cular dysfunction than larger particles of the same composition. However, it remains unclear if coronary microvascular endothelial function is affected to a similar degree. Rats were exposed to filtered air (control) or TiO_2 nanoparticles (primary particle diameter, ~21 nm) via inhalation at concentrations relevant to ambient air pollution (9.5 μg measured pulmonary deposition). Coronary arterioles (~150 μm in diameter) were isolated from the left anterior descending artery distribution and responses to flow (FID) (5-25 μL/min), acetylcholine (ACh, 10^{-7} – 10^{-5} M), and the Ca^{2+} ionophore, A23187 (10^{-8} – 10^{-6} M), were assessed. Endothelium-dependent FID was preserved in coronary arterioles from rats exposed to nano-TiO_2 compared to control rats. Conversely, a profound vasoconstriction (16±14, % constriction) resulted from cumulative additions of ACh in arterioles from rats exposed to nanoparticles, whereas control rats responded by vasodilation (73±4, % dilation). Similarly, nanoparticle exposure impaired arteriolar dilation to A23187 as compared to control rats. Sodium nitroprusside (10^{-3} M) produced comparable arteriolar dilation in both groups, indicating that vascular smooth muscle NO responsiveness remains intact after nanoparticle exposure. These results suggest that nanoparticle exposure significantly impairs Ca^{2+}-dependent microvascular responses to ACh and A23187, whereas responsiveness to shear stress is preserved. It is probable that such disturbances in coronary microvascular function contribute to the cardiac events associated with particle pollution exposure.
Support: NIH RO1-ES015022 and HEI #4730 (TRN)

PL 1351 TIME COURSE OF SYSTEMIC EFFECTS FOLLOWING A SINGLE EXPOSURE TO CARBON NANOTUBES.

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Pulmonary exposure to carbon nanotubes (CNT), in a mouse model, causes aortic mitochondrial DNA damage and enhanced thrombogenicity, prerequisites of atherosclerosis. The link between endpoint systemic effects and pulmonary exposure is unknown. We hypothesized that blood cell gene expression and serum protein analysis will provide insight into the relationship between CNT-induced lung and cardiovascular effects. C57BL/6 mice were exposed to 40ug of multi-walled CNT (MWCNT) and sacrificed at 4hr, 24hr, 7d and 28d post single exposure. We evaluated serum proteins and blood cell gene expression of biomarkers related to potential cardiovascular effects. Furthermore, the CNT effects on lung and cardiovascular tissues were characterized by a coordinated gene expression analysis. At 4hr, a marked systemic inflammatory response was evidenced by increased inflammatory serum proteins (e.g. IL-6, CXCL1) and upregulated blood cell gene expression of inflammatory mediators. Cardiovascular tissue, including heart and aorta, showed a generalized stress and inflammatory response. In addition, the expression of specific endothelial related genes was elevated in the aorta (e.g. E-selectin). The systemic effects at 4hr were mostly a reflection of the ongoing lung response. At 24hr, inflammatory serum proteins and blood cell gene expression had returned to baseline and the systemic tissue response had diminished. In exchange, serum acute phase proteins (e.g. C-reactive protein, serum amyloid P) and accompanying liver gene expression were increased. Furthermore, at both 4 and 24hr increased serum levels of the prothrombotic protein plasminogen activator inhibitor-1 were found. The late blood response (7 and 28d) was characterized by increased serum osteopontin levels in conjunction with increased lung expression of genes coding for a macrophage related response (e.g. arginase I, galectin-3, osteopontin). In conclusion, our data suggests a link between MWCNT-induced pulmonary toxicity and potential systemic effects related to cardiovascular dysfunction through alterations in blood parameters.

PL 1352 NANOPARTICLE INHALATION INCREASES MICROVASCULAR OXIDATIVE STRESS AND COMPROMISES NITRIC OXIDE BIOAVAILABILITY.

