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Thrombus formation in the left atrial appendage in the course of atrial fibrillation

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Abstract. – ***Background.*** **Thromboembolism in patients with nonvalvular atrial fibrillation is secondary to emboli arising from atrial cavities, particularly left atrial appendage. Stroke Prevention Atrial Fibrillation (SPAF) III study showed washing flow, left appendage ejection fraction, natural echocontrast, and left appendage volume and morphology, as risk parameters of thromboembolism.**

Methods. **The authors examined 69 patients by transesophageal echocardiography, subdividing them into 3 groups: 26 patients in sinus rhythm in Group A (Gr.A), 22 patients in atrial fibrillation without thrombi in the left atrial appendage in Group B (Gr.B), 21 patients with tromboembolism and with thrombus in the left atrial appendage (Gr.C)**

Results. **Atrial volume in sinus rhythm (SR) patients (41.9 ± 23.4 cm^3) was lower than the one in Gr.B (86.2 ± 47.9 cm^3, $p < 0.001$) and Gr.C (78.6 ± 28.5 cm3, $p < 0.01$), whereas no difference was found between Gr.B and Gr.C (86.2 vs. 78.6 cm^3; $p > 0.05$). No difference was found between Gr.A and Gr.B left atrial appendage fraction (31.8% versus 29.1%, $p > 0.05$), whereas it was found related to Gr.C (31.8% versus 15.4% $p < 0.01$). Flow velocity within left atrial appendage was significantly higher in Gr.A in relation to the other two groups ($p < 0.001$); flow velocity in Gr.B was lower than in Gr.A but higher than in Gr.C and in all cases such differences were statistically significant ($p < 0.001$). Gr.A flow duration was approximately twice as much compared to the one in Gr.B (616.8 ± 94.1 msec vs. 483.3 ± 172.6 msec, $p < 0.01$), whereas it was approximately four times higher compared to the one in Gr.C (616.8 ± 94.1 msec vs. 165.7 ± 53.7 msec; $p < 0.001$).**

Such duration, if related to the corresponding cardiac cycle, indicates the percentage of time during which blood flows through a cycle within the left atrial appendage; this value is about 85% of cardiac cycle in Gr.A, while it is 65% in Gr.B ($p < 0.01$) and about 21% in Gr.C ($p < 0.001$).

Conclusions. **Such results add a new parameter to the ones suggested in the SPAF III study for the evaluation of TE risk, that is flow duration measurement within the left atrial appendage, and its ratio to the cardiac cycle. The availability to measure this parameter, by recording the transesophageal pulse wave sample volume positioned in the atrial appendage, makes the evaluation of TE risk more reliable.**

Key Words:

Left atrial appendage thrombus.

Introduction

Transthoracic and transesophageal echocardiograms, although essential as for thromboembolic risk evaluation and correct patient selection for cardioversion in atrial fibrillation (AF), have not reached the degree of specificity and sensitivity we wish.

Availability of techniques and/or procedures allowing a correct TE risk stratification helps to optimize medical treatment, antiaggregating or anticoagulant, with definitely different benefits and risks concerning embolic and bleeding events prevention[5-7].

The present work, using transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE)[1,8-10], aimed at studying new parameters, starting from Virchow's principle about thrombus production.

Materials and Methods

Cohort Studied

Only 69 patients (pts) were included in this work, out of a starting cohort of 107, meeting the following inclusion criteria in the litera-

ture: (A) age over 40 and under 75; (B) AF pts without valvular heart disease; (C) no clotting factor abnormalities; (D) negative liver and/or kidney disease laboratory tests; (E) non-chronic AF (within 6 months and 1 year); (F) no thromboembolic events in SR pts.

69 pts were studied, of whom 26 in sinus rhythm (SR) and 43 in atrial fibrillation, for about 15 months.

