

WHAT'S NEW IN TRANSFUSION MEDICINE FOR TRAUMATIC HEMORRHAGIC SHOCK

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Director Blood Research Program

28 June 2017

DISCLOSURES

- Consultant or Research Funding
 - New Health Sciences
 - Entegriion
 - Vascular Solutions
 - Octapharma
 - Cerus
 - Cellfire
 - Haemonetics
 - ROTEM
 - TerumoBCT
 - US Department of Defense
 - NIH

OBJECTIVES

- RBC storage solution
- Does leukoreduction of whole blood reduce its hemostatic capacity
- Plasma products and derivatives
- Platelet products and derivatives
- Cryoprecipitate vs fibrinogen concentrates
- Factor concentrates vs plasma
- Empiric Tranexamic acid (TXA) vs goal directed
- Ratio vs TEG/ROTEM-guided hemostatic resuscitation



OPTIMAL PRODUCT CHARACTERISTICS

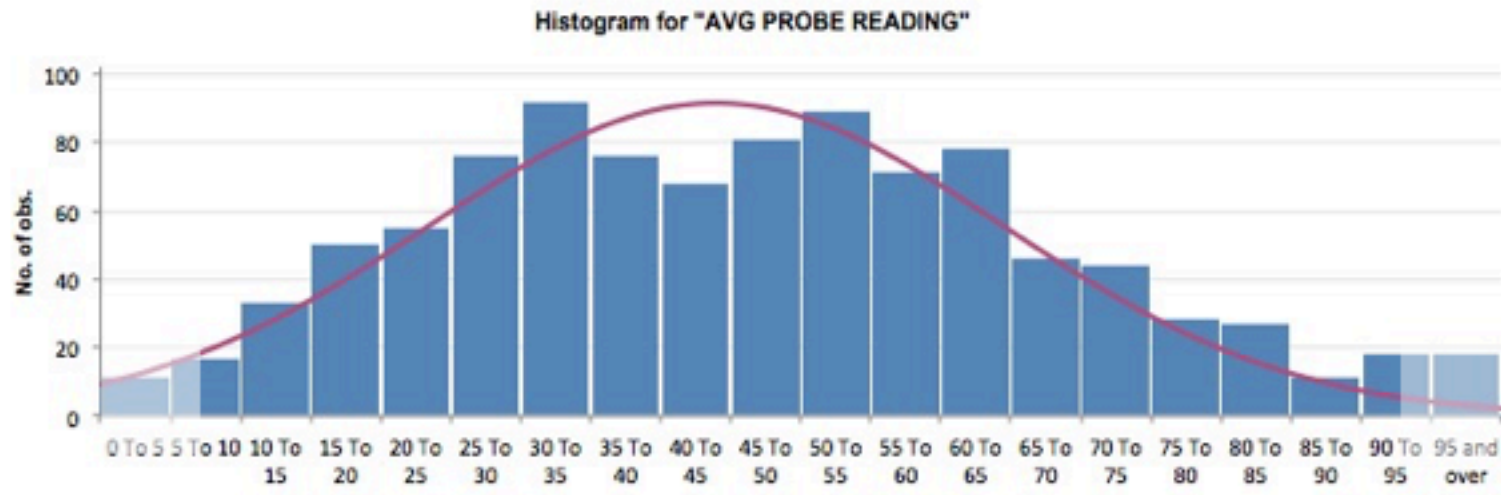
- Immediately available
- Maximal efficacy
 - Not just “good enough”
- Site specific action
- Maximal safety
 - Without sacrificing efficacy
- Low dose to dose variation
- Logistically simple to store and administer
- Economically feasible

DEOXYGENATED RBC STORAGE SOLUTION- HEMANEXT

- New Health Sciences
- Rationale for product is oxidation of stored RBCs
 - Reduces efficacy and increases adverse effects
 - RBC membrane injury
 - Reduced deformability
 - Hemolysis
 - Microparticles
 - Nitric oxide metabolism
- Improved RBC efficacy and safety is essential to address “Oxygen Debt”

OXYGEN CONTENT OF STANDARD RBC UNITS IS HIGHLY VARIABLE

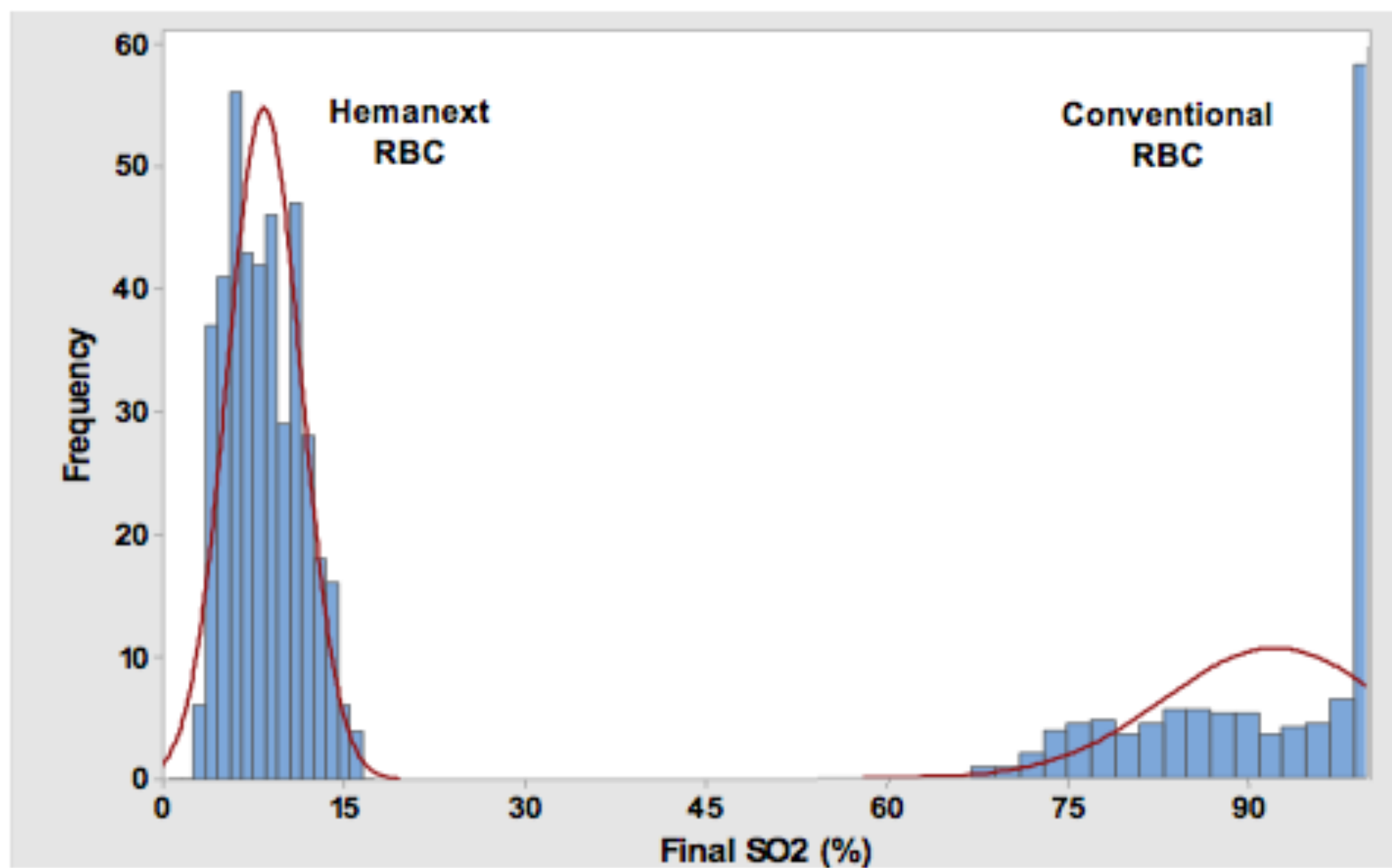
SO₂ distribution of LR-RCC (989 commercial units)



989 units of leukoreduced RCC— All 8-hour process:
PRP-platelet, cryoprecipitate, and apheresis RBC

