



Le future de la recherche pour le soin du blessé

Transformational Change in Combat Casualty Care Research

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Un nouveau problème – combat de haute intensité, à grande échelle



2001-2021

**Iraq, Afghanistan, Sahel/HoA:
contre-insurrection/terrorisme**

Futur (bientôt?)

***Large Scale Combat Operations (LSCO)
Multi-Domain Operating Environment
(MDO)***



Changing Adversaries → Changing Battlefield Medical Challenges



Afghanistan / Iraq:
IEDs, small arms, mortars,
RPGs →



*Low casualty density,
rapid evacuation to
surgery*

Russia / China:
Sophisticated / lethal
weapons, contested air →

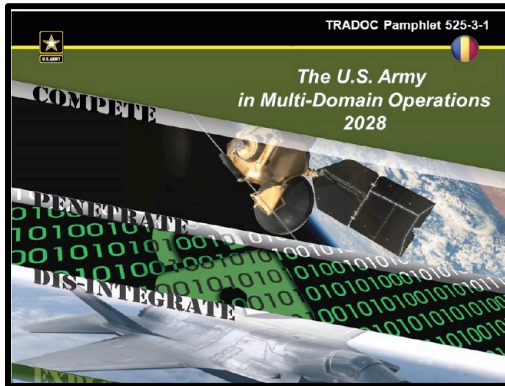


*High casualty density,
delayed evacuation to
surgery*





LSCO & MDO = PFC « Prolonged Field Care » (soin sur le champ prolongé)



La problématique de MDO:

- Cyber-attaque
- Canons/fusées avec précision à longue portée (70+ km)
- Défenses aériennes, drones



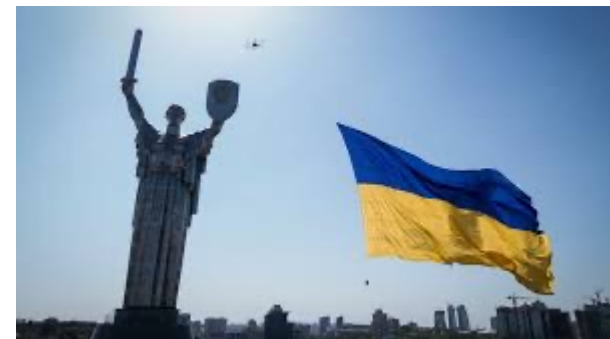
IMPACT:

- Forces très dispersées
- Communication dégradée
- Evacuations par air difficile/impossible
- Longue évacuation aux Rôles 2/3
- **Le blessé pourra être sur le champ pendant 6-72 heures -- pas 1 heure!**





LSCO & MDO = Ukraine aujourd'hui





Accès rapide à la transfusion et arrivée rapide en bloc opératoire = vies sauvées



Original Investigation

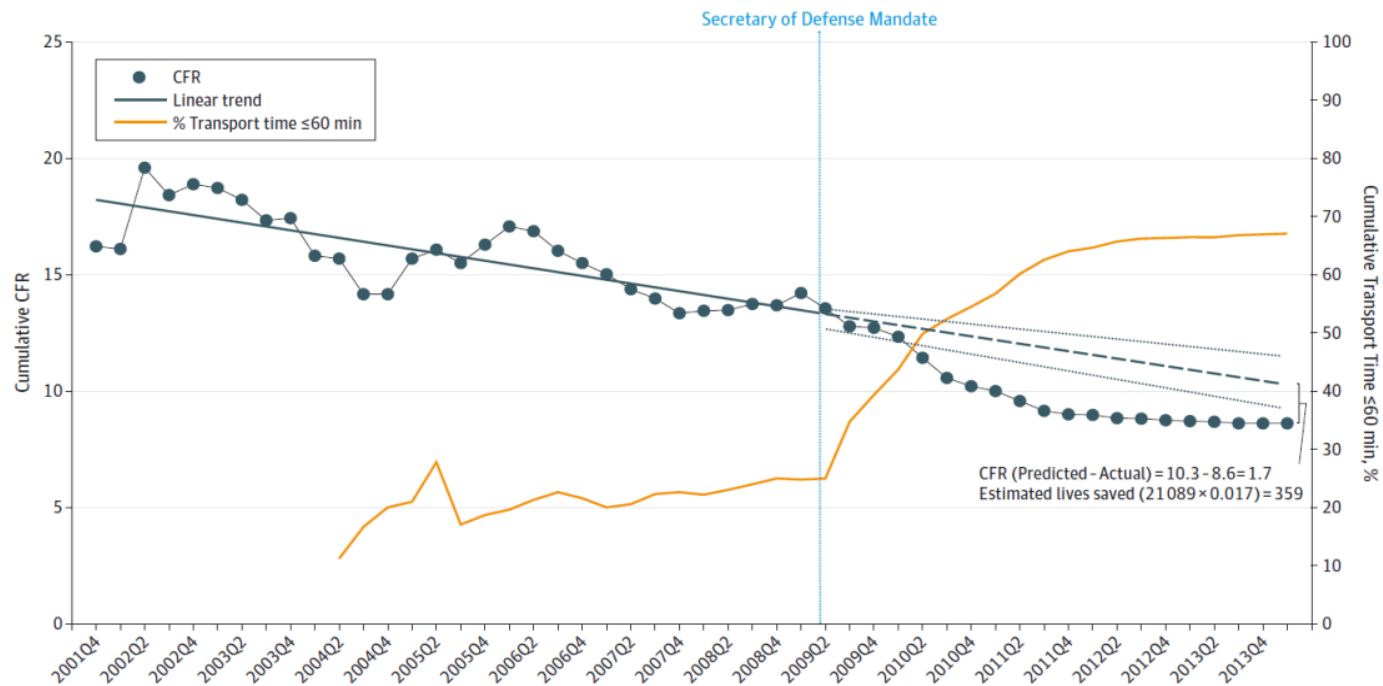
The Effect of a Golden Hour Policy on the Morbidity and Mortality of Combat Casualties

