

Microvascular Outcomes of Engineered Nanomaterial Inhalation

Phoebe A. Stapleton
West Virginia University
July 8, 2015

Overview

- How does something we inhale affect the cardiovascular system?
- Vascular Physiology and Common Methodologies
- Mechanistic Theories
- Unique Circulations and Special Populations

Epidemiological Studies

Air Pollution

- Epidemiologic evidence of cardiovascular effects of particulate air pollution. ¹
 - Increased incidence of myocardial infarction within 24 hours of inhaled particulate pollution. ²
- Overall, exposure to fine and ultrafine particulate air pollution has adverse effects on cardiopulmonary health. ^{3,4}

¹. Dockery, EHP, 2001

². Peters, Circulation, 2001

³. Pope, Circ Research, 2015

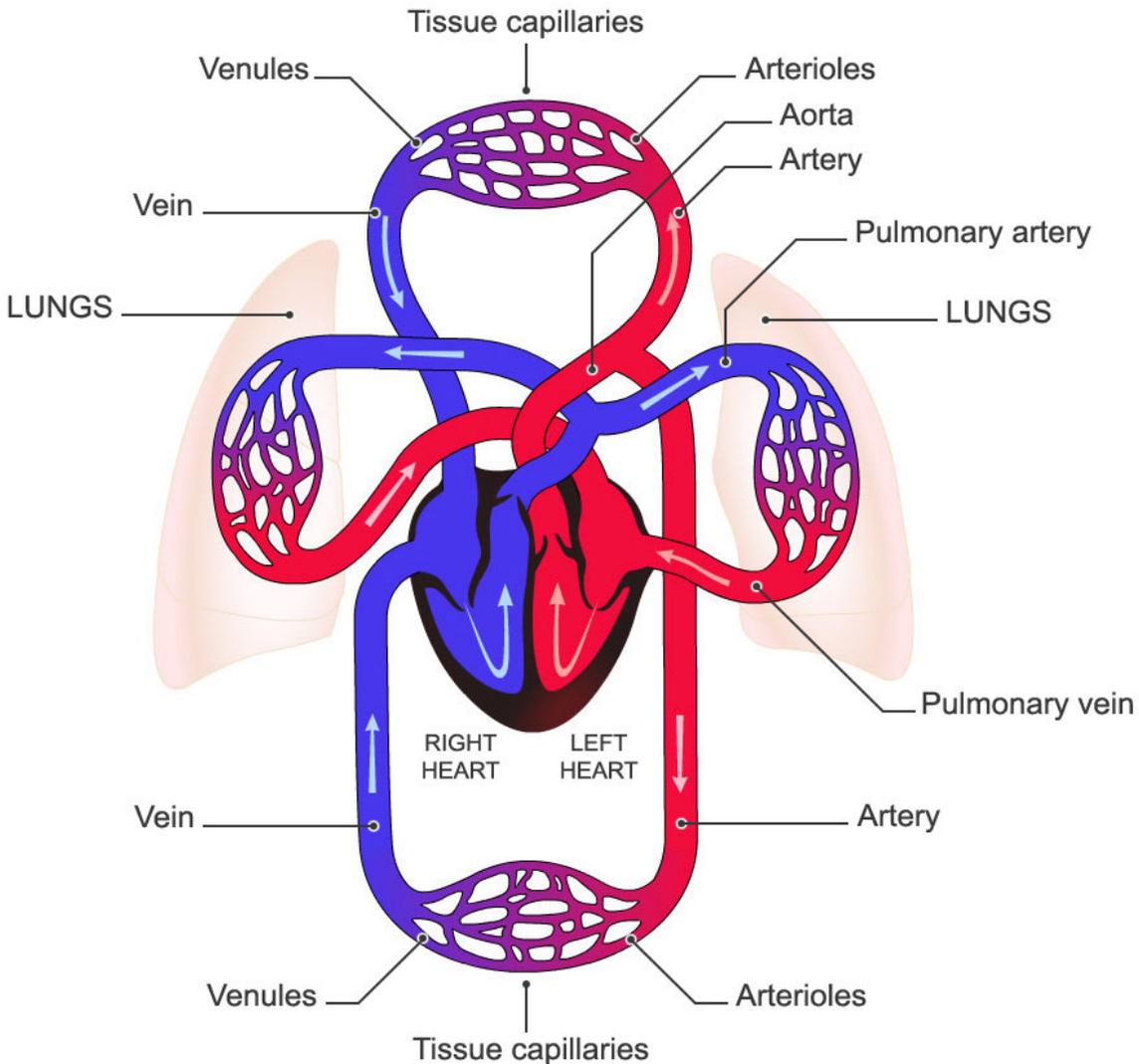
⁴. Van Eeden, J Toxicol. Environ. Health A, 2002

Nanomaterial

- Homogeneous composite of low-solubility and low-toxicity surrogate material.
 - However, previously identified as “ultrafine” size, studies demonstrated higher inflammatory, reactive stress, and toxicity potential than larger counterparts. ¹

