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 \( \approx 150 \, \mu \text{g/m}^3 \) 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, endothelium-dependent flow-mediated dilatation (FMD) and endothelium-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

Fine particulate air pollution <2.5 \( \mu \text{m} \) in diameter (PM\(_{2.5}\)) and ozone (O\(_3\)) are associated with increased cardiovascular mortality.\(^1\) Adults with underlying cardiopulmonary disease are at highest risk for acute cardiac events\(^2\) because even transient PM\(_{2.5}\) exposure may trigger myocardial infarctions in susceptible people.\(^3\) To reduce the substantial global health impact of air pollution, it is crucial to expand our limited understanding of the biological mechanisms underlying these observations.\(^4\)

We recently demonstrated increases in plasma endothelin (ET) 1 and 3 after short-term exposure to PM\(_{2.5}\) and O\(_3\) in animals\(^6\) and humans (R. Vincent, PhD, unpublished data, 2001). ET is a potent vasoconstrictor associated with vascular endothelial dysfunction and an adverse cardiovascular prognosis at increased systemic level.\(^6\) However, venous ET concentrations may not accurately reflect actual physiological alterations in arterial function. Therefore, to determine if exposure to common air pollutants indeed alters vascular function in a manner that promotes cardiac events, we investigated the effect of PM\(_{2.5}\) and O\(_3\) inhalation, at environmentally relevant concentrations, on basal arterial tone and reactivity.

Methods

The study was approved by the Human Subjects Review Committee of the University of Toronto and was performed at the Gage Occupational and Environmental Health Unit in Toronto. Subjects signed an informed consent form and were 18- to 50-year-old nonsmokers without cardiovascular disease or risk factors. Subjects were excluded for fasting glucose \( \geq 126 \, \text{mg/dL} \), total cholesterol \( \geq 240 \, \text{mg/dL} \), and for use of hypertension or lipid medications, antioxidants, folate, steroids, fish oil, or aspirin.

Exposure Protocol

Subjects fasted \( \geq 8 \) hours before and during each visit. Studies were performed at identical times during the morning to avoid the impact of diurnal variation on vascular tone/reactivity. Pre-exposure brachial artery vasoreactivity studies and blood pressure measurements were performed on arrival. Each subject then received 2 randomized, 2-hour exposures on separate days in the human exposure facility: a combined concentration of \( \approx 150 \, \mu \text{g/m}^3 \) of ambient PM\(_{2.5}\) (CAP) plus O\(_3\) (120 ppb); a control filtered air (FA) exposure of zero PM\(_{2.5}\) and very low O\(_3\). The PM\(_{2.5}\) and O\(_3\) levels selected represent conditions that occur during peak air pollution events and in certain outdoor microenvironments.\(^7\) Two subjects received 2.5 hours of CAP + O\(_3\), and 1 subject was exposed to 1 hour of FA. Within 10 minutes after exposure, brachial arterial vasoreactivity studies and blood pressure measurements were repeated. This single postexposure analysis did not allow us to determine the duration of alterations in vascular function, but it was chosen to investigate the immediate impact of air pollution inhalation and to minimize the potential influence of other confounding variables on arterial reactivity (eg, meals). At least 2 days later, subjects repeated the protocol, crossed-over to the alternate exposure type. Subjects were blinded to and unaware of the exposure conditions during the studies.
**TABLE 1. Subject Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25 (15 male/10 female)</td>
</tr>
<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 ± 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 with the use of 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.⁸

**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.⁹ 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.⁹ 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**

There were no significant differences in gaseous pollutant levels (CO, NOₓ, SO₂) between exposure days.

**Table 3. Vascular Responses After Exposures**

<table>
<thead>
<tr>
<th>Test</th>
<th>Before</th>
<th>After</th>
<th>Δ</th>
<th>Before</th>
<th>After</th>
<th>Δ</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAD, mm</td>
<td>3.89±0.68</td>
<td>3.90±0.68</td>
<td>0.01±0.18</td>
<td>3.92±0.65</td>
<td>3.82±0.62†</td>
<td>-0.09±0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>FMD, %</td>
<td>3.61±4.27</td>
<td>3.57±6.49</td>
<td>-0.03±6.63</td>
<td>4.22±4.52</td>
<td>4.52±3.69</td>
<td>0.29±4.11</td>
<td>0.88</td>
</tr>
<tr>
<td>NMD, %</td>
<td>14.69±6.40</td>
<td>18.15±8.94</td>
<td>3.46±7.92</td>
<td>14.88±5.25</td>
<td>18.76±6.12</td>
<td>3.87±5.43</td>
<td>0.83</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>120.5±13.5</td>
<td>121.3±8.9</td>
<td>0.8±10.3</td>
<td>120.4±10.4</td>
<td>120.8±11.8</td>
<td>0.4±8.6</td>
<td>0.61</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>71.2±8.7</td>
<td>70.8±9.2</td>
<td>-0.4±7.3</td>
<td>70.0±9.9</td>
<td>70.9±9.0</td>
<td>0.9±7.2</td>
<td>0.77</td>
</tr>
</tbody>
</table>

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

*Filtered 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.

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.

**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 and -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.¹

**Relevance of Conduit Artery Vasoconstriction**

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).¹⁰ 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,² 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.¹¹ Furthermore, the vasculature of patients with coronary risk factors is known to hyper-react to O₃...
BAD alterations after exposures. After CAP + O₃, 18 of the 24 subjects responded with a BAD vasoconstriction 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 alone 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 afferents 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 PM₅₀ 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

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References

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