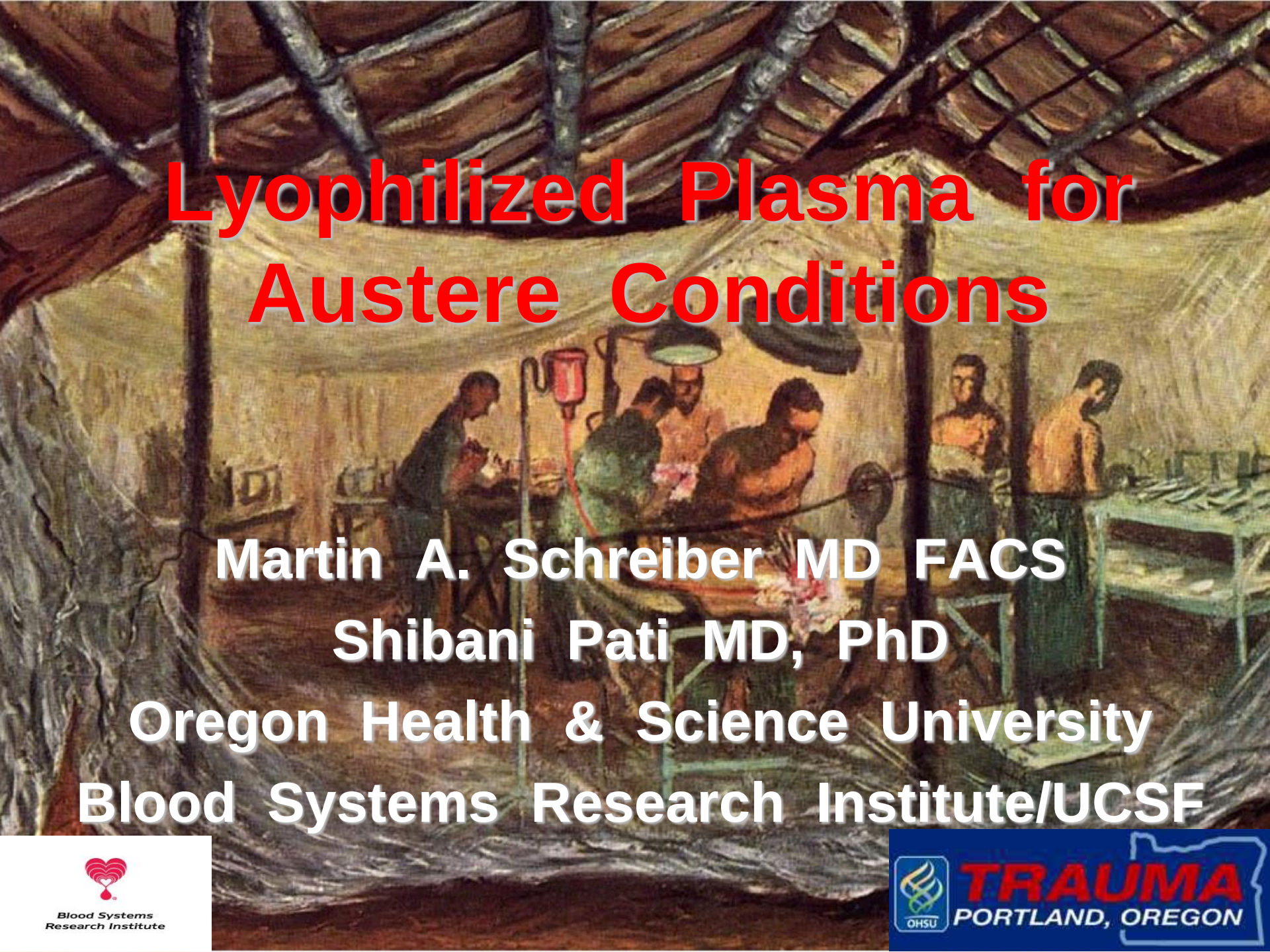


Lyophilized Plasma for Austere Conditions

Martin A. Schreiber MD FACS

Shibani Pati MD, PhD

Oregon Health & Science University

Blood Systems Research Institute/UCSF

Blood Systems Research Institute

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Introduction

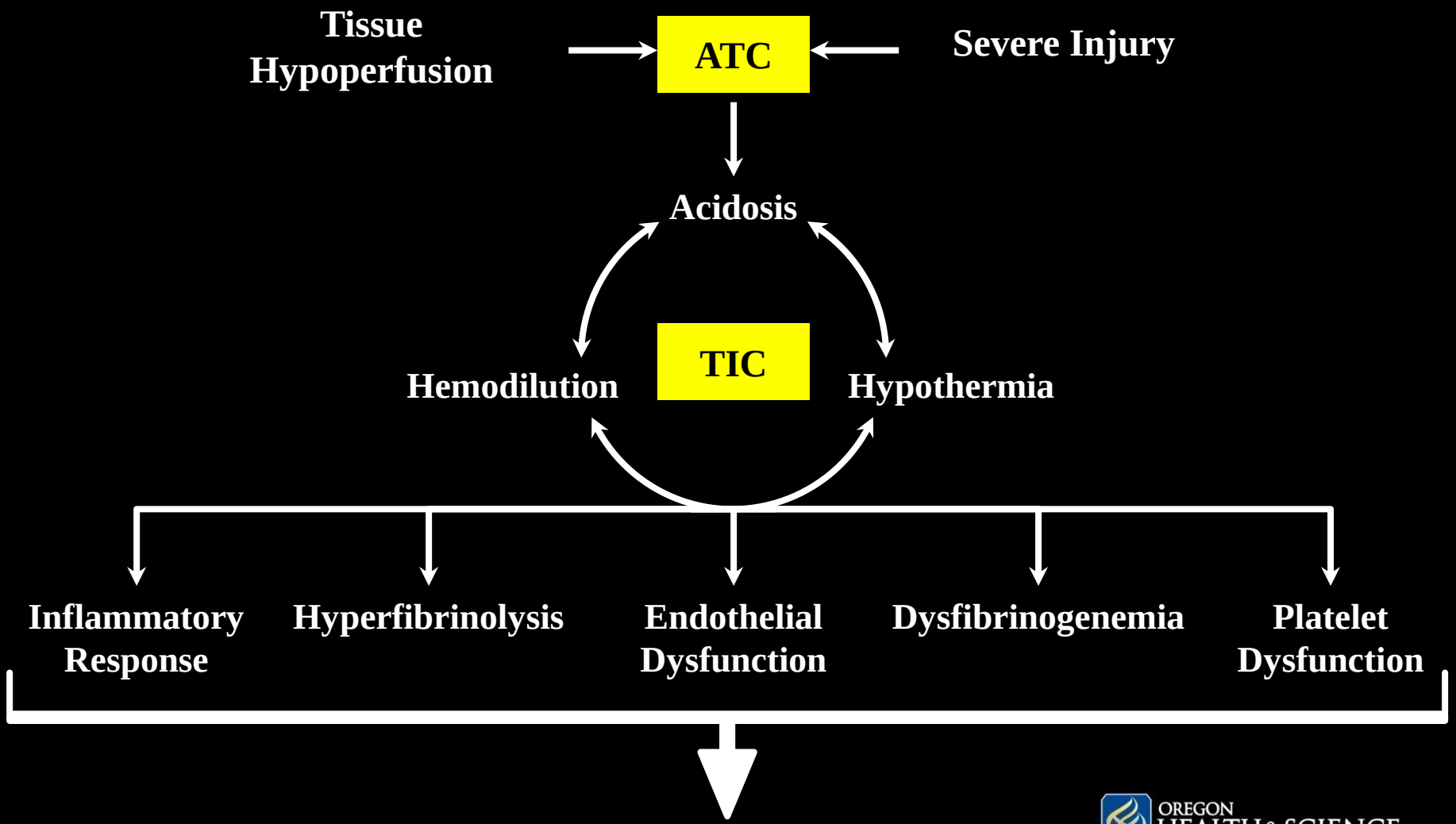
- Epidemiology and etiology of coagulopathy
- Damage control resuscitation
- Lyophilized plasma products in use
- Development and optimization of LP
- Advantages beyond coagulation

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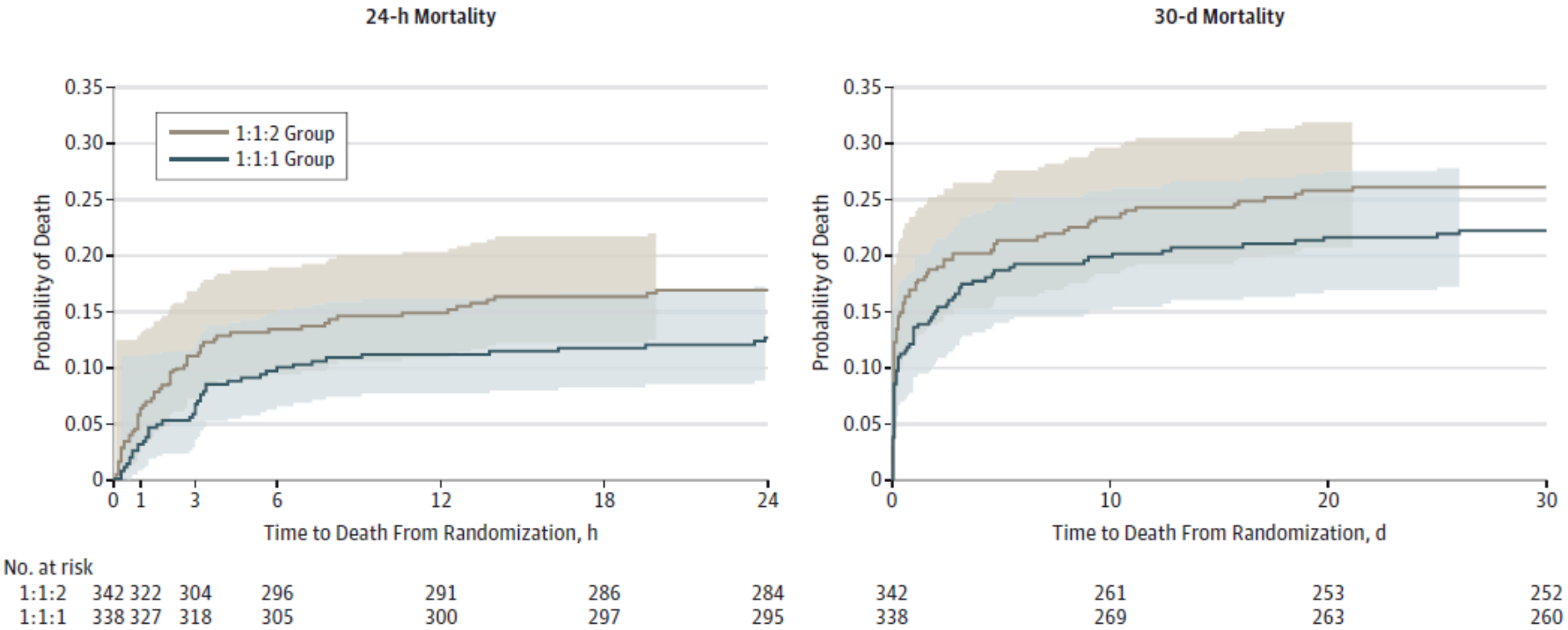
Acute Traumatic Coagulopathy (ATC)



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Kaplan – Meier Curves



Holcomb et al *JAMA* 2015;313:471 – 482.

