# The Protective Effects of Fresh Frozen Plasma (FFP) on Endothelial Function and Hemodynamic Stability are Time Dependent and Diminish Between Day 0 and Day 5 after Thaw

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# UTHSC-Houston and Memorial Hermann Hospital - TMC

# Epidemiology

Title

- 20 yo healthy male in a tire explosion
- Arrived with a SBP of 80, pulse 130, talking, weak DP pulse character
- CXR normal, pelvis with 10 cm diastasis and posterior elements disrupted
- Mult extremity fractures
- CT and then IR

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# Interventions and Resuscitation

- Operative
  - Embolize branch of right internal iliac
  - Ex fix pelvis and 2 extremities
  - Decompressve laparotomy and remove left eye and testicle
- Resuscitation over 2 days
  - RBC = 57
  - Plasma= 54
  - Platelets = 4 (6 packs) and only 16 liters of crystalloid
  - Cryo = 3 (10 packs)
  - Amicar

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# Globally, there are estimated to be over 5 million deaths per year due to injury.


Holder Y, Peden M, Krug E, Lund J, Gururaj G, Kobusignye O, eds. Injury Surveillance Guidelines. Geneva: World Health Organization and Atlanta, GA: US Department of Health and Human Services, CDC: 2001. Available at: Http://whqlibdoc.who.int/hq/2001/WHO_NMH_VIP_01.02.pdf. Accessed May 20,2008.

Approximately 10% of **all** global deaths are due to injury.

At a cost of over $518 billion annually.

**Butchart A, Harvey AP, Krug E, Meddings D, Peden M, Sminkey L. Preventing Injuries and Violence: A Guide for Ministries of Health. Geneva: World Health Organization; 2007. Available at http:/www.who.int/violence_injury_prevention/publications/injury_policy_planning/prevention_moh/en/. Accessed May 21, 2009.**

**Hofman K, Primack A, Keusch G, Hrynkow S. Addressing the growing burden of trauma and injury in low- and middle-income countries. Am J Pub Health 2005; 95: 13-17.**

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# Optimal Fluids for Resuscitation

Many groups have investigated the effects of fluid resuscitation in Hemorrhagic Shock and Trauma with the idea of improving outcome and preventing iatrogenic injury

- *McClelland RN, Shires GT, Baxter CR, Coln CD, Carrico CJ.* Balanced salt solution in the treatment of hemorrhagic shock. JAMA. 1967.
- ***FD Moore, Shires G.* Moderation. Anes Ana. 1968.**
- *Bickell WH, et al.* Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. NEJM. 1994.
- *Rhee et al.* Human neutrophil activation and increased adhesion by various resuscitation fluids. Crit Care Med. 2000.
- *Brandstrup B, et al.* Effects of IV fluid restriction on postop complications: a comparison of two perioperative fluid regimens. Annals of Surg, 2003.
- *NHLBI ARDS NET Clinical Trials Network; Wiedemann HP, et al*. Comparison of two fluid-management strategies in acute lung injury. NEJM 2006.
- *Cotton et. al.*, The Cellular, Metabolic and Systemic consequences of Aggressive Fluid Resuscitation Strategies. Shock, 2006.

# Serial changes in primary hemostasis after massive transfusion

**Surgery, 1985**

**Celestine Harrigan, Ph.D., Charles E. Lucas, M.D., Anna M. Ledgerwood, M.D., Daniel A. Walz, Ph.D., *and* Eberhard F. Mammen, M.D., *Detroit, Mich.***

- 18 patients, 28% mortality
- 21 units of blood, 1262 ml FFP (4:1)
- 19 liters of crystalloid
- No indication for prophylactic platelet transfusion unless medical bleeding
- No comparison groups

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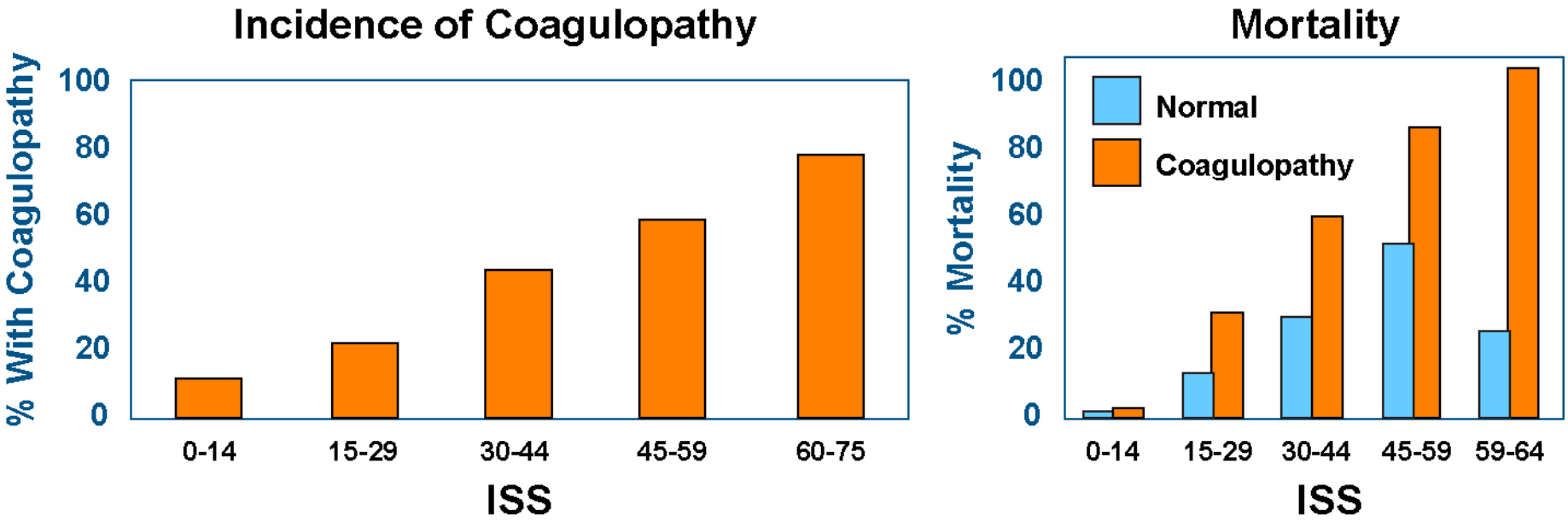
The Journal of TRAUMA® Injury, Infection, and Critical Care

*J Trauma*, 2003.

# Acute Traumatic Coagulopathy

*Karim Brohi, BSc, FRCS, FRCA, Jasmin Singh, MB, BS, BSc, Mischa Heron, MRCP, FFAEM, and Timothy Coats, MD, FRCS, FFAEM*




- Derangements in coagulation occur rapidly after trauma even after adjusting for ISS
- By the time of arrival at the ED, 1/3 of trauma patients had a coagulopathy associated with a poor outcome

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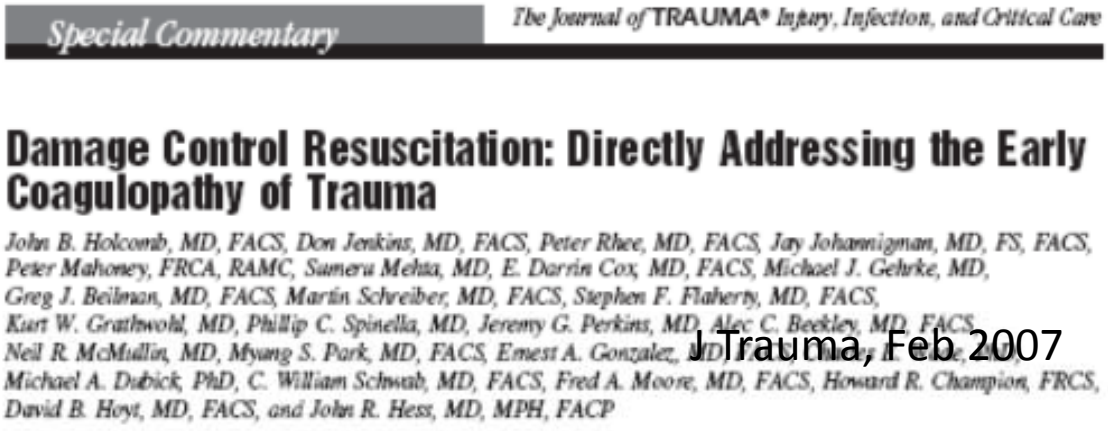
# Damage Control Resuscitation was developed to address the need for an optimal protocol to treat the lethal triad of trauma



Special Commentary

The Journal of TRAUMA® Injury, Infection, and Critical Care

**Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma**

*John B. Holcomb, MD, FACS, Don Jenkins, MD, FACS, Peter Rhee, MD, FACS, Jay Johannigman, MD, FS, FACS, Peter Mahoney, FRCA, RAMC, Sumeru Mehta, MD, E. Darrin Cox, MD, FACS, Michael J. Gehrke, MD, Greg J. Beilman, MD, FACS, Martin Schreiber, MD, FACS, Stephen F. Flaherty, MD, FACS, Kurt W. Grathwohl, MD, Phillip C. Spinella, MD, Jeremy G. Perkins, MD, Alec C. Beekley, MD, FACS, Neil R. McMullin, MD, Myung S. Park, MD, FACS, Ernest A. Gonzalez, MD, [illegible], Michael A. Dubick, PhD, C. William Schwab, MD, FACS, Fred A. Moore, MD, FACS, Howard R. Champion, FRCS, David B. Hoyt, MD, FACS, and John R. Hess, MD, MPH, FACP*

J Trauma, Feb 2007

- Lethal Triad: Hypothermia, acidosis and coagulopathy
- Damage control resuscitation addresses **diagnosis and treatment of the entire lethal triad** immediately upon admission

# Military Study:

*The Journal of* TRAUMA® *Injury, Infection, and Critical Care*

## The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

*Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD*

**Table 5** Odds Ratio Predicting Survival Using Multivariate Logistic Regression

| Variable | Odds Ratio (95% CI) | *p* Value |
|---|---|---|
| Plasma:RBC ratio | 8.6 (2.1–35) | 0.003 |
| AIS head/neck score | 0.76 (0.61–0.94) | 0.013 |
| AIS thorax score | 0.73 (0.57–0.92) | 0.009 |
| Systolic blood pressure | 1.0 (0.98–1.01) | 0.457 |
| Hemoglobin | 1.1 (0.91–1.2) | 0.501 |
| Base deficit | 0.89 (0.84–0.95) | <0.001 |

AIS, Abbreviated Injury Scale.

Oct, 2007;63

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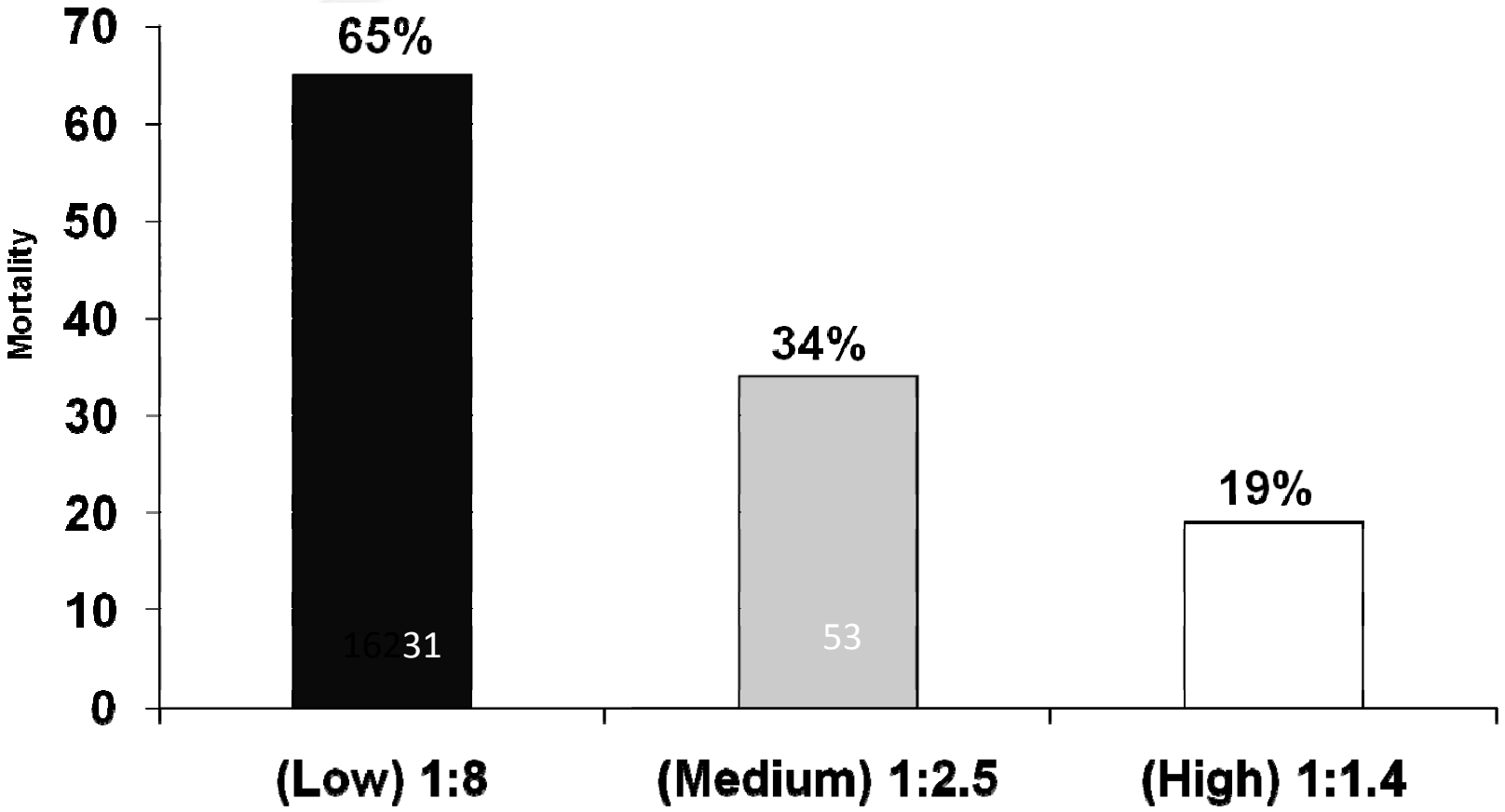
# Increased plasma:RBC ratio results in decreased mortality




The ratio of blood products transfused affects mortality in patients (252) receiving massive transfusions at a combat support hospital. *Borgman MA, et.* J Trauma, 2007.

