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Modelling of thrombin generation under flow in realistic left anterior descending geometries

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ABSTRACT

Currently there are no available methods for prediction of thrombotic complications in Coronary Artery disease. Additionally, blood coagulation tests are mainly performed in a steady system while coagulation in vivo occurs under flow conditions. In this work, a phenomenological model for coagulation up-to thrombin generation is proposed; the model is mainly based on the results of thrombin generation assays and therefore it can account for the variation of the coagulability that is observed in different individuals. The model is applied on 3 cases of left anterior descending arteries (LAD) with 50% maximum stenosis placed at a different location and have been statistically assessed as of different complication risk. The simulations showed that parameters of thrombin generation assays obtain different values when they refer to thrombin generation under realistic coronary flow conditions. The flow conditions prevailing locally because of the geometric differences among the arterial trees can lead to different initiation times and thrombin production rates and it also alters the spatial distribution of the coagulation products. Similarly, small changes of the coagulation characteristics of blood under identical flow conditions can allow or prevent the initiation of coagulation. The results indicate that combined consideration of geometry and coagulation characteristics of blood can lead to entirely different conclusions compared to independent assessment of each factor.

1. Introduction

Coronary artery disease (CAD) is the formation of plaques in the interior of the coronary vessel walls. This condition often leads to thrombus related complications that make CAD the leading cause of mortality worldwide [1]. Thrombus formation in coronary artery is believed to be triggered by the rupture of an atheromatous plaque and subsequent exposure of tissue factor (TF) and collagen. The triggering is followed by a series of biochemical reactions that result in the activation of fibrin by thrombin and the formation of the clot that narrows or blocks the flow in the coronary artery. As some of these reactions occur much faster on the membrane of platelets and endothelium cells the contemporary description of the process is cell-based [6]. Intracoronary ultrasound findings have suggested that a ruptured plaque does not necessary leads to thrombosis [3–5]. This can be attributed to any of the three factors, traditionally known as Virchow's triad, that influence the process: (1) specific conditions on vessel's wall (2) coagulability of blood and (3) local flow conditions [2].

During the last three decades, there were several attempts to investigate aspects of the process of thrombus formation using computational simulations. Based on in-vitro experiments on the enzymatic reactions (indicatively [7]) zero-dimensional models that reproduce the temporal evolution of the coagulation system have been developed., The first model consisted of 14 reaction rate constants, describing the activation and inhibition of four coagulation factors [8], while following works included up to 50 constants and focused on the extrinsic [9,10] or the intrinsic [11] pathway. Such models were used to investigate specific parts of the coagulation process, as the function of positive feedback loops and threshold concentrations for the initiation of the process [12], the triggering threshold with respect to Tissue Factor Pathway Inhibitor (TFPI) concentration [13], the inhibition mechanism of APC [14] or the effect of stochastically induced small variation of enzymes concentration [15]. For the simulation of thrombus formation the temporal evolution of the process is coupled with the diffusion and transport of the substances, initially as fluxes or with the use of few reactions [16,17]. The model of Sorensen et al., although focused on platelet aggregation, could also fit into this category [18]. While there are recent works using simplified reaction models, [19]. The trend is towards more complicated

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multi-scale and multi-phase models. These models, in addition to the set of equations that represents the reactions, may incorporate the movement of cells, the localization of equations and the change of blood properties due to blood clotting. Kuharsky and Fogelson [20] proposed an integrated model for thrombin generation under a simplified flow field, using a system of 59 equations that also included the binding of substances and the localization of reactions on surfaces. In following publications by the same group additional processes were incorporated in the model: the alteration of the rheological properties of blood due to clotting, by modelling platelet–platelet and platelet–wall interaction as reversible elastic links [21]; the APC mechanism and the transport of substances between plasma and endothelium cells [22]. Additionally, a small scale discrete model using an immersed boundary method [23] for platelets was utilized to develop a continuous model for platelet aggregation

[24]; the latter was also applied in simulations with pulsating flow in an idealized two dimensional vessel bifurcation [25] and with the inclusion of transport within the thrombus, was used to demonstrate the effects of flow conditions and the quantity of TF exposed on thrombus growth [26]. A similar model was presented by Xu et al. [27], which later included a cellular pot model [28] for discrete cells and an energy-based stochastic process for cell motion. The simulation involved differentiation of cell movements depending on fibrin levels and cell–cell or cell–surface interaction and bonds. The model was used to evaluate the role of fVII in venous thrombus formation [29] and to examine the impact of pulsating flow and the non-Newtonian characteristics of blood on thrombus growth [30]. Anand et al. [31] presented another multi-process model that used a viscoelastic model to simulate flow for both free vessel lumen and clot. This model also incorporated the activation of platelets due to excessive shear stress and fibrin production and lysis. In a similar work, a model for the viscosity of blood depending on fibrin concentration was proposed and used in a three-dimensional simulation of blood coagulation in a tube [32].