Russ S. Kotwal, MD, MPH; Jeffrey T. Howard, PhD; Jean A. Orman, ScD, MPH; Bruce W. Tarpey, BS; Jeffrey A. Bailey, MD; Howard R. Champion, FRCS; Robert L. Mabry, MD; John B. Holcomb, MD; Kirby R. Gross, MD

JAMA Surg. doi:10.1001/jamasurg.2015.3104

Published online September 30, 2015.

Figure 1. Case Fatality Rate and Transport Time





Accès rapide à la transfusion et arrivée rapide en bloc opératoire = vies sauvées



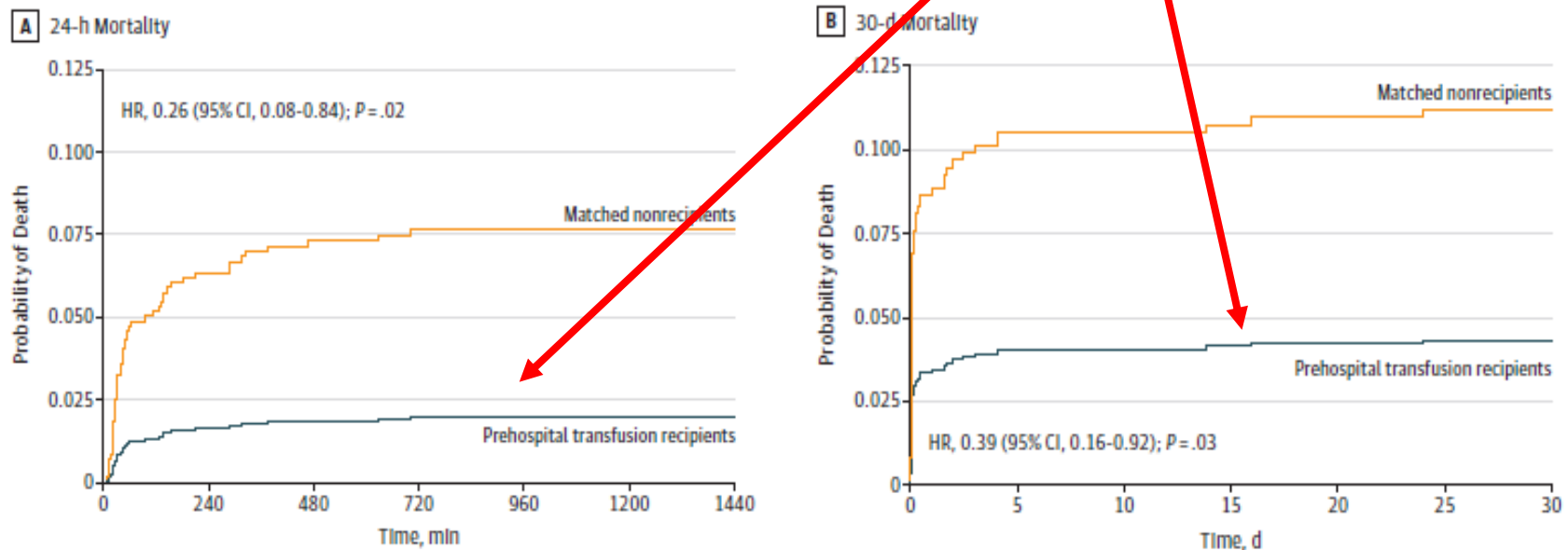
JAMA | Original Investigation

Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival

Stacy A. Shackelford, MD; Deborah J. del Junco, PhD; Nicole Powell-Dunford, MD; Edward L. Mazuchowski, MD, PhD; Jeffrey T. Howard, PhD; Russ S. Kotwal, MD, MPH; Jennifer Gurney, MD; Frank K. Butler Jr, MD; Kirby Gross, MD; Zsolt T. Stockinger, MD

Lower mortality w/ prehospital transfusion

Figure 3. Mortality of Prehospital Transfusion Recipients vs Matched Nonrecipients





Le grand défi



Comment va-t-on soigner les combattants blessés sans accès rapide à la transfusion et la chirurgie?

