Admission rapid thrombelastography predicts development of pulmonary embolism in trauma patients

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BACKGROUND: Injury leads to dramatic disturbances in coagulation with increased risk of bleeding followed by a hypercoagulable state. A comprehensive assessment of these coagulation abnormalities can be measured and described by thrombelastography. The purpose of this study was to identify whether admission rapid-thrombelastography (r-TEG) could identify patients at risk of developing pulmonary embolism (PE) during their hospital stay.

METHODS: Patients admitted between September 2009 to February 2011 who met criteria for our highest-level trauma activation and were transported directly from the scene were included in the study. PE defined as clinically suspected and computed tomography angiography confirmed PE. We evaluated r-TEG values with particular attention to the maximal amplitude (mA) parameter that is indicative of overall clot strength. Demographics, vital signs, injury severity, and r-TEG values were then evaluated. In addition to r-TEG values, gender and injury severity score (ISS) were chosen a priori for developing a multiple logistic regression model predicting development of PE.

RESULTS: r-TEG was obtained on 2,070 consecutive trauma activations. Of these, 2.5% (53) developed PE, 97.5% (2,017) did not develop PE. Patients in the PE group were older (median age, 41 vs. 33 years, $p = 0.012$) and more likely to be white (69% vs. 54%, $p = 0.036$). None of the patients in the PE group sustained penetrating injury (0% vs. 25% in the no-PE group, $p < 0.001$). The PE group also had admission higher mA values (66 vs. 63, $p = 0.050$) and higher ISS (median, 31 vs. 19, $p = 0.002$). When controlling for gender, race, age, and ISS, elevated mA at admission was an independent predictor of PE with an odds ratio of 3.5 for mA > 65 and 5.8 for mA > 72.

CONCLUSION: Admission r-TEG mA values can identify patients with an increased risk of in-hospital PE. Further studies are needed to determine whether alternative anticoagulation strategies should be used for these high-risk patients. (*J Trauma Acute Care Surg*. 2012;72:1470–1477.

LEVEL OF EVIDENCE: Prognostic study, level III.

KEY WORDS: Thrombelastography; venous thromboembolism; pulmonary embolism; hypercoagulable; trauma.

Venous thromboembolism (VTE) is a well-recognized phenomenon after injury and carries with it significant morbidity and mortality.[1,2] The reported incidence of VTE remains quite varied because of demographic and injury severity heterogeneity in the populations studied, discrepancies in capture of these complications, and the aggressiveness of VTE surveillance and screening.[3–8] In a recent report from the National Trauma Data Bank (NTDB), Knudson et al.[5] demonstrated an incidence of VTE (both deep venous thrombosis [DVT] and pulmonary embolism [PE]) of less than 1% in the general trauma population. With respect to the incidence of PE, this same study noted that its incidence was increasing but still remained below 0.5%.

Major trauma remains one of the most potent risk factors for VTE and has been reported to increase the risk by 10-fold.[1,2] Injury leads to dramatic disturbances in coagulation with initial increased risk of bleeding followed by a hypercoagulable state.[9] As such, the injury severity score (ISS) is closely correlated with increased risk of VTE.[10,11] Of the different anatomic regions, head, chest, and lower extremity injuries appear to contribute the most to this increased VTE risk.[4,5,10,11] In addition, increasing age, venous injuries, and increased ventilator days consistently appear as major risk factors even in multivariate regression models.[1] As well, even ABO blood group differences among injured patients carry a variable risk of VTE after injury.[2] Those with non-O blood type (specifically, A1 and B alleles) have a 60% higher age adjusted risk of VTE than those with O blood type.[12,13]

Despite knowledge of these risk factors, increase VTE guideline compliance and increasing aggressiveness with postinjury chemoprophylaxis, the rate of symptomatic VTE is increasing.[14] Even more concerning is the increased incidence of PE, which carries even higher risk of morbidity and mortality.[5] Recent data suggests that PE can be predicted in trauma patients, various postoperative states, and those admitted to a surgical intensive care unit (ICU) through the use of thrombelastography (TEG).[9,15–17] Given our institution's increasing use of this technology in management of the bleeding patient, we set out to determine how TEG might be used in predicting PE.[18] The purpose of this study was to identify whether admission rapid-TEG (r-TEG) values could identify patients at risk of developing PE during their hospital stay.

