ABSTRACT FORM ECAT SYMPOSIUM 8 – 9 NOVEMBER 2018

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Title:

A paradigm shift in measuring blood coagulation

Abstract:

Global testing of blood coagulation is currently done by mixing an activator, such as tissue factor or factor XII activator, with a blood or plasma sample and watch the time to gelation of the fibrin. Similarly, in such mixtures, thrombin formation can be recorded.

In the nineties of the previous century, Russian investigators (F. Ataullakhanov cs) developed another model --clot growth-- in which the activation starts from a focal point or surface and extends in the fluid. This was described as a wave model (like waves from dropping a stone in the water). It became further evident that in these moving waves the damping was very low, and waves continued for a prolonged time with closely similar amplitudes. This was described as “excitable waves” and formed the basis for clot growth from a focal point or surface.

The mechanism of continued wave stimulation (excitable waves) was found to be due to the thrombin activation of factor XI. This resulted in thrombin peak waves generated away from the surface activator and travelling away from the focal activation point. These thrombin peaks also developed in defibrinated plasma.

The same Russian investigators developed equipment to follow the clot growth from a surface in plasma by video microscopy: thrombodynamics. In this equipment the fibrin clot growth can be monitored as well as the thrombin waves.

A standard clot growth method was designed with a fixed amount of surface bound tissue factor, addition of 4 µM lipids, and CTI to prevent contact activation.

Evaluation of the characteristics of fibrin clot growth identified (a) dependence of clot growth rate and size of factor VIII, IX and XI in the normal and high range, and reduced growth when factor V and X were below 25%, (b) growth was insensitive to endogenous coagulation inhibitors. Added NOACs did inhibit and all worked on the growth module (VIII, IX, XI). Mechanistic evaluation showed that factor Xa activated factor VIII.

The thrombin waves, driven by factor XI activated in the clot, were sensitive to TFPI, antithrombin, PC, PS and Factor V Leiden.

It is proposed that clot growth is a relevant pharmacodynamic model for coagulation and coagulation inhibition. It represents a new option in coagulation testing, to be recognized as paradigm shift.

We currently apply the test in various clinical conditions to test effects of clotting defects and treatments and whether testing can predict recurrent VTE, risk of arterial disease, efficacy/bleeding risk of anti-Xa inhibitors.