

# The New Coagulation Cascade and Its Possible Influence on the Delicate Balance Between Thrombosis and Hemorrhage

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The article published by Navarro et al<sup>1</sup> in this issue of *Revista Española de Cardiología* reports the experience of 4 anticoagulation units located in large referral hospitals in Spain. The article also illustrates the appropriateness of monitoring treatment in specialist units to maintain the level of anticoagulation within the very narrow margin that allows prevention of thrombosis without causing bleeding complications.

All thrombotic processes have their origin in the dysfunction or rupture of the vascular endothelium, leading to release of tissue factor, which initiates the process of coagulation, and of collagen and von Willebrand factor, which initiates adhesion and activation of platelets. Alteration of the homeostatic balance between prothrombotic and antithrombotic factors during anticoagulation therapy can result in insufficient inhibition of coagulation (thrombosis) or the occurrence of bleeding due to excessive antithrombotic treatment.

The interpretation of the coagulation process described by MacFarlane<sup>2</sup> in 1964 (the “MacFarlane cascade”) has been of use for many years in beginning to understand the complex problem of thrombus formation. According to MacFarlane, there are 2 pathways: the extrinsic pathway, involving tissue factor and factor VII, and the intrinsic pathway, in which factors XII, XI, IX, VIII, and V participate. Both pathways converge to activate factor X and lead to transformation of prothrombin into thrombin and, through the action of thrombin, of fibrinogen into fibrin. The role of platelets in coagulation was considered independent.

During the following 3 decades, numerous studies were undertaken, culminating in almost simultaneous publications from groups in Houston (Schafer et al<sup>3</sup>) and

North Carolina (Monroe et al<sup>4</sup>). Both groups described a “new cascade” (Figure) that has been internationally accepted, as demonstrated by the recently published position paper from the Task Force of the European Society of Cardiology.<sup>5</sup> This new perspective built on the classic cascade in the following ways:

1. The complex formed by tissue factor and factor VII participates in the activation of factor IX, indicating that the intrinsic and extrinsic coagulation pathways are linked almost from the beginning of the process.

2. The complete process does not occur continuously but rather requires 3 consecutive phases: an initial phase, an amplification phase, and a propagation phase. Platelets and thrombin are actively involved in the last 2 phases.

## Initial Phase

The tissue factor–factor VII complex activates factor X, either directly or indirectly via factor IX, and transforms prothrombin into thrombin in small amounts that are insufficient to complete the process of fibrin formation.

## Amplification Phase

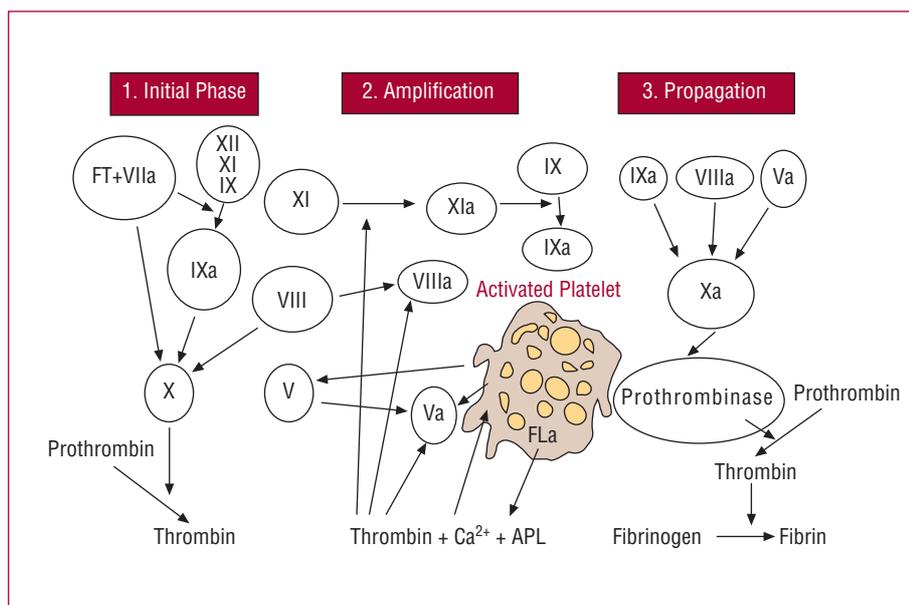
The thrombin that has been formed, along with calcium from the blood and acidic phospholipids derived from platelets, actively participates in a positive feedback process for the activation of factors XI, IX, VIII, and V, and, especially, to accelerate platelet activation. Simultaneously, the factors mentioned are attracted through chemotactic mechanisms to the surface of the platelets, where very rapid and extensive activation and amplification occurs.