Mean: 46.1%

SD: 21.0%



Reisz et alae, Blood 2016 128:e32-e42

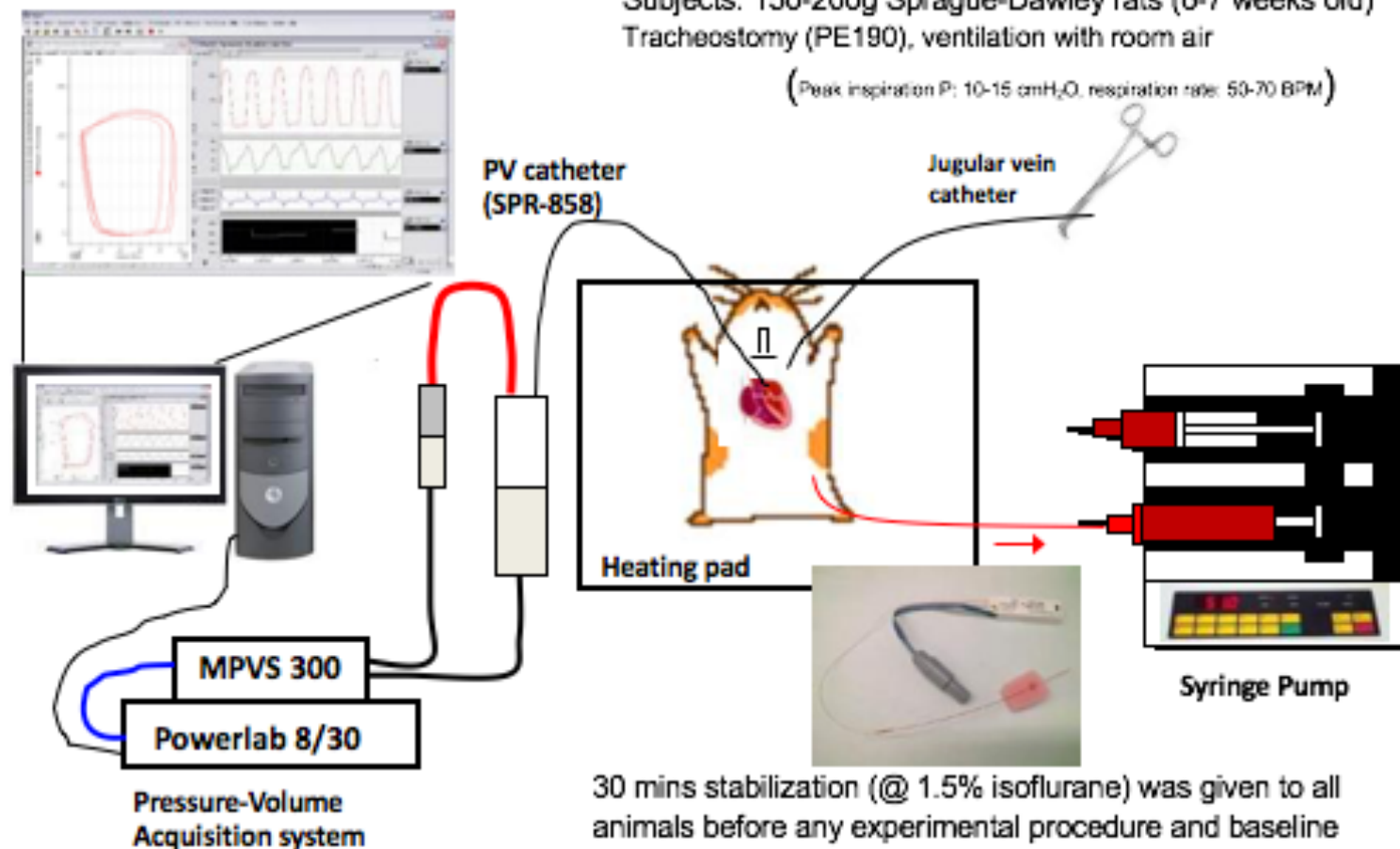
D'Alessandro et alae, in preparation

Rat hemorrhage model – UCSD Dr. Pedro Cabrales Lab

Subjects: 150-200g Sprague-Dawley rats (6-7 weeks old)

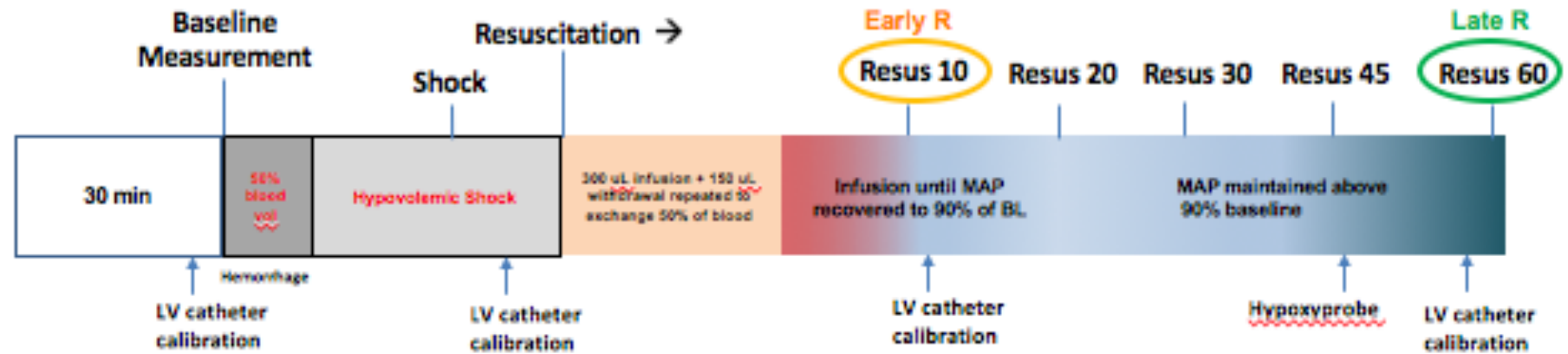
Tracheostomy (PE190), ventilation with room air

(Peak inspiration P: 10-15 cmH₂O, respiration rate: 50-70 BPM)

