Medical Engineering & Physics 36 (2014) 196–204

Contents lists available at ScienceDirect

Medical Engineering & Physics

journal homepage: www.elsevier.com/locate/medengphy

Editor's comment: Thrombosis is a major complication of surgery, often with life-threatening consequences, and the failure to manage effectively blood coagulation and haemostasis is implicated in the failure of cardiovascular devices. While its relationship to blood flow, surface chemistry and haematological factors is well known, models that describe the kinetics of thrombus formation in patient-specific terms, and which are amenable to incorporation into large-scale numerical simulations, are few in number. The paper by Papadopoulos et al. presents a new phenomenological approach that draws on empirical data generated by thrombin generation assays to specify the parameters of interest. The model lends itself to the study of thrombus formation under realistic flow conditions according to the haematological status of the individual or patient.

Richard Black, Editor in Chief

A simplified mathematical model for thrombin generation

Konstantinos P. Papadopoulos*, Manolis Gavaises, Chris Atkin

School of Engineering and Mathematical Sciences, City University London, Room: C171, Northampton Square, London, EC1V 0HB, United Kingdom

ARTICLE INFO

Article history:
Received 28 May 2013
Received in revised form
30 September 2013
Accepted 15 October 2013

Keywords:
CFD
Coagulation
Simulation
Thrombus

ABSTRACT

A new phenomenological mathematical model based directly on laboratory data for thrombin generation and having a patient-specific character is described. A set of the solved equations for cell-based models of blood coagulation that can reproduce the temporal evolution of thrombin generation is proposed; such equations are appropriate for use in computational fluid dynamic (CFD) simulations. The initial values for the reaction rates are either taken from already existing model or experimental data, or they can obtained from simple reasoning under certain assumptions; it is shown that coefficients can be adjusted in order to fit a range of different thrombin generation curves as derived from thrombin generation assays. The behaviour of the model for different platelet concentration seems to be in good agreement with reported experimental data. It is shown that the reduced set of equations used represents to a good approximation a low-order model of the detailed mechanism and thus it can represent a cost-effective and-case specific mathematical model of coagulation reactions up to thrombin generation.

1. Introduction

The formation of thrombus in blood is involved in a number of life threatening situations like coronary artery disease and mechanical heart valve complications; it is a multi-scale phenomenon both in respect of time and space, involving a number of biochemical substances, blood circulating minerals and cellular responses. While the formation of blood clot is a physiological response of human body to vessel injury, it can be initiated when blood contacts certain substances like those exposed after the rupture of atheromatous plaques in stenosed vessels [1] and when pathological flow conditions prevail in a region [2]. Between the initiation and the formation of a thrombus, a series of enzymatic reactions takes place also known as coagulation cascade [3], classically divided in three parts: (1) the extrinsic or tissue factor (TF) pathway, (2) the intrinsic or contact pathway and the (3) common pathway. In every step of the process a circulating zymogen is activated, with the activation reaction being catalyzed by the products of previous steps. However, as most of these enzymatic reactions take place on cell membranes, the current approaches for coagulation are cell-based models and the process is divided in three discrete phases, initiation, amplification and propagation. Thrombin (factor IIa) and platelets play critical roles in the coagulation process. Thrombin in the final step catalyses the conversion of fibrinogen (factor I) to fibrin (factor Ia), a protein that through polymerization creates a mesh clot that also traps circulating blood cells. In addition, thrombin activates factor XIII (that forms bonds that crosslink the fibrin strands [4] causes the activation of platelets [5], the activation of factors V and VIII and their inhibitor protein C (APC). Platelets on the other hand, after activation by chemical or mechanical stimulation [6] become adhesive and form aggregates on the materials exposed after arterial damage [7] or plaque rapture [8,9] or in flowing blood. In addition they play a major role in thrombin formation [10,11] and they enhance the coagulation process by supporting on their membrane some of the coagulation reactions [12], releasing chemical substances and micro-particles [13] that influence the progress of coagulation and activate other platelets.

* Corresponding author. Tel.: +44(0)2070408115; fax:+44(0)2070408566.
E-mail addresses: Konstantinos.Papadopoulos.1@city.ac.uk (K.P. Papadopoulos), m.gavaises@city.ac.uk (M. Gavaises).

1350-4533/$ – see front matter © 2013 IPEM. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.medengphy.2013.10.012

The advance of computational techniques and increase of computational power have made possible the emergence of in silico studies that reproduce a part of or the whole process in greater or lesser detail, simulating either the whole process of thrombus formation or only the coagulation reaction system up to thrombin or fibrin production. The first mathematical simulation of thrombin and fibrin generation in plasma used exponential time functions as fixed inputs for concentration of some enzymes [14]. In vitro measurements of the reaction rate constants [15] were used for the development of a system of 20 reactions, including formation and breakage of complexes, in a study that mainly focused on the effect of variation of the concentration of different factors [16]. A similar model was proposed for the intrinsic pathway including fibrin production and APC inhibition mechanism, and was used to investigate threshold values for some enzymes and the spatial propagation of coagulation from the reacting site due to diffusion [17,18]. Subsequent work included more chemical substances and biochemical processes [19] up to thrombin production, resulting in a system consisting of 27 reactions and 42 reaction rate constants that later was combined with a Monte Carlo simulation method, in order to detect changes to the cascade initiation behaviour, due to small variation of the concentration of enzymes induced by the stochastic approach [20]. At the same time some studies used simulations to investigate a specific part of the coagulation cascade, as the function of positive feedback loops and threshold concentrations for cascade initiation [21], the triggering threshold with respect to tissue factor pathway inhibitor (TFPI) [22] or the inhibition mechanism of APC [23].