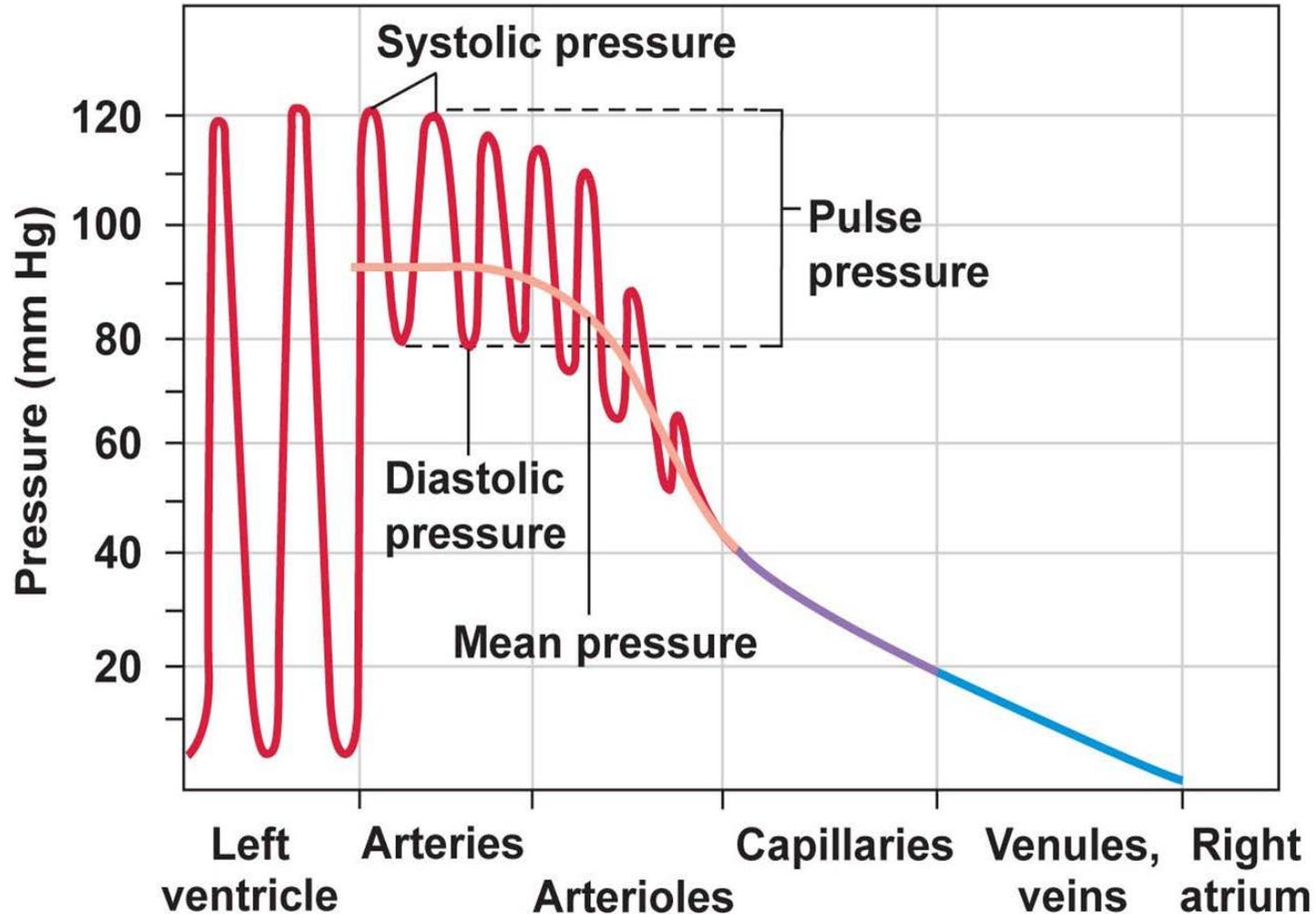
¹. Stone, IEEE Trans Nanobioscience, 2007

Vascular Anatomy



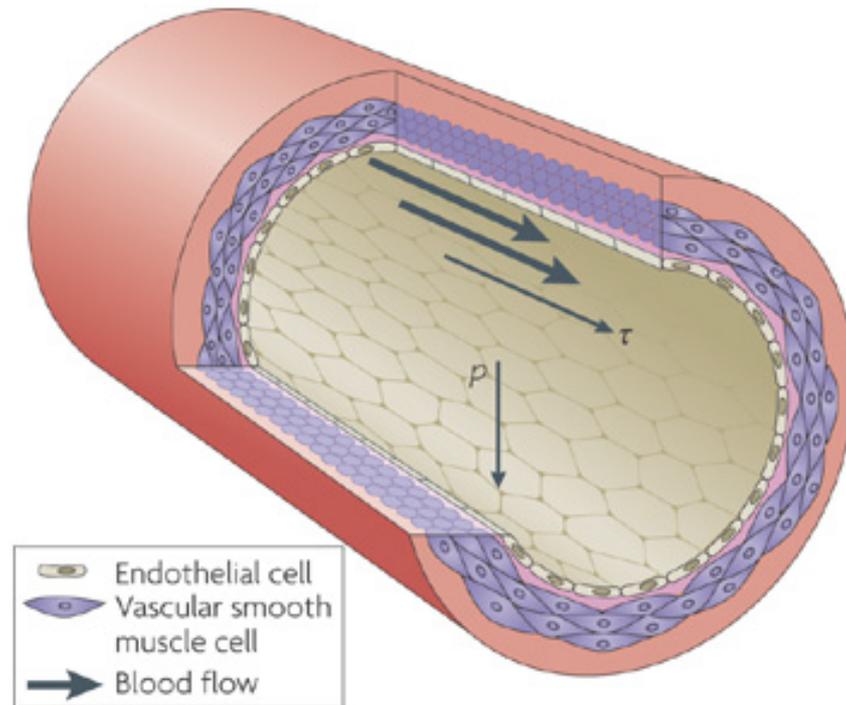
- Heart
 - Variability
 - Arrhythmias
- Macrocirculation
 - Aorta
 - Large Arteries
- Microcirculation
 - Peripheral Resistance
 - Tissue of Interest

