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Quantification of Hypercoagulable State After Blunt Trauma: Microparticle and Thrombin Generation Are Increased Relative to Injury Severity, While Standard Markers are Not

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Abstract

Objective—Major trauma is an independent risk factor for developing venous thromboembolism (VTE). While increases in thrombin generation and/or procoagulant microparticles (MP), have been detected in other patient groups at higher risk for VTE, such as cancer or coronary artery disease, this association has yet to be documented in trauma patients. This pilot study was designed to characterize and quantify thrombin generation and plasma MP in individuals early after traumatic injury.

Methods—Blood was collected in the trauma bay from 52 blunt injured patients (case) and 19 non-injured outpatients (controls) and processed to platelet poor plasma for 1) isolation of MP for identification and quantification by flow cytometry; and 2) in vitro thrombin generation as measured by calibrated automatic thrombography (CAT). Data collected are expressed as either mean $\pm$ standard deviation or median with interquartile range.

Results—Among cases, 39 men and 13 women (age = 40 ± 17), the injury severity score was 13 ± 11 , INR 1.0 ± 0.1 , PTT 25 ± 3 (sec), and platelet count 238 ± 62 (thousands). The numbers of total (cell-type not specified) procoagulant MP, as measured by Annexin V staining, were

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increased compared to non-trauma controls ($541 \pm 139/\mu\text{l}$ and $155 \pm 148/\mu\text{l}$, respectively, $p < 0.001$). There was no significant difference in the amount of thrombin generated in trauma patients compared to controls; however, peak thrombin was correlated to injury severity, (Spearman correlation coefficient $R = 0.35$, $p = 0.02$).

Conclusion—Patients with blunt trauma have greater numbers of circulating procoagulant MP and increased *in vitro* thrombin generation. Future studies, to characterize the cell-specific profiles of MP and changes in thrombin generation kinetics post-traumatic injury will determine whether they contribute to the hypercoagulable state observed after injury.

INTRODUCTION

Trauma Induced Coagulopathy (TIC) detected early after injury reflects injury severity and is prognostic for blood transfusions and death.^{1–2} Maintenance of hemostasis, often with blood products aimed at limiting hemorrhage, comes with a price of increased risk of venous thromboembolism (VTE).^{3–5} Although major trauma is an independent risk factor for VTE, injury in itself is not predictive of VTE for an individual patient; indeed, most trauma patients do not develop symptomatic VTE. The two faces of TIC, the hypo- and the hypercoagulable states, are poorly understood. Standard coagulation tests, which include prothrombin time (PT) and activated thromboplastin time (aPTT) assays, are measurements of the canonical extrinsic and intrinsic clotting pathways. They utilize excess concentrations of tissue factor or contact activator, which makes these tests relatively insensitive to perturbation of the clotting cascade because the end-points of these assays coincide with the onset of the propagation phase of clotting where >95% of thrombin is still to be generated.^{6–7}

Clearly, tools having enhanced sensitivity and specificity are needed to understand the basis for TIC, to explore its relation to VTE, and to target risky, anticoagulant-based prophylaxis to those patients who would benefit most. To this end, two unconventional methods to assess hyper-coagulation were employed in this study. First is the Calibrated Automated Thrombogram (CAT), a plate-based assay that measures the rate of thrombin generation and inhibition in citrated plasma, and has been used to quantify procoagulant activity in several diseases including VTE and coronary artery disease.^{8–10} The clinical utility of *in vitro* thrombin generation however, remains to be determined in trauma patients.

Second, circulating procoagulant microparticles (MP) have emerged as possible contributors to, or markers for, the hypercoagulable state. These sealed membrane vesicles arise from cell stress and other metabolic perturbations, and are shed into circulation from platelets, leukocytes, and endothelial cells. Increases in circulating MP have been associated with inflammatory and thrombotic processes and represent an opportune analyte owing to facility of access to peripheral blood samples and available technology, such as flow cytometry, can identify both the procoagulant nature and the cell source of MP in plasma samples.

The objective of this study was to characterize and quantify procoagulant activity and MP in plasma obtained from individuals after traumatic injury.

