Air pollution: Systemic effects?

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Overview

• Introduction statements
• Effect of air pollution on the lung
• Systemic inflammation induced by air pollution
• Impact of air pollution on blood vessels
• What can we do to attenuate these systemic effects
Effect of ambient air pollution on mortality

Deaths predominantly cardiopulmonary


Laden et al Am J Respir Crit Care Med. 2006
Deposition of Particles into the lungs

Particulate Matter:
- Carbon nucleus
- Polycyclic aromatic hydrocarbons
- Transition metals (iron, copper)
- Biologic's (LPS etc)

Nemmar A et al. Circulation. 2003
PM$_{10}$ in alveolar macrophages and epithelial cells

Van Eeden et al Proc Am Thorac Soc 2005
Cytokine produced by human AM exposed to PM

Cytokines produced by human bronchial epithelium following exposure to PM

Fujii et al Am J Respir Cell Mol Biol. 27:34-41. 2002
Hypothesis

PM$_{10}$ induced lung inflammation

- Lung Macrophages
- Lung Epithelial cells

Pro-inflammatory mediators

Systemic Inflammatory Response
Smoke Exposure Causes bloodstream inflammation

Changes in circulating IL-8 induced by fire fighting

Swiston et al Eur Resp J 2008
South-East Asia haze of 1997
Air pollution levels in Singapore 1997

Tan & van Eeden 2001, AJRCCM
Blood Stream inflammation causes by Woodsmoke

Tan & van Eeden 2001, AJRCCM
Blood Stream inflammation causes by Woodsmoke

IL-6 pg/ml

Haze

Post-haze

PM$_{10}$ (µg/m$^3$)

10

5

0

0 50 100 150 200

IL-6, p<0.09
PM$_{10}$, p<0.001

IL-1β pg/ml

Haze

Post-haze

PM$_{10}$ (µg/m$^3$)

15

10

5

0

0 50 100 150 200

IL-1β, p<0.05
PM$_{10}$, p<0.001

Tan & van Eeden 2001, AJRCCM
Possible Biological Mechanisms for PM$_{10}$ adverse health effects

**Seaton hypothesis:** PM$_{10}$ induces inflammation in the lung that have systemic effects

**Particles hypothesis:** Particles themselves are toxic to tissue
Arterial and Venous IL-6 At 4 Hours

**: P<0.01, *: P<0.05

Saline

Low dose PM10

High dose PM10

**: P<0.01, *: P<0.05

BAL versus Arterial IL-6

Log BALF IL-6 (pg/ml)

Log Aortic Serum IL-6 (pg/ml)

R² = .234  P<0.0001

Hypothesis

PM$_{10}$ induced lung inflammation

Systemic Inflammatory Response

Bone marrow Stimulation (leukocytes and platelets)

Cytokines production

Development and destabilization of atherosclerotic plaques

\{ Heart attacks, Strokes \}
First direct evidence that air pollution causes blood vessel disease

- Lacks LDL Receptor
- Hyperlipidemia
- Hypercholesterolemia
- Rapid development of AS-lesions

Suwa et al. J Am Coll Cardiol. 2002
Air pollution stimulate lipid uptake in Atherosclerosis plaques

Lipids in Plaques

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<thead>
<tr>
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<th>PM$_{10}$ n=9</th>
<th>Control n=6</th>
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<td></td>
<td>* 34.2</td>
<td>*p&lt;0.05</td>
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Suwa JACC 2001
Fibrous cap in advanced lesions in aorta

A trichrome stained AS lesions. The arrow delineating border between the fibrous cap and atheromatous core.

Suwa et al, JACC 2002
Effect $\text{PM}_{10}$ on plaque morphology

Control WHHL Rabbits

- Thinner Fibrous Cap
- Increased and redistribution of lipids
- Increase Inflammatory cells

$\text{PM}_{10}$
Air Pollution and blood vessel responses (endothelial dysfunction)

Myograph

Tamagawa et al AJP 2008
Circulating IL-6 and vessels vasodilation

R² = 0.406, p-value = 0.014

Tamagawa et al AJP 2008
Impact of IL-6 on PM-induced vascular dysfunction

Suda et al AJCMB 2010
Exposure Type

Brachial Artery Diameter Change (mm)

