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Choice of a hemodynamic model for occlusive thrombosis in arteries

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ABSTRACT

Intravascular thrombosis can lead to heart attacks and strokes that together are the leading causes of death in the US (Kochanek, K.D., Murphy, S.L., Xu, J.Q., 2014). The ability to identify the offending biofluid mechanical conditions and predict the timescale of thrombotic occlusion in vessels and devices may improve patient outcomes. A computational model was developed to describe the growth of thrombus based on the local hemodynamic shear rate. The model predicts thrombus deposition based on initial geometric and fluid mechanical conditions, which are updated throughout the simulation to reflect the changing lumen dimensions. Thrombus growth and occlusion from whole blood was measured in *in vitro* experiments using stenotic glass capillary tubes, a PDMS microfluidic channel, and a PTFE stenotic aorto-iliac graft. Comparison of the predicted occlusion times to experimental results shows excellent agreement. The results indicate that local shear rate plays a critical role in acute thrombosis, and that hemodynamic characterization may have clinical utility.

1. Introduction

Intravascular thrombosis is blood clot formation inside a blood vessel. Arterial thrombosis is particularly debilitating because the blood clot prevents oxygen from reaching an end organ such as the heart or brain. When this happens, the patient experiences a heart attack or a stroke. Likewise, intra-arterial thrombosis can occur with surgical procedures such as coronary artery bypass or insertion of a left ventricular assist device (LVAD). For the surgeon, the sudden thrombosis of an artery could be catastrophic to the patient, but so could the lack of hemostasis, which may lead to uncontrollable bleeding.

Blood clots can form from two very different pathways. The mechanism most described in standard medical textbooks is that of *coagulation*, where blood clotting is initiated by a cascade of 13 proteins being activated, ending in a fibrin clot that traps red blood cells (RBCs) and looks like a *red clot* by the naked eye (Cadroy et al., 1989). Virchow recognized 150 years ago that this pathway of coagulation requires stagnant blood or, in fluid mechanical terms, blood exposed to very low shear rates for extended duration.

Stagnation is the opposite of what happens in most arteries, especially arteries that are narrowed due to atherosclerotic disease. The alternative mechanism for arterial thrombosis comes from the accumulation of large amounts of platelets that aggregate into a *white clot* that has few red blood cells (Cadroy et al., 1989). These white clots can completely occlude a pressurized artery to stop hemorrhage with trauma. The mechanism behind the accumulation of the platelets at a specific site has been an area of much recent discovery. Platelets circulate in the bloodstream around the periphery in a process called margination as a consequence of large, flexible RBCs moving towards the center of the flow (Reasor et al., 2012). The platelets effectively get trapped in a boundary layer near the wall that is relatively free of RBCs. In contrast with coagulation, the capture and accumulation of platelets is greatest at supra-physiologic shear rates, are enabled by a completely different protein called von Willebrand Factor (vWF), and do not require any of the coagulation proteins (Reininger et al., 2006). While fibrin can form to stabilize a platelet thrombus, the histology and mechanism of thrombosis in arteries is predicated on factors and forces quite different from coagulation.

The prediction of the attachment and accumulation of a platelet thrombus under arterial flow conditions is the goal of this perspective. Our hypothesis is that arterial occlusion can be predicted for whole blood over collagen by assessing the local hemodynamic conditions and response of blood platelets and vWF without significant inclusion of coagulation factors. We then test our hypothesis by comparing our model predictions with three situations of experimental thrombosis.

2. Computational model

Several mathematical or computational models of thrombosis exist. An excellent recent review by Fogelson and Neeves (2015)

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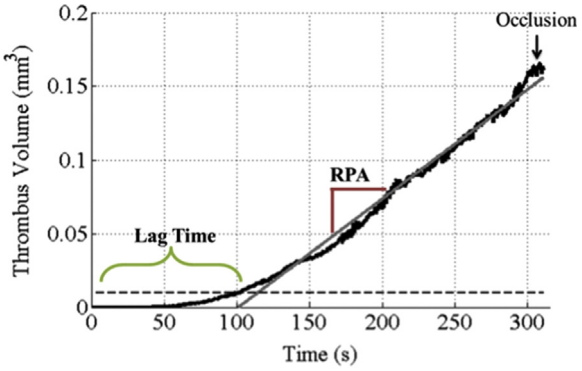

$$V_{thromb} = \sum_{i=1}^{n} J_i(\dot{\gamma})\Delta t_i$$

Fig. 1. Graph of total thrombus volume as a function of time during human whole blood perfusion of a collagen coated stenosis. The initial slow growth is called a lag time and corresponds to hundreds of platelets attaching to the surface. Rapid platelet accumulation (RPA) occurs after about 2 min with very high growth rates that can lead to occlusion of all blood flow. Occlusion for this experiment occurred at 300 s after initiation of blood flow through the stenosis. (Previously published in Mehrabadi et al., 2016).

