

Numerical Modeling of the Dynamics of Blood Flow through Thrombosis.

S.D. Maussumbekova, A.O Beketaeva

Abstract— Thrombosis not only helps of stopping excessive bleeding in case of trauma, but is also often associated with pathological conditions of blood that interferes with its flow. The study of thrombosis is crucial for understanding and developing new methods for treating deep vein thrombosis, pulmonary embolism, etc. For the last two decades, there has been an exponential growth in studies related to the formation of a blood clot using computational tools and experiments. Despite this growth, a full the mechanism of thrombus formation is not yet known. In this paper, we considered the mathematical model of blood flow through region with thrombus. Blood flow is modelled as homogeneous incompressible fluid by the two-dimensional Navier-Stokes equations, when the formation of the thrombus described by equations of main regulators of fibrin polymerization. The numerical algorithm of solution of the basic equations is based on the immersed boundary method. It allows to take into account the moving thrombus. The presence of the immersed boundary is accomplished by adding a special function to the equations of motion, which make it possible to accurately represent the boundary of the streamlined region. In the present study, we analyze the effects of influence of various fluid parameters as Reynolds, Peclet numbers, gradient of pressure. It has been revealed that the increase of blood flow velocity leads to a change in the qualitative structure of the thrombus, that is, instead of simple form of thrombus appear thrombus with a complex structure.

Keywords— Navier-Stokes equations, incompressible fluid, the immersed boundary method, thrombus, activator and inhibitor.

I. INTRODUCTION

The dynamics of blood flow in blood vessels with thrombin is one of the urgent problems of hemodynamics. Various methods of experiments are used to predict the occurrence of stenosis in the blood. There are more reviews that describe theoretical studies of blood coagulation [1, 2] and platelet-dependent hemostasis and thrombosis [2, 3, 4]. The numerical methods are the most interesting for calculating hemodynamic parameters in the region of thrombus formation. The construction of mathematical models is the main means of studying the real problems of hemodynamics, which is associated with the extreme complexity of the biological system. Because the functioning of them depend nonlinearly on a large number of factors, while analytical methods of solution have a very narrow field of application. The calculating of the

main hemodynamic parameters of the blood flow and the prognosis of the development of stenosis are possible due to the numerical methods. Note that the flow of a fluid with nontrivial rheological properties in vessels of a given geometry has been studied repeatedly in the continuum mechanics, including with reference to the flow of blood [5-7]. The classical Poiseuille work [8] is the most widely known research among specialists, which has not lost its importance to this day. The normal functioning of the blood coagulation system ensures the maintenance of blood in the liquid fluid state. The ability to provide a fast local response of the organism in response to local disturbance is a feature of the blood coagulation system. In real blood vessels, clotting is activated by factors that are released at the site of injury. These factors trigger a cascade of biochemical reactions leading to the appearance of thrombin [9,10]. The model describes chemical interaction between the activator of coagulation and the inhibitor, and also simulates the production of fibrin, which is a chemical present in thrombus.

Mathematical modeling has become a very widely used tool for investigation of the mechanisms of coagulation in the blood vessel [10-12]. One of the most important problems in the field of hemostasis and thrombosis is related to the question how a thrombus grows and how it stops growing, it is not clear how and when a thrombus stops to grow in order to avoid a complete occlusion of the vessel [13]. Numerical results have been proposed to explain the mechanism of thrombus growth stopping [14]. Various mechanisms have been suggested to act under different conditions, including thrombomodulin-dependent pathway [15], action of flow parameters [16]. All these mechanisms require fibrin formation, and it is known to be strongly inhibited by the flow [17]. In the works [18] the mathematical model is constructed taking into account the fact that the dynamics of the blood coagulation system is determined by the production and distribution of two types of substances over the space: coagulation factors and factors that prevent coagulation. The effect of convective transfer on the spatial distribution of clotting factors that affect thrombus growth was analyzed, but the influence of the growing thrombus on the change in the flow around it was not taken into account [19].