Vascular Physiology



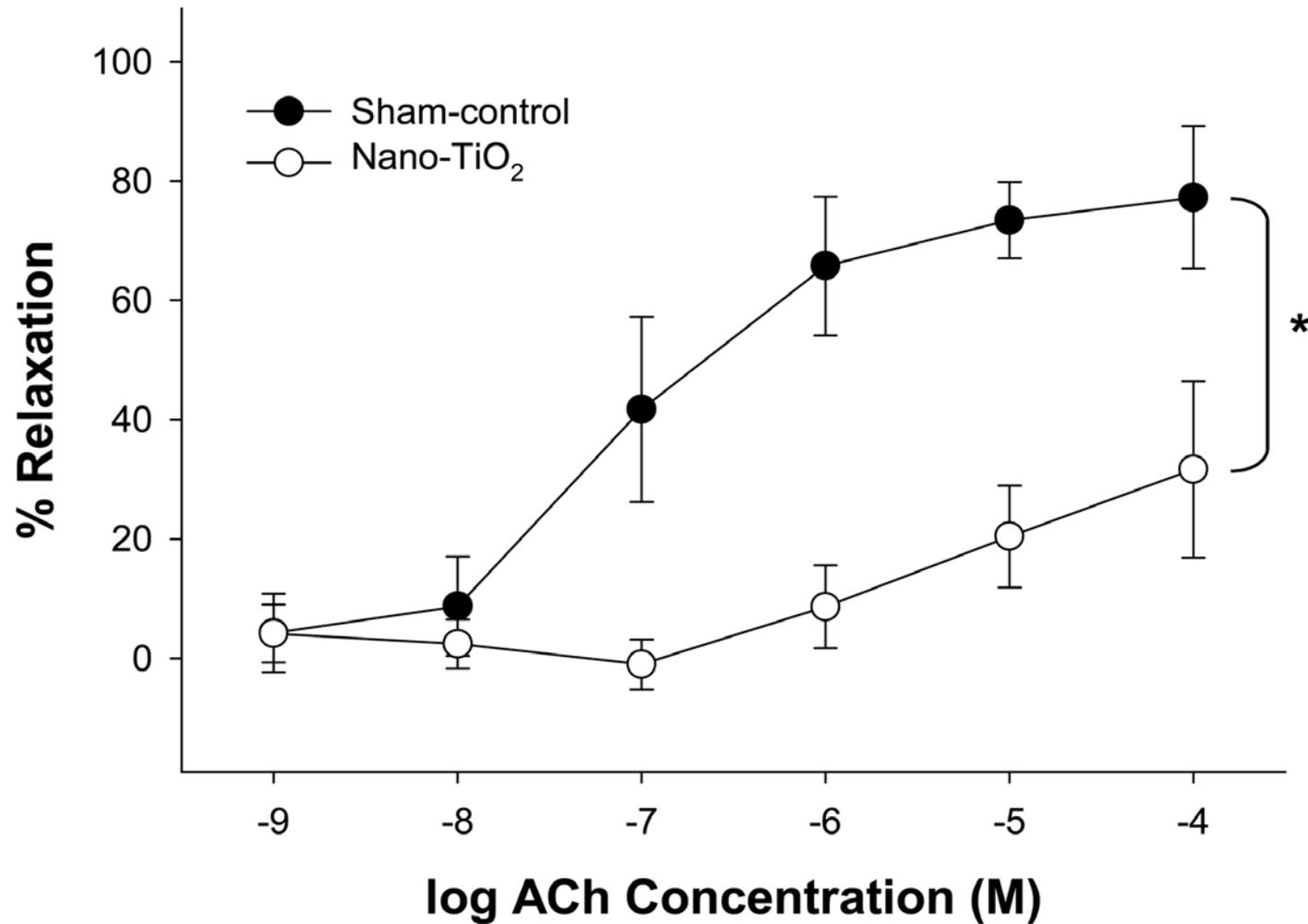
Copyright © 2009 Pearson Education, Inc.