Group A (Gr.A): 26 pts in SR, made up of 12 males (M) and 14 females (F), average age 50.2 ± 13 and 50.6 ± 19 respectively and total age 50,5 ± 17,1 (43-75). 2 pts had bicuspid aorta with hemodynamically insignificant regurgitation, 4 pts had mitral valve prolapse with hemodynamically insignificant regurgitation, 5 pts had aneurismatic ascending aorta, 6 pts had arterial hypertension and 9 pts had coronary heart disease.

Group B (Gr.B): 22 pts with thrombi-free atrium (NTAF), made up of 15 M and 7 F, average age 56.7 ± 4 and 60.7 ± 9 respectively and total age 55.7 ± 7 of whom 8 affected by hyperthyroidism and 14 by arterial hypertension. Among the latter ones, 11 had non-A.M.I. coronary artery disease. AF was of recent onset, not over 1 year (average time 84 ± 53 days).

Group C (Gr.C): 21 pts with thrombus in the left atrial appendage (TAF), made up of 15 F and 6 M, average age 58.2 ± 5 and 57.2 ± 7 respectively and total age 57.7 ± 6; they all affected by arterial hypertension, blood lipid abnormalities and non-A.M.I. coronary artery disease. AF was of recent onset, not over 1 year (average time 237 ± 42 days)

No pt in Gr.A nor in Gr.B reported any previous thromboembolic events, whereas 17 pts out of 21 did report a stroke event in Gr.C, of whom 9 T.I.A. during the last 30 days.

All pts signed an informed consent.

Echocardiographic Examination

Every patient, in the resting state, underwent TEE with both CW and PW Doppler, by ATL 5000 echocardiograph with multiplane probe.

All pts lied on the couch, on their left lateral position, lifted about 30°. They all underwent TTE in the standard views and measures were taken according to the criteria of the American Society of Echocardiography[13].

Before the TEE examination, every patient received antibiotic prophylaxis, i.v. ranitidine as for gastric protection, and topic pharyngeal anesthetics.

The whole examination was videotape-recorded, so that all parameters could be revaluated.

Analysis Mode

The left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes both with the Teichholz and the Simpson's formula, M-Mode left atrium transverse diameter, left atrial volume in atrial systole (LASV) and in atrial diastole (LADV) by the double ellipsoid formula, were measured.

As for atrial systole and diastole measurement, in SR pts the image was frozen at the end of the PQ tract and after QRS, whereas in AF pts atrial maximal emptying and maximal filling were timely related to the top of R wave and end of the T wave, respectively.

The appendage longitudinal diameter and the transverse orifice diameter were used to calculate appendage area, volume and ejection fraction. Left ventricular diameters and volumes were used to calculate ventricular shortening fraction and ejection fraction.

Mitral transvalvular flows including diastolic deceleration time (DT), PHT (protodiastolic halftime flow), presence of regurgitation and its estimation, were evaluated by Doppler scan.

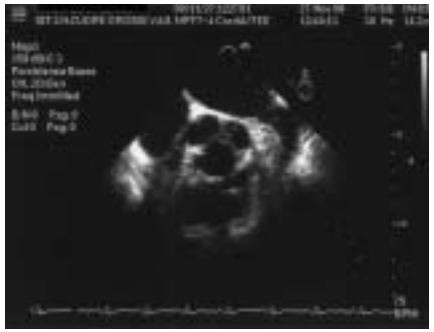
The morphological study of the appendage was carried out from the lower and upper middle transesophageal view and, placing PW Doppler sample volume above the proximal portion of the appendage, flow velocity (maximal and minimal) and its duration within an RR interval were measured.

