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Features of Left Atrial Appendage Thrombosis in Patients With Persistent Nonvalvular Atrial Fibrillation After COVID-19

Aim	To evaluate the incidence and characteristic features of left atrial appendage (LAA) thrombosis in patients with persistent nonvalvular atrial fibrillation (AF) after COVID-19.
Material and Methods	Transesophageal echocardiography (TEE) was performed for 469 patients (57.4% males; mean age, 64.0 [58.0; 70.0] years) with persistent nonvalvular AF before scheduled sinus rhythm restoration. In 131 of these patients (27.9%), the most recent episode of arrhythmia developed during the coronavirus infection. The time from the onset of COVID-19 to TEE was 145 [62; 303] days. All patients received an adequate anticoagulant therapy, in most cases, with direct oral anticoagulants for at least 3 weeks preceding the study.
Results	A LAA thrombus was detected in 20 (5.9%) patients who have had no coronavirus infection and in 19 (14.5%) patients after COVID-19 (p=0.0045). 18 of 19 (94.7%) thrombi found in patients who have had COVID-19 were mural whereas only 5 (25.0%) of such thrombi were found in patients who have had no COVID-19 (p<0.0001). In the absence of LAA thrombus, the LAA emptying velocity was 32.0 [25.0; 40.0] cm/sec whereas in the presence of a mural thrombus, it was 25.0 [20.0; 32.3] cm/sec, and in the presence of a typical thrombus, it was 17.0 [13.5; 20.0] cm/sec (p<0.0001). A Kaplan–Meier analysis showed that the median time of mural thrombus dissolution was 35.0 (95% confidence interval (CI), 24.0–55.0) days and for a typical thrombus, this time was 69.0 (95% CI, 41.0–180.0) days (p=0.0018).
Conclusion	Patients with persistent AF who have had COVID-19 had LAA thrombosis 2,5 times more frequently and, in most cases, the thrombus was mural. Mural thrombi, in contrast to typical, are not associated with a pronounced decrease in LAA emptying velocity and dissolve twice as fast as typical thrombi with an adequate anticoagulant treatment.

Keywords	Atrial fibrillation; transesophageal echocardiography; left atrial appendage thrombosis; COVID-19
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Clinical and medico-social value of atrial fibrillation (AF) is due to its high prevalence and thromboembolic complications peculiar to this type of arrhythmia, which are associated with thrombosis of the left atrial appendage (LAA) in 92–98% of cases [1, 2]. A number of studies have shown that reduced LAA ejection velocity caused by atrial systolic dysfunction is the main cause of thrombosis, and anticoagulant therapy is the only effective way to treat and prevent it [3, 4]. Intravascular vessel wall damage, the third element of the Virchow's triad, is generally not regarded as a causative factor for LAA thrombosis. The COVID-19 pandemic resulted among other things in higher prevalence of persistent AF with the onset of a paroxysm during the acute period of the disease [5, 6]. Coromilas et al. [7] showed that cardiac arrhythmias occur in 12.9% of COVID-19 cases, 61.5% of which are AF. LAA thrombosis is parietal and more common in patients with a history of COVID-19 than those without. This suggests that clotting is caused by damage to the endocardium [8]. This suggestion was based on a relatively small number of observations insufficient to conduct statistical analysis. A lot of new observations were collected since then, which allowed us to perform a comprehensive analysis, the results of which are present in this paper.

Objective

Estimate the incidence and characteristics of LAA thrombosis in patients with persistent AF and a history COVID-19.

Material and methods

The study was carried out following the Good Clinical Practice and the Declaration of Helsinki and approved

by the local ethics committee of Tver State Medical University. When being admitted to the hospital, all patients signed the informed consent using the study results for scientific purposes.

