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Trauma Resuscitation Considerations: Sex Matters

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Abstract

Background—Sex dimorphisms in coagulation have been recognized but whole blood assessment of these dimorphisms and their relationship to outcomes in trauma have not been investigated. This study characterizes the viscoelastic hemostatic profile of severely injured patients by sex and examines how sex-specific coagulation differences affect clinical outcomes, specifically massive transfusion (MT) and death. We hypothesize that severely injured females are more hypercoagulable and thus, have lower rates of MT and mortality.

Study Design—Hemostatic profiles and clinical outcomes from all trauma activation patients from two Level I trauma centers were examined with sex as an experimental variable. As part of a prospective study, whole blood was collected and thrombelastography (TEG) was performed. Coagulation profiles were compared between sexes and association with MT and mortality were examined. Poisson regression with robust standard errors was performed.

Results—Overall, 464 patients (23% female) were included. By TEG, females had a more hypercoagulable profile, with a higher angle (clot propagation) and maximum amplitude (MA, clot strength). Females were less likely to present with hyperfibrinolysis or prolonged activating clotting time than males. In the setting of depressed clot strength (abnormal MA), female sex

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conferred a survival benefit, and hyperfibrinolysis was associated with higher case-fatality rate in males.

Conclusions—Severely injured females have a more hypercoagulable profile than males. This hypercoagulable status conferred a protective effect against mortality in the setting of diminished clot strength. The mechanism behind these dimorphisms needs to be elucidated and may have treatment implications for sex-specific trauma resuscitation.

Precis

In severely injured trauma patients, female patients were more hypercoagulable than male by thrombelastography. In female patients, measurements of clot propagation and strength were higher and hyperfibrinolysis and prolonged clot formation occurred less frequently. In the setting of depressed clot propagation and strength, female sex conferred a survival benefit.

Keywords

Sex dimorphisms; coagulation; thrombelastography; massive transfusion

INTRODUCTION

Sex dimorphisms in coagulation are well-established, with females manifesting a more hypercoagulable profile(1–3). Whether this dimorphism impacts outcomes following trauma is timely, as trauma-induced hemorrhage remains a leading cause of early postinjury death(4). The effect of sex dimorphisms on clinical outcomes following trauma, including complications and mortality, has been controversial(5–12). Several multi-center studies report decreased morbidity and mortality among females, while other investigations have found increased mortality among females or failed to identify sex-related differences at all(5, 7–15). However, none of these studies have accounted for the whole blood hemostatic state. Despite potentially distinct coagulation profiles and responses to trauma between males and females, sex has often been controlled for during regression analysis in these large population investigations and rarely treated as an experimental variable.

Differences in coagulation between males and females following trauma have yet to be evaluated using thrombelastography (TEG), a whole blood assay which provides a comprehensive description of hemostasis with measurements of clot initiation, propagation, strength, and fibrinolysis(16). While plasma-based conventional coagulation assays, such as prothrombin time/international normalized ratio (PT/INR), have been used to quantify deranged hemostasis in the setting of trauma, a growing body of literature suggests that these plasma-based assays overestimate coagulopathy in trauma and surgical patients(17). Additionally, in contrast to PT/INR, the comprehensive description of the kinetics of clot formation provided by TEG can guide resuscitation in the setting of massive transfusion for specific blood component therapy(18). As such, precise description and comparative evaluation of sex-specific coagulation profiles in severely injured patients is timely. The effects of sex dimorphism in relation to MT requirement and risk of mortality require evaluation. We sought to evaluate sex dimorphisms in coagulation by TEG following severe injury and to assess the effect of sex-related differences in coagulation on clinical outcomes.

We hypothesize that females are more hypercoagulable than males and that this female-specific hypercoagulable phenotype decreases postinjury massive transfusion (MT) and mortality.

METHODS

Study Design for Evaluation following Trauma

Data were prospectively collected at two urban Level-1 trauma centers: Ernest E Moore Shock Trauma Center at Denver Health Medical Center (DHMC) in Colorado and Zuckerberg San Francisco General Hospital (SFGH) in California from 2010–2017. These studies were approved by their respective regional Institutional Review Boards (DHMC COMIRB#13–3087 & SFGH IRB#10–04417) and performed under waiver of consent. Criteria for inclusion in this study were patients ≥ 18 years old who presented to the Emergency Department as trauma activations with severe injuries (Injury Severity Score [ISS] >15). Criteria for MT at both institutions were based on the physiologic Resuscitation Outcome Consortium criteria: systolic blood pressure (SBP) < 70 mm Hg or SBP 70–90 mm Hg with heart rate (HR) > 108 beats/minute), in addition to any of the following: penetrating torso wound, unstable pelvic fractures, or abdominal ultrasound suspicious of bleeding in more than one region(19). Resuscitation is initiated based on clinical and injury criteria and starts with a ratio delivery of 2U FFP:4U RBC. The TEG assessed on arrival then directs ongoing blood product resuscitation, including MT, by viscoelastic parameters as we described previously (18). Exclusion criteria were any patient < 18 years, pregnant, or incarcerated. Clinical data collected include: age, sex, mechanism of injury, BMI, ISS, presence of traumatic brain injury (TBI), initial SBP, Glasgow Coma Scale (GCS), INR, PTT, PT, base deficit, and units of red blood cells (RBCs) transfused. Significant TBI was defined as an Abbreviated Injury Scale (AIS) for head or neck ≥ 3.