On ne peut pas continuer à faire les mêmes chose que l'on a fait depuis 20 ans!

« WE NEED BREAKTHROUGHS! »



Le progrès en traumatologie a été lent et incrémental...



Bandages / Poultices:
Imhotep, Egypt 3000 BC



Blood Transfusion at the Frontlines: WWI, 1918



Tourniquet: 200 BC;
17th century

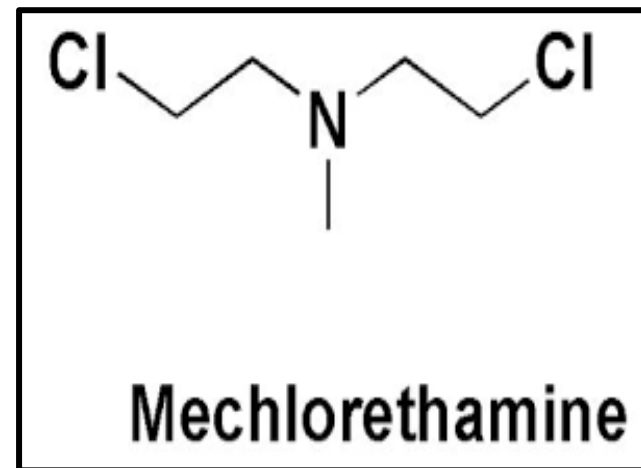
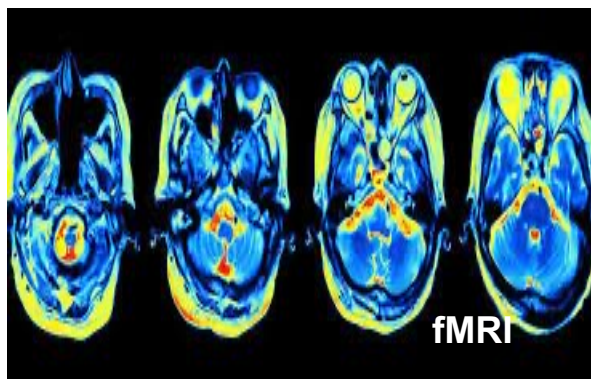
Freeze-dried plasma:
1930s, WWII



TXA: 1960s



Nous devons avoir des changements transformationnels!



