Particulate Matter Inhalation Impairs Coronary Microvascular Reactivity

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Summary

We hypothesized that microvascular reactivity is impaired after particulate matter (PM) exposure in rat coronary arterioles. Rats were exposed to filtered air (control), fine PM, or ultrafine (UF) PM via inhalation at concentrations relevant to ambient air pollution (10 and 67 μg measured pulmonary deposition). Coronary arterioles were cannulated and responses to flow, acetylcholine (ACh), endothelin (ET) and dea-NONOate were assessed. Exposure to fine and UF PM impaired flow-dependent dilation, but not ACh responsiveness. Vascular smooth muscle NO sensitivity and vasoconstriction to ET were decreased after exposure to UF PM, but not fine PM. These results suggest that UF PM exposure causes more coronary microvascular dysfunction than fine PM and could contribute to cardiac events associated with PM exposure.

Introduction

Ambient air pollution is a heterogeneous mix of various particle sizes or modes. This includes the fine, and UF components (mean aerodynamic diameters ≤ 2.5 ìm and ≤ 100 nm, respectively). Exposure to airborne pollutants, such as PM, significantly increases all-cause morbidity and mortality (2, 3, 5). PM exposure affects tissues and organs outside the respiratory tract, as evidenced by the occurrence of cardiovascular dysfunction on high pollution days (5). Previous research has shown that PM exposure impairs vasodilator capacity in the systemic microcirculation, with greater microvascular dysfunction after UF PM (4). PM exposure may similarly alter coronary blood

flow, which subsequently could lead to myocardial ischemia, malignant ventricular arrythmias, or coronary thrombosis (1). However, the coronary microvascular effects of exposure to such particles are unknown.

Materials and Methods

Inhalation Exposure: A fluidized-bed aerosol generator dispersed bulk powders. Aerosol concentration and exposure duration were calculated: *PM deposited = (aerosol level)·(minute ventilation)·(exposure duration)·(deposition fraction)*, where deposition fraction is estimated from the mean particle diameter and published deposition curves (4). Rats were exposed to filtered air (control), fine TiO_2 (~1 ≤m), or UF TiO_2 (~21 nm) at concentrations relevant to ambient air pollution (10 and 67 μg measured pulmonary deposition). These doses produce equivalent levels of microvascular dysfunction in the spinotrapezius muscle (4). After inhalation exposure, all rats recovered for 24 hrs prior to experiments.

Coronary Arteriole Isolation and Experimental Protocol: Sprague-Dawley rats (7-8 wks) were anesthetized (thiopental, 100 mg/kg, i.p.), and the heart was removed from the chest and resistance arterioles from the left anterior descending artery distribution were isolated at 4° C. The arterioles were cannulated on pipettes and pressurized at 60 cm H_2O. The vessels developed spontaneous tone (≥ 20% less initial diameter) at 37° C. Vasoreactivity was evaluated by assessing the response to flow (2-49 nl/sec), ACh (10^{-9}–10^{-4} M), 2-(*N,N*-dimethylamino)-diazenolate-2-oxide (dea-NONOate, $3x10^{-9}$–10^{-4} M), and ET (10^{-11}–10^{-7} M). At the end of all experiments, passive diameter was achieved in a Ca^{2+}-free solution with sodium nitroprusside (10^{-4} M).

Results

Twenty-four rats were studied: 9 sham-control, 8 rats exposed to 10 μg UF TiO_2, and 7 rats exposed to 67 μg fine TiO_2. Exposure to fine and UF TiO_2 did not alter spontaneous tone compared to coronary arterioles from control rats (Control: 27±2, UF: 32±2, Fine: 30±2; % maximum dilation). Inhalation of either fine or UF TiO_2 resulted in decreased flow-induced vasodilation in coronary arterioles compared to sham-control rats (Fig 1). There were no group differences in vasodilation to ACh (Fig 2). Smooth muscle sensitivity to NO was significantly decreased by exposure to UF TiO_2, but not fine TiO_2 (Fig 3). Coronary arterioles from rats exposed to UF TiO_2 exhibited a reduction in vasoconstriction to endothelin (Fig 4).