METHODS

Study Setting

The University of Texas Health Science Center-Houston and the Memorial Hermann Hospital Institutional Review Boards approved this study. Memorial Hermann Hospital is an American College of Surgeons verified Level I trauma center that is the primary teaching hospital for the University of Texas Health Science Center. Memorial Hermann is one of only two Level-I trauma centers in Houston, TX, the fourth largest city in the United States. The hospital is an 800-bed facility within Texas Medical City and is home to the John S. Dunn Helistop, the busiest heliport in the United States for its size. The trauma center admits well over 5,000 trauma patients annually with the most severely injured cared for in the 25-bed shock-trauma ICU.

Selection of Participants

Using the institution's Trauma Registry of the American College of Surgeons database, we evaluated all adult trauma patients admitted between September 2009 and February 2011 who were the institution's highest-level trauma activation. Patients who were younger than 18 years, had burn wounds greater than 20% total body surface area, or who died within 30 minutes of arrival were excluded.

Laboratory Setting and Processing of Specimens

All r-TEG specimens were run on a TEG thrombelastograph 5000 (Hemoscope Corporation, Niles, IL). Blood

specimens for r-TEG were obtained as part of the usual blood samples acquired during the primary or secondary survey evaluation of all major trauma activations. Given the previously described limitations of performing r-TEG at our institution with a noncitrated whole blood sample, we used a citrate "reversal" method.[18] Briefly, the specimen was collected in a small (3 mL) citrated tube, transported to the Stat Laboratory along with other trauma laboratories. There it was immediately reversed with the addition of calcium chloride according to the manufacturer's recommendations within the r-TEG package insert. After this, standard tissue factor plus kaolin activated r-TEG was performed.

Staff laboratory technicians in the Memorial Hermann Emergency Department (ED) Stat Laboratory performed all the r-TEG and standard during the defined study period. These same technicians performed all the quality controls on the TEG analyzers, doing so every 8 hours. QC was performed per the package insert form the Hemonetics Company.

Measurements

The r-TEG's activated clotting time (ACT) (normal range, 0–118 seconds) is the time in seconds between initiation of the test and the initial fibrin formation and is increased with factor deficiency and decreased with enzymatic hypercoagulopathy.[18] The r value (reaction time) is also another representation of the time to the beginning of clot formation. The alpha (α) angle (normal range, 66–82 degrees) is the slope of the tracing that represents the rate of clot formation, increasing with hyperfibrinogenemia or increased platelet aggregation. The maximal amplitude (mA) (normal range, 54–72 mm) is the greatest amplitude of the tracing and reflects platelet contribution to clot strength. High mA values correspond with states of platelet hypercoagulability. The *G* value (normal range, 5.3–12.8 K dynes/cm^2) is a measure of absolute clot strength (both enzymatic and platelet contributions) and is increased in hypercoagulable states. LY30 (normal range, 0.0–7.5%) represents the percent amplitude reduction at 30 minutes after mA and reflects the degree of fibrinolysis.

Definitions and Outcomes

PE was defined as those events detected by helical computerized tomography angiography of the chest (obtained for clinical suspicion) and recorded in the Division of Acute Care Surgery's Morbidity and Mortality database. Age, gender, ISS, and weighted Revised Trauma Score were abstracted from the Trauma Registry of the American College of Surgeons database. Other comparative trauma panel laboratory values were accessed through a query of the hospital's electronic medical record system.

Statistical Analysis

Continuous data were presented as medians with 25th and 75th interquartile range with comparisons between groups performed using the Wilcoxon rank sum (Mann-Whitney *U* test). Categorical data were reported as proportions and, where appropriate, tested for significance using χ^2 or Fisher exact tests. The primary data analysis evaluated each r-TEG variable and their ability to predict PE during hospital admission. All statistical tests were two tailed with $p < 0.05$ set as significant.