Damage Control Resuscitation

- Primary Goals
  - Hemorrhage control
  - Avoid lethal triad
- Risk factors for MT
  - SBP < 110
  - HR > 105
  - HCT < 32
  - pH < 7.25
- Transfusion Goal – 1:1:1

85% chance of Massive Transfusion

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A
AB
POSITIVE
O
Rh POSITIVE

Damage Control Resuscitation

- Last in first out
- FWB only if components not available or patient not responding
- Platelets obtained in theater
- Additional fibrinogen required
- rFVIIa option if coagulopathy persists
- TXA for patients requiring MT

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@1500
15 PRBC
15 FFP
2 Cryo
2 Plt
ADULT 11

Advantages of Dried Plasma

- Logistically superior
- Stored as a powder for years
- Rapidly reconstituted in water
  - FFP 30 minutes to thaw
- Could be widely available
  - FFP availability problematic in rural areas, pre-hospital and far forward
- Retains factor function
  - FFP 60 – 70% activity after thawing

South African Dried Plasma

- South African Bioplasma FDP
  - Lyophilized, pooled, solvent detergent treated
  - 1500 donors, ABO universal, frozen < 6 hours
  - Stored below 25C
  - Prospectively studied in CPB patients and equivalent to plasma

Chapanduka et al. *S Afr Med J* 2002; 92: 356 – 357.


Bioplasma FDP
Fresh Human Plasma
50 ml
Bioplasma FDP
Fresh Human Plasma
200 ml

German LyoPlas

- German LyoPlas
  - Single donor (Blood type compatibility)
  - Stored up to 15 months
  - 200,000 TFNs – 0.023% major complications similar to FFP



French Flyp

- Up to 11 donors/unit (Universal)
- Stored up to 24 months
- Available to US SF on IRB protocol
- 1000 transfusions with no major adverse events

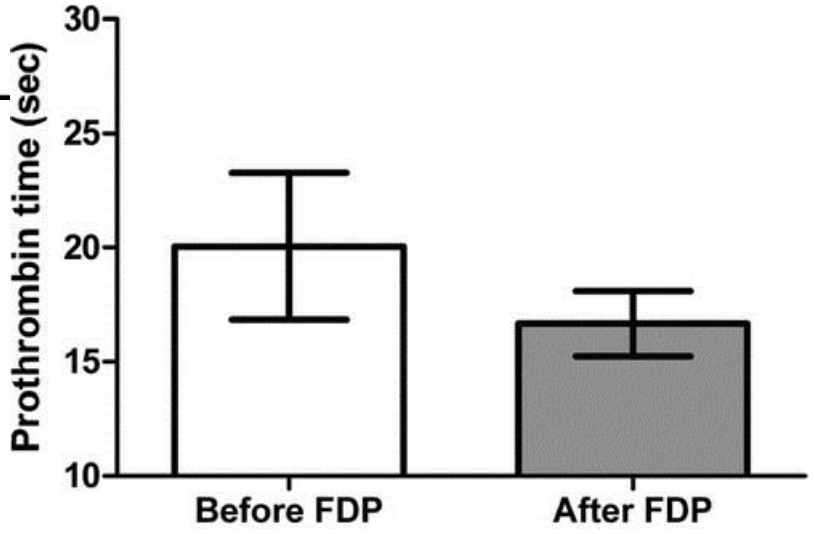


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Kabul Data

TABLE 1. Transfusion Data Before Administration of FDP

Blood Products, Fluids, and Agents Given Before the Use of FDP	Median	Range	Percent of Patients
Red blood cells (units)	3	1–13	32
Whole blood (units)	4	1–7	5
Crystalloid (L)	1	0.2–5	56
Colloid (mL)	500	100–8,000	15
rFVIIa (mg)	2	1–7	9
Fibrinogen (g)	1.5	1–3	6



Martinaud et al *J Trauma* 2011;71:1761-1765.

Swine Studies with LP

- US products in early FDA trials
- Whole blood sterilely removed from swine
- Plasma component separated
- Lyophilized by HemCon® Medical Technologies, Inc.
- Powdered plasma returned
- Reconstituted prior to transfusion



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Preparation of LP

- LP very alkalotic
- Requires addition of acid to reconstitution fluid
- Vitamin C utilized
- Reconstitute to original volume

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Methods: Swine Model

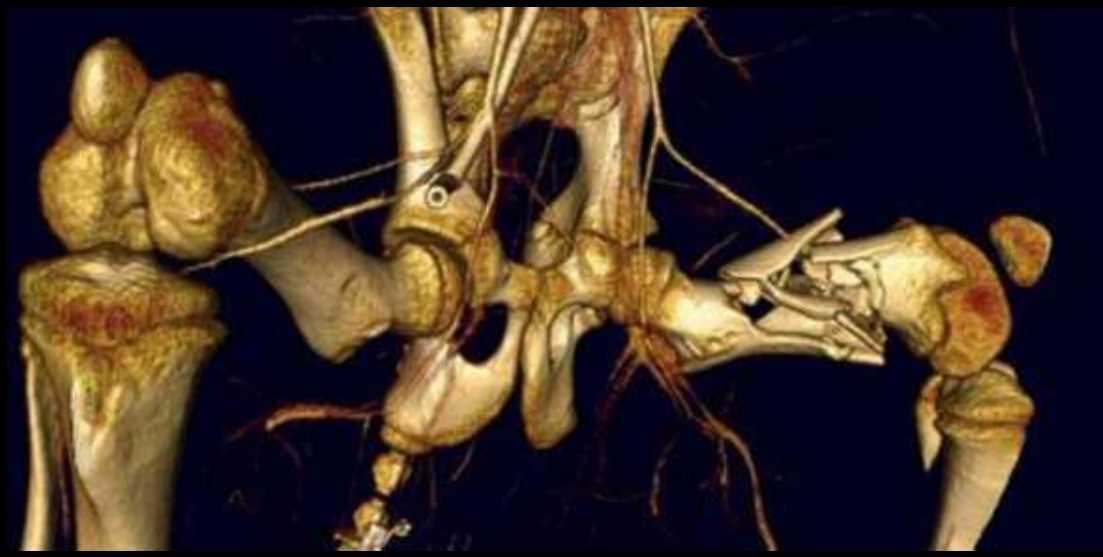
- Multi - center pre – clinical trial
- OHSU, USAISR, Mass General
- Previously validated model
- 32 Yorkshire crossbred swine
- Anesthetized, mechanically ventilated
- Carotid and jugular catheters placed

•Syverud et al, *Resuscitation* 1988
•Wladis et al, *Shock* 2001
•Kiraly et al, *J Trauma* 2006
•Cho et al, *Shock* 2008

