RELATIONS BETWEEN DIMENSIONAL AND DIMENSIONLESS VALUES AND VARIABLES

We choose the whole vessel’s length $L$ as a unified reference scale for any lengths in our model. Therefore, dimensionless quantities may be introduced: scaled vessel’s radius $\rho_0 = r_0/L$, inner radius of the lumen $\rho = r/L$, length of thrombus $\lambda = l/L$.

For convenience we define typical scale for hydraulic resistance as:

$$ [R] = \frac{8\eta}{\pi L}. $$

As for the flow rate scale, it is convenient to express this value through combination of blood flow rate at the outlet of the heart $Q_0$ and the shunting hydraulic resistance $R_w$: $[Q] = Q_0 R_w/[R]$. Pressure difference is thus scaled to a factor $[\Delta p] = Q_0 R_w$.

Shear rate in the stenosed vessel $\dot{\gamma}$ was scaled to the initial shear rate (when no thrombus yet grown):

$$ \dot{\gamma}_0 = \frac{\Delta p \rho_0}{2\eta} = \frac{Q_0 R_w r_0}{2\eta L}, $$

so that dimensionless shear rate $G = \dot{\gamma}/\dot{\gamma}_0$.

Let’s denote the timescale as $\tau$. The scaled amplitude of the growth rate $\Psi = \psi^1_{\dot{\gamma}_0}^{1-\beta} \tau/L$ may be set to unity by the appropriate choice of $\tau$. Here we see that $\Psi$ doesn’t change the occlusion dynamics qualitatively, but only the time required to reach the final size of the thrombus. If we choose $\tau = 1/\dot{\gamma}_0$, then $\Psi = \psi^1_{\dot{\gamma}_0}^{1-\beta}/L$. The scaled version of adhesion parameter $\xi_d$ is $\xi = \xi_d \cdot \dot{\gamma}_0/\psi$.

SOLUTION OF POISEUILLE PROBLEM FOR A THROMBOTIC BLOOD VESSEL OF AN ARBITRARY SHAPE

The hydraulic resistance and distribution of shear forces on thrombus we find from the solution of Poiseuille problem to Eq. (4) within the thrombotic domain. We treat the thrombus impermeable to blood plasma and impose a no-slip condition on surfaces of vessel and thrombus.

As confirmed by our numerical results, the only significant pressure variations are those along the vessel, and within the cross-section the pressure is almost uniform. This is equivalent to a uniform height of thrombus along its entire length. Therefore, the hydrodynamics in the thrombotic domain reduces to quasi-steady two-dimensional Poiseuille problem, where all hydrodynamic values (e.g., fluid velocity, shear rate, etc.) depend on the transversal coordinates $y$ and $z$ much stronger than on the longitudinal $x$ coordinate. According to these findings, the problem formulates in the following way.

Consider the cylindrical channel (blood vessel) parallel to the $x$ axis, and it is assumed to be translationally invariant in that direction. The cross-section in the $yz$-plane is denoted $\Omega$ with boundary $\partial \Omega$. A constant pressure difference $\Delta p_x$ is maintained over a vessel’s segment of length $l$. The viscosity of fluid $\eta$ is constant. In this general case problem may be formulated as follows. First, we introduce the function $g$ determined as a solution to the boundary value problem:

$$ \nabla^2 g = -1, \quad g|_{\partial \Omega} = 0, $$

so that, obviously, the fluid velocity component, parallel to the vessel’s centerline, reads

$$ u = \frac{\Delta p_x}{\eta l} g(y, z). $$

The inverse of hydraulic resistance of the considered seg-
moment is
\[ R_x^{-1} = \frac{1}{\eta l} \int_\Omega g(y, z) \, d\Omega \] (6)

where integration is over the lumen area of vessel’s cross-section. Now, to calculate this value, all we require is the exact information about the shape of the vessel’s cross-section. Note that we don’t need to know the pressure drop \( \Delta p_x \) to find \( R_x \), this is the main advantage of introducing the function \( g(y, z) \). However, in order to find the fluid velocity and, which is more important, the shear rate distribution, we have to find \( \Delta p_x \) as follows.

The well-known Hagen-Poiseuille law proposes a linear relation between flow rate and pressure drop for each segment of the circulatory system:
\[ Q \cdot R = \Delta p, \] (7)

where \( R \) is the hydraulic resistance of the segment, which is constant for low-Reynolds number flows typical in microvasculature. Hydrodynamic resistance of aorta and major arteries depend on Reynolds number and the pressure drop, though it is negligible compared to that of microcirculatory vessels. In fact, arterioles (and also venules) with diameter < 100 \( \mu \)m provide the biggest contribution to the hydraulic resistance of the circulatory system, being relatively long vessels (\( L \sim 1 \) cm) with small cross-sectional area.

