Ultrafine Particle-Induced Oxidative Stress

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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

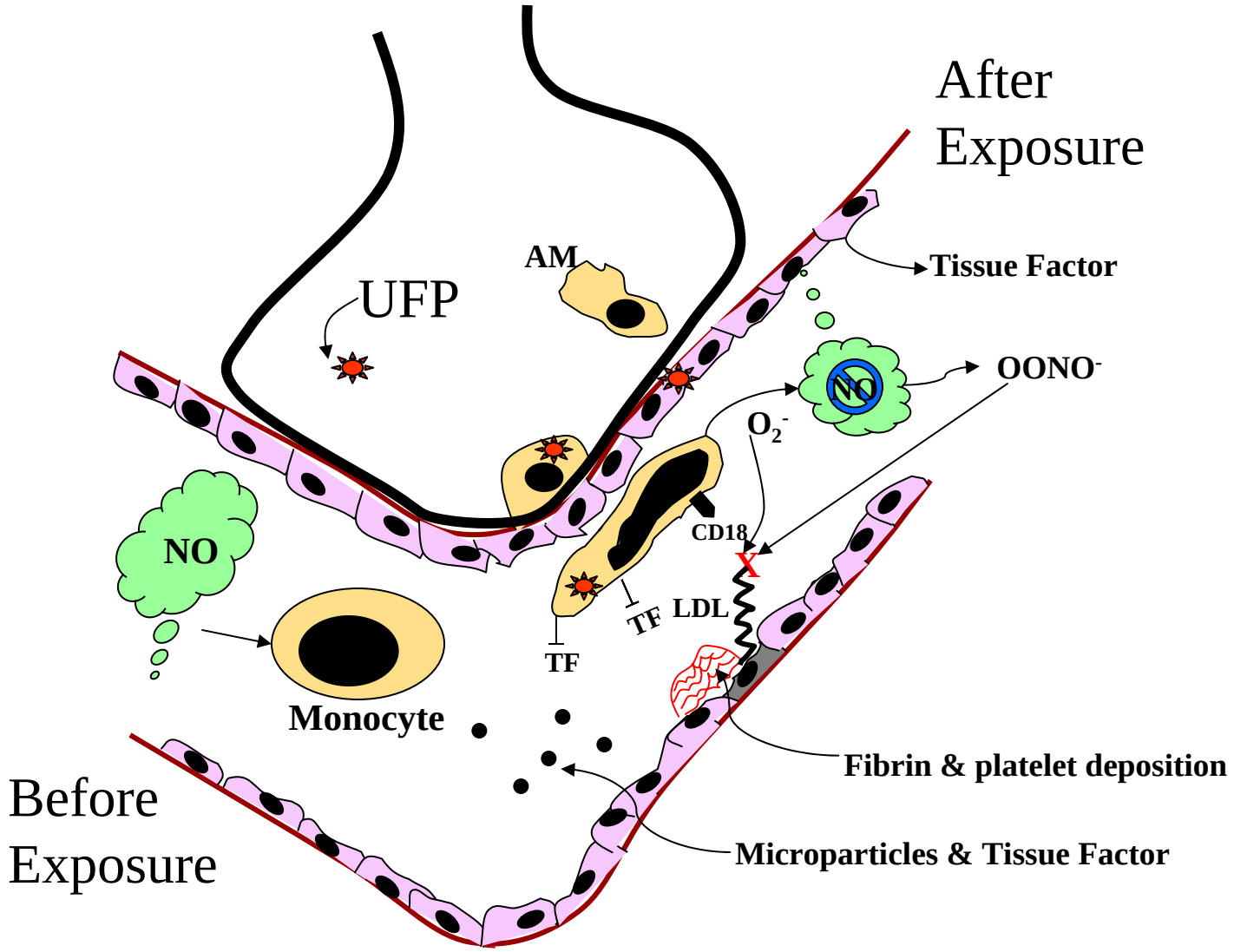
- Endothelial dysfunction is a key marker and precursor of atherosclerotic vascular disease
- Endothelial dysfunction is an NO deficiency state
- Antioxidants improve endothelial function
- UFP have oxidant capacity

