When children become adults and adults become most hypercoagulable after trauma: An assessment of admission hypercoagulability by rapid thrombelastography and venous thromboembolic risk

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Background: Thrombelastography (TEG) maximal amplitude (mÂ²) has also been shown to reflect hypercoagulability and increased venous thromboembolism (VTE) risk in adult trauma patients. Based on these previous works, we sought to identify when children become adults with respect to TEG mÂ² values and whether this correlated with VTE risk.

Methods: We evaluated all trauma patients admitted from January 2010 to December 2013 who were highest-level activations. Age was evaluated as a continuous variable, followed by a categorical evaluation. TEG mÂ² values were evaluated as continuous and dichotomous (hypercoagulable, mÂ² â‰¥ 65 mm). Logistic regression was then conducted controlling for age categories, sex, and injury severity to assess the association with TEG mÂ² values and VTE risk.

Results: A total of 7,194 Level 1 trauma patients were admitted during this time frame (619 were <18 years of age). The likelihood of mÂ² equal to or greater than 65 mm remained at 35% to 37% through age 30 years with significant increases observed at ages 31 years to 35 years (45%) and 46 years to 50 years (49%), both P < 0.01. When controlling for injury severity, race, and sex, logistic regression demonstrated that every 5-year increase in age (after age 30 years) was associated with a 16% increased likelihood of hypercoagulability at admission. Beginning with age 1 year, VTE risk remained at 1.5% or less until age 13 years where it increased to 2.3%, increasing again at age 15 years to 5.1%. Two additional significant increases were identified between ages 31 years and 35 years (5.5%) as well as 46 years and 50 years (7.6%), both P < 0.001. Logistic regression demonstrated a 3.4-fold increased risk for VTE among those aged 31 years to 50 years compared with those who are younger than 30 years. The same model noted a 2.3-fold increased risk compared with those who are older than 50 years.

Conclusion: Beginning at age 13 years, children transition toward adult hypercoagulability, as evidenced by elevated TEG mÂ² values and VTE risk. However, the greatest VTE risk (and highest likelihood of hypercoagulable mÂ²) is among those adult 31 years to 50 years of age. (J Trauma Acute Care Surg. 2016;80: 778–782. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

Level of Evidence: Prognostic and epidemiologic study, level III.

Key Words: Trauma, pediatric, hypercoagulability, thrombelastography, venous thromboembolism.

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are considered to be a major source of morbidity and mortality among adult trauma patients. Rates of venous thromboembolism (VTE) as high as 58% have been reported after trauma; however, no widely accepted screening protocol exists. Therefore, the literature has shown that Medicare's inclusion of VTE after trauma as a "never event" should be questioned.2 Expensive and potentially harmful maneuvers such as aggressive screening or prophylactic inferior vena cava filters are not supported as the standard of care for DVT and PE identification and prophylaxis.12 Early, accurate recognition of injury severity is critical for optimal trauma triage and management.

Injury leads to dramatic disturbances in coagulation with increased risk of bleeding followed by a hypercoagulable state.5-8 Rapid thrombelastography (r-TEG) is an efficient method for the rapid identification of coagulopathy in the trauma population, including adults and children.5-11 TEG assesses coagulation factor function, platelet function, clotting strength, and fibrinolysis. Admission r-TEG maximal amplitude (mÂ²) values have been shown to identify adult patients with an increased risk of in-hospital PE.11,12 Furthermore, a postoperative hypercoagulable state, as determined by mÂ² values, is associated with myocardial infarction and stroke.12

A recent exploration of the National Trauma Data Bank (NTDB) demonstrated that VTE risk increases in children during adolescence beginning at 13 years and peaking at age 16 years, independent of other VTE risk factors.13 The most important triggering risk factors for VTE among pediatric patients are the presence of central venous lines, cancer, and chemotherapy. Pathologic conditions such as severe infection, sickle cell disease, trauma, and antiphospholipid syndrome are associated with the presence of a hypercoagulable state in children.6 On the basis of these previous works, we sought to identify when children transition toward adults with respect to TEG mÂ² values and whether this correlates with VTE risk.

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PATIENTS AND METHODS

Study setting
The University of Texas Health Science Center at Houston and the Memorial Hermann Hospital institutional review boards approved this study. Memorial Hermann Hospital is one of two American College of Surgeons–verified Level I trauma centers in Houston and is the primary teaching hospital for the University of Texas Health Science Center. Children's Memorial Hermann Hospital is one of only two Level I pediatric trauma centers in the city of Houston.

Selection of Participants
Using the institution’s Trauma Registry of the American College of Surgeons (TRACS) database, we evaluated all trauma patients admitted between January 2010 and December 2013 who met highest-level trauma activation criteria. Patients who had burns greater than 20% total body surface area or who died within 30 minutes of arrival were excluded.

