Blood Clot Dissolution Dynamics Simulation during Thrombolytic Therapy

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Nonocclusive blood clots only partially fill blood vessels and together with the adjacent vessel wall form a channel through which blood flows at usually much higher velocities than in normal vessels. Our aim was to find a theoretical explanation for the experimentally observed fact that fast flowing blood through the channel has a large effect on the increase of the clot dissolution rate compared to the dissolution rate in the absence of flow. Blood flow through the channel increases transport of dissolution agents to the clot and also exerts large forces to the surface of the clot along the channel. Proposed is a model for clot dissolution which assumes that the clot dissolution rate is proportional to the forces of flowing blood to the surface of the clot multiplied by the average blood velocity. The model has been verified by fitting to experimental magnetic resonance imaging data obtained by dynamical magnetic resonance microscopy of clots dissolved by recombinant tissue plasminogen activator in an artificial blood flow system.

INTRODUCTION

The aim of thrombolytic therapy is to dissolve blood clots and restore normal vessel functions. Thrombolytic therapy is used in the treatment of ischemic strokes,[1−3] the treatment of pulmonary embolisms,[4,5] and the treatment of acute arterial thrombosis[6] and remains the mainstay of the treatment of myocardial infarctions in hospitals that do not provide emergency percutaneous transluminal angioplasty.[7] Properties of the thrombolytic agent, structure of the thrombus, and characteristics of molecular transport into the thrombus[8] are three major conditions that determine the success of thrombolyis. Nonocclusive clots have one or more channels created by slowly penetrating plasma containing thrombolytic agents. The clots are almost never completely dissolved when blood flow is reestablished along the remaining clot.[8−10] The residual clot impedes normal blood flow and poses a risk for rethrombosis. Thrombolytic processes in occlusive clots[9−13] have been fairly well described; however, relatively little is known about the influence of fast axial blood flow on the thrombolysis of nonocclusive clots. Experimental results of Sakharov and Rijken[14] as well as our own work[15] show that fast blood plasma flow significantly enhances blood clot dissolution under optimal biochemical conditions, but a consistent theoretical model has not been presented yet.

Our hypothesis is that mechanical forces of flowing blood are high enough to play an important role in the dissolution of nonocclusive blood clots in addition to the biochemical reactions that are responsible for chemically degrading the clot. The forces may do mechanical work, cause strain deformations and surface vibrations, and may therefore help the dissolution agent to more efficiently migrate into the clot and faster chemically degrade it. We assume that the clot dissolution rate is proportional to the mechanical power of the forces, i.e., to the product of the force and the average blood velocity. Mechanical forces have a viscous origin when blood flow is slow − laminar, and a kinematic origin when blood flow is fast − turbulent. Since kinematic forces increase quadratically with the blood velocity and viscous forces just increase linearly, significantly faster clot dissolution may be expected at the turbulent blood flow regime than at the laminar one.

THEORETICAL BASIS

Let us assume that a cylindrical blood vessel is narrowed in one segment by a nonocclusive blood clot. The cylindrical clot with a diameter R has initially a cylindrical blood flow channel of a radius r_0 that is parallel to the clot axis and is positioned next to the vessel wall. After a pharmacologic concentration of a thrombolytic agent is added to the blood that flows in our idealized two-segment vessel the nonocclusive clot begins to dissolve, and the nonobstructed channel along the clot expands as thin layers of the clot are gradually removed by the flowing blood. The channel keeps its tangential position with the vessel border also when the clot dissolves, i.e., the channel widens to radius r (Figure 1).

Let us also assume that the volume flow of blood through the vessel is constant during the entire dissolution process. This may not be true at the beginning as the clot strongly impedes blood flow and may pose a larger resistance to blood flow than other blood vessels. However, the assumption significantly simplifies our model and is not very far from the real situation especially when the clot is well canalized.

Our hypothesis is that the rate of thrombolysis, i.e., the progression rate of lysing front dr/dt is proportional to the

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Figure 1. Nonocclusive clot (red) fills in the middle section of a vessel with diameter 2*R* except in the small flow channel (blue) of diameter 2*r* next to the vessel's wall.