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We have shown that pulmonary nanoparticle exposure impairs endothelium dependent dilation in systemic arterioles. However, the mechanism(s) through which this effect occurs are unclear. The purpose of this study was to identify alterations in the production of oxidative stress and endogenous nitric oxide (NO) after nanoparticle exposure, and determine the relative contribution of hemoproteins and oxidative enzymes in this process. Rats were exposed to TiO_2 nanoparticles via inhalation (primary particle diameter ~21 nm) at depositions of 4-90 μg/rat. The spinotrapezius muscle was prepared for intravital microscopy 24 hrs after exposures. Intraluminal infusion of the Ca^{2+} ionophore A23187 was used to evaluate endothelium-dependent arteriolar dilation. Endogenous microvascular NO production was measured with an electrochemical sensor. Oxidative stress in the microvascular wall was quantified via dihydroethidium fluorescence (O_2^- probe). Histological sections of pulmonary tissue revealed nanoparticle uptake by alveolar macrophages, and migration to nearby lymph tissue. TiO_2 nanoparticles quenched spontaneous NO signals generated in vitro by S-Nitroso-N-acetyl-D,L-penicillamine (550 mM). As in previous experiments, A23187 produced dose-dependent arteriolar dilations (10-69% of maximum response). Nanoparticle exposure robustly attenuated this to 6-16% of the maximum response. Nanoparticle exposure also increased microvascular oxidative stress by ~60%, and decreased NO production. Inhibition of either myeloperoxidase (4-aminobenzoic hydrazide, 10 μm) or NADPH oxidase (apocynin, 10^{-4} M) partially restored NO production and normal microvascular function. These results indicate that in conjunction with microvascular dysfunction, nanoparticle exposure also increases local oxidative stress and decreases NO bioavailability. Support: R01-ES015022 and HEI#4730 (TRN).

PL 1353 MECHANISTIC LINKS BETWEEN THE LUNG AND THE SYSTEMIC MICROCIRCULATION AFTER NANOPARTICLE EXPOSURE.

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Previous studies in our laboratory have shown that pulmonary nanoparticle exposure causes peripheral microvascular dysfunction. This dysfunction is characterized by impaired endothelium-dependent arteriolar dilation and venular leukocyte adhesion. The mechanisms that produce these effects remain poorly understood. The purpose of this study was to determine if neurological mechanisms and/or circulating leukocytes play a fundamental role between pulmonary exposure and peripheral microvascular dysfunction. Rats were exposed to TiO_2 nanoparticles via inhalation (primary particle diameter ~21 nm) at depositions of 4-90 μg/rat. Some rats received a bolus dose of cyclophosphamide (200 μg/g, i.p.) 3 days prior to nanoparticle exposure to deplete circulating neutrophils. The spinotrapezius muscle was prepared for intravital microscopy 24 hrs after exposures. Intraluminal infusion of the Ca^{2+} ionophore A23187 (10^{-7} M, pipette concentration) was used to evaluate endothelium-dependent arteriolar dilation. Histological sections of the spinotrapezius muscle and lung were prepared, and plasma was sampled from each rat for multiplex analyses. Following nanoparticle exposure, plasma IL-1, 2, 13 and ICAM-1 were altered. Consistent with previous experiments, nanoparticle exposure significantly limited arteriolar dilation (in response to A23187) to 0-7% of the normal maximum response. Co-incubation with the fast Na^+ channel antagonist tetrodotoxin (TTX, 10^{-6} M) restored dilation by as much as 54%. Neutrophil depletion similarly resored dilation by as much as 42%. These mechanistic data support prominent hypotheses that suggest peripheral vascular effects associated with particle exposure are due to neurogenic and/or inflammatory mechanisms.
Support: NIH RO1-ES015022 and HEI#4730 (TRN)

PL 1354 CARDIOVASCULAR EFFECTS OF ULTRAFINE PARTICULATE MATTER ON SPONTANEOUSLY HYPERTENSIVE RATS.

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Exposure to particulate air pollution has been associated with increased cardiovascular morbidity and mortality. A suggested mechanism for this association is the development of oxidative stress and inflammation with exposure to ambient particulate matter. Exposure to ultrafine particles may result in greater oxidative stress and inflammation than exposure to larger particles due to a larger surface area to mass ratio and greater ability to translocate to other areas of the body. Spontaneously hypertensive rats, an animal model of arterial hypertension, were implanted with telemetry devices to measure heart rate and blood pressure. The rats were exposed to concentrated ultrafine particles or filtered air for 5 hours per day, 4 days per week for 12 weeks in Riverside, CA. Rats exposed to ultrafine particles showed greater serum levels of the inflammatory cytokines IL-1β, IL-6, IL-12, TNF-α, and IFN-γ, the anti-inflammatory cytokine IL-10, monocyte chemoattractant protein-1, and eotaxin. Cell differential counts from bronchoalveolar lavage fluid showed higher levels of mononuclear cells and neutrophils in the ultrafine particle exposed rats. Analysis of telemetry data from exposed animals showed a depression in blood pressure during exposure periods compared to non-exposure periods. In addition, rats exposed to ultrafine particles showed a decrease in heart rate compared to the control animals. These results indicate a change in cardiovascular function with exposure to ultrafine particulate matter. Further analysis is needed to determine the mechanistic relationship between the increase in inflammatory biomarkers and change in cardiac parameters.

