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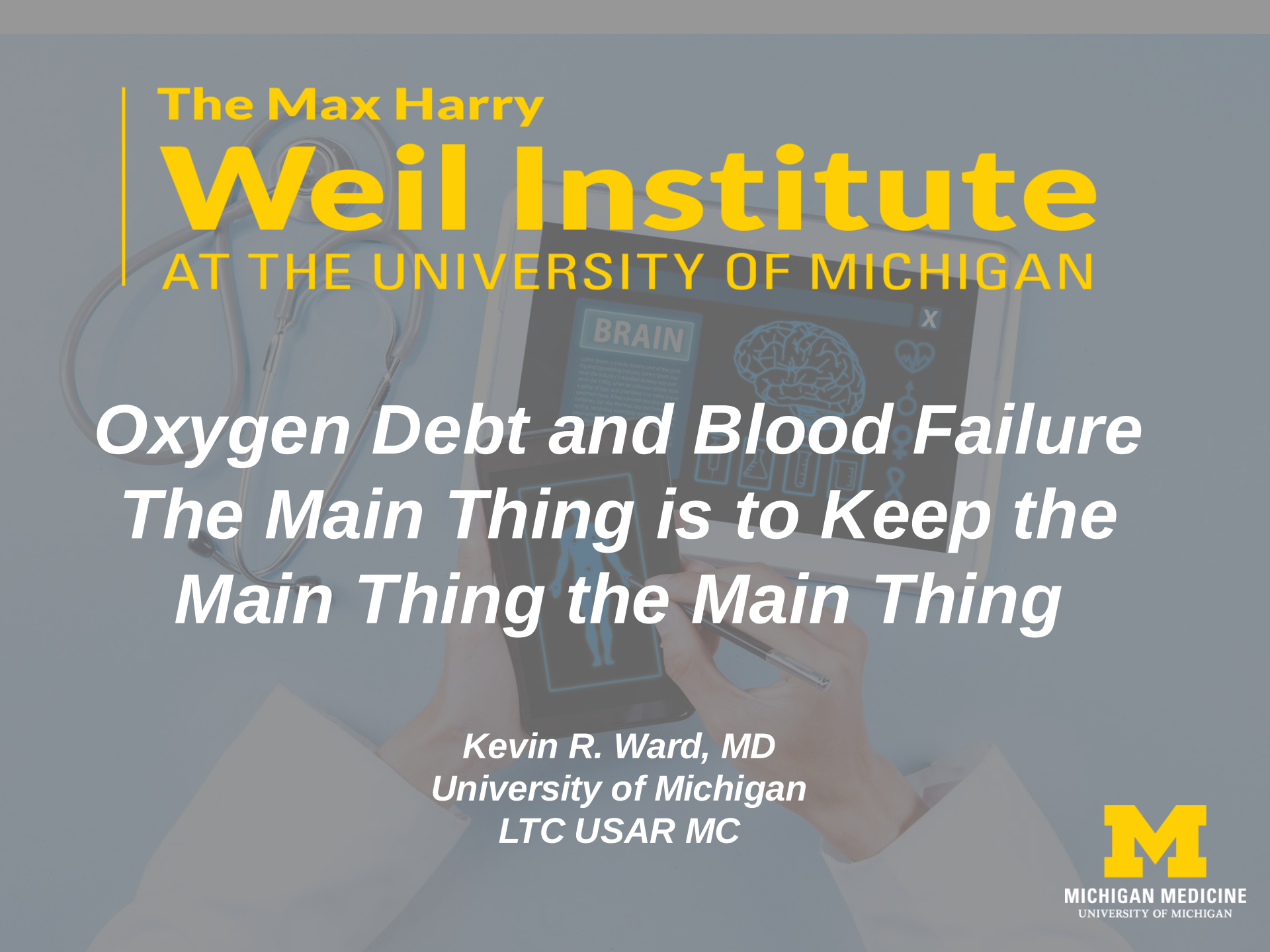

Oxygen Debt and Blood Failure The Main Thing is to Keep the Main Thing the Main Thing

Kevin R. Ward, MD
University of Michigan
LTC USAR MC

MICHIGAN MEDICINE
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COI Disclosures
Convergence of Interest

- Funding from the NIH, DoD, NSF, Industry, University of Michigan
- Intellectual Property Owned by U. Mich and VCU: Licensed to: New Vital Signs, Pendar Medical, Rapid Oxygen, Fifth Eye, Z-Medica, Cook Medical Precision Trauma and InspireRx, etc.
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- LTC US Army Reserves Medical Corps.
  - My opinions do not necessarily reflect those of the DoD

Rao Ivatury, MD: 1947-2024

On Behalf of the Weil Institute

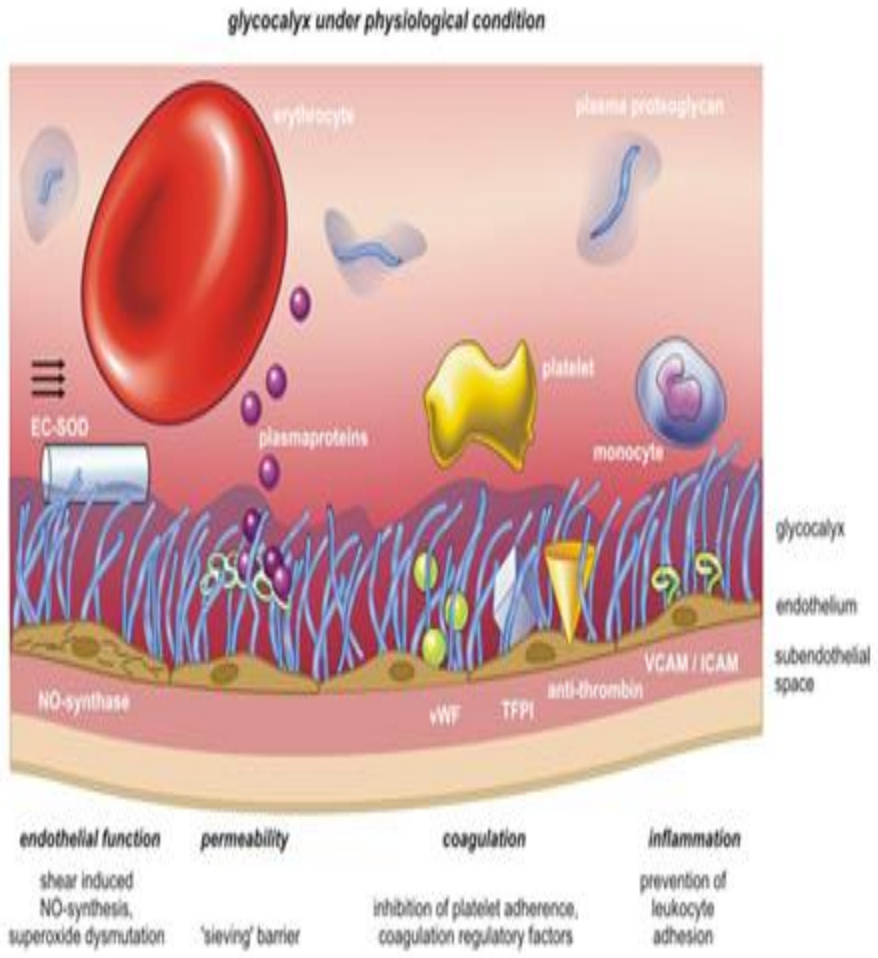
Ward's Principle

You are Entitled to Have Your Own Opinion

But

You are NOT Entitled to Have Your Own Physiology

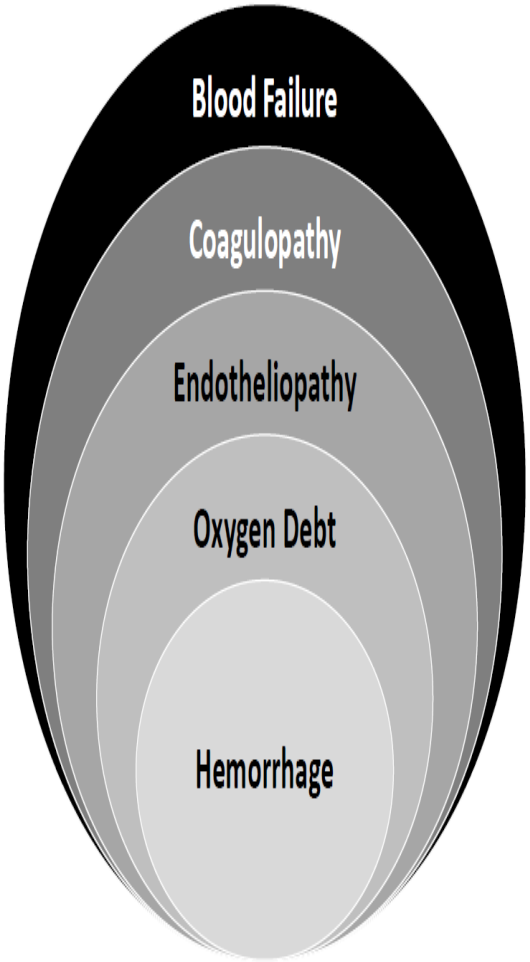
Blood as an Organ= Blood + Endothelium



- Blood: RBCs, WBCs, Platelets, Plasma
- Endothelium 10^{13} Cells
- Micorcirculation Estimated to cover an area of up to 7000 m^2
- Largest organ system.

Blood as an Organ and Blood Failure

BLOOD FAILURE: An emergent state of blood leading to coagulopathic dysfunction resulting from the physiologic and biochemical exhaustion of the blood-endothelium interface caused by a combination of hemorrhage driven shock and tissue hypoxia, tissue injury and blood cellular and plasma component loss.

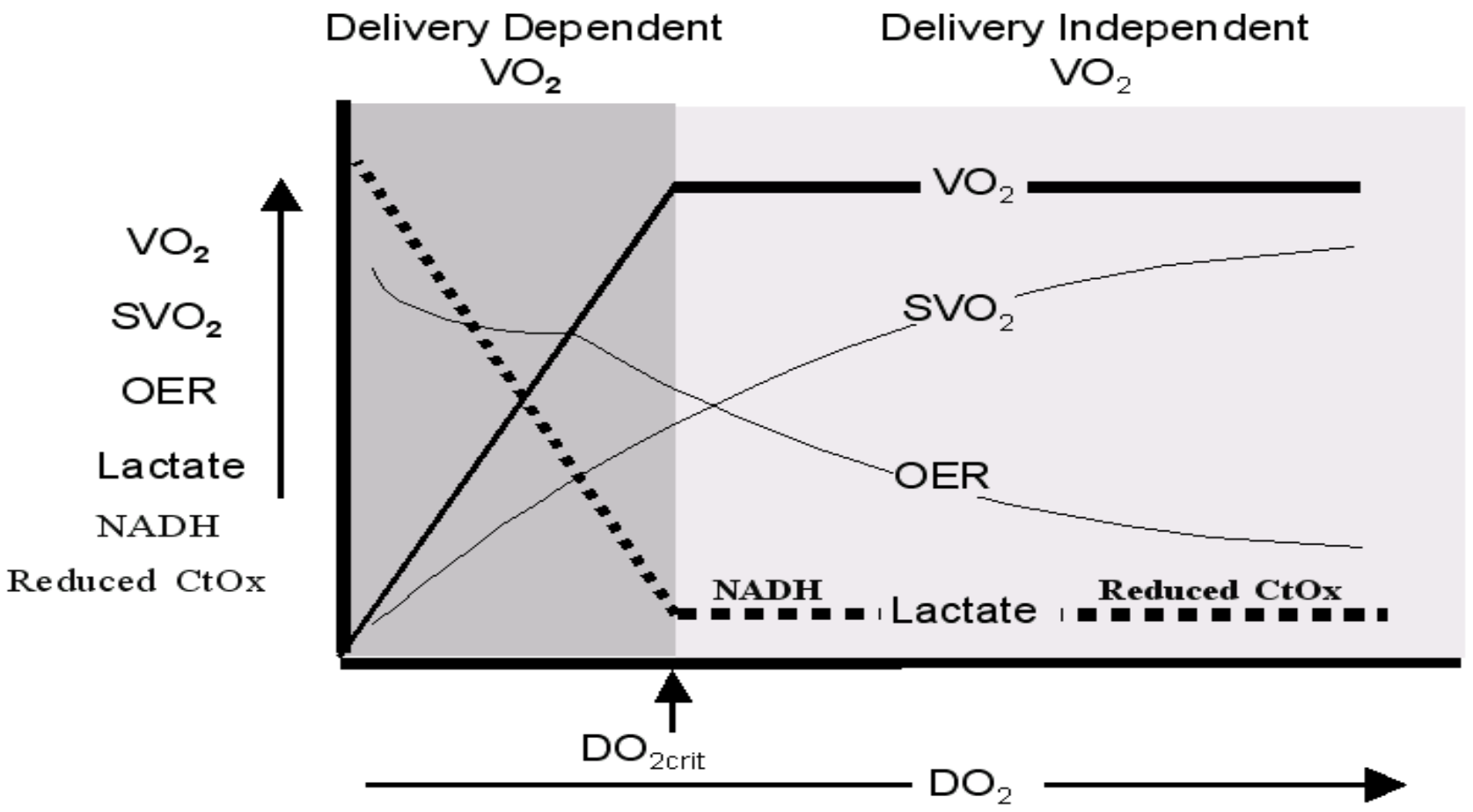


Pre-surgical resuscitation phase (RDCR and DCR) are designed to limit ongoing hemorrhage and to produce or preserve an adequate level of physiologic reserve to deliver a casualty that can be salvaged with the follow-on strategy of DCS.

