

# Computational Model for Hyperfibrinolytic Onset of Acute Traumatic Coagulopathy

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**Abstract**—The onset of acute traumatic coagulopathy in trauma patients exacerbates hemorrhaging and dramatically increases mortality. The disease is characterized by increased localized bleeding, and the mechanism for its onset is not yet known. We propose that the fibrinolytic response, specifically the release of tissue-plasminogen activator (t-PA), within vessels of different sizes leads to a variable susceptibility to local coagulopathy through hyperfibrinolysis which can explain many of the clinical observations in the early stages from severely injured coagulopathic patients. We use a partial differential equation model to examine the consequences of vessel geometry and extent of injury on fibrinolysis profiles. In addition, we simulate the efficacy of tranexamic acid treatment on coagulopathy initiated through endothelial t-PA release, and are able to reproduce the time-sensitive nature of the efficacy of this treatment as observed in clinical studies.

**Keywords**—Coagulopathy, Trauma, Computational medicine, Partial differential equations, Fibrinolysis, Tissue-plasminogen activator, Tranexamic acid.

## INTRODUCTION

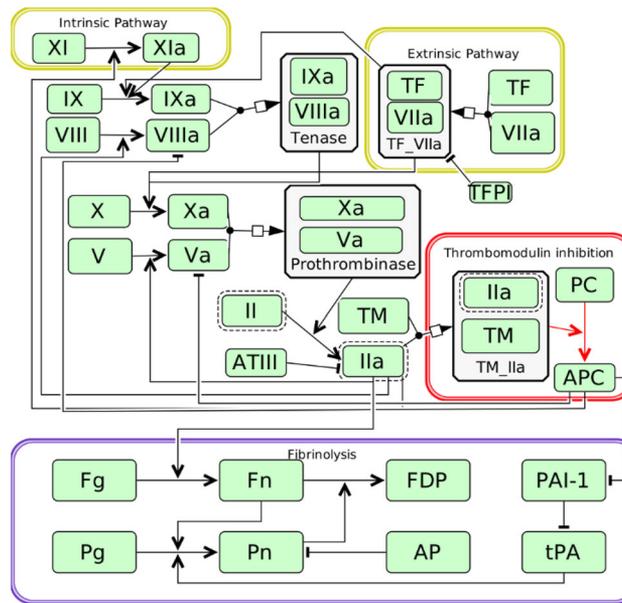
Severe trauma often induces a coagulopathic state known as Acute Traumatic Coagulopathy (ATC) that manifests in increased bleeding and resultant mortality.<sup>4</sup> The mechanisms underlying ATC are not yet fully understood. In this paper, we propose a mechanism that can produce some of the observed phenotypes associated with the early stages of ATC, and investi-

gate its viability and implications *via* a computational model.

The coagulation process is a complex network of reactions (Fig. 1) in which an over-expression or deficiency in many different proteins could lead to the hemorrhaging exhibited by ATC patients. There exists a very well-studied network of blood protein interactions from *in vitro* studies<sup>5,6,17</sup> and recent *in vivo* analysis of trauma patient data.<sup>8,35</sup> Despite this, the mechanism(s) that best explain ATC are still hotly debated.<sup>20,32,33</sup> Some of these mechanisms include factor consumption,<sup>34</sup> hemodilution,<sup>37</sup> increased protein C activation,<sup>3</sup> and hyperfibrinolysis.<sup>8</sup> In addition, there are also many who assert that the condition itself is non-uniform and must be treated on a case-by-case basis.<sup>36</sup> Some of the confounding characteristics of the disease include persistence despite massive transfusion,<sup>35</sup> tissue-specific coagulation profiles,<sup>24</sup> a strong correlation with shock<sup>10</sup> and the time sensitive efficacy of treatments such as tranexamic acid (TXA).<sup>31</sup>

To study ATC within a mechanistic framework, we introduce a partial differential equation model to simulate *in vivo* coagulation in blood vessels. This model builds on well-established reaction models and incorporates them into a spatial setting, which allows us to explore conditions that could provide a mechanistic explanation for the phenomena present in ATC. There are two primary modes for poor coagulation: (1) poor clot formation,<sup>37</sup> and (2) excessive clot lysis.<sup>8,29</sup> While previous computational studies on ATC have performed detailed analysis on clot formation through coagulation factor depletion and dilution,<sup>15,26–28</sup> the

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**FIGURE 1. Simplified Diagram of Coagulation-Fibrinolysis System.** Clotting factors become activated *via* the intrinsic and/or extrinsic pathway, which culminate in the production of thrombin (IIa). Thrombin then converts fibrinogen (Fg) to fibrin (Fn). The clot formed from fibrin is degraded by plasmin (Pn) which is converted from plasminogen (Pg) by tissue-plasminogen activator (t-PA). Additional notation: Tissue Factor (TF), Anti-Thrombin III (ATIII), Tissue Factor Plasma Inhibitor (TFPI), Thrombomodulin (TM), Thrombin (IIa), Protein C (PC), Activated Protein C (APC), Fibrin Degradation Products (FDP), Plasminogen Activator Inhibitor-1 (PAI-1),  $\alpha$ 2-antiplasmin (AP), Roman numerals represent the corresponding coagulation factors, and the letter “a” denotes that the factor is activated.

