Thrombocytopenia affects plasmatic coagulation as measured by thrombelastography

Wilfried W.H. Roeloffzen\textsuperscript{a}, Hanneke C. Kluin-Nelemans\textsuperscript{a}, André B. Mulder\textsuperscript{b} and Joost Th.M. de Wolf\textsuperscript{a}

Thrombelastography (TEG) is used as a point-of-care test of hemostasis. Different components of the test tracing are considered to reflect various parts of the hemostatic system and to distinguish low platelet count, platelet dysfunction or both from lack of plasmatic coagulation factors. To analyze the influence of one single element of the coagulation system, namely the platelet count, we used TEG serially in patients with well documented transient thrombocytopenia. A total of 188 TEG analyses were performed from 16 patients with a hematological malignancy in remission, receiving consolidation courses of chemotherapy. TEG outcomes using unmanipulated and citrated blood samples at a median of 11 times (range 1–17) in the same patients during the decrease of platelet count in response to chemotherapy were compared with outcomes in 120 healthy adults from various age categories. We found a correlation ($r = 0.7$, $P < 0.001$) between TEG clot strength (maximum amplitude) and platelet count. Moreover, platelet count was correlated respectively with the initial rate of clot formation (reaction time and clotting time), the rate of clot growth (alpha angle), and also with maximum thrombus generation, time to maximum thrombus generation and total thrombus generation. We conclude that platelet count not only affects the strength of clot formation, as was expected, but also all other phases of plasmatic coagulation. Citration of the blood sample, aiming at easy storage of the material, masked some of the important biological parameters of coagulation. Blood Coagul Fibrinolysis 21:389–397 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction
To determine the relative contribution of the different components of hemostasis, conventional coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen concentration and platelet count are measured. The limitation of these classical coagulation assays is that only information on the plasma coagulation factor levels is provided. Moreover, as most of these tests are performed in a central laboratory, it often takes time to obtain results, making the test less suitable as a perioperative test of hemostasis. In recent years the Thrombelastograph (Haemoscope Corporation, Niles, Illinois, USA) has gained popularity as a useful point-of-care coagulation monitor in the perioperative setting [1–4]. TEG is a whole blood test that gives information not only on plasma coagulation factors but also on the influence of platelets, leukocytes and erythrocytes on hemostasis, defining TEG as a more physiological instrument [5]. The different components of the TEG profile reflect different parts of the coagulation process and are used to assess the need for blood component therapy [6].

The purpose of the present study was to examine the influence of one single component of the coagulation system, the platelet count, on all available TEG parameters as measured in both native and citrated native whole blood. Although often used in clinical practice, we decided not to add activators of the coagulation process in order to improve interpretation of the initial part of the TEG line. We investigated patients with a hematological malignancy receiving chemotherapy, and assessed TEG multiple times during the chemotherapy-induced decrease of platelet count. Thus, in a single patient, all variables remained constant except for the changing platelet counts. The analyses were performed in a standardized way and results were compared with ranges obtained from healthy controls. We hypothesized that the platelet count correlates with the strength of clot formation, and that this TEG parameter is sensitive in detecting clinically relevant thrombocytopenia.

Patients and methods
Patients and controls

The institutional review board approved the study and informed consent was obtained from all patients ($n = 16$) and control persons ($n = 120$). Patients were treated for hematological malignancies and admitted for their second or third course of chemotherapy. For all patients, the underlying disease was in complete

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\textsuperscript{a}Department of Hematology and \textsuperscript{b}Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence to Joost Th.M. de Wolf, MD, PhD, Department of Hematology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

Tel: +31 90 361 2584; fax: +31 90 361 4862; e-mail: j.t.m.de.Wolf@int.umcg.nl

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remission after the preceding chemotherapy, precluding any effect of the underlying disease on the coagulation process. Also, the bone marrow function had to be restored to normal with concomitant normal peripheral blood counts. In these 16 patients, we studied the TEG performance multiple times (median 11, range 1–17) during the decrease and subsequent recovery of platelet count. The 120 controls were healthy adults from all age categories. For both study patients and controls, the following exclusion criteria were used: coagulation disorders, use of anticoagulants, use of acetylsalicylic acid within the preceding 10 days, use of nonsteroidal anti-inflammatory drugs within the last 24 h, renal diseases or plasma concentration of creatinine more than 120 μmol/l and liver disease or increased plasma concentration of aspartate aminotransferase (ASAT) (>50 U/l) or alanine aminotransferase (ALAT) (>50 U/l). Patients with septicemia, diffuse intravascular coagulation or thrombosis during the study period were also excluded. Finally, patients with a recent history (<1 week) of platelet or red blood cell (RBC) transfusion were also not eligible.

