CENTER FOR INTEGRATIVE RESEARCH IN CRITICAL CARE
UNIVERSITY OF MICHIGAN

Oxygen is Good: Blood Goes Round and Round:

Importance of Oxygen Delivery

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Disclosures

- Funding from the NIH, DoD, NSF, Industry, University of Michigan
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- Company Ownership: New Vital Signs, Rapid Oxygen, Fifth Eye

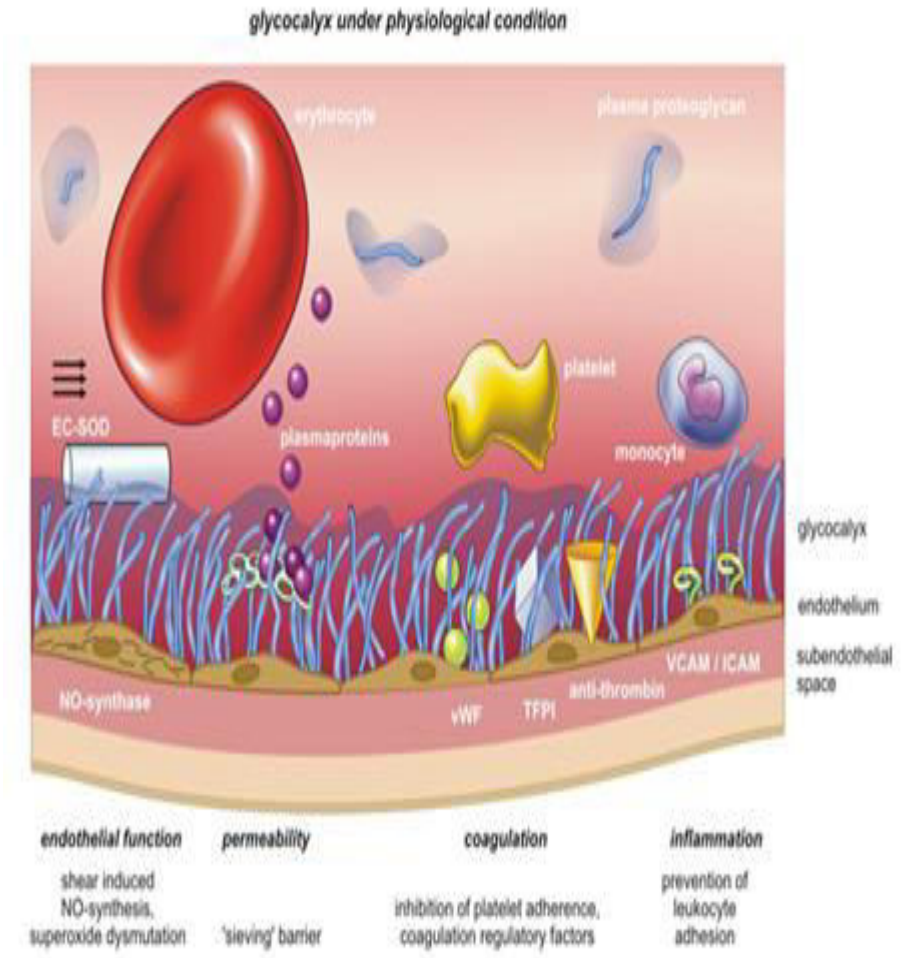
Ward's Principal

You Should Feel Free to Have Your Own Opinion

But

You Cannot Have Your Own Physiology

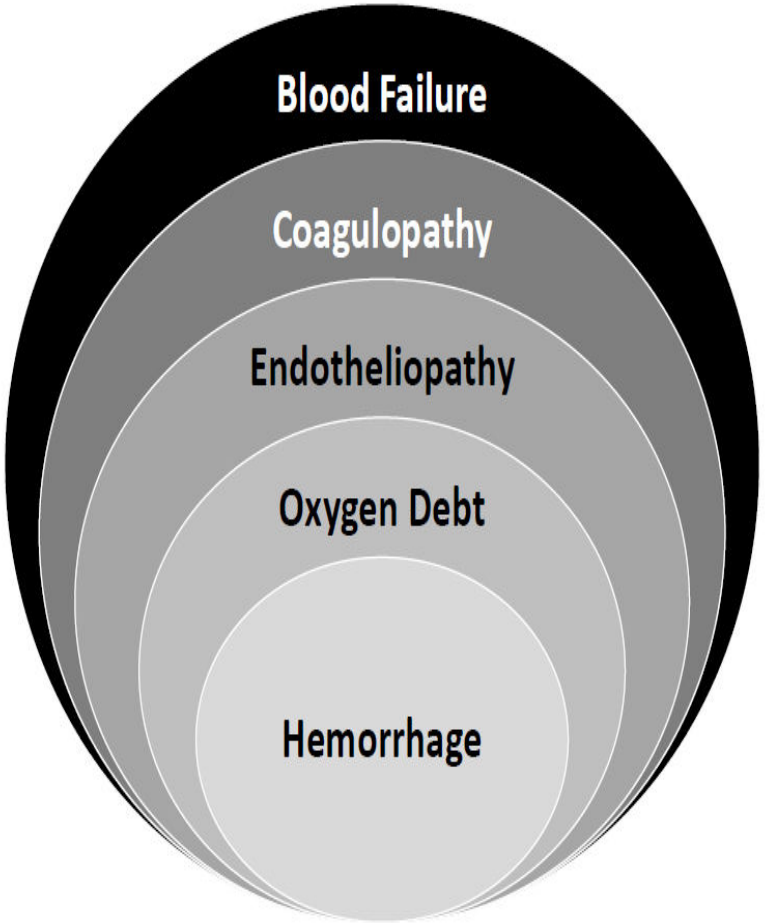
Blood as an Organ= Blood + Endothelium



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

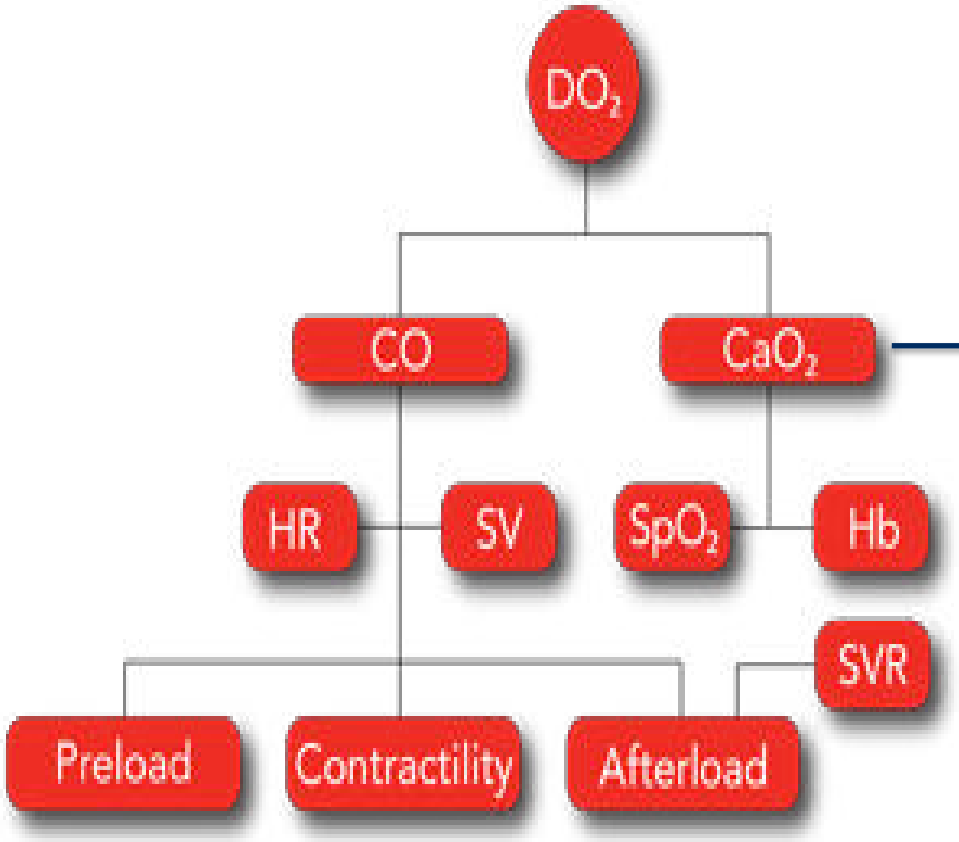
Blood as an Organ and Blood Failure

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.

Oxygen Delivery: DO2: The Simple Version

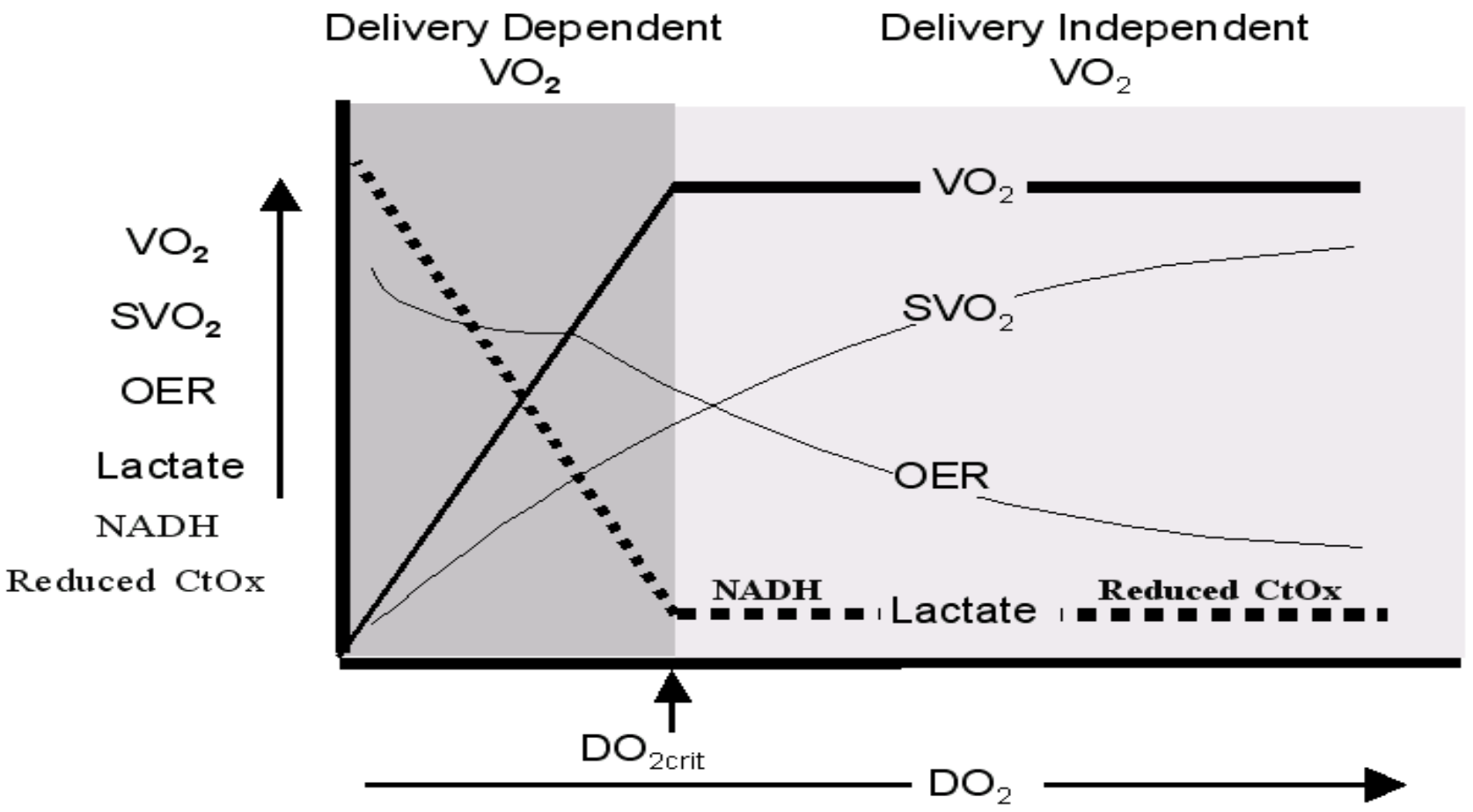


CaO2: Arterial Oxygen Content

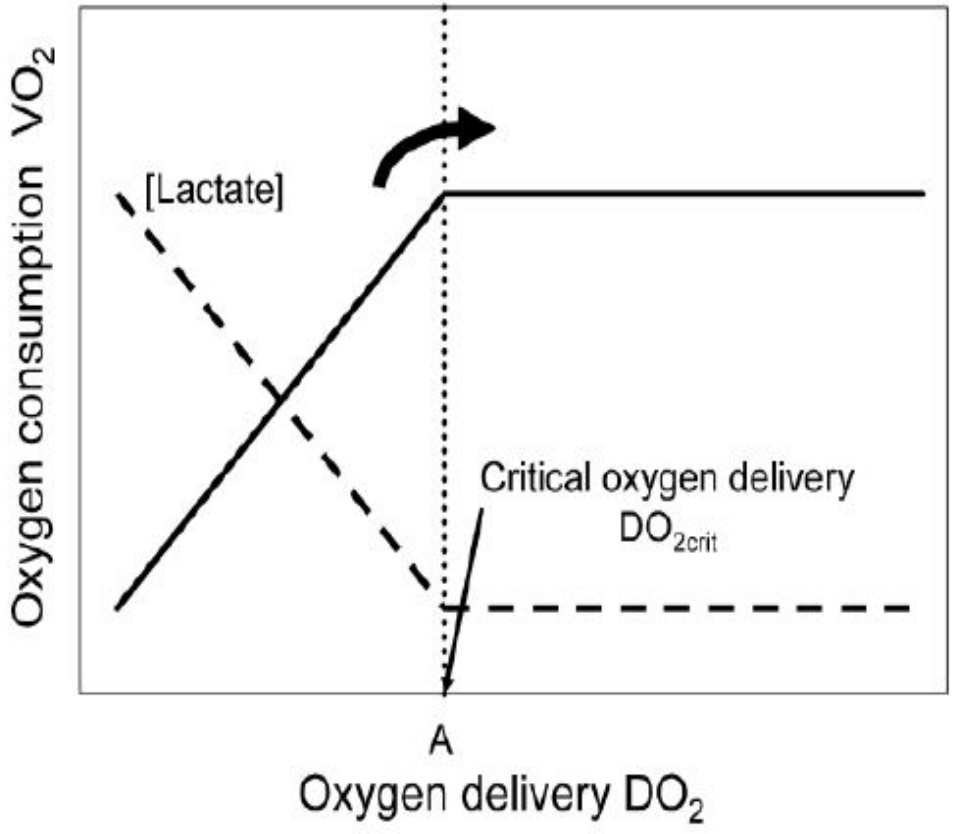
$$CaO_2 = (Hb \times 1.36)\frac{(SaO_2)}{100} + (PaO_2 \times 0.0031)$$