Purposeful regression modeling was then used to construct a multivariate linear and then a multivariate logistic regression model evaluating the development of PE during hospital stay. This was done using the technique of purposeful selection of covariates described by Hosmer and Lemeshow.[19] In an effort to minimize the risk of falsely identifying significant results with multiple comparisons, all variables were prespecified and judged a priori to be clinically sound. These independent variables included age, gender, race, ISS, ED vitals and laboratories, and prehospital and hospital fluid administration and transfusions. After this, the variables were entered into step-wise regression that generated four variables of significance (age, gender, race, and ISS). These were then applied to a multivariate logistic regression analysis evaluating these four variables and admission mA values. STATA Statistical software (version 10.1; College Station, TX) was used for analysis.

RESULTS

Demographic and Baseline Data

After excluding those who were younger than 18 years or had >20% total body surface area burns, 2,070 major trauma patients met inclusion criteria. Of these, 53 developed PE (PE group) during their hospital stay, whereas 2,017 did not (no-PE group). This translates to a 2.5% rate of PE in our most severely injured patients. Median time to PE was 6 days with 25th and 75th percentiles of 3 and 12, respectively. The mean time was 8.3 days with a standard deviation of 6.7 days, consistent with the distribution being skewed right. The range of time to PE was 2 days to 31 days. A comparison of demographics and injury scoring for these groups is shown in Table 1. Patients in the PE group were older, more likely to have sustained blunt mechanism, and more likely to be white. Arrival laboratories obtained as part of the routine trauma panel and r-TEG values obtained at admission are shown in Table 2. The r-TEG values of α angle, mA, and the *G* value were higher in the PE patients,

TABLE 1. Demographic and Injury Severity Differences Between PE and Non-PE Groups

	PE Group (n = 53)	No PE Group (n = 2,014)	*p*
Median age, yr (IQR)	41 (32–53)	33 (23–50)	0.012
Male gender	69%	76%	0.295
Blunt mechanism	100%	75%	<0.001
White race	69%	54%	0.036
Median ED SBP, mm Hg (IQR)	127 (103–147)	140 (117–156)	0.010
Median ED HR, bpm (IQR)	98 (82–110)	97 (80–117)	0.731
Median Head AIS (IQR)	4 (3–4)	3 (3–5)	0.355
Median Chest AIS (IQR)	4 (3–4)	3 (3–4)	0.148
Median Abdomen AIS (IQR)	3 (2–4)	3 (3–4)	0.228
Median Extremity AIS (IQR)	2 (2–3)	2.5 (2–3)	0.991
Median ISS (IQR)	31 (19–41)	19 (11–29)	0.002

IQR, 25th and 75th interquartile range; SBP, systolic blood pressure; HR, heart rate; bpm, beats per minute; AIS, abbreviated injury scale.

TABLE 2. Comparison of Admission Laboratory Values for PE and Non-PE Groups

	PE Group (n = 53)	No PE Group (n = 2,014)	*p*
Common trauma laboratory values			
Median PT, s (IQR)	14.1 (13.6–15.2)	14.5 (13.8–15.8)	0.035
Median PTT, s (IQR)	27.5 (24.1–28.6)	27.3 (24.7–28.6)	0.080
Median fibrinogen, mg/dL (IQR)	297 (264–318)	270 (209–329)	0.549
Median platelet count (IQR)	232 (197–324)	240 (195–288)	0.590
Median hemoglobin, g/dL (IQR)	13.7 (12.2–14.9)	13.5 (12.0–14.7)	0.825
Median creatinine (IQR)	1.1 (0.9–1.4)	1.1 (1.0–1.3)	0.635
Median base value (IQR)	−3 (−5 to 0)	−4 (−7 to −1)	0.060
Median lactate (IQR)	2.9 (2.4–4.8)	3.3 (2.4–4.6)	0.626
r-TEG values			
Median ACT, s (IQR)	113 (105–121)	113 (105–128)	0.212
Median *r* value, min (IQR)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.147
Median α angle, deg (IQR)	73 (71–79)	72 (68–76)	0.053
Median mA, mm (IQR)	66 (61–72)	63 (59–67)	0.050
Median *G* value, dynes/cm^2 (IQR)	9.4 (7.9–12.5)	8.7 (7.2–10.4)	0.052
Median LY30% (IQR)	0.5 (0.0–1.3)	0.6 (0.1–1.7)	0.115

IQR, 25th and 75th interquartile range; PT, prothrombin time; PTT, partial thromboplastin time.

suggesting a hypercoagulable state. Surprisingly, patients developing PE had lower prothrombin time and partial thromboplastin time.