**Blood sampling and assays**

Blood samples were obtained simultaneously for TEG analysis and standard laboratory and coagulation tests (i.e., complete blood count, white blood cell differentiation, creatinine, ASAT, ALAT, PT, aPTT, fibrinogen and anti-thrombin (AT)). Platelet aggregation assays with ADP, adrenaline, ristocetin and arachidonic acid were performed once at study entrance to exclude an underlying thrombopathic disorder. Venous blood samples were drawn from an indwelling central venous catheter (patients) or collected by vein puncture at the antecubital fossa using a 21-gauge butterfly needle (controls). Two examiners obtained all blood samples, both were experienced in performing phlebotomy. Blood was collected into a 20-ml polypropylene syringe to prevent contact with glass. To minimize the effects of using a tourniquet and to exclude effects of heparin in the central venous catheter, the first aspirate of 10 ml blood was discarded. In addition to the native whole blood (native) test, some of the collected blood, 3.5 ml, was filled into two Vacutainers (Greiner bio-one, Kremsmünster, Austria), containing 0.5 ml coagulation medium citrate 3.2% for subsequent standard coagulation tests and TEG analysis (recalcified citrated native whole blood; citrated native). All standard coagulation tests were performed on the STA-R coagulation analyzer (Roche, Basel, Switzerland); PTT with Thromboelast S reagents and aPTT with Actin FS reagents (DadeBehring Marburg GmbH, Marburg, Germany), fibrinogen with excess thrombin (BioPool US Inc., Ventura, California, USA) according to the Clauss method and AT with thrombin as enzyme (STACHROME ATIII, Roche kit). Normal values for these parameters are PT 11–16 s, aPTT 26–36 s, fibrinogen 1.7–3.5 g/l and AT 75–125%.

Thromboelastographic assays were carried out using a computerized TEG coagulation analyzer (Model 5000; Haemoscope Corp). All analyses were performed with TEG disposable cups and pins as devised by the manufacturer. Polypropylene and polyethylene pipettes were used to handle reagents and blood.

TEG measurements (and standard blood laboratory evaluation) took place at study entrance, before starting chemotherapy, and three times a week afterwards until the platelet count dropped below 10 × 10^9/l. From that point onwards, TEG analyses and blood tests were performed daily until a patient needed a RBC transfusion (hemoglobin < 8 g/dl) or a platelet transfusion (platelet count < 10 × 10^9/l).

For TEG analysis in native blood, 360 μl whole blood was pipetted into the prewarmed TEG cup, and measurements were performed within 6 min from sampling [7]. Recalcification and TEG measurements in citrated native blood were performed after storage at room temperature (RT) for 1 h, as described previously [8]. Twenty microliter 0.2 mol/l calcium chloride was pipetted into the prewarmed TEG cup. The citrated native blood was gently inverted to ensure mixing of the sample. Then 340 μl citrated native blood (RT) was added to the prewarmed TEG cup. The following TEG parameters were recorded: the reaction time (R, min), representing the rate of initial fibrin formation; the clotting time (K, min), representing the time until a fixed level of clot firmness is reached; the angle (α, degrees), which is closely related to K time and represents the rate of clot growth; the maximum amplitude (mm), is a measurement of maximum strength or stiffness of the developed clot; the shear elastic modulus strength (SEMS or G, dynes/cm^2) is a parametric measure of clot firmness expressed in metric units calculated from maximum amplitude as follows: $G = \frac{5000 \times \text{maximum amplitude}}{(100 - \text{maximum amplitude})}$. R time, K time and α are prolonged by anticoagulants and coagulation factor deficiencies, maximum amplitude is especially influenced by platelet count and platelet function as well as fibrinogen level.

