Host: Welcome to the Anesthesiology journal podcast, an audio interview of study authors and editorialists.

Dr. James Rathmell: Hello, I'm Jim Rathmell, Professor of Anesthesia at Harvard Medical School and Chair of the Department of Anesthesiology Perioperative and Pain Medicine at Brigham and Women's Hospital. I'm one of the executive editors for Anesthesiology and you're listening to an Anesthesiology podcast that we've designed for physicians and scientists interested in the research that appears in the journal.

Today we're going to talk with one of the authors of an original research article and the author of an accompanying editorial that appear in the January 2022 issue. With us today is Dr. Ross Davenport. Dr. Davenport is senior lecturer in trauma sciences at the Centre for Trauma Sciences and consultant trauma and vascular surgeon at Royal London Major Trauma Center, Barts Health NHS Trust Center for Trauma Sciences.

The Center for Trauma Sciences is a world leading Center of Excellence for translational research, at Barts and the London School of Medicine and Dentistry, Queen Mary University of London in the United Kingdom. Dr. Davenport is the senior author on an article that appears in the January 2022 issue of the journal titled, "Temporal Transitions in Fibrinolysis after Trauma. Adverse Outcome is Principally Related to Late Hypofibrinolysis." Dr. Davenport, thank you for joining us.

Dr. Ross Davenport: Thank you. My pleasure.

Dr. James Rathmell: Also with us today is Dr. Robert Medcalf. Dr. Medcalf is professor in the Molecular Neurotrauma and Hemostasis Laboratory within the Australian Centre for Blood Diseases at Monash University in Victoria, Australia. Together with Dr. Paul Myles, Dr. Medcalf authored an editorial that accompanies Dr. Davenport's original research article, also in the January 2022 issue of the journal, and it's titled "Fibrinolysis in Trauma Outcomes." Dr. Medcalf, welcome and thank you for joining us.

Dr. Robert Medcalf: Thank you for the invitation. I'm pleased to be here.

Dr. James Rathmell: Dr. Davenport, congratulations on the publication of your study. Let's start with what we knew before your new study. We knew that hypo and hyperfibrinolysis after traumatic injury are both associated with poor outcomes. And we knew that we could measure fibrinolysis using thromboelastography. We also knew that empiric administration of tranexamic acid to inhibit hyperfibrinolysis can improve outcomes.

But the ways in which early changes between lysis states affect clinical outcomes and the impact of tranexamic acid are not well understood. So your group set out to use rotational thromboelastography or ROTEM, after major trauma to better understand changes in lysis states and their impact on outcomes. What was the original hypothesis of this study?

Dr. Robert Medcalf: So using a large (inaudible) study that we've been running for over ten years now, we've been particularly interested in understanding both the natural history of fibrinolysis in trauma, but how tranexamic acid may modulate that response. And equally how both of those two things, both tranexamic acid and the fibrinolysis that's occurring in response to injury impacts clinical outcome.

So we can understand a little bit more about who should perhaps receive tranexamic acid and actually what those changes in the dynamic process of fibrinolysis over the early phase after injury, what that actually means for the patient that we see in terms of clinical outcomes such as multiple organ failure.

Dr. James Rathmell: So this was a secondary analysis of a previously collected data from trauma patients enrolled in an ongoing prospective cohort study. Can you tell us just a little bit about the primary study and then how you carried out this secondary analysis?

Dr. Ross Davenport: Yeah, so as I said, we've been running a study for over ten years called the Activation of Coagulation and Inflammation in Trauma, which we set up in 2008. In essence it's a bio-bank to collect samples from trauma patients as soon as they hit the doors at the Emergency Department through the bleeding episode and then up to seven days after injury.

And in particular for this study we looked at the subgroup of patients who had major trauma, so injuries (inaudible) 15 were either shocked with the standard metrics of high lactate or high base deficit, the presence of coagulopathy, such as an INR greater than 1.2, or had received significant blood transfusion. We felt that this particular group of patients were most at risk of having dynamic changes in the fibrinolytic response.

And so we collect a huge amount of data on these patients, which is designed in essence to look at any element of coagulation or inflammation abnormality. In particular we also collect the timing of tranexamic acid use and the clinical outcomes related, particularly for this study, multiple organ failure, mortality and the presence or absence of (inaudible) thromboembolic events.

Dr. James Rathmell: So the primary outcomes were multi organ dysfunction syndrome and 28 day mortality. What did you find?

Dr. Ross Davenport: Well, it was surprising in some respects to actually see such a strong signal to multiple organ dysfunction in patients with a particular dynamic change in their fibrinolytic profile. Much has been written in the literature around mortality, in particular patients who have a low level of fibrinolysis on admission. And what we set out to try to answer is that if you have a low level of fibrinolysis at 24 hours, is that the same as somebody who starts off with a low level? Is there a difference in those patients that transition to a low level?

