PM Health Effects: Biological Plausibility and Mechanisms

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Office of Research and Development

PM Center Directors' Meeting

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State of the Science in 1998

- **More than 30 epidemiology studies from around the world report associations between ambient PM and cardiac mortality and morbidity.**

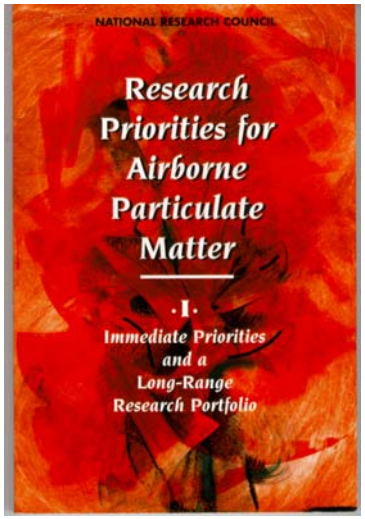
- **PM levels are very low compared with other particle exposures.**

  One cigarette = 10x more than a typical 24 hr exposure to PM

- **No widely accepted pathophysiological process or mechanism that could explain how a person could die following an acute exposure to such low levels of air pollution particles.**

The First NRC Report

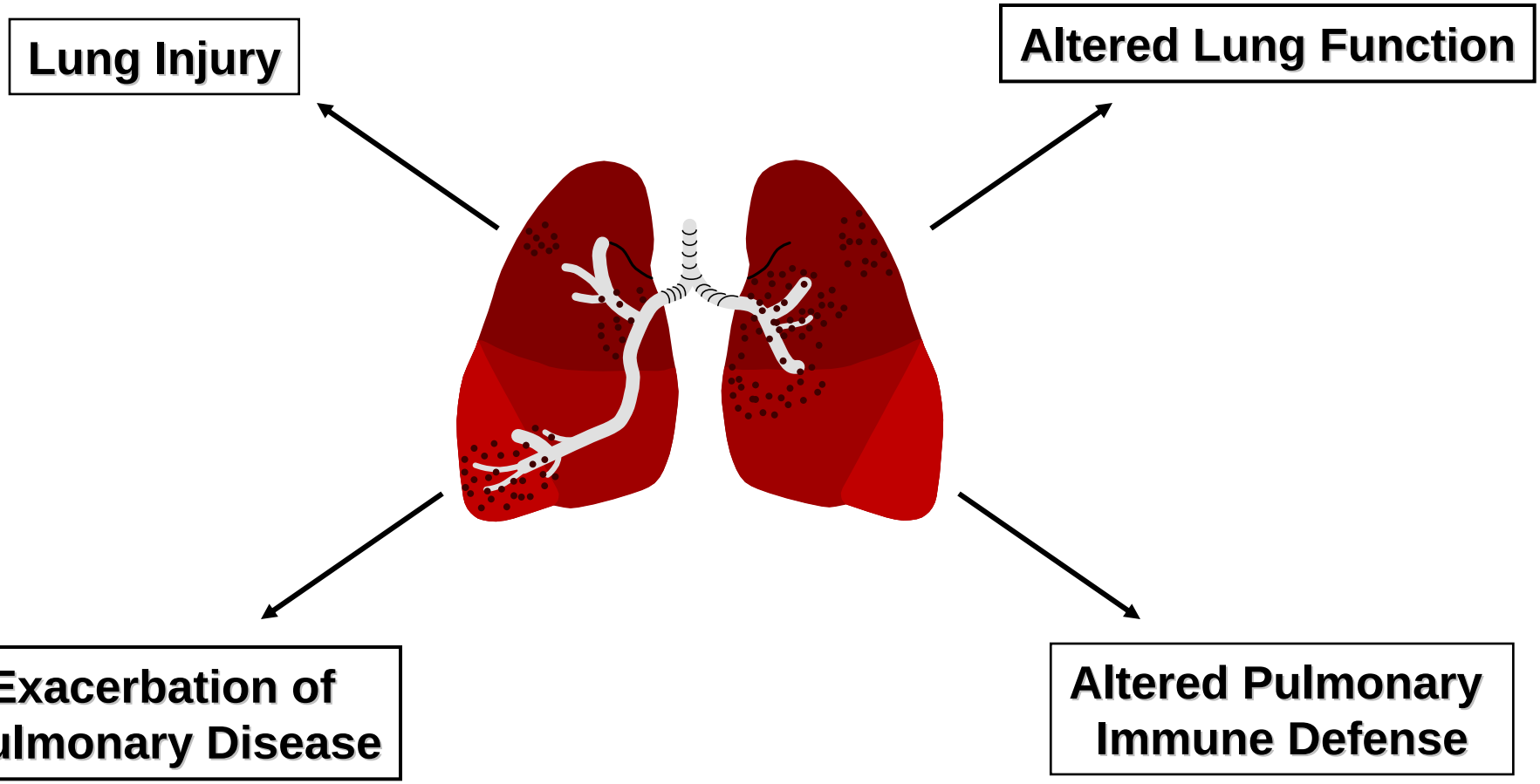
What are the underlying mechanisms (pulmonary, vascular, cardiac) that can explain the epidemiological findings of mortality and morbidity associated with exposure to ambient particulate matter?



PM Presented A New Challenge to Air Pollution Toxicologists

- **Traditionally, toxicologists have focused on respiratory tract responses to air pollutants**
  - **ozone, NO_2, SO_2**
- **The association between PM and cardiovascular effects required a new approach to the study of air pollution**
  - **cardiac effects (e.g. arrhythmias)**
  - **vascular effects (e.g. blood clot formation)**