Vascular Endothelium

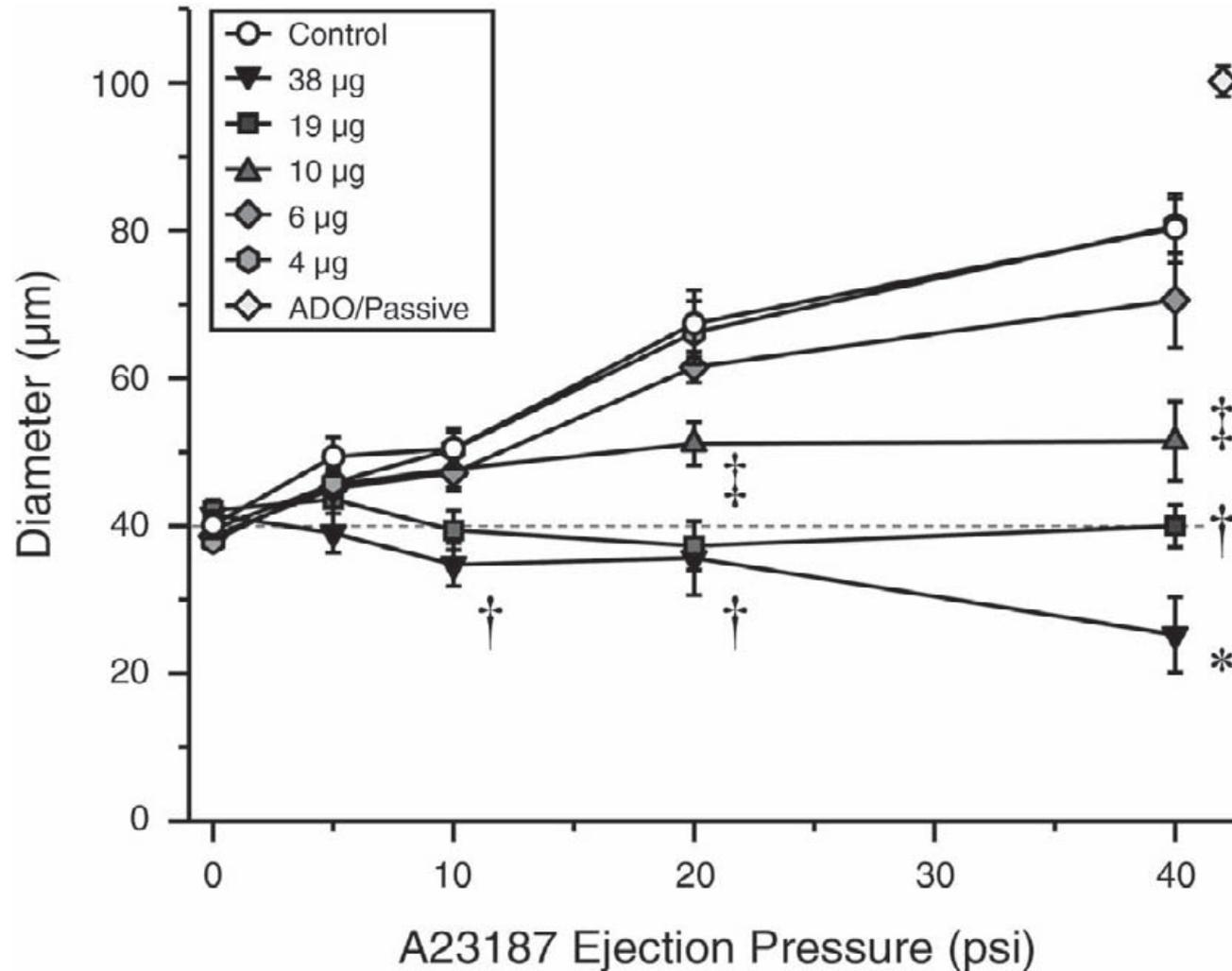


Nature Reviews | Molecular Cell Biology

