Inhalation of Fine Particulate Air Pollution and Ozone Causes Acute Arterial Vasoconstriction in Healthy Adults

Robert D. Brook, MD*; Jeffrey R. Brook, PhD*; Bruce Urch, MSc; Renaud Vincent, PhD; Sanjay Rajagopalan, MD*; Frances Silverman, PhD

Background—Fine particulate air pollution and ozone are associated with increased cardiovascular events. To help explain the mechanism behind these observations, we investigated the effect of air pollution exposure on vascular function.

Methods and Results—Twenty-five healthy adults underwent a randomized, double-blind, crossover study comparing the vascular response to the 2-hour inhalation of \( \approx 150 \, \mu g/m^3 \) of concentrated ambient fine particles (CAP) plus ozone (120 ppb) versus the response to the inhalation of filtered air. High-resolution vascular ultrasonography was used to measure alterations in brachial artery diameter, endothelial-dependent flow-mediated dilatation (FMD) and endothelial-independent nitroglycerin-mediated dilatation (NMD). Exposure to CAP plus ozone caused a significant brachial artery vasoconstriction compared with filtered air inhalation (\(-0.09 \pm 0.15 \, \text{mm} \) versus \(+0.01 \pm 0.18 \, \text{mm} \), \( P=0.03 \)). There were no significant differences in FMD (\(+0.29 \pm 4.11\% \) versus \(-0.03 \pm 6.63\% \), \( P=0.88 \)) NMD (\(+3.87 \pm 5.43\% \) versus \(+3.46 \pm 7.92\% \), \( P=0.83 \)), or blood pressure responses between exposures.

Conclusions—Short-term inhalation of fine particulate air pollution and ozone at concentrations that occur in the urban environment causes acute conduit artery vasoconstriction. (Circulation. 2002;105:1534-1536.)

Key Words: vasculature ■ endothelin ■ endothelium ■ air pollution
There were no significant differences in gaseous pollutant concentration. Subject characteristics are presented in Table 1. Concentration differences between the exposure and postexposure conditions were determined by flow-mediated dilatation (FMD) and nitroglycerin-mediated dilatation (NMD), respectively.

When analyzing images, the technician was blinded to subject identity and exposure type. The alterations in vascular function after each exposure were determined by subtracting pre-exposure BAD, FMD, NMD, and blood pressures from the respective postexposure values. The vascular responses of 1 subject were not included in the analyses because of excessive variation (>2 standard deviations) in the baseline pre-exposure BAD between visit days, which likely reflected an error in imaging site.

When analyzing images, the technician was blinded to subject identity and exposure type. The alterations in vascular function after each exposure were determined by subtracting pre-exposure BAD, FMD, NMD, and blood pressures from the respective postexposure values. The vascular responses of 1 subject were not included in the analyses because of excessive variation (>2 standard deviations) in the baseline pre-exposure BAD between visit days, which likely reflected an error in imaging site.

**TABLE 1. Subject Characteristics**

<table>
<thead>
<tr>
<th>Number</th>
<th>25 (15 male/10 female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34.9 ± 10</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.6 ± 2.87</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>120.6/71.3 ± 13.4/9.5</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>183.1 ± 29.5</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>110.4 ± 31.6</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>52.5 ± 15.1</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>101.1 ± 53.2</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>81.6 ± 6.7</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD.

**Human Exposure Facility**

PM₁₀ exposures were produced using a high-flow multi-stage virtual impactor system, which utilizes ambient particles drawn from outside the laboratory. O₃ was produced by an arc generator and was introduced to the exposure upstream of the concentrator. The human exposure facility has been described previously.

**Brachial Artery Vasoreactivity Studies**

Brachial artery vasoreactivity measurements were performed as previously described using an HP 4500 ultrasound system (Hewlett Packard) with a 7.5 linear array transducer. Basal brachial artery diameter (BAD) was measured after subjects rested supine for ~10 minutes. In previous validation studies, the mean difference between BAD measurements performed on 2 separate mornings was 0.04 ± 0.001 mm. Endothelial-dependent and -independent vasomotion were determined by flow-mediated dilatation (FMD) and nitroglycerin-mediated dilatation (NMD), respectively.