Definition of Shock

Insufficient oxygen delivery to meet the metabolic demands of tissues

Biphasic Oxygen Delivery/Consumption Relationship: Curve of Life

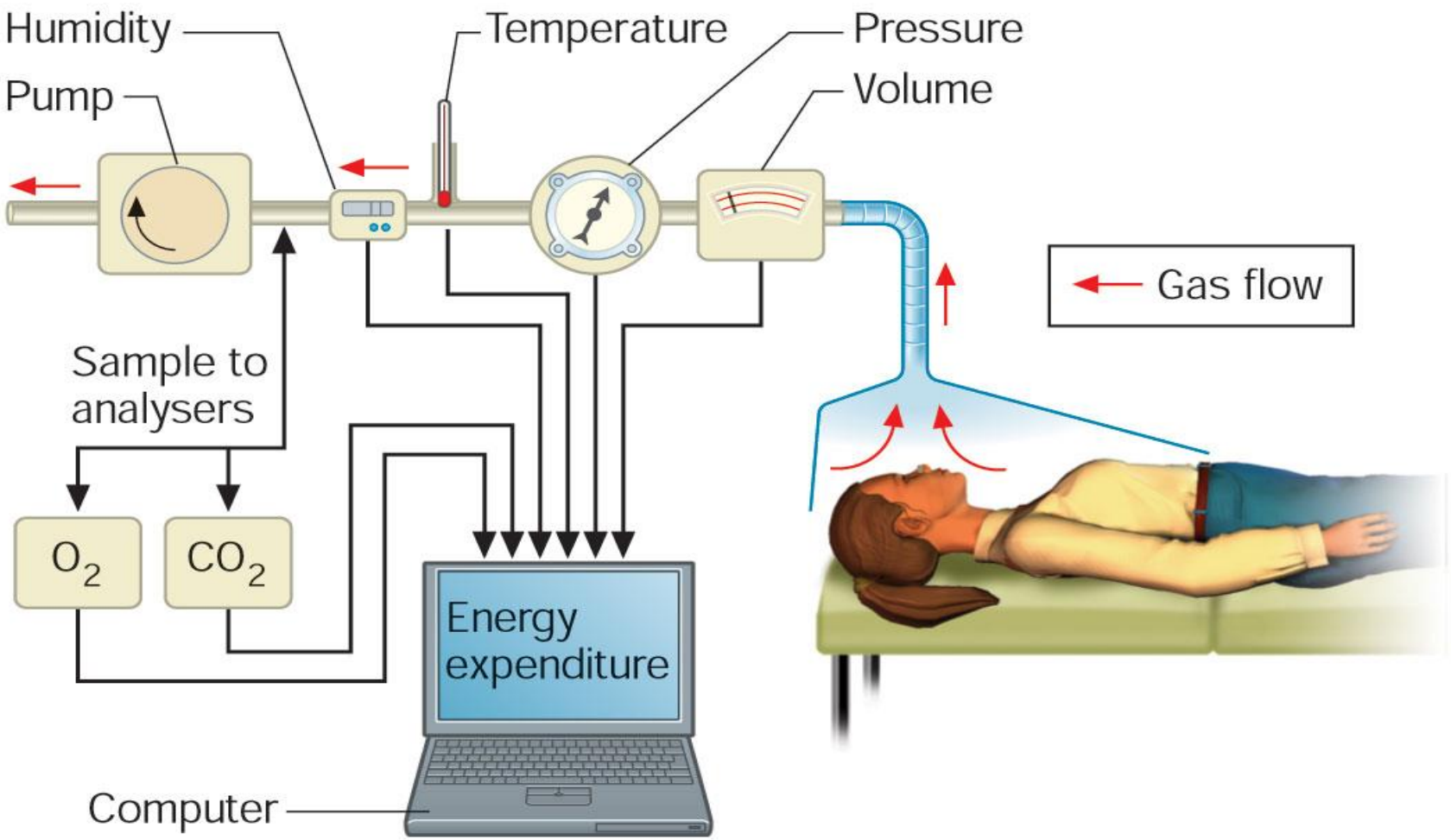


Oxygen Debt

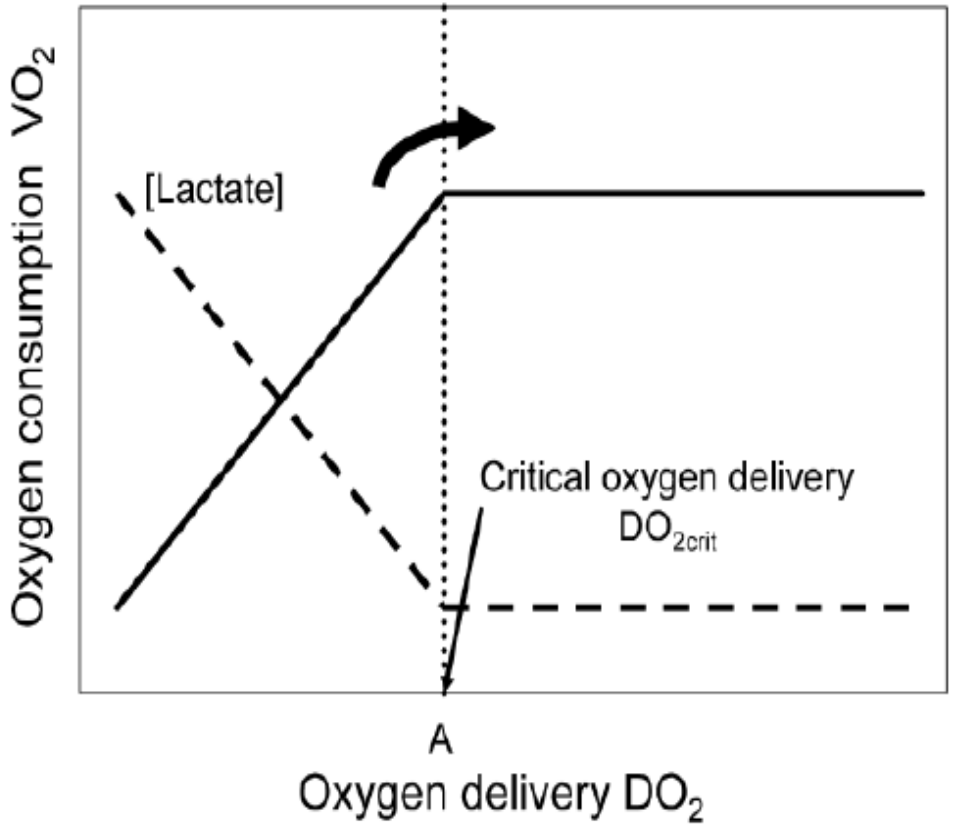
- The Magnitude (Degree and Time) that VO2 is Below Critical DO2

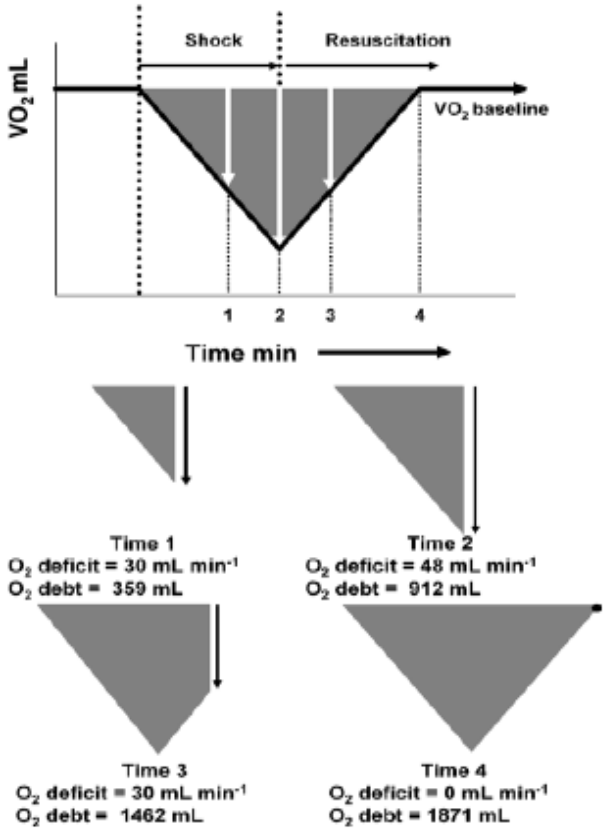
- Magnitude of Total Body Ischemia?

Indirect Calorimetry for Oxygen Debt Measures



Accumulated Oxygen Deficit = Oxygen Debt
Think of Debt as Whole Body Ischemic Burden



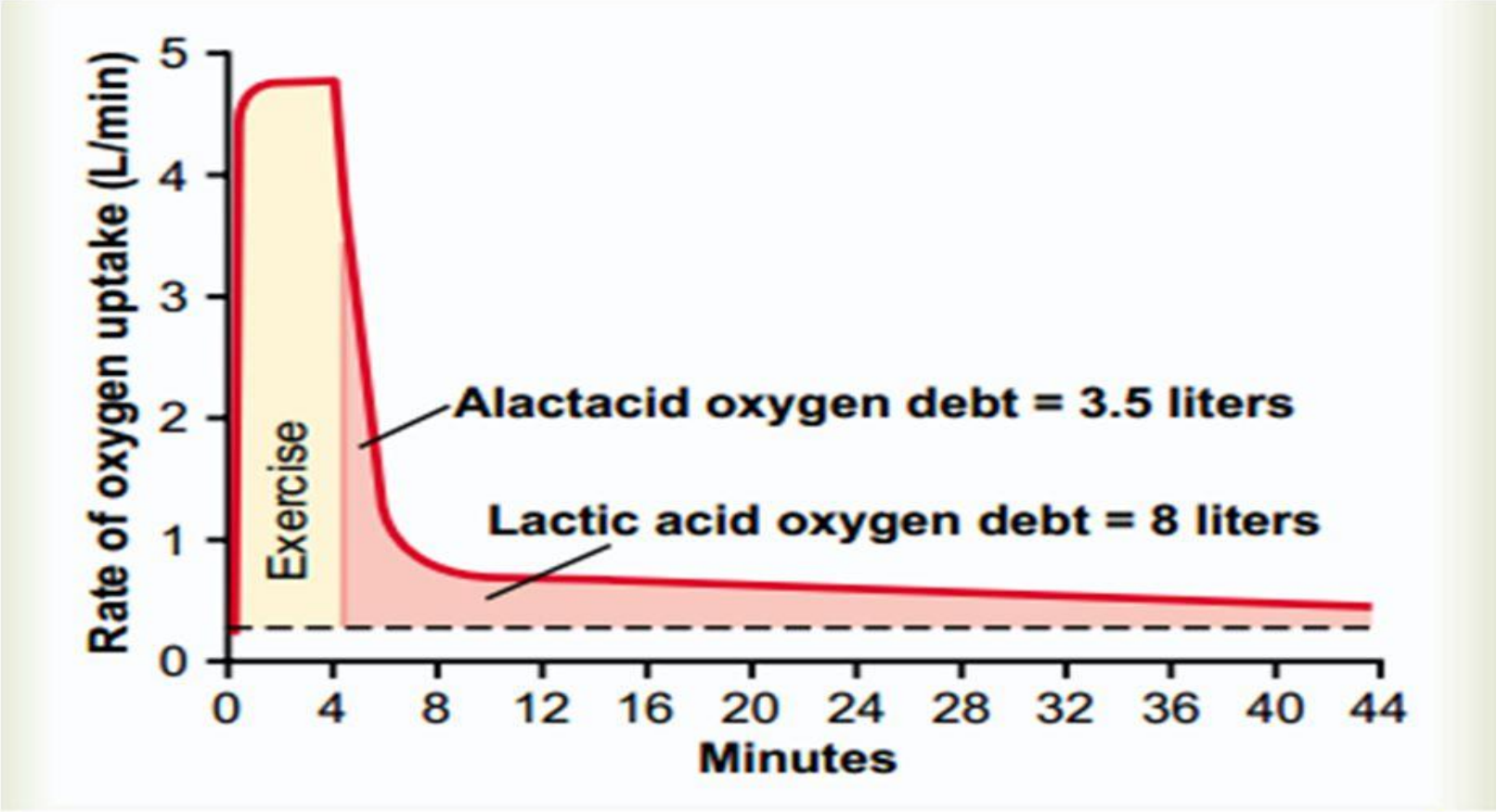


Barbee RW, Reynolds PS, Ward KR. Shock. 2010 Feb;

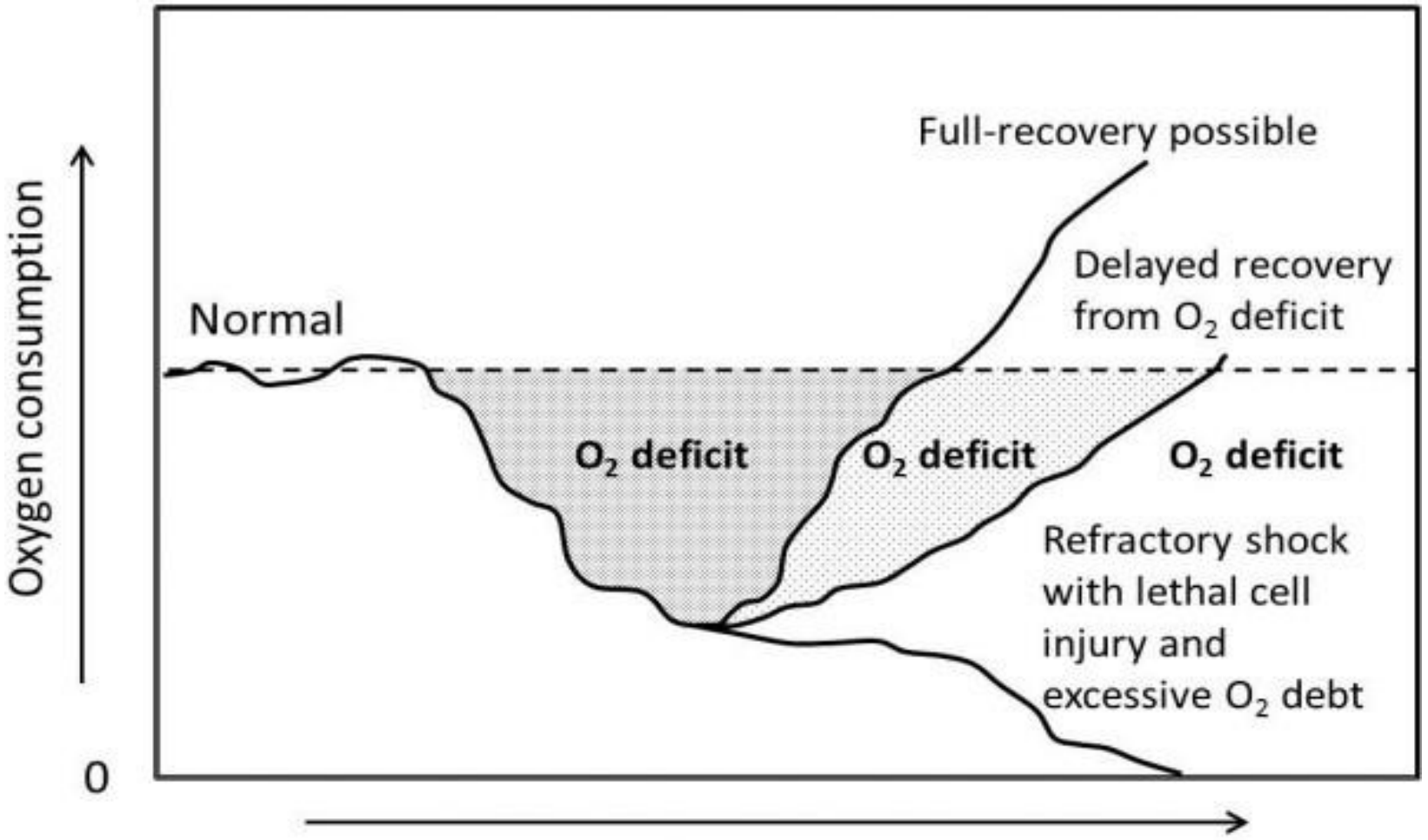
Repaying the Debt: Think of Sleep Debt

- Not enough just to Resolve Delivery Dependent VO2
- Lessons Learned From Exercise
  - Oxygen Already Stored
    - 0.3 liters stored in muscle
    - 1 liter stored in hemoglobin: 0.25 liters in other fluids
    - 0.5 liters stored in lung
  - Replenish Energy
    - 2 liters to replenish phosphagen system
    - 8 liters to replenish glycogen-lactic acid system

Lessons from Exercise Physiology



Lessons and Misinterpretation from Surgery: William Shoemaker, MD FACS



Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med.

In the Beginning!

OXYGEN DEFICIT AND IRREVERSIBLE HEMORRHAGIC SHOCK

J. W. CROWELL AND E. E. SMITH

Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi

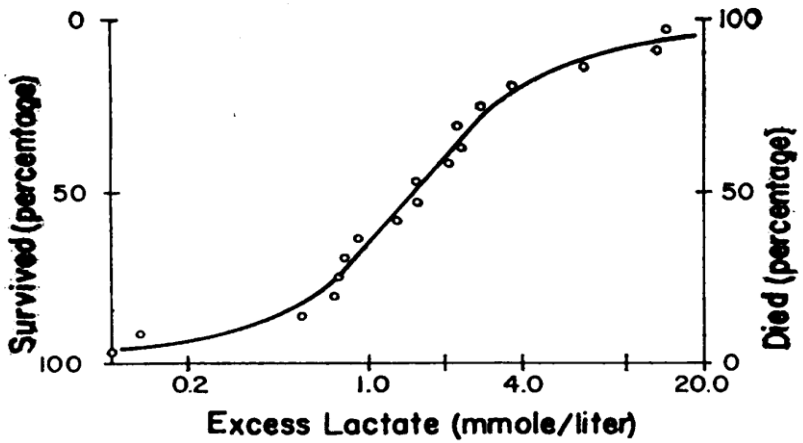
Am. J. Physiol., *206:* 313–316, February, 1964

Irreversible hemorrhagic shock can be produced by a wide variety of variations in bleeding volume or arterial pressure levels. If irreversibility has a single cause, one possible explanation for the diversity in its initiation is that the actual parameter which must be altered quantitatively to produce irreversibility is not altered in a consistent pattern by the different processes of hemorrhage. It seemed possible that, if the total oxygen deficit were measured, it might be a better criterion to indicate the onset of irreversible shock than the different hypotensive methods based on time or other factors.