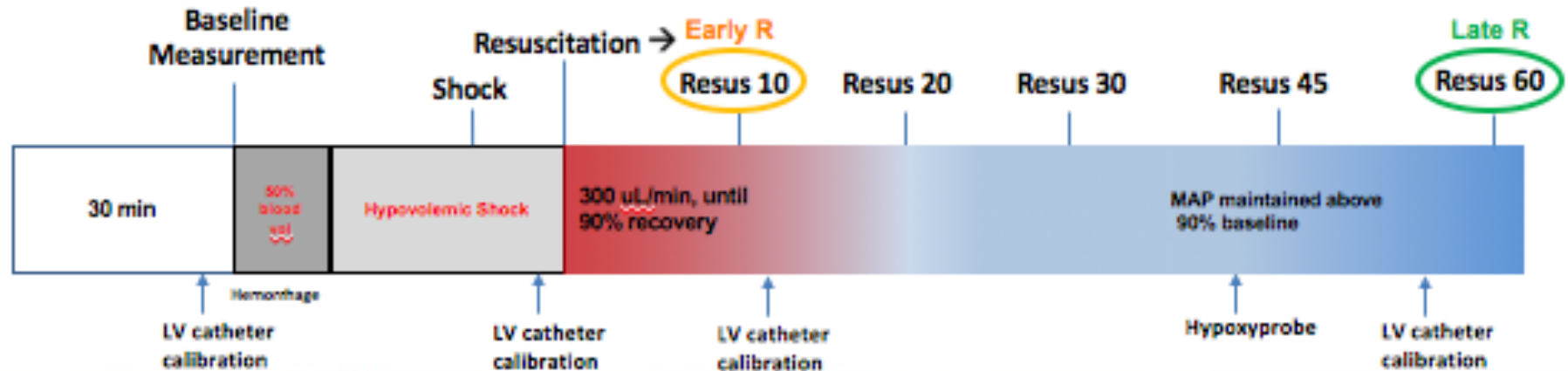


EXPERIMENT TIMELINE

1 Week Blood

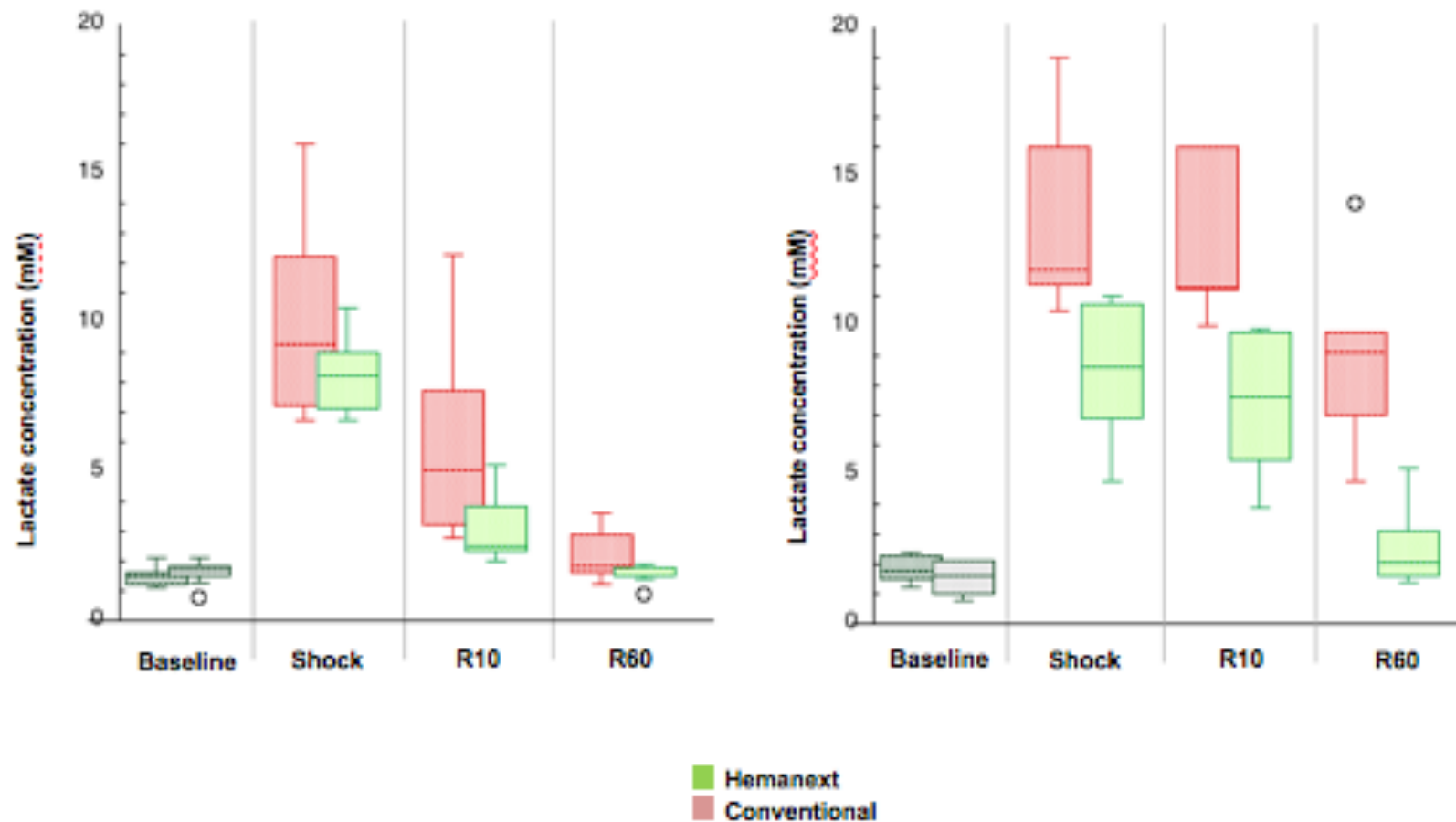


3 Week Blood



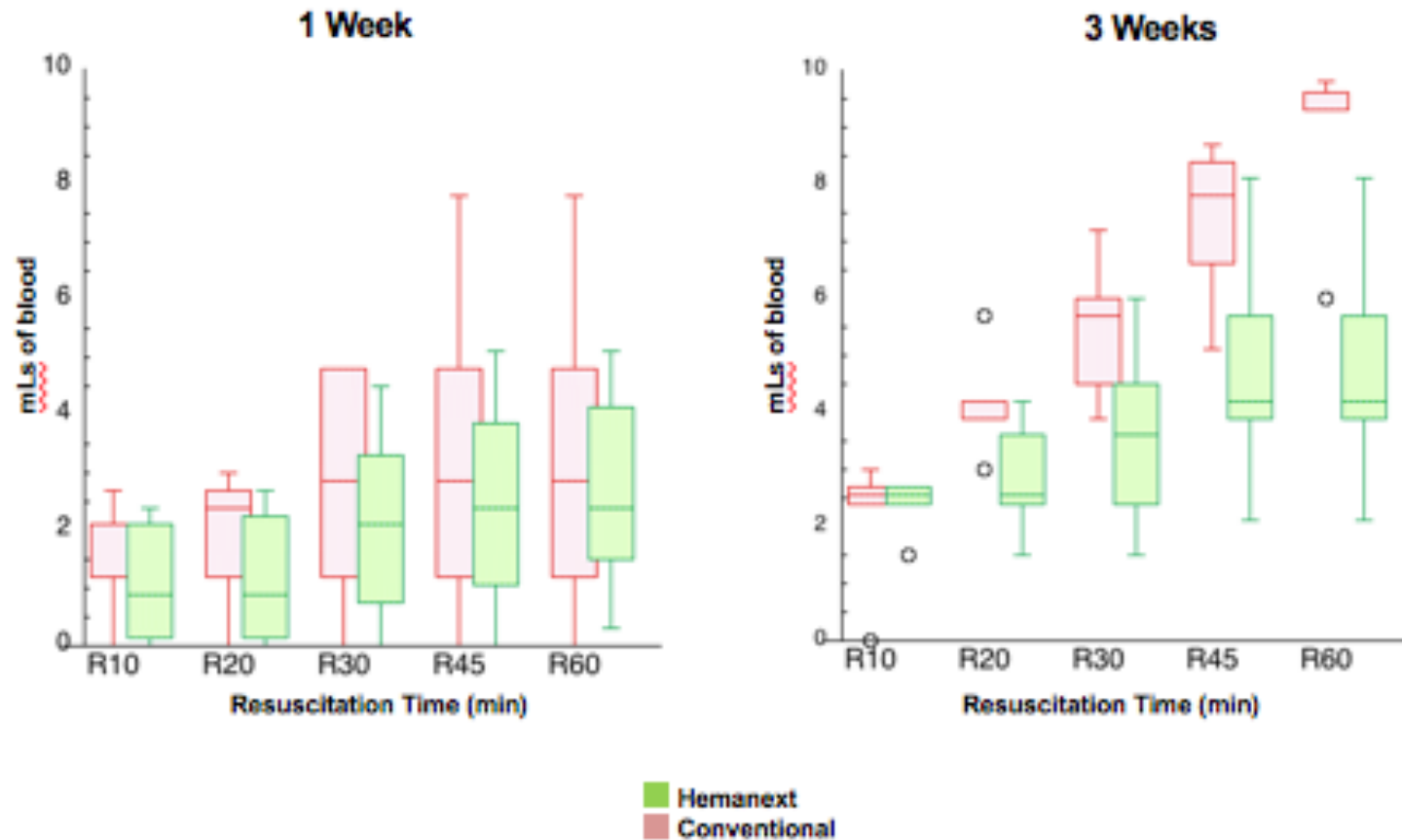
UNPUBLISHED DATA

Lactate Levels



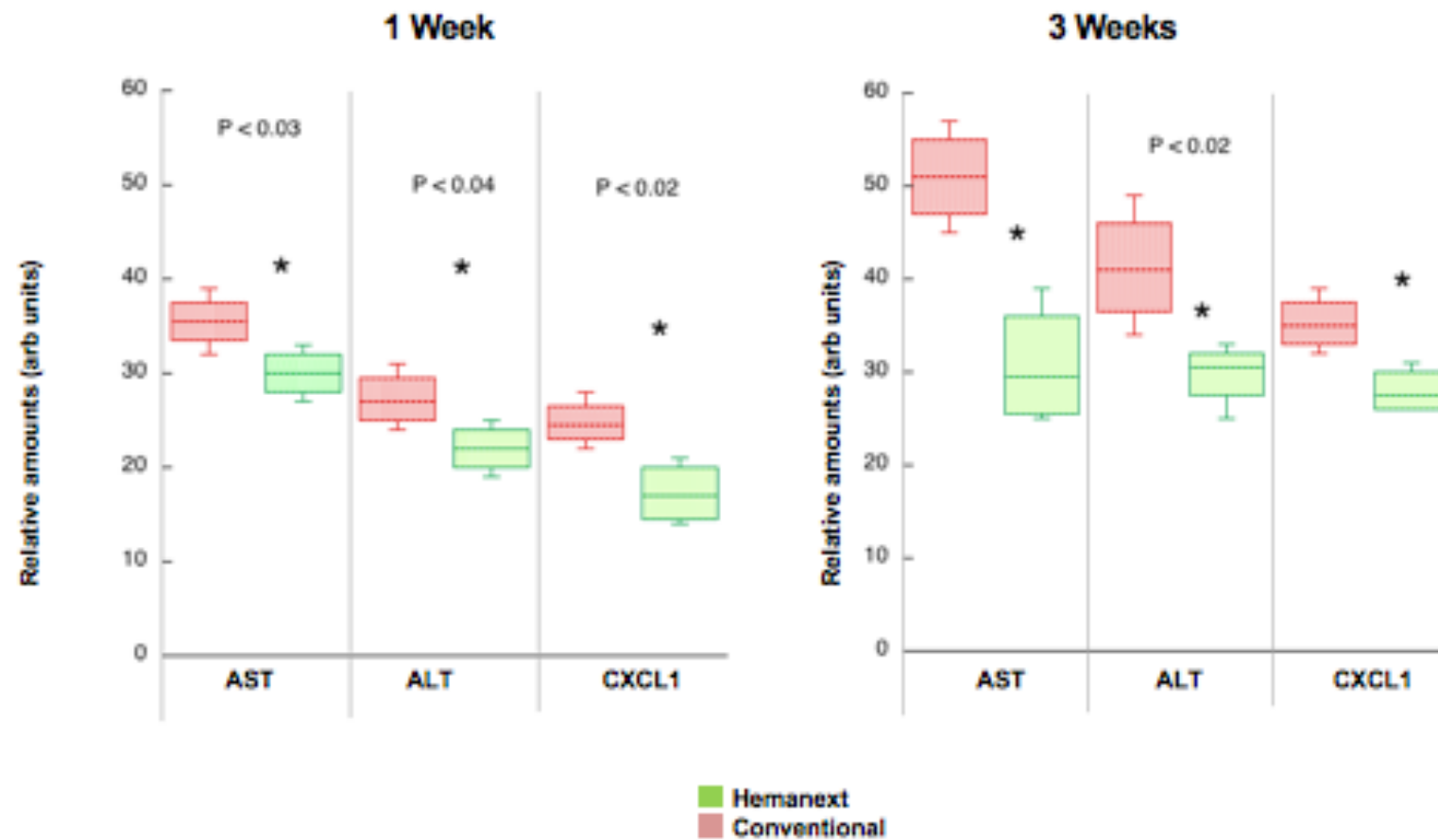
UNPUBLISHED DATA