Diabetes and Vascular Disease

Diabetics have:

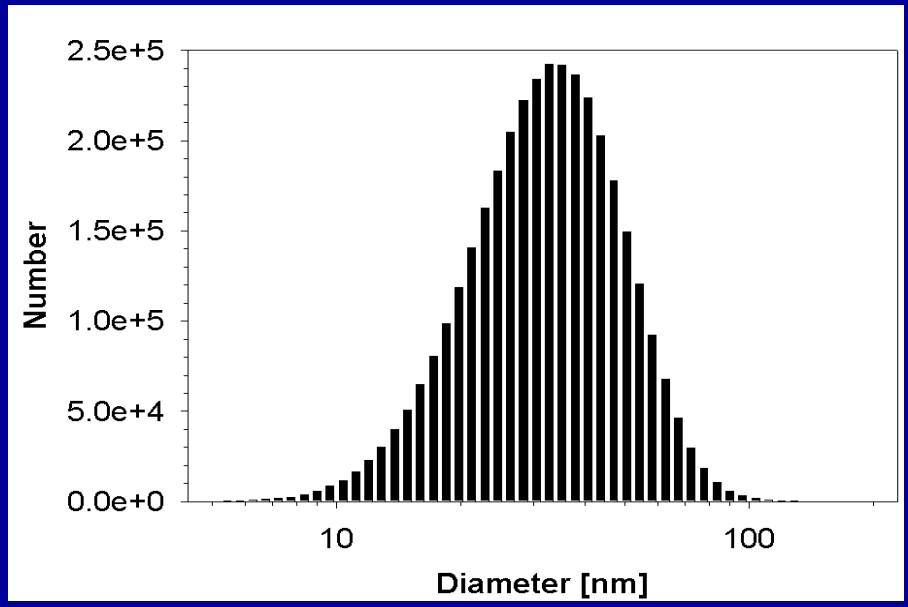
- Protein glycoxidation $\rightarrow$ endothelial injury
- Leukocytes primed for release of O_2^-
- Endothelial dysfunction
- Activation of tissue factor pathway
- More cardiovascular disease