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Cho, et al. *Shock* 2008

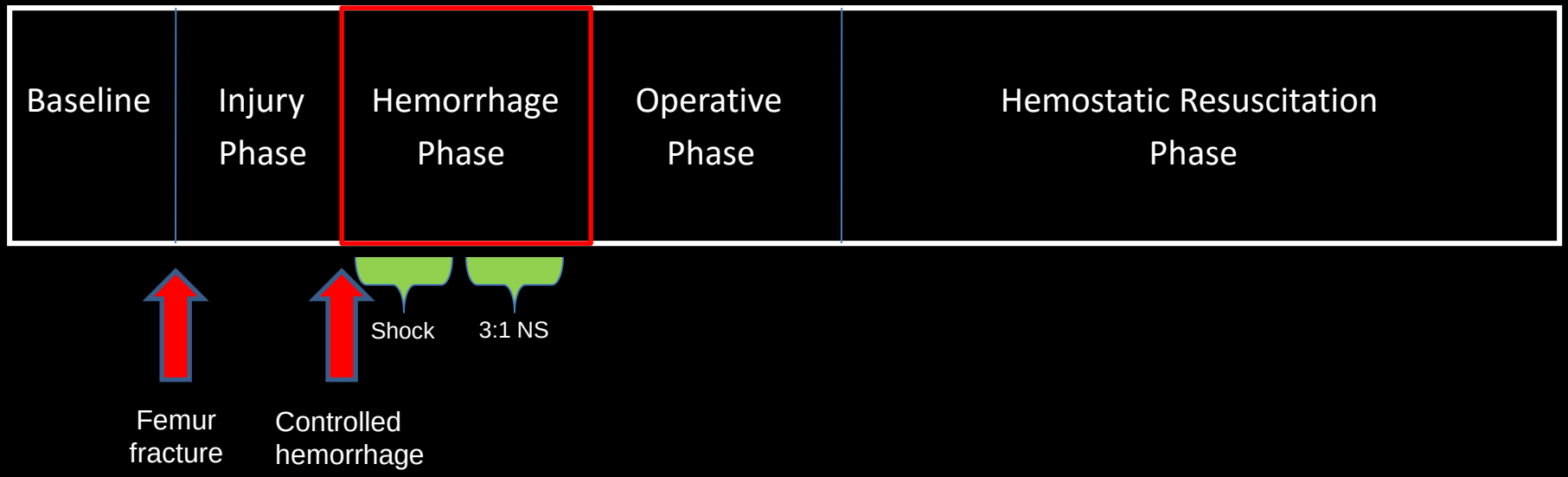


Shuja, et al, *J Trauma* 2008

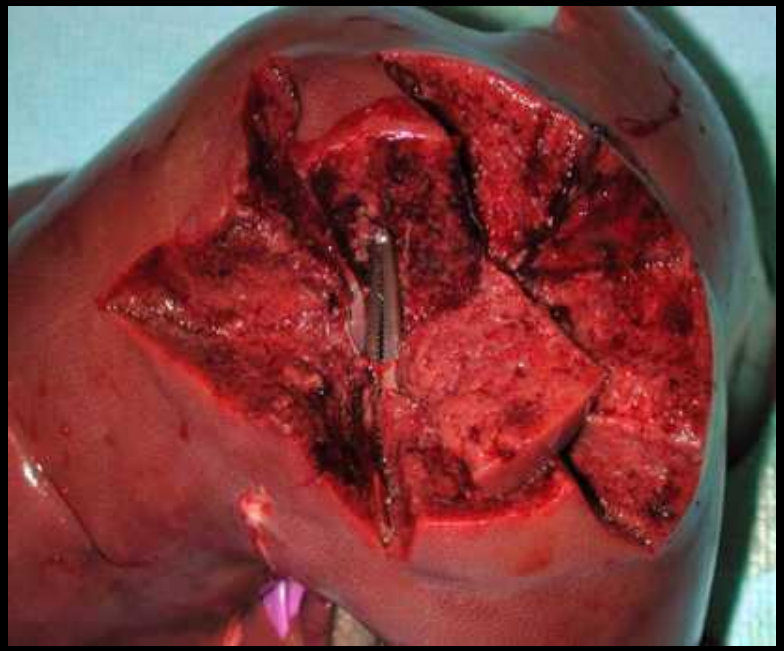
Baseline	Injury Phase	Hemorrhage Phase	Operative Phase	Hemostatic Resuscitation Phase



- 60% of estimated blood volume removed
- Hypothermia, acidosis, coagulopathy induced
  - Active cooling
  - Saline infusion







Baseline	Injury Phase	Hemorrhage Phase	Operative Phase	Hemostatic Resuscitation Phase

Shock

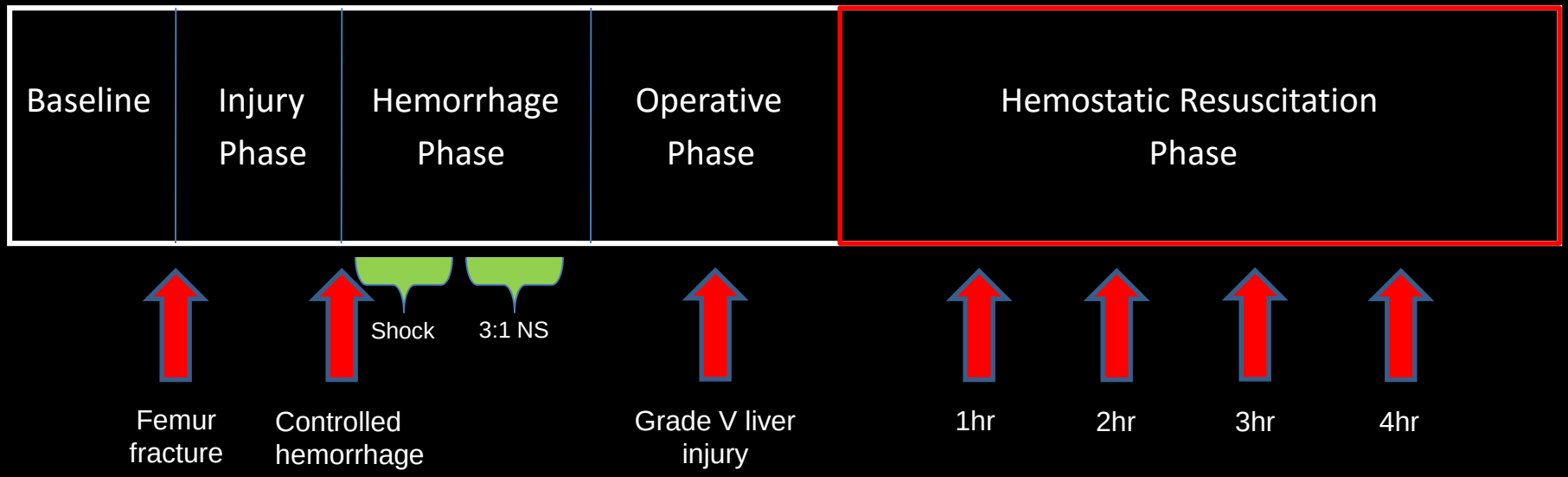
3:1 NS

Femur fracture

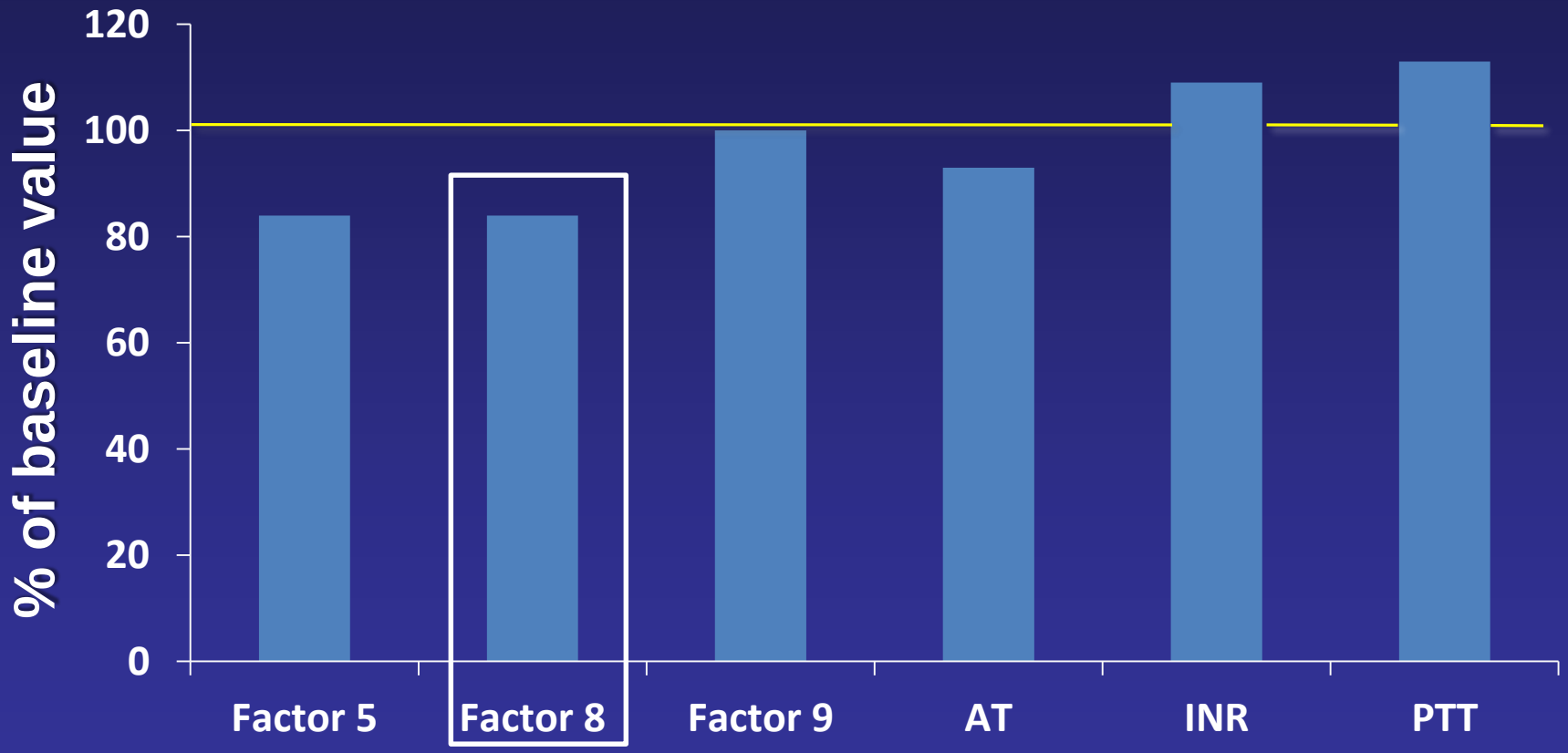
Controlled hemorrhage

Grade V liver injury

- 4 randomized groups
  - FFP
  - LP
  - FFP : PRBC
  - LP : PRBC
- Volume equal to controlled hemorrhage
- Re-warmed to 37°C
- Labs drawn hourly