The methods of immersed boundaries allow us to take into account the complex structure of the considered region. This method was first introduced by Peskin [20] for the study of flow patterns around heart valves and then applied successfully

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to many other problems in biological fluid dynamics [21-24].

Thus, for today not all possible mechanisms of influence on the growth of thrombus have been studied. The purpose of this work is to study the effect of blood flow parameters, as well as the conditions of appears thrombin on the structure of thrombus formation

II. MATHEMATICAL MODEL

In this model of blood clotting, blood is considered like an incompressible liquid with a constant viscosity, biochemical processes of interaction of key metabolites controlling the clotting of blood are taken into account. The mechanisms of the reaction ensuring the production of anti-coagulant factors have not been fully studied, so in this paper we confine ourselves to a simplified mathematical model that describes the kinetics of production and the diffusion over space of only two factors: coagulation factor-thrombin and clotting factor. The mathematical model reduces to two-dimensional equations for the flow of a viscous incompressible fluid supplemented by parameters of the convective transport of metabolites [25,26]:

$$\operatorname{div} V = 0 \quad (1)$$

$$\frac{\partial V}{\partial t} + (V \nabla) V = \Delta p + \mu \Delta V \quad (2)$$

$$\frac{\partial \theta}{\partial t} = D_1 \Delta \theta - \operatorname{div}(V \theta) + \frac{\alpha \theta^2}{\theta + \theta_0} - \gamma \theta \phi - \chi_1 \theta, \quad (3)$$

$$\frac{\partial \phi}{\partial t} = D_2 \Delta \phi - \operatorname{div}(V \phi) + \beta \theta (1 - \phi / C) \left(1 + \frac{\phi^2}{\phi_0^2} \right) - \chi_2 \phi, \quad (4)$$

$$\frac{\partial \psi}{\partial t} = k \theta \quad (5)$$

V - velocity of blood flow, p - pressure, μ - dynamic viscosity, θ - concentration of coagulation activator (thrombin), ϕ - inhibitor concentration. Thrombin catalyzes the conversion of a fibrin-fibrinogen precursor into a fibrin monomer which concentration is denoted by ψ , which in turn is polymerized under the condition $\psi > \psi^c$ of giving a thrombus. Here D_1, D_2 - are diffusion coefficients; $\alpha, \beta, \gamma, \chi_1, \chi_2, \theta_0, \phi_0$ are kinetic parameters from [23,27]. The kinetic term $\frac{\alpha \theta^2}{\theta + \theta_0}$ describes activator autocatalysis and $\gamma \theta \phi$ accounts for inhibitor influence on the activator production in the domains where both activator and inhibitor concentrations are large enough. The nonlinear item in the (4) equation simulates inhibitor production where activator occurs. The kinetic terms $-\chi_1 \theta$, $\chi_2 \phi$ describe passive escapes of metabolites. The equation (5) shows that fibrin is produced mainly due to the thrombin reactions. A detailed discussion of them and values can be found in [28]. The analysis of stability loss of the

homogeneous stationary state of model has also been considered [29].

The boundary conditions for the Navier-Stokes equations were taken as follows: no slip conditions were assumed on the walls of the vessel and the surface of the thrombus. Pressure values were set on the left and right boundaries of the considered region. At the input, the vertical components of velocity were assumed to be zero, at the output the boundary conditions were free. Boundary conditions for the metabolite - thrombin: the initial concentration was determined at the site of the vessel lesion.

