

Ultrafine Particle-Induced Oxidative Stress

Mark W. Frampton MD

Pulmonary and Critical Care

University of Rochester Medical Center

Hypotheses

- Ultrafine particle (UFP) exposure injures/activates endothelium via reactive oxygen species
- Exposure to ambient UFP increases expression of tissue factor and activation of coagulation
- Type 2 diabetics are more susceptible to UFP vascular and coagulation effects.
- Vascular effects predicted by UFP oxidant capacity and by level of glycemic control

Background

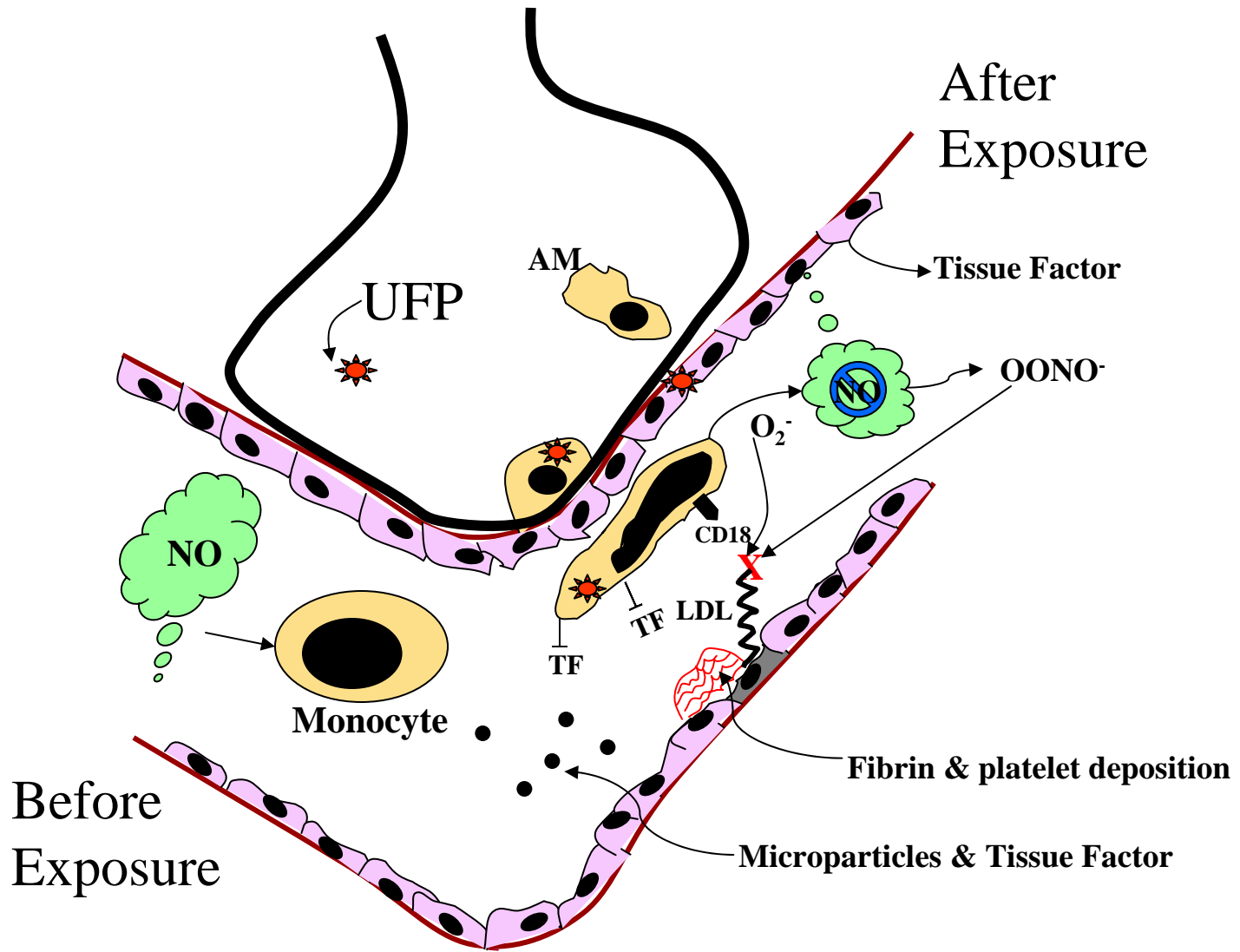
- Endothelial dysfunction is a key marker and precursor of atherosclerotic vascular disease
- Endothelial dysfunction is an NO deficiency state
- Antioxidants improve endothelial function
- UFP have oxidant capacity

