First report of the point-of-care TEG: A technical validation study of the TEG-6S system

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Abstract

Thrombelastography (TEG) measured by the TEG5000 Hemostasis Analyzer is an established but labor-intensive method for assessing global hemostasis. The first true point-of-care TEG, the TEG6s system, uses resonance-frequency viscoelasticity measurements and a disposable multi-channel microfluidic cartridge to assess hemostasis and response to antiplatelet therapy. TEG assays (n = 5,100) were performed on the blood of healthy volunteers (n = 157) and patients undergoing coronary revascularization at three hospitals (n = 300). The results from the TEG6s were compared with the conventional TEG5000 in accordance with Clinical and Laboratory Standards Institute (CLSI) and FDA recommendations. Precision testing was conducted using blood from healthy donors, all assays were run for 5 consecutive days in duplicate using multiple operators, lots, and instruments. Reference ranges were comparable between the TEG systems. Deming regression analysis demonstrated a strong correlation between the two systems for the standard hemostasis tests (R = 0.932, MA = 0.972, LY30 = 0.938). Method comparison analysis showed an acceptable agreement between PlateletMapping (PM) assays for measuring arachidonic acid (indicator of aspirin response)- and adenosine diphosphate (indicator of P2Y12 inhibitor response)-induced platelet aggregation (total agreement = 90%, and 72%, respectively). TEG6s precision testing yielded low variability (CV 0–13%) in all measures. The new point-of-care TEG6s is associated with greater ease of use than the TEG5000 and provides precise results. The results correlated between methods for all variables. TEG6s is a promising device for near-patient hemostasis monitoring and future trials of personalized therapy designed to reduce bleeding and thrombosis.

Introduction

Hemostasis is the result of complex interactions involving diverse biochemical reactions, feedback systems, and cellular elements. Depending on the disease state and balance between antithrombotic and prothrombotic factors, the hemostasis process results in either cessation of bleeding – a physiologic response, or thrombosis- hemorrhage- pathologic responses. Disease, injury, or administration of pharmacological agents may alter hemostasis, requiring laboratory monitoring in a wide range of clinical environments [1]. In this scenario, a comprehensive evaluation of the patient’s global hemostatic properties and response to anticoagulant and antiplatelet agents offers a platform for personalized therapy to improve both efficacy and safety.

Since its first documented clinical use in 1960’s, thrombelastography, which measures whole blood viscoelastic properties, has been used in clinical practice to quantify coagulability, fibrinolysis, and the effects of anticoagulant and antithrombotic therapy [2]. The Thrombelastograph® (TEG® 5000, Haemonetics Inc., Braintree MA) analyzer has been used in the settings of liver transplantation, cardiovascular surgery and other surgical interventions, percutaneous coronary intervention (PCI), trauma, and coagulation disorders [3–6]. It has also been used in the fields of obstetrics, pediatrics, veterinary medicine, and basic research. The TEG5000 with PlateletMapping® (PM) assay has been utilized to personalize antiplatelet treatment in patients undergoing percutaneous coronary intervention (PCI) and to determine the timing of coronary artery bypass grafting surgery (CABG) in patients on dual antiplatelet therapy [7–10].

The TEG5000 has been marketed since 2000, but ease-of-use issues, labor, and time intensive operation have limited more widespread use in practice and in large-scale clinical trials. A novel point-of-care TEG instrument, the TEG6s system (Haemonetics, Braintree, MA under license from Coramed Technologies, Niles, IL) has been developed to mitigate these limitations. In this first report on the TEG6s we sought to: (1) determine equivalency by correlating TEG6s results with those of the TEG5000 System in patients undergoing PCI or open heart surgery; (2) characterize the precision of the TEG6s; and (3) establish reference ranges for TEG6s assays in healthy volunteers.