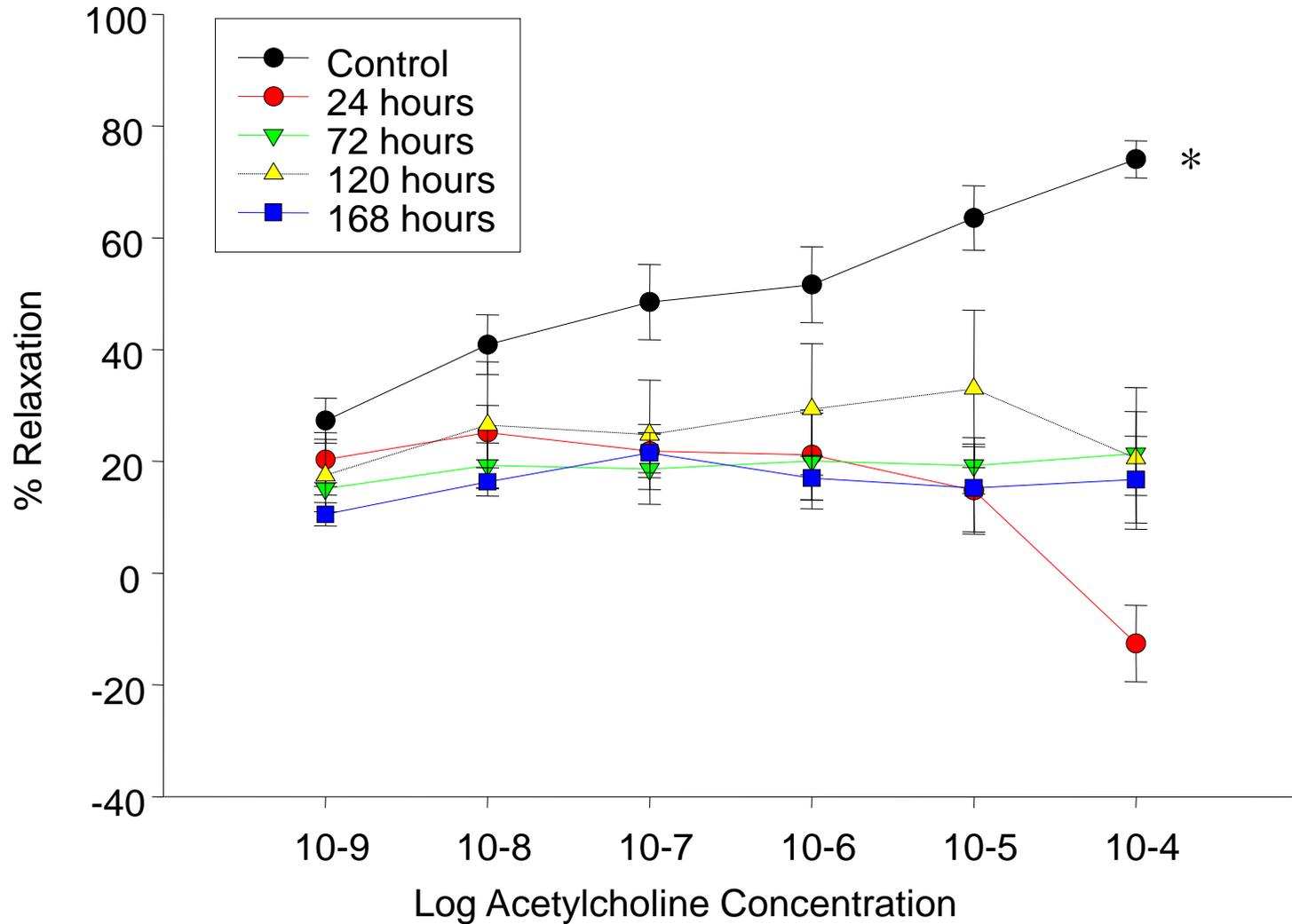
Microvasculature Dysfunction of the Heart