When analyzing images, the technician was blinded to subject identity and exposure type. The alterations in vascular function after each exposure were determined by subtracting pre-exposure BAD, FMD, NMD, and blood pressures from the respective postexposure values. The vascular responses of 1 subject were not included in the analyses because of excessive variation (>2 standard deviations) in the baseline pre-exposure BAD between visit days, which likely reflected an error in imaging site.

**Statistical Methods**

Data were stored and analyzed using SPSS 9.0 for Windows (SPSS, Inc). The vascular alterations after CAP + O₃ were compared with those after FA by 2-tailed paired t tests with a significance level of 0.05.

**Results**

Subject characteristics are presented in Table 1. Concentrations of PM₁₀ and O₃ during exposures are shown in Table 2. There were no significant differences in gaseous pollutant levels (CO, NOₓ, SOₓ) between exposure days.

**TABLE 2. Fine Particle and Ozone Concentrations**

<table>
<thead>
<tr>
<th>Test</th>
<th>Concentration</th>
<th>Before</th>
<th>After</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM₁₀, μg/m³</td>
<td>Filtered Air</td>
<td>1.6 ± 1.7</td>
<td>153.0 ± 34.8</td>
<td>8.5 ± 5.3</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD.

Vascular and blood pressure responses are shown in Table 3. Pre-exposure BAD showed no significant day-to-day variation (0.03 mm). Inhalation of CAP + O₃ caused a significant reduction in the postexposure BAD compared with the response after FA (Figure). There was a significant brachial artery vasoconstriction after CAP + O₃ inhalation (P = 0.007), whereas FA did not alter BAD. FMD, NMD, and blood pressure responses did not significantly differ between exposure types.

**TABLE 3. Vascular Responses After Exposures**

<table>
<thead>
<tr>
<th>Test</th>
<th>Concentration</th>
<th>Before</th>
<th>After</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAD, mm</td>
<td>Filtered Air</td>
<td>3.89 ± 0.68</td>
<td>3.90 ± 0.68</td>
<td>0.01 ± 0.18</td>
</tr>
<tr>
<td>FMD, %</td>
<td>Filtered Air</td>
<td>3.61 ± 4.27</td>
<td>3.57 ± 6.49</td>
<td>-0.03 ± 6.63</td>
</tr>
<tr>
<td>NMD, %</td>
<td>Filtered Air</td>
<td>14.69 ± 6.40</td>
<td>18.15 ± 8.94</td>
<td>3.46 ± 7.92</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>Filtered Air</td>
<td>120.5 ± 13.5</td>
<td>121.3 ± 8.9</td>
<td>0.8 ± 10.3</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>Filtered Air</td>
<td>71.2 ± 8.7</td>
<td>70.8 ± 9.2</td>
<td>-0.4 ± 7.3</td>
</tr>
<tr>
<td>CAP + O₃, mm</td>
<td>Filtered Air</td>
<td>3.92 ± 0.65</td>
<td>3.82 ± 0.62</td>
<td>-0.09 ± 0.15</td>
</tr>
<tr>
<td>FMD, %</td>
<td>Filtered Air</td>
<td>4.22 ± 4.52</td>
<td>4.52 ± 3.69</td>
<td>0.29 ± 4.11</td>
</tr>
<tr>
<td>NMD, %</td>
<td>Filtered Air</td>
<td>14.88 ± 5.25</td>
<td>18.76 ± 6.12</td>
<td>3.87 ± 5.43</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>Filtered Air</td>
<td>120.4 ± 10.4</td>
<td>120.8 ± 11.8</td>
<td>0.4 ± 8.6</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>Filtered Air</td>
<td>70.0 ± 9.9</td>
<td>70.9 ± 9.0</td>
<td>0.9 ± 7.2</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD. Δ indicates pre-exposure to postexposure change.

*Filter air Δ vs CAP + ozone Δ, by 2-tailed, paired t test.
†P = 0.007 for post-BAD (CAP + ozone) vs pre-BAD (CAP + ozone), by 2-tailed, paired t test.