# Military Study:

## Acute Traumatic Coagulopathy in Combat Casualty Care

S Niles, D McLaughlin, J Perkins, CE Wade, Y Li, JB Holcomb

*The Journal of* TRAUMA® *Injury, Infection, and Critical Care*

### Increased Mortality Associated With the Early Coagulopathy of Trauma in Combat Casualties

*Sarah E. Niles, MD, MPH, Daniel F. McLaughlin, MD, Jeremy G. Perkins, MD, Charles E. Wade, PhD, Yuanzhang Li, PhD, Philip C. Spinella, MD, and John B. Holcomb, MD*

*J Trauma*, 2008

- Retrospective cohort study on 391 patients who received a transfusion
- Patient outcomes of ISS and mortality were assessed.
- The prevalence of acute coagulopathy in this cohort was 38% and increased with ISS.

# Initial Studies with DCR:

- Majority of clinical studies (civilian and military) show administration of higher FFP to RBC ratios in MT patients results in a survival benefit.
  There are have been a few civilian studies that question this practice this concept
  - Kashuk et al . J Trauma 2008
  - Scalea et al. Annals of Surgery 2008
  - Snyder et al, J Trauma 2009
- The traditional rationale for the use of FFP in MT patients has primarily focused upon correcting disturbances in coagulation

# The Relationship of Blood Product Ratio to Mortality: Survival Benefit or Survival Bias?

*Christopher W. Snyder, MD, Jordan A. Weinberg, MD, Gerald McGwin, Jr., MS, PhD, Sherry M. Melton, MD, Richard L. George, MD, Donald A. Reiff, MD, James M. Cross, MD, Jennifer Hubbard-Brown, BS, Loring W. Rue, III, MD, and Jeffrey D. Kerby, MD, PhD*

J Trauma 2009

- Very important paper, not only for this topic, but all uncontrolled studies
- "They lived long enough to receive a treatment, not that the treatment caused them to live longer"
- However at UAB, they don't give plasma early
  - Median of 18 min vs 93 (RBC vs plasma administration)

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*Annals of Surg*, 2008

# Civilian Study:

## Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

*John B. Holcomb, MD,* Charles E. Wade, PhD,* Joel E. Michalek, PhD,† Gary B. Chisholm, PhD,† Lee Ann Zarzabal, MS,† Martin A. Schreiber, MD,‡ Ernest A. Gonzalez, MD,§ Gregory J. Pomper, MD,¶ Jeremy G. Perkins, MD,‖ Phillip C. Spinella, MD,** Kari L. Williams, RN,* and Myung S. Park, MD**

- 16 Multicenter  Retrospective Massive Transfusion Study
- Increased Plasma and Platelet to RBC Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

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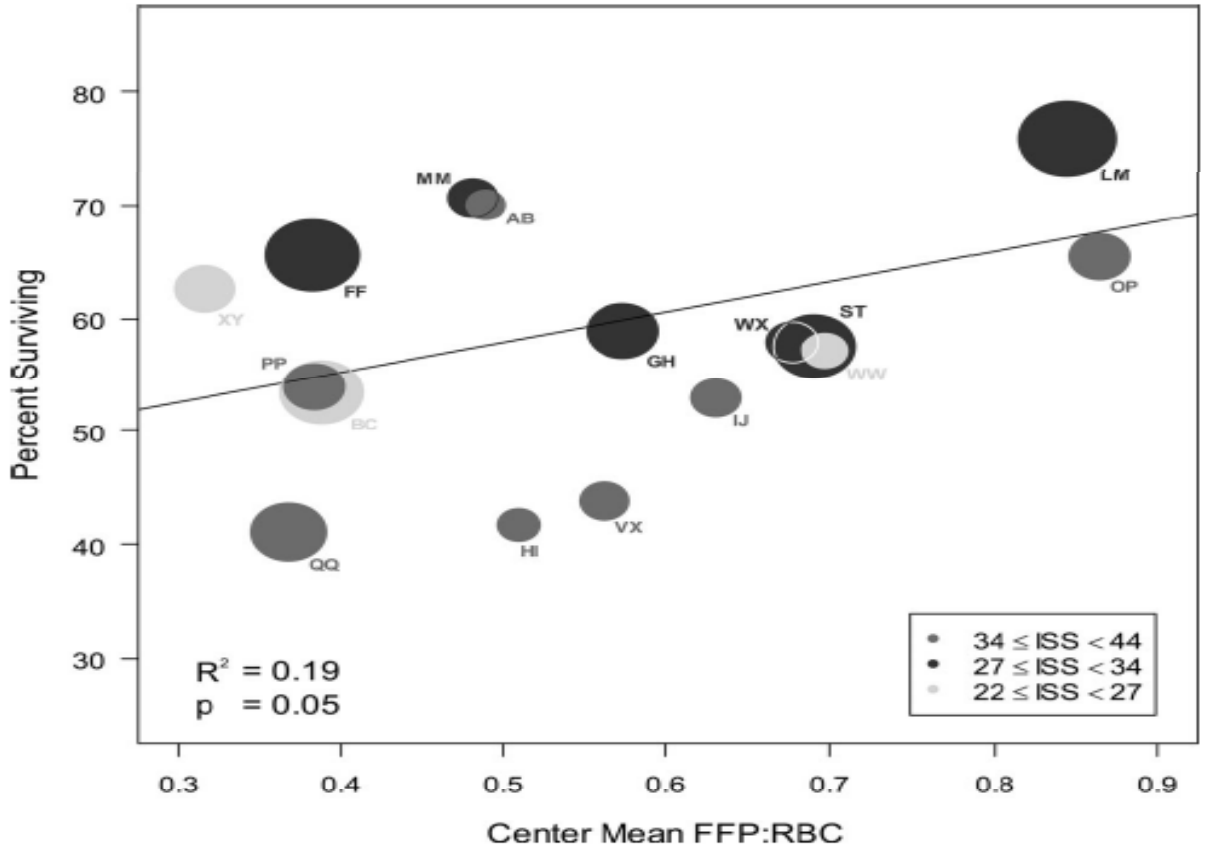
# Mortality vs. mean FFP/RBC ratio by Center and Variability




Holcomb et al., *Annals of Surg,*2008

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# High Plasma and Platelet to RBC ratio (>1:2) is associated with increased survival

| | High Plasma (%) | | Low Plasma (%) | | |
|---|---|---|---|---|---|
| | High Platelets (n = 151) | Low Platelets (n = 101) | High Platelets (n = 83) | Low Platelets (n = 83) | *P* |
| Survival (%) | 71 | 52 | 66 | 41 | <0.001 |
| Survival at 6 h | 98 | 86 | 83 | 58 | <0.001 |
| Survival at 24 h | 87 | 75 | 77 | 50 | <0.001 |
| Survival at 30 d | 73 | 54 | 68 | 43 | <0.001 |
| Median time-to-death, (hours) | 35 | 18 | 6 | 4 | <0.001 |
| Cause of death | | | | | |
| Truncal hemorrhage (%) | 10 | 25 | 22 | 44 | <0.001 |
| Head injury | 13 | 15 | 6 | 14 | 0.3 |
| MOF | 5 | 7 | 6 | 3 | 0.45 |
| Airway | 0 | 1 | 2 | 2 | 0.24 |
| Other | 3 | 6 | 4 | 4 | 0.85 |
| Clinical outcomes | | | | | |
| Hospital-free days | 6 ± 8 | 3 ± 6 | 5 ± 8 | 3 ± 7 | <0.001 |
| ICU-free days | 5 ± 7 | 3 ± 6 | 6 ± 7 | 4 ± 7 | <0.001 |
| Ventilator-free days | 6 ± 8 | 2 ± 5 | 7 ± 8 | 4 ± 7 | <0.001 |

High plasma- or platelet-to-RBC ratio ≥1:2. Low plasma- or platelet-to-RBC ratio <1:2.

Holcomb et al., *Annals of Surg,* 2008

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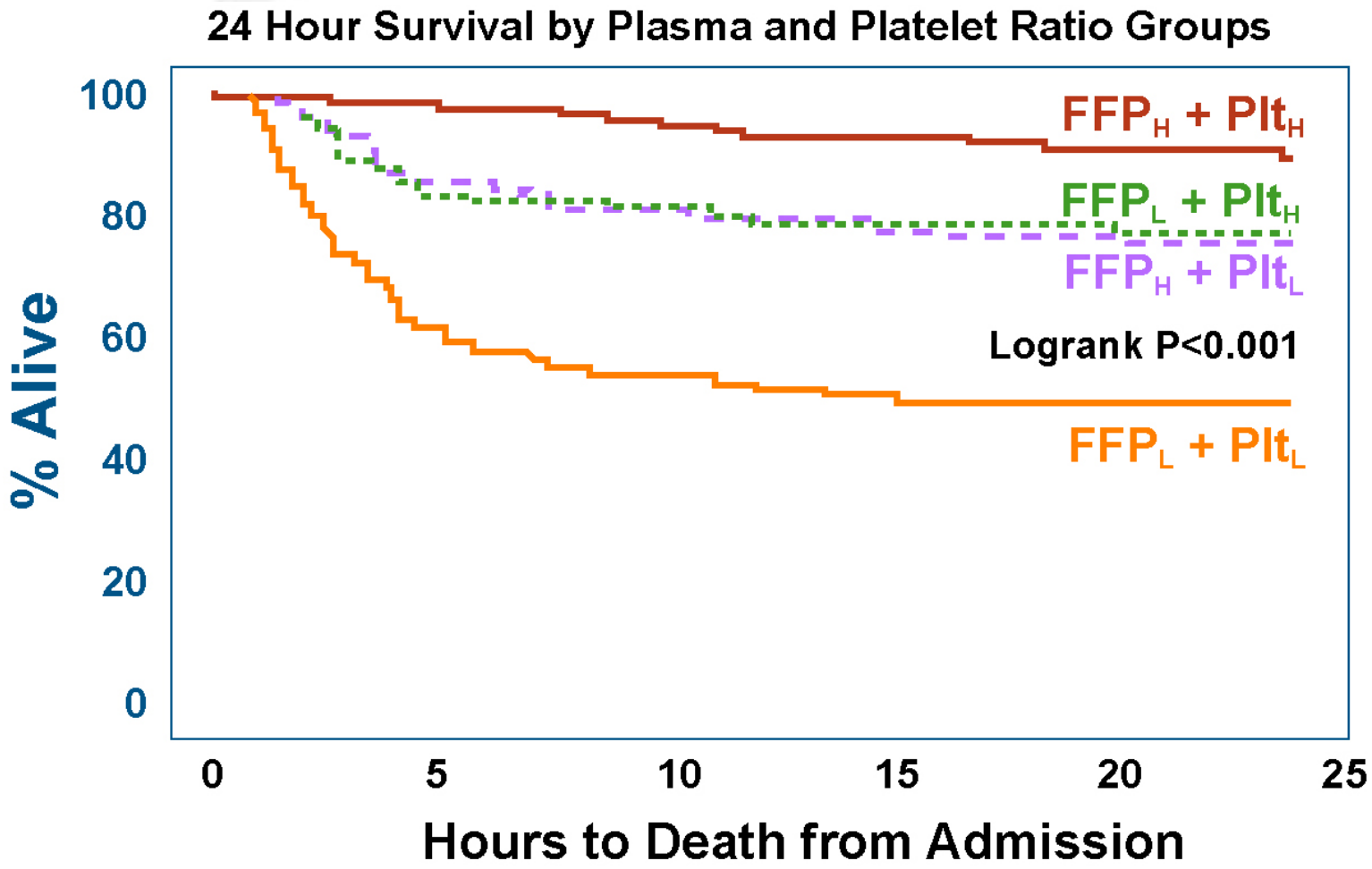
# 24 hour Kaplan-Meier




Holcomb et al., *Annals of Surg,* 2008

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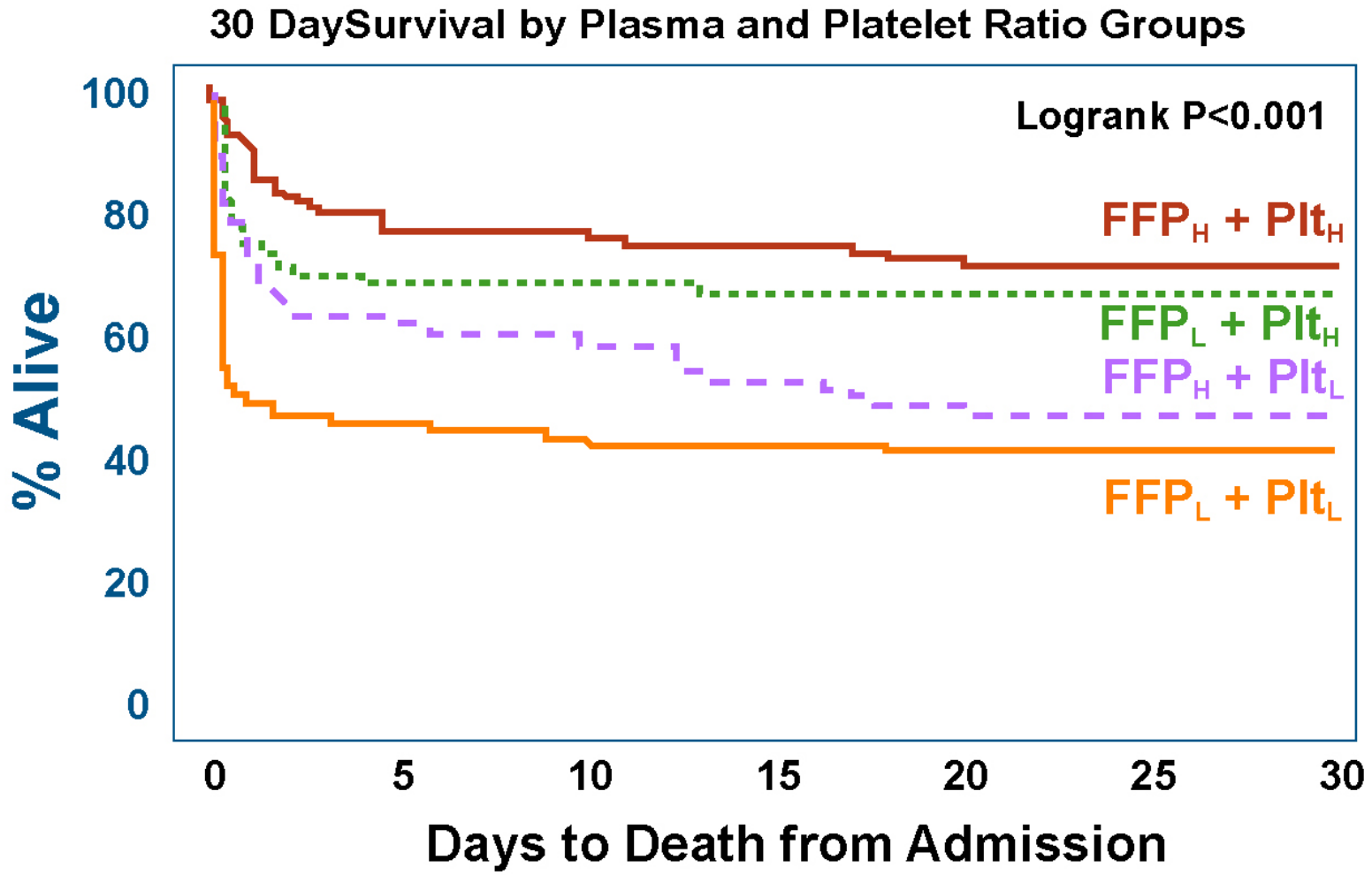
# 30 day Kaplan-Meier