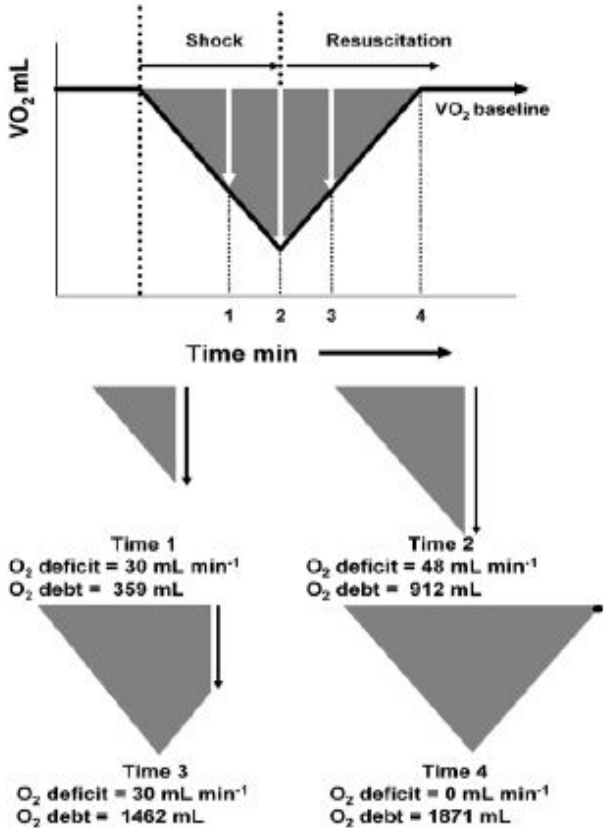
Similar to How Einstein's Physics of Relativity breaks down at the Quantum level so does Central DO2 at the tissue microcirculatory level.

Biphasic Oxygen Delivery/Consumption Relationship: Curve of Life



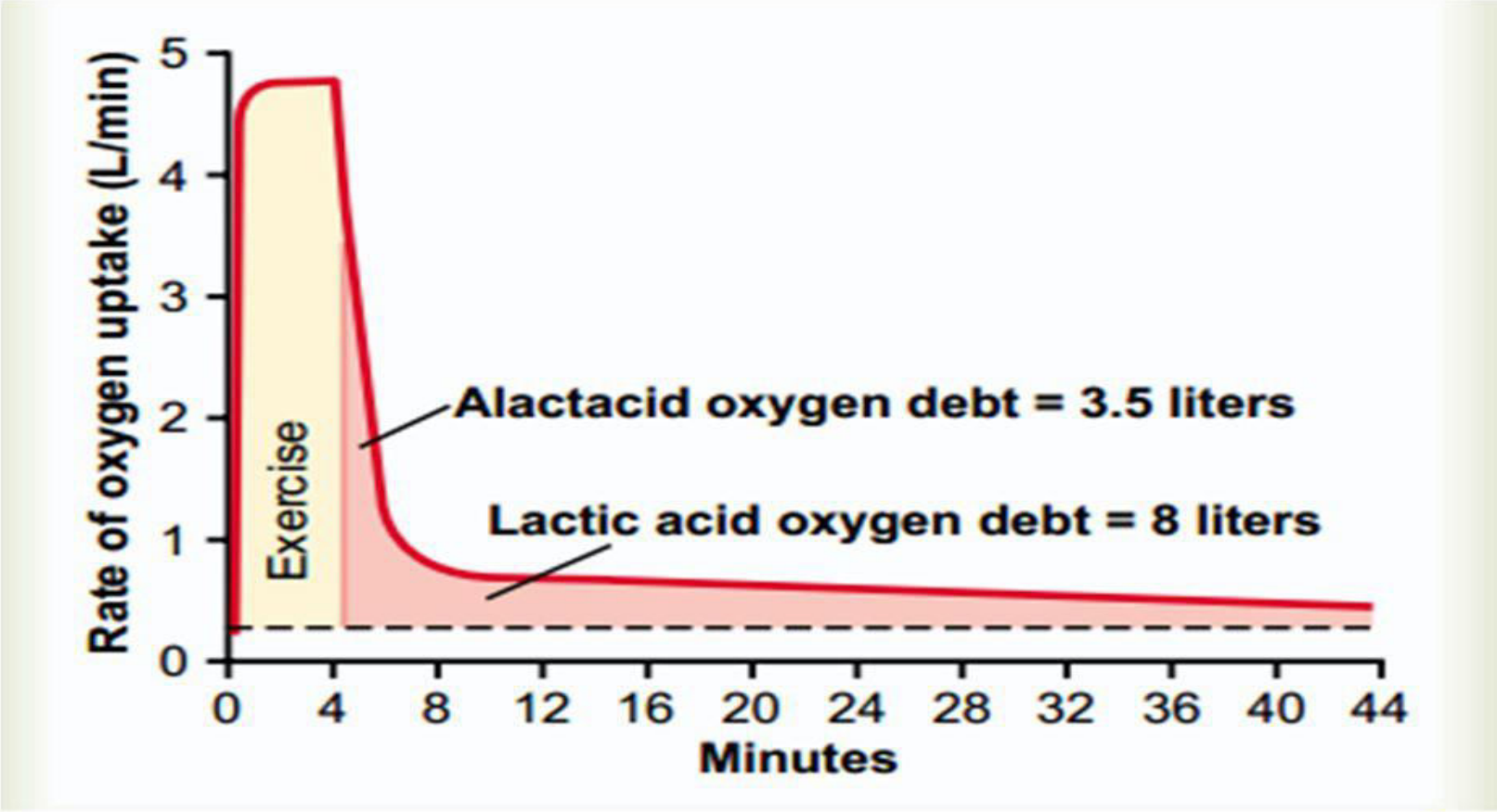
Accumulated Oxygen Deficit = Oxygen Debt
Think of Debt as Whole Body Ischemic Burden



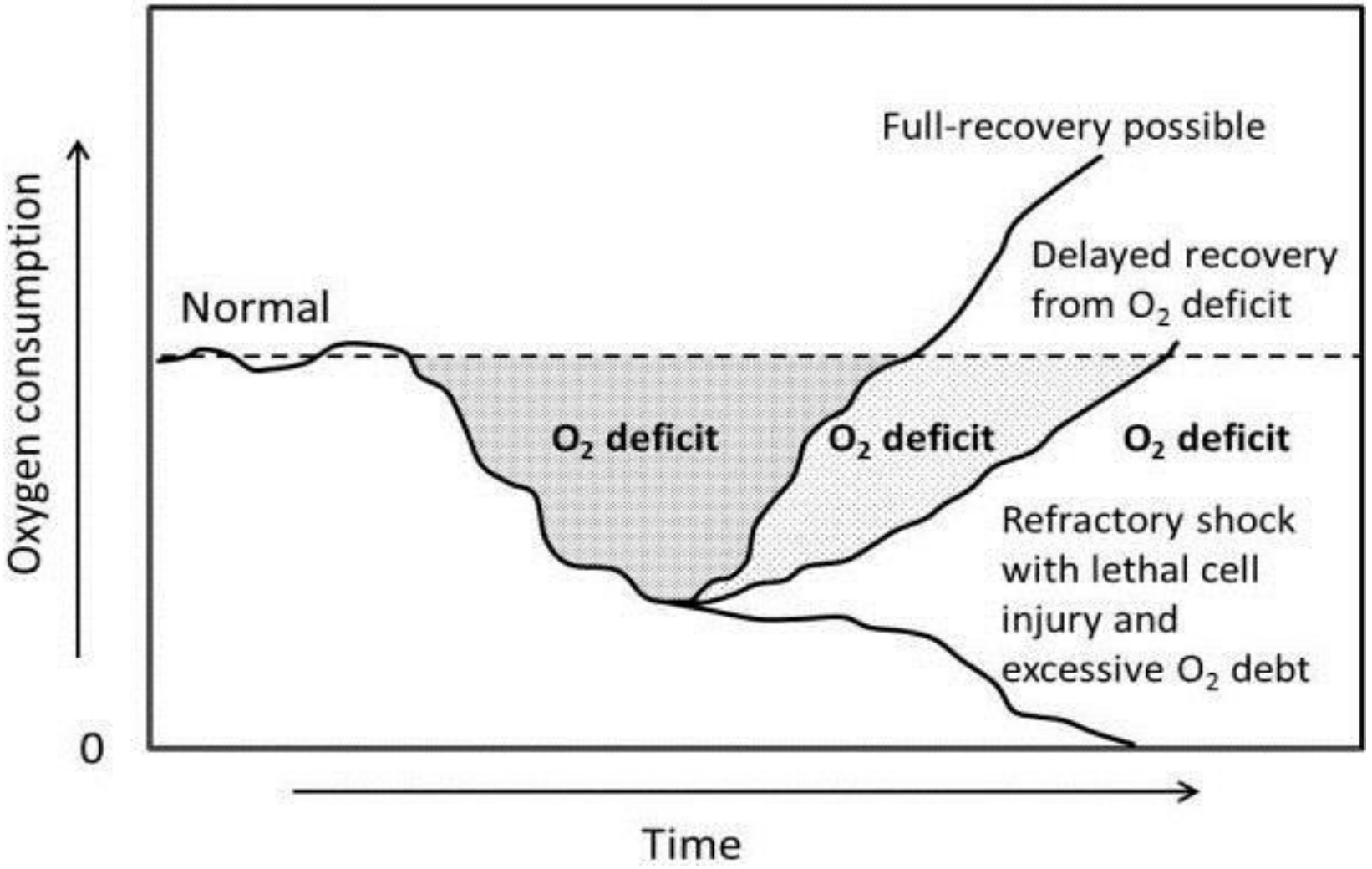


Barbee RW, Reynolds PS, Ward KR. Shock. 2010 Feb;

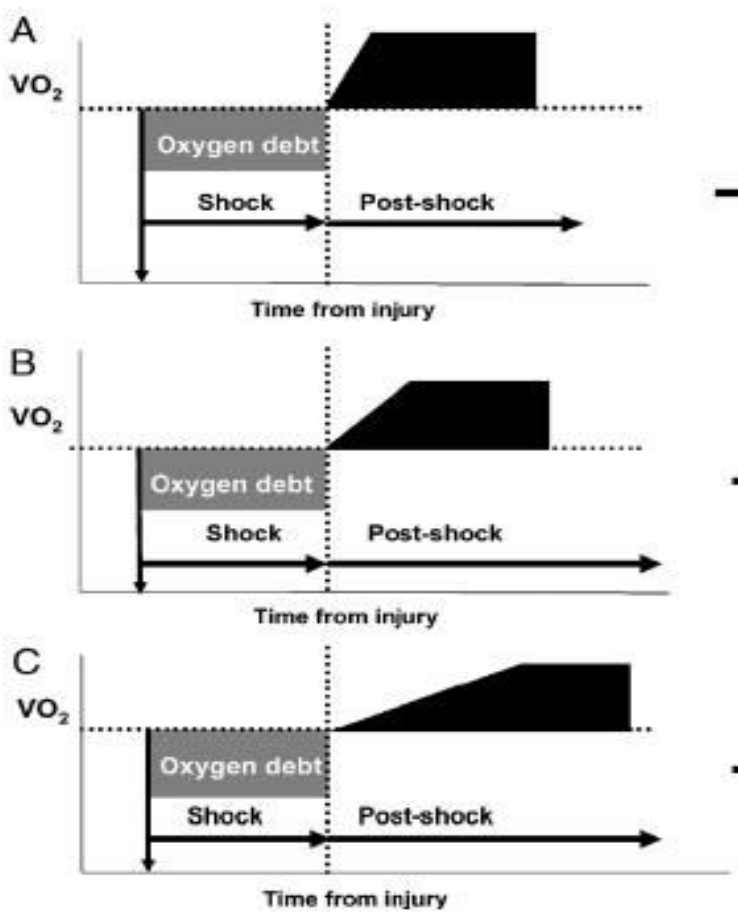
Lessons from Exercise Physiology

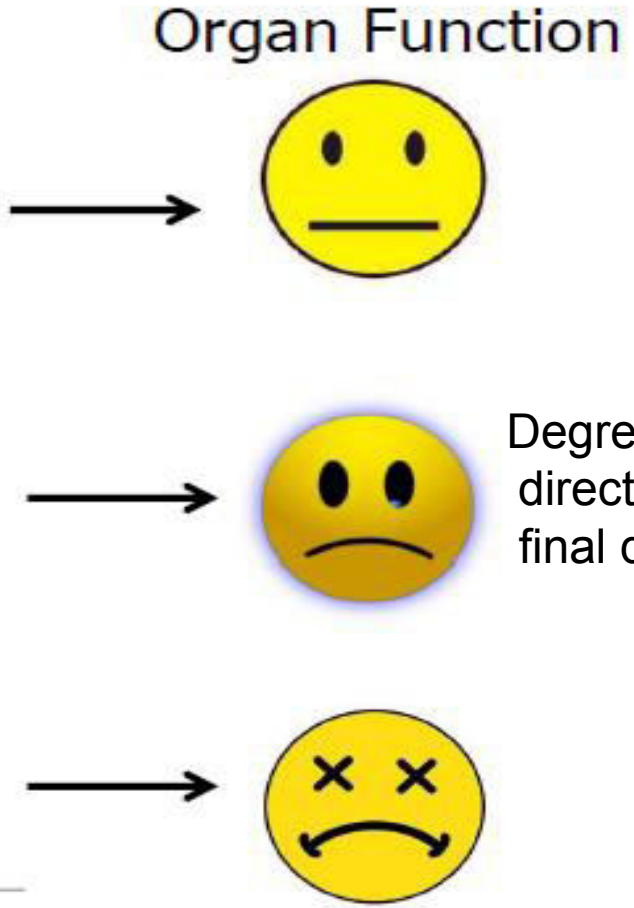


Lessons from Surgery:



