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(REVIEW ARTICLE)

Fibrinolytic activity in atrial fibrillation

Negreva Mariya [1,*], Georgiev Svetoslav [2] and Zarkova Ana [3]

[1] *Associate professor at Department of Cardiology, Medical University of Varna, First clinic of cardiology, University Hospital "St. Marina"-Varna, Varna, Bulgaria; address: 1 Hr Smirnenski bulv., Varna 9000, Bulgaria.*
[2] *Professor at Department of Cardiology, Medical University of Varna, Second Clinic of Cardiology, University Hospital "St. Marina"-Varna, Varna, Bulgaria; address: 1 H. Smirnenski blvd, Varna 9010, Bulgaria.*
[3] *Doctor at the National Specialized Hospital for Active Treatment of Hematologic Diseases, Sofia, Bulgaria; address: Plovdivsko pole str. 6.*

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Abstract

Atrial fibrillation (AF) is one of the most common causes of thromboembolic cerebrovascular accidents. This is a prerequisite for the significant scientific and clinical interest in hemostatic disorders in AF. Despite the large number of studies on the topic, the exact mechanisms of thrombosis remain unclear. A well established fact is the significant activation of the coagulation cascade, therefore AF is often defined as a hypercoagulable state. The presence of a genetically determined link between coagulation and fibrinolysis inevitably raises the question of fibrinolytic activity in the disease.

Our review of fibrinolysis in AF showed that compared to studies on the coagulation system, data are significantly smaller in number. Components of fibrinolysis, its functionality in general, as well as its relationship with the arrhythmia itself and associated thromboembolic disorders, have been studied in both experimental and clinical models. However, single indicators have been examined and the obtained results are absolutely contradictory, presenting the system in both end states - from hypofunction to hyperfunction. One of the main weaknesses of the studies is the heterogeneity of the populations in terms of demographic and clinical characteristics, which in itself is a prerequisite for compromising the results. Most often, the fibrinolytic process is studied independently, without comparison with coagulation activity, which complicates the interpretation of the results. The question of causal relationship between changes in coagulation and fibrinolytic system in AF, as well as their contribution to the clinical manifestation of the disease and related thromboembolic complications, remains open.

Keywords: Atrial fibrillation; Fibrinolytic activity; Plasminogen activators; Plasminogen inhibitors

1. Introduction

The term fibrinolysis was first used by Giovanni Morgagni and John Huter in the 18th century, and since 1950, fibrinolysis is recognized as "*a system that regulates hemostasis*" [1]. Recent studies show that it is engaged in a number of physiological and pathological processes, namely involved in degradation of the extracellular matrix, embryogenesis, cell migration, angiogenesis, as well as activation of growth factors of myelopoiesis, apoptosis and others. [2, 3]. Although its roles are growing, it remains mainly associated to hemostatic balance. According to the classical notion, fibrinolysis is a complex enzymatic cascade process with a dominant involvement of serine proteases, which localizes and limits thrombus formation, lyses fibrin clots and restores vascular patency. In the light of thromboembolic events, of great interest is the established genetically determined link between coagulation and fibrinolysis, providing a precise balance between these processes and the fluid state of blood [4, 5]. Any activation of coagulation necessarily initiates

* Corresponding author: Negreva Mariya

an increase in the potential of the fibrinolytic system, which limits excessive thrombus growth and its premature lysis [6]. The precise balance between fibrinolysis and coagulation systems is crucial for hemostasis in general.

Undoubtedly, atrial fibrillation is a prothrombotic state, one of the most common causes of thromboembolic cerebrovascular accidents [7]. The social significance and high frequency of the disease are prerequisites for the significant scientific and clinical interest in hemostatic disorders in atrial fibrillation. Despite the large number of studies in this direction, the exact mechanisms of thrombosis remain unclear [8].

The purpose of this review was to systematically present the data on the fibrinolytic system in atrial fibrillation, its components and functionality, as well as its relationship with the arrhythmia itself and thromboembolic disorders observed in it. We conducted an in-depth review of original and review articles on the problem, presented in MEDLINE, PubMed and Google Scholar for the period 2000-2019. The following keywords were used: (non) paroxysmal, persistent, permanent atrial fibrillation, fibrinolytic system/activity, fibrinolysis, plasminogen, tissue plasminogen activator (t-PA), alpha2-antiplasmin, plasminogen activator inhibitor 1 (PAI-1) and vitronectin. We included studies with a clear protocol and definition of AF, reliable sources of medical records, methods of clinical evaluation and follow-up of relevant subgroups of patients.