In addition to the former ‘classical’ TEG parameters, we made velocity calculations, describing thrombus generation during blood clotting, from the signature graph produced by TEG. These dynamic parameters are considered to give better insight into the initial part of the TEG trace by differentiating the entire initial time course [9]. The following thrombus generation parameters were recorded: maximum thrombus generation (MTG), time to maximum rate of thrombus generation (TMG) and total thrombus generation (TTG). First, the MTG (dynes/cm^2 per s), representing the velocity by which clot strength increases, beginning as SEMS starts to increase and ending after clot strength, has been stabilized. The information from this parameter is equivalent to...
the information from the $\alpha$ angle; however, MTG provides a more parametric evaluation than the determination of $\alpha$. The second variable is TMG (s), which is the time it takes to reach MTG. Finally, we determined TTG (dyne/cm²), which is the area under the velocity curve, representing the total change in elastic resistance until clot strength stabilization occurs. MTG, maximum thrombus generation; TTG, total thrombus generation.

**Statistical analysis**

For statistical analysis, SPSS 14.0 software for Windows (SPSS Inc., Chicago, Illinois, USA) was used. Variables are expressed as mean ± SD. Mean values of the TEG parameters were tested by an unpaired $t$-test comparing controls with study patients with different levels of thrombocytopenia. Significance levels were set at 0.05 (two tailed). The correlations of changes in platelet level and individual TEG variables were calculated using Spearman rank correlations.

**Results**

To obtain our own reference values, 120 controls, age 50 ± 18 years, range 20–80 years, 10 women and 10 men per decade, were studied. In Table 1, the values of the TEG parameters for native and citrated native blood are presented. The study group consisted of 16 patients (seven women and nine men), median age 45 years, range 18–62 years. Ten patients were treated for acute leukemia, five for multiple myeloma and one for Hodgkin’s lymphoma. In these patients, a total of 189 TEG analyses were performed. In 16 patients, 121 TEG analyses in native blood were performed (median 7, range 1–15). In 10 patients, 68 TEG analyses in citrated native blood were performed (median 7, range 2–17). At study entrance, each patient had normal classical coagulation tests as well as normal platelet aggregation assays (data not shown).

**Native whole blood**

Thrombocytopenia strongly influenced the TEG performance. Of the 121 TEG analyses, 30 (25%) could not be evaluated because no fibrin formation was detected. This phenomenon was related to decreasing platelet counts. No coagulation at all could be detected in 18 of 29 (62%) patients with platelet counts less than $25 \times 10^9$/l, in five of 18 (28%) patients with platelet counts between 25 and $50 \times 10^9$/l and in seven of 74 (9%) patients with platelet counts more than $50 \times 10^9$/l. In all of these patients, however, classical coagulation tests showed normal plasmatic coagulation as measured by PT, aPTT, AT and fibrinogen (data not shown).

**Relation between platelet count and thrombelastography parameters**

Fibrin formation could be measured in 91 patient samples by TEG. Figures 2 and 3 illustrate the effect of decreasing platelet count on TEG tracings, velocity profiles, as measured in one patient. Identical TEG patterns were found in all other study patients with increasing thrombocytopenia. Table 1 shows the results of TEG parameters from controls and patients with decreasing platelet counts. Bar charts presenting TEG parameters found at different platelet counts are shown in Figs 4 and 5. At a platelet count below $100 \times 10^9$/l, we found an increase in time to clot initiation ($R$ time and $K$ time were significantly prolonged) as well as a decrease in clot propagation ($\alpha$ angle) compared with controls. Remarkably, only at platelet levels below $25 \times 10^9$/l, clot strength (maximum amplitude) became significantly inferior as compared with the control group. Clot propagation (MTG) and total change in elastic resistance (TTG) declined significantly as compared with controls even at platelet count more than $100 \times 10^9$/l (in this group one-third of the patients had a platelet count below $150 \times 10^9$/l). Statistically significant correlations were found between platelet count and, respectively, maximum amplitude ($r = 0.7, P < 0.0001$), $R$ time ($r = -0.5, P < 0.0001$), $K$ time ($r = -0.7, P < 0.0001$), $\alpha$ angle ($r = 0.8, P < 0.0001$), MTG ($r = 0.6, P < 0.0001$), TMG ($r = -0.3, P < 0.008$) and TTG ($r = 0.6, P < 0.0001$) (Fig. 6a–g). In other words, both the time until clot initiation and propagation increased, and the ultimate clot strength and (change in) viscoelastic properties decreased significantly at lower platelet counts. In contrast, no significant correlations were found between platelet count and PT ($r = -0.2, P = 0.1$), aPTT.
Thrombelastography parameters in controls and in patients at different platelet counts, in native and citrated native whole blood