Holcomb et al., *Annals of Surg,* 2008

# Another Civilian Study:

*The Journal of* TRAUMA® *Injury, Infection, and Critical Care*

## Impact of Plasma Transfusion in Massively Transfused Trauma Patients

*Pedro G. R. Teixeira, MD, Kenji Inaba, MD, MS, Ira Shulman, MD, Ali Salim, MD, Demetrios Demetriades, MD, PhD, Carlos Brown, MD, Timothy Browder, MD, Donald Green, MD, and Peter Rhee, MD, MPH*

**Table 2** Predictors of Mortality After Stepwise Logistic Regression

| Step | Variable Selected | $R^2$ | Adjusted Odds Ratio (95% CI) | *p* |
|---|---|---|---|---|
| 1 | GCS ≤8 | 0.25 | 6.8 (3.3–14.0) | <0.001 |
| 2 | FFP:PRBC ratio | 0.11 | 0.02 (0.01–0.07) | <0.001 |
| 3 | Uncrossmatched blood transfusion | 0.05 | 3.1 (1.2–7.8) | 0.02 |
| 4 | Abdominal AIS ≥3 | 0.02 | 2.5 (1.3–4.5) | <0.001 |
| 5 | Age ≥55 | 0.02 | 2.0 (1.4–2.8) | <0.001 |
| 6 | SBP <90 | 0.01 | 2.2 (1.2–4.1) | 0.01 |
| 7 | Vascular injury | 0.01 | 1.8 (1.1–3.2) | 0.03 |

SBP, systolic blood pressure; AIS, Abbreviated Injury Severity Score.

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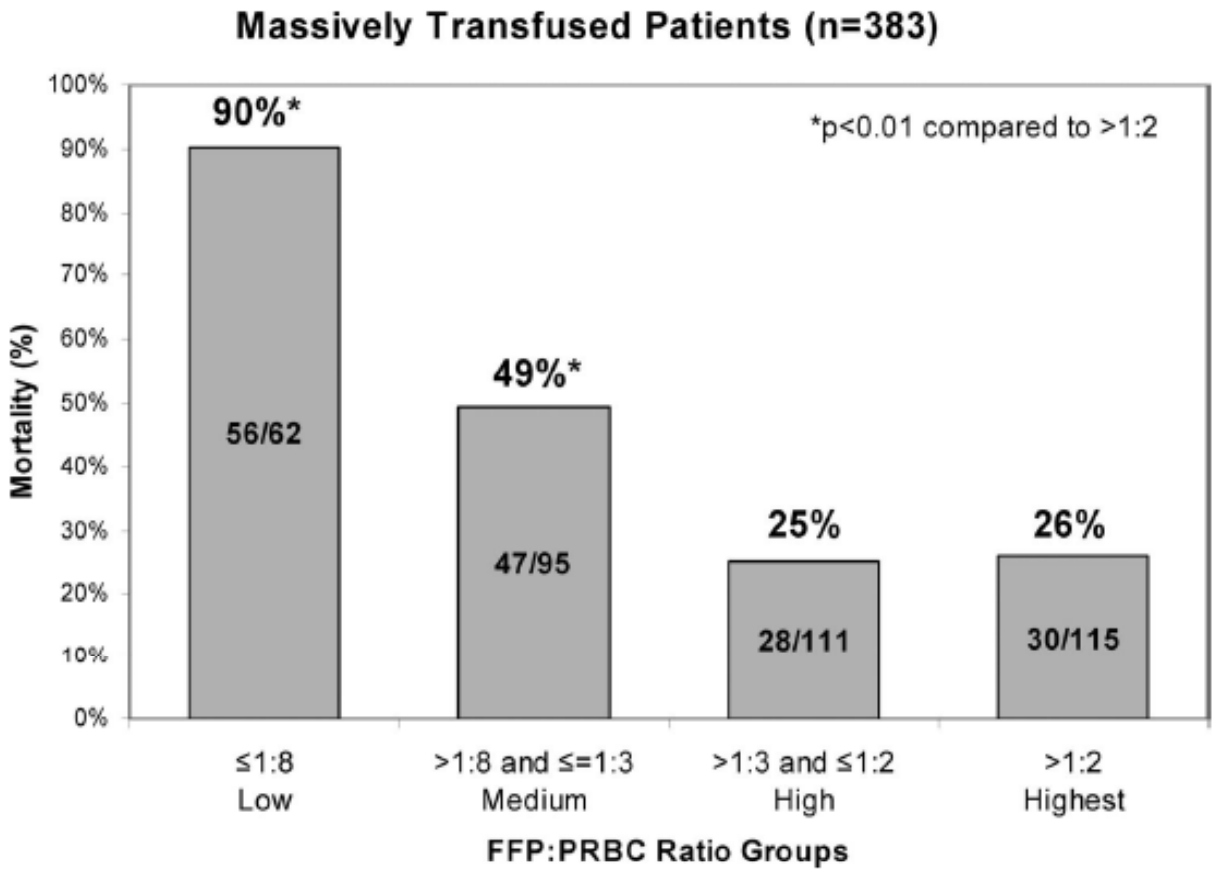
# There is a mortality decrease with higher FFP: RBC ratios in MT patients




**4.** *Mortality decrease with higher FFP:PRBC ratios. FFP, fresh-frozen plasma; PRBC, packed red blood cells.*

Teixeiria et al., *J. Trauma* 2009

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# The Principles of Damage Control Resuscitation

- Used in massively bleeding patients
- Primarily use blood and blood products
  - 1:1;1 (Plasma:RBCs:Platelets)
- Minimize crystalloid use
- Pay close attention to reversing and preventing coagulopathy

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# The Mechanism of Action of FFP

Very little is known about how plasma resuscitation “works” (if it does)

What do those 1000 proteins in each bag of plasma really do?

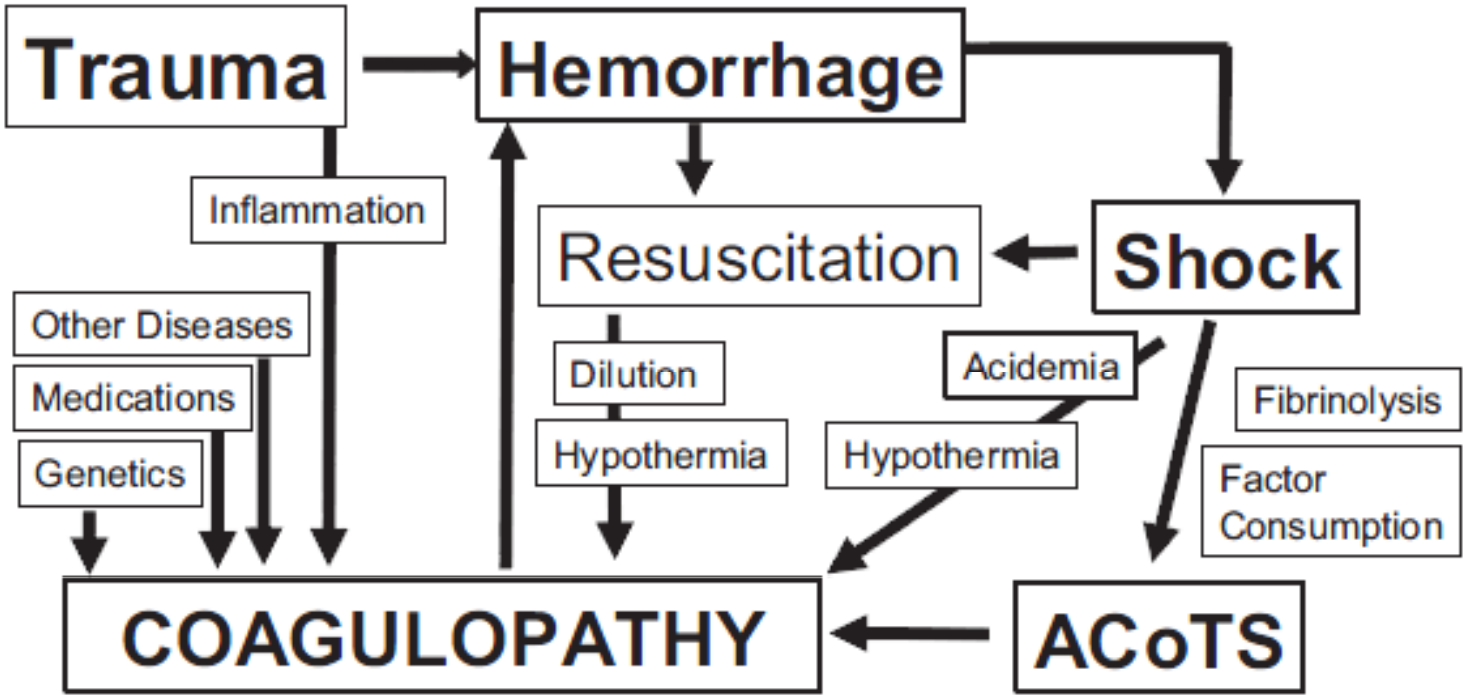
Review Article

The Journal of TRAUMA® Injury, Infection, and Critical Care

# The Coagulopathy of Trauma: A Review of Mechanisms

*John R. Hess, MD, MPH, FACP, FAAAS, Karim Brohi, MD, Richard P. Dutton, MD, MBA, Carl J. Hauser, MD, FACS, FCCM, John B. Holcomb, MD, FACS, Yoram Kluger, MD, Kevin Mackway-Jones, MD, FRCP, FRCS, FCEM, Michael J. Parr, MB, BS, FRCP, FRCA, FANZCA, FJFICM, Sandro B. Rizoli, MD, PhD, FRCSC, Tetsuo Yukioka, MD, David B. Hoyt, MD, FACS, and Bertil Bouillon, MD*

*J Trauma*, Oct 2008



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# Background: Use and Storage of FFP

- Recent data on FFP in HS has initiated patterns of change in blood product many trauma centers around the country
- AABB practice allows FFP to be thawed and kept up to 5 days at between 1-6 degrees C (in the US)
- This practice is based upon the presence of adequate coagulation factor activity necessary for hemostasis.

- **Advantages of storage are:**
  -it can be present upon arrival in the in the ED
  -can be used as a primary resuscitative fluid
  -Decreases waste by 60-70%

- **basic scientist comments**


- *Malone DL, Hess JR, Fingerhut A. Comparison of practices around the globe and suggestion for a massive transfusion protocol. J Trauma, 2006.*
- *Armand R, Hess JR. Treating coagulopathy in trauma patients. Transfus Med Rev 2003.*

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# Current practice has focused upon a few key variables that influence post-thaw quality of FFP

The storage lesion has been studied extensively for RBCs and less so in platelets. Very little has been investigated in the area of plasma storage.

## MAJOR POINT for Plasma

- **age of storage after thawing**

•Variation in Clotting Factor Activity

• Donor variability (ie. vWF and FVIII between ABO blood groups )

•Type and strength of anticoagulant used for collection

•Length of time and temperature whole blood or plasma has been stored prior to separation

•Whether Plasma is leukocyte depleted

•Pathogens- Bacterial or Viral Contamination

•Whether plasma is from male or female donors (FXII and FVII cold activation) and TRALI

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# In our studies we asked 2 very basic questions about FFP

1) Are the beneficial effects of FFP seen clinically solely due to modulation of the derangements seen in coagulation or could they be due to stabilizing effects on the vascular endothelium?