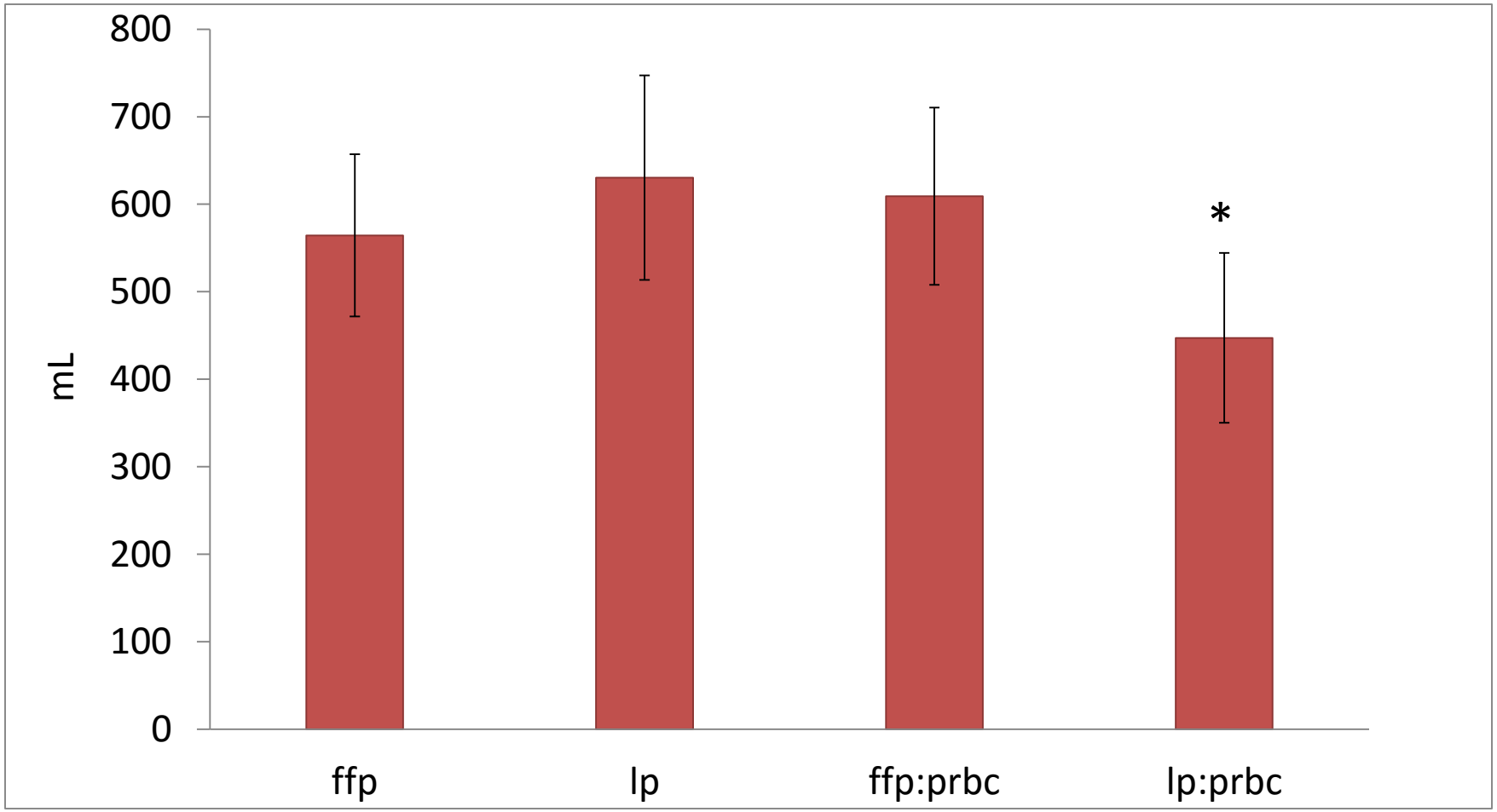
Residual Activity



Spoerke et al. *Arch Surg* 2009;144:829-834.

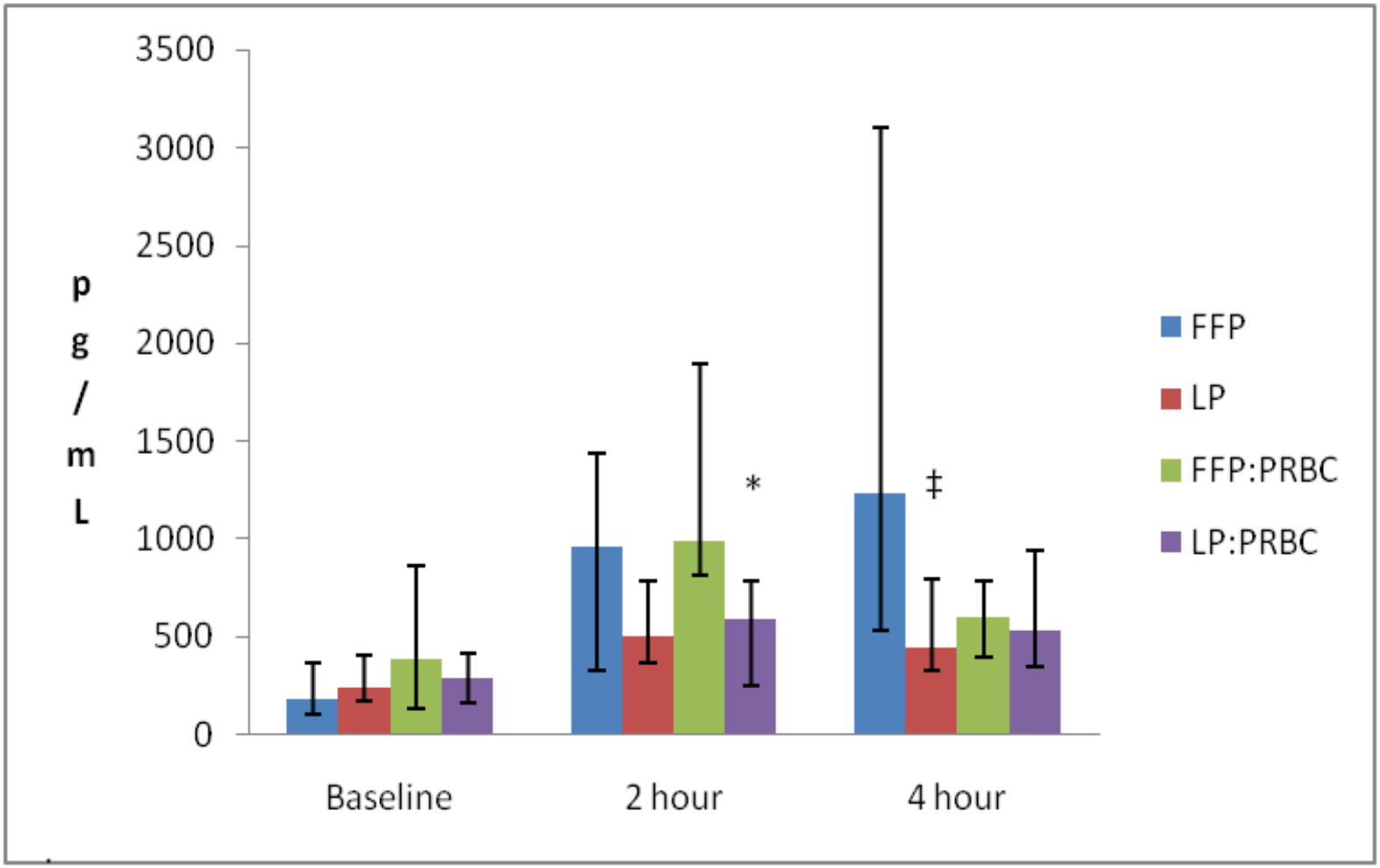
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Blood loss after liver injury



Spoerke et al. *Arch Surg* 2009;144:829-834.

IL-6



Spoerke et al. *Arch Surg* 2009;144:829-834.

Optimization of LP

- Minimize fluid for reconstitution
  - 50% equivalent
- Optimize reconstitution fluid
  - H_2O best
- Optimize anti-oxidants
  - Vitamin C dosed to correct pH
  - Effects unchanged 7.5 mM – 22.5 mM

Back to the Future





How does plasma work mechanistically?

- Over 1000 proteins in plasma
- Many are biologically active
- Many have unknown functions in health and disease

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Working Hypothesis:

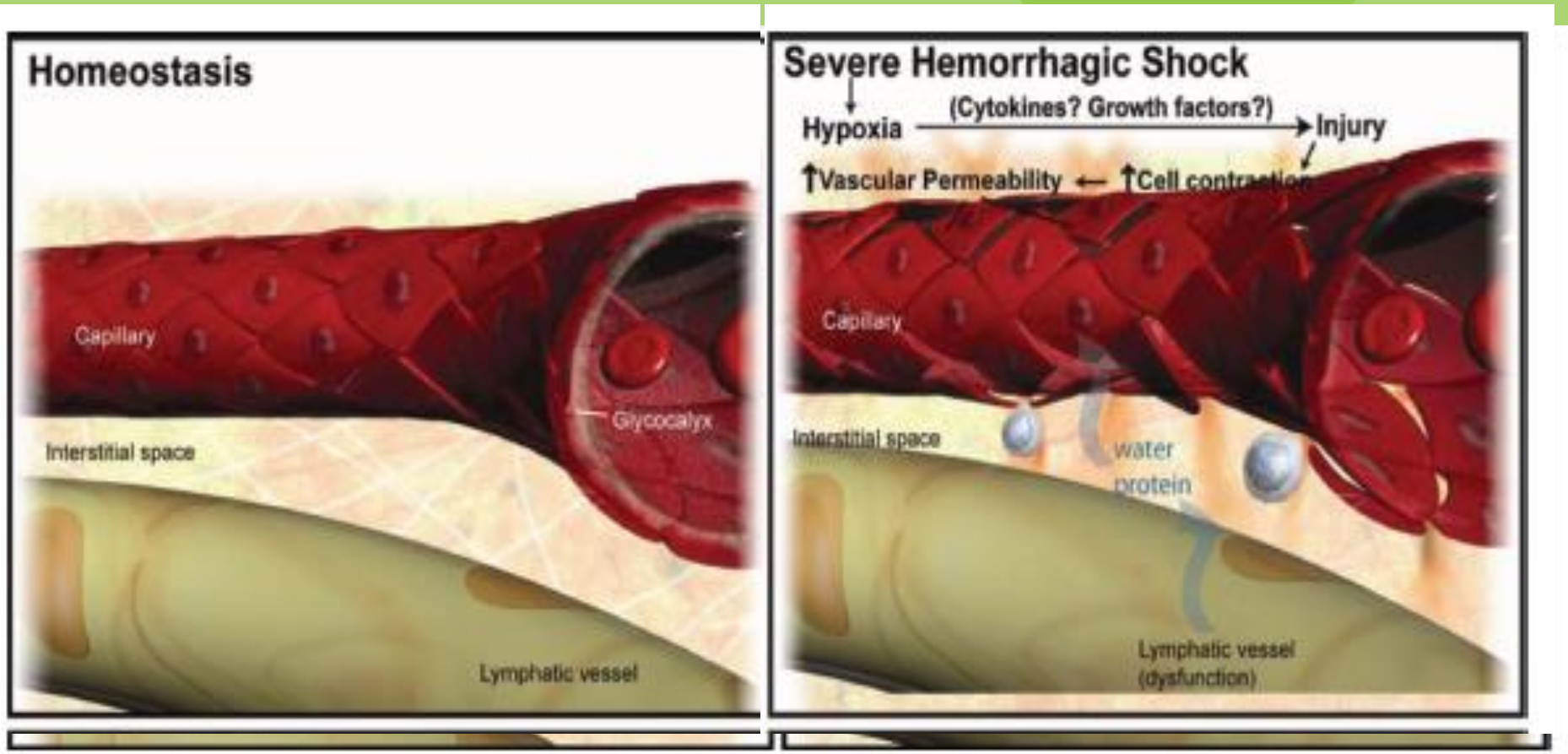
- We have formed the fundamental hypothesis:

that if we prevent or repair endothelial dysfunction **early** after traumatic injury – we can improve immune function and coagulation disturbances associated with trauma

- We hypothesize that plasma decreases inflammation and repairs endothelial injury and dysfunction.

