Blood coagulation: a puzzle for biologists, a maze for mathematicians

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Abstract

Blood coagulation is a process of extreme complexity and of fundamental importance that has been studied since antiquity. In this talk we shall go briefly through the historical stages of the studies on blood coagulation, and we will devote most of the time to illustrating the modern view (the so-called cell based model), in contrast to the theories that have dominated till recent times (~2005). A discussion on the complex mechanisms of blood clotting cannot be disjoint from an analysis (necessarily superficial) of bleeding disorders and thrombophilia.
In a very recent survey paper [1] we have summarized the main features of the process and we have illustrated both the modern approach, and some history, presenting also a concise review of mathematical models. The material collected there will be the subject of this lecture, which consists of two presentations: the fist talk (presented by prof. Antonio Fasano) will deal with the biological introductory part, while the second talk (delivered by prof. Adelia Sequeira) will be devoted to mathematical models.

Keywords: blood coagulation, bleeding disorders, models of hemodynamics, blood rheology, biochemical and mechanical factors

1. Part I: Biological mechanisms and models of blood coagulation.

The circulatory system is equipped with an incredibly complex chemical and mechanical machinery ready to repair lesions which may occur to blood vessels by sealing them with a *clot* (or *thrombus*). A clot is a gel like structure consisting of a polymer (*fibrin*) network entrapping various blood components. The ingredients necessary to lead to the clot formation are either present in the blood, or reside in the endothelium of the blood vessels. Actually, the ones contained in the blood vessel walls become available immediately after a lesion of the *tunica intima*, so even in the presence of a tiny internal lesion. Indeed the clotting process (accompanied by the clot dissolution process) is taking place continuously in the organism on a small scale, so to keep the circulatory system in good shape. Of course, it also occurs on a larger scale when needed.
It is absolutely crucial that the clotting mechanism is set in motion only when it is really necessary, remaining silent in normal conditions, and at the same time that the coagulation process is terminated before it occludes the vessel, allowing blood to flow normally. Indeed, after the process of *hemostasis* is completed, the thrombus will be gradually removed by means of another process known as *fibrinolysis*. To be more precise, it is not correct to look at these processes in a sequential way. The hemostasis and the fibrinolysis machines are both active at the same time and whether a thrombus is growing or retreating is the result of an unbalance between the two processes.

The clotting process takes place in two steps: *primary* and *secondary* hemostasis. Primary hemostasis occurs very rapidly: *platelets* form a compact network with the help of a multimer available at the injury site, known as *von Willebrand Factor*. Both platelets and von Willebrand Factor have multiple roles also in the next phase. Secondary hemostasis goes through a chain of reactions with a highly positive feedback, in which many other "Factors" intervene (the very first one being the *Tissue Factor*, present in the blood vessels wall). Such factors (numbered from I to XIII) come in two forms: activated and non-activated. Some of them form complexes that perform specific actions. For instance, the combination of the activated form of Factors V and X gives rise to an enzyme (*prothrombinase*), which triggers the final stage of coagulation. The reaction cascade has the aim of producing fibrin, making the skeleton of the thrombus, which is further consolidated by the production of cross links in the network. Fibrinolysis is likewise a chemical process with positive feedback, eventually producing the enzyme that can break the fibrin structure.
Many drugs can be effectively used to inhibit coagulation, interfering with the action of specific elements in the chain. This is another big chapter in blood coagulation.

Since we are addressing a composite audience, we will not enter the intricate world of the chemical structure of the numerous proteins and enzymes and on the details of the reactions, but we will try to describe the basic mechanisms in the simplest possible way. Moreover, it is very important to point out that hemostasis (both primary and secondary) *is not just of chemical nature*, but some crucial steps (the *activation* of platelets, as well as the action of von Willebrand Factor) require the intervention of *shear stress* beyond some threshold. Thus chemistry and fluid dynamics are strongly coupled, clearly making the problem extremely complicated.

Besides the physiological process of hemostasis following an injury, it is well known that unwanted coagulation can take place due to temporary reduced blood flow rate or stasis, leading to *deep vein thrombosis* (DVT), and stimulating puzzling questions concerning the absence of the triggering mechanical stress.

A lot can be learned from what may go wrong in the processes of hemostasis and fibrinolysis. Many different kinds of bleeding disorders have been studied, progressively identifying their cause in the deficiency or dysfunction of one of the many elements having some role in the formation or in the dissolution

of the clot. For that reason we will devote some time in reviewing the most important bleeding disorders.

