RDCR without blood:
Making the best of a bad situation?

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Disclaimer:

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Disclosures:

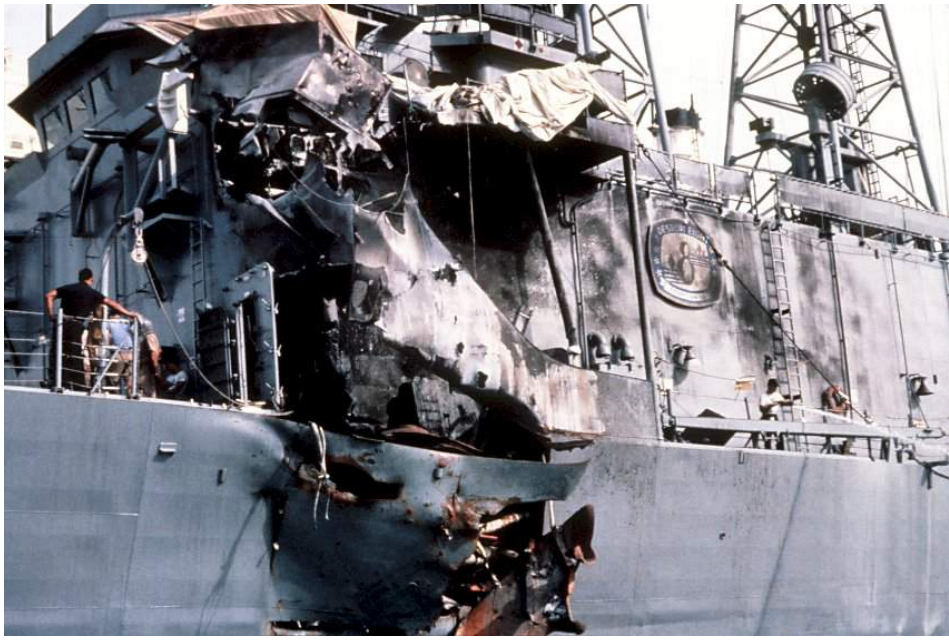
I have no relevant conflicts of interest.

I am an active duty officer in the U.S. Army.

Remote

No Level 1 Trauma Center within 1 hour…

+ Damage Control



Damage Control:

First, only do the things essential to keeping the ship afloat.

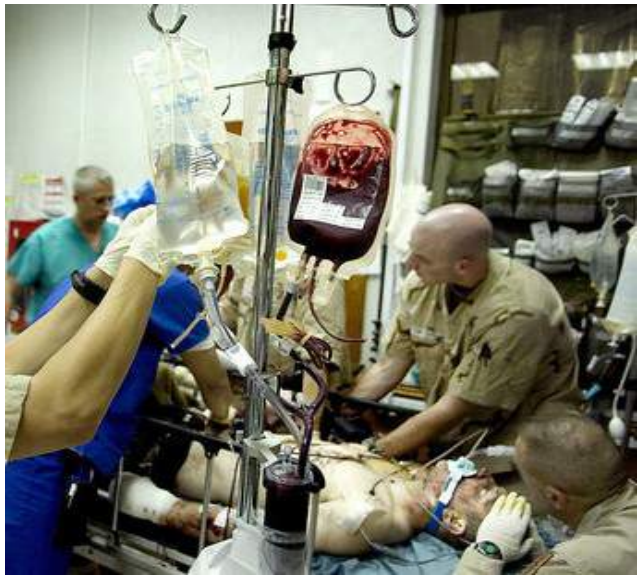
Rotondo MF, Schwab CW, et al. J Trauma. 1993;35(3):375-82.

+ Resuscitation

Emergency treatment to restore:

Circulating volume
Aid oxygen delivery
Replace hemostatic potential

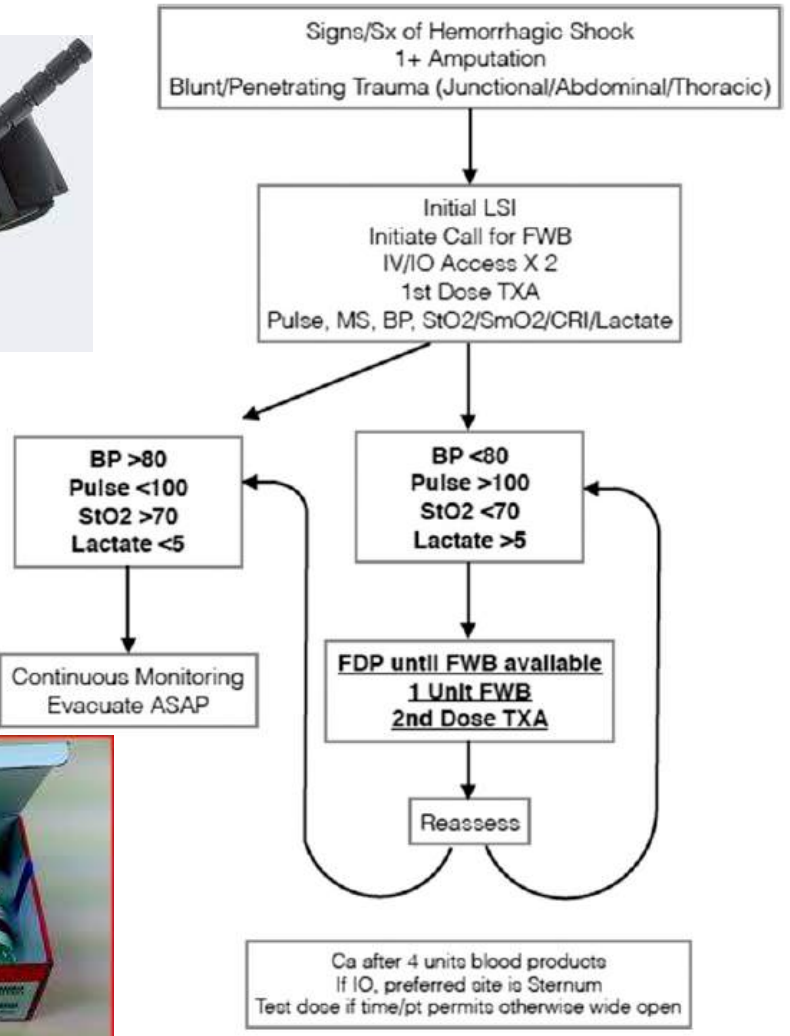
(and a few other things…)



= RDCR (today)

The essentials:

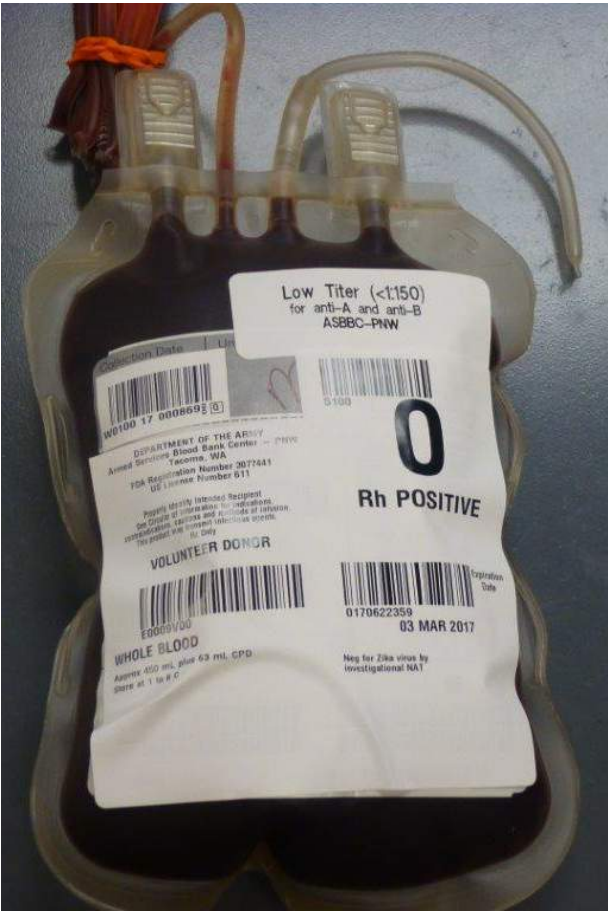
- ***Hemorrhage control***
- ***Resuscitation***
  - **TXA**
  - ***WHOLE BLOOD***
  - **Avoid clear fluids**
  - **Plasma (FDP) as a bridge to WB**



75th Hemorrhagic shock.

