Left atrial appendage thrombi relate to easily accessible clinical parameters in patients undergoing atrial fibrillation transcatheter ablation: A multicenter study

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Word count: 3,948 words, 3 tables, 1 figure and 22 references

Short title**:** left atrial appendage thrombus and ablation

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Abstract

Background. Transesophageal echocardiography (TEE) is routinely performed before atrial fibrillation (AF) transcatheter ablation to exclude the presence of left atrial (LA) or LA appendage (LAA) thrombi. Aim of the study is to evaluate if easily accessible clinical parameters may relate to the presence of LA or LAA thrombi to identify patients who could potentially avoid TEE.

Methods and Results. Between January 2012 and September 2014, data from 1,539 consecutive patients undergoing TEE, as a work-up before AF transcatheter ablation, in six large volume centers were collected. Baseline clinical features, CHA_2DS_2-VASc score, transthoracic echocardiography and presence of thrombi at TEE were recorded. Exclusion criteria were valvular, hypertrophic or dilated cardiomiopathy, previous heart surgery or an ejection fraction Ò35%. Mean age was 59.6 ± 10.4 years, 1,215 (78.9%) were males; 951 (62.9%) presented in sinus rhythm (SR) on admission, 324 (21.1%) had undergone at least one previous ablation and 900 (58.5%) had CHA_2DS_2-VASc score 0-1. Thrombi were encountered in 12 patients (0.8%). SR at TEE independently related to the absence of thrombi (OR 5.15, 95% CI 1.38-19.02, p 0.015); in addition to this, no patient with a CHA_2DS_2-VASc score 0-1 and SR on admission presented thrombi at TEE (specificity 100%, p=0.011).

Conclusion. In a selected population of patients referred for AF ablation, LA/LAA thrombi prevalence is low. No patients in SR with CHA_2DS_2-VASc score 0-1 presented LAA thrombi at TEE, identifying a significant subset of patients who could potentially safely be spared from pre-procedural TEE.

Key words: LAA thrombus; catheter ablation ï atrial fibrillation; transesophageal echocardiography.

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia. Its prevalence increases with age and the number of patients is expected to increase in the next years[1]. Percutaneous transcatheter ablation has proven to be safe and effective and the number of procedures performed worldwide is progressively increasing[2]. A pre-procedure evaluation, using a transesophageal echocardiogram (TEE), is commonly used to rule out the presence of thrombi in the left atrium (LA) or left atrial appendage (LAA)[2,3]. This examination is generally safe, technically simple and offers the unique advantage to accurately rule out the presence of LA/LAA thrombi before a procedure which can be associated with a significant risk of symptomatic[3] and asymptomatic thromboembolic events[4]. On the other side, this procedure can be time and resource consuming, often scarcely tolerated by patients and presents a not negligible rate of complications, which can rarely be life-threatening[5]. A very low prevalence of LA/LAA thrombi, moreover, is reported in patients undergoing AF ablation[6], making a discussion about the risk/benefit ratio of this exam in this setting mandatory.

For these reasons, it would be of utmost importance to evaluate if any clinical feature may predict the absence of LA/LAA thrombi and identify those patients who could potentially be spared from a TEE before AF ablation. The present multicenter study assesses the prevalence of LA/LAA thrombi at TEE in patients referred for AF ablation procedure in search of easily available clinical parameters that may relate to LA/LAA thrombosis.

Methods

Medical records of all consecutive patients planned to undergo AF ablation from January 2012 to September 2014 in six Italian high volume centers were retrospectively reviewed. Inclusion criteria were all consecutive patients undergoing pre-procedural TEE before (Ò48 hours) elective AF transcatheter ablation. In fact, at the time of collection of these data, all centres involved in the study routinely performed TEE to all patients undergoing AF ablation. Exclusion criteria were the presence of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), constrictive pericarditis and valvular cardiomyopathy, defined as valvular defect of at least moderate grade, previous heart surgery and a left ventricle ejection fraction (EF) Ò35%.

General and clinical data were recorded. Hypertension, dyslipidemia, disthyroidism, diabetes mellitus were defined and classified according to the current international guidelines; CHA_2DS_2-VASc score was computed for each patient.