Quantity of RBC needed to stabilize mean arterial pressure (MAP)



UNPUBLISHED DATA

Liver Injury and Inflammation (lower better)

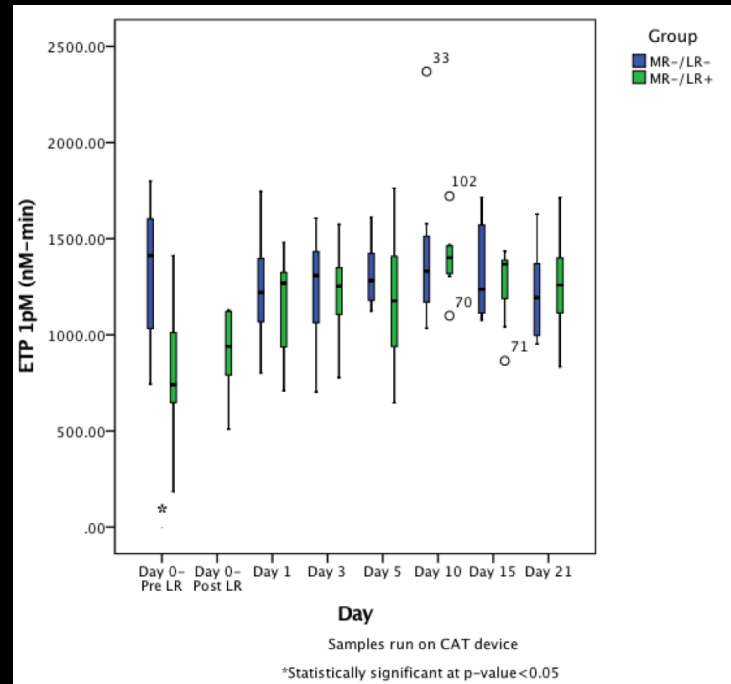
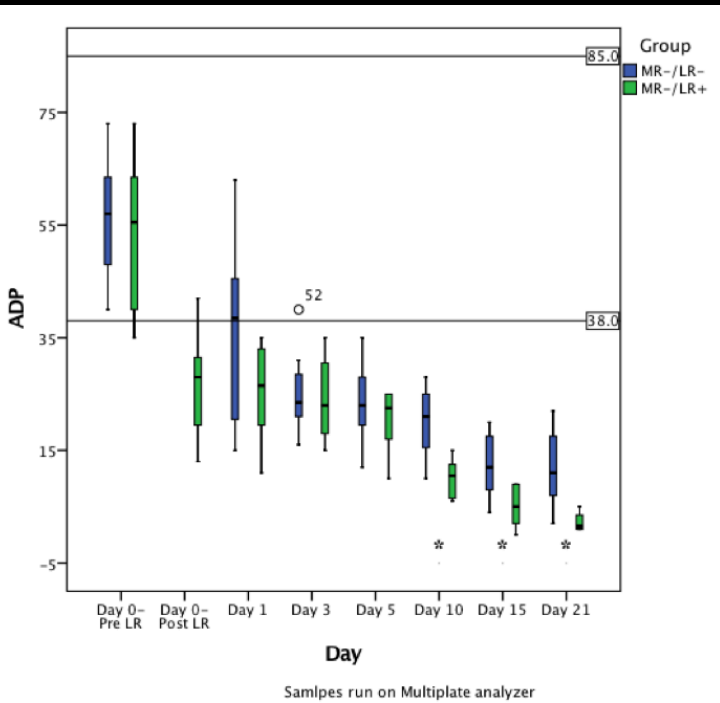
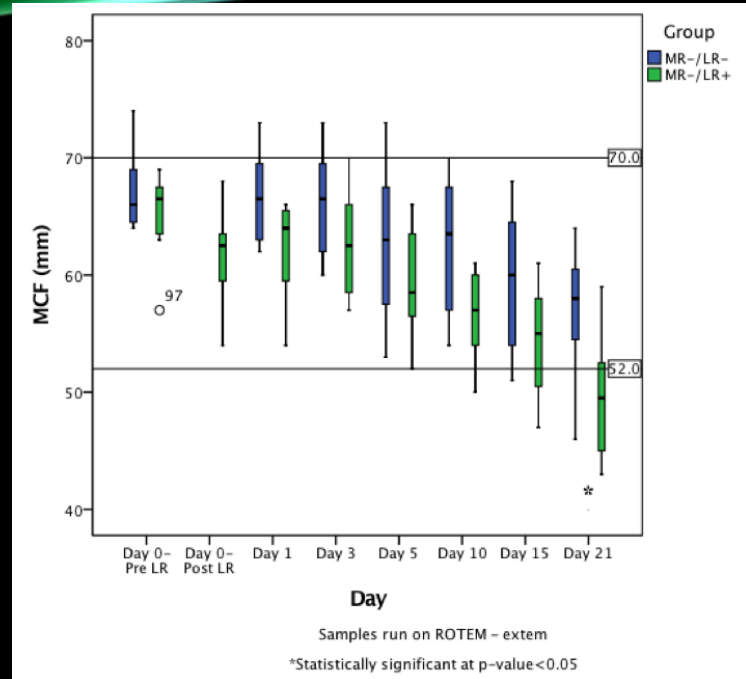
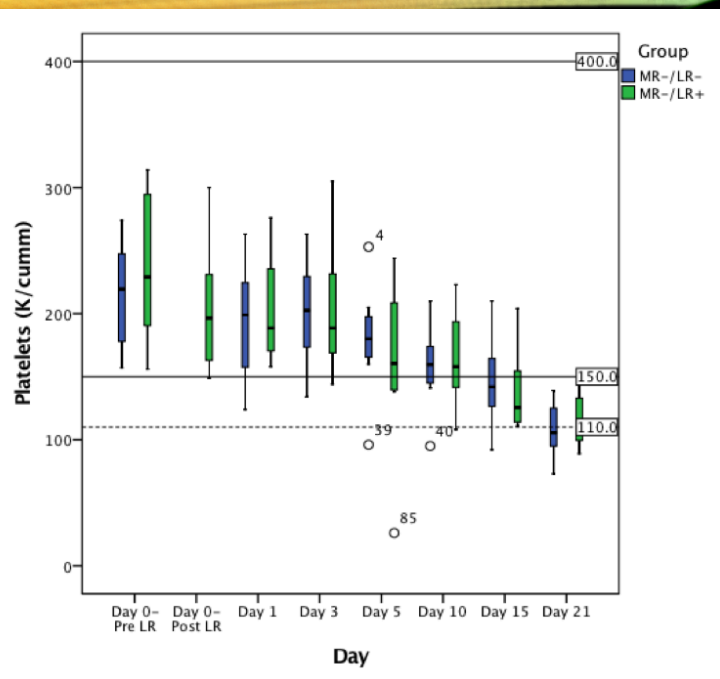