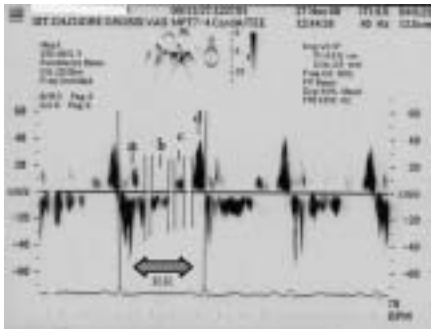
Each measurement of the total flow duration was related to the respective cardiac cycle (Figure 1)

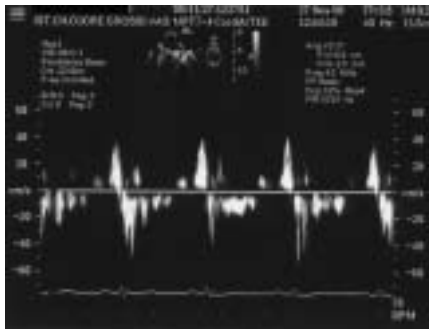
Presence or absence of natural echocontrast (NEC) was estimated by the Fatkin's[14] criterion. All measurements were carried out by 3 different operators, and autonomously. Each reported measure is the mean of 5 evaluations on different cardiac cycles.

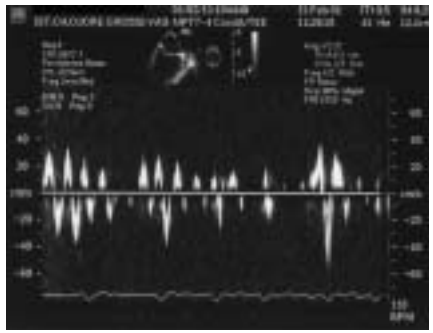
Statistical Analysis

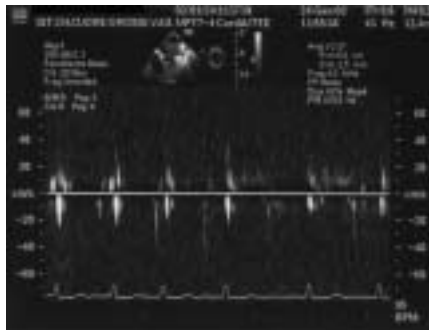
The mean and standard deviation of data was calculated in the statistical survey.











a+b+c+d = Flow duration measurement within a cardiac cycle (F)

RR = Mean interval

F/RR = % Flow duration measurement within a cardiac cycle/RR

Sinus rythm

Atrial fibrillation: with thrombi-free atrium (NTAF)

Atrial fibrillation: with thrombus in the left atrial appendage (TAF)

Figure 1. Each measurement of the total flow duration.

Student's t test for non-coupled data was used to compare the mean of values; significativity was considered when $p < 0.05$. All data were tabbed and surveyed with the help of Microsoft Excel.

Results

The average age (50.5 ± 17.1) of the 26 pts in Gr.A does not differ ($p > 0.05$) from the one of the pts in Gr.B and Gr.C, respectively 55.7 ± 7 and 57.1 ± 6.

The body surface of pts in Gr.A is 1.77 ± 0.2 sqm and is not different ($p > 0.05$) respect the one of pts in Gr.B and Gr.C, respectively 1.74 ± 0.13 m^2 and 1.70 ± 0.18 m^2.

As for the data concerning the anatomic-functional study of the heart, the ejection fraction (EF) in Gr.A (EF = 63%) is not statistically different ($p > 0.05$) from the one in Gr.B (EF = 59%); on the contrary, Gr.C with EF = 48% presents a *significant Student's t* both respect Gr.A ($p < 0.001$) and Gr.B ($p < 0.001$).

Left atrial systolic volume (41.9 ± 23.4 cm^3) in SR pts, although slightly above normal, is statistically lower than the one in Gr.B (86.2 ± 47.9 cm^3 with $p < 0.001$) and the one in Gr.C (78.6 ± 28.5 cm^3 with $p < 0.01$); on the contrary, left atrial systolic volume bears no difference between Gr.B and Gr.C (86.2 cm^3 versus 78.6 cm^3 with $p > 0.05$).

Left atrial appendage volume presents different mean values both diastolic (4.6 cm^3 in Gr.A versus 8.7 cm^3 in Gr.B; 4.6 versus 6.5 cm^3 in Gr.C) and systolic (3.1 in Gr.A versus 6.5 cm^3 in Gr.B; 3.1 versus 5.7 cm^3 in Gr.C); yet the mean among them is not statistically different ($p > 0.05$), obvious consequence of the high standard deviations, mainly in the groups of AF pts.