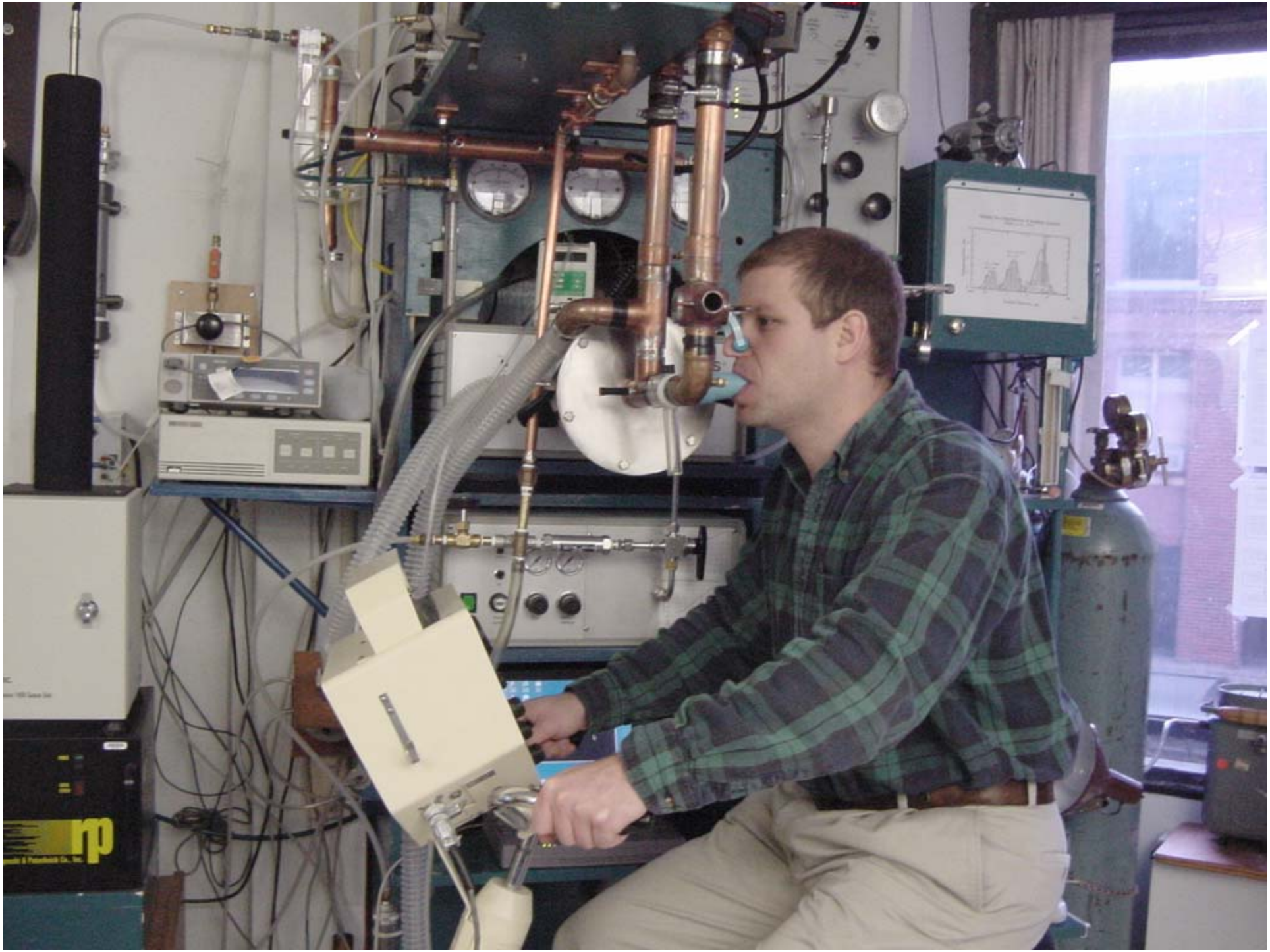
Proposed UFP Vascular Effects



Preliminary Data: Exposure to Carbon UFP

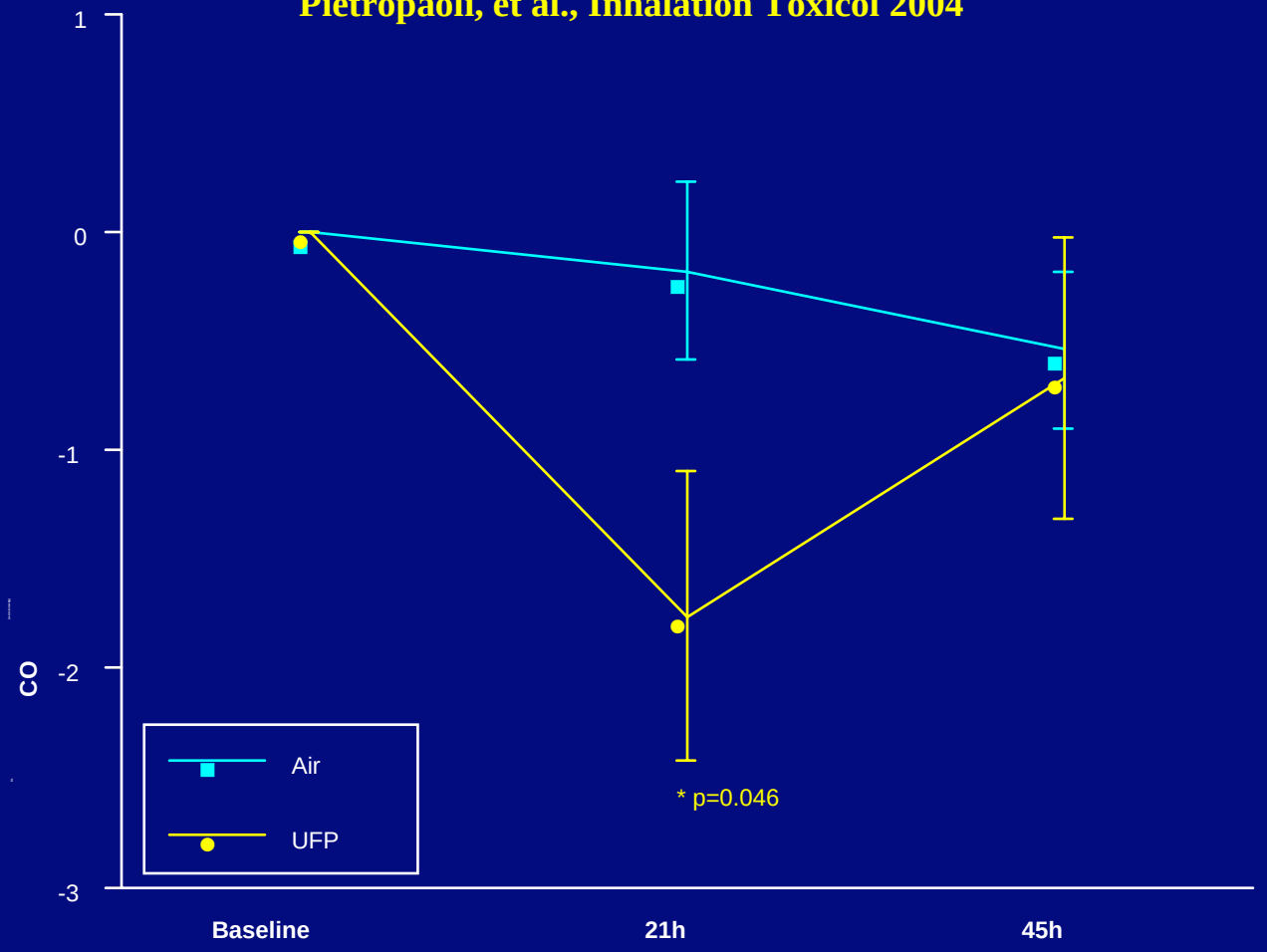
- Count median diameter ~26 nm, GSD ~1.6
- 2 hrs by mouthpiece
- Intermittent exercise





Change in Diffusing Capacity after 2 hr Exposure to 50 µg/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*

