Changes in Thrombelastograph™ Variables Associated with Aging

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Aging is associated with hypercoagulability. To assess thrombelastography (TEG®) variables associated with aging, 132 adult patients of various ages undergoing orthopedic surgery for fracture repair had venous blood samples withdrawn for testing of recalcified TEG® before the induction of anesthesia. Age was weakly correlated with all TEG® variables: \( r \) time (R) (\( r = -0.45, P < 0.001; R = 19.5 - 0.09 \times \text{age} \)), \( k \) time (K) (\( r = -0.49, P < 0.001; K = 6.5 - 0.04 \times \text{age} \)), maximum amplitude (MA) (\( r = 0.25, P < 0.01; \text{MA} = 53.3 + 0.07 \times \text{age} \)), and \( \alpha \) (\( r = 0.52, P < 0.001; \alpha = 52.8 + 0.2 \times \text{age} \)).

The correlation was stronger for men than for women. Only R was significantly correlated with age when the women were separately analyzed. Part of the correlation may be attributable to a concurrent decrease in hemoglobin with aging, but age remained an independent predictor of R, K, and \( \alpha \) on forward stepwise linear multiple regression analysis. Aging was weakly associated with changes in TEG® variables, which should be allowed for when interpreting TEG® measurements in the elderly.

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Thrombelastography® (TEG®; Haemoscope Corp., Skokie, IL) is a useful point-of-care global coagulation monitor. One of the advantages of TEG® over conventional coagulation tests is its ability to demonstrate rapidly hypercoagulable states (1).

Advancing age is associated with hypercoagulability. Increased plasma concentrations of fibrinogen, factor VII, factor VIIIc, and factor IX are associated with aging (2–4). Increased plasma concentrations of thrombin and fibrin markers such as thrombin-antithrombin complex (3,4), fibrinopeptide A (4,5), and prothrombin fragment 1 + 2 (F1 + 2) (2–5) have also been demonstrated. Antithrombin III concentrations are also smaller (3), and platelet aggregation is increased (6). These differences are even more pronounced in centenarians (4) and are not dependent on ethnicity (7).

Because TEG® is highly sensitive to hypercoagulability, perhaps the “normal” ranges of the various TEG® variables may change with aging. This study examined the changes in TEG® associated with aging.

Methods

With approval from the University of Hong Kong Ethics Committee and informed consent from patients, ASA status I–III patients presenting for elective orthopedic operations were recruited. All recruited patients had fractures presenting for fixation. Most of the elderly patients had hip fractures, whereas the younger patients had various upper or lower limb fractures. Patients with current malignancy or a history of malignancy, with a known preexisting hypercoagulable state, or with a known preexisting bleeding tendency or who were taking drugs such as nonsteroidal antiinflammatory drugs, aspirin or other antiplatelet drugs, warfarin, or any other drug known to interfere with coagulation were excluded. Patients with cardiovascular or metabolic diseases and patients taking 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors were not excluded. On the day before operation, venous blood samples were collected from all patients for measurement of complete blood count, serum albumin (ALB), blood urea nitrogen (BUN), and serum creatinine (Cr). No premedication was ordered.

On the patient’s arrival in the operating room, 10 mL of venous blood was collected before the induction of anesthesia. Blood samples were collected with the double-syringe technique from a clean venipuncture at the antecubital fossa. The first 6 mL of each sample was discarded. Whole blood 3.5 mL was then collected in a bottle containing 3.2% sodium citrate...
(blood to citrate 1:9 by volume; Vacuette™, Greiner GmbH, Germany) and stored at room temperature. Recalcification and TEG® measurements were performed after storage for 1 h, as described previously (8). TEG® variables recorded included r time (R), k time (K), maximum amplitude (MA), and angle (α). Briefly, R is similar to a whole-blood clotting time, K and α measure the rate of increase of elastic shear modulus of the developing clot, and MA indicates the strength of the clot formed (9).