same level of attention has not been given to modeling ATC through hyperfibrinolysis. These studies astutely demonstrate the deleterious effects of dilution-inducing therapies but they do not address mechanisms of trauma-induced coagulopathy prior to resuscitation. While it is likely that ATC is the result of both modes acting in tandem, we posit that excessive clot lysis is the driving mechanism behind many of the clinical phenotypes exhibited by patients with ATC.

To understand the causes of excessive lysis, our model focuses on tissue-plasminogen activator (t-PA), one of the primary proteins involved in fibrinolysis. It converts the inactive zymogen plasminogen into the active serine protease plasmin, which breaks down fibrin clots.<sup>43</sup> T-PA in plasma comes almost exclusively from endothelial cells,<sup>41</sup> where it is stored in large quantities.<sup>12,40</sup> If the vessel walls sustain a large injury, the ruptured endothelial cells can release enough t-PA into the local plasma to trigger hyperfibrinolysis. Using our model, we show that parts of the vasculature with higher surface-area-to-volume ratios are more susceptible to the hypocoagulable state exhibited in ATC (Fig. 2).

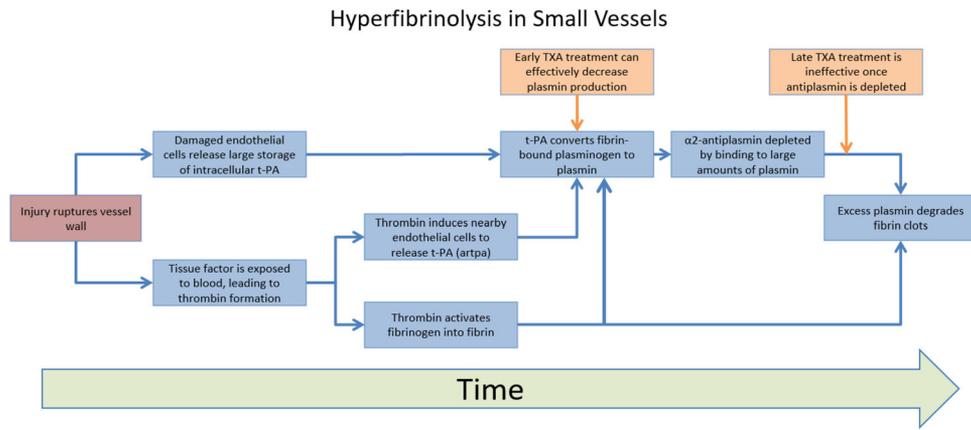
In our study, we also examine how our model of ATC would respond to treatment by tranexamic acid, an anti-fibrinolytic used to reduce bleeding in surgery, trauma and menstruation. The use of TXA for trauma has been somewhat controversial as it appears that the

treatment improves patient outlook if administered early but worsens outlook if administered after 3 h post-admission.<sup>31</sup> Using excessive t-PA to simulate the bleeding phenotypes of ATC, we were able to qualitatively reproduce the time-sensitive nature of the efficacy of TXA treatment reported in clinical trials.<sup>31</sup>

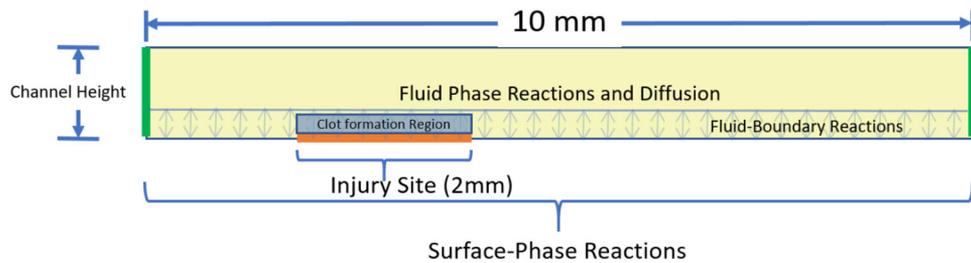
## MATERIALS AND METHODS

### *Model Construction*

We constructed a 2D rectangular domain (Fig. 3) to represent our damaged blood vessel. The width of the domain is 10 mm, and the height is varied between 10, 25, 50 and 100  $\mu$ m, which covers the range of diameters in venules. In this domain, we model the vessel as a reaction–diffusion partial differential equation (PDE) system. The domain is split into two parts, the fluid domain representing the lumen of the blood vessel and the surface domain representing the vessel wall. The simulations reported in this paper were undertaken with no convective flow (reaction and diffusion only). According to a recent study of patient microcirculation, heavy endothelial damage and shock is associated with poor flow in the microcirculation.<sup>30</sup> Since we are particularly interested in situations in which the patient has sustained a massive amount of injury, we assume a system without flow. This allows us to focus on the