Considering the blood circulatory system, one can obtain a formal expression for the relation between the flow rate \( Q_x \) and the applied pressure difference \( \Delta p_x \) using Hagen-Poiseuille law and Kirchhoff’s circuit laws:
\[ Q_x(t) = \frac{Q_0 R_w}{R_w + (R^t + R^o) + R_x(t)}. \] (8)

The pressure drop \( \Delta p_x = p_x^{in} - p_x^{out} = Q_x(t) \cdot R_x(t) \) is found to be:
\[ \Delta p_x(t) = \frac{Q_0 R_w R_x(t)}{R_w + (R^t + R^o) + R_x(t)}. \] (9)

Then, by finding \( \Delta p_x(t) \), one may determine the wall shear rate distribution:
\[ \dot{\gamma} = \frac{\Delta p_x \nabla g}{\eta l} \bigg|_{\partial \Omega} \] (10)

Evaluation of wall shear rate \( \dot{\gamma} \) at each time step was followed by the calculations of effective growth rate \( k_{eff} \) at each point of thrombus’s surface with the consequent alterations of thrombus’s form. Time step was chosen small enough to make the calculated dynamics of thrombosis independent of it.

The example studied in the main text deals with the particular shape class of the thrombus, which is the segment of the circle, determined by its radial protrusion \( r(t) \) and angular size \( \Theta(t) \), see Fig.1D. Both parameters were allowed to change during the simulation, while the length of the thrombus was fixed. Dimensionless equations governing the dynamics of thrombus growth were deduced from Eq.(1) of the main text:
\[ - \dot{\rho} = \Psi \langle K_{eff} \rangle_{top}, \] (11)
\[ (\rho_0 + \rho) \dot{\Theta} = 2\Psi \langle K_{eff} \rangle \Theta, \] (12)

where \( \langle K_{eff} \rangle_{top} \) and \( \langle K_{eff} \rangle \) are the integral-averaged growth rates at respectively top and flank surfaces of thrombus. These values are generally not equal to each other, since there are different shear rates at different parts of thrombus’s surface, Fig. S2.

**DEPENDENCE OF SHEAR RATE ON SHAPE OF VESSEL’S CROSS-SECTION**

One may use an approximate formula [1] for hydraulic resistance of a stenosed domain:
\[ R_x \approx \frac{2 \eta l P^2}{S^3} \] (13)

with \( S \) being the cross-sectional lumen area and \( P \) - the perimeter of lumen cross-section. From the second Newton’s law one may find the wall shear rate, averaged over the lumen perimeter:
\[ \dot{\gamma}_{aver} \approx \frac{\Delta p_x}{\eta l} \frac{S}{P} \] (14)

where \( \Delta p_x \) is still determined by the interplay of hydraulic resistance values of thrombotic and healthy domains of the vessel.

Dimensionless shear rate averaged over the cross-section within the stenosed region reads:
\[ \dot{\gamma}_{aver} = G_{aver} \approx \frac{Z^{1/2} \Gamma^{1/2}}{\lambda + (1 - \lambda) Z \Gamma^2}, \] (15)

where \( \Gamma = S/(\pi r_0^2) \) is \( \text{1} \text{ Stenosis} \) and \( Z = 4\pi S/P^2 \) is the characteristic of lumen’s shape. For a given degree of stenosis \( Z = 1 \), the whole variety of lumen cross-section’s shapes is now described by different values of \( Z \). This indeed would cause some quantitative changes, but the qualitative relation between shear stresses exerted on thrombus and the length of thrombus remains the same, as in the axisymmetric case. Moreover, according to isoperimetric inequality, \( Z \leq 1 \), and \( Z = 1 \) corresponds to circular shape. The highest possible peak value \( G_{aver}^{max} \) is attained for \( Z = 1 \), as follows from Eq.(15), i.e. circular cross-section.

**AXISYMMETRIC THROMBOTIC SEGMENT**

For axisymmetric thrombus (when thrombus grows over the whole perimeter of vessel’s cross-section, \( \Theta = \)
2π) the lumen has a circular shape with inner radius \( r(t) < r_0 \), and the hydrodynamic problem may be solved exactly

\[
g_{2π}(y, z; r(t)) = \frac{1}{4} (r(t)^2 - q^2), \quad q^2 = y^2 + z^2, \tag{16}
\]
\[
u_{2π}(y, z; r(t)) = \frac{Δp_x}{4ηl} (r(t)^2 - q^2), \tag{17}
\]
to yield the hydraulic resistance

\[
R_x(t) = \frac{8ηl}{πr(t)^4}, \tag{18}
\]
and shear rate at surface of thrombus

\[
\dot{γ} = \frac{Δp_x \cdot r(t)}{2ηl}. \tag{19}
\]

Flow rate through the stenosed vessel and corresponding pressure drop change as follows from Eqs. (8) and (9).

