Cellular Energetics in Heart Failure and Hemorrhagic Shock

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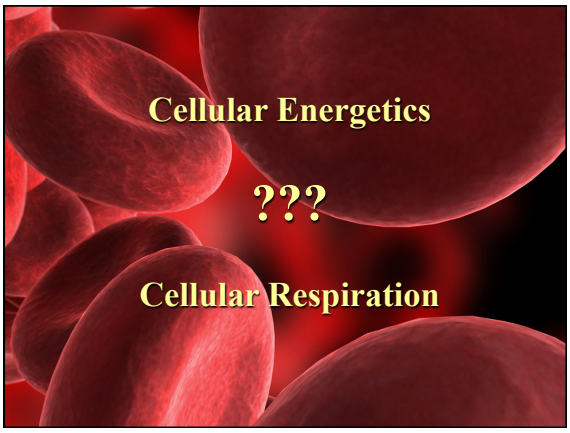
Outline

1. Define cellular energetics and cellular respiration
2. Mitochondria and bioenergetics
3. Diastolic heart failure and altered bioenergetics
4. Hemorrhagic shock, bioenergetics and reperfusion injury
5. Case history of ICU diastolic heart failure patients and what changed with the use of ubiquinol and d-ribose
6. Future treatment for ICU heart failure and hemorrhagic shock patients

Bioenergetics - Literature

- Medicine – over 21,000 articles
- Critical Care Medicine – over 375
- Critical Care Other Health Professions - 218
- Nursing – 3
  - Review article mitochondria, obesity, nutrition
- Critical Care Nursing – 1 (nutrition)

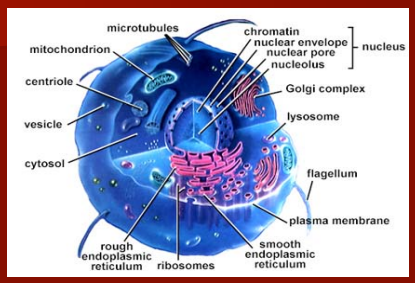


Definition of Bioenergetics

The biology of energy transformations and energy exchanges within and between living things and their environments.

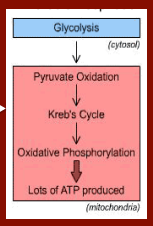
A system o th y that com hing and body exerc sycholoc ner nd the free expres of impu nd em s and that is held to ir e w ng by re g blocked physical an ergy

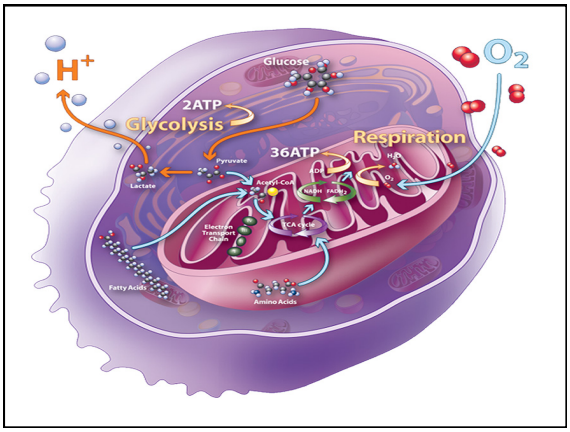
Anatomy of the Cell



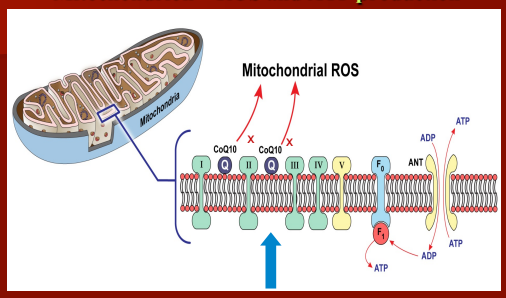
Bioenergetics = Energy from ATP is transferred to glucose to initiate glycolysis