**FIGURE 2. Simplified Sequence of Events Leading to Local Hyperfibrinolysis.** After injury, the tissue plasminogen activator (t-PA) contents of ruptured endothelial cells are released into the surrounding fluid. In small vessels, this release results in a disproportionately high concentration of t-PA because of the high surface-area-to-volume ratio, leading to excessive plasmin formation. If antiplasmin becomes depleted from binding to large amounts of plasmin, the excess plasmin can break down the fibrin clot, resulting in hyperfibrinolysis. Tranexamic Acid (TXA) can delay or prevent hyperfibrinolysis if provided early by decreasing the effective concentration of plasminogen, but has little effect if administered after antiplasmin has been depleted. Conditions can be exacerbated under conditions of shock, in which flow is impaired and/or the vessel is constricted.



**FIGURE 3. The Computational Model.** The model is separated into two domains: the plasma containing fluid species that undergo fluid-phase reactions and diffusion, and the vessel surface with surface species that undergo surface-phase reactions in which surface species react with each other. The injury site is a 2 mm region on the surface containing additional surface species to represent the injury. There are also fluid-surface reactions at the interface which allow the two domains to exchange species. The results reported in this paper are the average concentrations in a  $2\text{ mm} \times 10\text{ }\mu\text{m}$  area above the injury site, which we designate as the clot formation region. The height of the channel varies between 10, 25, 50 and  $100\text{ }\mu\text{m}$ .

effects of the release of endothelial contents into the injury.

The bottom boundary represents the endothelial surface, including the site of injury. The single layer of nodes in this region represents our surface domain, which contains reactions between surface species and exchanges between the surface and the fluid, which we model by introducing positive and negative fluxes in and out of the boundary to simulate species being produced by or bound to the endothelium.

We took the injury site to be 20% (2 mm) of the length of the channel, starting 3 mm into the channel. This portion of the bottom surface also contains tissue-factor, which is exposed to plasma upon injury, as well as platelet binding sites (PBS), the sites that coagulation factors bind to once platelets are activated and attached to the injury surface. To compare results between different sized vessels, we designate a  $2\text{ mm} \times 10\text{ }\mu\text{m}$  area above the injury site as the *clot*

*formation region*. The mean concentrations of the nodes of this area are reported in the results.

#### Model of Fibrin Formation and Degradation

The network of reactions used in our model includes the reactions for thrombin generation, fibrin formation and fibrin degradation in plasma. These reactions and their associated rate constants are taken from models based on *in vitro* experimental results, and most of them can be found in previously published ODE models.<sup>5,17,28</sup> These reactions are categorized into three types: (1) fluid-phase, (2) surface-phase and (3) fluid-surface interactions. The full list of reactions can be found in the Supplemental Information (SI). To model fibrin deposition and polymerization, restrict fibrin species from diffusion after formation. As a result, concentrations of fibrin near the injury site can exceed the initial concentration of fibrinogen. This also results

in simulations in larger vessels which have more fibrinogen molecules to accumulate higher concentrations of fibrin at the injury site, compared to the simulations with smaller vessels.

#### *T-PA Release from Endothelial Cells*

In addition to these reactions, we model t-PA release from the endothelial cells in the vessel wall with a boundary flux reaction, in which t-PA in the surface nodes is converted into fluid-phase t-PA. We model three types of endothelial t-PA release: (1) constitutive release, (2) acute release, and (3) intracellular release. Constitutive release is the slow, steady release from endothelial cells that establishes the basal concentration of t-PA together with the basal concentration of plasminogen activator inhibitor-1 (PAI-1). The main contributors to the region-specific susceptibility to hyperfibrinolysis are acute release and intracellular release. Acute release refers to the endothelial cell response of releasing t-PA in the presence of thrombin, and intracellular release refers to intracellular t-PA storage that can be dumped into the plasma instantaneously when cells rupture from injury.<sup>40</sup> Both these sources are much more rapid than constitutive release, and the magnitude of the increase in t-PA concentration scales inversely with vessel diameter because surface-area-to-volume ratio also scales inversely with vessel diameter.

#### *PAI-1 Release from Platelets*

To regulate fibrinolysis, there are two local anti-fibrinolytic responses at the injury site, one from endothelial cells and one from platelets. When exposed to inflammatory markers, endothelial cells can be induced to secrete PAI-1, which is the primary inhibitor to t-PA. However, trauma-induced increases in PAI-1 secretion in endothelial cells over the basal rate is slower than the t-PA response as PAI-1 is not stored in significant amounts in endothelial cells and therefore must be synthesized prior to release.<sup>42</sup> For this reason, this response was not included in our model.

