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Development of a platelet adhesion transport equation for a computational thrombosis model

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ABSTRACT

Thrombosis is a significant issue for cardiovascular device development and use. While thrombosis models are available, very few are device-related and none have been thoroughly validated experimentally. Here, we introduce a surface adherent platelet transport equation into a continuum model to account for the biomaterial interface/blood interaction. Using a rotating disc system and polyurethane-urea material, we characterize steady and pulsatile flow fields using laser Doppler velocimetry. In vitro measurements of platelet adhesion are used in combination with the LDV data to provide further experimental validation. The rotating disc system is computationally studied using the device-induced thrombosis model with the surface platelet adherent transport equation. The results indicate that the flow field is in excellent agreement to the experimental LDV data and that the platelet adhesion simulations are in good agreement with the in vitro platelet data. These results provide good evidence that this transport equation can be used to express the relationship between blood and a biomaterial if the correct platelet adhesion characteristics are known for the biomaterial. Further validation is necessary with other materials.

1. Introduction

Thrombosis often limits the widespread use of mechanical circulatory support devices, prosthetic valves, and other blood contacting devices (Daemen et al., 2007; Mehra et al., 2014; deBiasi et al., 2015; Marchena et al., 2015). Their design typically warrants extensive in vitro, hemocompatibility, animal, and clinical testing. While computational fluid dynamics (CFD) would ideally reduce the need for testing (Stewart et al., 2013) and the mathematical underpinnings of thrombosis models are available (Leiderman and Fogelson, 2014), there needs to be experimental validation of the models.

Groups have been developing computational thrombosis models focused on cellular interactions (Xu et al., 2011; Wang and King, 2012; Cito, 2013; Leiderman and Fogelson, 2014). While they have been able to grow a thrombus as a result of injury, most lack significant experimental validation. We recently published a device-induced thrombosis model using activated and non-activated platelets and ADP to grow a thrombus (Taylor et al., 2016). Experimentally acquired data of thrombi formed in an expansion using magnetic resonance imaging was used to test the model (Taylor et al., 2014). However, platelet adhesion was not included and is the focus here.

Platelet adhesion is a necessary precursor to macroscopic thrombus deposition and growth. Consequently, it is frequently used as a metric to assess device efficacy. There have been numerous modeling approaches for platelet adhesion, including Lagrangian approaches to more accurately simulate biomechanics on a cellular level (e.g., Mori et al., 2008; Fogelson and Guy 2008; Tokarev et al., 2011) or Eulerian approaches to better simulate larger spatial scales (e.g., Strong, 1987; Sorensen, 1999a; Goodman et al., 2005). Yet, no one has incorporated platelet adhesion into a thrombosis model capable of making quantitative predictions in three dimensions and on the spatial and temporal scales relevant to medical devices.

In an effort to integrate platelet adhesion into the thrombosis model from Taylor et al. (2016), we use in vitro platelet adhesion experiments from Navitsky et al. (2014) to calibrate a transport equation for surface adherent platelets (SAPs) under steady and pulsatile conditions. The in vitro platelet adhesion data were collected using polyurethane-urea (PUU): a clinically relevant biomaterial (Yamanaka et al., 2005). The blood-contacting properties

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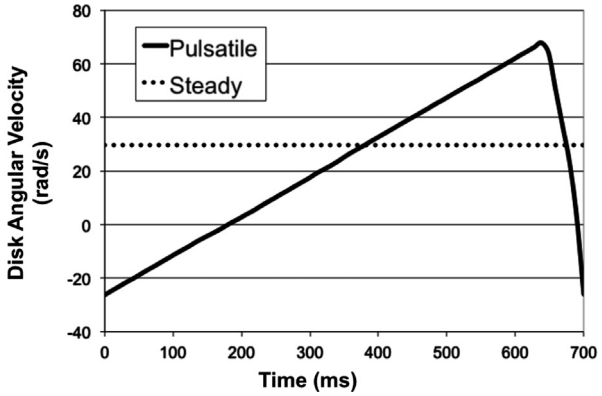

Fig. 1. The two waveforms used to control disc rotation. The pulsatile waveform has an RMS angular velocity of 29.63 rad/s (equal to the steady waveform) and has a clinically relevant period of 700 ms.

of PUU have been studied extensively (Milner et al., 2006; Topper et al., 2014).

The transport equation for platelet adhesion is based on Strong et al. (1987) and is added to the framework of a blood coagulation model developed by Fogelson (1992). A macroscopic and continuum framework is vital for making predictions of platelet adhesion on the spatial and temporal scales relevant to medical devices, as it eliminates the need to model prohibitively complex cellular interactions. Additionally, it allows the entire computational domain, even a growing thrombus, to be treated as a fluid, as demonstrated by Taylor et al. (2016).

In the present work, a rotating disc system (RDS), comparable to the experimental setup of Navitsky et al. (2014), is simulated and provides a means to assess model predictions of platelet adhesion. In an effort to isolate platelet adhesion, we focus on laminar conditions to eliminate the increase in complexity that would come along with turbulent flow. Nevertheless, our considered conditions encompass a wide range of physiologically relevant wall shear stresses (WSS), and we introduce a novel method for developing an SAP transport equation.

