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The profile of patients with atrial fibrillation scheduled for cardioversion or catheter ablation hospitalized in a Romanian rehabilitation hospital

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Abstract

Objectives - Structural cardiac, mainly atrial remodeling in non-valvular atrial fibrillation (NVAF) creates conditions for thromboembolic complications, despite the optimization of oral anticoagulant treatment over the past years. This study aims to provide a comparative analysis of patients with NVAF, with and without atrial thrombotic masses, in an integrated approach using clinical, electrocardiographic, anatomohemodynamic cardiac findings assessed by echocardiography, as well as an evaluation of the inflammatory status based on the usual screening blood markers. **Methods** – The study was based on the anonymous analysis of the medical records of 50 patients with NVAF monitored in a center of cardiology in Cluj-Napoca between March 2019 – February 2020, who received optimal oral anticoagulant treatment, all undergoing transesophageal ultrasound prior to cardioversion or ablation therapy. The statistical data processing methods were based on the "chi square" test and overall model fit logistic regression. **Results** – Atrial thrombotic complications were found in 7 (14%) patients with NVAF. These had, compared to patients without thrombotic masses, a mean CHA2DS2-VASc scale of 3 versus 2.76 ($p=0.05$), more frequently other atrial tachyarrhythmias ($p<0.01$), a more expressed inflammatory reaction ($p=0.02$), as well as a reduction of LVEF ($p<0.01$) and the peak left atrial appendage emptying velocity ($p<0.01$). **Conclusions** – In addition to a high CHA2DS2-VASc score, left anatomohemodynamic cardiac alteration, atrial arrhythmic complexity and background inflammatory status create conditions for high thromboembolic risk in patients with NVAF.

Keywords: *non-valvular atrial fibrillation, cardiac thrombosis, left ventricular ejection fraction, inflammatory status, peak left atrial appendage velocity,*

INTRODUCTION Atrial fibrillation (AF) represents the most usual sustained cardiac arrhythmia in adults, being at the same time the most frequent arrhythmic cause of hospitalization (1). In the presence of AF, the risk of thromboembolic complications – in the first place ischemic stroke – as well as the development of heart failure increases (biunivocal relationship).

Non-valvular atrial fibrillation (NVAF) evolves with a 5-fold increase in the risk of ischemic stroke. At present, NVAF benefits from the oral anticoagulant therapeutic contribution of both antivitamins K (AVK) and direct oral anticoagulants – non-vitamin K oral anticoagulants (NOAC), the therapy being monitored in relation to the CHA2DS2-VASc thromboembolic risk scale and the HAS-BLED hemorrhagic risk scale, according to current guidelines (2,3).

While the detrimental effects of NVAF on hemodynamics are well known and some factors that underlie the development of arrhythmia are also known (age, hypertension, diabetes mellitus, high body mass index, cardiomyopathy), no simple and reliable markers are available which allow accurately predicting the risk of arrhythmia as well as intracardiac (intraatrial) thrombosis. Analyzed separately, inflammatory markers, natriuretic peptides and adiponectin – although recognized as risk markers – are not specific enough to be used in a simple predictive manner (4).

Atrial fibrosis – a revealing element of atrial myopathy in patients with NVAF – develops in the context of the activation of coagulation proteins (it is currently accepted that AF entails a state of hypercoagulability) and of a concomitant increase in collagen synthesis (5). In close relationship with structural remodeling in NVAF is ionic remodeling, which has a strong arrhythmogenic effect (6,7,8).

Atrial remodeling in patients with NVAF has been the object of many echocardiographic studies over the past 3 decades, some of which relatively recent (9,10).

An extensive comparative analysis of patients with NVAF, related to the presence or absence of extensive cardiac (atrial) thrombosis, conducted by using clinical, electrocardiographic, anatomohemodynamic cardiac (left) findings assessed by echocardiography, as well as by evaluating the behavior of usual blood screening markers of the inflammatory status, was the object of the current research.

Material and methods

The studied cases were included in a retrospective observational study, performed by the anonymous analysis of the medical record documentation in the period March 2019 – February 2020 in the Clinic of Cardiology of the Clinical Rehabilitation Hospital in Cluj-Napoca, in a group of 50 patients with NVAF. All patients were on treatment with oral anticoagulants, NOAC or AVK and underwent transesophageal ultrasound prior to cardioversion (CV), sinus rhythm (SR) or ablation therapy (AB). The relationship between oral anticoagulant treatment and NVAF was flexible, in accordance with the current guidelines (11,12).

The general design of the research was focused on two distinct subgroups of patients with NVAF, with and without current cardiac (atrial) thrombosis or spontaneous (echocardiographic) contrast. The study inclusion criteria were based on the (documented) current or past presence of NVAF.