III. ALGORITHM OF THE NUMERICAL SOLUTION

In the present study, the immersed boundary method [30] is used to account of the thrombus, that is, a discrete time artificial force f_i is introduced into the momentum equation like in the work of Kim J. and ets. [31], that is applied only on the surface of the obstruction (thrombus) and inside the body. The points of application of force are located in a node where the velocity components are defined. When the forcing point coincides with the virtual boundary, the artificial force is applied so that the no slip wall boundary conditions on the obstacle are fulfilled. The parameters in the cell containing the virtual boundary may not satisfy the mass conservation equation. Therefore, the source / sink of the mass q is entered for this cell. Taking into account the artificial force and, after the procedure of dimensioning, the system (1) - (5) will be rewritten in the another form with the following choice of characteristic scales: the concentration θ_0 and ϕ_0 , the linear dimension L , and the characteristic velocity V :

$$\operatorname{div} V - q = 0 \quad (6)$$

$$\frac{\partial V}{\partial t} + (V \nabla) V = \Delta p + \frac{1}{\operatorname{Re}} \Delta V + f_i \quad (7)$$

$$\frac{\partial \theta}{\partial t} = \frac{1}{\operatorname{Pe}} \Delta \theta - \operatorname{div}(\theta V) + \frac{1}{M} \left(\frac{\theta(\theta - \chi_1)}{\theta + 1} - \gamma \theta \phi \right) \quad (8)$$

$$\frac{\partial \phi}{\partial t} = \frac{1}{\operatorname{Pe}} \Delta \phi - \operatorname{div}(\phi V) + \frac{1}{M} \left(b \theta (1 - \varepsilon \phi) (1 + \phi^2) - \chi_2 \phi \right) \quad (9)$$

Where:

$$M = \frac{V}{a_* L}, \quad a_* = \alpha - \chi_1, \quad \operatorname{Pe} = \frac{LV}{D}, \quad \chi_1 = a_* \bar{\chi}_1, \quad \chi_2 = a_* \bar{\chi}_2,$$

$$b = \frac{\beta \theta_0}{\phi_0 a_*}, \quad \varepsilon = \frac{\phi_0}{C}, \quad \operatorname{Re} = LV / \nu.$$

The splitting method by physical parameters [32] is applied for the numerical solution of the equations of a viscous incompressible fluid (6)-(7). In the first stage, the intermediate velocity values are determined without taking pressure into account, in the second step, the pressure field is calculated from the calculated Poisson equation using of the intermediate

velocity values. The speeds on the next time layer are calculated at the third stage. The force is determined at the fourth stage of the numerical algorithm from equation (7) at the boundary points of the moving body (thrombus). At the same points mass source is calculated from equation (6). Implicit second-order scheme for approximating the spatial variables was used to solve the equation (8)-(9) which described the dynamics of the distribution of the main metabolites of the blood coagulation system.

Wave of the activator, which has speed $V_* = \sqrt{D_1(\alpha - \chi_1)}$ in non-convective conditions. It forms a polymerizing clot that blocks the bloodstream with velocity V . As observed by Ataullakhanov [27] the stopping of bleeding as a result of thrombus growth is possible when these rates are commensurable. The counteraction of the flow to the auto wave of coagulation can be characterized by a dimensionless parameter $Gu = V/V_* = V/\sqrt{D_1(\alpha - \chi_1)}$.

IV. ANALYSIS OF THE NUMERICAL RESULTS

The numerical algorithm for determining the dynamic characteristics of the blood flow was tested on the problem of flow past one obstacle, the results of a numerical solution of which are shown in Figure 1. Here the streamlines are shown at different instants of time. The qualitative picture coincides with the results from [33-34] and the known field observations by Van Dyke [35], which makes it possible to apply the proposed algorithm for solving this problem.