- We further hypothesize this effect of plasma transfusion leads to increased survival and improved secondary outcomes related to injury- ie organ failure and long term disabilities

Working Biological Model Endotheliopathy of Trauma

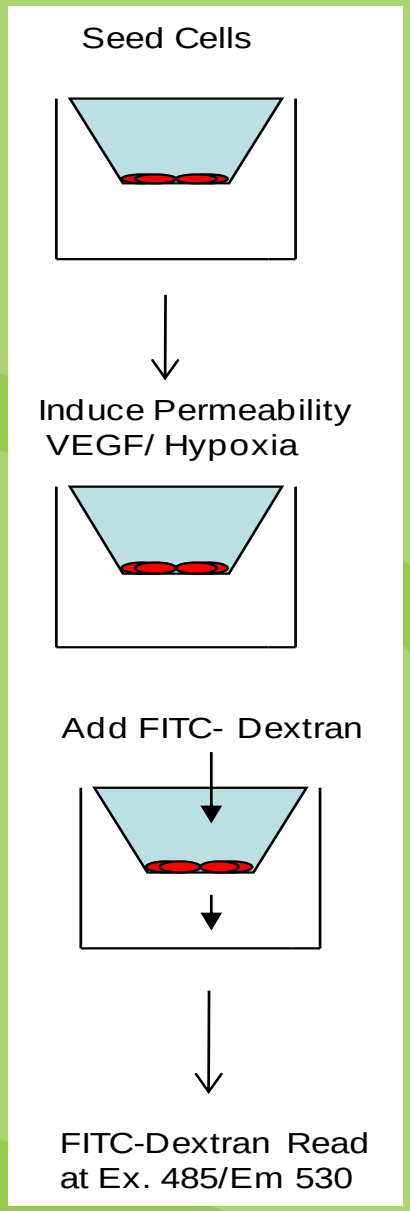


Pati et al. *J Trauma* 2010;69 Suppl 1:S55 – S63.

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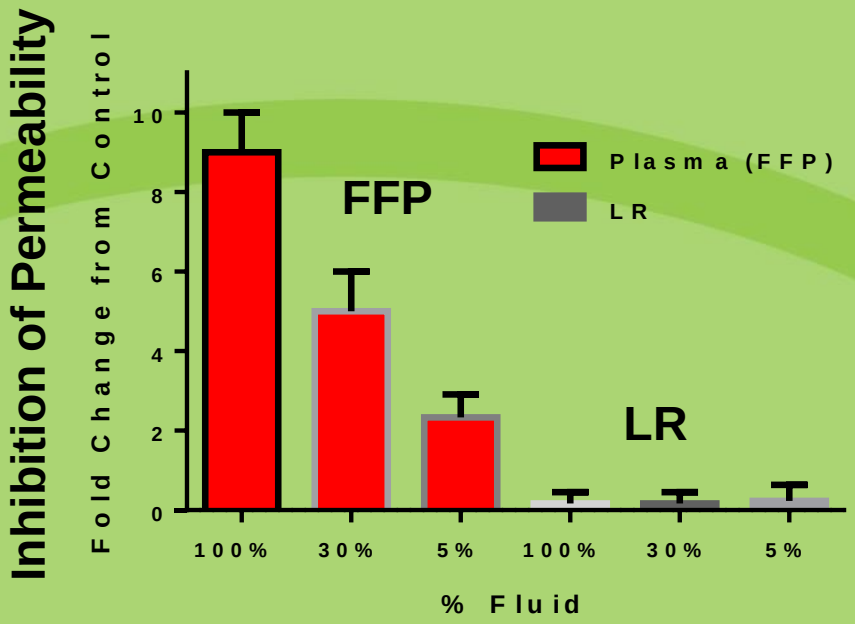
Assay of Endothelial Permeability



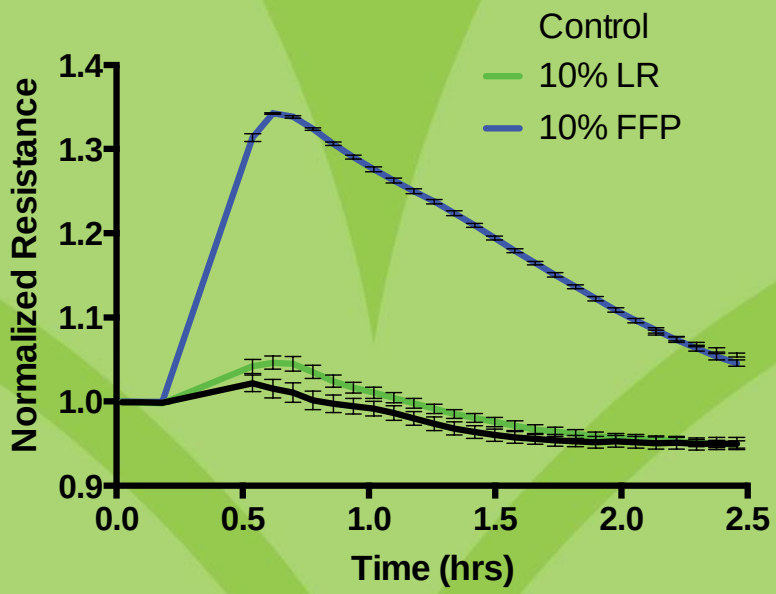
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FFP Inhibits Vascular Endothelial Permeability and Tightens the Junctions Between Endothelial Cells



Net: Decreased Permeability



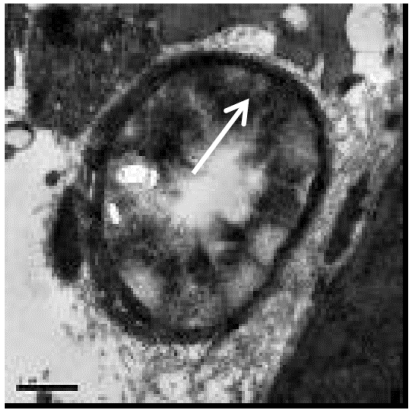
Net: Increased Resistance

Pati et al. *J Trauma* 2010;69 Suppl 1:S55 – S63.

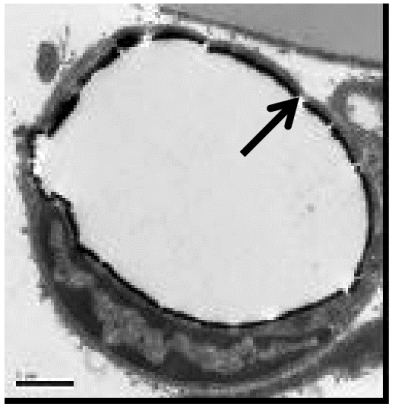
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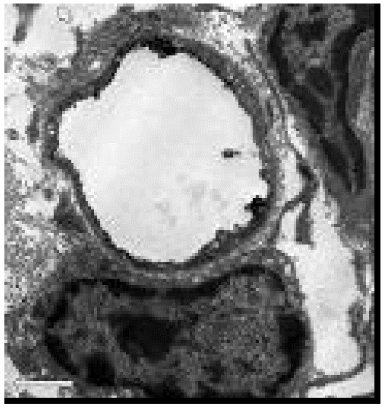
FFP Protects the Endothelial Glycocalyx