Potential Effects of PM on the Pulmonary System



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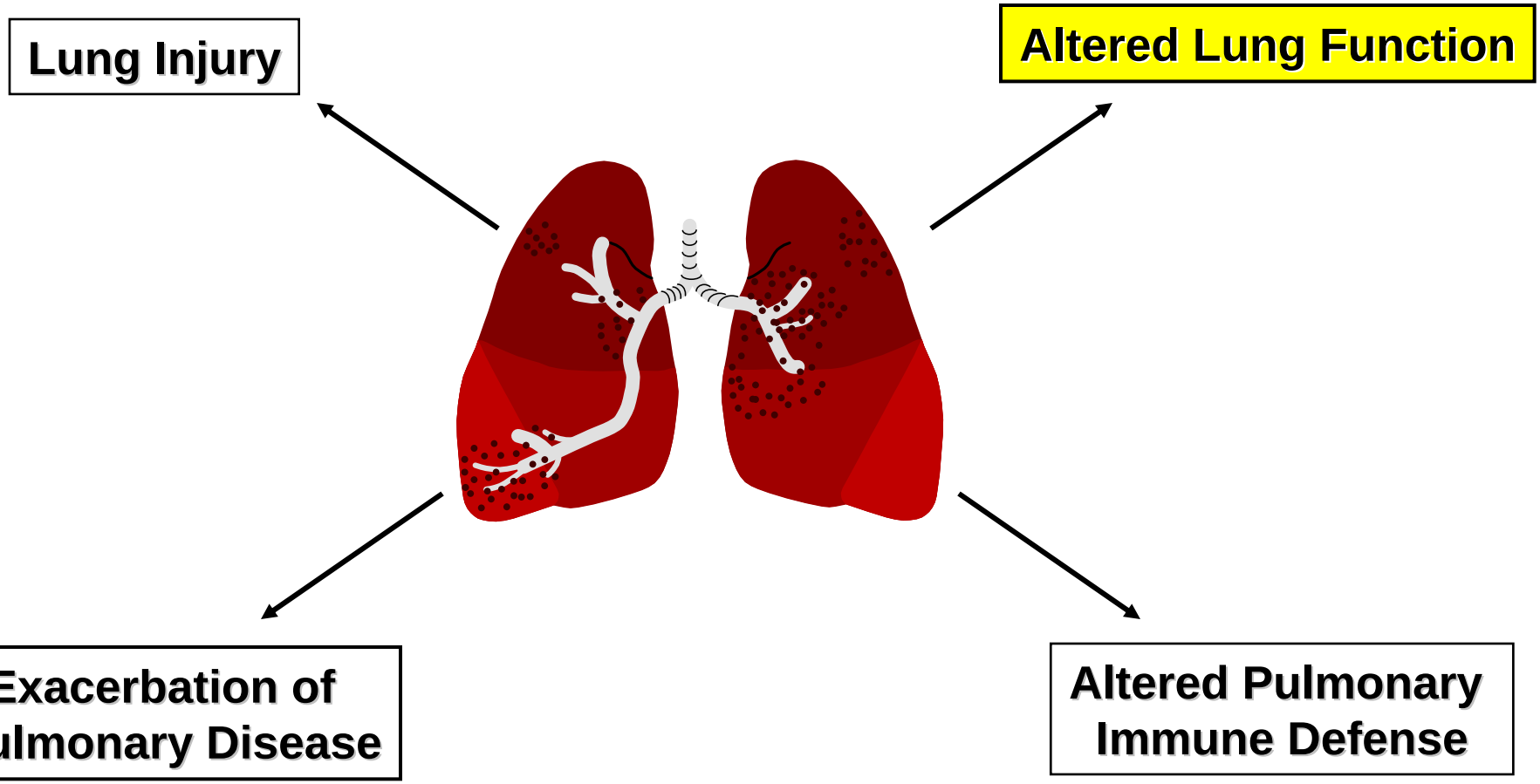
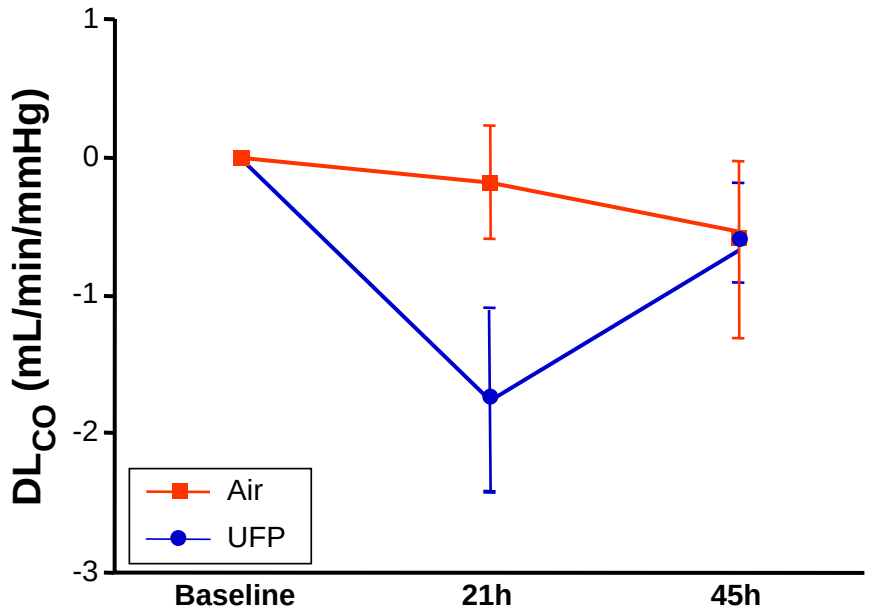


PM Causes Changes in Lung Function

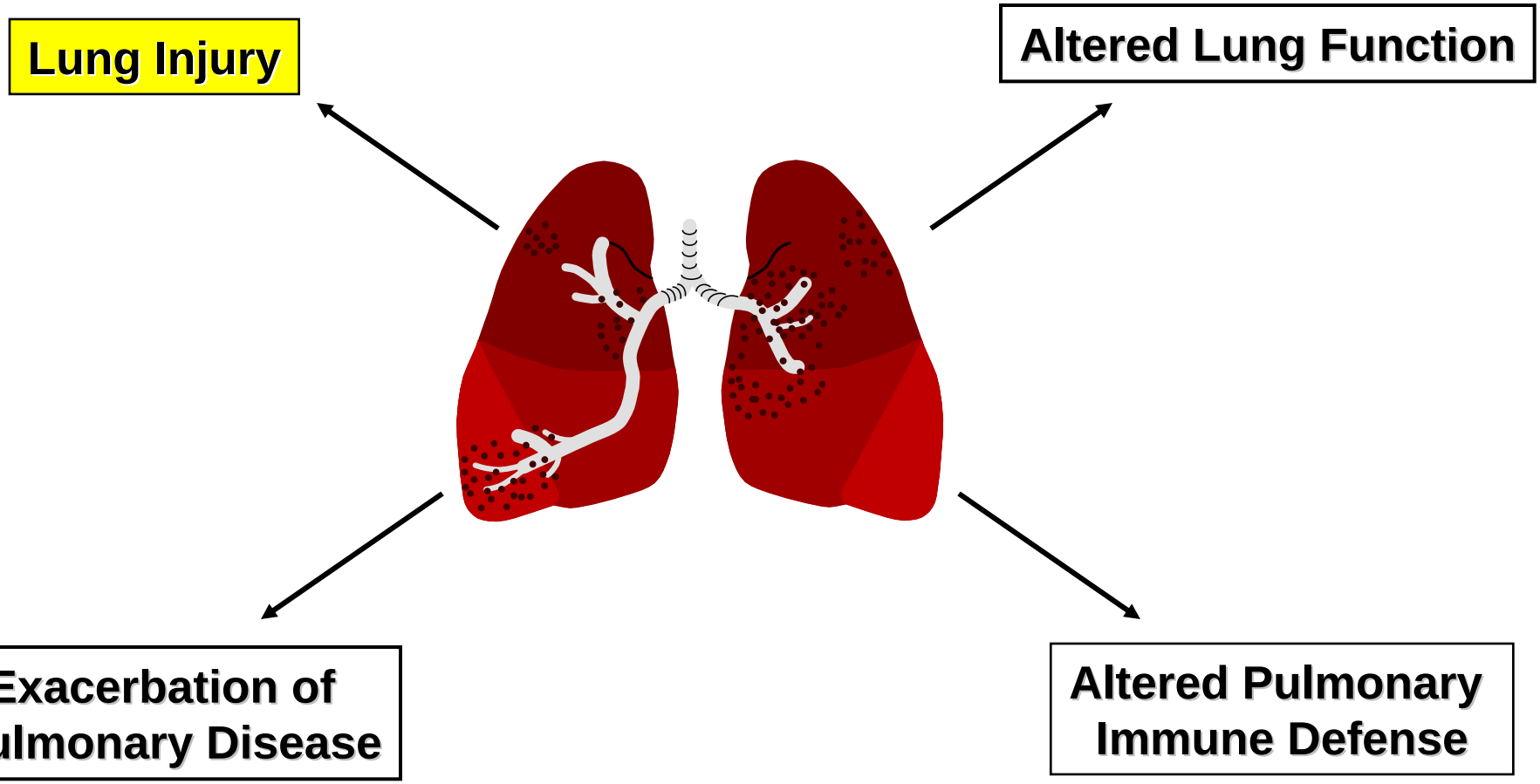
Humans exposed to ultrafine particles have decreased diffusing capacity.



