Ozone and Health: Clinical Studies

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QUESTIONS

• What do we know about respiratory effects of ozone?

• Are there acute cardiovascular effects of ozone?

• The obesity epidemic: ozone susceptibility?

• What’s new since last ozone Integrated Science Assessment (ISA)?
What do we know about respiratory effects of ozone?
WHAT OZONE DOES TO THE FORCED VITAL CAPACITY

FEF = forced expiratory flow  FVC = forced vital capacity  RV = residual volume

Effects of ozone on lung function.
Variability of Ozone Response

Variability of Ozone Response

![Graph showing variability of ozone response.

- FEV1, % CHANGE for BASELINE, 2HR, and 4HR.
- Baseline FEV1 values decrease from 0 to -60.
- 2HR and 4HR values showing similar trends, indicating variability in response.

Graph labels:
- Y-axis: FEV1, % CHANGE
- X-axis: BASELINE, 2HR, 4HR

The graph illustrates the variability in FEV1 (forced expiratory volume in one second) response to ozone exposure at different time points: Baseline, 2 hours, and 4 hours.
220 ppb 4 hours with exercise:
Smokers are less responsive to Ozone
Frampton et al., AJRCCM 1997
Age and Lung Function Effects of Ozone
PMN in Bronchial Lavage

220 ppb 4 hours

Torres et al., AJRCCM 1997

PMN = polymorphonuclear neutrophils
Are there acute cardiovascular effects of ozone?
### Human Clinical Studies of Ozone Cardiovascular Effects

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects/Conditions</th>
<th>Ozone Concentration</th>
<th>Time</th>
<th>Changes in Cardiovascular Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tank et al., PLoS One, 2011</td>
<td>14 ozone inflammation-responsive subjects, 250 ppb 3 hrs</td>
<td>No Δ BP, HR, HRV, cardiac output, PAI-1, muscle sympathetic activity</td>
<td></td>
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</tr>
<tr>
<td>Devlin et al., Circulation, 2012</td>
<td>23 subjects, 300 ppb 2 hrs</td>
<td>↓ HRV (HF only), ↑ IL-8 &amp; CRP, ↓ PAI-1 (fibrinolysis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barath et al., Toxicol Sci, 2013</td>
<td>36 men, 300 ppb 75 min</td>
<td>↑ Vasodilation. No Δ BP, HR, HRV, fibrinolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arjomandi et al., Am J Physiol, 2015</td>
<td>26 subjects (10 mild asthma), 100 &amp; 200 ppb 4 hrs</td>
<td>↑ CRP, ↓ HRV (HF). No change PAI-1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frampton et al., Inhal Toxicol, 2015</td>
<td>24 subjects (12 GSTM1 null), 100 and 200 ppb 3 hrs</td>
<td>↓ BP. No Δ HR, periph. art. tonometry, arterial and venous nitrite, cardiac output, platelet activation, microparticles. HRV not measured.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP = blood pressure; CRP = C-reactive protein; GSTM1 = glutathione S-transferase mu 1; HF = high frequency; HR = heart rate; HRV = heart rate variability; IL-8 = interleukin 8; PAI-1 = plasminogen activator inhibitor type 1; ppb = parts per billion
OZONE, BLOOD CLOTTING, AND TEMPERATURE

300 ppb, 2 hours

Kahle et al., Environ Health Perspect 2015

D-dimer = a fibrin degradation product; PAI-1 = plasminogen activator inhibitor type 1; tPA = tissue plasminogen activator; vWF = von Willebrand Factor
Multicenter Ozone Study of oldEr Subjects (MOSES)

- UCSF, UNC, URMC. Identical protocols. Central labs and data management.
- 87 healthy nonsmokers 55 to 70 years of age.
- 0, 70, 120 ppb ozone, intermittent moderate exercise.
- HRV, repolarization, ST segment, vascular function, platelet function, coagulation, oxidative stress, systemic inflammation, respiratory outcomes.
- GSTM1 genotyping.

UCSF = University of California–San Francisco; UNC = University of North Carolina–Chapel Hill; URMC = University of Rochester Medical Center
HRV = heart rate variability; GSTM1 = glutathione S-transferase mu 1
MOSES: Lung function and airway inflammation
MOSES:
Evidence for lung injury (Club Cell 16)
MOSES: What about frequency-domain HRV?

LF = low frequency; HF = high frequency
MOSES Bottom Line:

- Subtle but clear respiratory effects.
- Not completely resolved 22 hours after exposure.
- No convincing evidence for cardiac or vascular effects.
- No interactions with GSTM1 genotype.

Could subjects’ exposures to ambient ozone or other pollutants affect results of MOSES?
MOSES 2: Impacts of Personal and Ambient Pollutant Concentrations

- Personal ozone and NO$_2$ monitoring 72 hours before.
- Ambient pollutant concentrations up to 96 hours before.
- 3 Aims:
  1. Pollutant effects on pre-exposure biomarkers.
  2. Pollutant effects on pre to post change, independent of ozone.
  3. Pollutant modification of biomarker responses to controlled ozone.
# Ambient Ozone Concentrations

