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A Novel Platelet Function Assay for Trauma

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Abstract

Background: Platelet function tests such as thrombelastography platelet mapping and impedance aggregometry have demonstrated universal platelet dysfunction in trauma patients. In this study, we introduce the measurement of platelet contraction force as a test of platelet function. We hypothesize that force will correlate with established coagulation tests such as thrombelastography, demonstrate significant differences between healthy subjects and trauma patients, and identify critically ill trauma patients.

Methods: Blood samples were prospectively collected from level 1 trauma patients at initial presentation, assayed for force of and time to contraction and compared with thrombelastography. Blood from healthy subjects was assayed to establish a reference range. Results from trauma patients were compared with healthy controls and trauma patients that died.

Results: The study includes one hundred trauma patients with mean age 45 y, 74% were male, and median injury severity score of 14 ± 12 . Patients that survived ($n = 90$) demonstrated significantly elevated platelet contraction force compared with healthy controls ($n = 12$) (6390 ± 2340 versus 4790 ± 470 μN , $P = 0.043$) and trauma patients that died ($n = 10$) (6390 ± 2340 versus 2860 ± 1830 μN , $P = 0.0001$). Elapsed time to start of platelet contraction was faster in trauma patients that survived compared with healthy controls (660 ± 467 versus 1130 ± 140 s, $P = 0.0022$) and those that died (660 ± 470 versus 1460 ± 1340 s, $P < 0.0001$).

Conclusions: In contrast with all existing platelet function tests reported in the literature, which report platelet dysfunction in trauma patients, contractile force demonstrates hyperfunction in surviving trauma patients and dysfunction in nonsurvivors. Platelet contraction reflects platelet metabolic reserve and thus may be a potential biomarker for survival after trauma. Contractile force warrants further investigation to predict mortality in severely injured trauma patients.

Keywords

Platelet contraction; Thrombelastography; Mortality

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Introduction

Platelet function contributes a major portion of hemostatic potential.¹ In the bleeding trauma patient, platelets respond to hemorrhage by 1) adhering to sites of disrupted endothelium via exposed collagen, 2) forming aggregates with strands of fibrin to build a hemostatic plug, and 3) metabolizing energetic substrates to drive platelet contraction and clot stiffening. Each phase of activation has a unique biomechanical signature which reflects underlying platelet bioenergetics.² Dysfunction of any of these phases of platelet activation leads to unstable clot formation and continued hemorrhage.^{3,4}

Several devices translate platelet function after trauma into meaningful clinical information. Each device measures one or multiple phases of platelet activation including adhesion, aggregation, or contraction. The PFA-100 (Siemens Medical Solutions Inc, Malvern, PA) measures platelet adhesion and aggregation. The primary device metric is time to occlusion of a micropore coated with collagen and either epinephrine or adenosine diphosphate (ADP).⁵ The Multiplate (MP) analyzer (Roche Diagnostics, Mannheim, Germany) measures platelet aggregation by detecting change in electrical impedance as platelets adhere to metal sensor wires immersed in a blood sample. Agonists such as ADP, arachidonic acid (AA), thrombin receptor-activating peptide (TRAP), or ristocetin are added to blood samples anticoagulated with citrate to induce platelet aggregation.⁶ Thrombelastography platelet mapping (TEG PM, Haemonetics Corporation, Brain-tree, MA) detects clot strength by measuring torsional forces between a rotating sample cup and immersed sensor pin. The TEG PM signal isolates the contributions of clot stiffening due to platelet contraction and distinguishes it from fibrin formation. The pathway-specific agonists AA and ADP activate platelets and inhibition of platelet function is calculated relative to maximal clot activation with kaolin.⁷ The hemostasis analysis system (Hemodyne Inc, Richmond, VA) measures platelet contraction force and clot elastic modulus without stimulation by pathway-specific agonists. Blood is injected between two parallel plates and a clot forms. Platelets within the forming clot contract and force is recorded by a strain gauge.⁸

All previously mentioned platelet function devices report results as relative or nonmechanical units except for the Hemodyne, which measures the process of platelet contraction in units of force (Newtons). This distinction is important because the measured phases of platelet function involve mechanical forces.^{2,9} Measuring in units of force is mathematically significant as observations from TEG PM, MP, or the PFA-100 cannot be extended using mathematical principles such as integration or derivation to yield insights into energy production. Specifically, the integral of the force curve yields the physical quantity work which should yield insights into metabolic efficiency of platelets. In addition, reporting platelet function in device-specific relative units confuses attempts at creating a standard platelet function assay for trauma.