Diffusing capacity is a measure of oxygen transfer from the lungs to the blood

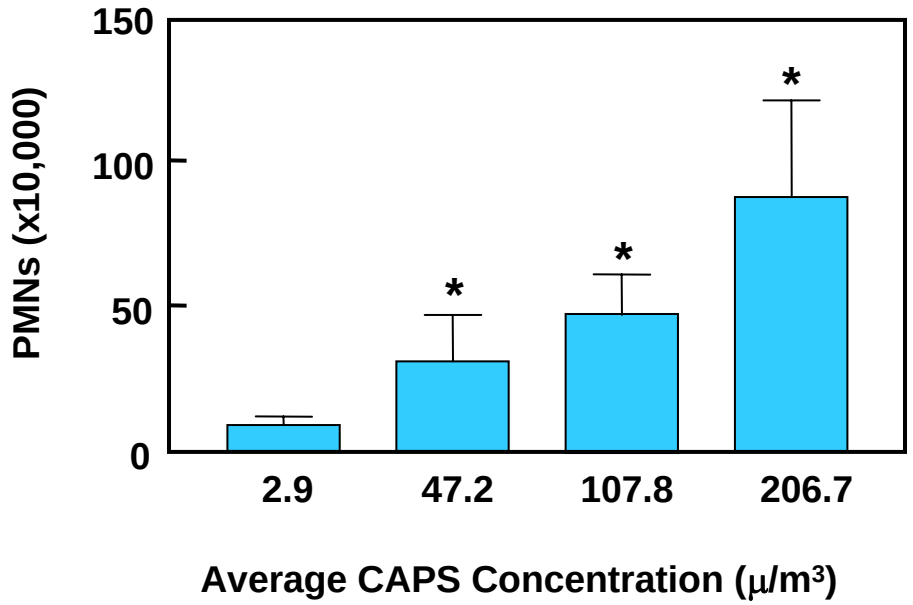
Pietropaoli, et al., 2004

Potential Effects of PM on the Pulmonary System



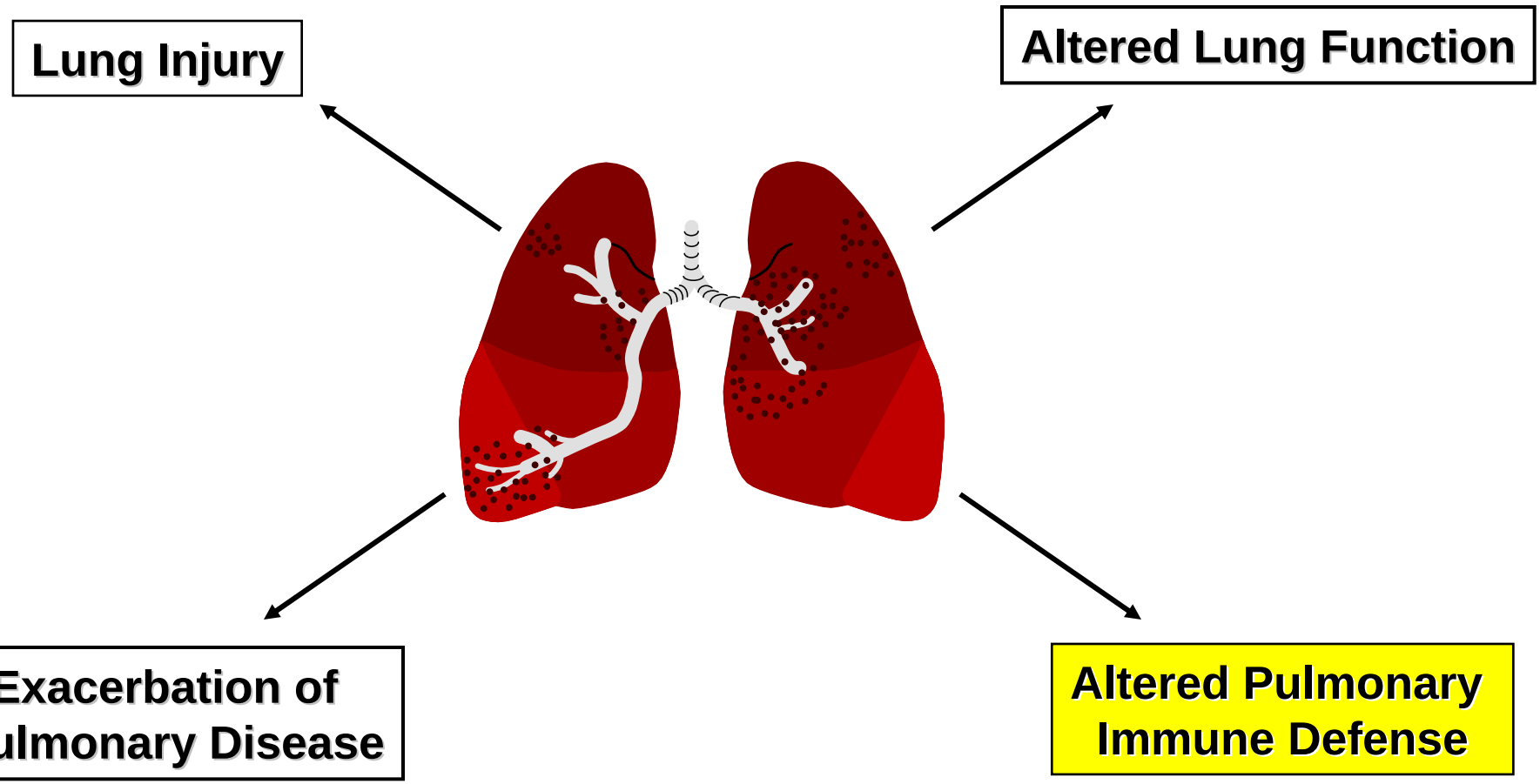
PM Causes Lung Inflammation

Healthy young volunteers exposed to concentrated ambient air particles (CAPs) experience mild pulmonary inflammation



Ghio et al., 2001

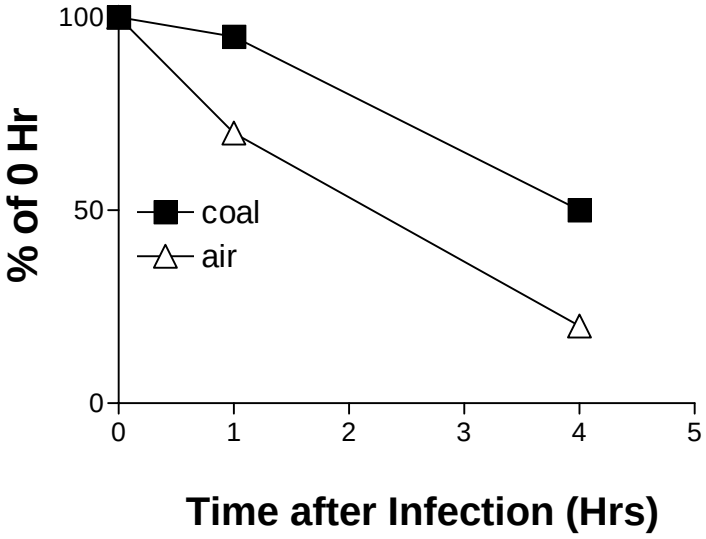
Potential Effects of PM on the Pulmonary System



PM Depresses Clearance and Inactivation of Bacteria

Epidemiology studies report associations between PM and increased incidence of hospitalization for respiratory infections.