The exclusion criteria referred in the first place to patients diagnosed with valvular AF (mechanical prostheses, moderate or severe hemodynamic mitral stenosis).

In the second place, patients with NVAF who had one of the following conditions over the last six months were not included in the analysis:

- acute myocardial infarction
- acute infections (with or without acute cardiac involvement)
- surgical interventions (mainly for neoplasms), associated or not with radiotherapy and/or chemotherapy

To evaluate the risk of initiation and development of the prothrombotic intracavitary cardiac status, we used in the research three categories of study methods by which we analyzed four categories of parameters: clinical, electrocardiographic, echocardiographic and biohumoral blood parameters.

This clinical population study aimed to evaluate the demographic data (mainly patients' age and sex), history of stroke, as well as peripheral ischemic embolic events and NYHA classification. Based on the data collected from each patient, we calculated the scores of CHA2DS2-VASc thromboembolic risk and HAS-BLED hemorrhagic risk. The means of these two scores were analyzed comparatively in the two subgroups of patients with NVAF. In the clinical study, we also monitored the possible individual presence of a gastrointestinal and/or hepatic disease with a risk of hemorrhagic events, as well as of other medication, possibly interfering with the oral anticoagulant treatment. The patients were enrolled individually taking into consideration the type of NVAF, clinically defined as a first episode, paroxysmal (with or without recurrences), persistent (with or without recurrences), persistent in the long term, and permanent, according to current guidelines. In the clinical study, we also analyzed the conventional electrocardiographic examination of all patients (single or repeated), as well as Holter electrocardiographic monitoring (performed in some patients), in order to evidence other potential, clinically suggested atrial tachyarrhythmias, alongside or in association with NVAF.

The analyzed blood (laboratory) examinations referred on the one hand to the functional biochemical hepatorenal status and on the other hand, to the possible presence of a background inflammatory status of the patients, supported by the usual screening examinations – ESR, CRP, fibrinogen, uric acid – those with pathological values (between 1-4) being retained, without aiming to extend this objective by using much more sensitive biomarkers.

The echocardiographic examination of patients with NVAF was aimed in the first place at quantifying the anatomohemodynamic cardiac (mainly left) status with focus on the left atrial cavity size, on the main morphofunctional parameters of the left atrial appendage (LAA), as well as the left ventricular ejection fraction LVEF. In the second place, we monitored the possible presence of thrombotic cavity masses and/or the spontaneous contrast (SC) image, in the given arrhythmic context. We used the data obtained from transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). We assessed the values of the left atrial (LA) telesystolic diameter (mm), LAA emptying velocity (m/sec) – LAA Vmax –, LAA opening (cm) – LAAO –, LVEF values (%), all this alongside the topography of the thrombotic intracavitary masses or the SC image.

Statistical analysis

For statistical processing, based on the data of the investigated patients – data initially collected in EXCEL format –, the second storage file ("database") processed in Stat view format was created. To compare the parametric variables, the Student t test was used, with the significance level set at $p \leq 0.05$. The measurement of the "association", among categorical variables was performed with the "chi square" test (x^2), the significance of the association being similar to that for p values <0.05.

The correlation of two parametric variables such as LVEF, of the values of the studied parameters in LA and LAA, of thromboembolic and hemorrhagic risk scales as well as inflammation biomarkers (IFBM) was expressed by means of Pearson's correlation coefficient or r. The correlation was considered significant at $p < 0.05$. The correlation of non-parametric values (e.g. the clinical type of NVAF versus NYHA class) was expressed using Spearman's correlation coefficient, with the same significance value of $p<0.05$. In the categories of parametric as well as non-parametric variables, to express the influence of a variable considered "independent" (predictive factors) on other variables considered

"dependent" (outcome variables), the simple and multiple linear regression model was used, the correlation, regression coefficients and the intercept being interpreted in the spirit of statistical requirements, according to the accepted level of significance (13). The numerical categorical parameters with statistical significance underlying multivariate analysis were expressed distinctly, but also synthetically (multivariate score) using ROC curves. Statistical analysis was based on the IBM SPSS software, version 22.

Results

Of the 50 patients with NVAF, 7 (14%) patients had, in a cumulated manner, an echocardiographic image of cardiac thrombosis (CT) – 6 patients, and spontaneous contrast (SC) – one patient. The thrombotic cavitary masses were distributed as follows: LAA – 3 patients, right atrium (RA) – 2 patients, LA – 1 patient. The SC image was also found in LA.

The comparative evaluation of clinical, electrocardiographic, echocardiographic, biohumoral blood parameters of inflammation and statistical analysis, using the Student t test, in patients with NVAF with and without CT/SC are shown in Table 1.

The mean age of patients with NVAF and thrombotic cardiac complications was 65.28±7.8 years, compared to those without these complications (62.06±9.5 years), a statistically insignificant difference (p=0.31).