Filtered Air  CAP + Ozone

\( \text{a) CAP + O}_3 - \downarrow \Delta \text{BAD} \)

0.003

0.092

Brook et al. Circulation 2002
Air Pollution where you live: Atherosclerosis

Kunzli et al. Environ Health Perspect. 2005
Living near a heavy traffic route:
Coronary Heart Disease

Coronary Plaque

Hoffmann B et al., Circulation, 2007
Figure 2. Univariate analyses for association between onset of MI and 24-hour average concentrations of PM$_{2.5}$. Odds ratios and 95% CIs for an increase of 20 $\mu$g/m$^3$ PM$_{2.5}$. 

Peters et al Circ 2001;103;2810
Cardiovascular Morbidity and Mortality associated with Air Pollution

- Mortality due to PM exposure is predominantly cardiovascular in nature (Pope et al 2002)
- Hospital admission within hours of an increase in PM (Schwartz et al 1994).
- Cardiovascular admissions for arrhythmia’s, unstable angina, MI’s and heart failure (Dockery et al 1993).
- Hospitalization and mortality form Stroke  Haidong 2003
- Predominantly the elderly at risk (Schwartz J 1994)
- M & M correlates the best with particle levels (Bates DJ 1992)
How air pollutants aggravate heart and lung disease

Air pollution

Lung inflammation

Blood stream inflammation

Pneumonia
Asthma Attacks
COPD Attacks

Heart Attacks & Strokes
What can we do to attenuate the impact of PM air pollution on blood vessels?
Pleiotropic Effects of Statins

- TXA\(_2\)
- Platelet Activation

- Nf-kB

- Rho

- Rac 1

- Endothelial Function

- Cholesterol

- Anti-inflammatory

- Immunomodulatory

HMG-CoA Reductase Inhibitors
Animals: New Zealand White rabbits
(12-week-old, female)

Interventions: i) +/- Lovastatin (5 mg/kg, 8 weeks)

ii) PM$_{10}$ or saline instillation
(direct intratracheal instillation; 1.0 mg/kg, 3 days a week. 4 weeks)
Statins reduce Lung Inflammation

Cell Differential Counts in BAL Fluid

Statins reduces cytokines in airspaces

### Transit times of PMN through bone marrow

<table>
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<th>Group</th>
<th>Transit Time (hrs)</th>
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<tr>
<td>Saline</td>
<td>47.9 ± 0.7</td>
</tr>
<tr>
<td>Saline + Lovastatin</td>
<td>42.7 ± 3.7</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>21.3 ± 4.3 ***</td>
</tr>
<tr>
<td>PM$_{10}$ + Lovastatin</td>
<td>38.2 ± 0.5 ###</td>
</tr>
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Two-way factorial analysis of variance (ANOVA) with PM10 exposure and statin treatment as independent variables, followed by Bonferroni post-hoc test. Transcripts with a significant PM10 exposure × statin treatment interaction ($p < 0.05$) were additionally analyzed with a one-way ANOVA followed by Newman-Keuls post-hoc test for comparison of individual treatment groups. ***$p < 0.001$ compared to saline; ### $p < 0.001$ compared to PM$_{10}$

Miyata et al Am J Physiol 2012
Statins attenuates PM-induced Atherosclerosis

Miyata et al Tox Appl Pharm 2013
Statins attenuates PM-induced endothelial dysfunction

Maximum vasoconstriction at PE $10^{-4}$ mM

**$P < 0.001$ vs. saline; **$P < 0.01$ vs. PM$_{10}$**, Two-way factorial ANOVA

Miyata et al Tox Appl Pharm 2013
Summary

• Overwhelming epi-evidence that PM$_{10}$ air pollution is associated with heart and vascular disease

• PM$_{10}$ exposure causes a systemic inflammatory response that increases CRP/IL-6 which stimulates the bone marrow.

• This systemic response activate blood vessels (endothelial dysfunction) and enhanced the development of atherosclerosis and induced instability in plaques.

• Statins attenuate the effects PM air pollution on blood vessels.
Policy Implications

• Size of air pollution particles matter

• Rethink urban development

• Should work on near-term solutions to mitigate adverse effects of PM
Breathing Clean Air Promotes Heart & Lung Health