Inactivation

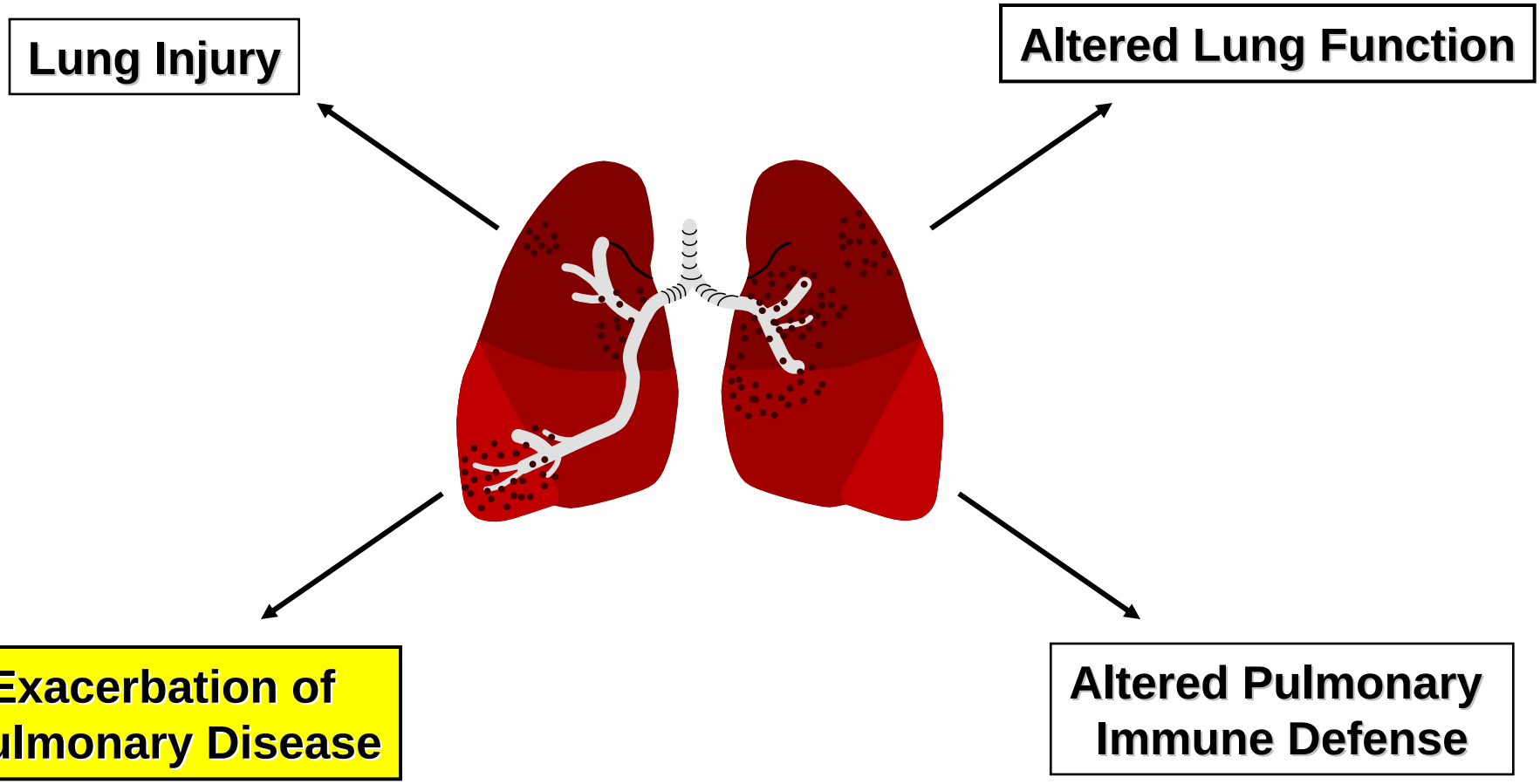


Host Resistance Model

	Control	Woodstove
% Mortality (Streptococcus)	0	21

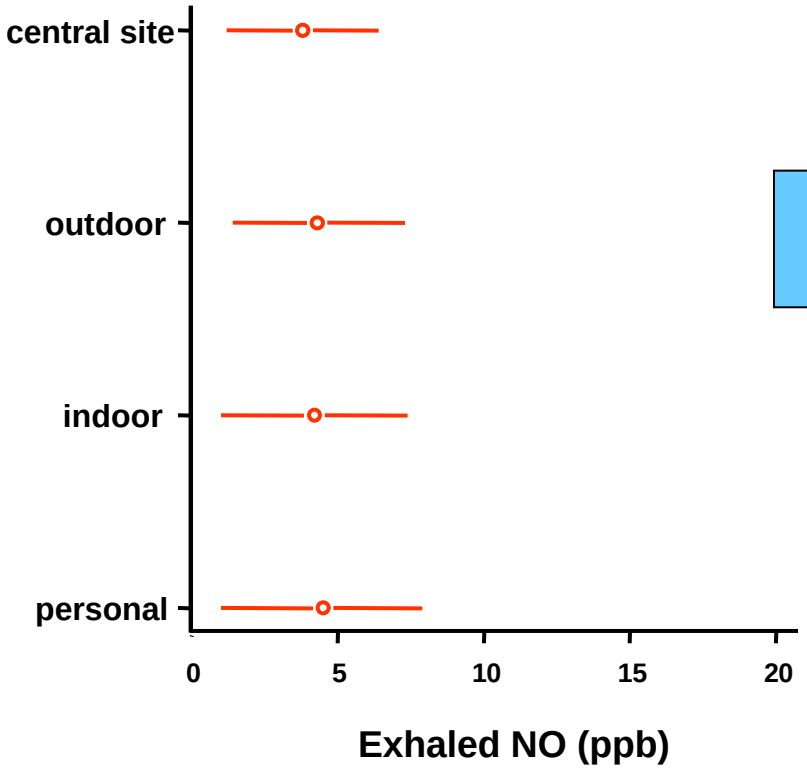
Gilmour et al., 2002

Potential Effects of PM on the Pulmonary System



PM Exposure Exacerbates Asthma

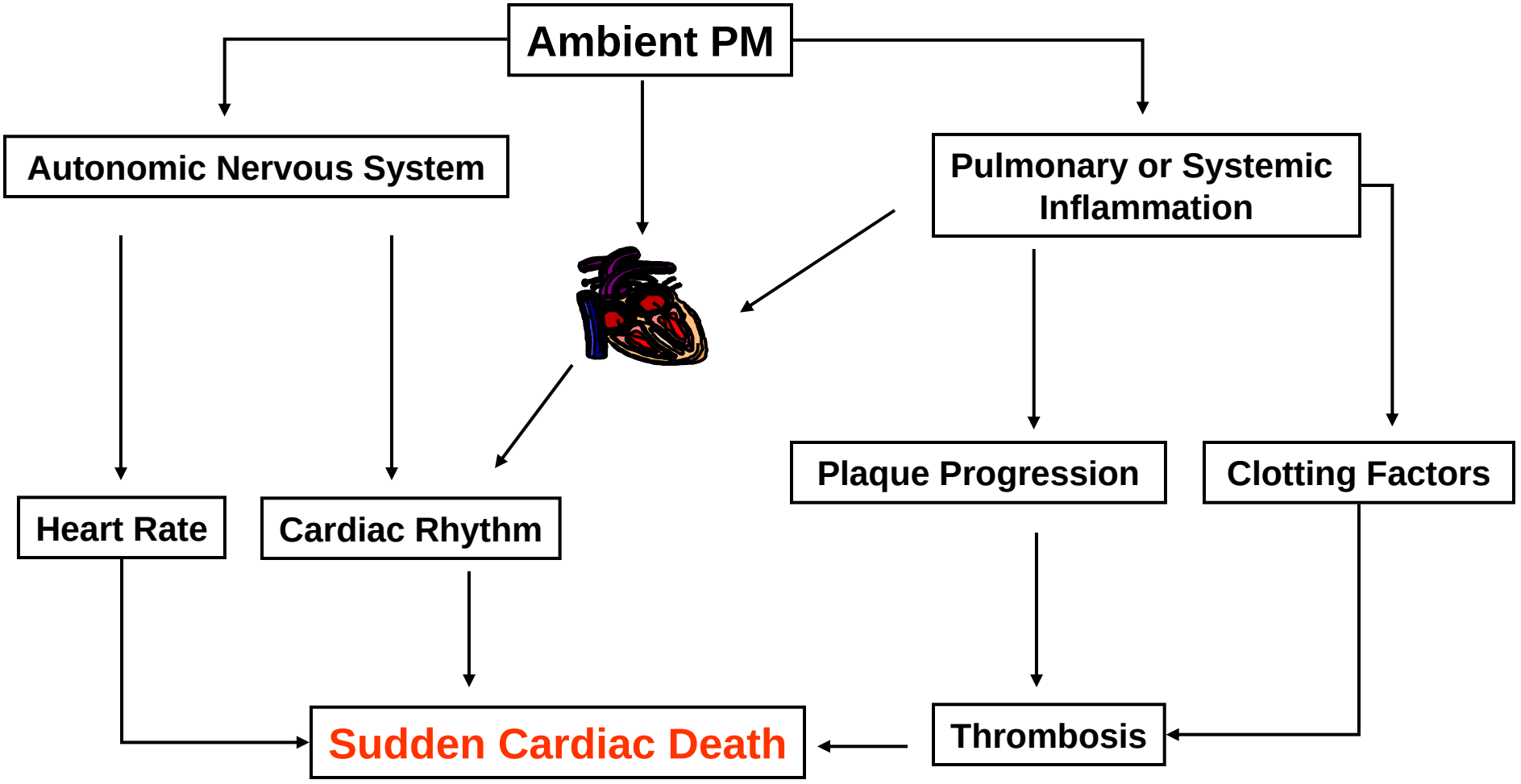
Change in exhaled nitric oxide per 10 μg/m^3 increase in $PM_{2.5}$ in children with asthma



