An Assessment of Clinical Interchangeability of TEG (R) and RoTEM (R) Thromboelastographic Variables in Cardiac Surgical Patients

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Thromboelastography is increasingly used for point-of-care assessment of the viscoelastic clot strength in whole blood. Clinically, 2 major systems are used: the TEG® system and the RoTEM® system. There are several differences between these 2 systems affecting the results of the measurements. As a consequence, the clinical interpretation of the obtained results with each device may be different.

Simultaneous use of both systems has been reported in clinical settings.1–3 Both systems were compared in a laboratory setting with purified and activated plasma.4 These studies suggest that the results obtained with both devices are not completely interchangeable.

However, a clinical comparison of both systems has not been performed in patients. This is important, because several transfusion algorithms have been published that use thromboelastography for interventions.5–7 In addition, thromboelastography is increasingly used in a variety of conditions to guide clinical management, for example, the application of recombinant factor VIIa,8 and the hypercoagulability in patients with malignancies.9

The aim of this study was to assess the interchangeability of TEG® and RoTEM® thromboelastographic variables in a clinical setting with patients scheduled for cardiac surgery in a 2 × 2 study design (2 devices, 2 different measurements on each device, each measurement consisting of 4 variables) using Bland–Altman (BA) plots and mixed-model analysis. To assess the repeatability of the 2 devices, we made 7 replicated consecutive measurements in 2 volunteers using the same 2 × 2 design.

METHODS

Study Design

In this study 2 devices were used: the TEG® system (Hemoscope, Niles, Illinois) and the RoTEM® system (Pentapharm, München, Germany). In the TEG® system, 2 measurements were performed: the kaolin TEG® (kaoTEG®, i.e., with the addition of kaolin as activator) and the native TEG® (natTEG®, i.e., without addition of activator). In the RoTEM® system 2 measurements were also performed: the intrinsic RoTEM® (inTEM, i.e., with the addition of partial thromboplastin/phospholipids and CaCl2) and the extrinsic RoTEM® (exTEM, i.e., with the addition of tissue factor and CaCl2). For each device, each measurement consisted of the following 4 variables. For the TEG®: reaction time (R), the time from the start of the recording until the amplitude reaches 2 mm; coagulation
time (K), the time from the end of the reaction time until the amplitude reaches 20 mm; maximum amplitude (MA), which represents the absolute strength of the clot; and angle (α), formed by the slope from the R value to the K value. These parameters correspond with the RoTEM® for coagulation time (CT), clot formation time (CFT), maximum clot firmness (MCF), and angle (α), respectively. For sake of clarity the abbreviations R, K, MA, and α will be used for both systems.

Patients
After ethical committee approval and written informed consent, 46 patients scheduled for elective cardiac surgery were included. Patients older than 80 years of age and patients with known coagulation abnormalities were excluded. Anticoagulation therapy was discontinued according to institutional guidelines.

Immediately after induction of anesthesia, native blood samples (Vacutainer, 4 mL, BD Diagnostics, Plymouth, United Kingdom) and citrated blood samples (Vacuette, 3.5 mL with sodium citrate 3.2%, Greiner, Austria) were taken from a 20-G radial artery pressure monitoring line without heparin flush. Within 4 minutes after the blood was collected, 1 TEG® cup was filled with 360 μL of this kaolin-activated blood was filled. The TEG® system was set at 37°C. After installation of the blood samples in the TEG® system, the citrated blood sample was used for the RoTEM® system, also set at 37°C. Using an electronic calibrated micropipette, we filled 1 RoTEM® cup with 20 μL CaCl2 20 μL partial thromboplastin/ phospholipid activator, and 300 μL of blood according to the instructions on the computer screen to assess the intrinsic coagulation pathway (inTEM). Then, again using an electronic calibrated micropipette, we filled another RoTEM cup with 20 μL CaCl2 20 μL thromboplastin activator, and 300 μL of blood according to the instructions on the computer screen to assess the extrinsic coagulation pathway (exTEM).