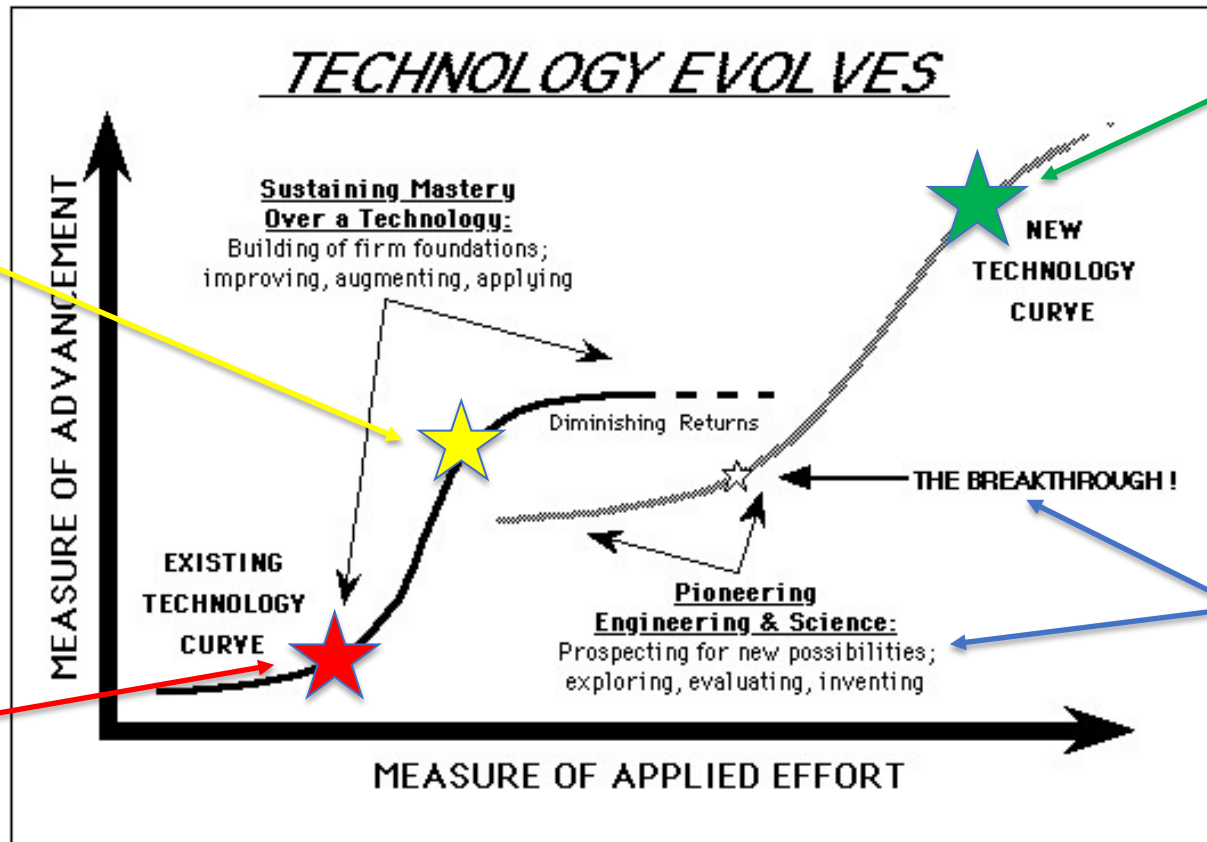


Nous avons besoin d'innovation radicale!



Combat
Casualty
Care 2021

Combat
Casualty
Care 2001



Where we
need to be for
MDO/LSCO

What we need
to do NOW!



Fundamental Challenges of Prolonged Field Care: the 5 Pillars



Prolonged Survival

Prevent, Detect, Treat

Blood &
Shock
Resuscitation

Pillar 1

Hemorrhage
& vascular
dysfunction

Pillar 2

Organ support
automation
technology

Pillar 3

Combat
wound care

Pillar 4

Pain, sensory
trauma

Pillar 5

Acute (0-1 hours)

Blood / Airway Loss
→ ↓ DO₂ → ↓ ATP →
↓ pH → ↑ K⁺
→ Cell death
→ Endothelial
dysfunction
→ Coagulopathy

Intermediate (2-6 hours)

Vascular dysfunction / edema /
thrombosis
→ Organ failure: brain, heart,
kidney, lung
Wound contamination &
colonization

Delayed (6-24 hours)

Inflammatory second hit
Progression of organ failure
Wound progression, thrombosis & infection



Clinical Problems Associated with the 5 Pillars

Clinical Challenges

Prevent, Detect, Treat

Blood &
Shock
Resuscitation

Pillar 1

Hemorrhage
& vascular
dysfunction

Pillar 2

Organ support
automation
technology

Pillar 3

Combat
wound care

Pillar 4

Pain, sensory
trauma

Pillar 5

- | | | | | |
|---|--|--|--|---|
| <ul style="list-style-type: none">• Inadequate blood supply vs. demand• Excessive "Shock dose"/ oxygen debt → irreversible shock | <ul style="list-style-type: none">• Non-compressible hemorrhage• Endotheliopathy, coagulopathy, thrombosis → organ failure, bleeding• Compartment syndrome | <ul style="list-style-type: none">• ARDS, blast lung, inhalation injury• Renal failure• Cardiac ischemic injury, contusion | <ul style="list-style-type: none">• Contaminated wounds• Complex soft tissue / long bone injury• Burns | <ul style="list-style-type: none">• Pre-hospital pain management• Post-operative pain management w/ delayed evacuation |
|---|--|--|--|---|

Overwhelmed providers lacking sensors, automation, decision support, telehealth to enable solutions



Promising Technologies for Clinical Problems Associated with the 5 Pillars



Future Solutions

Prevent, Detect, Treat

Blood &
Shock
Resuscitation

Pillar 1

- Shock drugs (e.g., PHDi, PDHKi)
- Enhanced forward blood availability & delivery (FDP, UAV, etc.)

Hemorrhage
& vascular
dysfunction

Pillar 2

- Partial REBOA
- Endothelial stabilizer drugs (e.g., BKr antagonist, TIE2 agonist, etc.)

Organ support
automation
technology

Pillar 3

- ECMO, CRRT capability forward, w/ safer anticoagulants
- Decision support systems, automation, telehealth

Combat
wound care

Pillar 4

- Pathogen agnostic anti-infective dressings
- Enhanced fracture stabilization
- Wound care bundle

Pain, sensory
trauma

Pillar 5

- Pre-hospital loco-regional pain management
- Ketamine autoinjectors
- Novel analgesics

New technologies to fundamentally change what is possible in the prehospital environment!