Patients who developed PE were similar to those in the no-PE group with respect to RBC (median 5 U vs. 6 U, p = 0.481), plasma (median 5 U vs. 5 U, p = 0.624), and platelet (median 6 vs. 6, p = 0.396) transfusions in the first 24 hours. As well, the ratio of plasma:RBC was similar between the groups (median of 1.00 for group and 0.92 for no-PE; p = 0.211). Thirty-day mortality was higher in those that developed PE versus those in the no-PE group (9.3% vs. 3.7%, p = 0.036). In the PE group, those who died had higher admission mA values (median, 73 mm vs. 65 mm, p = 0.482) compared with those who survived. Other r-TEG values were not predictive of mortality in the PE group. Among those in the no-PE group, however, admission mA values were lower in those who died (median, 60 mm vs. 64 mm in survivors, p = 0.001). Other r-TEG values were associated with mortality in the no-PE group (ACT: median, 121 vs. 113 seconds, p = 0.031; α angle, 69 vs. 72 degrees, p = 0.002; and *G* value, 8.2 vs. 8.7 dynes/cm^2, respectively). It was the LY30, however, that had the greatest difference between those who died and those who survived in the no-PE group (median, 2.2% vs. 0.7%, $p < 0.001$). In fact, each incremental increase in LY30% was associated with an increased risk of death. An LY30 < 3% had an 8% mortality whereas ≥3% had a 20% mortality, ≥4% had a 35% mortality, and ≥5% had a mortality 58% (all $p < 0.001$).

Simple linear regression was then performed to evaluate the ability of r-TEG values to predict PE. ACT (coefficient, −0.003, 95% confidence interval [CI], −0.009 to 0.0004; p = 0.363), *r* value (coefficient, −0.003, 95% CI, −0.0216 to 0.0158; p = 0.762), and α angle (coefficient, −0.0008, 95% CI, −0.00001 to 0.0018; p = 0.071) failed to predict PE by linear regression. However, both mA (coefficient, 0.0013, 95% CI, 0.00004–0.0021; p = 0.016) and *G* value (coefficient, 0.0034, 95% CI, 0.0006–0.0062, p = 0.040) predicted the development of PE.

Multivariate Analyses

Multivariate linear regression was then performed to address the results noted in the simple linear model. Age, gender, race, ISS were developed through purposeful regression modeling. Although we attempted to include blunt mechanism of injury, this variable was noted to predict "perfectly" the development of PE (all PE's were in patients who sustained blunt trauma). As such, the regression model "dropped" the variable and analysis was continued with the remaining four variables plus mA. This model was then repeated for the *G* value. When controlling for age, gender, race, and ISS, mA predicted development of PE (coefficient 0.002, 95% CI, 0.0002–0.0047, p = 0.033). Similarly, when the above covariates were controlled for, *G* value predicted PE development during hospital stay (coefficient 0.006, 95% CI, 0.0008–0.0123, p = 0.026).

Scatter plot analysis for mA and *G* values (along the *x* axis) and log development risk of PE (along the *y* axis) were performed to identify inflection points. Two distinct inflection points were identified at 65 mm and 72 mm. A similar distinct distribution could not be found for *G* value. Therefore, we then constructed a multivariate logistic regression model for mA alone. After controlling for age, gender, race, and ISS, admission mA >65 was an independent predictor of PE during hospital stay (Table 3). Even more impressive, when controlling for these same variables, admission mA >72 had an even greater prediction of PE risk with an odds ratio (OR) of almost 6.0 (Table 4). Using a cut-off of >65, the sensitivity of admission mA alone was 82% with a specificity of 53%. With a cut-off value for admission mA >72, the sensitivity drops to 49% whereas the specificity improves to 87%.