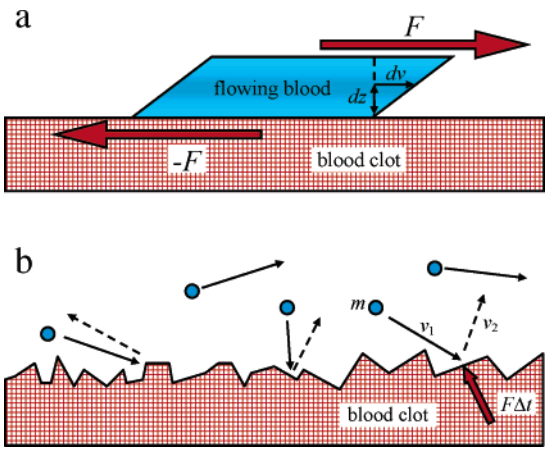

Figure 2. Forces of the flowing blood to the surface of the clot in the flow channel are (a) viscous when flow is slow-laminar and (b) become kinematic, i.e., increase with the blood velocity squared, when flow is fast-turbulent. Viscous forces originate in the strain velocity of blood, whereas kinematic forces originate in the change of momentum of molecules as they bounce from the rough surface of the clot.

average mechanical power of the flowing blood to the surface of the flow channel (Figure 2). The power P is equal to the force F of the flowing blood to the clot surface multiplied by the average blood velocity in the flow channel v. The force F is also equal to the product of the pressure drop Δp across the flow channel multiplied by the cross-section area of the flow channel S, from where follows $P = Fv = \Delta pSv$. The pressure drop is equal to $\Delta p = 8\pi\eta\, vl/S$ when flow is laminar and is equal to the $\Delta p = f\rho\, lv^2/\sqrt{S}$ when flow is turbulent.[16] Here η is the blood viscosity, ρ is the blood density, and f is a frictional coefficient, which was experimentally determined to be approximately equal to 0.011 for most round tubes.[16] The mechanical power of flowing blood is therefore equal to $P = 8\pi\eta v^2 l$ when flow is laminar and is equal to $P = f\rho l v^3\sqrt{S}$ when flow is turbulent, from where it may be obtained

$$\mathrm{d}r/\mathrm{d}t = a_l v^2 \tag{1}$$

and

$$\mathrm{d}r/\mathrm{d}t = a_t v^3\sqrt{S} \tag{2}$$

for laminar and turbulent flow, respectively. Other parameters η, ρ, l, and f do not change during dissolution and are therefore not included in the model equations for the dissolution. The flow channel radius r, its cross-section area S, and the average blood velocity v are not independent. They are related by the following relations: $S = \pi r^2$ and $v = \phi_V/S = \phi_V/\pi r^2$. Using these relations the two differential equations for clot dissolution change to $\mathrm{d}r/\mathrm{d}t = a_l(\phi_V/\pi r^2)^2 = R^5/(5\tau_5 r^4)$ and to $\mathrm{d}r/\mathrm{d}t = a_t(\phi_V/\pi r^2)^3\sqrt{\pi r^2} = R^6/(6\tau_6 r^5)$. These differential equations can be easily integrated, and the following dependence of the channel radius on time can be obtained

$$r(t) = R\sqrt[n]{(r_0/R)^n + t/\tau_n} \tag{3}$$

where $n = 5$ for laminar flow and $n = 6$ for turbulent flow; here r_0 denotes the initial radius of the flow channel. For further analysis it is convenient to define a new variable $x \equiv 1 - S/S_\infty = 1 - (r/R)^2$, which corresponds to the relative clot area, i.e., the ratio between the clot and the vessel area. The quantity x also denotes the level of obstruction for blood flow through the clot. In addition to parameters τ_5 and τ_6 which regulate the dynamics of clot dissolution another parameter T may be introduced. T corresponds to the delay between injection of the thrombolytic agent into a blood circulation system to the time when it reaches the clot and starts chemically degrading it. Finally, the following model equation for the relative clot area as a function of time is obtained

$$x(t) = \begin{cases} 1 - (r_0/R)^2 & t < T_n \\ 1 - ((r_0/R)^n + (t - T_n)/\tau_n)^{2/n} & t \geq T_n \end{cases} \tag{4}$$

Whether flow is laminar or turbulent may be determined by a criterion based on the Reynolds number[16]

$$Re = \frac{2r\rho v}{\eta} \tag{5}$$

It was experimentally determined[17] that for normal smooth surfaces flow is most likely turbulent when Re is more than 3000 and laminar when it is less than 2000. Transition between laminar and turbulent flow is usually not very sharp, and there may be some intermediate phenomena (typically when $2000 < Re < 3000$); flow in this regime is usually still laminar close to the walls of the vessel and turbulent in the center; for Re higher than 3000 flow becomes fully turbulent. A flow regime may turn into a fully developed turbulent flow also at Re much lower than 3000 if the walls are rough.[18] Based on electron micrographs of recanalization channels through blood clots[19] it is clear that nonocclusive blood clots have rough walls and first turbulences are expected at Re lower than 2000.