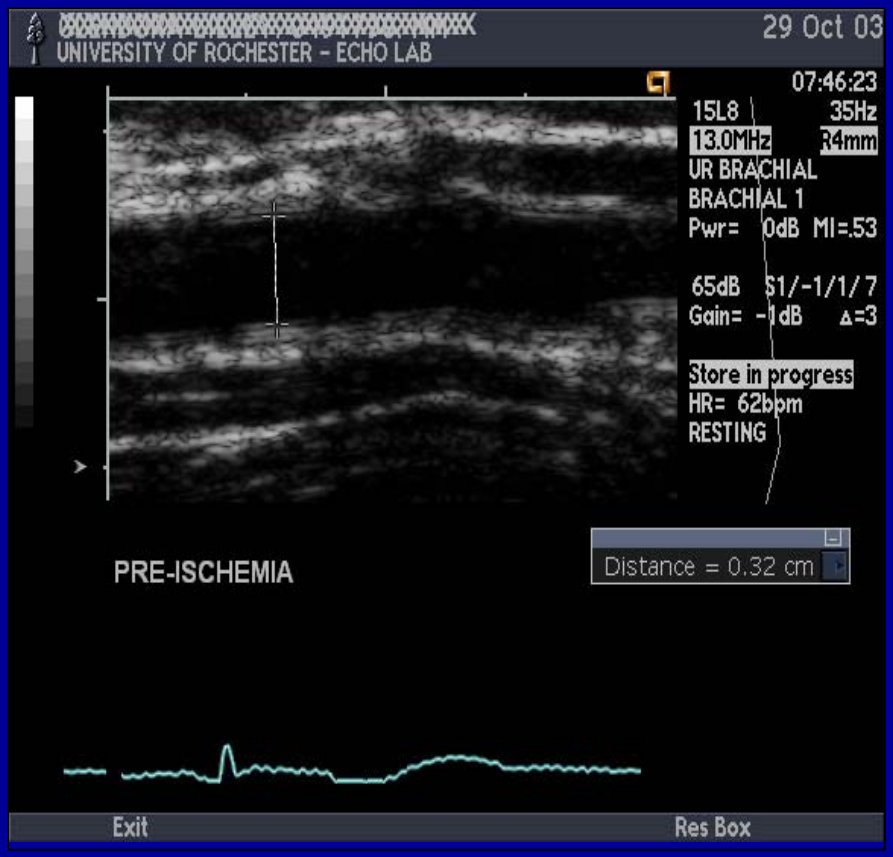
Markers of Oxidative Stress

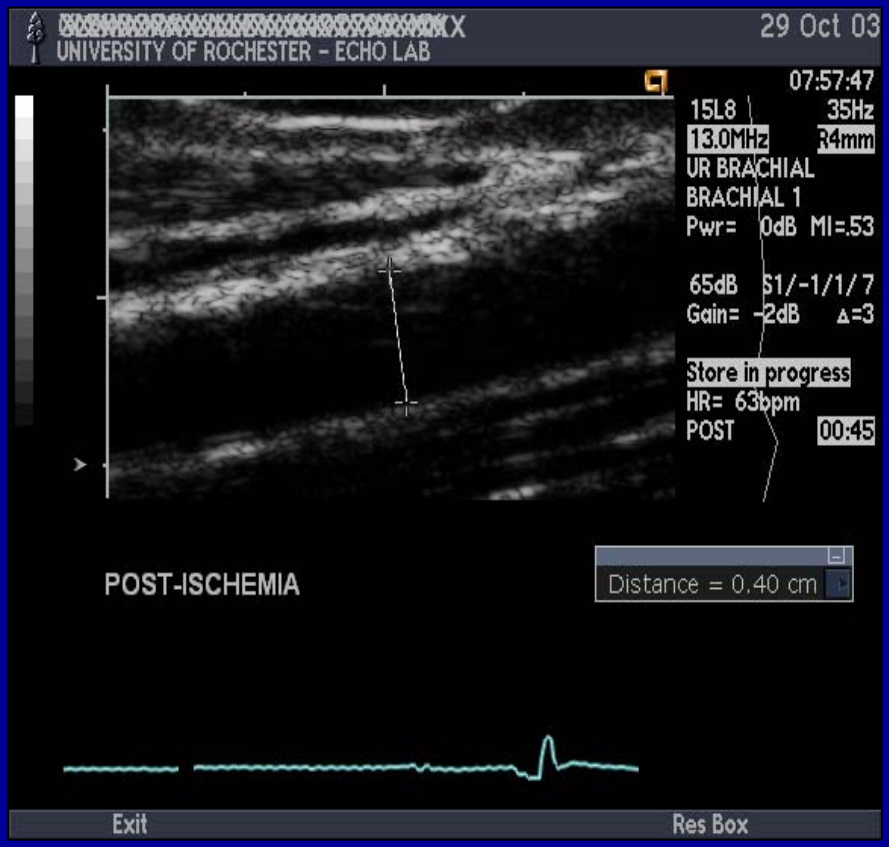
- UFP-associated ROS
- Plasma GSH redox status
- Plasma oxidative capacity
- Blood leukocyte generation of ROS

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
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- 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