Patients with persistent non-valvular AF were sequentially included to the study and were subjected to transesophageal echocardiography (TEE) to exclude contraindications to scheduled cardioversion. Patients were included from 07.09.2020, when the first patient with a history of COVID-19 was examined, to 31.05.2022. During this period, 469 patients with persistent AF were examined, 131 (27.9%) of whom had the most recent paroxysm of arrhythmia during the coronavirus infection.

Patients were included to the group of patients with a history of COVID-19 according to the medical records confirming that AF paroxysm developed precisely during the coronavirus infection (results of the PCR test for SARS-CoV-2 and computer tomography findings). During the COVID-19 infection, 39 (29.8%) patients had intact lung, 39 (29.8%) had ≤ 25% of lung involved, 39 (29.8%) had 26–50%, 12 (9.2%) had 51–75%, and 2 (1.5%) patients had > 75% of the lung tissue involved. All patients had negative PCR for SARS-CoV-2 at the time of TEE.

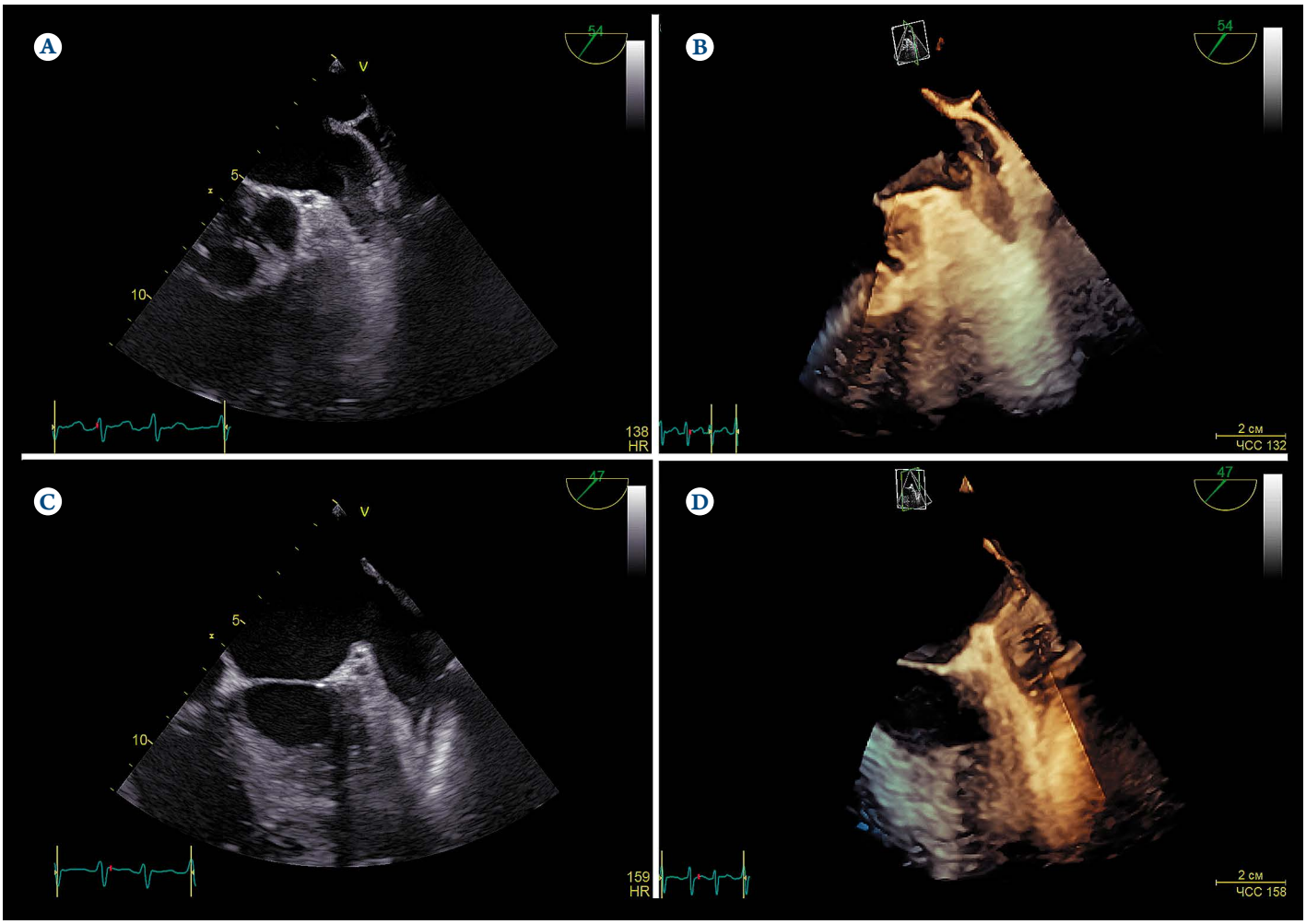
TEE was performed using a Vivid S70 system (GE, USA) and a 6VT-D transesophageal multiplanar phased array transducer (2D/3D/4D). LAA was scanned via a mid-esophagus access in sections from 0 to 180° with 10–30° steps. LAA clots were defined as discrete echo-positive masses with density different from that of the endocardium and pectineal muscles. The identified LAA clots were classified as typical and atypical clots based on the ultrasound findings.