ROLO!

Basic idea: treat the organ failure syndrome with organ replacement



Don’t make things worse (clear fluids)!

Give the patient what he or she is losing!

Keep it simple (one product)!

WHAT? NO WHOLE BLOOD???

What are the priorities of DCR?

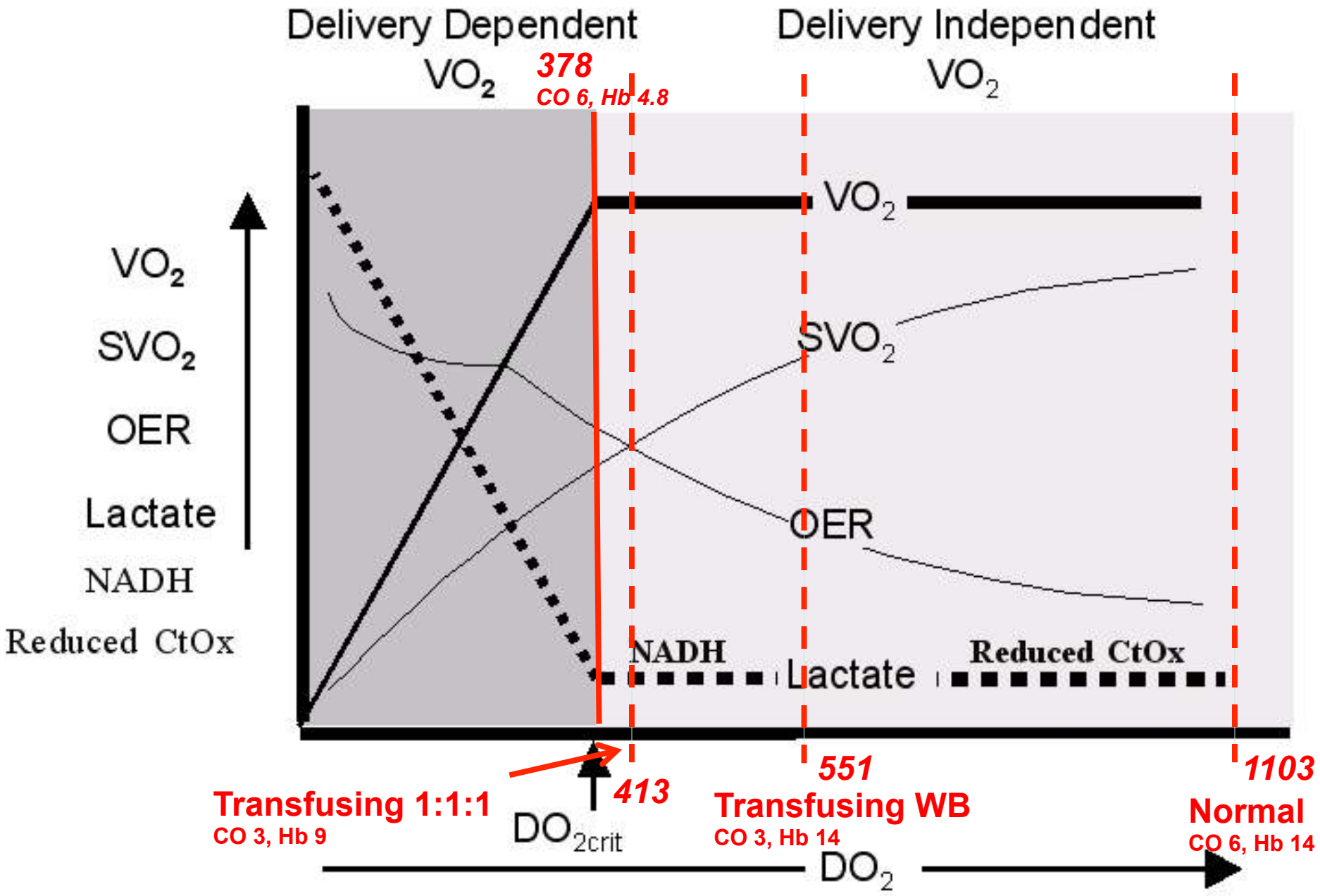
Control Hemorrhage

Treat Oxygen Debt

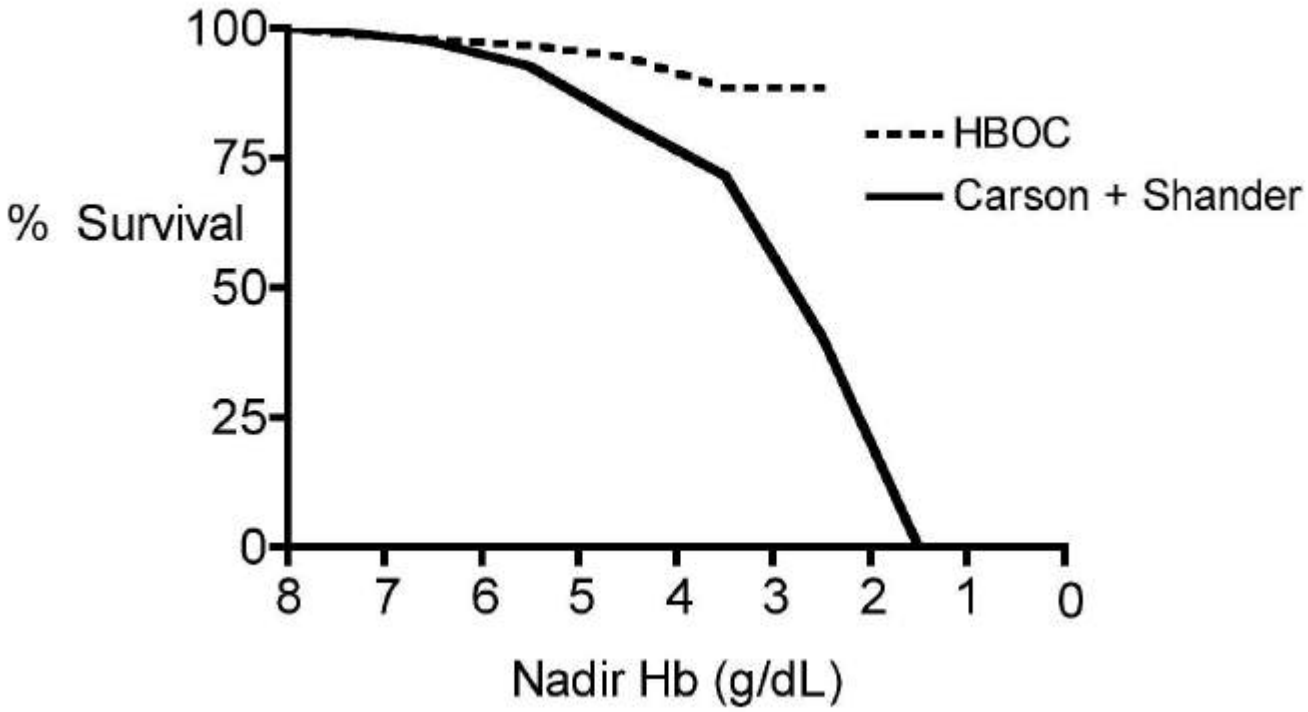
Mitigate coagulopathy

- ***Plasma dysfunction***
- ***Platelet dysfunction***
- ***Decreased RBCs (affect clot structure, platelet margination)***
- ***Endothelial dysfunction***
- ***Innate immune activation***

Fick's Equation: D02 = 1.34 x Hgb x Sa02 x CO



Potential Role for HBOC?



Not approved in US/EU

Promising data from HBOC-201 Expanded Access IND (when blood is not an option) Weiskopf *Transfusion* 2017.