A device was constructed to record continually the oxygen consumption of a dog, and to summate as the oxygen deficit the difference between normal oxygen use and oxygen use during hypotension. A series of 100 dogs was subjected to hypotension of 30 mm. Hg and various oxygen deficits were allowed to accumulate. It was found that oxygen deficits below 100 ml. per kg. did not result in irreversibility. As the oxygen deficit increased to 120 ml. per kg., half of the dogs died, and oxygen deficits of 140 ml. per kg. or above were uniformly fatal to all control animals. Fifty animals were digitalized with ouabain upon restoration of their normal blood volume. They uniformly withstood oxygen deficits of 140 ml. per kg. However, as the oxygen deficit increased to 165 ml. per kg., half of these treated animals died, and oxygen deficits above 200 ml. per kg. were uniformly fatal to these dogs.

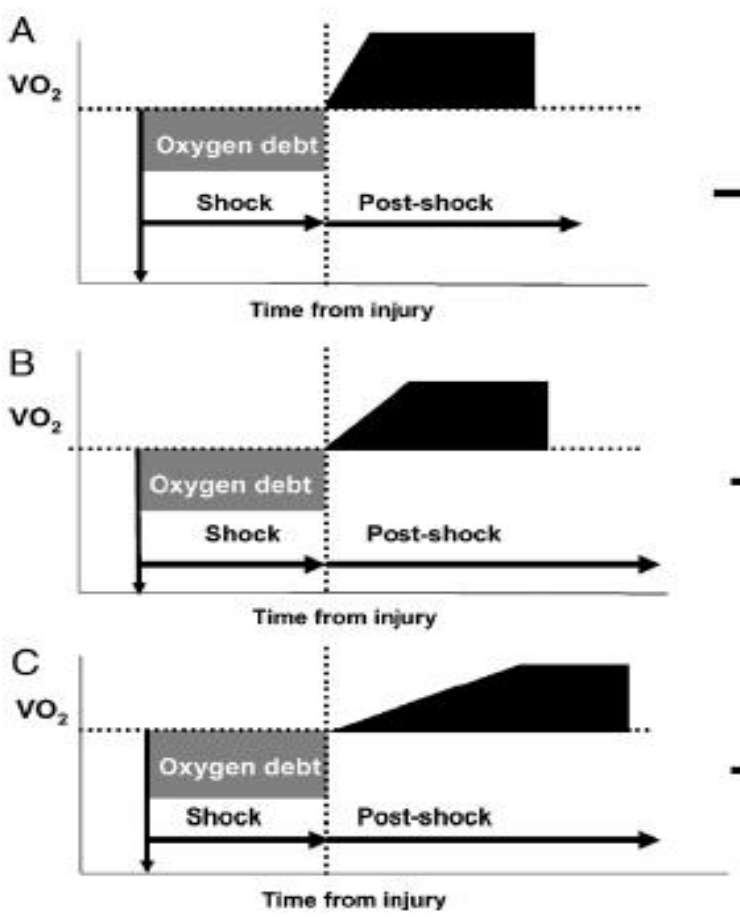
The time required for an animal to show a given oxygen deficit varied tremendously. During hypotension, the dogs showed very different percentages of their previous oxygen usage, and variability from one animal to another was quite sufficient to explain why some animals survived a longer period of hypotension than others. However, it would appear that measuring the oxygen deficit may be a way of producing quantitative information in the field of shock.

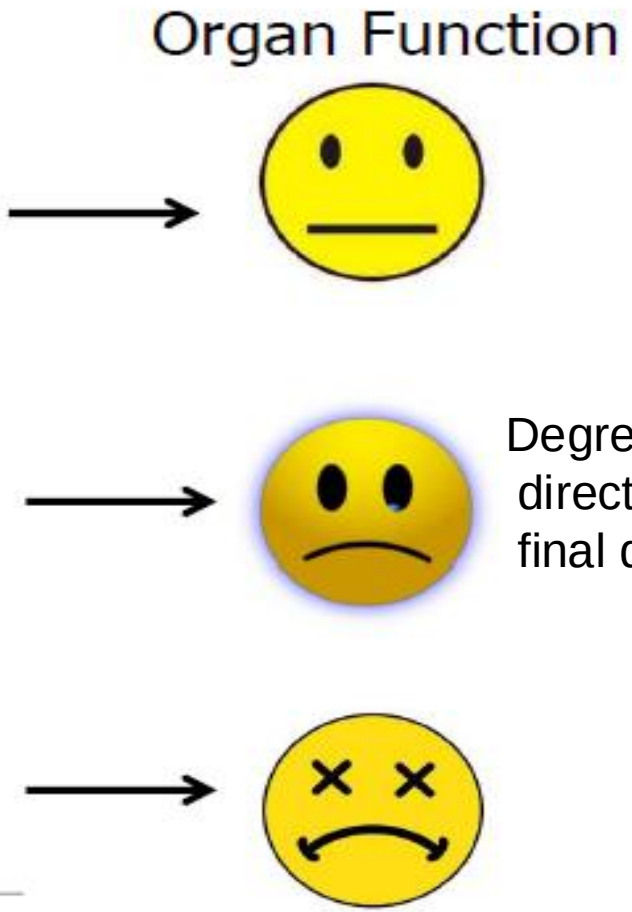
Many drugs and methods have been suggested as changing the susceptibility of an animal to shock. Among the drugs that are supposed to increase the animal's susceptibility are epinephrine and norepinephrine. This study showed that, if the experiment was based on time alone, the catecholamines were detrimental. Dibenzylene and conditioning to hypotension have been suggested as preventing hemorrhagic shock. This study showed that these factors did increase the time required for the animal to develop irreversible shock. If the total oxygen deficit required to cause death was used as a criterion, none of these drugs and methods had any effect.



- GUYTON AC, CROWELL JW. Dynamics of the heart in shock. Fed Proc. 1961 Jul;20(Suppl 9):51-60.
- BRODER G, WEIL MH. EXCESS LACTATE: AN INDEX OF REVERSIBILITY OF SHOCK IN HUMAN PATIENTS. Science. 1964 Mar 27;143(3613):1457-9.
- CROWELL JW, SMITH EE. OXYGEN DEFICIT AND IRREVERSIBLE HEMORRHAGIC SHOCK. Am J Physiol. 1964 Feb;206:313-6.

Ramifications of Debt Repayment:
Unclear How Much Repayment Over What Period of Time to Prevent Death and MSOF:
Think of Sleep Debt



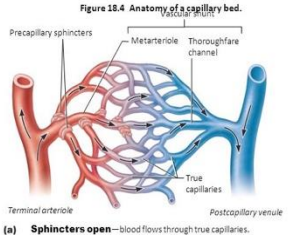


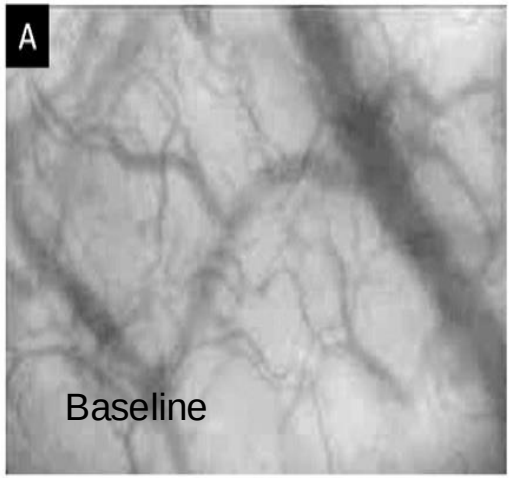
Degree of inflammation directly proportional to final degree of oxygen debt

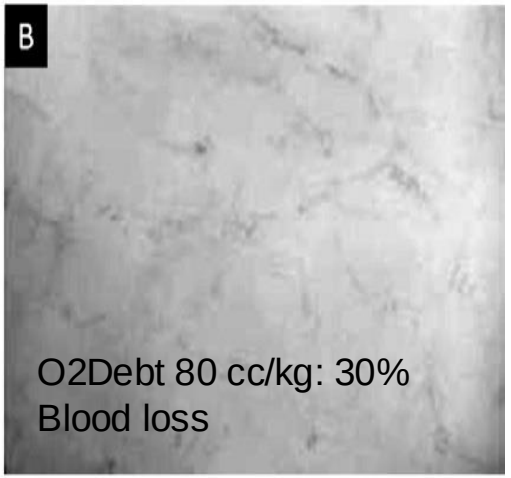
Barbee RW, Reynolds PS, Ward KR. Shock. 2010

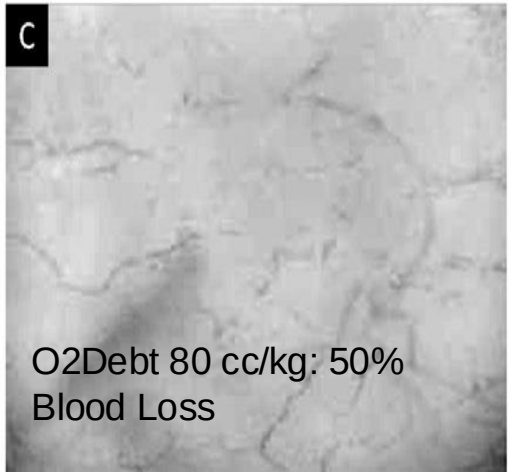
Shock: Microcirculatory Issues: Individuals Vary

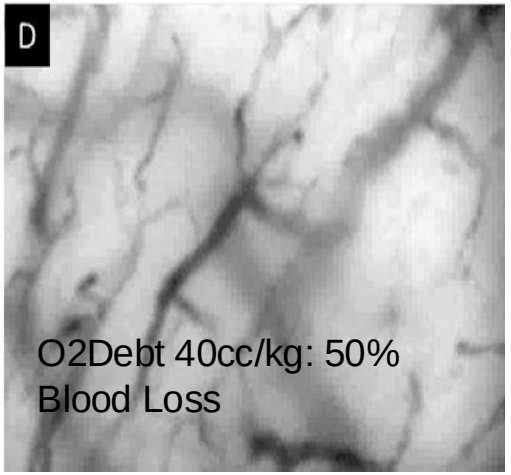
- Difficult to quantitate blood loss
- Rate of bleeding probably important
- Lots of individual variability
- Microcirculation difficult to open up once it is shut down
- Reason why early transfusion is best











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Additional Models and Data: Like Other Things in Medicine there is an LD50

- **Bench-to-bedside review: Oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and posttraumatic shock**

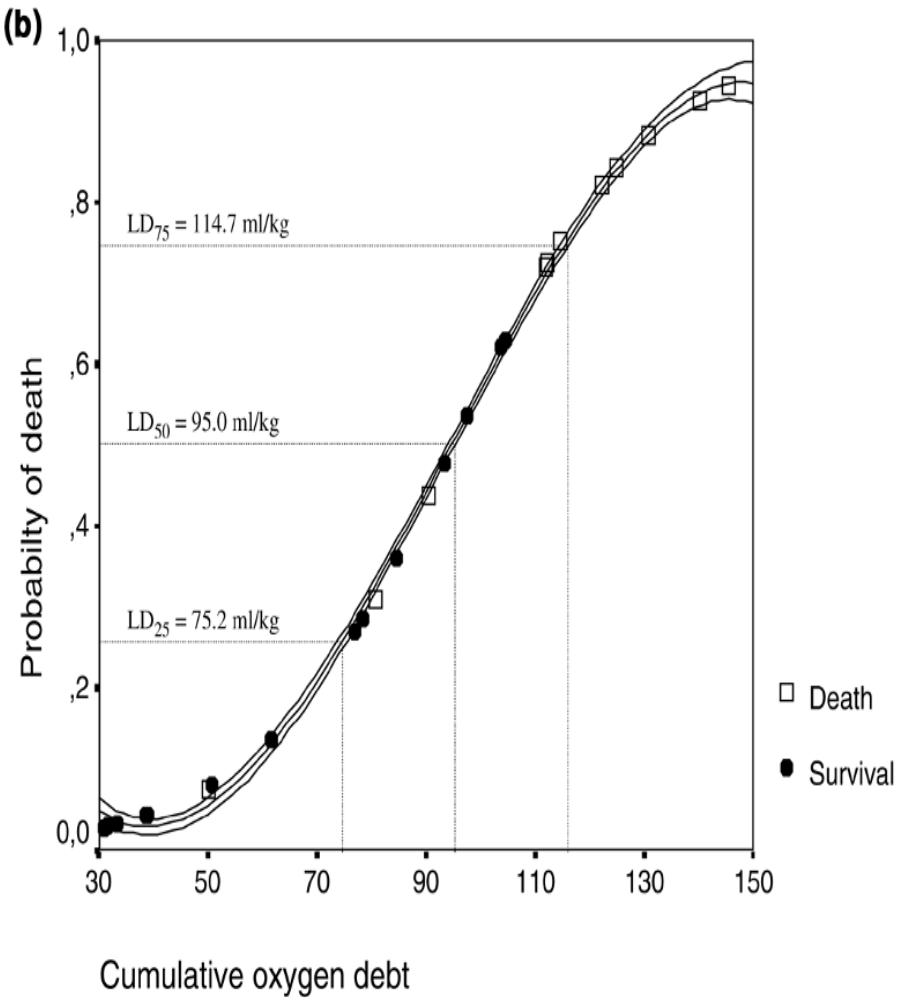
Rixen D, Siegel JH. Bench-to-bedside review: oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shock. Crit Care. 2005

Oxygen debt and metabolic acidemia as quantitative predictors of mortality and the severity of the ischemic insult in hemorrhagic shock