However, we do account for PAI-1 that is rapidly released from thrombin-activated platelets.<sup>19</sup> To account for the potential effects of PAI-1 released from platelets, we used a value of  $266 \text{ pM m}^{-2}$  for the surface concentration of PAI-1 stored at the injury site. This approximated value was obtained using the maximum platelet concentration in a spatial model from Fogelson,<sup>23</sup> and measured levels of PAI-1 release in thrombin stimulated platelets were taken from Huebner.<sup>19</sup> This allows us to obtain an upper bound on the amount of PAI-1 which can be released at the injury site. However, since the time resolution in the

measurements in Huebner<sup>19</sup> was too coarse to obtain an accurate rate of release, we were only able to obtain a crude model that roughly simulates the reported results. Therefore, these reactions were only used to gain an understanding of the potential effects of platelet PAI-1 rather than of incorporating them into all other simulations.

#### *Model for TXA Treatment*

We simulated the effects of two methods of treatment: (1) Tranexamic Acid (TXA) and (2)  $\alpha$ 2-Antiplasmin (AP or antiplasmin) replenishment. TXA binds to plasminogen, preventing the binding of plasminogen to fibrin. When plasminogen cannot bind to fibrin, the activation of plasmin by t-PA is drastically impaired.<sup>18</sup> By inhibiting this binding, TXA effectively lowers the concentration of plasminogen in the system. We calculated that the standard dosage of TXA binds to roughly 90% of the plasminogen in the body based on pharmacokinetic properties in McCormack<sup>25</sup> If administered intravenously, plasma concentrations can be maintained at this level for up to 5–6 h.<sup>25</sup> Thus, to model TXA treatment, we instantaneously reduce the concentration of plasminogen to 10% of its current concentration in the system at various time points. Since TXA does not interact with other species in the model, rather than incorporating the binding kinetics of TXA as others have done,<sup>38</sup> modeling the downstream effects of TXA treatment accomplishes the same task at a lower computation cost. To model antiplasmin replenishment treatment, we instantaneously increase the concentration of antiplasmin in the body by  $1 \mu\text{M}$  at various time points. Additional details regarding the details of the model can be found in the Supplemental Information.

## RESULTS

### *Fibrinolysis Studies*

We ran our simulations with and without intracellular t-PA release, to show the potential impact of the release of the endothelial storage of t-PA in triggering ATC. The magnitude of the impact depends on the extent of the injury. In our model, the simulations that included intracellular t-PA release used injury intensities of 25, 50, 75 and 100%, referring to the initial concentration of intracellular t-PA released if that percentage of the cells at the injury site were injured. The initial surface concentrations are held constant when comparing channels of different sizes, but result in different volumetric concentrations due to the differences in the surface-area-to-volume ratio. We re-

duce the rate of constitutive release and acute release by the same amount to account for the reduced number of cells.

### Effects of Vessel Size and Injury

We examined fibrin concentrations in vessels of differing diameters, in response to injury. In our simulations without intracellular t-PA release (Fig. 4a), we see that the size of the vessel has two effects on fibrin concentration. First, the peak fibrin concentration is lower in the smaller vessels. This is due to the larger control volumes in large vessels that allow for more fibrin to accumulate, as there is more fibrinogen which can diffuse toward the injury site, while the fibrin formed at the injury site cannot diffuse out as fibrin species are restricted from diffusion in our model. Secondly, in the 25, 50 and 100  $\mu\text{m}$  channels, the degradation is very slow, suggesting a very stable clot. However, in the 10  $\mu\text{m}$  channel, we see that fibrin degradation starts to accelerate. The lower peak concentration and faster fibrinolysis suggest that smaller channels will be more susceptible to hyperfibrinolysis. When we incorporate an intracellular t-PA release from a 50% injury, fibrinolysis is increased in all vessels but the effect is far more pronounced in the two smaller vessels (Fig. 4b).

We find that the rate at which fibrinolysis increases is more sensitive to the amount of t-PA released from the injury site in the smaller vessels compared to larger vessels (Fig. 5). This suggests that vessels of different size have a different threshold of t-PA to trigger hyperfibrinolysis. Once the t-PA threshold for hyperfibrinolysis has been exceeded, further t-PA exposure can exacerbate the situation. We also find that if we include the release of PAI-1 from platelets in the