TABLE 3. Multiple Logistic Regression Model Predicting the Development of PE Based on Admission mA Value of >65

	OR	95% CI	*p*
r-TEG maximal amplitude >65	3.50	1.694–7.238	0.001
Male gender	0.81	0.392–1.679	0.569
White race	2.67	1.210–5.872	0.015
ISS	1.09	1.021–1.178	0.011
Age (yr)	1.04	0.939–1.165	0.939

TABLE 4. Multiple Logistic Regression Model Predicting the Development of PE Based on Admission mA Value of >72

	OR	95% CI	*p*
r-TEG maximal amplitude >72	5.80	2.858–11.777	<0.001
Male gender	0.80	0.379–1.705	0.570
White race	2.63	1.168–5.919	0.020
ISS	1.11	1.031–1.191	0.005
Age (yr)	1.04	0.933–1.162	0.466

DISCUSSION

Despite increased aggressiveness in initiating chemoprophylaxis for VTE and more liberal use of vena cava filters, the incidence of PE in trauma patients continues to increase.[5,14,20] Fortunately, there has been a concurrent reduction in PE-related mortality. The source of both of these trends (increasing incidence, decreasing lethality) is likely the increased use of helical computed tomography. However, postinjury PE remains a considerable burden carrying with it an increased risk of mortality. In fact, the incidence of PE directly causing or contributing to death in hospitalized patients has remained at ~15% for the last 40 years.[21–23] Given ongoing debates on the appropriate timing for initiating chemoprophylaxis and our recent observation of increasing PE at our institution, we set out to determine whether TEG values on admission could identify high-risk patients. This study noted that admission mA values independently predicted development of PE during hospital stay, even after controlling for other known risk factors of age, gender, and injury severity.

TEG technology is based on measurements of the viscoelastic properties of a whole blood specimen and the various activities that transpire in coagulation (enzymatic clot, platelet clot, and fibrin production and breakdown).[24] As it is able to provide an assessment of the clot initiation and formation and stability of the clot, it is ideally suited to demonstrate both hypo- and hypercoagulable states. TEG has been shown to predict VTE, vascular graft occlusion, and myocardial infarction risk in various patient populations.[16,25,26] The TEG value most commonly used to quantify a patient's risk of VTE is the mA value. The mA on TEG is the greatest amplitude of the tracing and reflects platelet (and to a lesser extent, fibrin) contribution to clot strength. McCrath et al.[16] evaluated postoperative thrombotic complications in 240 patients undergoing various noncardiac surgical procedures. The authors found that mA > 68 mm (within 2 hours of the operation) was associated with increased risk of thrombotic complications, including myocardial infarction (OR, 1.16). Kashuk et al.[15] recently evaluated the performance of r-TEG in 152 critically ill patients in a surgical ICU. This group demonstrated that for every unit increase in *G* value, the odds of a VTE increased by 25%. We noted that although several r-TEG values were associated with an increased risk of PE, the most consistent predictor was an elevated mA (which increased the odds of developing PE by 250% to 500%).

Injury, as a disease process, has long been known to increase the risk of VTE and has more recently been shown to have definitive hypercoagulable profiles by TEG and other sensitive tests of coagulation.[9,15,27–29] Schreiber et al. noted that female trauma patients were more hypercoagulable by TEG and thrombin-antithrombin complexes, although this did not translate into increased clinical events of VTE. Our study demonstrated no statistical difference in PE by gender. When specifically looking at risk factors for PE (rather than for PE and DVT), increasing injury severity of the chest, pelvis, and lower extremities are significant and independent risk factors.[5] Knudson et al. noted that severe chest injury, in particular, conferred a much higher risk of PE. In this study, although we identified a definite impact of overall ISS values, we did not see a significant difference in individual Abbreviated Injury Scale scores. However, there was a trend toward higher PE and chest Abbreviated Injury Scale, and this may have been statistically significant in a larger population.