OK, "volume" to increase cardiac output? In a bleeding patient?

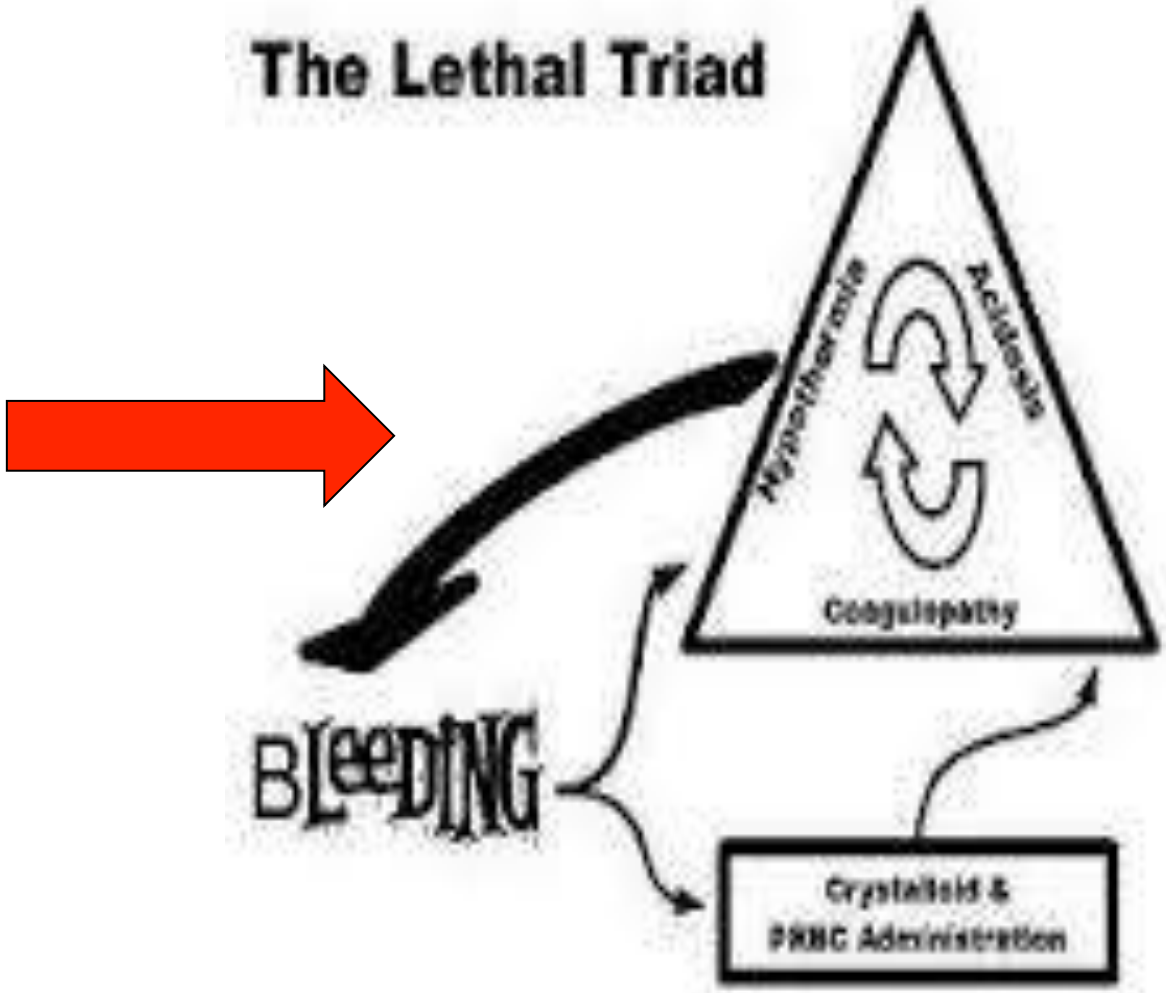
- **Crystalloid**
  - Doesn't stay intravascular: you can't carry enough to make the slightest difference.
  - Bickell (NEJM 1994) demonstrates that withholding crystalloid improves survival even in short term.
  - Hemodilution, acidosis, electrolyte imbalances…
- **Colloid**
  - Even more hemodilution
  - Starch belongs in potatoes, not your bloodstream (platelet inhibition, vWF/FVIII defect)
  - ALBUMIN: only colloid that does not worsen outcomes (at least it buffers) and it's the main protein in plasma

Where is the oxygen-carrying capacity?

Where is the hemostatic potential?

Let's face it, in the RDCR context, if this is all you have, you better also have some training in palliative care…

Clear Fluid = Wishful Thinking
Bickell: don't do it!



Harmful: Hextend

- Contraindicated in lactic acidosis
- Incompatible with blood administration
- Causes acquired VWD/VIII deficiency
- Increased risk of bleeding
- Increased risk of renal failure
- Increased risk of death

Discontinue use of HES at the first sign of coagulopathy.

A retrospective study of **trauma** patients (N=2225), 22% (N=497) of whom received HES 450/0.7 as part of their fluid resuscitation regimen, reported **increased risk of acute kidney injury**: relative risk 1.73 (1.30 to 2.28); **increased mortality**: relative risk 1.84 (1.48 to 2.29); and increased risk of death or acute kidney injury: relative risk 1.90 (1.59 to 2.27) in HES patients.[14]

FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings

Excess bleeding
In a **meta-analysis of 18 RCTs** in patients undergoing **open heart surgery** in association with cardiopulmonary bypass,[15] use of different HES products, irrespective of molecular weight or degree of molar substitution, was associated **with increased bleeding**. FDA considers excess bleeding a **class effect** warranting addition of this new safety information to the Warning and Precautions Section of the PI.

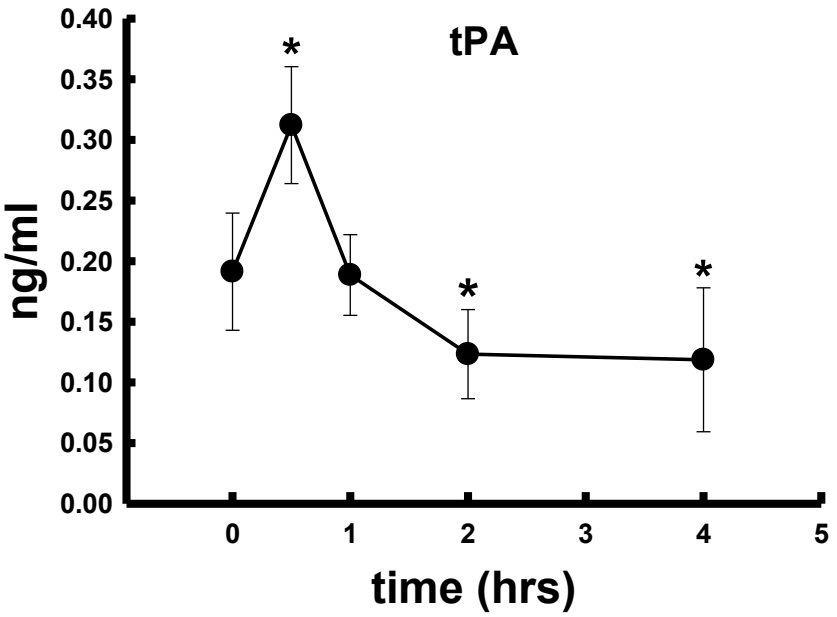
Least bad "volume" option: 25% albumin?