For axially symmetric thrombus equation for the lumen radius in the stenosed region of vessel in dimensionless form reads

\[
\dot{ρ} = -ΨK_{\text{eff}}(G), \tag{20}
\]
where \( ρ = r(t)/L \) is the dimensionless radius of lumen, \( G = \dot{γ}/\dot{γ}_0 \) is dimensionless shear rate related to the wall shear rate in non-stenosed vessel, and \( Ψ \) is the constant amplitude of the growth rate, which determines the typical time span required to occlude the vessel or to reach the steady state.

**DIFFERENT MODELS FOR THE EFFECTIVE GROWTH RATE**

We use several models for the effective growth rate. The first one is the model with power-law dependence of platelet in-flux on the shear rate \( j_{in} \sim ψ\dot{γ}^{1-β} \) and the out-flux being a linear function of the shear rate \( j_{out} = ξd\dot{γ} \), where \( ξd \) is a constant with a dimensionality of length that can be considered as a characteristic thickness of a layer of weakly attached platelets, which are relatively mobile and can be easily detached from the thrombus. Dimensionless version of the effective growth rate in Eq. (20) reads

\[
K_{\text{eff}}(G) = G^{1-β} - ξG, \tag{21}
\]
with \( G = \dot{γ}/\dot{γ}_0 \), \( β \) being the one of model parameters, which is approximately equal to 0.2 for human blood, as it was measured earlier [3]. Here \( ξ \) is an adhesion parameter, which characterizes the relative significance of hydrodynamic forces exerted on a platelet in respect to the adhesion forces, by which it attaches to the thrombus or subendothelium, so that the bigger \( ξ \) the weaker adhesion is.

Another model considered in the paper is the model with constant platelet influx

\[
K_{\text{eff}}(G) = K_0 - ξG, \tag{22}
\]
which is actually the particular case of the power-law model for \( β = 1 \). Here \( K_0 \) is the constant dimensionless influx \( j_{in} \). This parameter may be varied as long as the amplitude of the growth rate \( Ψ \). To be certain, in this case (with no loss of generality) we set \( K_0 = 1.2 \) and regulate adhesion dynamics changing \( Ψ \) only.

We also use the model with activation of platelets, enabling their irreversible attachment described via Bell’s law. In this model a two-stage [3] aggregation mechanism is expected: the first stage is reversible attachment governed by the aforesaid power-law dependence on shear rate, the second stage involves the fact of shear-dependent activation of particular membrane proteins of platelets (integrins), which provide firm attachment. The effective growth rate \( k_{\text{eff}} \) we take from [2] with a slight modification, so that it resembles the well known Bell’s law (note that in the original paper shear-dependency of integrin activation was linear). This allows coverage of a wider range of shear rates:

\[
k_{\text{eff}} = \frac{ψ\dot{γ}^{1-β}}{1 + \frac{ψ\dot{γ}^{1-β}}{k_0 \exp(-ξd\dot{γ})}}, \tag{23}
\]
or in dimensionless form:

\[
K_{\text{eff}}(G) = \frac{G^{1-β}}{1 + \frac{G}{K_0 \exp(-ξG)}}. \tag{24}
\]

**PRESSURE DISTRIBUTION IN THROMBOTIC VESSEL**

Healthy regions of the stenosed vessel provide the resistance

\[
R' + R'' = [R]. \frac{(1 - λ)}{ρ_0^3} \tag{25}
\]
and the thrombotic domain has the resistance

\[
R_x = [R]. \frac{λ}{ρ^3(t)}. \tag{26}
\]

Let’s denote the initial resistance of thrombotic vessel (when thrombus height is zero) as \( R_0 = R' + R'' + R_0(0) = [R]/ρ_0^3 \). According to our estimates, the initial hydraulic resistance of arteriole (venule) \( R_0 \sim 10^4 - 10^5 \text{ Pa} \cdot \text{s/cm}^3 \) is much bigger than that of the remaining circulatory network, \( R_w \ll R_0 \). Therefore, \( (ρ_0 R_w/[R]) \ll 1 \) should be considered as a small parameter.

In dimensionless variables Eqs. (8) and (9) take form

\[
\frac{Q_x}{Q_0} = \frac{(R_w/[R])}{(R_w/[R]) + (1 - λ)/ρ_0^3 + λ/ρ^1}. \tag{27}
\]
\[ \delta p = \frac{\Delta p_x}{Q_0 R_w} = \frac{\lambda/\rho^4}{(R_w/[R]) + (1 - \lambda)/\rho_0^4 + \lambda/\rho^4}. \] (28)

Both values change as thrombus grows and stenosis increases.