2. Association of fibrinolytic indicators with atrial fibrillation

The number of studies presenting coagulation cascade activation in AF patients is significant, therefore it is often defined as a hypercoaguluble state [9]. Data on fibrinolytic system in AF are significantly less in number, which gave us a prerequisite for conducting this review.

Plasma levels of tissue plasminogen activator (t-PA) and activity of its major inhibitor, plasminogen activator inhibitor 1 (PAI-1), are the most commonly studied fibrinolytic parameters in AF, probably due to their key role. It is well known that t-PA is the major plasminogen activator of intravascular fibrinolysis [10]. PAI-1 is one of the most important inhibitors of plasma fibrinolytic activity, determining about 60% of its total potential [11].

Identification of specific hemostasis markers, closely associated with AF manifestation, is essential for understanding the etiology, development and prognosis of the disease. Detection of abnormalities in hemostasis in AF patients is important, but extremely insufficient from a clinical point of view. It is necessary to specify to what extent the abnormal levels are a consequence of AF, its cause or related to present comorbidities. The exact mechanisms of association between changes in hemostatic markers and the arrhythmia need to be clarified.

Berg et al. conducted a study on 63 patients aged 75 with paroxysmal and non-paroxysmal atrial fibrillation and 126 sinus rhythm controls [12]. The aim was to study the effect of the disease itself on plasma t-PA levels and PAI-1 activity. In the patient group, PAI-1 activity was significantly elevated [12.9 U/mL (6.6-17.1) vs 9.0 U/mL (4.6-14.0), p=0.0005] compared to controls, and the deviations persisted after gender (p = 0.007) and age (p = 0.028) adjustment.

This gave the authors a reason to believe that the changes are closely related and result from the disease itself and not from demographic and clinical characteristics of patients. However, plasma t-PA levels in patients and controls showed no significant differences (p>0.05). As a whole, the results showed reduced fibrinolytic activity, a prerequisite for prothrombotic state and thromboembolic events. The established hemostatic changes were present in the absence of clinical manifestation (no reported thromboembolic), which, according to the authors, emphasizes the need for fibrinolysis to be screened even in visibly healthy AF patients.

Reduced fibrinolytic activity in AF was also established by Roldan et al. [13]. They studied the chronic form of the disease in the context of one of the most commonly associated diseases, namely mitral stenosis. In their study group of 36 people with chronic AF, levels of PAI-1 (42.78±22.85 ng/mL vs 8.80±5.04 ng/mL, p<0.05) and t-PA-PAI-1 complex (0.77±0.33 ng/mL vs 0.37±0.38 ng/mL, p<0.05) were significantly increased. This was present in both patients with mitral stenosis and those with structurally healthy hearts, which suggests the independence of the hemostatic disorder from valve pathology. There were no deviations in the values of t-PA (2.31±0.90 ng/mL vs 2.88±1.58 ng/mL, p<0.05) and plasmin-antiplasmin complex (275.31±151.69 ng/mL vs 232.5±65.7 ng/mL, p<0.05). Disorders of fibrinolytic function were defined as independent of coagulation activity and even considered as a stand-alone option for a therapeutic approach to thromboembolic events in AF. However, as the authors themselves emphasize, the studied patient population was heterogeneous in terms of clinical characteristics and arrhythmia duration, which is a serious limitation of the study.

Fibrinolytic activity in AF and mitral stenosis is also discussed by Marin et al. [14]. They examined plasma levels of t-PA and PAI-1 activity in three groups: patients with mitral stenosis in sinus rhythm, patients with mitral stenosis and AF,

and a healthy control group. The results did not show significant differences in t-PA levels between the three groups (2.30(2.04–2.72) vs 1.78(1.43–2.78) vs 2.92(1.41–4.80) ng/mL, p>0.05). In mitral stenosis, plasma concentrations of PAI-1 were elevated both in sinus rhythm and AF (p<0.05). Changes were observed in the anterior-posterior atrial diameter subgroup ≤45 mm (45.9(24.4–58.9) ng/mL vs 28.5(15.5–53.0) ng/mL vs 7.3(5.6–9.2) ng/mL, p<0.05) as well as the group with diameters >45 mm (46.0(28.4–52.2) ng/mL vs 21.0(10.0–38.6) ng/mL vs 7.3(5.6–9.2) ng/mL, p<0.05). Mitral stenosis was associated with fibrinolytic dysfunction even in normal left atrial size and sinus rhythm. Summarizing the data, the authors conclude that AF is characterized by significant changes in fibrinolytic function, which, however, undoubtedly depend on the underlying structural heart diseases. Decreased fibrinolytic function is a consequence of concomitant diseases rather than the arrhythmia itself.