Methods

Study design

The study was a multicenter investigation conducted in healthy volunteers (n = 157) to determine TEG6s reference ranges and in
Thromboelastography parameters

Thromboelastography measures the viscoelastic properties of a clot through all phases of hemostasis - from the enzymatic phase through the fibrinolytic phase and displays results numerically and as a TEG tracing. The standard TEG parameters measured are (1) clotting time (R), recorded in minutes from the start of the sample run to the point of clot formation corresponding to an amplitude of 2 mm, a quantitative representation of the initiation phase of enzymatic clotting; (2) clot kinetics (K), recorded in minutes, a measure of the time to reach 20 mm of clot strength from 2 mm; (3) clot strengthening rate (α, angle), the angle recorded in degrees, formed by the tangent to the TEG tracing measured from R, reflects the velocity of clot strength generation; (4) maximum clot strength (MA, maximum amplitude) recorded in millimeters, reflects the maximal platelet-fibrin clot strength, and (5) clot breakdown (LY 30), recorded as the % reduction in amplitude at 30 min after MA has been reached, reflective of clot lysis (Supplement Figure 2).

TEG5000 method

In the two-channel TEG5000, the time-varying physical properties of the clot are measured with a mechanism similar to a low-strain concentric cylinder oscillatory rheometer (Supplement Figure 3). Native or anticoagulated whole blood samples are combined with reconstituted dry reagents, then manually pipetted into a small cylindrical sample cup and placed into the instrument for analysis. Two samples can be run concurrently.

The sample cup holding the blood oscillates through an angle of 4° 45' in 10-second cycles. A stationary pin suspended in the blood from a thin tungsten wire is monitored for motion. As fibrin and/or fibrin-platelet bonding begins to link the cup and pin together, the pin begins to move in phase with the cup. The strength and rate of formation of the clot, balanced by the torsional stiffness of the tungsten wire, determines the degree of pin rotation. As the clot retracts, rotation diminishes. A non-contact rotation sensor allows a computer to monitor the pin motion, producing graphical and numeric representation of clot strength.

The TEG5000 assays were performed on citrated blood combined with calcium chloride (0.01 M) and lyophilized reagents reconstituted with distilled water: (1) kaolin (CK), (2) kaolin + tissue factor (CRT; RapidTEG), (3) kaolin + heparinase (CKH),
and (4) kaolin + tissue factor + abciximab (CFF, Functional Fibrinogen) (Table III). Blood sample volume ranged from 340 ul to 360 ul per channel. Each assay required one channel for a total of four channels (two TEG instruments).

The Functional Fibrinogen (FF) reagent is a blood modifier intended to measure the contribution of functional fibrinogen to MA. The FF reagent is composed of tissue factor (TF) to activate the clotting process, along with a platelet inhibitor (PI) to exclude the contribution of platelets to the MA (MAₚ) thus measuring only the functional fibrinogen contribution to clot strength (MAFF). MAFF is measured in millimeters and is transformed to functional fibrinogen level (FLEV) in milligrams per deciliter [11].

The PM assays on heparinized blood included four reagent-treated samples: (1) kaolin, (2) reptilase + factor XIII (ActF, Activator F), (3) ADP + Activator F, and (4) AA + Activator F. Blood sample volume was 360 ul per channel. One channel was
required for each reagent, for a total of four channels (2 TEG instruments). The standard parameters are displayed for the kaolin sample, where \( \text{MA}_K \) represents maximal clot strength. \( \text{MA}_{\text{ADP}} \) and \( \text{MA}_{\text{AA}} \) are displayed, which reflect clot strength induced by stimulation of platelet ADP receptors and thromboxane (Tx)A_2 receptors, respectively. Corresponding calculated % aggregation and % inhibition are displayed. For calculations of percentage of clot strength reduction, percent aggregation is

\[
\left\{ \frac{\text{MA}_P - \text{MA}_{\text{ActF}}}{\text{MA}_K - \text{MA}_{\text{ActF}}} \right\} \times 100
\]

where \( \text{MA}_P \) can be either \( \text{MA}_{\text{ADP}} \) or \( \text{MA}_{\text{AA}} \). Percent inhibition is calculated as 100- percent aggregation.

