blocker, ruthenium red (2.5 mg/kg), not only inhibited substance P synthesis in nodose ganglia and the increased phosphorylation level in cardiac proteins, but also prevented the above cardiovascular changes induced by pulmonary exposure to UFTiO2. Our results suggest that the effects of pulmonary exposure to UFTiO2 on the cardiovascular system are most likely influenced by a lung-nodose ganglia-regulated pathway via the activation of TRP channels located on the endings of c fiber sensory neurons in the lung. Activation of this neuronal pathway may contribute to an increased incidence of cardiovascular diseases associated with pulmonary inhalation of small-sized particle components from ambient air.

PS 1496 CARDIOVASCULAR EFFECTS AFTER PULMONARY EXPOSURE TO WELDING FUME.

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Epidemiological studies have found positive associations between air pollution and adverse cardiovascular outcome. Whether exposure to welding fumes cause similar cardiovascular dysfunction remains unclear. The present study investigated the effects of manual metal arc-hard surfacing (MMA-HS) on the heart and the vascular system. Rats were intratracheally instilled with MMA-HS (2 mg/rat, once a week) or saline for seven weeks. On days 1 and 7 after the last treatment, rats were implanted with indwelling catheters and cardiovascular function in response to increasing levels of adrenoreceptor agonists was assessed. Pulmonary exposure to MMA-HS decreased the basal level of left ventricular pressure and the positive dp/dt of the heart at 1 day post-exposure. The negative dp/dt of the heart in response to isoproterenol decreased 7 days after exposure to MMA-HS. Exposure to MMA-HS slightly reduced blood pressure in response to norepinephrine at 1 day post-exposure, but this change was not statistically significant. In addition, pulmonary exposure to MMA-HS reduced the phosphorylation level of cardiac troponin I in the heart. This was consistent with the reduced heart muscle contractility indicated by decreases in left ventricular pressure, positive and negative dp/dt. These findings suggest that the heart may be more prone to developing dysfunction than the vascular system after exposure to welding fumes.

PS 1497 NI IN AMBIENT PM CAUSES MICROVASCULAR DYSFUNCTION VIA NO AND NADPH PATHWAYS.

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Exposure to PM2.5 (<2.5μm) has been associated with endothelial dysfunction in humans and animal models. We have shown that systemic inflammation and atherosclerosis in residents of two China cities, Jinchang (JC) and Zhangye (ZH), were linked to specific PM2.5 compositions. Despite similar PM2.5 concentrations, JC had levels of nickel, selenium, copper, and arsenic that were 76, 25, 17, and 7 fold higher than in ZH, respectively. The aim of this study was to use unique PM2.5 samples from these cities to identify the mechanism(s) that drive pulmonary and systemic effects. Male FVBN mice received a single or repeated oropharyngeal aspiration of water or aqueous suspension of PM2.5 from JC, ZH or ZH spiked with Ni (ZH+Ni) at the same concentrations found in the JC PM, followed by evaluation of pulmonary inflammation. Mesenteric arteries were isolated 24hr post exposure for gene activity or functional response ex vivo. To investigate Ni-induced changes in NO and NADPH pathways, functional response was also assessed using LNAME or Apocinin, respectively. Plasma cytokine and cardiovascular markers were measured using a Mesoscale Discovery multiplex assay. Lung lavage revealed significant pulmonary inflammation from the JC and ZH+Ni; $p<0.001$. No differences were seen in artery contractile function, however, there was significantly less artery relaxation in JC and ZH+Ni; $p<0.001$. Percent relaxation was also altered among groups after LNAME and Apocinin incubation. There was significantly higher gene expression in JC and ZH+Ni (TNF-α, IL-6, Nos2; $p<0.01$ for all; NOX4 $p<0.05$). Lastly, multiplex results showed significantly higher concentrations of VEGF and IL-10 in JC and ZH+Ni ($p<0.01$, $p< 0.001$; respectively). These data suggest that changes in vascular responses can be driven by nickel found in PM2.5. Both short and long-term exposures can induce an acute systemic inflammatory response, trigger endothelial damage via eNOS uncoupling and NADPH oxidase pathways, and result in vascular dysfunction.