The left atrial appendage shortening velocity in Gr.A is not different from the one in Gr.B (31.8 ± 16.3 % versus 29.1 ± 16.3 % with $p > 0.05$), whereas it is statistically different respect the one in Gr.C ($p < 0.01$; 31.8 ± 16.3 versus 15.4 ± 8.6 %); the same difference exists between Gr.B and Gr.C with $p < 0.01$.

NC was detected only in 63% of pts in Gr.C with a wide class ranging according to Fatkin's criteria (from level II to IV), whereas it was absent in Gr.A and Gr.B.

The mean RR interval, calculated to compare both heart rate among the groups and to evaluate heart cycle length, presents no statistical difference ($p > 0.05$) both between Gr.A versus Gr.B and Gr.C, and between Gr.B versus Gr.C.

Measures are 751.9 ± 126.7 msec, 743.2 ± 126.6 msec, 799.7 ± 141.8 msec, respectively.

The evaluation of flow velocity within the left atrial appendage, both as for maximal and minimal value, has shown *statistical difference* among the 3 groups: Gr.A presents statistically higher velocity than the other two groups ($p < 0.001$); flow velocity in Gr.B was lower than in Gr.A but higher than in Gr.C and in all cases such differences were statistically significant ($p < 0.001$); in Gr.C values are lower and statistically different ($p < 0.001$) respect the other two groups.

Flow duration measurement within a cardiac cycle is *different* among the 3 groups. We find out in Gr.A flow duration was approximately twice as much compared to the one in Gr.B (616.8 ± 94.1 msec vs. 483.3 ± 172.6 msec) with $p < 0.01$), whereas it was approximately four times higher compared to the one in Gr.C (616.8 ± 94.1 msec. vs. 165.7 ± 53.7 msec) with $p < 0.001$).

This value, expressed as percentage related to the cardiac cycle (RR interval), allows to observe that *flow duration* in Gr.A is about 85% of the cardiac cycle whereas in Gr.B it is about 65% ($p < 0.01$) and in Gr.C it is about 21% ($p < 0.001$).

We refer to Table I and II for a full view of results and related statistical significance.

Discussion

In the elderly, since AF-related TE risk is particularly high[15], anticoagulation is highly recommended. The decision to start anticoagulation in the elderly must be based on a wider thinking.

The bleeding risk associated to oral anticoagulant treatment (OAT) is significantly higher in the elderly and this represents an important drawback for such treatment[16-18].

OAT in patients with NVAF lowers the incidence of systemic TE events from 5% to 1.4% per year[19,20,21-23]; on the other hand bleeding complications are significantly in-

Table I.

	Gr A (sinus rhythm)	Gr B (NTFA)	Gr C (FTA)
N° pts	26	22	21
Age	50.5 ± 17.1	55.7 ± 7	57.7 ± 6
B.S.	1.77 ± 0.2	1.74 ± 0.13	1.70 ± 0.18
E.F.	0.63 ± 0.07	0.59 ± 0.09	0.48 ± 0.03
LAV(cm^3)	41.9 ± 23.4	86.2 ± 47.9	78.6 ± 28.5
RR (msec)	751.9 ± 126.7	743.2 ± 126.6	799.7 ± 141.8
Fl.Dur. (msec)	616.8 ± 94.1	483.3 ± 172.6	165.7 ± 53.7
Fl.Dur./RR (%)	84.6 ± 20.5	64.9 ± 19.2	21.2 ± 6.6
V_{max} (cm/s)	52.4 ± 19.7	34.5 ± 11.2	21.1 ± 4.2
V_{min} (cm/s)	19.1 ± 6.6	13.7 ± 4.2	10 ± 4.7
L.Ap. diastolic (mm^3)	4.6 ± 2.6	8.7 ± 9.5	6.5 ± 6
LAp. systolic (mm^3)	3.1 ± 1.9	6.5 ± 8.1	5.7 ± 5.9
LASV (%)	31.8 ± 16.3	29.1 ± 16.3	15.4 ± 8.6

