Assessing the Methodology for Calculating Platelet Contribution to Clot Strength (Platelet Component) in Thromboelastometry and Thrombelastography

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The viscoelastic properties of blood clot have been studied most commonly using thrombelastography (TEG®) and thromboelastometry (ROTEM®). ROTEM®-based bleeding treatment algorithms recommend administering platelets to patients with low EXTEM clot strength (e.g., clot amplitude at 10 minutes [A10] <40 mm) once clot strength of the ROTEM® fibrin-based test (FIBTEM) is corrected. Algorithms based on TEG® typically use a low value of maximum amplitude (e.g., <50 mm) as a trigger for administering platelets. However, this parameter reflects the contributions of various blood components to the clot, including platelets and fibrin/fibrinogen. The platelet component of clot strength may provide a more sensitive indication of platelet deficiency than clot amplitude from a whole blood TEG® or ROTEM® assay. The platelet component of the formed clot is derived from the results of TEG®/ROTEM® tests performed with and without platelet inhibition. In this article, we review the basis for why this calculation should be based on clot elasticity (e.g., the E parameter with TEG® and the CE parameter with ROTEM®) as opposed to clot amplitude (e.g., the A parameter with TEG® or ROTEM®). This is because clot elasticity, unlike clot amplitude, reflects the force with which the blood clot resists rotation within the device, and the relationship between clot amplitude (variable X) and clot elasticity (variable Y) is nonlinear. A specific increment of X (ΔX) will be associated with different increments of Y (ΔY), depending on the initial value of X. When calculated correctly, using clot elasticity data, the platelet component of the clot can provide a valuable insight into platelet deficiency in emergency bleeding. (Anesth Analg 2015;121:868–78)

Clot amplitude is a standard parameter derived from viscoelastic methods of coagulation monitoring with thrombelastography (TEG®; Haemonetics Corp, Braintree, MA) or thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany). This variable is interpreted as a measure of clot strength. Although red blood cells make up over 90% of blood clot volume,[1] clot strength is derived from the interaction of the fibrin network and platelets.[2,3] Fibrin-based clot strength is dependent mainly on factor XIII and fibrinogen,[4] whereas platelets contribute to overall clot strength by binding and tightening fibrin fibers.[3] The platelet component of clot strength can be inhibited pharmacologically with, for example, a glycoprotein IIb/IIIa receptor antagonist or cytochalasin D. The platelet component of clot strength is defined as the difference in shear modulus measured with and without platelet inhibition.[5–7] The calculation is shown in Table 1. The platelet component of clot strength is usually expressed either dimensionless in the same way as "clot elasticity" (CE) or in units of dyne/cm^2 (e.g., G, which is numerically 50 times the TEG® parameter E or the equivalent ROTEM® parameter CE). Dyne is a unit of force that, although superseded by the SI system (1 dyne/cm^2 = 0.1 N/m^2 = 0.1 Pa), is still used in the scientific literature pertaining to viscoelastic coagulation assessment. It is important to note that the assessment of the platelet component to clot strength may lead to misleading results if the calculation is performed using clot amplitude instead of CE. In this article, we explore parameters used for defining platelet deficiency with TEG® and ROTEM®.

Viscoelastic Coagulation Monitoring

TEG® and ROTEM® are photokymographic[8] devices designed to measure coagulation under conditions with oscillation but without blood flow.[9] This reflects in vivo conditions of trauma and surgery, where blood vessels are cut or disrupted; blood flow is interrupted and the clot functions to close the vessel (hemostatic clot). It should also be considered that blood is unlikely to be fully static in vivo. The oscillations that characterize the TEG® and ROTEM® devices, which reduce clot strength compared with quiescent conditions,[10] mimic the "nonflow"/"sluggish flow" conditions of surgery and trauma.

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Table 1. Equations for Calculating Parameters of Interest

Coagulation property	Equation
Platelet component	Platelet component = $(100 \times A_T)/(100 - A_T) - (100 \times A_F)/(100 - A_F)$ [Equation used today, for correct calculation of platelet component from clot amplitude] A_T represents amplitude (total), without platelet inhibition; A_F represents amplitude under platelet inhibition (F denotes fibrin).
Shear modulus	$\varepsilon = (100 \times a)/(100 - a)$ [Source: Hartert, 1960[20]] a represents clot amplitude $G = (100 \times s)/(100 - s)$ [Source: Hartert & Schaeder, 1962[21]] s stands for deflection of the light beam (mm) G has arbitrary units $G = (5000 \times A)/(100 - A)$ [Equation used today] A represents clot amplitude G, defined as shear elastic modulus strength (dyne/cm^2)
Clot elasticity	$CE = (100 \times A)/(100 - A)$ A represents clot amplitude
Maximum clot elasticity	$MCE = (100 \times MCF)/(100 - MCF)$ MCF stands for maximum clot firmness (i.e., the peak value of clot amplitude)
Clot elasticity attributable to platelets (i.e., platelet component)	$CE_{platelet} = CE_{EXTEM} - CE_{FIBTEM}$ $MCE_{platelet} = MCE_{EXTEM} - MCE_{FIBTEM}$

In common with many other biological tissues, blood clots have viscosity and elasticity properties. Application of stress to a blood clot results in a molecular rearrangement known as "creep," characterizing viscosity. However, when the stress is removed, the clot's elasticity returns to its original form. The Maxwell model takes into account a material's viscoelastic properties in relation to stress, strain, and changes in these parameters over time. Early consideration of clot properties suggested that a blood clot could be considered to behave as a Maxwell body.[11] However, recent porcine studies indicate that the Zener model may be more appropriate.[12,13] The Zener model (also referred to as "the standard linear solid model") is an alternative method of modeling the behavior of a viscoelastic material which, unlike the Maxwell model, includes a description of creep.