Contraction is the final common pathway of platelet function. Platelets develop force by the ratcheting action of actin and myosin, which is an extremely well-characterized molecular motor. Regulation of actomyosin cycling is known to occur via the myosin light chain kinase/phosphatase pair, which is in turn regulated by the upstream rho-kinase/ROCK pathways.¹⁰ Thus, any defects in force detected by this system represent targets for

additional investigation of the signal transduction cascade that lies upstream of myosin light chain.

The natural response of platelets after trauma, either inhibition or activation, is unclear. Previous studies demonstrate varying results using different platelet function devices.¹¹ In addition, there is only one study investigating platelet contractile force in trauma and it lacks comparison with healthy controls.¹² Thus, this study aims to investigate platelet contraction forces in a severely injured cohort of trauma patients and compare them with healthy controls. In addition, results are compared with TEG, a common measure of coagulation function in trauma. We hypothesize that force will correlate with established coagulation tests such as TEG, demonstrate significant differences between healthy subjects and trauma patients, and identify critically ill trauma patients.

Methods

Human subjects

This prospective observational study was conducted at the Memorial Hermann Hospital within the Texas Medical Center, Houston, Texas. Before the study, approval was obtained from the Institutional Review Board (HSC-GEN-12-0059). Patients meeting the highest level of trauma team activation were included in the study from August 2017 to March 2018. Patients were excluded from the study if they were younger than 16 y, pregnant, prisoners, enrolled in other studies, found to be pharmacologically anticoagulated by antiplatelet agents such as aspirin or clopidogrel, or declined to give informed consent. The patients from whom we could not obtain an admission blood draw were excluded from the study. Informed consent was obtained from the patient or a legally authorized representative within 72 h of admission. A waiver of the informed consent was obtained for those patients who were discharged or died within 24 h. In the remaining cases in which the informed consent could not be obtained, the patients were excluded from the study and their blood samples were destroyed.

Blood sample collection

Blood samples from trauma subjects were drawn with the initial sample within 5 min after arrival to the hospital. 2 mL of blood was drawn through venipuncture into a Vacutainer tube containing 3.2% citrate and inverted to assure proper anticoagulation. Platelet contractile force was measured within 4 h after sample collection.^{13,14} Samples obtained from healthy subjects were assessed in a similar manner. Vital signs, injury data, injury severity score (ISS), laboratory data, and demographic variables were also obtained. Moderate to severe brain injury was defined as head abbreviated injury scale (AIS) ≥ 3 .¹⁵ Coagulation parameters measured with rapid TEG included activated clotting time (ACT) and maximal amplitude (MA). TEG assays were all run within an hour of collection.

Measurement of platelet contractile force

Force was measured using a bent-wire cantilever (Fig. 1). Platelet force was previously proven to correlate with optical aggregometry and TEG in a study of healthy controls with an intra-assay variability of 6%.¹⁶ To perform the assay, 270 μ L of citrated whole blood was

recalcified to a concentration of 6 mmol CaCl₂ and then immediately injected into the device. A void between two plastic sensor discs was filled with blood. The discs were separated by 1 mm and had a diameter of 6 mm which defined a volume of 28 µL. Blood in this sensor volume clotted and adhered to the sensor discs. The bottom disc was fixed in place and the top disc was attached to a nickel wire cantilever. Platelets within the sensor volume contracted and drove the top disc downward. Deflection of the cantilever attached to the top disc was recorded with a camera and force was calculated using beam equations. The assay lasts 5000 s and time to platelet contraction (TPC) is marked when 500 µN of force is reached. Maximum platelet contraction force is marked when the highest force is recorded. The assays were run in duplicate and force curves were averaged. All assays were run within 4 h 25% of samples were run within 30 min of collection, 50% of samples were run from 30 min to 2 h, and the remaining 25% were run from 2 h to 4 h. There was no correlation between time to assay and their force curves.