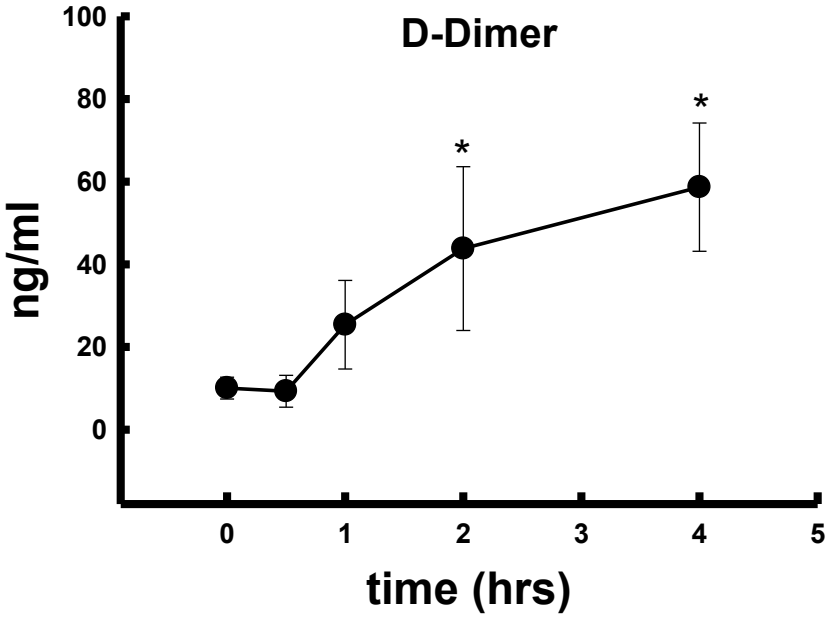
- Major protein constituent of plasma
- Buffering capacity
- "endothelial friendly"
- Shelf stable
- Cheap (ish) & widely available
- Not associated w/ increased mortality (TBI?)
  - SAFE patients got 4% albumin
  - SAFE patients received albumin in ICU for long periods – relevance?
  - ≥ 10% albumin looks good in animal models
- Still hemodilutes: need to do SOMETHING for hemostasis if bleeding
  - Give with fibrinogen and TXA
  - Add PCC???
- *Efficacy if already extravascularly depleted?*

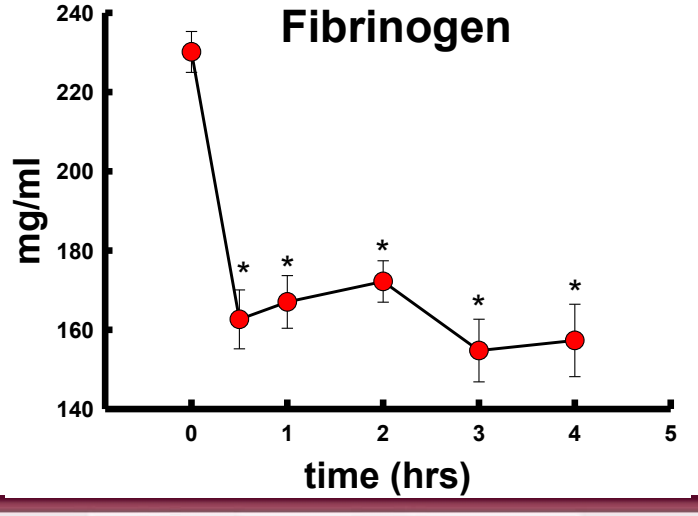
NB: comes from blood…

Studer et al. *JSOM* 2017.

Fibrinolysis is a major driver of ATC





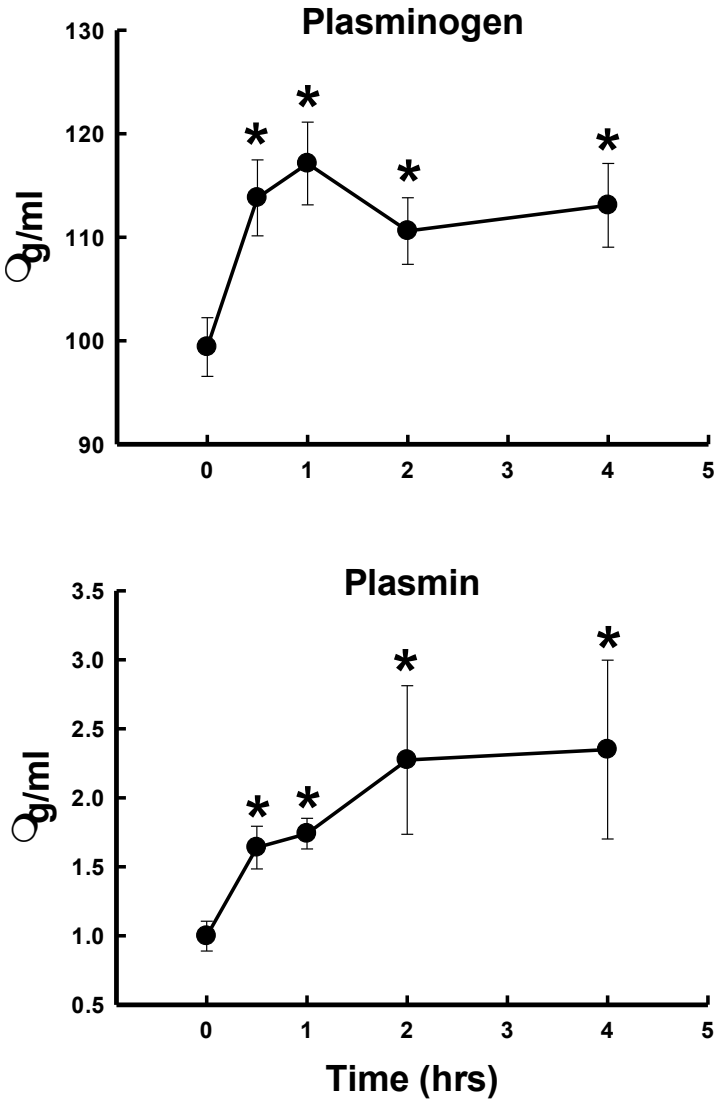


Note that fibrinogen is also being consumed!

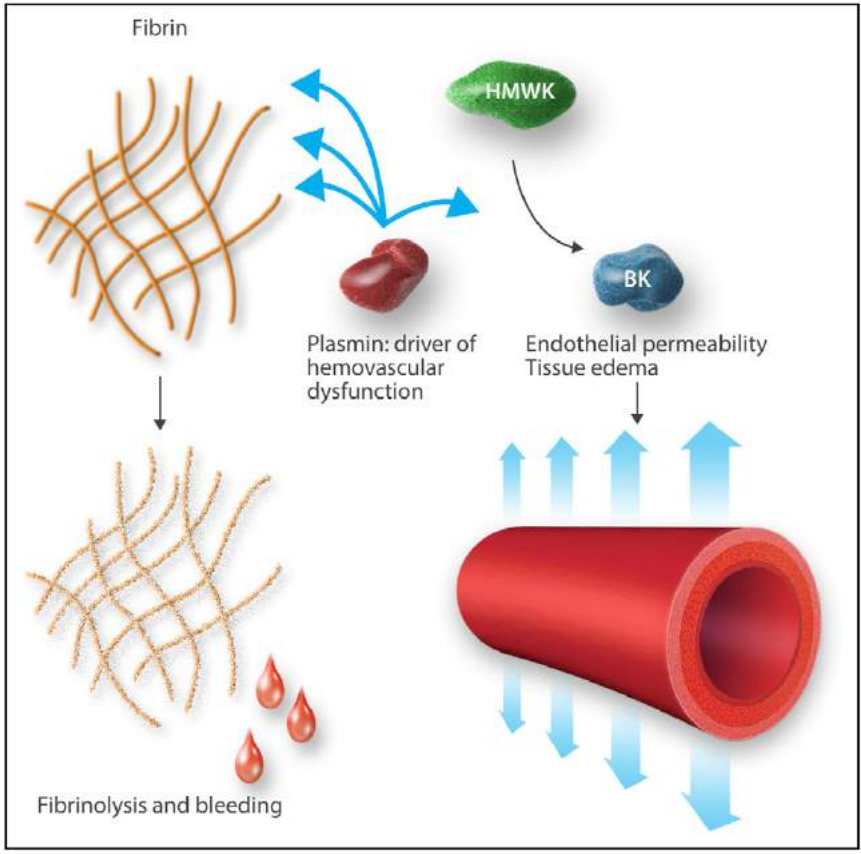
Drowning victims: hypoxia alone can drive fibrinolysis (tPA release).