Decreased fibrinolytic activity was also found by Jabati et al. [15]. In the AF group, PAI-1 levels were significantly elevated (19.55±2.17 pg/mL vs 5.39±3.77 pg/mL, p<0.0001), while t-PA had no abnormalities (4.14±2.09 ng/mL vs 4.50±3.80 ng/mL, p=0.58). The patient group was heterogenous in terms of arrhythmia duration and the antithrombotic treatment, two facts that significantly limit the interpretation of the results and do not allow to clarify the relationship between fibrinolytic changes and the presence of the disease.

Wang et al., however, demonstrate completely opposite results [16]. They present data on increased fibrinolytic activity during clinical manifestation of AF, which are independent of gender, BMI, systolic blood pressure, total cholesterol and triglyceride levels, and left ventricular systolic function (p>0.05). The study was conducted among 53 patients with accidentally diagnosed AF. Significantly elevated plasma t-PA levels were observed compared to sinus rhythm controls (mean values 12.8 vs 8.1 ng/mL, p<0.01). However, the study population was quite heterogeneous in terms of comorbidities and treatment, which raises the question of their role in increased fibrinolytic activity.

Enhanced fibrinolysis has been found in a number of other studies [17, 18]. It is associated with elevated plasma levels of t-PA and PAI-1 and low values of plasmin-antiplasmin complex. It is well known that t-PA plays a key role in fibrinolysis by directly catalyzing the conversion of plasminogen to plasmin, and PAI-1 is its major antagonist. The identified changes were considered as a pathophysiological response to a hypercoagoluble state. At the same time, however, high values of t-PA and PAI-1 are present in a number of cardiovascular diseases, such as ischemic heart disease, heart failure, hypertension and others. This raises the question of whether abnormalities in the fibrinolytic system are associated with AF or are only present due to comorbidities. In this regard, prospective studies have established a direct correlation between the values of some fibrinolytic parameters and AF manifestation. Elevated t-PA levels have been shown to be an independent predictor of postoperative AF, in addition to age and previous history of arrhythmia episodes [19]. They are also an independent predictor for success of electrical cardioversion in AF patients [20]. In the attempts to clarify the relationship between the clinical manifestation of AF and fibrinolytic activity, the question arises about changes in fibrinolytic parameters as a consequence of other pathological processes associated with AF, such as inflammation [21].

The contradictory results regarding changes in the fibrinolytic system in AF gave us reason to conduct our study on 51 patients with recent-onset paroxysmal atrial fibrillation (duration of the arrhythmia episode <24 hours) and 52 controls, corresponding in terms of sex, age and clinical characteristics. [22]. We established elevated plasminogen levels (159.40±4.81% vs 100.2±2.88%, p<0.001) and t-PA activity (11.25±0.35 ng/mL vs 6.05±0.31 ng/mL, p<0.001), and decreased PAI-1 (7.33±0.37 AU/mL vs 15.15±0.52 AU/mL, p<0.00), alpha2-antilasmin activity (112.9±2.80% vs 125.60±3.74%, p<0.05) and decreased vitronectin plasma levels (134.7±5.83 vs 287.3±10.44 mcg/mL, p<0.001). Results suggest fibrinolytic system activity in the paroxysmal atrial fibrillation (PAF) group was significantly increased in the early hours (< 24th hour) of the clinical manifestation of the disease. This is most likely a pathophysiological response to an enhanced coagulation process, as evidenced by high D-dimer levels (0.53±0.07 vs 0.33±0.02 ng/mL, p <0.05). The close demographic and clinical characteristics of the patient and control group and lack of concomitant prothrombotic diseases among them are a prerequisite to assume that changes in the fibrinolytic system most likely result from the arrhythmia and are not caused by "co-existing factors".