Now we assure that pressure across microcirculatory vessels \( \Delta p_{12} = p_1 - p_2 \) remains almost constant:

\[ \Delta p_{12} = Q_0 \frac{R_w (R'_w + R''_w + R_x)}{R_w + R'_w + R''_w + R_x} = \]

\[ = Q_0 R_w \frac{(1 - \lambda)\rho^4 + \lambda\rho_0^4}{\rho^4 \rho_0^4 ([R]/R') + (1 - \lambda)\rho^4 + \lambda\rho_0^4}. \] (30)

Since relation \( \rho_0^4 ([R]/R') \ll (1 - \lambda) \) in microvessels is valid for \( \lambda < 0.990 \), then \( \Delta p_{12} \approx Q_0 R_w = \text{const.} \)

Dimensionless wall shear rate at stenosed region of the vessel for Poiseuille flow reads exactly:

\[ G = \frac{\gamma}{\gamma_0} \approx \frac{\delta p_x}{\lambda} \cdot \frac{\rho}{\rho_0}. \] (31)

and the pressure gradient across the thrombus may be approximated with high accuracy as follows:

\[ \frac{\delta p_x}{\lambda} \approx \frac{1}{(1 - \lambda)(\rho/\rho_0)^4 + \lambda}. \] (32)

**CONTRIBUTION OF FRONT (UPSTREAM) AND BACK (DOWNSTREAM) SIDES OF AN AXISYMMETRIC THROMBUS IN ACCUMULATION OF PLATELETS FROM THE STREAMING BLOOD**

Equation for thrombus volume dynamics in that case reads:

\[ \frac{d}{dt} V_{\text{thromb}} = \left( \psi^{(1-\beta)} - \xi_d \psi \right) \cdot (2A_{\text{side}} + A_{\text{top}}) \] (33)

where \( A_{\text{side}} = \pi (r_0^2 - r^2) \) is the area of side surfaces of thrombus, \( A_{\text{top}} = 2\pi rl \) is the top surface area (see Fig.1).

Introducing dimensionless variables, we obtain:

\[ -\rho \dot{\psi} = \Psi K_{\text{eff}}(G) \left[ \frac{\rho_0^2 - \rho^2}{\lambda} + \rho \right] \] (34)

\textbf{FITTING PARAMETERS OF PLATELET ADHESION FROM EXPERIMENTS}

The values of \( \psi \) and \( \xi_d \) seem to depend only on properties of platelets, hematocrit and blood plasma viscosity, and not on the geometrical sizes or hydrodynamics. Specifically, we found these values by fitting the results of experiment [4] in a venule of 60 µm diameter (initial wall shear rate \( \dot{\gamma}_0 \approx 320 \text{ s}^{-1} \)) with our power-law model (\( \beta = 0.2 \)): the amplitude of platelet influx \( \psi \approx 6.1 \cdot 10^{-3} \text{ µm/s}^{0.2} \), and thickness of the shear-responsive layer of thrombus (amplitude of platelet outflux) \( \xi_d \approx 1.2 \cdot 10^{-3} \text{ µm} \). The parameter \( \xi_d \) turns out to be of order of several nanometers, which is much smaller compared to the platelet’s size, however, it should be considered as an effective value, defining the perception of thrombus to hydrodynamic shear forces. For this venule we found \( \lambda_\text{cr} = l_\text{cr}/L \approx 0.02 \) (with length of the vessel \( L = 5.34\text{mm} \)). That gives us \( l_\text{cr} = 106 \mu\text{m} \), while the actual size of injury was reported to be slightly bigger \( l = 120 \mu\text{m} \), which means the occlusion was an imminent result in that case. The critical shear rate that should be exceeded to prevent occlusion we found as \( \dot{\gamma}_\text{cr} = (\psi/\xi_d)^{1/\beta} \approx 3400 \text{ s}^{-1} \).

On using the fitted values of \( \psi \) and \( \xi_d \) in our model, we have succeeded in describing the experimental thrombosis dynamics in the arteriole of 42 µm in diameter from the same work [4]. According to data from the original paper, injury length was \( l = 168 \mu\text{m} \) and initial wall shear rate \( \dot{\gamma}_0 \approx 1900 \text{ s}^{-1} \), see Fig. S5B for plot.

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**SUPPORTING FIGURE LEGENDS**

**Figure S1**

Hydrodynamic simulations of blood velocity (the component along the vessel) in different slices (cross-sections) of the thrombotic vessel. Top and bottom panels show longitudinal fluid velocity through stenosed segment with 100 µm and 500 µm -length thrombi respectively. Diameter of the vessel equals 100 µm, the length of presented segment \( L=1 \text{mm} \), additionally laminar inflow and outflow of lengths 100 µm each were implemented in the model. The pressure drop along the vessel was kept the same for all presented situations (100 Pa). Digits in color legend correspond to dimensional values in mm/s. Maximal fluid velocity in the top panel is 96 mm/s (short thrombus), and 71 mm/s in the bottom one (longer thrombus). Longer thrombus produces higher hydraulic resistance, which reduces blood velocity and,
Figure S2

Typical distributions (normalized values) of longitudinal fluid velocity (top panels) and shear rate (bottom panels) in a cross-section of microvessel with a non-symmetric thrombus (white).