The core of the talk will be the most recent approach to hemostasis. The biological model of secondary hemostasis that has been used for four decades till very recently is known as the Cascade Model. Such a model was characterized by two distinct pathways able to start the coagulation process independently of each other: the *intrinsic* pathway, originated within the blood, and the *extrinsic* pathway, triggered by elements liberated at the wound site. The two pathways, when both present, merge in the *common* pathway eventually leading to fibrin production. During the last years some criticism has been moved against the Cascade model, based on the fact that it fails to explain the presence or absence of symptoms of bleeding disorders in correspondence of the deficiency of some key factors. The Cascade model, which anyway correctly describes some stages of coagulation, has been gradually replaced by the so called *Cell based* model, in which the extrinsic origin prevails. Nevertheless, the occurrence of DVT dramatically poses the question of an intrinsically originated coagulation. That can be identified in the ability of neutrophils to deliver the Tissue Factor in abnormal conditions.

The introductory part of the talk will be of historical character, from ancient times to the discovery of platelets, followed by the first attempts of indentifying some of the biochemistry involved, and then reviewing the efforts of assembling and disassembling this very complicated biological puzzle till our days. Mathematicians have to face the task of combining this puzzle with the complexity of hemodynamics in a geometry which varies with the thrombus growth.

Despite the substantial literature on the subject, a comprehensive mathematical model incorporating the recent progress made on the biological side is still missing, and it should move from the ascertained features of the cell-based model.

2. Part 2: Mathematical modelling of blood coagulation

The phenomena of platelet activation and blood coagulation is quite complicated and not yet completely understood. Numerous experimental studies recognized that thrombus formation occurs not in regions of parallel flow, but primarily in regions of stagnation point flows within blood vessel bifurcations, branching and curvatures. Moreover, internal cardiovascular devices such as prosthetic heart valves, ventricular assist devices and stents, generally harbor high hemodynamic shear stresses that can cause platelet activation and result in coagulation. Thrombotic deposition encountered in these devices is a major cause of their failure and of severe pathologies such as bleeding or thromboembolic disorders. In the last case, thrombi can detach to form an embolus, which can lodge in a smaller vessel downstream from the site of thrombosis, induce ischemia of the irrigated tissues, and result in a stroke, heart attack or pulmonary embolism.

While there has been a considerable research effort in blood rheology, the constitutive models have thus far focused on the aggregation and deformability of the RBCs, ignoring the role of platelets in the flow characteristics. Of all the components of blood, platelets are by far the most sensitive to chemical and physical agents and play a critical role in the coagulation process. Reliable phenomenological models that can predict regions of platelet activation and deposition (either in artificial devices or in arteries), have the potential to help to optimize design of artificial devices and also to identify regions of the arterial tree susceptible to the formation of thrombotic plaques and possible rupture in stenosed arteries.

Comprehensive mathematical models of the blood coagulation and fibrinolysis processes, describing either the classical concept of *Coagulation Cascade* or the recently adopted *Cell-Based* model, and taking into account physiologic and mechanical factors, have the potential to identify regions of the arterial tree susceptible to the formation of blood clots and could contribute to a better understanding of these complex phenomena. Kinetic models generally consist of a nonlinear system of partial differential equations of advection-diffusion-reaction type or a set of ordinary differential equations (ODEs), along with appropriate initial and boundary conditions. Each equation in the system describes the evolution of the concentration of each species entering the process that leads to blood clotting and dissolution. Boundary conditions simulate the beginning of the whole process following a vessel wall injury. Due to the size of the system and to its nonlinearity, a solution in a closed form is out of sought and numerical simulations are necessary. We should note that numerical simulations are useful, not only from a mathematical point of view but also from a biological perspective. In fact, a specific perturbation in the hemostatic system, which usually cannot be assessed through laboratory tests, can easily be introduced in a phenomenologic mathematical model and predictions on the effects of that specific perturbation can be evaluated through numerical simulations and their corresponding results.

As mentioned above, blood coagulation is a very complex process. It is therefore not reasonable to expect to be able to build a mathematical model that fits all' the features of clot formation and lysis. Indeed, the important influence of shear stress (both on platelets activation and on the mechanical interaction of the blood flow with the clot) should be captured by the model. The path for an overall understanding of the whole process seems to be constructing mathematical models that look upon a particular phase or aspects of the process, along with numerical simulations. For example, the role of Tissue Factor in the initiation of blood coagulation, or that of other activators or inhibitors, from a threshold point of view; or, the main step leading to clot formation, and how much Thrombin is formed; existence and control of the several feedbacks in the chain of chemical reactions (positive and negative); existence of different time scales that, in some cases, allow for a reduction in the size or in the nature of the differential system; or the important role of platelets in the whole process, how they aggregate and their behavior under shear flow conditions. Bleeding disorders or deficiencies leading to diseases can also be taken into account in a mathematical model. Moreover, blood rheology and the specific flow regime for blood clotting cannot be neglected. These are the main issues that will now be considered, while giving a short overview of some relevant mathematical models of blood coagulation proposed in the literature. It is important to notice that there remains a pressing need for further experimental data to validate these models and to develop new ones in order to understand better the interplay between biochemical and mechanical factors under different flow conditions found in the human vasculature.

References

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