Recently, in 2018, the American Heart Association presented a scientific statement discussing the relationship of AF burden to cardiovascular and neurological outcomes in AF [23]. It stated that AF should be considered beyond the binary entity (present/absent), as a dynamic value that cumulate in time. Review of recent data shows that higher AF burden is associated with higher rate of embolic events [24-26]. In this regard, it is quite logical that fibrinolysis, as important determinant of prothrombotic load, should be considered as a quantity with a possible dynamic characteristic over time. Therefore, its main indicators have been studied in both paroxysmal and persistent forms of the disease. For example, Drabik et al. found elevated t-PA levels in both paroxysmal (11.9±2.5 vs 9.4±2.1 ng/mL, p<0.001) and persistent atrial fibrillation (12.8±1.8 vs 9.4±2.1 ng/mL, p<0.001). [27]. Levels of its main inhibitor PAI-1 were significantly increased in both forms of arrhythmia (25.0-30.4 vs 17.4-29.9 ng/mL, p<0.001; 23.8-30.4 vs 17.4-29.9

ng/mL, p<0.001), paroxysmal and non-paroxysmal, respectively. Results show a tendency to form more compact fibrin clots and fibrinolytic resistance in the presence of the disease, even when patients are in sinus rhythm. However, arrhythmia duration does not determine significant differences in fibrinolytic activity.

Different conclusions were made by Mondillo et al. [28]. In a study of 45 patients with chronic non-rheumatic AF and 35 sinus rhythm controls, plasma levels of t-PA (20.371±7.8 vs 9.8±13.21 ng/mL, p<0.05) and PAI-1 (15.2±6.2 vs 9.33±4.8 ng/mL, p<0.05) were significantly increased. The changes correlated with the size of the left atrium, which suggests that the disease, and in particular its duration, is related to hemostasis.

Ischemic stroke is undoubtedly a serious AF complication. The hemostatic profile of patients with previuos thromboembolic stroke associated with AF is important and essential for adequate antithrombotic approach. According to Skov et al., the formation, structure and tendency to lysis of fibrin clot play an essential and equal role in the process of thrombosis [29]. Based on this, they examined fibrinolytic capacity of AF patients with and without a history of cardioembolic stroke and found that t-PA-induced fibrinolysis (79.6(51.9-92.6)% vs 55.3(42.4-77.0)%, p=0.005) and total fibrinolytic potential (20.4(11.7-30.9)% vs 13.6(9.7-20.5)%, p=0.004) were significantly higher in the group that experienced an embolic event. In this sense, they define the fibrinolytic system as directly associated with AF-related embolic events. Its increased activity logically determines an increased risk of embolization of thrombi present in the left atrium. The results support the hypothesis that increased fibrinolytic activity is responsible for AF embolism. At the same time, it is noteworthy that in the studied patient population, patients with a history of stroke have a significantly higher incidence of concomitant diseases such as diabetes, hypertension, heart failure, peripheral arterial disease, etc., which in themselves alter hemostasis.

Of particular interest is the study by Topcuoglu et al. [30]. Their research interests include patients with lone atrial fibrillation who do not have structural heart disease or other concomitant diseases that determine embolic risk. This population is considered to have the lowest embolic risk among patients with known AF. Plasma concentrations of t-PA and PAI-1 were studied in 24 patients with acute occlusion of the middle cerebral artery and lone atrial fibrillation and were compared to two control groups, patients with this type of arrhythmia, but without registered embolic incidents (n = 23) as well as with healthy sinus rhythm controls (n = 15). There were no significant differences in t-PA concentrations between the three groups (p = 0.89). PAI-1 levels were significantly higher among stroke patients. Results show reduced fibrinolytic activity in the conditions of an acute cerebrovascular event, most likely closely related and playing a key role in its manifestation. The authors define hemostatic changes as opportunities for new therapeutic approaches and prognostic tests.