Intracardiac thrombotic /SC masses were found in 5 male patients and 2 female patients with NVAF, with a similar percentage distribution of men in the group with CT/SC (71.42%) and without CT/SC (62.76%).

The functional cardiac behavior expressed by NYHA classes in patients with NVAF with and without CT/SC is also of interest. If in the first situation, 85.72% of the patients were assigned to NYHA classes II and III (distributed in equal proportions in these classes) and the rest of 14.28% belonged to NYHA class I, in the second situation NYHA class I included 58.13% of patients, the rest being distributed in NYHA classes II and III.

Patients with NVAF and CT/SC have a history of cumulated thromboembolic cerebral or peripheral events 6 times more frequently than those without current CT/SC, the difference being statistically significant for AVK (p=0.02).

In 4/5 of patients with NVAF – both in the group with and without CT/SC – the clinical types of AF, found in similar proportions, were represented by paroxysmal-recurrent and persistent AF.

Of all patients with NVAF, 11 (22%) patients had associated intermittent atrial flutter (AFL) and/or focal atrial tachycardia (FAT).

An important difference of the subgroups of patients with NVAF, in relation to the presence/absence of CT/SC, is the association of other atrial tachyarrhythmias (AFL, FAT) in a much higher percentage in the first situation (85.71%) compared to the second (11.62%) (p<0.01).

The cardiogenic substrate of NVAF was dominated by ischemic heart disease (IHD) in over ¾ of the cases, in both groups of patients (with and without CT/SC).

High values of the usual inflammation biomarkers (IFBM) evaluated in all patients with NVAF and CT/SC were also found in a high percentage in patients without CT/SC, the difference being however statistically significant (p=0.02).

Oral anticoagulation in patients with CT/SC was dominated by the use of AVK. This was performed in 71.42% of the patients compared to patients with NOAC (28.56%), while in patients without CT/SC, the percentages of AVK (51.16%) and NOAC (48.84%) were relatively similar.

The CHA2DS2-VASc thromboembolic risk score in both groups of patients with NVAF ranged between 1-5, having a slightly higher mean value in the subgroup of patients with CT/SC – 3 – compared to patients without CT/SC – 2.76, reaching the level of statistical significance (p=0.05).

The HAS-BLED hemorrhagic risk score had a slightly higher mean value in the case of patients with NVAF and CT/SC, compared to those without thrombotic complications (1.85 versus 1.72).

The analysis of echocardiographic anatomohemodynamic and functional parameters of the left heart provided interesting results regarding patients with and without CT/SC. The mean values of the LA telesystolic diameter, slightly increased compared to the upper limit of normal, were similar in the two subgroups (42.42 versus 43 mm). However, the considerable decrease of the mean LAA Vmax value (0.31 m/sec) in patients with CT/SC, compared to the mean value of 0.59 m/sec found in patients without CT/SC, highly statistically significant (p<0.01), is of interest. In the same line falls the decrease in the mean LAAO values in patients with CT/SC compared to those without CT/SC, without reaching the threshold of statistical significance.

Extremely relevant among echocardiographic parameters is the mean LVEF value, considerably decreased in patients with NVAF and CT/ SC (42%), compared to the mean value of patients without CT/SC (51.93%) (p<0.01).

The study of the correlations between two parametric values that reached the threshold of statistical significance, using Pearson's correlation coefficient or r, expressed a variation in the same direction (direct correlation) when analyzing the behavior of LAA Vmax (m/s) versus LVEF (%) (Figure 1).

We found a significant indirect correlation between IFBM and LVEF (Figure 2), LAA Vmax (m/s) respectively (Figure 3).

In univariate analysis, the impact on thrombogenesis/thromboembolism – as an endpoint – of LAA Vmax, LVEF and IFBM is found by testing the sensitivity and specificity of ROC curves, illustrated in Figure 4.

The multivariate analysis of prothrombotic/thromboembolic risk – according to the mathematical model of logistic regression adapted to the studied cases – allowed including maximum 5 variables of the group of those with certain statistical significance. The representation of the 4 categories of studied parameters (clinical, electrocardiographic, echocardiographic, blood IFBM) was taken into consideration. For clinical parameters, we chose to include the history of thromboembolic events (stroke), over the CHAD2DS2-VASc scale (due to the strength of statistical significance, more obvious in the first situation). Thus, the logistic regression mode included the personal history of thromboembolic events, LAA Vmax and LVEF, arrhythmic complexity (instability) defined by the presence of other atrial arrhythmias, in addition to atrial fibrillation and usual inflammation IFBM. The LAA Vmax – atrial arrhythmic complexity (instability) pair was detached, reaching each a final p value =0.04. The details of mathematical-computer processing are illustrated in Table 2.

