Cardiovascular Health and Exposure to Ultrafine Particles

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Ultrafine PM characteristics

- magnitudes higher particle number concentration & surface area than larger particles;
- can carry large amounts of adsorbed or condensed toxic air pollutants (oxidant gases, organic compounds & transition metals) having pro-inflammatory effects, partly a result of ROS;
- high pulmonary deposition efficiency;
- translocates into the pulmonary interstitium & then systemically → vascular endothelium.
Hypothesized pathways leading to adverse cardiovascular health effects from exposure to UFP

1. Ultrafine PM Exposure
   - Pulmonary Deposition
   - Interstitial Translocation to Circulation
     - Redox Active PM Components

2. Pulmonary Oxidative Stress Responses from ROS:
   - Mononuclear Cell Activation
   - Pulmonary Neuroinflammation:
     - Release of Cytokines: e.g., IL-1β, IL-6, TNFα
     - Liver Hepatocyte Release of Acute Phase Proteins: e.g., C-reactive protein & Fibrinogen
     - Hemostasis & Clot Formation

3. Phase I & II enzyme polymorphisms
   - Peripheral Vascular Oxidative Stress Responses from ROS
     - Endothelial Cell Activation
     - Upregulation of Endothelial Adhesion Molecules: VCAM-1, ICAM-1
     - Endothelin-1 and ↓ NO; Oxidation of phospholipids

Acute: Systolic and diastolic BP; ↓ HRV; Angina and associated ECG abnormalities (ST Segment Elevation/Depression); cardiac arrhythmias; and cardiac arrest.
Chronic: Progression of atherosclerotic lesions.
Background: Time Series Studies

- Daily ambient \( PM_{10} \) & \( PM_{2.5} \) mass concentrations have been associated with cardiovascular hospital admissions & mortality:
  - National Morbidity, Mortality and Air Pollution Study in 90 U.S. cities.
  - 14 U.S. cities: \( PM_{10} \) from mobile source emissions & oil combustion (EPA estimates) showed the strongest associations with cardiovascular admissions vs. fugitive dust (coarse PM), wood burning, coal.
Background: American Cancer Society Cohort Study

- 319,000-500,000 subjects, 16 years follow-up across all U.S. urban areas.

- 10 $\mu g/m^3$ increase in PM$_{2.5}$ was associated with 8-18% increases in mortality due to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest.

Pope et al. 2004; Circulation 109:71-77
Netherlands Cohort Study on Diet and Cancer

- 5,000 persons with 8 years follow-up

- Cardiopulmonary mortality was associated with indicators of traffic-related air pollutants:
  - living near high traffic density, RR 1.95 (95% CI: 1.09, 3.52)
  - 10 µg/m³ black smoke from background + local (proximity to streets), RR 1.71 (95% CI: 1.10, 2.67)
  - 30 µg/m³ background + local NO₂, RR 1.81 (95% CI: 0.98, 3.34).

Hoek et al. 2002
Case-crossover study of 691 cases of MI, Augsburg Registry, subjects surviving at least 24h completed a time-activity diary.

Positive association between reported exposure to traffic and onset of MI one hr later: OR = 2.92 (95% CI: 2.22, 3.83), p < 0.001.

Little change after adjusting for exercise.

Most common exposure was in a car, but associations were also found with public transport.
What is driving M&M associations?

- Causal pollutant components and sources?
- Biological mechanisms?
  - Autonomic dysfunction: ↓HRV, arrhythmias
  - ↑Inflammation & coagulation/thrombosis
  - Endothelial dysfunction: vasoconstriction (↓NO / ↑ET-1), upregulation of adhesion molecules.
Relative Risks of Future MI among Apparently Healthy Middle-Aged Men: *Physician’s Health Study*

Lipoprotein(a)
Homocysteine
Total Cholesterol
Fibrinogen
tPA Antigen
TC:HDL-C
hs-CRP
hs-CRP + TC/HDL-C

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Risk Factors for Future Cardiovascular Events: WHS


Lipoprotein(a)
Homocysteine
IL-6
TC
LDL-C
sICAM-1
SAA
Apo B
TC:HDL-C
hs-CRP
hs-CRP + TC:HDL-C

Relative Risk of Future Cardiovascular Events
PM, Systemic Inflammation & Thrombosis

- Inflammation/endothelial dysfunction may determine plaque stability in CHD:
  - Unstable plaques have increased leukocytic infiltrates
  - T cells, macrophages predominate rupture sites
  - Cytokines and metalloproteinases influence both stability and degradation of the fibrous cap

- PM exposures have been associated with systemic hypercoagulability & inflammation:
  - increased cytokines, acute phase proteins and plasma viscosity.
  - major mechanism: PM-induced oxidative stress.
PM-induced oxidative stress

- ROS from PM → endothelial dysfunction and subsequent acute changes leading to plaque instability and rupture.
- Chronic changes -- atherosclerosis.

Diagram:
- Vascular smooth muscle cell migration
- Foam-cell formation
- Inflammatory cell activation
- Adherence and aggregation of platelets
- Adherence and entry of white blood cells

Acute changes leading to plaque instability and rupture.