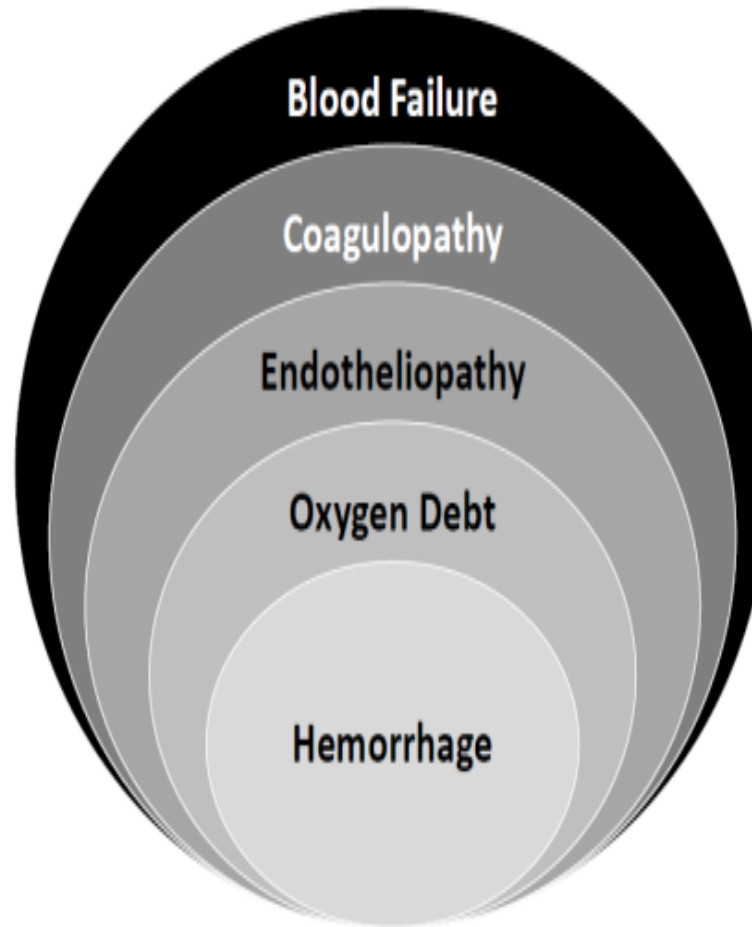
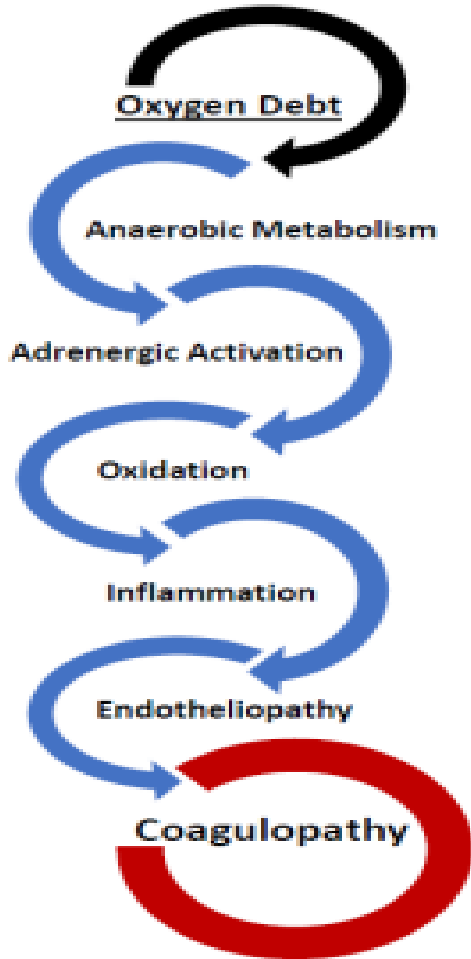
Exemple de nouveau concept: la défaillance du sang « *Blood Failure* »



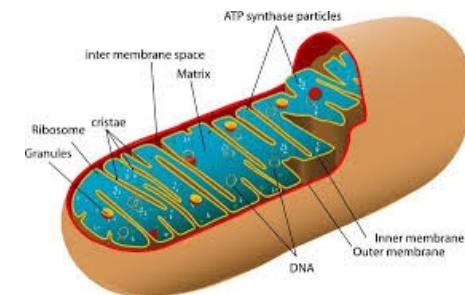
- Réaliser que le sang est un organe, pas une fluide de remplissement
- Réaliser que le sang existe en symbiose avec l'endothélium
- Réaliser que l'hypoxie mène à la faillite du métabolisme dans le choc, et que la coagulopathie et l'endothéliopathie y sont liés
- Chercher des interventions **transformationnelles** à la base de la pathophysiologie



Loss of Blood → hypoxia → metabolic failure → endotheliopathy → coagulopathy → **Blood Failure**