Diabetes and Vascular Disease

Diabetics have:

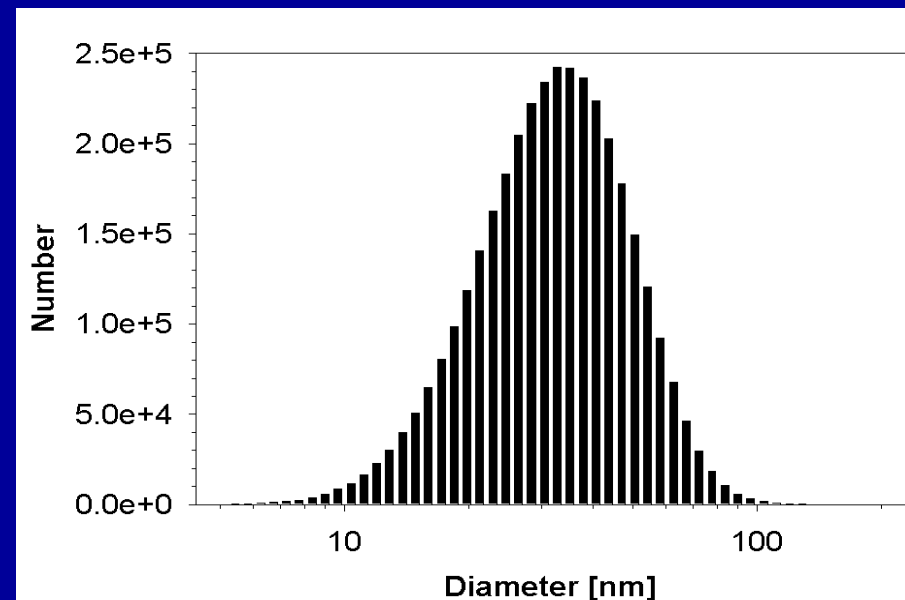
- Protein glycoxidation \checkmark endothelial injury
- Leukocytes primed for release of O_2^-
- Endothelial dysfunction
- Activation of tissue factor pathway
- More cardiovascular disease