MATERIALS AND METHODS

Artificial whole blood clots were prepared in 3 cm long glass tubes with a 3 mm diameter, as described before.[15] The procedure was the following: citrated venous blood was clotted by the addition of thrombin (Thrombin, Sigma, Germany) in a final concentration of 1 NIH unit/mL of blood and calcium (50 μL $CaCl_2$ at 2 mol/L per mL of blood), and clot retraction was inhibited[20] by the phosphodiesterase inhibitor UDCG 212 (Boehringer, Germany). After at least an hour at room temperature to allow for fibrin formation, a hole of 0.7 mm diameter was made in the clot lengthways by a needle to create a flow channel. The initial relative clot area was therefore equal to $x = 0.946$. The glass tube with the clot was connected by a flexible hose to a pump that was generating a constant pressure of 15 000 Pa. The hose connecting the pump and the clot was 1.7 m long and also had a 3 mm inner diameter. The artificial circulation system was in each experiment filled with approximately 0.5 L of blood plasma at the room temperature, which was in most

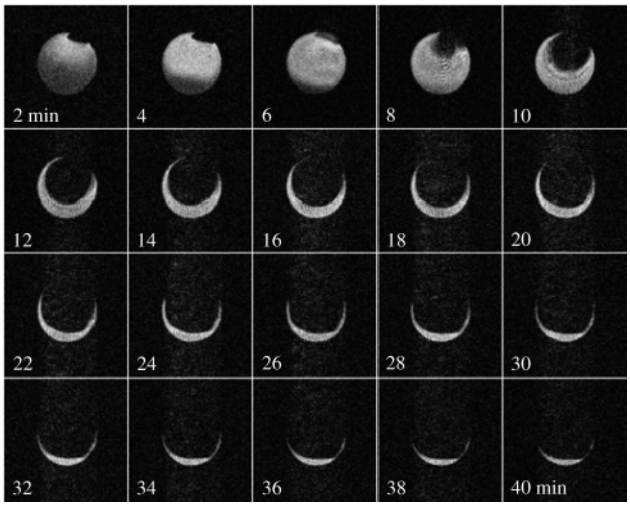

Figure 3. Time sequence of magnetic resonance images of a blood clot in an axial cross-section during dissolution process. Flowing blood in the channel cannot be seen in images as it moves out of the imaging plane before signal acquisition.

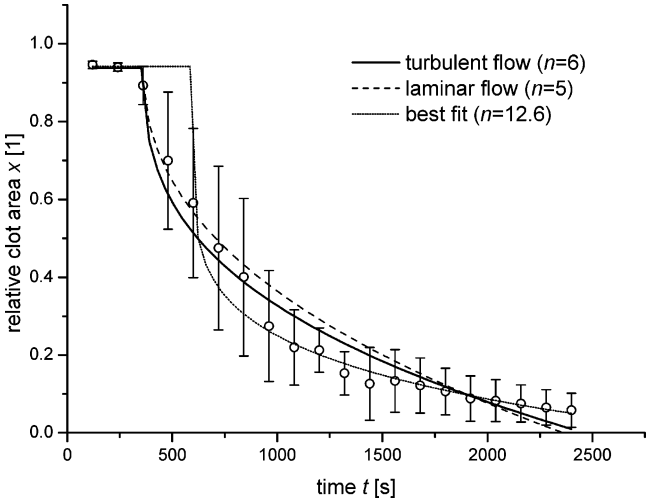

Figure 4. Curves representing the best fit between the experimental data of the relative clot area as a function of time (circles) and models of clot dissolution (eq 4): turbulent (solid line), laminar (dashed line), and the variable n model (dotted line).

Table 1. Model Parameters that Yield the Best Fit between the Dissolution Model (Eq 4) and Experimental Data for the Relative Clot Area as a Function of Time

	T [s]	τ [s]	n [1]	χ^2
turbulent flow	358 ± 2.6	2100 ± 120	6	0.44
laminar flow	353 ± 8.9	2010 ± 95	5	0.76
best fit	590 ± 23	2500 ± 580	12.6 ± 3.8	0.26

experiments at about 20 °C. According to the literature the viscosity of blood plasma is 1.8 times higher than is the viscosity of water, which yields an estimate value for viscosity of 0.0018 Ns/m^2, whereas the density of plasma is practically identical to the density of water, i.e., 1000 kg/m^3.

Volume flow was measured without the addition of a thrombolytic agent in a system with the clot and without a clot in the glass tube. From these measurements average plasma velocities in the flow channel were calculated. These were equal to 4.26 m/s at the beginning ($x = 0.946$) and 0.86 m/s at the end ($x = 0$) from where it follows that the Reynolds number (eq 5) was equal to $Re = 1660$ at the beginning of the dissolution and was equal to $Re = 1430$ at the end of the dissolution.