Statistical analysis

Statistical analysis was performed with Stata 14.2 (College Station, TX). Shapiro–Wilk analysis was used to determine the normality of continuous data. For normally distributed data, Pearson’s correlation was used to compare device results; otherwise, Spearman’s rank correlation coefficient was used. Other data are expressed as the mean and standard deviation if normally distributed; otherwise, they are expressed as the median and interquartile range. To determine the differences between clinical outcomes, Student’s *t*-test was used for normally distributed data and Mann–Whitney *U*-test was used for significantly skewed data. Analysis of variance with Tukey post hoc analysis was used to compare multiple groups of normally distributed data. Nonparametric receiver operator characteristic (ROC) analysis was performed to determine the ability of continuous device measurements to classify binary clinical outcomes. Youden index was used to define threshold values for mortality. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are all presented as percentages. For all analyses, statistical significance was set to $P < 0.05$.

Results

Patient characteristics and laboratory values

One hundred trauma patients were enrolled into this study. Patient demographics, vital signs, laboratory data, and coagulation function of all patients and patients stratified by mortality are presented in Table 1. Blunt injury accounted for 73% of injury patterns. The mean ($\pm$ standard deviation) age of the trauma cohort was 45 ± 19 y, 74% were male, and median ISS was 14 (4, 23) with 10% mortality. Of the 10 deaths, 7 were due to traumatic brain injury (TBI), 1 from hemorrhage within 24 h of arrival, and 2 were after 2 wk due to sepsis and multiorgan failure. Trauma patients surviving to discharge were significantly younger, with higher GCS, lower ISS, and higher platelet count compared with those that died. Base excess, pH, white blood cell count, and lactate were not different between surviving trauma patients and those that died.

Coagulation function and platelet function in trauma deaths versus survivors

TEG MA was significantly higher in trauma patients that survived compared with nonsurvivors; however, there was no difference in TEG ACT (Table 1). Force developed by platelets was more than two-fold higher in trauma survivors compared with trauma subjects that died. However, platelet count was significantly lower in subjects that died; therefore, we normalized for platelet count by calculating maximum force per 100,000 platelets. Normalized platelet contraction force of trauma survivors remained significantly higher than those that died. Unlike force, TPC was independent of platelet count; thus, it was not normalized in this study. TPC was significantly faster in trauma survivors compared with trauma subjects that died.

Platelet function in healthy controls compared with trauma patients

Platelet function of healthy controls measured by force, normalized force, and TPC was compared with trauma survivors and those trauma patients that died (Fig. 2). Average platelet count of healthy controls was 234 ± 71 K/ μ L. Force, not normalized to platelet count, was significantly different among the three groups (Fig. 2A). Mean force in healthy controls was 4790 ± 470 μ N and establishes a normal baseline contraction force. Normalized force of healthy controls was not significantly different from either trauma group (Fig. 2B). As mentioned previously, normalized force of trauma survivors was significantly higher than those that died. TPC demonstrated a similar trend in platelet function (Fig. 2C). Control TPC was 1130 ± 140 s and was significantly slower than that of trauma patients who survived. TPC of trauma patients that died was not different from healthy controls. As mentioned previously, TPC of trauma survivors was significantly faster than those that died.

Platelet contraction force and time to platelet contraction as potential identifiers of mortality

ROC analysis was performed to determine the potential ability of either normalized force or TPC to predict mortality in trauma. In addition, TEG MA and ACT were considered (Fig. 3). According to their ROC curves, force and TPC were strong predictors of mortality. The optimal cutoff value for force was 4010 mN, which correctly classifies mortality in 75.3% of patients with 75.6% sensitivity, 72.7% specificity, 96.2% PPV, and 31.8% NPV. The optimal cutoff value for TPC was 914 s, which correctly classifies mortality in 86.2% of patients with 66.7% sensitivity, 88.2% specificity, 96.4% PPV, and 41.2% NPV. TEG MA and ACT were not significantly different from chance.