Laboratory Setting and Processing of Specimens
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 (r-TEG samples are obtained within 15 minutes of presentation). All r-TEG specimens were run on a TEG thrombelastograph 5000 (Hemoscope Corporation, Niles, IL). Staff laboratory technicians in the Memorial Hermann ED Stat Laboratory performed all r-TEGs during the defined study period. These same technicians performed all the quality controls on the TEG analyzers, doing so every 8 hours. Quality control was performed as per the package insert from the Haemonetics Company.

Definitions and Outcomes
PE was defined as those events detected by helical computed tomography (CT) angiography of the chest (obtained for clinical suspicion) and recorded in the joint adult and pediatric TRACS database. DVT was defined as those events detected and confirmed by duplex ultrasonography and recorded in the same registry. VTE events were defined as the documentation of PE and/or DVT during hospital stay. Age, sex, Injury Severity Score (ISS), and weighted Revised Trauma Score (w-RTS) were abstracted from the TRACS database. The mA is the greatest amplitude of the tracing and reflects platelet contribution to clot strength. High mA values correspond with states of platelet hypercoagulability. Hypercoagulability was defined based on previously published data using admission r-TEG mA value of 65 mm or greater.11

Management Strategy and Protocols
All patients admitted to the adult trauma service (>15 years) are evaluated for VTE prophylaxis using strict criteria outlined in a thromboembolism guideline. High-risk patients are those anticipated to be hospitalized for more than 24 hours and have one or more of the following risk factors: anticipated immobilization for more than 2 days; history of DVT, PE, or hypercoagulable disease; traumatic brain injury with Glasgow Coma Scale (GCS) score of lower than 8 or unable to respond to commands (contraindications are discussed later); pelvic fracture; long bone fracture; spine fracture; lower extremity venous injuries; cancer; obesity (body mass index > 30); or multiple rib fractures. Relative contraindications to initial anticoagulation include ongoing hemorrhage, coagulopathy, nonoperative management of splenic injuries, nonoperative management of liver injuries, traumatic brain injury (specific contraindications include intracranial hemorrhage, evolving mental status/GCS, or after neurosurgical consultation), or a history of heparin-induced thrombocytopenia (consider consult hematology). Anticoagulation (usually with Enoxaparin) and compression devices are initiated at admission on high-risk patients without a contraindication. Inferior vena cava filter placement is considered for certain, specific high-risk patients with a VTE and/or those who have prolonged contraindications to anticoagulation. Compliance with this protocol is closely monitored through quality improvement data collection/evaluation and exceeds 95%.

Statistical Analysis
Age was evaluated as a continuous variable, followed by a categorical evaluation according to previously published cutoff points as well as bundling of age categories by inflection points noted on scatterplot analysis (admission mΑ vs. age and VTE rate vs. age).14 Initial age categories were defined as younger than 13, 13 to 18, 18 to 30, 31 to 50, and older than 50 years. When potential differences were detected within these groups, these ages were further broken down into the following: younger than 13, 13 to 15, 15 to 18, 18 to 25, 26 to 30, 31 to 35, 36 to 40, 41 to 45, 46 to 50, 51 to 55, 56 to 60, 61 to 65, 66 to 70, 71 to 75, 76 to 80, and older than 80 years, to better identify significant age cutoff points.

TEG mA values were evaluated as continuous and dichotomous ("hypercoagulable" defined as mA ≥ 65 mm).3 Continuous data are presented as medians with 25th and 75th interquartile range (IQR) with comparisons between groups performed using the Wilcoxon rank-sum (Mann-Whitney U-test). Categorical data are reported as proportions and, where appropriate, tested for significance using χ2 test or Fisher's exact test.

The primary data analysis evaluated mA values at admission by age and then by age category. This was followed by analysis of the prevalence of VTE events by age and then by age category. All statistical tests were two-tailed with p < 0.05 set as significant. Purposeful regression modeling was then used to construct a multivariate logistic regression model evaluating the development of VTE during hospital stay. This was performed using the technique of purposeful selection of covariates described by Hosmer and Lemeshow.15 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 categories, sex, race, and injury severity (ISS). These were then applied to an analysis evaluating these four variables and admission mA values. STATA Statistical Software (version 12.1, College Station, TX) was used for analysis.

RESULTS
Demographics and Baseline Data
A total of 7,194 patients met study criteria. Of these patients, 6,375 were 18 years or older and 819 were younger than 18 years. Of the 819 who were younger than 18 years,
205 patients (25%) were 5 years or younger. Overall, the median age was 34 years (IQR, 23–51 years); the population was 74% male and 49% white. Median ISS was 17 (IQR, 9–26). The population was 75% blunt trauma mechanism, and 19% of the patients were transfers. Overall mortality was 14%.