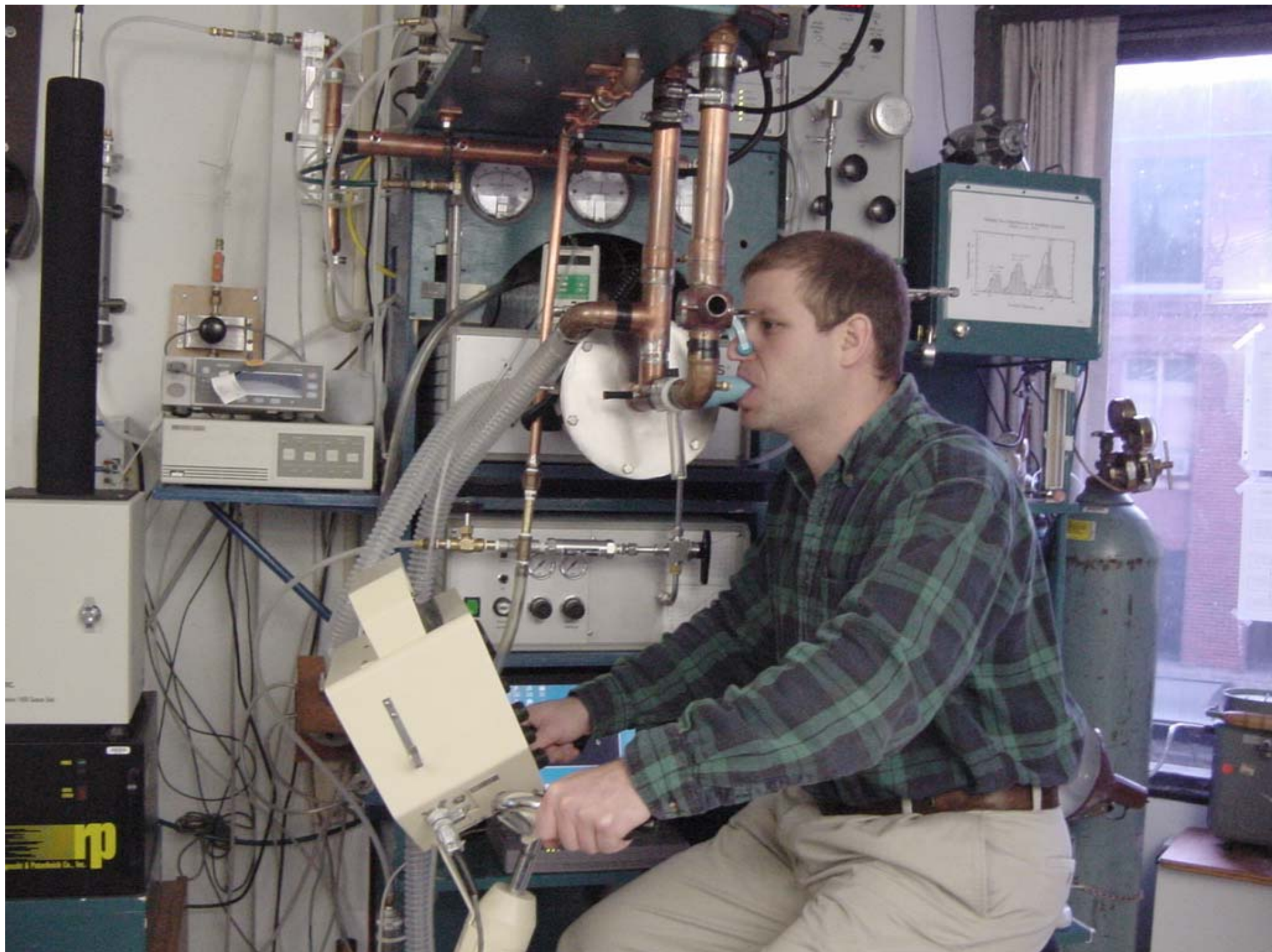
Proposed UFP Vascular Effects



Preliminary Data: Exposure to Carbon UFP