In addition to factor XIII,[4] platelets and fibrin/fibrinogen are recognized as the key determinants of whole blood clot strength.[14,15] After platelets have bound to fibrin via the glycoprotein IIb/IIIa receptor, the clot contracts through the action of cytoplasmic motility proteins inside platelets, such that fluid (serum) is expelled.[16] With TEG® and ROTEM® devices, the clot is attached to both the pin and the cup, and clot retraction is therefore hindered. However, the clot contractile forces may contribute to clot stiffness, which translates into increased clot amplitude. It has been proposed that the relative contributions of platelets and fibrin to the clot amplitude (strength) are approximately 80% and 20%, respectively.[17,18] Two points should be raised regarding this proposition. First, the estimation of the platelet and fibrin contribution to clot strength should, theoretically, be based on CE and not on clot amplitude. For example, using rabbit whole blood samples, Nielsen et al.[7] calculated that platelets contribute 87% of CE in the absence of tissue factor and 94% upon exposure to tissue factor. Second, the extent to which platelets contribute to hemostasis probably differs from their contribution to CE: there is no evidence that platelets make an 80% to 95% contribution to hemostasis.

In 1948, Hartert[19] introduced a viscoelastic device for measuring the shear modulus of a blood clot. Whole blood was added to a cup, and a plunger (pin) was immersed in the blood. The apparatus was designed so that rotation of the plunger was recorded via deflection of a light beam, with a 100-mm deflection representing the maximal rotation of 4°45′ (the scale of 0–100 mm was chosen arbitrarily). Hartert used the symbol ε to denote CE.[19] In 1960, he used the same symbol to denote shear modulus of the clot and defined its relationship with clot amplitude as shown by the equation in Table 1.[20] The equation was written slightly differently by the same author in 1962 (Table 1).[21] Importantly, the equation shows that the relationship between deflection of the light beam (subsequently defined as clot amplitude) and shear modulus is not linear. The symbol ε was used synonymously with G in the 1962 publication. This is confusing, because within the same publication Hartert calculated the shear modulus of a clot with amplitude 2.5 cm to be 5000 dyne/cm^2.[14] This is the basis for today's calculation of G (defined as shear elastic modulus strength in units dyne/cm^2) from clot amplitude (A) (Table 1).[22,23] Numerically, G (dyne/cm^2) has a value 50 times that of Hartert's parameter G with arbitrary units.

In a discussion of Hartert's work, Copley stated that the name Hartert gave for his method—thromboelastography—was ill-chosen and even misleading, because the term "thrombus" is reserved for intravascular clotting, whereas blood clot in Hartert's device is formed in vitro.[20] Copley suggested the term "coaguloelastograph" or "blood clot elastograph" for Hartert's apparatus[20]; these suggestions were reiterated by Evans et al.[24] in 2006.

Today, the principles of using either TEG® or ROTEM® remain similar to the early work of Hartert. Whole blood or plasma is placed into a cup, although unlike in Hartert's experiments reagents, such as celite or kaolin, are added to stimulate coagulation. Similarities between the current TEG® apparatus and that designed by Hartert are that the angle of rotation is the same for both devices (4°45′) and the TEG® oscillation period is 10 seconds (6 full oscillations per minute) compared with 9 seconds (6.7 oscillations per minute) with Hartert's apparatus.[21,23] The principles of the ROTEM® device are similar to those of TEG®, although with ROTEM® the oscillation period is 12 seconds (5 full oscillations per minute) and the central pin, instead of the

Table 2. Major Parameters Associated with Thrombelastography and Thromboelastometry

Coagulation property	TEG® parameter	ROTEM® parameter	Parameter used by Hartert
Clot strength	A (amplitude at any specific time) [mm]	A (amplitude at any specific time [A_5, A_{10}, etc. = amplitude at 5 min, 10 min, etc.]) [mm]	a or s (amplitude at any specific time)
	MA (maximum amplitude) [mm]	MCF (maximum clot firmness) [mm]	ma
Clot elasticity	G (shear elastic modulus at any specific time) [dyne/cm^2]		
	E ("normalized G parameter" at any specific time) [dimensionless[a]]	CE (clot elasticity at any specific time) [dimensionless]	G[b] or ε (clot elasticity at any specific time) [dimensionless]
	EMX (E at maximum amplitude) [dimensionless[a]]	MCE (maximum clot elasticity) [dimensionless]	mε (maximum clot elasticity) [dimensionless]

[a]The user manual for TEG® states that E and EMX have units dyne/cm^2,[23] but it may be argued that these parameters should be considered as dimensionless.[14]
[b]G was used by Hartert to represent dimensionless clot elasticity, a departure from conventional use of G to represent shear elastic modulus.

cup, is rotated so that resistance to its rotation is measured (resistance increases as the clot forms). With both TEG® and ROTEM®, the principal measurement is clot amplitude, which shows the extent to which rotation is either triggered (TEG®) or resisted (ROTEM®) by clot formation. The scale for clot amplitude with both TEG® and ROTEM® generally ranges from 0 to 100 mm, with the maximal value chosen arbitrarily. Both elasticity and viscosity of the forming blood clot contribute to the clot amplitude.[24]