AF was classified according to current European Society of Cardiology guidelines as paroxysmal, persistent and long-standing persistent[7]. Arrhythmia duration was intended as time from the onset of the first recorded arrhythmic episode.

Patients were treated according to the available latest AF ESC guidelines, particularly regarding long-term oral anti-thrombotic prophylaxis[7]. Oral anticoagulation (OAC) prior to AF ablation could be withdrawn or prosecuted according to physicians and treating centersô preference; in any case, for patients withdrawing OAC and/or not on long-term OAC a minimum of a 5 day-course of low-molecular weight heparin at weight adjusted dose (80-100U/Kg every 12 hours) was prescribed.

All patients underwent pre-procedural trans-thoracic echocardiography, and LA/ LAA thrombi or spontaneous echo contrast (SEC) were searched for by conventional TEE[5]. Thrombi were defined as circumscribed and uniformly echodense intracavitary masses distinct from the underlying LA or LAA endocardium[8]. Patients in whom a thrombus was described were temporarily withdrawn from the AF ablation procedure. Ejection Fraction, antero-posterior LA diameter and LAA dimensions

were classified according to the current guidelines on Chamber Quantification [9].

The study was performed in accordance to the latest Declaration of Helsinki and patients at each center provided written informed consent to undergo TEE.

Statistical Analysis

Categorical variables are reported as counts and percentages, while continuous variables as means and standard deviations. Correlations between parameters and study groups were tested in cross tabulation tables by means of the Pearson Chi-Square or Fisherôs Exact Test and by one-way ANOVA respectively for categorical and continuous variables. Sensitivity and specificity predictive values were assessed for clinical features reporting significant relation with LAA thrombi. Multivariate analysis was performed by a logistic binary regression model including parameters known to predict LAA thrombi and/or with a statistically significant relationship ($p < 0.05$) with the presence of LAA thrombi at univariate analysis.

A two sided p-value <0.05 was considered statistically significant; all analyses were performed with SPSS 21.0 (IBM Corporation, Armonk, NY, USA).

Results

A total of 1,539 patients were enrolled, of whom 1,215 (78.9%) males; 864 (56.2%) presented paroxysmal AF, 753 (48.9%) had hypertension and 66 (4.5%) suffered previous stroke or transient ischemic attack (TIA); on admission, 951 (62.9%) were in sinus rhythm (SR, Table 1). Nine hundred patients (58.5%) presented a CHA_2DS_2-VASc score of 0-1. Overall, 589 (56.2%) were on active OAC treatment with a vitamin-K antagonists (VKA), 6 (0.4%) with novel oral anticoagulants (NOAC). Overall, 164 (10.7%) patients were excluded due to the following exclusion criteria: 11 for HCM, 39 for DCM, one for constrictive pericarditis, 79 for valvular heart disease, 18 for previous heart surgery, 16 for EF Ò35%.

At TEE performed before the AF ablation procedure, LAA thrombi were detected in 12 patients (0.8%). All patients with LAA thrombi were on OAC with VKA, excepted two with CHA_2DS_2-VASc score 1. Among the patients with thrombi at TEE (Table 2), all of those with a CHA_2DS_2-VASc score 0-1 were in AF at the moment of the TEE, while the remaining 3 patients that were in SR during TEE presented a CHA_2DS_2-VASc score of 2 or higher. Seven of these patients were undergoing a first ablation procedure; only one was in SR at the moment of TEE (CHA_2DS_2-VASc score 3). At univariate analysis (Table 1), presence of AF during TEE and undergoing a redo procedure, related to the presence of thrombi at TEE (p=0.024, p=0.001, respectively). No patient with CHA_2DS_2-VASc score Ò1 and SR on admission presented thrombi at TEE (p=0.011, Figure 1). Only one patient on SR undergoing a first procedure presented a thrombus at TEE (CHA_2DS_2-VASc score 3). At multivariate analysis, adjusting for SR during TEE, CHA_2DS_2-VASc score 0-1, undergoing a first procedure, only SR at TEE significantly related to the absence of thrombi (OR 5.15, 95% CI 1.38-19.02, p 0.015).