Age and race have been associated with increased risk of VTE and increased hypercoagulability demonstrated by TEG.[30,31] This study found both race and age to be significant on univariate analysis but noted that only race was an independent predictor of PE in multivariate modeling. Finally, blunt mechanism of injury, which has been associated with higher "volume" of tissue trauma and generalized coagulopathy, was noted to be highly predictive of PE. In fact, none of the patients who developed PE in our series sustained penetrating trauma, as such blunt trauma could not be included in our multivariate regression model. Although blunt trauma is dominant injury mechanism in those who develop VTE, and PE in particular, this percentage (100%) is higher than previously reported. The largest study to date (from the NTDB) evaluating the development of 3,738 postinjury PE found that 90% of patients had blunt mechanism compared with 83% for the population as a whole. The reason for the difference between our population and that of the NTDB may reflect captures of the diagnosis through our morbidity and mortality process, aggressiveness of screening, and sample size.

This study is larger than any previous study evaluating the use of thromboelastometry or TEG. However, this was a single center study and only included 53 patients with PE. As well, we admit more than 5,000 patients per year, but this study only evaluated those who were our highest level trauma activations, excluding a great number of patients. The group studied, however, represents not only the most severely injured patients we care for but also the only group in which we routinely obtain admission r-TEG values. Another significant limitation of this study is that we did not include those patients who developed DVT (in the absence of PE). This decision was made a priori as we do not screen for DVT at our center and would be missing a considerable number of patients. To the contrary, we aggressively pursue the diagnosis of PE and begin treatment in all patients without strong contraindications. Finally, these mA values represent only admission r-TEG values and not those obtained after leaving the ED. Serial r-TEG values may have provided more insight as could have values obtained postoperatively or on arrival to floor or ICU. We are currently engaged in a multicenter study to hopefully address some of these issues, deficits, and limitations.

CONCLUSIONS

Admission r-TEG (using elevated mA values) can identify patients with an increased risk of in-hospital PE. Compared with previous studies stratifying risk factors and those proposing algorithms for VTE prophylaxis, an admission mA value of >65 mm exceed those ORs for "high risk" factors such as pelvic and lower extremity fractures, spinal cord injury, and severe head injury.[4] Moreover, mA values >72 mm exceed or equal the ORs of those noted to be "very high risk" factors for developing PE. Further studies are needed to determine whether alternative or more aggressive anticoagulation strategies should be used for these high-risk and very high-risk patients.

AUTHORSHIP

B.A.C., J.P., C.E.W., and J.B.H. designed this study. B.A.C., K.M.M., Z.A.R. conducted literature searches. B.A.C., K.M.M., Z.A.R. and J.P. collected data. B.A.C., N.M., E.P., C.E.W., R.A.K., and J.B.H. analyzed data. B.A.C., N.M., E.P., R.A.K., C.E.W., and J.B.H. interpreted the data. All authors participated in writing, revising, and editing the manuscript. B.A.C., K.M.M., and Z.A.R. created the figures and tables.

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DISCUSSION

Dr. Preston R. Miller (Winston-Salem, North Carolina): Overall, this looks like a paper that answers some questions and creates a lot of questions as to what we're doing with respect to pulmonary embolism and thromboembolism prophylaxis in our patients.

Some of the things that stood out to me in the paper that might be helpful for others reading the paper to know to help interpret these data, first, in trauma patients what is your standard thromboembolism prophylaxis practice? And what proportion of the patients in the PE group and the non-PE group were receiving these?

Number 2, there is a reasonable incidence of intrinsic genetic hypercoagulable states in the population at large. Do you know if there were any of these states present such as Protein C or S deficiency or factor V leiden were present in the pulmonary embolism group which might skew your results in these 53 patients?

Number 3, on the TEG maximal amplitude or MA is mostly reflective of platelet activity. The elevated MA being associated with pulmonary embolism certainly may argue that platelet dysfunction is a problem.

Does this argue for a potential role for antiplatelet agents in future pulmonary embolism and thromboembolism prophylaxis in trauma patients?