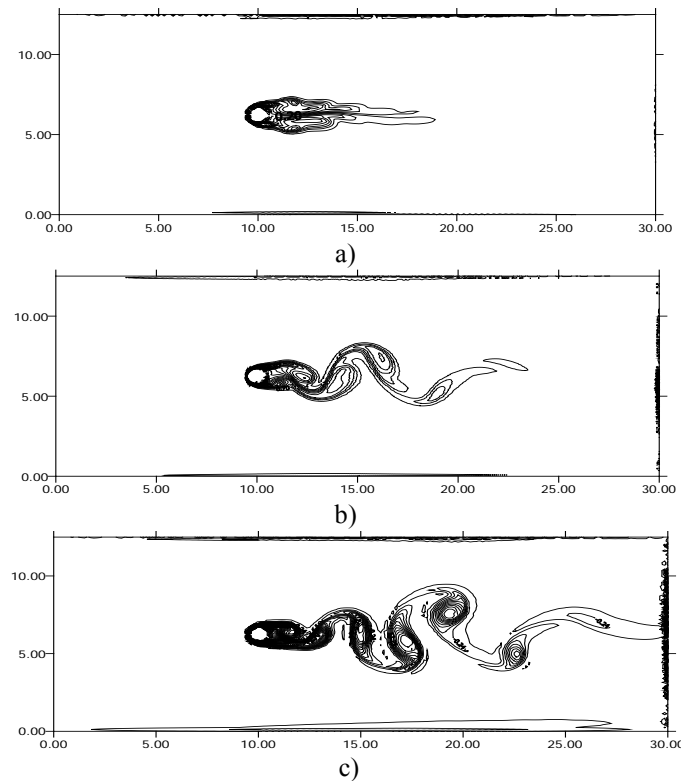


Fig. 1 pattern for flow around one cylinder at $t = 30$ (a), $t = 45$ (c), $t = 90$ (s),

The transitions from one type of characteristic spatio-temporal behavior to a qualitatively different one is interesting in study of macroscopic formation dynamics in the blood stream. The conditions of activation processes of the blood coagulation system that lead to the formation of a localized thrombus are investigated. The question of the conditions under which the localized thrombus formation is replaced by a multiple one is also investigated. The growth of blood clots is determined by the conditions of their flow around, and the flow characteristics in turn depend on the size of growing thrombus.

Figure 2 shows the results of calculations with the following parameters: $Re = 0.01$, $Pe = 10$, $Gu = 1.2$ at different times.

