Thromboelastometry and Thrombelastography Analysis under Normal Physiological Conditions – Systematic Review

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Summary
Background: Studies investigating thromboelastometry or thrombelastography analyses in a physiological context are scattered and not easy to access. Objective: To systematically retrieve and describe published reports studying healthy subjects and targeting at the correlation of ROTEM® and TEG® measurements with conventional parameters of hemostasis. Methods: Systematic Review: Papers were searched in Medline, Scopus and the Science Citation Index database. Reference lists of included studies and of reviews were screened. To be included papers had to report ROTEM or TEG data on healthy subjects. Two reviewers screened papers for inclusion, read full texts of potentially relevant papers, and extracted data of included papers. Results: Searches identified 1,721 records of which 1,713 were either excluded immediately or after reading the full text. The remaining 8 studies enrolled 632 subjects. The association of conventional parameters of hemostasis with ROTEM and with TEG was investigated in one and two studies, respectively. Overall correlation was limited and ranged from 0.0 to 0.40 (total thrombus generation vs. fibrinogen; clotting time INTEM vs. activated partial thromboplastin time). Conclusions: Studies assessing the relationship between thromboelastometry or thrombelastography analyses and conventional parameters of hemostasis in healthy subjects remains scarce, and correlations are limited. Further research is needed to understand the physiology of thromboelastometry and thrombelastography parameters.

Introduction
Back in 1978, Loop and Lusted [1] proposed the first phased evaluation of new medical tests. To date, after the publication of at least 18 additional recommendations, (reviewed in [2]) there is a broad consensus that first evaluations should address parameters of technical efficacy such as minimal detection level, circadian fluctuation, reproducibility, and correlation with established tests in healthy volunteers in order to understand the physiology of the analyzed parameters. It has been recognized that sophisticated and expensive tests that are disseminated without suitable evaluations can subsequently be found to have marginal clinical value and economic benefit. Well known examples include the carcinoembryonic antigen test in the diagnosis of colon cancer [3], iodine-125-labeled fibrinogen scans in the diagnosis of deep venous...
Thromboelastometry (ROTEM®) and thrombelastography (TEG®) analysis, two methods evaluating hemostasis, are increasingly used in clinical practice, based on the anticipation that they improve the management of acute bleeding [6, 7]. Several possible advantages over conventional laboratory parameters promote their use in emergency units and operating rooms. The analyzer is easy to use, and tests are readily available. Results are displayed graphically, allowing an intuitive interpretation [8]. Furthermore, tests claim to provide global information on all aspects of hemostasis, including fibrinogen level, platelet function, coagulation cascade, cross-linking of fibrin, and fibrinolysis. In addition, whereas the therapeutic consequences of results obtained with conventional parameters of hemostasis immediately [9]. Several studies explored their role in the detection of coagulopathies and changes in bleeding management as well as in the perioperative setting [10–14]. However, despite a vast amount of investigations, the clinical value of these methods has been challenged repeatedly [15–19]. It has been argued that the lack of rigorous examinations assessing the correlation of thromboelastometry and thrombelastography measurements with conventional parameters of hemostasis jeopardizes its clinical interpretation and usefulness [8, 20, 21].

To the best of our knowledge, however, there is no systematic review assessing the available evidence on thromboelastometry and thrombelastography examinations under physiological conditions in healthy volunteers. We therefore set out to systematically search, describe and inventory published reports on ROTEM and TEG data in healthy subjects, targeting at the correlation of thromboelastometry and thrombelastography measurements with conventional parameters of hemostasis.

**Material and Methods**

The present systematic review was done according to the PRISMA statement [22].

**Search Strategy**

To identify papers investigating correlations of ROTEM and TEG measurements with conventional parameters of hemostasis under physiological conditions, we searched (PRE-)MEDLINE (PubMed interface) using a search string including the two Medical Subject Headings (MeSH) ‘Thrombelastography/methods’[Mesh], ‘Blood Coagulation Tests’[Mesh] and the free text terms thromboelastography, thromboelastometry, ROTEM, and TEG. SCOPUS was searched using the following algorithm: TITLE-ABS-KEY(thromboelastography OR thromboelastometry) AND (valid*) AND (LIMIT-TO(DOCTYPE, ‘ar’) AND (LIMIT-TO(SUBJAREA, ‘MED’))). We also searched the Web of Science database entering 4 seminal papers [8, 23–25] and checked their citations for potentially relevant papers. Searches were complemented checking reference lists of included studies and of a recently published Cochrane review [15]. Electronic searches were done from inception to November 2016.