Data Measurements and Clinical Outcomes

Whole blood samples were collected in citrated tubes (3.5 mL, 3.2% sodium citrate, Greiner Bio-One, Monroe, North Carolina) at the scene or upon hospital arrival. Citrated Rapid TEG (CR-TEG) was performed using the TEG 5000 Thrombelastography Hemostasis Analyzer per manufacturer's instructions(20). This whole blood assay involves the addition of tissue factor to blood to elicit a thrombin burst and accelerate clot formation, providing results within 15 minutes(16). The rapidity of these results allows for prompt, clinically relevant assessment of the hemostatic profile of trauma patients to direct blood component resuscitation in real-time. CR-TEG yields the following variables: activated clotting time (ACT, time from initiation of assay to clot formation in minutes), angle (rate of clot strength increase, degrees), maximum amplitude (MA; maximal clot strength achieved, millimeters) and percent clot lysis 30 and 60 minutes after reaching MA (LY30 and LY60, %). An ACT > 128 seconds, angle < 65 degrees and MA < 55 mm are considered deranged coagulation measurements(18). LY30, due to its multimodal distribution, was expressed as previously published: fibrinolysis shutdown (LY30 0–0.8%), physiologic fibrinolysis (LY30 0.9–2.9%), and hyperfibrinolysis (LY30 ≥ 3%)(21). We evaluated the initial coagulation status present on the admission TEG (with the aforementioned measurements) for prediction of need for transfusion and the analysis of subsequent clinical endpoints, given serial TEGs during

transfusion reflect changes in coagulopathy secondary to components received. Primary outcomes assessed included massive transfusion (defined as >10 units of RBCs transfused within six hours of presentation or death within six hours of presentation to account for survivor bias) and 30-day mortality, as well as hypercoagulable morbidities including venous thromboembolism (VTE), including both pulmonary emboli (PE) and deep venous thrombosis (DVT), and cerebral vascular accident (CVA). DVT was determined by venous duplex ultrasound, and PE was diagnosed by computerized tomography angiography of the chest. Per current Chest guidelines, our institution does not routinely survey patients for VTEs; only symptomatic patients are submitted to clinical investigation(22). CVA was diagnosed by head computerized tomography.

Statistical Analysis

Univariate analysis used t-tests and Wilcoxon tests or Chi-square and Fisher Exact tests as appropriate. Multivariate analysis was conducted using Poisson regression with robust standard errors to account for intra-center cluster effects. Effect modification was assessed including interactions in logistic regression models.

Due to the suspected role of sex hormones in coagulation dimorphisms, pre-menopausal and post-menopausal (based on age cut-off of 54 years) females were compared and then an additional analysis of age-matched males and females (matching “nearest” 1:1) was conducted, accounting for tissue injury (ISS), shock (SBP), and blunt mechanism(6, 7). Statistical analyses were performed using SAS for Windows version 9.4 (SAS Institute, Cary, NC, USA). All tests were two-tailed, with significance established at $p < 0.05$.

RESULTS

Demographics and injury characteristics

Overall, 464 trauma patients were eligible for this study, 241 from SFGH and 223 from DHMC (Table 1). Differences were detected between institutions in ISS, TBI and SBP (eTable 1). Women accounted for 23% of the overall sample. The median age of males was 34.0, whereas females were older with a median age of 48.0 years ($p = 0.001$). Blunt mechanism was more common among females (92% vs. 72% in males, $p < 0.0001$) and time from injury to arrival was longer for females compared to males (28 vs. 24 minutes, $p = 0.03$). The median ISS was 27.0, with no difference between sexes. There was no difference in lactate or base deficit, however, the median arrival SBP was lower in females (114 versus 128 mm Hg in males, $p = 0.02$).

Hematology and thrombelastography values

Hemoglobin was lower and platelets were higher in females ($p = 0.01$) (Table 1). Whole blood TEG demonstrated sex dimorphisms in coagulation, while plasma-based conventional coagulation assays (PT/INR and PTT) failed to detect a difference. On univariate analysis, angle and MA were significantly higher in females compared to males (73.9° versus 71.1° in males and 64.9 mm versus 61.5 mm in males respectively; $p = 0.01$ and $p = 0.0001$) (Table 1). There were no sex-specific differences in ACT or LY30 as a continuous variable. In terms of fibrinolytic phenotypes, on univariate, males were more likely to present with

hyperfibrinolysis than females (26% versus 15% of females, $p=0.03$). After adjusting for covariates (age, blunt mechanism, ISS, SBP and TBI) on multivariate analysis, men were more likely to present with a prolonged ACT (>128 sec; RR 1.11, 95% CI 1.10–1.11) and decreased MA (<55 mm; RR 1.35, 1.13–1.60) (Table 2), as well as were more likely to present in hyperfibrinolysis (RR 1.73, 95% CI 1.32–2.25).

Clinical outcomes and association with TEG measurements

Overall mortality rate was not different between sexes (25% in men versus 33% in women) on unadjusted analysis, despite the fact that women were older, had longer time from injury to ED presentation, and lower arrival SBP ($p=0.08$). On unadjusted analysis, there was no difference in case-fatality rate among hyperfibrinolytic patients (21% [20/94] in males versus 6% [1/16] in females, $p=0.29$). However, all males with hyperfibrinolysis died from coagulopathy or hemorrhagic shock, whereas only one female with hyperfibrinolysis died and the cause of her death was a devastating TBI, unrelated to coagulopathy. Case-fatality rate did not differ between males and females for physiologic lysis (11% in males versus 17% in females, $p=0.30$) or fibrinolytic shutdown (7% in males versus 11% in females, $p=0.50$).