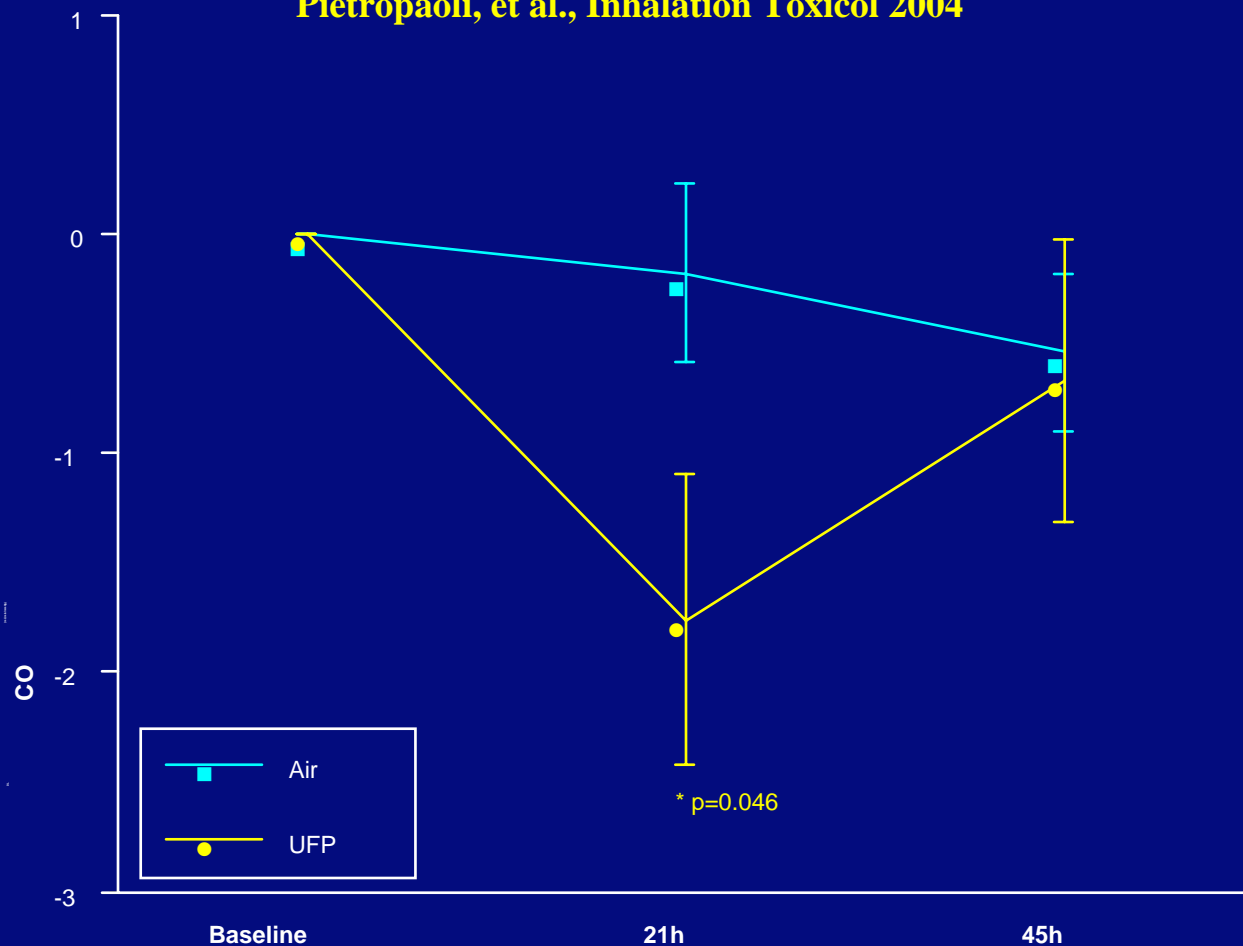
- Count median diameter ~ 26 nm, GSD ~ 1.6
- 2 hrs by mouthpiece
- Intermittent exercise