A clot with the base occupying the LAA apex and the free part forming an acute angle with LAA wall in its cavity was considered typical (Figure 1 A, B). A clot filling the LAA apex and extending to its base tightly adjacent to its wall was considered atypical (Figure 1 C, D).

LAA ejection velocity was measured using pulse-wave Doppler ultrasound with the control volume located in the LAA ostium. Mean peak velocity of 10 consecutive cardiac cycles was calculated.

Spontaneous echocardiographic contrast (SEC) was defined as a dynamic vortex in the left atrial cavity and

Figure 1. Typical (A, B) and atypical (C, D) LAA clots in two-dimensional (A, C) and three-dimensional (B, D) transesophageal echocardiography



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evaluated by four grades from mild to severe according to the classification by Fatkin et al. [9].

If a clot was detected in the LAA, cardioversion was canceled. The patient was offered to continue taking anticoagulant drugs and undergo repeated TEE in 3–5 weeks. Repeat transesophageal examinations (from 1 to 5) were performed in 29 of 39 patients with a LAA clot detected during the initial examination.

Statistical processing was performed in MedCalc v. 20.110 (MedCalc Software Ltd.). The medians and interquartile ranges (Me [Q1; Q3]) were estimated for quantitative variables and the percentages (%) were calculated for qualitative variables. The intergroup comparisons were performed using the Mann-Whitney test or the two-tailed Fisher's exact test; multiple comparisons were made using the Bonferroni correction. A logistic regression analysis was performed by sequential exclusion of independent variables to identify factors affecting the likelihood of LAA thrombosis. The Kaplan–Meier method was used to investigate the effect of the anticoagulant treatment duration on the likelihood of the LAA clot dissolution (survival analysis). The results of the analysis were considered statistically significant with a probability of an alpha error of less than 5% ($p<0.05$).

Results

The age of the patients examined ranged from 23 to 88 years with 89.1% of middle-aged or elderly patients (45–74 years). Male patients prevailed, the majority of patients had concomitant arterial hypertension (AH), 50% had obesity, every fifth had diabetes mellitus (DM) (Table 1). Coronary heart disease (CHD) and congestive chronic heart failure (CHF) were significantly less common. More than 50% of the examined patients face a high risk of stroke according to the CHA2DS2 VASc score (>1 in male patients and >2 points in female patients). All patients received appropriate anticoagulant therapy for at least 3 weeks before TEE, and direct oral anticoagulants (DOACs) were administered in 92.1% of cases. TEE showed a LAA clot in 39 (8.3%) patients.

