Cardiovascular Effects of Urban and Rural Coarse Particulate Matter in Adults (COARSE-CAP)

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**PLAUSIBLE BIOLOGICAL MECHANISMS**

1. **Autonomic Imbalance**
2. **Systemic Inflammation**
3. **Deposition in Alveoli**

**Mediators of Oxidative Stress**
- Transition metals (Zn, V, Fe, Ni)
- Organics, PAH, quinones
- Ultrafine PM Vapors: SVOC, VOC

**Circulating PM constituents**

**Arrhythmia** (sudden death)

**Vascular Dysfunction** (Vasoconstriction, Hypertension)

**Altered Blood Rheology** (Increased viscosity, pro-thrombotic)

**Atherosclerosis** (plaque progression & instability)

**Hierarchical Oxidative Stress Response Model**
Few Studies with Controlled Exposure to Coarse PM

- Exposure to concentrated coarse air pollution particles causes mild cardiopulmonary effects in healthy young adults
    Chapel Hill CAP (2 hr x 89 µg/m³) to 14 healthy young adults
    - 20 hrs post ↓ TPA (32.9%), ↓ SDNN (14.4%)
    - No PFT changes, mild increase in lung PMN 20 hrs post-CAP

- Altered heart-rate variability in asthmatic and healthy volunteers exposed to concentrate
    Los Angeles suburb (2 hr x 157 µg/m³) to 12 asthmatics and 4 healthy adults
    - Small ↑ HR and ↓ SDNN 4-24 hrs post-CAP (more in healthy)
Updated Overall Hypothesis

Short-term exposure to coarse PM, from both rural and urban sources, promotes pro-vasoconstrictive vascular dysfunctions via biological pathways related to autonomic imbalance (rapid) and endothelial dysfunction (delayed) with (a) larger effects in obese vs lean subjects and (b) promotes metabolic insulin resistance syndrome.
Brachial Artery Diameter Changes in Response to Air Pollution versus Filtered Air

\[ \text{Exposure Type} \]

\[ \text{Brachial Artery Diameter Change (mm)} \]

\[ p = 0.03 \]

\[ n = 25 \]

\[ \text{Filtered Air} \]

\[ \text{CAP + Ozone} \]
Blood Pressure Responses to Concentrated Ambient PM$_{2.5}$ (CAP) versus Filtered Air

![Graph showing the relationship between Organic carbon (µg/m³) and Change in DBP at 2 hr (mm Hg). The graph indicates a positive correlation with r=0.53 and p=0.009. The change in DBP is 6 mm Hg.]

Environ Health Perspectives 2005; 113: 1052-55.
CLEANAIR STUDY: DBP Changes during Exposures in Toronto

FA (filter air); O3 (ozone); CAP (concentrated ambient fine particulate matter); DBP (diastolic blood pressure)

DBP Slope (mmHg / 30 min)
- FA = 0.32 ± 0.32 (p=0.32)†
- O3 = 0.11 ± 0.27 (p=0.68)†
- CAP = 0.71 ± 0.21 (p=0.002)†
- CAP + O3 = 0.89 ± 0.22 (p=0.0003)† p=0.01*

DBP correlates: (1) ↑ CAP mass* (2) ↓ heart rate variability (SDNN)

† vs slope = 0
* For “CAP effect” = slopes of [CAP + (CAP+O3)] vs [O3 + FA]

Hypertension 2009; 54: 659-667

*β = 1.6 mmHg per 100 µg/m³
Endothelial Function (Toronto)

N=31

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change (± SD)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>FA</td>
<td>2.7 ± 9.0% (n=30)</td>
<td>0.11</td>
</tr>
<tr>
<td>O3</td>
<td>-0.9 ± 7.5% (n=29)</td>
<td>0.50</td>
</tr>
<tr>
<td>CAP</td>
<td>-2.9 ± 6.2% (n=28)</td>
<td>0.02</td>
</tr>
<tr>
<td>CAP+O3</td>
<td>-2.3 ± 6.4% (n=28)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

No change in NMD at any time point, or FMD immediately post exposures

↓ FMD correlates: ↑ CAP mass*, ↑ TNFα**

*β = -2.3% per 100 μg/m³
**r = -0.26, p=0.023

Hypertension 2009; 54: 659-667
Coarse-CAP

Specific Aim 1
To demonstrate that coarse CAP exposure causes acute vascular dysfunctions in health adults (n=50)

- Coarse PM (CAP) [150-300 μg/m³] for 2 hrs triggers vascular dysfunctions at rural (Dexter) + urban (Dearborn) sites (vs filtered air).
  
  Primary outcomes: ↓ brachial artery diameter (vasoconstriction)
  ↑ intra-exposure diastolic blood pressure (BP)

- The vascular dysfunctions are mediated by CV autonomic balance
  ↓ HRV correlated and temporally related to vasoconstriction.
  Update: ↑BP related to autonomic Δ; ↓FMD related to systemic inflammation

- To further elucidate the CV impact of coarse PM by novel CV outcomes
  • Continuous BP/hemodynamics (Finometer)
  • Central aortic hemodynamics, arterial compliance (SphygmoCor)
  • Microvascular endothelial function (EndoPAT2000)
  Update: Novel metabolic, pro-inflammatory biomarkers and outcomes
Specific Aim 2
To explore potential differences in outcome responses between obese (BMI>30, n=25) versus lean (BMI<27, n=25) adults elicited by both CAP sources (urban vs rural locations).