The studies that simulate thrombus formation and growth, simultaneously with blood flow and concentration of related substances, necessitate a less detailed sub-model for the coagulation cascade. While for the first studies of this kind the production rates of substances were mainly modelled as fluxes or with the use of few reactions [24,25], the increase of computational power allowed more complicated multi-scale and multi-phase models to emerge, that include an integrated coagulation sub-model. The authors in Kuharsky and Fogelson [26] proposed an integrated model of thrombus formation under flow conditions, taking into account the localization of reactions on surfaces, with the inclusion of the available binding sites on cell membranes for enzymes and using a system of 59 equations to simulate the coagulation system up to thrombin generation. A study that modelled platelet–platelet and platelet–wall interaction as reversible elastic links demonstrated the influence of these interactions on the flow field and predicted thrombus evolution and emboli formation [27]. The initial model was later improved with the addition of the APC mechanism and the transport of substances between plasma and endothelium cells [28]. The same concepts for cells and reactions were combined with an immersed boundary method [29,30] for modelling platelet movement and the interaction between platelet membrane sites and chemicals or endothelium. The results of this micro-scale model were also used to develop a continuous model for platelet aggregation (with platelets as continuous phase with movement limitations) describing the alterations in blood flow due to the presence of aggregated platelets [31] The macro-scale model was tested in simulations with pulsating flow in an idealized two dimensional vessel bifurcation [32]. The continuous model, with coupling of flow with thrombus growth and including flow and transport within the thrombus, was used to demonstrate the effects of flow conditions and the quantity of TF exposed in thrombus growth [33]. Anand et al. [34,35] 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 with a reacting site; in this study the area where fibrin concentration exceeded a specific value interpreted as the area occupied by the clot [36]. In Xu et al. [37] another multi-scale model was proposed that included a cellular pot model [38] for discrete cells and cell movement was simulated through an energy-based stochastic process. 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 due to vessel injury [39] and to examine the impact of pulsating flow and the non-Newtonian characteristics of blood on thrombus growth [40].

While the detailed description of coagulation included in these works makes them appropriate for studying the influence of different factors, unfortunately it increases dramatically the computational cost; thus published applications mainly refer to small two dimensional regions ($\sim$100 μm) while the dimensions of computational regions for studying thrombus formation in a coronary artery or in mechanical heart valves are much larger (typically, the diameter of the coronary artery is about 4 mm while the diameter of the aortic root is of some cm) with the flow distribution being three-dimensional and strongly time dependent preventing use of simplified flow models. In addition, these models do not have patient-specific characteristics, as the use of reaction rate constants derived from experiments do not allow the significant variability of thrombin generation observed for different individuals [41]. At the same time, it has been shown that the resulting thrombin generation curve predicted by such models under steady state conditions can be simulated in different ways by a much simpler system of 6 equations [42]. As the process between the initial stimulation and the formation of thrombin consist the main part of the coagulation reactions, our motivation is to develop a phenomenological model for thrombin formation that would be efficient enough to be used with three dimensional computational fluid dynamic (CFD) simulations while also being adjustable in order to reflect measured differences existing in data of different individuals. A case-specific simplified model like this, though not including the full biochemical details of the process, could be used for comparison of different cases of clinical interest.

2. Materials and methods

The aim of the study is to propose a set of equations that describe the thrombin generation in blood using the minimum possible number of parameters but which are able to describe with acceptable accuracy the whole process. The model is validated against experimental results for thrombin generation in vitro from Thrombin Generation Assays (TGA). The proposed model for thrombin production is based on the cell-based models of coagulation [12]; the full description of the biochemical processes are mainly based on Hoffman and Monroe [11]. For a detailed modelling of coagulation the localization of the different reactions makes the task more complicated, as it requires taking into account additional parameters such as the binding rate of the substances on cell membranes and the expression, concentration and availability of appropriate binding sites on the cell surfaces. For the development of a simplified model however, it can function as an advantage, as the processes can be grouped in respect to the location they occur (on platelet surface, on the vessel wall or in plasma). This approach is rigorous in cases where the transport of reactants is mainly due to convection such as arterial flow conditions, or in cases where the different species are well mixed. The generation of thrombin and generally the coagulation process is mainly attributed to activated platelets, while the initiation phase is localized on the reacting site of the vessel surface. The burst of thrombin generation is considered to occur when the small amounts of thrombin