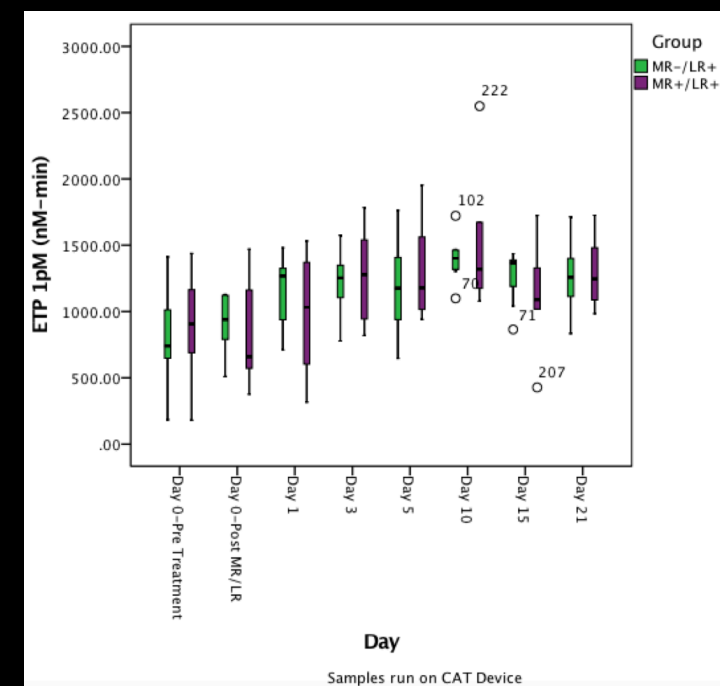
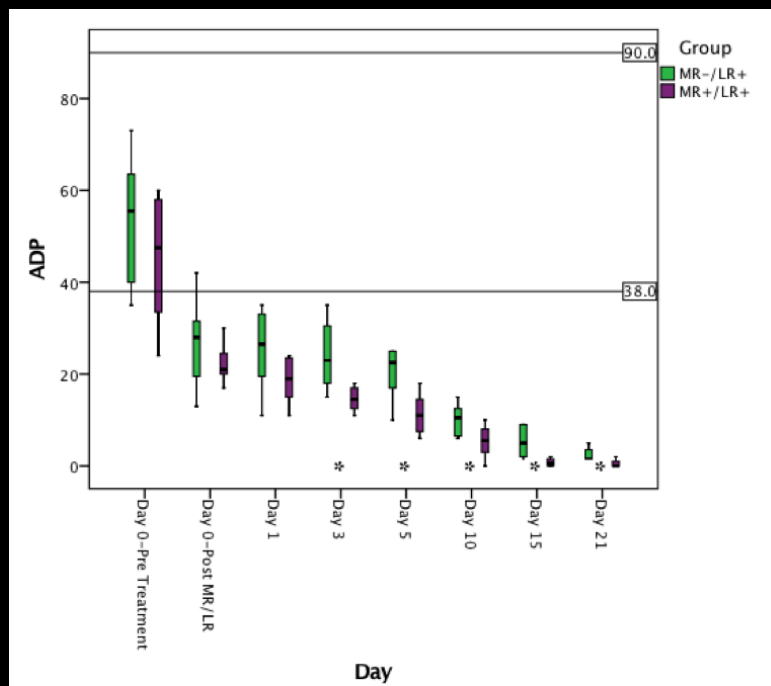
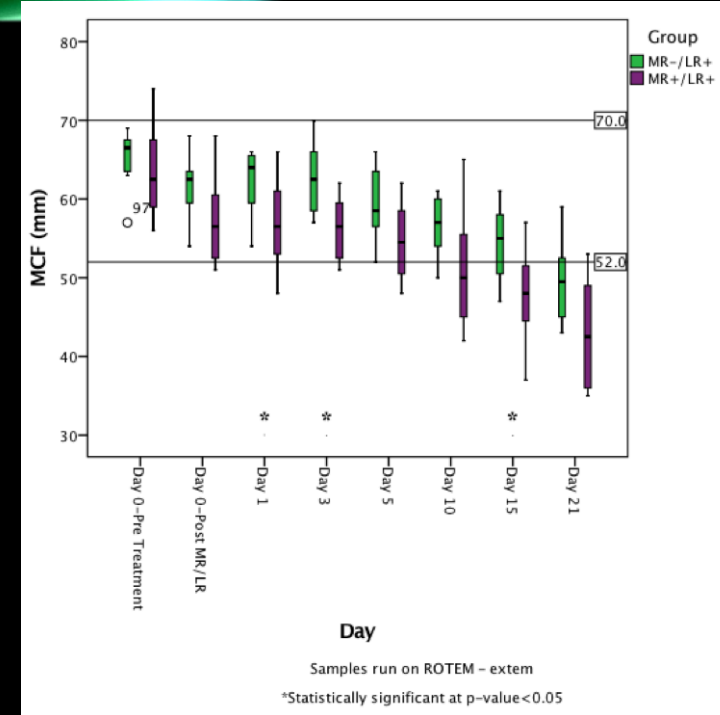
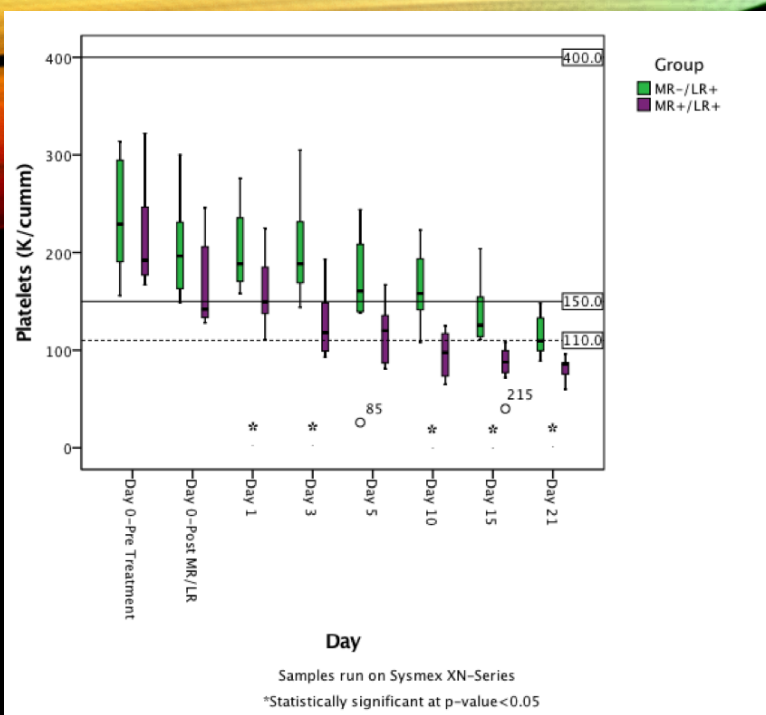
DOES LEUKOREDUCTION OF WHOLE BLOOD REDUCE ITS HEMOSTATIC CAPACITY?

- Imuflex SP filter licensed 2006
 - Spares platelets
 - Based on platelet count
 - Function of platelets and effects on hemostasis have not been thoroughly evaluated
- Yazer published data LR PLT function not reduced in WB that is LR
 - TEG measured for 10 days of storage at 4C
- Stubbs data in press indicating LR of whole blood reduces platelet function
 - Aggregometry measured for 7 days at 4C
- Neither group compared LR to non-LR groups nor did they go up to 21 days

EFFECT OF LR ON HEMOSTATIC CAPACITY OF WHOLE BLOOD STUDY

- Preliminary results from Spinella Lab at Wash U – Unpublished
- Funded by TerumoBCT/US Department of Defense
- In vitro study
 - Whole blood collected by local blood collection center
 - 8 donors in each of 4 study groups
 - LR-/MR-, LR+/MR-, LR-/MR+, LR+/MR+
 - Whole blood stored at 4C for up to 21 days
 - Platelet count, ROTEM, Multiplate aggregation, Thrombin generation
 - sCD40L, Platelet factor 4 and Thromboxane A2





CONCLUSIONS

- LR does not reduce hemostatic capacity compared to non LR samples
-IN VITRO
- Conflicting results over time between
 - Multiplate aggregometry data vs ROTEM/thrombin generation data
 - Don't know which measures of hemostasis are more clinically relevant
- For centers that must LR it appears OK to LR whole blood
- For centers that don't want to do it, that is OK too
- Mirasol treatment with LR minimal reduction in hemostatic capacity

PLASMA

- Frozen plasma
 - FFP
 - FP24
 - Immediate use and thawed for days
- Liquid (never frozen) plasma
- Pathogen Reduced
 - Solvent Detergent
 - Mirasol
 - Intercept
- Dried products
 - Freeze dried
 - Spray dried



Outcomes Related to the Use of Frozen Plasma or Pooled Solvent/Detergent-Treated Plasma in Critically Ill Children