Statistical analysis was performed by using the software program Statistica, Release 4.5 (StatSoft, Tulsa, OK). A P value of <0.05 was considered statistically significant. Scattergraphs were first drawn with age as the independent variable against R, K, MA, and α as the dependent variables, and the graphs were visually inspected. A linear relationship between age and the TEG® variables R, K, MA, and α would be sought if the visual inspection did not suggest an obvious non-linear relationship between the variables. Linear relationships were sought by calculating the Pearson’s correlation coefficient (r). Simple linear regression was then performed to define the relationship between age and any TEG® variable that had a statistically significant r. Because there is a known effect of sex on TEG® variables (10), the correlation was repeated for male and female patients separately.

In addition, patients were divided into 3 groups according to age. Group Y (young) consisted of patients <50 yr of age, Group M (middle) included patients aged 50 to 79 yr, and Group E (elderly) consisted of patients aged 80 yr or older. R, K, MA, and α were compared among these 3 groups by using analysis of variance followed by Student’s t-tests with the Bonferroni correction.

To explore the possible contribution of other factors to variations in R, K, MA, and α, r was also calculated among R, K, MA, α, hemoglobin (Hb), platelet count (PLT), total leukocyte count, neutrophil count, lymphocyte count (LYM), ALB, BUN, and Cr. Spearman’s correlation coefficient was calculated for smoking habits.

The linear relationship between age and Hb, PLT, total leukocyte count, neutrophil count, LYM, ALB, BUN, and Cr was also sought by calculating r. This allowed identification of any multicollinearity between variables for subsequent multiple regression analysis.

To evaluate the contribution of age per se on predicting changes in R, K, MA, and α, four linear multiple regression models were constructed. R, K, MA, and α were selected as the dependent variable in each of these models. The independent variables included sex (female = 0; male = 1) and all other variables that were found to have significant correlation with R, K, MA, or α in the earlier analysis. The forward stepwise method was used to feed the independent variables into the model, with F set at 3 for variable entry and F set at 1 for variable removal. Tolerance was set at 0.3 to control for multicollinearity between independent variables. Only coefficients from the final model were reported.

There were no data in the literature on the strength of correlation between age and R, K, MA, and α. A correlation hypothesis of r = 0.3 was assumed in this study for the purpose of sample size determination. To measure such a correlation coefficient at an α error of 0.01 and with 80% power, a sample size of 125 was required.

### Results

One-hundred-thirty-two patients completed the study. The age distribution of these patients is presented in Figure 1. Other patient demographics are summarized in Table 1.

Age was significantly correlated with all four TEG® variables (R, K, MA, and α). Increasing age was associated with a tendency toward hypercoagulability with shortening of R and K and widening of MA and α. The scatter diagrams and regression equations of R, K, MA, and α versus age are presented in Figure 2. When the male and female patients were analyzed separately, the same pattern of correlation was observed in the male patients, but age was significantly correlated only with R in females. The coefficients of the male and female correlations are presented in Table 2. As expected, a number of blood tests were closely correlated with the TEG® variables (Table 3).

Four forward stepwise linear multiple regression models were constructed with R, K, MA, and α as dependent variables. The independent variables were those with a P < 0.01 in earlier correlation analysis—namely, Hb, LYM, PLT, ALB, and BUN (Table 3)—plus sex and age. Age was an independently significant predictor in three of these four models: R, K, and α. The best multiple regression models for R, K, and α were as follows:

\[
R = 12.86 \ (95\% \ CI, \ 5.86–19.86) \\
- \ 0.072 \ (95\% \ CI, \ 0.036–0.11) \ \text{age} \\
+ \ 0.44 \ (95\% \ CI, \ 0.005–0.88) \ \text{Hb} \\
\text{with an adjusted } R^2 \text{ of } 21.7\%
\]

