Spontaneous echo-contrast and prothrombotic status in patients undergoing left atrial appendage occlusion

Eco contraste espontáneo y estado protrombótico en pacientes tratados con cierre percutáneo de la orejuela izquierda

To the Editor,

Percutaneous left atrial appendage occlusion (LAAO) has emerged as an alternative to anticoagulation for preventing thromboembolic events in patients with nonvalvular atrial fibrillation (NVAF). Despite the growing evidence in support of LAAO, device-related thrombosis (DRT) after LAAO remains a concern because its presence has been related to ischemic events.[1] Although it is known that the origin of DRT is multifactorial, involving both patient characteristics and procedure-related factors, the relationship between the presence of spontaneous echo-contrast (SEC) in the left atrial appendage (LAA) prior to LAAO and the development of DRT is unclear.[2,3] The presence of SEC seems to be related to low blood velocities and flow turbulence, creating a prothrombotic environment that may translate into a higher risk of DRT.[4] However, there is currently no biological evidence supporting this latter notion in the setting of LAAO. For this purpose, the present study aimed to evaluate the relationship between the presence of SEC and the presence of a prothrombotic state in patients undergoing LAAO.

This study included 30 consecutive patients with NVAF who underwent LAAO in our institution between June 2019 and May 2020. LAA SEC was defined as an echogenic, swirling pattern of blood flow at the standard gain setting during the cardiac cycle and was graded according to the Fatkin classification.[5] Only moderate and severe LAA SEC findings were included in our analysis. Patients were stratified by the presence or absence of SEC. Hemostatic status was assessed by thromboelastography as an indicator of overall coagulopathic status. In addition, 3 different biomarkers were used to evaluate inflammatory and prothrombotic states: *a)* VCAM-1 (vascular cell adhesion molecule; *b)* tumor-necrosis factor receptor 1 (TNFR1), and *c)* Von Willebrand factor (vWF) antigen. Fasting blood samples were collected and were anticoagulated with citrate before the procedure on the same day as LAAO and at 90 days after the procedure. For each study participant, blood samples were analyzed using the standard thromboelastography analyzer of our institution, with the INTEM (intrinsic pathway) and EXTEM (extrinsic pathway) tests. Immunoassays were used to determine laboratory levels of VCAM-1, TNFR1, and vWF antigen. Preprocedural imaging was mainly performed with transesophageal echocardiography. The device and antithrombotic treatment (ATT) after LAAO were selected according to LAA anatomy and physician preference, respectively. A follow-up transesophageal echocardiogram was performed 3 months after LAAO, and patients underwent clinical follow-up at 3 and 12 months after the procedure. Prospectively collected data were transferred to a dedicated database. The study was approved by the institutional committee and all participants gave informed consent. The study conformed to the guiding principles of the Declaration of Helsinki.

Categorical variables are presented as frequencies, and differences were assessed using the chi-square test. Continuous variables are presented as mean ± standard deviation or as median. The Kolmogorov-Smirnov test was applied to ensure normal distribution. Continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test, as appropriate. For all analyses, a 2-tailed *P* value < .05 was used as the criterion for statistical significance. Follow-up was considered to terminate at 3 months. Analyses were performed using Stata software (V14.0, Stata Corp LP, College Station, TX, United States).

