Mathematical Model of Platelet Thrombus Formation

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Abstract

The mathematical model of the platelet thrombus formation has been investigated. The model of platelet transport on the shear flow is shortly described. The model can be applied for studying of inflammatory diseases of kidneys.

Introduction

Traditionally, when studying *in vitro* blood coagulation process, more attention was paid to the fibrin thrombus formation. Donor blood plasma, which was used for experiments, contained no blood corpuscles.

Meanwhile, *in vivo* are usually formed platelet thrombi at first. The secreted thrombin is one of the blood factors which lead to formation of fibrin thrombus. The later formation of the thrombus is mixed, it is carried out due to both fibrin polymerization and embedding of the activated platelets into the thrombus.

Here we consider a simple mathematical model for platelet thrombus formation in the blood flow. Note, that such mathematical model was derived for describing experiments *in vitro* in the artificial system, which excludes donor blood plasma.

Mathematical model

We consider an inner problem of the liquid flow with dissolved chemicals in the cylindrical vessel of variable cross-section. The cross-section of the vessel can change in time due to thrombus formation. We used the Navier-Stokes equations [1] for describing the liquid flow. Under this approximation blood or blood plasma are considered as Newtonian incompressible fluid. The permanent Poiseuille profile of velocity is maintained at the vessel entrance.

We consider a simple kinetic model of platelet transport in the shear flow. We neglect the aggregation of the platelets in the flow. Let us assume that platelets are warp-free spherical particles (usually platelets are of ellipsoidal shape).

To estimate the result of platelet collision in the blood flow let us assume that: the platelet size is sufficiently less then the radius of the vessel, the velocity of the center of mass of platelet couple doesn't change at collision and is equaled to local velocity of the blood at the couple location. We also neglect the spin of the platelet. As a result, the platelet couple would rotate around its center of mass until the contact between the platelets is broken. The contact breaks when both platelets have the same axial velocity. The platelets in the blood flow change their location relative to the flow with the collision rate so that the center of mass of each platelet couple doesn't shift relative to the flow. We assume that the velocity of the flow is big enough to neglect the axial shift of the platelet during the time of collision. Thus we can consider only radial component of platelet transport.

The rate of collisions for control platelet can be calculated as an integral:

$$\nu = 2\int_0^{2a} 2c(r+x)\Delta v(r,x)\sqrt{(2a)^2 - x^2}\,dx. \tag{1}$$

where a — is the radius of the platelet, $c(r+x)$ — concentration of the platelets, $v(r,x)$ — relative velocity.

We used simplified view of platelet state evolution. It assumed that platelets can be differentiated by following characteristics: passive-active and full-empty. For a platelet to go from passive to active state activator (thrombin) is needed, and when a platelet goes from full to empty state, it releases thrombin to the flow. The kinetics of state changes is described by a system of equations [2]:

$$\frac{\partial\, w}{\partial\, t} = -k_w w + k_1 c_f + (\mathbf{V}, \nabla w) + D_w div(\nabla w), \tag{2}$$

$$\frac{\partial\, c_p}{\partial\, t} = -f(c_p, w) + (\mathbf{V}, \nabla c_p) + div(\mathbf{D}_\parallel \nabla_\parallel c_p + \mathbf{D}_\perp \nabla_\perp c_p), \tag{3}$$

$$\frac{\partial\, c_f}{\partial\, t} = f(c_p, w) - k_2 c_f + (\mathbf{V}, \nabla c_f) + div(\mathbf{D}_\parallel \nabla_\parallel c_f + \mathbf{D}_\perp \nabla_\perp c_f), \tag{4}$$

$$\frac{\partial\, c}{\partial\, t} = f(c_p, w) + (\mathbf{V}, \nabla c) + div(\mathbf{D}_\parallel \nabla_\parallel c + \mathbf{D}_\perp \nabla_\perp c) \tag{5}$$