### Admission mA values

Median mA values at admission were similar when evaluating by age categories (62–66 mm, p = 0.219) (Table 1). However, when evaluating age as a continuous variable, linear regression identified an increase in admission mA values with increasing age (coefficient, 0.175; 95% confidence interval, 0.104–0.236; p < 0.001). When evaluating for the prevalence of hypercoagulable admission mA values (>65 mm), the likelihood of mA equal to or greater than 65 mm remained at 35% to 37% through age 30 years, but significant increases were observed at ages 31 years to 35 years (45%) and 46 years to 50 years (49%), p = 0.009 and p < 0.001, respectively.

### Multiple Logistic Regression Analysis of Admission mA and Age

After controlling for age, race, sex, and ISS, logistic regression demonstrated that every 5-year increase in age (after age 30 years) was associated with a 16% increased likelihood of hypercoagulable admission mA of equal to or greater than 65 mm (Table 2).

### In-Hospital VTE Risk

Beginning with age 1 year, VTE risk remained at 1.5% or less until age 13 years, at which point it increased to 2.3% (Fig. 1). While it increased again at age 15 years to 5.1%, it fell and remained at 3.6% or less from age 16 years to 30 years. Two additional significant increases were identified between ages 31 years and 35 years (5.5%) as well as 46 years and 50 years (7.6%), both p < 0.001. Interestingly, the risk decreased to 5.3% after the age of 50 years. A more robust analysis of the adolescent increased risk of VTE is shown in Figure 2.

### Table 1. Admission r-TEG Values by General Age Categories

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
</tr>
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<tr>
<td>&lt;13 y</td>
<td>323</td>
<td>121 (113–128)</td>
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<tr>
<td>13–17 y</td>
<td>496</td>
<td>121 (113–128)</td>
<td>121 (113–128)</td>
<td>121 (113–128)</td>
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<tr>
<td>18–30 y</td>
<td>2,017</td>
<td>105 (113–128)</td>
<td>105 (113–128)</td>
<td>105 (113–128)</td>
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<tr>
<td>31–50 y</td>
<td>1,911</td>
<td>105 (113–128)</td>
<td>105 (113–128)</td>
<td>105 (113–128)</td>
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<tr>
<td>&gt;50 y</td>
<td>2,167</td>
<td>105 (113–128)</td>
<td>105 (113–128)</td>
<td>105 (113–128)</td>
</tr>
</tbody>
</table>

### Table 2. Multivariate Logistic Regression Predicting Hypercoagulable Admission r-TEG mA of Equal to or Greater Than 65 mm

- Increase in age, 5 years: Odds Ratio 1.16, 95% CI 1.099–1.230, p < 0.001
- Male sex: Odds Ratio 0.45, 95% CI 0.399–0.539, p < 0.001
- White race: Odds Ratio 1.06, 95% CI 1.001–1.119, p = 0.048
- ISS: Odds Ratio 1.03, 95% CI 1.021–1.039, p < 0.001

Multiple Logistic Regression Analysis of In-Hospital VTE Risk and Age

Controlling for sex, race, ISS, and admission mA of equal to or greater than 65 mm, logistic regression demonstrated a 3.4-fold increased risk for VTE among those aged 31 years to 50 years compared with those who are younger than 30 years (Table 3). The same model noted a 2.3-fold increased risk compared with those who are older than 50 years.

**DISCUSSION**

Van Arendonk et al. recently evaluated children and adolescents in the NTDB and found that those younger than 12 years had extremely low rates of VTE after injury (0.1%), only increasing toward 1.0% at age 16 years. However, after controlling for injury severity and other known risk factors, patients 13 years to 15 years old and 16 years to 21 years old had significantly higher odds of VTE after injury compared with those who are younger than 12 (odds ratio, 1.96 and 3.77, respectively). Viscoelastic testing has recently been demonstrated to identify patients at increased risk of VTE following injury and surgery. Using an mA value of equal to or greater than 65 mm, Cotton et al. noted that patients who were hypercoagulable at admission had a 3.5-fold increased odds of developing PE. The current study found that the likelihood of
Figure 2. VTE risk specifically during adolescent/teenage years.

hypercoagulable r-TEG at admission remained at 35% to 37% through the age of 30 years, with significant increases noted at ages 31 years to 35 years (45%) and 46 years to 50 years (49%). While the VTE risk remained low through age 13 years (≤1.5%), this risk increased at the age of 13 years (2.3%) and again at 15 years (5.1%). However, the greatest risk of VTE was noted in those aged 31 years to 35 years (5.5%) and 46 years to 50 years (7.6%). Moreover, even when controlling for hypercoagulable admission r-TEG, trauma patients 31 years to 50 years had a 3.4-fold increased risk of VTE compared with the younger ages and a 2.3-fold odds of VTE compared with those who are older than 50 years.