| TEG parameter | Controls | >100 | 100–50 | 50–25 | <25 |
|---------------|----------|------|--------|-------|-----|
| N (n = 120)   | (n = 46) | (n = 21) | (n = 13) | (n = 9) |
| CN (n = 120)  | (n = 38) | (n = 12) | (n = 10) | (n = 9) |
| R time (min)  | N 11 ± 2 | 13 ± 3  | 17 ± 3  | 15 ± 3  |
|               | CN 3 ± 1  | 3 ± 1   | 7 ± 3   | 9 ± 3   |
| K time (min)  | N 9 ± 1  | 9 ± 3  | 19 ± 4  | 30 ± 6  |
|               | CN 3 ± 1  | 3 ± 2   | 7 ± 3   | 9 ± 3   |
| α (°)         | N 26 ± 8 | 30 ± 10 | 17 ± 9  | 10 ± 8  |
|               | CN 56 ± 7 | 54 ± 12 | 51 ± 7  | 34 ± 10 |
| MA (mm)       | N 46 ± 7 | 58 ± 9  | 54 ± 10 | 45 ± 10 |
|               | CN 58 ± 6 | 61 ± 17 | 55 ± 10 | 49 ± 9  |

SEMS (dyne/cm²) | 4506 ± 1392 | 7288 ± 3371 | 6323 ± 2471 | 4333 ± 1654 | 2182 ± 489
| CN 7082 ± 1545 | 8504 ± 3103 | 6608 ± 2464 | 5046 ± 1543* | 3049 ± 727* |
| MTG (dyne/cm² per s) | N 4.1 ± 1.3 | 3.2 ± 1.3* | 2 ± 1.1* | 1.6 ± 0.9* | 1.4 ± 0.6* |
|               | CN 10.6 ± 2.8 | 6.6 ± 3.2* | 5.6 ± 2.7* | 2.6 ± 1.4* | 2.8 ± 1.5* |
| TMG (s)       | N 1747 ± 693 | 2340 ± 1404* | 3639 ± 2621* | 4359 ± 2572* | 5088 ± 4254* |
|               | CN 764 ± 147 | 981 ± 809* | 771 ± 242 | 1747 ± 1956* | 1184 ± 653* |
| TTG (dyne/cm²) | N 769 ± 114 | 552 ± 91* | 511 ± 83* | 449 ± 85* | 347 ± 44* |
|               | CN 959 ± 88 | 559 ± 113* | 504 ± 83* | 426 ± 167* | 400 ± 63* |
| TMA (min)     | N 49 ± 10 | 56 ± 18* | 99 ± 45 | 117 ± 40* | 140 ± 30* |
|               | CN 31 ± 4 | 34 ± 10 | 34 ± 5 | 51 ± 16* | 55 ± 14* |
| R + K (min)   | N 30 ± 8 | 35 ± 13 | 66 ± 32* | 82 ± 27* | 107 ± 25* |
|               | CN 13 ± 3 | 16 ± 6 | 14 ± 4 | 24 ± 12* | 24 ± 9* |

α, Angle; CN, citrated native; K time, clotting time; MA, maximum amplitude; MTG, maximum thrombus generation; N, native; R time, reaction time; R + K, R time plus K time; SEMS, shear elastic modulus strength; TEG, thrombelastography; TMA, time to maximum amplitude; TMG, time to maximum thrombus generation; TTG, total thrombus generation. * P < 0.05 different between control and study group.

Predictive value of thrombelastography parameters regarding low platelet count

As TEG maximum amplitude is considered the parameter most reflecting functional thrombocytopenia, we calculated the sensitivity of maximum amplitude in detecting clinically significant thrombocytopenia (<50 x 10⁹/l). We found a sensitivity of 79%, with a specificity of 93% and a positive predictive value (PPV) and negative predictive value (NPV) of 79 and 94%, respectively, of TEG maximum amplitude in detecting important thrombocytopenia. The test characteristics for all TEG parameters are shown in Table 2.