So in essence what is the importance of the 24 hour, low level lysis? Is it that you're there at low level lysis, is actually changing your trajectory and your status of multiple organ dysfunction? Does it matter how you get there if you started off with a normal level of lysis? So it is really trying to tease these things out.

Dr. James Rathmell: There's a lot in your findings. You enrolled 731 patients, 299 or 41% received tranexamic acid, and 432 or 59% were untreated. There were two different cohorts with low maximum lysis at 24 hours that you identified. And one was those with severe brain injury, and the second was those with admission shock and hemorrhage. And multiple organ dysfunction syndrome was greatest in those with this low maximum lysis on admission and at 24 hours. And late mortality was four times higher in patients who remained normal during the first 24 hours.

Patients that transitioned to or remained in the low maximum lysis had increased odds of organ dysfunction. Tranexamic acid abolished hyperfibrinolysis on admission, increased the frequency of persistent low maximum fibrinolysis and was associated with reduced early mortality. But regardless of the fibrinolysis transition patterns, you didn't observe any increase in late death beyond 24 hours after admission. So what did you conclude? What were your summary conclusions after all of this?

Dr. Ross Davenport: Well, it's clear for us that the actual pattern that occurs in the first 24 hours is absolutely key. And that patients cannot be discriminated on terms of their clinical trajectory on their admission parameters alone. There appears to be two particular groups at risk of a poor outcome. Those are those patients with persistent hyperfibrinolysis, which as you described are those with the severe brain injury. But also those that transition from a normal state to a low lytic state. Those typically are the patients that we found to be in shock and hemorrhage early on.

And so it is really helpful I think to think of this as another tool to actually understand prognostication for patients who may look the same when they arrive with some degree of injury and some degree of bleeding. But actually they may go off in different ways. There is a recovery pattern in some patients who start off with a low level of fibrinolysis. But there are those that then persist with this low level of fibrinolysis at 24 hours. And it's that group that have the very high incidence of multiple organ failure.

Dr. James Rathmell: Dr. Medcalf, I want to turn to your editorial. Together with Dr. Paul Myles you authored an editorial, and it accompanies Dr. Davenport's original research article in the January 2022 issue. It's titled, "Fibrinolysis and Trauma Outcomes." You do a terrific job of putting this

article into perspective, and I want to start by reading the first part of your editorial as it provides a perfect orientation.

Severe trauma can cause dramatic changes in hemostasis, resulting in a severe coagulapathic state. There's been heightened interest in the fibrinolytic system for its role in exacerbating or increasing this risk of bleeding during the acute post-trauma period and its relationship to subsequent patient outcomes. Walk us through the mechanism that leads to fibrinolysis after severe trauma.

Dr. Robert Medcalf: Thank you for the question, but I don't have a simple answer. What we've learned in recent times following trauma, the host's fibrinolytic system is very dynamic, as Dr. Davenport just described. There's a large variation between individuals that will be influenced by the location and the severity of injury. But generally speaking the fibrinolytic system is increased following trauma. Mostly likely due to large increases in the fibrinolytic enzyme tPA that's released from endothelial cells, probably as a result of an inflammatory trigger.

So tPA itself can then do a few things, but most relevant is its activation of the plasma protein plasminogen into its active form plasmin that in turn breaks down blood clots. So if we lose control of plasmin we can be in a bit of trouble, as too much plasmin will increase risk of devastating bleeding, and which you can manage with tranexamic acid, as Dr. Davenport just described. But this seems to be a very transient state, and things can change very quickly.

Others have reported that the (inaudible) tPA can be reduced by its natural inhibitor, which is called PAI-1 and plasmin activity itself can be restricted through it, a natural inhibitor anti-plasmin. And both PAI-1 and anti-plasmin themselves can have different temporal relationships following trauma. But as revealed in Dr. Davenport's paper, some patients who have low fibrinolysis at the outset, that is within two hours of injury, (inaudible) because the fibrinolytic system had already been increased and then shut itself off. Truly hard to know what happened there.

The other thing I'd like to mention is that when we talk about fibrinolysis, we immediately focus on the accidents of plasmin on fibrin removal, hence the name fibrinolysis. However, I think it's important to realize that plasmin, the main enzyme here, can influence many other processes as well. It can be also pro-inflammatory, anti-inflammatory, again depending on severity. So some of these effects are plasmin as a consequence of the fibrinolytic activation can be helpful and others not.

The other point to raise is that not all current approaches used to evaluate fibrinolysis, they all rely on the activity in blood samples. What we don't know is the extent to which these dynamic changes in fibrinolysis are occurring in the damaged tissue that may not be reflected in the blood samples taken for the ROTEM testing.

Dr. James Rathmell: You describe strengths and weaknesses of thromboelastography for measuring fibrinolysis. Can you elaborate on those strengths and limitations, and are there more definitive measures available for clinicians to look at fibrinolysis?