## Propagation Phase

The amplification of the process through feedback mechanisms involving thrombin and platelets and the activation of all these factors allow large quantities of factor X to be activated and form the prothrombinase complex to convert prothrombin into thrombin and, through the action of thrombin, fibrinogen into fibrin. The final process, always occurring on the surface of the platelets, accelerates and leads to the explosive generation of large quantities of thrombin and fibrin.

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**Figure.** Phases of coagulation according to the new cascade. a indicates activated (Roman numerals represent the coagulation factors); APL, acidic phospholipids; Ca<sup>2+</sup>, calcium; TF, tissue factor.

## The Role of Platelets

Activation of platelets alters the permeability of the membrane and allows entry of calcium and release of chemotactic substances that attract coagulation factors to the surface. At the same time, factor V and acidic phospholipids are released, providing the necessary complement for the coagulation process.

Research into counteracting the tendency toward thrombosis has focused on inhibiting the factors involved in the cascade (tissue factor, factor X, prothrombin, or thrombin) or counteracting the action of other important factors such as factor VIII. Research into inhibiting the tissue factor–factor VII complex is still ongoing but has not yielded results that can be applied in clinical settings. Phase II/III trials of factor X and thrombin inhibition are more promising, although recent trials of a thrombin inhibitor (ximelagatran) were suspended due to hepatic toxicity.<sup>6</sup> Factor VIII, although not part of the main pathway of the cascade, is a very important factor and its inhibition with the different forms of heparin has been, and continues to be, used successfully due to its ease of monitoring and very low risk of bleeding complications. However, its use is limited by the requirement for parenteral administration and the inadequate antithrombotic effect in certain situations.

Inhibition of prothrombin with anti-vitamin K drugs (warfarin, acenocoumarol) is the most widely used treatment for the chronic prevention of thrombosis, as reported by Navarro et al.<sup>1</sup> Their study, undertaken by specialist units with extensive experience in monitoring anticoagulant therapy, illustrates the common difficulty associated with maintaining a level of anticoagulation that prevents thrombotic events. It also illustrates how excessive inhibition of a single factor in the cascade (prothrombin) puts patients at risk for severe or fatal

hemorrhage. The use in Spain of acenocoumarol (Sintrom<sup>®</sup>) represents an added difficulty due to the dosage inadequacy of the commercially available drug, which does not allow patients to take the same dose every day.

The new coagulation cascade presents fibrin formation as the result of 2 complementary processes: coagulation (represented by thrombin) and platelet activation. Strong and combined inhibition of both processes necessarily leads to severe bleeding, as was soon documented in international studies.<sup>7</sup> However, the combination of pharmacologic inhibitors of both processes at doses corresponding to the lower level of the therapeutic range can achieve an effective antithrombotic effect without risk of bleeding complications. The clinical trials undertaken by the Working Group on Thrombosis of the Spanish Society of Cardiology into moderate inhibition of prothrombin and platelet activity are an example of the clinical application of the new cascade<sup>8-10</sup> and may represent a starting point for studies aimed at determining the ideal combination and dose of the 2 drugs to achieve the desired balance between prevention of thrombosis and development of bleeding complications.<sup>11</sup>

The study by Navarro et al<sup>1</sup> yielded interesting data regarding the increased use of anticoagulation therapy compared with the results of previous studies.<sup>12</sup> The percentage of follow-ups in which the international normalized ratio (INR) was within the intended range indicates a good level of control, similar to that seen in other countries.<sup>13</sup> However, it should be noted that the selected range of anticoagulation was very wide (INR between 2.0 and 4.0) and is not recommended according to the guidelines of the Spanish Society of Cardiology or international guidelines.<sup>14,15</sup> In most situations, the guidelines recommend INR values of between 2.0 and 3.0, except in patients with metallic prostheses, in whom

a range of 2.5 to 3.5 is preferred. In addition, we should add that Robert Hart, principal investigator for the SPAF studies, recommends an INR of between 2.0 and 2.5 in patients with atrial fibrillation.<sup>16</sup> A meticulous retrospective analysis of randomized trials that included the risk of bleeding complications and vascular death led him to recommend levels of anticoagulation lower than those previously used.

The results of the study by Navarro et al<sup>1</sup> have little clinical application in cardiology since they did not analyze risk factors or report clinical follow-up to determine the true incidence of interruption of INR monitoring or the date. Consequently, the number of patients followed for 1 year cannot be determined in order to calculate the frequency of events, which would allow comparison with standard clinical reports. The results are of great use, however, to small and large anticoagulation units for use as reference values to allow assessment of the quality of monitoring of anticoagulation therapy.

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