Figure S3

Different models of effective thrombus growth rate \( K_{\text{eff}} \) as function of dimensionless shear rate at the surface of thrombus \( G = \dot{\gamma}/\dot{\gamma}_0 \) in microvessel with axisymmetric thrombus (\( \Theta = 2\pi \)): power-law model with \( \beta = 0.2, \xi = 0.63 \) (solid), linear model with \( K_0 = 1.2, \xi = 0.12 \) (dash) and model of irreversible platelet adhesion with \( K_0 = 1.2, \xi = 0.3 \) (dash-dot).

Figure S4

Effective thrombus growth rate \( K_{\text{eff}} \) as function of the relative height of axisymmetric thrombus \( h/r_0 = (r_0 - r)/r_0 \) for three different platelet accumulation models: power-law model with \( \beta = 0.2, \xi = 0.63 \) (solid), linear model with \( K_0 = 1.2, \xi = 0.12 \) (dash) and model of irreversible platelet adhesion with \( K_0 = 1.2, \xi = 0.3 \) (dash-dot); relative vessel’s radius \( r_0/L = 0.02 \). Relative thrombus length: (A) \( l/L = 0.01 \) is below critical value; and (B) \( l/L = 0.03 \) is bigger than the critical value. Considering the thrombus growth as the evolution of a dynamical system, this figure represents its phase portrait, i.e. dependence of velocity on the coordinate. Linear and power-law models demonstrate qualitatively similar behavior (for given sets of parameters). In panel (A), where injury length is smaller than the occlusion threshold, the diagram predicts that a thrombus of height \( h/r_0 \approx 0.6 \) would be stable. The model with irreversible platelet attachment instead of a total stoppage predicts the essential decrease of growth rate, which is equivalent to the prevention of occlusion in the framework of our consideration. In panel (B), where size of injury exceeds the occlusion threshold, the effective growth rate is always non-negative, thus the occlusion is the only steady situation for this length of thrombus.

Figure S5

Comparison of computed thrombus dynamics with experiments. (A) Contribution of front (upstream) and back (downstream) sides of an axisymmetric thrombus in accumulation of platelets from the streaming blood. This figure depicts time course for changes in relative thrombus height in venule. The corrected model (SI Text) with power-law dependence of growth rate on shear rate (dash line) is compared to the experiments of Sato and Ohshima [Microvascular Research (1986) 31: 66–76] (dots). Model parameters obtained from this fitting are: \( \Psi = 0.023, \rho_0 = 5.62 \cdot 10^{-3}, \lambda = 4\rho_0, \xi = 0.63 \), which correspond to platelet accumulation amplitude \( \psi = 6.1 \cdot 10^{-3} \mu m/s^{0.2} \), thrombus’s susceptibility to shear rate \( \xi_d = 1.2 \cdot 10^{-3} \mu m \). Dotted line corresponds to the case when platelets are allowed to adhere only at the top surface of the thrombus for the same parameter set, and to fit experiment with such a simplified model we need a bigger value of \( \Psi \) (namely, \( \Psi = 0.026 \), as in Fig.4C of the main text). (B) The experiment from the same authors in a 42\( \mu m \)-diameter arteriole (dots) is well described by our model (dash line) for axisymmetric thrombus growth with the parameters of platelet accumulation \( \xi_d \) and \( \psi \) obtained from the experiment in venule (A). In this experiment the initial wall shear rate \( \dot{\gamma}_0 \approx 1900 s^{-1} \), the length of injury \( l \approx 168 \mu m \). We found critical thrombus’s length for this arteriole \( l_{\text{cr}} \approx 176 \mu m \) and \( \lambda_{\text{cr}} = 0.255 \). The length of arteriole was calculated \( L = 690 \mu m \) (since it was not reported in the original paper).

SUPPORTING FIGURES
FIG. S1.

FIG. S2.
FIG. S3.

FIG. S4.

FIG. S5.
Threshold of microvascular occlusion: injury size defines the thrombosis scenario

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Damage to the blood vessel triggers a cascade of processes leading to the formation of a thrombus, which is meant to prevent bleeding. However, the same phenomenon may result in a total blockade of a blood vessel, causing severe medical conditions. Here we develop a mathematical model of thrombus growth in a microvessel, which demonstrates that the size of vascular injury acts like a switch between the regimes of thrombus growth. When the length of injury exceeds the critical value, thrombus occludes the vessel, otherwise the growth stops due to hydrodynamic shear forces. Our findings explain an experimentally observed distinctions between thrombosis induced by chemical lesion and laser injury. We suggest that the specifics of platelet adhesion in combination with microvascular hydrodynamics can be a major reason for cessation of thrombus growth in vivo.

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Aggregation of blood platelets is an essential part of hemostatic response aimed at prevention of bleeding upon injury [1, 2]. However, intravascular aggregates, called ‘thrombi’, may cause dangerous conditions, e.g., complete vascular occlusion. Experimental data on thrombosis are highly controversial. Chemical initiation of thrombosis by ferric chloride application [3, 4] leads to occlusion in all reported cases. The most advanced contemporary works study thrombosis initiated by laser-induced vessel wall injury [5, 6], ultrasound rupture of atherosclerotic plaque [7], or mechanical micropipette piercing [8, 9]. Provided real-time in vivo microscopic imaging of growing thrombi [5, 6] reveals that initially rapid platelet accumulation eventually slows down and stops, thus no occlusion occurs.

