Physiological Thrombophilia Screening Assay Platform

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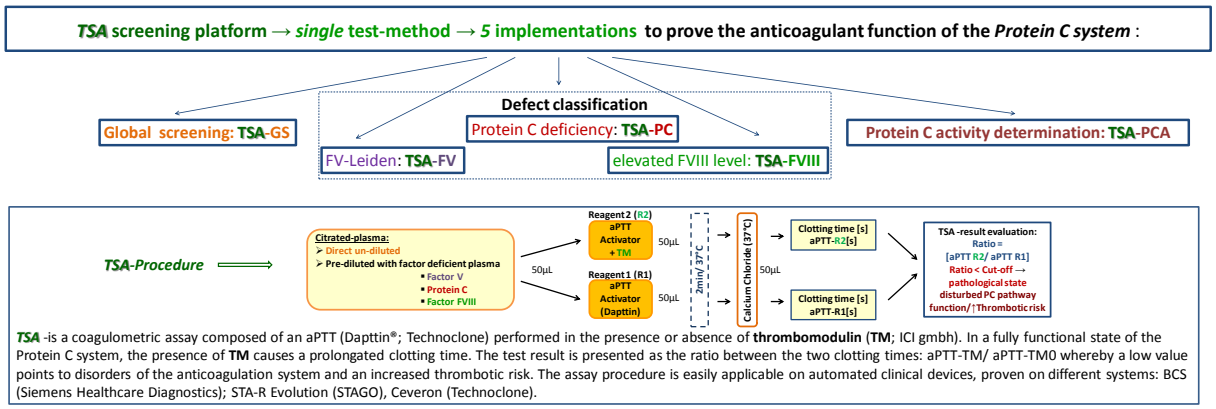
The Physiological Thrombophilia Screening Assay Platform (TSA) represents the results of recent efforts of ICI's R&D activities in the field of coagulation and haemostasis.

The determination of dysfunctional states in the defence systems against thrombosis is the aim of thrombophilia diagnostics. The protein C pathway is the system with the most impact on prevention of thrombotic events and comprises a complex interaction of several components. Dysfunctional states of hereditary or acquired origin in this pathway lead to enhanced thrombotic risks. Therefore, it is of major importance to have diagnostic tools at hand which allow reliable determination of failures emerging either from single or multiple components in this pathway.

For this, we have developed and evaluated a thrombophilia screening assay platform named TSA that is based on the physiological thrombomodulin[1] mediated activation of the protein C system and utilizes a single test method for a compact analysis of the entire system from global screening up to differentiation for specific defects (APC resistance; protein C; factor VIII) and quantification of protein C activity.



Summarized, we have developed the TSA - thrombophilia screening assay platform -with two major advantages compared to conventional test systems:

1.) The physiological activation of the protein C system via soluble thrombomodulin

2.) A single test method / less heterogeneity for performing global, differentiated and quantitative analysis of dysfunctional states in the protein C pathway:
   - global screening with high overall sensitivity for factor V Leiden; protein C deficiency; elevated factor VIII; protein S deficiency and combined failures
   - defect classification for factor V Leiden, protein C, elevated factor VIII level with high differentiation specificity
   - protein C activity determination based on clotting background; with low interference by other defects; and a high comparability to the chromogenic assay

[1] recombinant soluble human thrombomodulin is manufactured by ICI

Our approach was successfully implemented in laboratory practice and the results were presented at the 57th and the 58th Annual Meetings of the Society of Thrombosis and Haemostasis Research.

Our results demonstrate that the TSA platform fulfils all requirements for a new diagnostic tool in the field of thrombophilia.

APPENDIX: EXTENDED TSA INFORMATION

The value of our diagnostic product for the medical practice and the commercial market use is further outlined below:

1.) The most important diagnostic advantage of the TSA assay for the field of thrombophilia is represented through its test concept: It is the physiological activation of the protein C (PC) pathway employing thrombomodulin which is a natural transmembrane receptor for thrombin and potentiates its ability to activate the PC pathway. Therefore, thrombomodulin has a key function in the inhibition of blood coagulation. Its application in our test system ensures the investigation of the involved factors for failures in their natural environment. Our method guarantees a high specific activation of the PC pathway. As a global tool it allows testing for all components contributing *in vivo* to the activation pathway. This is the main benefit of our method compared to present commercially available (global or single factor specific) diagnostic tools. In these assays the PC pathway activation is not natural; the activation occurs via snake venom proteases and is therefore much more unspecific and burdened with activation side effects influencing the test results.

2.) The next advantage is represented by the platform concept - the possibility to use one single method for 5 different demands in thrombophilia screening: Global screening; classification of single defects for the 3 main thrombophilic risk factors (factor V Leiden; protein C, deficiencies and elevated factor VIII levels) and determination of protein C activity.

   a. The physiological activation of the protein C pathway via thrombomodulin in the test method by itself position all 5 screening approaches above other products on the market investigating the same failures (arguments already listed in point 1).

   b. For the global screening approach an additional benefit over the single factor testing (representing the state of art in the thrombophilia screening today) is the ability to proof the overall functional potential of all in the proven pathway participating (known and unknown) factors at the same time. More specifically, the result of this approach is reflecting not only its impact of failures rising form single factors alone, but also from two and more components having a synergistic effect. Furthermore, since same defects may have a differently severe manifestation in two persons, such a result may lead to a personalized therapeutic consequence for each patient. Therefore, the TSA also fulfilled the today's request of a personalized medicine.

c. Another fact pointing to the need of a reliable global screening tests (represented by TSA) in the thrombophilia diagnostic is the actual discussion about the need of thrombophilia screening at al (how important is this screening for a patient who has no history of thrombotic events personally or in his/her family). Fact is that a hypercoagulability stage in a patient is pathological and may have a life-threatening consequence in certain situations. Therefore, the information about the thrombophilic state is gaining more and more importance. To questioning such screening is caused by high costs associated with investigating each factor separately and the fact, that only in half of the investigated patients the defect causing the thrombophilic states can be determined. The clear disadvantage of this practice is to look at the clotting cascade in isolation and this even on a non-physiological basis. Therefore, the inclusion of our TSA global approach into the screening algorithm would lead to cost-effectiveness and true conclusive personalized results.

3.) The further advantage of our test is its ability to be performed on devices routinely used in medical diagnostic laboratories. The test is easily applicable and performs robust (high precision and reproducibility) on the common automated, as well as on manual coagulation devices. This is a prerequisite for being accepted by costumers.

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