Dynamics of clot dissolution was measured by dynamical magnetic resonance microscopy. Clots in glass tubes were inserted into a 25 mm radio frequency probe and connected to the artificial flow system. The flow system was then tested for stability, ensuring that were no air bubbles in the system which could obstruct plasma flow. Then, the probe with the clot was inserted into a 100 MHz (proton frequency) horizontal bore Oxford superconducting NMR magnet equipped with a Bruker microimaging gradient system with maximum gradients of 300 mT/m. The magnet and the gradients were controlled by a TecMag NMR/MRI spectrometer. Before each experiment, a thrombolytic agent rt-PA (recombinant tissue activator of plasminogen, Actylise, Boehringer, Germany) was added to the plasma in a pharmacologic dose of 2 μg/mL. Also, the magnetic resonance imaging contrast agent Gd-DTPA (Magnevist, Berlex Lab., Germany) was added to the plasma. Immediately thereafter, dynamical MR imaging was started. Blood clots were imaged by a T_1 weighted spin−echo MR imaging method in a transversal cross-section every 2 min. The imaging sequence parameters were as follows: echo time and repetition rate TE/TR = 8/400 ms, imaging field of view 2 cm, slice thickness 2 mm, and imaging matrix 256 × 256. Dissolution was monitored for 40 min by a time sequence of 20 images. A representative set of dynamical MR images of a dissolving clot is shown in Figure 3. After MR images were acquired, cross-section areas of the flow channel through the clot were measured as a function of time for each clot in the study to get time dependence of the relative clot area $x(t)$. For the image analysis the Image-J program (Java version of the NIH-Image program) was used.

The experimental data for the relative clot area $x(t)$ were then analyzed by the mathematical model given by eq 4. The model equation (eq 4) was fitted to experimental data by the OriginPro program (OroginLab Corporation, Northampton, MA). Three different fits and corresponding parameters (T and τ) were calculated for three different parameters n: $n = 6$ (turbulent flow), $n = 5$ (laminar flow), and for the third fit n was used as a fitting parameter.

RESULTS AND DISSCUSSION

Parameters of the dissolution model in eq 4 were optimized so that the best fit between the model for the relative clot area $x(t)$ and experimental MRI data x_i was obtained. The best fit model curves for the turbulent flow model ($n = 6$), the laminar flow model ($n = 5$), and the model with variable n as well as the experimental data are presented in Figure 4, and corresponding model parameters are shown in Table 1. It can be seen in Figure 4 that the turbulent model curve (solid line) fits better with the experimental data than the laminar model curve (dashed line). The same can be seen also in Table 1, where the turbulent model has a lower fit error than the laminar model ($\chi^2 = 0.44$ as opposed to $\chi^2 = 0.76$). These results can be expected also from the presented theory. Namely, during the dissolution experiment, the Reynolds number in the flow channel was always between $1430 < Re < 1660$ which simulated a severely narrowed artery, and since the surface of blood clots is rough, it is most likely that the flow in the channel was turbulent at all

times. Therefore the most appropriate model for dissolution is the turbulent model (eq 4 at $n=6$) and not the laminar model (eq 4 at $n=5$). However, the best fit between the data and the model was obtained for the model with variable n, where the fit error of $\chi^2 = 0.26$ was obtained with $n = 12.6$. This indicates that perhaps in reality the dissolution rate may increase even faster than with the third power of the average blood velocity. The reason for this may be that turbulences in addition to exerting mechanical forces may also increase the concentration gradients of plasminogen and rt-PA in the dissolving layer of the clot.

The parameter τ denotes the time that is needed from the beginning of a chemical clot degradation to the complete dissolution of a clot. This was in our model equal to $\tau = 2100$ s for turbulent flow and $\tau = 2010$ s for laminar flow, whereas it was slightly longer ($\tau = 2500$ s) in the model with variable n. From the experimental data it seems that this time is too short, and the model does not give the correct prediction for the end of the dissolution process. In most instances a clot is not completely dissolved, and its dissolution resembles an infinitely long process. An important reason for this is that when the clot's cross-section area is significantly reduced it no longer represents an obstacle for blood flow. The pressure drop along the clotted area of the vessel is very low, and therefore very little thrombolytic agent is transported into the remaining clot by convection and also very little mechanical work is done by the flowing blood to the clot. Thrombolysis could have stopped also if the concentration of plasminogen in plasma would be reduced significantly; however, that does not happen with thrombolytic agent rt-PA. In the experiment the concentration of plasminogen in plasma dropped from the initial 1.01 ± 0.57 of the normal pooled plasma value before adding 2 μg/mL of rt-PA to 0.72 ± 0.04 after 60 min.[15]