And, finally, based on these results, what's our next step? Should we change our practice? Should we change what we're doing to try to phrophylax these people? What are you thoughts on this?

I appreciate having the paper early and very much appreciate the opportunity to discuss this paper. Thanks very much.

Dr. Steven R. Shackford (San Diego, California): Bryan, that was an excellent paper. I have two questions for you.

The first is the reason that maybe Peggy is noticing in the NTDB that there is an increasing incidence of PE is because we have surveillance bias now. Instead of getting the pulmonary angio we're getting now a CT scan, which is much easier to get. Could you comment on that, please?

Second, have you taken this to the next step? And that would be: since most pulmonary emboli are asymptomatic and you're only looking at the symptomatic people, reverse it. Look at patients, get a routine CT, say, on patients with a 72 and get them at three or four days, and do it to see if these patients have asymptomatic PEs.

Dr. Jeffry Kashuk (Saginaw, Michigan): Bryan, I'm glad to see you guys are continuing with your work in TEG. I have a couple of questions.

On one location in your discussion in your previous work you said MA is a parameter indicative of overall clot strength. In another place in your discussion you said G is a measure of absolute clot strength. Could you clarify what MA versus G really is?

Secondly, if one uses the simple math formula that the manufacturer gives and plugs in the formula for, for instance, an MA of 54, one would get a 10% increase in going from an MA of 54 to 60, whereas the G would increase from 5.3 to 7.5 or have about a 29% increase, suggesting that the G increases exponentially whereas the MA increases linearly. Given that, how can you explain the fact that you found the MA to be a better predictor of the changes that you noted?

What do you think is the origin of the hypercoagulability? Do you think it's platelets? Do you think it's enzymatic? Do you think it's both? This is critical as we look forward to treatment regimes.

And, lastly, I think it's really essential to look at the hospital length of stay and the ICU length of stay (the stasis component of Virchow's triad) in the regression models. Please comment.

Dr. Mitchell Jay Cohen (San Francisco, California): As you know, we've discussed this extensively and have shown that hypercoagulability seems to happen as a result of tissue injury. If you add shock you get hypocoagulability and many of us have published on that.

Are there any patients that had the switch from hypocoagulability to hypercoagulability later? Did you see any change in the TEGs? And did those patients get PEs? Can you track that with your data?

Dr. Hasan B. Alam (Boston, Massachusetts) Bryan, very nice paper. My question relates to the strength of the association. What percentage of the patients that had high R value actually developed PE? You have shown that for an R value of more than 65 the odds ratio was 3, but for white race it was 2.5 and for high ISS it was only 1.5. It does not make any sense that white race is more strongly associated with PE compared to the severity of injury. So can you please comment about the strength of association?

Dr. Ajai K. Malhotra (Richmond, Virginia): You have shown an association of TEG anomaly or TEG value that is associated with later on development of PE. But is it possible that a specific injury, say a head injury or something like that, is causing both the TEG value and the inability to give prophylaxis and leading on to a PE development? You have shown the association but you don't drill down any more that, yes, these patients were equally prophylaxed.

Dr. A. Brent Eastman (San Diego, California): Peggy Knudson wrote a provocative paper that we all read last year about a subset of patients that may have de novo emboli or not emboli but thrombus forming in the pulmonary vascular system as a result of blunt trauma. I wondered if you could look at those patients and were they any different in terms of their predictive value of your study?

Dr. Sandro Rizoli (Toronto, Ontario, Canada): One quick question: how good is this test? What is the sensitivity? Specificity? Positive predictive value? Negative predictive value? Thank you.

Dr. Bryan A. Cotton (Houston, Texas): Thank you for those questions and comments.

With respect to a standard protocol for venous thromboembolism prophylaxis, we are fairly aggressive with this but, again, we don't practice in a vacuum and despite what I want to say goes that doesn't always happen, especially with neurosurgeons or orthopaedic surgeons amongst us.

All the patients, for what it's worth, our prophylaxis guidelines receive 30 milligrams of Lovenox Q 12 or 5,000 of Heparin Q 8, depending on the renal function status, unless they have a traumatic brain injury; and that's held for 48 hours but we start it at the 48-hour mark and we're pretty aggressive about that.