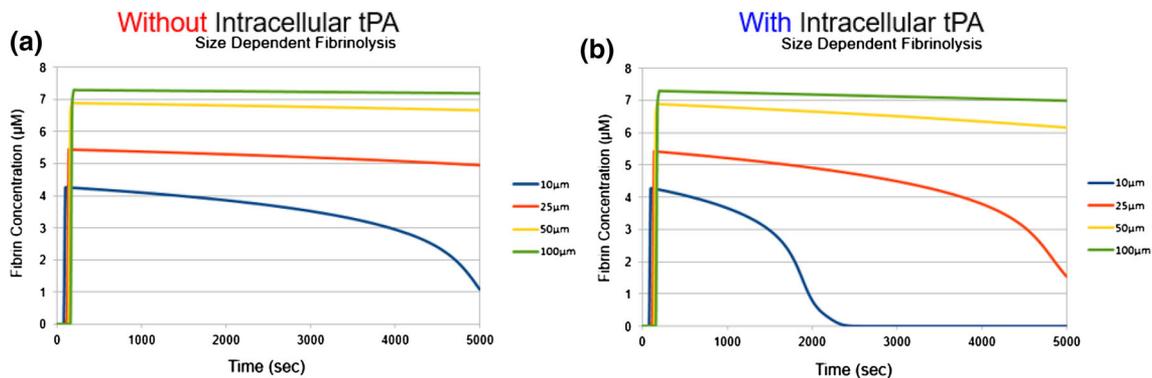
model, it can delay the onset of hyperfibrinolysis, possibly increasing the t-PA threshold, but has little potential to prevent it (Fig. 6). This demonstrates that, although in theory a localized release of PAI-1 could offset the localized release of t-PA, the difference in magnitude of available t-PA and PAI-1 make this possible only if the amount of t-PA released during injury is close to its threshold.

The mechanism behind the acceleration of fibrinolysis in the smaller vessels is apparent when we examine the concentrations of plasmin and plasmin-antiplasmin (PAP) complex (Fig. 7). The concentration of PAP approaches 1  $\mu\text{M}$  (the initial concentration of antiplasmin) around the time that fibrinolysis starts to accelerate. This depletion of antiplasmin causes plasmin generation to go unregulated, which results in accelerated fibrin degradation.

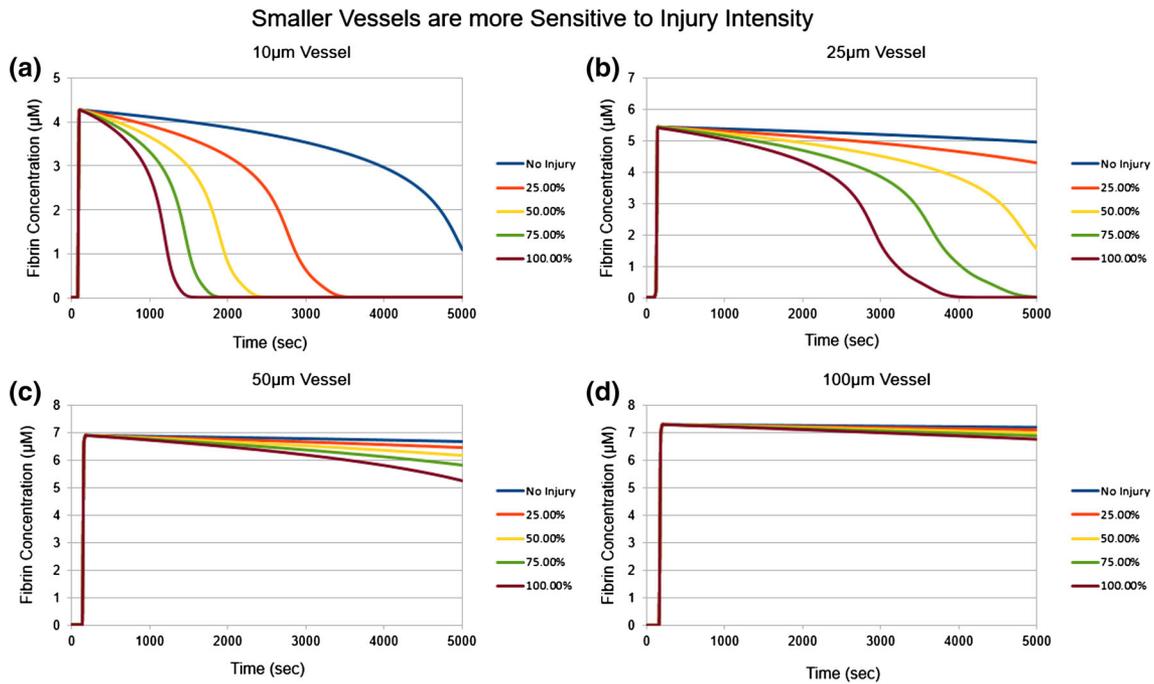
### TXA and Antiplasmin Studies

We use the 25  $\mu\text{m}$  vessel with 100% injury simulation as our surrogate for coagulopathic conditions because it allows us to apply the treatments at different stages of ATC in the 5000 s computation window. With that, we simulated the effectiveness of TXA treatment (Fig. 8a). We found that if TXA is provided before fibrinolysis starts to accelerate, it can effectively re-stabilize the rate of fibrinolysis. However, the efficacy of TXA treatment falls off tremendously when treatment is provided after hyperfibrinolysis sets in. One discrepancy between these results and the clinical observations of the CRASH-2 studies<sup>31</sup> is that not only did TXA become ineffective when administered late, it also *increased* hemorrhaging. This is likely related to the unmodeled dynamics between TXA-bound plas-