Pediatric Critical Care Medicine

Maraya N. Camazine, BS¹; Oliver Karam, MD, PhD^{2,3}; Ryan Colvin, MPH¹;
Stephane Leteurtre, MD, PhD^{3,4}; Pierre Demaret, MD, MSc^{3,5}; Marisa Tucci, MD⁶;
Jennifer A. Muszynski, MD⁷; Simon Stanworth, MD^{8,9}; Philip C. Spinella, MD, FCCM¹; on behalf of
the PlasmaTV Investigators and the Pediatric Critical Care Blood Research Network (Blood Net)

TABLE 1. Relationship Between Type of Plasma and Population Characteristics

Candidate Independent Variables	Fresh Frozen Plasma/ Frozen Plasma 24 hr (<i>n</i> = 357)	Pooled Solvent/Deter- gent-Treated Plasma (<i>n</i> = 62)	<i>p</i>
Gender, <i>n</i> (%)			0.78
Male	152 (42.6)	25 (40.3)	
Female	205 (57.4)	37 (59.7)	
Age, yr, median (IQR)	1.1 (0.2–6.4)	0.8 (0.3–6.3)	0.80
Reason for admission, <i>n</i> (%)			0.88
Medical only	142 (39.8)	23 (37.1)	
Surgical only	133 (37.3)	25 (40.3)	
Combination of medical and surgical	82 (23.0)	14 (22.6)	
Primary indication for plasma transfusion, <i>n</i> (%)			< 0.001
No bleeding, no procedure	128 (35.9)	17 (27.4)	
Critical bleeding	81 (22.7)	10 (16.1)	
Minor bleeding	64 (17.9)	27 (43.6)	
Preparation/planned procedure	44 (12.3)	6 (10.0)	
High risk of postoperative bleeding	40 (11.2)	2 (3.2)	
Pediatric Logistic Organ Dysfunction -2 score at transfusion, median (IQR)	7 (5–10)	7 (5–9)	0.26
INR prior to transfusion, median (IQR) ^a	1.6 (1.3–2.0)	1.5 (1.2–1.9)	0.89
Change in INR, posttransfusion minus pretransfusion, median (IQR) ^b	–0.2 (–0.4 to 0)	–0.2 (–0.3 to 0)	0.80
Highest lactate on day of transfusion, median (IQR) ^c	2.6 (1.5–5.0)	2.3 (1.6–4.3)	0.72
Extracorporeal life support during transfusion, <i>n</i> (%)	36 (10.1)	4 (6.5)	0.49
Continuous renal replacement therapy during transfusion, <i>n</i> (%)	28 (7.8)	6 (9.7)	0.62
Intermittent hemodialysis	4 (1.1)	1 (1.6)	0.55
Total volume of plasma (mL/kg), median (IQR) ^d	21.4 (11.1–55.4)	15.0 (10.0–40.9)	0.07
Mortality, <i>n</i> (%)	104 (29.1)	9 (14.5)	0.02

TABLE 5. Multiple Logistic Regression Model of Independent Variables and ICU Mortality

Candidate Independent Variables	OR (95% CI)	<i>p</i>
Reason for admission		0.01
Surgical only	Reference	
Medical only	2.76 (1.39–5.46)	0.004
Combination of medical and surgical	2.09 (0.94–4.65)	0.07
Day 1 Pediatric Logistic Organ Dysfunction-2 score	1.24 (1.14–1.35)	< 0.0001
Highest log lactate on day of transfusion	1.45 (1.00–2.10)	0.05
Plasma type		0.05
Fresh frozen plasma/frozen plasma 24 hr	Reference	
Solvent/detergent-treated plasma	0.40 (0.16–0.99)	0.05
Continuous renal replacement therapy during transfusion, yes vs no	2.50 (1.08–5.79)	0.03
Log total volume of plasma (mL/kg)	1.59 (1.26–2.00)	< 0.0001

OR = odds ratio.

Variables placed in the model that were not reported due to nonsignificance include indication for plasma transfusion, patient age, and use of extracorporeal life support.

Area under the curve = 0.85

DRIED PLASMA PRODUCTS

- Freeze dried products from France and Germany licensed for use outside of the USA
 - US Special Forces have access to French product
- Products in the USA being developed by
 - Entegriion
 - Spray dried, Solvent Detergent treated.
 - Completed phase 1 in healthy volunteers
 - In discussion w FDA/DoD for phase 2 trial in patients with hepatic disease
 - Vascular Solutions
 - Freeze dried, single donor plasma
 - Phase 1 to start in healthy volunteers

DRIED PLASMA PRODUCTS

- TerumoBCT
 - Assessing the feasibility of developing a small pool freeze-dried plasma product, most likely with pathogen reduction.
 - Preclinical development
- Cerus
 - In preclinical development of freeze dried plasma product
- Velico
 - Device that will spray dry plasma onsite
 - Similar coagulation factor and thrombin generation profile vs FFP
 - Licensure pursued for single donor plasma only
 - Goal to submit for licensure by early 2019



PLATELETS

- Platelets at 22 C and 4C
 - Suspended in plasma or additive solutions
- PRT platelets
 - 22C storage
 - 4C storage
- Freeze dried platelets
- Frozen platelets

4C PLATELETS

- Clinical development, trials in CT surgery patients
 - University of Haukeland (Kristofferson, Strandenes, Hervig, et al.)
 - Phase II study in CT surgery patients
 - TerumoBCT (Pidcocke)
 - In discussion with FDA regarding trial
 - Pediatric Critical Care Blood Research Network (Spinella/Steiner/Zantek)
 - Early trial design phase
- Preclinical
 - Intercept 4C platelets - Cerus

CRYOPRESERVED PLATELETS IN THE USA

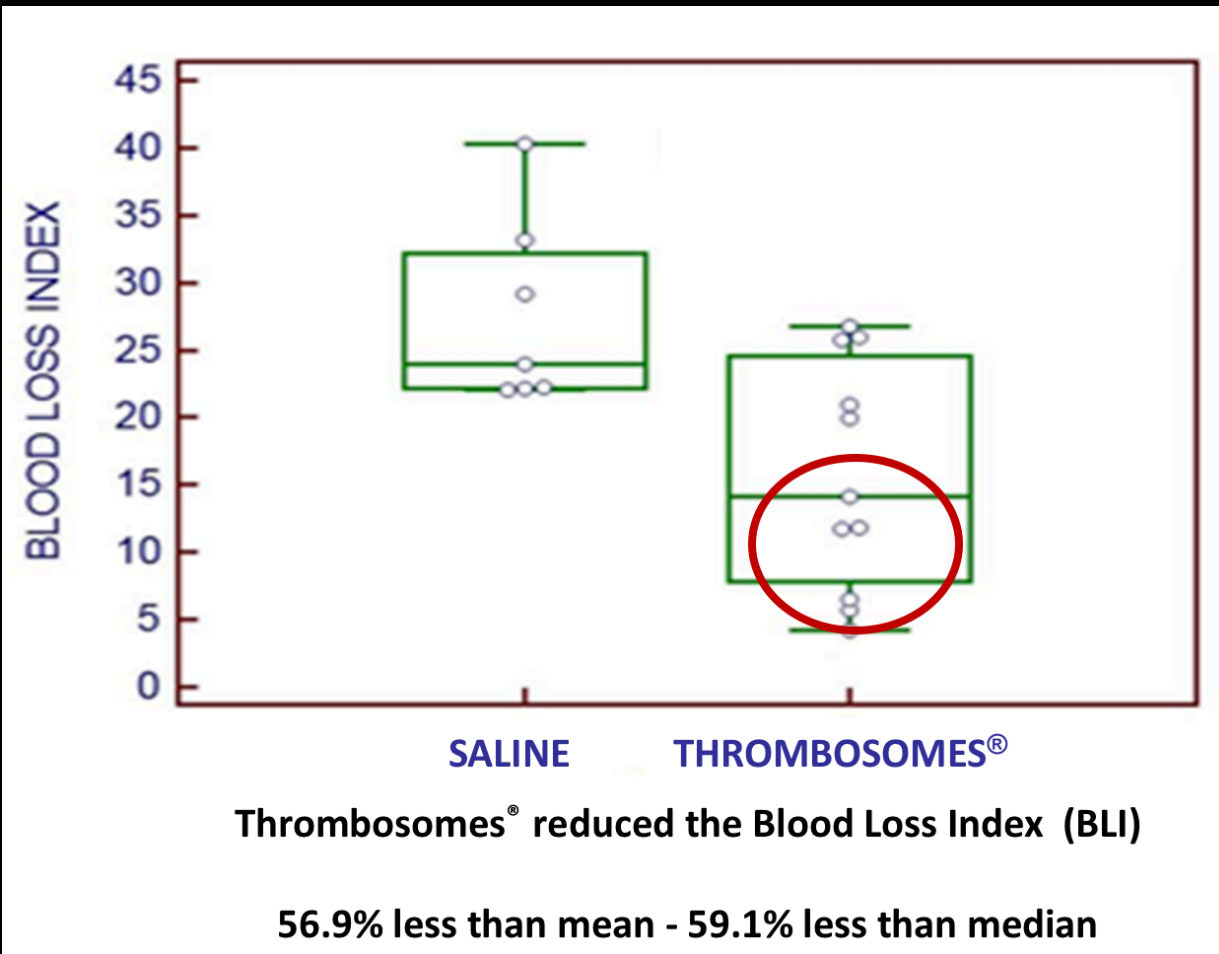
- Larry Dumont, Blood Systems Research Institute, Denver
- DoD funded
- Phase 1 in 24 hypoproliferative thrombocytopenic bleeding patients -completed
- Phase 2 studies in bleeding CT surgery patients are under development
- Similar product to the one used by Netherlands except
 - Re-suspended in saline vs plasma
 - Considering using PAS/plasma instead