TEG6s method

The TEG6s system is a fully automated diagnostic instrument (Figure 4), that uses a four-channel microfluidics cartridge. An unmetered whole blood sample (~0.4 ml) is pipetted into the entry port in the cartridge (Figure 1). The sample is metered under instrument control into four separate analysis channels. Dried reagents resident within each channel are reconstituted by movement under microfluidic valve and bellow action. After reconstitution, approximately 20 µl of prepared sample is delivered to individual test cells at the terminus of each microchannel, where clotting is monitored. Excess sample is directed into a waste chamber. The test cell is a short vertical tube open at both top and bottom ends, in which blood is supported by surface tension. The slightly convex meniscus that naturally forms at the bottom opening of the tube is positioned at the focus of an optical detection system. When the blood is excited with a multi-frequency signal by a piezoelectric actuator, the resulting meniscus motion can be optically monitored with a photodetector. A Fast Fourier Transform is performed on these frequency components to identify the resonant frequency at which the sample has had the greatest amplitude due to a coagulation event. As clotting occurs, resonant frequencies increase. These frequencies were converted to TEG equivalent units using a mapping function derived in previous \textit{in vitro} studies (personal communication from Coramed).

The standard hemostasis assay cartridge (Citrated Multi-Channel, CMC) uses a citrated blood sample that is mixed with dried reagents within each of the 4 channels, each with calcium chloride (to reverse the sodium citrate) and: (1) kaolin, (2) kaolin + tissue factor activated (RapidTEG), (3) kaolin + heparinase, and (4) kaolin + abciximab (functional fibrinogen) (Table III). The PM cartridge used to monitor response to oral antiplatelet agents employs a heparinized blood sample that is mixed with dried reagents within each of the 4 channels of the cartridge: (1) kaolin + heparinase, (2) Activator F + abciximab, (3) ADP + Activator F, and (4) AA + Activator F. The same parameter results are displayed as in the TEG5000.

In-vitro studies

In order to cover the full analytical measurement range, samples from the healthy subjects

(up to 11 subjects per site, ~10% of all samples) were treated with either: (1) abciximab (ReoPro®, Eli Lilly and Company), at concentrations of 4 and 20 µg/ml to inhibit glycoprotein (GP)IIb/IIa receptor, (2) heparin, at a concentration of 1.5 USP/ml, to prolong the R, or (3) alteplase (Activase, Genentech USA, South San Francisco, CA) at concentrations of 100–200 ng/ml, to increase the % reduction in MA at 30 minutes (LY30). The results of these \textit{in-vitro} treated samples were incorporated with results of the patient samples for method comparison. The assay cut-off values for platelet aggregation detection were identified using the reference ranges data from healthy individuals (and determined by the 10% probability quintile for both the ADP- and AA-induced aggregation). In addition, based on the TEG5000 and the TEG 6s cut-off values we measured the positive (PPA), negative (NPA), and total percent agreements (TPA) between the systems for ADP-and AA-induced aggregation in patient samples.

Statistical analysis

Statistical analyses were performed with R Studio (RStudio, Inc.). Descriptive statistics were reported for subjects’ age, gender, race, medications, and primary diagnosis for surgery.

Reference ranges were estimated using the CLSI C28-A3c Guideline (www.clsi.org) on three reference sample groups, and constructed using the Shapiro-Wilk test to determine normality of the variable. If normality was satisfactory \((p > 0.10)\), then the reference interval was constructed as mean \( \pm 2 \) SD. If the Shapiro-Wilk test indicated non-normality \((p < 0.10)\), the 95% reference limits were used as estimates of the reference interval.

Method comparisons were carried out using Weighted Deming regressions and Bland Altman analysis. In the Deming Regression analysis, outputs of the two TEG methods are plotted against each other allowing measurement error (imprecision) in outputs from both methods. The Bland Altman analysis method calculates the mean difference between the two methods of measurement, called the \textit{bias}. The limits of agreement (LOA) refer to lower and upper 95% CI of the mean difference.

Results

Demographics

Healthy volunteers \((n = 157)\) were representative of a broad population with respect to age, gender, and race (Supplement Table II). Among cardiac patients, 264 patients underwent open heart surgery and 36 underwent PCI (at Sinai Hospital only). Fifty-seven percent of patients were on aspirin therapy and 7% and 12% of patients were on P2Y_12 inhibitor therapy and anticoagulant therapy prior to procedure, respectively (Supplement Table III).