2)Does the age of FFP after thaw affect these beneficial effects ? The storage lesion has been well described for RBCs but not FFP

There are no published studies correlating the age of plasma and clinical outcomes


# Effects of FFP and Storage on Endothelial Permeability and Survival

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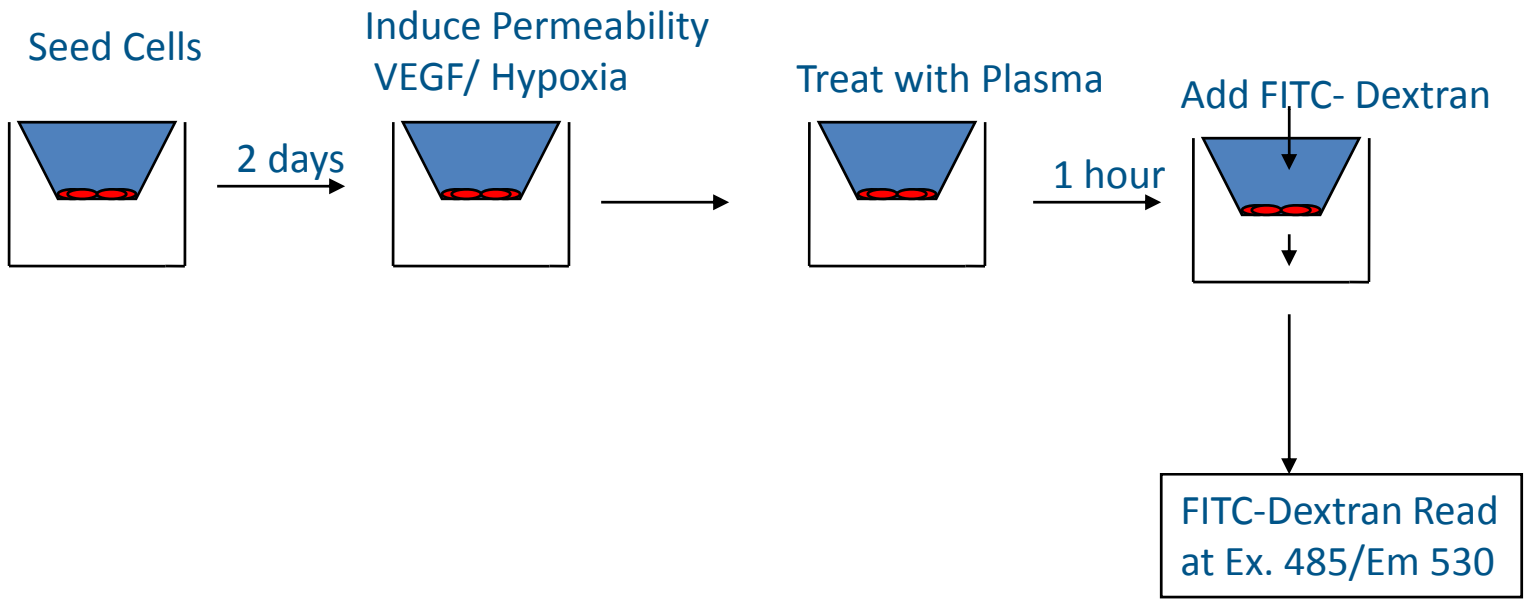
# Assay for *In Vitro* Endothelial Permeability



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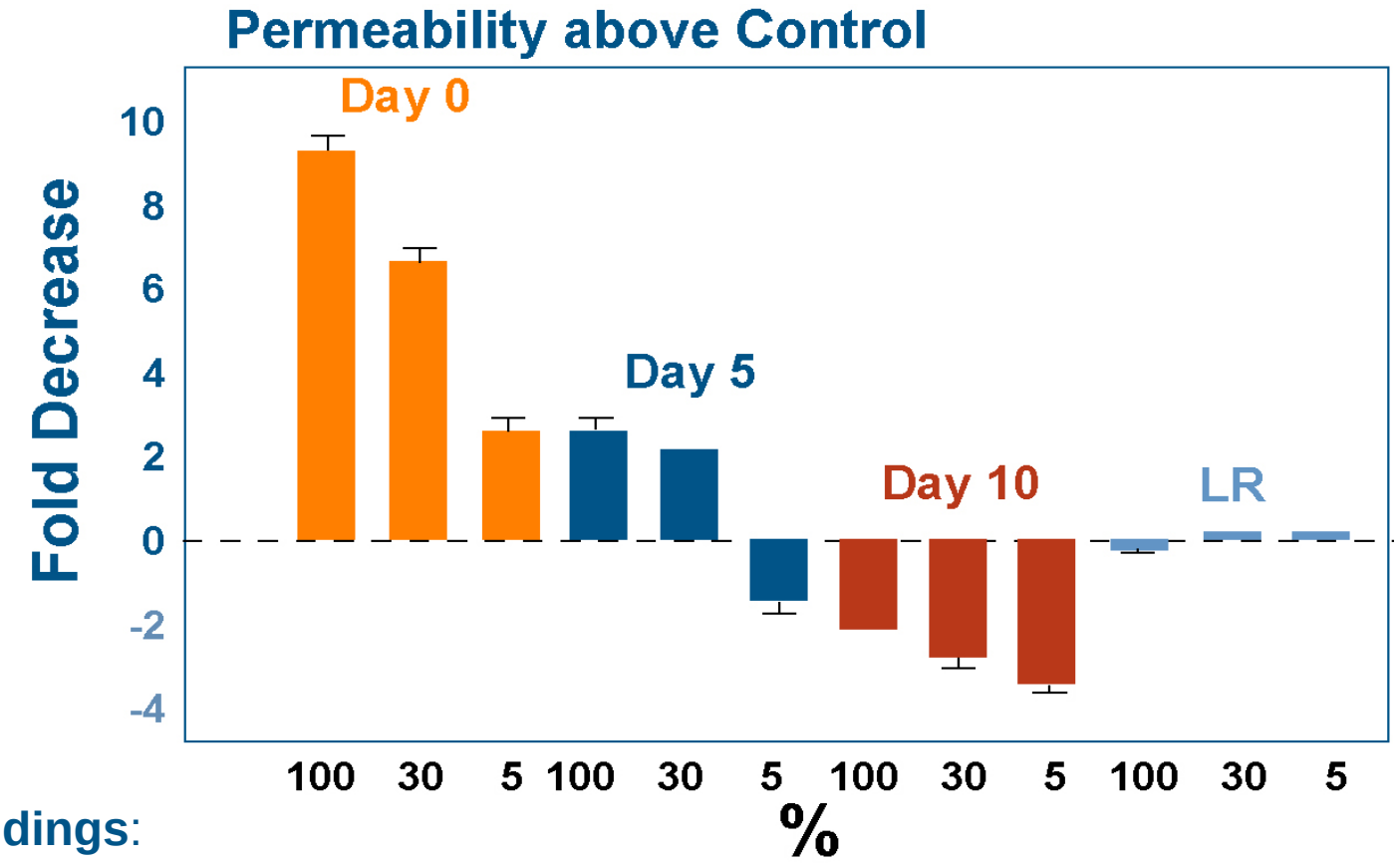
# FFP but not LR inhibits endothelial permeability: Effect diminishes by Day 5 after thaw




**Findings**:

1. Plasma is Protective against EC permeability induced by Hypoxia
2. LR has no protective effects on EC permeability
3. The protective effects of plasma diminish with storage time

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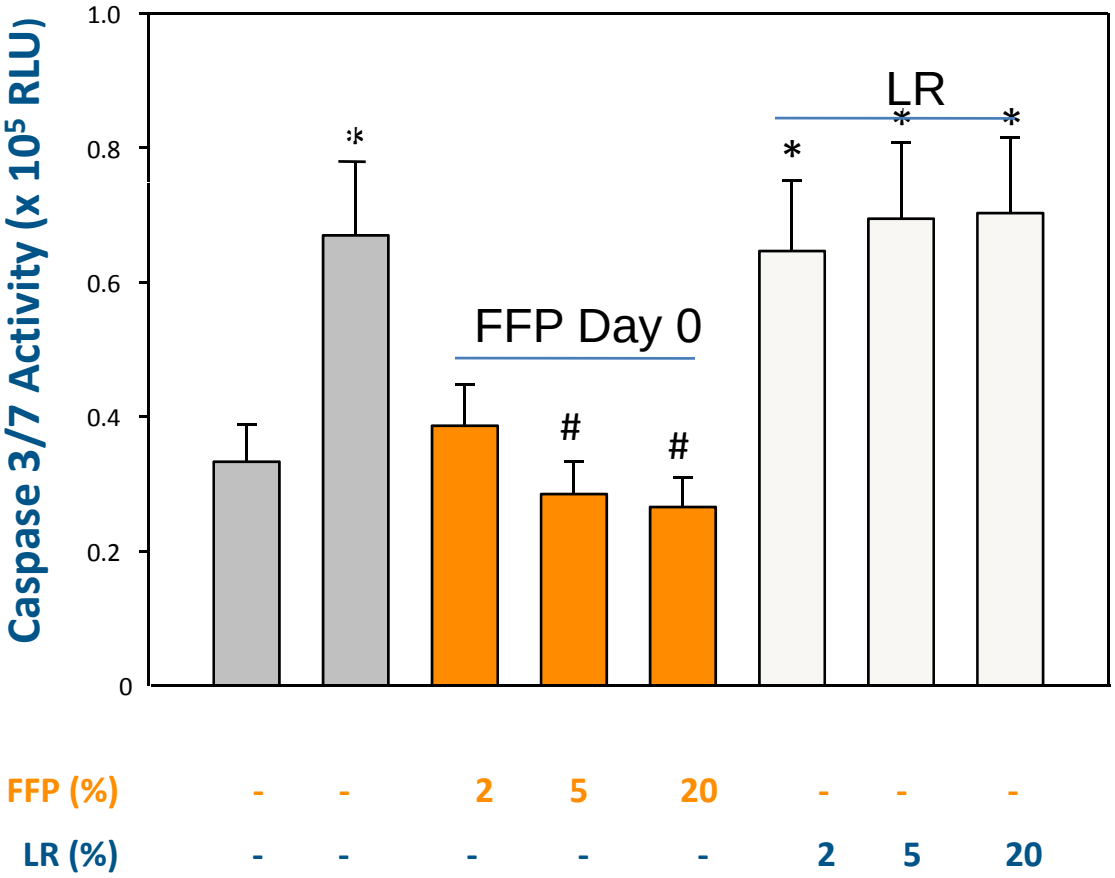
# FFP Protects Endothelial Cells from Death by Apoptosis vs LR



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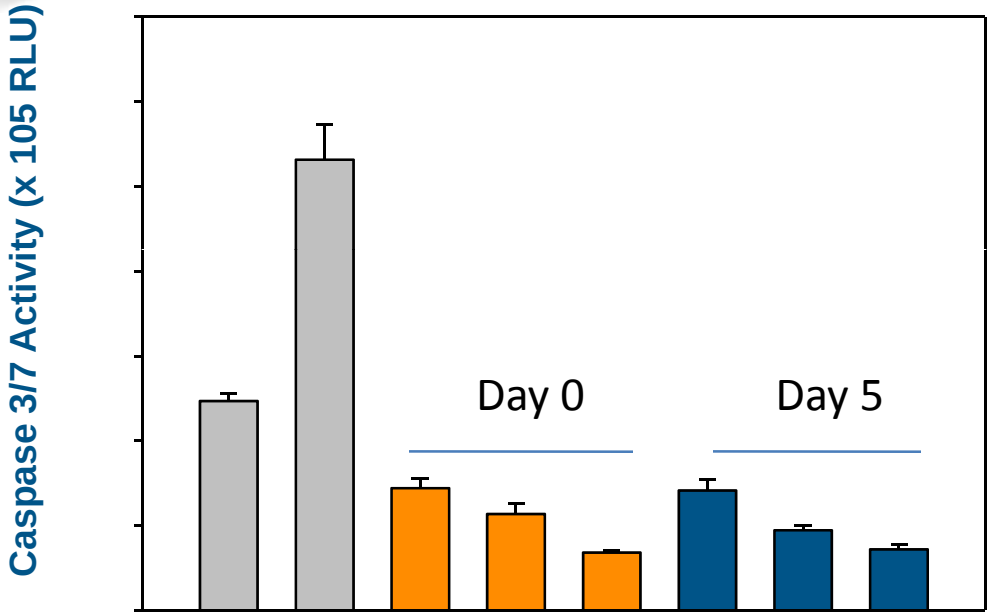
# Day 0 and day 5 FFP are equally protective on endothelial cell death




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| FFP, Day 0 (%) | - | - | 2 | 5 | 20 | - | - | - |
| FFP, Day 5 (%) | - | - | 2 | 5 | 20 | - | - | - |

- * : $p$ <0.05 compared to group 1
- # : $p$ <0.01 compared to group 2

# Effects of FFP and Storage on Coagulation

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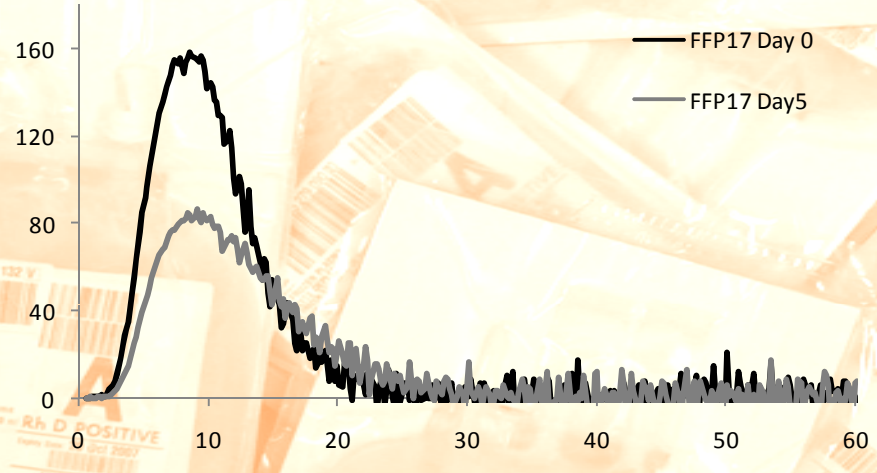
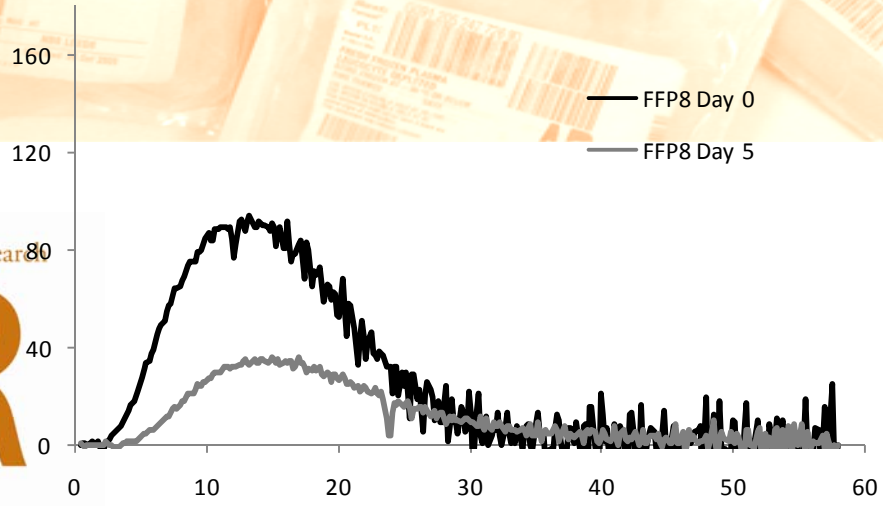
# Coagulation factor Changes between Day 0 and Day 5 FFP