There were no statistically significant differences between persistent AF patients with or without a history COVID-19 in terms of age, prevalence of obesity, concomitant AH, CAD and congestive CHF, and the percentage of patients receiving DOACs. However, there were significantly fewer male patients among those with a history of COVID-19, but more patients with concomitant DM and a high risk of stroke according to CHA2DS2 VASc. LAA thrombosis was almost 3 times more common in patients with a history of COVID-19 than in those without a history of COVID-19. Mean LAA ejection velocity and the prevalence SEC grade III–IV did not differ (see Table 1).

The logistic regression analysis showed that a history of COVID-19 and congestive CHF have an independent effect on the likelihood of LAA clotting: area under the error curve (AUC) 0.662 (95% confidence interval (CI) 0.617–0.706; p=0.0011). A history of COVID-19 increased the risk of clotting and CHF 3.157 (95% CI 1.577–6.318) times (p=0.0012) and 2.741 (95% CI 1.035–7.260) times (p=0.0425), respectively. Other factors of interest did not have a statistically significant effect on the likelihood of LAA thrombosis.

A similar analysis was performed in the subgroups of patients with and without a history of COVID-19. In the former case, a weak statistically significant effect of congestive CHF on the likelihood of LAA clotting was shown: AUC 0.582 (95% CI 0.527–0.636; p=0.0405),

Table 1. Characteristics of the examined patients with persistent non-valvular atrial fibrillation

Parameter	All patients	Onset of a paroxysm during COVID-19		p
	(n=469)	No (n=338)	Yes (n=131)	
Age, years	64.0 [58.0; 70.0]	64.0 [58.0; 70.0]	64.0 [58.0; 71.0]	0.7687
Male, n (%)	269 (57.4)	203 (60.1)	66 (50.4)	0.0616
Obesity, n (%)	231 (49.3)	165 (48.8)	66 (50.4)	0.8370
AH, n (%)	325 (69.3)	235 (69.5)	90 (68.7)	0.9112
CAD, n (%)	56 (11.9)	40 (11.8)	16 (12.2)	0.8754
Congestive CHF, n (%)	36 (7.7)	26 (7.7)	10 (7.6)	1.0000
Diabetes mellitus, n (%)	91 (19.4)	56 (16.6)	35 (26.7)	0.0186
High risk, n (%)	241 (52.5)	162 (47.9)	79 (60.3)	0.0386
Duration of paroxysm, days	53.0 [20.5; 103.0]	45.0 [14.0; 94.0]	76.5 [42.5; 130.5]	0.0105
DOACs, n (%)	432 (92.1)	308 (91.1)	124 (94.7)	0.2534
LAA clot, n (%)	39 (8.3)	20 (5.9)	19 (14.5)	0.0045
LAA velocity, cm/sec	31.0 [24; 40]	31.0 [24.0; 40.0]	31.0 [25.0; 37.8]	0.9800
SEC grade III-IV, n (%)	20 (4.3)	15 (4.4)	5 (3.8)	1.0000

The data are expressed as the medians and interquartile ranges or the absolute and relative numbers.
DOACs, direct oral anticoagulants; LAA, left atrial appendage; SEC, spontaneous echocardiographic contrast

odds ratio 4.042 (95% CI 1.216–13.44; p=0.0227). None of the factors of interest demonstrated a statistically significant effect on the likelihood of atrial clotting in the group of patients with a history of COVID-19. No relationship was shown between the likelihood of thrombosis and the severity of COVID-19 assessed by the presence and degree of lung tissue involvement.