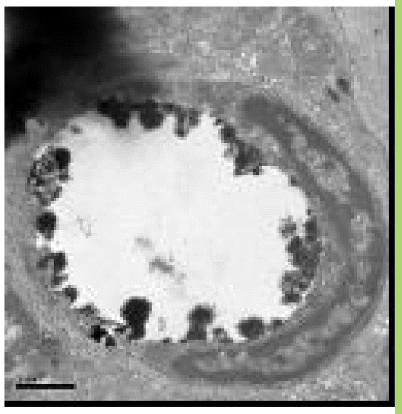
Sham



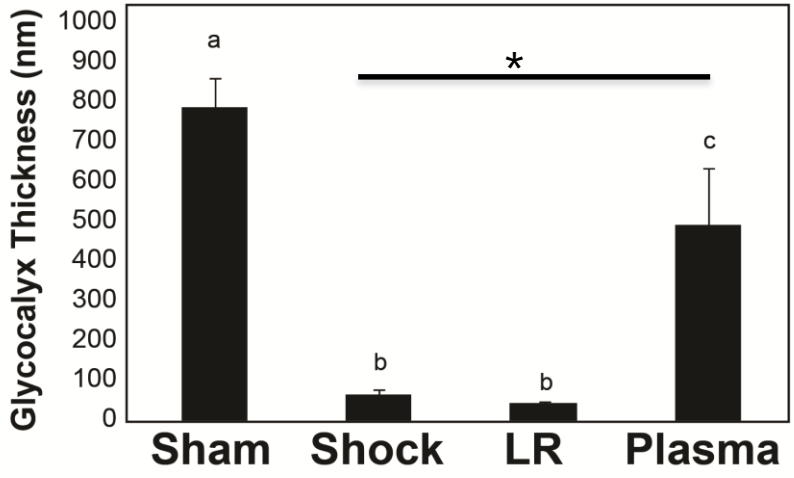
HS alone



HS + LR



HS + fresh plasma



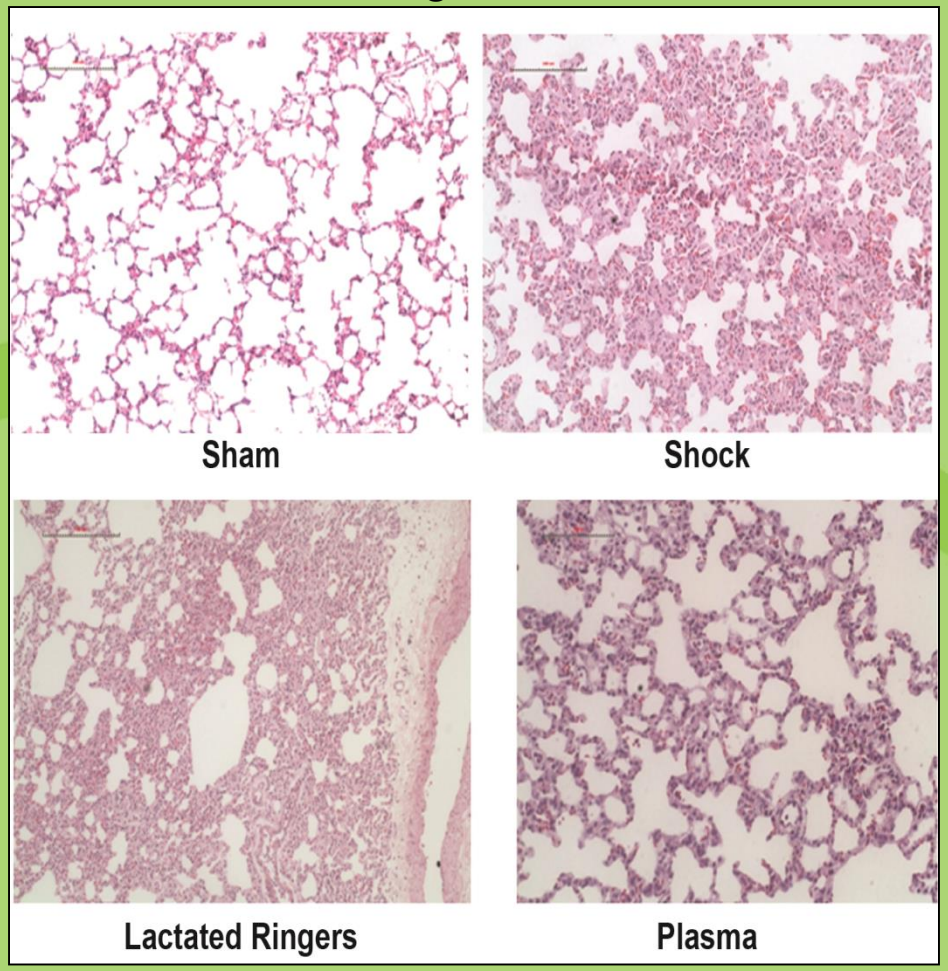
The glycocalyx is a ubiquitious barrier that protects the underlying endothelium

Kozar et al *Anesthesia Analgesia* 2011;112:1289 – 1295.

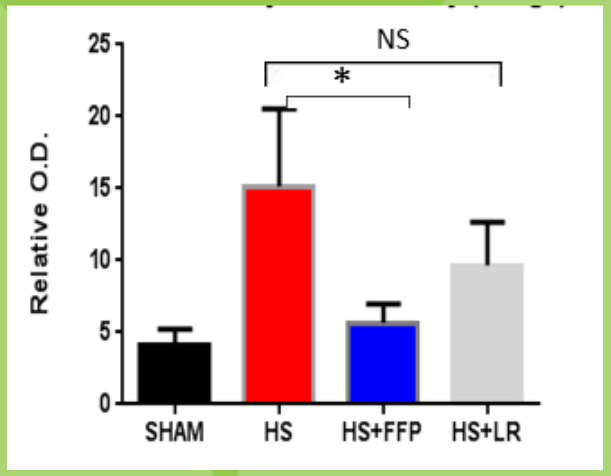
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Lung Injury in HS is inhibited by FFP

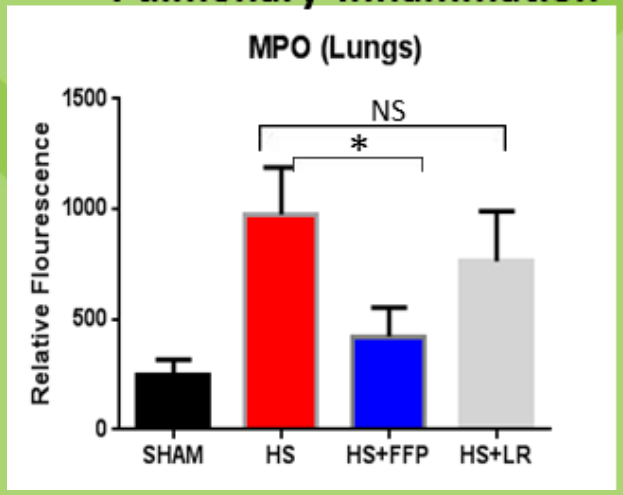
Lung Tissue



Pulmonary Vascular Leak



Pulmonary Inflammation

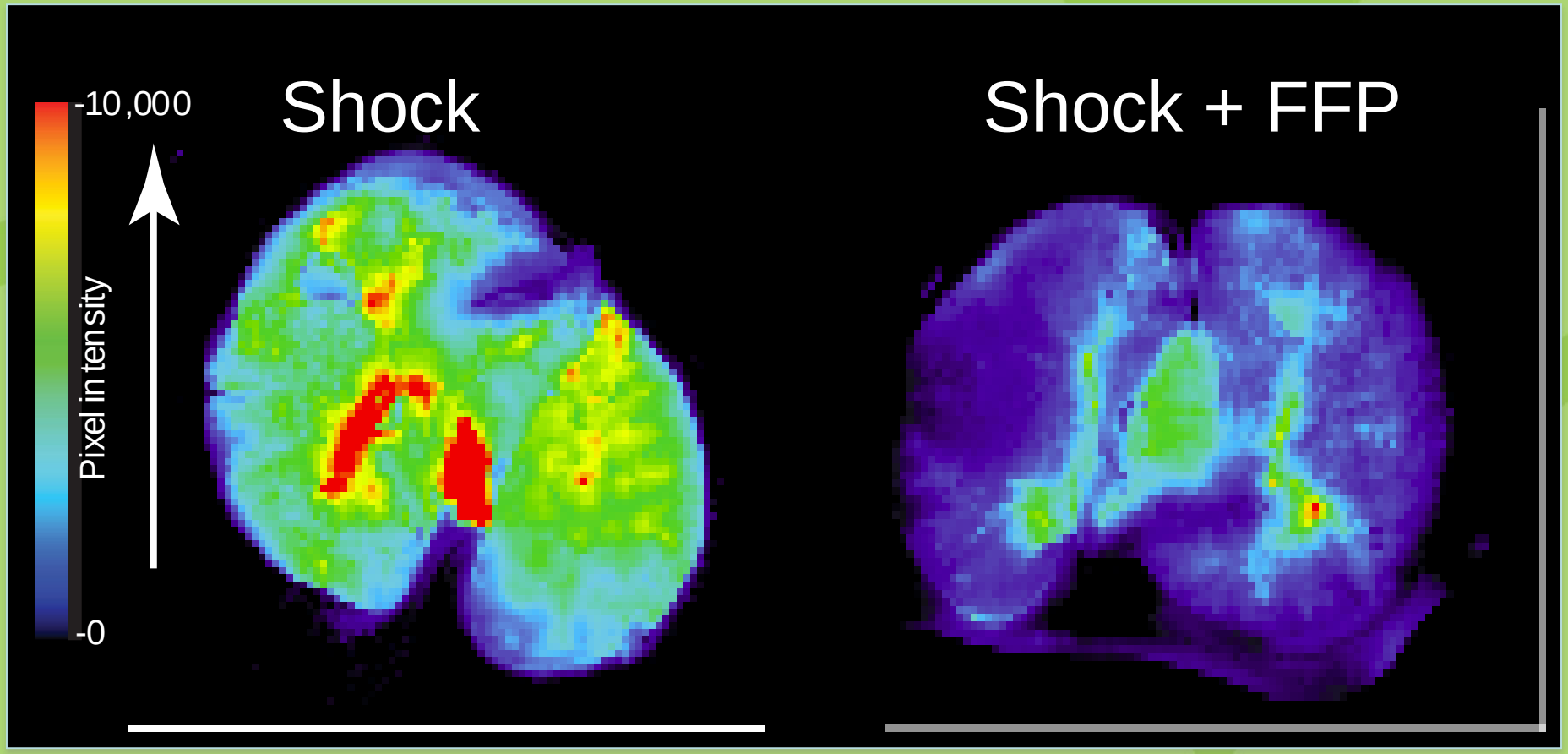


N=5 mice/group

Peng et al *Shock* 2013;40:195 – 202.

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Lung Vascular Permeability in HS is Inhibited by FFP



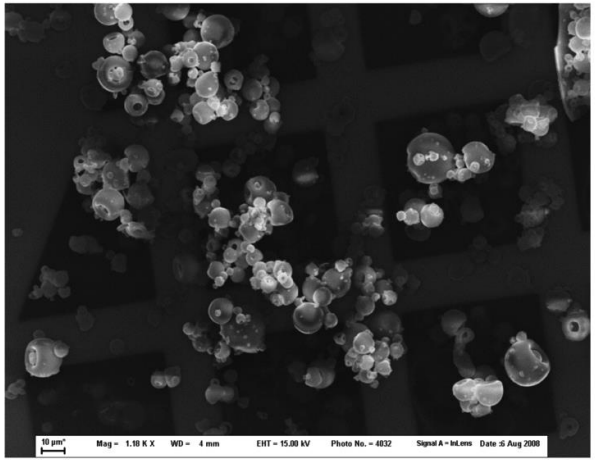
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Spray Dried Plasma: Resusix combines dried plasma with Pathogen reduction

- Entegrion Inc. and Velico Inc.
- Plasma is pooled (150 donors, type AB)
- Pathogen reduced via solvent detergent treatment
  - TnBP and Octoxinol
- Spray Dried
  - Powder has 2-5% of original moisture content
  - Allows the plasma to be concentrated





Images © Entergion Inc.