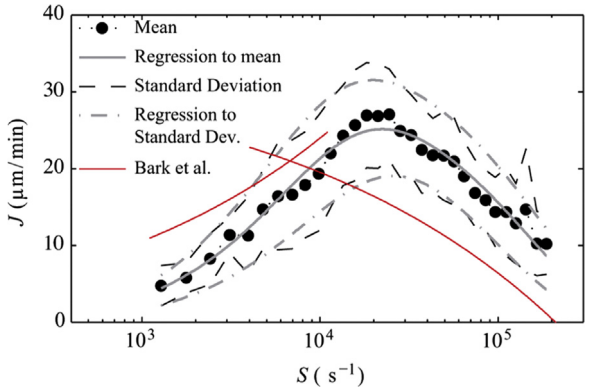

Fig. 2. Thrombus growth rate (J) at different shear rates (S), plotted on a linear-logarithmic scale. Note that the growth rate increases by an order of magnitude over a wide range of very high shear rates. (Previously published in Mehrabadi et al., 2016).

describes many of these models. Most of the models describe the attachment of 1 to 100 platelets for low shear rates below 1000 s^{-1}, or the activation of platelets without volume accumulation (Folie and McIntire, 1989; Jesty et al., 2003). Our studies have focused on macroscopic thrombotic occlusion of medium-sized arteries that would require attachment of millions to billions of platelets, which many of the previous models do not address.

Our computational model for thrombosis prediction utilizes the growth rate versus shear rate in an experiment of thrombus growth over 10 min in a simulated coronary stenosis. The details of the experimental methods are described previously (Para and Ku, 2013; Mehrabadi 2016). Platelet thrombosis under high shear rates routinely follows a bi-phasic pattern (Fig. 1). Initially, platelets attach to a collagen surface in a slow process where hundreds of inactivated platelets stick via soluble vWF from the blood (Reininger et al., 2006). The surface attachment is called the lag time and is shear dependent. Next, the thrombus volume grows rapidly where millions of platelets rapidly accumulate (Rapid Platelet Accumulation) within a few minutes. This rapid thrombus growth is typically visible with the naked eye and can grow to occlude a large vessel of several millimeters in diameter.

The relationship of platelet accumulation growth rate versus shear rate in a series of experiments using human whole blood is shown in Fig. 2. The graph demonstrates that thrombus growth rate is slow at physiologic shear rates below 1000 s^{-1}, but can be almost an order of magnitude faster in the 10,000 s^{-1} range. Surprisingly, thrombus growth can continue even with shear rates greater than 200,000 s^{-1} with a correspondingly high drag force on the thrombus, typical of a coronary artery nearing occlusion (Bark and Ku, 2010). The thrombi in these experiments were all white on gross examination, and contained predominantly platelets and vWF on histological analysis.

The growth rate as a function of shear of a platelet thrombus can be built into a computational simulation of thrombus growth over time for a given geometry and blood flow condition (Bark et al., 2012; Mehrabadi et al., 2016). To construct the thrombosis model, lag times and thrombus growth rates are calculated as a function of shear. On average, the lag time, t_{lag}, as a function of shear rate, γ, is represented as:

$$t_{lag}(\gamma) = 1.69 \times 10^6 \gamma^{-1.2}. \quad (1)$$

Thrombus growth rate is a piecewise function:

$$J(t,\gamma) = \begin{cases} 0, & t < t_{lag}(\gamma) \\ -31.3e^{-1.45\times10^{-4}\gamma} + 30.7e^{-6.81\times10^{-6}\gamma}, & t > t_{lag}(\gamma) \end{cases} \quad (2)$$

where J is the rate of thrombus growth at a particular position as a function of shear rate, γ. The growth rate constants were determined experimentally. To model volumetric thrombus growth in a particular geometry, the initial geometry and flow conditions (driving pressure or flow rate) are specified. After discretizing the geometry, the wall shear rate at each location is determined by computational fluid dynamics. Thrombus deposition is simulated after the lag time at each node is reached. The geometry is updated at each time step and the wall shear rates recalculated. The computational model continues to grow the thrombus at each time step until a pre-determined occlusion condition is reached (e.g. decrease in lumen diameter, decrease in flow rate, or increase in hydraulic resistance).

The algorithm is shown in Fig. 3. For the simulation, the thrombus grows and the wall shear rates are recalculated in an iterative manner. Flow can be designated as pressure-driven or other physiologic conditions such as inclusion of fractional flow reserve. Total thrombus volume is then computed as the integral of the growth rate over time. No embolism term is included, although this can be included as a subtraction term in the growth rate Eq. (2).

3. Experimental thrombosis

The computational model was compared against three different thrombus occlusion experiments (Mehrabadi, 2016). The first condition is with a microfluidic channel where the isolated test section had a rectangular cross-section of 82 × 480 μm similar to parallel plate flow. The flow rate was adjusted to yield an initial shear rate of 4000 s^{-1}. Whole human blood flows through the test section only once with no recirculation (single pass). The computational model predicted an occlusion time of 5.4 min. The experiments yielded a mean occlusion time of 5.2 ± 2.2 min.

A second condition was to independently predict occlusion in an independent hourglass shaped stenosis (67% by diameter) with nominal upstream diameter of 1.5 mm and a throat minimal diameter of 0.5 mm. The computational model predicted an occlusion time of 10 min. The experiments yielded a mean occlusion time of 10 ± 2 min.

A third condition was to recreate thrombosis in a nominal 10 mm PTFE vascular graft with a focal stenosis with a throat of