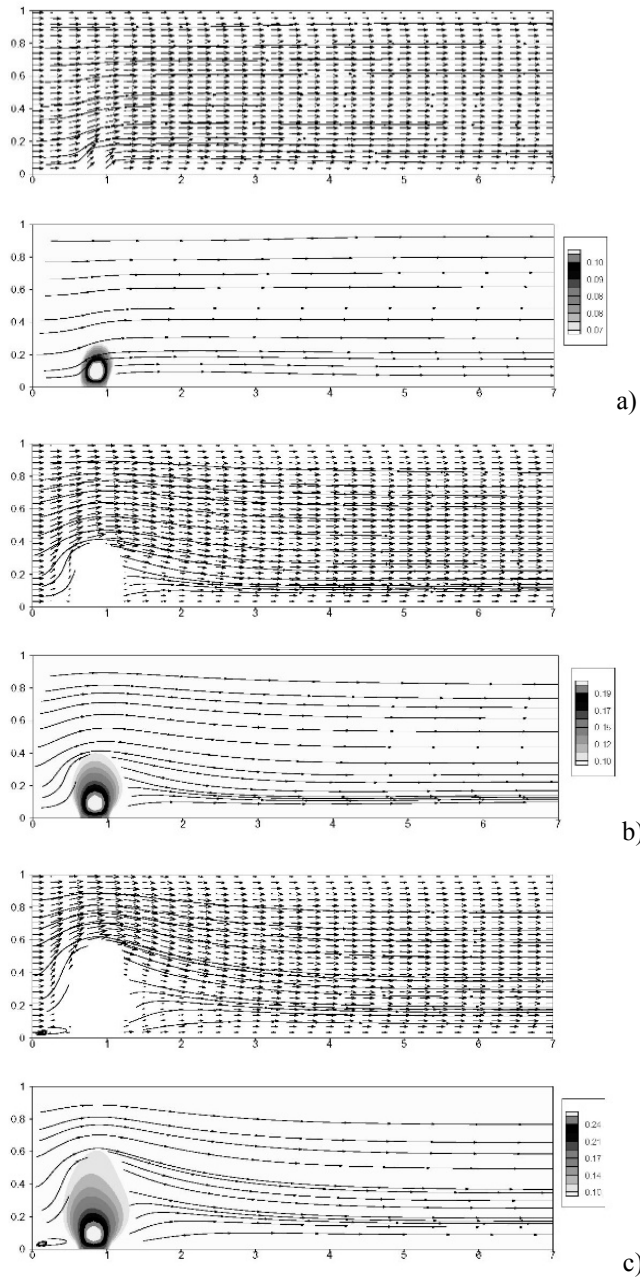


Fig. 2 the dynamics of thrombus formation for $Re = 0.01$, $Pe = 10$, $Gu = 2.7$, $n = 100$ (a), $n = 400$ (b), $n = 500$ (c).

In the low blood flow velocities case, the primary wave of activation of clotting (the initial perturbation wave) is extinguished by the inhibitor wave and the growth of the thrombus stops. The thrombus covers up to one-third of the transverse vessel size as in work [36]. As can be seen from the pictures the blood flow is displaced from the injury area. Localized thrombus formation is determined by the interaction of the activator and the inhibitor with each other also by the hydrodynamic flow.

An increase of the Reynolds number leads to the destruction of the thrombus along the direction of the flow, as can be seen

from Figure 3, the thrombus assumes an asymmetric shape.

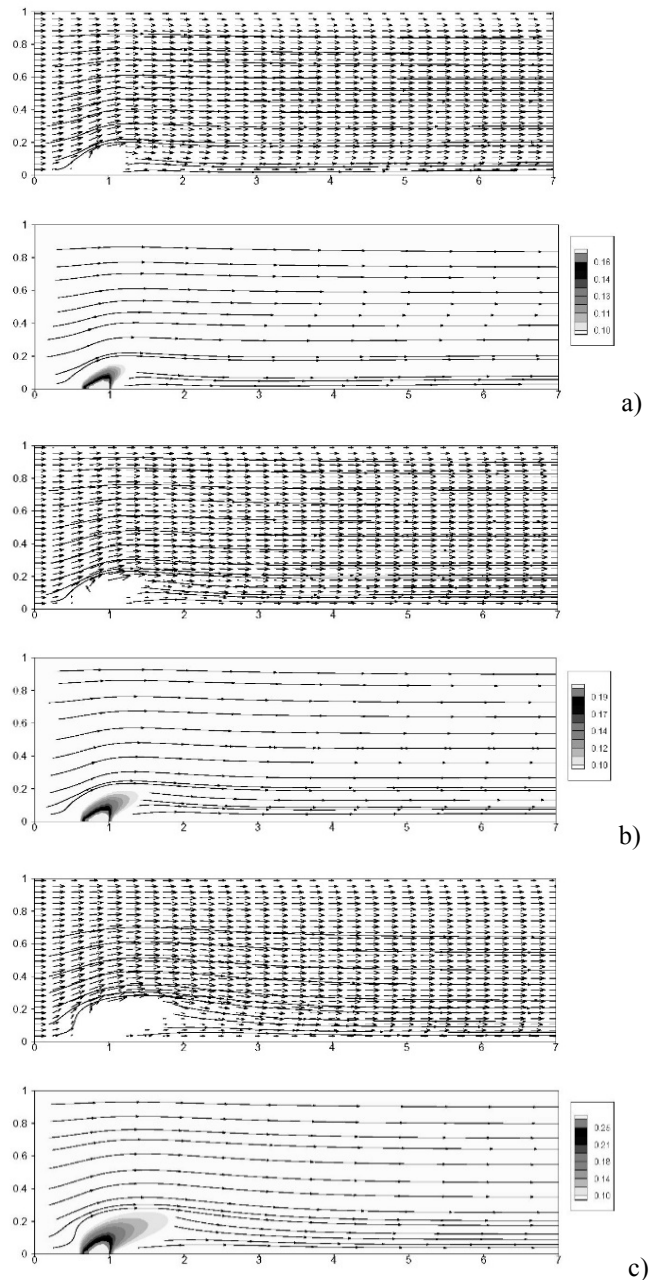


Fig. 3 the dynamics of the formation of a thrombus for $Re = 1$, $Pe = 10$, $Gu = 1.2$, $n = 100$ (a), $n = 400$ (b), $n = 500$ (c).