Ramifications of Debt Repayment:
Unclear How Much Repayment Over What Period of Time: Think of Sleep Debt



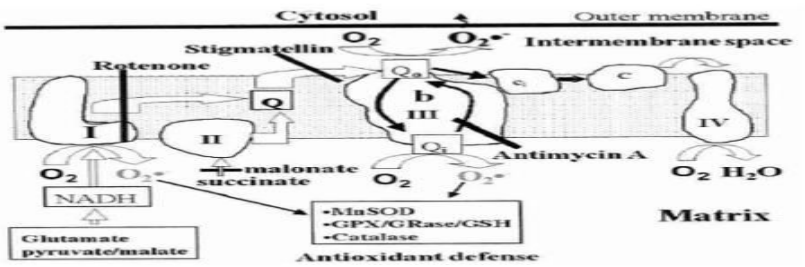


Degree of inflammation directly proportional to final degree of oxygen debt

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

Debt and the Role of Reperfusion Injury: Degree of Injury and Inflammation Related to Debt

ROS and Oxidation



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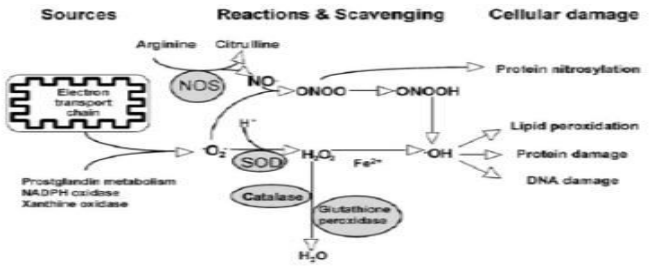
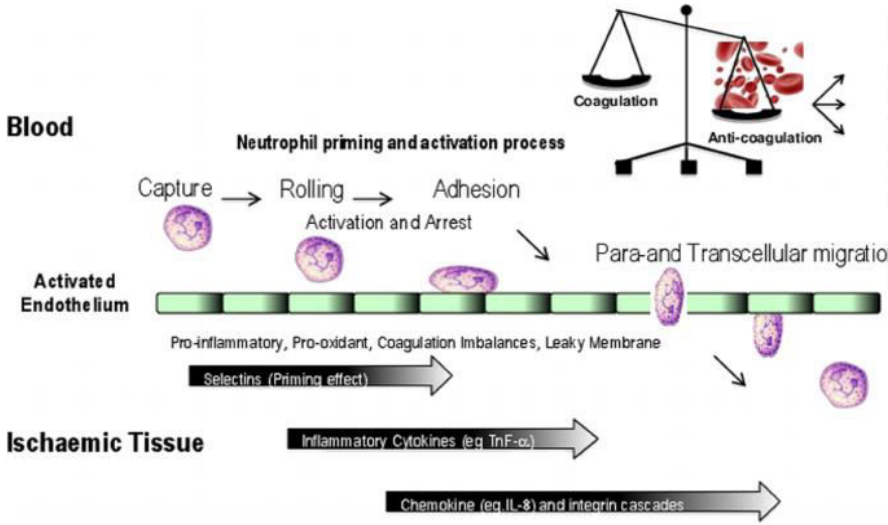


Kyaw M *et al* / Acta Pharmacol Sin (2004) 8: 977-985



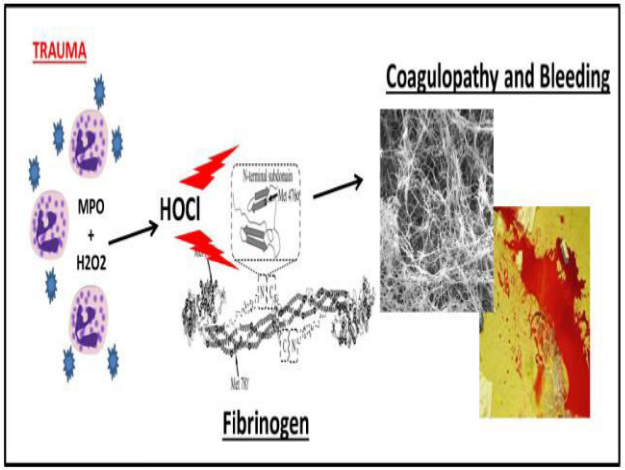
Acute Hypocoagulopathy

- ↑ Activated protein C
- ↓ Thrombin availability
- ↑ Protein C receptor activity
- ↓ Tissue Factor availability
- ↑ Fibrinolysis
- ↑ Platelet Dysfunction

Depolarised Endothelial Membrane Potential

Oxidative "Attack" (Tissue Damage)

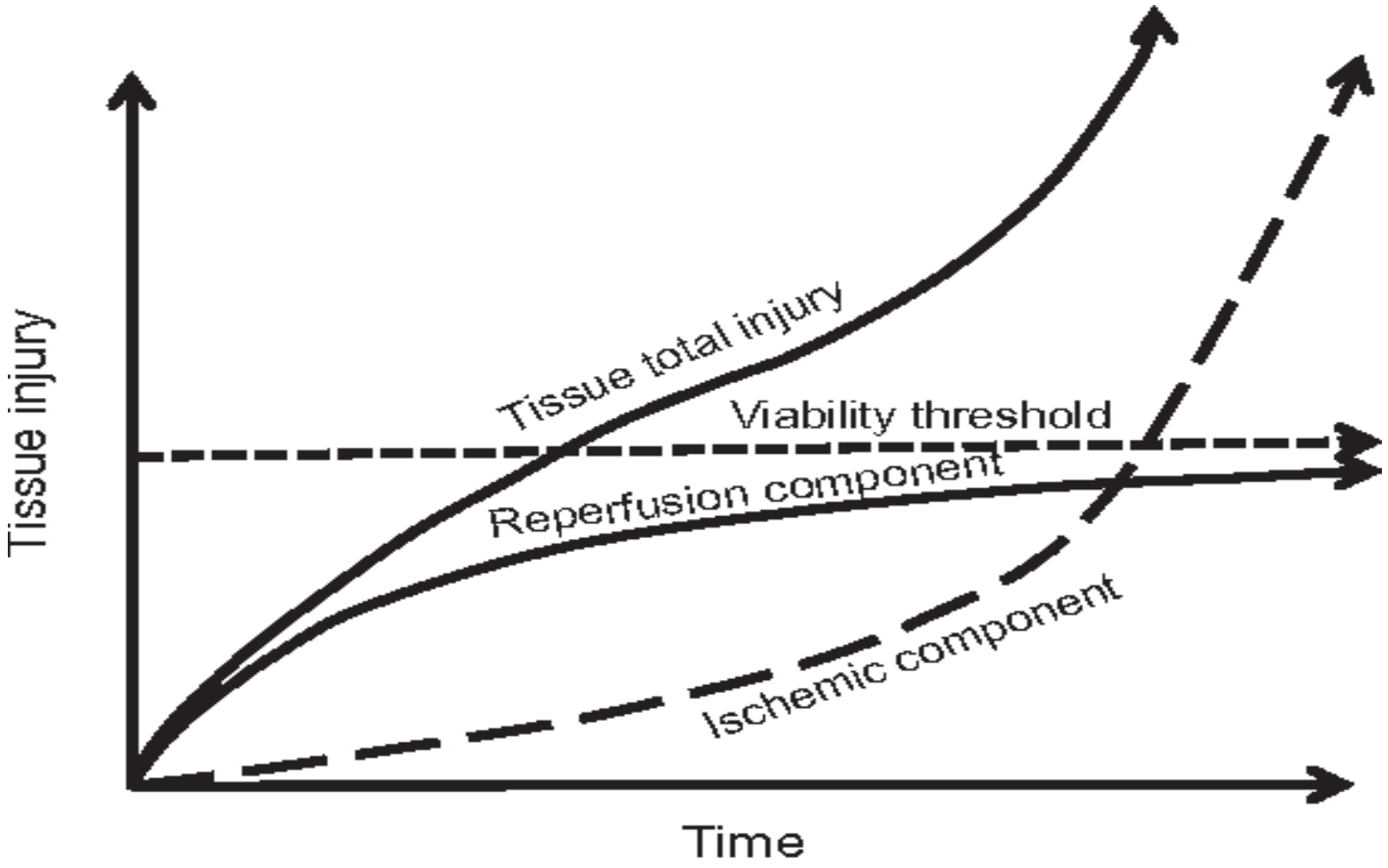
- ↑ Inflammatory cytokines
- ↑ Microparticle Formation
- ↑ Free radicals (superoxide, hydrogen peroxide)
- ↑ Cytotoxic metabolites (proteases cathepsin G, proteinase 3, elastase)



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

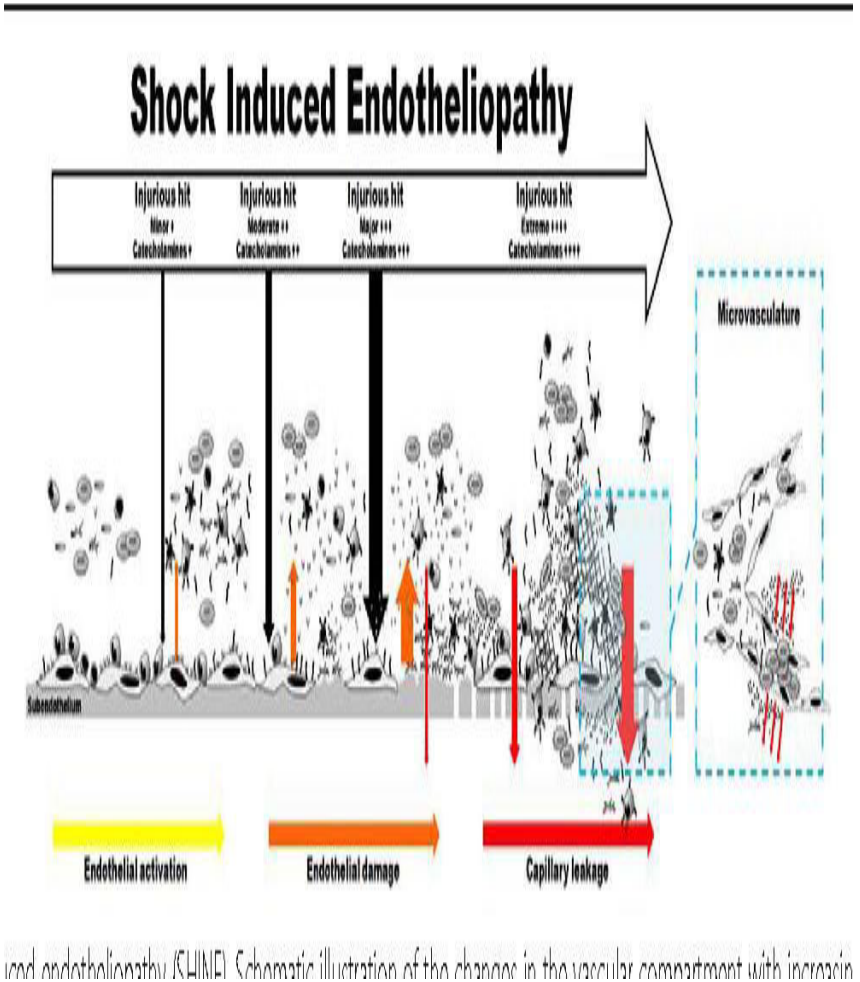
MCIRCC

Synergistic Connection Between Ischemic Time, Reperfusion and Total Tissue Injury