FREEZE DRIED PLATELETS

- Thrombosomes – Platelet derived particles
 - Rehydrated with sterile water
 - Cellphire
- Preclinical phase of development – complete
- Phase 1 trials ongoing
 - Early phase 1 trial completed in 2016
 - 15 subjects
 - No safety concerns identified
 - Proposed Phase 1 in discussion w FDA
 - Dose escalation trial
 - To evaluate for safety issues

NON HUMAN PRIMATE MODEL – UNCONTROLLED HEMORRHAGE

- Intervention 15 minutes after liver injury
- 15 min treatment period
- Laparotomy at 120 min from injury
 - Blood loss measured
- **UNPUBLISHED DATA** from US Navy





PATHOGEN REDUCED PLATELETS

- Cerus product
 - Licensed in Europe and US
 - Clinical development phase in Canada
- TerumoBCT product
 - Licensed in Europe
 - Clinical development phase in Canada and US
- Controversy regarding the efficacy of PRT platelets

ORIGINAL PAPER

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Patient outcomes and amotosalen/UVA-treated platelet utilization in massively transfused patients

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¹Central Institute for Blood Transfusion and Immunology, Medical University Hospital Innsbruck, Innsbruck, Austria

²Cerus Corporation, Concord, CA, USA

INTERCEPT VS STANDARD APHERESIS PLATELETS

- Retrospective cohort study of 306 patients requiring massive transfusion
 - Approximately 3 years total
 - Mix of cardiac, liver, trauma surgery
- No difference in demographics, transfusion ratios and severity of illness
- No difference in
 - Blood product use
 - Day 1 and day 7
 - Overall mortality
 - 27 vs 24%, $p=0.37$

INTERCEPT VS STANDARD APHERESIS PLATELETS

- Analysis did not adjust for
 - Use of hemostatic adjuncts
 - ISS in trauma
 - APACHE or MELD score for non-trauma
 - Time period since practice may have changed between 2011 and 2014
- Important study
- Reassuring that intercept platelets have similar efficacy in MT cohort with mortality around 25%

Every minute counts: Time to delivery of initial massive transfusion cooler and its impact on mortality

David E Meyer, MD, MS (David.E.Meyer@uth.tmc.edu) – University of Texas Health Sciences Center and McGovern School of Medicine, Houston, TX

- 680 patients from PROPPR Trial
- Median (IQR) time from arrival to MTP activation was 9 (3-20) min
- Median (IQR) time from MTP activation to delivery of blood products was 8 (5-11) min

Table 2. Multivariate regression predicting 24-hour mortality

	Odds ratio	95% C.I.	p-value
Time to receipt of first cooler (min)	1.05	1.01-1.10	0.035
Anatomic injury severity (ISS)	1.03	1.02-1.05	<0.001
Disturbed arrival physiology (w-RTS)	0.69	0.60-0.81	<0.001
Randomization group (1:1:2)	1.69	1.01-2.86	0.047
Resuscitation Intensity (units)	1.12	0.60-2.05	0.719

95% C.I.: 95% confidence interval; min: minutes; ISS: injury severity score; w-RTS: weighted revised trauma score

Table 3. Multivariate regression predicting 30-day mortality

	Odds ratio	95% C.I.	p-value
Time to receipt of first cooler (min)	1.05	1.01-1.09	0.016
Anatomic injury severity (ISS)	1.05	1.03-1.06	<0.001
Disturbed arrival physiology (w-RTS)	0.61	0.53-0.69	<0.001
Randomization group (1:1:2)	1.46	0.92-2.29	0.102
Resuscitation Intensity (units)	1.03	0.60-1.44	0.184

95% C.I.: 95% confidence interval; min: minutes; ISS: injury severity score; w-RTS: weighted revised trauma score

Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial

Petra Innerhofer, Dietmar Fries, Markus Mittermayr, Nicole Innerhofer, Daniel von Langen, Tobias Hell, Gottfried Gruber, Stefan Schmid, Barbara Friesenecker, Ingo H Lorenz, Mathias Ströhle, Verena Rastner, Susanne Trübsbach, Helmut Raab, Benedikt Tremel, Dieter Wally, Benjamin Treichl, Agnes Mayr, Christof Kranewitter, Elgar Oswald

Vol 4 June 2017

RETIC TRIAL

- Single Center, non-blinded, RCT
- Innsbruck, Austria
- 94 patients
 - 44 in FFP
 - 50 in Factor Concentrate (Fibrinogen, PCC, XIII)
- 18-80 yrs, estimated ISS>15, clinical bleeding
- Reduced FIBTEM MCF or increased EXTEM CT
- Primary endpoint: Multiple Organ Failure

RETIC TRIAL INTERVENTIONS

- FFP Group (15ml/kg dose)
 - FIBTEM A10 < 9 mm
 - EXTEM CT > 90 sec or Prothrombin time index <35%
- Concentrate Group
 - Fibrinogen Concentrate (50mg/kg)
 - FIBTEM A10 < 9 mm
 - Kcentra (20IU/kg)
 - EXTEM CT > 90 sec or Prothrombin time index <35%
 - Factor XIII (20IU/kg)
 - Every second fibrinogen dose and bleeding score 2-3 with XIII < 60%
- Rescue therapy provided if ROTEM results did not correct after "double dose"

RETIC TRIAL OUTCOMES

- No differences between study groups
 - Except time to initial treatment
 - Concentrates
 - 10 min vs FFP 50 min
- No differences in MOF
 - FFP 66% vs Concentrates 50% ($p=0.15$)
- Adjusted analysis
 - Increased MOF in FFP group
 - OR 3.13 (1.19-8.88), ($p=0.025$)
- Increased risk of failure to correct ROTEM values
- Increased rate of massive transfusion

FACTOR CONCENTRATES VS PLASMA

- Debate Continues
 - RCT not conclusive in my opinion
- High value in using concentrates in a precision medicine approach
- Still need to replace circulating volume for patients with hemorrhagic shock
 - Concentrate only approach requires colloid/crystalloids
 - If platelet units are used they contain plasma

FIBRINOGEN VS CRYO DEBATE

	Fibrinogen Concentrate	Cryoprecipitate	Cryo-5 day, jumbo (under development)
Storage condition	Lyophilized	frozen	Thawed up to 5 days
Availability-immediate	Yes	No	Yes- when thawed, 5 days
Hemostatic factor content	Fibrinogen	Fibrinogen, vWF Factor VIII and XIII	Fibrinogen, vWF Factor VIII and XIII
Waste	No	High	Less than Cryo
Degradation with storage at room temp	No	No	No
Safety	Pathogen reduced	Pathogen reduced	Pathogen reduced
Cost	High	Low	Unknown