Reference ranges

Since Shapiro-Wilk test indicated non-normality \((p < 0.10)\), the 95% reference limits were used as estimates of the reference interval. Reference ranges for all TEG6s tests are shown in Table I and are similar to the established TEG5000 values except LY30 in Kaolin channel, and K and LY30 in Rapid TEG assay \([12, 13]\).

TEG5000 vs. TEG 6s method comparison

Deming regression analysis demonstrated a good correlation between the two systems for the standard hemostasis tests \((R = 0.932, K = 0.627, \text{angle } r = 0.627, \text{MA } r = 0.972, \text{LY30 } r = 0.938)\) and a low coefficient of variation for the TEG6s system (Figure 2A-E). The MA, R, K, and Alpha parameters had a minimal bias and good agreement, indicating that the measures are comparable between the 2 assays. In contrast, the LY30 had a substantial bias of 0.57 and wide limits of agreement (Figure 3A-E).

PM assay

For ADP-induced aggregation, the PPA (95%CI), NPA (95%CI), and TPA (95%CI) values were 72% (67–78%), 66% (60–73%),
Table I. Thrombelastography tests and TEG6s reference ranges.

| Assay/Channel | Sample Type | Reagents Purpose | Test* | TEG6s | TEG5000 |
|---------------|-------------|-----------------|-------|-------|---------|
| Kaolin†       | CK          | Kaolin           | R     | 4.6–9.1 | 5–10 |
|               |             | Sample activation; standard hemostasis profile | K     | 0.8–2.1 | 1–3  |
|               |             |                  | α     | 63–78   | 53–72 |
|               |             |                  | MA    | 52–69   | 50–70 |
|               |             |                  | LY30  | 0.2–6   | 0–7.5 |
| Kaolin with heparinase† | CKH | Kaolin + heparinase | R     | 4.3–8.3 |         |
|               |             | Heparinase neutralizes heparin to test for effect of residual heparin in blood sample | K     | 0.8–1.9 |         |
|               |             |                  | α     | 64–77   |         |
|               |             |                  | MA    | 52–69   |         |
| RapidTEG†     | CRT         | Kaolin + tissue factor | ACT   | 82–152  | 86–118 |
|               |             |                  | K     | 0.8–2.7 | 34–138 |
|               |             |                  | α     | 60–78   | 64–80  |
|               |             |                  | MA    | 52–70   | 52–71  |
|               |             |                  | LY30  | 0–2.2   | 0–7.5  |
| Functional fibrinogen† | CFF | Kaolin + tissue factor + abciximab | MA_{PI} | 15–32  |       |
|               |             | Abciximab inhibits platelets to determine contribution of functional fibrinogen to clot strength (MA) | FLEV  | 278–581 | 200–445 |
| PlateletMapping‡ | HKH | Kaolin + heparinase | R     | 4.2–9.8 |         |
|               |             |                  | K     | 1–2.9   |         |
|               |             |                  | α     | 57–75   |         |
|               |             |                  | MA    | 53–68   |         |
|               |             |                  | MA_{PI} | 2–19   |         |
|               |             |                  | ActF/P1 | Activator F + abciximab |       |
|               |             |                  | ADP/P2 | Activator F + ADP |       |
|               |             |                  | AA/P3  | Activator F + AA |       |
|               |             |                  |       |         |         |

†Standard hemostasis assay cartridge
‡PlateletMapping assay cartridge
R = clotting time, K = clot kinetics, MA = maximum clot strength or maximum amplitude, α = clot strengthening time, LY30 = clot breakdown, MA_{PI} = maximum amplitude in the presence of platelet inhibitor, ACT = activated clotting time, FLEV = functional fibrinogen level, ActF = activator F, ADP = adenosine diphosphate.