On adjusted analysis (age, blunt mechanism, ISS, SBP, and TBI), higher mortality was observed in hyperfibrinolytic and shutdown groups in both sexes with equivalent case-fatality rates. Female sex conferred a survival benefit in the setting of decreased MA, with an increased risk of death in males (OR 2.89, 95% CI 1.48–5.64) compared to females (OR 0.65, 95% CI 0.17–2.48) (Table 3). Sex was not found to have an effect on the association of abnormal ACT, angle, or LY30 with massive transfusion or death. There was no difference in transfusion requirement, MT, or hypercoagulable morbidities between sexes on univariate or multivariate analysis (Table 1).

Matched analysis

Before performing age-matched analysis, pre- and post-menopausal women were compared. Post-menopausal women had less severe indicators of shock (higher SBP, less base deficit, and less lactate), a shorter ACT and decreased LY30, but higher angle and MA compared to pre-menopausal women (Table 4). The outcomes discussed in sections above were also analyzed among a cohort of age-matched male and female trauma patients. Among the 105 age-matched males and females, there were no differences in MT (14.3% in males versus 12.4% in females) or mortality (13.3% in both sexes) ($p=0.84$ and 0.99 respectively). This lack of statistical difference persisted even when matching for mechanism, shock and tissue injury, with a MT rate of 12.4% in females and 14.3% in males and mortality rate of 13.3% in females versus 12.4% in males ($p=0.83$ and 0.99 respectively).

DISCUSSION

Female hypercoagulability has been described, but not characterized with comprehensive whole blood evaluation, such as TEG, in the setting of trauma(3, 23). The effect of this hypercoagulable state on clinical outcomes following trauma, including massive transfusion and mortality, is not well-established. In the present data, when treating sex as an

experimental variable, females had a more hypercoagulable profile than their male counterparts, presenting less coagulopathic after severe injury (less clot formation prolongation, higher MA and angle and less hyperfibrinolysis). This hypercoagulability was protective and conferred a survival advantage in the setting of decreased clot strength (lower MA). Further, no females died from hemorrhage associated with hyperfibrinolysis, unlike their male counterparts.

Documenting a more hypercoagulable state among females compared to males is consistent with previous literature in healthy volunteers. Francis *et. al.* first described the CN-TEG profile of 40 healthy volunteers and noted sex-based differences: females demonstrated shorter R time and higher MA versus males(24). Gorton *et. al.* described similar native TEG results among healthy volunteers, specifically 50 males, 50 pregnant females and 50 nonpregnant, premenopausal females(1). Non-pregnant females demonstrated shorter R time and higher angle and MA, and these differences were further increased in pregnant females compared to non-pregnant females(1). These data suggest that female sex hormones convey a hypercoagulable state. This highlights the importance of evaluating sex as an independent variable and accounting for estrus state of females when examining coagulation. The presented data support the contention that sex hormones contribute to a hypercoagulable state in that female patients had a more hypercoagulable profile than males. However, within our study, there were no differences in our findings when comparing pre-menopausal versus post-menopausal females to age-matched males. This suggests the mechanisms responsible for dimorphisms in outcomes are not explained by circulating sex hormone levels alone. For example, epigenetic or post-translational processes may exist from lifetime exposure to the milieu of female sex hormones, as suggested by the myriad of genomic and nongenomic effects of sex hormones on platelets(25, 26). This could impart functional alterations in female platelet progenitors or cellular clotting biology and result in hypercoagulable potential which persists through menopause. Additionally, there is data from animal models and clinical work demonstrating low hemoglobin and elevated platelets confer a hypercoagulable profile on thrombelastography(27–30). These data suggest that the relative anemia and elevated platelet count in females compared to males may partially explain their sex-specific hypercoagulability. While the differences in hemoglobin and platelets levels between sexes themselves may not be clinically significant, their effect on coagulation must be considered. Ultimately, the mechanisms behind the sex-specific distinct coagulation profiles are likely multifactorial, complex, and include a composite of the aforementioned variables. The hypercoagulable profile described in healthy females in the aforementioned literature persisted in the setting of trauma in our investigation. Male trauma patients presented with lower clot propagation and clot strength and were more likely to present with a prolonged time to clot formation (ACT) and hyperfibrinolysis than females. Given penetrating trauma is associated with a higher rate of hyperfibrinolysis compared to blunt trauma, the higher rate of penetrating trauma within the male population suggest a partial explanation for this finding(31). Another explanation may be that a higher angle and MA among females results in a stronger clot that is more resistant to fibrinolysis. Despite the higher risk of hyperfibrinolysis in males, there was no difference in transfusion requirement or MT. This could be due to the fact that neither institution has a sex-specific trigger for massive transfusion and all patients were resuscitated with TEG-based algorithms, as we

