

The dynamics of thrombin generation

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SUMMARY

The thrombin generation (TG) assay is a global coagulation assay used in research and in clinical settings. The advantage of measuring TG is that various coagulation abnormalities can be detected with this assay, that can result in an increased risk for developing a bleeding or thrombosis. This is in contrast to the conventional tests, such as the clotting times routinely used in the clinic, which, for example, cannot shorten and therefore cannot detect an increased risk of thrombosis. However, some specific coagulation abnormalities cannot be identified by TG alone. Kremers et al. developed a new method to investigate the main pro- and anticoagulant processes underlying TG through computational analysis of the dynamics of thrombin formation. By applying the thrombin dynamics method, one can obtain the course of prothrombin conversion into thrombin, and of the thrombin inactivation, which occur both during TG. The thrombin dynamics analysis has been described previously for analyzing TG measured in platelet-poor plasma, and several clinical studies have demonstrated its utility for explaining altered TG profiles in various pathologies. In this thesis, we further investigated the clinical relevance of thrombin dynamics in platelet-poor plasma and determined the thrombin dynamics of TG data measured with the ST Genesis, which is a new and fully automated TG assay. In addition, we applied the thrombin dynamics method in platelet-rich plasma from healthy donors.

Chapter 2

In chapter 2 we investigated the influence of individual coagulation factors of the prothrombinase complex and natural thrombin inhibitors on prothrombin conversion and thrombin inactivation using TG and thrombin dynamics analysis. We showed that prothrombin conversion is influenced not only by the procoagulant clotting factors prothrombin and factor (F)X, but also by antithrombin, a natural thrombin inhibitor. Thrombin inactivation is mainly dependent on the thrombin inhibitors and on fibrinogen. We also determined reference values for thrombin dynamics that provide guidance for future clinical studies. We found that in a normal population, men have lower thrombin activity than women. In addition, the use of oral contraceptives (OC) significantly increases prothrombin conversion and thrombin inactivation, which may explain the increased risk of thrombosis in women taking OC. In addition, we showed that prothrombin conversion and thrombin inactivation were significantly lower in hemophilia A patients compared to healthy controls.

Chapter 3

In chapter 3, we collected plasma samples from 55 healthy donors and 189 HIV patients, of whom 96 were treated with abacavir, 93 with tenofovir disoproxil fumarate (TDF) and 19 with other drugs. TG was measured and thrombin dynamics was performed to quantify prothrombin conversion and thrombin inactivation. Patients treated with abacavir had an increased prothrombin conversion in combination with an increased thrombin inactivation, which led to a rebalanced TG. The higher prothrombin conversion in the abacavir-treated patients revealed a pro-clotting mechanism, which could explain the higher risk of thrombosis in these patients. On the contrary, patients treated with TDF had an increased thrombin inactivation, but an unchanged prothrombin conversion, which resulted in a lower TG. This could, among other things, explain the fact that these patients have a lower risk of developing thrombosis compared to abacavir-treated HIV patients.

Chapter 4

In chapter 4 we measured TG with the ST Genesis in platelet-poor plasma. With this new device, we determined the reference values in 112 healthy donors for all parameters of the thrombin dynamics method. For this study, we used the three ST Genesis reagent kits, namely STG-BleedScreen, STG-ThromboScreen and STG-DrugScreen. These reference values can be used for future research and in clinical studies. In addition, our data showed that the parameters of thrombin dynamics did not differ between men and women that did not take OC. Remarkably, the use of OC increased almost all TG and thrombin dynamics parameters.

Chapter 5

In chapter 5 we performed thrombin dynamics analysis in platelet-rich plasma and studied the effect of the difference in platelet count on TG and thrombin dynamics parameters in 117 healthy individuals. We have shown that increasing the platelet count mainly affects the rate of prothrombin conversion and TG, rather than affecting the total amount of thrombin formed. In addition, we determined the reference values of TG and thrombin dynamics in platelet-rich plasma of these healthy subjects.

Conclusion

In this thesis we have further explored the clinical relevance and biological modulators of

the thrombin dynamics analysis. In addition, we determined the reference values in healthy donors for the analysis of thrombin dynamics in platelet-poor and platelet-rich plasma. Finally, we also investigated the effect of platelets on the individual parameters of the thrombin dynamics method.