Stopping bleeding as a result of thrombus growth is possible when these rates are commensurable. As indicated above, the counteraction to the flow of an auto-coagulation wave can be characterized by a dimensionless parameter, like the number Gu . The results of numerical experiments were obtained, where a change in the number Gu leads to an intensity of convective thrombus transfer. The further growth of the thrombus stops by anti-coagulation wave. The displacement of the blood flow is more significant. In these conditions there is no separation of the thrombus as have been shown by numerical experiments

(Figure 4.).

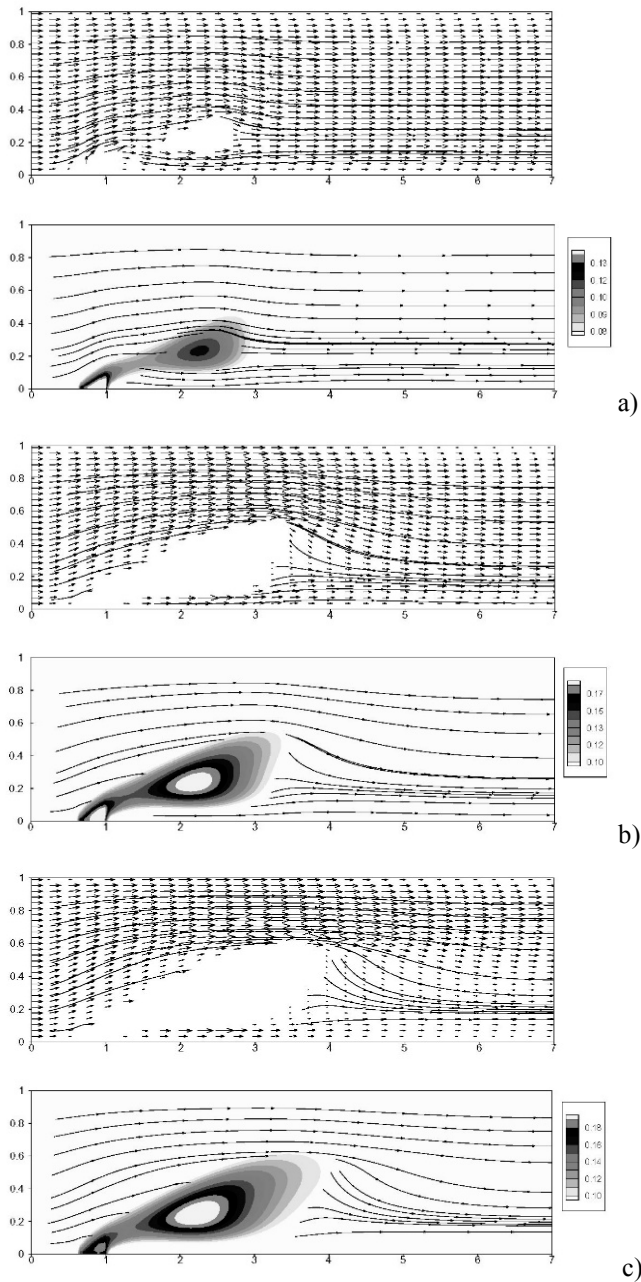


Fig. 4 the dynamics of the formation of a thrombus for $Re = 1$, $Pe = 10$, $Gu = 2.7$, $n = 100$ (a), $n = 400$ (b), $n = 500$ (c).

The complex topological structure of thrombus is the result of nonlinear interactions of activators and inhibitors with each other and with the flow in the varying geometry region. When the blood flow velocity exceeds a certain threshold value, the thrombus formation pattern takes a dramatic scenario, which is the reason for the inability of inhibitor to stop the development of a clotting activator. The structure of the flow shows multiple thrombogenesis, that is, secondary thrombus arise downstream of the site of the vessel damage. This scenario is the

development of thromboembolism, leading to obstruction of blood vessels (Figure 5.).