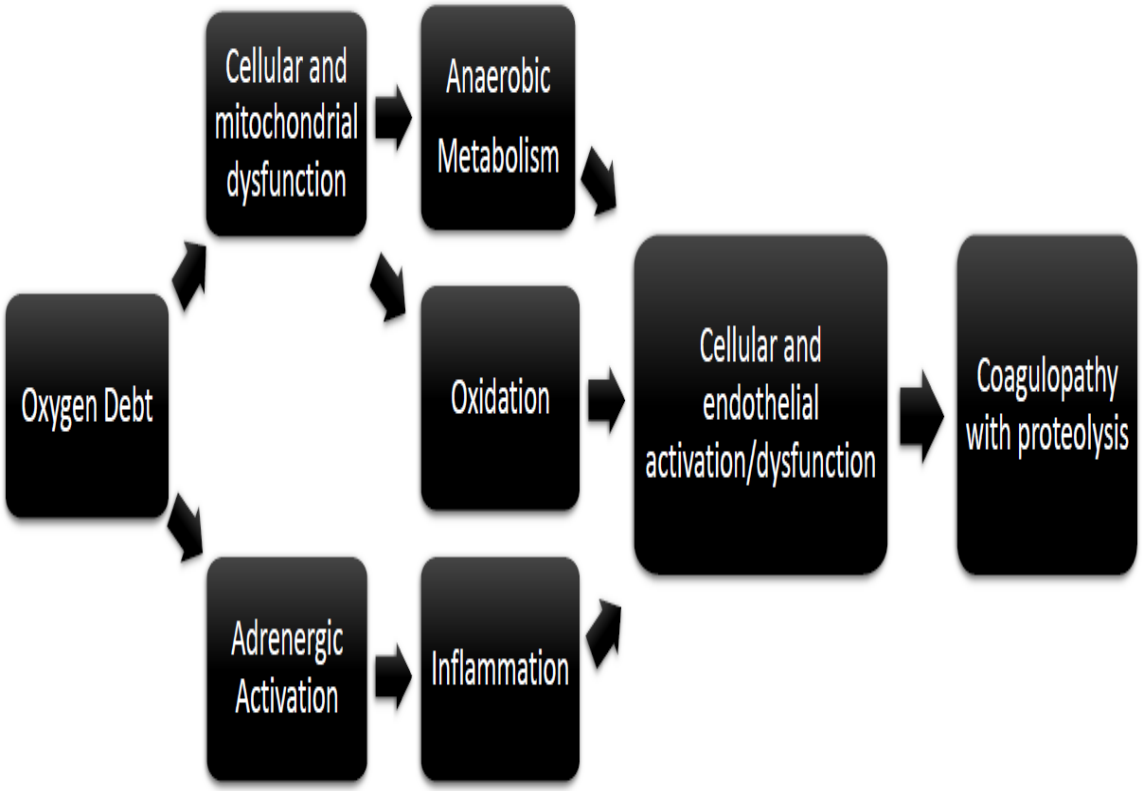


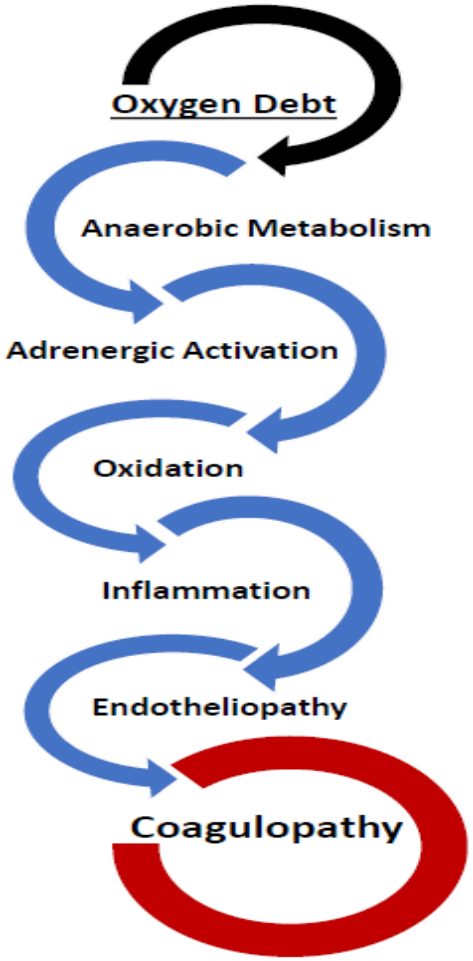
Role of Catecholamines:

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

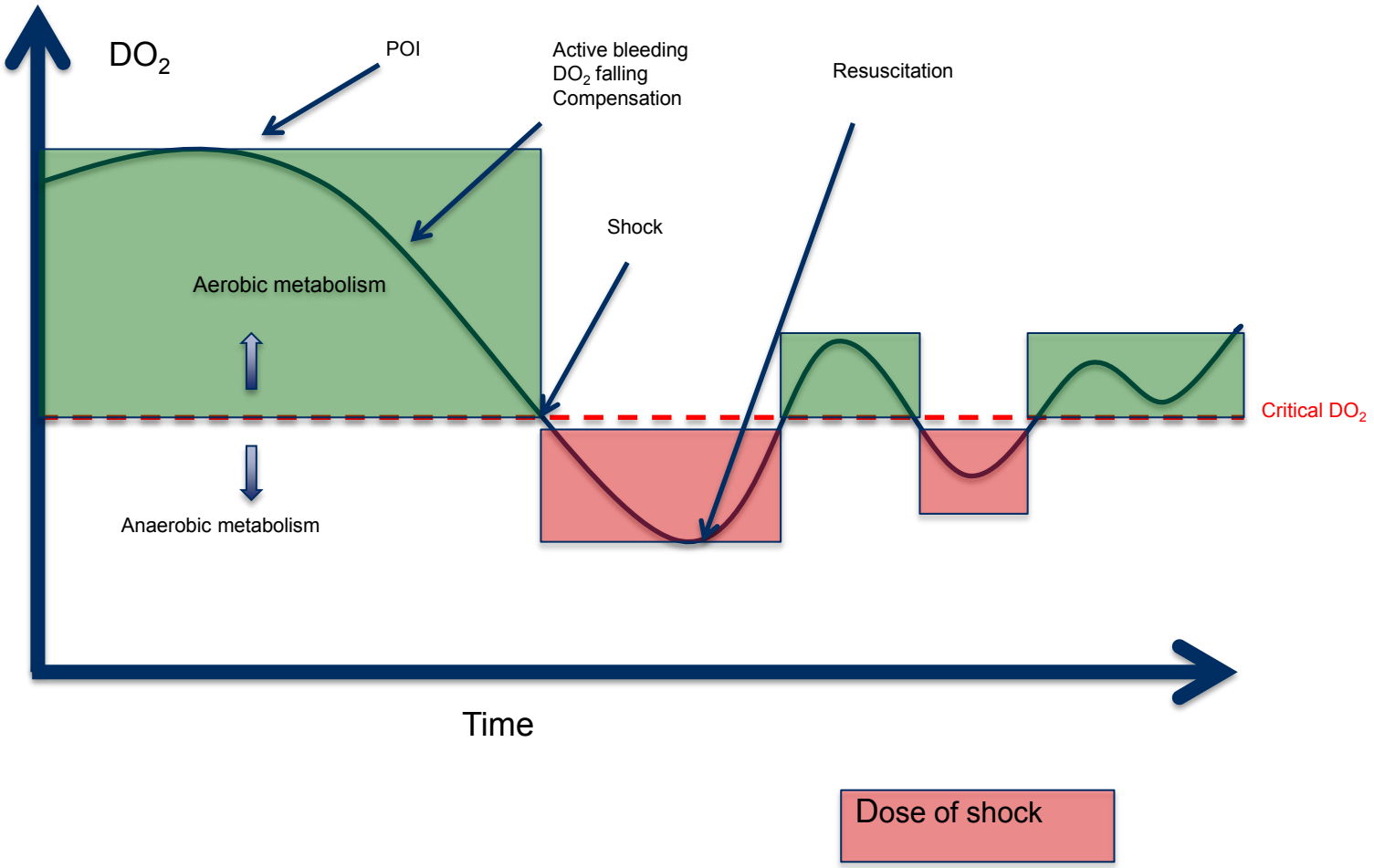


Putting it All Together

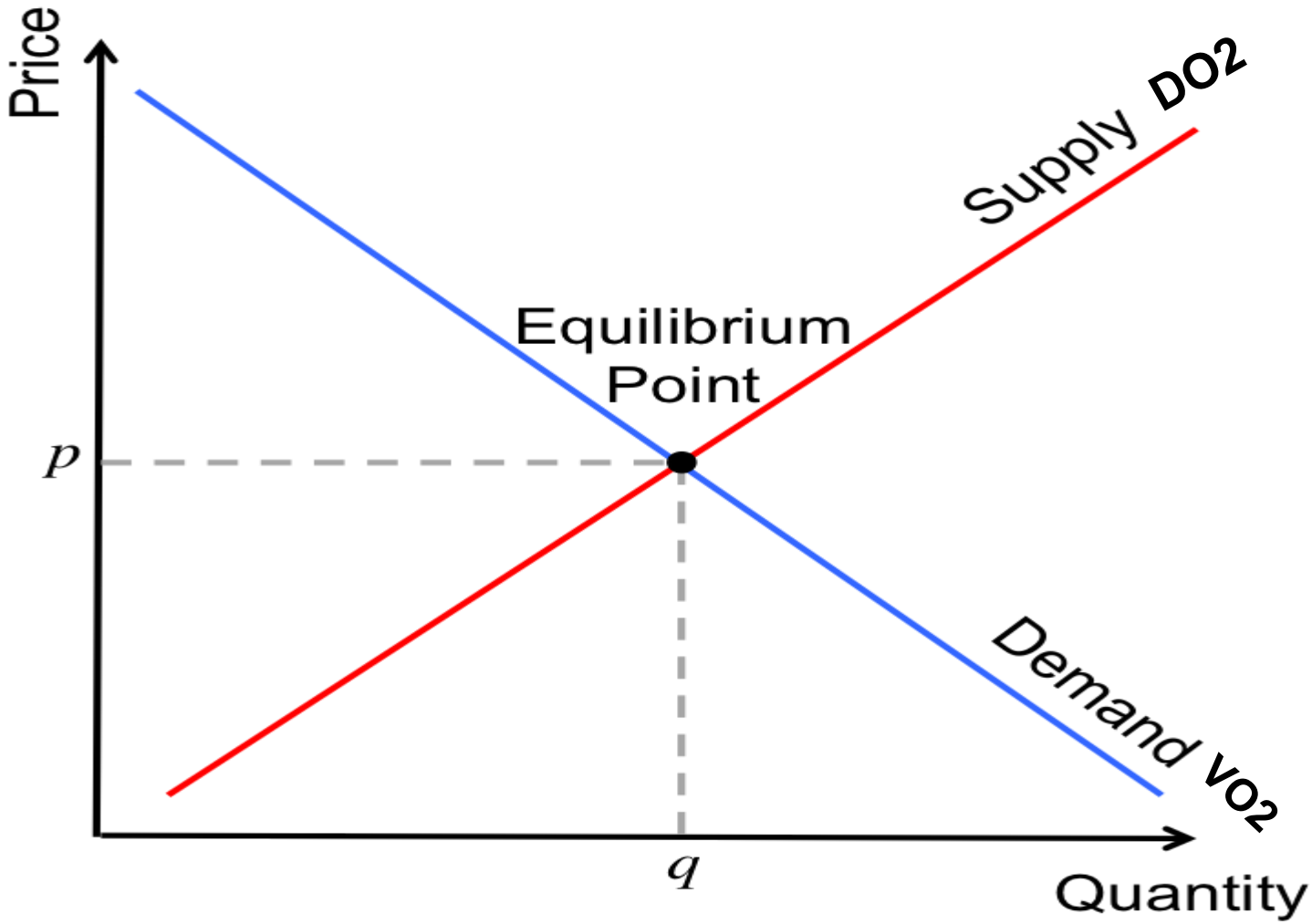




The Reality of Injury and Resuscitation



The Price of Supply and Demand: The Economics of Shock: Everything Has a Cost!

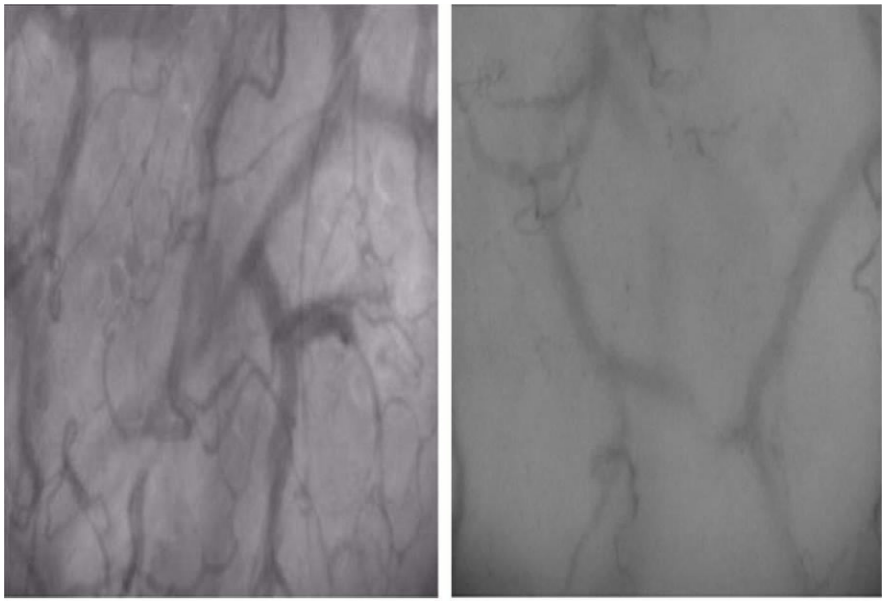


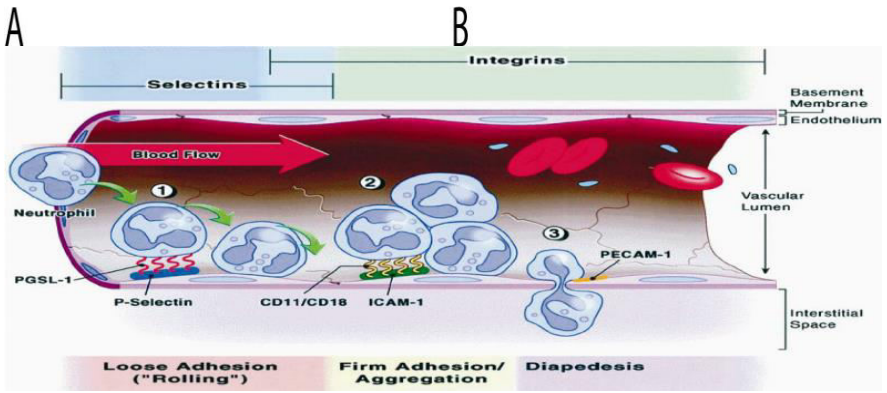
How to Increase/Maintain DO2?