| Analyte | Day 0 (n=9) | Day 5 (n=9) | % Change | P-value |
|---|---|---|---|---|
| PT (sec) | 11.0 (0.6) | 13.4 (0.7) | 20.7 | <0.001 |
| APTT (sec) | 36.6 (4.1) | 41.3 (5.9) | 12.8 | <0.001 |
| Fibrinogen (mg/dL) | 298 (61) | 292 (58) | - | NS |
| Factor II (%) | 99.9 (7.3) | 92.1 (5.9) | 7.8 | 0.002 |
| Factor V (%) | 77.9 (18.8) | 51.9 (17.4) | 33.4 | <0.001 |
| Factor VII (%) | 102.5 (20.7) | 82.1 (15.5) | 19.9 | <0.001 |
| Factor VIII (%) | 79.2 (17.6) | 54.9 (16) | 30.7 | <0.001 |
| von Willebrand factor: Ag (%) | 118.6 (55.7) | 101.4 (55.2) | 14.5 | 0.05 |
| von Willebrand factor: activity (%) | 89.1 (25.8) | 65.7 (30.9) | 26.3 | 0.006 |
| Factor IX (%) | 116.1 (13.2) | 107.1 (11.2) | 7.8 | <0.001 |
| Factor X (%) | 97.7 (10) | 94.0 (9.0) | - | NS |
| Factor XI (%) | 98.3 (16.3) | 95 (16) | 3.4 | 0.001 |
| Factor XII (%) | 108.9 (24.7) | 106.3 (24.5) | 2.4 | 0.03 |
| Factor XIII (%) | 133.6 (34.6) | 126.5 (32.4) | 5.3 | 0.003 |
| Antithrombin (%) | 97.2 (6.6) | 96.8 (6.3) | - | NS |
| Protein C (%) | 110.0 (20.4) | 112.5 (20.9) | - | NS |
| Protein S (%) | 84.1 (13.4) | 56.9 (23) | 32.3 | 0.004 |
| Free Protein S (%) | 82.8 (10.6) | 82.0 (11.1) | - | NS |
| Plasminogen (%) | 97 (10.3) | 97.1 (10.4) | - | NS |
| Plasmin inhibitor (%) | 104.8 (6.8) | 103.3 (7.9) | - | NS |
| DD (ng/mL) | 214.7 (115.5) | 219.8 (105.1) | - | NS |

# Thrombin Generation Capacity is Diminished in Day 5 FFP

## CAT Assay

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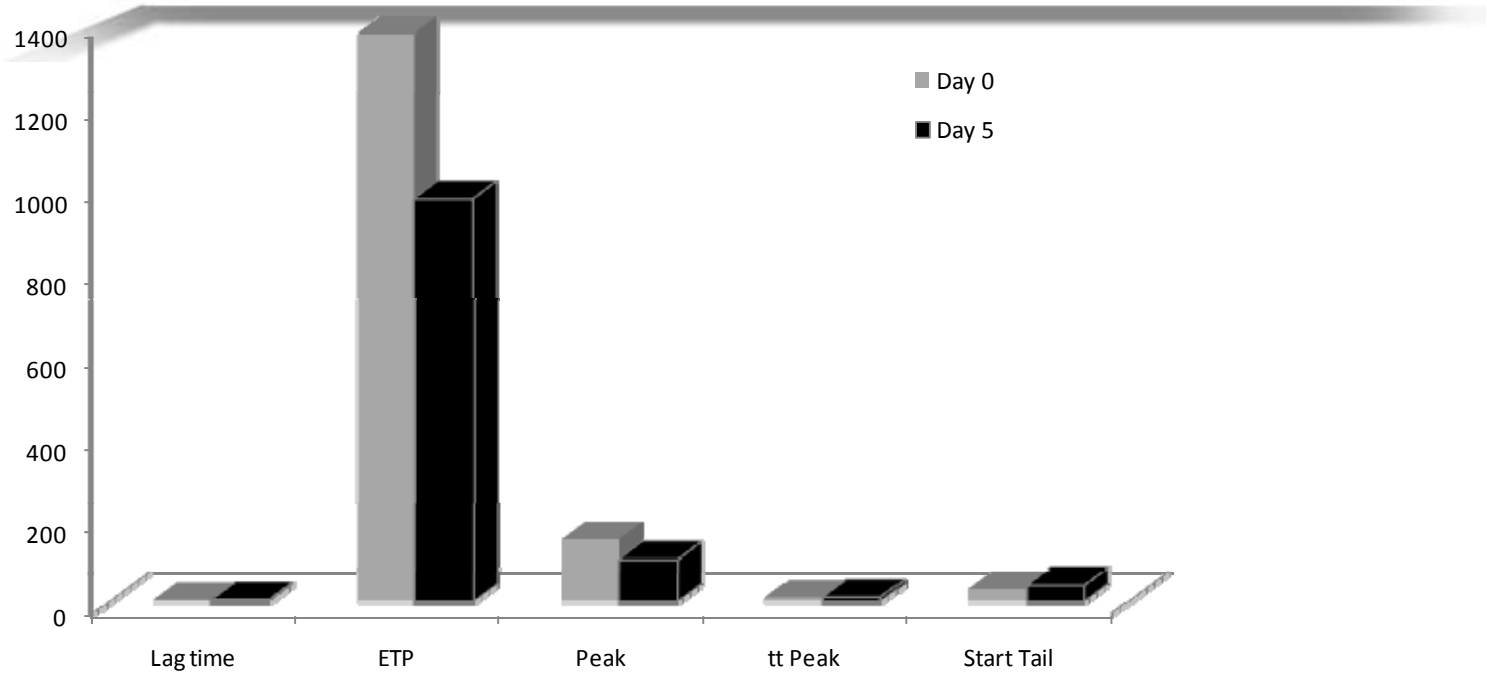
# Measures of Thrombin Generation are altered in Day 5 FFP




| Measures | Day 0 | Day 5 | p-value |
|---|---|---|---|
| Lag time (min) | 3.7 (2.9-6.0) | 4.5 (1.7-7.7) | <0.001 |
| ETP (nM thrombin*min) | 1377 (984-1751) | 972 (660-1614) | <0.001 |
| Peak thrombin (nM) | 149 (87-303) | 96 (34-225) | <0.0001 |
| Time to peak (min) | 9.2 (5.5-13.3) | 10.3 (5.4-14.8) | 0.003 |
| Start tail (min) | 30.8 (20-43) | 39.9 (19.3-58) | <0.001 |

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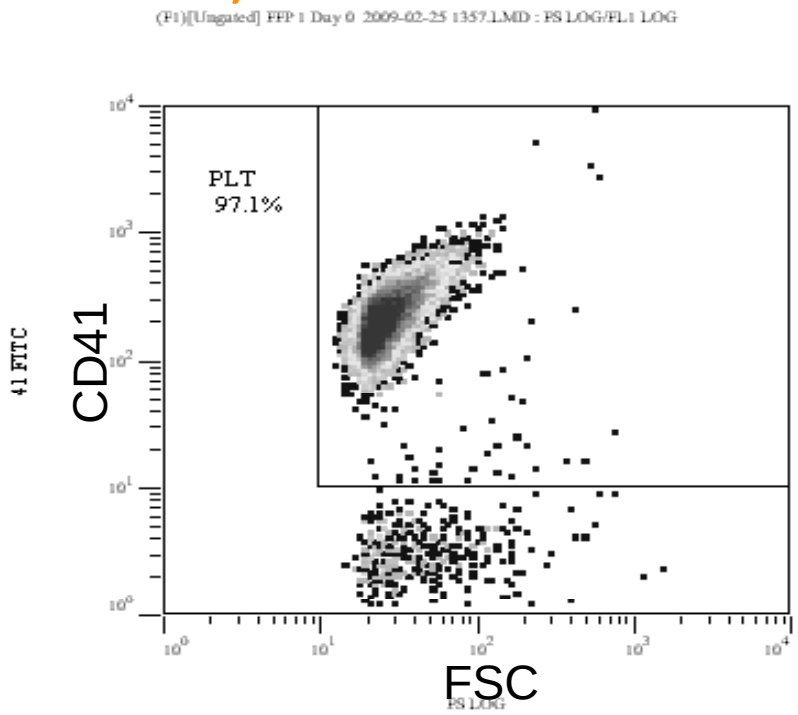
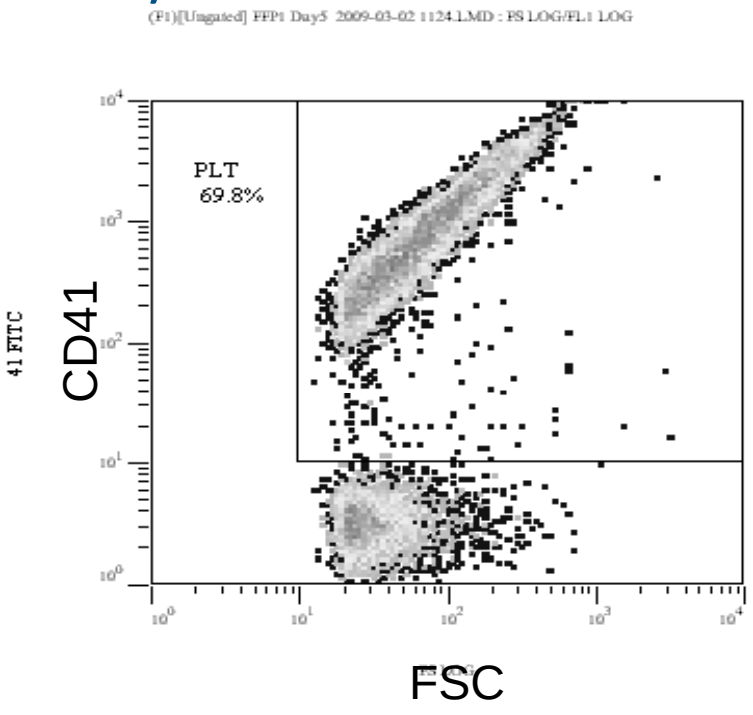
# Platelet activation occurs in FFP stored at 4ºC between Days 0 and 5

## Day 0




## Day 5




Preparations of FFP contain platelets which can vary from donor to donor between 1500/ul and 72,0000/ul

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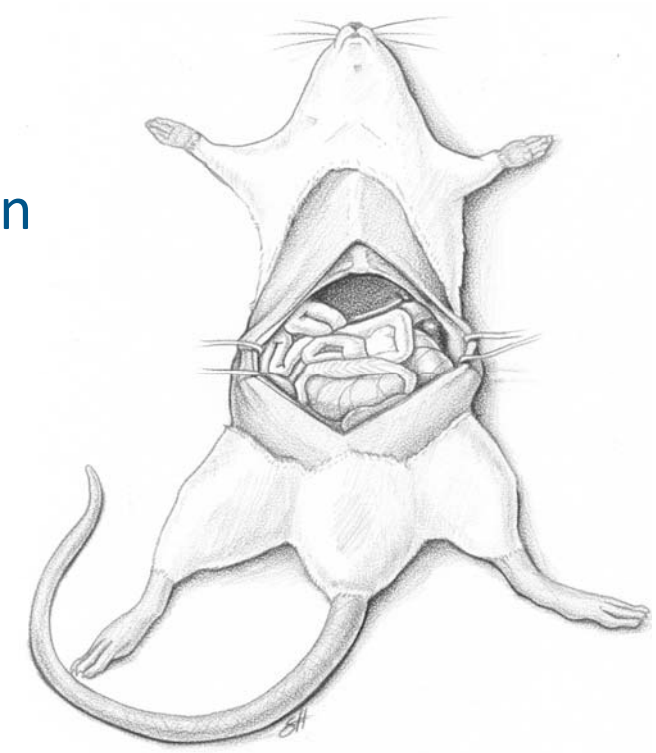
# Rat Hemorrhagic Shock Model

- **Acute Preparation**
- Intubation/Surgery under Isoflurane anesthesia
- Tygon catheters introduced in femoral artery (BP, HR) and jugular vein (blood withdrawal)
- Baseline measurements
- Hemorrhagic shock 2 ml/kg over 10 min



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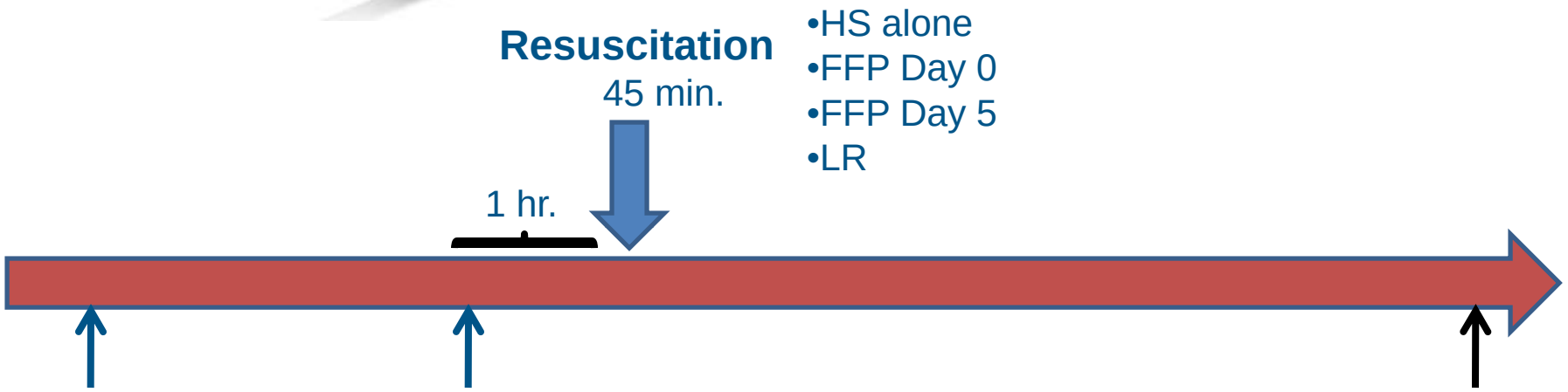
# Experimental Design for *In Vivo* HS Rat Model




