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Losing the forest for the trees: the complexities of fibrinolysis will never be explained with one variable alone

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Social Media Summary:

Fibrinolytic shutdown (versus hypofibrinolysis) = plasmin burst followed by diminished fibrinolysis. After thrombin and plasmin burst, fibrinolysis is inhibited, mediated by increased TAFI. #TAFI #TIC #surgscience @JuliaColemanMD @CUDeptSurg @DenverHealthMed @OhioStateSurg @mitchelljayc

We appreciate Dr. Zhu's readership of our recent work advancing the understanding of fibrinolytic shutdown. In our observational cohort study, we collected blood from trauma activation patients at a single, level-1 trauma center and then performed thrombelastography (TEG) and a variety of plasma-based assays (measuring thrombin, antithrombin, thrombin-antithrombin, thrombin-activatable fibrinolysis inhibitor [TAFI], plasminogen, antiplasmin, plasmin-antiplasmin [PAP], tissue plasminogen activator [tPA], plasminogen activator inhibitor-1 [PAI-1], and tPA-PAI-1).[1] Among our 56 patients, cluster analysis revealed that patients with diminished fibrinolysis had significantly higher PAP and TAFI, suggesting fibrinolytic shutdown is indeed characterized by an initial plasmin burst (increased PAP) followed by diminished fibrinolysis (mediated in part by TAFI).[1] We appreciate Dr. Zhu echoing the literature which has also suggested linkage between TAFI and fibrinolytic shutdown[2].

While the findings from our study are consistent, this is by no means an assertion that TAFI is the sole driver of fibrinolytic shutdown. Fibrinolysis is a prodigiously complex process that cannot be explained with any single variable. For example, while we agree with Zhu that PAI-1 is an important player, we do not believe the complexity of fibrinolytic shutdown

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can be attributed to PAI-1 alone (nor TAFI alone, as explained in our work). Moreover, in our study, the differences in PAI-1 between these two groups were not statistically significant (while we agree larger sample sizes can be helpful, please refer to the power analysis which justifies our work). Why would there be differences in TAFI, but not PAI-1, in our patients with lower fibrinolysis? This is likely explained by the physiology of the protein release cascade post-injury. PAI-1, which is produced by endothelial cells, is generally seen to rise approximately 60 minutes after injury, with a half-life of two hours[3,4]. Our previous work has documented the time dependent changes in PAI-1 following severe injury[5]. In contrast, activated TAFI, which is synthesized in the liver and circulates in plasma as a plasminogen-bound zymogen, spikes much earlier after injury and has a shorter half-life of approximately 15 minutes (can be variable depending on glycosylation of the activation peptide)[6]. Therefore, our work in question, which includes blood draws from patients immediately upon arrival to the emergency department, best characterizes diminished fibrinolysis after injury in the *immediate* setting. If we included blood draws at later intervals, we would undoubtedly observe increasing PAI-1 levels and the importance of PAI-1 in driving prolonged fibrinolytic shutdown. In fact, this has been previously demonstrated by our group and others[5,7,8].

We appreciate the opportunity to clarify the methodology and patient population used in the manuscript. This study included all trauma activation patients at a single level-1 trauma center. As part of an ongoing prospective observational cohort study, we collected blood from these patients immediately upon arrival to the hospital and then performed thrombelastography (and banked the remaining plasma, which was snap-frozen for interval investigations). We excluded patients in hyperfibrinolysis since our group previously described these patients in a similar analysis[9] and the focus of this work was on differentiating patients with diminished versus physiologic fibrinolysis. We then performed a cluster analysis, specifically a hierarchical cluster analysis. Hierarchical cluster analyses group together objects that are “close” to one another through repeated calculation of distance measures between objects and between clusters once objects begin to be grouped into clusters, yielding a dendrogram. Much to our fascination, our non-hyperfibrinolytic patients clustered by LY30 (the fibrinolysis metric on TEG), with a group with predominantly physiologic fibrinolysis and a group with predominantly fibrinolytic shutdown (or diminished fibrinolysis). The LY30 values were included in the manuscript results: Group 2 had significantly lower fibrinolysis with a median LY30 of 1.1% [IQR, 0.1–1.9%] versus 2.1% [IQR, 0.5–2.8%] in Group 1 while the median LY30 was within physiologic range, 48% of patients in Group 2 were in shutdown versus 19% in Group 1.

In closing, we fervently agree with Dr. Zhu’s sage charge to the scientific community – “more work should be done to uncover the mechanisms underlying the complex process of pathologic fibrinolysis after injury”. While TAFI is contributing to the early process of fibrinolytic shutdown, it is not the only contributor, just like PAI-1 is unlikely to be the sole contributor in the process later on. We, as scientists, must not lose the forest for the trees when trying to understand the intricacies of fibrinolysis.

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Conflicts of interest:

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