Several hypotheses emerged trying to explain why some thrombi grow to occlusion and others reach stable size. The mechanism of thrombosis regulation was ascribed to either biochemical reactions and platelet activation [7, 9], or changing porosity of the hemostatic plug [10], or non-uniform structure of platelet thrombi [11, 12]. Unified picture is not present yet.

Early studies demonstrate that thrombosis is governed by two competing factors: the rate of platelet income from bloodstream and the intensity of hydrodynamic forces that prevent platelets from adhering to the thrombus [12, 17]. It was revealed that platelet aggregation rate does not simply increase with blood flow velocity, yet exhibits a maximum with a subsequent decrease due to growing hydrodynamic forces that inhibit platelet adhesion [13, 14, 18]. The combination of hydrodynamic features of microvasculature with non-monotonous shear-dependent platelet aggregation rate, in principle, may stop the growth of thrombus. In present study we use mathematical modeling to check validity of this hypothesis. In this paper we focus on principal physical effects, which drive thrombosis.

Model overview – We account for closure of blood circulatory system and deduce hydrodynamic conditions within the thrombotic vessel (Fig. 1(a)). Heart acts as a pump, providing a systole-averaged constant flow rate...
Q_{0} \text{ (Fig.1(b))}. Pulses are negligible in microvasculature. Thrombotic vessel consists of a stenosed segment (with resistance \( R_{x} \)) and two healthy ones (\( R' \) and \( R'' \)). A large number of healthy vessels with overall resistance \( R_{w} \approx 100 \text{ Pa} \cdot \text{s} / \text{cm}^{3} \) provide a slant through which blood can bypass thrombotic vessel. The resistance of bigger vessels (e.g. aorta) may be neglected compared to that of microvasculature. Let \( L \) be the length of a thrombotic blood vessel measured between two consequent bifurcations. Healthy segments have circular cross-section, and the lumen shape of the stenosed one is disturbed by thrombus, Fig.I(c,d). In our numerical model the actual shape of thrombus is approximated by cylindrical segment, protruded into the vessel and characterized by \( l, r \) and \( \Theta \). The angular size of the thrombus \( \Theta \) and its height \( h \) are allowed to change in time, while \( l = \text{const} \). Resistance of damaged segment \( R_{x}(t) \) changes due to growing stenosis, and consequent changes happen to pressure and flow rate in whole circulatory system. Pressure difference \( \Delta p_{12} = p_{1} - p_{2} \) between vessel ends may change due to thrombus, as well as pressure drop across thrombus \( \Delta p_{x} = p_{x}^{\text{in}} - p_{x}^{\text{out}} \) and flow rate \( Q_{x} \) through the vessel \[ \text{Fig.1} \]. Thus, hydrodynamics and thrombus growth are coupled and should be considered within a unified self-consistent model. Within our approach at each timestep for a given thrombus’s configuration hydrodynamic values (shear rate, \( \Delta p_{x} \) and \( Q_{x} \)) were found numerically as a solution of linearized Navier-Stokes equation for incompressible flow (for details see [19]), then thrombus shape was adjusted according to hydrodynamics-dependent growth rate.

**Platelet accumulation** - Platelets circulate in the blood relatively inactive and do not adhere to healthy vessel walls. Damage of vessel wall starts a cascade of processes leading to formation of a thrombus [1]. Its volume increases due to attachment of platelets supplied by the bloodstream. Platelet adhesion at early stage is reversible [2], and thrombus growth rate is the balance of rates of platelet attachment \( j_{in} \) and detachment \( j_{out} \):

\[
\frac{d}{dt} V_{\text{thromb}} = \int_{\text{surf}} (j_{\text{in}} - j_{\text{out}}) \, dA, \tag{1}
\]

where the integral is taken over the surface of thrombus capable to catch platelets. Platelet aggregation depends on hydrodynamic conditions. For platelet accumulation rate we use power-law function \( j_{\text{in}} \approx \psi \dot{\gamma}^{1-\beta} \) proposed earlier [18, 20] with \( \beta \approx 0.2 \) for human blood. Here \( \psi \) is a parameter defined by the form and size of platelets and RBCs, near-wall concentration of platelets in blood and hematocrit. Thrombus erosion rate \( j_{out} \) should be proportional to viscous shear stress per unit area of thrombus \( \eta \dot{\gamma} \), where \( \eta \) is the viscosity of blood plasma, inversely proportional to inter-platelet adhesive forces and should depend on shape and density of platelet aggregate: \( j_{\text{out}} = \xi_{d} \dot{\gamma} \), where \( \xi_{d} \) is a constant with a dimensionality of length, which accounts for all non-hydrodynamic effects. The effective growth rate \( k_{\text{eff}} = (j_{\text{in}} - j_{\text{out}}) \) is a power function of wall shear rate:

\[
k_{\text{eff}} = \psi \dot{\gamma}^{1-\beta} - \xi_{d} \dot{\gamma}. \tag{2}
\]

This value may change its sign if \( \dot{\gamma} \) reaches exceedingly high values, in particular \( \dot{\gamma} > \dot{\gamma}_{cr} \), where \( \dot{\gamma}_{cr} = (\psi / \xi_{d})^{1/\beta} \) corresponds to balance between the influx and the outflux of platelets (\( k_{\text{eff}} = 0 \)).