described previously(18). In our previously published randomized trial, a TEG-based resuscitation algorithm resulted in less blood product transfusions and improved survival. Thus, detection of differences in transfusion and survival outcomes by sex, which may be observed in sex-indiscriminate fixed ratio transfusion strategies, may have been therapeutically mitigated or underestimated by TEG-based resuscitation. Ultimately, fixed ratio administration may result in females receiving more products than they need for hemostasis. Notably, seminal studies examining fixed ratio transfusion, such as the PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial and related studies, have not accounted for sex in transfusion practice or examined sex-based differences in transfusion requirement, highlighting the need to better characterize sex-specific transfusion triggers(32, 33). The lack of transfusion differences between males and females has been described in other studies including a multi-center prospective cohort study of 2,007 trauma patients which found no difference in 24-hour transfusion requirement between males and females(11, 15). However, to our knowledge, current models to determine triggers for massive transfusion in trauma do not account for sex-related differences in coagulation and apply an empiric practice for males and females. Our data suggest that females may not need platelet transfusion for the same MA threshold as males, given their ability to tolerate a lower clot strength. These data ultimately support a consideration for the need to re-calibrate the TEG-based thresholds for transfusion, which were previously established in a population with a male-dominated demographic(18). Despite an older age, longer time from injury to ED presentation and lower arrival SBP, females did not have higher mortality. In fact, female sex-specific hypercoagulability was protective among trauma patients and conferred a survival advantage in the setting of decreased clot strength (lower MA). Additionally, the case-fatality rate among females with hyperfibrinolysis was lower than that of males. This sex-specific hypercoagulability did not appear to increase the risk of thrombotic morbidity. The findings from this study may serve to explain the reason for higher mortality among male trauma patients in larger scale studies, including a multi-center study of 47, 295 trauma patients, an analysis of a trauma registry including 18,133 patients and a review of 48,394 patients in the National Trauma Database, all of which describe a higher mortality rate among males(5, 7, 10). While another multi-center study of outcomes among trauma patients, stratified by coagulopathy (defined by INR >1.5), found increased mortality among females, those findings were in the context of defining coagulopathy by INR, not by TEG as our study does(11). The distinction of coagulopathy definitions by INR versus TEG is relevant, given recent work indicating that INR overestimates coagulopathy in trauma(17). The mechanism behind an inferior tolerance for decreased clot strength and hyperfibrinolysis among males is unclear. There are multifactorial effects on MA in males, including a lower fibrinogen and platelet count, as well as reduced platelet function, compared to females(34, 35). The increased functional fibrinogen level (FLEV) on citrated functional fibrinogen TEG (a measurement of fibrinogen contribution to clot strength in a fibrinogen-specific TEG in the healthy female volunteers (unpublished data) suggests that fibrinogen in females may contribute more to clot strength than platelets compared to males, explaining a better tolerance to coagulopathy in females(36). It may also be that coagulopathy associated with an abnormal MA does not increase mortality risk in females because they present with, or convert to, a more hypercoagulable profile earlier than their male counterparts, attenuating risk of death from hemorrhage. This has been suggested in

serial blood draws and TEG of male versus female trauma ICU admissions(23). Ultimately, platelets are known to be affected by shock, tissue injury, acidosis, and other elements present in trauma, therefore, the mechanism behind the survival advantage is likely a composite of several factors versus clot strength reflected by MA alone(37). Translationally, the hypercoagulability and increased tolerance of coagulopathy in females has treatment implications in that males in trauma-induced coagulopathy may need to be resuscitated earlier and more aggressively with blood components. Further, while we did not observe increased thrombotic morbidity in females, given their hypercoagulability, it calls into question the relative risk of thrombosis or transition to fibrinolysis shutdown with transfusions of cryoprecipitate or the administration of antifibrinolytics.

Limitations of this study include a relatively small sample size among the trauma population, which may contribute to a lack of power to detect morbidity and overall mortality differences. The small number of females in hyperfibrinolysis further limits the ability to draw firm conclusions on case-fatality, however the fact that there were no deaths from hemorrhage in females with hyperfibrinolysis highlights a relationship worth investigating with a higher-powered study. Our findings support other larger-scale studies which have found increased survival in females and we believe this investigation focused on sex-specific coagulopathy suggests a potential mechanism behind this survival. However, wide application of these findings requires additional multi-center investigation to support this analysis. As previously mentioned, another limitation is the inability to correlate increased survival in females with a decreased MA (compared to males) to the TEG measurement itself; while MA and platelet function are affected by a myriad of factors, it is likely that the composite of these variables is what ultimately confers the improved survival. While this study includes VTE, CVA and ALI as clinical events related to the hypercoagulable state, to comprehensively evaluate for all sequelae of hypercoagulability, a prospective, multi-center trial with screening duplex ultrasound and consistent definitions of clinical endpoints of hypercoagulability (myocardial infarction, CVA, VTE) would better address these outcomes. While all TEGs were conducted within one hour of venipuncture and conducted at the same time for each patient, some variability existed between time from venipuncture and running assays. Lastly, the trauma patient analysis did not include data on pharmacologic contraception or estrus cycle timing among females.

CONCLUSION

Sex-specific dimorphisms in coagulation persist in the setting of trauma such that following severe injury, female trauma patients are less coagulopathic. This female-specific hypercoagulability was protective from mortality in the setting of trauma-induced coagulopathy. These data challenge the clinical bias of unified transfusion strategy and suggest there should be a differential transfusion trigger and strategy for females given their more hypercoagulable profile or for males given their more coagulopathic profile. Our data also suggest that females may require less blood product transfusion and be less likely to require antifibrinolytics because of their hypercoagulable profile, and antifibrinolytic therapy may disproportionally increase risk of venous thromboembolic events in females. The results of this study highlight the need to further investigate sex as a biological variable in

studies of trauma populations and how these sex dimorphisms may warrant differential transfusion practices or resuscitation following severe injury.