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In vitro: SDP is functionally equivalent to FFP in inhibiting endothelial permeability and inflammation

Spray-dried plasma and fresh frozen plasma modulate permeability and inflammation in vitro in vascular endothelial cells

K. Wataha, T. Menge, X. Deng, A. Shah, A. Bode, J.B. Holcomb, D. Potter, R. Kozar, P.C. Spinella, and S. Pati

TRANSFUSION Volume 53, January 2013 Supplement

- *In vitro* Assays show both SDP and FFP equivalently
  - Inhibit endothelial cell permeability
  - Inhibit leukocyte binding
  - Reconstitute endothelial adherens junctions after VEGF treatment

In Vivo- SDP is Equivalent to FFP

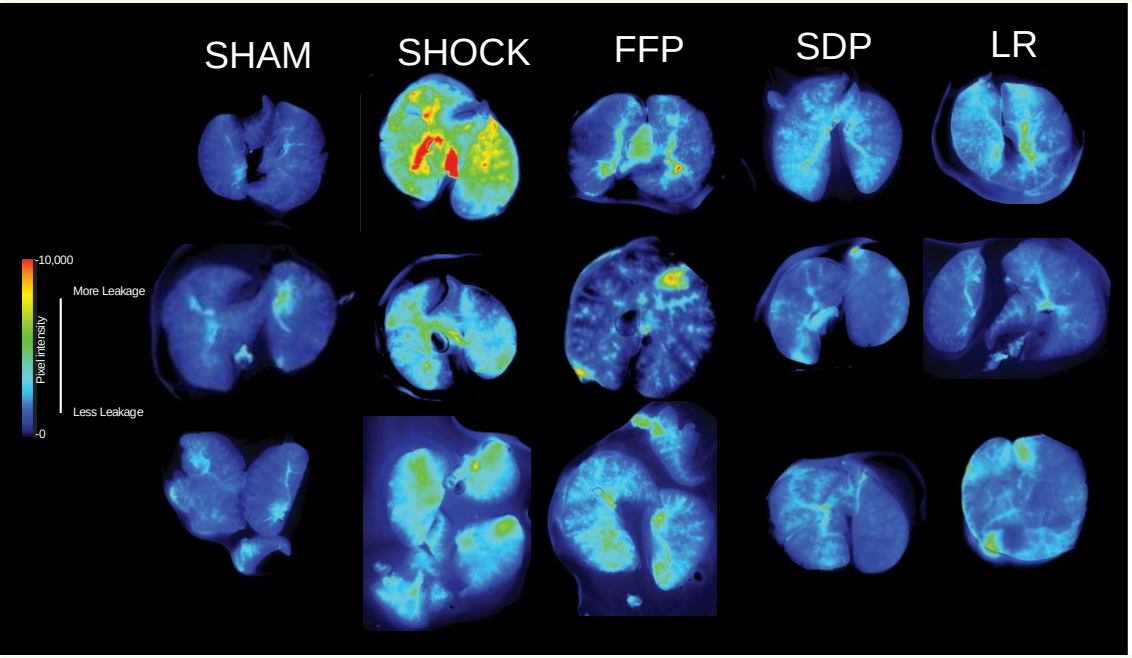
FFP and SDP are equivalent in reversing the endotheliopathy of trauma *in vivo* in a mouse model of hemorrhagic shock and trauma.

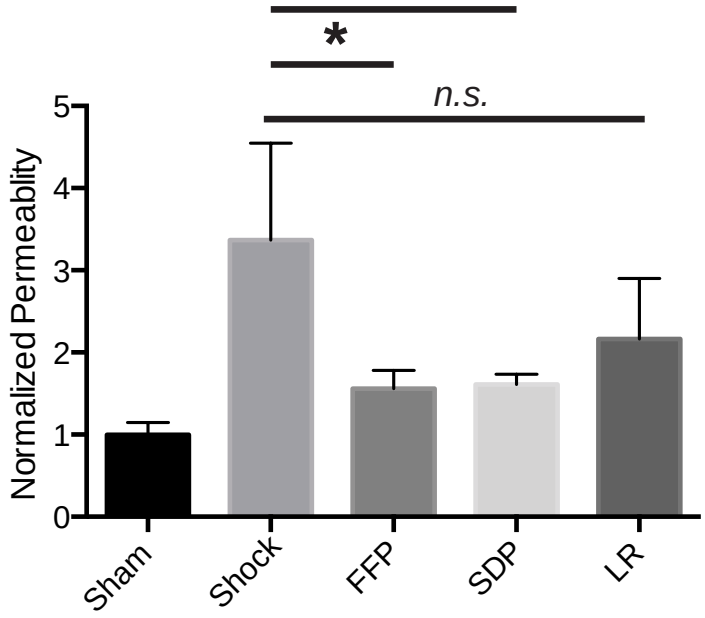
Fresh frozen plasma and spray-dried plasma mitigate pulmonary vascular permeability and inflammation in hemorrhagic shock

Daniel R. Potter, PhD, Gail Baimukanova, MD, PhD, Sheila M. Keating, PhD, Xutao Deng, PhD, Jeffrey A. Chu, Stuart L. Gibb, PhD, Zhanglong Peng, PhD, Marcus O. Muench, PhD, Marina E. Fomin, PhD, Philip C. Spinella, MD, Rosemary Kozar, MD, PhD, *and* **Shibani Pati, MD, PhD,** *San Francisco, California*

J Trauma Acute Care Surg
Volume 78, Number 6, Supplement 1

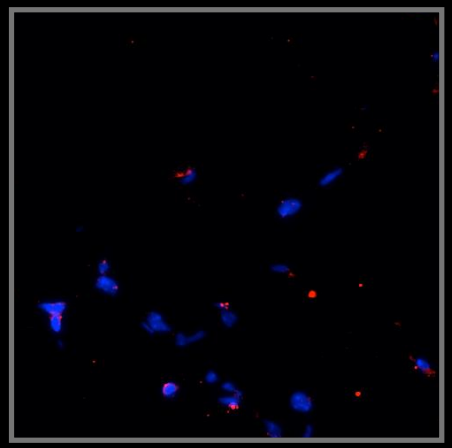
FFP and SDP equivalently inhibit pulmonary vascular permeability induced by hemorrhagic shock in mice



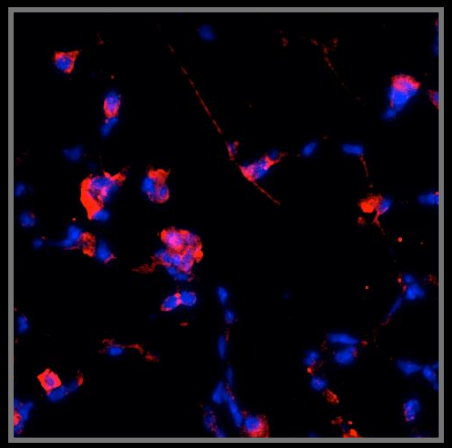


CD68 positive monocytes and macrophage infiltrates are decreased by SDP and FFP resuscitation but not LR