As expected, prevalence of SEC was significantly higher in patients with LAA thrombi (91 (6.1%) vs. 5 (50%), $p < 0.001$).

Specificity and predictive values for the absence of thrombi at TEE were assessed for the

clinical variables emerged at univariate analysis or known to relate to LA/LAA thrombi. Individually CHA_2DS_2-VASc score as well as undergoing AF ablation for the first time reported a low specificity (58.5% and 41.7, respectively), while a higher specificity (75.0%) was reported for heart rhythm on admission and, even more, for presenting with SR at TEE while referred for the first procedure (90.0%). No patients with CHA_2DS_2-VASc score 0-1 and SR at TEE presented LAA thrombi at TEE, with a positive predictive value of 100% for the absence of thrombi for the combination of these two parameters.

Discussion

The main findings of our study are 1) that prevalence of LA/LAA thrombi in selected, consecutive patients referred for AF ablation is extremely low; 2) presence of SR on admission and a low-intermediate CHA_2DS_2-VASc score, especially in patients undergoing first AF ablation, relate to the absence of LA/LAA thrombi at TEE.

AF ablation is an interventional procedure that is becoming a mainstay in the management of AF [7,10]. Despite its widespread diffusion, questions concerning pre-procedural management, as the systematic need for TEE to exclude LA/LAA thrombi, still remain open. Not even the 2012 HRS/EHRA/ECAS consensus document on AF ablation reached an unanimous agreement on pre-procedural TEE indications, only suggesting TEE should be reserved to patients with AF on admission, especially when persisting from more than 48 hours[11]. In fact, to date, given the difficulty of certifying OAC effect over the weeks preceding the procedure and the hazard of presenting a thrombi despite therapeutic OAC, the majority, but not all, of the centers routinely perform TEE before the AF ablation despite correct anticoagulation [2,3,12]. In fact, in Europe, about 2 out of 3 patients undergo TEE prior to AF ablation, without major significant regional differences[13].

Our study included a selected population of patients without major structural cardiomyopathies undergoing AF ablation and is, to the best of our knowledge, the largest available series assessing this issue. Despite the strict selection criteria, the population included in our study is well representative of a relevant share of subjects undergoing AF ablation in European centers in the time span considered for our analysis[13]. A very low prevalence of LA/LAA thrombi is reported, however the prospective study by Puwanant et al. reported a similar prevalence of LAA thrombi (0.6%)[6]; in the European Atrial Fibrillation Ablation Pilot Study 7 patients out of 1410 did not undergo AF ablation due to a LAA thrombus. A slightly higher prevalence was reported instead in other experiences (ranging between 1.6%-3.6%), that, however, included patients at higher risk of thrombotic events who were excluded in our multicenter study (e.g. history of congestive heart

failure, structural heart disease, cardiomyopathies and valvular heart disease) [14, 15,16,17, 18,19].

In the population included in the present study, SR at TEE, and referral for first AF ablation procedure significantly related to the absence of thrombi at TEE. Of note, also the presence of SEC at TEE related to the presence of LA/LAA thrombi (5.9 vs. 50.0%, respectively in patients without and with LA/LAA thrombi; $p<0.001$). Given the aim of the study to identify easily available features relating to the presence of LA/LAA thrombi, this parameter has intentionally not been considered within predictors; in any case, its presence, provided that no thrombi were detectable, did not prevent patients from undergoing the procedure.

SR at TEE was the only independent predictor of LA/LAA thrombi at multivariate analysis. In addition, no patients in SR and with a CHA_2DS_2-VASc score of 0-1 presented thrombi at TEE. These results are consistent with those reported in previous studies: in seven prior series, only 5 patients with a $CHADS_2$ or CHA_2DS_2-VASc score of 0 presented thrombi at TEE[6,14,15,16,17,18,19]. Of these five patients only two were on SR at the time of TEE[14,17,18,19]. The present findings therefore confirm that a clinical assessment combining two simple parameters, heart rhythm and CHA_2DS_2-VASc score, may help to identify a relevant amount of patients (35.1% in our series) with a very low probability of presenting LA/LAA thrombi at TEE prior to AF ablation. A history of a previous AF ablation, instead, related to the presence of LA/LAA thrombi also in a previous study of Wallace et al[18]. This result may depend on the fact that a previous transcatheter ablation may determine increased atrial fibrosis[20], while AF relapses following failure of a first procedure may relate to decreased atrial function and increased LA dimensions[21], all predisposing substrates for thrombus formation and consequent thromboembolic risk.

