Microvascular Outcomes of Engineered Nanomaterial Inhalation

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Overview

• How does something we inhale affect the cardiovascular system?

• Vascular Physiology and Common Methodologies

• Mechanistic Theories

• Unique Circulations and Special Populations
Epidemiological Studies

Air Pollution

• Epidemiologic evidence of cardiovascular effects of particulate air pollution. ¹
• Increased incidence of myocardial infarction within 24 hours of inhaled particulate pollution. ²
• Overall, exposure to fine and ultrafine particulate air pollution has adverse effects on cardiopulmonary health. ³,⁴

Nanomaterial

• Homogeneous composite of low-solubility and low-toxicity surrogate material.
• However, previously identified as “ultrafine” size, studies demonstrated higher inflammatory, reactive stress, and toxicity potential than larger counterparts. ¹

¹. Dockery, EHP, 2001
². Peters, Circulation, 2001
³. Pope, Circ Research, 2015

Vascular Anatomy

- Heart
  - Variability
  - Arrhythmias

- Macrocirculation
  - Aorta
  - Large Arteries

- Microcirculation
  - Peripheral Resistance
  - Tissue of Interest
Vascular Physiology

Pressure (mm Hg)

- Systolic pressure
- Pulse pressure
- Diastolic pressure
- Mean pressure

Left ventricle - Arteries - Arterioles - Capillaries - Venules, veins - Right atrium

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Vascular Endothelium
Microvasculature Dysfunction of the Heart

LeBlanc, J Toxicol. Environ. Health A, 2009
Dose-Dependent Response

Nurkiewicz et al., Health Effects Institute, 2011
Time Course

% Relaxation vs. Log Acetylcholine Concentration

- Control
- 24 hours
- 72 hours
- 120 hours
- 168 hours

*p<0.05 vs. All Exposures

Stapleton et al., International Journal of Molecular Science, 2012
How does something you inhale cause cardiovascular issues?

Stapleton et al., Microcirculation, 2012
Autonomic Control and Neurological Alterations

- Augmented Sympathetic Control. ¹, ²
- Altered Neurotransmitter Release. ², ³
- Tissue Specific Receptor Populations

². Stapleton et al., Microcirculation, 2012;
³. Knuckles, Nanotoxicology, 2012
Inflammation

- Systemic signaling cascade following exposure. 1, 2
  - Increase in circulating cyto- and chemokines
- Increased leukocyte activity. 1, 3
- Local mediators leading to a reduction in metabolite bioavailability. 3, 4

Direct Particle Interaction

MWCNT Translocation

• Evidence to suggest interactions and/or translocation: brain, liver, spleen, kidney, and heart. ¹, ²
• Direct particle-tissue interaction (inflammation, reactive species). ², ³
• Are they getting back out? (excretion) ⁴

Systemic Distribution of Inhaled Multi-Walled Carbon Nanotubes

<table>
<thead>
<tr>
<th>Organ</th>
<th># of MWCNT Fibers</th>
<th>% Lung Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>$646.8 \times 10^6$</td>
<td>99.99890</td>
</tr>
<tr>
<td>Kidney</td>
<td>$1533 \pm 530$</td>
<td>0.00024</td>
</tr>
<tr>
<td>Liver</td>
<td>$4535 \pm 1100$</td>
<td>0.00070</td>
</tr>
<tr>
<td>Heart</td>
<td>$525 \pm 1260$</td>
<td>0.00008</td>
</tr>
</tbody>
</table>

Models of Exposure

All of our past research using young, healthy, male models of occupational exposure, differing cardiovascular assessments indicate cardiovascular dysfunction.

2010 Census:
- Male (15-30): 10.7% American Population
- Median Age: 37.2 years

Additional Applications:
- Domestic Applications
- Theranostics
Models of Exposure

• With respect to health, these models represent the best of the best society has to offer. What about other populations?
Unique Circulations

“Pregnancy Therapeutic Window”

Maternal

Placenta

Fetal

Uterine Circulation

Barry, Theriogenology, 2008
Gestational Exposure

• Maternal coronary, uterine, and umbilical reactivity impairments. 1,2

• Development of a hostile gestational environment. 1

• Fetal arteriolar dysfunction. 1

• Dysfunction is maintained in the heart and uterus of the F1 generation. 3

• Behavioral/memory deficits within the F1 generation. 4,5

Applicability/Special Populations

• Nanomaterial Fate
• Numerous studies have shown the propensity for vascular impairments in susceptible populations.
• As the uses for ENM increase, as will potential for exposure of varying populations.

Consider:
• Female Subjects
• Pregnancy
• Children
• Elderly
• Diabetic Patients
• Obese
• COPD
• Sickle-Cell Disease
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