Journal of Thrombosis and Haemostasis, **14**: 1–2

LETTER TO THE EDITOR

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

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To cite this article: Rijken DC, Abdul S, Malfliet JJMC, Leebeek FWG, Uitte De Willige S. Compaction of fibrin clots reveals the antifibrinolytic effect of factor XIII: reply. *J Thromb Haemost* 2016; DOI: 10.1111/jth.13544.

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 α_2-antiplasmin to fibrin, which prevents the plasmin inhibitor from being expelled from the clot during compaction or retraction [2]. This mechanism primarily involves α_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.

References

1 Gurewich V. Compaction of fibrin clots reveals the antifibrinolytic effect of factor XIII: comment. *J Thromb Haemost* 2016. doi: 10.1111/jth.13546.

2 Rijken DC, Abdul S, Malfliet JJ, Leebeek FW, Uitte de Willige S. Compaction of fibrin clots reveals the antifibrinolytic effect of factor XIII. *J Thromb Haemost* 2016; **14**: 1453–61.

3 Rijken DC, Sakharov DV. Molecular transport during fibrin clot lysis. *Fibrinolysis Proteol* 2000; **14**: 98–113.

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DOI: 10.1111/jth.13544

4 Carmeliet P, Schoonjans L, Kieckens L, Ream B, Degen J, Bronson R, De Vos R, van den Oord JJ, Collen D, Mulligan RC. Physiological consequences of loss of plasminogen activator gene function in mice. *Nature* 1994; **368**: 419–24.
5 Singh I, Burnand KG, Collins M, Luttun A, Collen D, Boelhouwer B, Smith A. Failure of thrombus to resolve in urokinase-type plasminogen activator gene-knockout mice: rescue by normal bone marrow-derived cells. *Circulation* 2003; **107**: 869–75.
6 Gurewich V, Emmons F, Pannell R. Spontaneous clot lysis in whole human plasma by endogenous tissue type and urokinase type plasminogen activators: demonstration of a promoting effect by t-PA and by platelets on urokinase. *Fibrinolysis* 1988; **2**: 143–9.
7 Rijken DC, Lijnen HR. New insights into the molecular mechanisms of the fibrinolytic system. *J Thromb Haemost* 2009; **7**: 4–13.
8 Chandler WL, Jascur ML, Henderson PJ. Measurement of different forms of tissue plasminogen activator in plasma. *Clin Chem* 2000; **46**: 38–46.
9 Emeis JJ. Local fibrinolysis. *J Thromb Haemost* 2005; **3**: 1945–6.
10 Abdul S, Leebeek FW, Rijken DC, Uitte de Willige S. Natural heterogeneity of alpha2-antiplasmin: functional and clinical consequences. *Blood* 2016; **127**: 538–45.