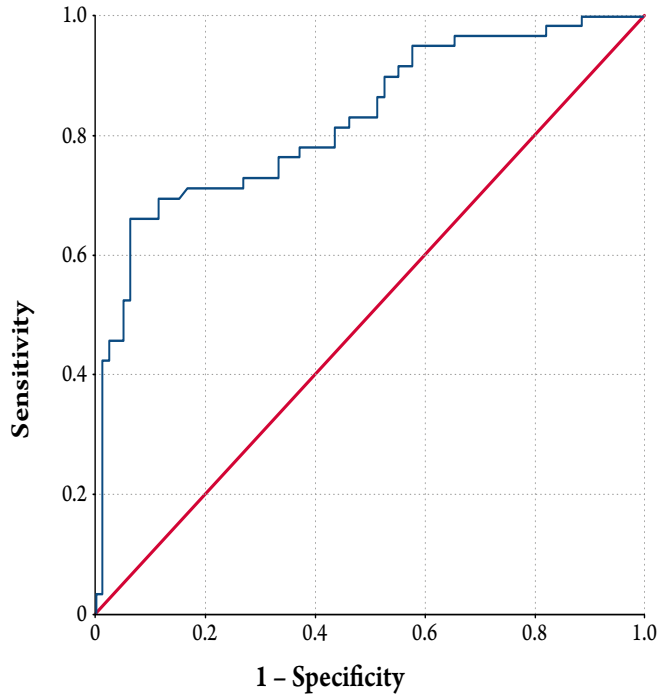
The effect of CHF on clotting appears to be associated with a more pronounced decrease in LAA ejection velocity. Patients without a LAA clot (n=430) had the mean LAA ejection velocity of 32.0 [25.0; 40.0] cm/s, with 33.0 [26.0; 40.0] cm/s in patients without CHF (n=400) and 27.5 [23.0; 36.0] cm/s in patients with CHF (n=30) (p=0.0430).

Going back to the Table 1 data, it should be noted that the most pronounced differences between patients with and without a history of COVID-19 were related to the prevalence and features of LAA thrombosis. First, a LAA clot was detected 2.5 times more often in patients with a history of COVID-19 than in those without: 14.5 (95% CI 9.49–21.5) % versus 5.92 (95% CI 3.86–8.96) %, p=0.0045. Second, 18 (94.7%) of the 19 clots identified in patients with a history of COVID-19 were atypical (parietal), and 5 (25.0%) such clots were detected in patients without a history of COVID-19 (p<0.0001).

The presence of a clot in the LAA was associated with lower ejection velocity and higher SEC grade. However, the changes were significantly less pronounced in the case of an atypical clot than in the case of a typical clot (Table 2).

Repeat transesophageal examinations (from 1 to 5) were performed in 29 of 39 patients with a LAA clot detected during the initial examination. The Kaplan-Meier analysis showed that atypical blood clots dissolve faster during anticoagulant therapy than typical clots (Figure 2). The median dissolution of atypical clots was 35.0 (95% CI 24.0–55.0) days versus 69.0 (95% CI 41.0–180.0) days in the case of typical clots (p=0.0018). With equal duration of anticoagulant therapy, the likelihood of the dissolution of atypical clots is 4.190 (95% CI 1.708–10.29) times higher than that of typical ones.

Figure 2. Kaplan–Meier curves of the likelihood of typical and atypical clot survival in the left atrial appendage during anticoagulant therapy



Discussion

This study showed that patients with persistent non-valvular AF and a history of COVID-19 were 2.5 times more likely to have LAA thrombosis than patients without a history of COVID-19 (14.5% and 5.9%, respectively; p=0.0045). Of the 19 clots detected in patients with a history of COVID-19, 18 (94.7%) clots were closely adjacent to the LAA wall (see Figure 1), with only 5 (25.0%) parietal clots of the 20 clots detected in patients without a history of COVID-19.