The complete unfolding of the mathematical logistic regression model, in a synthetic form, of prothrombotic/thromboembolic risk in the studied cases with NVAF is also found in the multivariate risk score, illustrated in Figure 5.

Last, but not least, hemorrhagic complications, absent in patients with NVAF and CT/SC, were found in 13.95% of patients without CT/SC, being represented by ecchymoses, epistaxis, gingivorrhagia, macroscopic hematuria.

Discussions

The thrombogenic/thromboembolic context in the analyzed NVAF cases was assessed using four categories of parameters. These were clinical, electrocardiographic, echocardiographic and biohumoral blood parameters. For clinical parameters, we analyzed the CHA2DS2-VASc thromboembolic risk scale, as well as the presence of personal thromboembolic history. Electrocardiographically, by conventional monitoring we evaluated atrial arrhythmic complexity (instability), retaining the presence of other atrial tachyarrhythmias alongside atrial fibrillation, at various succession moments. Echocardiographically, we assessed the behavior of some anatomohemodynamic parameters (of the left heart), focusing on LA, LAA Vmax, LAAO, LVEF, alongside the presence of intracardiac thrombotic masses and/or SC appearance. For the usual blood screening biomarkers of inflammatory status, we analyzed the behavior of ESR, CRP, fibrinogen and uric acid.

NVAF is an important condition of thromboembolic risk with a cardiac starting point. The presence of thrombosis located in LA increases the risk of stroke 2.5-3 times (14). This requires permanent anticoagulation of patients with NVAF. About one fifth of the causes of ischemic stroke are based on the cardioembolic mechanism (15). AF is known to be the most frequent cause of cardioembolic ischemic stroke (16). Research over the past decade has highlighted the fact that excessive extrasystolic supraventricular ectopic activity is correlated with a high risk of AF and stroke (17). At the same time, it was emphasized that LA can be a source of thromboembolic ischemic stroke secondary to atrial myopathy, even in the absence of AF (18, 19, 20). Currently, the idea is accepted that if after ischemic stroke the presence of frequent atrial extrasystoles is found, this is associated with atrial remodeling and dysfunction, revealing elements of early left atrial remodeling (21). Furthermore, the increase in LA volumes – an aspect observed in our cases as well – and the alteration of LA function are associated with a decrease in the LAA emptying velocity, which we also found in our cases, predominantly in NVAF cases that developed thrombosis located in LA, LAA respectively.

The identification of the intermittent presence, in the context of NVAF, in our study, in a proportion higher than 85% of other atrial tachyarrhythmias (AFL, FAT, independent or associated) is an argument for the presence of atrial remodeling in the group of patients who developed CT and central or peripheral cardioembolic events.

Atrial remodeling in patients with NVAF approached by echocardiography is considered not only through the morphological component – focused on LA size – but also through the functional component. The integrated approach of these 2 components underlay the definition of the concept of atrial remodeling (22). This is a dynamic process, in which atrial fibrosis, contractile status alteration, inflammation, fat infiltration, ischemia and ion channel dysfunction with the generation of electrical instability, the main actor being the calcium ion, play a role (23). The behavior of the right atrium (RA) in patients with NVAF was also monitored, which opened the way to the concept of biatrial remodeling in patients with NVAF (24).

In patients with NVAF, high LA values associated with the arrhythmic context and stasis represent a triad of prothrombotic intracavitary risk.

TEE, complementing the findings of TTE, provided in TM and two-dimensional modes, has a major contribution to the anatomohemodynamic evaluation of LA and LAA, offering significant diagnostic elements, both regarding prothrombotic cavitary risk in patients

with NVAF and the diagnosis of developed intracavitary thrombotic masses. TEE allows an accurate evaluation of the LA surface (25). In LAA, using TEE, biphasic pulsed Doppler flow is recorded (positive flow meaning emptying and negative flow being recorded during filling). An emptying velocity value <0.25 m/s shows the presence of a LA with thromboembolic arterial risk. The normal velocity of LAA flow is >0.4 m/s. Values lower than 0.20-0.25 m/s are considered to have the significance of major cardioembolic risk. In our cases with NVAF who developed CT, the mean LAA emptying velocity value was 0.31 m/s, lower than in patients with NVAF without thrombotic masses of LA or LAA, where the mean value of this parameter by TEE was 0.59 m/s. The opening of LAA was also evaluated by TEE; the mean value in patients with NVAF and CT was 0.97 cm, compared to 1.52 cm in patients with NVAF without CT. The presence of SC and sludge in LA and LAA is also evidenced using TEE. The decrease of LVEF <50% correlated with the mentioned LA and LAA abnormalities significantly increases cardioembolic risk in patients with NVAF. TEE also allows assessing the behavior of thrombotic masses formed in LA or LAA.