In the present study, less than 60% of the patients not presenting a thrombus and slightly more than 30% of the patients in SR with low-intermediate CHA_2DS_2-VASc score were on long-term OAC before ablation. On the whole, all patients received at least a course of 5 days of low-molecular weight heparin before the TEE, remarking how the risk of LA/LAA thrombi is, in reality, in a general

population referred for AF ablation, quite low. These results may lead, in any case, to reconsider the appropriateness of executing TEE in all patients undergoing AF ablation.

In general, the present is a highly selected population with a low probability of LAA thrombi. Generalization of the present findings is therefore bound to subjects with similar characteristics. In fact, enrolment in the study was obtained after thorough TTE assessment in search of the declared exclusion criteria. Previous literature has proposed several TTE parameters, not considered in the present study, potentially related to an increased prevalence of LAA thrombi (i.e diastolic dysfunction, pulmonary hypertension, severe right atrial enlargement, poor LA function at speckle tracking[22]). These TTE features, especially when the hereby-proposed features suggest sparring a TEE, therefore candidate as reliable parameters to minimize potential residual risks. Indeed TEE is a safe and low expensive exam, which offers undeniable results in the search of LA/LAA thrombi, but the risk-benefit ratio of its use in the AF ablation setting should be carefully re-assessed. TEE presents a low, but still not negligible, risk of complications (0.8-2.8%)[5], and, in addition, may determine an unjustified increase in the health-care related costs other than being often poorly tolerated by the patients[23]. In conclusion, in our opinion, a careful risk/benefit ratio evaluation and prospective studies are needed to corroborate the comparative safety of an extensive vs. selective use of TEE prior to AF ablation.

Study limitations

The following limitations must be taken into account. First, this report is retrospective: study cohort may therefore be biased by patient selection by physician in charge. Second, multivariate analysis is based on a low number of events and is consequently limited in statistical power. The results of our study have consequently to be considered primarily as hypothesis generating. Third, as the aim of our study was to identify easily available features relating to the presence of LA/LAA thrombi, advanced and TEE parameters were

intentionally not included in the analysis. More specifically, thorough diastolic (i.e. DTI E/e') or LA function (i.e. by strain and/or speckle tracking) assessment, number of LAA lobes and peak flow velocity were not available, as they were not part of clinical routine when excluding thrombi at pre-procedural TEE; eventually LAA morphology was not assessed due to need for 3D segmentation techniques not routinely performed in all the centers involved[24 25]. Eventually, data concerning anticoagulation relate to prescribed and not effective treatment; for this reason, any conclusion on this topic has been avoided. Moreover, very few patients on NOAC were included, limiting generalization to patients on NOAC.

Conclusions

The present study shows that careful patient selection and a simple clinical assessment including CHA_2DS_2-VASc score, heart rhythm on admission, and ablation history may identify a relevant subset of patients with a very low probability of LA/LAA thrombi, who could be potentially safely spared from TEE before AF transcatheter ablation.

Acknowledgments: to all the cardiologists, cardiology fellows and paramedics assisting or performing the procedures and collecting the data that contributed to the realization of this study.

Conflicts of interest / Funding sources: none declared

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Table 1. Baseline clinical and echocardiographic characteristics of the study population stratified according to the presence of left atrial appendage thrombi. Values reported as counts and percentage, if not differently stated. P value by Pearson Chi-Square/Fisherôs Exact Test or ANOVA.