\[
K = 2.68 \ (95\% \ CI, \ -0.089 \ to \ 5.45) \\
- \ 0.028 \ (95\% \ CI, \ 0.015–0.041) \ \text{age} \\
+ \ 0.34 \ (95\% \ CI, \ 0.19–0.49) \ \text{Hb} \\
- \ 0.005 \ (95\% \ CI, \ 0.002–0.008) \ \text{PLT}
\]
with an adjusted $R^2$ of 39.3% 

$$\alpha = 76.46 \ (95\% \ CI, 63.68 \text{-} 89.24)$$

$$+ \ 0.13 \ (95\% \ CI, 0.071 \text{-} 0.19) \ \text{age}$$

$$- \ 2.0 \ (95\% \ CI, 1.29 \text{-} 2.71) \ \text{Hb}$$

$$+ \ 0.025 \ (95\% \ CI, 0.009 \text{-} 0.041) \ \text{PLT}$$

with an adjusted $R^2$ of 45.3%, where CI indicates confidence interval. Age was not an independent predictor of MA. The regression coefficients are presented in Table 4.

Dividing the patients into three groups showed significant differences in R, K, MA, and $\alpha$. The analysis results are summarized in Table 5.

**Table 1. Patient Demographics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>53:79</td>
</tr>
<tr>
<td>Smoking (Y:N)</td>
<td>21:111</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>56.5 ± 12.3</td>
</tr>
</tbody>
</table>

Values are $n$ or mean ± sd.

Discussion

Although TEG® is a useful bedside global hemostatic monitor that is simple to operate, interpretation of the TEG® variables requires care. In particular, the normal ranges of the variables may not apply under different operating and patient conditions. For example, performing the test on a fresh whole blood sample (the "native" TEG®) will give normal ranges that are quite different from those when the test is performed on citrated and subsequently recalcified samples. Men and women have different normal ranges (10), children younger than 12 months of age have faster clot formation (9), and pregnancy also causes important TEG® changes (11). A venous sample will also have different normal ranges compared with an arterial sample (12). However, the effect of advancing age on TEG® variables in adults is unknown.

This study confirmed the association of TEG® changes suggestive of hypercoagulability with advancing age. Shortening of R and K and widening of MA and $\alpha$ developed as the age of the patient increased. The necessary adjustments can be approximated by the regression equations for R, K, MA and $\alpha$:

$$R (\text{mm}) = 19.5 - 0.09 \ \text{age (yr)}$$

$$K (\text{mm}) = 6.5 - 0.04 \ \text{age (yr)}$$

$$\text{MA (mm)} = 53.3 + 0.07 \ \text{age (yr)}$$

$$\alpha (^\circ) = 52.8 + 0.2 \ \text{age (yr)}$$

In other words, for a patient aged 80 years, R is approximately 68% (95% CI, 52%–85%), K is approximately 57% (95% CI, 35%–78%), MA is approximately 108% (95% CI, 104%–112%), and $\alpha$ is approximately 121% (95% CI, 117%–125%) of the value at age 20. These magnitudes of differences can be relevant clinically. For example, an approximately 18%–20% difference in $\alpha$ was found to separate bleeders from nonbleeders after cardiopulmonary bypass (13,14), and an approximately 40% reduction in K was equivalent to the magnitude of difference in K seen in samples with PLT differing by approximately $80 \times 10^9/L$ (15).

The findings of this study agree with known changes in plasma concentrations of coagulation factors, fibrinogen, and thrombin and fibrin markers with...
There was no previous study in the literature reporting changes in TEG® measurements with aging. However, a study in patients undergoing cardiac surgery demonstrated shorter R in extrinsic TEG® and shorter R and K in intrinsic TEG® when patients younger than 60 years of age were compared with those older than 80 (16). Their findings were contradictory to those of this study and were rather surprising, because they have also found larger fibrinogen and smaller antithrombin III concentrations in the older group. This apparent paradox in patients with significant coronary artery disease may be explained in an analogous manner to the “smokers’ paradox” found in thrombolysis for myocardial infarction (17,18). Younger patients who presented for coronary bypass in the study by Boldt et al. (16) may have had more frequent and severe thrombophilic risk factors, such as smoking, compared with older patients. Therefore, their TEG® findings may not apply to noncardiac surgery patients.