TTE examination was also focused on the evaluation of LVEF. For each patient, the mean value of three LVEF determinations, in the arrhythmic context of NVAF was retained. The assessment of the contractile status of the left ventricle, starting from its importance in the determinism of left ventricular systolic performance in patients with NVAF, adds to the value of the LA cavity size an additional pathogenic significance in the determinism of cardioembolic risk in patients with NVAF.

In relation to the thrombogenic process, in patients with NVAF, assessing their background inflammatory status is also of interest, as it is known that prothrombotic status and thrombogenesis are closely related to IF and endothelial dysfunction. In our cases, we analyzed the presence of IFBM evaluated as part of the routine screening (ESR, CRP, fibrinogen, uric acid). The numerical presence, isolated or associated in various combinations, of their pathological values was 100% in patients who developed thrombotic masses and 88.37% in those without thrombotic masses. In addition to this general context, in patients with NVAF and intraatrial/or LAA thrombosis, the presence of altered anatomohemodynamic parameters such as the reduction of LVEF, LAA Vmax, atrial dilation increases thrombogenic and cardioembolic risk (26,27).

The predictors of stroke in NVAF in our cases are represented by LA dilation, the presence of the SC image in LA, the presence of thrombosis in LAA (half of the cases with thrombi are located here), and the decrease in LAA Vmax to a value of 0.31 m/s and in LVEF, along with an increase in atrial electrical instability through the increase of arrhythmic complexity at atrial level.

Relevance and limitations of the study

The approach through a multimarker analysis of thromboembolic risk in NVAF, by evaluating some clinical parameters (clinical type of AF, NYHA class, presence of thromboembolic history, evaluation of thromboembolic and hemorrhagic risks, by specific risk scales), echocardiographic anatomohemodynamic cardiac parameters – mainly of the left heart – in addition to the diagnostic impact of intracardiac thrombotic masses, electrocardiographic parameters of complex atrial arrhythmic instability, as well as taking into consideration a possible contributive thrombogenic quota of patients' background inflammatory status in a retrospective evaluation over one year represents an integrated approach, in a personal concept, of the research. Certainly, this intention leaves the way open for future research, especially by integrating the contribution of a more extensive study on inflammation, its interrelation with hemodynamic and oxidative stress in patients with NVAF, resulting in the diagnostic optimization of the thrombogenesis process, as well as the efficiency of oral anticoagulant therapy.

The limitations of the study are represented in the first place by a relatively reduced number of cases, given the study inclusion criteria for patients with NVAF (exclusion of patients with valvular F) in the year preceding the COVID-19 pandemic.

A second limitation of the study is using, with the aim of unifying the collected data – within the anatomohemodynamic cardiac parameters evaluated by echocardiography – the telesystolic diameter of LA, less reliable than its area or especially its volume. We used LA diameter because this was found in all echocardiographic results, the other two atrial parameters being mentioned sporadically and separately.

Conclusions

The mean CHA2DS2-VASc value, statistically significantly higher in patients with NVAF and intracardiac thrombotic masses compared to that of patients with NVAF without intracardiac thrombotic masses, confirms the value of element revealing thromboembolic risk of this scale. In the given context, the alteration of left cardiac anatomohemodynamic status, associated with atrial arrhythmic complexity, occurring on an inflammatory background, forms a triad of increased thromboembolic risk in patients with NVAF.

Abbreviations

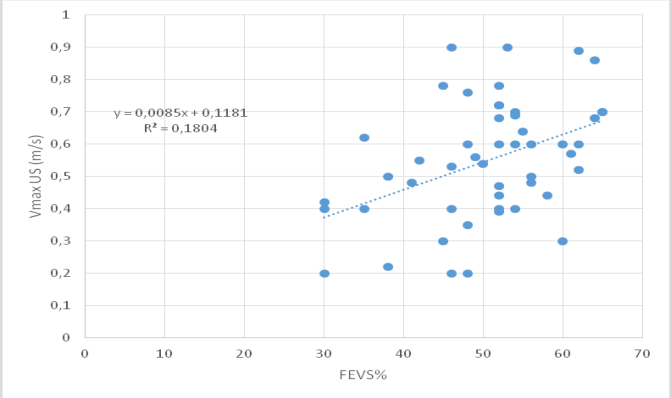
AB = ablation, RA = right atrium ,LA = left atrium, AVK = antivitamins K, IFBM = inflammatory biomarkers, CF = control of frequency, IHD = ischemic heart disease, SC = spontaneous contrast, CV = cardioversion, LAAO = left atrial appendage opening , TEE = transesophageal echocardiography, TTE = transthoracic echocardiography, AF = atrial fibrillation, NVAF = non-valvular atrial fibrillation, LVEF = left ventricular ejection fraction, AFL = atrial flutter, IF = inflammation, NOAC = non-vitamin K oral anticoagulant,