**Selection Criteria for Inclusion**

To be included a paper had to use whole blood or citrated blood obtained from healthy volunteers and had to assess either ROTEM or TEG. Additional criteria had to be fulfilled for inclusion of correlation studies: ROTEM and TEG data in combination with at least one established parameter of hemostasis such as activated partial thromboplastin time (aPTT), prothrombin time (PT), platelet count (PLT), fibrinogen level, or d-dimers.

**Exclusion Criteria**

We excluded papers assessing trauma patients, patients undergoing cardiac surgery, and other patients with severe illness as well as studies including pregnant women, children, or patients with sepsis if the study did not include any kind of control arm with healthy subjects.

Head-to-head comparisons between ROTEM and TEG were also excluded, if they were assessed in absence of an established hemostasis method.

**Selection Process and Data Abstraction**

In the case of multiple publications on the same participants, the most complete report was chosen for each study. We extracted data in duplicate, and a third reviewer resolved any discrepancies if the two reviewers disagreed. Of each study we extracted participants’ age, number of female participants, the total number of included subjects, the device employed (ROTEM, TEG), and the hemostasis parameter assessed. In case of TEG studies these were reaction time (R time), time to maximum clot formation (K time), a, angle, MA (maximal amplitude), SEMS (shear elastic modulus strength), COI (coagulation index), MTG (maximal thrombus generation), TMG (time to maximal thrombus generation), and TGT (total thrombus generation). In the ROTEM studies CT (clotting time), CFT (clot formation time), alpha angle, and MCF (maxim clot firmness) for both INTEM and EXTEM assay were recorded. Finally, we also extracted which of the established methods was used as the comparator test and what type of correlation or concordance parameters was used.

**Thromboelastometry/Thrombelastography Analysis**

The analytical principle of thromboelastometry and thrombelastography analysis is discussed in detail elsewhere [13, 20, 26–28]. In brief, the viscoelastic properties of a forming clot are assessed by recording the oscillations of a pin or a cup containing a citrated whole blood sample. Different aspects of clot formation are represented as parameters of the analysis. For example, the time from addition of the reagent until start of clot formation is denoted as CT in case of ROTEM, and R time in case of TEG; the clot strength is reported as MCF, or MA. Parameters are measured after addition of different activators. By analogy with PT, tissue factor reagent is added in case of EXTEM (ROTEM) and Rapid-TEG. Comparable to the aPTT, contact phase activators are added in case of INTEM (ROTEM) or standard TEG.

**Results**

**Selection Process**

Searches retrieved 1,721 records of which 1,588 had to be excluded after screening title or abstract. Full texts of 133 articles were examined for inclusion. Of these, 125 articles fulfilled at least one exclusion criterion leaving 8 articles for detailed examination [24, 29–35]. The selection process is described in figure 1.

**Included Studies**

Thromboelastometry or thromboelastography measurements in healthy volunteers have been performed in 8 studies, enrolling 632 subjects (table I) [24, 29–35]. Five studies reported thromboelastometry/thrombelastography results but did not investigate correlations with conventional parameters of hemostasis [24, 29, 30, 34, 35]. Lang and colleagues [24] conducted a multicenter study to establish reference values for ROTEM thromboelastome-
try. 262 individuals were included in five centers in Germany, Austria, and France. Even though considerable variation between centers existed, ‘orientating reference ranges’ were calculated for INTEM, EXTEM, and FIBTEM parameters (CT, CFT, α angle, A10, A20, A30, MCF, CLI30, and ML). Tripodi and co-workers [35] conducted ROTEM measurements in 58 healthy volunteers to establish reference ranges for an observation study in cirrhosis patients. However, results were not reported, and no correlation studies have been done. 20 healthy women were studied using TEG in an investigation by Huissoud and colleagues [30], serving as a control for thromboelastometry patterns in pregnancy. Median values and inter-quartile ranges of EXTEM, INTEM, FIBTEM, and APTEM parameters were reported. TEG was conducted in 5 volunteers in a study by Foley et al. [29] aiming to improve the thromboelastography assay, and individual measurements were reported.