Repeatability Measurements in 2 Volunteers
The comparison of the repeatability of each method is relevant to method comparison studies, because the reproducibility of 2 methods of measurement limit the amount of agreement that is possible. Therefore 7 blood samples from 2 volunteers were determined in rapid succession. Thus, each of the 7 measurements started with a new venapuncture. After puncture of an antecubital vein with a 21-G Venoject Quick Fit Needle (Terumo, Leuven, Belgium), the tourniquet was removed and free-flowing blood sampled. The first 4 mL was discarded to minimize contamination of the samples by tissue thromboplastins released at the time of venapuncture. Four milliliters of native blood was then collected in a tube without additives (Vacutainer, BD Diagnostics, Plymouth, United Kingdom), and 3.5 mL of blood was collected in a citrated tube (Vacuette, sodium citrate 3.2%, Greiner, Austria). These blood samples were processed by the same operator in the TEG® and RoTEM® systems as is described above.

| Table 1. Number of Outliers in the Variables of Log-Converted TEG® and RoTEM® Measurements in 46 Patients |
|-------------------------------------------------|----------------------------------|-----------------|-----------------|-----------------|
| Procedure            | R                  | K                  | MA               | α                | Sum              |
| natTEG®             | 1                  | 0                  | 1                | 1               | 3                |
| kaoTEG®             | 2                  | 0                  | 1                | 1               | 3                |
| inTEM               | 5                  | 2                  | 0                | 5               | 12               |
| exTEM               | 5                  | 0                  | 0                | 0               | 5                |
| Sum                 | 13                 | 2                  | 2                | 6               |                  |

Outliers were defined as having values of at least 3 SD from the mean. R, K, MA, and α refer to the elements of the thromboelastographic tracings; R is reaction time, K is coagulation time, MA is maximum amplitude, and α is the angle alpha. KaoTEG®, the kaolin TEg®, natTEG®, the native TEG®, inTEM, intrinsic RoTEM®, exTEM, extrinsic RoTEM®. There was a difference between the TEG® and RoTEM® systems (P < 0.01, chi-square test).

| Table 2. Descriptive Data of the TEG® and the RoTEM® Systems from 166 Measurements in 46 Patients |
|-------------------------------------------------|----------------------------------|-----------------|-----------------|-----------------|
| R (seconds) | K (seconds) | MA (mm) | α (degrees) |
| kaoTEG® | 345 ± 102 | 78 ± 18 | 71 ± 6.5 | 72 ± 4.1 |
| 311–379 | 72–84 | 69–73 | 71–73 |
| 156–738 | 48–126 | 44–82 | 62–79 |
| natTEG® | 1141 ± 561 | 462 ± 41 | 57 ± 11.8 | 38 ± 18.3 |
| 966–1316 | 325–500 | 53–60 | 32–43 |
| 228–3768 | 85–2160 | 26–75 | 7–78 |
| inTEM | 179 ± 74 | 75 ± 52 | 67 ± 5.2 | 76 ± 7.0 |
| 157–202 | 59–91 | 65–68 | 74–78 |
| 0–391 | 32–294 | 57–78 | 51–83 |
| exTEM | 55 ± 28 | 61 ± 24 | 69 ± 6.3 | 78 ± 4.5 |
| 6–166 | 28–129 | 58–83 | 68–84 |

Values are given as mean ± SD (upper row), 95% confidence limits for the mean (middle row), and range (lower row). R, K, MA, and α refer to the elements of the thromboelastographic tracings: R is reaction time, K is coagulation time, MA is maximum amplitude, and α is the angle alpha. KaoTEG®, the kaolin TEG®, natTEG®, the native TEG®, inTEM, intrinsic RoTEM®, exTEM, extrinsic RoTEM®.