For the case of coronary thrombosis, a typical value for the diameter of the artery is around 4 mm and the flow is strongly three-dimensional and time dependent, preventing utilization of simplified flow fields. Additionally there is significant variability of the response of the coagulation system observed for different individuals [33]. From the reviewed works, only the latest was applied on 3D geometries, while the typical used regions are 2D simplified geometries with dimensions of $100 \times 100\ \mu m^2$. In most studies the flow field is simplified and predefined. Finally, the inclusion of a large number of processes makes the application of the models computationally expensive while at the same time they require a large amount of experimental data in order to be adapted for different patients. Due to these limitations of the existing methods there is no connection between modelling of thrombus formation and clinical practice.

In this work, we propose a model for coagulation under realistic flow conditions up to the stage of thrombin generation that compensates for some of these difficulties. The proposed phenomenological model has the following characteristics: (1) computational effectiveness, so that it can be coupled with transient flow simulations; (2) ability to obtain patient specific character in a manner that can be directly related to clinical practice, drawing data directly from clinical tests.

2. Materials and methods

2.1. Thrombus modelling

For the description of the coagulation process the cell based approach (Fig. 1) was followed. The computational model was realized in three steps: (i) a zero dimensional sub-model for thrombin generation was developed; (ii) the thrombin-sub model was modified for application under flow and (iii) a sub-model for platelet aggregation under flow was added. For the simulation of the coagulation reactions up to thrombin generation our previously published phenomenological model was used [34], consisting of the 4-lumped equations of Table 1. These equations express the concentration of 4 species in a zero-dimensional system. The outcome is the temporal evolution of thrombin concentration. The reaction rate constants of the model are derived directly from thrombin

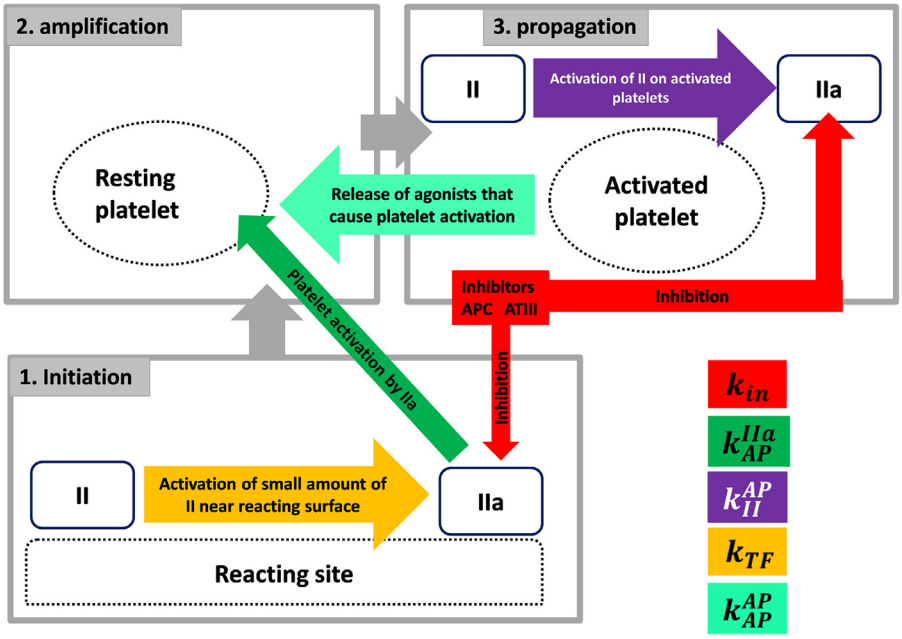

Fig. 1. *Phenomenological thrombin generation model.* The simplified cell based concept used for the development and application of the thrombin sub-model under flow. The different colours of arrows indicate the processes that are lumped in each reaction rate constant used. $\boldsymbol{K_{in}}$: thrombin inhibition; $\boldsymbol{k_{AP}^{IIa}}$: activation of platelets by thrombin; $\boldsymbol{k_{II}^{AP}}$: thrombin activation due to activated platelets; $\boldsymbol{k_{TF}}$: initiation by exposed TF; $\boldsymbol{k_{AP}^{AP}}$: activation of platelets due to the presence of activated platelets.

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