2. Methods

2.1. Experimental measurements

Platelet adhesion to PUU was studied using a rotating disk and is thoroughly described in Navitsky et al. (2014). In brief, a 20 mm diameter circle of smooth PUU was adhered to the bottom of a 20 mm diameter metallic disc. The disc was attached to a shaft and motor, suspended in a cylindrical, acrylic reservoir, and rotated according to four pulsatile and one steady waveforms, which yielded a wide range of physiologically relevant WSS on the disc surface. The reservoir was filled with bovine platelet rich plasma (PRP), reconstituted after centrifugation to maintain a constant platelet concentration of 350×10^6 platelets/mL, and the disc was rotated for two hours. Six experiments were performed for each waveform, and platelet adhesion data were collected at nine radial locations: 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9 mm. SAP concentrations were quantified with confocal microscopy after fixation and fluorescent labeling of platelets. SAP concentration was calculated by counting adherent platelets within a 0.011 mm^2 interrogation region.

We discuss one steady and one pulsatile disc rotation (Fig. 1), which correspond to the steady and +25% ramp waveforms used in Navitsky et al. (2014). The steady waveform produces a constant rotation rate of 29.63 rad/s (283 RPM) and the pulsatile waveform maintains an RMS rotation rate of 29.63 rad/s. The pulsatile waveform produces minimum and maximum rotation rates of −26.3 and 68 rad/s, and angular accelerations of 150 and −1500 rad/s^2 on the up and down slopes. The pulsatile waveform has a period of 700 ms. The steady waveform Reynolds number (Re) is 1950, while the pulsatile waveform has a maximum Re and an RMS Re of 4500 and 1950, respectively.

To define the pulsatile flow field, laser Doppler velocimetry (LDV) data were collected every 1 mm along a radial line 100 μm beneath the disc surface, from $r=0$ mm to $r=10$ mm, using a refractive index matched analog fluid with a kinematic viscosity of 1.51 cSt. Details of the LDV system and acquisition can be found in Navitsky et al. (2014). Velocity realizations ($n=20{,}000$) are collected, and the 700 ms period is divided into 20 ms bins for analysis. There are more than 500 realizations per bin, which is sufficient to accurately calculate mean near-disc velocity throughout the cardiac cycle but can result in large error bars due to time averaging.

3. Computational methods

3.1. Model governing equations

We adopt a continuum approach throughout so that the laminar flow of a Newtonian fluid governed by Eqs. (1) and (2) are used to calculate the velocity ($\boldsymbol{u}$) and pressure (p) fields, where ρ is the density and ν is the kinematic viscosity.

$$\nabla \bullet \boldsymbol{u} = 0 \tag{1}$$

$$\frac{\partial \boldsymbol{u}}{\partial t} + (\boldsymbol{u} \bullet \nabla)\boldsymbol{u} = -\frac{1}{\rho}\nabla p + \nu \nabla^2 \boldsymbol{u} \tag{2}$$

Bulk concentrations of four species are calculated in each computational cell: non-activated platelets, activated platelets, SAPs, and adenosine diphosphate, ADP (a chemical activator). Platelet agonists or high shear stress can activate platelets either chemically or mechanically, respectively, and include ADP, thromboxane A_2, and thrombin; participating in feedback loops that continue to activate platelets even if the initial activating stimulus is removed. The proposed model focuses on ADP, which has been shown to be the primary chemical activator of platelets (Fogelson, 2008).

The concentrations of non-activated, ϕ_n, and activated, ϕ_a, platelets are calculated using Eqs. (3) and (4), respectively, based on Fogelson (1992) though the cohesive stress tensor was removed. Terms that are equal in magnitude but opposite in sign, $[A_C(ADP)]\phi_n + \left[A_M\left(\phi_f, \tau\right)\right](\phi_a + \phi_n)$, quantify the total rate of platelet activation (a sink for non-activated platelets and a source for activated platelets), based on chemical (A_C) and mechanical (A_M) stimuli, where τ is the shear stress and ϕ_f is the fraction of activated platelets in the system. This ensures that mass is conserved in the platelet population. The transport equations for non-activated and activated platelets are modified to account for the loss of platelets from both sub-populations as they adhere to a surface ($k_{ns}\phi_n$ and $k_{as}\phi_a$, respectively, where k_{ns} represents the reaction rate for non-activated platelets and k_{as} represents the activated platelet adhesion to a surface). While both sub-populations are allowed to adhere to a surface, any platelets that embolize from a surface are assumed to be in the activated state. Therefore, any platelets that are removed from a surface ($k_{off}\phi_{sa}$, where k_{off} is the reaction rate for the removal of platelets from a surface) are added to the activated platelet population. Eqs. (3) and (4) also include D_n and D_a, the diffusivity for non-activated platelets and activated platelets.

$$\frac{\partial \phi_n}{\partial t} + (\boldsymbol{u} \bullet \nabla)\phi_n = D_n \nabla^2 \phi_n - \left\{[A_C(\mathrm{ADP})]\phi_n + \left[A_M\left(\phi_f, \tau\right)\right](\phi_a + \phi_n)\right\} - k_{ns}\phi_n \tag{3}$$

$$\frac{\partial \phi_a}{\partial t} + (\boldsymbol{u} \bullet \nabla)\phi_a = D_a \nabla^2 \phi_a + \left\{[A_C(\mathrm{ADP})]\phi_n + \left[A_M\left(\phi_f, \tau\right)\right](\phi_a + \phi_n)\right\} - k_{as}\phi_a + k_{off}\phi_{sa} \tag{4}$$

Chemical platelet activation uses a function of ADP concentration $[A_C(\mathrm{ADP})]$, Eq. (5). This term is a linear rate equation with an activation threshold (ADP_t) and is identical to one used by Sorensen et al. (1999a). The rate of chemical platelet activation