Table II. Platelet aggregation cut-offs and agreement.

|                  | N  | TPA (95% CI) (values are in %) | PPA (95% CI) (values are in %) | NPA (95% CI) (values are in %) | TEG 5000 Cut-off (values are in %) | TEG 6s Cut-off (values are in %) |
|------------------|----|-------------------------------|-------------------------------|-------------------------------|-----------------------------------|----------------------------------|
| ADP-induced      | 261| 72 (67–78)                    | 66 (60–73)                    | 90 (82–97)                    | <80                               | <83                              |
| AA-induced       | 267| 90 (86–94)                    | 91 (87–95)                    | 85 (73–96)                    | <80                               | <89                              |

ADP = adenosine diphosphate, AA = arachidonic acid, TPA = total percent agreements, PPA = positive percent agreements, NPA = negative percent agreements, CI = confidence interval

and 90% (82–97%), respectively. For AA-induced aggregation, the PPA (95%CI), NPA (95%CI), and TPA (95%CI) values were 90% (86–94%), 91% (87–95%), and 85% (73–96%), respectively (Table II).

PM assay agreement for ischemia risk between the systems were compared by using the TEG5000 cutoff of MA_{ADP} ≥47 mm, as previously defined [8]. Using a non-linear regression model between the TEG5000 and the TEG 6s MA_{ADP} results, MA_{ADP} >56.1 mm defined the ischemia risk cutoff for the TEG 6s. Qualitative agreement between systems for ischemia risk identification was evaluated based on the cutoffs, with a sensitivity and specificity of 83% and 83%, respectively, for all samples collected (data not provided).

**Method performance**

Precision results are presented for each reagent and parameter for the citrated multichannel (CMC) and the PM assays as mean, SD, and coefficients of variability (CV) in Tables III and IV. Imprecision was very low within reagent lot, operator, and instrument (≤2.1%) for all tests. Within day, within run, and total precision ranged between 0.8% and 10% for tests except K for CK sample type, which was 13.0%. Imprecision was very low in the PM assay within reagent lot, operator, and instrument (≤4.1%) for all tests. Within run and total precision ranged between 0.3% and 12.9% for tests except MA_{AA}, which was 45.8%. The latter was due to a low value for the mean (3.7 ± 1.69). For comparison, previously published values for within run precision on the TEG5000 for MA_{ADP} and MA_{AA} were 9% and 6%, and total precision were 8% and 7%, respectively.15

**Discussion**

The current study provides the first description of a point-of-care TEG. Our study demonstrated that the TEG6s provided data that are comparable to the established TEG5000 with respect to parameters reflecting global hemostasis and platelet function, and that the precision of the TEG6s was high.

Currently, available coagulation tests are mostly plasma based and ignore the role that platelets play and their interaction with coagulation factors in hemostasis. Therefore, an effective measurement of hemostasis requires a whole blood assay to measure the net effect of interactions between cellular and soluble factors. The TEG system with its associated assays reports the net effect of plasmatic and platelet factors that contribute to hemostasis. The TEG has been
Validation of the TEG-6S

Table III. Method precision, standard hemostasis tests.

| Sample type | Test | Mean* | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
|-------------|------|-------|----|-----|----|-----|----|-----|----|-----|----|-----|
| CK          | R    | 6.5   | 0.56| 8.7% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.49 7.6% 0.49 7.6% |
|             | K    | 1.4   | 0.19| 13.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.16 12.0% 0.16 12.0% |
|             | a    | 72.1  | 2.07| 2.9% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 1.73 2.4% 1.73 2.4% |
| CKH         | MA   | 59.4  | 1.24| 2.1% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 1.37 2.4% 1.37 2.4% |
|             | CRT  | R    | 6.0  | 0.46| 7.7% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% |
|             | ACT  | 94   | 0.98| 10.0% 0.38 0.4% | 0.51 0.5% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 8.11 8.6% 8.11 8.6% |
|             | K    | 1.4   | 0.11| 7.8% 0.03 0.2% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% |
|             | a    | 74.4  | 0.75| 1.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% |
|             | MA   | 62.7  | 0.52| 0.8% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% |
| CFF         | FLEV | 376.8 | 7.15| 1.9% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% |
|             | MA   | 20.6  | 0.39| 1.9% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% | 0.0% 0.0% |