Whole Blood, Blood Components (RBC, Plasma, Platelets), Blood Substitutes, etc. Should Not and Cannot Be the Only Answer!

Microcirculatory Vasodilation and Repair: Once Wrecked, Its Hard to Repair

- Use of vasodilators
  - Nitric oxide, Carbon Monoxide, CO2
    - Inhalation, Precursors (CORMS, L-Arginine), Vibration induced NO
  - Angiotensin Converting Enzyme Inhibitors
  - Reduce adrenergic output?
    - Clonidine???
    - Better pain control
- Use of antioxidants and anti-inflammatory agents
  - Reduce ROS damage and Neutrophil plugging/damage
  - Vitamin C, Carbon Monoxide
  - Hypothermia

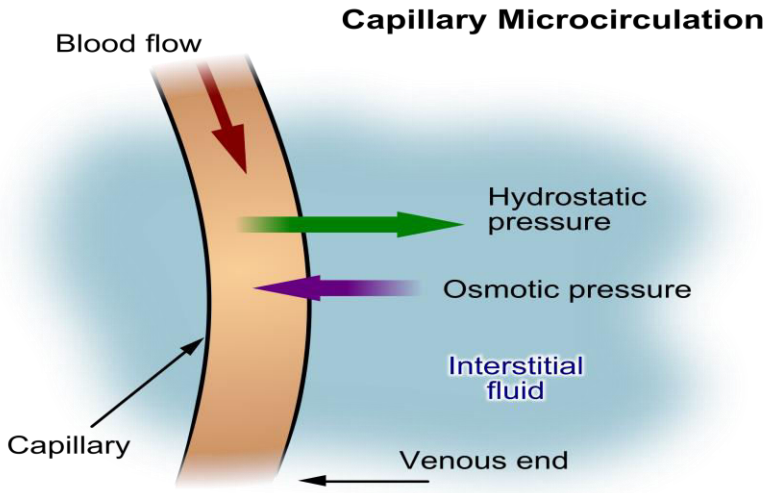


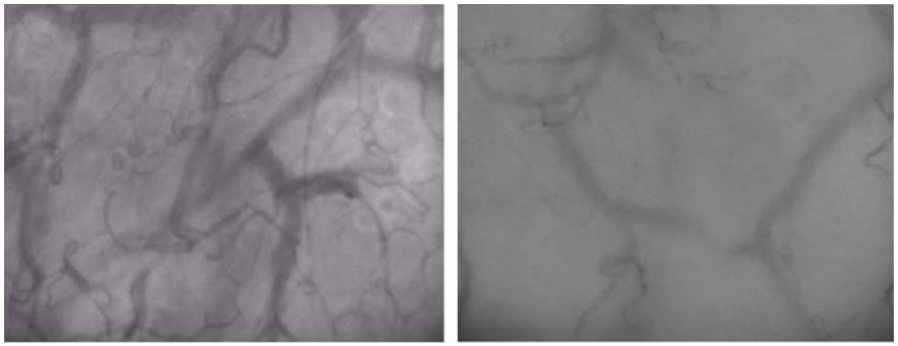


Maintaining Critical Hydrostatic Pressures: Pertinent to Permission Hypotension

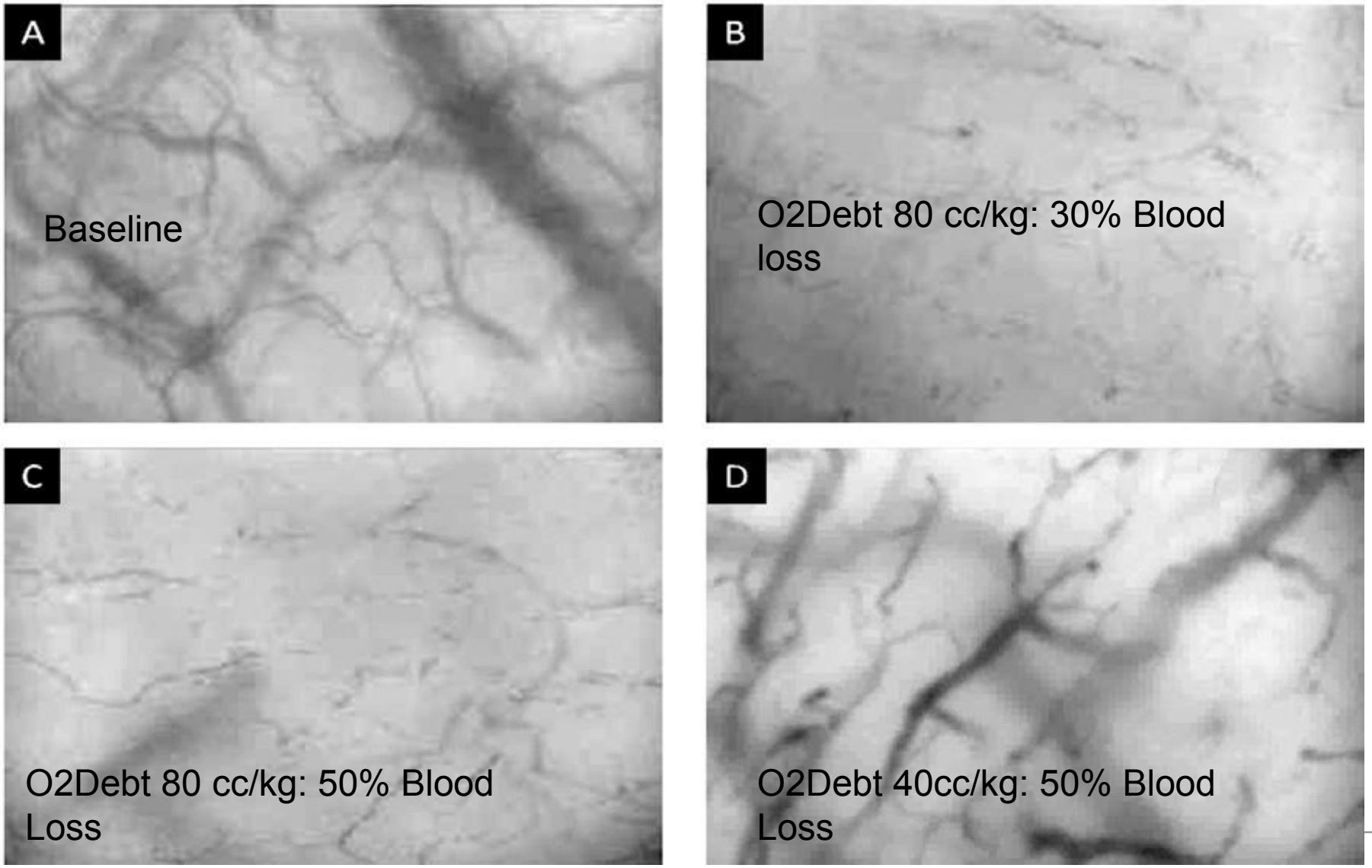
- Vasopressors (non-catecholamines)?
  - Phenylephrine
  - Vasopressin
- Volume expansion
  - Polyethylene Glycol
  - Plasma/Albumin
  - Rate may count

Again…Once Collapsed Its Very Hard to Open: Shunting (Non-Nutritive) Flow Occurs



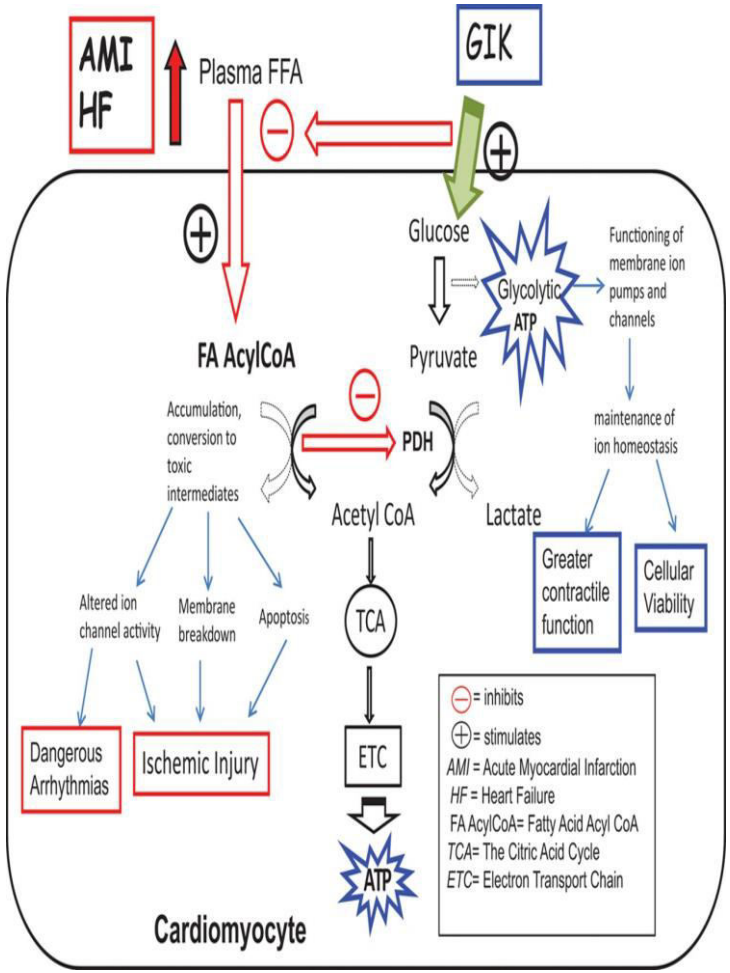


Challenges in Variability: Non-linearity of Response to Hemorrhage



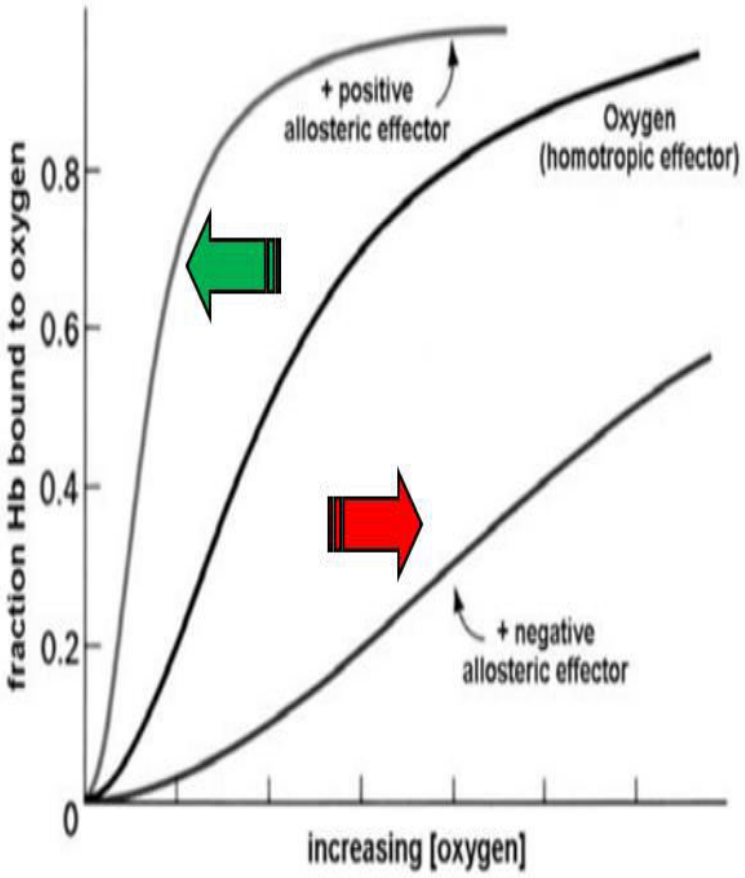
Increasing Cardiac Output (Without Volume and Catecholamines)

- Glucose-Insulin-Potassium (GIK)
- Glucagon and glucagon receptor chemistry
- Amrinone: PDE III inhibition



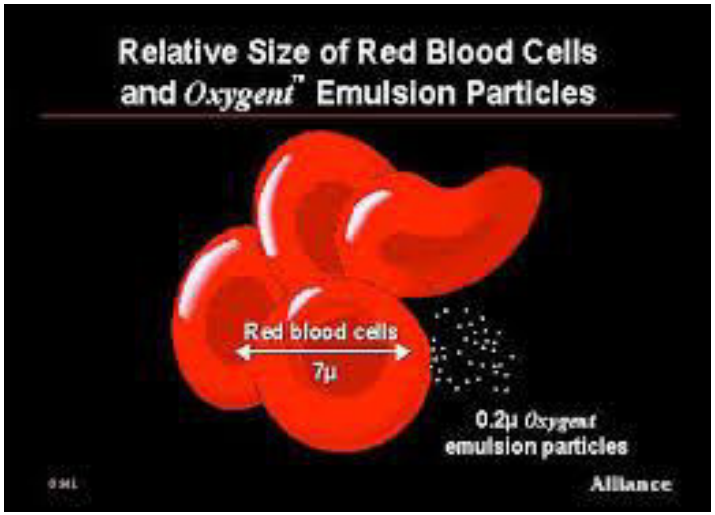
Allosteric Modification of Hemoglobin

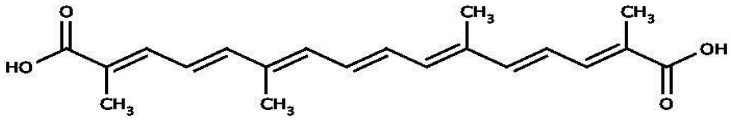
- Drugs that move the oxy-hemoglobin curve to the right or the left
  - Changes Hb P50 (27 mmHg)
  - Right: P50 40-50 mmHg
  - Left: P50 5-10 mmHg
- Controversy on which may be better
- May have vaso-active effects
  - Reducing hemoglobin Nitric Oxide scavenging, etc.