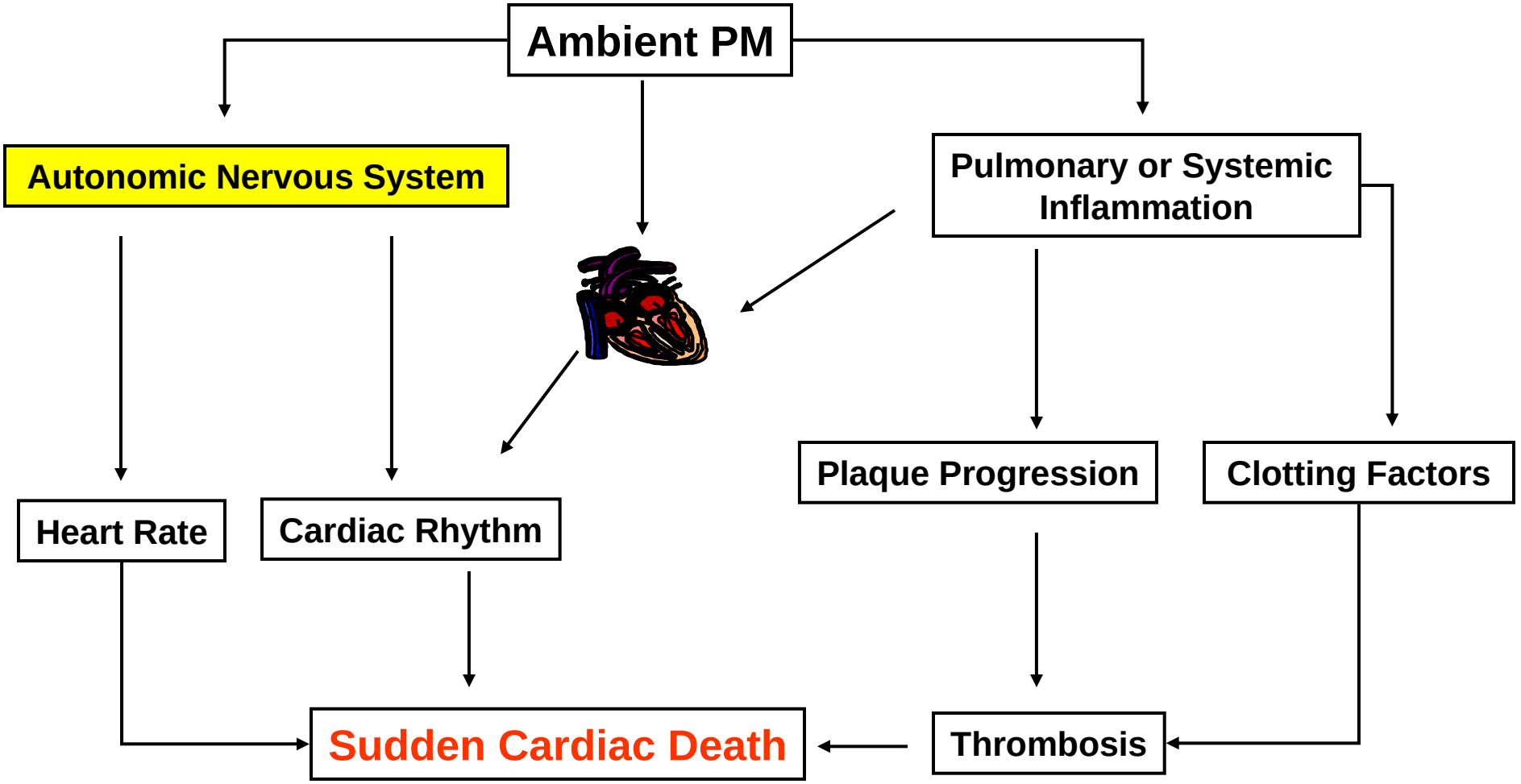
NO is an indication of pulmonary inflammation

Koenig et al., 2003

Potential Effects of PM on the Cardiovascular System

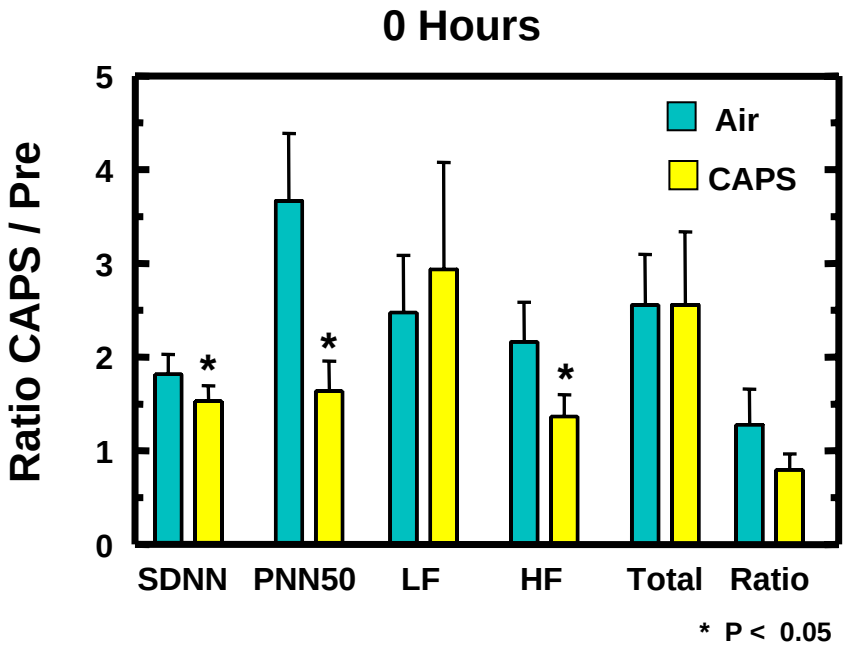


Potential Effects of PM on the Cardiovascular System



PM Affects Autonomic Nervous System Control of the Heart

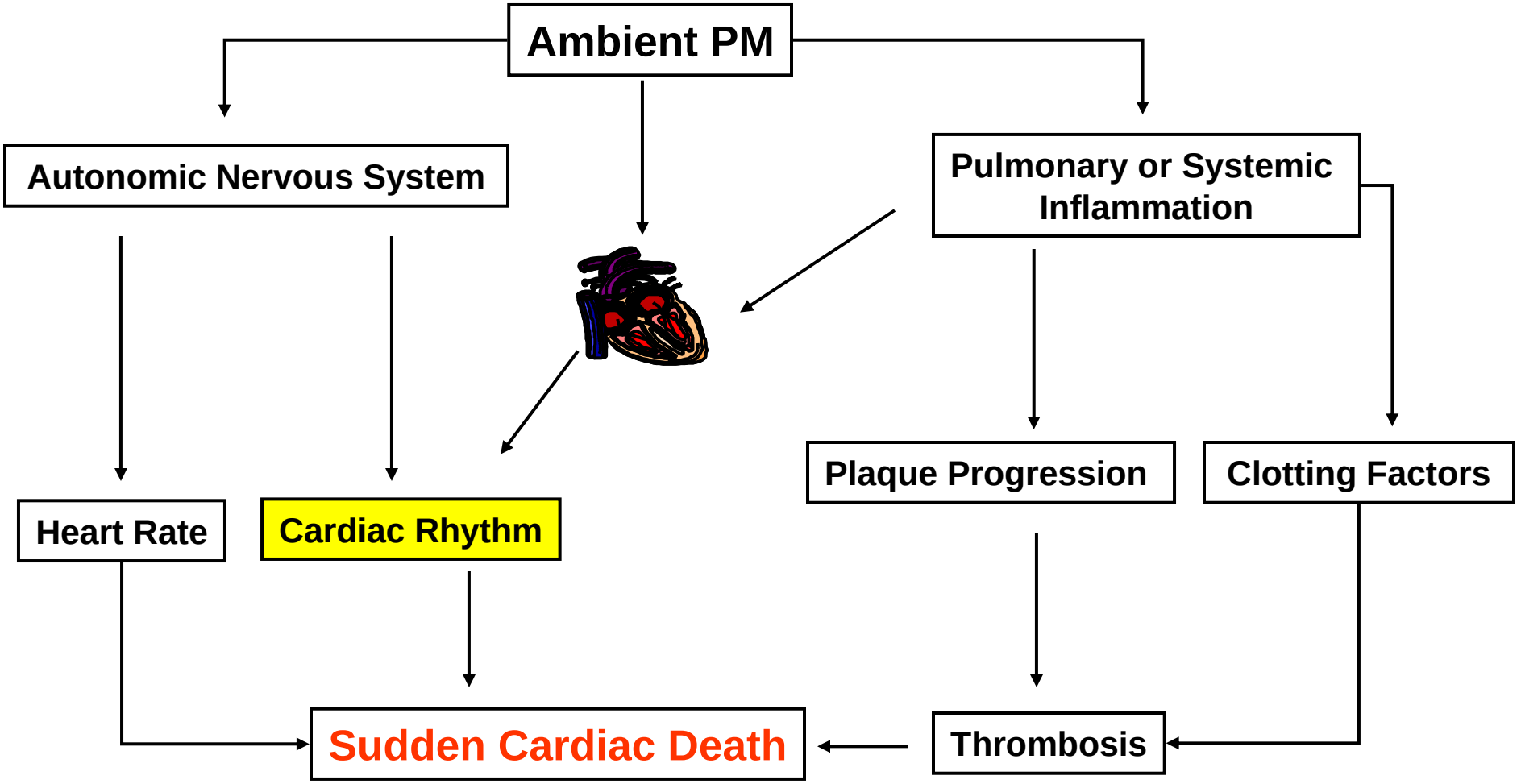
Elderly humans exposed to fine CAPS experience decreases in heart rate variability (HRV).