Standard parameters used to characterize the coagulation process using TEG® or ROTEM® are summarized in Table 2. The lower section of the table is described as relating to the elasticity of the clot. This is not strictly true because both viscosity and elasticity contribute to clot amplitude,[24] and it is not possible with TEG® or ROTEM® to ascertain the contributions that each of these properties of blood clots contribute to the amplitude. As a result, the true elasticity of a blood clot cannot be calculated from TEG®/ROTEM® data. However, the elasticity parameters are directly related to the force with which the blood clot resists rotation within the device. In addition, it is believed that viscosity makes only a small contribution to clot amplitude.[20] We will therefore continue to use the term CE within this article, in relation to the parameters G, E, EMX, CE, and maximum clot elasticity (MCE).

As with Hartert's original device, clot amplitude has a nonlinear relationship with elasticity (Fig. 1). Although the scale for elasticity ranges between zero and infinity, it would have been possible to configure the TEG® or ROTEM® device to display elasticity as the primary reading instead of amplitude. Had this approach been adopted (Fig. 2), calculation of the platelet component from TEG® or ROTEM® results would have been more straightforward from the beginning. Such adjustment could now be implemented by modifying the device software. Thus, future presentation of the platelet component as a primary TEG®/ROTEM® parameter, as shown in Figure 2, is conceivable.

With the TEG® device, the cup rotates both clockwise and counterclockwise, with movement that can be described as oscillatory. Amplitude is derived from rotation of the plunger, occurring as the blood forms a bond between these 2 parts of the apparatus. The clockwise and counterclockwise rotation angles of the plunger are recorded, and the central point at which the plunger remains before the clot is formed represents no rotation. With the ROTEM® device, it is the plunger that rotates (oscillates); the cup remains stationary and the rotation angle is decreased as the clot forms. As with TEG®, clot amplitude is calculated from the maximal rotation angle of the plunger. There is a question with both devices whether clot amplitude represents the difference between the central point and the full rotation in one direction or the difference between full rotation in one direction versus full rotation in the opposite direction. With Hartert's device, the maximal rotation was 4°45′, representing 2°22.5′ clockwise from the resting point and the same rotation counterclockwise. Therefore, the 100-mm maximal deflection represented 50 mm in each direction from the resting point. The ROTEM® device provides measurements from a single point in the rotation cycle (i.e., maximal rotation in one direction). The measured deflection from the resting point is doubled to obtain clot amplitude (A), and the generation of traces showing both positive and negative deflection is artificial. With TEG®, readings are taken more frequently, so that values are obtained for rotation in both directions. Consequently, Figure 2 could be represented differently with TEG®; the curves above and below the x-axis would have equal weighting, and the y-axis scale could go downward to −50 and upward to +50. However, clot amplitude with TEG® (A) represents both positive and negative deflection, meaning that, in practice, TEG® clot amplitude values correspond to those of ROTEM® (although differences in cup size/geometry and in assay components mean that values are not directly comparable between the 2 devices).

PARAMETERS FOR ASSESSING PLATELET CONTRIBUTION TO CLOT STRENGTH

ROTEM®

Results from 2 ROTEM® tests are used to guide platelet administration: EXTEM and FIBTEM. The EXTEM test provides a measure of clot strength with extrinsic activation of whole blood coagulation via tissue factor. Both