With respect to factor V leiden, protein C and NS deficiencies, things like that, we did not test for that. It was a little bit more of a blunt tool here with the assessment of what was in the database. We did not have those criteria.

We could go back and hone in on at least those 53 and maybe pull out a sample of the other ones that did not get it and look at those. But, again, we did not test for that specifically. But, again, an excellent point.

With respect to what we're going to do next and where the platelet inhibition comes in, we do have several of our faculty that we have talked with and we go back and forth at our faculty meetings every Monday about starting aspirin and Lovenox or just starting Lovenox or where to go from here and we don't really have the perfect answer yet.

We are currently trying to develop an algorithm and a guideline based on initiating aspirin in addition to our Lovenox.

We haven't necessarily incorporated our filters into it although I will tell you that we do have some faculty opinions that if the MA is high enough, especially greater than 72, that given some other risk factors that if we were on the margin for putting in a filter that that might actually push us over.

With respect to where we go now, again to test the impact in a more aggressive fashion with chemoprophylaxis and see if we have a difference, I know Marty Schreiber is doing a study looking at chemoprophylaxis and looking at a Delta R

on his and seeing if he can find a difference in the development of DVT and PE but we have not employed that yet.

And, applying more aggressive prophylaxis, adding aspirin to it may be a way to go.

With respect to Dr. Shackford, I appreciate your comments. There was an increased risk with obviously the symptomatic ones.

We did not look at those who were asymptomatic as we were trying to define PE by its strictest terms that we set out a priori.

As far as the others, we think those are very — I think those are very reasonable comments with your second question and we hope to address those again with the paper and with the revisions.

Dr. Kashuk's questions, the MA and the G value, the G value is overwhelming a portion of the MA. In fact, besides numbers derived into that mathematical equation, the only value you put into it is the MA. And so that is an overwhelming part of that.

We brought that out and we tested MA and G value and ACT and alpha. Every value was interrogated to the nth degree but only the MA was the one that fell out with all of our models.

Now, I will say for the linear regression the G value was important but when we tried to dichotomize it, the G value did not offer up a nice clean cut point and, hence, the reason that we did not push forward with the G value.

With respect to your third question I believe platelets are the major contributor to this because, again, it's an MA heavy predictive model. And then, again, we only had 53 patients so we weren't able to address your other questions.

With respect to Mitch Cohen, there weren't serial labs involved with this. Hopefully we will have that answer soon. And, again, these were asymptomatic patients.

With respect to Dr. Hasan Alam's question, these were multi-logistic regression models that were developed. The factors were chosen a priori and plugged in.

I will tell you these were fairly reproducible. If you look at the MA of 65, the MA of 72, the race, the gender, the ISS, their contribution to it or their contribution to the overall model strength didn't really change much.

When we broke up ISS and broke it into AIS scores, those didn't change much as well so I, there is not much more I can extrapolate on that.

With Dr. Malhotra, we did not break them down into AIS, very similar to the other questions, did not break those down into individual AIS scores for the purpose of the publication.

We did that for the statistical evaluation and surprisingly the AIS individual components which we were predicting based on Dr. Knudson's work and Dr. Shackford's work to have a lot of contribution to it, be more powerful, they were actually not.

And they were actually more powerful in aggregate. And when they were brought together in the ISS score that seemed to have more power.

With respect to Dr. Eastman's questions, again, we did not break up the DVT and the PE. That would be much more interesting to bring all of those back together and see if overall if the clot, if the hypercoagulable state can be detected.

We'd like to start employing the TEGs in more of our patients. Right now we've only been doing them in our major traumas which, again, has only been a quarter of our population.

With Dr. Rizoli's comments to the specificity and sensitivity, if it's a greater than 65 yields an 82% sensitivity and about a 53 specificity.

When you flip that, and depending on how aggressive you want to be, you put your cut point at 72 and you improve your specificity well above 80% but your sensitivity drops to just below 50%.

Again, I appreciate all the questions and comments and look forward to talking to you guys in the hall. Thank you.