Sufficient evidence has been accumulated so far on the development of severe hemostatic disorders during COVID-19 that cause the development of thrombosis and thromboembolic complications. Deep vein

Table 2. LAA flow velocity and patients with high-grade SEC

Parameter	LAA clot			p
	No clot – Group 1 (n=427)	Typical clot – Group 2 (n=16)	Atypical clot – Group 3 (n=23)	
LAA velocity, cm/sec	32.0 [25.0; 40.0]	17.0 [13.5; 20.0] p_{1-2}<0.0001	25.0 [20.0; 32.3] p_{1-3}=0.0021 p_{2-3}=0.0030	<0.0001
SEC grade III-IV, n (%)	5 (1.2)	10 (62.5) p_{1-2}<0.0001	5 (21.7) p_{1-3}=0.0001 p_{2-3}=0.0552	<0.0001

p is the statistical significance of LAA thrombosis effect on a parameter of interest, which is estimated using the Kruskal–Wallis in the case of blood flow velocity and chi-square test for a percentage of subjects with SEC grade III-IV. p1–2, p1–3, p2–3 is the statistical significance of intergroup differences estimated using Bonferroni correction. LAA, left atrial appendage; SEC, spontaneous echocardiographic contrast.

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thrombosis is detected in 17.3–25.0% of patients with severe COVID-19 [10, 11], and thromboembolism of the small pulmonary arteries is observed in 40–81% of cases [12, 13]. The incidence of LAA thrombosis in COVID-19 patients is not described in the literature, but ischemic stroke is observed in 5.7% of cases of the critical course of the disease [13, 14].

COVID-19 can cause thrombosis during the acute disease and long after the time of infection. Fan et al. [15] described four cases of arterial thrombosis in young (mean age 38.5 years) healthy men in a mean of 78 days after asymptomatic COVID-19. Having analyzed the results of the examinations and the literature data, the authors concluded that the cause of thrombosis could be persistent endothelial dysfunction caused by its damage during the acute infection.

Blagova et al. [16] detected SARS-CoV-2 RNA in the myocardium in 5 of 6 patients with morphologically verified post-COVID-19 myocarditis (mean age 49.0±9.2 years), the symptoms of which appeared a mean of 5.5±2.4 months after COVID-19. The maximum time after COVID-19 to detecting the virus in the myocardium of patients with active myocarditis was 9 months. Endocardial biopsy detected the signs of lymphocytic endocarditis with endocardial thickening and sclerosis in 2 patients; individual biopsies were represented completely by thrombotic masses composed of fibrin, erythrocytes, and neutrophils. Biopsy showed mural thrombosis without endocarditis in another 1 case.

In the light of the above, the high prevalence of LAA thrombosis in persistent AF patients with a history of COVID-19 seems understandable, but the question remains on triggers of the clotting. It can be assumed that clots identified in patients with a history of COVID-19 were formed during the acute disease and survived until TEE, which was conducted a mean of 76.5 days after the onset of the disease. However, this assumption runs counter other findings of this study.

First, the present study did not find a relationship between the incidence of thrombosis and the severity of COVID-19 in the acute stage as assessed by the presence and volume of the lung tissue involvement. According to the literature, venous thrombosis and thromboembolic complications are observed in the acute period of COVID-19 mainly in patients with massive lung damage [11, 13]. Second, according to the prospective study, post-COVID-19 parietal (atypical) clots dissolve faster than typical clots in AF patients without a history of COVID-19 (median survival is 35.0 days and 69.0 days, respectively; p=0.0018). Third, the assumption on clotting in the acute period of COVID-19 related to severe hemostasis disorders leaves the question on the causes of parietal LAA clotting in patients with a history of COVID-19.

In our opinion, it seems plausible to assume that endocardial damage caused by the SARS-CoV-2 persistence in the LAA myocardium and/or endocardium plays a leading role in the development of thrombosis in persistent AF patients with a history of COVID-19 [8]. This explains the parietal nature of LAA thrombosis in patients with a history of COVID-19 (see Figure 2), since the parietal location is characteristic of clots formed after the damage of the vascular wall or endocardium [17, 18]. It should be noted that, according to Blagova et al. [16], patients with post-COVID-19 myocarditis had parietal thrombosis. Two patients with a history of COVID-19 described by Fan et al. [15] had parietal aortic thrombosis.

