Editor—A key aspect of improving care for patients suffering from life-threatening haemorrhage as a result of trauma or major perioperative bleeding, is a better understanding of mechanisms involved in coagulation and haemostasis around the injury site. Prevailing models of coagulation, like the cascade or waterfall model, are limited, describing haemostasis as a set of complex interactions between coagulation factors and other blood components, but not taking into account the context in which haemostasis takes place at the injury site. However, decades ago it was established that other mechanisms, such as vasoconstriction and the formation of extraluminal soft clots, are key mechanisms involved in the initiation of haemostasis in ruptured vessels (see Table 1 for a selection of evidence from relevant studies).

The initial experiments hinting at the importance of injury-site vasoconstriction and formation of extraluminal clots are more than 50 yr old. Although we recently demonstrated the importance of injury site clot formation in haemostasis using ultrasound elastography (see also Table 1), it seems that these mechanisms, despite their obvious importance, have been largely overlooked in recent research. We believe that the lack of appropriate models may be the main reason why these mechanisms have not received more attention. One method of particular interest for studying thrombus formation in vivo is intravital confocal microscopy. Advances in real-time live confocal microscopy have made it possible to visualize thrombus formation as it occurs in vivo. Until now, this method has been helpful for increasing our understanding of certain aspects of coagulation, such as the interaction between fibrin generation and platelet deposition during the process of thrombus formation. However, a major shortcoming of current in vivo models is that intraluminal thrombus formation is generally induced with ferric chloride injections or laser beams targeted at blood vessels. The fact that vessels are not cut and local blood flow and pressure are not also considered, means it is impossible to investigate haemostatic mechanisms specifically involved in perioperative bleeding.

We believe that coagulation following cut-vessel injury differs significantly from what is observed with present intravital thrombus models, where the thrombus forms under normal flow conditions. Conversely, in cut vessels, the thrombus instead forms in the extraluminal space. We therefore believe that an intravital model for confocal microscopic assessment of cut-vessel outflow is needed to study these mechanisms in greater detail. Such a model would allow for a thorough investigation of mechanisms specific to perioperative bleeding, such as injury-site vasoconstriction and formation of extraluminal soft clots described previously. Challenges in developing this model include the creation and validation of molecular tools for visualizing fibrin formation and other coagulation processes under these conditions with high sensitivity and specificity. Furthermore, as cut vessels are not static because of contraction, retraction and pulsation, obtaining high-quality confocal imagery under these conditions represents a challenge.

Although developing an intravital model of cut-vessel outflow will be challenging, the rewards in terms of increased understanding of bleeding could be major. Therefore, preparations for the development of a method that will allow for real-time live confocal microscopic assessment of cut-vessel outflow in a rodent model are underway. The utility of intravital microscopy for imaging biopsies to assess organ function was recently demonstrated, and it should be feasible to adapt this method to image cut-vessel outflow. Such a model, with adaptations for arterial or venous blood flow simulation, has the potential to have a large impact on our understanding of perioperative bleeding that could translate into improved treatments. Considering the risks associated with severe bleeding and the importance of properly managing coagulopathy, such a model is way overdue.
Acknowledgements

Editorial assistance was provided by Meridian HealthComms Ltd, funded by CSL Behring.

Declaration of interest

C.S. is an employee of CSL Behring and previously received speaker honoraria and research support from Tem International and CSL Behring and travel support from Haemoscope Ltd (former manufacturer of TEG®). N.J.W. reports receiving one-time travel support from CSL Behring, a maker of fibrinogen concentrate, and is cofounder and stockholder for Stasys Medical Corp, a maker of blood coagulation diagnostic devices. G.H. is an employee of CSL Behring. D.F. has received study funding, payments, and travel funding from Austrian National Bank, AOP Orphan, Astra Zeneca, Baxter, B. Braun, Biotest, CSL Behring, Fresenius Kabi, Glaxo, Hemogem, Lilly, LFB, Mitsubishi Pharma, Novo Nordisk, Octapharma, and TEM International. M.H. has no conflicts of interest to declare.

References


doi:10.1093/bja/aew037

Table 1. Selected evidence of injury-site mediated haemostatic mechanisms

<table>
<thead>
<tr>
<th>Authors</th>
<th>Methods</th>
<th>Results/observations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen and Tsai</td>
<td>Haemostasis following puncture coincided with arterial constriction/retraction. Even in heparinized rabbits no serious or prolonged bleeding occurred.</td>
<td>Haemostasis coincided with arterial constriction/retraction. Even in heparinized rabbits no serious or prolonged bleeding occurred.</td>
<td>Arterial vasoconstriction plays a key role in haemostasis following cut vessel injury.</td>
</tr>
<tr>
<td>Shaftan and colleagues (1964, 1965)</td>
<td>Haemostasis was assessed following transection-induced arterial haemorrhage. Subsequently, b.p was increased by epinephrine injection or blood transfusion.</td>
<td>A significant drop in b.p from blood loss was required before spontaneous haemostasis. Investigation of the injury site revealed that the area surrounding the arterial ends were covered by a newly developed blood clot. Removing the clot or increasing b.p resulted in resumption of bleeding.</td>
<td>Haemorrhage control is also mediated by the formation of extraluminal soft clots that contain rather than thrombose bleeding arteries and are susceptible to rupture by increasing b.p.</td>
</tr>
<tr>
<td>White and colleagues (2015)</td>
<td>In a swine model, arterial bleeding was induced and ultrasound elastography was used to visualize clot formation in vivo.</td>
<td>Elastography and visual inspection of the haematoma revealed that haemostasis coincided with the formation of a single large clot around the injured artery.</td>
<td>The results confirm that clot formation within the peri-wound haematoma is an integral component of haemostasis.</td>
</tr>
</tbody>
</table>

Correspondence | 555

Downloaded from https://academic.oup.com/bja/article-abstract/116/4/554/2566164
by guest
on 28 April 2018