Steps of cellular respirations



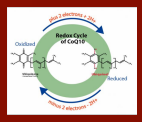


Mitochondrion – ROS and ATP production



Electron Transport Chain: Complexes I-V

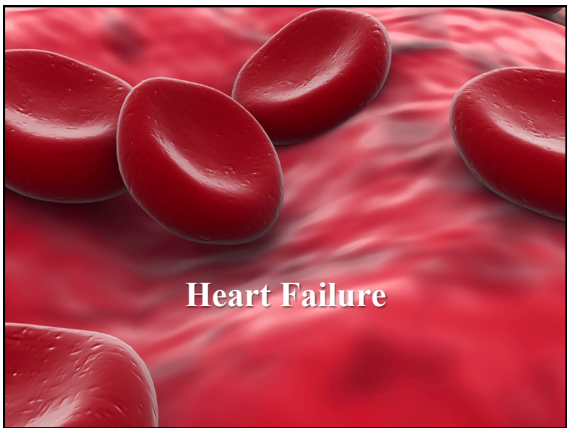
Different Types of CoQ10



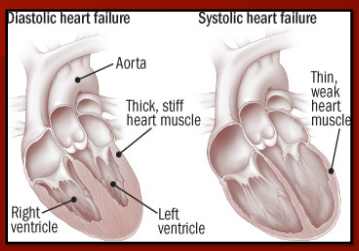
- 3 redox states of coenzyme Q10:
  1. fully oxidized (ubiquinone)
  2. semiquinone (ubisemiquinone)
  3. fully reduced (ubiquinol)
- The body's ability to produce CoQ10 declines with age, as does the ability to convert it into ubiquinol. Ubiquinol levels have been shown to be suppressed in older individuals and those with cardiovascular, neurological, liver- and diabetes-related conditions

Coenzyme Q10

- Critical component of the electron transport chain in mitochondrial respiration
- Plays important roles in cellular energetics and is a potent antioxidant
- CoQ10 inhibits lipid peroxidation by preventing the production of lipid peroxyl radicals. $CoQH_2$ reduces the initial perferryl radical and singlet oxygen, with concomitant formation of ubisemiquinone and H_2O_2. This quenching of the initiating perferryl radicals, which prevent propagation of lipid peroxidation, protects not only lipids, but also proteins from oxidation
- There are two forms of CoQ10
  - Ubiquinone (oxidized form)
  - Ubiquinol (reduced form)



Types of Heart Failure (Diastolic and Systolic)



1. Heart Failure with Preserved Ejection Fraction
2. Heart Failure with Reduced Ejection Fraction

500,000 new people with heart failure each year

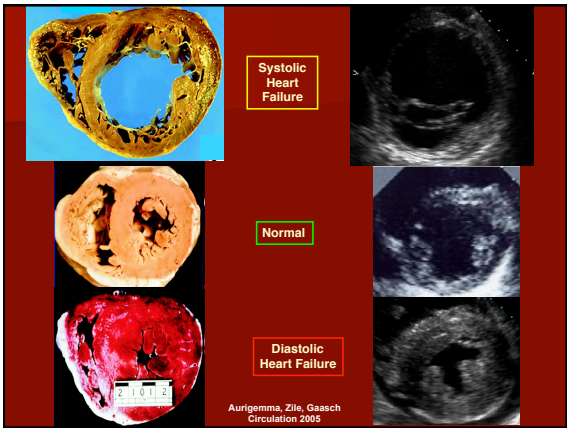
- 1/3 Diastolic Heart Failure
- 1/3 Systolic Heart Failure
- Often a mixture of the two

Diastolic Heart Failure

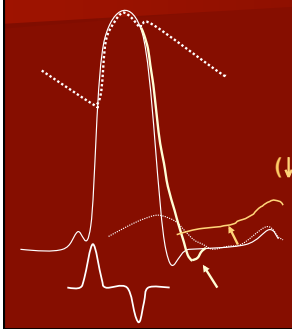
- Abnormalities of active relaxation or passive stiffness of the left ventricle leading to elevated filling pressures
- Signs and symptoms of heart failure fatigue, shortness of breath
- EF greater than 50%

Pathophysiology of HFpEF (Diastolic Heart Failure)

- Abnormal diastolic function
- Subtle abnormalities of systolic function
- Ventricular-arterial coupling
- Decreased arterial distensibility
- Chronotropic incompetence



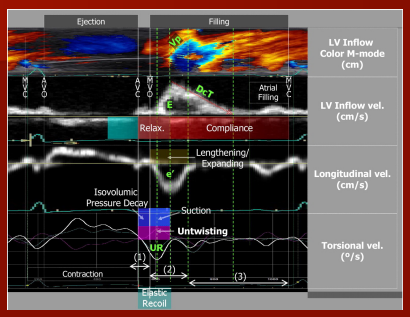
Mechanisms for Diastolic Dysfunction



Delayed relaxation (↑ Tau)