PATIENTS AND METHODS

Study Design

The study was approved by the Mayo Clinic IRB (# 09-000713) and was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPPA) Regulations. A prospective cohort study included consecutive patients from southeastern Minnesota, northern Iowa, or western Wisconsin arriving at the Mayo Clinic Trauma Center after suffering from blunt (including closed head injury) or penetrating injury. The patients

were transported to the Mayo Clinic Emergency Department (ED) by ambulance or helicopter. Exclusion criteria were: age < 18 years, active treatment for anticoagulation (e.g., heparin, warfarin) or antithrombotic therapy (e.g., thienopyridine; excluding aspirin or non-steroidal anti inflammatory drugs), preexisting coagulopathy, more than 12 hours from time of injury, any transfusion of blood products prior to blood sample collection, active malignancy, sepsis or renal failure, or burn injuries. The clinical practice of the Trauma Service does not involve routine DVT surveillance by any form of routine, serial, noninvasive imaging in asymptomatic patients either during or after hospital discharge, in accordance with the guidelines of the American College of Chest Physicians on prophylaxis for VTE.¹¹ Clinical data were collected and included: injury severity score (ISS), Glasgow Coma Scale (GCS), body temperature, lactate, cell blood count (CBC), activated partial thromboplastin times (aPTT) and international normalized ratio (INR). These particular parameters were collected as they have been shown to be affected by traumatic injury.^{12–16}

Outpatients with no prior history of thrombosis (i.e., stroke, myocardial infarction or venous thromboembolism) seen at the Mayo Clinic during the same time period, provided blood samples for MP and CAT (n=19) reference (control) analyses. The individuals were not receiving anticoagulation (heparin, warfarin) or taking antithrombotics (e.g., thienopyridine; including aspirin or non-steroidal anti inflammatory drugs) within 7 days prior to blood sample collection.

Sample Collection and Processing

To minimize the impact of confounding therapy, a one-time blood sample was collected either at the scene of the injury or, if the pre-hospital team was unable to collect the sample, in the ED. Whenever possible, written informed consent was obtained from the patient prior to collection of blood sample. When patients were unable to provide consent at the time of the trauma, consent was obtained from the patient or legal guardian prior to patient discharge; otherwise, the study sample was appropriately discarded. The study was approved by the Mayo Clinic Institutional Review Board.

Blood samples

A total of 18 mL of blood was collected by antecubital venipuncture into 1) an anticoagulant containing hirudin (inhibits thrombin) plus soybean trypsin inhibitor (inhibits factor Xa) for the MP analysis 2) a 3.2% citrate tube for CAT analysis. Multiple aliquots of platelet poor plasma (PPP) were prepared by two (2) centrifugations (3000g, 15 minutes) and then frozen at –80 ° C until analysis.

CAT assay

Procoagulant activity of plasma samples to which 50 ug/mL corn trypsin inhibitor (CTI, Haematologic Technologies Inc. Essex Junction, VT) had been added were assayed with the Calibrated Automated Thrombogram (CAT) as described by Hemker et al^{17–18} and Owen et al.¹⁹ For the canonical CAT, 5 nM exogenous tissue factor (TF) and 4 nM phospholipids (PL) was added to trigger thrombin generation. The CAT assay can be configured without addition of exogenous triggers, and is referred to as native CAT (nCAT).^{19–20} The rationale for using native CAT was to be able to detect all procoagulant activity, particularly tissue factor (TF) generated after traumatic injury that might be otherwise masked by addition of high concentrations of exogenous activators.

MP Analysis

Isolation and characterization of MP was carried out as described by Jayachandran et al.¹⁹ Briefly, MP were collected by high speed centrifugation (20,000g for 30 min) and then

stained with a platelet-specific fluorescent antibody (anti-CD42) and with fluorescent annexin V, which binds to procoagulant phosphatidylserine. The stained MP were counted with a FACSCanto flow cytometer (BD Biosciences, San Jose CA), with use of an internal standard of microbeads.

Statistical Analyses

Data analysis was performed using SigmaStat 3.50 (Systat Software, Point Richmond, CA, USA). Student's t-test and the Mann-Whitney Rank Sum Test (as appropriate) were used to assess differences in mean values between the enrolled subjects and controls. Correlation was assessed with Spearman rank correlation analysis using Sigmaplot 8 (Systat Software, Inc. San Jose, CA). Data are expressed either as mean $\pm$ standard deviation (SD) or as median values with interquartile range; a $p < 0.05$ considered to be significant.