Thrombelastography and bedside monitoring

TEG is considered a ‘near-patient’ bedside test allowing rapid assessment of hemostasis. A fast way to obtain an early impression of the TEG curve is to look at the initial part of the TEG trace represented by time to maximum amplitude (TMA) and the sum of R and K times. The results of TMA and R + K time at different platelet counts as compared with controls are shown at the bottom.

![Thrombelastography tracings in the same patient at decreasing platelet counts.](image)

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of Table 1. This demonstrates that with platelet counts of less than \(100 \times 10^9/l\), it took about 1–1.5 h to get this ‘early’ impression, whereas with platelet counts of less than \(25 \times 10^9/l\), it took 1.5–2.5 h to obtain results.

**Recalcified citrated native whole (citrated native) blood**

All the 68 analyses in citrated native blood could be evaluated because fibrin formation was detected (R time, K time or both were detectable).

**Platelet count and TEG parameters**

Table 1 shows the effect of decreasing platelet count on TEG parameters. We found a correlation between platelet count and clot strength (maximum amplitude, \(r = 0.75, P = <0.001\)). At platelet counts below \(50 \times 10^9/l\), maximum amplitude became significantly smaller than the maximum amplitude in healthy controls. No significant correlation was found between platelet count and clot initiation (R time; \(r = 0.2, P = 0.07\)). Significant correlations were found between platelet count and, respectively, K time (\(r = -0.3, P = 0.03\), \(\alpha\) angle (\(r = 0.6, P < 0.0001\)), maximum amplitude (\(r = 0.7, P < 0.0001\)), SEMS (\(r = 0.7, P < 0.0001\), MTG (\(r = 0.4, P = 0.003\) and TTG (\(r = 0.6, P < 0.0001\)). In other words, in citrated native blood, platelet count influenced both (the velocity of) clot propagation as well as the ultimate strength and elasticity of the formed clot.

**Predictive value of thrombelastography parameters regarding low platelet count**

With citrated native blood, the sensitivity of a maximum amplitude in detecting clinically significant thrombocytopenia (\(<50 \times 10^9/l\)) was 85%, with a specificity of the test of 82% and a PPV and NPV of, respectively, 65 and 95%. The test characteristics for all TEG parameters are shown in Table 2.

**Thrombelastography and bedside monitoring**

The results of TMA and \(R + K\) time at different platelet counts, compared with controls, are shown at the bottom.
of Table 1. After storage for 1 h (equilibration time), it took another 0.5–1 h to obtain an early impression of the coagulation profile at platelet counts below $25 \times 10^9/l$.

**Discussion**

By studying the effect of different levels of thrombocytopenia on TEG parameters, we found that platelet count not only influenced the strength of clot formation (maximum amplitude) – an expected result – but also all other elements of the system. The finding of a correlation between platelet count (at levels $< 100 \times 10^9/l$) and $R$ time, respectively, $K$ time as well as $\alpha$ angle and MTG suggests an important role of platelets in initiating and propagating the coagulation cascade. A possible explanation for this observation is that platelets, but also platelet-derived micro particles, have a major role in providing membrane surface for the assembly of the reactants of the blood coagulation cascade [10]. Moreover, platelets are a storage compartment for many proteins involved in blood coagulation and its regulation [11].
Low platelet counts (<50 x 10^9/l) are considered as a major risk factor for bleeding complications [12]. TEG maximum amplitude is considered as the parameter best reflecting the effect of platelet count. However, in our study, a significant decrease in maximum amplitude was noticed only after the platelet count dropped below 25 x 10^9/l. On the contrary, in native whole blood, both K time and α angle had a high sensitivity as well as high NPVs in detecting platelet counts below 50 x 10^9/l. This emphasizes again the importance of platelets in initiating the coagulation process. Also, the novel thrombus generation parameters, MTG and TTG, were very sensitive and had high NPVs for low platelet counts, as measured in both native and citrated native whole blood. TEG is considered a bedside test, capable of delivering an impression of platelet count and function, coagulation proteins and fibrinolytic system within 30 min. We demonstrated that with decreasing platelet count both TMA and R + K time substantially prolong to more than 60 min, making rapid assessment of the coagulation process impossible. In order to circumvent this problem, perioperative TEG is performed with coagulation activator (e.g. kaolin, celite and diluted tissue factor). The coagulation activator makes blood clotting less dependent on platelets with R and K times more reproducible as compared with R and K times obtained with nonactivated samples. However, manipulation of the blood sample (by adding activators) is something we wanted to minimize, in order to eliminate artificial influences and to get more realistic data. The present study suggests an important
Another advantage of TEG over classical coagulation tests is that the assay provides information on the kinetics of the coagulation cascade as well as the quality and firmness of the resultant clot. The latter is calculated from the maximum amplitude and is defined as SEMS (dyne/cm²). As with maximum amplitude, a significant reduction in SEMS was noticed as compared with controls in native blood, only if the platelet count dropped below 25 x 10⁹/l. In citrated native blood, SEMS decreased earlier at platelet counts between 50 and 25 x 10⁹/l.