The age-related changes in TEG® variables were much more pronounced in male than in female patients. This agreed with the findings of Gorton et al. (10) that young female subjects were more hypercoagulable than male subjects, probably because of the effects of female sex hormones. This hormonal effect will decrease as the woman ages, which may cancel out some of the hypercoagulability that will otherwise develop, as seen in men.

Figure 2. Correlation and linear regression of age with r time (R), k time (K), maximum amplitude (MA), and angle (α); r = Pearson’s correlation coefficient; CI = confidence interval. The individual regression equation is shown in each graph. Fine dotted lines are 95% confidence limits of the regression equations. Thick dotted lines are normal ranges according to thrombelastograph (TEG®) Analytical Software Version 3 (Haemoscope Corp., Skokie, IL).

Table 2. Correlation of Age with thrombelastograph (TEG®) Variables in Male and Female Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male (n = 53)</th>
<th>Female (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R (mm)</td>
<td>r 0.48, P &lt; 0.001</td>
<td>r 0.25, P = 0.025</td>
</tr>
<tr>
<td>K (mm)</td>
<td>r 0.47, P &lt; 0.001</td>
<td>r 0.16, P = 0.16</td>
</tr>
<tr>
<td>MA (mm)</td>
<td>r 0.30, P = 0.027</td>
<td>r 0.06, P = 0.61</td>
</tr>
<tr>
<td>α (°)</td>
<td>r 0.52, P &lt; 0.001</td>
<td>r 0.18, P = 0.11</td>
</tr>
</tbody>
</table>

The TEG® variables analyzed were r time (R), k time (K), maximum amplitude (MA), and angle α.
Table 3. Correlation of thrombelastograph (TEG™) Variables and Age with Blood Tests and Smoking

<table>
<thead>
<tr>
<th>Variable</th>
<th>R (mm) (n = 132)</th>
<th>K (mm) (n = 132)</th>
<th>MA (mm) (n = 132)</th>
<th>α (°) (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>r</td>
<td>P value</td>
<td>r</td>
<td>P value</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>-0.52*</td>
<td>&lt;0.001</td>
<td>0.37*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WCC (×10⁹/L)</td>
<td>0.016</td>
<td>0.85</td>
<td>0.23</td>
<td>0.007</td>
</tr>
<tr>
<td>NEU (×10⁹/L)</td>
<td>0.099</td>
<td>0.26</td>
<td>-0.035</td>
<td>0.69</td>
</tr>
<tr>
<td>LYM (×10⁹/L)</td>
<td>-0.36*</td>
<td>&lt;0.001</td>
<td>0.31*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLT (×10⁹/L)</td>
<td>-0.19</td>
<td>0.03</td>
<td>0.005</td>
<td>0.99</td>
</tr>
<tr>
<td>ALB (g/L)</td>
<td>-0.49*</td>
<td>&lt;0.001</td>
<td>0.31*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>0.41*</td>
<td>&lt;0.001</td>
<td>-0.22</td>
<td>0.010</td>
</tr>
<tr>
<td>Cr (μmol/L)</td>
<td>0.13</td>
<td>0.14</td>
<td>-0.20</td>
<td>0.024</td>
</tr>
</tbody>
</table>

The TEG™ variables analyzed were r time (R), k time (K), maximum amplitude (MA), and angle α. The blood tests were hemoglobin (Hb), white blood cell count (WCC), neutrophil count (NEU), lymphocyte count (LYM), platelet count (PLT), serum albumin (ALB), blood urea nitrogen (BUN), and serum creatinine (Cr).

Spearman’s rank order correlation; correlation with age not done.