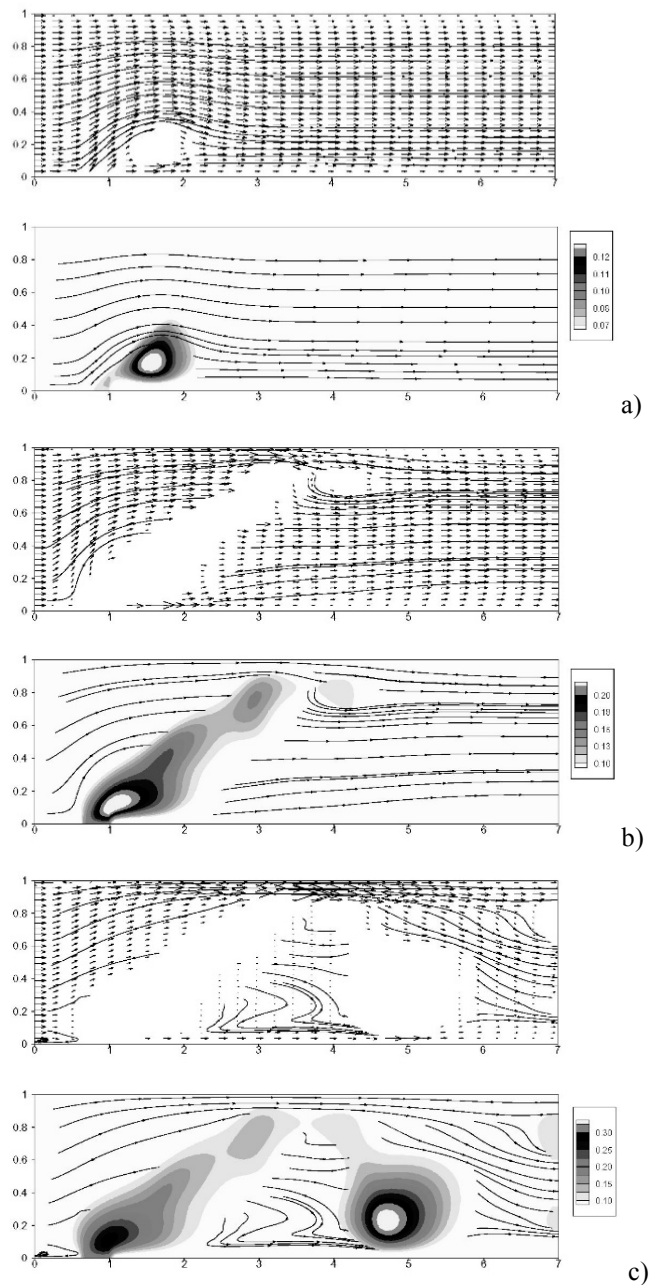


Fig. 5 - the dynamics of the formation of a thrombus for $Re = 1$, $Pe = 24$, $Gu = 2.7$, $n = 100$ (a), $n = 400$ (b), $n = 500$ (c)

V. CONCLUSION

In the present work the mechanisms of thrombus formation in the blood stream were numerically studied, where the two-dimensional Navier-Stokes equations for an incompressible fluid described dynamics of blood and the equations for metabolites of blood clotting described the process of blood coagulation. To solve the initial equations, the immersed boundary method was used which gives for taking into account

the thrombus formation. Numerical results showed that in the case of high blood flow velocities, the primary wave of clotting activation (initial disturbance wave) is cancelled by the inhibitor wave and the growth of the thrombus stops. When the blood flow velocity and the velocity of wave activator are commensurable, bleeding may stop. Nonlinear interactions of activators and inhibitors with each other and with the flow lead to a complex topological structure of thrombus.

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