This assumption allows us to explain other features of LAA thrombosis in post-COVID-19 patients, particularly the fact that the severity of COVID-19 does not affect the prevalence of parietal thrombosis. According to the literature, the endocardial and/or endothelial damage is not associated in post-COVID-19 patients with a severe course of the disease. According to Fan et al. [15], patients with arterial thrombosis had a history of asymptomatic COVID-19, and in the study by Blagova et al. [16], only 4 of the 15 patients with post-COVID-19 myocarditis had been hospitalized for acute COVID-19. These data are fully consistent with the findings of this study, which did not reveal the effect of the disease severity on the prevalence of LAA thrombosis.

Another feature of parietal LAA clots is the lack of CHF effect on their prevalence. Reduced LAA ejection velocity associated with left atrial systolic dysfunction is the leading factor in the development of LAA thrombosis in AF [19, 20]. It is shown in this study that, in the absence of a LAA clot, the LAA ejection velocity is lower in patients with CHF than those without (33.0 cm/s versus 27.5 cm/s, respectively; p=0.0430). It can be assumed that the effect of CHF on the likelihood of LAA thrombosis is implemented through a decrease in the blood flow velocity detected both in the general group of the examined patients and in the subgroup of patients without a history of COVID-19. No such effect was noted in post-COVID-19 patients, which may be due a small number of patients in this group (n=112) and the persistence of the SARS-CoV-2 in the LAA myocardium or endocardium, a factor not included in the analysis but having a pronounced effect on the clotting process.

A third feature of parietal clots is faster dissolution compared to typical clots floating in the LAA cavity and characteristic of patients without a history of COVID-19. As shown in this study, parietal clots cause a smaller decrease in the LAA ejection velocity compared to typical

clots. To recall, the mean ejection velocity is 32.0 cm/s in the absence of a LAA clot and decreases to 17.0 cm/s in typical thrombosis and 25.0 cm/s in atypical thrombosis ($p<0.0001$). The relatively high ejection velocity prevents the violation of blood rheology, which is evidenced by the rare combination of parietal clots and high-degree SEC (21.7% vs. 62.5% in the case of typical clots; $p=0.0552$), and ultimately contributes to the dissolution of the clot.

Thus, the results of this study provide an adequate explanation given the consideration that the SARS-CoV-2 persistence in the LAA myocardium or endocardium is one of the causes of LAA thrombosis in patients with persistent non-valvular AF and a history of COVID-19.

Limitations

The results of this study provide indirect evidence of the SARS-CoV-2 involvement in the development of LAA thrombosis in patients with persistent non-valvular AF and a history of COVID-19. However, this study did not provide the direct evidence of this. This could be the detection of the SARS-CoV-2 virus in the LAA myocardium or endocardium in patients with a history of COVID-19 and parietal thrombosis and the absence of signs of viral damage to these structures in patients without LAA thrombosis. However, this is impossible due to the technical problems of in-life biopsy. The identification of laboratory signs of inflammation and endothelial dysfunction in patients with parietal thrombosis and the absence of such signs in patients without thrombosis or in the presence of typical clots could provide sufficiently strong indirect evidence of the involvement of endocardial inflammation in the genesis of LAA thrombosis. The suggestion of a relationship between LAA thrombosis in AF patients with a history of COVID-19 will remain only a hypothesis until such evidence is obtained.

Conclusion

Left atrial appendage thrombosis is detected 2.5 times more often in patients with persistent atrial fibrillation and a history of COVID-19 than in patients without a history of COVID-19. The majority of post-COVID-19 patients and only every fourth patient without a history of COVID-19 have a parietal left atrial appendage clot. Unlike typical clots, parietal clots are not associated with a pronounced decrease in the left atrial appendage ejection velocity and high-grade spontaneous echocardiographic contrast. Parietal clots dissolve during appropriate anticoagulant therapy twice as fast as typical clots.

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No conflict of interest is reported.

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