Wu *AJP* 2015
Schwameis CCM 2015

tPA → Plasmin → bradykinin…

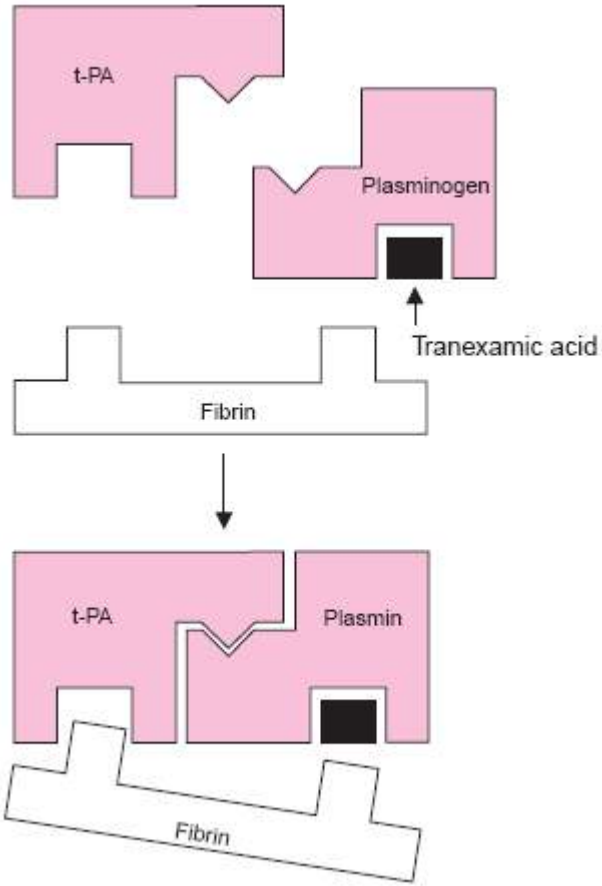


This is why tranexamic acid (TXA) reduces mortality in trauma.



CRASH-2 *Lancet* 2010
Wu *AJP* 2015
Cap *Blood* 2017
Marcos-Contreras *Blood* 2017

We can do something about plasmin…



TXA is essential, but…

Hypoxia and Fibrinolysis: Need TXA & FGN source

Drowning = perfect hypoxia model

Hypoxia→ tPA release →massive fibrinolysis
(& auto-heparinization)

Treat this with:
-- **TXA**
-- **Fibrinogen**

If the hypoxia is due to Blood loss, will need:
-- RBC
-- volume
-- coag factors
-- platelets
i.e, whole blood

Schwameis CCM 2015.

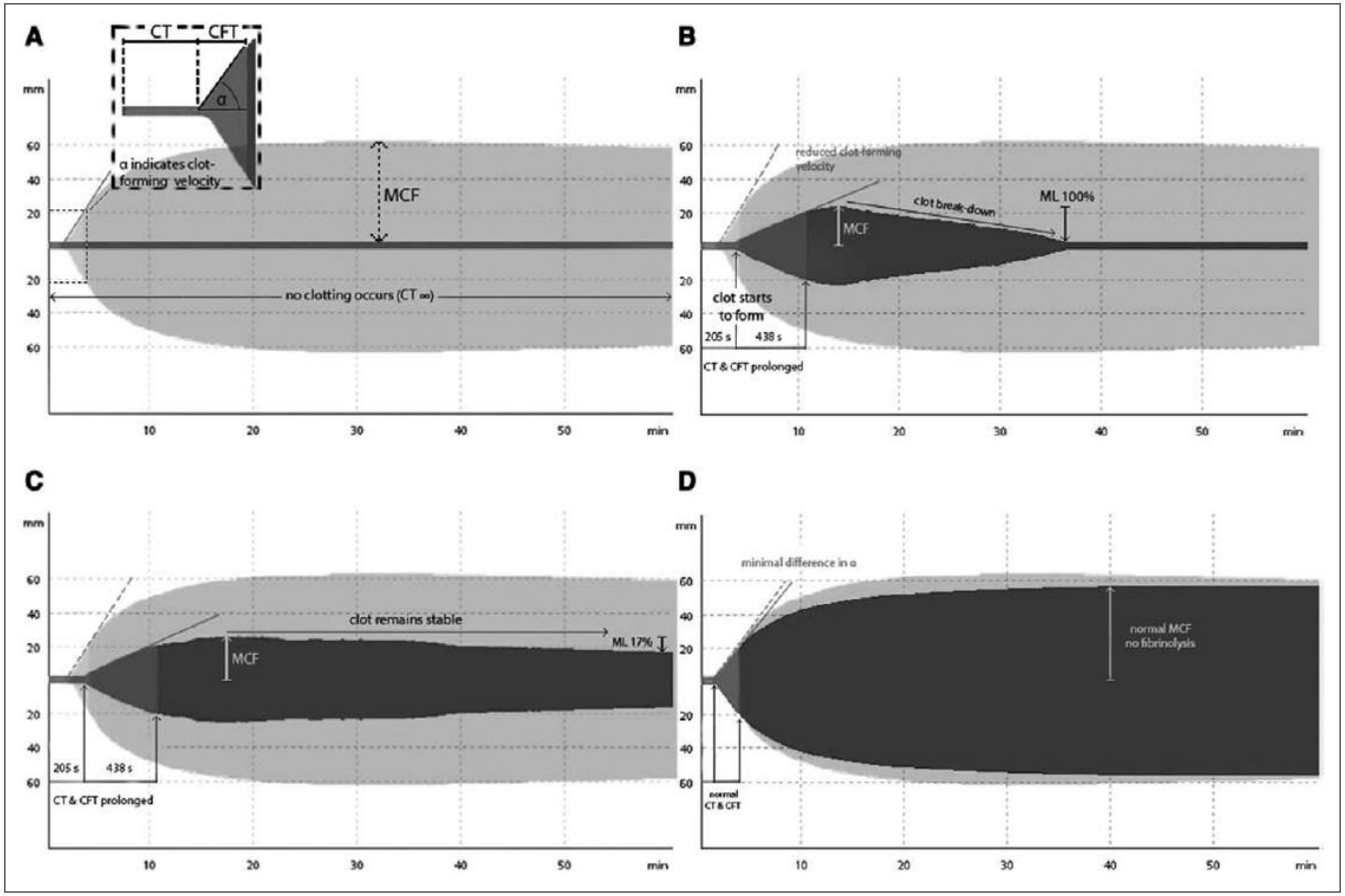


Figure 1. Tissue factor activates extrinsic hemostasis (EXTEM) traces from admission to 6 hr after arrival of a drowning victim. A reference rotational thrombelastometric analysis trace (25% opacity) is used as overlay to visualize differences from normal clotting. Parameters analyzed are clotting time (CT, s: time from adding starting reagent until clot begins to form; range, EXTEM [35–80 s], kaolin activates contact phase [INTEM, 100–240 s]), clot formation time (CFT, s: time from CT until a trace amplitude of 20 mm is reached; range: EXTEM [36–160 s], INTEM [35–110 s]), alpha angle (α, °: angle of tangent at 2-mm amplitude: kinetic of clot formation), maximum clot firmness (MCF, mm: maximum trace amplitude, range: EXTEM, INTEM: [53–72 mm]) and maximum lysis (ML,%, difference between MCF and lowest trace amplitude in %; range: EXTEM, INTEM: [< 15%]). **A**, Admission, **(B)** 100 min, **(C)** 180 min, and **(D)** 360 min after first presentation. Hyperfibrinolysis progressively resolved and MCF increased over time, after tranexamic acid (1,000 mg) and fibrinogen (4,000 mg) had been given IV.

We could have fibrinogen concentrate…

BUT:
1 gm/vial
10 min to reconstitute
4 gm starting dose?

