PS 1129 Diesel Exhaust-Induced Cardiac Dysfunction Is Mediated by Sympathetic Dominance in Heart Failure-Prone Rats.

A. P. Carll[1, 2], M. S. Hazari[2], C. M. Perez[3, 2], Q. Krantz[2], C. King[2], D. W. Winsett[2], D. L. Costa[4] and A. K. Farraj[2]. *[1]Gillings School of Global Public Health, University of North CarolinaChapel Hill, Chapel Hill, NC; [2]Environmental Public Health Division, US EPA, Research Triangle Park, NC; [3]Curriculum in Toxicology, University of North Carolina Chapel Hill, Chapel Hill, NC; [4]ORD, US EPA, Research Triangle Park, NC.*

Short-term exposure to vehicular emissions is associated with adverse cardiac events. Diesel exhaust (DE) may provoke cardiac events through defective co-ordination of the two main autonomic nervous system (ANS) branches. We exposed heart failure-prone rats once to DE (500 μg/m^3 $PM_{2.5}$, 4 h, whole-body inhalation) and tested for ANS-mediation of cardiotoxicity by several interventions, including post-DE sympathetic agonism (dobutamine) before and after parasympathetic ablation (vagotomy) and, separately, sympathetic or parasympathetic inhibition (atenolol or atropine) during–and treadmill exercise after–DE exposure. Left ventricular pressure (LVP), heart rate (HR), HR variability (HRV), and blood pressure (BP) were measured to determine cardiac function and autonomic balance. During exposure hour 2, DE markedly increased HR, BP and contractility in saline-pretreated rats, and atenolol entirely inhibited these effects, indicating DE caused mid-exposure sympathetic excitation. DE increased body temperature regardless of pretreatment. Upon exercise recovery at 4 h post-exposure, HRV and HR indicated that DE increased parasympathetic influence. Conversely, during exercise recovery at 21 h post-exposure, DE increased sympathetic influence in saline-pretreated rats, while it impaired contractility and decreased systolic BP in saline- and atropine-pretreated rats. Atenolol inhibited all of these effects. LVP at 1 d post-DE indicated systolic and diastolic dysfunction and changes in diastolic and chronotropic responses to dobutamine mediated partly through sympathetic dominance. Thus, DE-induced autonomic dysregulation of the heart involves time-dependent oscillations between sympathetic and parasympathetic dominance, with the former mediating DE's cardiotoxic effects. *(Does not reflect EPA policy. Funded by EPA/UNC CR-83515201-0)*

PS 1130 Remote Subcutaneous and Intravenous Administration in Large Animals: Impact on Cardiovascular Safety Pharmacology Data and Sensitivity.

R. Mikaelian[1], S. Authier[1, 2], A. Ascah[1], M. Pouliot[1], E. Troncy[2] and R. Forster[1]. *[1]CIToxLAB North America, Laval, QC, Canada; [2]Faculty of Veterinary Medicine, University of Montréal, St-Hyacinthe, QC, Canada.*

The regulatory guideline S7A supports the use of unrestrained models for safety pharmacology assays. Parenteral bolus administrations including the intravenous (IV) and subcutaneous (SC) routes are associated with CMax achieved immediately or within minutes of dosing for some compounds. In this context, animal handling can constitute a major interference to data quality and can obscure pharmacodynamic responses. The current investigation compared cardiovascular changes after remote SC and IV delivery in telemetered cynomolgus monkeys and Beagle dogs with restrained administration in the same species. Remote parenteral administrations were associated with a substantial decrease in data variance and consequently improved minimum detectable differences. Mean heart rate variations from baseline in the first 30 min after restrained IV saline dosing reached a maximum of 27% compared to 9.7% for remote administration. Baseline systolic arterial pressure following remote SC saline dosing in cynomolgus monkeys ranged from 93.7 and 116.4 mmHg while post-dose values in the initial 60 min post-dose ranged from 94.0 and 116.3 mmHg. Recovery of cardiovascular parameters to baseline levels after animal handling was 25 to 120 minutes in both species which can constitute a major confounder to evaluation of short half-life drug candidates. Remote dosing presented optimal results when the animals remained completely undisturbed (i.e. no staff present in the animal room). Remote IV dosing is generally recognized to improve telemetry data quality but the current investigation also demonstrate beneficial effects of remote SC injections on sensitivity of cardiovascular investigations in safety pharmacology studies using telemetry in cynomolgus monkeys and Beagle dogs.

PS 1131 Acute Silver Nanoparticle Exposure Increases Cardiac Ischemic/Reperfusion Injury in Sprague-Dawley Rats.