Increased stiffness (↓chamber compliance)

Sequence of Mechanical Events in Diastole



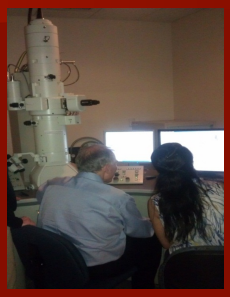
Notomi, Y. et al. J Am Coll Cardiol Img 2009;2:717-719

JACC Imaging

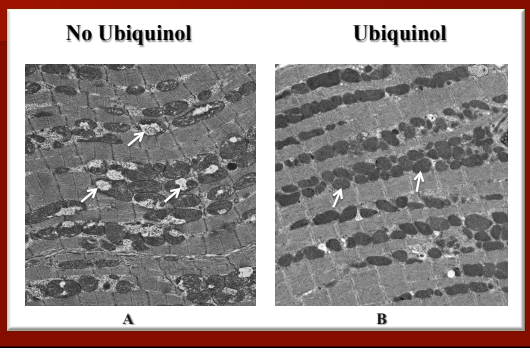
Current Treatment of HFpEF

- Diuretics
- Verapamil
- Digoxin
- Beta blockers
- Hydralazine/ISDN
- Ace inhibitors/ ARBs

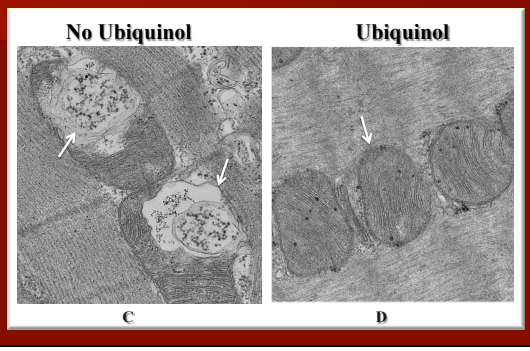
Transmission Electron Microscopy (TEM)