BTW, fibrinogen comes from blood…

Dilution worsens fibrinolysis: plasma inhibitors of lysis would be nice…

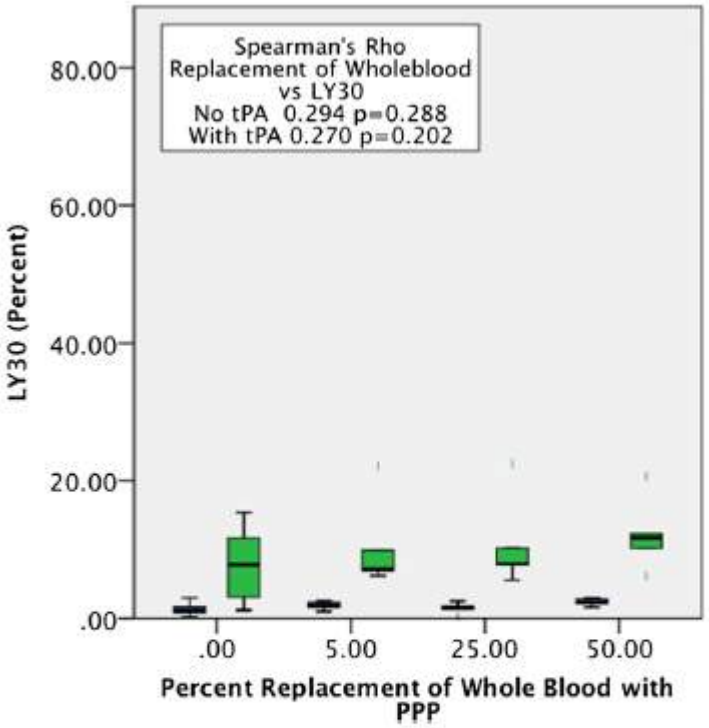


Figure 2. Plasma dilution of whole blood does not alter sensitivity to tissue plasminogen activator (tPA)-mediated fibrinolysis. The y axis represents the percent fibrinolysis quantified by LY30 (amount of blood clot lysed 30 minutes after reaching maximum amplitude). The x axis represents progressive dilution of whole blood with platelet poor, with largest dilution on the right. Blue bar, whole blood with no tPA added. Green bar, whole blood mixed with tPA. PPP, platelet poor plasma.

Plasma Is the Physiologic Buffer of Tissue Plasminogen Activator-Mediated Fibrinolysis: Rationale for Plasma-First Resuscitation after Life-Threatening Hemorrhage

(J Am Coll Surg 2015;220:872–879.

Hunter B Moore, MD, Ernest E Moore, MD, FACS, Eduardo Gonzalez, MD, Gregory Wiener, BA, Michael P Chapman, MD, Monika Dzieciatkowska, PhD, Angela Sauaia, MD, Anirban Banerjee, PhD, Kirk C Hansen, PhD, Christopher Silliman, MD, PhD

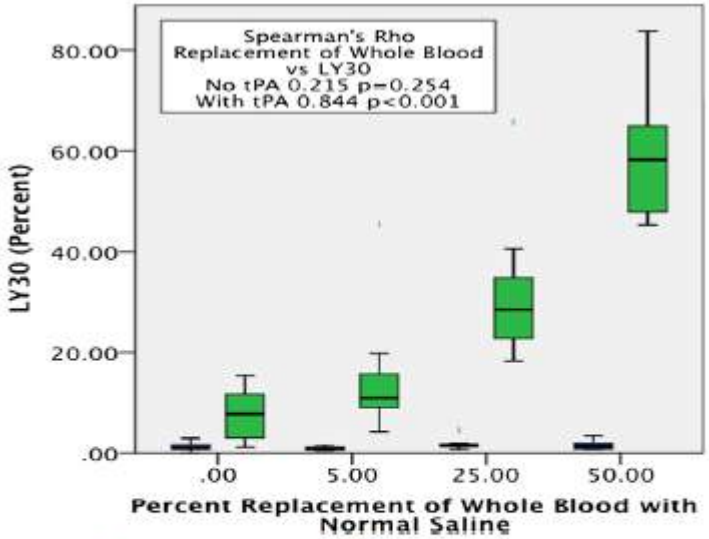
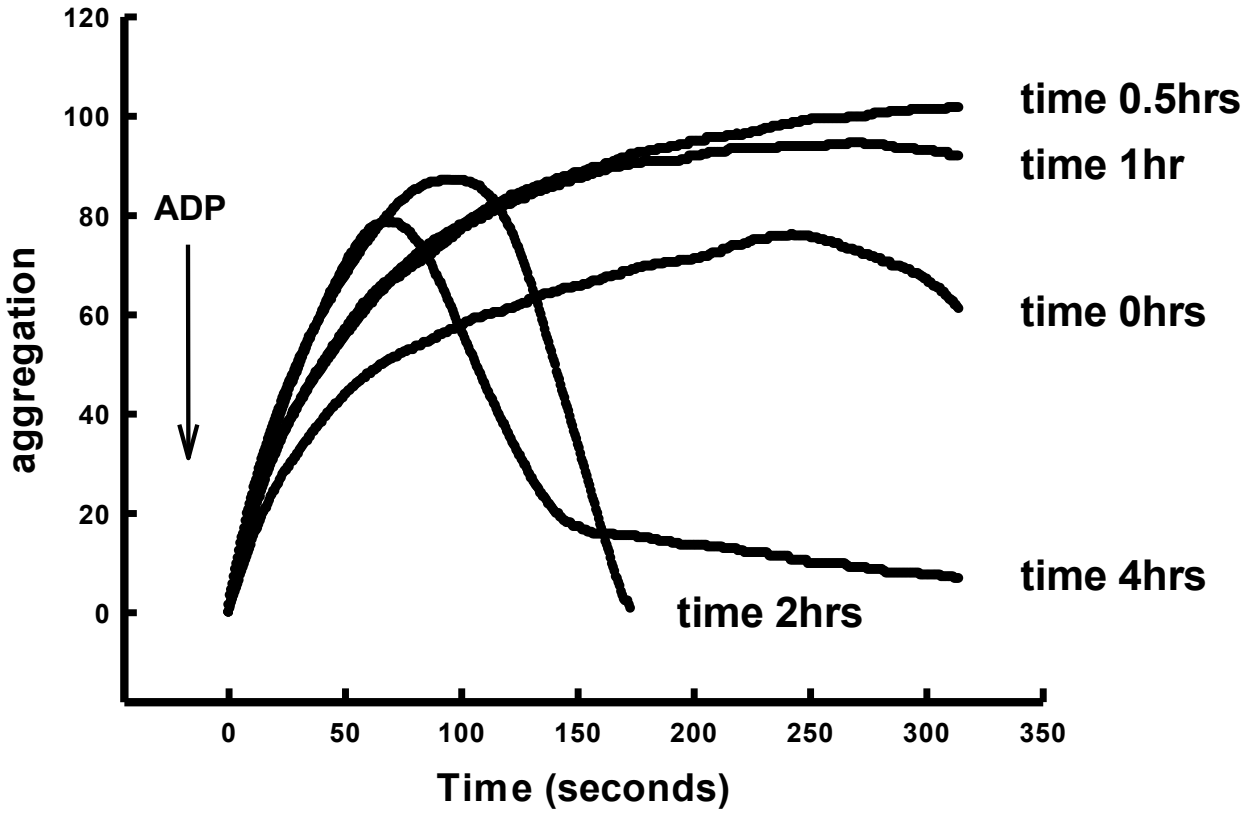


Figure 1. Normal saline (NS) dilution of whole blood increases sensitivity to tissue plasminogen activator (tPA)-mediated fibrinolysis. The y axis represents the percent fibrinolysis quantified by LY30 (amount of blood clot lysed 30 minutes after reaching maximum amplitude). The x axis represents progressive dilution of whole blood with saline, with largest dilution on the right. Blue bar, whole blood with no tPA added. Green bar, whole blood mixed with tPA.

Platelets can't maintain aggregation response!