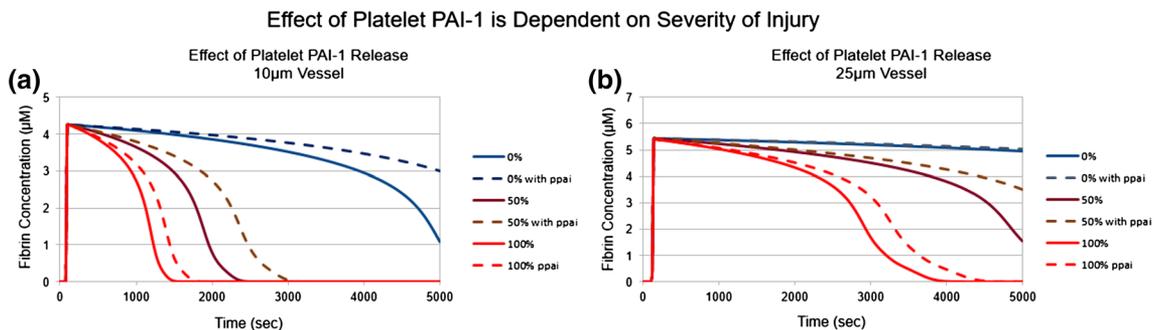
### Damaged Endothelial Cells Provide the Additional tPA Necessary to Induce Hyperfibrinolysis in Small Vessels



**FIGURE 4.** Simulations of Fibrin Concentrations in Various Sized Vessels in the (a) Absence and (b) Presence of intracellular t-PA release. (a) Fibrin concentrations are very stable for the 25, 50, and 100  $\mu\text{m}$  vessels under both conditions. In the case of the 10  $\mu\text{m}$  simulation, fibrin degradation accelerates rapidly toward the end. (b) When intracellular t-PA from a 50% injury is added, there is little effect on fibrinolysis for the 50 and 100  $\mu\text{m}$  vessels, but there is a very pronounced effect for the 10 and 25  $\mu\text{m}$  vessels.



**FIGURE 5. Simulations of the Effects of Injury Intensity on the Rate of Fibrinolysis on Vessels of Height: (a) 10  $\mu\text{m}$  (b) 25  $\mu\text{m}$  (c) 50  $\mu\text{m}$  and (d) 100  $\mu\text{m}$ .** (a) In the 10  $\mu\text{m}$  vessel, the rate of fibrinolysis is very sensitive to the level of injury, however it seems that hyperfibrinolysis has begun for all injury levels. (b) In the 25  $\mu\text{m}$  vessel, we find that the range of t-PA release in our model includes the critical point for which at low injury levels fibrinolysis may be stable, but at higher levels it can switch to becoming hyperfibrinolytic. In the larger vessels (c) and (d), we find that the rate of fibrinolysis is not very sensitive to the level of injury, probably because the concentration of t-PA in the system has not reached the threshold necessary to induce hyperfibrinolysis.



**FIGURE 6. Simulations of Fibrinolysis in the Presence and Absence of Platelet PAI-1 Release in (a) 10  $\mu\text{m}$  and (b) 25  $\mu\text{m}$  Vessels.** In both vessels, we see that platelet PAI-1 release reduces the effective amount of t-PA released from the injury. This delays the onset of hyperfibrinolysis but does not prevent it from occurring.

minogen and urokinase-type plasminogen activator (u-PA) in which TXA induces a shape change in plasminogen, making it a better substrate for uPA.<sup>16</sup>

