US EPA ARCHIVE DOCUMENT
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 and endothelial injury
- Leukocytes primed for release of $O_2^-$
- Endothelial dysfunction
- Activation of tissue factor pathway
- More cardiovascular disease
Proposed UFP Vascular Effects

Before Exposure

- UFP
- AM
- Monocyte
- NO
- O2
- OONO-
- LDL
- CD18
- TF

After Exposure

- Tissue Factor
- Fibrin & platelet deposition
- Microparticles & Tissue Factor
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/m³ Carbon UFP

Pietropaoli, et al., Inhalation Toxicol 2004

* p=0.046
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
  - D-dimer
  - PAI-1
  - F1.2
  - vWF
  - 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 …

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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