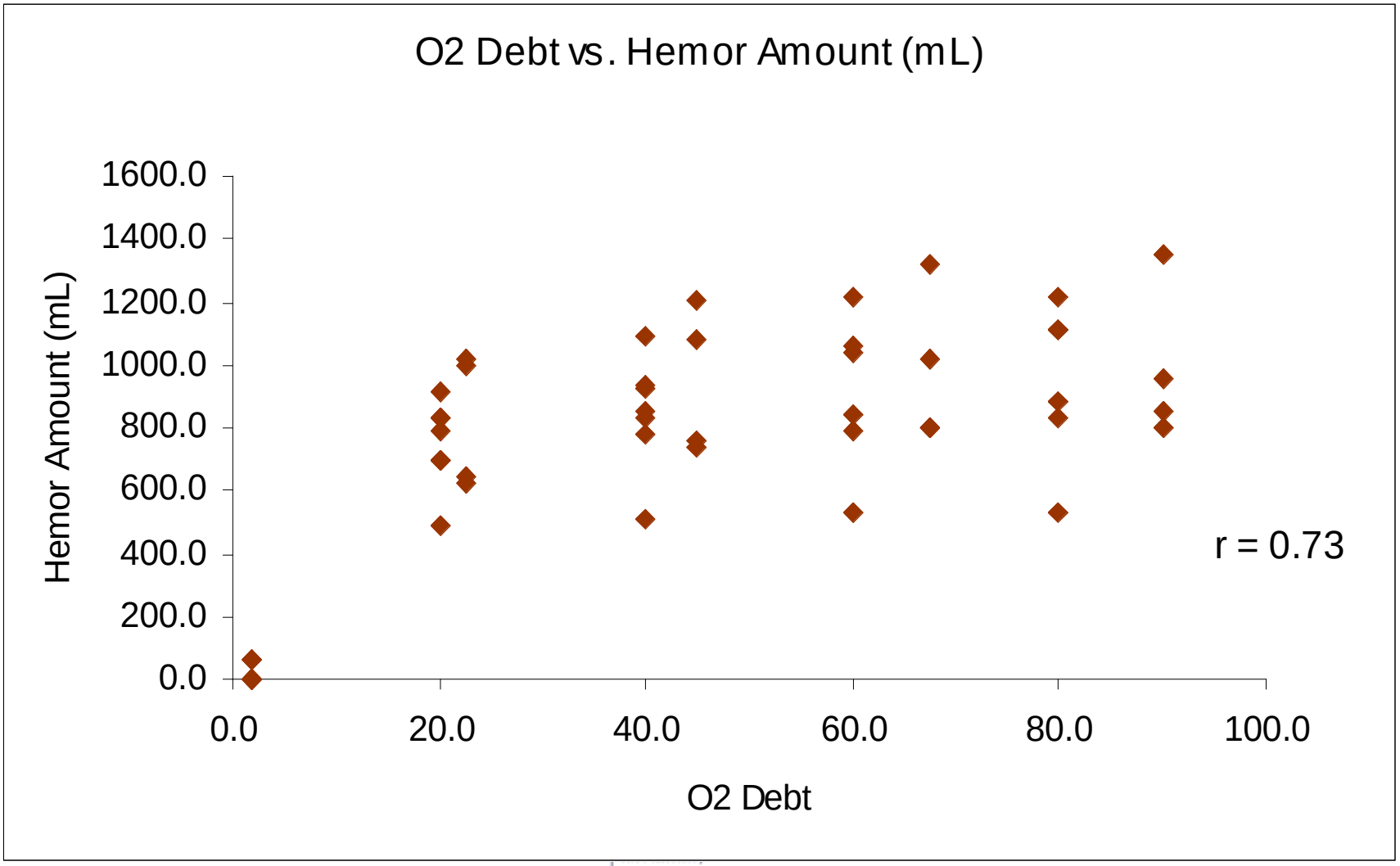
Dunham CM, Siegel JH,. Oxygen debt and metabolic acidemia as quantitative predictors of mortality and the severity of the ischemic insult in hemorrhagic shock. Crit Care Med. 1991

Metabolic Correlates of Oxygen Debt Predict Post-trauma Early Acute Respiratory Distress Syndrome and the Related Cytokine Response

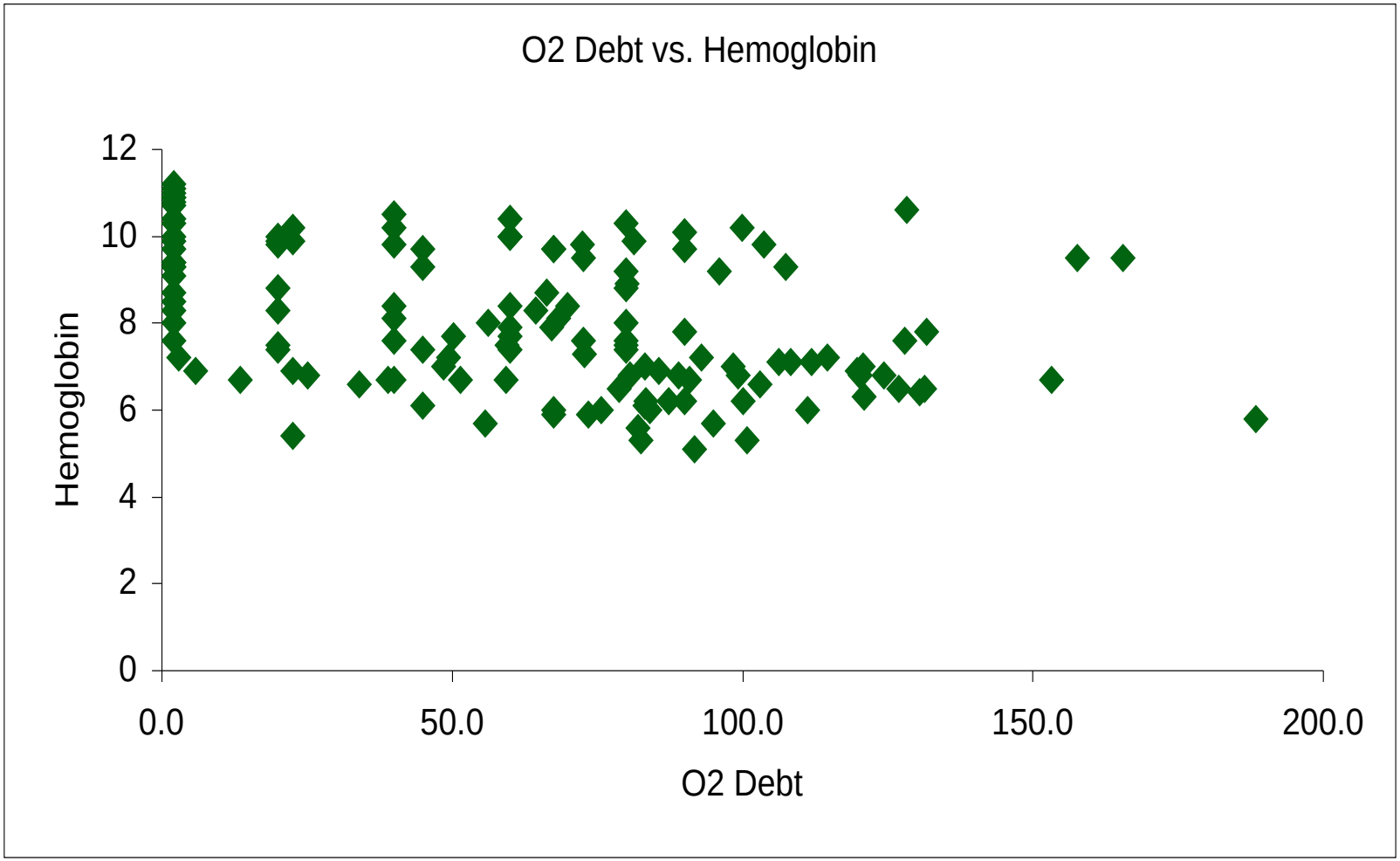
Rixen D, Siegel JH. Metabolic correlates of oxygen debt predict posttrauma early acute respiratory distress syndrome and the related cytokine response. J Trauma.



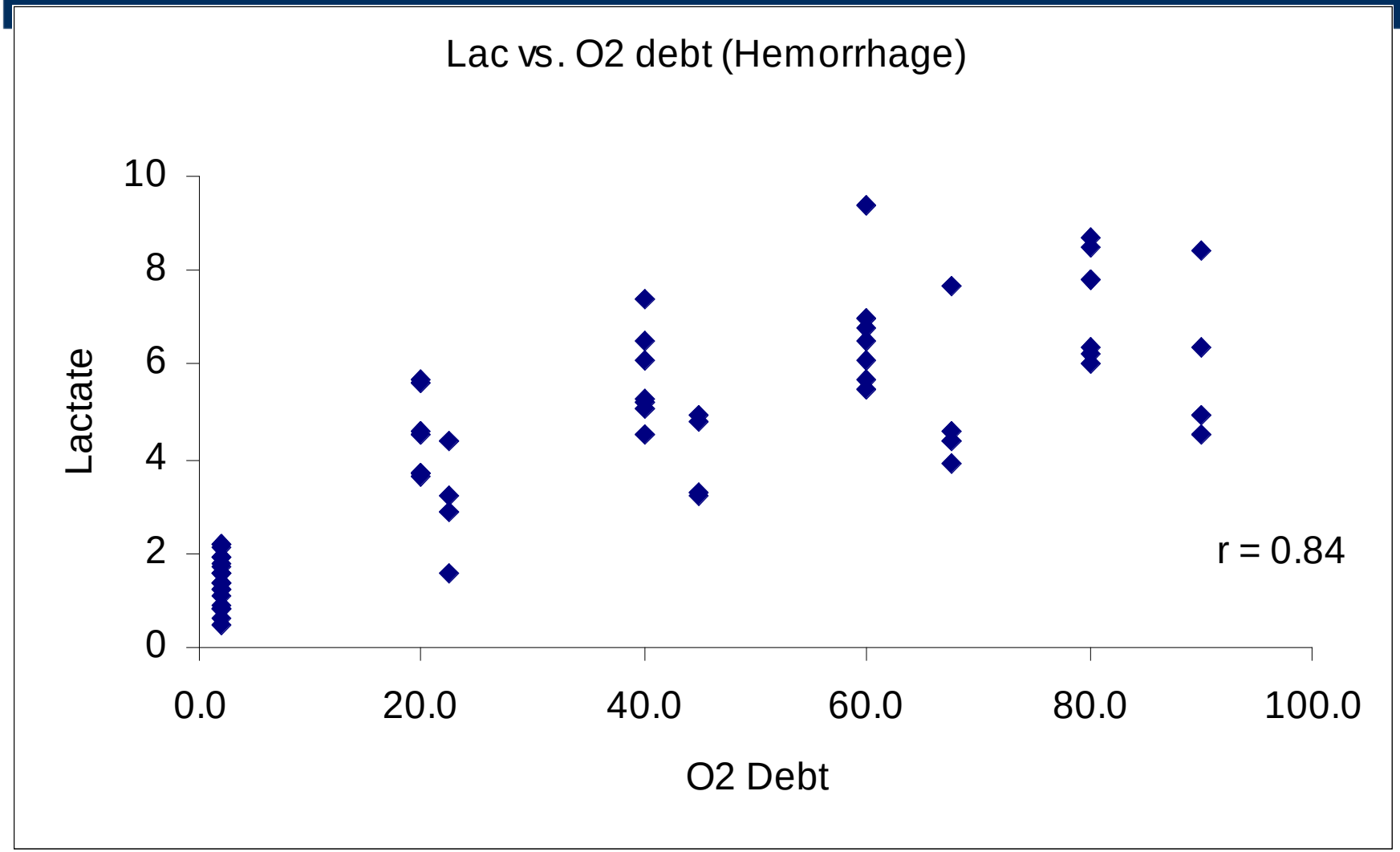
O2 Debt vs. Hemorrhage Volume: A Word About Precision Medicine



