INHALED PARTICULATE MATTER: SIZE AND RISK – THE HEART OF THE MATTER

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Overview

1. Air pollution is linked to cardiovascular diseases.
2. Components of air pollution are associated with inflammation and oxidative stress.
3. We will address 4 questions;
   - Do real-world events affect cardiovascular function?
   - Can some cardiovascular effects be explained by direct effect of PM or components on the heart?
   - Do components of inhaled pollutants increase the risk, or accelerate the progress, of cardiovascular diseases?
   - Which components???
Epidemiological Studies Link Air Pollution to Cardiovascular Disease

An increase in air pollutants leads to increased mortality and hospital admissions because of cardiovascular diseases (Analitis A. et al. 2006, Zanobetti et al. 2003, Dominici et al. 2006, Peel et al. 2007). Exposure to elevated levels of particulate matter (PM) in ambient air leads to an increased heart rate (HR) and a decreased heart rate variability (HRV) in elderly patients (Dubowsky Adar S. et al. 2007, Luttmann-Gibson et al. 2006).

Individuals in the >65 year-old age bracket are more susceptible to air pollution-associated heart-related morbidity and mortality. Cardiovascular effects are stronger from particles of smaller size (i.e. fine and ultrafine PM).
Ambient Pollutants that are Associated with Adverse Cardiovascular Effects

Particles: Definition according to the particle size:
- PM10: Particles with an aerodynamic diameter $\leq 10\ \mu m$
- PM2.5: Particles with an aerodynamic diameter $\leq 2.5\ \mu m$
- UFP (ultrafine particles): Particles with an aerodynamic diameter between 0.01 and 0.1 $\mu m$, measuring size: count/cm³

Definition according to chemical composition:
- OC, EC: organic and elemental carbon
- Gases: NO, NO₂: nitrogen monoxide, nitrogen dioxide
- CO: carbon monoxide
SOURCE APPORTIONMENT of PM

Mass

San Gabriel 1 IN
San Gabriel 1 OUT
San Gabriel 2 IN
San Gabriel 2 OUT
San Gabriel 3 IN
San Gabriel 3 OUT
Riverside IN
Riverside OUT

µg/m³

SOA
rs-Dust
nss-Sulfate
SS
SHIP
LDV
HDV

Warmer Phase
Colder Phase

Vehicles

highest contribution: 24-47%

Similar indoor and outdoor (vehicles)

Higher Sulfate, SOA & rs-Dust in warmer phase

Cooking was not apportioned
What are the health-relevant components of urban air?

- Emissions from power plants, motor vehicles, dust.
- Pollutant gases: Ozone and NO\textsubscript{2} are major problems in California. SO\textsubscript{2} and organic vapors are also important.
- Particles or Particulate Matter (PM): Particles are associated with increased heart-related deaths during air pollution episodes. Toxicology studies show that PM\textsubscript{2.5} accelerates the development of atherosclerosis. The strongest associations with human heart-related illness and death are with PM.
Particles Vary in Size and Shape

Adapted from The Particle Atlas, McCrone and Delly, 1973
Particles of Different Size Deposit in Different Places in the Respiratory System. Size Influences Target Sites in the Lung.
Soluble Particles Clear Quickly But Less Soluble Particles Can Be Retained For Long Periods

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Components of PM could be Causal Agents (or Surrogates)

Cardiovascular mortality is more tightly linked to PM exposure than is total mortality.

EC, OC, nitrate and Zn may be important based on some epidemiological findings.

Some toxicological studies have identified Ni and V as possibly being causal agents.

In California Air Pollution is Strongly Associated with Heart-Related Deaths

Mortality data are consistent with PM exposures on a regional basis in California. Cardiovascular Mortality Represents about ½ of all Deaths.

Regional Mortality
Deaths per $10^6$ People

Adapted from Ostro et al., 2007
There are several potential mechanisms at play

Indirect Effects
Driven by Mediators Induced in The Lung

Direct Effects
Driven by Particles that Translocate from the Respiratory System and Impact the Vascular Endothelium and Myocardium

Adapted from: Pope, 2006, Ischemic heart disease events triggered by short-term exposure to fine particulate air pollution., Circulation :114, 2443 -8
Controlled Studies Using Models of Diseases Can Be Used to Identify Causal Agents and Mechanisms

- Rats Aged (geriatric)
- MI Hypertensive (SHR)
- Mice ApoE-/- (3, 4 and 6 month studies)
- Nrf2-/- (in progress)
- Diabetes (proposed)
Rats or Mice Can Be Exposed to Purified Air or CAPs in Sealed Chambers. The Sealed Chambers Can Be Placed Onto Racks to Facilitate Transport.
Various Endpoints Can Be Measured Before, During and After Exposures

- Biochemistry
  - Blood Samples
    - Acute phase proteins
    - Cytokines
  - Expired Breath
- Cardiac Physiology
  - Heart Rate and HRV
  - Blood Pressure
    - Systolic
    - Diastolic
    - Mean
  - Developed Pressure
  - Contractility
- Molecular Biology
  - Gene/protein expression from lung, heart, brain
  - In-situ hybridization for effects localization
These Mobile Systems Can Be Readily Deployed Near Sources

Case in point – Wildfires in Southern California

Rats exposed before, during and after the fires.