The parameter T corresponds to the delay between the injection of the thrombolytic agent to the time when it starts chemically degrading the clot. This is equal to approximately $T = 350$ s for both the turbulent and the laminar model (approximately 6 min) and is almost twice longer in the model with variable n. This delay depends on several external conditions such as the average blood velocity in vessels, the vessel length from the injection point to the clot, migration dynamics of the dissolution agent into the clot, and of course the degrading efficiency of the dissolution agent. In the presented experiment the time elapsed between the injection to the time when the agent reached the clot was approximately 10 s. Therefore most of the time was spent for migration of the agent into the clot and for setting the corresponding chemical reactions that start degrading the clot. Penetration of Gd-DTPA-labeled plasma into the clots was measured by MRI as a surrogate for the penetration of the thrombolytic agent. The medium-sized, paramagnetic Gd-DTPA remains confined to the extracellular space because it is hydrophilic and does not bind to proteins;[21] therefore, it may overestimate the transport rate of rt-PA and plasminogen that bind to fibrin in the clot. After 6 min of flow, the Gd-DTPA-permeated areas extended 2.0 ± 0.4 mm from the border of the flow channel into the clot.

The proposed model has been applied to explain our experimental data and has resulted in a reasonably accurate fit. Our results therefore support the concept that clot degradadtion is governed not only by the biochemical processes of fibrinolysis but also by viscous and kinematic forces of blood flowing along the clot, which has been experimentally demonstrated previously.[22] Resistance of the fibrin network to the combined proteolytic and shear stress-mediated degradation is governed by the interaction of fibrin with platelet glycoprotein[23] IIb/IIIa and by the mechanical properties of the fibrin strands.[24] Although our model gives a useful overview, it has several limitations. Some physical phenomena may not have been accounted for in detail as well. For example, the model assumes that the volume flow through the clotted area is constant. This however is not entirely true at the beginning of dissolution, especially if the flow channel is very narrow. In that case the flow channel poses a very strong resistance for blood flow, and a much higher pressure between both ends of the circulation system would be required to keep the flow constant in comparison with conditions at the end of the experiment. In our experiment as well as in the human body, the pressure difference between the ends of the circulation system is constant. Therefore, volume flow at the beginning of dissolution is lower than at the end. If the flow is very fast, the transition phenomena at the entry point into the flow channel and at the exit point may become important, too. At these two points blood velocity changes rapidly as the cross-section of the relatively wide blood vessel changes into a narrow channel through the clot or vice versa. Because of the conservation of blood volume flow at these two points, blood velocity is changed and blood flow is accelerated or decelerated. This phenomenon has not been accounted for in our equations. It was assumed that pressure drops linearly along the channel through the clot. More exact calculations of blood pressure distribution along the flow channel may be obtained by solving the Navier−Stokes equation[25] of flow for this particular geometry. This is quite difficult as it implies solving partial differential equations numerically. The other option would be to measure a velocity map of flowing blood through the clot by magnetic resonance flow imaging techniques.[26] From these, pressure distribution around the clot may be calculated, too.

CONCLUSION

Tangentially oriented blood flow along the clot in combination with biochemical reactions can significantly increase dissolution of nonocclusive blood clots. First, the thrombolytic agent accumulates in the superficial layers of the clot in the first few minutes after injecting a pharmacological dose of the thrombolytic agent into the blood. This is followed by the start of the most rapid phase of clot degradation that is enabled by the fast turbulent, axially directed blood flow and a steady state of fibrinolytic biochemistry. The flow channel then very rapidly expands, and as it widens blood velocity decreases due to the conservation of volume flow, and the rate of clot degradation decreases, too. In the last stage, the channel is already so wide that the clot no longer represents a substantial obstacle for the flowing blood. Since there is practically no pressure drop along the flow channel, very little work is done by the flowing blood, and thrombolysis reverts to a regime governed purely by diffusion-limited fibrinolytic biochemistry. This may preclude complete dissolution of the clot if the biochemical circumstances are unfavorable.

The dynamics of clot dissolution is proportional to the square of the blood velocity in the flow channel when the flow is laminar and to the third power of blood velocity when the flow is turbulent. For any set of biochemical and biophysical circumstances during dissolution, the dissolution dynamics can be described by a few relatively simple parameters such as the dissolution rate constant that incorporates biochemical properties of the system and a time delay parameter.

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