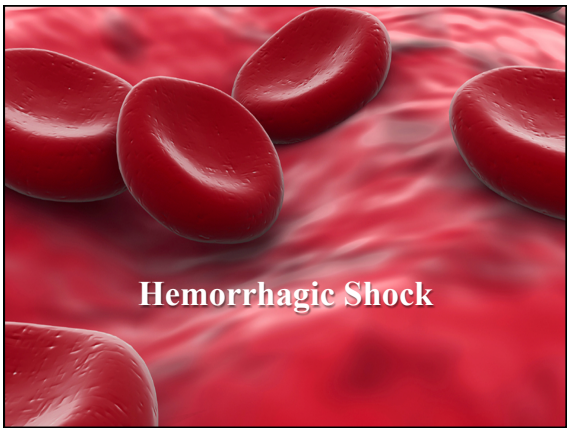
Heart Mitochondria



Heart Mitochondria

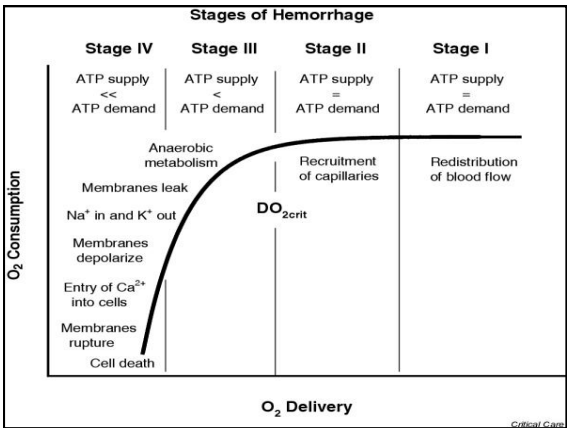


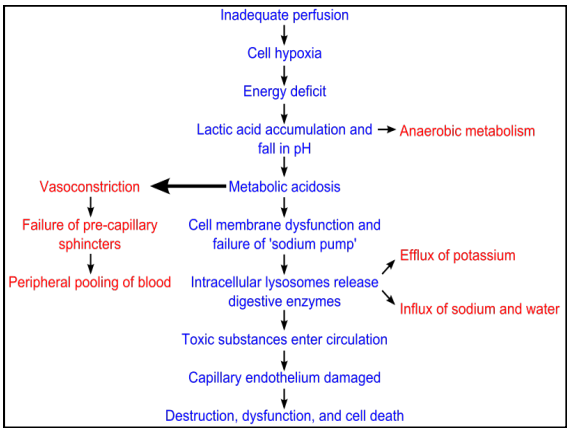
Case Histories



Hemorrhagic Shock

Class	Blood loss	Response	Treatment
I	<15 %(0.75 l)	Slight heart rate, normal blood pressure	minimal
II	15-30 %(0.75-1.5 l)	fast heart rate, min. low blood pressure	intravenous fluids
III	30-40 %(1.5-2 l)	very fast heart rate, low blood pressure, confusion	fluids and packed RBCs
IV	>40 %(>2 l)	critical blood pressure and heart rate	aggressive interventions



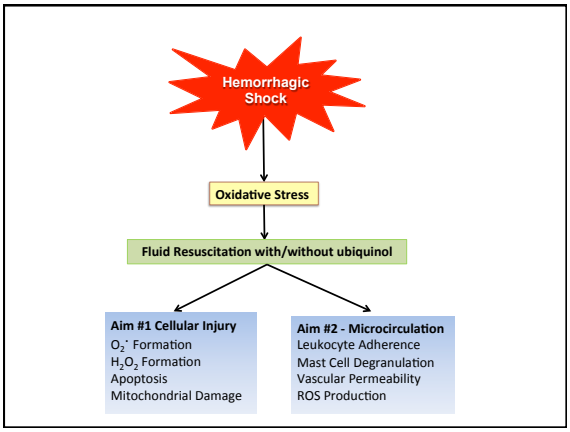


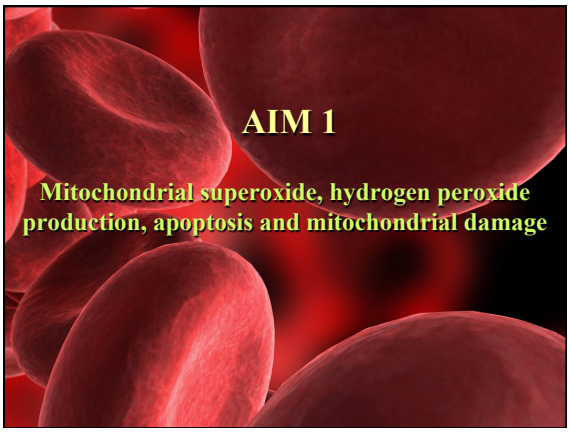
Hemorrhagic Shock

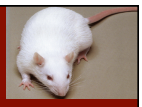
- Microvascular hypoperfusion creates hypoxic conditions that:
  1. Uncouple the mitochondrial membrane
  2. Activate peroxisome and cause generation of free electrons, the agents of oxidative tissue injury

Reperfusion Injury

- Reperfusion injury is the tissue damage caused when blood supply returns to the tissue after a period of ischemia or lack of oxygen
- The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than restoration of normal function


Hemorrhagic Shock
Oxidative Stress
Fluid Resuscitation with/without ubiquinol
Aim #1 Cellular Injury
$O_2^{\cdot}$ Formation
H_2O_2 Formation
Apoptosis
Mitochondrial Damage
Aim #2 - Microcirculation
Leukocyte Adherence
Mast Cell Degranulation
Vascular Permeability
ROS Production


AIM 1
Mitochondrial superoxide, hydrogen peroxide production, apoptosis and mitochondrial damage



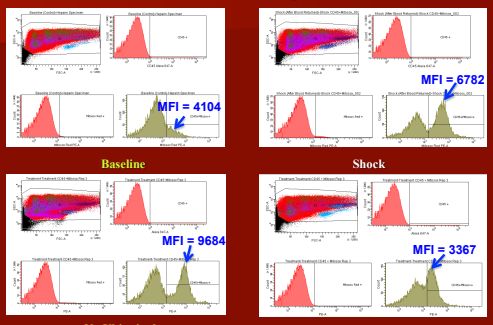
Methodology

- Male Sprague-Dawley rats
- Administered anesthesia (Sodium Pentobarbital, IP)
- Performed tracheostomy
- Inserted carotid arterial catheter
  - Used to measure hemodynamic variables
- Inserted femoral arterial catheter
  - Used for exsanguination & infusion of fluids
- Over 60 minutes, arterial blood was removed and blood pressure maintained at a mean arterial pressure < 50 mmHg
- Over the next 10 minutes, the removed blood was reinfused and twice that amount of LR administered with or without CoQ10
- The animal was monitored every ten minutes for a total treatment period of 120 minutes