PS 1498 TREADMILL STRESS TEST AFTER DIESEL EXHAUST PARTICULATE EXPOSURE REVEALS A TIME-DEPENDENT SHIFT FROM PARASYMPATHETIC TO SYMPATHETIC DOMINANCE.

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Epidemiological studies suggest that particulate matter (PM) air pollution is a major trigger of acute cardiac events—including arrhythmia—especially in those with preexisting cardiac disease. Diesel exhaust (DE) contributes the majority of urban fine and ultrafine PM, and is thus likely a key trigger of acute cardiac events. Research suggests that several interrelated mechanisms underlie the acute cardiotoxicity of PM, including autonomic nervous system imbalance. Abnormal heart rate (HR) and HR variability (HRV) responses to treadmill challenge are indicative of autonomic dysfunction and predictive of cardiovascular mortality. We hypothesized that a single intra-tracheal instillation (IT) of DE particles (DEP, 500 μg/kg) in hypertensive heart failure-prone rats would provoke abnormal HR and HRV responses to treadmill. Rats were monitored by radiotelemetry during treadmill challenge at 24-h pre-IT and 3- and 24-h post-IT. Relative to saline-instilled rats, DEP significantly decreased HR and low-to-high frequency ratio of HRV (LF/HF) while increasing time domain HRV parameters (SDNN & RMSSD) during treadmill deceleration and recovery at 3 h post-IT, suggesting parasympathetic dominance. Upon 24-h post-IT treadmill challenge, DEP significantly increased HR while decreasing SDNN and RMSSD during acceleration, indicating sympathetic dominance relative to saline. During treadmill challenge, DEP did not affect arrhythmia counts, peak HR, or HR recovery. The treadmill stress test is useful in unmasking the latent cardiovascular effects of air pollutant exposure, which in this study included autonomic imbalance characterized by early parasympathetic dominance followed one day later by an excess in sympathetic tone. Collectively, these effects indicate increased risk for adverse cardiovascular events. (Abstract does not reflect EPA policy; Supported by UNC/EPA CR83323601.)

PS 1499 CHRONIC EXPOSURE TO DIESEL EXHAUST PARTICULATE INDUCES VENTRICULAR REMODELING AND DYSFUNCTION.

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In the United States, approximately 60,000 deaths annually are attributed to particulate matter (PM). Chronic PM exposure increases the risk of cardiovascular disease in urban residents, predisposing them to the development of diseases including heart failure. Diesel exhaust particulates (DEP) accounts for 90% of outdoor air pollution. DEP is a heterogeneous mixture composed of inorganic compounds and polyaromatic hydrocarbons (PAH). Chronic PAH exposure is associated with ventricular dilation and wall thinning. Although the mechanisms are unknown, we hypothesized that chronic exposure to DEP induces ventricular remodeling and dysfunction. Male Sprague-Dawley rats were exposed to nose-only nebulization of DEP (SRM 2975, 0.23 mg/mL) or vehicle for 20 min/day x 5 weeks. Echocardiographic measures of left ventricular (LV) end diastolic diameter and posterior wall diameter taken at baseline and weekly thereafter-demonstrated DEP induced chamber dilation and posterior wall thinning compared to vehicle. After 5 weeks, LV function using pressure volume catheter indicated systolic dysfunction in these DEP animals. Morphological analysis using Picrosirius Red staining of LV collagen revealed that DEP reduced cardiac interstitial collagen. AhR activation has been linked to impaired extracellular collagen remodeling through suppression of the hypoxic inducible factor (HIF)-1α pathway. Our studies showed DEP exposure was associated with reduced expression of cardiac HIF-1α. Furthermore, these animals had reduced cardiac expression of VEGF and TGF-β; both mediated by HIF-1α activation and stimulate collagen production. Attenuation of either VEGF or TGF-β signaling is associated with chamber dilation, contractile dysfunction, and impaired cardiac growth. Moreover, DEP animals exhibited greater cardiac AhR / HIF-1α expression suggesting that blockade of these signaling molecules may be due to the activation of the AhR pathway in the heart. Furthermore, activation of the AhR in the heart may play a significant role in ventricular remodeling and dysfunction through the impairment of collagen turnover.

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