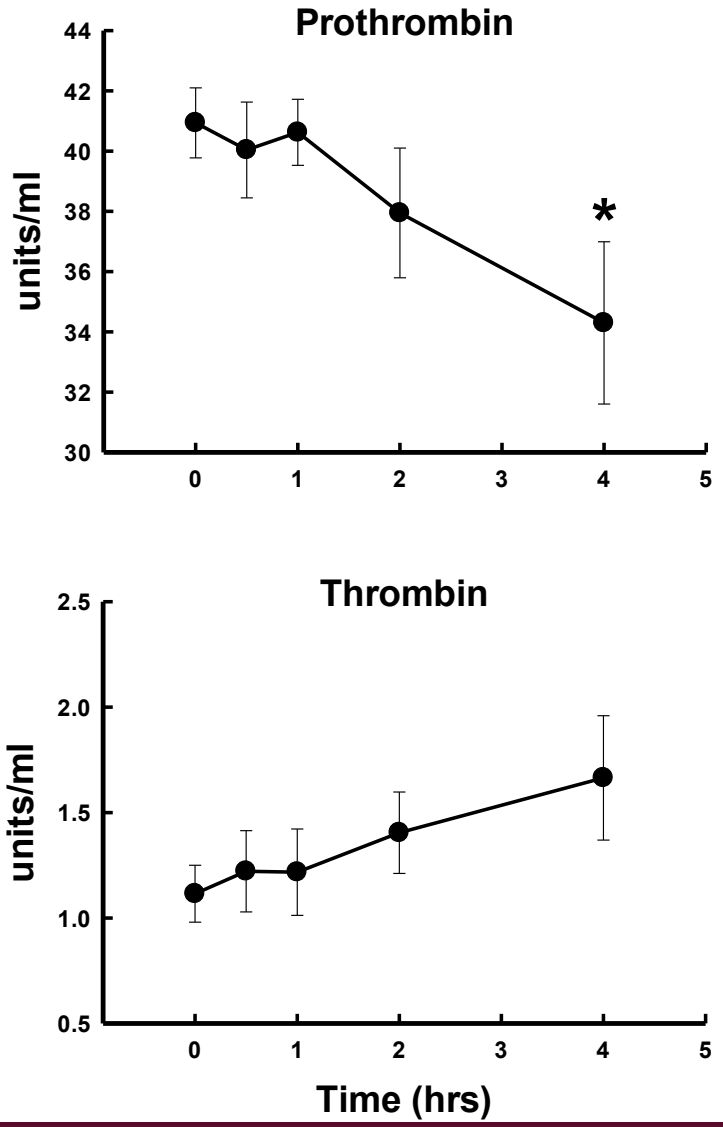


No platelet option yet…

<u>R&D stage:</u>
Lyophilized PLT?
Engineered nanoparticles?

Promising but not currently available anywhere.

Is thrombin the problem?



Animal model data: thrombin generation increased

Human observational data: elevated TAT (implies ↑ thrombin)

RCT data: no survival benefit to rVIIa

Maybe over time or with crystalloid/colloid dilution but no validated role for PCC or rVIIa

Wu *AJP* 2015

PCC in trauma RCT?

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

Lancet Haematol 2017

Published Online
April 27, 2017
http://dx.doi.org/10.1016/
S2352-3026(17)30077-7

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 Treml, Dieter Wally, Benjamin Treichl, Agnes Mayer, Christof Kranewitter, Elgar Oswald

	CFC (n=50)	FFP (n=44)	Estimated difference or odds ratio* (95% CI)	p value
FFP				
Patients†	2 (4%)	44 (100%)	∞ (126·35 to ∞)	<0·0001
Dose (U)	5 (5 to 5)	14 (10 to 14)	−9 (−16 to −2)	0·023
Fibrinogen concentrate				
Patients†	50 (100%)	23 (52%)	0 (0 to 0·10)	<0·0001
Dose (g)	8 (5 to 10)	5 (4·5 to 8)	1 (0 to 3)	0·11
Four-factor PCC				
Patients†	8 (16%)	2 (5%)	0·25 (0·02 to 1·37)	0·098
Dose (IU)	2000 (1875 to 3000)	850 (675 to 1025)	1500 (300 to 4500)	0·046

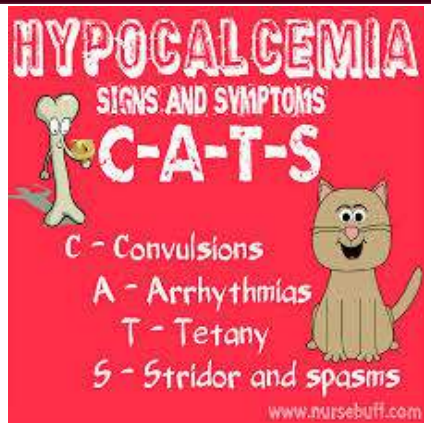
This was a study of early FGN vs. late plasma

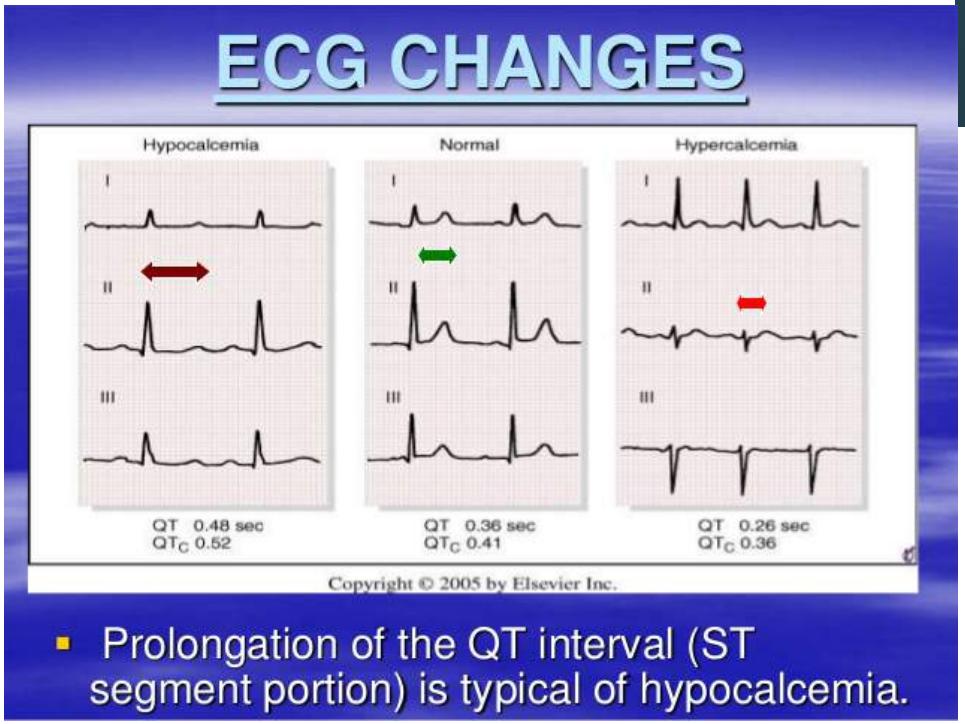
Not enough data on PCC (10/94 patients total)

ROTEM guided

NB: PCCs are blood-derived…

What are other drivers of death?





Acidosis
Hypothermia,
Hypocalcemia
hypomagnesemia…

Treat hypocalcemia early

CALCIUM: hypoCa → long QTc, decreased cardiac output, coagulopathy, seizures, etc.