*N = 120
CK = Kaolin, CKH = Kaolin + heparinase, CRT = Kaolin + tissue factor, CFF = Kaolin + tissue factor + abciximab, R = clotting time, K = clot kinetics, MA = maximum clot strength or maximum amplitude, α = clot strengthening time, FLEV = functional fibrinogen level, SD = standard deviation, %CV = percent coefficient of variance

Table IV. Method precision, platelet mapping.

| Assay | Variable | Level | Mean† | Total precision | Within reagent lot | Within operator | Within instrument | Within Run | Within Day |
|-------|----------|-------|-------|-----------------|-------------------|-----------------|------------------|------------|------------|
| AA    | %Aggregation | Normal | 100.0 | 0.34 0.3% | 0.00 0.0% | 0.00 0.0% | 0.00 0.0% | 0.00 0.0% | 0.34 0.3% |
|       | %Inhibition   | Abnormal | 97.4 | 2.99 3.1% | 0.00 0.0% | 0.00 0.0% | 0.00 0.0% | 0.00 0.0% | 2.90 3.0% |
| MA    | Normal       | 69.2  | 1.11 1.6% | 0.00 0.0% | 0.16 0.2% | 0.00 0.0% | 0.00 0.0% | 0.99 1.4% |
| MA    | Abnormal     | 3.7   | 1.69 45.8% | 0.00 0.0% | 0.25 0.6% | 0.00 0.0% | 0.00 0.0% | 1.65 44.7% |
| ADP   | %Aggregation | Normal | 99.4 | 0.81 0.8% | 0.24 0.2% | 0.00 0.0% | 0.24 0.2% | 0.69 0.7% |
|       | %Inhibition   | Abnormal | 43.1 | 5.55 12.9% | 1.65 3.8% | 0.00 0.0% | 0.24 0.2% | 2.19 5.1% |
| MA    | Normal       | 67.4  | 0.84 1.2% | 0.00 0.0% | 0.00 0.0% | 0.00 0.0% | 0.35 0.5% |
| MA    | Abnormal     | 26.9  | 3.08 11.4% | 1.11 4.1% | 0.00 0.0% | 0.00 0.0% | 1.26 4.7% |
| HKH   | Normal       | 63.6  | 0.78 1.2% | 0.30 0.5% | 0.28 0.4% | 0.00 0.0% | 0.57 0.9% |

Note: (*) Higher CV is due to the small value of the mean, since small deviations in the mean cause exaggerated increase in CV.
†N = 120
AA = adenosine diphosphate, AA = arachidonic acid, MA = maximum amplitude, HKH = kaolin + heparinase, SD = standard deviation, %CV = percent coefficient of variance.

most widely used to manage blood product usage in patients requiring liver transplantation, in patients undergoing open heart surgery, in trauma patients, and in non-surgical diseases [3–7]. The TEG5000 is not a true point-of-care device and requires the skillset of a trained technician, manual sample pipetting and mixing, frequent quality control activities, calibration, careful cleaning due to exposed blood, and leveling. These barriers have limited the widespread use of the system in multi-center clinical trials and in routine clinical practice.

The new TEG6s system has been developed to overcome the limitations of the TEG5000. The TEG6s is an automated thrombelastograph that allows for continuous measurement of clot viscoelasticity in the presence of coagulation factors and inhibitors during clot initiation, formation, retraction and subsequent fibrinolysis. In contrast to the TEG5000, the TEG6s system is a stand-alone, self-contained unit that has the same physical footprint size as the TEG5000. The technical issues related to the torsion wire have been eliminated, and therefore there is no requirement to level the instrument or guard against vibratory surfaces. No computer and software installation is required, and operator training is minimal. The automated sample handling within the cartridge-based system reduces the time needed to set up and start a test from approximately 10–15 minutes on the TEG5000 to less than one minute on the TEG6s. No pipetting, adding, reconstitution or mixing of reagents is required, reducing exposure to open containers of blood, reagents, or used sample cups and pins. Overall operation is now streamlined due to simplified quality control procedures resulting in part from a self-test performed before running each sample, along with reduced preventive maintenance requirements.