B.S. = body surface; E.F. = ejection fraction; LAV= Left atrial volume; RR= mean RR interval; Fl. Dur. = Flow duration measurement within a cardiac cycle; Fl.Dur./RR = Flow duration measurement within a cardiac cycle/RR; V_{min} = Flow velocity minimal; V_{max} = Flow velocity maximal; LAp. = left atrial appendage volume; LASV = left atrial appendage shortening velocity.

creased (literature data are contrasting) by about 1-3% for major bleeding events per year[24-29]. Due to this bivalence of events OAT should always be used with great caution, weighing the risk-benefit ratio.

Several studies[26] tried to stratify the TE risk observing the coexistence of NVAF with other diseases increases the risk; under the same pathophysiologic conditions the morpho-functional state of the heart deeply modifies such incidence.

The use of the transesophageal probe in the echocardiographic technique has become useful over the years, if not essential.

The display of left and right atrium, appendage and interatrial septum has been optimized by TEE, with sensitivity, specificity and diagnostic accuracy of about 100% (versus intraoperatively view)[10,30]. Such tecnique has allowed further quantification of TE risk

The study of left atrium and left appendage by TEE has allowed to show the presence of

Table II. (t. Student).

	Gr A (sinus rhythm)	Gr B (NTFA)	Gr C (FTA)
Age	n.s.	n.s.	n.s.
B.S.	n.s.	n.s.	n.s.
E.F.	n.s.	$p < 0.001$	$p < 0.001$
LAV (cm^3)	$p < 0.001$	n.s.	$p < 0.01$
RR (msec)	n.s.	n.s.	n.s.
Fl. Dur. (msec)	$p < 0.01$	$p < 0.001$	$p < 0.001$
Fl. Dur/RR	$p < 0.01$	$p < 0.001$	$p < 0.001$
V_{max} (cm/s)	$p < 0.001$	$p < 0.001$	$p < 0.001$
V_{min} (cm/s)	$p < 0.01$	n.s.	$p = 0.001$
LAp. diastolic (mm^3)	n.s.	n.s.	n.s.
LAp. Systolic (mm^3)	n.s.	n.s.	n.s.
LASV	n.s.	$p < 0.01$	$p < 0.01$

B.S. = body surface; E.F. = ejection fraction; L.A.V. = Left atrial volume; RR = mean RR interval; Fl. Dur. = Flow duration measurement within a cardiac cycle; Fl.Dur./RR = Flow duration measurement within a cardiac cycle/RR; V_{min} = Flow velocity minimal; V_{max} = Flow velocity maximal; LAp. = left atrial appendage volume; LASV = left atrial appendage shortening velocity; n.s. = $p < 0.05$;

thrombi: the latter ones have been detected in 19-21% of pts with previous T.I.A.[1,9], in 12-15% of pts with arterial hypertension[29,31] and in 19% of pts with low left ventricular compliance[1,9].

Such percentages increase from 21% to 25%, from 15% to 23% and from 19% to 25%, if natural echocontrast (NEC)[26,28] is detected during TEE.

Thanks to TEE studies could be done to understand the relationship existing between appendage morphology and haemostatic mechanisms, which predispose to thrombus formation. Tabata et al.[32] observed a relationship between left atrial appendage function and mean left atrial pressure. Carerj et al.[33] demonstrated a relationship between left atrial appendage shortening fraction and values of the valve area, in a cohort with mitral valve disease. Mugge et al.[34] identified two different patterns of left appendage emptying in pts with NVAF: one with velocity higher than 25 cm/sec (defined "high profile") and the other with velocity lower than 25 cm/sec (defined "low profile"). Both left atrial appendage thrombosis and TE events have been more often reported in "low profile" patients.

The outcome of SPAF III study[26,35] showed a high incidence of appendage dysfunction, with low profile flow, in pts at high risk and exactly in 40% of pts with a previous TE event, in 37% of women over 75 years, in 33% of pts with systolic arterial hypertension and in 35% of pts with altered left ventricular performance.