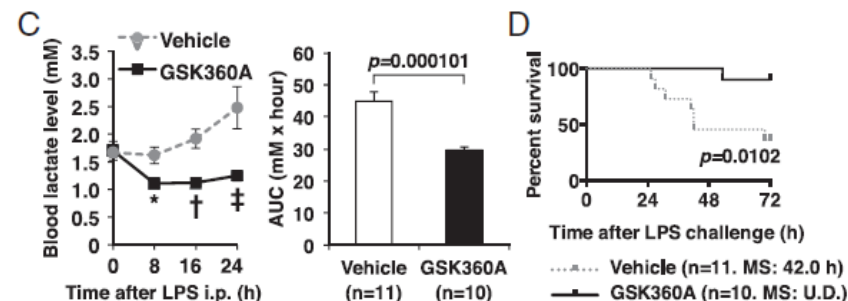
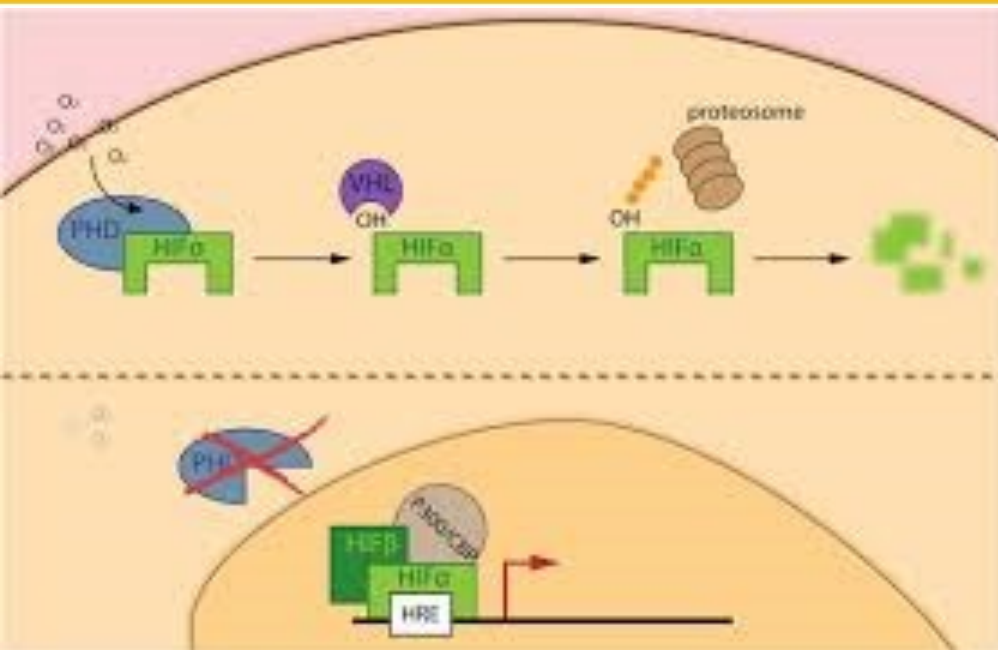
Mitochondrial Dysfunction



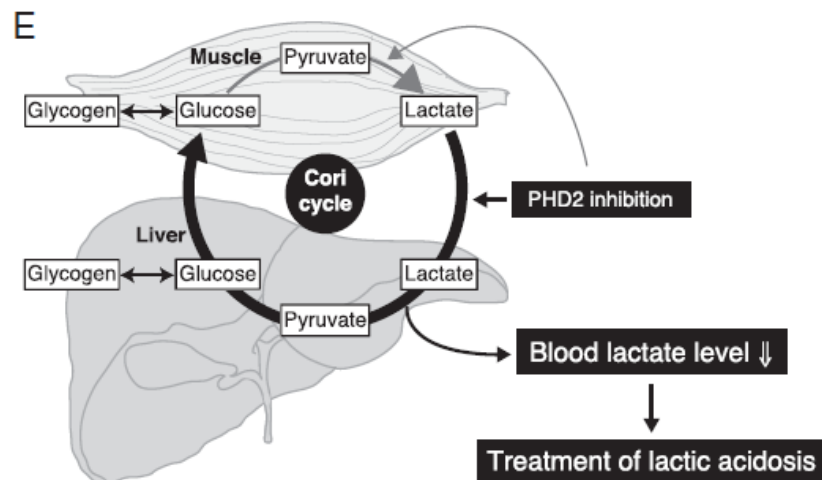
Bleeding → hypoxia → metabolic failure → blood failure → **bleeding** → hypoxia...
Need blood ASAP & “shock drug” to break the cycle!



Harness the body's hypoxia response: *Clear lactate via gluconeogenesis*



Suhara PNAS 2015.