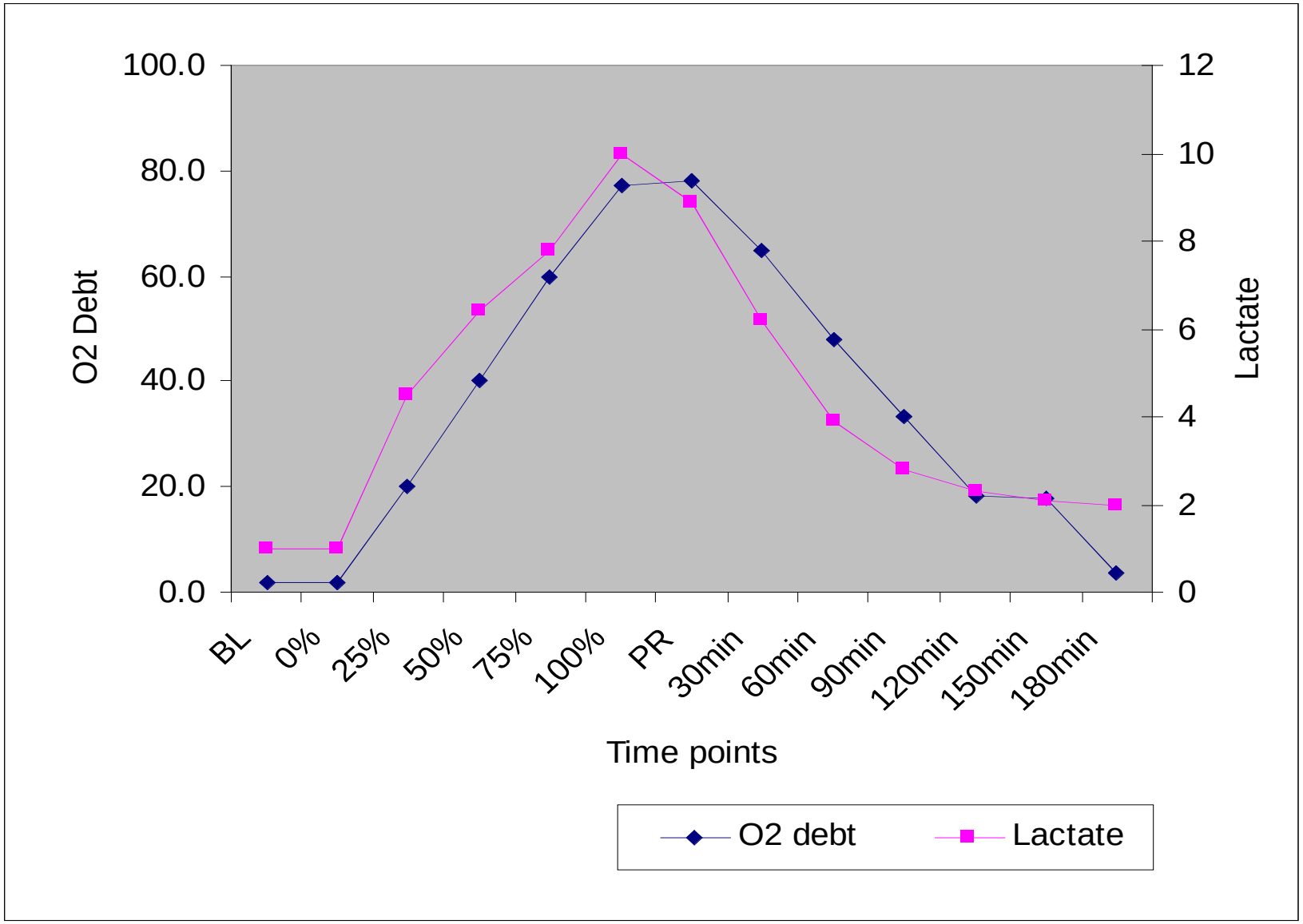
O2 Debt vs. Hemoglobin Levels



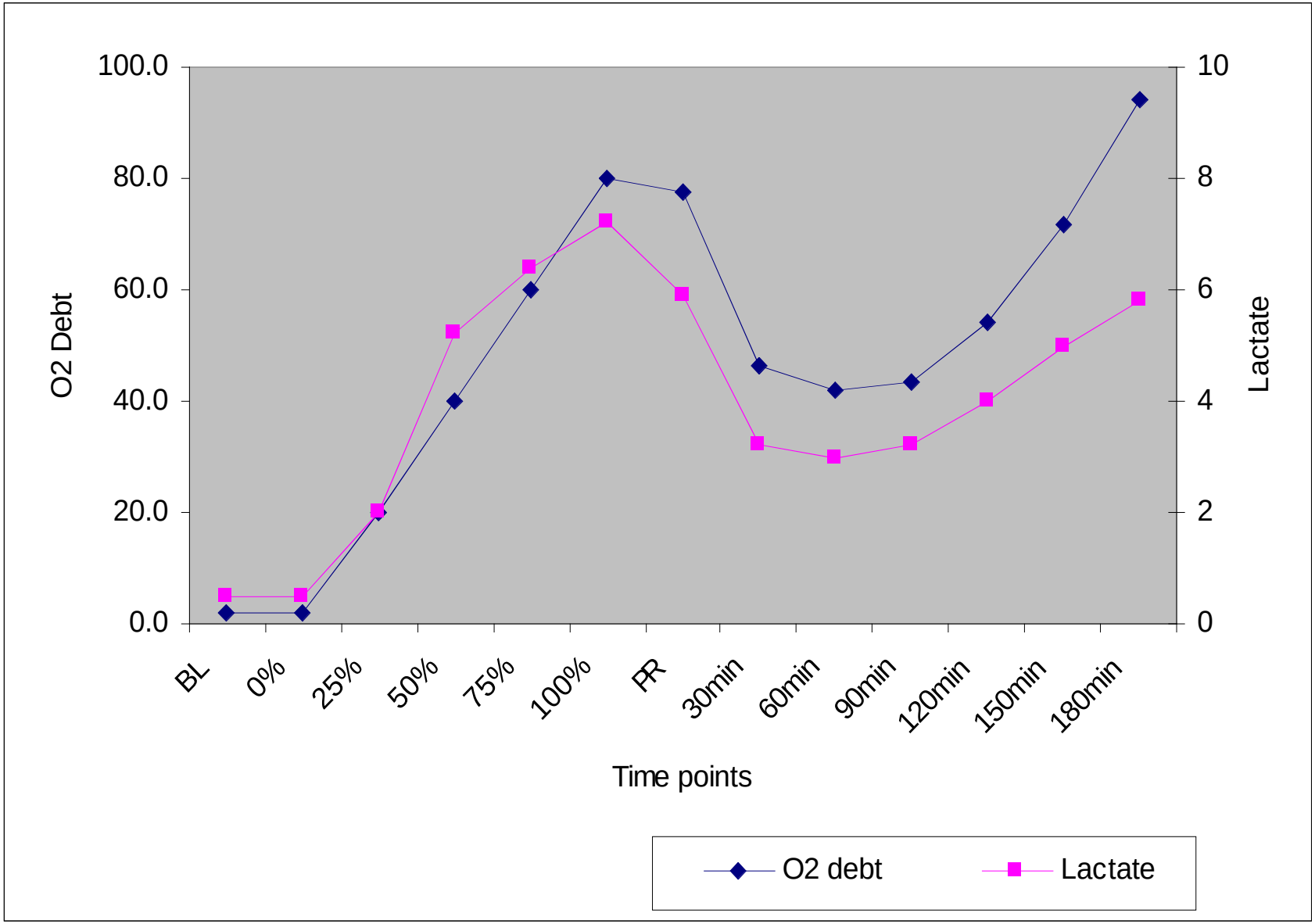
O2 Debt vs. Lactate



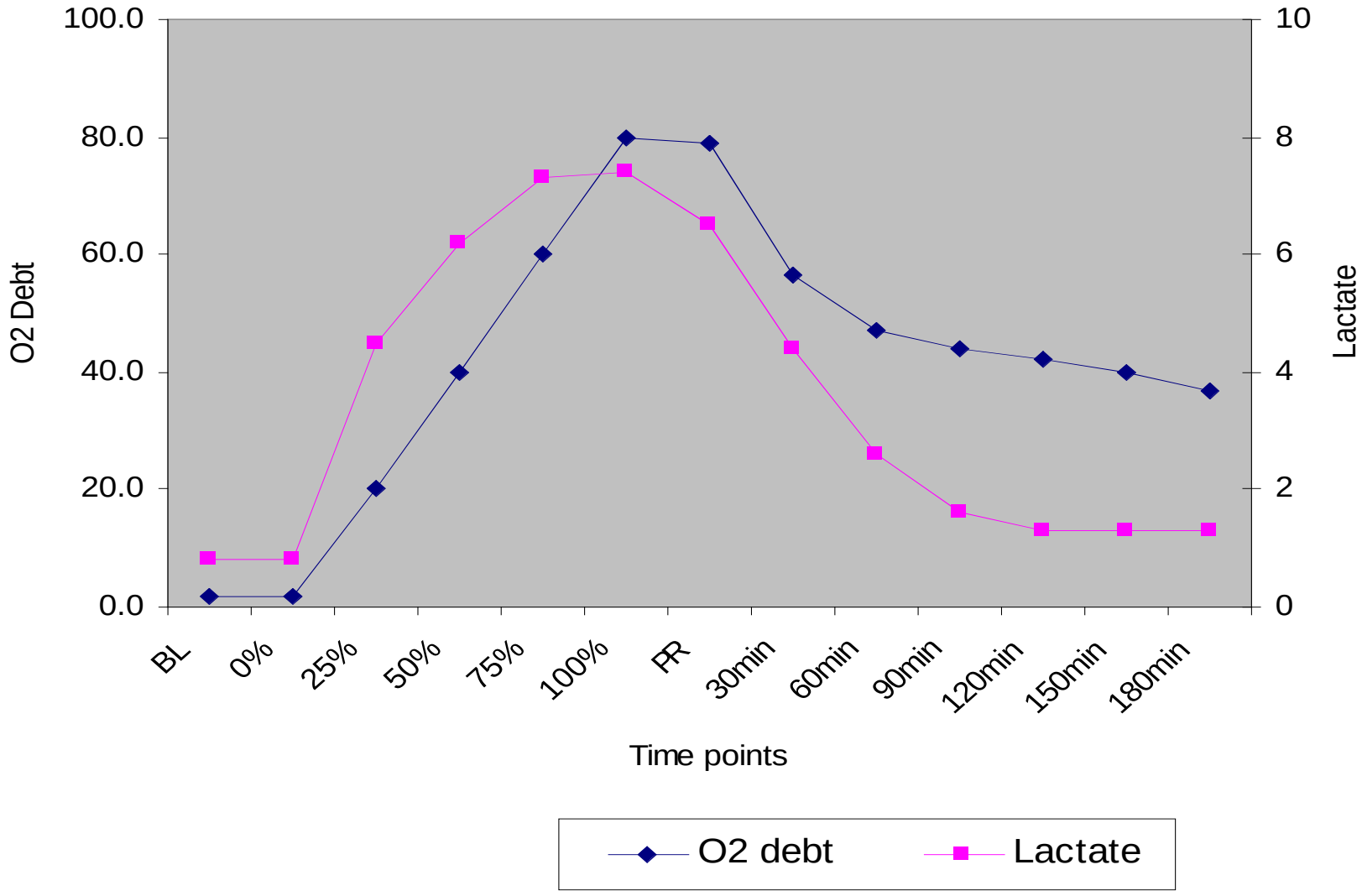
Paying back debt and lactate normalizing



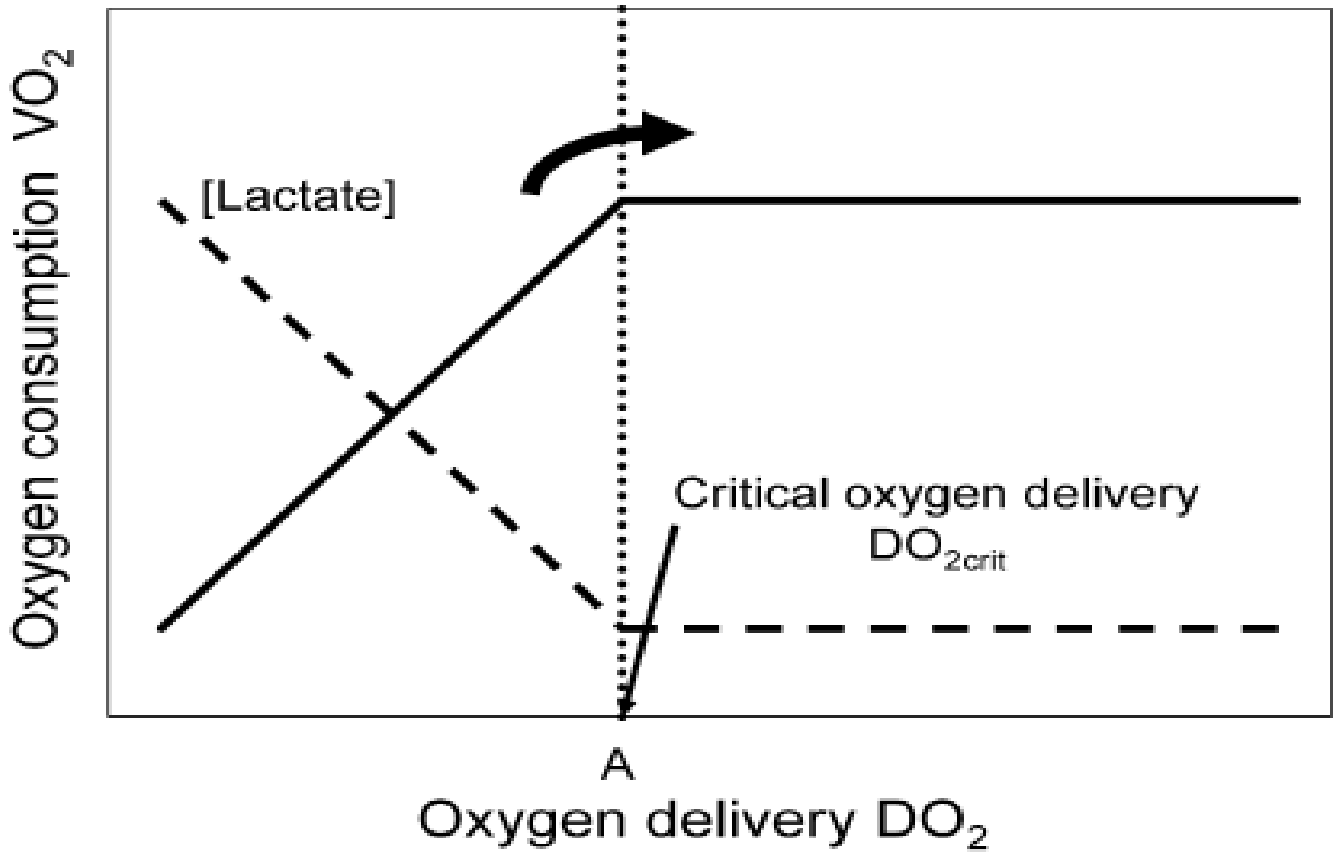
Re-accumulating debt with lactate going up



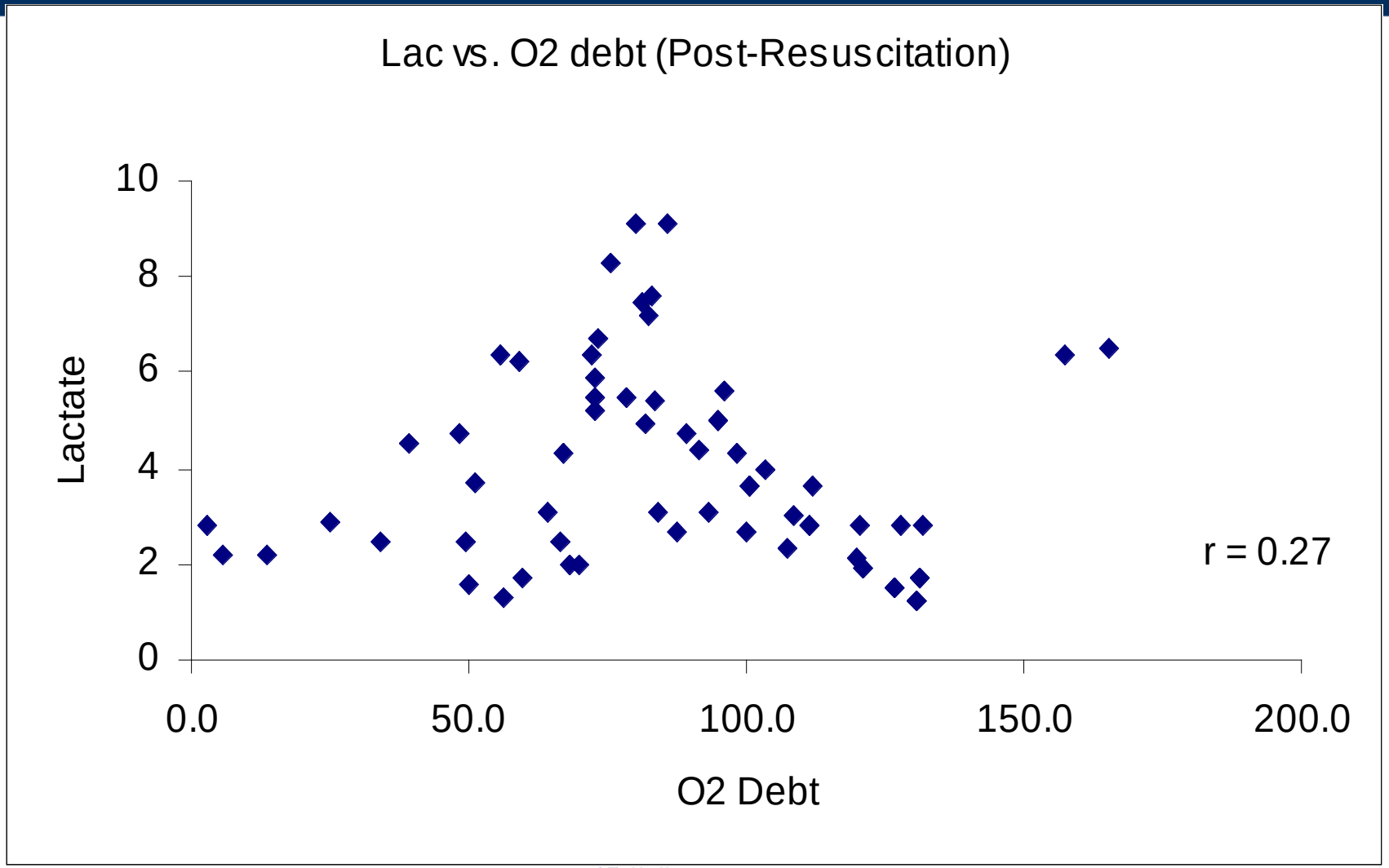
Partially paying back debt and lactate normalizing