Table 4. Regression Coefficients (β) of Relevant Independent Variables with R, K, and α

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>P value</th>
<th>β</th>
<th>P value</th>
<th>β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>0.18</td>
<td>0.09</td>
<td>0.36</td>
<td>0.08</td>
<td>-0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLT (×10⁹/L)</td>
<td>—</td>
<td>—</td>
<td>-0.22</td>
<td>0.07</td>
<td>0.21</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>-0.36</td>
<td>&lt;0.001</td>
<td>-0.35</td>
<td>&lt;0.001</td>
<td>0.34</td>
<td>0.08</td>
</tr>
</tbody>
</table>

β values are presented as estimate ± se.

Table 5. Comparison of thrombelastograph (TEG™) Variables in Group Y Versus Group M Versus Group E

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Y (n = 26)</th>
<th>Group M (n = 51)</th>
<th>Group E (n = 55)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R (mm)†‡</td>
<td>16.4</td>
<td>4.3</td>
<td>13.6</td>
<td>4.0</td>
</tr>
<tr>
<td>K (mm)†‡</td>
<td>5.3</td>
<td>2.4</td>
<td>3.7</td>
<td>1.2</td>
</tr>
<tr>
<td>MA (mm)‡</td>
<td>55.3</td>
<td>7.1</td>
<td>58.5</td>
<td>4.6</td>
</tr>
<tr>
<td>α (°)†‡</td>
<td>59.4</td>
<td>9.9</td>
<td>66.5</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Values are mean ± so. Comparison was performed by analysis of variance.

R = r time; K = k time; MA = maximum amplitude.

† P < 0.05, Group Y versus Group M by Student’s t-test with the Bonferroni correction.
‡ P < 0.05, Group M versus Group E by Student’s t-test with the Bonferroni correction.

Apart from age, another strong predictor of TEG® variables was Hb. The trend toward hypercoagulability that developed with aging was partially attributable to a concurrent decrease in Hb. This was demonstrated with multiple regression, although age still remained an independent predictor for changes in R, K, and α. A small Hb concentration, such as that occurring during acute hemodilution, causes hypercoagulable changes on the TEG® (19,20).

There is little doubt that the hypercoagulability associated with aging is genuine and clinically relevant (21–23). The findings of this study confirm that this hypercoagulability will affect TEG® measurements. The magnitude of changes is not negligible. According to our findings, we can calculate that in a 20-year-old patient, compared with an 80-year-old patient, some TEG® variables will differ by a magnitude similar to what has been reported to be associated with relevant differences in surgical blood loss and PLT (13–15). However, this was a descriptive and not an outcome study. It was therefore not possible to demonstrate directly in this study the effect of interpreting the TEG® in the elderly, with or without taking these “normal” variations into account. We believe that the findings of this study should always be applied when TEG® data are interpreted in future studies that involve the use of TEG®. In addition, there are some
useful TEG\textsuperscript{\textregistered}-based algorithms that can guide the administration of blood products. These algorithms all use one cut-off value irrespective of the patient's age (24,25). Whether the elderly may have delays in receiving appropriate blood product therapy if these algorithms are used is not known.

There were a number of limitations to this study. First, from our regression equations, the TEG\textsuperscript{\textregistered} algorithms are used is not known. Whether the elderly may have delays in re-use one cut-off value irrespective of the patient should still be valid. Another limitation is that only ever, unless the magnitude of these fracture-related fractures do cause coagulability changes (26). However, unless the magnitude of these fracture-related changes differs with age, the findings in this study should still be valid. Another limitation is that only the cited sample was used for TEG\textsuperscript{\textregistered} measurements in this study, and the observed changes may not apply to other methods of TEG\textsuperscript{\textregistered} measurement.

In conclusion, this study demonstrated a clear tendency toward hypercoagulability in all TEG\textsuperscript{\textregistered} variables associated with aging. Normal ranges of TEG\textsuperscript{\textregistered} variables may need to be developed separately for the elderly.

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References