Characteristics	Overall population n = 1539	No LAA thrombus n = 1527	LAA thrombus n = 12	p value
Age (years)	59.6 ± 10.4	59.6 ±11.3	59.1 ± 19.4	*0.887*
Male	1215 (78.9)	1206 (79.0)	9 (75%)	*0.724*
BMI	19.0 ± 12.7	19.0 ±12.7	23.3 ± 11.5	*0.412*
Hypertension	753 (48.9)	745 (48.8)	8 (66.7)	*0.256*
Dislipidemia	237 (18.4)	235 (18.4)	2 (16.7)	*0.990*
PreviousStroke/TIA	66 (4.5)	65 (4.5)	1 (8.3)	*0.800*
Diabetes	89 (6.2)	89 (6.3)	0 (0)	*0.371*
Cha_2ds_2Vasc				
0	405 (26.3)	403 (26.4)	2 (16.7%)	
1	495 (32.2)	492 (32.2)	3 (25.0%)	*0.297*
2	382 (24.8)	379 (24.8)	3 (25.0%)	
Ó3	257 (16.7)	253 (16.6)	4 (33.3%)	
Paroxysmal AF	864 (56.2)	860 (56.4)	4 (33.3)	
Persistent AF	620 (40.3)	615 (40.3)	5 (45.5)	
Long-standing persistent AF	48 (3.1)	48 (3.1)	0 (0.0)	
AF duration (months)	56.3 ± 66.0	56.4 ± 66.1	47.2 ± 48.5	*0.756*
First AF ablation procedure	1215 (79.0)	1208 (79.1)	7 (58.4)	***<0.001***
Sinus rhythm at admission	951 (62.9)	948 (63.2)	3 (25.0%)	***0.024***
OAC	589 (56.2)	579 (55.9)	10 (83.3%)	*0.078*
TT Echocardiographic parameters				
LVEF (%)	60.5 ± 6.6	60.0 ± 5.6	60.6 ± 6.5	*0.819*
LA volume (ml)	84.8 ± 39.3	117.7 ± 25.4	84.7 ± 39.4	*0.149*
Left atrium AP diameter (mm)	45.2 ± 6.7	45.2 ± 6.7	51.5 ± 8.9	*0.061*

BMI, body mass index; TIA, transient ischemic attack; AF, atrial fibrillation; AP, antero-posterior; LA, left atrium; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; OAC, oral anticoagulation; TT, transthoracic

Table 2. Detailed clinical features of patients presenting with left atrial or left atrial appendage thrombus at transesophageal echocardiography.

Patient	Age	Sex	CHA_2DS_2-VASc score	First procedure	Long term OAC	Heart rhythm at TEE	Oral anticoagulation
1	67	M	2	NO	Yes	AF	Yes
2	65	F	5	No	Yes	SR	Yes
3	77	M	3	No	Yes	AF	Yes
4	63	M	1	Yes	No	AF	No
5	59	F	1	No	No	AF	No
6	65	M	2	No	Yes	SR	Yes
7	56	M	0	Yes	Yes	AF	Yes
8	63	M	3	Yes	Yes	SR	Yes
9	69	F	2	Yes	Yes	AF	Yes
10	58	M	2	Yes	Yes	AF	Yes
11	35	M	0	Yes	Yes	AF	Yes
12	67	M	1	Yes	Yes	AF	Yes

Table 3. Sensitivity and specificity predictive values for the clinical features showing a significant correlation for the absence of left atrial/left atrial appendage thrombi.

	Specificity	Sensitivity	PPV	NPV
CHA_2DS_2-VASc 0-1	58.5	58.3	99.4	1.1
SR at TEE	75.0	62.1	99.7	1.9
First Procedure	41.7	79.1	99.4	1.6
CHA_2DS_2-VASc score 0-1 and SR at TEE	100.0	35.2	100.0	1.2
SR at TEE and First Procedure	90.0	50.2	99.9	3.9
SR at TEE and CHA_2DS_2-VASc 0-1 and First Procedure	100.0	55.5	100.0	1.7

NPV, negative predictive value; PPV, positive predictive value

Figure titles and legends:

Figure 1. **Heart Rhythm,** CHA_2DS_2-VASc **score and Left Atrial or Left Atrial Appendage Thrombi.** Prevalence of left atrial or left atrial appendage thrombi stratified according to heart rhythm on admission and CHA_2DS_2-VASc score (SR, sinus rhythm; AF, atrial fibrillation).