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REFERENCES

1. Gorton HJ, Warren ER, Simpson NA, et al. Thromboelastography identifies sex-related differences in coagulation. *Anesthesia Analgesia* 2000;91:1279–1281. [PubMed: 11049922]
2. Hobson AR, Qureshi Z, Banks P, Curzen N. Gender and responses to aspirin and clopidogrel: insights using short thrombelastography. *Cardiovascular Therapeutics* 2009;27:246–252. [PubMed: 19903188]
3. Scarpelini S, Rhind SG, Nascimento B, et al. Normal range values for thromboelastography in healthy adult volunteers. *Brazilian J Med Biologic Res* 2009;42:1210–1217.
4. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma* 1995;38:185–193. [PubMed: 7869433]
5. Bolandparvaz S, Yadollahi M, Abbasi HR, Anvar M. Injury patterns among various age and gender groups of trauma patients in southern Iran: A cross-sectional study. *Medicine* 2017;96:e7812. [PubMed: 29019874]
6. George RL, McGwin G Jr, Windham ST, et al. Age-related gender differential in outcome after blunt or penetrating trauma. *Shock* 2003;19:28–32. [PubMed: 12558140]
7. Haider AH, Crompton JG, Chang DC, et al. Evidence of hormonal basis for improved survival among females with trauma-associated shock: an analysis of the National Trauma Data Bank. *J Trauma* 2010;69:537–540. [PubMed: 20838123]
8. Mitchell R, Curtis K, Fisher M. Understanding trauma as a men's health issue: sex differences in traumatic injury presentations at a level 1 trauma center in Australia. *J Trauma Nursing* 2012;19:80–88.
9. Napolitano LM, Greco ME, Rodriguez A, et al. Gender differences in adverse outcomes after blunt trauma. *J Trauma* 2001;50:274–280. [PubMed: 11242292]
10. Croce MA, Fabian TC, Malhotra AK, et al. Does gender difference influence outcome? *J Trauma* 2002;53:889–894. [PubMed: 12435939]
11. Brown JB, Cohen MJ, Minei JP, et al. Characterization of acute coagulopathy and sexual dimorphism after injury: females and coagulopathy just do not mix. *J Trauma Acute Care Surg* 2012;73:1395–1400. [PubMed: 23064602]
12. Magnotti LJ, Fischer PE, Zarzaur BL, et al. Impact of gender on outcomes after blunt injury: a definitive analysis of more than 36,000 trauma patients. *J Am Coll Surg* 2008;206:984–991. [PubMed: 18471739]
13. Lopez MC, Efron PA, Ozrazgat-Baslanti T, et al. Sex-based differences in the genomic response, innate immunity, organ dysfunction, and clinical outcomes after severe blunt traumatic injury and hemorrhagic shock. *J Trauma Acute Care Surg* 2016;81:478–485. [PubMed: 27306446]
14. Eachempati SR, Hydo L, Barie PS. Gender-based differences in outcome in patients with sepsis. *Arch Surg* 1999;134:1342–1347. [PubMed: 10593332]

15. Trentzsch H, Lefering R, Nienaber U, et al. The role of biological sex in severely traumatized patients on outcomes: a matched-pair analysis. *Ann Surg* 2015;261:774–780. [PubMed: 25029437]
16. Coleman JR, Moore EE, Chapman MP, et al. Rapid TEG efficiently guides hemostatic resuscitation in trauma patients. *Surgery* 2018;164:489–493. [PubMed: 29903508]
17. McCully SP, Fabricant LJ, Kunio NR, et al. The International Normalized Ratio overestimates coagulopathy in stable trauma and surgical patients. *J Trauma Acute Care Surg* 2013;75:947–953. [PubMed: 24256665]
18. Gonzalez E, Moore EE, Moore HB, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. *Ann Surg* 2016;263:1051–1059. [PubMed: 26720428]
19. Bulger EM, May S, Kerby JD, et al. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. *Ann Surg* 2011;253:431–441. [PubMed: 21178763]
20. Haemonetics. TEG 5000 System User Manual. P/N 06–510-US, Manual revision: AC Niles, IL: Haemonetics Corporation, Haemoscope Division; 2010.
21. Moore HB, Moore EE, Liras IN, et al. Targeting resuscitation to normalization of coagulating status: hyper and hypocoagulability after severe injury are both associated with increased mortality. *Am J Surg* 2017;214:1041–1045. [PubMed: 28969894]
22. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e351S–e418S. [PubMed: 22315267]
23. Schreiber MA, Differding J, Thorborg P, et al. Hypercoagulability is most prevalent early after injury and in female patients. *J Trauma* 2005;58:475–480; discussion 480–481. [PubMed: 15761339]
24. Francis JL, Francis DA, Gunathilagan GJ. Assessment of hypercoagulability in patients with cancer using the Sonoclot Analyzer and thromboelastography. *Thrombosis Research* 1994;74:335–346. [PubMed: 8085235]
25. Unsworth AJ, Flora GD, Gibbins JM. Non-genomic effects of nuclear receptors: insights from the anucleate platelet. *Cardiovascular Research* 2018;114:645–655. [PubMed: 29452349]
26. Heldring N, Pike A, Andersson S, et al. Estrogen receptors: how do they signal and what are their targets. *Physiological Reviews* 2007;87:905–931. [PubMed: 17615392]
27. Smith SA, McMichael MA, Gilor S, et al. Correlation of hematocrit, platelet concentration, and plasma coagulation factors with results of thromboelastometry in canine whole blood samples. *Am J Veterinary Res* 2012;73:789–798.
28. McMichael M, Smith SA, McConachie EL, et al. In-vitro hypocoagulability on whole blood thromboelastometry associated with in-vivo expansion of red cell mass in an equine model. *Blood Coagulation Fibrinolysis* 2011;22:424–430. [PubMed: 21508831]
29. Roeloffzen WW, Kluin-Nelemans HC, Mulder AB, et al. In normal controls, both age and gender affect coagulability as measured by thrombelastography. *Anesthesia Analgesia* 2010;110:987–994. [PubMed: 20357143]
30. Li L, Yang J, Sun Y, et al. Correction of blood coagulation dysfunction and anemia by supplementation of red blood cell suspension, fresh frozen plasma, and apheresis platelet: results of in vitro hemodilution experiments. *J Crit Care* 2015;30:220e1–12.
31. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg* 2014;77:811–817. [PubMed: 25051384]
32. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015;313:471–482. [PubMed: 25647203]
33. Meyer DE, Vincent LE, Fox EE, et al. Every minute counts: Time to delivery of initial massive transfusion cooler and its impact on mortality. *J Trauma Acute Care Surg* 2017;83:19–24. [PubMed: 28452870]