RF = radiofrequency, SR = sinus rhythm, CT = cardiac thrombosis, emptying velocity
LAA = left atrial appendage, LAA Vmax = left atrial appendage

Table 1. Structure and main characteristics of the subgroups of patients with NVAF, with and without cardiac thrombosis or spontaneous contrast (echocardiographic)

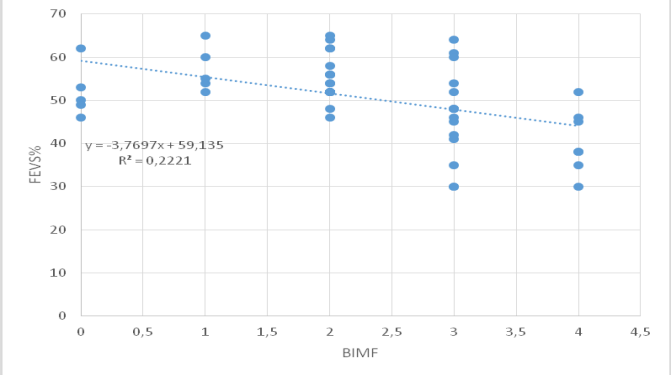
Total number of patients with NVAF (n=50)	NVAF with CT/SC (n=7)	NVAF without CT/SC (n=43)	P
Age (years)	65.28±7.8	62.06±9.5	0.31
Men (n%)	5/7(71.42%)	27/43(62.76%)	0.99
NYHA class			
I	1/7(14.28%)	25/43(58.13%)	0.08
II	3/7(42.86%)	14/43(32.55%)	0.92
III	3/7(42.86%)	4/43(9.32%)	0.07
Thromboembolic history			
Stroke	4/7(57.14%)	5/43(11.62%)	0.02
SE	1/7(14.28%)	0/43	0.48
NVAF - type			
Paroxysmal	1/7(14.28%)	3/43(6.97%)	0.48
Paroxysmal-recurrent	3/7(42.86%)	18/43(41.86%)	0.72
Persistent	3/7(42.86%)	17/43(39.53%)	0.80
Persistent-recurrent	0/7	3/43(6.97%)	0.45
Permanent	0/7	2/43(4.65%)	0.50
AF+other atrial arrrhythmias	6/7(85.71%)	5/43(11.62%)	<0.01
NVAF substrate			
IHD	5/7(71.42%)	35/43(81.39%)	0.92
HC	1/7(14.28%)	3/43(6.97%)	0.93
TCM	1/7(14.28%)	2/43(4.65%)	0.89
IDCM	0/7	1/43(2.32%)	0.60
ASD	0/7	1/43(2.32%)	0.60
VSD	0/7	1/43(2.32%)	0.60
Oral anticoagulation			
NOAC	2/7(28.56%)	21/43(48.84%)	0.56
AVK	5/7(71.42%)	22/43(51.16%)	0.56
Blood IFBM	7/7(100%)	38/43(88.37%)	0.02
CHA_2DS_2-VASc score			
1	0/7	9/43(20.93%)	0.68
2	3/7(42.86%)	10/43(23.22%)	0.53
3	2/7(28.56%)	11/43(25.58%)	0.77
4	1/7(14.28%)	8/43(18.60%)	0.80
5	1/7(14.28%)	5/43(11.62%)	0.67
Mean of the CHA_2DS_2-VASc scale	3	2.76	0.05
HAS-BLED score			
1	1/7(14.28%)	18/43(41.86%)	0.33
2	6/7(85.71%)	18/43(41.86%)	0.08
3	0/7	7/43(16.28%)	0.90
Mean of the HAS-BLED score	1.85	1.72	0.69
Echocardiographic parameters			
LA (mm)	42.42	43	0.76
LAA Vmax (m/s)	0.31	0.59	<0.01
LAAO (cm)	0.97	1.52	0.21
LVEF (%)	42	51.93	<0.01
Treatment			
CV	0/7	19/43(44.18%)	0.12
AB	0/7	20/43(46.51%)	0.10
CF	7/7(100%)	4/43(9.31%)	<0.01
Hemorrhagic complications	0/7	6/43(13.95%)	0.097

Data represent the mean ± SD, number and percentage of patients (%). NVAF, non-valvular atrial fibrillation; IHD, ischemic heart disease; HC,
hypertensive cardiomyopathy; TCM, tachyarrhythmic cardiomyopathy; IDCM, ischemic dilated cardiomyopathy; ASD, atrial septal defect;
VSD, ventricular septal defect; IFBM, inflammation biomarkers; CV, cardioversion; AB, ablation; CF, control of frequency; LA, left atrium;
LAA, left atrial appendage; LVEF (%), LV ejection fraction; LAA Vmax, LAA emptying velocity; LAAO, LAA opening; SC, spontaneous contrast; CHA_2DS_2-VASc, thromboembolic risk score; HAS-BLED hemorrhagic risk socre; ES, systemic embolism; CT, cardiac thrombosis; SC, spontaneous contrast; NOAC, non-vitamin K antagonist oral anticoagulants; AVK, antivitamins K; p>0.05, statistically insignificant (NS).