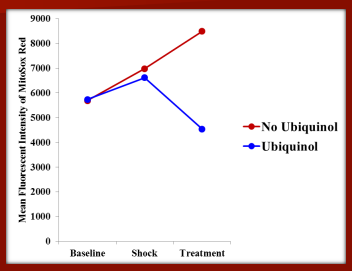
Surgical Preparation

Results

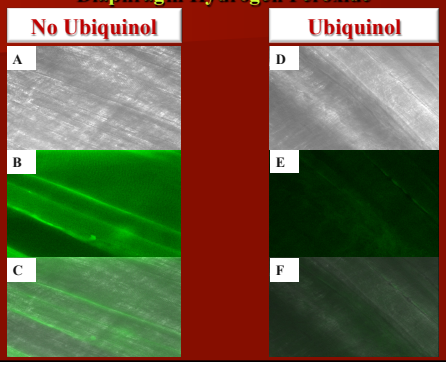
Mitochondrial Superoxide



Results
Mitochondrial Superoxide



Results
Diaphragm Hydrogen Peroxide

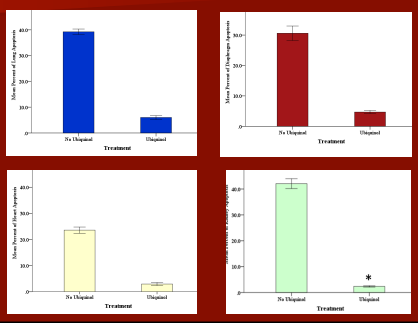


Results
Diaphragm Hydrogen Peroxide

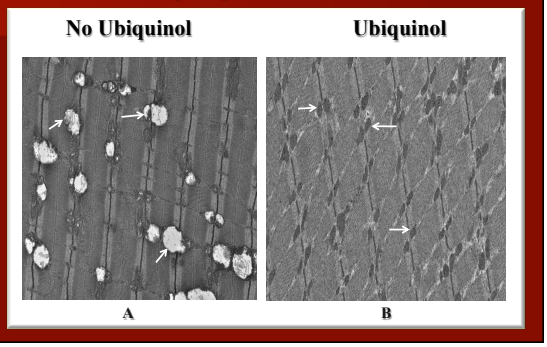
Treatment	Mean Fluorescence Intensity	SEM
No Ubiquinol	23513	± 5098
Ubiquinol	4193 *	± 333

n = 8 for each group. SEM = standard error of mean.
T test: $t_{7, 0.05} = 3.782$ ($p = 0.007$)

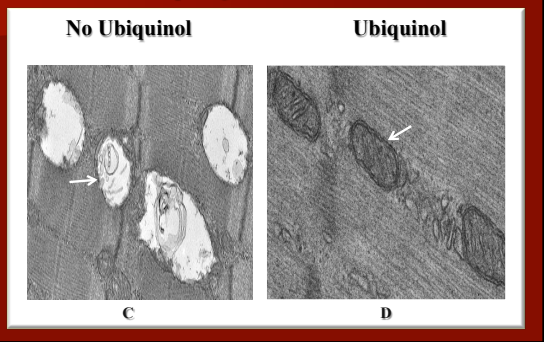
Apoptosis



Results
Diaphragm Mitochondria



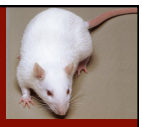
Results
Diaphragm Mitochondria



Discussion

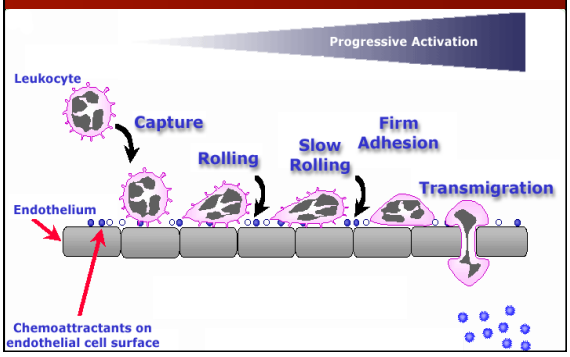
- Ubiquinol is a potent antioxidant that scavenges excessive production of ROS (e.g., hydrogen peroxide) following hemorrhagic shock and fluid resuscitation
- Ubiquinol has a protective effect on the structure of myocyte mitochondria by reducing ROS