TEG analysis was performed with both native and recalcified citrated native blood to determine which test technique gives best insight into the effects of thrombocytopenia on hemostasis. From a scientific point of view, TEG analysis with native blood is superior to TEG with citrated native blood and is for a long time considered the gold standard [13]. However, in clinical practice, TEG with citrated native blood seems more feasible because this can take place in the coagulation laboratory after 1-h equibrillation time as compared with TEG with native blood, which has to take place within 6 min after sampling [14]. The correlations found between TEG variables and platelet counts with both techniques are comparable. However, in case of severe thrombocytopenia (platelets <50 x 10⁹/l), TEG performed with native blood showed a flat line in over more than 40% of the analyses, which makes it insensitive to detect these low platelet counts. Moreover, at these low platelet counts, it often took more than 2 h until TMA was reached, making the test with (nonactivated) native whole blood unsuitable as a rapid test of hemostasis. In contrast, TEG performed with citrated native blood at low platelet counts showed clot formation in all cases, and TMA was reached within 1 h in most of these cases. The latter suggests that citration could not completely prevent the activation of coagulation and platelets. This is in accordance with the findings of Camenzind et al. [8] who demonstrated progressive acceleration of blood coagulation during 30–60 min citrate storage, with a decrease in reaction time, coagulation time and angle. Others [15] demonstrated that coagulation analyses using blood exposed to citrate followed by recalcification do not yield reliable depictions of the natural dynamics of blood coagulation processes.

Although TEG performances with different platelet counts have been studied before [1,16,17], we consider our study unique at several points. First, multiple serial TEG measurements were performed in patients in whom only one component of the hemostatic system was altered, namely the platelet count. The latter is in contrast to studies in which the examined patients suffered from multiple hemostatic derangements, making analysis of the different underlying coagulopathies much more complex. Second, the fact that all measurements were performed ex vivo instead of using an in-vitro model, making our results more robust [18,19]. More recently, Larsen et al. [20], using ROTEM technology, found that the coagulopathy associated with thrombocytopenia in recalcified citrated blood was characterized by a reduced MTG and maximum amplitude. Similar to our results, they found that the minimum amount of platelets required to obtain a healthy MTG of whole blood clot formation was estimated to be 65 x 10⁹/l. In their model, however, platelet preactivation cannot be excluded, as they used a model of mixing platelet-poor plasma with platelet-rich plasma to obtain different levels of thrombocytopenia.

Third, we compared TEG outcomes in study patients with our own normal values obtained from a large series of healthy controls from all age categories. In all these controls, TEG was performed in a uniform way by the same examiners, thereby reducing interobserver bias.

A limitation of our study is that we cannot preclude any direct or late effect of chemotherapy on the coagulation system. Also, the underlying hematological condition, although in remission, may have affected study results. On the contrary, no significant changes were seen in the classical coagulation tests during the entire study period in these individuals.

Analysis of hemostasis by TEG cannot replace conventional coagulation tests, but can be seen as a valuable tool, giving extra insight into the kinetics of hemostasis, taking into account the interactions of all other cellular blood elements.

We conclude that platelet count not only affects the strength of clot formation, but also all other phases of
plasmatic coagulation. Remarkably, TEG variable maximum amplitude was insensitive in detecting the hemostatic effects of severe thrombocytopenia (<50 × 10^9/l).

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