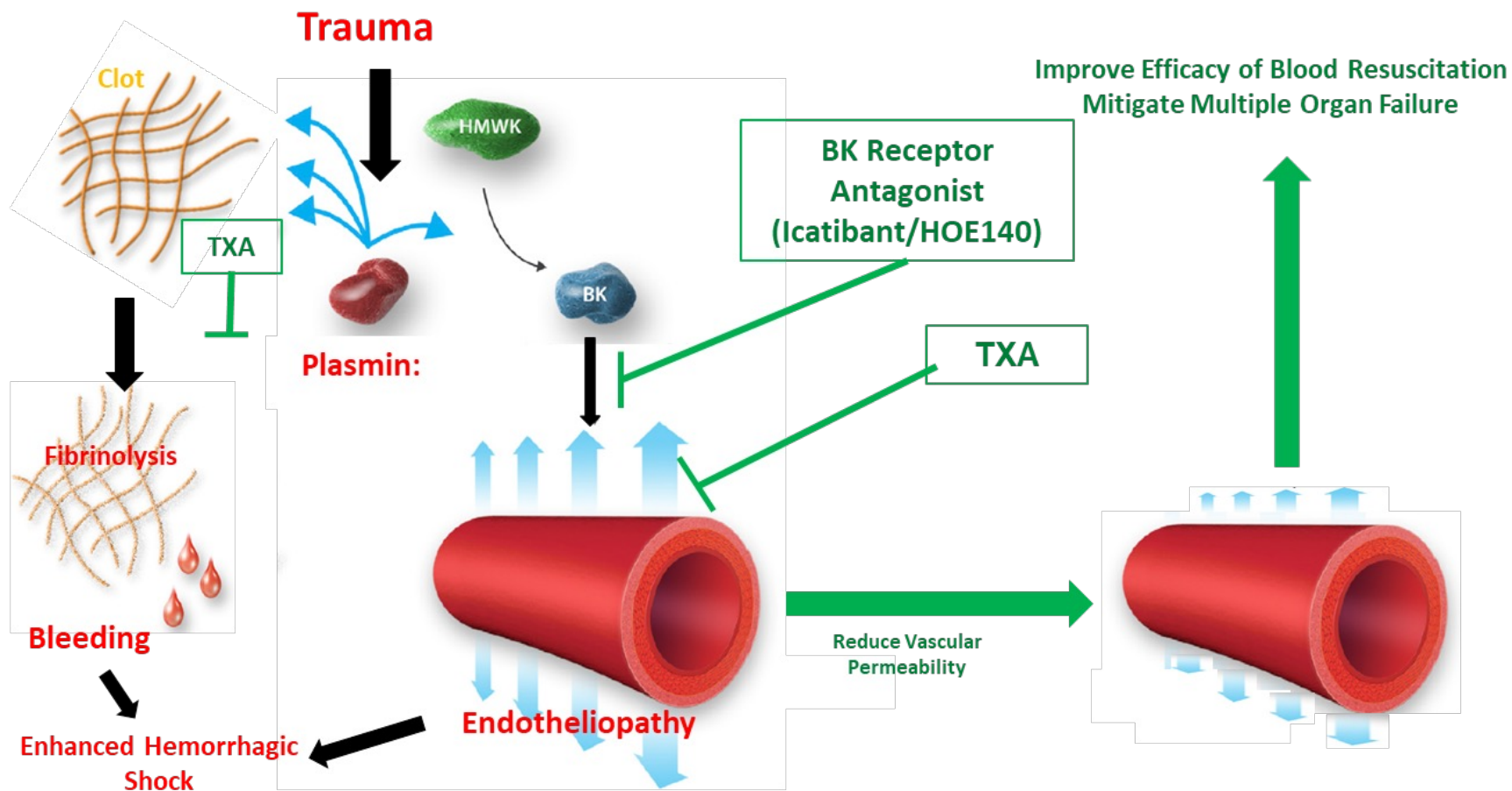


Under development in CKD to
treat anemia (Roxadustat; see
NEJM 2019)

-- Acute timeframe of action



Icatibant and Tranexamic Acid: targeting plasmin (a driver for hemovascular dysfunction)





New target for evaluation in hemorrhagic shock: Angpt1/2 – Tie2



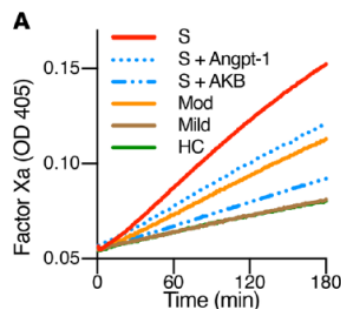
Tissue Barriers 3:1-2, e957508; January-June 2015; © 2015 Taylor & Francis Group, LLC

The angiopoietin-Tie2 signaling axis in the vascular leakage of systemic inflammation

Katelyn E Milam¹ and Samir M Parikh^{1,2,*}

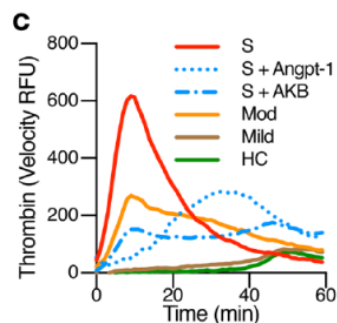
¹Center for Vascular Biology Research; Beth Israel Deaconess Medical Center and Harvard Medical School; Boston, MA USA; ²Division of Nephrology; Beth Israel Deaconess Medical Center and Harvard Medical School; Boston, MA USA

