Acute Traumatic Coagulopathy: Thrombin Is the Driver!

To the Editor:

We read with great interest the article by Davenport *et al.*[1] about activated protein C (aPC)–induced acute trauma coagulopathy (ATC) demonstrated in trauma patients. In their study, the authors state that aPC-induced anticoagulation is not the primary mechanism of ATC and argue that aPC-induced fibrinolytic activity is the central mechanism of fibrinogen depletion in ATC. However, the evidence presented in this article does not fully support their claims due to study design and technical issues, as described below.

First, the authors measured D-dimer as one of the indicators of systemic fibrinolysis. D-dimer is a measurement of plasmin-digested fibrin (after cross-linking by activated factor XIII). No fibrinogen degradation marker was included in this study. Elevated D-dimer here indicated the massive thrombin generation, fibrin formation, and ongoing fibrin degradation. Indeed, prothrombin fragment one plus two and D-dimer levels were higher in those with hypofibrinogenemia and elevated aPC.

Second, they argue that factor V is particularly vulnerable to aPC-mediated proteolysis, whereas overall endogenous thrombin potential is maintained. These are some concerns about the interpretations. Factor V activity tends to be underestimated using a one-stage assay,[2] and the extent of its reduction was not much different from other factors, such as prothrombin (see Supplemental Digital Content 1 in Davenport *et al.*[1]). The results of endogenous thrombin potential are highly dependent on tissue factor reagents, and their failure to detect a subtle change might have been due to the use of the standard reagent (5 pM tissue factor).[3] Taken together, all of the procoagulant factors are similarly consumed in the trauma patients with the highest degree of injury.

Lastly, the timing of the evaluation of ATC is crucial in understanding its mechanisms. Their data represent a single time point in 300 subjects who were admitted within 2 h of injury.[4] Fibrin formation (*i.e.*, loss of fibrinogen) is an acute response (less than 5 to 10 min) after major injury, whereas fibrinolysis and aPC generation are subsequently observed according to the level and duration of stimulation.[5,6] It is important to point out that the authors previously demonstrated high levels of D-dimer and activated thrombin-activatable fibrinolysis inhibitor levels in the most severe case of injury.[1] Both aPC and thrombin-activatable fibrinolysis inhibitor have a short half-life *in vivo* (approximately 10 to 15 min), and they are generated most efficiently by circulating thrombin captured by thrombomodulin. The lack of fibrinolysis inhibition (*i.e.*, D-dimer reduction) by thrombin-activatable fibrinolysis inhibitor in their cohort suggests that aPC and thrombin-activatable fibrinolysis inhibitor were activated by circulating thrombin at a later point in time than fibrin formation and plasmin activation.[4]

In summary, the data presented by Davenport *et al.*[1] provide important evidence that uncontrolled thrombin generation in massive injury drives aPC levels high. Their data are in agreement with postcardiac surgical patients who demonstrate worse outcome in the presence of high thrombin generation and aPC.[7]

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Prof. Tanaka and colleagues for their interest in our article[1] and for their thoughts on the interpretation of our findings. We believe that overall they are in agreement with the main thrust of our article, which is that activation of protein C (aPC) is central to the pathogenesis of acute traumatic coagulopathy (ATC). Most of their points address

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