Conclusions

Among particulates and concentrations used herein, UF TiO_2 exposure impairs both vasodilation and vasoconstriction in coronary arterioles. Inhalation of fine and UF TiO_2 attenuated flow-induced vasodilation, but did not alter ACh responses. Although both flow- and ACh-induced dilations are

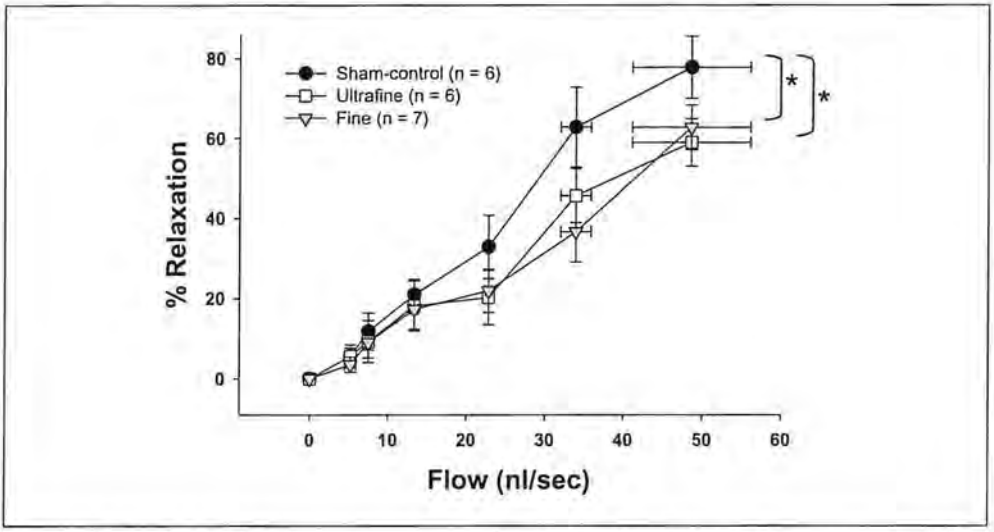

*Figure 1. UF and fine TiO_2 exposure attenuates flow-induced vasodilation in coronary arterioles. * $P \leq 0.05$ vs. sham-control.*

endothelium-dependent responses, PM exposure may target different intracellular mechanisms. Only UF TiO_2 exposure contributed to decreased smooth muscle NO sensitivity. This impairment in the ability to respond to NO could also contribute to the decrease in flow-induced vasodilation in coronary arterioles from rats exposed to UF TiO_2. UF TiO_2 exposure also reduces arteriolar

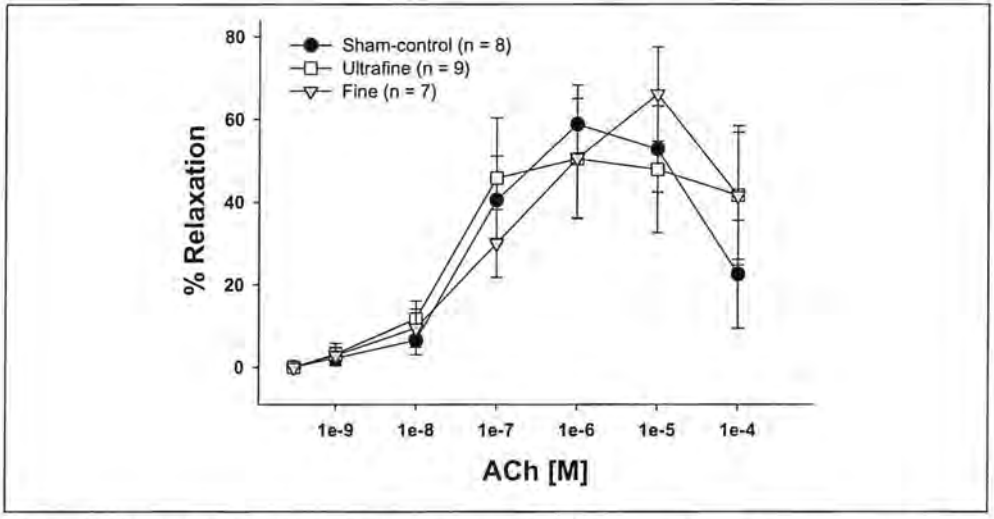

Figure 2. Neither UF nor fine TiO_2 exposure alters ACh responsiveness in coronary arterioles.