Methodology
Microcirculation

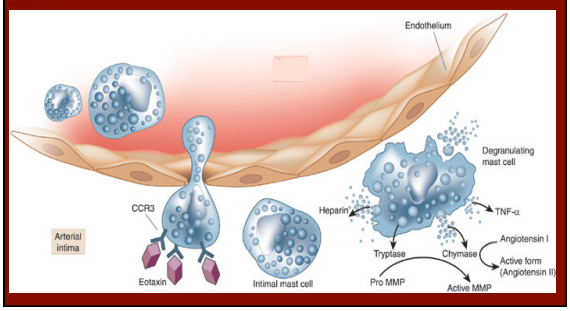


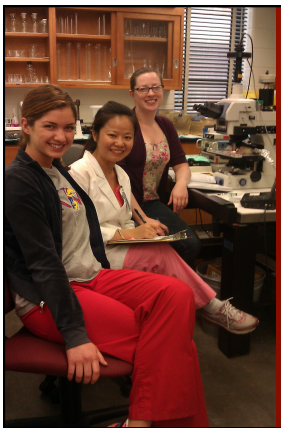
- Similar surgery as the other experiments except:
  1. A 5 cm abdominal incision was made using an electrocautery and a section of small intestine was exteriorized and positioned over a glass coverslip and the Plexiglas sheet
  2. A 100 µm length of mesenteric venule was visualized under an inverted microscope to observe leukocyte adherence and mast cell degranulation

Endothelial Injury



Mast Cell Degranulation



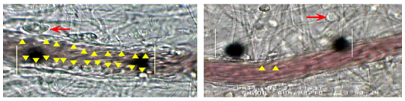


Microcirculation Measurements

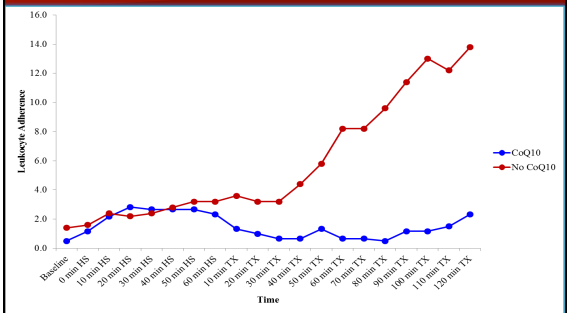
Leukocyte adherence

The number of leukocytes that remain stationary for ≥ 30 seconds

No Ubiquinol | Ubiquinol



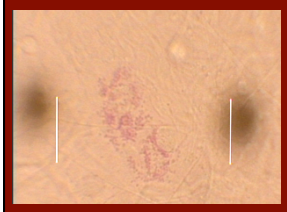
Results
Leukocyte Adherence

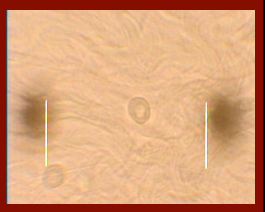


Results
Mast Cell Degranulation

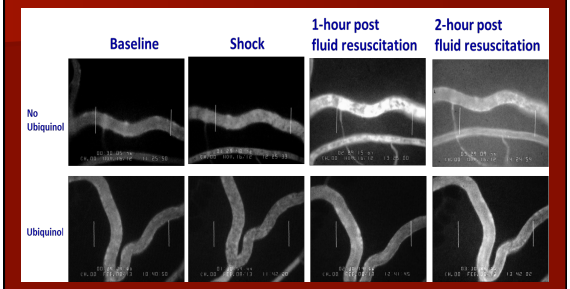
No CoQ10
Degranulated Mast Cell

CoQ10
Intact Mast Cell

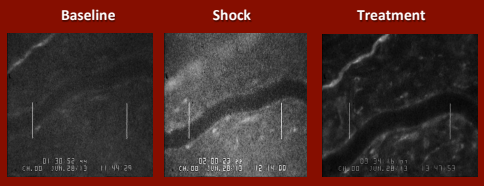




Vascular Permeability



- Dihydrorhodamine (DHR) was used to assess ROS levels within the venular wall



Conclusion

Ubiquinol is an effective antioxidant treatment in reducing ROS and cellular injury following hemorrhagic shock and fluid resuscitation

Acknowledgement

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