Platelet function in traumatic brain injury

Brain injury predicts platelet dysfunction as measured by some assays. In this study, there were 24 patients with head-AIS ≥ 3 and confirmed brain injury after review of their initial brain CT scan. These 24 patients had significantly slower TPC than the 76 non-TBI patients (789 ± 430 versus 608 ± 340 s, $P = 0.039$) and the two groups demonstrated no difference in force. There were no differences between those patients whose brain injury worsened determined by interval brain scans and those that remained stable. Of the 24 TBI patients, 7 died within 24 h and 2 died later of multiorgan failure. Head-AIS was not significantly different between TBI survivors and those that died (4.7 ± 0.7 versus 4.4 ± 0.7 , Mann–

Whitney $P=0.243$) and total ISS was not different between the two TBI groups (29.6 ± 15 versus 27.3 ± 7.4 , $P=0.67$). Platelet contractile force of those TBI patients that died was significantly decreased compared with those that survived (2800 ± 1930 versus $6900 \pm 2,950$, $P=0.001$) (Fig. 4A). Normalized force of those that died was also significantly decreased compared with those that survived (16.1 ± 6.2 versus 30.3 ± 10.9 $\mu\text{N}/100,000$ platelets, $P=0.0006$) (Fig. 4B). In addition, their TPC was significantly longer compared with those that survived (1150 ± 590 versus 625 ± 254 s, $P=0.01$) (Fig. 4C).

Platelet contraction forces correlate with TEG MA

TEG is a global measure of coagulation used in trauma to identify coagulopathy and guide resuscitation. Force was compared with TEG MA to determine if the two assays correlated. Because both devices are affected by platelet count, normalization was deferred. A power curve function fitted to the comparison data has a correlation coefficient of $r=0.80$ and $P<0.001$ (Fig. 5). TPC and TEG ACT did not correlate well with $r=0.3$.

Discussion

Our data demonstrate a significant increase in force and normalized force as well as faster TPC in surviving trauma patients compared with those that die. Surviving trauma patients also have increased force and faster TPC than healthy controls. ROC analysis identified force and TPC as potential predictors of mortality, whereas TEG MA and ACT were not. Patients with moderate to severe TBI who survived demonstrated significantly higher normalized force and faster TPC than those with similar head-AIS and ISS that died. Finally, force correlated with TEG MA. This study is clinically relevant because it identifies platelet contraction as a potential predictor of mortality in trauma patients and specifically those who suffer from TBI. In addition, it demonstrates platelet hyperactivity in surviving trauma patients in the early stages after their injury.

No single platelet function assay has been accepted for use in trauma; however, MP is one device widely reviewed in the literature. Solomon *et al.* in 2011 initially studied MP in 163 trauma subjects with median ISS of 18. They demonstrated platelet dysfunction defined by decreased aggregation with TRAP, ADP, and collagen agonists (13.7%, 13.9%, and 5.6% of patients, respectively). Platelet dysfunction was significantly more common in non-survivors compared with survivors in the TRAP and ADP agonist pathways, similar to findings in our study of platelet contraction in trauma nonsurvivors.¹⁷ Kutcher *et al.* in 2012 demonstrated decreased platelet function using MP in 101 trauma patients with mean ISS of 23. 46% of patients had below-normal platelet aggregation in response to at least one agonist on admission and none demonstrated an increase in platelet function. Platelet hypofunction on admission correlated with a 10-fold increase in mortality.⁴ Sillesen *et al.* in 2013 studied MP using a swine model of TBI and hemorrhage and demonstrated significant decreases in ADP aggregation compared with controls. No changes in collagen or AA aggregation were observed.¹⁸ These studies suggest that trauma leads to a universal decrease in platelet function measured by MP that is worsened in nonsurvivors.

