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Response to Letter to the Editor submitted by Dr. Wada and Dr. Yamakawa re: Trauma-Induced Coagulopathy: The Past, Present, and Future

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Abstract

It is with equal appreciation and enthusiasm that we have the opportunity to participate in these valuable scientific discussions with our respected colleagues Dr. Wada and Dr. Yamakawa, as we did with Dr. Gando and Dr. Otomo on their analogous disseminated-intravascular coagulation (DIC)-centric views of trauma-induced coagulopathy (TIC). We welcome and appreciate Drs Wada and Yamakawa's expounded descriptions on their areas of their expertise specific to the critical thrombin-specific biologies. We find their additions valuable to the overall framing of the state of the science and controversies that exists in TIC investigations. However, we continue to support that it would be erroneous to continue to force an inflexible view of the complex biology of TIC, thereby failing to acknowledge the various competing mechanisms and mediators described throughout the literature, including the sometimes contradictory biomarker phenotypes that are 'impaired' in TIC. In addition, much of our following response to Drs Wada and Yamakawa's letter will involve referring back to what was already addressed within the manuscript that appears to have been overlooked. However, of absolute importance, we would like to stress that TIC remains open science should therefore be regarded with open minds and without siloed opinions.

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Authorship Details

L.Z. Kornblith., H.B. Moore, and M.J. Cohen contributed equally to this letter to the editor response. This is original work, not previously published and is not under consideration of publication elsewhere. This response has been read and approved for submission to JTH by all qualified authors.

Conflict of Interests

Dr. Moore reports is a Co-Founder and Board Member with Thrombo Therapuetics Incorporated and Served on the Advisory Committee for Instrument Laboratories. Dr. Cohen and Dr. Kornblith have no actual or potential conflict of interest capable of influencing their judgment.

Thrombin

It must be clarified that the word ‘impair’ used throughout the manuscript does not impose the meaning ‘decrease’, nor ‘hypocoagulable’. Rather, we repeatedly use it in the context of altered or damaged biology. In fact, we distinctly outlined that ‘impair’ is not synonymous with ‘decrease’ or ‘hypocoagulable’, when we recognized TIC as “complex … covering a wide range of impaired clot formation and lysis, in combination with failure of vascular homeostasis and immunoactivation resulting in multiple clinical phenotypic states that can cause pathologic bleeding, clotting, organ failure, and death.” This specifically acknowledges that the impaired biology in these pathways is complex and not synonymous with hypocoagulable phenotypes of the various biomarkers studied, including thrombin. Furthermore, we clearly state within the manuscript that: “both hypocoagulable and *hypercoagulable* thrombin generation profiles have been associated with trauma with variable associations to bleeding and thromboembolic outcomes”, and that there is “variable evidence supporting both *increases* and decreases in thrombin levels” [1–3].

Additionally, we must remain cognizant of the fact that the majority of our understanding of TIC in humans is based primarily on in vitro assays lacking flow and endothelium, both critical to vascular biology. Specifically, thrombin generation is usually measured in plasma (platelet poor or platelet rich) by exogenous addition of tissue factor and phospholipids to imitate vessel wall damage [4]. In this setting, it remains true that altered thrombin generation profiles consistent with both hypocoagulable and hypercoagulable states following injury have been identified, with variable associations with bleeding and venous thromboembolic outcomes [2, 3, 5–7]. Whole blood thrombin generation assays allow for the presence of erythrocytes and other cells, and may have the potential to allow for a better assessment of thrombin generation [8]. Yet, we cannot ignore the fact that thrombin generation exists on endothelial cells, which do not exist in these assays. This is of importance when considering the biology that thrombomodulin binds thrombin with affinity at the endothelial cell surface [9]. In overwhelming tissue injury and shock, it is biologically supported that resultant early enhanced generation of activated factors including thrombin leads to formation of complexes of thrombin-thrombomodulin from thrombomodulin expressed on endothelial cells, with consequent activation of protein C, and ensuing inactivation of Factor Va, Factor VIIIa, and plasminogen activator inhibitor-1. This may be followed by decreasing thrombin generation via reduced fibrinogen utilization and enhanced fibrinolysis, following inhibition of Factor Va and VIIIa [10–12]. Furthermore, it should be noted that the addition of thrombomodulin in thrombin generation assays can prolong the lag time and decrease the peak and endogenous-thrombin potential [13, 14], which may contribute to the various thrombin generation profiles seen following injury. In the interest of remaining open minded ourselves, we recognize that soluble thrombomodulin is less active than membrane bound thrombomodulin, and therefore relevance of measures of increased thrombomodulin and resultant effects in trauma remain under debate. Additionally, it should be noted that thrombin generation assays are sensitive to elevated antithrombin levels because of the potential to degrade thrombin, and factors IX, X, XI, XII [15, 16].