In TEG6s, 4 assays are run simultaneously in a single cartridge, instead of using two TEG5000 instruments. The use of automated cartridges in the TEG6s system removes sample preparation variability, derived from operator and instrument factors, as demonstrated in the performance data. Agreement of results was demonstrated across multiple operators. The variability due to instrument and user is <1% in most instances. The TEG6s method generates reproducible results, has a short turnaround time, and can be run by non-trained personnel. The novel microfluidics cartridge-based device offers a simple, rapid, and accurate system for evaluating hemostasis status, enabling thrombelastography to be conveniently used in near patient settings and in the management of critical care.

The current validation study was performed with blood samples collected from both healthy volunteers and patients with cardiovascular disease. The results including precision testing...
Hypercoagulability as indicated by high thrombin induced-platelet fibrin clot strength (>72 mm), and high ADP-induced-platelet fibrin clot strength measured by TEG have been shown to be associated with both short- and long-term clinical events in patients undergoing PCI [9]. It is well established that high on-treatment platelet reactivity to adenosine diphosphate (HPR) during clopidogrel therapy measured by various platelet function assays is an independent risk factor for ischemic event occurrences in post-percutaneous coronary intervention (PCI) patients [14]. In addition, recent data suggest that low on-treatment platelet reactivity to ADP (LPR) is associated with a higher risk of bleeding and a therapeutic window [14,15]. However, recent prospective randomized trials evaluating personalized antiplatelet therapy based on PFT in PCI populations did not demonstrate a clinical benefit, thus questioning whether treatment modification based on the results of PFT can actually influence outcomes [13]. These trials were associated with limitations including enrollment of low risk patients, and use of high-dose clopidogrel, a suboptimal strategy to overcome HPR. Most importantly, all these trials used VerifyNow P2Y12 assay which may not be effective in identifying high risk patients [14].

We have demonstrated that clopidogrel-treated patients undergoing first time on-pump coronary artery bypass grafting had the same perioperative bleeding as clopidogrel-naïve patients when their surgery was timed on the basis of a preoperative assessment of platelet reactivity by TEG [10]. In the 2012 Society of Thoracic Surgeons guidelines there is a class IIa recommendation for PFT in clopidogrel-treated patients to shorten the wait time for operation [16]. In addition, 2014 ESC/EACTS Guidelines on myocardial Revascularization states that platelet function testing should be used to guide antiplatelet therapy interruption rather than arbitrary use of a specified period of delay in patients undergoing CAGB surgery (Class IIa recommendation) [17].

Inclusion of a new point-of-care TEG6s system with PM assay in future personalized antiplatelet therapy trials may assist in identifying high risk patients for modified therapy to reduce the risk of both ischemic and bleeding event occurrences. In addition, the ease of use of the TEG6s system may facilitate future investigations of precision medicine. Finally, since clinical outcomes were not included in the current study, future studies will be required to establish the TEG 6s as a valid tool to detect etiologies of bleeding and thrombosis.

In conclusion, the new point-of-care TEG6s is associated with greater ease of use as compared to the TEG5000 and has high precision. Results correlated well between the two systems and there was acceptable agreement for all tests. The TEG6s is a promising new point-of-care device for measuring hemostasis in general practice and in future trials of personalized therapy designed to reduce bleeding and thrombotic risk.

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Addendum
PA Gurbel, KP Bliden, and US Tantry contributed to concept and design, enrollment of subjects, data acquisition and analysis, handled funding and supervision, drafted manuscript and made critical revisions of manuscript. E Cohen, G Raviv, and C G Lopez-Espinia contributed to concept and design, data acquisition and analysis, handled funding and supervision, and made critical revisions of manuscript. A Monroe, WL Slusser, DL Haugen, and MH Ereth contributed enrollment of subjects and reviewed the manuscript. AA Muresan contributed data acquisition and analysis and supervision and critical revisions of manuscript. NE Brunner contributed to concept and design, data analysis, and made critical revisions of manuscript PR Delmenico contributed to concept and design and made critical revisions of manuscript.