People with cardiovascular disease who have decreased HRV have a higher risk of getting a heart attack.

Devlin et al, 2003

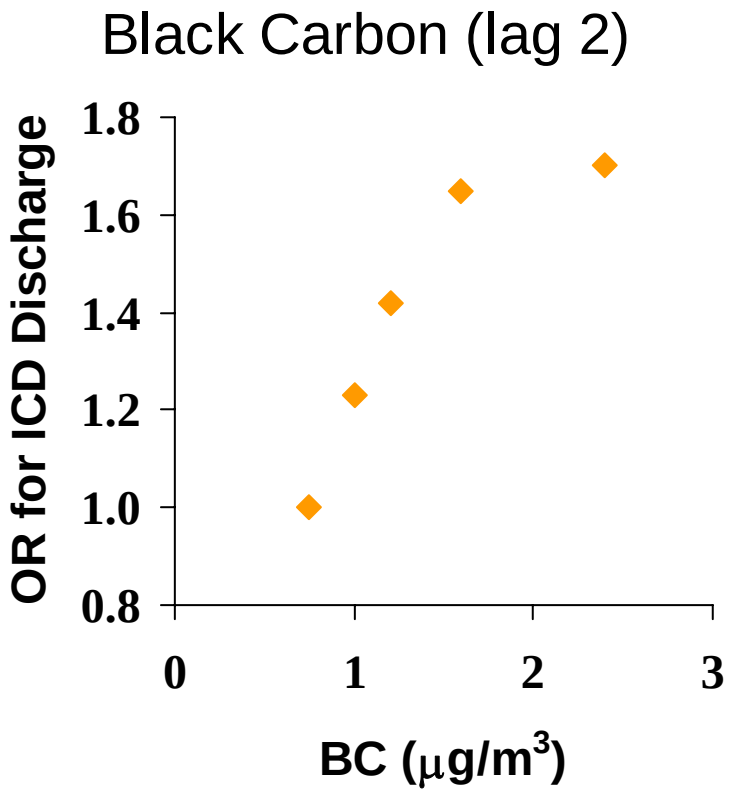
Potential Effects of PM on the Cardiovascular System



PM Triggers Cardiac Arrhythmias in Humans

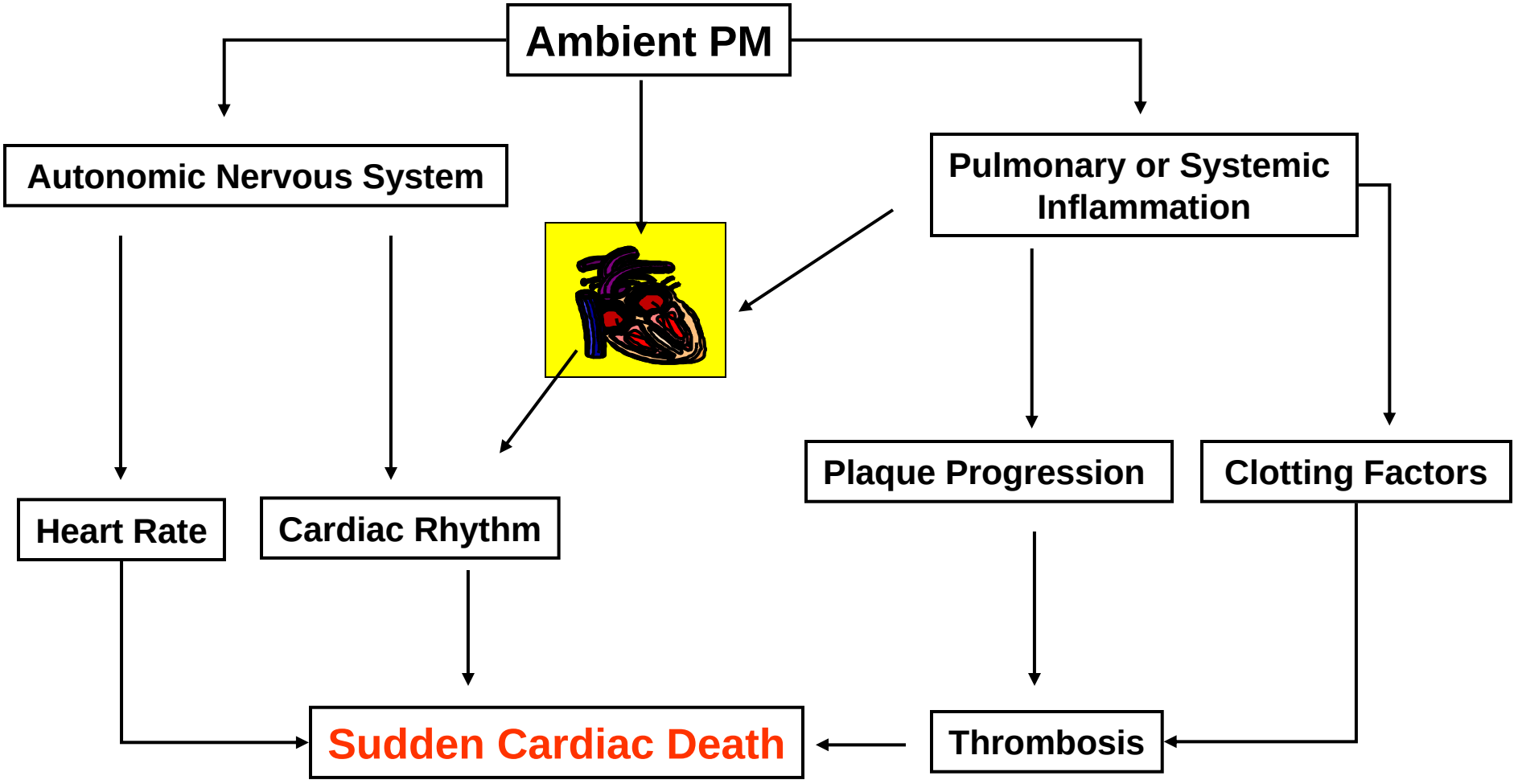
The number of times that implanted defibrillators discharged were related to prior days levels of PM and PM components

- $PM_{2.5}$ 1.22 (0.7,2.0)
- BC 2.16 (1.0,4.9)