Table 1. Characteristics of identified evaluation studies in healthy volunteers

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Mean age (SD), years</th>
<th>Age range, years</th>
<th>Female, n (%)</th>
<th>Total (n)</th>
<th>Device</th>
<th>Correlation/concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lang et al., 2005 [24]</td>
<td>45.4 (17.6); 43.1 (15.9); 38.8 (14.4)</td>
<td>–</td>
<td>161 (61.5%)</td>
<td>262</td>
<td>ROTEM</td>
<td>–</td>
</tr>
<tr>
<td>Rivard et al., 2005 [32]</td>
<td>–</td>
<td>–</td>
<td>2 (50%)</td>
<td>4</td>
<td>TEG</td>
<td>linear/non-linear regression</td>
</tr>
<tr>
<td>Tripodi et al., 2009 [35]</td>
<td>30 (median)</td>
<td>26–33</td>
<td>20 (100%)</td>
<td>20</td>
<td>ROTEM</td>
<td>–</td>
</tr>
<tr>
<td>Huissoon et al., 2009 [30]</td>
<td>36.8 (11.2)</td>
<td>–</td>
<td>40 (34%)</td>
<td>118</td>
<td>TEG</td>
<td>–</td>
</tr>
<tr>
<td>Roedeloffzen et al., 2010 [33]</td>
<td>49.5 (25.5)</td>
<td>19–87</td>
<td>60 (50%)</td>
<td>120</td>
<td>TEG</td>
<td>Pearson’s correlation coefficients</td>
</tr>
<tr>
<td>Foley et al., 2012 [29]</td>
<td>29–32</td>
<td>0 (0%)</td>
<td>5</td>
<td>TEG</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Kim et al., 2013 [31]</td>
<td>44</td>
<td>22–71</td>
<td>19 (42%)</td>
<td>45</td>
<td>ROTEM</td>
<td>Pearson’s correlation / linear regression</td>
</tr>
</tbody>
</table>

**Fig. 1.** Study flow.

**Correlation with Conventional Parameters of Hemostasis**

Three studies reported the extent of association between thromboelastometry/thromboelastography parameters and conventional coagulation assays [31–33]. The details are reported in table 2. Two studies focused on thromboelastography [32, 33]. In a study enrolling 120 participants (50% female) of 49.5 years on average, Roedeloffzen and colleagues [33] compared R time with the aPTT, K time with the hemoglobin level, aPTT and the fibrinogen level, α angle with aPTT and the fibrinogen level, MA with the fibrinogen level, SEMS with the fibrinogen level, the CI with aPTT and the fibrinogen level, MTG with the fibrinogen level, TMG with aPTT, and the TTG with the fibrinogen level. Pearson’s correlation coefficient was reported and varied between 0.21 (TMG vs. aPTT) and 0.40 (TTG vs. fibrinogen level). Rivard and co-workers [32] studied the association between a TEG parameter used as surrogate for TTG with thrombin generation as measured using thrombin/antithrombin complexes (TAT) in 4 volunteers. A correlation coefficient of 0.85 was determined from a linear regression and a correlation coefficient of 0.94 from a linear regression using the ln of TAT.

Associations between thromboelastometry parameters and conventional parameters of hemostasis were investigated in one study only [31]. Kim and co-workers [31] correlated CT, CFT, α angle, CFR, and MCF with PT as well as aPTT. No significant correlation was found between any EXTEM or INTEM parameters and PT. For INTEM, the CT value was significantly correlated with aPTT only (r = 0.41).

**Discussion**

**Main Findings**

Using comprehensive retrieval methods, our systematic review only found few studies assessing thromboelastometry as well as thromboelastography and correlations thereof with established parameters of hemostasis in healthy volunteers. The studies revealed only a weak correlation.

**Findings in Context**

There are several studies investigating the relationship of thromboelastometry or thromboelastography in animals, e.g.,
Table 2. Correlation of thromboelastometry/thrombelastography parameters with conventional parameters of hemostasis in healthy volunteers

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Device</th>
<th>Test</th>
<th>Pearson's correlation coefficient</th>
<th>Hb</th>
<th>aPTT</th>
<th>PT</th>
<th>fibrinogen</th>
<th>TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roeloffzen et al., 2010 [33]</td>
<td>120</td>
<td>TEG</td>
<td>R time</td>
<td>-0.27 (p &lt; 0.05)</td>
<td>NS</td>
<td>0.24 (p &lt; 0.05)</td>
<td>NS</td>
<td>-0.28 (p &lt; 0.05)</td>
<td>0.37 (p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>K time</td>
<td>-0.27 (p &lt; 0.05)</td>
<td>NS</td>
<td>0.24 (p &lt; 0.05)</td>
<td>NS</td>
<td>0.37 (p &lt; 0.05)</td>
<td>-0.37 (p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a angle</td>
<td>-0.21 (p &lt; 0.05)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.25 (p &lt; 0.05)</td>
<td>0.27 (p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MDMS</td>
<td>-0.21 (p &lt; 0.05)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.25 (p &lt; 0.05)</td>
<td>0.40 (p &lt; 0.05)</td>
</tr>
<tr>
<td>Rivard et al., 2005 [32]</td>
<td>4</td>
<td>TEG</td>
<td>TTG</td>
<td>-</td>
<td>-</td>
<td>0.85 / 0.94† (p &lt; 0.05)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kim et al., 2013 [31]</td>
<td>45</td>
<td>ROTEM</td>
<td>CT EXTEM</td>
<td>-0.223 (p = 0.17)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CFT EXTEM</td>
<td>-0.149 (p = 0.36)</td>
<td>-</td>
<td>-</td>
<td>-0.149 (p = 0.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α angle EXTEM</td>
<td>0.079 (p = 0.63)</td>
<td>-</td>
<td>0.005 (p = 0.89)</td>
<td>-0.053 (p = 0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MCF INTEM</td>
<td>-0.014 (p = 0.93)</td>
<td>-</td>
<td>0.003 (p = 0.98)</td>
<td>-0.014 (p = 0.93)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hb = hemoglobin level; K time = time to maximum clot formation; MA = maximal amplitude; MCF = maximum clot firmness; MTG = maximal thrombus generation; NS = not stated; PT = prothrombin time; R time = reaction time; SEMS = shear elastic modulus strength; TAT = thrombin/antithrombin complex.