Another platelet function device commonly reviewed in the literature for use in trauma is TEG PM. Platelet inhibition in TEG PM is defined by decreased clot stiffening in either the

AA or ADP channel compared with a kaolin control when controlled for the clot fibrin component. Wohlaue *et al.* in 2012 studied TEG PM in 51 trauma patients with mean ISS of 19. Compared with healthy controls, trauma patients exhibited marked platelet inhibition. In addition, rates of blood transfusion and base deficit correlated with the degree of platelet inhibition.³ In 2013, Davis *et al.* studied platelet function in 50 TBI patients using TEG PM. Similar to the study by Wohlaue, there was significant platelet inhibition compared with controls in the AA and ADP channels. The amount of ADP inhibition distinguished survivors and nonsurvivors, similar to the pathway independent findings in our study concerning platelet contraction in TBI patients.¹⁹ Sirajuddin *et al.* in 2016 demonstrated significant inhibition of platelet function measured by TEG PM in 459 trauma patients with mean ISS of 5. Even in these patients with minor injuries and no apparent coagulopathy, platelet function was inhibited in the AA and ADP channels of the assay. There was no correlation between TEG PM parameters and mortality.²⁰ These studies of TEG PM suggest that platelet inhibition after trauma is common and demonstrate clinical correlations that are pathway dependent.

These studies of MP and TEG PM in trauma attempt to demonstrate device correlation with clinical end points such as mortality, injury severity, and blood product administration. Despite their clinical relevance, however, the two devices correlate poorly with each other.²¹ They also universally report platelet inhibition compared with controls even in patients with low ISS, absence of coagulopathy, and without blood transfusions. None of these studies reports an instance of increased platelet function after trauma. This finding disagrees with a natural physiologic state of hypercoagulability after trauma that would be expected.²² By contrast, platelet contractile force demonstrates a distinction between platelet hyperactivity in those patients that survive and platelet dysfunction in those patients that die when compared with healthy controls. Although mortality is a crude measure of clinical outcomes, it serves as a foundation for discussion of expected results using different platelet function devices.

A study by Jacoby *et al.* in 2001 using the PFA-100 demonstrates patterns of platelet activation similar to our study. Jacoby examined a cohort of 100 trauma patients with mean ISS of 22. They demonstrate similar distinctions in platelet function to our study; however, these distinctions were not significant until 24 h after patient admission to the hospital. Surviving trauma patients demonstrated faster occlusion times when compared with healthy controls, or increased platelet function. Nonsurviving trauma patients demonstrated significantly slower occlusion times than surviving patients, or decreased platelet function.²³ A potential explanation for this similarity with our study is that activation in the PFA-100 is not dependent on a single pathway like in MP or TEG PM. PFA-100 device cartridges use a combination of collagen and either ADP or epinephrine, whereas MP and TEG PM are dependent on a single pathway for activation. Platelet contractile force is not pathway dependent, rather samples are activated by recalcification to initiate clotting and engage the coagulation cascade.

Platelet contraction is the terminal phase of platelet function and reflects the integrity of platelet biomechanics and energy metabolism. Its purpose is to strengthen a forming clot, appose edges of open wounds or vessels, decrease shear forces imparted onto a forming clot,

and reestablish blood flow in occluded vessels. Platelet contraction is an important measure of hemostatic potential because it is the final common pathway of platelet function and reflective of all antecedent phases of platelet activation. ATP derived from oxidative phosphorylation is the primary source of energy utilized by the actin and myosin proteins within platelets to drive contraction.²⁴ This phase of platelet activation is energy intensive and offers a mechanical signal with a wide dynamic range. In this study, measured force ranged from 600 μ N to 12,800 μ N, a twenty-fold difference. This is clinically advantageous and allows distinction of a wide range of platelet function. Other platelet function devices such as MP, TEG PM, or the PFA-100 do not approach this range of measurable signal.

Both force and normalized force provide relevant information regarding platelet function after trauma. However, it is possible that force is more clinically useful because it more accurately reflects bulk clot strength. In an injured trauma patient, force reflects the overall clot strength regardless of platelet count and offers an approximation of clot burst pressure. On the other hand, normalized force may be superior in describing function of individual platelets. It is possible that low normalized force could represent platelet metabolic exhaustion and serve as a biomarker for systemic metabolic dysfunction after severe injury. Further studies could elucidate novel metabolic therapies to correct this underlying cause of coagulopathy after trauma.

Limitations of this study include investigating only the initial patient blood sample rather than collecting serial samples. Future studies would benefit from studying samples after resuscitation and at 24 or 48 h time points. In addition, standard coagulation studies such as prothrombin time, international normalized ratio, or partial thromboplastin time were not included in this study and could potentially add perspective because they are commonly used to estimate hemostatic potential. We also acknowledge that other variables in the blood samples such as fibrinogen concentration and total protein were not recorded and could affect platelet contractility.