In particular, for axisymmetric thrombus (\( \Theta = 2\pi \)) the model permits analytical consideration. When thrombus grows over the whole perimeter of vessel’s cross-section, the lumen has a circular shape with inner radius \( r(t) < r_{0} \). Since the only variable that determines the size of an axisymmetric thrombus is the inner lumen radius \( r(t) \), in that case Eq.1 reads

\[
-2\pi rl \cdot \frac{dr}{dt} = k_{\text{eff}} (\dot{\gamma}) \cdot A, \tag{3}
\]

where \( A \approx 2\pi rl \) is the area capable of accumulating platelets, and \( \dot{\gamma} = \Delta p_{x}(t) \cdot r(t) / (2\eta l) \) is the shear rate at thrombus’s top surface [19].

For convenience we introduce the following dimensionless values that determine thrombosis dynamics: the relative thrombus length \( \lambda = l / L \), the adhesion parameter \( \xi = (\dot{\gamma}_{0} / \dot{\gamma}_{cr})^{\beta} = \xi_{d} \cdot \dot{\gamma}_{0}^{\beta} / \psi \) that characterizes stability of platelet aggregates subjected to hydrodynamic forces in a vessel, and \( \Psi = \psi / (L \dot{\gamma}_{0}^{\beta}) \) that determines the timescale for dynamics of thrombosis.

**Results** - We performed a series of numerical simulations in order to reveal the mechanism of thrombosis regulation. Fig.2 suggests that longer thrombus experiences lower shear stress on its surface due to re-distribution of pressure and flow rates in circulatory network. In Fig.2(a-c) the maximal shear rate (and, thus, the force) on top of the plug gradually reduced 4-fold, when length of thrombus was increased from 50 \( \mu \text{m} \) to 500 \( \mu \text{m} \). Our analytical calculations for axisymmetric case (\( \Theta_{0} = 2\pi \)) also support these findings, as illustrated in Fig.2(d). Note non-monotonous dependence of shear rate on the degree of stenosis: when \( \lambda < 1 \), shear rate increases with growing stenosis, reaches maximum \( \dot{\gamma}_{\text{max}} \) and then goes to zero as occlusion occurs. That is consistent with earlier observations [15, 21]. Hydrodynamic shear forces \( f_{\text{h}} \propto \dot{\gamma} \) may prevent occlusion, if \( \dot{\gamma}_{\text{max}} \) is high enough. Therefore, longer thrombi tend to be more occlusive. Increase of relative shunting resistance lessens \( \dot{\gamma}_{\text{max}} \), Fig.2(e), yet not changing qualitative picture of thrombosis. For realistic system the limit \( R_{w} \rightarrow 0 \) (equivalent to \( \Delta p_{12} = \text{const} \)) is a good approximation [19].

Typical time course of a ring-shaped thrombus growth are presented in Fig.3(a) for different thrombus lengths. The analysis shows that there exists a critical injury length \( \lambda_{cr} \), which differentiates the regimes of occlusion and thrombosis stoppage. For \( \lambda > \lambda_{cr} \) the occlusion occurs in a finite period of time, and for \( \lambda < \lambda_{cr} \) thrombus reaches finite size.
FIG. 2. (Color online) (a-c) Mapping of scaled shear rate $\dot{\gamma}/\dot{\gamma}_0$ over the thrombus’s surface and walls of the blood vessel computed with finite-difference simulation for different lengths of a thrombus: 50 $\mu$m (a), 100 $\mu$m (b) and 500 $\mu$m (c). Vessel diameter is 100 $\mu$m. Pressure drop between vessel’s ends $\Delta p_{12} = 100$ Pa. (d) Dependence of shear rate on stenosis degree for $l/L = 0.01$ (solid), 0.1 (dash-dot) and 0.75 (dash). Here $R_w/[R] = 10^{-3}$, $[R] = 8\eta/(\pi L^3)$. (e) Shear rate vs. stenosis for different hydraulic resistances of the shunt: $R_w/[R] = 10^{-3}$ (solid), 1 (dash-dot), 10 (dash); thrombus length $l/L = 0.01$.