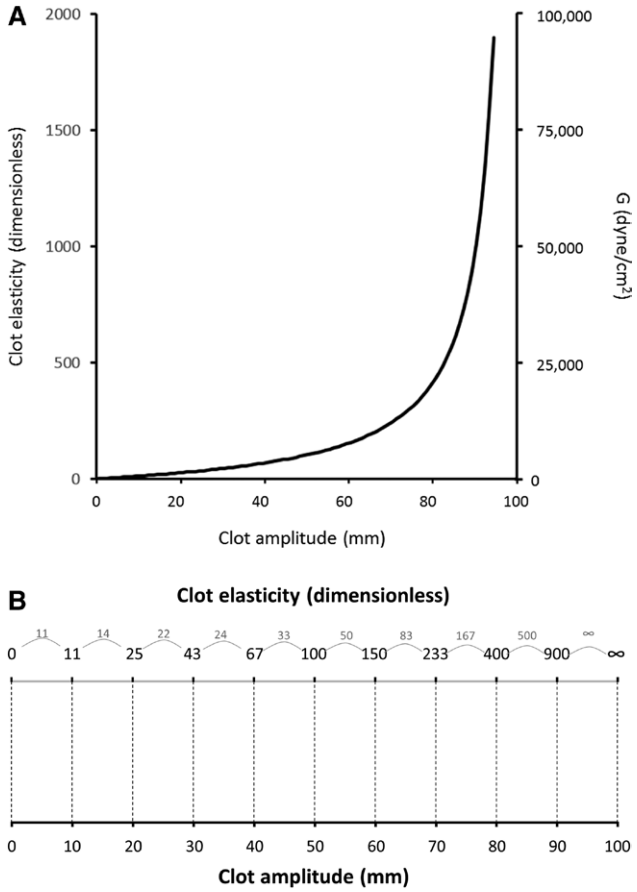

Figure 1. Relationships of clot amplitude (e.g., A) with clot elasticity (e.g., E for TEG®; CE for ROTEM®) and shear modulus (G). Because a specific increment of clot amplitude is associated with different increments of clot elasticity or shear modulus, depending on the initial value of clot amplitude, the relationship between amplitude and elasticity or shear modulus is nonlinear. In A, the single curvilinear line can show relationships of clot amplitude with both G and clot elasticity because G is 50 times clot elasticity. With respect to TEG® parameters, E = (100 × A)/(100 − A) while G = (5000 × A)/(100 − A). The conversion scale in B illustrates in a different way how clot amplitude is converted to clot elasticity; 10-mm increments in clot amplitude are associated with variable increments in clot elasticity. Configuration of a viscoelastic device so that the primary output is clot elasticity would enable the platelet component to be calculated by subtracting the primary FIBTEM reading from the primary EXTEM reading. A = Clot amplitude at any specific time (TEG® or ROTEM® notation); E = clot elasticity at any specific time (TEG® notation); CE = clot elasticity at any specific time (ROTEM® notation); G = shear modulus at any specific time.

fibrin and platelets contribute to EXTEM clot strength, meaning that EXTEM alone does not provide a specific measure of the platelet contribution to clot strength. The FIBTEM test is the same as EXTEM but with the addition of cytochalasin D to prevent platelets from contributing to the clot strength. By comparing results from the EXTEM and FIBTEM tests, a specific assessment of the contribution of platelets to clot strength (platelet component) can be obtained.

The platelet component is calculated from the elasticity results. First, CE (a dimensionless quantity) is obtained from clot amplitude (A) as shown in Table 1. MCE is calculated in the same way from maximum clot firmness (MCF) (Table 1). After such conversion, the platelet component can be calculated from EXTEM and FIBTEM results (Table 1).[5,6,25] It is important that the calculation of platelet component be performed using elasticity (e.g., CE, MCE) as opposed to clot amplitude (e.g., A, MCF) because of the nonlinear relationship between clot amplitude and CE,[6,7,21,26–28] as indicated in Figure 1 and Table 3. Unlike amplitude, CE may be considered a reflection of the force with which the blood clot resists rotation within the device. Where there is a nonlinear relationship between 2 variables X and Y, a specific increment of X (ΔX) will be associated with different increments of Y (ΔY), depending on the initial value of X. Therefore, an increment ΔX from baseline X′ cannot be considered as equivalent to the same increment ΔX from baseline X″. The European Society of Anaesthesiology guidelines for the management of perioperative bleeding highlight the fact that MCE and G have a curvilinear relationship with maximum amplitude (MA) and MCF.[29] An illustration of the comparison between platelet component, correctly calculated from CE (in this case, EXTEM- and FIBTEM-MCE values) and incorrectly calculated from clot amplitude (MCF values), is presented in Table 3. This theoretical model shows that, across a range of platelet counts (from 10,000 to 100,000/μL), ΔMCF remains unchanged, whereas ΔMCE increases with platelet count. Therefore, it is clear that ΔMCF is not appropriate for calculating the platelet component.

In the literature, there are publications where the contribution of platelets to clot strength has been calculated appropriately (i.e., using CE; Table 4). However, as also shown in Table 4, there are numerous examples where unsuitable methodology has been used, with calculations based on clot amplitude. Where the overall conclusions of a publication are based on possible incorrect calculation of platelet component (i.e., where the subtraction is performed using values for clot amplitude as opposed to CE), the findings should be interpreted with caution until the calculations have been repeated using correct methodology.

TEG®

With the TEG® device, the standard kaolin-activated TEG® assay is most commonly used in relation to assessing the platelet contribution to clot strength. However, there is also a commercially available TEG® assay with platelet inhibition (Functional Fibrinogen assay), which is based on the same principle as FIBTEM. The platelet component of clot strength may be calculated by comparing elasticity results from the Functional Fibrinogen assay and from a standard assay without platelet inhibition. For example, the platelet component could be calculated as E (elasticity) obtained using the RapidTEG™ (Haemonetics Corp) assay minus E obtained using the Functional Fibrinogen assay, where E is a "normalized G parameter,"[23] calculated in exactly the same way as Hartert's shear modulus ε (Table 1). [Note that G is shear elastic modulus strength, with units dyne/cm² (Table 1)].[23] The parameter E may be considered as equivalent to the CE parameter of ROTEM®. The units of E are commonly referred to as dyne/cm².[23] However, CE is considered dimensionless and, because E is calculated in the same way as CE, we would argue that E should also be considered dimensionless. A is the equivalent of the ROTEM® parameter A (clot amplitude, in mm). For maximum values, EMX