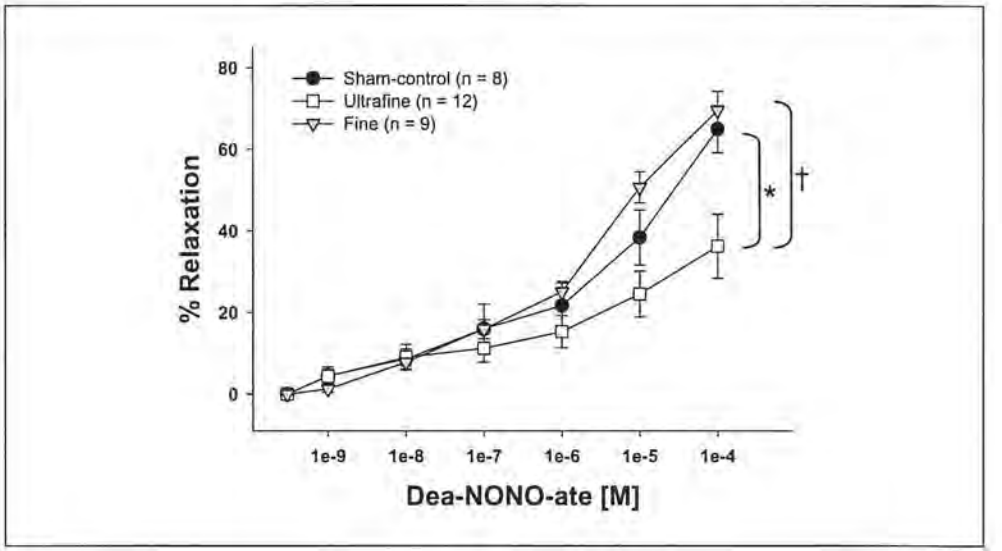

*Figure 3. UF TiO_2 exposure decreases coronary arteriolar responsiveness to the NO donor dea-NONOate. *≤ 0.05 vs. sham-control, † P≤0.05 vs. fine TiO_2.*

responsiveness to ET, a potent vasoconstrictor peptide important in regulating myocardial blood flow. Collectively, these findings suggest that UF PM exposure may play a greater role in coronary microvascular dysfunction than

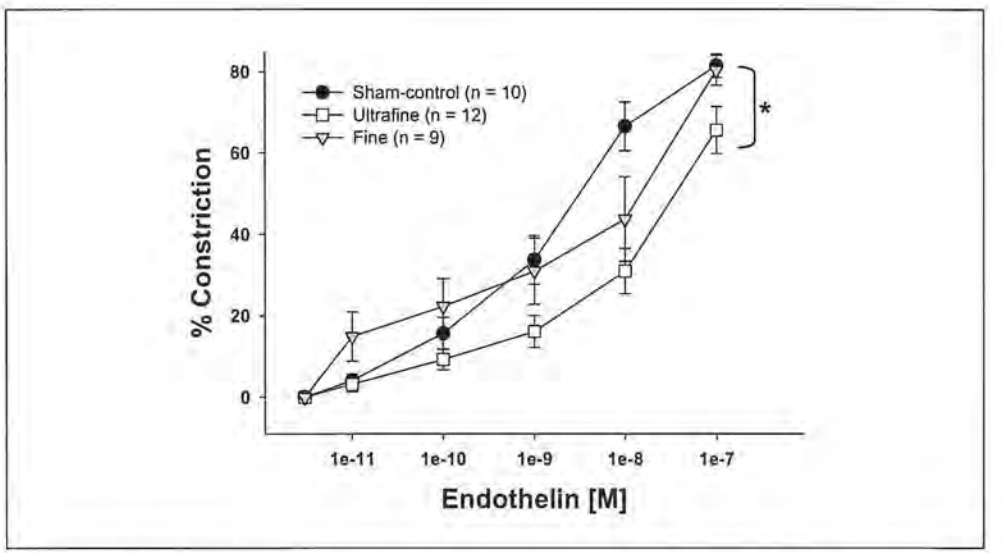

*Figure 4. UF TiO_2 exposure decreases coronary arteriolar responsiveness to ET. * P≤0.05 vs. sham-control.*

fine PM, and this dysfunction is consistent with cardiac events associated with exposure to particle pollution.

Support

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Disclaimers

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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