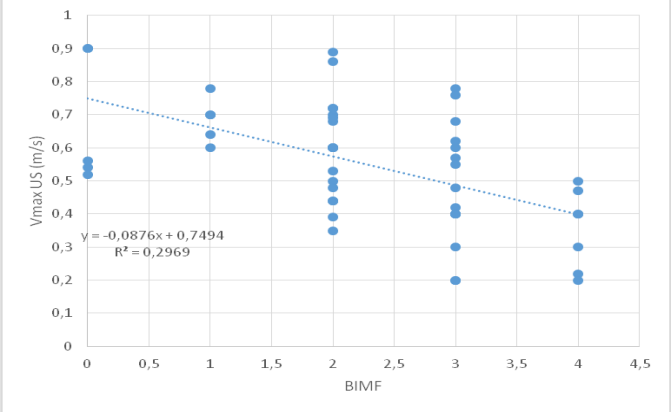
r=0.424744 p=0.02

Fig. 1. The LAA Vmax (m/s) / LVEF (%) correlation



r= -0.471248 p=0.01

Fig. 2. The LVEF (%) / IFBM (n) correlation



r= -0.54486 p<0.01

Fig. 3. The LAA Vmax (m/s) / IFBM (n) correlation

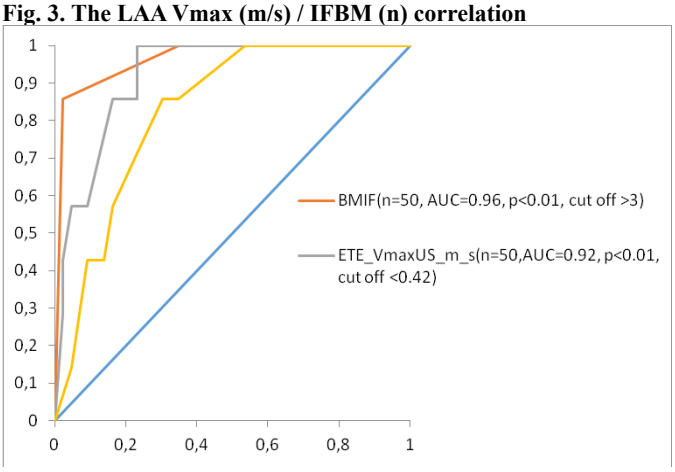


Fig. 4. ROC curves of IFBM, LAA Vmax and LVEF in relation to thrombogenic/thromboembolic risk in patients with NVAF

Table 2. Multivariate analysis, by logistic regression, of prothrombotic/thromboembolic risk in the studied patients with NVAF

Logistic regression

Overall Model Fit	
Null model -2 Log Likelihood	40.496
Full model -2 Log Likelihood	10.208
Chi-squared	30.288
DF	2
Significance level	P < 0.0001
Cox & Snell R^2	0.4543
Nagelkerke R^2	0.8185

Coefficients and Standard Errors				
Variable	Coefficient	Std. Error	Wald	P
TEE_LAA Vmax_m_s	-25.49805	12.85457	3.9346	0.0473
Other atrial arrhythmias_n	6.42251	3.13857	4.1874	0.0407
Constant	5.6994			
Variables not included in the model				
IFBM				
TTE_LVEF%				
APP2_n				

Odds Ratios and 95% Confidence Intervals		
Variable	Odds ratio	95% CI
TEE_LAA Vmax_m_s	8.44E-12	9.64521E-023 to 0.7385
Other atrial arrhythmias_n	615.5475	1.3112 to 288976.6688

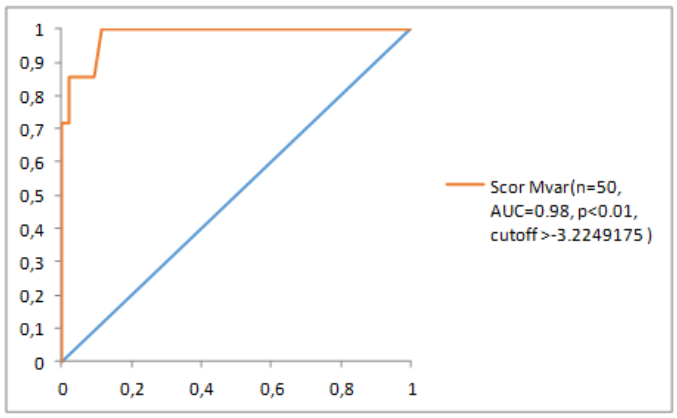


Fig. 5. Multivariate prothrombotic/thromboembolic risk score of the studied patients with NVAF

References

1. Benjamin EJ, Muntner P, Alonso A et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. Circulation. 2019; 139: e56 – e528.

2. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax J, Lundqvist BC, Boriani G, Castella M, Dan GA, Dilavelis PE, Fauchier L, Filippatos G, Kalman JM, Meir ML. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with European Association of Cardio-Thoracic Surgery (EACTS). The Task Force for the diagnosis and management of atrial fibrillation of the Europeam Society of Cardiology. Eur Heart J. 2020;42:373498.
3. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan V, Rowel N, Sinnaeve P, Collins R, Camon AJ, Heidbuchel H. The 2018 European Heart Rhythm Association Practical Guide of the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330-1393.
4. Machered F, Bartz TM, Djousse L, et al. Higher circulating adiponectin levels are associated with increased risk of atrial fibrillation in older adults. Heart. 2015;101: 1368-1374.
5. Sproneck HMH, De Jong AM, Verheule S, et al. Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. Eur Heart J. 2017; 38: 38-50.
6. Richard S, Thireau J. Physiopathologie de canaux calciques de type I. cardiaques. Arch Mal Coeur Vaiss Prat. 2014; 225: 28-32.
7. Hatem SN, Coulombe A, Balse E. Specificities of atrial electrophysiology: Clues to a better understanding of cardiac function and the mechanisms of arrhythmias. J Mol Cell Cardiol. 2010; 48: 90-95.
8. Algalarondo V. Physiopatologie de la fibrillation atriale à l'échelle cellulaire. Arch Mal Coeur Vaiss Prat. 2015; 235: 27-31.
9. Soulat-Dufour L, Lang S, Ederhy S, et al. Biatrial remodeling in atrial fibrillation: A three – dimensional and strain echocardiography insight. Arch of Cardiovasc Dis 2019; 112: 585-593.
10. Thomas L, Abhayaratna WR. Left atrial reverse remodeling: mechanisms, evaluation, and clinical significance. JACC Cardiovascular Imaging. 2017; 10: 65-77.
11. Cohen A, Ederhy S, Lang S, Boccara F. Bleeding risk and use of oral anticoagulant. Arch of Cardiovasc Dis. 2016; 8: 288-302.
12. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Eurospace 2015; 17: 1467-1507.
13. Dumitrașcu D, Dumitrașcu DL. Introducere în cercetarea științifică, Editura Dacia, Cluj Napoca, 2007.
14. The Stroke, Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with non-valvular atrial fibrillation. Ann Intern Med. 1998;128:639-647.
15. Palacio S, Hart RG. Neurologic manifestations of cardiogenic embolism: an update. Neurol Clin. 2002;20:179-193.
16. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. New Engl J Med. 2014;370:2467-2477.
17. Binici Z, Intzilakis T, Nielsen OW, et al. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation 2010;121:1904-1911.
18. Kamel H, Okin PM, Elkind MS, et al. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. Future Cardiol. 2015;11:323-331.
19. Okin PM, Kamel H, Devereux RB. Electrocardiographic left atrial abnormalities and risk of incident stroke in hypertensive patients with electrocardiographic left ventricular hypertrophy. J Hypertens. 2016;34:1831-1837.
20. Overvad TF, Nielsen PB, Larsen TB, Sogaard P. Left atrial size and risk of stroke in patients in sinus rhythm. A systematic review. Thromb Haiemost. 2016;116:206-219.
21. Agathe Py, Mathieu S, Suzanne D, et al. Atrial premature activity detected after an ichaemic stroke unveils atrial myopathy. Arch Cardiovasc Dis. 2020;113:220-236.
22. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS EUR Heart J. 2016; 37: 2893-2962.
23. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol. 2014; 63: 2335-2345.
24. Műller H, Noble S, Keller PF, et al. Biatrial anatomical reverse remodeling after radiofrequency catheter ablation for atrial fibrillation: evidence from real – time three – dimensional echocardiography. Europace. 2008; 10: 1073-1078.
25. Ursula W, Kruk J. Handbuch der Echokardiographie, Georg Thieme Verlag,2019
26. Choudhury A, Odell JA, Pengo V. Atrial fibrillation and the hypercoagulable state: from basic science in clinical practice. Pathophysiol Haiemost Thromb. 2003;33:282-289.
27. An K, Mei J, Zhu J, et al. Endocardial changes in non-valvular atrial fibrillation without atrial thrombus-thrombomodulin and tissue factor pathway inhibitor. Clin Appl Thromb Hemost. 2018;24:1148-1152.