Enhancing the Solubility of and Reducing Resistance of Oxygen in Plasma

- Diffusion based on Fick's Law
  - Plasma accounts 70-90% resistance
- 0.023 ml O2 per ml of plasma at 760 torr O2
- 50 ml O2 per ml of Perfluorocarbon at 760 torr O2
- Trans Sodium Crocetin:
  - Alters hydrogen boding of water
  - Increases oxygen diffusivity





Strategies being used to enhance tumor susceptibility to Radiation Therapy

Alternative/Complimentary Forms of Oxygenation

- GI Tract: 25-30% of whole body VO2
- Intestinal absorptive surface area
  - 250 sq meter or 2700 sq ft.
- Counter current structure of microvilli:
  - Prone to sever hypoxia
- Direct oxygenation of lumen
  - Oxygen gas
- Indirect oxygenation of lumen
  - Oxygen precursors (H2O2)

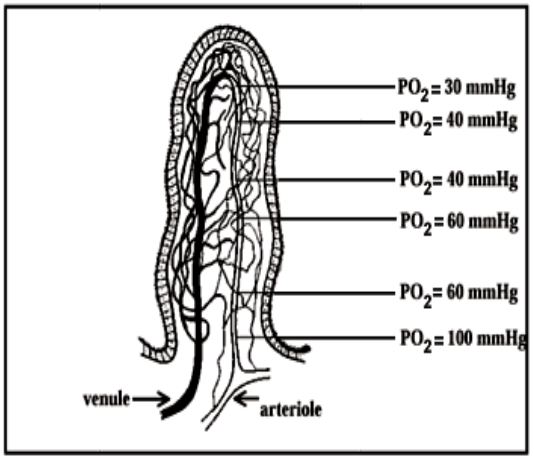
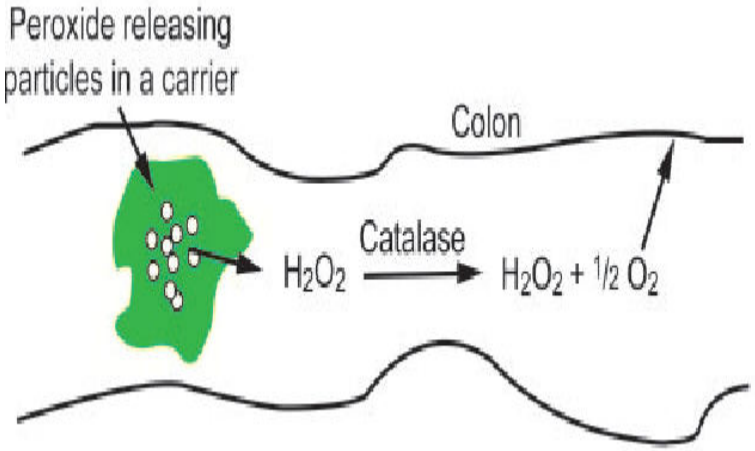


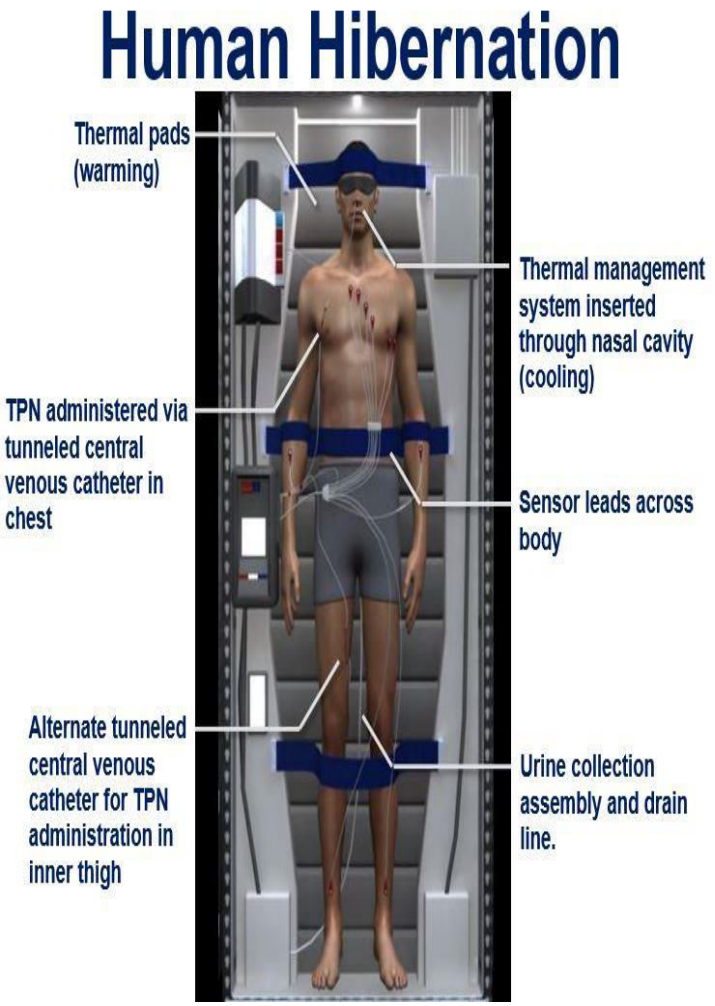
Figure 1 - Countercurrent exchange of O_2 between arteriole and venule within the intestinal villi, showing the progressive decrease in arteriolar PaO_2



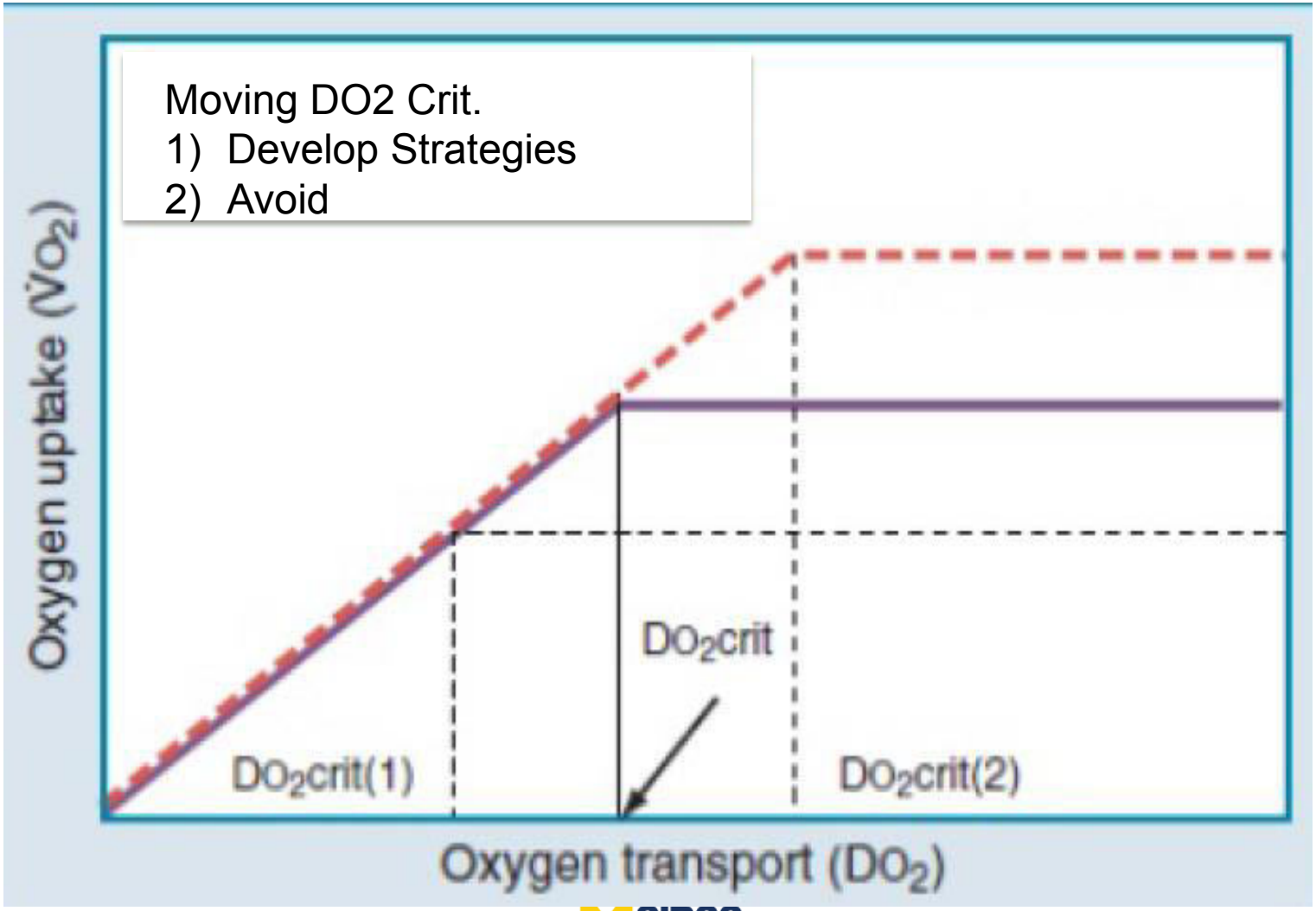
Reducing DO2 dependent VO2 and Enchancing Cell Survival Strategies

Suspended Animation

- Metabolic Down Regulation
  - Hypothermia
    - Not from inadequate DO2
    - Up to 7% decrease in VO2 for each 1º decrease in temp.
  - Protein Synthesis Inhibition
  - Revisit Hydrogen Sulfide
- Alternative fuel strategies
  - Ketones, lactate, etc.
- Cell Survival Strategies
  - Histone Deacetylase Inhibitors
    - Valproic Acid
  - Ischemia Preconditioning
    - Transient Ischemia Reperfusion
    - Adenosine, Lidocaine, Magnesium