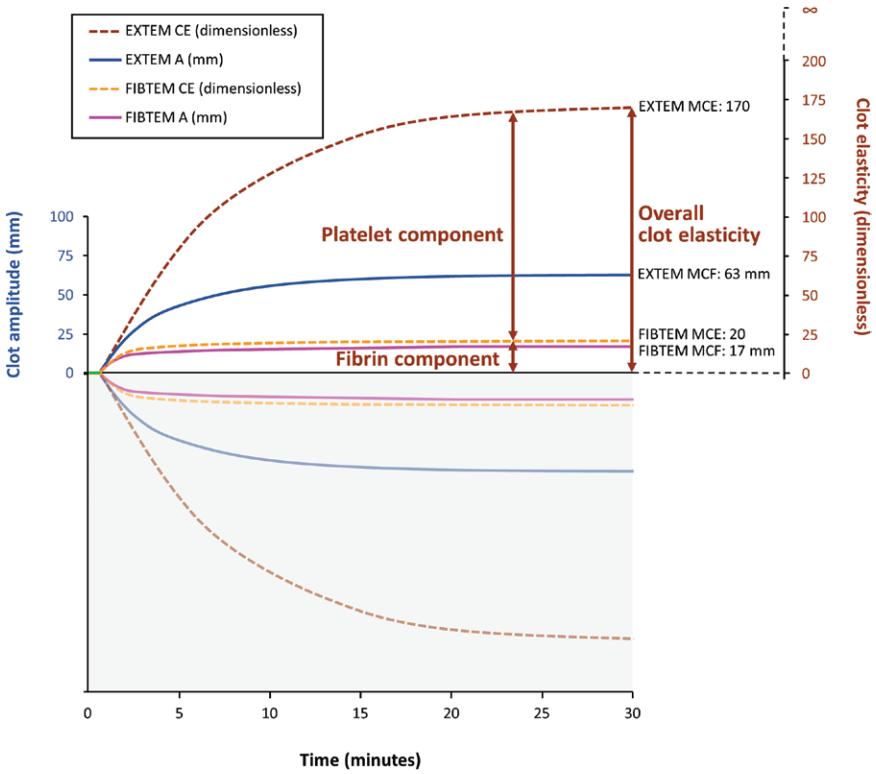

Figure 2. Derivation of the platelet component from viscoelastic assays performed in whole blood, in the presence and absence of platelet inhibition. The graph represents data obtained from a healthy volunteer with coagulation parameters in the normal range (roTEG®05 device; software version 2.95–2.99, December 2001; readings taken every 10 s are represented by curves of best fit). The platelet component is defined as the difference in clot elasticity between values obtained from assays with and without platelet inhibition. Conversion of clot amplitude to clot elasticity is therefore needed for calculation of the platelet component. As shown with ROTEM®, calculation of the platelet component requires data from the EXTEM and FIBTEM assays. With TEG®, the RapidTEG and Functional Fibrinogen assays could be used for this purpose; the procedure for calculating the platelet component would be the same. A = clot amplitude; CE = clot elasticity; EXTEM = ROTEM® extrinsically activated test; FIBTEM = ROTEM® test designed to assess fibrin-based clotting; MCE = maximum clot elasticity; MCF = maximum clot firmness.

Table 3. Theoretical Data to Illustrate the Difference Between the Platelet Component (Based On the Difference in MCE Between EXTEM and FIBTEM) and the Difference in MCF Between EXTEM and FIBTEM

Platelet count (/μL)	FIBTEM MCF (mm)	FIBTEM MCE[a]	EXTEM MCF (mm)	EXTEM MCE[a]	MCF contributors: fibrin, platelets	MCE contributors: fibrin, platelets	ΔMCF (EXTEM – FIBTEM)	ΔMCE (EXTEM – FIBTEM) (platelet component)
100,000	40	67	70	233	57.1%, 42.9%	28.8%, 71.2%	30	167
50,000	20	25	50	100	40.0%, 60.0%	25.0%, 75.0%	30	75
35,000	15	18	45	82	33.3%, 66.7%	22.0%, 78.0%	30	64
30,000	10	11	40	67	25.0%, 75.0%	16.4%, 83.6%	30	56
20,000	5	5	35	54	14.3%, 85.7%	9.3%, 90.7%	30	49
10,000	0	0	30	43	0.0%, 100.0%	0.0%, 100.0%	30	43

[a]MCE = (100 × MCF)/(100 − MCF).

EXTEM = ROTEM® extrinsically activated test; FIBTEM = ROTEM® test designed to assess fibrin-based clotting; MCE = maximum clot elasticity; MCF = maximum clot firmness.

(E at maximum amplitude[23]; equivalent to MCE) would be used instead of E, in which case MA would be used instead of A. As an illustration of the need to use CE, Chandler[14] stated that an increase in thrombelastograph clot amplitude from 50 to 67 mm (34% increase) corresponds with a 2-fold increase in CE. Thus, the principles discussed earlier in relation to ROTEM® apply to TEG® in the same way. Although the platelet component of clot strength can be derived from E or EMX, its calculation from G values may also be considered. The calculation of G by using the constant "5000," and subsequent interpretation of G as an absolute value for shear elastic modulus may be flawed, however, for the following reasons: First, the strain imparted by the TEG® device is large enough to modify clot structure (i.e., the strain is too large for a linear viscoelastic response to be maintained).[10,24] Second, the constant 5000 was derived from experiments reported by Hartert and Schaeder[21] in 1962, and it is possible that differences in geometry or oscillation speed between today's devices and that used by Hartert may mean that the value of 5000 should be redetermined experimentally using today's devices. Until such experiments have been performed, using an elasticity parameter that does not rely on a constant (i.e., E) may, arguably, be considered preferable. Despite these considerations, as indicated earlier, G is mathematically a simple multiple of CE (e.g., G = 50 × E). This means that the mathematical approach for calculating the platelet component from G would be the same as that with E. However, we are not aware of published reports where the platelet component, based on TEG® data, has been correctly calculated and used to guide treatment for perioperative or trauma-related bleeding. As with ROTEM®, there are numerous examples in the literature where the platelet contribution to clot strength has been inappropriately calculated from TEG® values for clot amplitude instead of CE (Table 4).