Conclusions

Platelet contraction is clinically relevant because it demonstrates platelet hyperactivity in trauma survivors and dysfunction in nonsurvivors. Force, a mechanical measure of platelet function, is increased in surviving trauma patients compared with healthy controls and trauma nonsurvivors. In addition, time to platelet contraction in surviving trauma patients decreases compared with nonsurvivors. These findings are similar in patients with moderate to severe traumatic brain injury. In addition, platelet contraction force correlates moderately with TEG.

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Disclosure

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Fig. 1 –. Schematic of the bent-wire cantilever. Labeled components in panel A and B include camera (1), wire cantilever (2), light emitting diode (3), alignment pin (4), heating element (5), thermocouple (6), bottom sensor disc (7), top sensor disc (8), glass vial (9), and cantilever holder (10).

Fig. 2 –.

Comparison of platelet function between healthy controls and trauma patients. Platelet contraction force is significantly different among all groups, being highest in trauma survivors, lowest in trauma patients that die, and at the baseline in healthy controls (A). Normalized platelet contraction force demonstrates similar but nonsignificant trends with regards to healthy controls (B). Time to platelet contraction is significantly shorter in trauma survivors compared with healthy controls (C).

Fig. 3 –.

Receiver operator characteristic curves as predictors of patient mortality. Platelet contraction force (A) and time to platelet contraction (B) are significantly different from chance. TEG maximal amplitude (C) and activated clotting time (D) are not. Area under the curve (AUC) with 95% confidence intervals shown in bottom right of graph. *AUC signifies 95% confidence intervals that are significantly differ from random chance.

Fig. 4 –.

Comparison of platelet function between trauma survivors and those that died with traumatic brain injury (TBI), head-AIS 3. Head-AIS and ISS are similar between the two groups. Platelet contraction force (A) and normalized platelet contraction force (B) is higher and time to platelet contraction is faster (C) in those TBI patients who survive.

Fig. 5 –.

Correlation of platelet contraction force with TEG MA. Platelet contraction force correlates moderately with TEG MA. A power curve function fits the data with $r = 0.8$.

Table 1 –

Patient demographics, injury, vitals, laboratory values, and coagulation function in all patients and stratified by mortality.

	All (n = 100)	Survivors (n = 90)	Deaths (n = 10)	P-value
Demographic data				
Age (y)	45 ± 19	42 ± 18	65 ± 19	0.001
Male (%)	74	76	90	0.315
Injury and vitals				
Blunt (%)	73	70	100	0.059
Systolic BP (mm Hg)	134 ± 31	134 ± 29	136 ± 48	0.83
Heart rate (beats per min)	102 ± 24	102 ± 23	104 ± 34	0.79
Glasgow coma score (GCS)	15 (3, 15)	15 (6, 15)	3 (3, 4)	<0.0001
Injury severity score (ISS)	14 (4, 23)	9 (4, 17)	25 (23, 31)	0.027
Laboratory values				
pH	7.29 ± 0.12	7.3 ± 0.11	7.25 ± 0.17	0.26
Base excess	-2.9 ± 5.6	-2.8 ± 5.4	-3.6 ± 7.3	0.67
WBC	12.8 ± 5.6	12.9 ± 5.6	12.3 ± 5.8	0.73
Lactate	3.8 ± 3.7	3.6 ± 3.7	5.4 ± 4.1	0.17
Platelet count (K/ μ L)	237 ± 73	244 ± 68	165 ± 84	0.001
Coagulation function				
TEG MA	63 ± 8	64 ± 6	56 ± 15	<0.0001
TEG ACT (s)	109 ± 15	108 ± 14	117 ± 17	0.06
Force (uN)	6010 ± 2520	6390 ± 2340	2860 ± 1830	<0.0001
Normalized force (uN/100,000 platelets)	25.8 ± 10.2	27 ± 9.9	16.2 ± 5.9	0.001
TPC (s)	748 ± 655	660 ± 467	1460 ± 1340	<0.0001