Data Presentation and Statistics
Analysis was performed using BA plots.10 The BA method calculates the mean difference between the 2 methods of measurement, called the bias. The limits of agreement refer to ±2 standard deviations of the mean difference. These values define the range within which 95% of the differences between measurements by the 2 methods will lie. Because the BA plots suggested a relationship between the difference and the mean, a logarithmic transformation was performed for all data according to Bland and Altman.10 As a consequence, the bias and the limits of agreement are presented as a dimensionless ratio due to back-transformation.11

This study started as an observational study, and therefore a power analysis was not performed. However, to assess the power of a study, one can also use confidence limits of relevant values. We felt, on the basis of expert opinion, that a difference of 10% of the MA would be clinically relevant. The confidence intervals are presented in Table 3 and are for the kaoTEG®, the inTEM, and the exTEM within the 10% MA limits. This indicates that the study has sufficient power. To test whether the mean values of the measured variables were equal, we used linear mixed-model statistics (MLwin version 2.02). A P value <0.05 was considered significant.
Thus, the mixed-model analysis reflects the differences between the groups, whereas the BA plots reflect the individual measurements.

RESULTS

The 46 patients (34 men and 12 women) were 66.8 ± 11.3 years old and had scheduled first-time surgery for coronary artery bypass grafting (n = 29), aortic valve replacement (n = 10), or a combination (n = 7). In total there were 46 × 4 = 184 measurements. Seventeen measurements were missing (device used for other patient (3), run out of reagent (3) or cup (1), wrong site of blood collection (2), technical computer failure (2), do not know (6)), leaving 167 measurements for analysis. From the 167 available separate measurements the number of outliers, defined as values exceeding at least 3 standard deviations, was determined. This is shown in Table 1. Most of the outliers were in the R time. Table 1 also suggests that outliers occurred more in the RoTEM® than in the TEG® measurements. The outliers were included in the statistical analysis. However, if at least 3 variables of 1 measurement were designated as outlier, this measurement was discarded. Therefore, 1 additional measurement (inTEM) was discarded, leaving a total number of 166 measurements for analysis.

Table 3. Results of the Mixed-Model Analysis of Log-Converted TEG® and RoTEM® Measurements in 46 Patients

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>K</th>
<th>MA</th>
<th>Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>kaoTEG®</td>
<td>1 (0.92–1.08)</td>
<td>1 (0.92–1.08)</td>
<td>1 (0.96–1.04)</td>
<td>1 (0.95–1.05)</td>
</tr>
<tr>
<td>inTEM</td>
<td>0.50 (0.41–0.62) &lt; 0.001*</td>
<td>0.85 (0.68–0.96) 0.11*</td>
<td>0.94 (0.90–0.99) 0.02*</td>
<td>1.05 (0.92–1.20) 0.43*</td>
</tr>
<tr>
<td>exTEM</td>
<td>0.14 (0.12–0.19) &lt; 0.001*</td>
<td>0.73 (0.60–0.90) 0.003*</td>
<td>0.98 (0.93–1.03) 0.38*</td>
<td>1.09 (0.96–1.24) 0.17*</td>
</tr>
</tbody>
</table>

Values are given as a ratio with kaoTEG® as reference in the upper row. The 95% confidence limits for the ratios are given within parentheses. The P values are indicated with an asterisk.

R, K, MA, and α refer to the elements of the thromboelastographic tracings: R is reaction time, K is coagulation time, MA is maximum amplitude, and α is the angle alpha. KaoTEG®, the kaolin TEG®; inTEM, intrinsic RoTEM®; exTEM, extrinsic RoTEM®.

Figure 1. Bland–Altman plots with limits of agreement of the kaolin-activated TEG® (kaoTEG) and the RoTEM® intrinsic (upper panels; inTEM) and extrinsic (lower panels; exTEM) activated coagulation in 46 patients presenting for cardiac surgery. Data were log converted; see text. Reaction time (R), the time from the start of the recording until the amplitude reaches 2 mm; coagulation time (K), the time from the end of the reaction time until the amplitude reaches 20 mm; maximum amplitude (MA), which represents the absolute strength of the clot; and angle (α), formed by the slope from the R value to the K value.