The platelet mapping assay should enable more specific assessment of platelet function with the TEG® device. This

Table 4. Methods Used in the Literature for Calculating the Platelet Component

Publications with appropriate methodology for calculating the platelet component

Publication	Device	Method for calculating the platelet component	Term used	Δ calculated?
Barua et al. 2010[30]	TEG®	GP = GWB – GF [GP = contribution of platelets to clot strength; GWB = whole blood clot strength; GF = clot strength with abciximab]	Contribution of platelet function to clot strength	Yes
Cartwright et al. 2015[31]	ROTEM®	Platelet elasticity component = (EXTEM-MCE – FIBTEM-MCE)	Platelet elasticity component	Yes
Chandler et al. 2001[32]	TEG®	Platelet-dependent clot strength = ESM_{total} – $ESM_{platelet\ independent}$ [ESM = elastic shear modulus = (5000 × AMP)/(100 – AMP)]	Platelet-dependent clot strength	Yes
Dekker et al. 2014[25]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	No
Djabir et al. 2013[33]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component/ platelet contribution	Yes (not shown in figures/tables but MCE_{EXTEM} and MCE_{FIBTEM} are presented in Table 1)
Haizinger et al. 2006[34]	roTEG or ROTEM®	Platelet component = EXTEM-MCE – FIBTEM-MCE	Platelet component	Yes
Kettner et al. 1999[26]	TEG®	ΔGMA = (5000 × standard MA)/(100 – standard MA) – (5000 × abciximab MA)/(100 – abciximab MA)	Platelet function/ contribution of platelets to clot strength	Yes (not shown in figures/tables but correlation with platelet count is presented in Table 1)
Lang and von Depka 2006[27]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	No (review)
Lang et al. 2009[6]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	Yes
Mahla et al. 2001[35]	roTEG	$G_p = G_t – G_c$ [G = (5000 × MA)/(100–MA); G_p = platelet contribution to clot strength; G_t = total clot strength; G_c = clot strength with abciximab and cytochalasin D]	Platelet component	Yes
Nielsen et al. 2000[7]	TEG®	G_p (%) = $(G_T – G_{SC}/G_T) \times 100$ [G = (5000 × MA)/(100–MA); G_p = G caused by platelet function; G_T = total G; G_{SC} = G caused by soluble components of coagulation]	G caused by platelet function	Yes
Nielsen and Geary 2000[36]	TEG®	$G_p = G_T – G_{SC}$ [G = (5000 × MA)/(100–MA); G_p = contribution of platelets to G; G_T = total G; G_{SC} = G attributable to soluble components of the coagulation pathway]	Contribution of platelets to G	Yes
Pérez-Ferrer et al. 2015[37]	ROTEM®	$MCE_{platelets} = MC_{EXTEM} – MCE_{FIBTEM}$	Platelet contribution to clot strength	Yes
Schöchl et al. 2012[28]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	Yes
Solomon et al. 2011[5]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	Yes
Solomon et al. 2011[38]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	Yes
Solomon et al. 2013[39]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	No
Solomon et al. 2013[40]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	Yes
Torres et al. 2013[41]	ROTEM®	$MCE_{platelet} = MCE_{EXTEM} – MCE_{FIBTEM}$	Platelet component	Yes

Publications with inappropriate methodology for calculating the platelet component

Publication	Device	Method for calculating the platelet component	Term used	Δ calculated?
Bontekoe et al. 2014[42]	TEG®	MA-PLTs = MA (CK test) – MA-fibrinogen (CFF test)	Contribution of platelets to MA	Yes
Cui et al. 2009[43]	TEG®	$MA_{platelet} = MA_{TEG'} – MA_{fibrinogen}$ [MA_{TEG} = absolute strength and elasticity of the clot; $MA_{fibrinogen}$ = contribution of functional fibrinogen to clot strength; $MA_{platelet}$ = functional platelet component of clot strength]	Functional platelet component of clot strength	Yes
Cui et al. 2010[44]	TEG®	$MA_{platelet} = MA_{TEG} – MA_{fibrinogen}$ [MA_{TEG} = absolute strength and elasticity of the clot; $MA_{fibrinogen}$ = contribution of functional fibrinogen to clot strength; $MA_{platelet}$ = functional platelet component of clot strength]	Functional platelet component of clot strength	Yes
Faybik et al. 2006[45]	TEG®	$MA_{PLT} = MA_{TEG'} – MA_{fibrinogen}$ [MA_{PLT} = contribution of platelets to clot firmness; MA_{TEG} = MA from standard TEG® assay; $MA_{fibrinogen}$ = MA from abciximab-modified TEG®]	Contribution of platelets to clot firmness	Yes
García-Monteavaro et al. 1986[46]	TEG®	$MA_{platelet} = MA_{PRP} – MA_{PPP}$	Platelet thrombodynamic action	Yes
Godier et al. 2010[47]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} – MCF_{FIBTEM}$	Platelet component	Yes

(*Continued*)

Table 4. *Continued*

Publications with inappropriate methodology for calculating the platelet component, continued