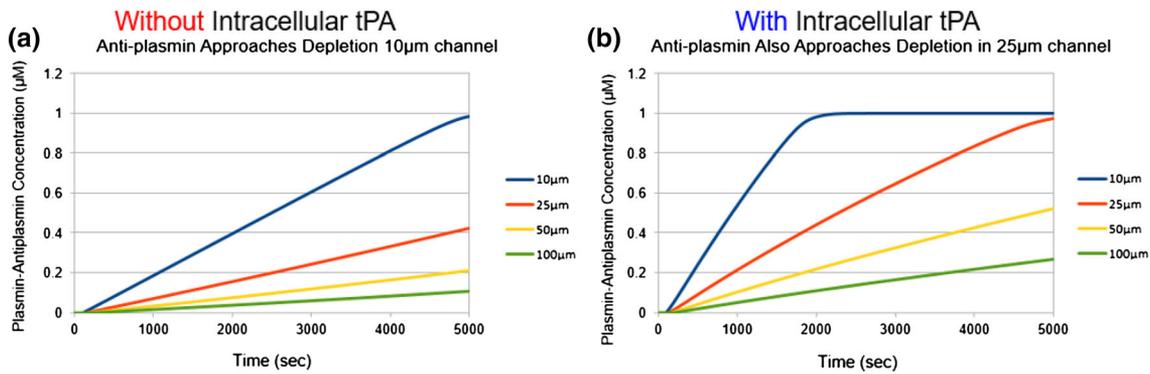
Since we know that antiplasmin depletion is the reason for accelerated fibrinolysis, we also simulated antiplasmin replenishment as a treatment to compare to TXA treatment (Fig. 8b). We see that TXA treatment is more effective than antiplasmin treatment early, but antiplasmin treatment is more effective than TXA treatment at later treatment times. Since neither treatment could restore fibrin concentration (i.e.; could only slow down the rate of fibrin degradation), it

is likely that fibrinogen replenishment is necessary in conjunction with these anti-fibrinolytic treatments.

## DISCUSSION

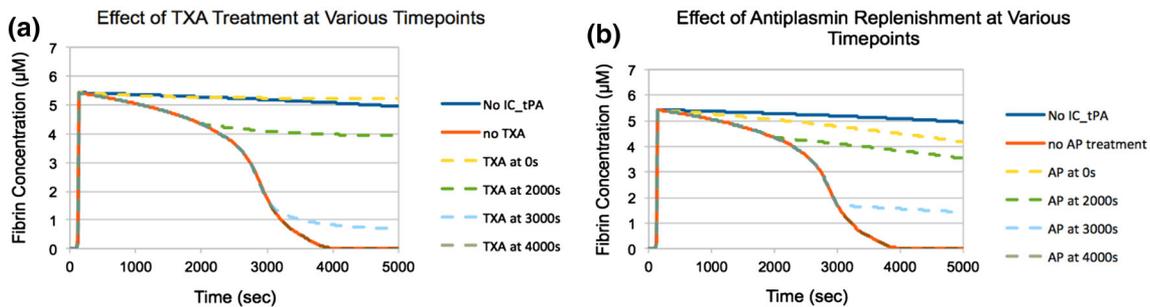
Our model provides a mechanism in which excessive clot lysis can play a substantial, and possibly dominant role in producing many of the phenotypes seen in the early phase of ATC. While correlation studies linking trauma mortality to low levels of various coagulation factors, fibrinogen, high levels of d-dimer, and high

Damaged Endothelial Cells Provide the Additional tPA Necessary to Induce Hyperfibrinolysis in Small Vessels



**FIGURE 7. Simulations of Plasmin-antiplasmin (PAP) Complex Concentrations in the (a) Absence and (b) Presence of intracellular t-PA release. (a) In the 10 µm vessel, the concentration of PAP approaches 1 µM, indicating that the antiplasmin is approaching depletion (initial concentration 1 µM). In contrast, in the 25, 50, and 100 µm vessels, the PAP concentration increases far more slowly. (b) The presence of intracellular t-PA release speeds up the rate at which PAP is formed in all vessels, and reaches saturation in the 10 µm vessel. The concentration of PAP approaches saturation in the 25 µm vessel and that’s why we see fibrinolysis accelerate in Fig. 4b. This explains why the additional t-PA from intracellular release has a greater impact on fibrin degradation in the 10 and 25 µm simulations.**

Model Predicts Time-Dependent Efficacy of Anti-fibrinolytic Treatment



**FIGURE 8. Simulations of Fibrinolysis Profiles when (a) TXA and (b) Antiplasmin (AP) Treatment is applied to a 25 µm vessel with 100% injury at Various Time Points. (a) Similar to reported clinical studies, the efficacy of TXA to slow down hyperfibrinolysis is very sensitive to the time at which it is administered. If applied early it is very effective, however if provided late, it can have little or no effect. (b) On the other hand, antiplasmin treatment is slightly less effective when given early but is better at slowing down the rate of fibrinolysis if provided later. However, neither treatment can restore the lost clot strength once fibrin generation has ceased.**

levels of t-PA<sup>33</sup> are often attributed as evidence for factor consumption and/or hemodilution leading to poor clot formation, a depletion of fibrinogen and elevated levels of d-dimer can be indicative of successful fibrin formation and subsequent excessive fibrinolysis. Although factor consumption and/or dilution will undoubtedly impact the overall coagulation profiles of trauma patients, it cannot explain the often simultaneous hypo and hypercoagulable profiles exhibited in severe trauma,<sup>21</sup> since factor consumption and dilution are systemic phenomena.