KaoTEG® Versus inTEM

The kaoTEG® had a longer R time than did the inTEM (P < 0.001, Tables 2 and 3). The kaoTEG® R time had a bias of 0.76, indicating that the kaoTEG® R time was about twice the inTEM R time (e0.76 = 2.14; Fig. 1, panel A). In contrast, the kaoTEG® K time was not different from the inTEM K time (P = 0.11, Table 3). The K time had a bias of 0.22 with wide limits of agreement. This was caused by 2 extreme measurements, as is shown in Figure 1, panel B. Omitting these 2 extreme measurements resulted in an improvement of the limits of agreement from 0.6/1.1 to 0.3/0.9, about 30%. The MA had a small bias of 0.05 (Fig. 1, panel C) and a good agreement, indicating that the MA could be used interchangeably. The α also had a low bias and a good agreement (Fig. 1, panel D).

KaoTEG® Versus exTEM

The kaoTEG® had a longer R time than did the exTEM (P < 0.001, Tables 2, 3) with a large variability. This resulted in a high bias of 1.97, indicating that the kaoTEG® R time was about 7 times larger than was the exTEM R time (e1.97 = 7.2; Fig. 1, panel E). The K time did not agree either. The bias was 0.36 with wide limits of agreement, quite similar to the limits of agreement of the inTEM measurements (Fig. 1, panel F).
Assessment of TEG® and RoTEM®


discussion

this study has 2 important findings. first, it demonstrates that the MA and the α correlate between both devices, whereas the R and K times had variability. second, on the basis of the reproducibility and the good agreement of the MA and α, the kaoTEG® and the exTEM had the best agreement.

previous reports note differences that exist between the TEG® and the RoTEM® systems. first, in the TEG® system the cuvette with blood rotates around a fixed wire. in the RoTEM® system the wire rotates in a fixed cuvette with blood. important differences as a result of friction forces could be reflected in the MA values, but was not found in our study. the MA and α measurements had a low bias and a good precision in the activated samples in both devices, suggesting that rotation of the wire or rotation of the cup does not influence the MA or α.

a second difference between the TEG® and RoTEM® systems is the larger and less diluted blood volume in the cuvette of the TEG® system. this might have implications for the R and K times. ruttmann et al. demonstrated an increased coagulation profile with a shortening of the R and K times after dilution with normal saline. nielsen also found a shortening of the R time after dilution. in the RoTEM® system the blood is diluted by about 10%. this may in part explain the faster onset of the coagulation in the RoTEM® system, and could also explain the differences in R time that we found while the K time was similar in the kaoTEG® and the inTEM because the dilution effects were most obvious in the R time.

third, in the TEG® system a kaolin phospholipid mixture is commonly used as activator of the coagulation process, whereas in the RoTEM® system either partial thromboplastin phospholipid (inTEM) or thromboplastin extracted from rabbit brain (exTEM) is used. we found that the kaoTEG® measurements had the best agreement with the exTEM measurements, and on the basis of the type of activator, agreement with the inTEM measurements was more likely. however, this agreement does not necessarily mean that the mechanism is similar. the data also suggest that the type of activator is important. we found the shortest times to clot formation in the exTEM measurements. tissue factor is a potent activator of coagulation. our data suggest that a potent activator such as tissue factor shortens the time to obtain results but does this at the cost of a reduced repeatability of R and K values of the measurements. this is in contrast to the findings of sorensen et al. using a velocity-based TEG® parameter, they found that the variability of the measurement decreased with the addition of tissue factor. nielsen also found in his in vitro study a shorter R time in the inTEM measurement with an almost similar variability in the kaoTEG® and the inTEM, but did not give data for the K time.

