

# Excessive Perioperative Bleeding

## Are Fibrin Monomers and Factor XIII the Missing Link?

PREDICTING perioperative blood loss is traditionally fraught with great difficulties. Medical history is certainly crucial in the risk assessment of perioperative blood loss because it provides information on bleeding history, the use of antiplatelet drugs, and oral anticoagulation.<sup>1</sup> However, so far there is no laboratory parameter that could reliably predict perioperative blood loss.<sup>2</sup>

According to the paper of Korte *et al.* in this issue of ANESTHESIOLOGY, there may be hope at least for surgical cancer patients.<sup>3</sup> In these patients, increased fibrin monomer levels, suggestive of preoperative coagulation activation, might be predictive of increased intraoperative blood loss.<sup>3-5</sup> The hypothesis of the authors is that the increase in fibrin monomer would be due to a preexisting imbalance between available factor XIII and thrombin.

Thrombin proteolytically cleaves fibrinogen to soluble fibrin monomers, which are incorporated into a cross-linked and thus stabilized or nonsoluble fibrin network in the presence of appropriate amounts of activated factor XIII. Thrombin also cleaves the A subunit of factor XIII to generate the enzymatically active factor XIII (FXIIIa), capable of cross-linking fibrin monomers into a fibrin strand (fig. 1). The authors hypothesize that a relative imbalance of thrombin in respect to activatable factor XIII would result in an accumulation of fibrin monomers due to the inadequate incorporation of monomers into a stable fibrin network. They further hypothesize that in patients with preoperatively elevated fibrin monomers, the surgical procedure may lead to an accentuation of the above-described imbalance that may be associated with increased perioperative blood loss.<sup>5,6</sup>

This Editorial View accompanies the following article: Korte WC, Szadkowski C, Gähler A, Gabi K, Kownacki E, Eder M, Degiacomi P, Zoller N, Devay J, Lange J, Schnider T: Factor XIII substitution in surgical cancer patients at high risk for intraoperative bleeding. ANESTHESIOLOGY 2009; 110:239-45.

The authors tested their hypothesis in a pilot study with 22 patients. Intraoperative factor XIII substitution resulted in a reduced decrease of fibrinogen concentration, a smaller decrease of mean clot firmness in rotational thrombelastography analysis, and reduced blood loss.

Interestingly, the authors were able to demonstrate in an earlier study that the developing clot had reduced maximum clot firmness before the exaggerated surgical blood loss was observed.<sup>4</sup> Most fascinating, by a single dose of factor XIII (30 U/kg) given 15 min into surgery, the exaggerated decrease of maximum clot firmness during surgery could largely be prevented, and this resulted in a reduced blood loss.<sup>3</sup>

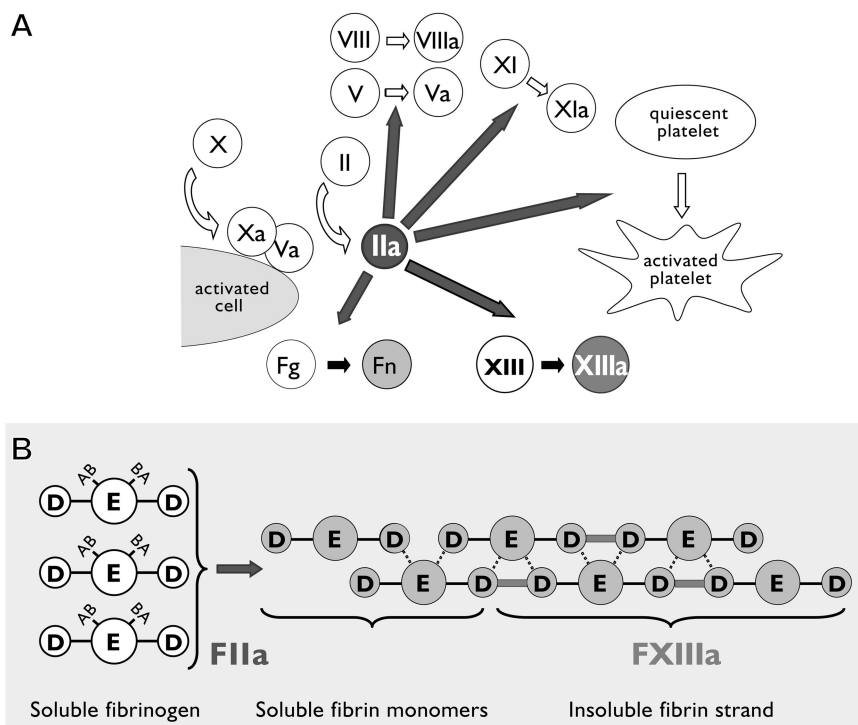
A potentially relevant characteristic of the study population of Korte *et al.* is that patients had pathologically low factor XIII activities at baseline (approximately 58% in the verum group *vs.* 55% in controls). The study population thus presented with increased fibrin monomer levels and (putatively) acquired factor XIII deficiency. Whether intraoperative factor XIII substitution will prove useful in patient populations without preexisting acquired factor XIII is an open question.

