Kinder und Jugendklinik
Direktor: Prof. Dr. med. Dr. h.c. Wolfgang Rascher

Universitätsklinikum
Erlangen

Validating the Role of Thrombelastography and the Thrombin Generation Assay for Routine Clinical Care in Children with Haemophilia

M. Rauh, H.-G. Topf

Introduction:

Bleeding patterns in haemophilia patients vary markedly, also within the group of patients with comparable factor VIII and IX levels. While laboratory assay play an essential role in the clinical management of patients with haemophilia, no single assay has been shown to reliably monitor therapy. Current available haemostasis assays measure levels and/or activities of individual factors and have largely been disappointing. The biologic factors that underlie this phenotypic variability remain poorly understood, but evidence is reviewed supporting a role for platelets and platelet related factors in modifying bleeding tendency. Global coagulation tests may show a better correlation with phenotype in haemophilia than traditional coagulation tests. These include the Calibrated Automated Thrombin generation assay (CAT) and modified thromboelastometry (TG) using low tissue factor.

Methods:

Thrombin generation in platelet poor plasma (PPP) and platelet rich plasma (PRP) was measured by calibrated automated thrombography. Additional PT, aPTT, and fibrinogen were examined. The platelet poor plasma reagent containing 5 pM tissue factor,and 4 µM phospholipids, the PRP reagent containing 1 pM tissue factor, and the thrombin calibrator was purchased from Thrombinoscope BV (Maastricht, The Netherlands). Assays were performed by means of Fluoroskan Ascent plate reader (Thermo Lab-systems, Helsinki, Finland) and Thrombinoscope software (Thrombinoscope BV, Maastricht, The Netherlands) as described by the manufacturer.

TEG analysis was performed with the ROTEM-Coagulation Analyzer (ROTEM delta, TEM, Munich, Germany). Four channels were available for simul-taneous measurements. Each test required 300 µl citrated whole blood. The blood was re-calcified with 20 µl 0.2 mol/L CaCl2 (star-TEM®) and activation of coagulation was performed with 40 µl PRP reagent (Thrombino-scope).

Results:

The present study evaluates dynamic coagulation profiles and thrombin generation in whole blood (WB) and platelet rich and poor plasma from children with haemophila before (mean ETP(PPP) 1002 nMmin, ETP(PRP) 526 nMmin) and after FVIII substitution (ETP(PPP) 1220 nMmin, ETP(PRP) 1296 nMmin). The correlation of thrombin generation parameters for PRP and PPP show significant differences between patient groups (hemophilia A patients before (n= 76) and after substitution (n = 24) and control samples (n = 74)). TEG parameters before and after substitution are compared. Significantly differences are seen for clotting time (CT), clot formation time (CFT) and the maximum of the first derivative of the clot curve (MAXV(t)).

Conclusion:

The data suggest that thrombelastography and the thrombin generation assay may be helpful for predicting the individual bleeding risk and for providing individually tailored regimens. Extensive evaluation in clinical practice is required.

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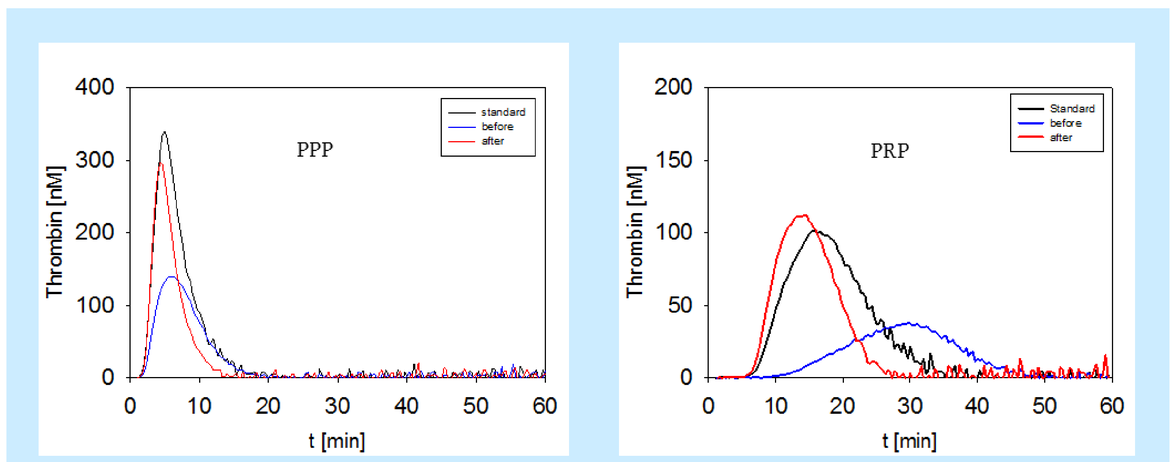

Figure 1: ETP: Haemophilia A patient before and after substitution.