BS = Blood Samples Taken at 0, 1,2,4,and 6 hours

HS = Hemorrhagic Shock

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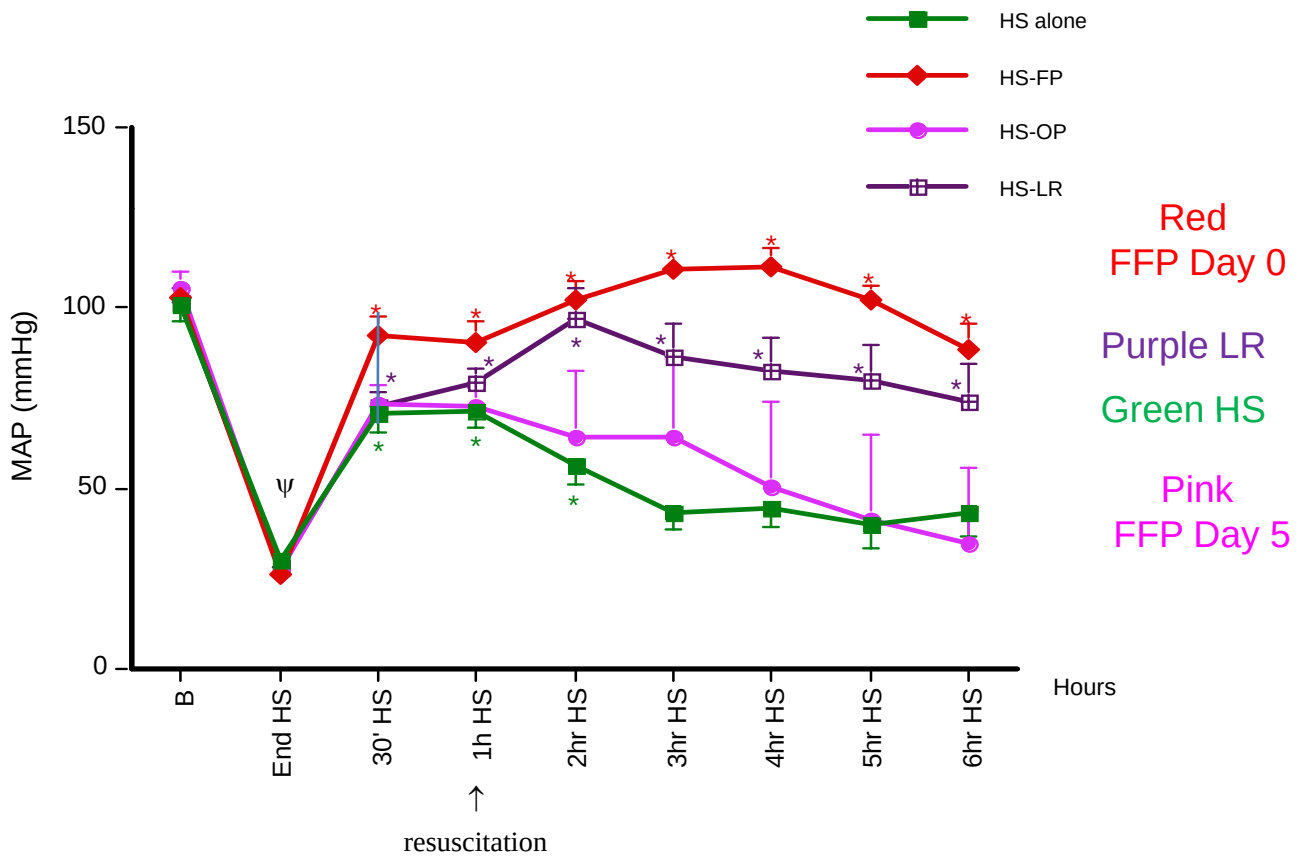
# Day 0 FFP is superior to day 5 FFP in restoring MAP after HS *In Vivo*




Red
FFP Day 0

Purple LR

Green HS

Pink
FFP Day 5

ψ $p < 0.05$ end HS vs B

* $p < 0.05$ HS/Resuscitation vs end HS

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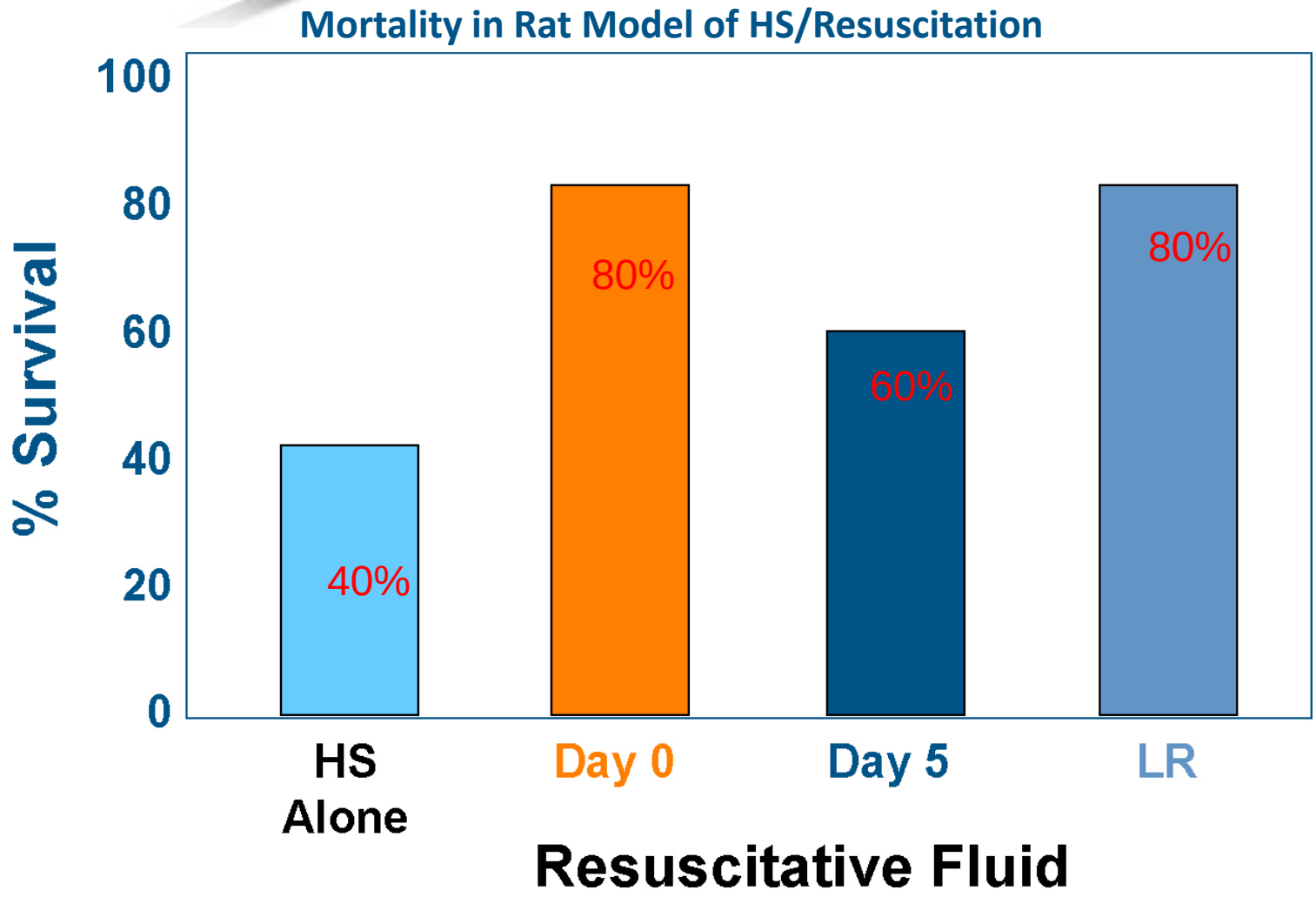
# Mortality in Day 0 FFP and LR resuscitated rats is lower than Day 5 FFP rats



# Resuscitation with FFP diminishes Lung Injury after Hemorrhagic Shock

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# Histopathology of Normal Sham HS Rat Lungs

## Normal Sham HS Rat Lungs

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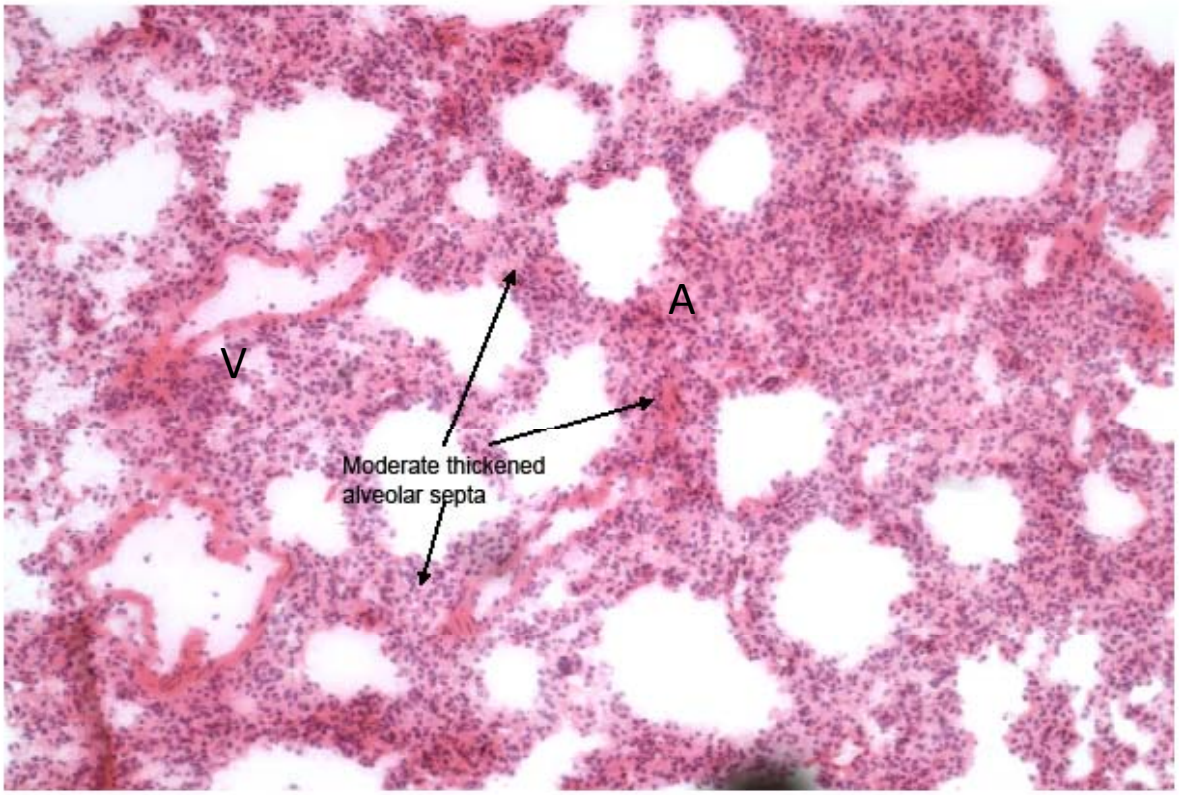
# Hemorrhagic Shock Alone




Finding: Thickened Alveolar Septae

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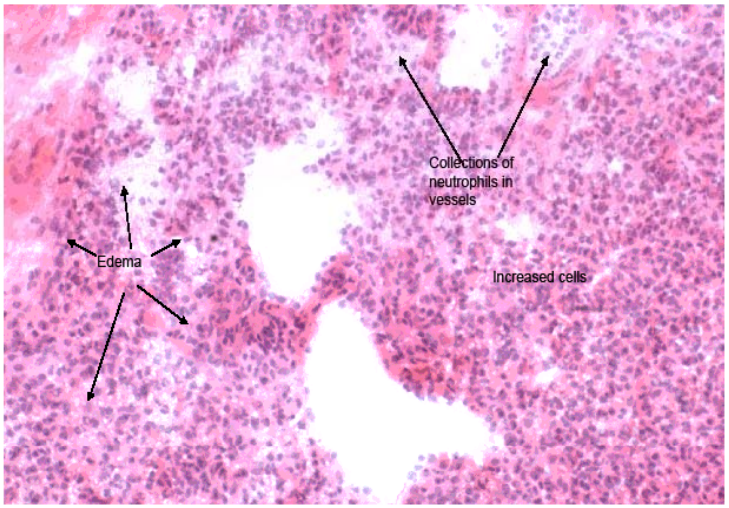
# Hemorrhagic Shock + LR

LR 4X


LR 20 X




Finding: Thickened Alveolar Septae and neutrophil infiltrates

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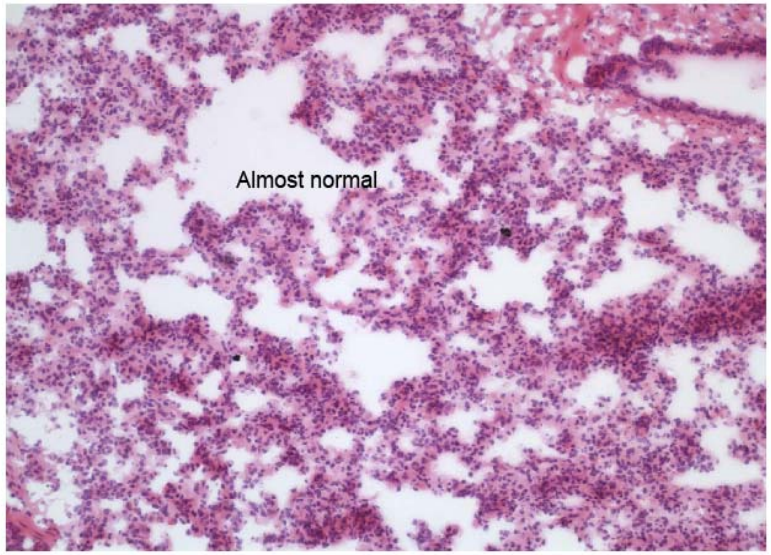
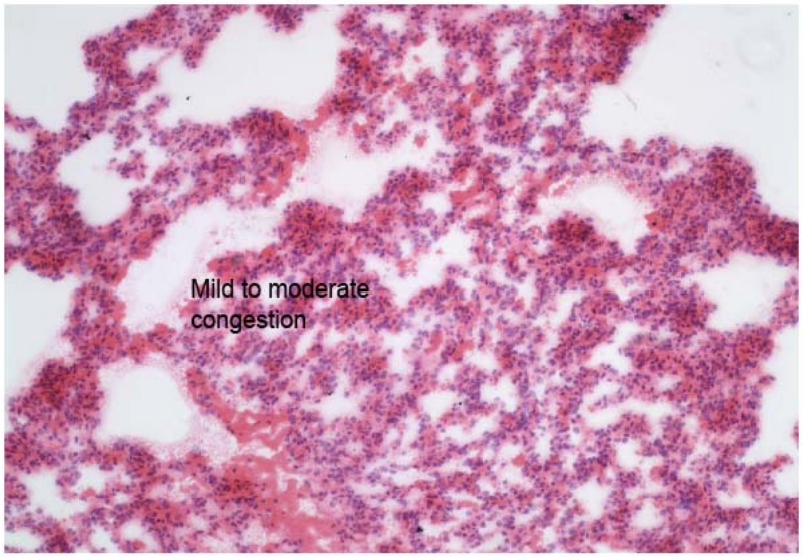
# Hemorrhagic Shock + FFP
# Day 0 vs. Day 5