Change in Diffusing Capacity after 2 hr Exposure to 50 $\mu\text{g}/\text{m}^3$ Carbon UFP

Pietropaoli, et al., Inhalation Toxicol 2004



Specific Aims

- **Determine effects of concentrated ambient UFP on pulmonary and systemic endothelial function and coagulation**
 - **Healthy subjects**
 - **Type 2 Diabetics**
- **Determine whether antioxidant vitamins ameliorate the vascular effects of UFP**

Clinical Protocols

1. 20 healthy subjects, age 30-60 yrs
2. 20 subjects with type 2 diabetes
3. Diabetics, pre-treated with vitamins C & E or placebo
 - *Double-blind, randomized, 2-period*
 - *2-hr exposures to concentrated ambient UFP and air*
 - *Outcome measures before and 3.5, 24, 48 hours after exposure*

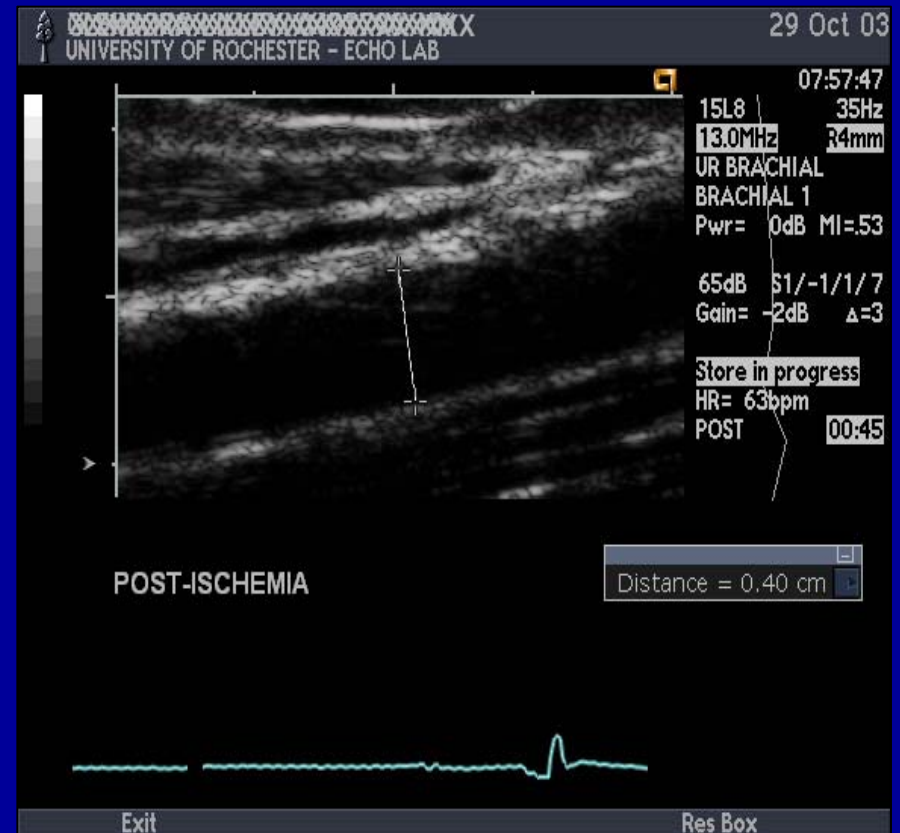
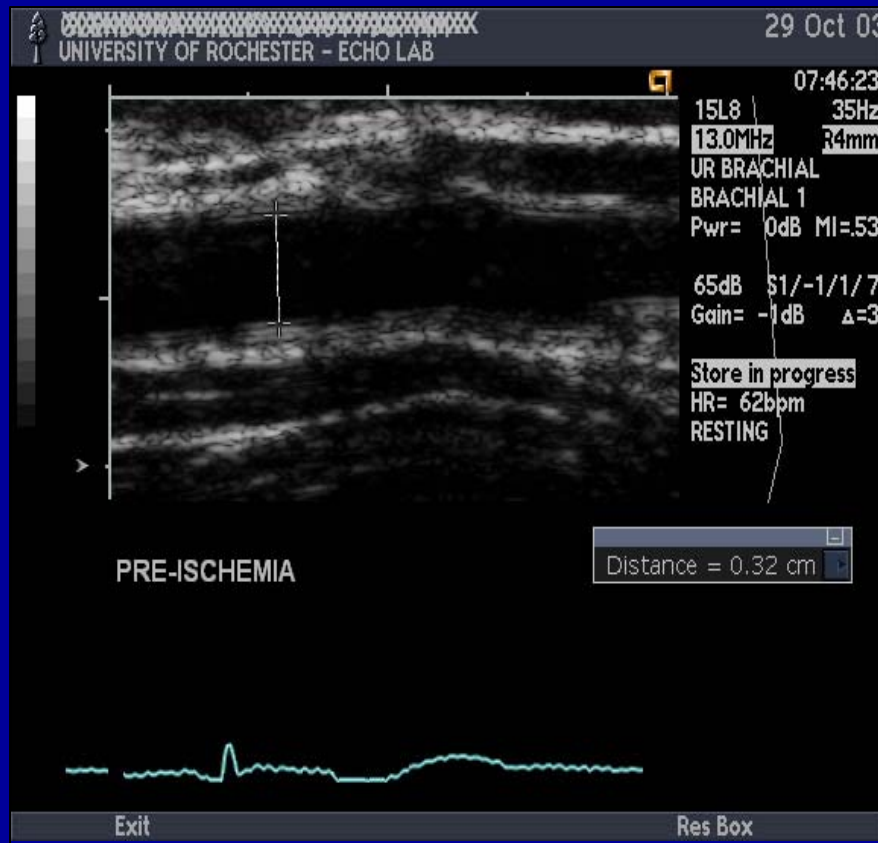
Markers of Oxidative Stress

- UFP-associated ROS
- Plasma GSH redox status
- Plasma oxidative capacity
- Blood leukocyte generation of ROS

Effects on Endothelial Function

- Flow-Mediated dilatation of brachial artery
- Pulmonary capillary blood volume (DLCO & DLNO)
- Plasma NO reaction products

Ultrasound Imaging of Brachial Artery: Flow-Mediated Dilatation



Effects on Coagulation

- Plasma TF
- Blood monocyte expression of TF
- Markers of coagulation & fibrinolysis:

Fibrinogen F1.2

D-dimer vWF

PAI-1 CRP

Expected Outcomes

- Reduced FMD and pulmonary capillary blood volume
- Reduced plasma NO products
- Increased systemic burden of ROS
- Activation of TF coagulation pathway
- UFP oxidant capacity predicts effects
- Effects in diabetics predicted by Hgb A1C
- Vitamins C & E mitigate vascular effects

Coinvestigators & Consultants ...

- Mark Utell
- Mark Taubman
- Charles Francis
- Xucai Chen
- Günter Oberdörster
- Arshed Quyyumi
- Petros Koutrakis

Endothelial Dysfunction is an NO Deficiency State

Vascular effects of NO:

- Vasodilation
- ⚡ Platelet adhesion & aggregation
- ⚡ Leukocyte adhesion
- ⚡ Leukocyte production of O_2^-
- ⚡ TF expression

Harvard Ultrafine Concentrated Ambient Particle System