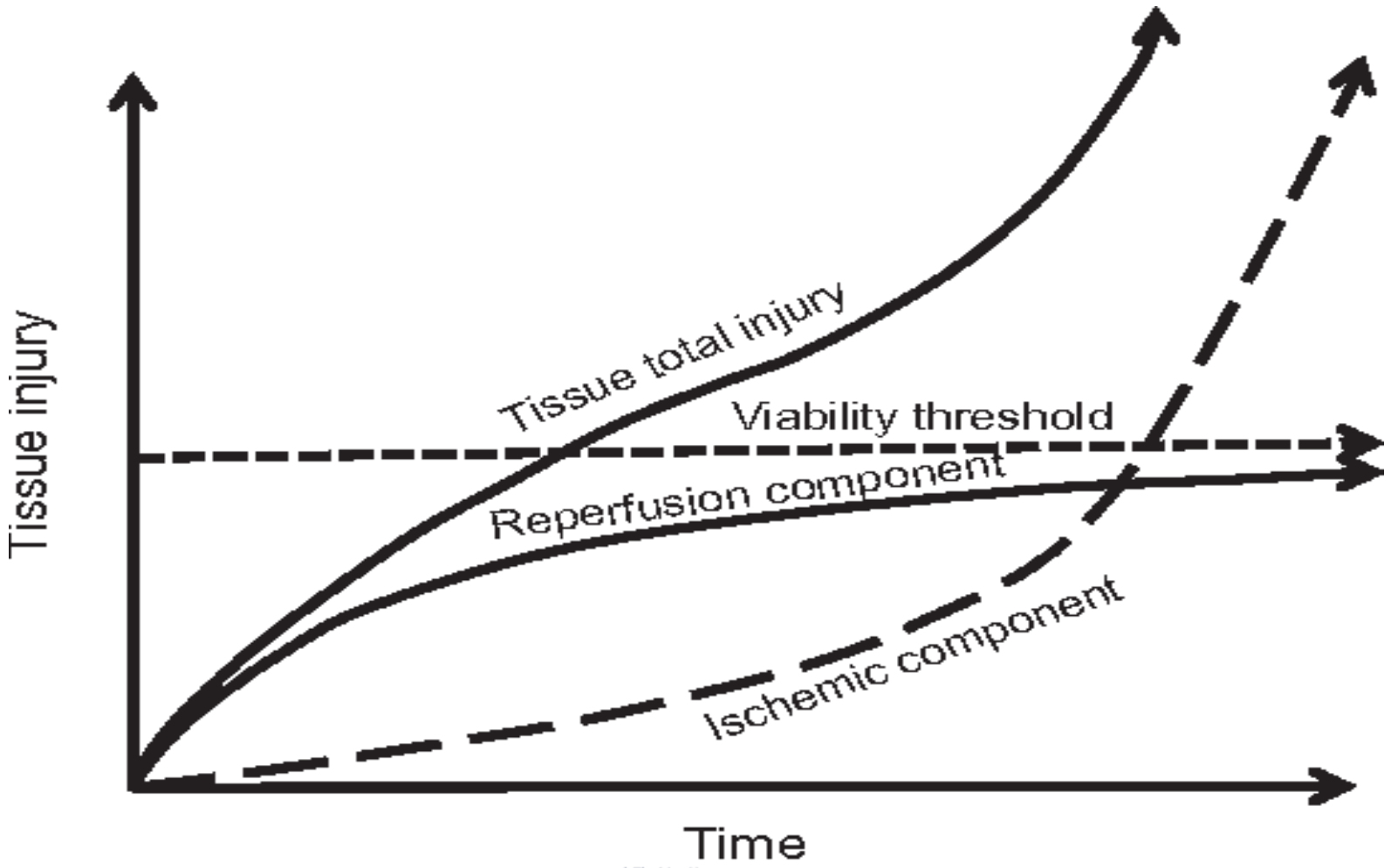
Remember the Relationship is Biphasic



O2 Debt vs. Lactate: Post-Resuscitation
Danger of Using Lactate

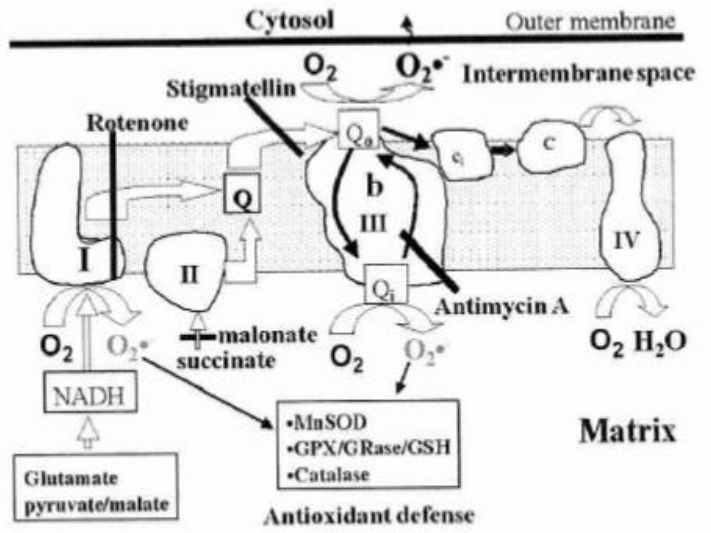


Synergistic Connection Between Ischemic Time, Reperfusion and Total Tissue Injury



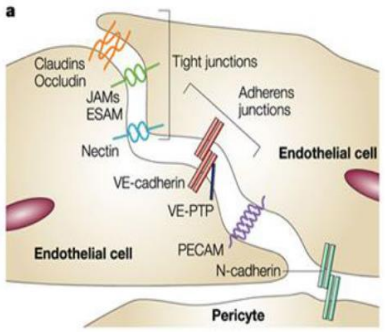
Setting the Stage for Reperfusion with Oxidative Injury including Endothelial Cell Injury Endotheliopathy

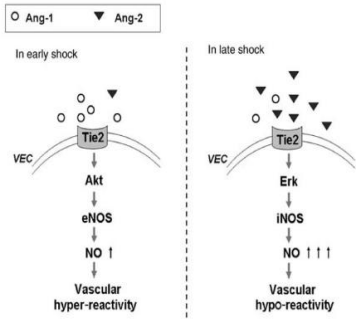
ROS and Oxidation



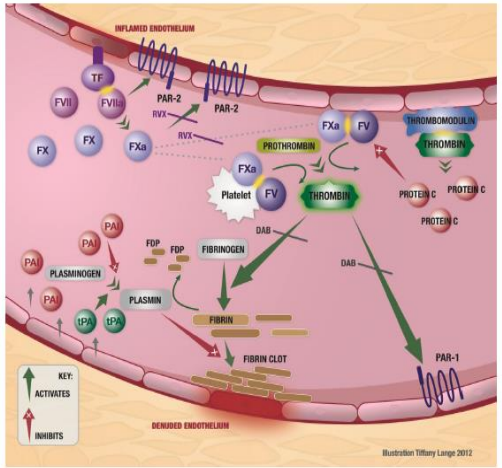
Best, B. Mechanisms of Aging.
http://www.benbest.com/lifeext/aging.html#mitochondria

Endothelium- Barrier Disruption





Endotheliopathy induces TIC

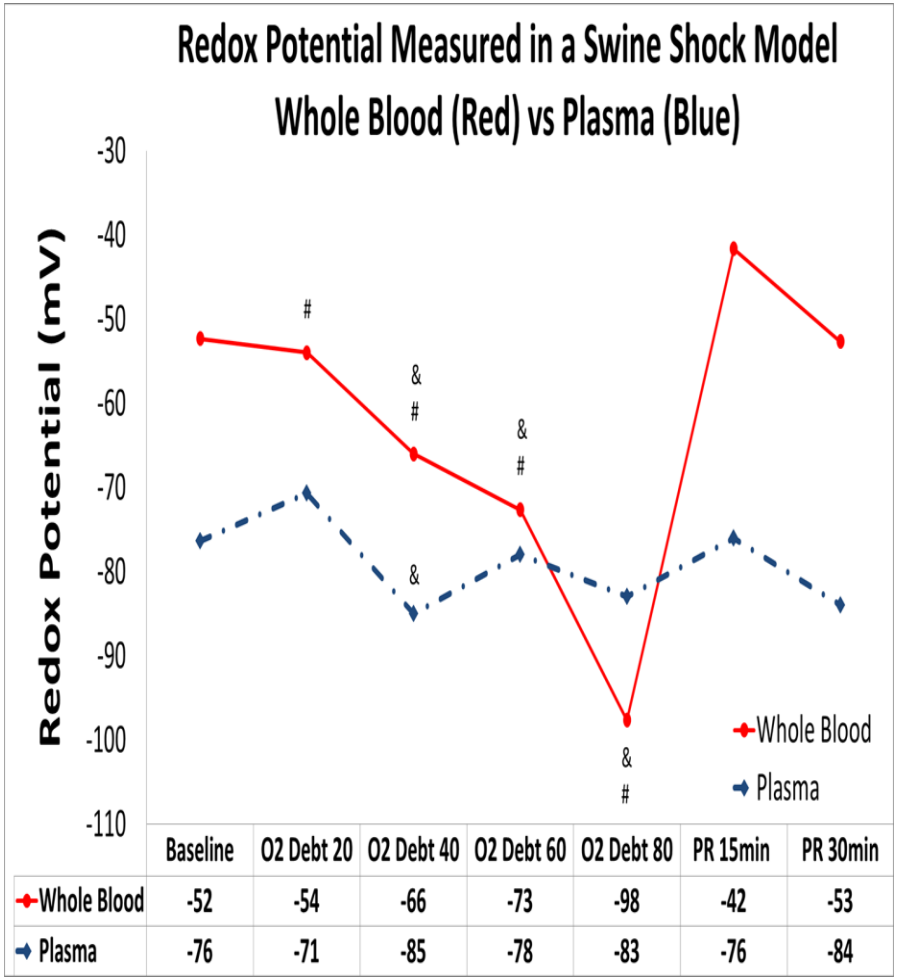


Plasmin

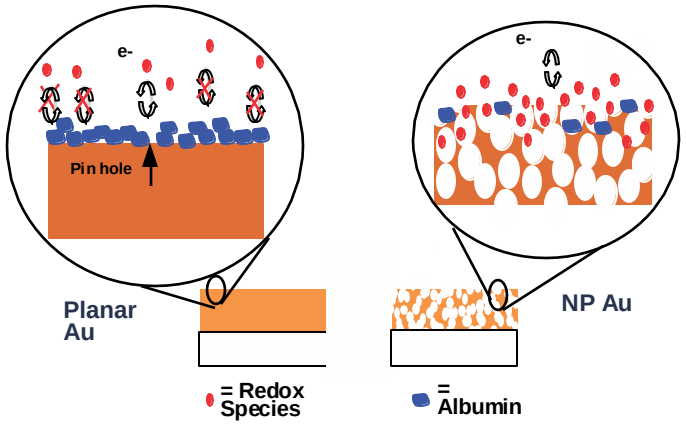
Targets

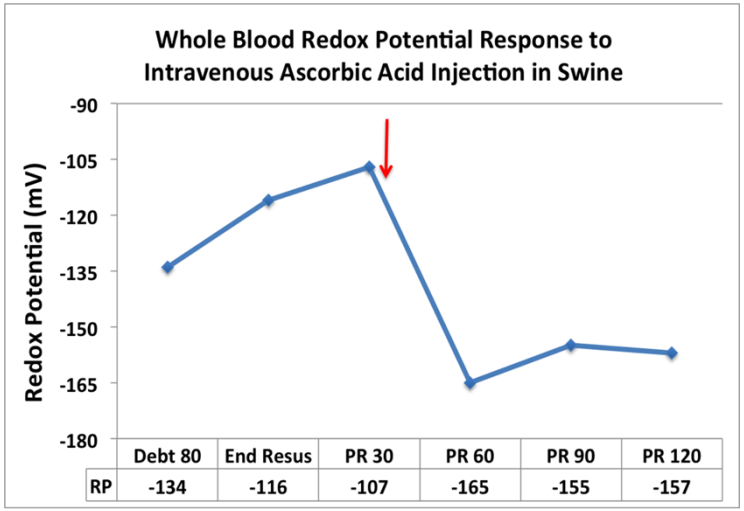
- Fibrinogen
- Fibrin
- Fibronectin
- Laminin
- von Willebrand factor
- Platelet Receptors (GPIb)
- Factor XIIIa

Whole Blood Oxidative Stress Monitor: Electron Pressure: Balance of Oxidants and Reductant: It Not All About the Protons



	Baseline	O2 Debt 20	O2 Debt 40	O2 Debt 60	O2 Debt 80	PR 15min	PR 30min
Whole Blood	-52	-54	-66	-73	-98	-42	-53
Plasma	-76	-71	-85	-78	-83	-76	-84





	Debt 80	End Resus	PR 30	PR 60	PR 90	PR 120
RP	-134	-116	-107	-165	-155	-157

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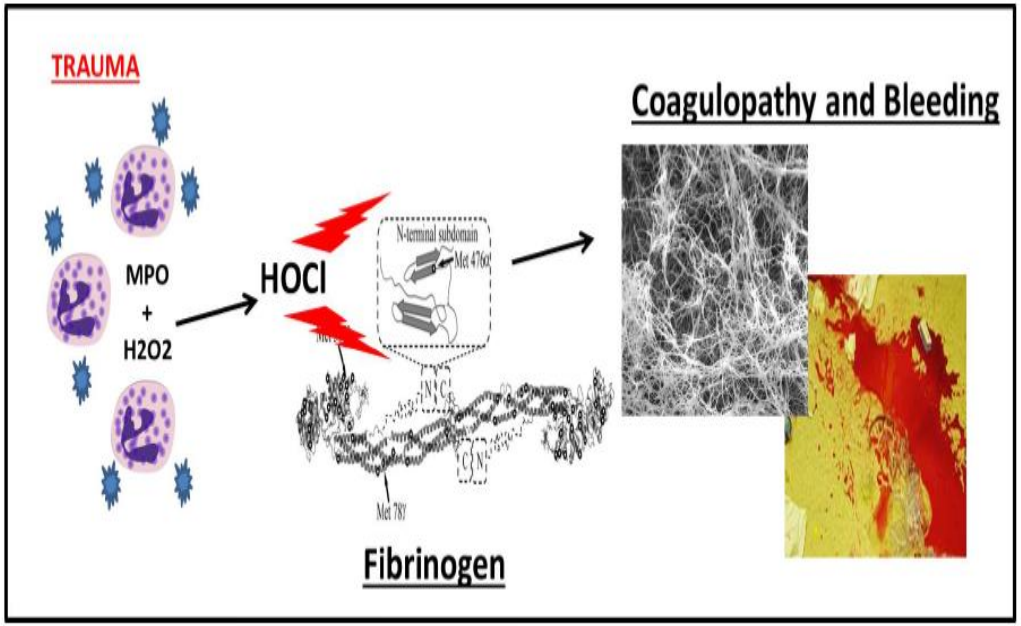
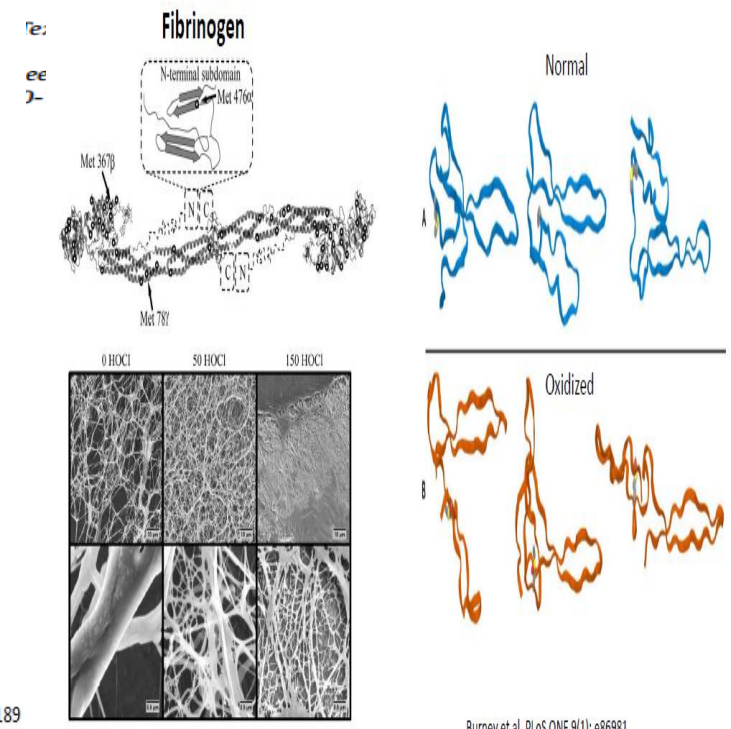
journal homepage: www.elsevier.com/locate/freeradbiomed

Post-translational oxidative modification of fibrinogen is associated with coagulopathy after traumatic injury

Nathan J. White [a,b,*], Yi Wang [b], Xiaoyun Fu [b], Jessica C. Cardenas [c], Erika J. Martin [d], Donald F. Brophy [d], Charles E. Wade [c], Xu Wang [a], Alexander E. St. John [a], Esther B. Lim [a], Susan A. Stern [a], Kevin R. Ward [e], José A. López [b], Dominic Chung [b]



White et al. Free Radical Biology and Medicine (2016)181–189

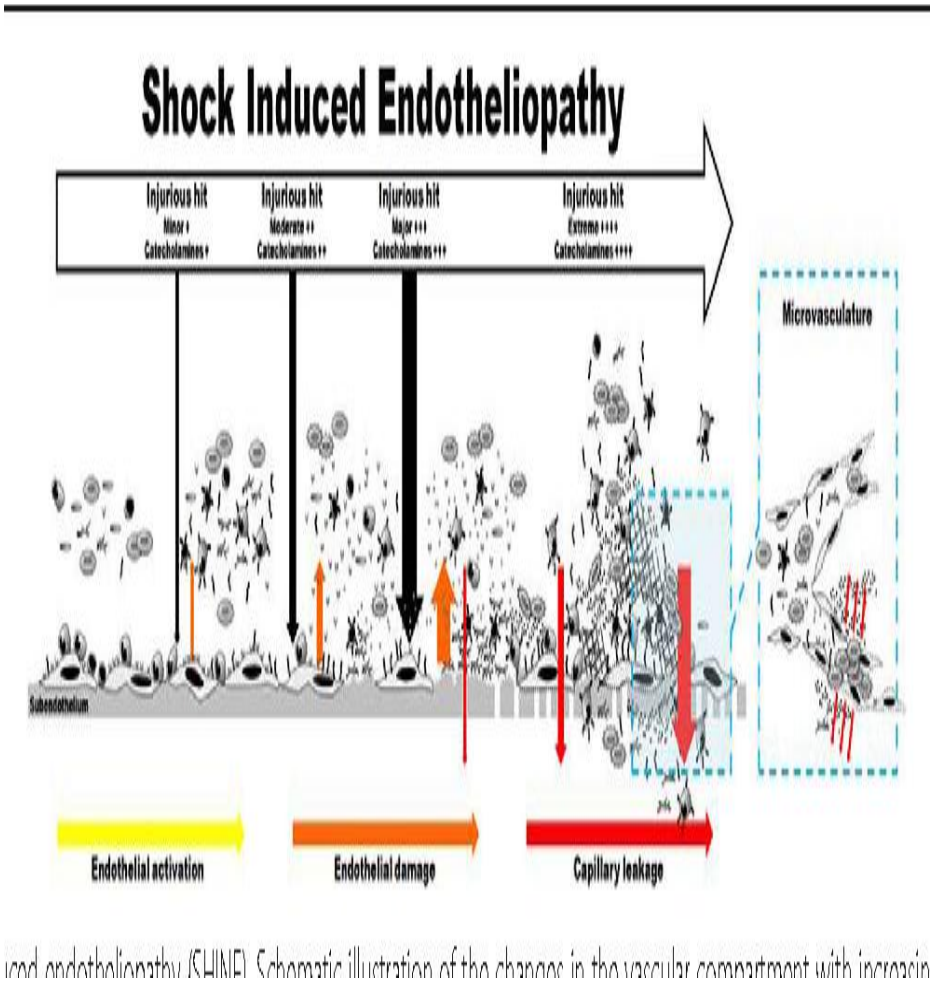


Weigandt et al. Biophysical Journal Volume (2012):2399–2407

Burney et al. PLoS ONE 9(1): e86981.