UNPUBLISHED DATA

Figure 3: Calibrated Automated Thrombogram Data from Apheresis FFP Cryo Samples

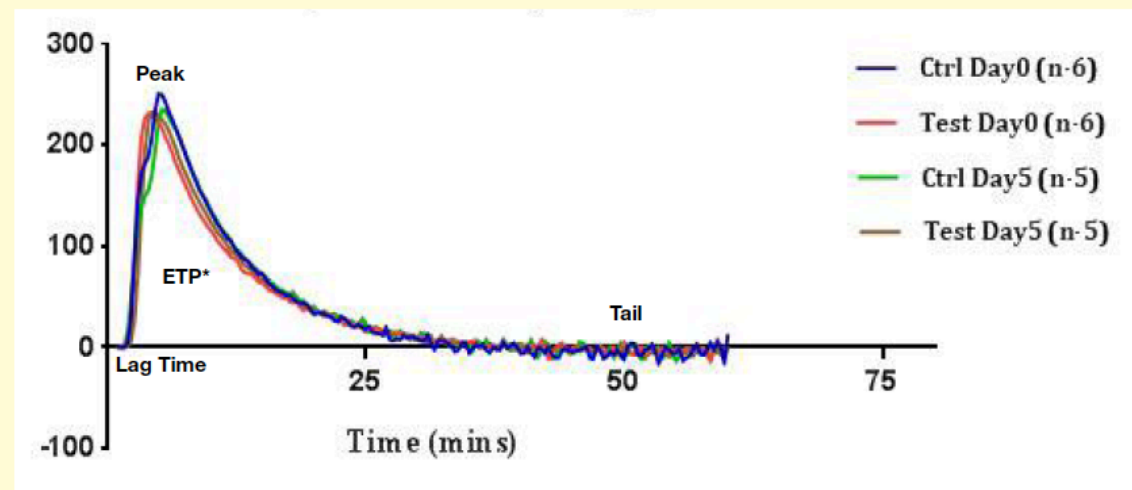


Table 2: Day 5 Total Fibrinogen (mg)

Total Fibrinogen (Avg (SD))				
All Groups Plasma		Day 0 (mg)	Day 1 (mg)	Day 5 (mg)
PR Treated	WBD Cryo	762 (134.7)	806 (150.8)	794 (127.2)
	Aph Cryo	954 (94)	997 (166.9)	1026 (143)
Control	WBD Cryo	319 (58.5)	320 (70.4)	345 (77)
	Aph Cryo	406 (105.9)	N/A	445 (84)

Poster presentation at Society Cardiovascular Anesthesia-2017, CERUS

Military use of TXA in combat trauma: Does it matter?

Jeffrey T. Howard, PhD^{1,2}, Zsolt T. Stockinger, MD^{3,4}, Andrew P. Cap, MD, PhD¹,

Jeffrey A. Bailey, MD^{5,6}, and Kirby R. Gross, MD¹

METHODS

- Retrospective study from DoD trauma registry
- Outcomes included mortality and DVT/PE
- Cohorts examined include
 - Massive transfusion
 - Propensity matched
 - US/NATO patients
- Multivariable proportional hazard models
 - Estimate Hazard Ratios



METHODS

- Inclusion criteria
 - Afghanistan, October 2010 – March 2014
 - Admitted to a level 3 hospital
 - Received at least 1 blood product

RESULTS

- Patients analyzed
 - Total population – 3,773
 - Massive transfusion – 784
 - Propensity matched – 1,030
 - US/NATO patients – 1,262
- TXA was not associated with mortality
 - Total population, HR 0.97 (0.62-1.53)
 - Massive transfusion, HR 0.84 (0.46-1.56)
 - Propensity matched, HR 0.68 (0.27-1.73)
 - US/NATO patients, HR 0.76 (0.3-1.92)

RESULTS

- TXA was independently associated with pulmonary embolism
 - Total population, HR 2.82 (2.08-3.81)
 - Massive transfusion, HR 3.64 (1.96-6.78)
 - US/NATO patients, 2.55 (1.73-3.69)
- TXA was independently associated with DVT
 - Total population, HR 2.0 (1.21-3.3)
 - US/NATO patients, HR 2.18 (1.2-3.96)

CONCLUSIONS

- Lack of analysis of TXA dose is a limitation
- Lack of association with reduced mortality
 - Similar HR to CRASH-2 Trial
 - Reduced power the issue or is there no benefit in this population?
- Results regarding PE and DVT are concerning – needs further evaluation
 - Benefit vs risk analysis is important
 - Number needed to treat argument is generous
- My opinion: Goal directed use of TXA may be the future
 - Empiric use for ALL traumatic bleeding **may not** be appropriate



Cochrane
Library

Cochrane Database of Systematic Reviews

**Thromboelastography (TEG) or thromboelastometry (ROTEM)
to monitor haemostatic treatment versus usual care in adults
or children with bleeding (Review)**

Wikkelsø A, Wetterslev J, Møller AM, Afshari A

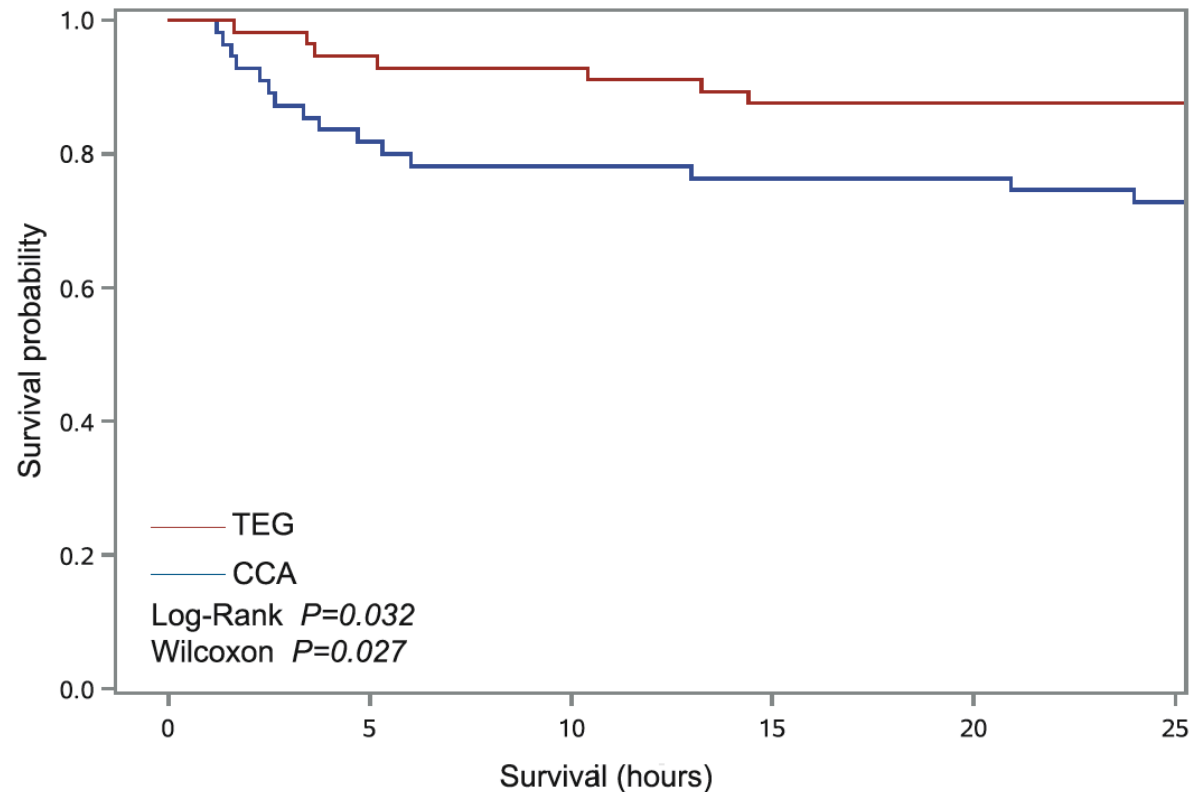
- 17 Studies
- TEG/ROTEM
 - Reduces Mortality
 - Reduces RBC, plasma, platelet transfusions
 - Reduces dialysis dependent renal failure

Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy

A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays

Eduardo Gonzalez, MD, Ernest E. Moore, MD,*† Hunter B. Moore, MD,* Michael P. Chapman, MD,* Theresa L. Chin, MD,* Arsen Ghasabyan, MPH,* Max V. Wohlauer, MD,* Carlton C. Barnett, MD,*† Denis D. Bensard, MD,*† Walter L. Biffl, MD,*† Clay C. Burlew, MD,*† Jeffrey L. Johnson, MD,*† Fredric M. Pieracci, MD, MPH,*† Gregory J. Jurkovich, MD,*† Anirban Banerjee, PhD,* Christopher C. Silliman, MD, PhD,*‡§ and Angela Sauaia, MD, PhD*¶*

(Ann Surg 2015;xx:xxx-xxx)



TEG DIRECTED VS EMPIRIC RATIO HEMOSTATIC RESUSCITATION

- Single center RCT of 110 patients
- Study groups similar in epidemiologic and severity of illness
- TEG group
 - Less mortality at 6 hours and 28 days
 - Less death from hemorrhage
 - More ICU free days and mechanical vent free days
- Small sample size may limit generalizability
- Supportive of TEG directed resuscitation



CONCLUSIONS

- Progress is being made in optimizing blood products
- Must remain vigilant in pursuit of optimization of blood products
- No clear answers in current controversies
- Need to remain critical of data published and continue to challenge dogma to achieve our goals of improving outcomes for patients with traumatic hemorrhagic shock