Dr. Robert Medcalf: Well, the good thing about TEG and ROTEM is that they provide a very convenient point of care test in about 30 minutes. Well, that 30 minutes can be a long time in the Emergency Department. But nonetheless these tests give relevant information about the clotting system, both the speed and the strength of coagulation and some information about fibrinolysis.

The drawback is that the dynamic range for fibrinolysis is very narrow and the sensitivity low. For example, there is likely to be changes in the fibrinolytic activity that simply cannot be detected by TEG or ROTEM. Unfortunately there are no other tests around that can be used to monitor fibrinolysis in real time. I mean, we all know about D-dimer and PAI-1 levels that you can evaluate as well.

But these take much longer to get the (sounds like: the drops) for anyway, and they only give a snapshot of what is actually occurring. Right now viscoelastic tests or the ROTEM or TEG are the best we have. But more research is needed to develop more sensitive tests to evaluate fibrinolysis in real time.

Dr. James Rathmell: So how does the uncertainty around the accuracy of thromboelastography measure, to measure fibrinolysis influence your own interpretation of this study?

Dr. Robert Medcalf: Well, I think the overall interpretation of the findings are basically correct despite the limitations of viscoelastic testing. But what is just less clear to me is the extent to which these blood-based assays reflect what is going on in the damaged tissue. That's all.

Dr. James Rathmell: You tell us that we should not conclude that hypofibrinolysis detected by ROTEM has a causal impact on trauma outcomes. Can you explain that?

Dr. Robert Medcalf: The conclusions of the study I think is sound. The authors found a very clear and important correlation between a hypofibrinolytic state, as measured by ROTEM, and poor outcomes after trauma. That is there is an association. But this should not be assumed to be causal. In our editorial that I did with Paul Myles, we provided a web link to a causal mediation diagram which highlights several potential confounding factors that may more likely link with early hypofibrinolysis and be the true causal mediator in the poor outcomes.

For example, the association could be explained by residual confounding effects, especially trauma severity and type, shock (inaudible) for example, large volume transfusions. The authors, in this study they used multi variable statistical adjustments for these but not other potent factors. And in any case the adjustments could be incomplete. Untangling causal and non-causal associations can be clarified by developing a conceptual model that includes other forms of analysis, aiming to shed light on the exposure outcome relationship.

But overall I think the study is very interesting and sound. I think it's just important to realize that cause and effect, association and cause can be different.

Dr. James Rathmell: All right, well I'm going to switch to Dr. Davenport for this final question. What do you think the take home message is for practicing anesthesiologists caring for patients immediately after severe trauma?

Dr. Ross Davenport: Well thank you to Dr. Medcalf for his comments there, and I would wholeheartedly agree. There are numerous limitations with the viscoelastic testing, ROTEM or TEG. But really it is the only usable diagnostic that we have to provide a result in a clinically meaningful timeframe for any clinical practice.

And then equally, what the results are showing in terms of the hypofibrinolytic profile, is really unclear actually what this means in terms of the true biomarkers of fibrinolysis that are occurring both locally and systemically. So certainly our follow up work we'll be trying to examine some of this and look at some of the newer diagnostics that are coming out and in the research field.

But the key take home I think would be for the anesthesiologist, is that if you see low levels of fibrinolysis without persistent or have a delayed onset of 24 hours, then this is a signal that this patient is at great risk of developing multiple organ dysfunction. And some of the other things that we've identified in the smaller subgroups and caution because they are smaller subgroups, is that these patients are particularly at risk of developing VTEs or PAES or DVTs. Early strategies to try to prevent this would be important.

My final take home message is, I think looking at the effect of tranexamic acid, in my mind is very clear. There has been much written about the potential risks of pushing patients into a low lytic state at 24 hours and beyond in patients who have received tranexamic acid. And whilst that is absolutely the case, it would appear, from the data that we have presented, this does not track through to worse outcomes later on. In fact it certainly saved lives based on a reduction in the early mortality. And that would be consistent with the data that's come out from a number of large randomized control trials showing benefit of tranexamic acid.

And I don't feel that there's any benefit to be gained in waiting for a ROTEM or a TEG trace to confirm whether or not the patient is in a low lytic state already. Because waiting for a result is potentially going

to introduce further delay, and we know that time to administration of anti-fibrinolytics is very important in preserving a strong efficacy of the drug.

Dr. James Rathmell: Terrific. I hope today's discussion will leave many of you listening to read this new article and the accompanying editorial that appear in the January 2022 issue of Anesthesiology, where you can learn more about temporal patterns of fibrinolysis after severe trauma and the use of thromboelastography. John Wanderer from Vanderbilt University and I also created an infographic that's titled "Fibrinolysis Transitions, Adverse Outcomes in Trauma," that summarizes the finding of the study. Drs Davenport and Medcalf, thank you for joining me and for the terrific explanations.

Host: You've been listing to the Anesthesiology journal podcast, the official peer reviewed journal of the American Society of Anesthesiologists. Check Anesthesiology.org for an archive of this podcast and other related content.