Modulating Critical DO2: Changing the Goal Post

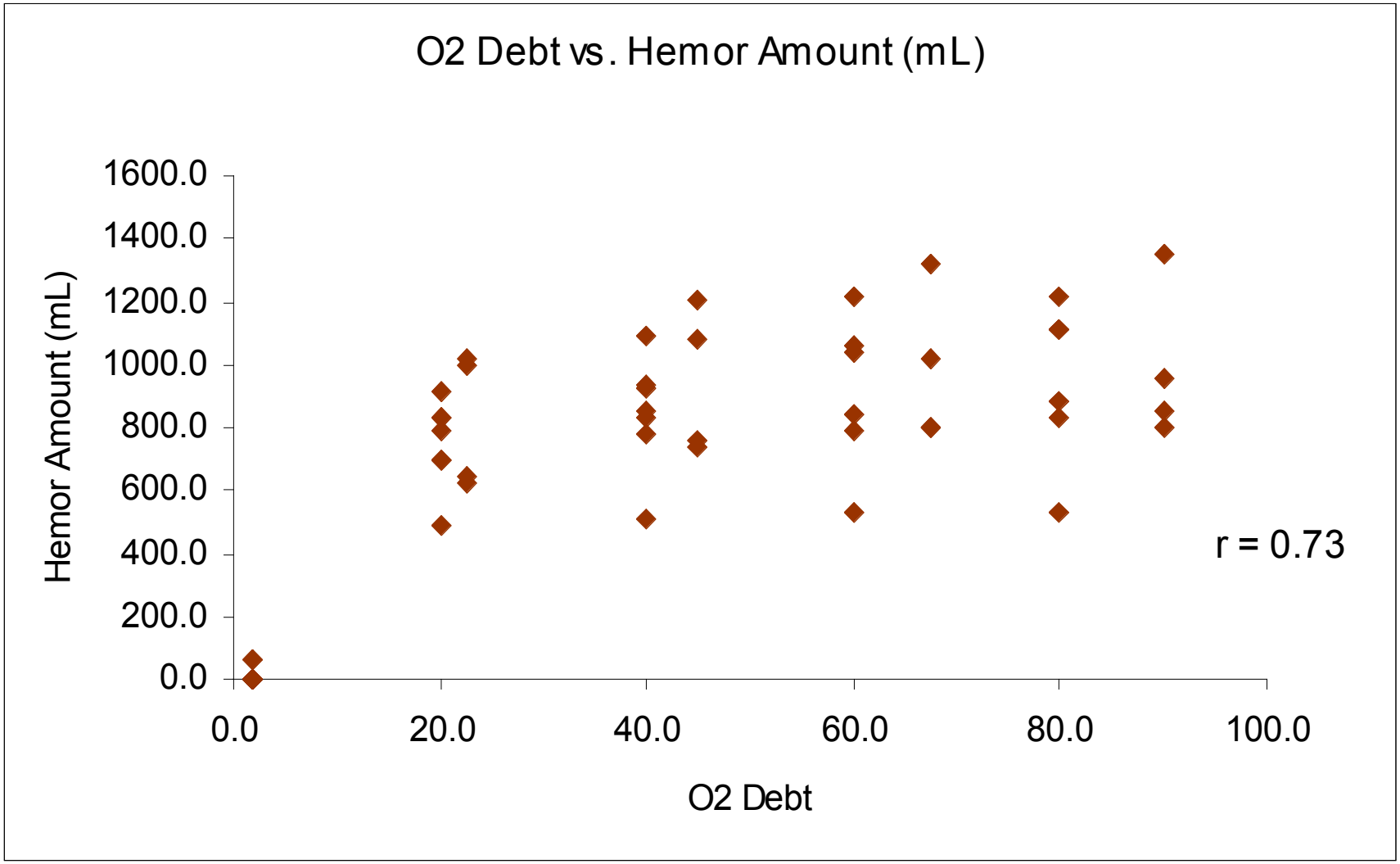


Other Considerations

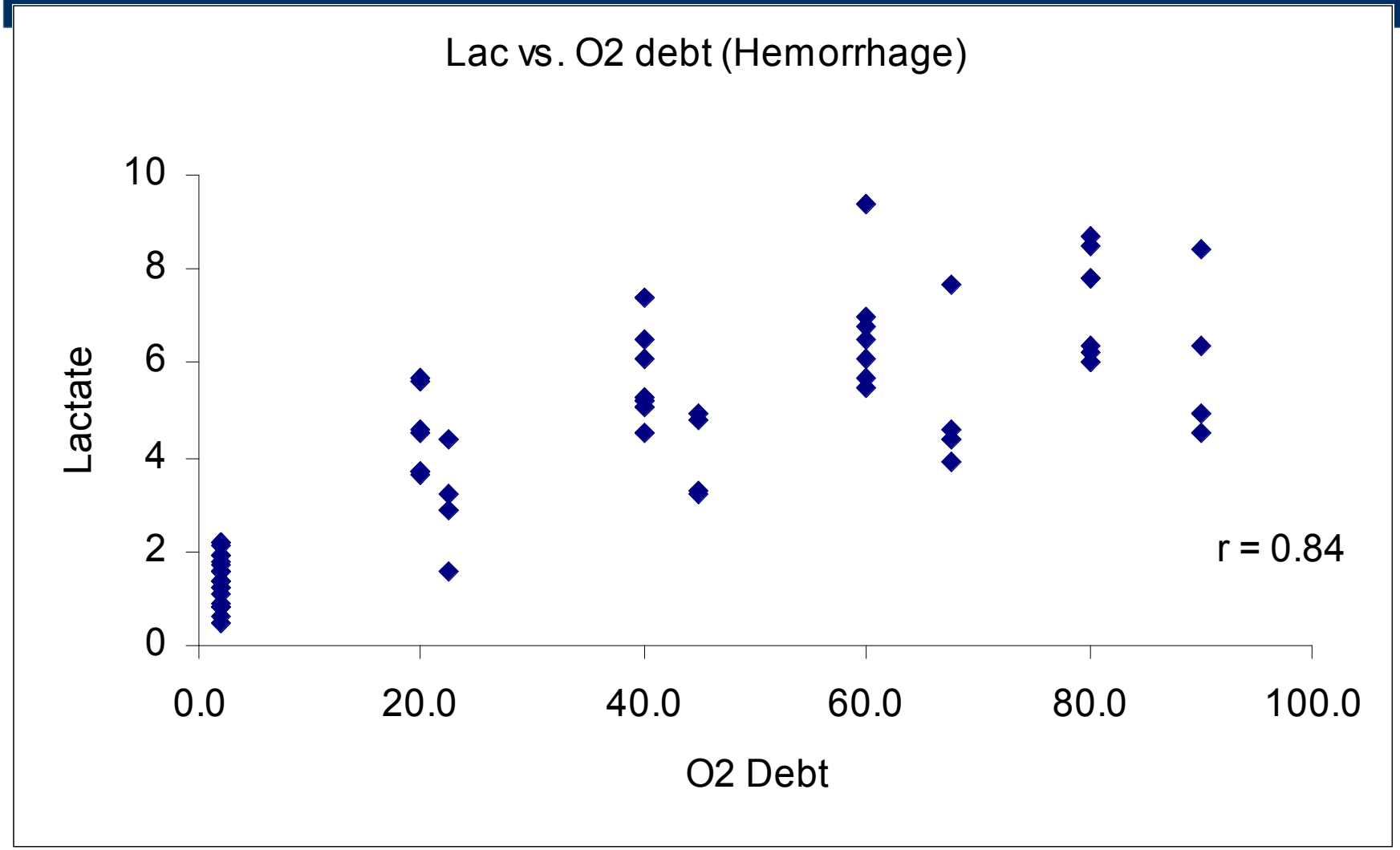
- How to Monitor?
- How to Monitor?
- How to Monitor

- Need Methods to Quantitate Oxygen Debt in real time
- End-points to Resuscitation
- Lactate and Hemorrhage Volumes Are Not the Holy Grail

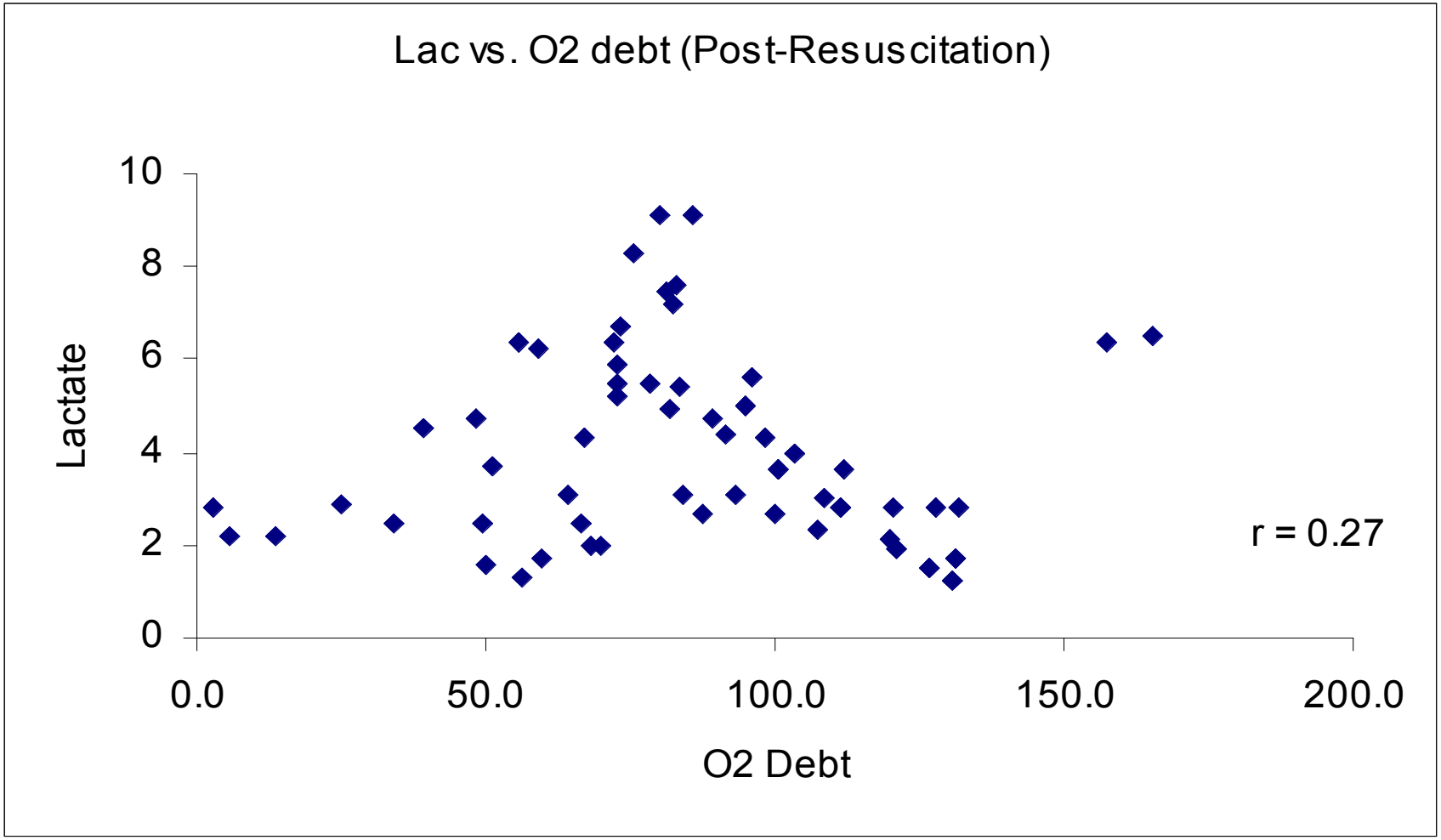
O2 Debt (cc/kg) vs. Hemorrhage Volume



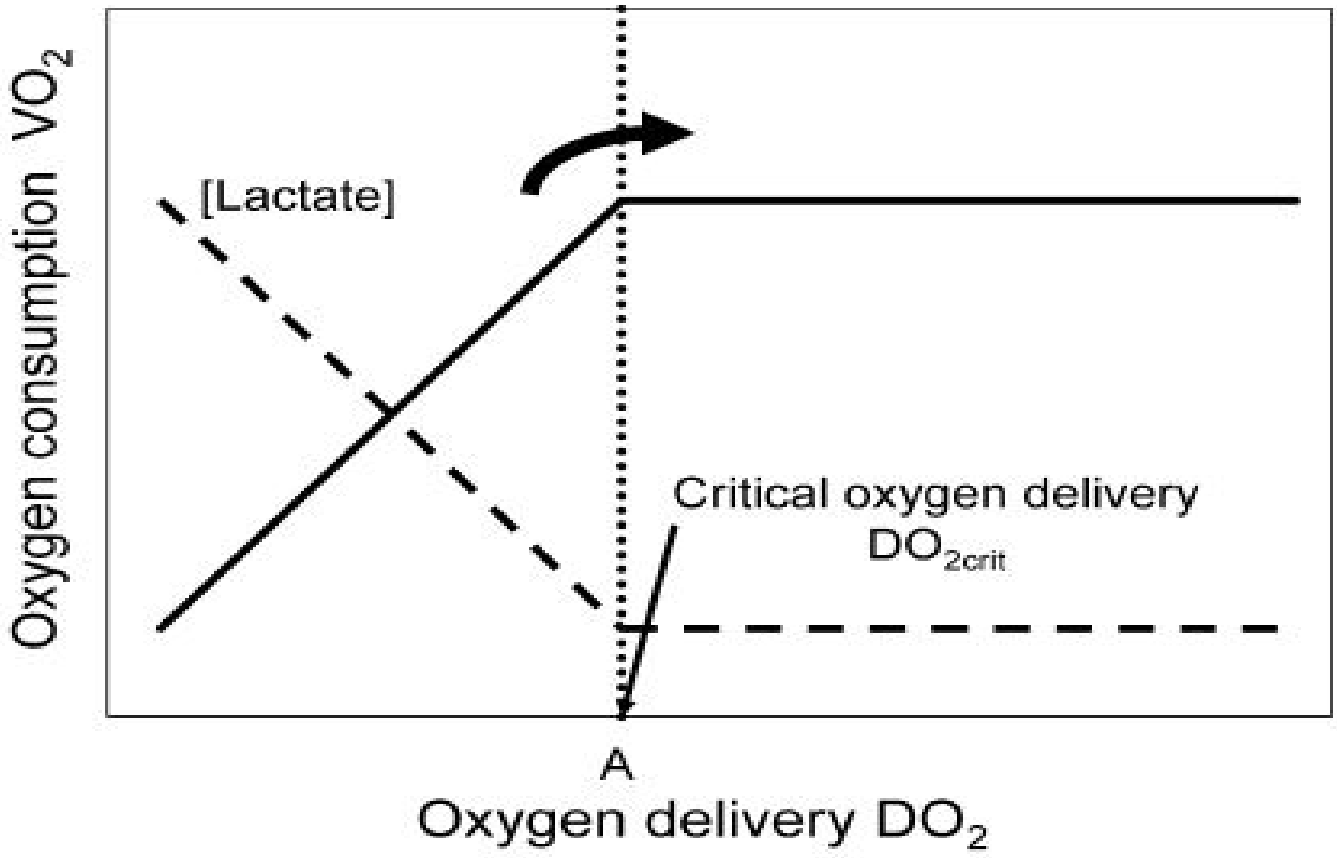
O2 Debt (cc/kg) vs. Lactate During Hemorrhage



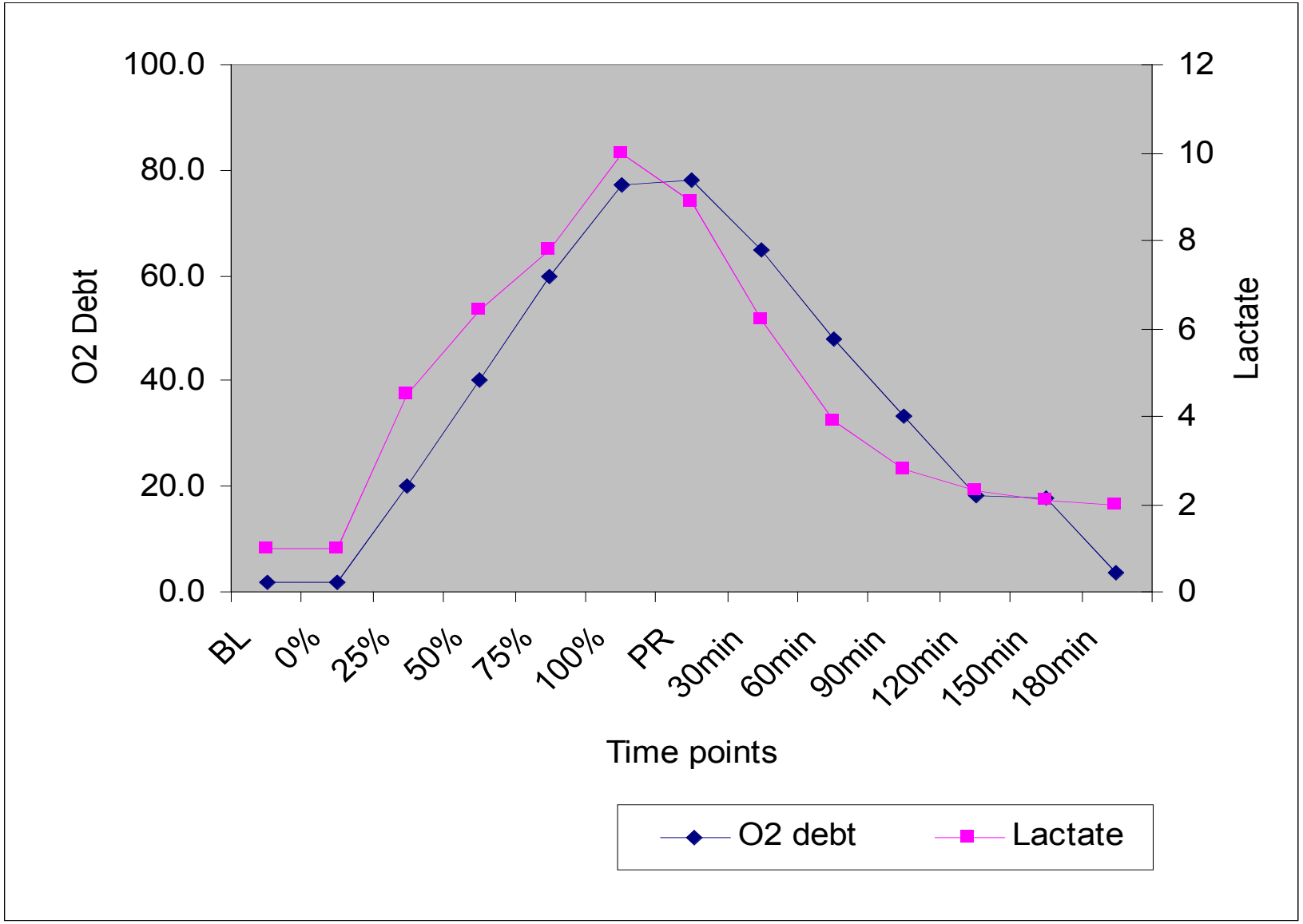
O2 Debt (cc/kg) vs. Lactate: During-Resuscitation