the addition of an activator did not result in different MAs in either system. our data suggest that once the incubation with activator is completed, the further the measured coagulation process is activator independent. one explanation may be that once thrombin is generated, indicated by the R time, the final step of fibrin polymerization, indicated by the MA, is minimally affected. this is supported by the findings of taketomi et al., who demonstrated that once a certain thrombin level was present, α and MA values were relatively constant. sorensen et al. reported that the initial activation of the coagulation system determined the thrombin burst, indicating that a higher initial activation should result in a higher MA. on the
other hand, Nielsen et al. found a reduction in MA when more tissue factor was added.¹⁸

Several studies addressed normal values and inter- and intraobserver variability of the TEG® and the RoTEM® systems.⁴,¹⁹–²¹ Some interassay observations had a high agreement. However, these observations were made with plasma in a strict laboratory setting. We found larger differences. Our repeatability measurements also included the retrieval of blood from the volunteers and were therefore not limited to the performance of the devices itself. In our view this most accurately represents the actual clinical point-of-care use of these devices. Thromboelastography is listed as a moderate complexity test by the Clinical Laboratory Improvement Amendment (Centers for Disease Control and Prevention, Atlanta, Georgia), requiring certain operator skills. In our study the measurements in the patients were performed by 4 investigators and in the volunteers by 1 investigator. The similar variability in the patient and volunteer observations suggests that interobserver effects are limited. However, this should be the subject of further study, because in daily practice different measurements may be performed for 1 patient by different observers.

Outliers influence the limits of agreement. Omitting the 2 extreme measurements shown in Figure 1, panel B, resulted in improvement in the limits of agreement of 30%. Outliers were included in the statistical analysis, except for 1 measurement (inTEM) that consisted of 3 outlier values. The other measurements of this patient (kaoTEG® inTEM, and exTEM) did not demonstrate outlier values. Therefore, it is likely that there were inaccuracies with the inTEM measurement itself.

Repeated measurements in the patient group would have improved the relevance of the data as proposed by Bland and Altman,¹⁰ but this approach was not feasible because of the long duration of the natTEG® measurements. We performed repeated measurements in 2 volunteers and found similar, acceptable variability in both. There is no reason to believe that the degree of within-subject variability would be significantly different in different subjects.

Another limitation is the number of missing data. Seventeen of 184 measurements were missing. It is important, however, in that these failures occurred in a random order and were not attributable to 1 device or 1 measurement. Thus it is highly unlikely that these missing data would affect the reported results.²⁰

This study may have clinical implications. Several transfusion algorithms use the R time to guide the transfusion of freshly frozen plasma and platelet concentrates.⁵–⁷,²² This study demonstrates that this determination has large variability in both devices. Thus, transfusion algorithms based on these determination are likely to be affected by type I errors, and therefore each device should be individually tested in parallel with more conventional laboratory determinations (prothrombin time, activated partial thromboplastin time, fibrinogen) to determine whether they are useful for guiding freshly frozen plasma transfusion. When α or MA values are used to guide cryoprecipitate or fibrinogen concentrate, either device seems to be reasonable.

Another drawback of transfusion algorithms using thromboelastography is that reference values are used from the normal population. Only Lang et al. presented normal values for cardiac surgical patients, who are different from the normal population.²⁰ Our data agree with their values. One additional benefit of this study is that we obtained normal values for a typical population of cardiac surgical patients for both devices.

In conclusion, the TEG® and the RoTEM® measurements correlated for the MA and the α, but not for the R and K. The measurements that are obtained with these 2 devices are therefore not completely interchangeable in a clinical setting, although the kaoTEG® correlated with the exTEM measurements. Given the poor repeatability of R and K times and the different patient populations and settings in which the devices are used, these measurements should be used with caution. The measurements of MA and α could be used interchangeably for both devices, but for a proper interpretation the whole coagulation process should be considered.

**REFERENCES**

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