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High Five for Low Five

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There is a considerable variability in bleeding phenotype within hemophilia A patients with similar factor VIII (FVIII) levels, which to date has not really been understood. In search of an explanation, many studies have been performed to find mechanisms for regulation or compensation of bleeding in hemophilia. Not long ago, hemophilia patients were found to have a 1.5-fold higher platelet factor V (FV) concentration compared to healthy blood donors.[1] The authors suggested this to be the consequence of a compensatory procoagulant response to hemophilia bleeding. Although the assumption of higher clotting factor levels having more procoagulant potential is appealing, recent insights have shed a different light on this topic.

The coagulation system is a highly complex network, where multiple proteins interact upon a platelet surface under flow conditions (Fig. 1). Nonlinear positive and negative feedback loops, individual thresholds and a dynamic continuum make it extremely difficult to study the contribution of individual proteins in the final coagulation properties in a single patient. One approach to systemically evaluate such complex network is through local or global sensitivity analysis, where the uncertainty in the output of a model can be appointed to different sources of uncertainty in the model input. Recently, Link et al performed a global sensitivity analysis in search for a modifier of thrombin generation in hemophilia A.[2] Potential candidates from this analysis were evaluated in a flow model of coagulation and by measuring thrombin generation by calibrated automated thrombography (CAT). After 110.000 simulations, they found that FV was responsible for 50% of the variance in their model. More strikingly, it appeared that low-normal levels of FV enhanced thrombin generation in FVIII-deficient plasma in this model of flow-mediated coagulation. In a next step, they confirmed their findings in flow assays and using CAT. In both experiments, inducing lower FV levels within the normal range (to 60%) resulted in clearly enhanced thrombin generation. These effects were amplified by high-normal prothrombin levels in both experimental models. Their hypothesis is that lowering FV reduces competition between FV and FVIII for factor Xa on activated platelet surfaces (Fig. 1), which enhances FVIII activation and rescues thrombin generation in FVIII-deficient blood.[2]

There is a rare bleeding disease with a combined congenital FV and FVIII deficiency (F5F8D). In the model of Link et al, very low FV levels (<5% of normal) combined with very low FVIII levels (1% of normal) produced little to no thrombin in the simulations.[2] Recently, Shao et al reported on

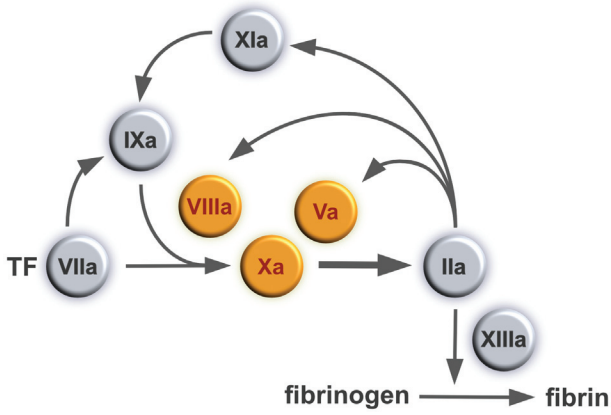

Figure 1. *Schematic representation of the coagulation cascade.* Factor V, factor VIII and factor X are indicated in color to highlight the possible competition between factor V and factor VIII for factor Xa. TF = tissue factor.

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The authors have no conflicts of interest to disclose.

HemaSphere (2020) 4:2(e355)
Citation: *HemaSphere*, 2020;4:2.
http://dx.doi.org/10.1097/HS9.0000000000000355

6 patients with F5F8D.[3] They found that the low FV in those patients (ranging from 7% to 18% of normal), accompanied by low tissue factor pathway inhibitor levels, had optimal procoagulant activity. Moreover, correcting FV levels to 100% of the normal range did not result in increased thrombin generation, but in an opposite effect. This indicates indeed that lower FV levels contribute to enhanced thrombin generation.

In light of the many therapeutic advances being made in the last years for hemophilia, mild inhibition of FV to low-normal levels could be an interesting strategy.

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