34. Miller CH, Rice AS, Garrett K, Stein SF. Gender, race and diet affect platelet function tests in normal subjects, contributing to a high rate of abnormal results. *Br J Haematol* 2014;165:842–853. [PubMed: 24617520]
35. Gee AC, Sawai RS, Differding J, et al. The influence of sex hormones on coagulation and inflammation in the trauma patient. *Shock* 2008;29:334–341. [PubMed: 18437714]
36. Carroll RC, Craft RM, Chavez JJ, et al. Measurement of functional fibrinogen levels using the thrombelastograph. *J Clin Anesthesia* 2008;20:186–190.
37. Davenport RA, Brohi K. Cause of trauma-induced coagulopathy. *Curr Opin Anaesthesiol* 2016;29:212–219.

Table 1.

Trauma Population Characteristics by Sex (n=464)

Characteristic	Female (n=106)	Male (n=358)	p Value*
Demographics, median (25 th –75 th IQR)			
Age, y	48.0 (27.8–61.6)	34.0 (25.3–51.0)	0.01
BMI, kg/m ²	25.3 (22.5–28.2)	25.8 (23.1–29.0)	0.18
Injury characteristic			
Time from injury to arrival, min	28 (20–38)	24 (19–32)	0.03
Blunt, n (%)	97 (91.6)	258 (72.1)	<0.01
ISS, median (25 th –75 th IQR)	29 (22–38)	27 (21–34)	0.06
GCS, median (25 th –75 th IQR)	10 (4–14)	11 (3–15)	0.55
TBI, n (%)	62 (58)	208 (58)	0.91
Physiologic marker, median (25 th –75 th IQR)			
SBP, mm Hg	114 (90–142)	128 (104–148)	0.02
Base deficit, meq/L	8.4 (6.0–13.0)	7.0 (4.0–10.6)	0.26
Lactate, mmol/L	4.1 (2.2–5.8)	4.2 (2.7–6.9)	0.21
Hematology/coagulation assays, median (25 th –75 th IQR)			
Hemoglobin, g/dL	12.6 (11.0–13.4)	13.8 (12.5–15.3)	<0.01
Hematocrit, %	38.2 (34.9–40.9)	41.8 (38.0–45.0)	<0.01
Platelets, 10 ⁹ /L	264 (216–369)	240 (191–301)	0.01
INR	1.2 (1.1–1.3)	1.2 (1.0–1.3)	0.96
PTT, sec	28.2 (25.2–34.4)	28.4 (25.0–35.0)	0.69
TEG measurements, median (25 th –75 th IQR)			
ACT, sec	113 (99–128)	113 (105–128)	0.37
Angle, degrees	73.9 (67.1–77.3)	71.1 (65.8–75.4)	0.01
MA, mm	64.9 (59.0–69.6)	61.5 (56.0–66.0)	0.01
LY30, %	1.4 (0.2–2.5)	1.4 (0.5–3.1)	0.72
Fibrinolytic phenotype, n (%)			
Fibrinolytic shutdown, LY30 < 0.9%	39 (37)	132 (37)	0.03
Physiologic lysis, LY30 0.9–2.9%	51 (48)	132 (37)	
Hyperfibrinolysis, LY30 ≥ 3.0%	16 (15)	94 (26)	
Outcome			
Mortality, n (%)	35 (33.0)	88 (24.6)	0.10
Transfusion (≥ 1U RBC) in 1st 24 h, n (%)	30 (28.3)	84 (23.5)	0.31
No. of U of RBC in first 6 h (among those transfused), median (25 th –75 th IQR)	6 (3–12)	6 (2–12)	0.98
Massive transfusion, n (%)	14 (13.2)	45 (12.6)	0.87
VTE, n (%)	13 (12)	29 (8)	0.25
CVA, n (%)	1 (1)	2 (1)	0.57
LOS, d, median (25 th –75 th IQR)	12 (6–20)	10 (4–18)	0.10

Characteristic	Female (n=106)	Male (n=358)	p Value*
VFD-28, d, median (25 th –75 th IQR)	21 (0–26)	23 (0–27)	0.33
ICUFD-28, d, median (25 th –75 th IQR)	21 (6–25)	22 (9–25)	0.26

* p Values from Mann-Whitney and chi-squared (2 outcomes for all categories except for fibrinolytic phenotype) as appropriate.

ISS, Injury Severity Score; GCS, Glasgow Coma Score; TBI, traumatic brain injury; SBP, systolic blood pressure; INR, International Normalized Ratio; PTT, partial thromboplastin time; ACT, activated clotting time; MA, maximum amplitude; LY30, lysis 30 min after MA; RBC, red blood cell; VTE, venous thromboembolism; CVA, cerebral vascular accident; LOS, length of stay; VFD-28, ventilator free days at 28 d; ICUFD-28, intensive care unit free days at 28 d.