97.4% of trauma MTP patients hypocalemic (<1.12mmol/L) [also most patients with sepsis/MOF]

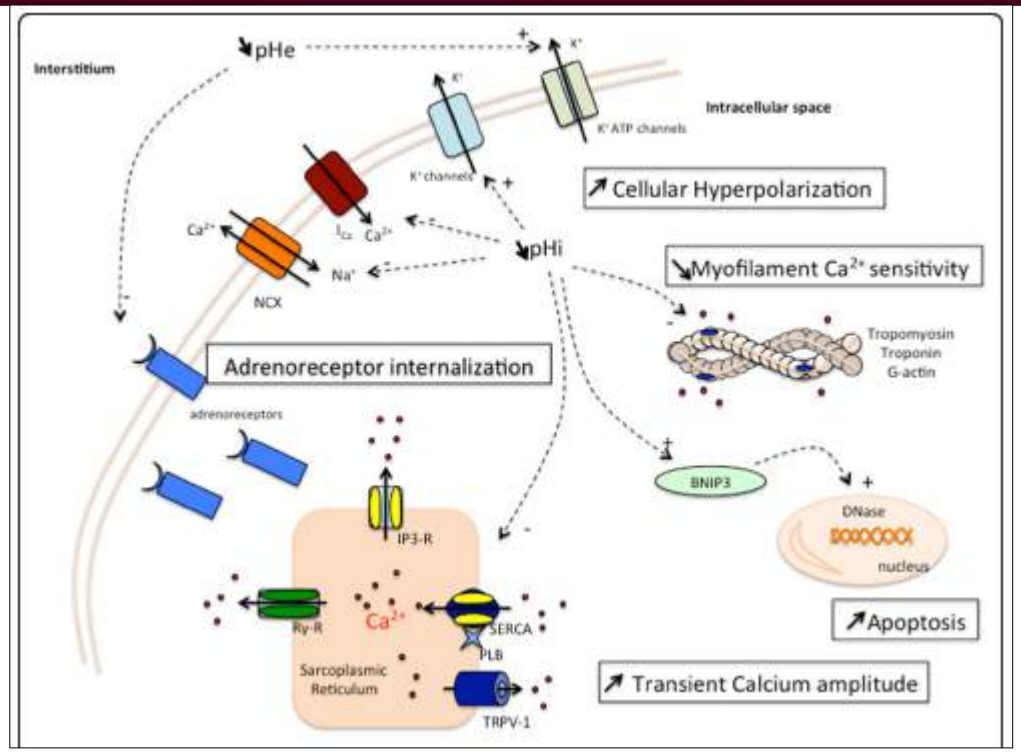
50-70% severe (<0.8-0.9mmol/L)
→ More coagulopathy
→ More blood transfused
→ Double mortality (49% vs. 24%)
→ Calcium replacement after 4U, but never resolved (still <1.12mmol/L)

One unit of citrated blood product can drop iCa

Give 2g CaCl or 6gm Ca gluconate EARLY (<4 U transfused)

Giancarelli. J Surg Res. 2016.
Ho. Anesth Intens Care. 2011.

How bad is the acidosis itself?



Depressed myocardial contractility
Reduced myocardial relaxation
iNOS expression, vasodilation
Reduced adrenergic responses
Membrane hyperpolarization (vasorelaxation)

CARDIOVASCULAR FAILURE

LACTIC ACIDOSIS:
-- altered Ca2+ transients/ electrical instability
-- mitochondrial failure
-- increased intracellular Ca2+/ caspase activation

CELL DEATH

It's a complex problem.
It's bad.
Need buffering.
Albumin? THAM?

Kimmoun *Crit Care* 2015.

What else can you do? Warm the patient!

- Hypothermia is metabolic as well as due to environmental exposure
- Need ACTIVE re-warming

Field-expedient heat sources?

Beware vasodilation if not yet resuscitated…

So, RDCR w/o blood?

Hemorrhage control plus…

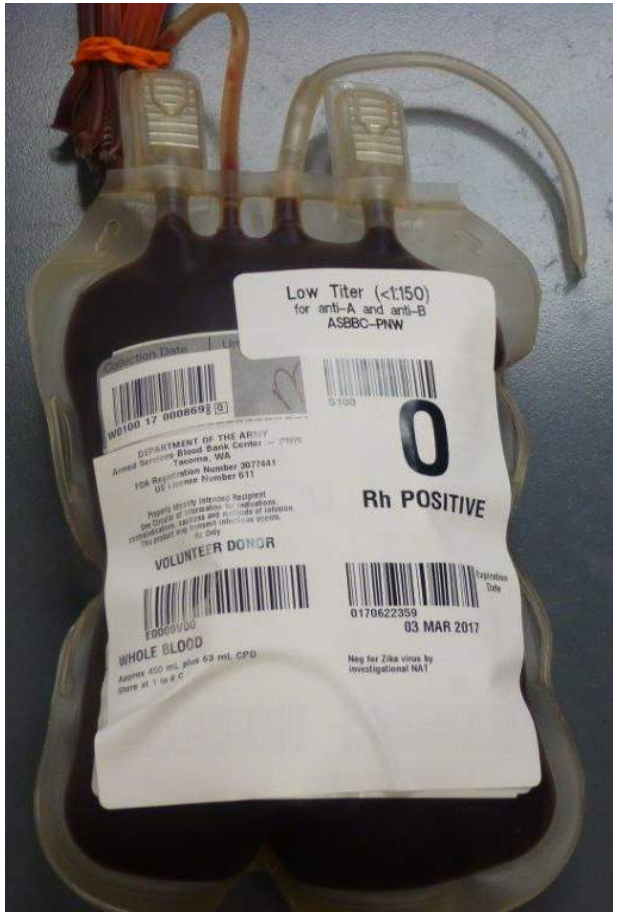
1) HBOC + FDP + TXA + Ca2+
2) FDP + TXA + Ca2+
3) Alb 25% (& plasmalyte?) + FGN + TXA + Ca2+

Re-warming

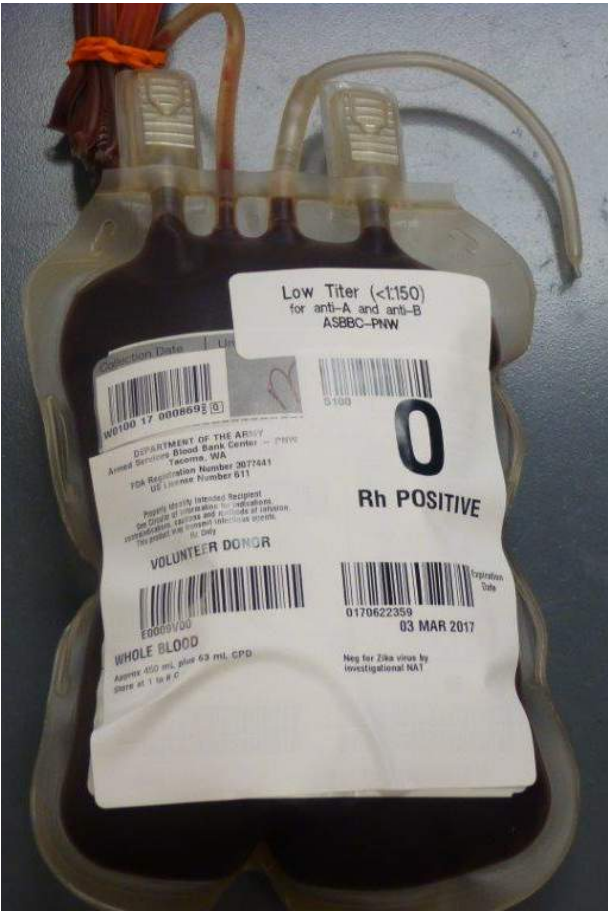
THAM?
PCC?
Dried/artificial PLT?

There are no simple solutions…

Except for Mother Nature's!



WB vs. non-blood: *Really?*



	WB 4°C	Non-blood! (Actually mostly blood-derived)
Hgb HCT	12-13 35-37	Lower than starting
PLT	138-165	Lower than starting
Fibrinogen, Factors	Normal @ baseline, FVIII ≥ 50% d7	Well, maybe with FGN & PCC…
TEG	Nearly normal d21	Reduced vs. WB
PLT aggregation	≥ 50% baseline d7-10	Not good
Practical aspects	One bag, one storage mode	Still have to bring lots of products…

RDCR

- Hemorrhage and injury cause **acute blood failure** or **hemovascular dysfunction**.
- **DCR treats drivers of blood failure simultaneously with blood (and TXA).**
- DCR is most effective if **started immediately: RDCR**.
- Risk-benefit of products should be considered in light of exsanguination mortality.
- Simplicity is a virtue: **LTOWB**.

THERE ARE NO GOOD SUBSTITUES FOR BLOOD… but there are things you can do to improve the patient's odds including: *TXA, calcium, warming and MAYBE HBOC+FDP, 25% albumin plus FGN*

LTOWB

Cold Platelets

Questions?

TXA

FDP