The Mechanisms of Air Pollution Mediated Cardiovascular Disease

Sanjay Rajagopalan
Case Cardiovascular Research Institute
Case Western Reserve University
University Hospitals, Harrington Heart and Vascular Institute
Cleveland OH

Disclosures: Grant Support from the National Institutes of Health
The Footprint of Pollution in the Anthropocene Era

Air Pollution Major Determinant of Climate Change

Air Pollution
- Particulate matter
- Ozone
- Volatile Organics
  - CO, SO\textsubscript{x}, NO\textsubscript{x}

Toxic Metals
- Lead (Pb)
- Arsenic (As)
- Mercury (Hg)
- Nickel (Ni)

Cardiovascular Disease

9.1 Million Deaths* (>50% from CVD)

Climate Change
- Temperature extremes
- Wildfires
- Increased PM\textsubscript{2.5} and O\textsubscript{3}

Manufactured Chemicals
- BPA
- Styrene
- PCBs
- Phthalates

Air Pollution: Major Determinant of Climate Change

Air Pollution Pathways Mediating Cardiovascular Risk

Obesity
Chronic Inflammation
Hypertension
Diabetes
Atherosclerosis
Cardiometabolic Disease

Reduced flow mediated dilation
Oxidized LDL
Endothelial injury
Foam cell
Macrophage retention
VCAM
TLR4
CD36
ROS
Platelet activation
Monocyte recruitment
Ly6Chi
CCR2
CNS
Air pollution
Neural reflex arc
Oxidative stress
Inflammation
Epigenomic Changes
Tissue Inflammation
Autonomic Imbalance
Immune System Activation
Plaque Instability
Endothelial Damage
Ion-Channel Activation
HPA Axis Activation
Inflammation
Oxidative Stress
Thrombosis
Vascular Dysfunction

END-ORGAN EFFECTOR MECHANISMS
TRANSMISSION PATHWAYS
INITIATING PATHWAYS

Levels in the US are mostly below NAAQS Annual Level of 12 $\mu$g/m$^3$

No lower threshold dose response

Chronic PM Exposure Potentiates Atherosclerosis and Vascular Inflammation

% Plaque area

* p<0.001 vs. FA-HFC
† p< 0.01 vs. FA groups

% Macrophage (CD 68)

* p<0.001 vs. FA-HFC
† p< 0.01 vs. FA-NC groups

% FA-NC PM-NC FA-HFC PM-HFC

* p<0.001 vs. FA-HFC
† p< 0.01 vs. FA groups

Sun et al. JAMA 2006.; 294

Tissue activities on $^{18}$F-FDG-PET/CT by PM$_{2.5}$ exposure. Tissue FDG increased with PM2.5 exposure and major adverse cardiovascular event.

Central Sympathetic Activation with PM$_{2.5}$ 12 Week Exposure (C57/Bl6)

C57Bl/6 (n=10-12/group) (5 days/wk, 6 hours/d) Cannulated with indwellling catheters prior to exposure.

---

Environ Health Perspect. 2014 Jan;122(1):79-86
Links Between Hypertension and Air Pollution: Summary of Evidence

- BP positively related to PM2.5 exposure ($\uparrow$ of 1.4 mmHg, 95% CI (0.87-1.91) and 0.89 mmHg, 95% CI (0.49-1.29) per 10 mcg/m3 increase for SBP and DBP respectively (1)).

- Both ultrafine and course particles mediate blood pressure increase acutely (2, 3, 4, 5)

- Evidence suggests a slower effect (hours to days) with ambient air pollution compared to controlled chamber studies

Chronic PM$_{2.5}$ Ambient Exposures (20 wk) Potentiates Inflammation/Insulin Resistance

In 2019, 20% of the Global Burden of Type 2 Diabetes is Attributable to PM$_{2.5}$ Exposure
SWI/SNF chromatin-regulatory complexes are ATP dependent complexes that are critical in determining genome wide transcriptional access. Mutations in subunits of the SWI/SNF complex are present in 25% of all cancers.
Healthy Clock

Disrupted Clock

Light Environmental Triggers?
PM$_{2.5}$ Induces Insulin Resistance and Causes Circadian Disruption Similar to Light at Night Exposure
PM$_{2.5}$ Disrupts Metabolism and Circadian Function

A. Energy expenditure

B. Respiratory Quotient

C. $\text{VO}_2$ Consumption

D. $\text{VCO}_2$ Production

E. Bmal1 mRNA

F. Clock mRNA

G. Per1 mRNA

H. Per2 mRNA

I. Cry1 mRNA

J. Cry2 mRNA

Conclusions

• PM$_{2.5}$ is the leading environmental cause of death and disability and the 4$^{th}$ leading cause of global mortality

• Atherosclerotic cardiovascular disease (ASCVD) dominates the mode of death due to PM$_{2.5}$.

• Compelling epidemiologic and mechanistic data implicates PM$_{2.5}$ in ASCVD initiation, progression and complications

• Coarse, fine and ultrafine PM$_{2.5}$ potentiates blood pressure through alterations in vascular autonomic tone. These changes occur acutely in response to exposure.

• PM$_{2.5}$ exposure induces hyperinsulinemia, adipose inflammation and altered metabolism (including impaired O2 consumption and energy expenditure)

• Air Pollution may induce circadian disruption akin to light at night exposure.