonstrated that the prevalence of thrombi detected by TEE was similar regardless of the arrhythmia type (3.1% vs. 5.4%, respectively). Despite anticoagulation, the population referred for ablation displayed significant LAA alteration, including thrombi that required management [7]. However, our observations support greater TEE scrutiny required to detect LAA thrombi. Therefore, we believe that our observations are relevant, and that the data are hypothesis-generating regarding the criteria used. Furthermore, although the incidence of thrombi appears to be low, stroke is clearly a devastating complication. Thus, systematic TEE has been intensely discussed in recent studies [5]. Especially two of them [37-38] concluded that performance of AFib ablation in patients on uninterrupted DOACs without TEE may be safe and feasible in high stroke-risk patients [37]. In the first one ICE imaging substituted TEE with visualisation of the LAA and detection of LAA thrombi before any trans-septal ponction. In the other one, there was no LAA visualisation neither with TEE nor ICE imaging with a low rate of thromboembolic events [38]. This approach may be very questionable for ethicals reasons such as the major consequences of stroke. None of these studies included AFL patients. Our results and those of other publications have proven that LAA thrombi are not uncommon in patients who are referred for cavotricuspid isthmus ablation, which exposes patients to stroke or cardio-embolism. Thrombi formation is more related to the CHA^2DS^2-VASc score, the presence of valvular prothesis and LA or LAA status. Indeed, our echocardiographic

analysis demonstrated that LA dilation and LAA functioning (based on LAA emptying velocity) exposed AFL patients to LA thrombi or severe LAA contrast. The different models tested found that AFL remains a significant factor of thrombosis or severe LAA contrast independently of AFib especially in presence of valvular prosthesis or in patients with LAA velocities alteration.

4.6 Limitations

Our study displays several limitations that must be acknowledged. First, this was a single-center study with a limited number of patients, which poses limitations about the generalizability of these findings. Thus, further higher-power multicenter studies are required. Second, a follow-up should be considered that includes the percentage of embolic events in the long term. Finally, while the multivariate analysis may have strengthened our study results, the number of factors studied is likely to limit the value of such an analysis. However, we cannot rule out that many patients exhibit alternating periods of AFib and AFL, despite our inclusion criteria. This makes it difficult to evaluate the risk of thrombus formation in pure AFL patients. Conversely, it must be stressed our data agree with real life conditions. Finally, the evaluation of the left atrial remodeling only based on a higher LA volume, severe LAA echo contrast and LAA velocities may be of critical value. Indeed, some recent studies highlighted the speckle tracking echocardiography left atrium function approach. This technic provided an independent and sensitive assessment of LA function throughout the cardiac cycle reflecting the total atrial activation time athat will be a surrogate for fibrosis and LA substrate remodelling [39]. This new criteria is already considered as a potential stroke predictive factor but it is hardly usable in daily practice due to technical limits.

5. Conclusions

The risk of LAA thrombi is better related to the presence of valvular prosthesis, CHA^2DS^2-VASc score and LA remodelling than the atrial arrhythmia itself. Accordingly, TEE should be recommended before right AFL ablation, especially in case of a valvular prosthesis, high CHA^2DS^2-VASc score or LA alteration.

Abbreviations

AFib: Atrial fibrillation

AFL: Atrial flutter

CI: Confidence interval

DOACs: Direct oral anticoagulants

LAA: Left atrial appendage

LA: Left atrium

LVEF: Left ventricular ejection fraction

SEC: Spontaneous echocardiographic contrast

TEE: Transesophageal echocardiography

VKAs: Vitamin K antagonists

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