Role of Catecholamines:

- Adrenergic Response
  - Tissue Trauma
  - Pain
  - Increases O2 Debt over Hemorrhage Alone
- Direct and Indirect Effects on Endothelium
  - Glycocalyx damage
  - Vasoconstriction



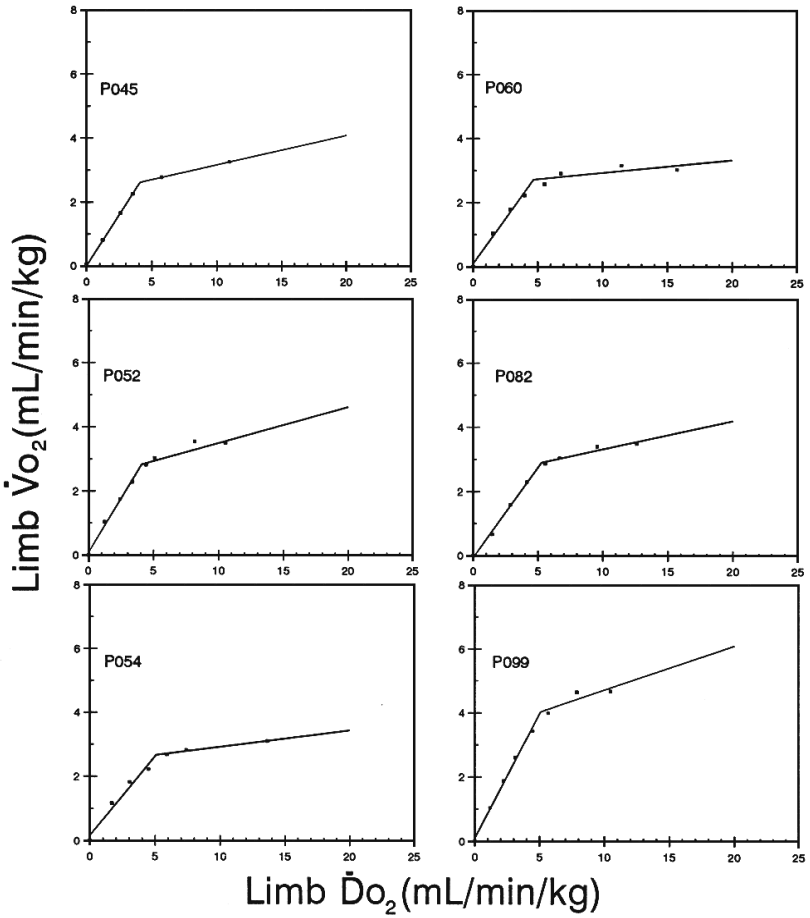
ced endotheliopathy (SHINE). Schematic illustration of the changes in the vascular compartment with increasin

Critical Oxygen Delivery and O2 Debt in Isolated Hind Limb and Langendorff Models

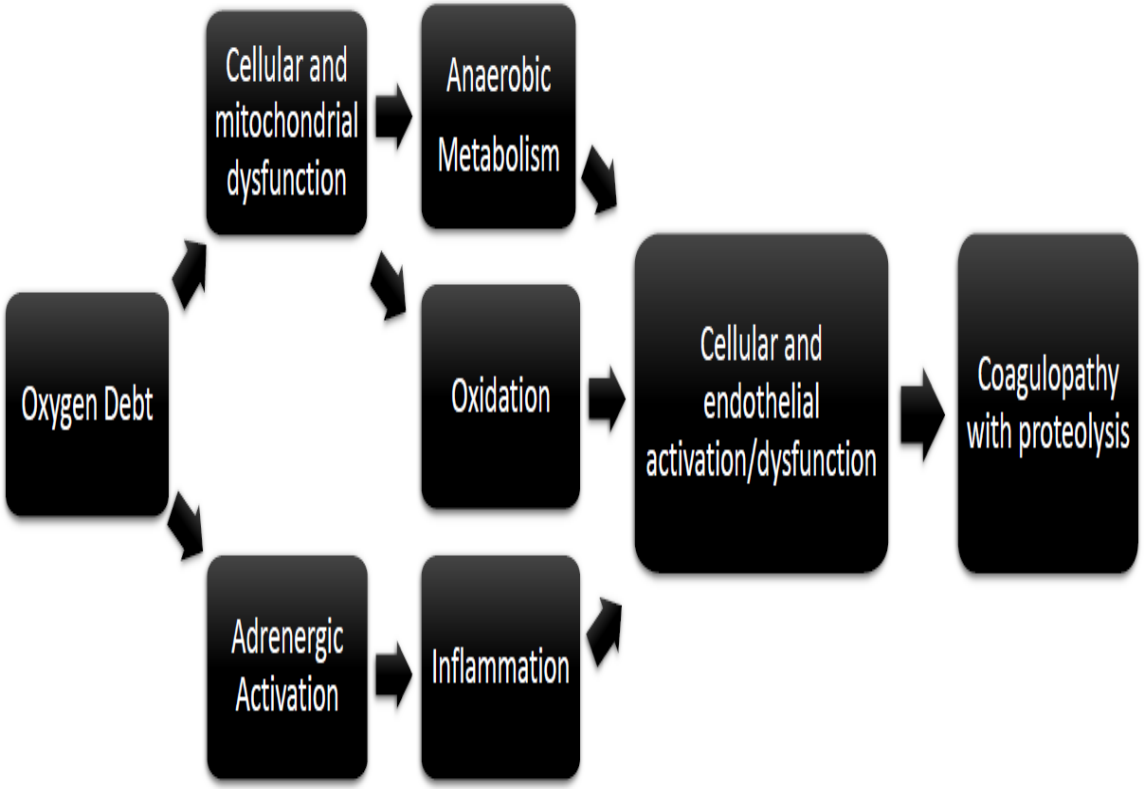
- Hofer, S. , van der Kleij, A. , Grundeman, P. , Scholten, E. & Klopper, P. (1995). Critical tissue oxygen tension defines tissue oxygen debt in the isolated hindlimb of the pig during progressive ischemia. *Critical Care Medicine*.

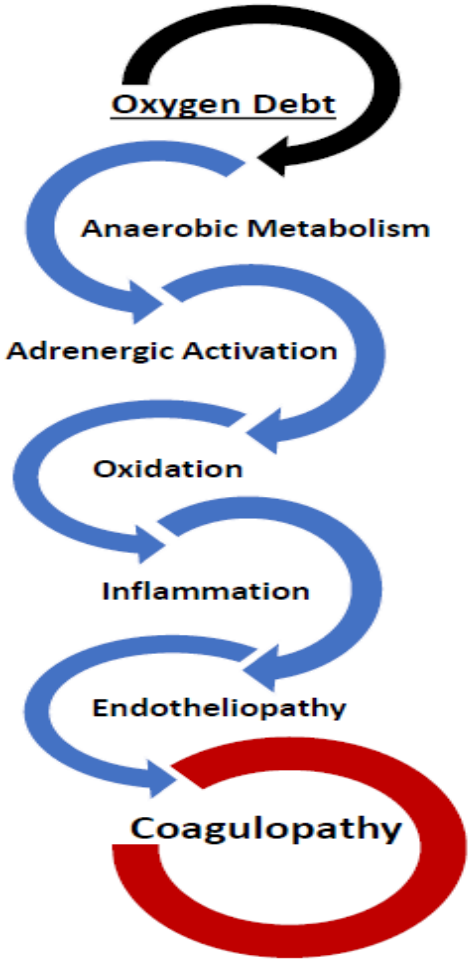
- Adams RP, Cain SM. Total and hindlimb oxygen deficit and "repayment" in hypoxic anesthetized dogs. J Appl Physiol Respir Environ Exerc Physiol. 1983

- Chandra M, Schwalb H, Yaroslavsky-Houminer E, Appelbaum Y, Uretzky G, Borman JB. New experimental technique to study blood cardioplegia in the isolated, perfused rat heart. Ann Thorac Surg. 1993

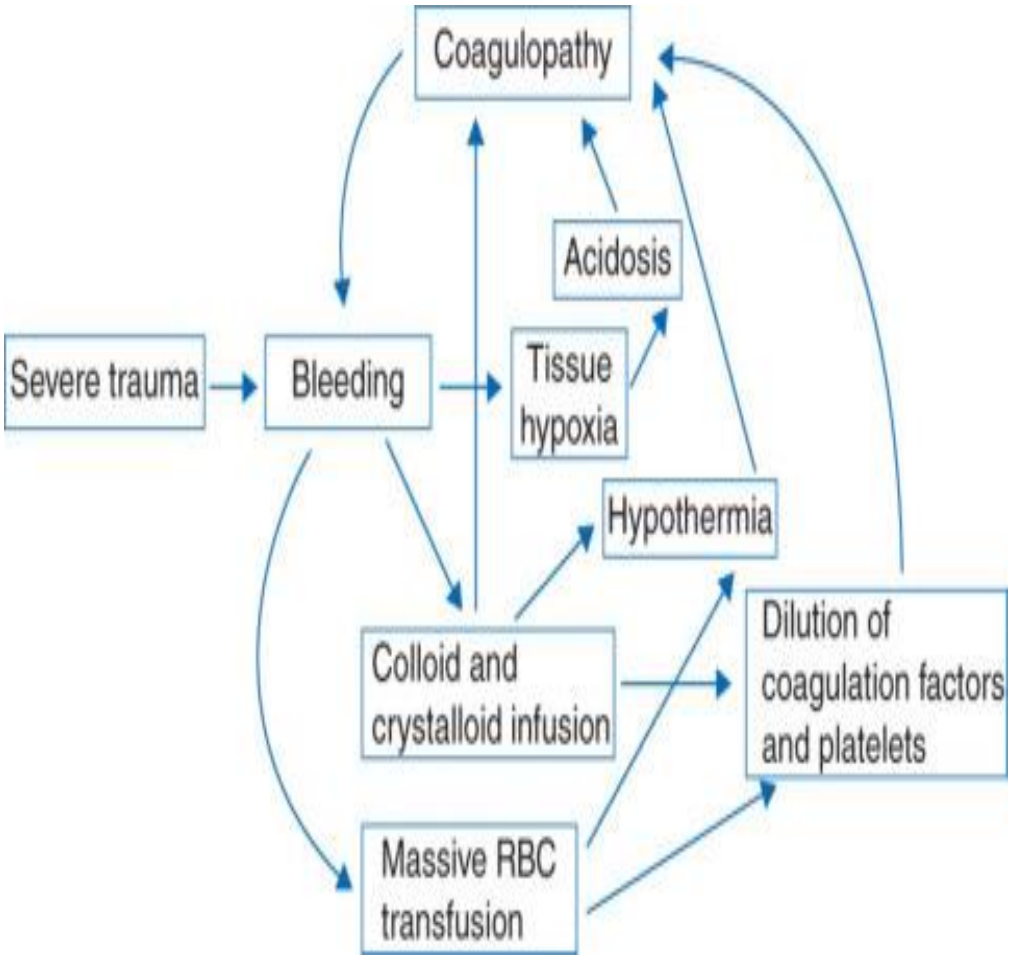


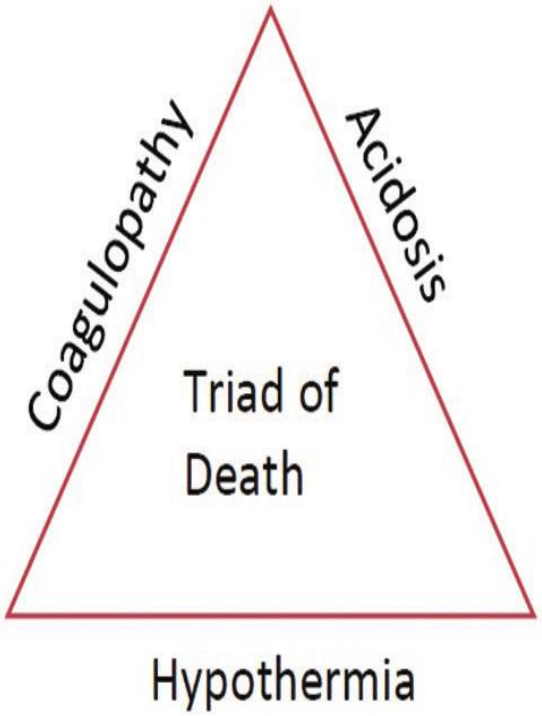
Putting it All Together





Vicious Cycles but All Related to O2 Debt





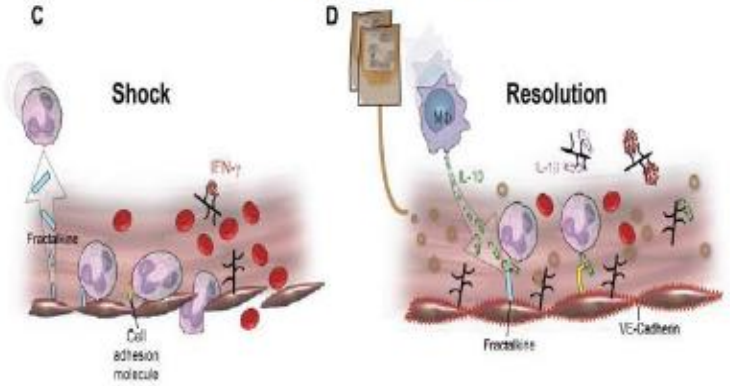
Major Cause of Hypothermia is poor perfusion and Oxygen Debt!!!