Thrombus growth rate $k_{eff}$ can be positive, or negative, depending on system’s parameters, so that thrombus can either grow or decrease in size. If we plot this value as a function of the thrombus’s height, Fig. 3(b), this phase portrait would characterize dynamics of thrombosis. If $\lambda$ is above critical the only stable point on the phase trajectory corresponds to occlusion. As $\lambda$ decreases, the shear rate grows, and two additional zeros of $k_{eff}$ appear. The one with smaller $h/r_0$ corresponds to a stable non-occlusive thrombus, and another one (empty circle in figure) is not stable, since any fluctuations of $h/r_0$ will make $k_{eff}$ either positive, leading to occlusion, or negative, eroding the thrombus to stable size.

The value of threshold thrombus length $\lambda_{cr}$ should be determined from the condition $\dot{\gamma}_{max} = \dot{\gamma}_{cr}$, where $\dot{\gamma}_{max}$ is the peak value of dimensionless shear rate and $\dot{\gamma}_{cr}$ is the shear rate for which average influx and outflux of platelets in Eq. (11) are balanced and $k_{eff} = 0$. This requirement leads to the equation

$$\lambda^3(1 - \lambda) = \frac{27}{256} \left( \frac{\dot{\gamma}_0}{\dot{\gamma}_{cr}} \right)^4.$$  

Note that $\dot{\gamma}_{cr}$ depends only on adhesive properties of platelets, hematocrit and sizes of blood cells, while $\dot{\gamma}_0$ is the initial wall shear rate, dependent on sizes of vessel and pressure. Solution of Eq. (4) determines critical relative thrombus length $\lambda_{cr} = l_{cr}/L$, so that if $\lambda > \lambda_{cr}$, the thrombosis always proceeds to occlusion, and for $\lambda < \lambda_{cr}$ the thrombus reaches stable non-occlusive size.

We found $\dot{\gamma}_{cr} \approx 3400$ s$^{-1}$ fitting the experimental data for axisymmetric thrombi with our theory (for details see [19]). A good consistency, Fig. 3(c), attests validity of our model. Fig. 3(d) summarizes our findings for axisymmetric thrombus in a form of a parametric diagram. $X$-axis of the diagram shows $\lambda = l/L$, and $y$-axis corresponds to $\dot{\gamma}_{cr}/\dot{\gamma}_0$. The upper-right corner of the diagram corresponds to parameters, for which the thrombus grows to occlusion. Domain of thrombosis stoppage is enclosed between line $\lambda_{cr} = f(\dot{\gamma}_{cr}/\dot{\gamma}_0)$, found from Eq. (4), and the horizontal line $\dot{\gamma}_{cr} = \dot{\gamma}_0$. Below the former one any platelet aggregate will be washed away by the bloodstream, as $\dot{\gamma}_0 > \dot{\gamma}_{cr}$.

Fig. 3(a) suggest that non-symmetric thrombi show
thrombosis regulation rests on the interplay between the non-trivial hydrodynamics-dependent of platelet aggregation law Eq. [2] and features of microcirculatory network. Namely, initial prevalence of adhesion favors the formation of a hemostatic plug, yet consequent increase of shear forces impede thrombus growth and may eventually stop it. However, if injury length exceeds the critical value, this mechanism fails to prevent occlusion due to lesser shear rates. This explains why ferric chloride-induced thrombosis characterized by vast injuries is always occlusive [3, 4], while small laser-induced thrombi may stop growing [6]. Interestingly, recanalization of occlusive thrombi [22, 23] and the risks of stent thrombosis [24] also depend on the thrombus’s length in the same threshold manner. Our principal conclusion is an existence of a threshold injury length $l_{cr} = \lambda_{cr}L$ demarcating regimes of thrombosis. This value depends on relative adhesion strength expressed via fraction of $\gamma_{cr} = (\psi/\xi)^{1/\beta}$ and initial wall shear rate $\dot{\gamma}_0$. Eq. (4). Threshold exists regardless of thrombus’s shape, yet its value may change depending on the angular size of the injury. It appears that axisymmetric injury is the most adverse situation for occlusion, i.e. if the ring-shaped thrombus grows to occlusion for given $\lambda$, then any injury with angular size $\Theta < 2\pi$ would result in occlusion as well. The reason for this effect is, probably, the emerging of an additional degree of freedom, by which the thrombus can avoid the stoppage point. Specifically, shear forces on top of thrombus increase preventing further growth in radial direction, yet favoring the increase of angular size.

This study predicts several effects that are not obvious. The most direct way to verify our predictions experimentally is to study thrombus formation under constant pressure conditions using different sizes of the damaged area. Our model predicts that there should be a triggering from occlusion to stable thrombus for a certain length of injury. Another way is to lower $\dot{\gamma}_{cr}/\dot{\gamma}_0$ by using platelets with partial adhesion receptor deficiencies, or increasing pressure $\Delta p_{12}$.

Presented work consolidates existing knowledge about microvascular thrombosis. We used basic physical principles, not involving complex biological concepts. Our findings resolve fundamental contradictions in experiments and make novel influential predictions of immense scientific and biomedical importance.

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