Dose-Dependent Response

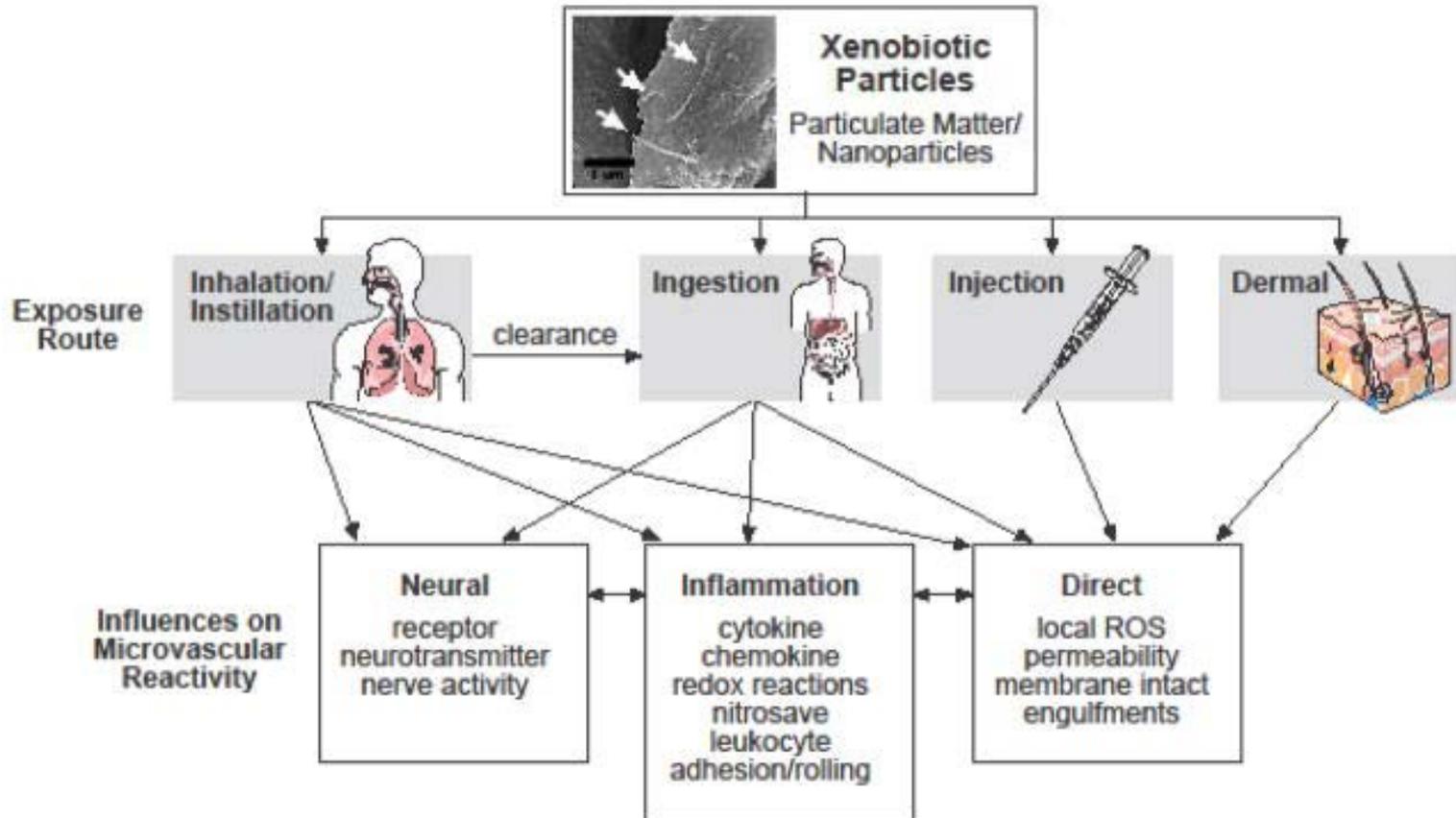


Time Course



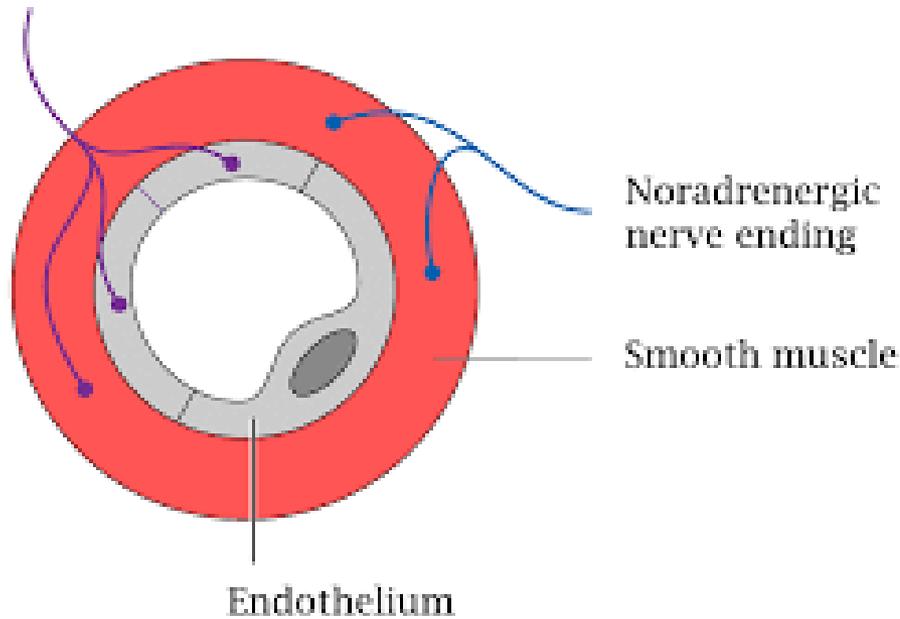
* p < 0.05 vs. All Exposures

How does something you inhale cause cardiovascular issues?