Furthermore, one study found that the major indicator of trauma-induced coagulopathy was high circulating levels of t-PA.<sup>8</sup> Interestingly, the authors were able to accentuate the difference in the clotting profiles

of healthy and coagulopathic patients with the addition of 1 nM extra t-PA in their Thromboelastogram (TEG) assays. Our results show that both the additional t-PA needed to induce hyperfibrinolysis and the region-specific hemostatic tendencies in coagulopathy can be explained by differential susceptibility to hyperfibrinolysis from a local endothelial t-PA release that is determined by vessel size and local injury intensity.

This mechanism allows for the excessive hemorrhaging brought on by accelerated fibrinolysis in some regions, while other regions can exhibit normal and possibly even excessive coagulation. This mechanism can also explain why hemorrhagic shock is often a predictor for ATC.<sup>3</sup> During hemorrhagic shock, the body redistributes blood flow away from “luxury”

organs *via* vasoconstriction to preserve function in the vital organs.<sup>39</sup> This causes an even higher surface-area-to-volume ratio and impaired blood flow in the portions of the vasculature, particularly in the microvasculature<sup>30</sup> around these “luxury organs”, thus further exacerbating the region’s susceptibility to hyperfibrinolysis. In addition, the connection between ATC and shock is often attributed to an increase in the activation of protein C and its subsequent inhibition of PAI-1.<sup>40</sup> While this mechanism cannot trigger hyperfibrinolysis by itself, it can amplify the effects of a large local influx of t-PA.

One major obstacle to understanding ATC comes from the methods used to diagnose the condition.<sup>7</sup> The current methodology uses blood that is often drawn from regions away from the injury site. Since coagulation is a local phenomenon, we do not expect blood composition to be uniform across the body, especially in cases of severe trauma in which flow is drastically impaired. This makes hyperfibrinolysis difficult to detect, resulting in a debate on the frequency of the condition and the appropriate metrics for identifying hyperfibrinolysis.<sup>11,20,32,33</sup> In addition, experiments investigating this should attempt to mimic the local conditions inside an injured vessel. An important step toward this goal would be to quantify the amount of t-PA in endothelial cells *in vivo*. Once this is established, appropriate amounts of t-PA and other endothelial proteins can be added to the blood to simulate the fibrinolysis inside different sized vessels.

Our model focuses on the concentrations of blood proteins to find a mechanism for ATC, as many of the competing hypotheses are based on protein interactions. Thus, it does not capture some important dynamics that other models may include, such as the complex dynamic flow during coagulation,<sup>13,23</sup> platelet dynamics,<sup>9</sup> as well as complex mechanisms for fibrin degradation.<sup>1,2</sup> Our model also does not capture the contribution of antiplasmin in stabilizing clots against fibrinolysis<sup>14</sup> which would further emphasize the pathological consequences of antiplasmin depletion. Spatial models are far more computationally costly than well-mixed models; because of this, the previously mentioned spatial models often use reduced-order reaction systems and choose to focus on other details.

Using our focused approach on reaction mechanisms, we can observe the effect of endothelial t-PA release in isolation to establish its importance. This mechanism can then be incorporated into more detailed models to answer more complex question on topics such as the effects of endothelial t-PA release on geometry of the clot during lysis. If extended to a model with flow, we must caution that the boundary conditions must be carefully chosen to reflect severe trauma. Most of the coagulation models with flow

simulate an open-flow scenario in which the concentrations of the inflowing plasma are fixed, which is not the case in coagulopathic patients.

Besides the region-specific coagulation profiles, our mechanistic explanation for ATC is consistent with other clinical observations as well. Hemorrhaging produced by this mechanism responds to TXA treatment in a similar time sensitive fashion as reported in clinical studies.<sup>31</sup> This phenomena cannot be explained by mechanisms of ATC associated with poor clot formation, as TXA does not improve the formation of clots, but instead it acts to slow down clot lysis.<sup>25</sup> Moreover, since the source of the increased fibrinolytic activity derives from the endothelium and not the plasma, our model is able to explain the limited effectiveness of transfusions to restore proper coagulation. Even if plasma concentrations are restored through transfusion, the local t-PA concentration from the damaged endothelium at these injury sites will eventually deplete the antiplasmin in the local blood, leading to post-resuscitation hemorrhaging.

In addition, we were able to compare the effects of two different treatments for ATC. TXA treatment represents treatments that inhibit the zymogen, plasminogen, while antiplasmin treatments, such as the drug aprotinin (Tryasol),<sup>22</sup> inhibit the serine protease plasmin. Because these treatments use a different mechanism to inhibit fibrinolysis, the results can be different depending on the time at which the treatment is administered. With a mechanistic understanding of this disease, we can explore different options for treatment.

## ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (<https://doi.org/10.1007/s10439-018-2031-9>) contains supplementary material, which is available to authorized users.

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