C. J. Wingard[1], R. Urankar[1], J. Shananhann[2], A. K. Vidanapathirana[1], L. C. Thompson[1], S. Sumner[3], T. Fennell[3], J. M. Brown[2] and R. M. Lust[1]. *[1]Physiology, East Carolina University, Greenville, NC; [2]Pharmacology & Toxicology, East Carolina University, Greenville, NC; [3]RTI International, Research Triangle Park, NC.*

The expanding use and production of silver nanoparticles (AgNP) as anti-bacterial/fungal agents is raising concerns regarding their safety to human health. The diversity of nanosized silvers (AgNP) and coatings for dispersion may produce combinations that minimize potential toxic effects on the cardiovascular system. We hypothesized that acute intratracheal (IT) exposure to 20 nm (S; small) or 110 nm (L; Large) AgNP coated with either polyvinylpyrorrolidone (P) or citrate (C) would increase the susceptibility of cardiac tissue to a regional ischemic reperfusion (I/R) injury. Young male Sprague Dawley rats were exposed to 200 μg of AgNP. 24 hrs post-exposure, cardiac ischemia was induced for 20 mins followed by 2 hrs of reperfusion in situ. Hearts were sectioned stained with Evans blue to demarcate Area at Risk (AAR) and counter stained with TTC to determine % of AAR infarcted. Bronchoalveolar lavage fluid (BALF) and serum was collected post I/R injury to evaluate pulmonary injury and circulating markers of injury. Neither P (22 ± 2% Infarct/AAR) nor C (24 ± 1% Infarct/AAR) altered the extent of infarcted cardiac tissue as compared to naive (22 ± 2% Infarct/AAR). However, the installation of all forms of AgNP significantly increased the extent of cardiac I/R injury. As a group the P-coated AgNP developed larger infarcts than C-coated. The 20 nm were more effective at enhancing I/R Injury (SP 43 ± 2.0 % Infarct/AAR, SC 37 ± 3 % Infarct/AAR) than the 110 nm size (LP 37 ± 3 % Infarct/AAR, LC 31± 2 % Infarct/AAR). The opposite pattern was observed in the BALF endpoints with P and L AgNP having greater effects. Our results suggest IT exposure to AgNP have differential effects on pulmonary and cardiac tissues following the application of I/R injury. This work is supported by NIEHS U19 ES019525.

PS 1132 Effect of Pulmonary Exposure to Welding Fumes on Cardiomyocyte Contractility.

H. Kan[1], J. M. Antonini[1], M. Ye[1], W. Zheng[1], R. Salmen[1], R. Popstojanov[2] and V. Castranova[1]. *[1]PPRB, NIOSH, Morgantown, WV; [2]West Virginia University, Morgantown, WV.*

Studies have found that pulmonary exposure to welding fumes is positively associated with a higher incidence of cardiovascular events. We reported previously that pulmonary exposure to welding fumes, manual metal arc-hard surfacing (MMA-HS), has a negative impact on cardiac function as evidenced by reduced heart contractility. However, the mechanisms underlying MMA-HS-induced depression of cardiac contractility remain unclear. To study the mechanisms, rats were given an intratracheal instillation of MMA-HS welding fumes (2 mg/rat) or saline once a week for seven weeks. Cardiomyocytes were isolated at 1 and 7 days post-exposure. Cardiomyocyte contractility and intracellular calcium level in response to increasing concentrations of adrenoreceptor agonist isoprenaline and extracellular calcium were assessed using a Myocyte Calcium Imaging/Cell Length System. Pulmonary exposure to MMA-HS blunted contractile function in response to both isoprenaline and calcium at 1 day post-exposure ($P < 0.01$; $P < 0.05$, respectively). A blunted contractile response was also observed with welding fume treated rats at 7 days post-exposure in response to isoprenaline and calcium ($P < 0.01$). Intracellular calcium level in response to extracellular calcium stimulation was reduced at 7 days post-exposure ($P < 0.05$). These findings suggest that pulmonary exposure to welding fumes impairs cardiac function by decreasing cardiomyocyte contractility through a defect in the adrenergic signaling pathway and intracellular calcium handling.

PS 1133 Silver Nanoparticle Exposure Increases Vasoconstrictor Response in Nonpregnant Female Sprague-Dawley Rats.

J. O. Dawkins[1], A. K. Vidanapathirana[1], L. C. Thompson[1], S. J. Sumner[3], T. Fennell[3], J. M. Brown[2] and C. J. Wingard[1]. *[1]Physiology, East Carolina University, Greenville, NC; [2]Pharmacology & Toxicology, East Carolina University, Greenville, NC; [3]RTI International, Research Triangle Park, NC.*

The use and production of silver nanoparticles (AgNP) is growing rapidly raising concerns regarding their safety to human health, particularly following translocation to the circulatory system. Previous findings from our lab have shown intravenous (IV) exposure to AgNP changes the vasoconstrictor response in both pregnant and male Sprague Dawley (SD) rats. We hypothesized, acute IV exposure to AgNP in non-pregnant females will increase vascular reactivity of arterial vessels

The Toxicologist

Supplement to *Toxicological Sciences*

52nd Annual Meeting and ToxExpo™

March 10–14, 2013 • San Antonio, Texas

An Official Journal of the Society of Toxicology

SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science of Toxicology

www.toxicology.org

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 132, Issue 1
March 2013

www.toxsci.oxfordjournals.org