- Compare CV responses due to urban (Dearborn) vs. rural (Dexter) coarse CAP in Michigan [and Toronto – ongoing Harvard EPA Center]

- Compare CV responses between obese and lean subjects and the interaction effects of BMI/metabolic syndrome parameters (e.g. basal BP) on corresponding outcomes
Why Obesity as an Effect Modifier

- WHI + Nurses’ Health Cohort studies
  - Higher RR in subjects with BMI>30 for CV mortality

- Obese subjects (BMI>30) have larger increase in BP related to ambient PM
  - Detroit Healthy Environments Partnership
    - Dvonch et al. Hypertension 2009
    - Traffic exposure in U.S. Boston Puerto Rican cohort

- Obesity increases risk for inflammation related to PM
  - NHANES (WBC); Seniors in St. Louis (CRP)
WHY METABOLIC PARAMETERS
Inter-relationships between the Cardio-metabolic Syndrome and Air Pollution

FACETS OF THE CARDIO-METABOLIC SYNDROME

- Elevated BP
- Vascular dysfunction

- Insulin Resistance
- Dyslipidemia
  - Impaired HDL

Reciprocal Relationship

PM$_{2.5}$ ± ozone exposure

Lifestyle factors
  (Obesity, high fat or sugar diet) + genetic susceptibility

Systemic inflammation and oxidative stress
Autonomic nervous system imbalance
“Common soil”
The Relationship Between Diabetes Mellitus and Traffic-Related Air Pollution

In Women
OR = 1.04 per 1 ppb NO₂
↑ IQR (4 ppb) NO₂ = ↑ 17% DM

N=7634

J Occup Environ Med 2008; 50: 32
Ambient Air Pollution Exaggerates Adipose Inflammation and Insulin Resistance in a Mouse Model of Diet-Induced Obesity

Circulation 2009; 119:538-46
Coarse-CAP Status

- Construction of Harvard 2-stage coarse concentrator
- Construction with Jack Harkema (MSU) of AIRCARE-2 and installation of concentrator and exposure chamber
- Experimental updates and IRB/University approvals
- Modifications to exposure site locations
- Oct 2010 – Completion of site modifications for electrical powering of AIRCARE-2 facility at Dexter
- Oct 2010 – Study protocols commence at Dexter
Coarse-CAP

Specific Aim 3
To elucidate the coarse CAP constituents and sources responsible for the CV responses.

- Detailed assessment of the differences in coarse PM composition and sources between the experimental sites.
- Correlate CAP composition with CV outcomes for insights into constituents and sources responsible for triggering biological CV responses.
Coarse-CAP

Coarse PM characterization:

Continuous PM by TEOM and TSI APS.

Teflon filters: gravimetric total mass.

Inductively coupled plasma-mass spectrometry (ICP-MS): trace elements (e.g., Fe, Ni, Zn, Cu)

Ion chromatography: sulfate, nitrate, chloride, potassium, sodium and ammonium.

Thermal-optical-transmission analysis: total organic and elemental carbon.

Biological: Endotoxin (LAL)

Source Apportionment:

PM will be quantified and categorized based on the chemical composition

Multivariate receptor modeling methods, Positive Matrix Factorization (PMF)

Associations between the health outcomes and the individual pollutants and CAP components as well as their likely sources
Study Overview

Medical Waste
Waste to Energy
Ambassador Bridge
Electric Utility
Coke
Zug Island
Steel Processing
Steel Coating
Steel
Lime
Lime
Oil Refinery
DBN

Dexter Site

40 miles

Dearborn Monitoring Site

DXT

Detailed Map
Monitoring Sites

Dexter

Dearborn
PM Dichotomous Mass - Spatial Results

USEPA-NERL / Univ-Michigan Collaborative Study (July-August 2007)
Spatial Results

Coarse PM Species (XRF)

USEPA-NERL / Univ-Michigan Collaborative Study (July-August 2007)
Updated Coarse-CAP Protocol

Coarse CAP = 150-300 µg/m³
*Exposure dose allowed to change along with ambient levels*

10 AM-12 PM
2-hour exposure

- Dexter Coarse RURAL
  - REGIONAL CAP
- Filtered Air
- Dearborn (URBAN)
  - Coarse CAP

2 PM
2 hr-post-exposure testing

- 25 Healthy adults
- 25 Obese adults

8 AM
20 hr-post-exposure testing

- Vascular Studies
  - AIRCARE Blood draws
  - Insulin sensitivity -HOMA-IR
- Vascular Studies
  - AIRCARE Blood draws
  - HOMA-IR
- Vascular Studies
  - CTSA Blood draws
  - FSIVGTT (CTSA)
- HRV
  - CTSA Blood draws
  - FSIVGTT (CTSA)
- HRV
  - CTSA Blood draws
  - FSIVGTT (CTSA)