According to a morphologic and functional analysis, an appendage is defined "at risk" when dilated (area > 6 cm^2), anatomically complex (multilobulated), with low flow (< 25 cm/sec), with NEC and markedly reduced shortening fraction (< 20%).

Starting from the above data we have undertaken this study, enlisting 69 pts of whom 26 in SR and 43 in AF Among the latter ones only 21 pts (Gr.C) had a thrombus in the left atrium-left atrial appendage.

The choice of pts in SR with heart disease rather than a healthy cohort was unavoidable, since no healthy person underwent TEE.

The advantage to ulilize pts in stable SR with heart disease, free of TE events, consists in having a non perfectly normal anatomic-functional condition, but with such anomalies to liken the ones in pts in cronic AF Moreover the choise was addressed to examine a cohort in NVAF, but with a diverse thromboembolic condition and, in particular, a thrombus-free left atrial appendage Gr.B (NTAF) and a Gr.C with such a thrombus (TAF). Gr.C, differently from what reported in the literature, presents an excessive incidence in TE events (80.9%; 17 out of 21 pts.). This group was selected to be compared to Gr.B, made up of NTAF. We could not enlist NVAF pts free of heart disease, but this has caused no influence in the estimation of the morpho-functional condition of the left atrium-atrial appendage.

The results of the present study agree with the ones reported in the literature. Indeed women have AF more often than men; EF both in Gr.A (EF = 63%) and in Gr.B (EF = 59%), with $p > 0.05$, is within the normal range, whereas in Gr.C (EF = 48%) is slightly lower than normal.

Left ventricular compliance is reduced in Gr.C whereas it is normal in Gr.A and Gr.B with a statistical difference in $p < 0.001$ between Gr.A and Gr.C and $p < 0.001$ between Gr.B and Gr.C, respectively; left atrial volume is lower ($p < 0.001$) in SR pts compared to the 2 groups in AF whereas there is no difference ($p > 0.05$) between Gr.B and Gr.C, even if inhomogeneous as for duration and onset of A.F., but anyway under 12 months, universally considered as a short duration A.F.

Particular attention must be focused on left atrial appendage volume. In the literature, the atrial appendage is considered at high risk when it presents volume > 6 cm^3.

According to our results, the diastolic appendage volume in Gr.A is 4.6 cm^3; in Gr.B it is 8.7 cm^3; in Gr.C it is 6.5 cm^3, whereas the systolic volume is 3.1 cm^3 in Gr.A; 6.5 cm^3 in Gr.B; 5.7 cm^3 in Gr.C. These values are clearly different, yet the mean among them is not statistically different ($p > 0.05$).

These data represent a quite peculiar meaning. The mean is not statistically different because the standard deviations are high in the group of pts in AF, due to a different anatomic-functional adaptation of the atrium-atrial appendage the hemodinamic state brought on by AF over the time; the atrial appendage volume in Gr.C (with high occur-

rence of TE events) is apparently lower than in Gr.B, but this may be due to a difficult estimation of the contour of the appendage wall when it is filled with thrombus. Related to the above, atrial appendage volume has *not* shown up as a fairly valid criterion to estimate TE risk.

Shortening fraction of the appendage wall is over 31% in SR Gr.A whereas in Gr.B, thrombus-free, it is 29.1 ± 16.3%. In Gr.C, with the presence of thrombus, the shortening fraction is 15.4 ± 8.6% with a significant difference ($p < 0.01$) between Gr.A versus Gr.C and between Gr.B versus Gr.C, whereas there is no difference between Gr.A versus Gr.B.

No NC was found in Gr.A and Gr.B although in a different electrical activity, whereas 37% of pts in Gr.C did not show any NC, despite TAF. The remaining 63% of pts in Gr.C showed up NC but with a wide class ranging according to Fatkin's criteria (from level II to IV); such findings, in this study, did not represent a significant evaluation as for TE risk.