The main baseline and procedural characteristics of the study population are listed in table 1. Rates of permanent atrial fibrillation were higher in patients in the SEC group than in the non-SEC group ($P < .05$). Although no statistically significant differences were found in ATT, 11% of patients with SEC did not receive any treatment compared with 5% of patients without SEC. These patients had an absolute contraindication to ATT due to a previous intracranial bleed or amyloid angiopathy. The results of the prothrombotic analysis are listed in table 2. At baseline, only α-angle—an indicator of prothrombotic status—was higher in the SEC group than in the non-SEC group (78.1 ± 3.0 vs 72.7 ± 6; $P = .003$). However, the differences between groups became more relevant at 3 months of follow-up, with clotting time being significantly lower (64.7 ± 16.3 vs 87.4 ± 19.1; $P = .006$) and the amplitude and maximum clot firmness being significantly higher in both the INTEM test (62.2 ± 6.2 vs 49.6 ± 15.1; $P = .012$ and 69.1 ± 5.2 vs 56.6 ± 12.9; $P = .004$; respectively) and in the EXTEM test (58.6 ± 7.94 vs 44 ± 16.3; $P = .01$ and 65.6 ± 6.10 vs 53.3 ± 12.0; $P = .005$; respectively) of the SEC cohort. Regarding biomarkers, VCAM-1 was higher in the SEC group than in the non-SEC group at 3 months of follow-up (21.6 ± 13.2 vs 12.9 ± 4.6; $P = .03$). Importantly, DRT after LAAO showed a trend toward a higher incidence in the SEC group (22% vs 0%; $P = .08$). Patients who developed DRT were receiving dual antiplatelet therapy or single antiplatelet therapy.

The negative impact of DRT on clinical outcomes after LAAO has been recently highlighted but remains poorly understood. DRT is considered a serious complication, associated with the recurrence of ischemic events, and is difficult to treat given the initial contraindication to full anticoagulation in most patients undergoing LAAO. The presence of SEC in the LAA acts as an indirect marker of prothrombotic states in patients with NVAF.[2,3] Likewise, it seems reasonable to believe that SEC could increase the risk of DRT in patients undergoing LAAO. Nonetheless, there are no reports of this biological plausibility. The results of our study suggest that the presence of SEC is associated with an increased hypercoagulable state, as shown by the thromboelastography analysis and the increase of VCAM-1 at follow-up. The ROTEM results obtained at baseline were not affected by oral anticoagulation, since patients were only treated with antiplatelet agents, which do not affect these results. Oral anticoagulation (apixaban at reduced doses) was prescribed after hospital discharge in 55% of the patients with SEC and in 33% of those without SEC. At the dose administered, apixaban increases, though slightly, computed tomography (CT) values at the ROTEM. Nevertheless, mean CT values were shorter in the SEC patients. In addition, the results on the 'amplitude' and 'maximum clot firmness' indicated a prothrombotic behavior in the SEC cohort compared with the non-SEC patients. The potential mechanism of this hypercoagulable state in patients with left atrial SEC may include a reduced LAA voltage. This is associated with fibrotic remodelling of the atrial substrate, leading to compromised contractility of the left atrial appendage.[3] In addition, DRT was more likely in the SEC cohort, although a stronger association was probably precluded by the limited sample size. Finally, it is important to point out that LAAO is feasible and safe in the presence of SEC, even with LAA thrombus.[6] In this context, the use of biomarkers may be helpful to tailor the optimal ATT after LAAO. In conclusion, the presence of SEC prior to LAAO was associated with an increased prothrombotic state that could lead to an increased risk of DRT.

This report has several limitations. The observational design and small sample precluded the detection of a significant association of these clotting analyses with clinical events, but our results should be considered as hypothesis-generating. LAA SEC was defined based on a semiquantitative method. In addition, the study did not include data on the exact time of diagnosis of

Table 1
Baseline, procedural, and 3-month follow-up characteristics.