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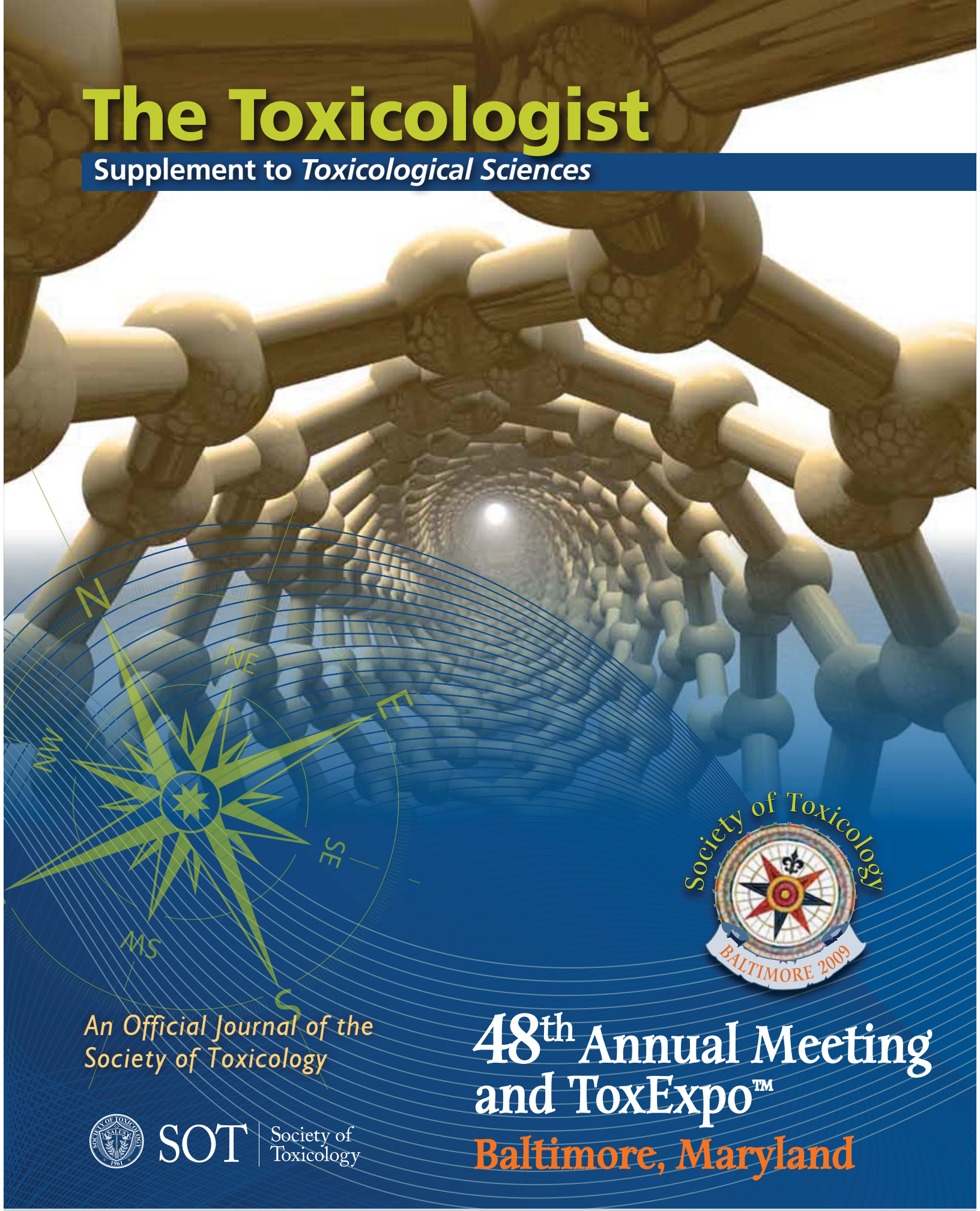

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