Declaration of interest
Dr. Gurbel reports serving as a consultant for Daiichi Sankyo, Bayer, AstraZeneca, Merck, Medtronic, CSL, and Haemometrics; receiving grants from the National Institutes of Health, Daiichi Sankyo, CSL, AstraZeneca, Harvard Clinical Research Institute, Bayer, Haemometrics, Sinnowa, Coramed, Accriva and Duke Clinical Research Institute; receiving honoraria and payment for lectures, consultations, including service on speakers’ bureaus from Daiichi Sankyo/ Lilly, AstraZeneca and Merck. Dr. Gurbel is holding stock or stock options in Merck, Medtronic, and Pfizer; and holding patents in the area of personalized antiplatelet therapy and interventional cardiology.

Muresan AA, Brunner NE, and Cohen E, Raviv G are employees of Coramed Technologies and Lopez-Espinia CG, and Delmenico PR, are employees of Haemometrics Corporation. Other authors report no disclosures.

Supplemental material
Supplemental data for this article can be accessed on the publisher’s website at www.tandfonline.com/iplh.

References
1. Roberts HR, Monroe DM, Escobar MA. Current concepts of hemostasis: implications for therapy. Anesthesiology 2004;100:722–730.
2. Marechal G, Leroux ME, Samama M. Thrombodynamography (thromboelastography). Its present place in clinical practice. Presse Med 1960;68:1919–1922.
3. Kang Y. Thromboelastography in liver transplantation. Semin Thromb Hemost 1995;21(Suppl 4):34–44.
4. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vel antic F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 1999;88:312–319.
5. Du Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK. Effect of thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Crit Care 2014;18:518.
6. Yeung MC, Tong SY, Tong PY, Cheung BH, Ng JY, Leung GK. Use of viscoelastichaemostatic assay in emergency and elective surgery. Hong Kong Med J 2015;21:45–51.
7. McCrath DJ, Cerboni E, Frumento RJ, Hirsh AL, Bennett-Guerrero E. Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. Anesth Analg 2005;100:1576–1583. PubMed PMID: 15920172.
8. Gurbel PA, Bilden KP, Navickas IA, Mahla E, Dichia J, Suarez TA, Antonino MJ, Tantry US, Cohen E. Adenosine diphosphate-induced platelet-fibrin clot strength: a new thromboelastographic indicator of long-term poststenting ischemic events. Am Heart J 2010;160:346–354.
9. Gurbel PA, Bilden KP, Guyer K, Cho PW, Zaman KA, Kreutz RP, Bassi AK, Tantry US. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STEMTING Study. J Am Coll Cardiol 2005;46:1820–1826.
10. Mahla E, Suarez TA, Bilden KP, Rehak P, Metzler H, Sequeira AJ, Cho P, Seil J, Fan J, Antonino MJ, Tantry US, Gurbel PA. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CAGB (TARGET-CABG) study. Circ Cardiovasc Interv 2012;5:261–269.
11. Carroll RC, Craft RM, Chavez JJ, Snider CC, Kirby RK, Cohen E. Measurement of functional fibrinogen levels using the Thrombelastograph. J Clin Anesth 2008;20:186–190.

12. TEG5000 User Manual. Haemonetics Corp. 2007.

13. Guide to PlateletMapping®. Haemonetics Corp. 2006.

14. Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, Stone GW, Curzen N, Geisler T, Ten Berg J, Kirtane A, Siller-Matula J, Mahla E, Becker RC, Bhatt DL, Waksman R, Rao SV, Alexopoulos D, Marcucci R, Reny JL, Trenk D, Sibbing D, Gurbel PA. Working Group on On-Treatment Platelet Reactivity. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–2273.

15. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, Ten Berg J, Janssen P, Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J 2015;36:1762–1771.

16. Ferraris VA, Saha SP, Oestreicher JH, Song HK, Rosengart T, Reece TB, Mazer CD, Bridges CR, Despotis GJ, Jointer K, Clough ER; Society of Thoracic Surgeons. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. Ann Thorac Surg 2012;94:1761–1781.

17. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knutsen J, Landmesser U, Lauer G, Neumann FJ, Richter DJ, Schaufele P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–2619.