where $\nabla_\parallel c$ denotes projection of concentration gradient vector parallel to the fluid velocity vector, $\nabla_\perp c$ — normal projection, $\mathbf{D}_\parallel$ is small, and $\mathbf{D}_\perp \approx a^2\nu$, ν is determined by (1), w — activator concentration, c_p — assive platelets concentration, c_f — concentration of full active platelets, c — concentration of all active platelets, k_1, k_2, k_w — constants of monomolecular reactions, k, w_0, m — constants of the function which determines transition of passive platelets to active state when interacting with activator:

$$f(c, w) = \frac{k \cdot w^m \cdot c}{w^m + w_0^m}.$$

The values of parameters are: $k_w = 2.0$, $k_1 = 15.0$, $k_2 = 0.5$, $k = 20.0$, $m = 2.0$. At the vessel entrance all concentrations are set constant, at the vessel exit free (unreflecting) boundary conditions are set. At the axis of the vessel symmetrical conditions are set, on the vessel wall diffusive flow of activator equals to zero $\frac{\partial w}{\partial \mathbf{n}} = 0$, the flow of platelets to the active zone of the wall is determined by $\mathbf{D}_\perp \frac{\partial c_i}{\partial \mathbf{n}} = c_i(R-2a)\frac{a}{\tau}$, $c_i = c_p, c_f, c$, where $c_i(R-2a)$ is the concentration of the platelets at $R-2a$ distance from the vessel wall.

Thrombus formation at inflammatory kindey diseases

We calculated a simplified variant of the problem. It is known, that at inflammatory kidney diseases (e.g. pyelonephritis) almost all platelets are active and thrombin concentration in the blood is highly elevated. We assume that in large blood vessels only platelet thrombi are formed and neglect the processes connected with fibrin polymerization. Such approach allows one to investigate medically important DIC syndrome, and also platelet formation in veins. In particular, one of the most dangerous areas of thrombus formation is abdominal vein. When all platelets are activated the system (2–5) is simplified and we can only consider evolution of active platelets using only one equation

$$\frac{\partial\, c}{\partial\, t} = f(c_p, w) + (\mathbf{V}, \nabla c) + div(\mathbf{D}_\parallel \nabla_\parallel c + \mathbf{D}_\perp \nabla_\perp c).$$

Below are represented results of numerical experiments. Diffusion coefficient was assumed to be constant for test experiments. The speed of thrombus formation increases with increasing of the flow velocity. The initial concentration was rather big, so at Re=100 concentration of the platelets behind the growing thrombus isn't zero, which happened in

the experiments with lower concentrations, when all the platelets coming to vessel adhered on the thrombus. Also the thrombus grows upstream. The time of thrombus growth was about 5s, which is several times faster than in vivo due to high concentration of the platelets and velocity of the flow. At slow velocities almost all platelets adhere on the wall in the vicinity of active zone. As a result, behind the thrombus is formed a region with almost zero concentration of the platelets.

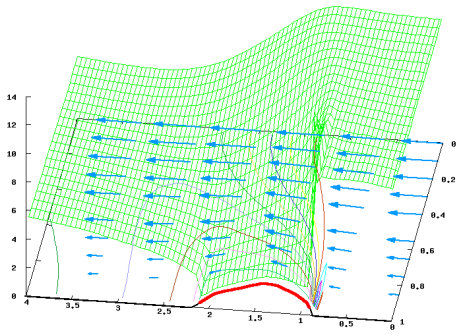

Figure 1: Platelet distribution (3d surface), vessel boundary and active zone and velocity field (arrows). Re=100.

Conclusions

Here we considered a mathematical model for platelet thrombus formation based on a simple model of particles transport in the shear flow. Numerical method was implemented which allows one to calculated thrombus formation on the linear parts of the vessels. A simplified model of thrombus formation when all platelets are active was investigated. It is known that large veins with relatively high velocity of the flow are more exposed to thrombus formation. The results of numerical experiments are in qualitative agreement with clinical data. The other area which is subject to thrombus formation are venules, where velocity of the flow is small. Within the framework of the examined model the formation of platelet thrombus in such vessels is slow. But the model doesn't include fibrin clots formation, which are more actively formed in slow flows. The development of the model is to integrate both platelet and fibrin models of thrombus formation.

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