We cannot estimate the statistical incidence of thrombus in the left atrium-atrial appendage in the whole of the population in AF, because the enlisting of patients was aimed and not at random.

Maximal flow velocity in atrium-atrial appendage in Gr.A and Gr.B was over 25 cm/sec, whereas in pts in TAF (Gr.C) the mean value of maximal velocity was 21.1 ± 4.2 cm/sec, lower to the criterion reported in the literature[34].

Not all pts presented these values, indeed 5 out of 21 (23.8%) had flow velocities slightly over 25 cm/sec.

Related to the above, atrial appendage flow velocity did *not* show up as a fairly valid criterion to estimate TE risk.

We wanted to apply the logic of Virchow's triad, which defines thrombotic risk as the existence of two out of the following three parameters, on the whole cohort: vessel wall abnormalities, marked slowing/absence of blood flow, abnormalities of coagulation cascade.

We calculated blood flow at the orifice of atrium-atrial appendage, and its duration within the RR interval, by PW echo-Doppler, on the whole cohort.

This time length, both indipendently from the positive or negative flow direction and from its velocity, was related to the cardiac cycle. This measurement, in our opinion, is an expression of blood flow within the atrial appendage and therefore allows the calculation of one of the 3 elements of Virchow's triad.

Total flow duration is 165.7 ± 53.7 msec in Gr.C versus 483.3 ± 172.6 msec in Gr.B, with $p < 0.001$.

If we evaluate the ratio of flow duration to the RR interval, we get a pure value which indicates the percentage of time blood flows within the appendage during a cardiac cycle.

We observe blood flows for about 65% of the cardiac cycle length in the NTAF group whereas it flows for about 21% in TAF group. In the SR group blood flow is equal to 616.8 ± 94.1 msec with a mean duration of cardiac cycle of 751.9 ± 126.7 msec, that is blood flows for about 85% of the cardiac cycle length. The statistical difference among the three groups is significant.

Another parameter in Virchow's triad is the wall structural alteration. As reported in the literature, pts affected by cronic NVAF with increased left atrial volume and morphologically dilated left atrial appendage present an altered wall structure[3-7,36-38], therefore both pts in Gr.B and in Gr.C can be considered affected by such alteration.

One of the inclusion items in this work has been the laboratory screening about clotting factors determination and values had to be in the normal range; therefore we can infer no patient was affected by clotting anomalies leading to thrombus formation.

Pts in Gr.B and in Gr.C have many common items, like heart rhythm and the morphologic feature of left atrium-atrial appendage, but show up different conditions about blood flow along the extreme atrial periphery.

This item, related to Virchow's triad, could bring on thrombus formation and its embolic evolution. SR pts in Gr.A, used as a reference sample, present characteristics (atrial structure, flow velocity, flow duration, no NEC) similar to Gr.B, yet have a normal electric heart activity and no TE events. All this confirms our opinion.

The choice of a cohort with diverse heart rhythm (SR and AF), and particularly the inclusion into the AF group of two subgroups, one with NTAF and the other with TAF evenly balanced (22 to 21 pts), has allowed to

verify both if new item could increase TE risk stratification reliability, and to quantify the difference.

Gr.A has been used as the normal sample, whereas the comparison has been aimed at Gr.B versus Gr.C.

In this work, the two groups in AF have demonstrated a significant statistical difference concerning maximal flow velocity within the atrial appendage.

The atrial appendage shortening fraction is of doubtful value, NEC is present with a wide variability, atrial appendage volume is not statistically valuable, whereas a sharp difference is evidenced about blood flow among the groups. The predictive value of this new item has not been calculated because the TAF group was not enlisted at random.

The easiness, in our opinion, with which this parameter can be calculated, makes this technique more reliable than the estimation of atrial appendage area and atrial appendage wall shortening fraction, which, very often, with the variability of measurement of a few millimeters, may mislead interpretations.

This observation won't be a contraddictory item against the others, but a hint at increasing statistical significance in TE risk stratification.

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