RESULTS

Patient and Normal Donor Characteristics

During a 6-week period, 6 April through 24 May 2009, one blood sample was collected from 80 of 147 patients admitted with major trauma (57 Level 1, based on physiologic criteria of instability and 90 Level 2 activations, based on mechanism of injury); five samples were collected in the pre-hospital setting, while the remainder were collected on arrival to the ED. Of these 80 patients, consent was obtained from 52; 13 were women (25%), and the overall mean age was 40 ± 17 years. The mean time between sample collection and time of injury was 2 hours (hrs) 51 minutes (min) $\pm$ 2 hrs 44 min (range 27 min – 9 hrs 22 min). All enrolled subjects had received blunt mechanical trauma and a mean injury severity score (ISS) of 13 ± 11 , Glasgow Coma Scale (GCS) of 13 (range 3–15), core body temperature of 37.0 ± 0.6 °C, systolic blood pressure of 144 ± 23 mmHg, and serum lactic acid concentration of 2.2 ± 0.9 mg/dL. The hemoglobin and platelets were 13.8 ± 1.8 g/dl and $238 \pm 62 \times 10^9/L$, respectively. In the overall patient population, the activated partial thromboplastin times (aPTT) and international normalized ratio (INR) of study patients were within the normal reference range and did not correlate with ISS (r of 0.17 and 0.26, respectively with $p > 0.05$). Five patients had a GCS < 8 on presentation, 8 patients went directly to the operating room (OR) from the ED, and 17 patients were admitted to the Intensive Care Unit after evaluation in the ED or directly from the OR. There were two deaths during the hospitalization. One patient, 48 year old woman with an ISS of 43, developed left arm swelling due to subclavian vein thrombosis that was confirmed by venous duplex ultrasonography.

The age of the 19 outpatients used for controls was 52 ± 17 (9 men and 10 women). None of the women was on hormonal replacement therapy.

Native Calibrated Automated Thrombinogram (nCAT)

The distribution of the values of Lag Time (minutes) and thrombin Peak Height (nM) among the trauma patients and the 19 controls were broad (Figure 1) and did not differ significantly between the two groups (Table 1). Similar to the findings of Dunbar and Chandler¹⁴ a commercial pooled control plasma (CryoCheck, Precision Biologic, Nova Scotia) had three times the Lag Time (61.4 ± 8.3 minutes) and 1/60 the Peak Height (1.3 ± 2.2 nM) of our control patients.. However, the range of peak thrombin displayed by trauma patients was nearly 30-times that compared to controls Furthermore, Lag Time and Peak Height (Figure 2) showed a significant correlation with ISS; Spearman rank correlations to Lag Time and Peak Height were $r = -0.325$ ($p = 0.04$) and $r = 0.352$ ($p = 0.02$), respectively (Figure 2). The one patient who developed VTE had a lesser Lag Time (9 minutes) and a much greater Peak Height (298 nM) than any of the controls.

Microparticle Analysis

Trauma patients had significantly increased total numbers of Annexin V (+) MP relative to the controls (Table 2) and with a substantially larger variance (Figure 3). The one patient who developed VTE had markedly increased numbers of Annexin V (+) MP (2,074/ μ L at the time of presentation to the trauma bay). Correlation between ISS and Annexin V (+) MP was significant with $r = 0.393$ ($p = 0.007$) (Figure 4). No significant correlation was found between ISS and total platelet [CD 42a (+)] derived MP ($r = 0.281$, $p = 0.059$). Interestingly, only in one patient did we detect CD 62E (+), endothelial cell-derived MP.

DISCUSSION

In this pilot study, we have observed that the numbers of circulating thrombogenic MP and endogenous procoagulant activity in patients with blunt trauma correlate with injury severity despite normal values for standard clotting assays. Response to injury appears to be variable between individuals as evidenced by a large variance around the regression lines. This variability is essential for exploration of an individual hypercoagulable response to trauma. Because this was a small study, we had only one patient with clinically relevant VTE. In addition, procoagulant activity in peripheral blood may continue to increase from the time of trauma and then decline as patients recover from their injuries. As we collected blood samples only at the time of patient presentation to the ED, it cannot be determined where each patient was on the injury response continuum. In our current study, serial blood draws are being obtained from trauma patient enrollees until their discharge. Our goal is to understand the importance of how changes in thrombin generation and MP distributions relative to time of injury might influence the development of VTE after trauma.