Autonomic Control and Neurological Alterations

Cholinergic nerve ending

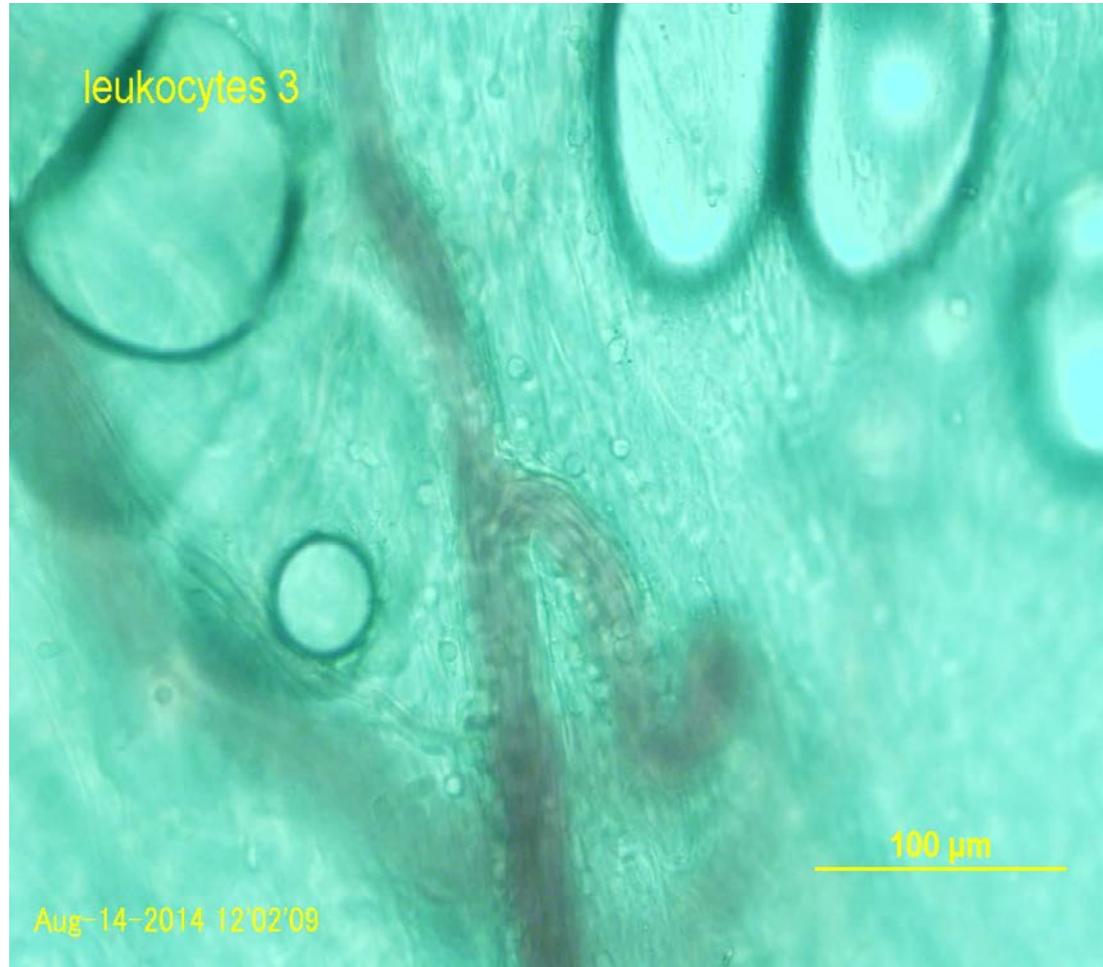


- Augmented Sympathetic Control. ^{1, 2}
- Altered Neurotransmitter Release. ^{2, 3}
- Tissue Specific Receptor Populations

¹. Mann, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol., 2012;

². Stapleton et al., Microcirculation, 2012; ³. Knuckles, Nanotoxicology, 2012

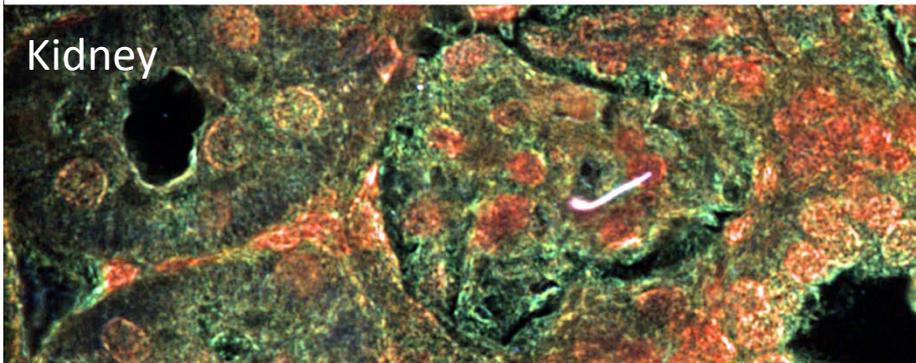
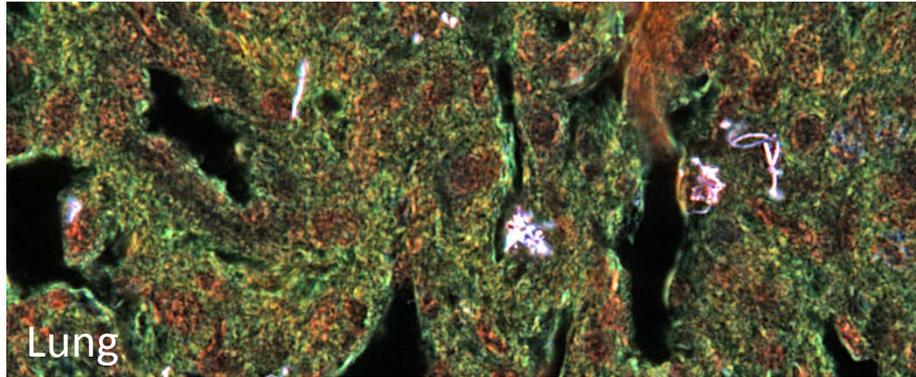
Inflammation



- Systemic signaling cascade following exposure.^{1, 2}
 - Increase in circulating cyto- and chemokines
- Increased leukocyte activity.^{1, 3}
- Local mediators leading to a reduction in metabolite bioavailability.^{3, 4}