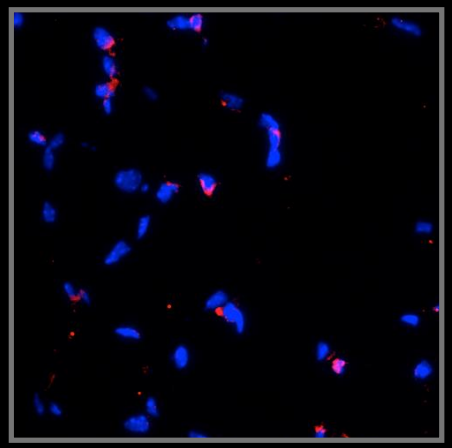
Sham



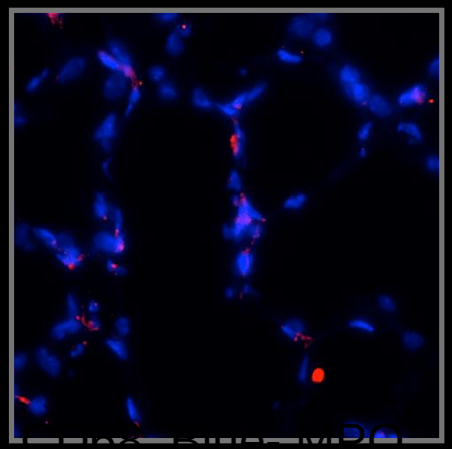
Shock



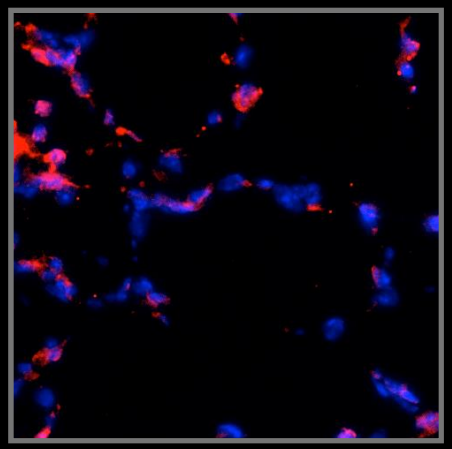
FFP



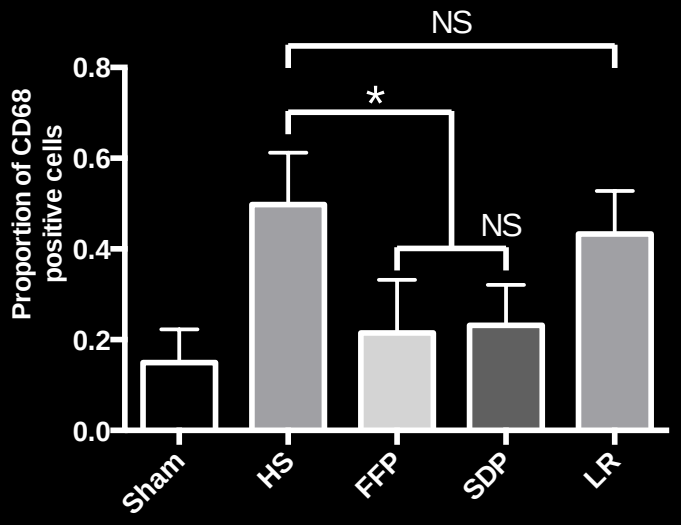
SDP



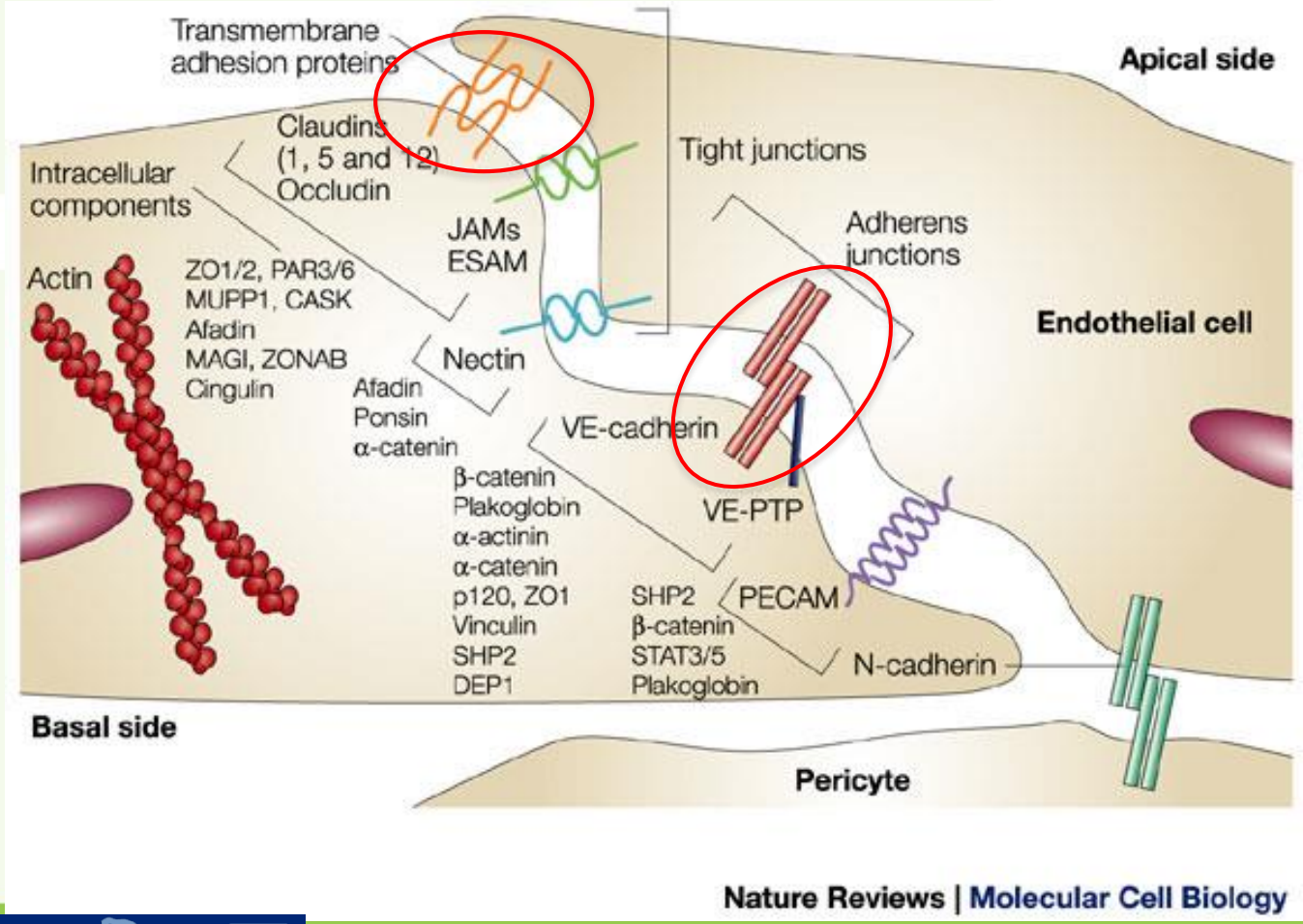
LR



CD68 Postive Cells

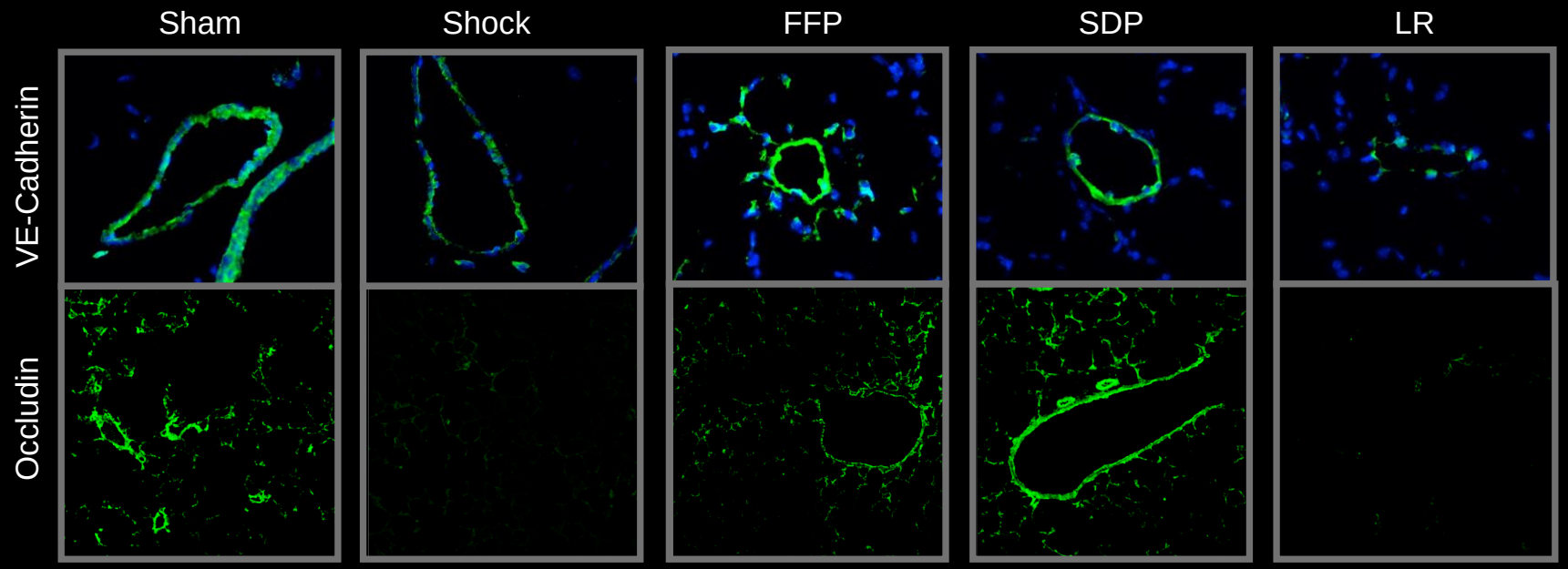


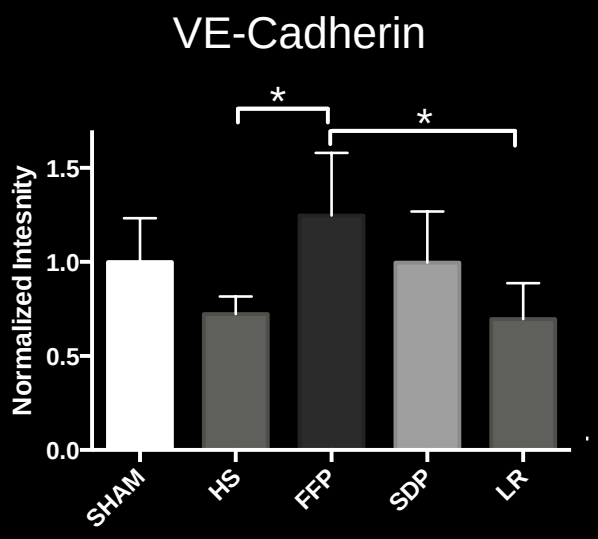
Overview of the endothelial cell junctions

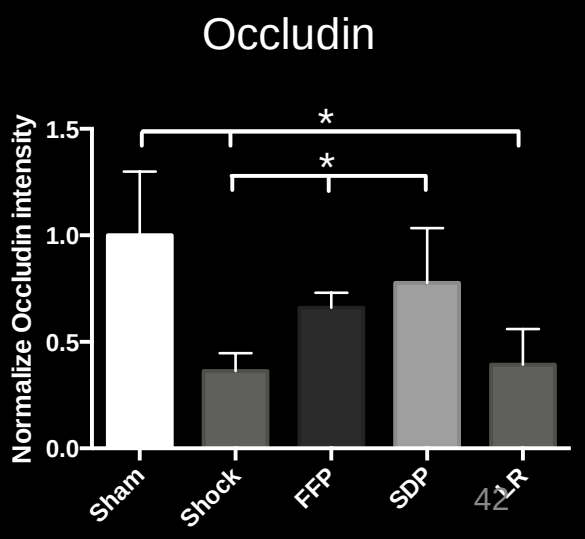


Dejana, E., Nature Reviews Molecular Cell Biology 5. 261-270

Tight and Adherens Junctions are Preserved in by FFP and SDP but not LR







Summary – Benefits of Plasma in Trauma

- Correction of coagulopathy of trauma
- Repletion of volume deficit
- Anti – Inflammatory
- Decreases vascular permeability
- Repairs the endothelium
- Decreases organ injury
- Superior to crystalloid

Dried Plasma Conclusions

- Logistically superior
- Functionally equivalent or superior to FFP
- Dried plasma can be pooled, pathogen reduced and stored for extended periods of time
- Dried plasma should be used in lieu of FFP in austere conditions

Thank you!