†Derived from log-linear regression analysis (ln(TAT)).
Mauch et al. [36]. In this study the intrarater and interrater validity of the ROTEM data was analyzed with blood from healthy pigs. Another prospective study compared the coagulation profiles of healthy foals using standard techniques (PT, aPTT, fibrinogen concentration, and antithrombin) with the TEG analyzer [37]. The validity of the ROTEM and TEG was verified through comparison with standard methods in the context of specific circumstances, as for example orthotopic liver transplantation [38–40], during aortic surgery [12, 41, 42], or in trauma patients [18, 43, 44]. We also found a few trials reporting on head-to-head comparisons between ROTEM and TEG [21, 45, 46]. Although these approaches also yield valuable information, we think that they do not make comparisons with standardized methods in healthy subjects superfluous.

Strength and Limitations

We applied up-to-date and rigorous systematic review methods to retrieve and assess the available evidence. In view of the risk that potentially relevant studies could be missed due to ambiguous indexing in the various databases, we applied an over-inclusive approach. These sensitive searches retrieved over 1,700 records. Screening for inclusion was made in duplicate to reduce the risk to miss relevant papers. We expected to find a reasonable number of studies that would allow us to provide quantitative summaries of various comparisons. Moreover, out of the many available, we hoped to depict those parameters from thromboelastometry and thrombelastography that would be most suited for investigations in various clinical settings such as acute bleeding, applications in emergency rooms, and for treatment of patients with specific hemostatic deficiencies. Despite our current evidence base impeded us from generating meaningful summaries for further research and clinical practice.

Implications for Clinical Practice

The small number of studies examining thromboelastometry or thrombelastography in a cohort of healthy volunteers and systematically comparing the so obtained findings to conventional assays of hemostasis is remarkable. One may argue that the clinical value of established coagulation parameters is limited as well. It is true that results of coagulation parameters such as PT not directly prompt any specific treatment. Nevertheless, they are still important biomarkers for the detection of coagulopathies in the setting of acute bleeding [47–49].

Implications for Research

Following existing guidelines of test evaluation (reviewed and discussed in [2]), we propose that further research should first investigate the distribution of normal values of ROTEM and TEG parameters in reasonably sized studies enrolling healthy subjects. Second, distributions should be assessed in groups of patients with a specific illness and compared to distributions of healthy subjects. In a third step, assessing test performance characteristics such as sensitivity and specificity should be performed, taking contextual clinical information into account. Fourth, studies should determine the added value of thromboelastometry/thromboelastography in context of other clinical information about the patients’ state that is available prior testing. Finally, decision-analytic models should be performed determining the optimal areas for clinical use, taking clinical outcomes into account.

Conclusions

Studies assessing the relationship between thromboelastometry or thromboelastography analyses and parameters of hemostasis in healthy subjects remains scarce. From a hemostaseologic standpoint, further physiologic research is needed to elucidate the significance of thromboelastometry and thrombelastography for clinical practice and research.

Disclosure Statement

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References

2 Lijmer JG, Leeflang M, Bossuyt PM: Proposals for a thromboelastography in a cohort of healthy volunteers and base impeded us from generating meaningful summaries for fur-


45 Casutt M, Kristoffy A, Schuepfer G, Spahn DR, Konrad C. Effects on coagulation of balanced (130/0.42) and non-balanced (130/0.4) hydroxyethyl starch or gelatin compared with balanced Ringer’s solution: an in vitro study using two different viscoelastic coagulation tests: ROTEM(R) and SONOCLOTM. Br J Anaesth 2010;105:273–281.


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