<table>
<thead>
<tr>
<th>Site</th>
<th>Lag Hrs</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>5th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>95th</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSF</td>
<td>0-23</td>
<td>73</td>
<td>23.1</td>
<td>8.9</td>
<td>4.4</td>
<td>8.9</td>
<td>17.3</td>
<td>23.3</td>
<td>28.6</td>
<td>37.6</td>
<td>44.9</td>
</tr>
<tr>
<td></td>
<td>0-71</td>
<td>73</td>
<td>23.2</td>
<td>7.8</td>
<td>7.1</td>
<td>8.4</td>
<td>18.5</td>
<td>23.9</td>
<td>27.5</td>
<td>37.0</td>
<td>42.1</td>
</tr>
<tr>
<td>UNC</td>
<td>0-23</td>
<td>70</td>
<td>26.6</td>
<td>10.2</td>
<td>0</td>
<td>12.3</td>
<td>19.6</td>
<td>26.1</td>
<td>35.0</td>
<td>42.7</td>
<td>45.9</td>
</tr>
<tr>
<td></td>
<td>0-71</td>
<td>70</td>
<td>28.2</td>
<td>9.3</td>
<td>0</td>
<td>14.3</td>
<td>21.9</td>
<td>28.6</td>
<td>36.0</td>
<td>41.2</td>
<td>45.7</td>
</tr>
<tr>
<td>URMC</td>
<td>0-23</td>
<td>92</td>
<td>27.0</td>
<td>9.1</td>
<td>10.6</td>
<td>13.4</td>
<td>20.7</td>
<td>26.0</td>
<td>32.9</td>
<td>43.5</td>
<td>52.4</td>
</tr>
<tr>
<td></td>
<td>0-71</td>
<td>92</td>
<td>26.6</td>
<td>7.4</td>
<td>9.7</td>
<td>15.3</td>
<td>21.1</td>
<td>26.2</td>
<td>31.3</td>
<td>38.4</td>
<td>45.8</td>
</tr>
</tbody>
</table>
MOSES 2 Conclusions

• Ambient ozone reduced pre-exposure heart rate variability (HRV).
• Ambient PM$_{2.5}$, CO, NO$_2$, but not ozone, reduced forced expiratory volume in 1 second (FEV$_1$); recovers during exposure session.
• Ambient PM$_{2.5}$, CO, NO$_2$, but not ozone, increased lung function effect of experimental ozone.
• No evidence that prior pollutant exposures affected MOSES cardiovascular results.
The obesity epidemic: ozone susceptibility?
Obesity Prevalence Still Increasing
CDC 2015

CDC = Centers for Disease Control and Prevention
Obesity and the Lung

- Lung restriction
- Increased work of breathing
- Increased oxygen demand
- Increased ventilation $\rightarrow$ increased ozone dose
- Increased systemic inflammation
- Altered gut microbiome
Obesity and the Lung

Peters et al., Chest 2018

Dietary factors

High fat diet

Low fiber diet

Western diets contribute to deposition of adipose tissue

Dietary factors directly affect immune function

Adipose tissue

Ventilatory control and cholinergic airway tone

Adipokines

Altered immune function in obesity

Gut microbiota modulate immune function through SCFA

Altered innate and adaptive immune function

Gut microbiome
Obesity & Ozone

• Increased lung function decrements in obese.
• Unclear whether gender difference.
• Obesity increases ozone effects on airway inflammation and responsiveness in mouse models—Stephanie Shore.
• Not clear in humans.
### Table 3. Mean (SD) decrements in lung function variables (delta % fall) expressed as \((\text{Pre-Post Ozone}/\text{Pre Ozone}) - (\text{Pre-Post Air}/\text{Pre Air})) \times 100.\)

<table>
<thead>
<tr>
<th></th>
<th>FVC (%)</th>
<th>FEV1 (%)</th>
<th>IC (%)</th>
<th>sGaw (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>12.5 (7.5)</td>
<td>15.9 (8.6)</td>
<td>16.7 (14.2)</td>
<td>12.6 (26.2)</td>
</tr>
<tr>
<td>Normal Wt</td>
<td>8.0 (5.8)</td>
<td>11.7 (7.1)</td>
<td>10.2 (13.2)</td>
<td>12.4 (21.0)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.05</td>
<td>0.11</td>
<td>0.12</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 6. Sputum PMNs (concentration and % of recovered cells) and Sputum IL-6 concentration (pg/ml).

<table>
<thead>
<tr>
<th></th>
<th>Concentration cells/mg median (25th, 75th %ile)</th>
<th>% of total cells mean (SD)</th>
<th>IL-6 (pg/ml) median (25th, 75th %ile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese Post Ozone</td>
<td>194.5 (25, 390.5) *</td>
<td>48 (28) *</td>
<td>13.1 (3.0, 24.4)</td>
</tr>
<tr>
<td>Obese Post Air</td>
<td>62.5 (7.5, 174)</td>
<td>22 (21)</td>
<td>7.9 (1.4, 10.8)</td>
</tr>
<tr>
<td>Obese Train</td>
<td>50 (16, 103.5)</td>
<td>19 (16)</td>
<td>2.2 (0.9, 10.1)</td>
</tr>
<tr>
<td>Normal Post Ozone</td>
<td>186.5 (15, 257.5) *</td>
<td>39 (25) ^</td>
<td>15.9 (6.7, 33.3) ^</td>
</tr>
<tr>
<td>Normal Post Air</td>
<td>64.5 (27, 100.5)</td>
<td>14 (10)</td>
<td>4.8 (2.6, 9.1)</td>
</tr>
</tbody>
</table>

IC = inspiratory capacity; IL-6 = Interleukin 6; NS = Not significant; sGAW = specific airway conductance
What’s new since the last ozone ISA in 2013?

- Airway effects in older subjects at 120 ppb: lung function, inflammation, injury.
- Acute cardiovascular effects of brief exposures remain unclear.
- Ambient but not chamber ozone (120 ppb) reduces HRV. Delayed effect?
- Prior traffic exposures may enhance ozone response.
- Obesity confers increased susceptibility to lung function effects.

ISA = Integrated Science Assessment; HRV = heart rate variability