**Angpt2 release from W-P bodies during
inflammation → antagonizes Tie2 signaling**

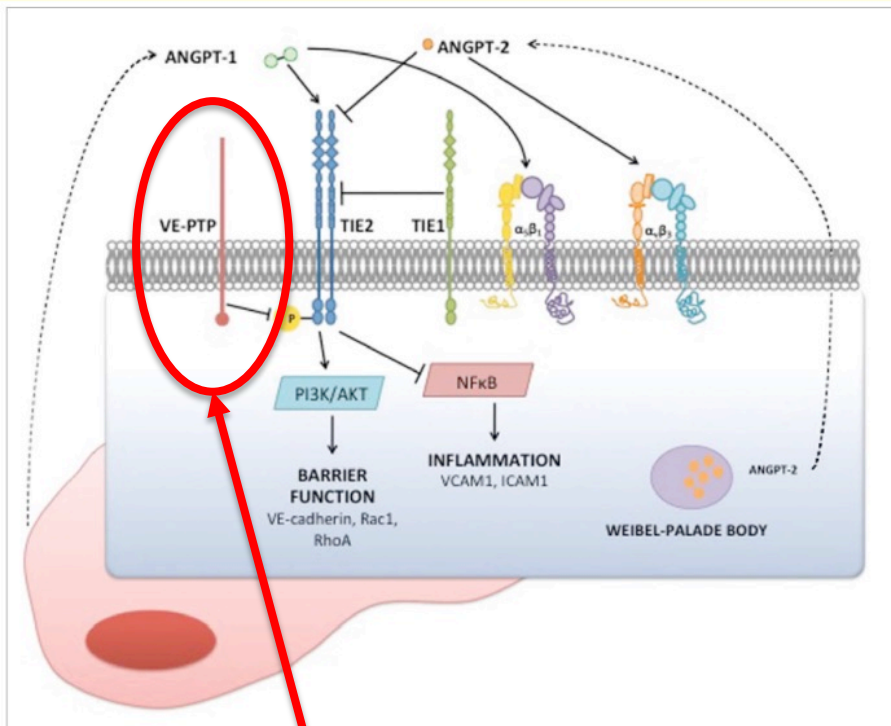


**AKB-9778
restores EC
anticoagulant
phenotype**

**-- less
consumptive
coagulopathy?**



**-- less
microvascular
thrombosis &
organ failure?**



**VE-PTP = Tie2 “off
switch” AKB-9778 target**

**Tie2 activation protects against
prothrombotic endothelial dysfunction in
COVID-19** JCI insight

Reference information: JCI Insight.
2021;6(20):e151527.
<https://doi.org/10.1172/jci.insight.151527>

Alex A. Schmaier,¹ Gabriel M. Pajares Hurtado,² Zachary J. Manickas-Hill,³ Kelsey D. Sack,^{2,4,5} Siyu M. Chen,⁶ Victoria Bhambhani,⁶ Juwera Quadir,⁶ Anjali K. Nath,⁶ Ai-ris Y. Collier,⁷ Debby Ngo,⁴ Dan H. Barouch,^{2,8} Nathan I. Shapiro,⁹ Robert E. Gerszten,¹ Xu G. Yu,^{3,10} MGH COVID-19 Collection and Processing Team,^{3,5,11} Kevin G. Peters,¹² Robert Flaumenhaft,¹³ and Samir M. Parikh^{14,15}



Past, Present and Future of Resuscitation?



Whole Blood is King!

Components are cool!

WW I

WW II

Korea

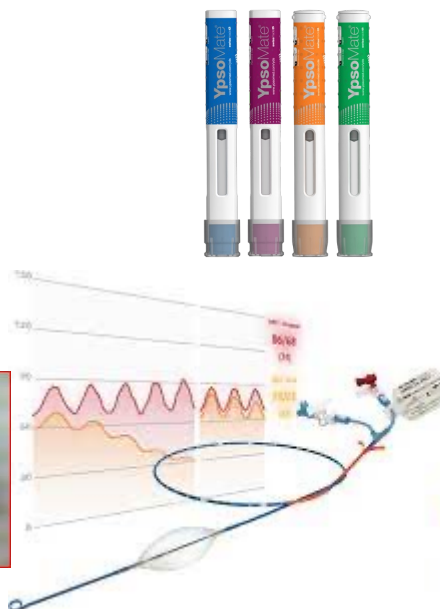
Vietnam

OIF/OEF

60 years of Blood

30 years of Clear Fluids

**Back to
the future!**



- **WB + plasma + ...???**
- **shock drugs**
- **vascular stabilizers**
- **Partial REBOA, ECMO**
- **Optimized forward wound care & pain control**



LTOWB





Questions?