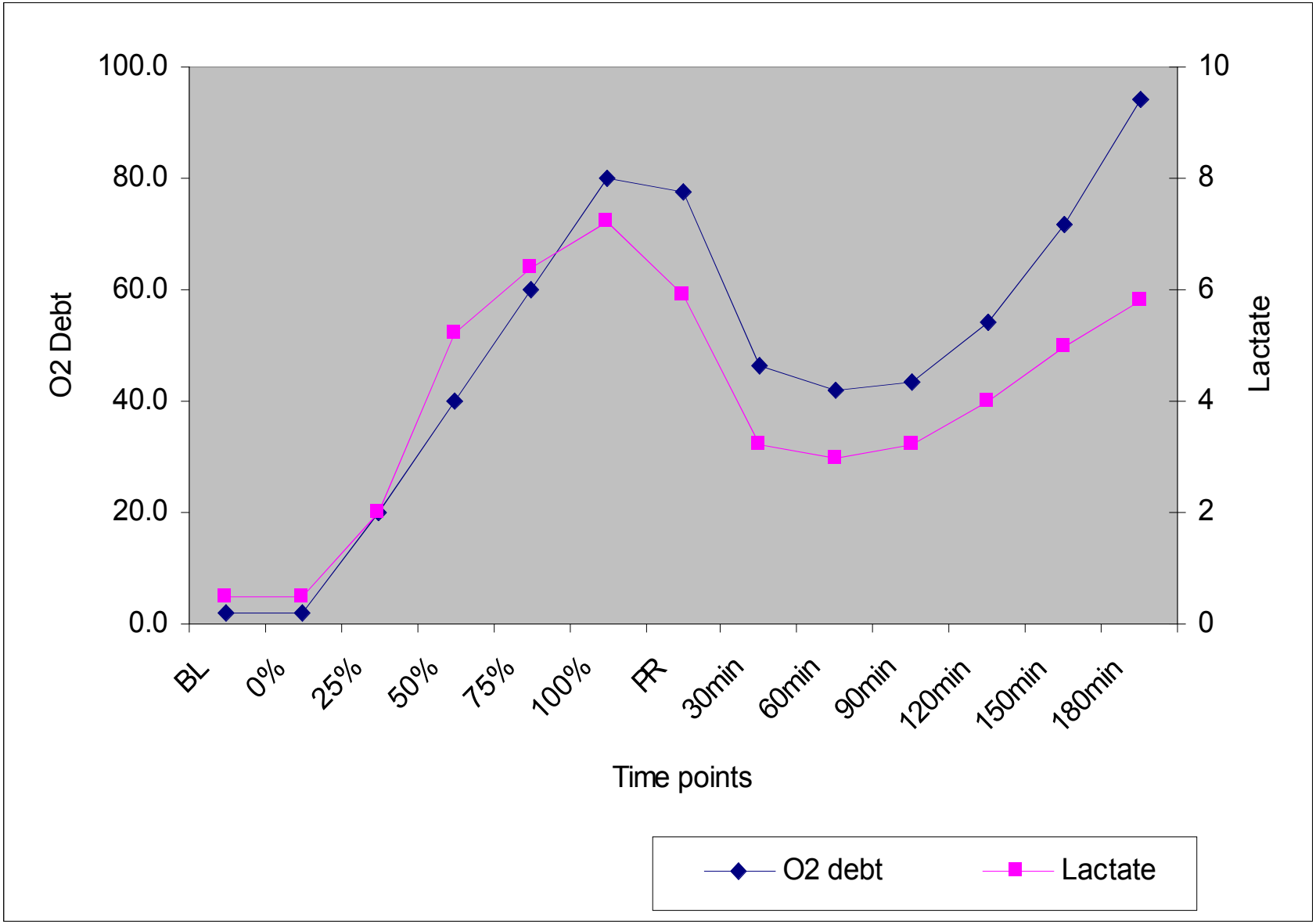
Remember the Relationship is Biphasic



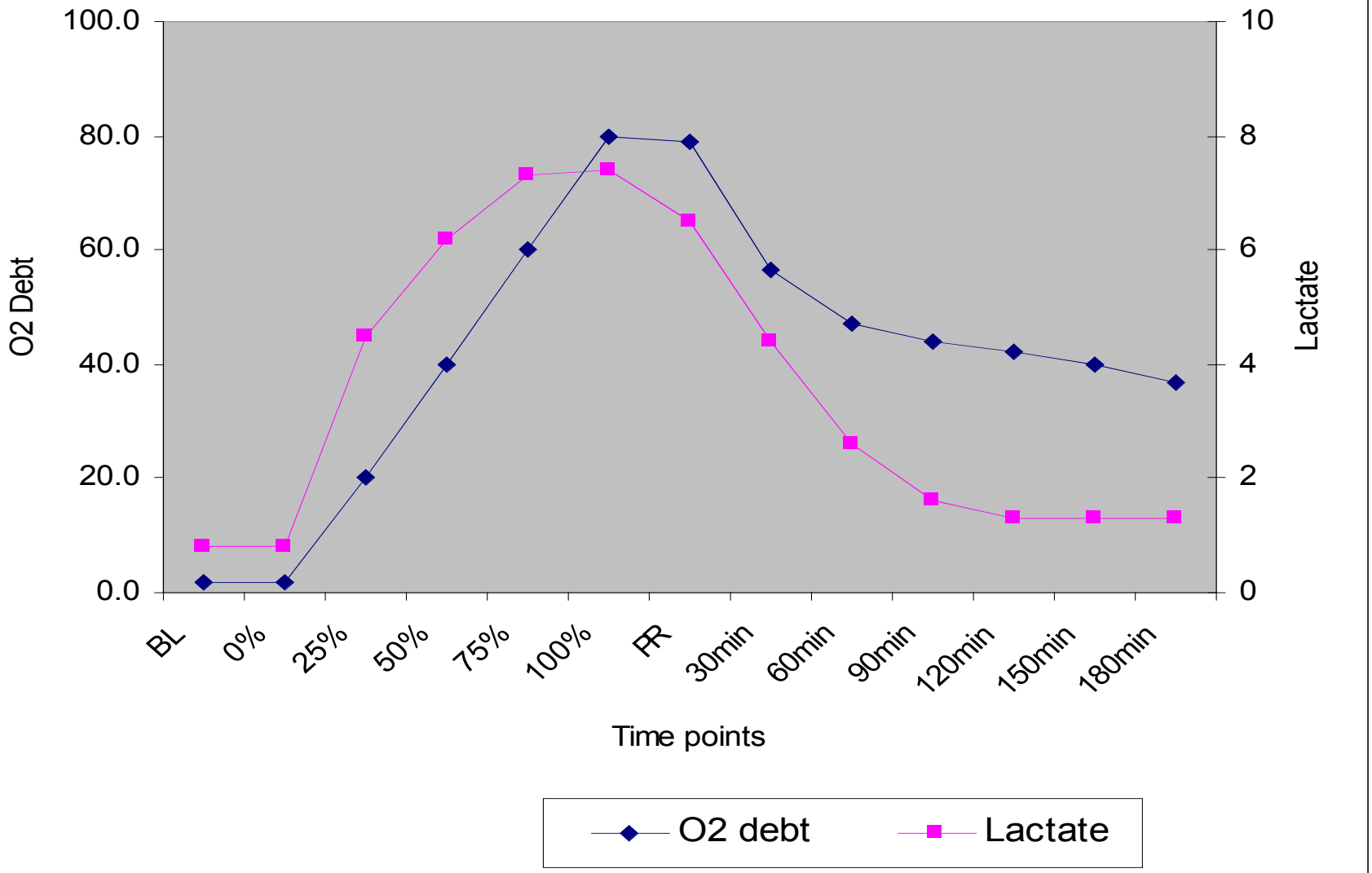
Paying back debt and lactate normalizing



Re-accumulating debt with lactate going up



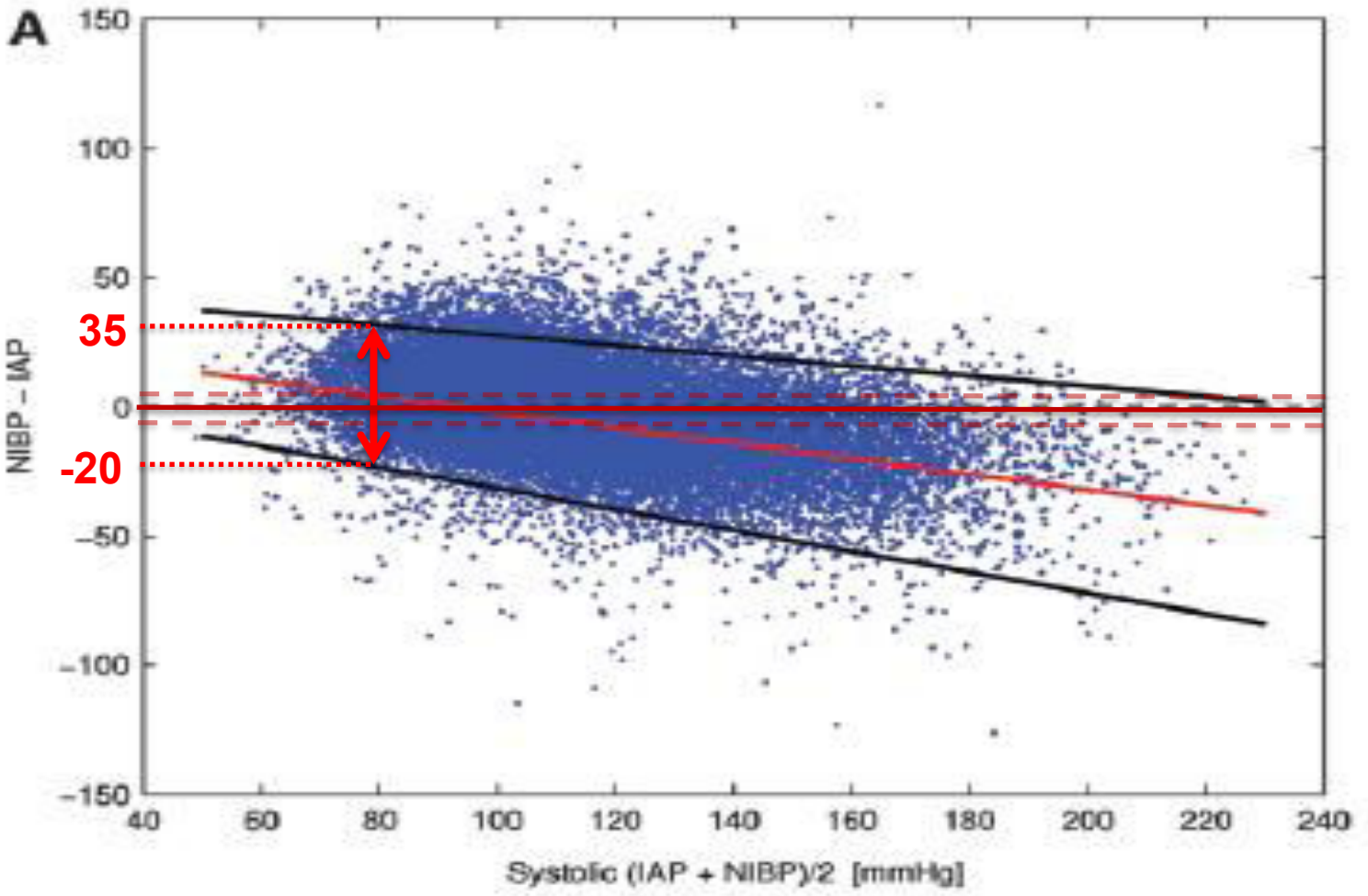
Partially paying back debt and lactate normalizing



Summary

- Shock and Its Magnitude (Oxygen Debt) is the main driver of Blood Failure
  - The Main Thing is to Keep the Main Thing the Main Thing
- Limiting Oxygen Debt and Rapidly Repaying a Critical Portion is Key
  - Consider as integral to hemostatic resuscitation
  - Challenges in use of Permissive Hypotension
  - Need to Study Non Blood (CaO_2) Strategies
  - Technology Challenges in Monitoring

Noninvasive Systolic Blood Pressure (NIBP) vs Intra-arterial Blood Pressure (IAP)



Lehman 2013