Rates of VTE among hospitalized pediatric patients have been shown to increase in adolescence. Among all hospitalized pediatric patients during a 15-year period, adolescents (age, 14–17 years) were four times more likely to develop a VTE compared with children age 2 years to 9 years. Other children with a central venous catheter, trauma was the most common reason for admission among pediatric patients who developed a VTE. A recent systematic review of pediatric trauma patients also identified several studies showing increased rates of VTE during adolescence (different studies identified increased rates between the age of 13 years and 15 years). Adding to these and the NTDB study, our findings suggest that patients “become adults,” from a VTE risk perspective, beginning at age 13 years and increasing toward adult risk through age 16 years. While immaturity of the coagulation system has been demonstrated during the first year of life (with prolonged clotting times using prothrombin and partial thromboplastin assays), differences have not been observed between ages 1 year to 18 years. The current study also failed to demonstrate a significant increase in r-TEG values during this time, although values did become more hypercoagulable between ages 31 years to 50 years, which brings us to the question of why the dramatic change in VTE risk during these adolescent years? Whether this represents an acute change in pro-thrombotic hormone levels or is related to a higher risk of injury in this age group remains poorly understood and under-investigated.

Given mounting evidence for increased VTE in adolescence, along with coagulation changes identified in this study, should prophylaxis recommendations change? Clearly, children with indwelling catheters, with multiple medical problems, high ISSs, with spine/spinal cord injuries, and/or in the adolescent age group are at higher risk for VTE. Historically, VTE events in children (and even adolescents) have been considered rare. However, with increased sensitivity of CT scans, increased surveillance, and a large number of these patients being admitted to adult trauma services, the prevalence seems to be higher than previously reported. These extremely low rates have led most centers and pediatric trauma services to not use VTE prophylaxis in their patients. Similar to the practice at Johns Hopkins, our center admits all patients 15 years and older to the adult trauma service, and they receive management such as VTE prophylaxis as with adult patients. This includes high clinical suspicion for working up potential VTE events (specifically pulmonary embolii) and aggressive initiation and maintenance of VTE prophylaxis (enoxaparin 30 mg every 12 hours). While there may be potential hormone-related risk factors associated with pubertal changes that could account for the significant increase in risk at these ages, our institution’s own practices and guidelines may have artificially created such an inflection point for increased VTE risk. However, this does not account for the increased likelihood on hypercoagulable admission r-TEG.

There are, however, several limitations to this study. First, while much of the data were collected prospectively, a large portion was abstracted from the trauma registry, and the current study meets the definition of being retrospective in nature. Specifically, only certain patients were evaluated for the presence of a DVT or PE, based on clinical status. Subclinical DVT and/or PEs may not have been identified. In addition, the study was confined to a single institution and suffers from the usual limitations of such a design. Moreover, we excluded a significant number of patients who were burn patients or not highest-level trauma activations. Finally, our prevalence of VTE is much higher than that of the NTDB study. Our center has previously described that we aggressively pursue the diagnosis of PE and likely are detecting clinically insignificant emboli after injury and that would not have been captured by previous generation CT scans. However, the NTDB has significant missingness of data and does not account for variability in aggressiveness of using duplex ultrasonography and helical CT for screening and diagnosing patients. Finally, these mA values represent only admission r-TEG and do not capture the trajectory of coagulation following injury. However, admission mA values have been shown in several studies to correlate with overall hypercoagulable profiles and risk of VTE.

| TABLE 3. Multivariate Logistic Regression Predicting In-Hospital VTE Risk |
|---------------------------------------------|------------------|-----------------|---------------|
| Age category 31–50 y                       | 3.44             | 1.063–11.120    | 0.039         |
| Male sex                                   | 0.78             | 0.562–1.087     | 0.144         |
| White race                                 | 1.20             | 0.688–2.231     | 0.290         |
| ISS                                         | 1.02             | 1.015–1.032     | <0.001        |
| Admission mA ≥ 65 mm                       | 1.19             | 0.997–1.435     | 0.093         |
CONCLUSION

While VTE risk remains extremely low in those younger than 13 years, we noticed that beginning in adolescence, children do transition to adults with respect to hypercoagulable TEG mA values and VTE risk. However, the greatest VTE risk and highest likelihood of hypercoagulable mA is among those adults 31 years to 50 years of age. Given these findings, our institution is now developing a VTE prophylaxis guideline for adolescents similar to that currently used at our adult trauma center.

AUTHORSHIP

DISCLOSURE
B.A.C. served as a consultant in 2014 for Haemonetics Australia. The other authors have no financial disclosures.

REFERENCES