A low factor XIII level has been shown, in keeping with the results of Korte *et al.*,<sup>3-5</sup> to be a risk factor for hemorrhage after intracranial<sup>7</sup> and coronary artery bypass surgery.<sup>8</sup> With factor XIII treatment, chest tube drainage and transfusion needs were indeed reduced in patients with a normal postoperative factor XIII level.<sup>9</sup>

The study by Korte *et al.*<sup>3</sup> is highly interesting and thought-provoking. If the conclusions hold true despite significant methodological shortcomings and findings that are difficult to interpret, we may in the future test patients for fibrin monomers preoperatively, and treat them if elevated with (a single dose of) factor XIII early into surgery. At the moment, such a conclusion is premature because this study has significant limitations. First, only 22 patients were analyzed. This limits the power of the study, and the sample size is far too small to allow any judgment on safety. All procoagulatory substances may be associated with adverse thrombotic and thromboembolic events. Second, the study was powered to show a difference of 30% in maximum clot firmness and was prematurely terminated because this threshold was achieved at a planned interim analysis with a *P* value of 0.04. Stop rules at planned interim analyses usually use significantly lower *P* values to avoid a false positive result due to an (initial) uneven patient allocation to the groups by chance and to preserve an overall two-sided type I error rate of 0.05.<sup>10</sup> Therefore, the question arises whether this trial may have been

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**Fig. 1. Roles of thrombin in coagulation and roles of thrombin and enzymatically active factor XIII (FXIIIa) in a simplified model of fibrin strand generation. (A)** According to the cell-based model of coagulation, thrombin (IIa) is generated on the surface of activated cells (*left in A*) by FXa-mediated proteolytic cleavage from its precursor molecule, prothrombin. Thrombin (*dark gray*) is a key enzyme in coagulation and has multiple functions, including the activation of FXIII to generate FXIIIa. (*B*) Fibrinogen molecules comprise three domains: a central E domain flanked by two D domains. Fibrinogen is activated to fibrin monomers through the thrombin-mediated cleavage (*dark gray in B*) of the fibrinopeptides A and B from the E domain. Fibrinopeptide cleavage permits electrostatic interaction (*dotted lines*) of E domains with D domains of other fibrin molecules resulting in the formation of a still soluble fibrin strand. It is only after FXIIIa (*light gray*) has cross-linked fibrin monomers by covalently linking D domains of adjacent fibrin monomers (*bold light gray lines*) that the strands or protofibrils become "stabilized" or insoluble. Bottom graph (*B*) modified, with permission of Elsevier, from Furie B, Furie BC: Molecular basis of blood coagulation, Hematology: Basic Principles and Practice, 4th edition. Edited by Hoffman R. Philadelphia, Elsevier, 2005, pp 1946. Copyright © Elsevier 2005.<sup>12</sup>



stopped prematurely. Third, estimated blood loss is only a weak surrogate outcome parameter. Fourth, the specificity of the fibrin monomer test used in this study with potential cross-detection of fibrin degradation products has been debated in the past. In future studies, harder outcome parameters such as the need for allogenic blood transfusion should be targeted. In addition, although a higher maximum clot firmness at higher factor XIII levels can be expected,<sup>11</sup> it remains speculative why fibrinogen would decrease less in factor XIII-treated patients than in control patients during surgery. One hypothesis may be that due to a lack of factor XIII activity fibrin monomers are insufficiently cross-linked, maximum clot firmness is compromised, and thus bleeding continues with further activation of the coagulation and fibrinogen consumption.

In conclusion, large multicenter studies in patients at risk of excessive perioperative blood loss are necessary to formally test the possible beneficial effect of intraoperative use of factor XIII. For the moment, the authors are to be congratulated for their innovative research and for having performed a proof-of-principle study in patients presenting with acquired functional factor XIII deficiency preoperatively.

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