FFP Day 0




FFP Day 5




Finding: Day 0 Lungs almost normal , Day 5 has congestion

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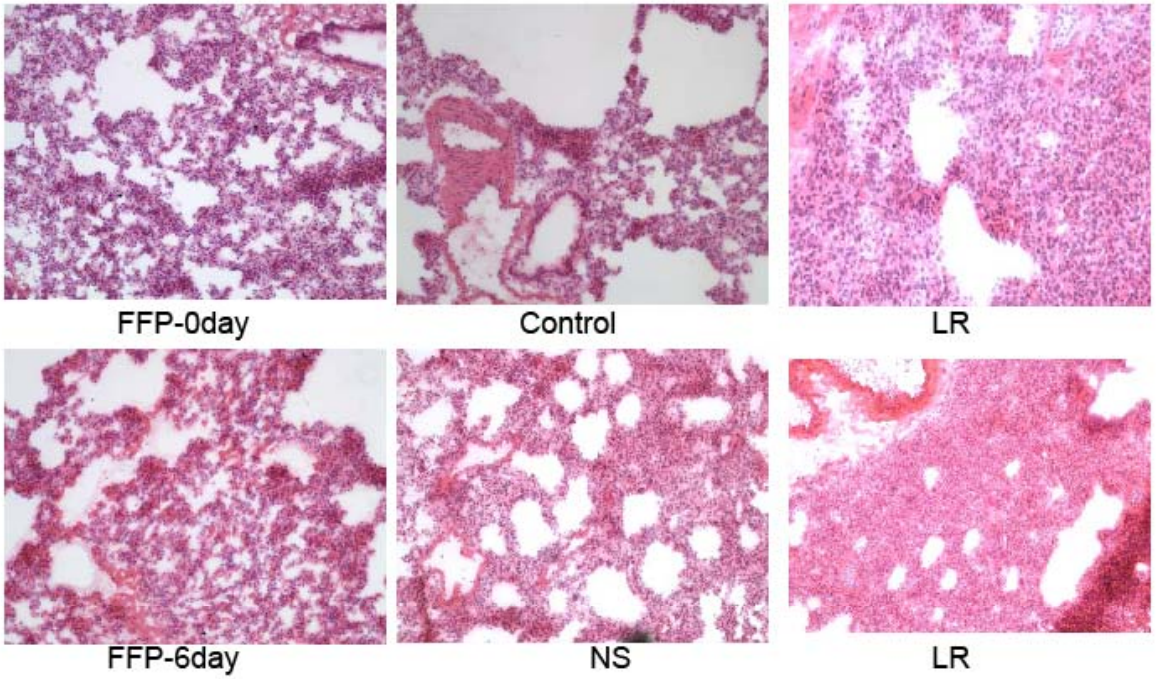
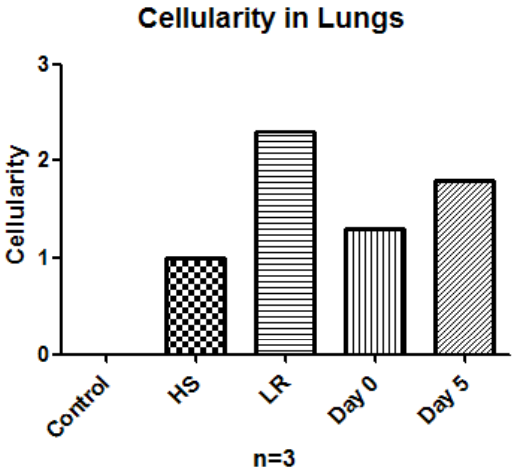
# Summary

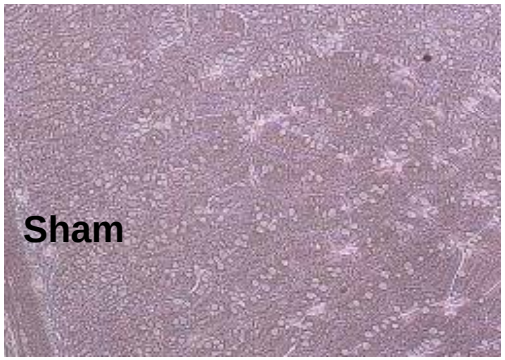


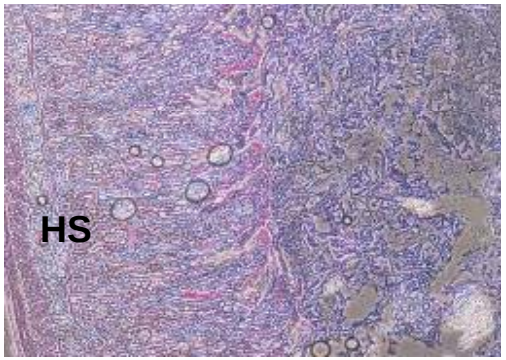



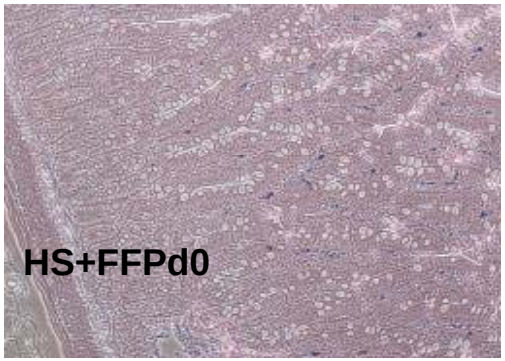

# Resuscitation with FFP inhibits cell death after Hemorrhagic Shock

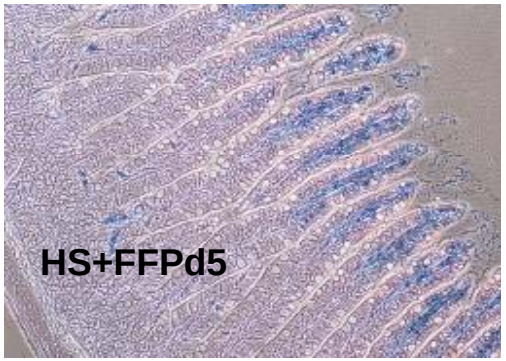
# FFP Protects the GI Organs Against HS-induced Apoptosis

Gut

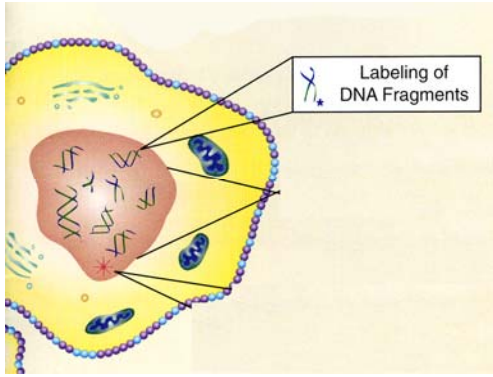


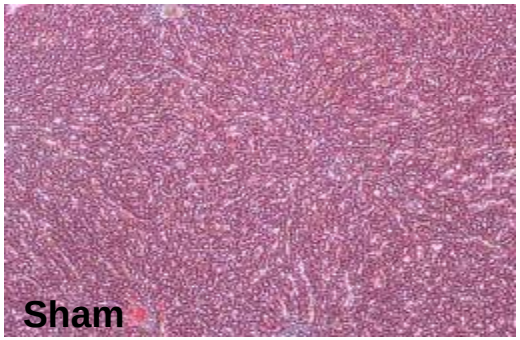



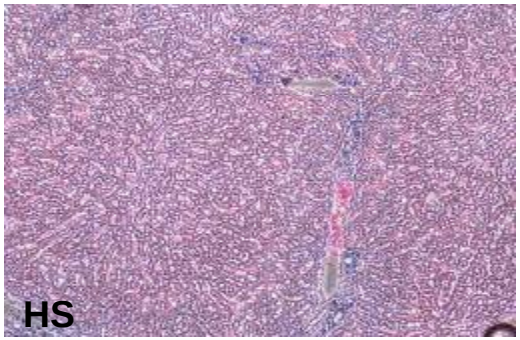


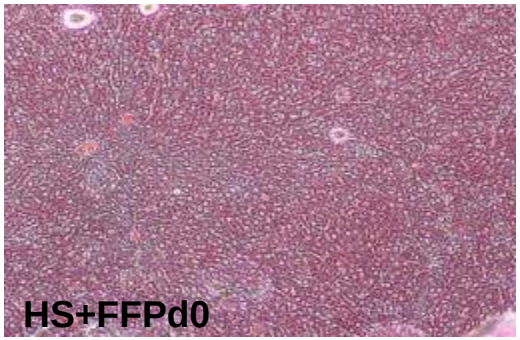


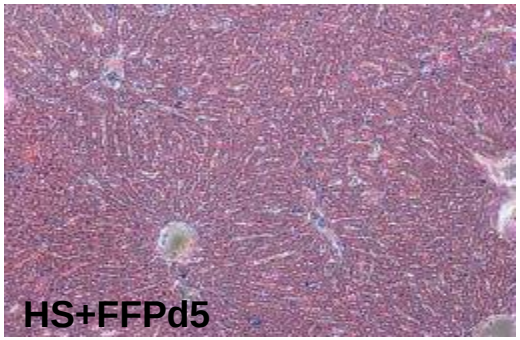
# FFP Protects the Liver Against HS-induced Apoptosis

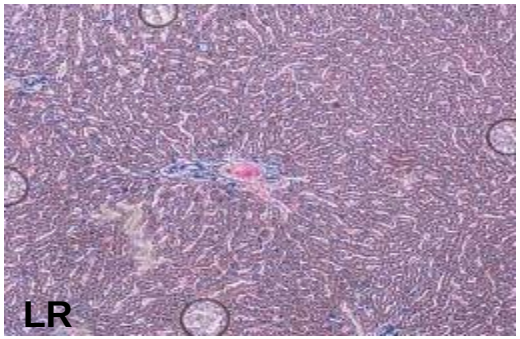
Liver

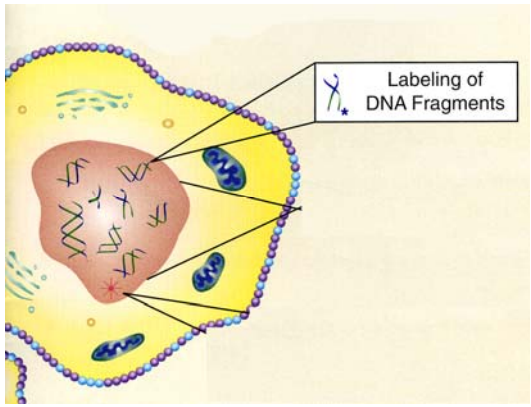


**What is a possible solution to the use of Day 5 FFP if future studies continue to support its diminished potential ?**

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# Back to the Future
## Lyophilized Plasma Resuscitation

FIGURE 159.—Administration of plasma on beach, only few feet from surf, to survivor of landing craft sunk off coast in first days of invasion of Normandy, June 1944.

Practice began during WWII

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# New Product LyP from HemCon

- The Army recently named HemCon to develop lyophilized human plasma (LyP)
- Significant logistical advantages compared to FFP

HemCons LyP

FFP

Advantages:

- Made from single donor plasma
- Traceable, Safe, No Pooling
- Universal Donor Anti-B removed from A
- Preserves coagulation factor levels
- Easy and Fast to reconstitute
- Stored at Room Temp

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# Why do we need a LyP?

| Current FFP | Universal LyP |
|---|---|
| Preparation/Delivery Time: 20-40 mins | Reconstitution/prep-time: < 5 mins = immediate transfusion treatment |
| Blood type specific and limited supply of Universal Type AB Plasma (4% population) | Universal – no ABO typing required |
| Potential Waste & Breakage: 4-37% | No Waste – reconstitute when needed |
| Shelf life: 1 year frozen, 5 day unfrozen | Shelf life: 2-3 years |
| Storage Requirements: Freezers/refrigerators | Storage Requirements: TBD (Room Temperature +) |
| Access limited to large trauma and acute care facilities | Expanded access: ***Military Field Use, Emergency use, Aero-med Flight Services, National Disaster Stockpile Programs*** |

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# The Questions for lyophilized Plasma:

- Can LyP treat the Lethal Triad?
- Does LyP function like Day 0 FFP?
- Is LyP better than Day 5 FFP or LR ?

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# Is Lyophilized Plasma is Equivalent to FFP?

The Journal of TRAUMA® Injury, Infection, and Critical Care

## Development and Testing of Freeze-Dried Plasma for the Treatment of Trauma-Associated Coagulopathy

*Fahad Shuja, MD, Christian Shults, MD, Michael Duggan, DVM, Malek Tabbara, MD, Muhammad U. Butt, MD, Thomas H. Fischer, PhD, Martin A. Schreiber, MD, Brandon Tieu, MD, John B. Holcomb, MD, Jill L. Sondeen, PhD, Marc deMoya, MD, George C. Velmahos, MD, and Hasan B. Alam, MD*

**Experiment:**

Swine ( n = 32) were subjected to complex polytrauma including extremity fracture, hemorrhage, severe liver injury, acidosis and hypothermia.