Variable	Total (N = 30)	Spontaneous echo-contrast (n = 9)	Nonspontaneous echo-contrast (n = 21)	*P*
Age, y	75.4 ± 8.1	74.6 ± 7.2	75.7 ± 8.5	.72
Men	19 (63)	6 (66)	13 (62)	.80
Hypertension	24 (80)	6 (67)	18 (86)	.23
Diabetes mellitus	9 (30)	3 (33)	6 (29)	.55
Coronary artery disease	11 (37)	5 (55)	6 (29)	.16
Previous heart failure	8 (27)	5 (24)	3 (33)	.45
Left ventricular ejection fraction, %	52.6 ± 10.1	50 ± 10.1	53.6 ± 8.9	.37
Permanent atrial fibrillation type	17 (57)	8 (89)	9 (43)	.04
Left atrial volume index, mL/m²	28.4 ± 6.3	30.5 ± 6.9	29 ± 6.2	.55
Stroke	14 (47)	5 (56)	9 (43)	.40
Prior bleeding	24 (80)	6 (67)	18 (86)	.24
CHA_2DS_2-VASc score	4.6 ± 1.43	4.22 ± 1.30	4.71 ± 1.48	.40
HAS-BLED score	3.8 ± 0.91	3.9 ± 0.91	3.8 ± 0.98	.83
In-hospital events				1.00
Stroke	0	0	0	
Major bleeding	0	0	0	
Cardiac tamponade	0	0	0	
Prosthesis embolization	0	0	0	
Antithrombotic treatment at discharge				.64
Aspirin	5 (17)	1 (11)	4 (19)	
Clopidogrel	2 (7)	0	2 (9)	
Aspirin + clopidogrel	9 (30)	2 (22)	7 (33)	
Anticoagulant	12 (40)	5 (55)	7 (33)	
None	2 (7)	1 (11)	1 (5)	
3-month follow-up events				
Stroke	1 (3)	1 (11)	0	.30
Major bleeding	4 (13)	1 (11)	3 (14)	.65
Thrombus device	2 (7)	2 (22)	0	.08
Prosthesis embolization	0	0	0	1.00

The data are expressed as No. (%), mean ± standard deviation.

Table 2
Activation of the coagulation markers.

Variable	Total (N = 30)	Spontaneous echo contrast (n = 9)	Nonspontaneous echo contrast (n = 21)	*P*
Baseline activation of coagulation markers				
Thromboelastometry–EXTEM values				
Clotting time, s	75 ± 14.8	78 ± 17.2	73.6 ± 14.0	.46
Clot formation time, s	74 ± 26.1	81.7 ± 35.8	70.6 ± 20.8	.30
Alpha-angle	76 ± 4.6	75.1 ± 5.8	76.4 ± 4.1	.50
Amplitude 10 min after CT, mm	60 ± 7.5	61.7 ± 6.3	57 ± 9.2	.12
Maximum clot firmness, mm	67.5 ± 6.6	69 ± 5.8	62.47 ± 7.4	06
Lysis index 30 min after CT, %	100 ± 0.4	99.8 ± 0.7	100 ± 0.22	.28
Maximum lysis, %	8.6 ± 10.6	11.1 ± 17.8	7.57 ± 5.6	.41
Thromboelastometry–INTEM values				
Clotting time, s	162.8 ± 52	167.4 ± 74.3	161.7 ± 41.2	.79
Clot formation time, s	103.8 ± 127.3	104.3 ± 47.3	103.6 ± 150.4	.99
Alpha-angle	76.4 ± 4.8	78.1 ± 3.0	72.7 ± 6	.003
Amplitude 10 min after CT, mm	57.3 ± 11.8	54.1 ± 8.85	58.7 ± 12.8	.34
Maximum clot firmness, mm	59.7 ± 18.3	54.8 ± 18.6	61.8 ± 18.2	.35
Lysis index 30 min after CT, %	99.8 ± 0.61	99.7 ± 1	99.9 ± 0.36	.44
Maximum lysis, %	11.8 ± 17.8	9.44 ± 12.2	12.9 ± 19.8	.64
Other markers				
vWF Ag, %	119.7 ± 57.8	111.8 ± 61.5	123 ± 57.4	.64
TNFR1, pg/mL	1008.7 ± 217.8	977.1 ± 177.9	1022.3 ± 235.5	.61

Table 2 *(Continued)*
Activation of the coagulation markers.