Changes in fibrinolysis, as directly related to and responsible for thromboembolic events in AF patients, were also studied by Zabczyk et al. [31]. They examined 62 patients with permanent atrial fibrillation, from which 19 people (30.6%) were registered with a thromboembolic incident (11 with stroke, 8 with myocardial infarction, 3 with pulmonary thromboembolism). It is noteworthy that the studied fibrinolytic parameters were quite numerous, which allowed to refine the pathophysiological mechanisms of impaired hemostasis. In patients with embolic incident, clot lysis time (CLT) was prolonged (112.2±16.4 min vs 95.4±16.6 min, p=0.0035), PAI-1 levels (28.3 (22.0–34.7) ng/mL vs 20.3 (17.2–29.4) ng/mL, p=0.025), α2-antiplasmin levels (112.5±8.9% vs 102.0±11.7%, p=0.007), TAFI activity and levels (36.4±6.8 mcg/mL vs 28.9±6.9 mcg/mL, p=0.002; 116.8±13.4% vs 106.9±14.3%, p=0.04; respectively) were elevated. There were no significant deviations in plasma plasminogen concentrations (98.3±12.2% vs 103.3±12.1%, p=0.22). There was a good correlation of CLT with PAI-1 (r=0.66, p<0.001), α2-antiplasmin (r=0.32, p=0.009), TAFI activity and levels (r=0.73, p<0.001; r=0.27, p=0.03, respectively). According to the authors, this was the first study to identify impaired fibrinolysis in patients with AF and thromboembolic event due to increased activity of key inhibitors of the process. Moreover, CHA2DS2-VASc scores correlated with CLT, which support authors' concept that impaired fibrinolysis is indicative and determines an increased risk of stroke and thromboembolism in AF patients. The lack of correlation between CLT and left atrial size suggests a lack of association between fibrinolytic changes found in the systemic circulation and local hemostasis in the left atrium. In the studied group of patients, reduced activity of the fibrinolytic process was found, mediated mainly by changes in PAI-1, α2-antiplasmin and TAFI. One of the main disadvantages of the study was the comorbidity of the studied population, as well as intake of oral anticoagulants in a large proportion of patients. There were also no data on coagulation activity, which would provide information on hemostasis in general and determine the role of the fibrinolytic system as a separate risk factor for thromboembolic events. There was no control group without AF data to determine the extent to which decreased fibrinolytic activity was a consequence or cause of embolic events.

The study of fibrinolytic activity in the left atrium of AF patients is intriguing because it is thought to be the most thrombogenic part of the heart. There is little data on this topic. The intervention itself is an invasive procedure with a potential effect on hemostasis, therefore, it is necessary to compare the patient group with a control group undergoing

the same intervention, but without anamnestic and clinical AF data. Toth et al. studied 38 patients with impending radiofrequency ablation [32]. In 24 of them the procedure was for AF, and in the remaining 14 for supraventricular tachycardia. Plasma activity of plasminogen, α2-plasmin inhibitor and PAI-1 did not show significant differences between the two groups ($p > 0.05$). In general, no difference was found between intracardiac and peripheral levels of the studied indicators, except for a small but significant reduction of plasminogen intracardiacly in the AF group ($p < 0.05$). Plasminogen-antiplasmin complex and D-dimer levels were significantly increased intracardiacly ($p > 0.05$), which was the reason for the authors to believe the changes were a consequence of the invasive procedure itself. The results do not support the generally accepted notion of increased intracardiac thrombogenicity as a major cause of thromboembolic events in AF. The fibrinolytic system as a whole was almost unchanged in AF patients.

Intracardiac fibrinolytic activity in AF was also studied by Wybreniec et al. [33]. At baseline, prior to radiofrequency ablation, no significant differences were found in the values of t-PA and PAI-1 tested in the left atrium and peripheral venous blood (6.81(5.81–7.98) ng/mL vs 6.99(5.87–8.06) ng/mL, p=0.83; 15.1(12.0–17.3) ng/mL vs 14.2(11.5–16.0) ng/mL, p=0.75, respectively). After the procedure, atrial t-PA levels increased (6.81(5.81–7.98) ng/mL vs 11.3(10.3–13.3), $p<0.01$), and those of PAI-1 had no significant deviations (15.1(12.0–17.3) ng/mL vs 16.5(15.6–18.5) ng/mL, p= 0.08). Changes in fibrinolysis were considered secondary, resulting from the manipulation. Absence of abnormalities in intracardiac fibrinolytic activity in AF patients was also demonstrated by Motoki et al. [34]. Plasmin-α2-plasmin inhibitor complex levels did not differ significantly between patients with paroxysmal atrial fibrillation outside the paroxysmal period, patients with permanent arrhythmia and controls ($p>0.05$). In another study on the effect of AF on fibrinolysis, Otto et al. examined plasma PAI-1 levels before ablation, in the first and third months after the procedure, and found a significant decrease in the first month (19.55±2.17 ng/mL vs 12.99±1.69 ng/mL, $p<0.01$) and retention of changes after two months (12.99±1.69 ng/mL vs 18.23±2.52 ng/mL, p=0.11) [35]. Results suggest an effect of the arrhythmia itself on fibrinolysis, but the patient group was too small, which limited definitive interpretation according to the authors.