Table 2.

Multivariate Analysis Assessing the Independent Effect of Sex (Female as the Reference Category) on Abnormal Thrombelastographic Measurements in Trauma Patients

Coagulation phenotype	Male relative risk	95% CI	p Value
Abnormal lysis, <0.9%, 3%	1.21	1.08–1.36	0.001
Hyperfibrinolysis, 3%	1.73	1.32–2.25	<0.0001
Fibrinolytic shutdown, <0.9%	1.02	0.91–1.13	0.100
Abnormal ACT, >128 s	1.11	1.10–1.11	<0.0001
Abnormal angle, <65 degrees	0.89	0.86–0.93	<0.0001
Abnormal MA, <55 mm	1.35	1.13–1.60	0.001

ACT, activating clotting time; MA, maximum amplitude.

Table 3.

Multivariate Analysis of the Modification of the Association Between Abnormal Activating Clotting Time, Angle, Maximum Amplitude, and Fibrinolysis with Death, by Sex

Coagulation phenotype	Analysis of conditional maximum likelihood estimate	Standard error	p Value
Abnormal ACT	1.06	0.35	0.003
Abnormal ACT + male sex	0.18	0.32	0.58
Abnormal angle	0.53	0.36	0.14
Abnormal angle + male sex	0.46	0.34	0.18
Abnormal MA	0.32	0.38	0.41
Abnormal MA + male sex	0.74	0.38	0.04
Hyperfibrinolysis	0.85	0.32	0.60
Hyperfibrinolysis + male sex	−0.39	0.31	0.21
Fibrinolysis shutdown	−0.25	0.33	0.46
Fibrinolysis shutdown + male sex	0.17	0.33	0.60

Abnormal activated clotting time: >128 s; abnormal angle: <65 degrees; Abnormal maximum amplitude: <55 mm; hyperfibrinolysis: LY30 (30 min after maximum amplitude) ≥3%; fibrinolysis shutdown: LY30 <0.9%.

ACT, activated clotting time; MA, maximum amplitude.

Table 4.

Female Patient Data, Stratified by Menopausal State

Data	Premenopausal females, 54 y (n=66)	Postmenopausal females, >54 y (n=40)	p Value
Demographics, median (25 th –75 th IQR)			
Age, y	31.8 (25.1–45.1)	67.5 (57.8–77.8)	<0.01
BMI, kg/m ²	25.3 (20.9–28.37)	25.1 (23.2–28.3)	0.57
Injury characteristic			
Time from injury to arrival, min, median (25 th –75 th IQR)	24 (18–37)	31 (24–46)	0.01
Blunt, n (%)	56 (85)	40 (85)	0.99
ISS, median (25 th –75 th IQR)	30 (22–41)	28 (22–37)	0.40
GCS, median (25 th –75 th IQR)	11 (3–14)	9 (5–15)	0.84
TBI, n (%)	32 (48)	30 (75)	0.01
Physiologic marker, median (25 th –75 th IQR)			
SBP, mm Hg	111 (90–134)	132 (91–161)	0.03
Base deficit, meq/L)	8.0 (5.9–12.6)	2.2 (1.0–6.1)	<0.01
Lactate, mmol/L)	4.1 (3.1–5.6)	2.0 (1.8–3.7)	<0.01
Hematology/coagulation assay, median (25 th –75 th IQR)			
Hemoglobin, g/dL	12.6 (11.2–13.5)	12.6 (11.4–13.5)	0.92
Hematocrit, %	38.0 (34.8–41.4)	38.5 (35.2–40.0)	0.66
Platelets, 10 ⁹ /L	273 (214–332)	232 (181–298)	0.13
INR	1.2 (1.1–1.3)	1.1 (1.0–1.2)	<0.01
PTT, s	28.7 (25.6–36.0)	28.5 (25.8–32.4)	0.75
TEG measurement, median (25 th –75 th IQR)			
ACT, s	113 (105–132)	105 (97–113)	0.01
Angle, degrees	71.6 (63.3–76.2)	76.9 (73.9–78.5)	<0.01
MA, mm	63.0 (55.9–68.8)	66.4 (62.1–71.0)	0.02
LY30, %	1.8 (0.7–2.7)	0.7 (0.0–2.0)	<0.01
Outcome			
Mortality, n (%)	16 (24)	19 (48)	0.02
Transfusion, 1U RBC in first 24 h, n (%)	35 (53)	24 (60)	0.55
No. of units of RBC in 1 st 6 hours (among those transfused, median (25 th –75 th IQR)	5 (3–13)	4 (3–6)	0.12
MT, n (%)	11 (17)	3 (8)	0.24
LOS (d, median (25 th –75 th IQR)	12 (5–20)	12 (5–27)	0.51
VFD-28 (d, median (25 th –75 th IQR)	23 (0–28)	16 (0–28)	0.66
ICUFD-28 (d, median (25 th –75 th IQR)	18 (4–26)	19 (7–28)	0.31

ISS, Injury Severity Score; GCS, Glasgow Coma Score; TBI, traumatic brain injury; SBP, systolic blood pressure; INR, International Normalized Ratio; PTT, partial thromboplastin time; ACT, activated clotting time; MA, maximum amplitude; LY30, lysis 30 min after MA; RBC, red blood cell; LOS, length of stay; VFD-28, ventilator free days at 28 d; ICUFD-28, intensive care unit free days at 28 d.

Comparison of Trauma Patients from Denver Health Medical Center and Zuckerberg San Francisco General Hospital (SFGH). Continuous data presented as median (25th–75th IQR).

eTable 1.