Variable	Total (N = 30)	Spontaneous echo contrast (n = 9)	Nonspontaneous echo contrast (n = 21)	*P*
VCAM-1, ng/mL	314.8 ± 173.9	431.23 ± 264.3	264.8 ± 91.6	.05
3-month activation of the coagulation markers				
Thromboelastometry–EXTEM values				
Clotting time, s	72.3 ± 19.1	64.7 ± 16.3	87.4 ± 19.1	.006
Clot formation time, s	100.8 ± 109.1	73.9 ± 25.7	154.6 ± 182.1	.11
Alpha-angle	74.5 ± 6.1	75.9 ± 4.9	71.9 ± 7.6	.17
Amplitude 10 min after CT, mm	58 ± 11.4	62.2 ± 6.2	49.6 ± 15.1	.012
Maximum clot firmness, mm	64.9 ± 10.2	69.1 ± 5.2	56.6 ± 12.9	.004
Lysis index 30 min after CT, %	99.9 ± 0.7	100 ± 0	99.6 ± 1,13	.16
Maximum lysis, %	7.5 ± 6.1	7.21 ± 6.6	7.86 ± 5.2	.82
Thromboelastometry–INTEM values				
Clotting time, s	220.7 ± 95.5	220 ± 83.8	222 ± 46.5	.97
Clot formation time, s	111.1 ± 72.9	79.29 ± 38.7	134.9 ± 78.6	.09
Alpha-angle	71.1 ± 11.6	74.3 ± 7.37	64.6 ± 16.0	.07
Amplitude 10 min after CT, mm	53.8 ± 13.1	58.6 ± 7.94	44 ± 16.3	.01
Maximum clot firmness, mm	61.5 ± 2.2	65.6 ± 6.10	53.3 ± 12.0	.005
Lysis index 30 min after CT, %	99.6 ± 1.0	99.6 ± 0.75	99.4 ± 1.5	.66
Maximum lysis, %	7.0 ± 6.3	7.71 ± 6.19	5.71 ± 6.8	.51
Other markers				
vWF Ag, %	116.7 ± 45.8	138.6 ± 54.2	107.3 ± 40.3	.17
TNFR1, pg/mL	997.2 ± 202.2	1094.7 ± 262.4	955.4 ± 164.4	.16
VCAM-1, ng/mL	380.9 ± 175.6	485.4 ± 107.9	221.4 ± 83.6	.03

CT, coagulation time; VCAM-1, vascular cell adhesion molecule 1; TNFR1, TNF receptor 1; vWF Ag, Von Willebrand factor antigen.
Values are expressed as No. (%) or mean ± standard deviation.

atrial fibrillation before the index procedure and right atrial area among the different groups.

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AUTHORS' CONTRIBUTIONS

X. Freixa, P. Cepas-Guillen, and E. Flores-Umanzor conceived and designed the analysis. E. Flores-Umanzor and PL. Cepas-Guillen performed the analysis. L. Sanchis, A. Regueiro and M. Díaz-Ricart reviewed and edited the manuscript. E. Flores-Umanzor and PL. Cepas-Guillen contributed equally to this work.

CONFLICTS OF INTEREST

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REFERENCES

1. López-Mínguez JR, Nogales-Asensio JM, Infante De Oliveira E, et al. Long-term Event Reduction After Left Atrial Appendage Closure. *Results of the Iberian Registry II Rev Esp Cardiol.* 2019;72:449–455.
2. Freixa X, Cepas-Guillen P, Flores-Umanzor E, et al. Pulmonary ridge coverage and device-related thrombosis after left atrial appendage occlusion. *EuroIntervention.* 2021;16:e1288–e1294.
3. Wang B, Wang Z, Fu G, et al. Left Atrial Spontaneous Echo Contrast and Ischemic Stroke in Patients Undergoing Percutaneous Left Atrial Appendage Closure. *Front Cardiovasc Med.* 2021;8:723280.
4. Khan AA, Lip GYH. The prothrombotic state in atrial fibrillation: pathophysiological and management implications. *Cardiovasc Res.* 2019;115:31–45.
5. Fatkin D, Loupas T, Jacobs N, Feneley MP. Quantification of blood echogenicity: evaluation of a semiquantitative method of grading spontaneous echo contrast. *Ultrasound Med Biol.* 1995;21:1191–1198.
6. Fontenla A, Gómez-Blázquez I, Corros-Vicente C, et al. Percutaneous left atrial appendage closure in the presence of thrombus: a single-center experience. *Rev Esp Cardiol.* 2021;74:886–888.

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