Cardiac Physiology Monitored During Exposures.
Blood Pressure

Blood Pressure Stable in Air-Exposed Rats

Significant Drop in Blood Pressure in UFP-exposed Rats During Fire, Superimposed on a Gradual BP Decline
Increased Particle Number to Mass Ratio Suggests Importance of UFP During Fires

Peak Exposure Concentrations Match Up With BP Depression

AQMD Data

Exposure System Data
Hearts from Rats Exposed to CAPs Show Influx of Inflammatory Cells

H & E staining in Sprague-Dawley hearts after 9 months of inhalational exposure to ultrafine particles

H & E staining in WKY rat hearts after 3 months of inhalational exposure to ultrafine particles
PM Exposure Causes Fibrotic Changes in Hearts

Picosirius red staining in Sprague-Dawley rat hearts after 9 months inhalational exposure.
Could Physiological Effects Be Explained by Direct Action of PM on Myocardium?
1-10 µg of UFP injected into venous return at $t_0$. 

Langendorff System
UF PM can directly alter heart physiology and cardiac function.

Measurements of contractile function and coronary flow at the end of 30 min of perfusion show that UF PM exposure reduced cardiac contractile function (LVDP, dP/dtmax and dP/dtmin).

The reduced contractile response to UFP exposure is closely correlated to changes in coronary flow.

Note that filled circles represent WKY rat hearts perfused with UFP (n=10); open circles represent WKY hearts perfused without UFP (n=10).
Organic components of UFP may be important contributors to the adverse effects on the heart. (Delfino et al EHP 2008)
Is the increase in particle number of semi volatile particles of concern while PM mass is going down with newer vehicles? 

*Le Monde, October 13, 2007*
PM Emissions from Newer Technologies

4 vehicles, 7 configurations, 3 driving cycles

Veh#1
1998 Cummins Diesel 11L, 360,000 miles, BASELINE VEHICLE

SCRT® systems used in this project are development prototypes, not commercial units.

Biswas et al ES&T 2009
Redox Activity (DTT assay) of Semivolatile and Total PM from Newer Diesel Trucks

- Samples including semivolatile PM
- Thermo-denuded samples
- Thermo-denuded samples
Semi-volatile faction accounts for over 80% of the per PM mass toxicity (Biswas et al, ES&T, 2009)
Changes in Heart Rate Variability Appear to be Mediated by Semi-volatile PM Components
Air Pollution Promotes Atherosclerosis

- 6 month study using ApoE-/- mice examined plaque development and acute phase biomarkers.
- 2 month study using ApoE-/- mice examined role of oxidative stress in PM-promoted atherogenesis.
After 8 weeks of Exposure to F PM in Riverside

Increased Plaque in mice after 2 months of CAPs Exposure

Note increased wall thickness due to plaque formation
Representative histological photomicrographs.

Aortic root sections from UFP mice (C,F) exhibited greater atherosclerotic lesions than sections from FA (A,D) and FP (B,E) mice.
PM May Contribute to Plaque Formation by Amplifying the Effect of Systemic Inflammation
Conclusions

- Inhaled PM has significant effects on the Cardiovascular System.
- There are strong and consistent associations between PM exposure and heart-related morbidity and mortality.
- PM exposure can alter autonomic control of blood pressure and heart rate.
- PM exposure dramatically accelerates atherosclerotic processes possibly by amplifying the biological activities of inflammatory factors in systemic circulation.
- The organic fraction of the fine and ultrafine PM strongly drives the adverse effects on the heart.
Collaborators

- Cardiovascular Project (ARB)
  - Chen, Li, Xian (Ultrasound)
  - Meacher, Gookin, Salazar, Willett (ECG, Physiology, Arterial Plaque Measurements)

- Atherosclerosis Mechanisms
  - SCPC Project 2 (Nel, Araujo, Kleinman, Harkema, Sioutas)

- Direct Effects of PM on Heart
  - EPA STAR Grant
    - GSH-Kloner and Simkovitch
  - UCI-Kleinman, Willett, Gookin, Salazar, Meacher
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