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# Initial Studies in a Swine Model of HS + Trauma Reveal Resuscitation with LyP to be Equivalent to FFP

## Results:

- LyP had decreased clotting factor activity by an average of 14%. Survival was similar between all groups.
- Swine treated with 1:1 FFP:PRBC were similar to those treated with 1:1 LyP:PRBC.
- Coagulopathy Corrected with Lyp and FFP
- Resuscitation with LyP resulted in a reduction in IL-6 expression compared to resuscitation with FFP.
- **Conclusions**:

LP can be used for resuscitation in a severe polytrauma and hemorrhagic shock swine model with equal efficacy to FFP

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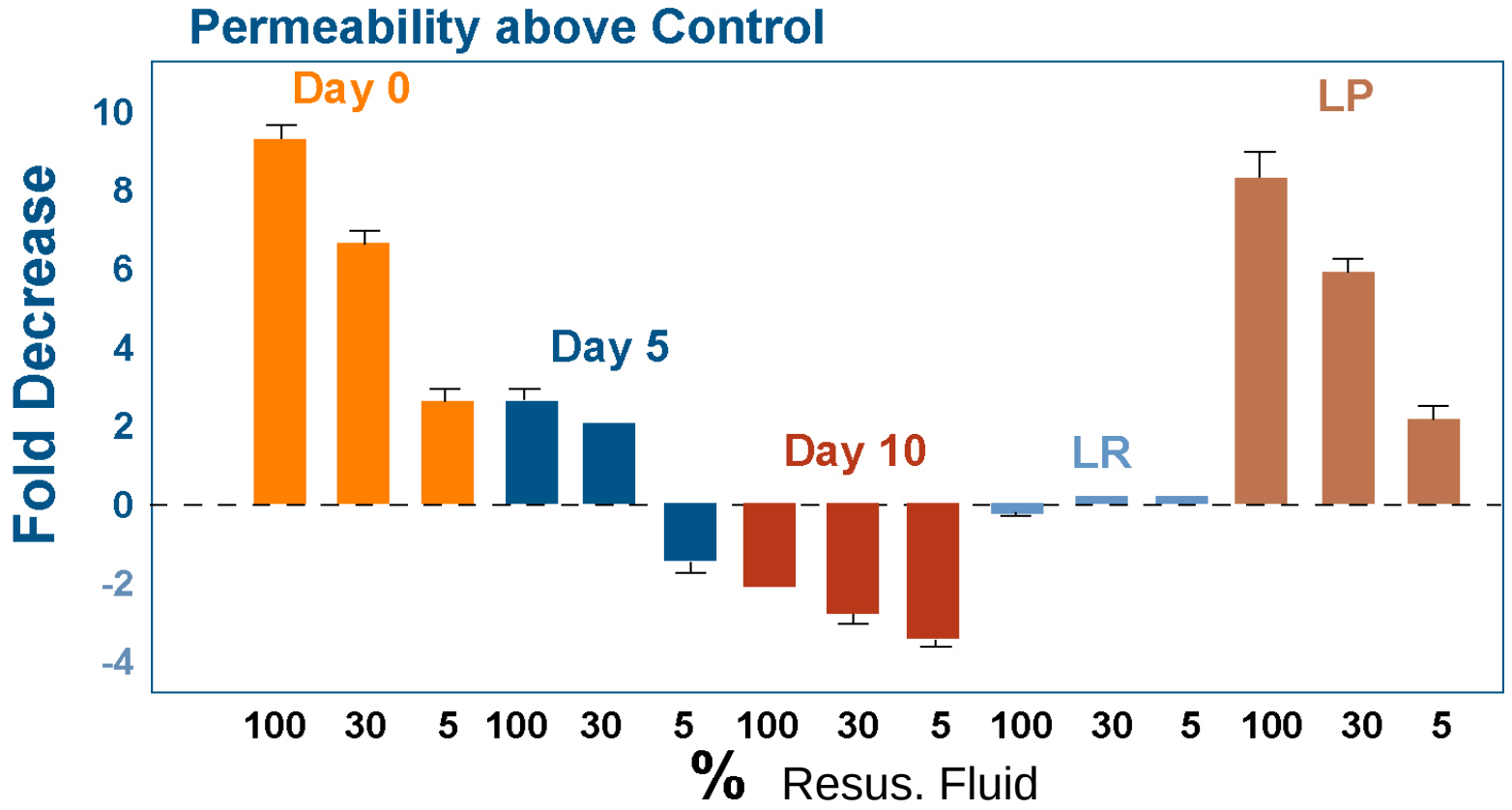
# LyP is equally as protective on EC permeability *In vitro*



# Mechanism

- Classic platelet clotting along with the proteins found in plasma
- However, I think it is simplistic to assume these positive effects are based solely on the classic clotting cascade

*Review Article* *The Journal of* TRAUMA® *Injury, Infection, and Critical Care*

J Trauma, Oct, 2008

**The Coagulopathy of Trauma: A Review of Mechanisms**

*John R. Hess, MD, MPH, FACP, FAAAS, Karim Brohi, MD, Richard P. Dutton, MD, MBA, Carl J. Hauser, MD, FACS, FCCM, John B. Holcomb, MD, FACS, Yoram Kluger, MD, Kevin Mackway-Jones, MD, FRCP, FRCS, FCEM, Michael J. Parr, MB, BS, FRCP, FRCA, FANZCA, FJFICM, Sandro B. Rizoli, MD, PhD, FRCSC, Tetsuo Yukioka, MD, David B. Hoyt, MD, FACS, and Bertil Bouillon, MD*

The NEW ENGLAND JOURNAL of MEDICINE

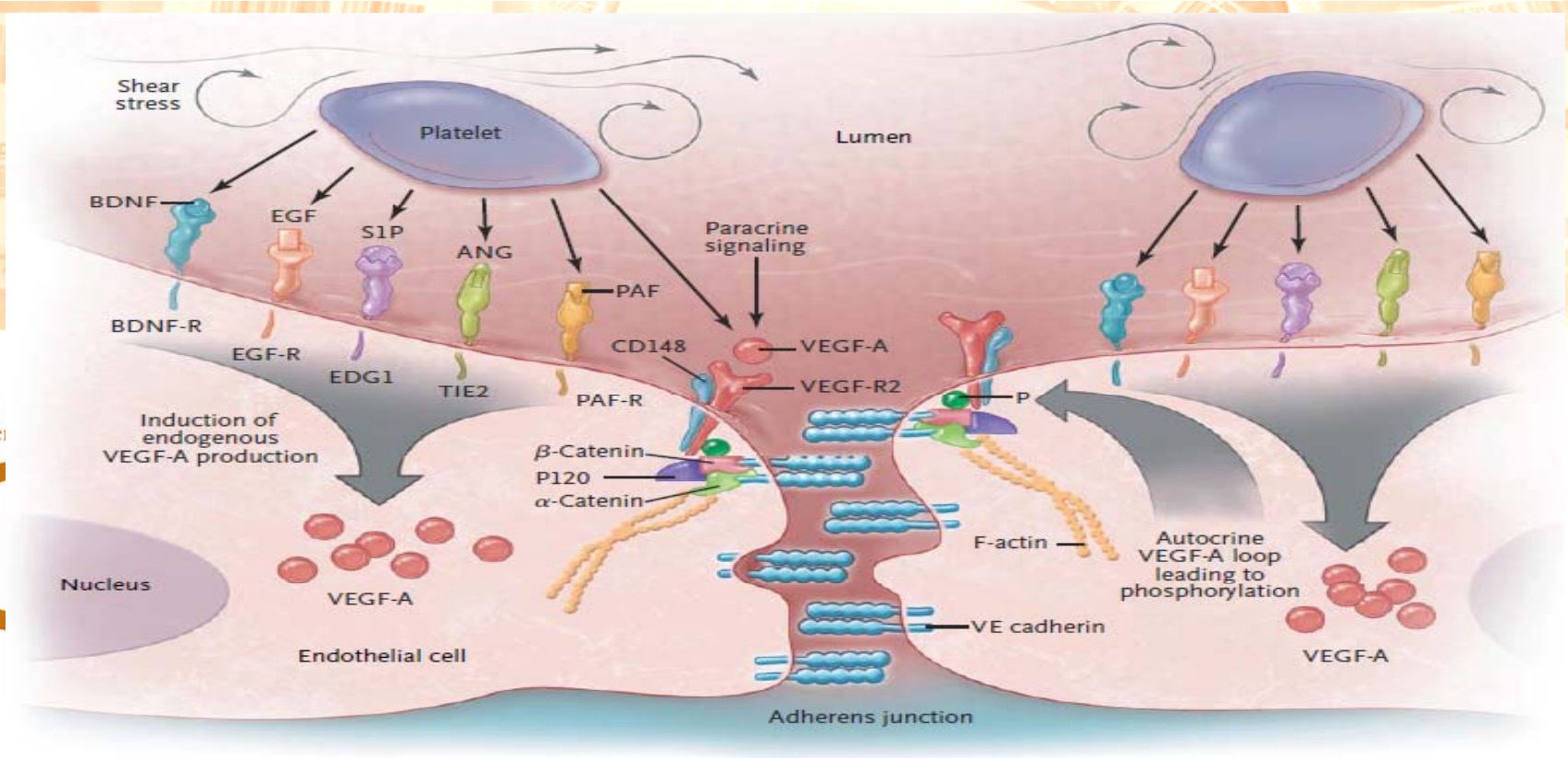
REVIEW ARTICLE

MECHANISMS OF DISEASE

# Platelets, Petechiae, and Preservation of the Vascular Wall

Sept 2008

Ralph L. Nachman, M.D., and Shahin Rafii, M.D.



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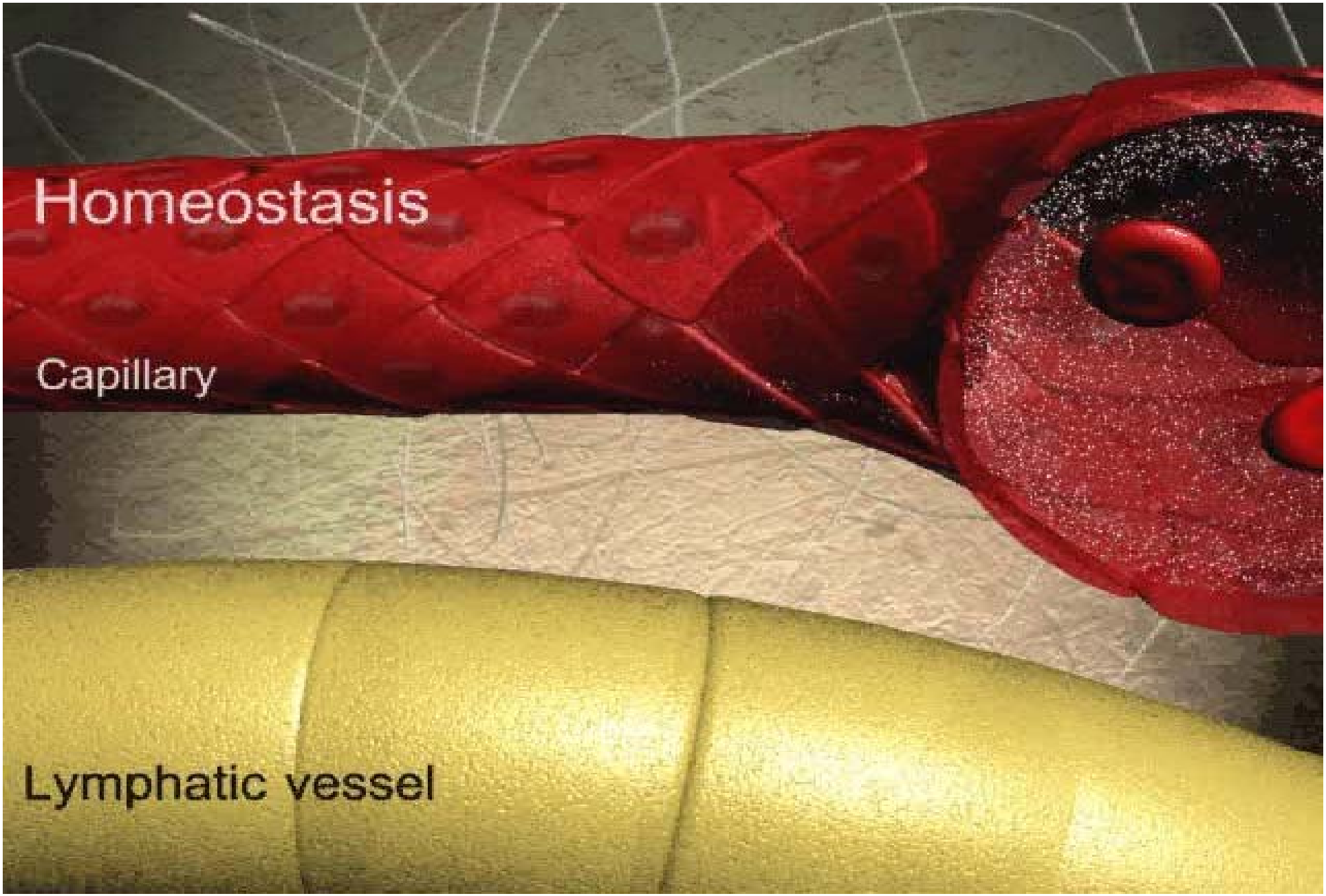
# Central Hypothesis:

FFP has the capacity to “normalize” injured endothelium

This capacity diminishes during 5 days of storage

# Depiction of our Central Hypothesis



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# Summary:

- Day 0 FFP has potent beneficial effects on endothelial function and hemodynamic stability *in vitro* and *in vivo* respectively; effects which diminish after 5 days of routine storage at $4^0$C.

- In our *in vitro* studies, we found that Day 0 FFP has the capacity to repair EC permeability induced by hypoxia and also inhibits EC apoptosis

- In addition, we show that this reparative capacity is diminished between Day 0 and Day 5 of storage at 4 $^0$C.

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# Summary Continued:

- In vivo we also find that resuscitation with Day 0 FFP inhibits cell death and inflammatory cytokine production and lymphocyte infiltration in the lungs compared to Day 5 FFP

- There are significant differences in coagulation proteins between Day 0 and Day 5 FFP, and there are changes in thrombin generation capacity (TGC), a global measure of coagulation potential.

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# Conclusion:

Resuscitation after major blood loss is a dynamic and complex process

The use of FFP has likely significantly changed mortality in massively transfused patients

Our preliminary studies suggest that plasma may be working through mechanisms other than the simple correction of coagulation factors

We propose a novel concept that plasma has the ability to “normalize” injured endothelium

# Future Studies:

To understand how the changes seen in permeability, coagulation, and HS affect outcome *in vivo* models of HS and also in patients.

There are no published studies correlating the age of plasma and clinical outcomes

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