**Discussion**

We have demonstrated for the first time that inhalation of common air pollutants affects the systemic vasculature of humans. Short-term exposure to PM₁₀ and O₃ at levels that occur in urban environments causes acute conduit artery vasoconstriction without producing immediate alterations in endothelial-dependent or -independent vasomotion. This finding is important because it suggests that alterations in arterial tone may be a relevant mechanism contributing to air pollution–mediated acute cardiac events and because it provides evidence that the observations shown by large epidemiological studies are biologically plausible.

**Relevance of Conduit Artery Vasocostriction**

It is reasonable to suspect that the coronary vasculature may respond similarly to air pollution exposure because brachial and coronary reactivity strongly correlate (r = 0.79, P < 0.001 for brachial versus coronary FMD). Even so, a reduction in coronary diameter of this relatively small magnitude (~0.1 mm) would have minimal impact on healthy adults. However, congruent with epidemiological findings that individuals at increased risk for acute air pollution–related cardiac events generally have pre-existing cardiovascular disease, this degree of sudden coronary vasoconstriction could promote cardiac ischemia in those with underlying flow-limiting obstructive lesions or could trigger instability of susceptible plaques. Furthermore, the vasculature of patients with coronary risk factors is known to hyper-react to
BAD alterations after exposures. After CAP + O₃, 18 of the 24 subjects responded with a BAD vasocostricton versus dilatation, a greater BAD vasoconstriction, or a blunted dilatation compared with FA. Bars represent mean BAD changes.

a variety of vasoconstrictors,¹²,¹³ which potentially increases their susceptibility for acute cardiac events after air pollution exposure. Additional investigations in the coronary circulation and in high-risk individuals are needed to confirm these hypotheses.

Mechanisms and Mediators of Vasoconstriction

Because this is the first study to investigate the effects of air pollution on the vasculature, a more complete understanding of the pathophysiological mechanisms underlying our observations and the specific pollutants involved requires further investigation. Substantial evidence links increased PM₂.₅ along with cardiac mortality.¹ However, our initial air pollution exposure was chosen to be PM₂.₅ plus O₃ because this mixture occurs in "real-life" settings. At present, an effect on the vasculature partially mediated by O₃ cannot be ruled out. Determinations of the relative importance of PM₂.₅ versus O₃ and specific components in fine particulate matter await follow-up studies now that a meaningful effect of urban air pollution on vascular function has been demonstrated.

Potential biological mechanisms for the vasoconstriction include a reflex increase in sympathetic nervous system activity via stimulation of pulmonary vagal afferents¹⁴ or an acute increase in vascular ET release, analogous to cigarette smoking.¹⁵ PM₂.₅ inhalation has been shown to induce systemic inflammation and cytokine production,¹⁶ possibly related to free radical activity of components in particulate matter.¹⁷ In turn, these have the capacity to enhance vascular ET expression by direct mechanisms or via activation of oxidative stress pathways.⁶ Indeed, we have previously demonstrated the presence of increased plasma ET levels acutely after PM₂.₅ exposure.⁵

In conclusion, alterations in arterial tone and reactivity in response to PM₂.₅ and O₃ exposure is a new arena for future research into the biological mechanisms linking air pollution with acute and potentially chronic cardiovascular events. Further investigations are needed to confirm and extend our findings to the coronary circulation and to subjects with existing heart disease.

Acknowledgments

This study was funded by a contribution from Health Canada Toxic Substance Research Initiative and Air Quality Health Effects Research Section, Government of Canada.

References

Inhalation of Fine Particulate Air Pollution and Ozone Causes Acute Arterial Vasoconstriction in Healthy Adults
Robert D. Brook, Jeffrey R. Brook, Bruce Urch, Renaud Vincent, Sanjay Rajagopalan and Frances Silverman

Circulation. 2002;105:1534-1536; originally published online March 11, 2002;
doi: 10.1161/01.CIR.0000013838.94747.64
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/13/1534

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/