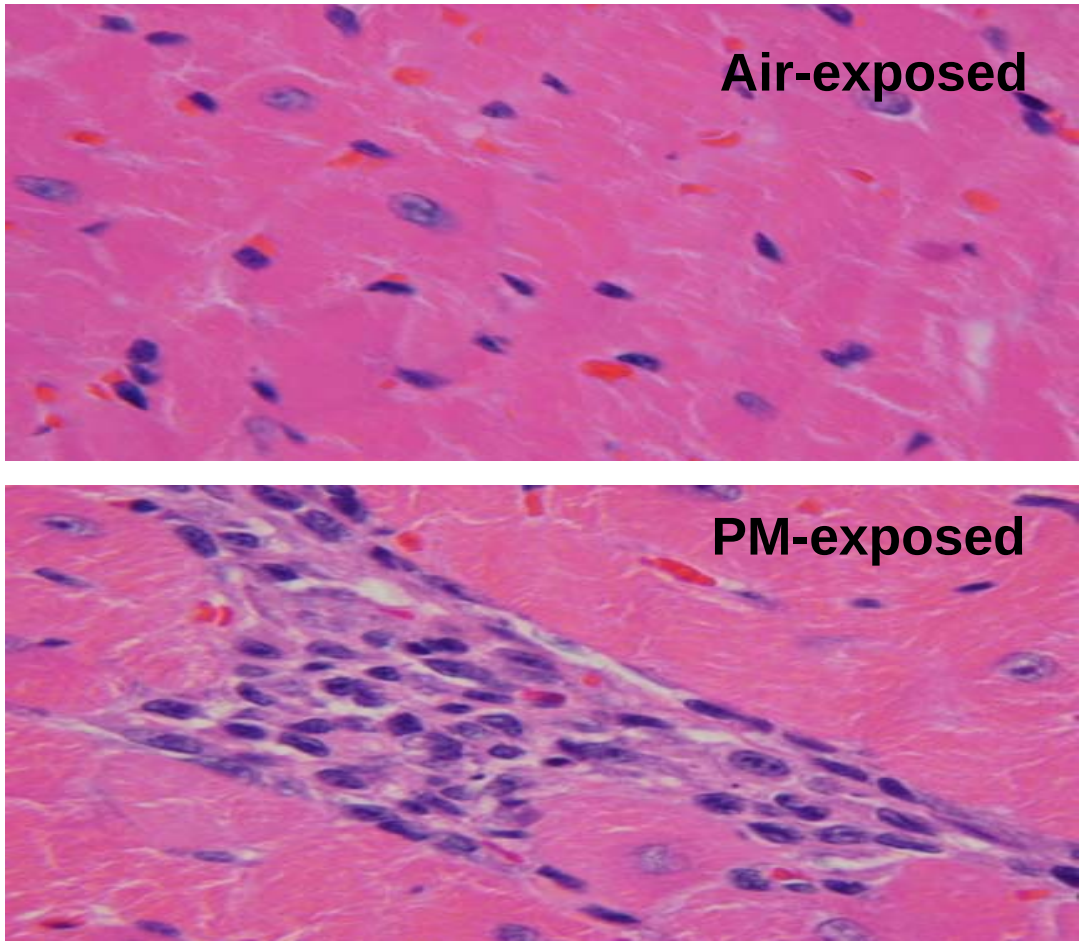


Peters et al, 2000

Potential Effects of PM on the Cardiovascular System



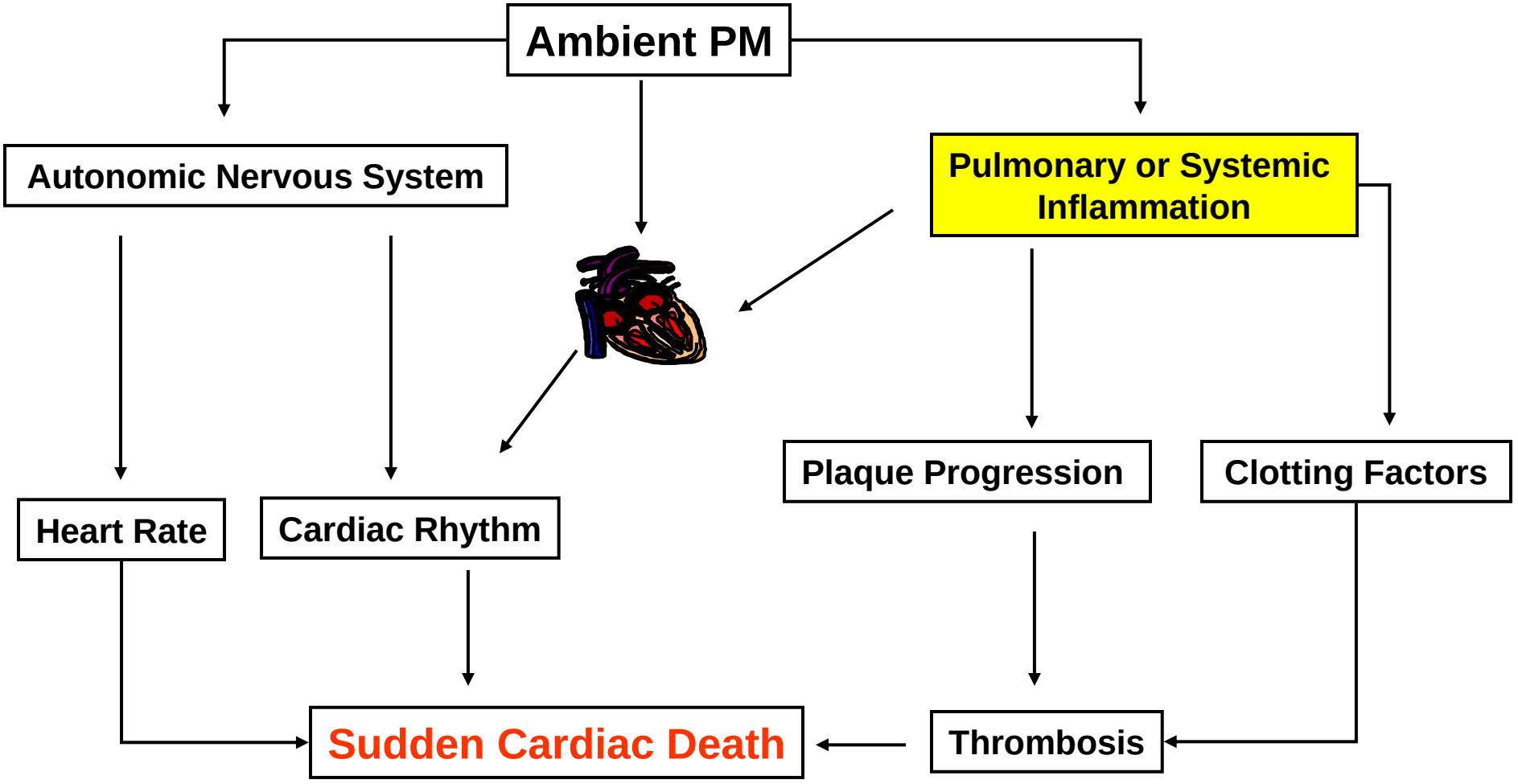
PM Causes Injury to Cardiac Cells



Rats exposed to ambient PM one day per week for 16 weeks

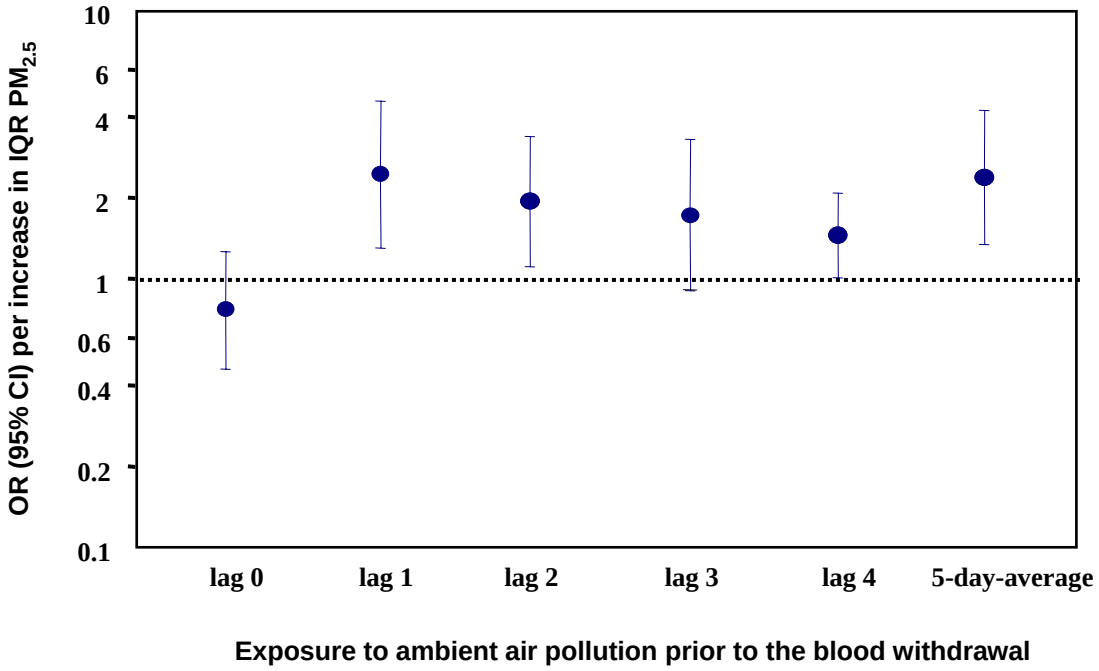
Kodavanti et al., 2003

Potential Effects of PM on the Cardiovascular System