Publication	Device	Method for calculating the platelet component	Term used	Δ calculated?
Gottumukkala et al. 1999[48]	TEG®	$MA_{plt} = MA_{wb} - MA_{fib}$ [MA_{plt} = contribution of platelets to clot strength; MA_{wb} = MA from celite-activated whole blood; MA_{fib} = MA from whole blood with abciximab]	Contribution of platelets to clot strength	Yes
Greilich et al. 1997[49]	TEG®	$MA_{WB-PPP} = MA_{wb} - MA_{PPP}$	Platelet contribution to clot strength	Yes
Harnett et al. 2002[50]	TEG®	$MA_{platelet} = MA_{whole\ blood} - MA_{fibrinogen}$ [$MA_{platelet}$ = MA attributed to platelets; $MA_{whole\ blood}$ = MA caused by fibrinogen and platelets; $MA_{fibrinogen}$ = MA caused by fibrinogen alone (whole blood with abciximab)]	Contribution of platelets to MA	Yes
Harnett et al. 2005[51]	TEG®	Platelet function = $MA_{whole\ blood} - MA_{whole\ blood + Reopro}$	Platelet function	Yes
Harr et al. 2013[18]	TEG®	$MA_{platelet} = MA_{TEG'} - MA_{fibrinogen}$ [$MA_{platelet}$ = contribution of platelets to clot strength; $MA_{fibrinogen}$ = MA from the Functional Fibrinogen assay; MA_{TEG} = overall clot strength]	Contribution of platelets to clot strength/individual component contribution to clot strength	No
Harr et al. 2013[17]	TEG®	Platelet contribution = $1 - (MA_{Fibrinogen}/MA_{Kaolin})$ [$MA_{Fibrinogen}$ = MA from the Functional Fibrinogen assay; MA_{Kaolin} = MA from kaolin-activated whole blood]	Platelet contribution to clot strength/individual component contribution to clot strength	Yes
Ichikawa et al. 2014[52]	ROTEM®	Platelet component = $MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet component	Not shown (letter)
Kessler et al. 2011[53]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet component	Yes
Kettner et al. 1999[26]	TEG®	ΔMA = standard MA – abciximab MA	Platelet function/ contribution of platelets to clot strength	Yes (not shown in figures/tables but correlation with platelet count is presented in Table 1)
Kornblith et al. 2014[54]	TEG®	$MA_{platelets} = MA_{TEG'} - MA_{FF}$	Platelet-based contribution to clot firmness/platelet contribution to clot strength	Yes
Kuitunen et al. 2006[55]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Effect of platelets on clot strength	Yes
Larsen et al. 2015[56]	TEG®	$MA_{platelets} = MA_{TEG} - MA_{FF}$	Contribution of platelets to clot strength	Yes
Lindroos et al. 2011[57]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Effect of platelets on clot strength	Yes (not shown in figures/tables but MCF_{EXTEM} and MCF_{FIBTEM} are presented in Figures 3 and 4)
Miller et al. 2004[58]	TEG®	$MA_{platelet} = MA_{WB} - MA_{ABCX}$ [$MA_{platelet}$ = contribution of platelets to clot strength; MA_{WB} = MA from the TEG® assay (whole blood); MA_{ABCX} = MA from the TEG® assay (whole blood with abciximab)]	Contribution of platelets to clot strength	Yes (not shown in figures/tables but MA_{WB} and MA_{ABCX} are presented in Tables 2 and 5, and the correlation with platelet count is presented in the text)
Monaca et al. 2014[59]	ROTEM®	Platelet component = $MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet component	Yes
Niemi et al. 2006[60]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Effect of platelets on clot strength	Yes
Olde Engberink et al. 2014[61]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Contribution of platelets to clot strength/platelet component	Yes
Ostrowski et al. 2013[62]	TEG®	$MA_{platelet} = MA_{TEG'} - MA_{FF}$	Platelet contribution to clot strength	Yes (in the text, MA_{TEG} and MA_{FF} presented in Table 2)
Oswald et al. 2010[63]	ROTEM®	Platelet component = $MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet component	Yes
Rahe-Meyer et al. 2010[64]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Contribution of platelets to clot firmness	Yes
Reid et al. 1998[65]	TEG®	$MA_{PLT} = MA_{PRP} - MA_{PPP}$	Platelet component	Yes
Schöchl et al. 2009[66]	ROTEM®	Platelet contribution = $MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet component	Yes
Schramko et al. 2009[67]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Effect of platelets on clot strength/platelet contribution to clot firmness	Yes (not shown, but MCF_{EXTEM} and MCF_{FIBTEM} presented in the tables)
Schramko et al. 2015[68]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet MCF	Yes
Sivula et al. 2009[69]	ROTEM®	$MCF_{platelet} = MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet contribution on clot strength	Yes
Tynngård et al. 2014[70]	ROTEM®	Platelet component = $MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet component	Yes
Winstedt et al. 2013[71]	ROTEM®	Platelet component = $MCF_{EXTEM} - MCF_{FIBTEM}$	Platelet-dependent clot strength	Yes

AMP = amplitude; EXTEM = ROTEM® extrinsically activated test; FIBTEM = ROTEM® test designed to assess fibrin-based clotting; FF = TEG® Functional Fibrinogen test; MA = maximum amplitude; PLT = platelet; PPP = platelet-poor plasma; PRP = platelet-rich plasma; TEG´ = TEG® kaolin-activated assay.

assay involves up to 4 cuvettes.[72,73] The first assesses citrated blood as in the standard method to determine the strength of the fully activated clot. The second cuvette is heparinized and contains reptilase plus factor XIIIa to measure strength of the full fibrin clot in the absence of platelet activation. The third and fourth cuvettes, also heparinized, measure the effects of adenosine diphosphate (ADP) and arachidonic acid stimulation on platelet aggregation. The platelet mapping assay was designed to provide an insight into the inhibitory effects of clopidogrel and aspirin. Conceivably, it could be used to guide platelet administration in a perioperative setting for patients who are bleeding without having taken platelet-inhibiting drugs. However, the results are analyzed by comparing MA values (e.g., percentage platelet inhibition in response to ADP = $[(MA_{ADP} - MA_{Fibrin})/(MA_{Thrombin} - MA_{Fibrin}) \times 100]$).[73] As described earlier, it may be preferable to base such analyses on CE.