Direct Particle Interaction

MWCNT Translocation



Systemic Distribution of Inhaled Multi-Walled Carbon Nanotubes

Organ	# of MWCNT Fibers	% Lung Burden
Lung	646.8×10^6	99.99890
Kidney	1533 ± 530	0.00024
Liver	4535 ± 1100	0.00070
Heart	525 ± 1260	0.00008

Direct Particle Interaction

- Evidence to suggest interactions and/or translocation: brain, liver, spleen, kidney, and heart. ^{1, 2}
- Direct particle-tissue interaction (inflammation, reactive species). ^{2, 3}
- Are they getting back out? (excretion) ⁴

1. Oberdorster, J Toxicol. Environ. Health A., 2002; ². Stapleton, IJMS, 2012 ;

³. Stapleton, Wiley Interdiscip Rev Nanomed Nanobiotechnol, 2014; ⁴. Choi, Nat Biotechnol, 2007

Models of Exposure

All of our past research using young, healthy, male models of occupational exposure, differing cardiovascular assessments indicate cardiovascular dysfunction.



Livestrong.com

2010 Census:

- Male (15-30): 10.7% American Population
- Median Age: 37.2 years

Additional Applications:

- Domestic Applications
- Theranostics

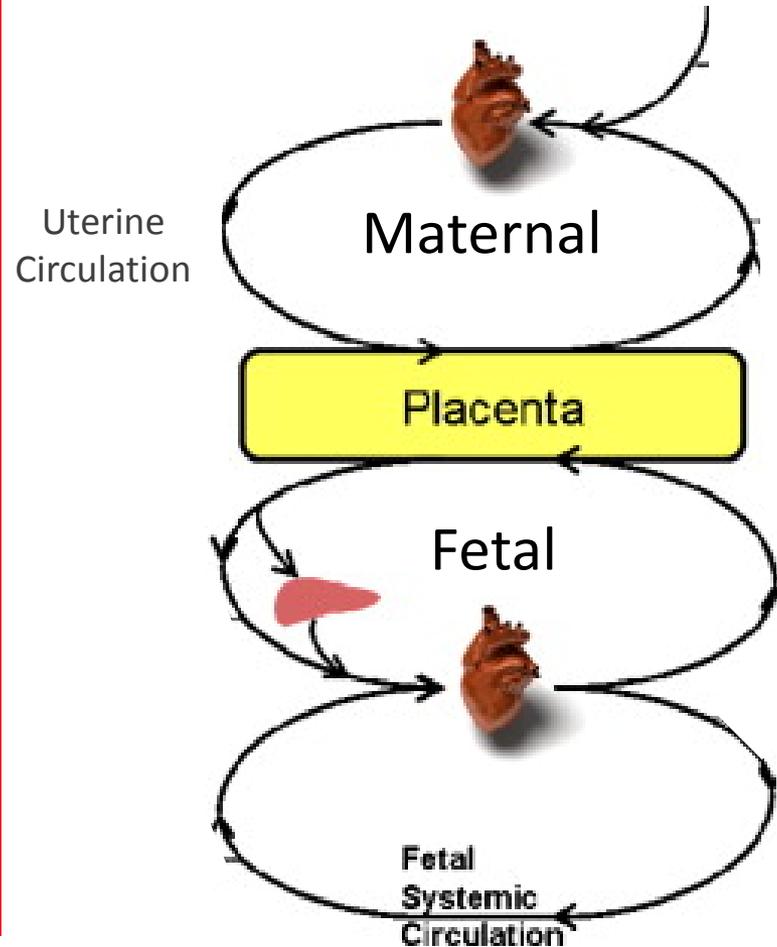
Models of Exposure

- With respect to health, these models represent the best of the best society has to offer. What about other populations?



Unique Circulations

“Pregnancy Therapeutic Window”



Gestational Exposure

- Maternal coronary, uterine, and umbilical reactivity impairments.^{1,2}
- Development of a hostile gestational environment.¹
- Fetal arteriolar dysfunction.¹
- Dysfunction is maintained in the heart and uterus of the F1 generation.³
- Behavioral/memory deficits within the F1 generation.^{4,5}



¹. Stapleton, Am. J. Obstet. Gynecol., 2013; ². Vidanapathirana, Reprod. Toxicol., 2014; ³. Stapleton, Nanotoxicology., 2014 [Epub]; ⁴. Hougaard, Part Fibre Toxicol., 2010; ⁵. Engler-Chiurazzi, Neurotoxicology and Teratology, (in review)

Applicability/Special Populations

- Nanomaterial Fate
- Numerous studies have shown the propensity for vascular impairments in susceptible populations.
- As the uses for ENM increase, as will potential for exposure of varying populations.

Consider:

- Female Subjects
- Pregnancy
- Children
- Elderly
- Diabetic Patients
- Obese
- COPD
- Sickle-Cell Disease



National Science Foundation
WHERE DISCOVERIES BEGIN



Support: NIH-K99-ES024783 (PAS), NIH-RO1-ES015022 (TRN), NSF-1003907 (TRN),
DGE-1144676 (VCM, TRN)