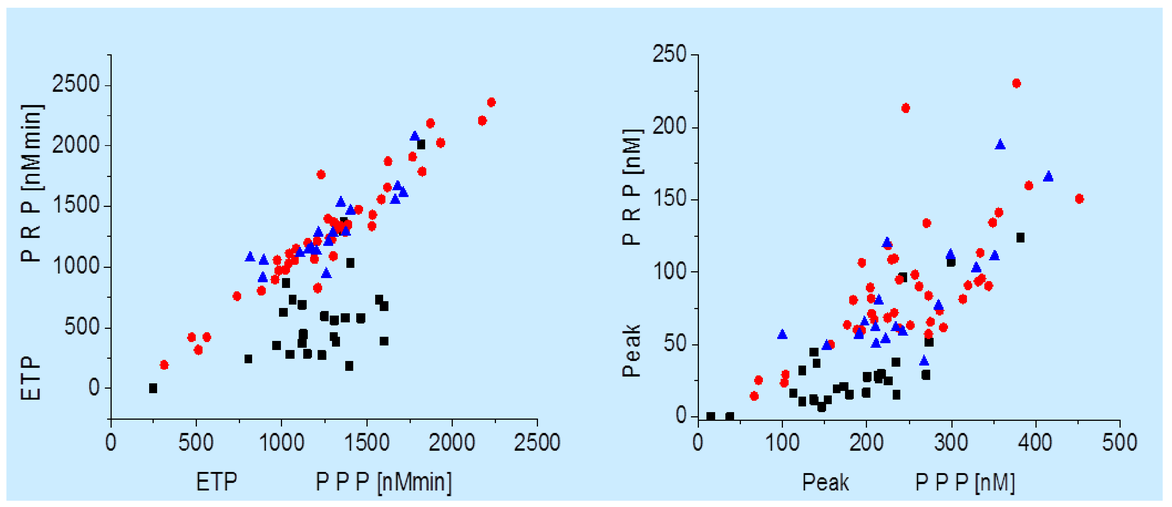

Figure 2: Comparison of ETP parameters: Haemophilia A patients before (n = 76, black symbols) and after substitution (n =24, blue symbols), controls (n= 74, red symbols).

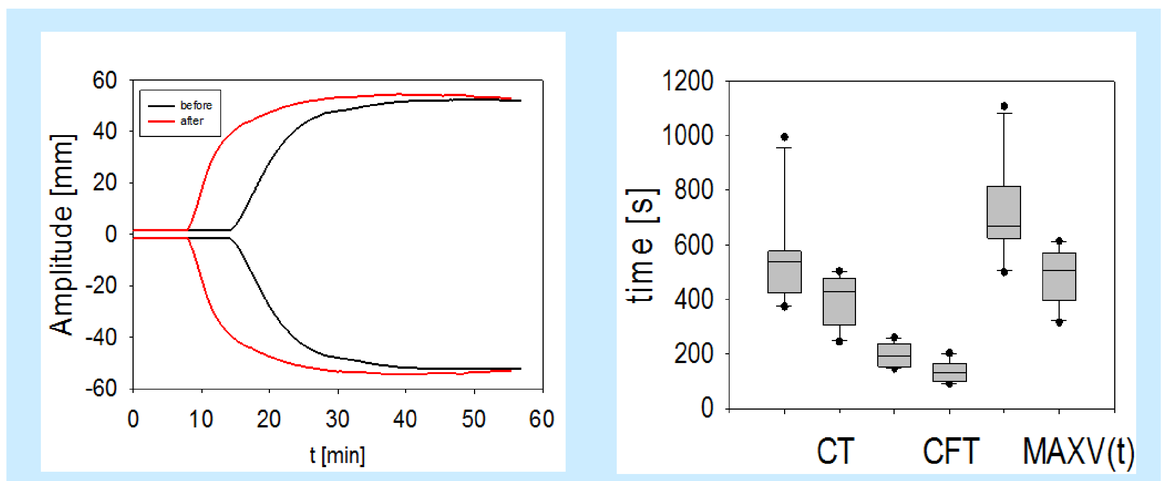

Figure 3: TEG parameters: Haemophilia A patients (n = 10) before and after substitution.

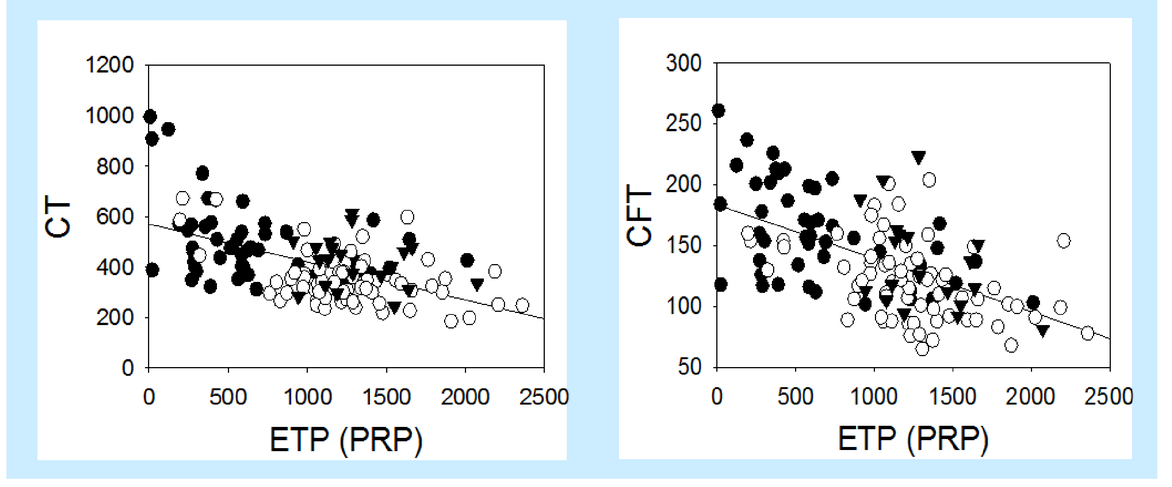

Figure 4: Correlation of TEG parameters and ETP (PRP).

FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG
MEDIZINISCHE FAKULTÄT

Kontakt:
Universitätsklinikum Erlangen, Kinder- und Jugendklinik, Loschgestr. 15, 91054 Erlangen, Germany
PD Dr. Manfred Rauh, manfred.rauh@uk-erlangen.de

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