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Review Article

A Review of Macroscopic Thrombus Modeling Methods

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ABSTRACT

Hemodynamics applied to mechanobiology offers powerful means to predict thrombosis, and to understand the kinetics of thrombus formation on areas of vascular damage in blood flowing through the human circulatory system. Specifically, the advances in computational processing and the progress in modeling complex biological processes with spatio-temporal multi-scale methods have the potential to shift the way in which cardiovascular diseases are diagnosed and treated. This article systematically surveys the state of the art of macroscopic computational fluid dynamics (CFD) Computational fluid dynamics techniques for modeling thrombus formation, highlighting their strengths and weaknesses. In particular, a comprehensive and systematic revision of the hemodynamics models and methods is given, and the strengths and weaknesses of those employed for studying thrombus formation are highlighted.

Contents

Introduction

A thrombus is a blood clot anchored to damaged vascular wall. Thrombus forms in the blood vessel because of the occurrence of various hemodynamics and biomechanical processes. These processes are often classified into two main sub-processes; platelet activation/aggregation and coagulation (or fibrin gel formation). The thrombus formation process in arteries can lead to heart attacks or ischemic strokes if the affected

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arteries are the coronary or the carotids, respectively [1–3]. Intracavitary thrombus can also be dislodged from the heart and be embolized to the brain producing cardiogenic strokes [4]. Nowadays, heart attacks and strokes due to pathological thrombosis constitute the leading causes of death in developed countries [3,5,6]. Hemodynamics variables such as shear rate, shear stress and elongational forces cover a central role in thrombus formation mechanisms [7–12].

Thrombus formation and its pathological role was reported for the first time in the Edwin Smith Papyrus [13], although it is solely with the discovery of platelets, during the second half of the nineteenth century, that the dilemma of thrombus formation started to be uncovered. For the first time in histology, Schultze [14,15] identified platelets and described them in detail. But the first who understood that platelets, through their aggregation process, are the predominant protagonists of the thrombus formation is Bizzozero [16]. Bizzozero, using the immersion microscope, observed that exerting with a needle a little pressure on the wall of an artery of a living animal to cause a wound, the platelets flowing in the blood stream started to aggregate in the vicinity of the injured part of the vessel. In the late ninetieth century, Virchow observed the influence of the blood flow conditions on the activation of platelets and consequently on the thrombus formation and describe the Virchow's triad in thrombus formation: flow, blood and substrate [17]. In the last years, most of the complex cascade of biological reactions leading to fibrin formation has been identified and is well documented in the literature [18–20]. With this knowledge at hand, many mathematical models aimed at describing the clotting process and some of its sub-processes were developed [21,22].

Analytical solutions to macroscopic blood clotting models are almost never possible. The only alternative is to approach them by means of numerical methods. The ever-increasing computing power of the computational architectures has further emphasized the advantage of using numerical methods for tackling complex mathematical models such as those involved in describing thrombus formation.

In this review, we summarize the characteristics of the main macroscopic computational blood clotting models present in the literature. We classified the models according to: their mathematical formulation and the properties and differences of the numerical methods employed to solve them. Firstly, we report the salient thrombus formation-related biological and biochemical concepts[2] (Biological background). Secondly, we review the mathematical equations employed to model the blood flow behavior, its biochemical reactions and intertwined multi-modal events. Thirdly, we systematically review the numerical methods used to simulate the models cited earlier (Blood clotting models and methods). Lastly, we provide a summary and a discussion of the most relevant macroscopic models and methods (Discussion).

Biological Background

Thrombus formation is a consequence of an abnormal functional behavior of hemostasis [25,26]. The wall of a damaged vessel is tended to be repaired by means of different intertwined mechanisms: vasoconstriction, primary and secondary hemostasis and, lastly, fibrinolysis (see Fig. 1).

The process of thrombus formation takes place both in hemostasis and in thrombosis, and depends on complex interactions among the vascular wall (endothelium), platelets, many enzymes and 13 chemical factors listed in Table 1. Thrombosis is mainly triggered by an endothelial damage and/or the stasis or blood flow condition [26,27]. The spatio-temporal evolution of the clot is regulated by approximately 80 kinetic reactions, the diffusion of the biochemical products of blood clotting and the convection forces of blood flow [28]. Detrimental events (for example, endothelial damage due to atherosclerosis) and flow conditions such as abnormal wall shear stress prevail in arterial thrombosis, whereas venous and aneurysm thrombosis are predominantly formed in the presence of stasis of blood [23–25,28–30].

The whole blood clotting process is a series of closely related and integrated sub-processes which form the hemostasis triad. Below, we provide a general description of the blood clotting process divided into four stages: endothelial injury, primary and secondary hemostasis, coagulation cascade and fibrinolysis.

Endothelial Injury

Vasoconstriction begins rapidly, is restricted to the area of the lesion and has the objective to prevent any loss of material. Vasoconstriction alter the red blood cells flow promoting the marginalization of the blood cells (RBCs)Red blood cell, creating an enriched near-wall platelet plasma layer near the injury site so as to facilitate the interactions between the platelets and the sub-endothelium. Vasoconstriction is compensated by the endothelium through the secretion of factors with vasodilator bioactivity such as NO, prostacyclin, and EDHF [31].

Primary and Secondary Hemostasis

Platelets are anucleated discoid cells with a diameter of 2–3 μm, average life of 10 days, and a concentration in the blood under physiological conditions of about 250,000 per μl. Platelets are primarily responsible for the formation of the primary hemostatic plug, which is characterized by the following processes: adhesion, platelet shape change, degranulation and reversible aggregation. During primary hemostasis, clot formation is reversible; platelets adhere to the damaged tissue, activate and start to aggregate. Simultaneously, coagulation factor respond in a complex coagulation cascade to form fibrin strands, which strengthen the primary hemostatic plug. This second process is known as secondary hemostasis. A detailed description of the role of the primary and secondary hemostasis can be found in other more specific reviews [32,33].

Coagulation Cascade

The coagulation cascade is a complex phenomenon not fully understood yet. In the last three decades, a remarkable effort has been expended to better comprehend all the mechanisms involved. An extensive review of such findings has been reported by Schenone et al. [25].

Several blood clotting models have been designed to simulate the coagulation cascade. Most of them model it as a sequence of reactions that convert fibrinogen into fibrin. Fibrin polymerizes to form a “mesh” and thus a hemostatic plug, or clot, entrapping aggregated platelets.

The coagulation cascade is traditionally separated into three pathways: intrinsic, extrinsic and common pathways (see Fig. 2). The extrinsic pathway involves the tissue factor and the factor VII complex, which activates factor X. The intrinsic pathway are regulated by kininogen, prekallikrein, factors XII, XI, IX and VIII. The extrinsic and intrinsic pathways converge at the activation of factor X. The common pathway leads to the factor X-mediated generation of thrombin from prothrombin (facilitated by factor V, calcium and platelet phospholipid), and ultimately converts fibrinogen into fibrin [18,34].

Fibrinolysis

Spontaneous fibrinolysis is a process of self-limitation of clot formation that degrades the stabilized clot once hemostasis has been achieved. The principal mediator of fibrinolysis is plasmin, which cleaves fibrin and produces fibrin degradation products. A detailed review of the fibrinolysis sub-mechanisms have been reported by Cesarman-Maus et al. [35]. By the time the clot is stabilized, the vessel starts an auto-healing process by means of a cell colonization over the clot. Thus, fibrinolysis causes the gradual fibrin-network degradation and concomitantly promotes the creation of new tissues.

[2] For a deep comprehension of these, the reader is referred to [22–25].