Importantly, Drs Wada and Yamakawa did not balance their citation of Dr. Cardenas’ [3] interpretations of the reduced thrombin-generating capacity found in 17% of their injured

cohort. In fact, Dr. Cardenas and colleagues recognized that there were multiple hypotheses for this, not solely explained by a loss of coagulation factors through massive bleeding and hemodilution. They highlighted their acknowledgement that the finding could also be explained by: 1) activation of anticoagulants or inhibitors [16], or 2) endothelial glycocalyx shedding (including glycosaminoglycans and heparan sulfates) causing an auto-anticoagulating effect (via modification of thrombomodulin with increased affinity for thrombin [14] or via heparan sulfate cofactor activity increasing thrombin inhibition via antithrombin [17]). Simplifying this concept to "hypercoagulability within the vessel and hypocoagulability outside the vessel namely at the site of injury due to consumption coagulopathy" is supportive of the DIC-centric view and again ignores the diversity of tissue injury and shock states in the setting of trauma, with resultant manifestations of a spectrum of phenotypes of coagulation and inflammation aberrancies that include mixed phenotypes of hypo and hypercoagulability [18]. It also ignores the importance of the Hoffman and Monroe proposed 'cell-based model of hemostasis'[19], regulated by cell surfaces rather than enzymatic protein and protease reactions and consumptive pathologies alone, and the robust data generated by independent groups of investigators using hierarchical clustering analyses to identify heterogeneity in phenotypes of clot formation and lysis in trauma populations [20–22]. Specific, these clustering analyses have confirmed that not all phenotypes of TIC can be explained by clotting factor changes or solely mediated by thrombin.

Endothelial markers and antithrombin

We are in agreement that antithrombin decreases as it neutralizes thrombin via a stoichiometric complexing of thrombin-antithrombin in which thrombin loses irreversibly its enzymatic activity, though the mechanisms of this remains of debate [23].

TIC and DIC

As we have previously extensively responded to Drs Gando and Otomo on their DIC-centric concept of TIC, we will not belabor the points that we have already made. However, it must be noted that in Drs Wada and Yamakawa's reactionary statement that "DIC should not be differentiated from TIC", they have significantly contradicted themselves [24, 25]. In fact, they have both authored publications this year in which they propose, in agreement with the other investigators of the Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis, that DIC is a final common event for separate and heterogenous coagulopathies that include: sepsis coagulopathy, cancer coagulopathy, pregnancy-related coagulopathy, hematologic malignancy coagulopathy, and notably trauma coagulopathy [24, 25]. We would summarize these points with our original statement in our review that "best evidence at this time suggests that … TIC encompasses the criteria of DIC." We would like to continue to suggest that it would be detrimental to our patients and to scientific advancements for our communities to ignore the large emerging fundamental, mechanistic, physiologic, and clinical biologies that are evidenced in TIC and cannot be solely explained by the final common pathway of DIC.

In closure, we do not believe any of the points shared by Drs Wada and Yamakawa are ‘fatal flaws’, but rather differences of opinions in a shared evolving field that is open science with unidentified and undiscovered advances ahead of us. It would be more progressive to view differences in the published scientific findings as valuable advances, and in fact we believe there remains mutual assent between our viewpoints on: 1) thrombin profiles, and 2) the existence of DIC in the end-stage of certain TIC phenotypes. We will continue to strongly disagree in the statement made in Dr Wada and Yamakawas’ table that “DIC should not be differentiated from TIC”, particularly as our overarching goal should remain to identify targeted and appropriate treatments of the diverse phenotypes of coagulopathies following injury to prevent progression to DIC.

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