Platelet Component and Bleeding Management

The platelet component derived from ROTEM® and TEG® analysis provides a measurement of the contribution that platelets make to the strength of the whole blood clot. This is different from both platelet count and platelet function (measured by aggregometry). Nonetheless, there may be potential for using the platelet component to guide the transfusion of platelets in the treatment of coagulopathic bleeding.

At present, the platelet component of blood clot strength is not commonly used as a direct basis for treatment decisions. Instead, low whole blood clot strength (extrinsic activation), in the presence of adequate fibrin-based clot strength, is the typical criterion for administering platelets. The European Society of Anaesthesiology guidelines for the management of perioperative bleeding state that "adequate TEG® Functional Fibrinogen test/FIBTEM clot strength in the presence of decreased overall clot strength in bleeding patients may indicate platelet deficiency," although specific thresholds for administering platelets are not provided.[29] In a ROTEM®-based coagulation management algorithm for cardiovascular surgery patients, platelets are administered if EXTEM A10 is ≤40 mm and FIBTEM A10 is >10 mm.[74] That is, these ROTEM® parameters suggest reduced overall clot strength in the setting of an adequate fibrinogen contribution to the clot. In a similar treatment algorithm for trauma-related bleeding, it is recommended that platelets are transfused if EXTEM CA10 <40 mm when FIBTEM CA10 >12 mm.[75] Few bleeding management algorithms based on TEG® results have been published. In one example, platelet transfusion was based only on MA,[76] a parameter with limited sensitivity to platelets. In the future, it is possible that platelet component, calculated from the difference in CE between the whole blood clot and the fibrin-based blood clot, could be integrated as one of the standard parameters of ROTEM® and that it might be validated against clinical parameters. The platelet component could then be used directly as a basis for quantitative treatment decisions.

Relationships Between Viscoelastic Coagulation Parameters and Platelet Count and Platelet Function

Correlations between EXTEM clot amplitude or CE and platelet count have been reported. In a prospective study involving patients undergoing cardiac surgery, EXTEM A5 significantly correlated with platelet count (Pearson correlation = 0.74; $P < 0.001$).[61] Analyses on platelet-rich plasma samples from healthy volunteers demonstrated a positive correlation between changes in MCE and platelet count ($r^2 = 0.88$; $P < 0.001$).[6] In trauma patients, a statistically significant but weak correlation has been reported between ROTEM® platelet component (defined as $MCE_{EXTEM} - MCE_{FIBTEM}$) and platelet count (correlation coefficient = 0.44; $P < 0.001$).[38] A more recent animal study also reported significant ($P < 0.05$) moderate correlation between these parameters.[77] Variability in the correlation between ROTEM® platelet component and platelet count may be attributable to the platelet component being a measure of platelet function, which may be distinct from platelet count. Similar considerations apply to TEG®, where correlations between platelet count and TEG® MA have been documented.[22,78,79] For example, a study on healthy volunteers and patients with peripheral arterial disease reported a strong correlation between $\log_{10}$ platelet count and TEG® MA in both groups (Pearson correlation = 0.97 and 0.89, respectively; $P = 0.0001$ in both groups).[79] However, a previous study by Nielsen et al.[7] in a rabbit whole blood model showed no significant correlation between the platelet contribution to G and the platelet count. We are not aware of clinical studies exploring the correlation between TEG® platelet component and platelet count. Overall, there is a need for additional investigation of the relationships between the platelet component (measured using either TEG® or ROTEM®) and the clinical status.

CONCLUSIONS

In this review, we provide evidence that the platelet component of clot strength should be calculated using CE as opposed to clot amplitude parameters from TEG® or ROTEM® analysis. This is because CE, unlike clot amplitude, reflects the force with which the blood clot resists rotation within the device, and the relationship between clot amplitude and CE is nonlinear. The platelet component has the potential to provide valuable insight into the clinical importance of a minor contribution of platelets to CE in emergency bleeding and might therefore help to guide treatment with platelet concentrate. However, this is conditional on the platelet component being calculated correctly. Certainly, clinical validation studies are needed to refine the interpretation of TEG® and ROTEM® results for the management of clinical bleeding.

DISCLOSURES

Name: Cristina Solomon, MD, MBA.
Contribution: This author helped design the study and wrote the manuscript.
Attestation: Cristina Solomon approved the final manuscript and attests to the integrity of the data presented. Cristina Solomon is the archival author.
Conflicts of Interest: Cristina Solomon is an employee of CSL Behring and previously received speaker honoraria and research support from Tem International and CSL Behring, and travel support from Haemoscope Ltd (former manufacturer of TEG®).

Name: Marco Ranucci, MD.
Contribution: This author helped prepare and critically revised the manuscript for important intellectual content.
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Name: Gerald Hochleitner.
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Conflicts of Interest: Gerald Hochleitner is an employee of CSL Behring.
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