Chronic changes -- atherosclerosis.
Epidemiologic evidence from acute exposure-response relationships

- **Panel Studies**, within-individual studies → evidence for possible pathophysiological mechanisms underlying the findings of epidemiologic time series.

- **Outdoor fixed site** PM exposures have been associated with:
  - **systemic hypercoagulability & inflammation**: increased cytokines, acute phase proteins and plasma viscosity.
  - **decreased heart rate variability (HRV)**, increased blood pressure, cardiac arrhythmia and ST segment depression during exercise.
100 subjects in eastern Massachusetts with implanted defibrillators (63,628 person-days of follow-up), ambient air pollution only.

Defibrillator discharge interventions for ventricular tachycardias or fibrillation (33 subjects) associated with:

- 26-ppb increase in NO\textsubscript{2} lagged 1 d, OR 1.8; 95% CI: 1.1, 2.9
- black carbon & PM\textsubscript{2.5} confounded by NO\textsubscript{2}
Ambient PM, NO₂, CO exposure and ischemia during submaximal exercise tests in 45 subjects with CHD in Helsinki, Finland

Significant three times increased risk for ST depression:
- 1000 particles/cm³ \( \text{NC}_{0.1-1} \)
- 10,000 particles/cm³ \( \text{NC}_{0.1} \), Independent of
- 10 μg/m³ \( \text{PM}_{2.5} \)
- NO₂ and CO were also associated.
In-vehicle study of 9 healthy male North Carolina Highway Patrol troopers.

In-vehicle 10 µg/m³ PM$_{2.5}$ increase was associated with:

- Decreased lymphocytes (−11%, $p = 0.03$),
- Increased red blood cell indices (1%, $p = 0.03$),
- Increased neutrophils (6%, $p = 0.04$),
- Increased CRP (32%, $p = 0.02$), and
- Increased von Willebrand factor (12%, $p = 0.02$)

NO$_2$ and CO were not significant
personal exposure to PN (TSI P-TRAK) and HRV over one 16-hr daytime period in 9 young healthy adults and 10 older subjects with lung function impairments.

Personal exposure to UFP NC was associated with decreased time-domain and frequency-domain HRV.
Subjects with CAD, 37 in Amsterdam, 47 in Erfurt 47 in Helsinki, in-clinic BP biweekly over 6 mo, single-site ambient PM.

- small decrease in systolic BP (~0.72 mm Hg) and diastolic BP (~0.70 mm Hg) associated with a 5-day mean 10,000 UFP particles/cm³.

- slightly stronger and more significant for 1,000 particles/cm³ PM$_{0.1-1.0}$

- smaller associations were found for 10 µg/m³ PM$_{2.5}$ mass.

- contrasts Zanobetti et al. (2004): ambient 5-d average PM$_{2.5}$ was positively associated with BP among 62 patients with pre-existing heart disease
Timonen et al. 2005 (ULTRA study) JEAEE in press online

- Same subjects as Ibald-Mulli 2004, in-clinic HRV biweekly over 6 mo, single-site ambient PM
- 10,000 particles/cm$^3$ UFP NC lag 2 was associated with changes in sympathetic/vagal tone:
  - 13.5% decreased LF/HF
  - 2.9% increased HF/ (LF+HF)
- UFP associations were consistent across each city.
- PM$_{2.5}$ was associated with LF/HF HRV only in Helsinki (6% decrease), HF/(LF+HF) only in Erfurt (1.3% increase), and HF in Helsinki (14% decrease).
Erfurt panel of 57 males with CAD – blood draws in clinic 12 times, every 2 weeks, in winter

All ambient PM size fractions were similarly associated with:

- Increased CRP (inflammation)
- Increased ICAM-1 and vWF (endothelial dysfunction)
- Increased prothrombin fragment 1+2, (coagulation) but not D-dimer, and Factor VII decreased

EC & OC associated with all outcomes except CRP

Similar associations for CO and NO₂
State of Knowledge is Limited by Exposure Data

- EPA regulates PM mass → focus of epi. research;
- Regulatory focus on toxic PM components is weak;
- Data on UFP toxicity by source is needed;
- UFP high spatial variability / proximity to sources;
- Identifying traffic-related sources of PM toxicity is relevant as it is likely the predominant UFP exposure.
Ultrafine vs. fine PM Spatial Distribution

Unanswered Questions

- Impact of UFP exposure on the CV health of a susceptible population: elderly, subjects with CV disease, diabetes, COPD, etc:

  - Long-term progression of atherosclerosis by repeated acute impacts on systemic inflammation / ox stress and thrombosis?

  - Acute risks (e.g., MI, stroke) posed by effects on cardiovascular autonomic function?

- Importance of UFP composition and related source characteristics to cardiovascular and inflammatory outcomes
  (toxicity? reactive oxygen species? primary vs. secondary?)
Problems with exposure data:
- Exposure misclassification due to reliance on pollutant data measured at central regional sites;
- Reliance on PM mass alone: components can vary independently over space & time.

Solutions proposed:
- Personal and microenvironmental PM exposures;
- Measurement of UFP mass & particle number conc.;
- Assessment of PM sources & components using tracer compounds and surrogates (e.g., EC + traffic proximity and in-vehicle assessment).
Thank-you