Assays that address the net effect of both pro- coagulant and anti-coagulant processes have a greater potential for detecting a hypercoagulable state than measurement of any single pathway. The CAT, which uses cell-deficient plasma, allow analysis of the composite soluble factors involved in the coagulation process, including the balance of pro- and anti-coagulant factors derived from a single individual. Compared to clotting time assays, such as prothrombin time (PT) and aPTT, which yield only 1 time point and evaluate clot formation early in the process of thrombin generation, CAT allows evaluation of total thrombin generated within a sample and is calculated as the area under the thrombin generation curve over time. Increased total thrombin generation has been associated in patients with clinical risk factors (e.g., obesity, increasing age, oral contraceptives) for VTE.^{22–24}

Using the modification of the CAT that eliminates exogenous trigger (TF/PL) limits thrombin generation in response to endogenous procoagulants which, in normal subjects, is substantially less than that with a TF/PL trigger. The median Lag Time and Peak Height of our sample of patients were not different from those of 19 outpatient controls but showed a substantially greater variance, which was reflected by a positive correlation between native thrombin generation and ISS. We found that native thrombin generation from commercial reference pooled donor plasma (CryoCheck) was essentially null. This difference warrants further investigation as a publication reporting an impact of trauma on native CAT used a similar commercial product for control values.²⁰

We observed significantly greater numbers of procoagulant (Annexin V+) MP in trauma patients relative to the 19 controls, and like nCAT, a high-variance correlation with ISS. MP normally found in plasma can potentially be derived from any cell type. In normal plasma, MP derived from platelets are most common (>80%), followed by MP derived from endothelial cells (<10%) and leukocytes (<10%).²⁵ The microparticles derived from platelets, which are the most abundant in plasma, express surface phosphatidylserine (Annexin V+) and are procoagulant in vitro.^{21, 26–28} Such a thrombogenic potential of MP

has been known for the past three decades, but the membrane vesicles containing phosphatidylserine (Annexin V+) are thrombogenic pharmacologically in vivo only with co-administration of a coagulant enzyme.^{29–30} Thus, endogenous MP expressing membrane phosphatidylserine may not contribute intrinsically to thrombosis but may drive thrombosis in an environment where procoagulant enzymes are generated, such as would be expected in peripheral blood of patients after major trauma.

Conclusion

In this pilot study of patients with blunt trauma, we observed an increase in thrombogenic MP and increased thrombin generation by CAT. Future studies to characterize the profiles of MP and thrombin response over time would enhance our understanding of their role in the hypercoagulable state observed after injury. It remains to be determined if the characterization of MP and thrombin generation could find practical applications either as diagnostic indicators or be predictive of post-injury thrombotic complications such as VTE. If so, bleeding complications related to chemoprophylaxis could be minimized by assessing the blood physiology of individual patients rather than utilizing population-based algorithms. Conversely, it may be determined that other patients require more aggressive chemoprophylaxis than is currently administered.¹¹

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Key Words

An V+	Annexin V binding positive
CAT	Calibrated Automated Thrombogram
LT	Lag Time (minutes)
MP	microparticles
PH	Peak Height (nM)

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Figure 1.

Peak Height distributions of native thrombin generation. The top of each box defines the 75th percentile, while the bottom of the box the 25th percentile and the line through the box indicates the median. The top whiskers define the 95th percentiles and the bottom whiskers define the 5th percentiles of the data. Each data point is represented by a symbol.

Figure 2. Correlations between Injury Severity Score and Peak Height. The data were fit using a linear regression model.

Figure 3. Distribution of Annexin V Positive Microparticles counts. Box and whisker variables as defined in figure 2. Note that there are 7 trauma patients that fall outside the 95th percentile.

Figure 4. Correlation of Injury Severity Score with Annexin V Positive Microparticle counts. Linear regression analysis as described in Figure 2.

Table 1

Native Calibrated Thrombinogram (nCAT) of Plasma

	PATIENTS (N = 40)	CONTROL (N=19)	P VALUE
Native Lag Time (min)	26.9 ± 14.9	22.6 ± 7.3 *	0.615
Native Peak (nM)	77.0 ± 62.0	76.9 ± 40.4 *	0.372

* From Mayo Clinic outpatients with no prior history of thrombosis.

Table 2

Microparticle with Platelet - Derived Annexin V Positive (Annexin V +) Microparticles (MP) in row 1; All Annexin V + MP in row 2

	PATIENTS (N = 47)	CONTROL (N = 19)	P VALUE
Platelet Derived Annexin V + MP	328 ± 1418	<u>151 ± 145</u>	<0.001
Total Annexin V + MP	541 ± 1981	<u>155 ± 148</u>	<0.001