

## Compaction of fibrin clots reveals the antifibrinolytic effect of factor XIII: reply

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See also Rijken DC, Abdul S, Malfliet JMC, Leebeek FWG, De Willige S. Compaction of fibrin clots reveals the antifibrinolytic effect of factor XIII. *J Thromb Haemost* 2016; 14: 1453–61 and Gurewich V. Compaction of fibrin clots reveals the antifibrinolytic effect of factor XIII: comment. *J Thromb Haemost* 2016; DOI: 10.1111/jth.13546.

We thank Dr Gurewich [1] for his critical evaluation of the impact of our recently published article on factor XIII (FXIII) [2]. This article reports that mechanical compaction or platelet-mediated retraction of plasma clots is essential to fully reveal the antifibrinolytic effect of FXIII on tissue-type plasminogen activator (t-PA)-induced plasma clot lysis. Gurewich argues that we cannot assume that these results are applicable to endogenous fibrinolysis *in vivo*, because endogenous fibrinolysis depends not only on t-PA, but also on urokinase-type plasminogen activator (u-PA).

We fully agree that the role of u-PA in fibrin degradation is frequently underestimated or even neglected in the literature on fibrinolysis, as discussed in our review on the molecular transport of fibrinolytic components during fibrin clot lysis [3]. The relative contributions of t-PA and u-PA to fibrinolysis, however, may depend on the design of the *in vitro* test system or on the particular thrombosis model applied in experimental animals [4,5]. In addition, it is quite possible that the relative contributions of t-PA and u-PA to fibrinolysis *in vivo* vary, depending on the mechanism and site of thrombus formation, and the speed of thrombus resolution.

Although we agree that the role of u-PA in fibrin degradation is frequently underestimated, we probably estimate the relative contribution of t-PA to endogenous fibrinolysis to be greater than Gurewich does. For instance, Gurewich *et al.* [6] observed only a limited role of t-PA in the spontaneous lysis of platelet-rich plasma

clots. The source of t-PA activity in their experiments was pooled normal plasma, which contains hardly any free t-PA, owing to the rapid formation of a complex with plasminogen activator inhibitor-1 [7]. In contrast, the t-PA activity in the plasma compartment of circulating blood is much higher, because a substantial proportion of t-PA in blood is in its free form [8].

In addition, it is still a matter of dispute whether endogenous fibrinolysis in a blood vessel depends on systemic levels of plasminogen activators, on local release of t-PA by injured endothelial cells, or on both [9]. If local release of t-PA is important, then the contribution of t-PA to endogenous fibrinolysis is more substantial than studies with isolated blood or plasma suggest.

Finally, the antifibrinolytic effect of FXIII is explained by the cross-linking of  $\alpha_2$ -antiplasmin to fibrin, which prevents the plasmin inhibitor from being expelled from the clot during compaction or retraction [2]. This mechanism primarily involves  $\alpha_2$ -antiplasmin, which is able to inhibit plasmin that is generated either by t-PA or by u-PA [10]. It is therefore likely that the new mechanism is also applicable to endogenous fibrinolysis, even if u-PA is the most prominent plasminogen activator.

### Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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