MODIFIED TIME LINE

Oct 2010-Sept 2011: Dexter coarse CAP + FA
Oct 2011- April 2012: Dearborn coarse CAP

INTRA-EXPOSURE TESTING
BOTH EXPOSURES
- Ambulatory BP monitoring
- HRV monitoring

Cross-over to randomized exposure scenarios
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<tr>
<th>Method</th>
<th>Effect Assessed</th>
<th>Specific Parameter Measured</th>
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<tbody>
<tr>
<td>Ultrasound</td>
<td>Basal vascular tone</td>
<td>Brachial artery diameter</td>
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<tr>
<td>Finometer</td>
<td>Arterial hemodynamics</td>
<td>Cardiac output and Systemic Vascular Resistance</td>
</tr>
<tr>
<td>Omron 780</td>
<td>Systemic BP</td>
<td>Brachial BP: Average of 2(^{nd}) and 3(^{rd}) arm BP</td>
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<tr>
<td>SphygmoCor</td>
<td>a) Arterial compliance</td>
<td>a) Carotid-femoral PWV</td>
</tr>
<tr>
<td></td>
<td>b) Pulse wave analyses</td>
<td>b) Central aortic BP levels, augmentation index Aix)</td>
</tr>
<tr>
<td>Terason</td>
<td>Brachial (conduit) vascular function</td>
<td>Flow-mediated dilatation (endothelial function)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Brachial (conduit) vascular function</td>
<td>Nitroglycerin-mediated dilation (NMD)</td>
</tr>
<tr>
<td>EndoPAT</td>
<td>Microvascular endothelial function</td>
<td>Finger tonometer-determined microvascular endothelial-dependent dilatation (RI)</td>
</tr>
<tr>
<td><strong>CV outcomes</strong></td>
<td><strong>to take place while subject is intra-chamber during 2-hour long exposure</strong></td>
<td></td>
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<tr>
<td>AMBP</td>
<td>Continuous BP/HR</td>
<td>Rapid systemic arterial BP change during exposure</td>
</tr>
<tr>
<td>Holter ECG</td>
<td>Continuous ECG/HRV</td>
<td>Time/frequency domain heart rate variability metrics.</td>
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## UPDATED BIOMARKERS AND OUTCOMES

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<th><strong>Plasma Endotoxin level</strong></th>
<th>Circulating blood endotoxin concentrations</th>
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<tr>
<td><strong>CARDIAC and VASCULAR BIOMARKERS</strong></td>
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<tr>
<td>EPC levels/function (flow cytometry)</td>
<td>Endothelial progenitor cell vascular repair function</td>
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<tr>
<td>Cardiac echo – RF tissue Doppler</td>
<td>Novel cardiac diastolic function parameter</td>
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<td><strong>PRO-INFLAMMATORY AND METABOLIC</strong></td>
<td></td>
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<tr>
<td>TLR-2 and TLR-4 (flow cytometry)</td>
<td>Monocyte Toll-like receptor expression</td>
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<tr>
<td>Monocytes CD(^{14+16+}) vs CD(^{14+16-})</td>
<td>Circulating monocyte pro-inflammatory sub-types</td>
</tr>
<tr>
<td>Adipocytokines/cytokines/CBC</td>
<td>Adipocyte function and cytokine changes</td>
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<tr>
<td>Adiponectin, IL-1beta, IL-6, TNF-alpha</td>
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<td>HDL function; PON-1 activity</td>
<td>Dysfunctional HDL particles</td>
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<td><em>Prevention of LDL oxidation</em></td>
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<tr>
<td>Lipoproteins (<em>NMR lipoprofile</em>)</td>
<td>Lipoprotein phenotypes (LDL-P#; LDL-P size)</td>
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<td>HOMA-IR (glucose x insulin/405)</td>
<td>Metabolic insulin sensitivity</td>
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<tr>
<td><strong>FSIVGTT using MinMOD (S(I))</strong></td>
<td>Metabolic insulin sensitivity</td>
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Coarse-CAP

- **Principal Investigator:**
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  Division of Cardiovascular Medicine, University of Michigan (UM)

  **Co-investigators:**
  - J. Timothy Dvonch, Gerald Keeler (School of Public Health, UM)
  - Niko Kaciroti (Biostatistics, UM)
  - Diane R. Gold (Harvard School of Public Health)

- **Consultants/collaborators:**
  - Bruce Urch, Jeffrey R. Brook, Frances Silverman (GAGE Toronto)
  - Sanjay Rajagopalan (Ohio State)  Monocyte biomarkers
  - Marianna Kaplan (UM, Rheumatology)  EPC testing
  - Elif Oral (UM, Endocrinology)  Metabolic testing
  - Jesus Araujo (USC)  HDL function
  - Ted Kolias (UM, Cardiology)  Echo diastolic function