Characteristic	Females (n=106)			Males (n=358)		
	DHMC (n=59)	SFMC (n=47)	P Value	DHMC (n=164)	SFMC (n=194)	p Value
Demographic, median (25 th –75 th IQR)						
Age, y	39.7 (26.1–50.4)	58.0 (39.0–75.0)	<0.01	32.6 (25.3–48.0)	36.0 (25.8–53.0)	0.25
BMI, kg/m ²	26.0 (22.7–24.5)	24.2 (21.0–27.8)	0.36	25.4 (23.2–28.6)	26.0 (23.0–29.7)	0.81
Injury characteristic						
Time from injury to arrival, min, median (25 th –75 th IQR)	29 (20–37)	27 (18–36)	0.83	25 (19–31)	25 (19–32)	0.85
Blunt, n (%)	52 (88.1)	45 (95.7)	0.27	111 (67.7)	147 (75.8)	0.10
ISS, median (25 th –75 th IQR)	29 (22–38)	30 (26–38)	0.38	26 (18–34)	29 (22–35)	0.02
GCS, median (25 th –75 th IQR)	13 (3–15)	9 (6–14)	0.71	14 (3–15)	11 (6–15)	0.70
TBI, n (%)	35 (59.3)	38 (80.9)	0.02	79 (48.2)	137 (71.1)	<0.01
Physiologic markers, median (25 th –75 th IQR)						
SBP, mm Hg	102 (83–130)	132 (107–159)	0.01	118 (90–140)	131 (112–155)	<0.01
BD, meq/L	8.4 (6.0–13.0)	1.8 (2.4–4.9)	0.16	7.0 (4.0–10.6)	3.0 (1.0–7.2)	0.33
Lactate, mmol/L	4.1 (2.0–6.4)	3.2 (2.2–4.9)	0.35	4.2 (2.7–6.9)	2.9 (2.3–5.6)	0.15
Hematology/coagulation assay, median (25 th –75 th IQR)						
Hemoglobin, g/dL	12.6 (10.8–13.6)	12.6 (11.0–13.2)	0.56	14.0 (12.5–15.5)	13.7 (12.6–15.0)	0.25
Hematocrit, %	38.6 (33.4–41.3)	37.8 (35.1–39.9)	0.86	42.4 (38.5–46.1)	40.7 (37.7–44.4)	0.30
Platelets, 109/L	264 (216–369)	245 (199–309)	0.14	240 (191–301)	261 (208–314)	0.03
INR	1.2 (1.1–1.3)	1.1 (1.1–1.2)	0.63	1.2 (1.0–1.3)	1.2 (1.1–1.3)	0.70
PTT, s	28.2 (25.2–34.4)	29.4 (25.7–32.8)	0.43	28.4 (25.0–35.0)	29.1 (26.8–34.2)	0.33
TEG measurement, median (25 th –75 th IQR)						
ACT, sec	121 (113–136)	97 (89–105)	<0.01	121 (113–136)	105 (89–121)	<0.01
Angle, degrees	72.2 (63.6–76.6)	76.8 (72.1–77.9)	0.01	69.7 (63.9–74.4)	72.5 (68.6–75.9)	0.05
MA, mm	63.8 (57.5–70.1)	66.4 (59.3–69.3)	0.16	60.5 (53.1–65.5)	62.1 (58.2–66.3)	0.66
LY30, %	1.6 (0.7–2.6)	0.8 (0.0–2.3)	0.13	1.9 (0.9–3.4)	0.8 (0.1–2.2)	0.01

Characteristic	Females (n=106)			Males (n=358)		
	DHMC (n=59)	SFMC (n=47)	P Value	DHMC (n=164)	SFMC (n=194)	p Value
Outcome						
Mortality, n (%)	14 (23.7)	21 (44.7)	0.04	37 (22.6)	51 (26.3)	0.46
Transfusion (1U RBC) in first 24 h, n (%)	30 (50.8)	23 (46.9)	0.99	84 (51.2)	65 (33.5)	0.01
No. of U of RBC in first 6 h, among those transfused, median (25 th –75 th IQR)	6 (3–12)	4 (3–9)	0.79	6 (2–12)	4 (2–8)	0.13
MT, n (%)	8 (13.6)	6 (12.8)	0.99	25 (15.2)	20 (10.3)	0.20
VTE, n (%)	4 (7)	9 (19)	0.07	10 (6)	19 (10)	0.24
CVA, n (%)	1 (2)	0 (0)	0.99	2 (1)	0 (0)	0.99
LOS, d, median (25 th –75 th IQR)	12 (6–20)	13 (4–29)	0.57	10 (4–18)	12 (5–25)	0.77
VFD-28, d, median (25 th –75 th IQR)	22 (0–26)	12 (0–25)	0.12	23 (0–27)	20 (0–26)	0.59
ICUFD-28, d, median (25 th –75 th IQR)	21 (6–25)	24 (10–25)	0.10	22 (8–25)	22 (14–26)	0.81

DHMC, Denver Health Medical Center; SFGH, San Francisco General Hospital; ISS, Injury Severity Score; GCS, Glasgow Coma Score; TBI, traumatic brain injury; SBP, systolic blood pressure; INR, International Normalized Ratio; PTT, partial thromboplastin time; ACT, activated clotting time; MA, maximum amplitude; LY30, lysis 30 min after MA; RBC, red blood cell; VTE, venous thromboembolism; CVA, cerebral vascular accident; LOS, length of stay; VFD-28, ventilator free days at 28 d; ICUFD-28, intensive care unit free days at 28 d.