Studies on the fibrinolytic system are significantly less than those concerning coagulation activity in AF patients. This is also confirmed in the meta-analyzes and systematic reviews of hemostatic changes associated with the disease, published in the last few years. In 2017, Wyemann et al., presented an analysis of the literature available in leading electronic databases, addressing the issue of coagulation and fibrinolysis in AF patients [36]. Of the 71 selected studies, only about 20% examined fibrinolytic changes were associated with the arrhythmia. Noteworthy is the small number of studied indicators, as well as significant heterogeneity of the patient populations regarding concomitant diseases and duration of the arrhythmia. The authors found elevated t-PA levels compared to controls (mean 10.97 ng/mL vs 8.61 ng/mL) with significant heterogeneity among the studies ($I^2=98.3\%$; heterogeneity $p<0.001$). Pooled assessment analysis indicated that t-PA in patients with AF was significantly higher compared to those with SR with WMD of 2.13 (95% CI: 1.04–3.21; $p<0.001$) using a random effect model. PAI-1 mean values were also higher (30.59 vs 19.58 ng/mL; $I^2=99.4\%$; heterogeneity $p<0.001$). Plasma levels of fibrinopeptide A were similar (7.33 vs 3.18 ng/mL; $I^2=99.6\%$; heterogeneity $p<0.001$). Summarizing the data, the authors conclude that fibrinolytic function is significantly altered in AF. Results suggest a direct link between the identified changes and the manifestation of the disease. Weymann et al. consider the fibrinolytic system as a mechanism involved not only in the prothrombotic state, but probably also in the pathophysiological processes responsible for the manifestation of the disease.

To support this view, the authors present data on additional effects (beside hemostasis) that some molecules of the fibrinolytic cascade exhibit. For example, PAI-1 is not only a direct t-PA inhibitor, but it also modulates a number of adhesive glycoproteins involved in tissue and myocardial remodeling [37]. At the same time, Weymann et al. clearly outline the weaknesses of the studies performed on fibrinolytic function that complicate interpretation of results. Patient populations are highly co-morbid, data on a number of key fibrinolytic molecules are insufficient, such as plasminogen, α2-antiplasmin, plasmin-antiplasmin complex and others. All this limits the possibility to clearly define the critical role of the fibrinolytic system in the mechanisms associated with the manifestation of the arrhythmia.

In the search for relationship between hemostatic markers and AF, a meta-analysis by Wu et al. is of particular interest [38]. Of more than 600 studies screened, only 11 look at changes in fibrinolytic parameters in AF patients. T-PA and PAI-1 levels were significantly elevated in the presence of the disease compared to controls [SMD[95% CI]: 0.86[0.04–1.67] and 0.87[0.28–1.47], respectively]. A subgroup analysis was performed according to anticoagulant treatment, as it is well known that values of hemostatic indicators are affected by it. Subanalysis showed that both indicators were slightly altered in AF. There was no significant association between t-PA, PAI-1 and the presence of AF, both in participants without anticoagulant therapy and in studies with different doses of anticoagulant. At the same time, heterogeneity among the studies was significant ($I^2=96.7\%$, $I^2=96.3\%$, respectively). Based on the results, Wu et al. believe that the exact role of the fibrinolytic system in thrombosis in AF is unclear. The results are contradictory, and studied indicators are few in number, which further limits and complicates their interpretation.

3. Conclusion

Atrial fibrillation thromboembolism is a consequence of complex pathophysiological mechanisms that meet the requirements of the Virchov's triad for thrombogenesis, namely: stasis, changes in the vessel wall and impaired coagulation/fibrinolysis balance. The exact mechanisms through which the disease causes thrombosis are unclear. The role of the fibrinolytic system in the pathophysiological mechanisms of this process is also undefined. Data on it are few in number, and results are contradictory. Only single indicators are examined. Most often, the fibrinolytic process is studied independently, without comparison with coagulation activity, which complicates interpretation of the results. The question of causal relationship between changes in coagulation and fibrinolytic system in AF, as well as their contribution to the clinical manifestation of the disease and related thromboembolic complications, remains open.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflict of interest to declare.

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