Treating Blood Failure

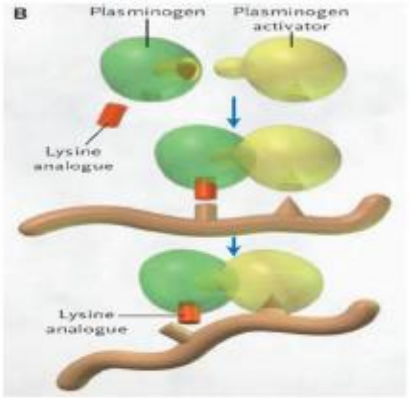
What is required to treat blood failure?

Repay Oxygen Debt

Restore the Glycocalyx

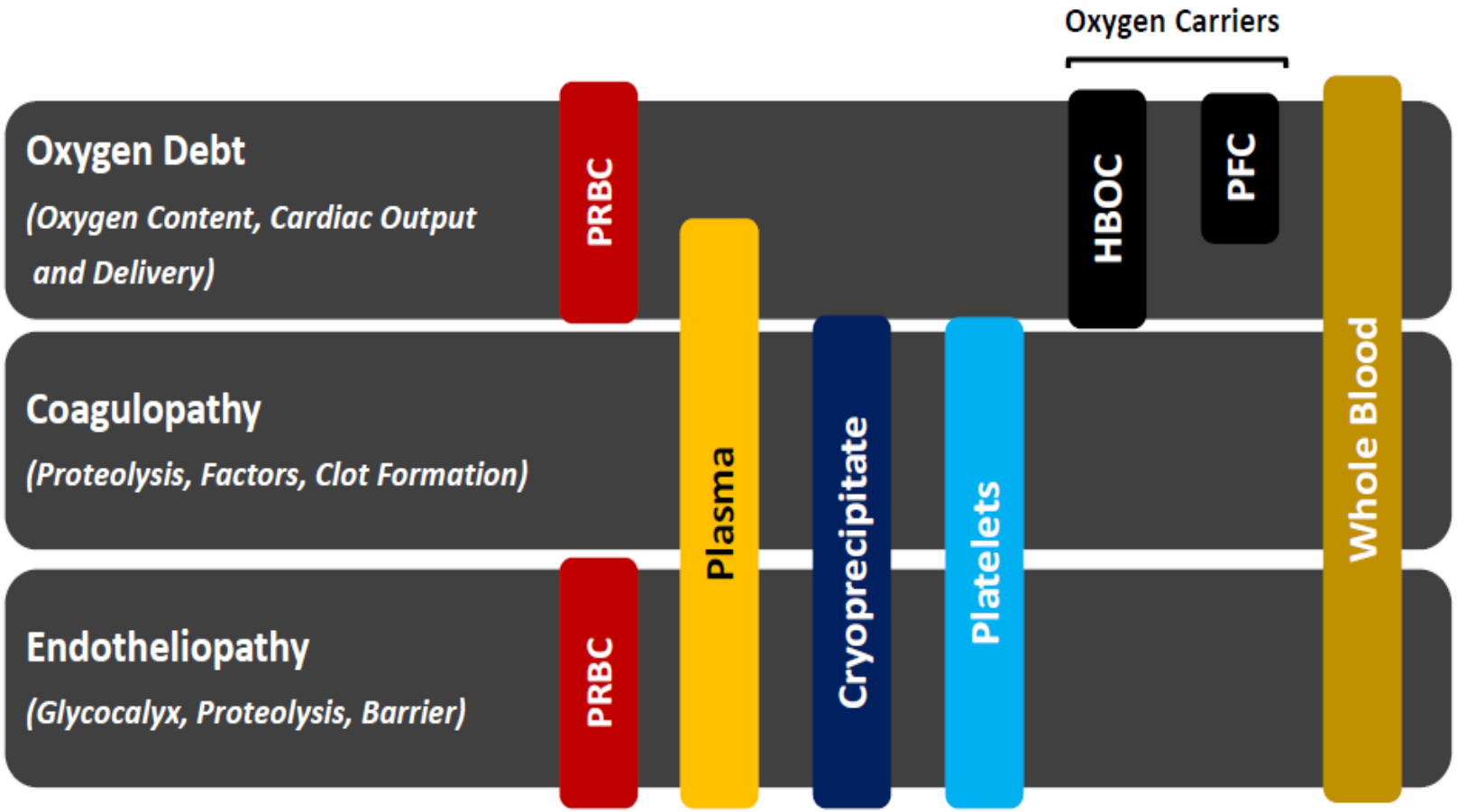


Stop Proteolysis



Replete the Coagulation System

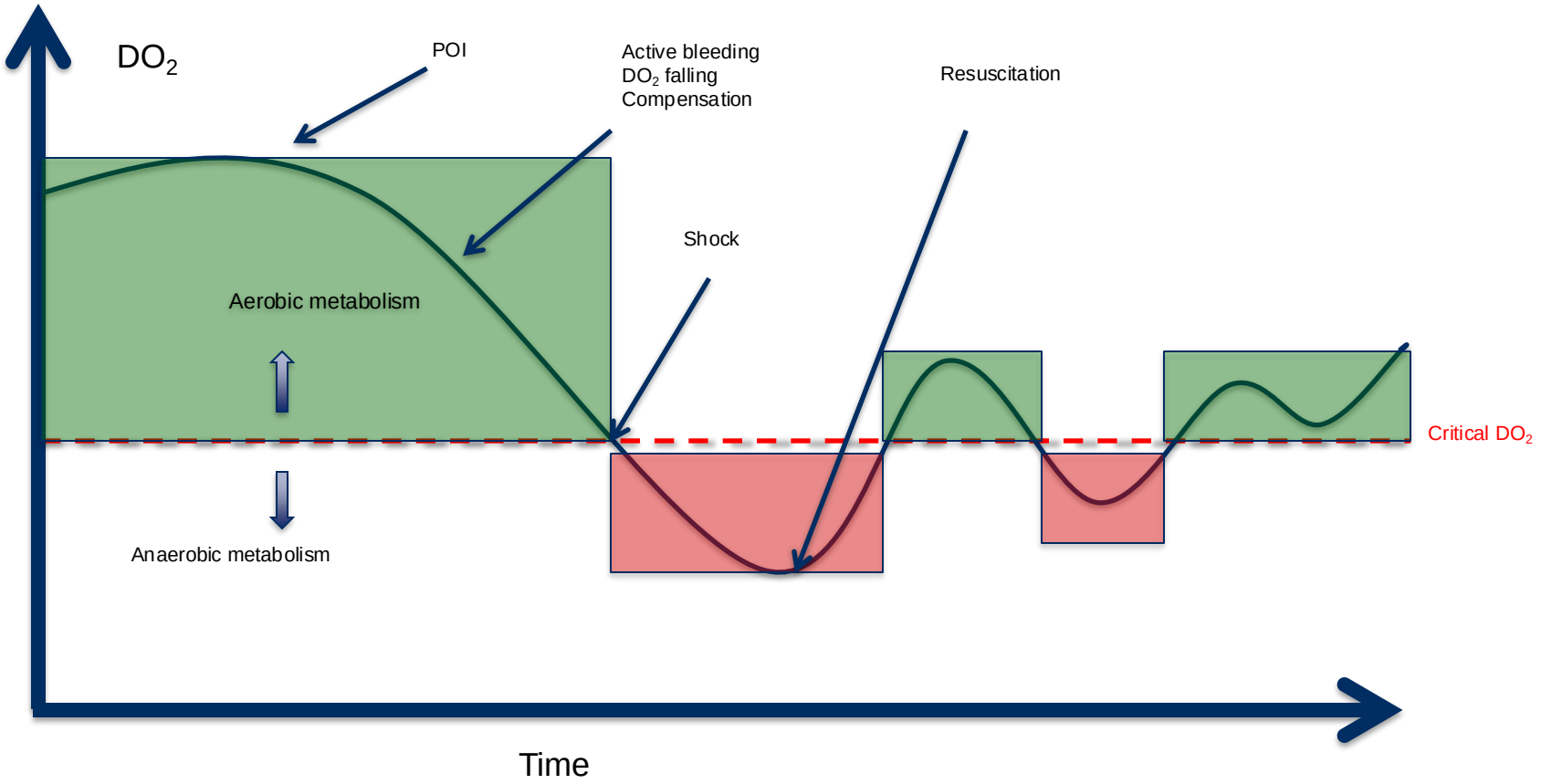
What's in Your Wallet?



Challenges: Prehospital vs Hospital in O2 Debt Prevention/Repayment for Hemostatic Resuscitation

- How to monitor? Deficit, Debt, Repayment
  - Vital signs: Shock Index?
  - Perfusion indicators: EtCO2, NIRS, HRV?
  - Biochemistry: Lactate, Redox, Coag?
- Dilemma of permissive hypotension
  - Time to definitive hemostasis
  - Stop O2 Debt accumulation maybe the best we can do prior to definitive hemostasis.
  - Closed loop

The Reality of Injury and Resuscitation



Dose of shock

Oxygen is Good
Blood Goes Round and Round

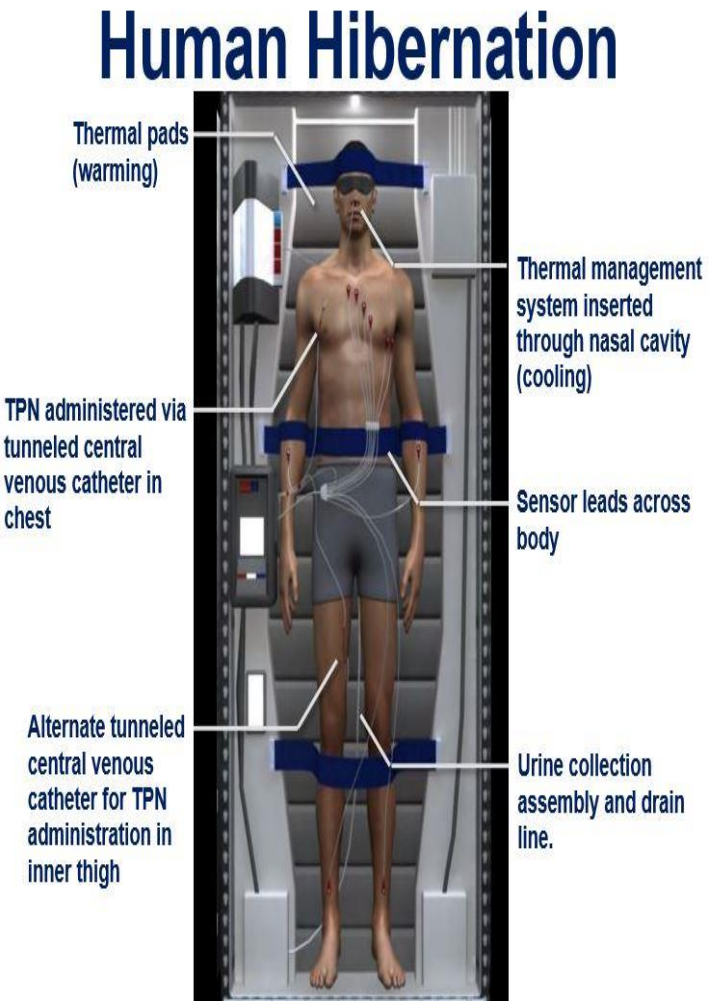
- Oxygen Carriers Should be Evaluated on their Ability to:
  - Repay oxygen debt and reduce tissue hypoxia
  - Modulate DO2crit on Re-bleeding
  - Reduce Coagulopathy
  - Reduce Need for Traditional Blood Components

Opportunities for Oxygen Carriers to Carry Other Therapeutic Gases, Agents to Modulate VO2, Microcirculation, etc….

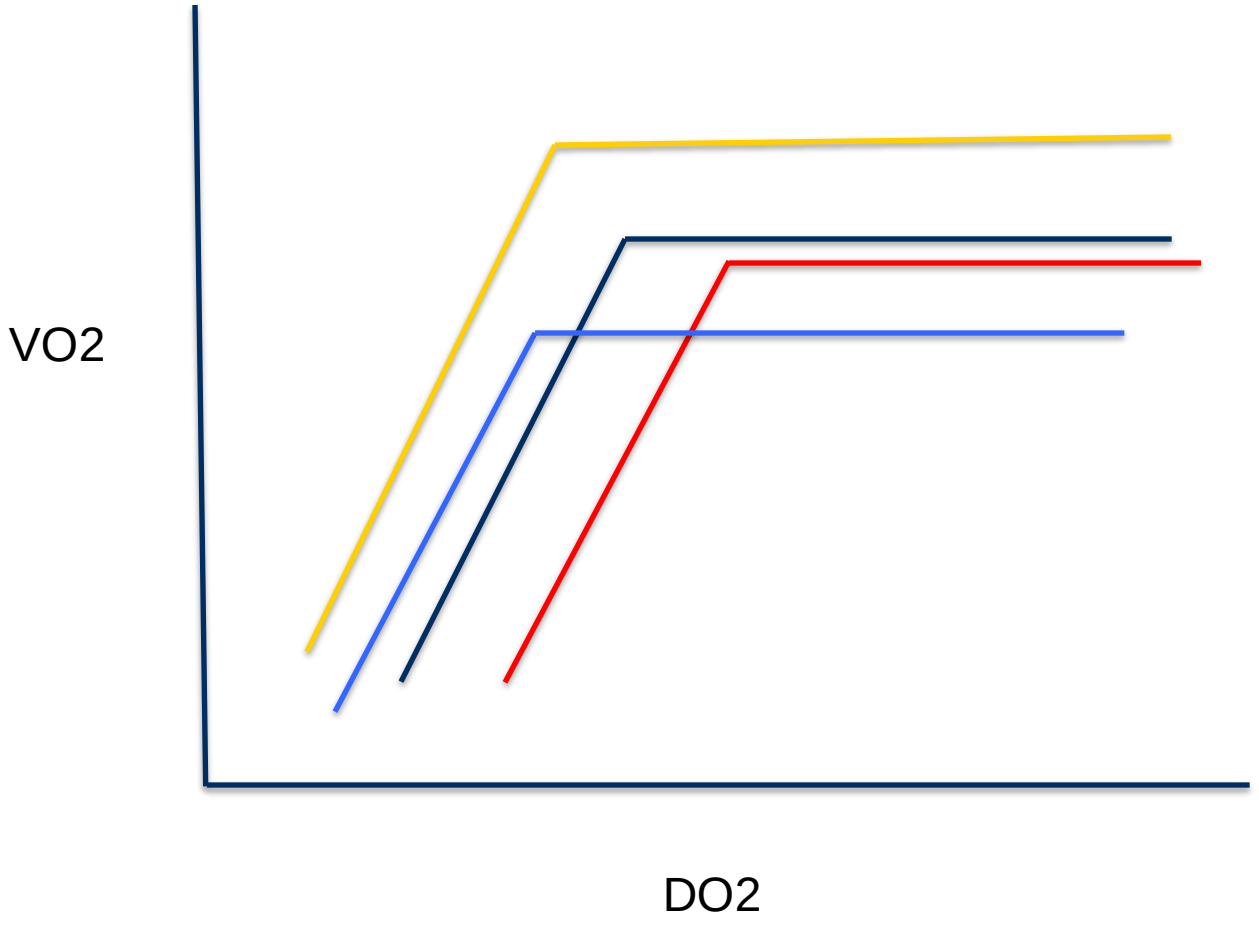
Reducing DO2 dependent VO2 and Enhancing Cell Survival Strategies

Suspended Animation

- Metabolic Down Regulation
- Alternative fuel strategies
- Cell Survival Strategies



Modulation of DO2crit: Re-Hemorrhage, Hypothermia, Pharmacology



Summary

- Shock and Its Magnitude (O2 Debt) is the Main Driver of Blood Failure
  - The Main Thing is to Keep the Main Thing the Main Thing

- Limiting O2 Debt and Rapidly Repaying is Critical
  - Must be considered as integral to hemostatic resuscitation
  - Challenges in use of Permissive Hypotension
  - Technology Challenges in Monitoring
  - Resuscitation strategies designed around O2 Debt