Clinical Chemistry

T2 Magnetic Resonance: A Diagnostic Platform for Studying Integrated Hemostasis in Whole Blood—Proof of Concept

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Guests: Dr. Tom Lowery is the Chief Scientific Officer at T2 Biosystems in Lexington, Massachusetts, and Dr. Douglas Cines is Professor and Director of the Special Coagulation Laboratory at the University of Pennsylvania.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Thrombosis and bleeding are among the foremost causes of morbidity and mortality, and the recent introduction of novel anticoagulants, anti-thrombotic, and hemostatic drugs has increased the need for rapid and accurate assessment of their activities. While the usual laboratory assessment of hemostasis, such as prothrombin time and other coagulation tests, are often effective, these methods may not identify all bleeding disorders.

In a paper published in the September 2014 issue of *Clinical Chemistry,* researchers from a number of centers published a Proof of Concept study applying transverse relaxation time magnetic resonance for the study of hemostasis in whole blood. Two of the authors of that paper are our guests in this podcast.

Dr. Douglas Cines is Professor and Director of the Special Coagulation Laboratory in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania.

And Dr. Tom Lowery is the Chief Scientific Officer at T2 Biosystems in Lexington, Massachusetts.

And Dr. Lowery, let's start with you, please explain the technology you are using for this study and how the project got started?

Dr. Tom Lowery: You bet! The technology we are using is T2 Magnetic Resonance. It's basically a miniaturized form of nuclear magnetic resonance from magnetic resonance imaging, so we use the same basic physics as those two methods.

The magnet is a small permanent magnet, about 4 inches on the side, a cube, and it's monitoring signals from water molecules inside of our samples. So these signals evolve over time as a clot is triggered and the dynamics of clotting and lysis occurs.

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And in this study what we did is we mapped out what these different signals are that are coming from the samples. We are measuring specifically something called T2 relaxation; it's a physical property of water.

And in this study we map out how those different relaxation times or T2MR values, as we call them, how they depend on the dynamics of clotting and how they depend on the wide range of platelet counts, high thrombin concentrations, hematocrit and so forth. We identify then how to use these different signals for a variety of measurements.

I will just add, the technology that we have here, we have products that are just for investigation and research use; they have not been cleared for use by the FDA.

Bob Barrett: Dr. Cines, in your clinical role as a Professor of Laboratory Medicine and Director of the Special Coagulation Laboratory, what interested you with this technology and this study, why is this important?

Dr. Douglas Cines: As a clinical laboratory physician I saw the T2MR technologies offering the opportunity to study multiple aspects of coagulation using a single platform. If successful, this would extend testing into laboratories that now must refer samples and even patients to specialized centers, sometimes at considerable distance.

Let me mention some features of the technology to address this point using platelet function as an example. First, relatively few laboratories offer platelet function tests because of the expertise required to isolate platelets without perturbing their function. The T2MR approach requires no sample modification because platelet function is studied directly in whole blood.

Secondly, it's difficult, and sometimes not possible, to study platelet function in children because of sample size requirements for standard light transmission aggregometry. The T2MR approach uses 40 microliter sample volumes, permitting even young children to be studied.

Third, platelet function can be measured in minutes from the time the blood is drawn by the T2MR rather than the additional time it takes to isolate platelet rich plasma in order to use light transmission aggregometry.

Fourth, sample volumes in rapid turnaround times not only should increase laboratory efficiency, but it also offers the potential for siting such tests in the operating room, trauma bay, etcetera. This would permit hemostasis and interventions to be assessed at appropriate time intervals, even in complex and rapidly changing clinical settings. And

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this should translate into improved clinical outcome and reduce administration of unnecessary and even deleterious blood products.

Fifth, outcomes of T2MR correlate closely with currently employed technologies, including standard prothrombin times, thromboelastograms and platelet function measured by light transmission aggregometry. However, T2MR also identifies biologically relevant aspects of platelet biology, such as platelet mediated clot contraction and the contribution of erythrocytes to hemostasis, that are not assessed by current approaches using clinical laboratories.

Bob Barrett: Doctor, you have discussed the first finding in this study surrounding the correlation of T2 Magnetic Resonance with existing diagnostic tests. In your role as a researcher in hemostasis, can you discuss the hypothesis of findings of the structural characterization of clots and what this could mean to patients and physicians?

Dr. Douglas Cines: I was excited by the possibility that the T2MR platform had the potential to provide new insights into the biology of clotting as it occurs in vivo by using whole blood. Analysis of whole blood reflects the integrated function of platelets and coagulation factors with white blood cells and erythrocytes as it occurs in vivo, and the platform is flexible enough to also permit study of individual components of coagulation alone or together in reconstituted systems.

One important unmet medical need is the identification of hypercoagulable states and their management. For example, we can now measure high levels of certain coagulation factors such as fibrinogen and factor VIII that may predispose the thrombosis, but there is a need for an assay that identifies patients who are actually in a hypercoagulable state, ideally using a platform amenable to clinical use.

In the course of our studies we found a unique T2MR signal. When we raise the concentration of fibrinogen or platelets or erythrocytes, or when we added high concentrations of thrombin to activate coagulation, this signal appeared early and was robust under these conditions, and the low T2 signature suggested to us that the ward of molecules within this region of the clot were highly constrained.

We hypothesized that this feature might derive from highly contracted clot that helps seal sites of vascular interruption, but also a clot that might be resistant to fibrinolysis and leads to vascular occlusion.

To test this hypothesis we isolated distraction of the clot and we found that it permitted only extremely slow diffusion of

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deuterated water, consistent with lack of permeability, and we found that it was indeed relatively resistant to lysis by tissue-type plasminogen activator, which rapidly lysed the remainder of the clot.

Our colleague John Weisel and his team performed scanning electron microscopy of this clot fraction. To his and our surprise, this clot, thought composed of fiber and coated with platelets on its exterior surface, contained within it a tightly packed arrays of erythrocytes, having a unique morphology that we call polyhedrocytes.

We went on to confirm the appearance using confocal microscopy and we found identical structures within human arteriovenous clots. We are currently performing clinical studies to determine the utility of this potential biomarker for a hypercoagulable state.

Bob Barrett: Well, finally Dr. Lowery back to you, looking forward, where do you see the future of this technology?

Dr. Tom Lowery: Yeah, I am really excited about it. In this Proof of Concept study we demonstrated the T2MR, we have the potential to provide rapid and sensitive identification of patients that are at risk of thrombosis or bleeding. But also, I think equally exciting, is the potential of identifying new biomarkers and therapeutic targets, all with this platform, that is simple to employ and maybe suitable for routine use, whether you are in a research setting or you are in a variety of clinical settings.

It's really uniquely positioned, as we show in the paper, there is a rich information that's delivered by the T2MR signatures, because we are using water molecules as the probe of this clot formation and clot dissolution, and so applications, I think they could include rapid, multiplex, point-of-care measurements or simpler platelet activity measurements, as Dr. Cines mentions, or measurement of new thrombotic risk markers for diagnosis or drug development or to guide therapeutics development.

So we are really excited about the potential. We are excited about this work that we are able to publish in *Clinical Chemistry* and we look forward to the upcoming developments.

Bob Barrett: Dr. Tom Lowery is the Chief Scientific Officer at T2 Biosystems in Lexington, Massachusetts, and Dr. Douglas Cines is Professor and Director of the Special Coagulation Laboratory at the University of Pennsylvania. They have been our guests in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!

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