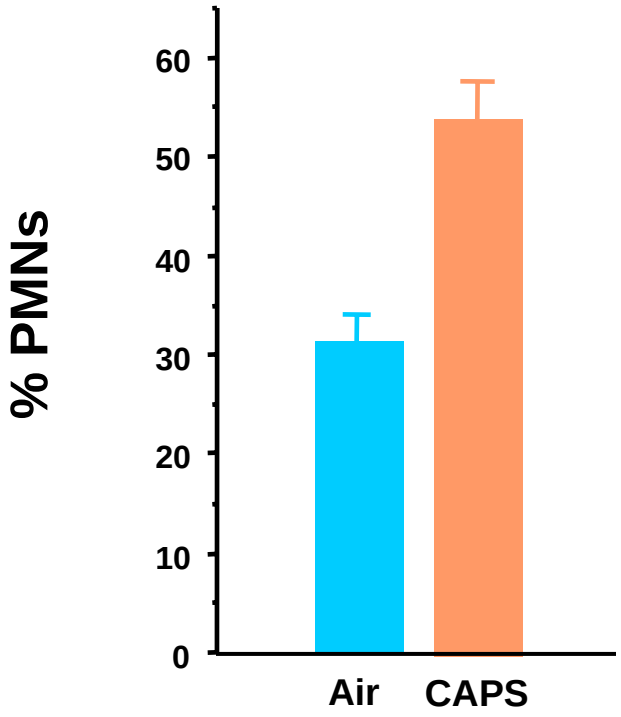
PM Increases Vascular Inflammation

Increase in blood C Reactive Protein in Humans



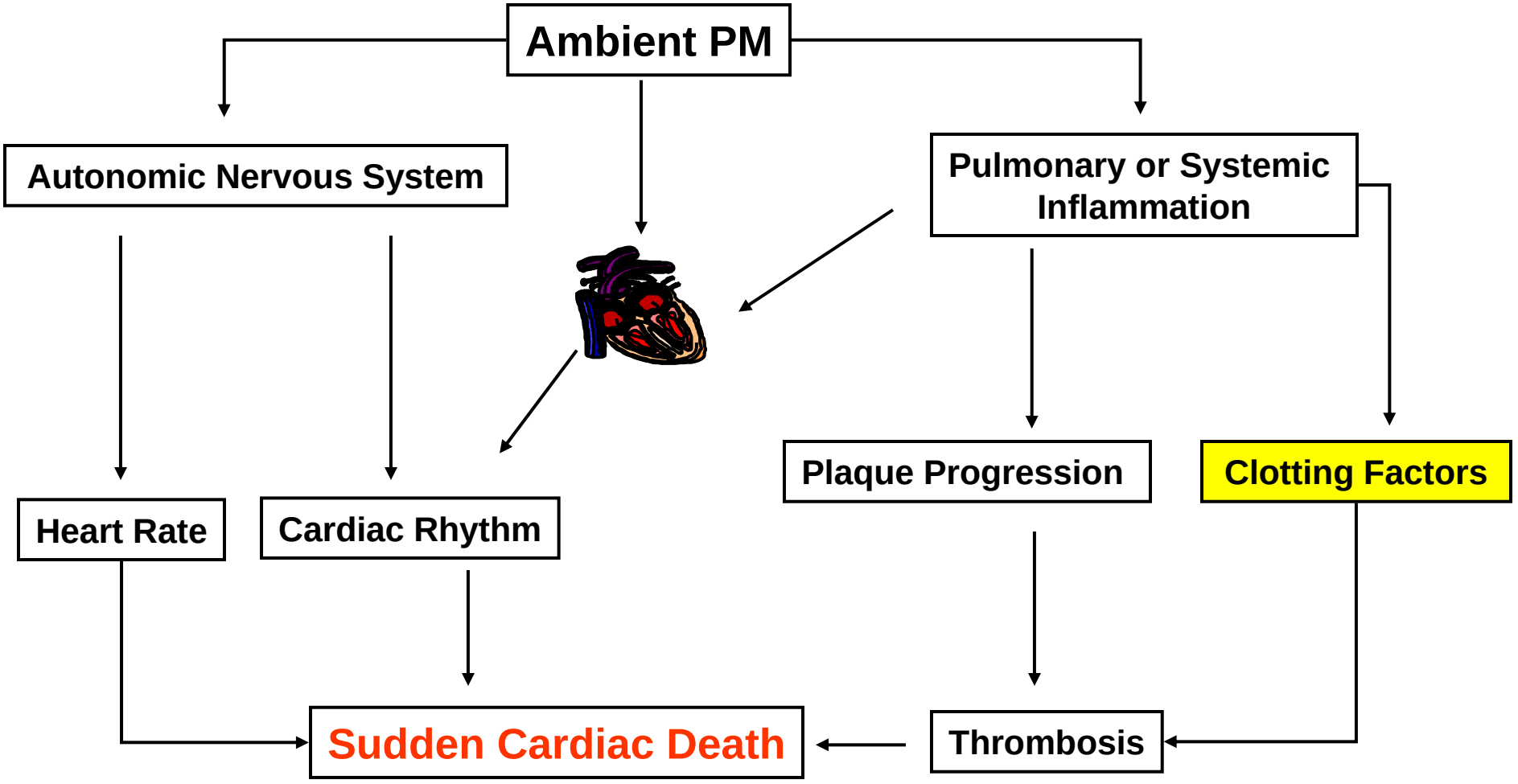
Rueckerl et al., 2004

Increase in blood PMNs in Rats Exposed to CAPS



Gordon et al., 2000

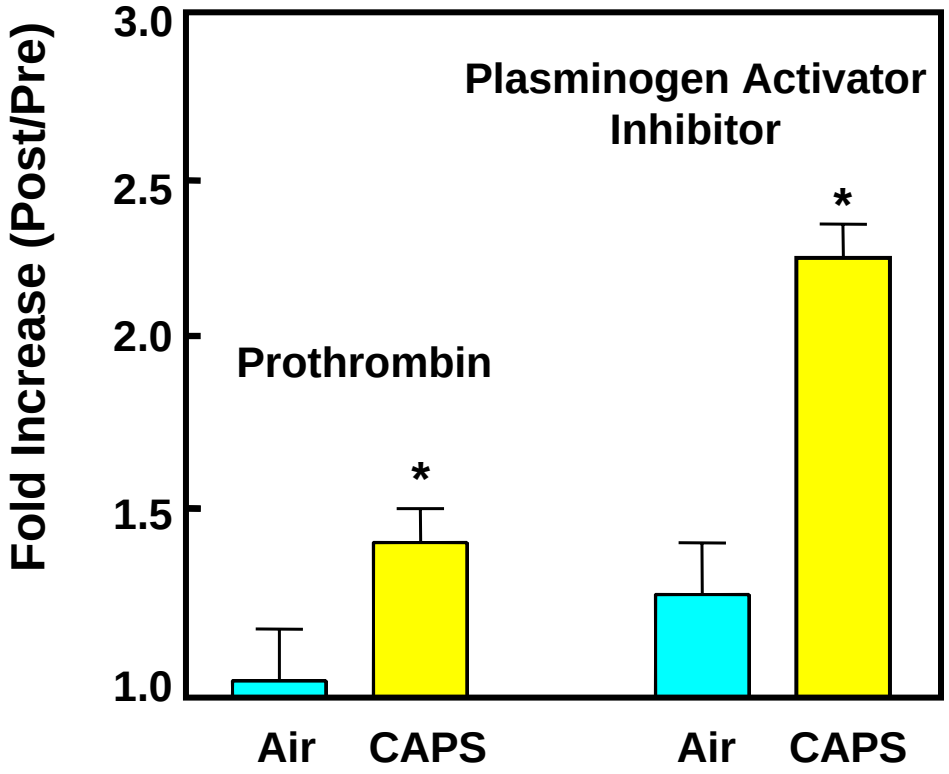
Potential Effects of PM on the Cardiovascular System



PM Increases Levels of Clotting and Coagulation Factors

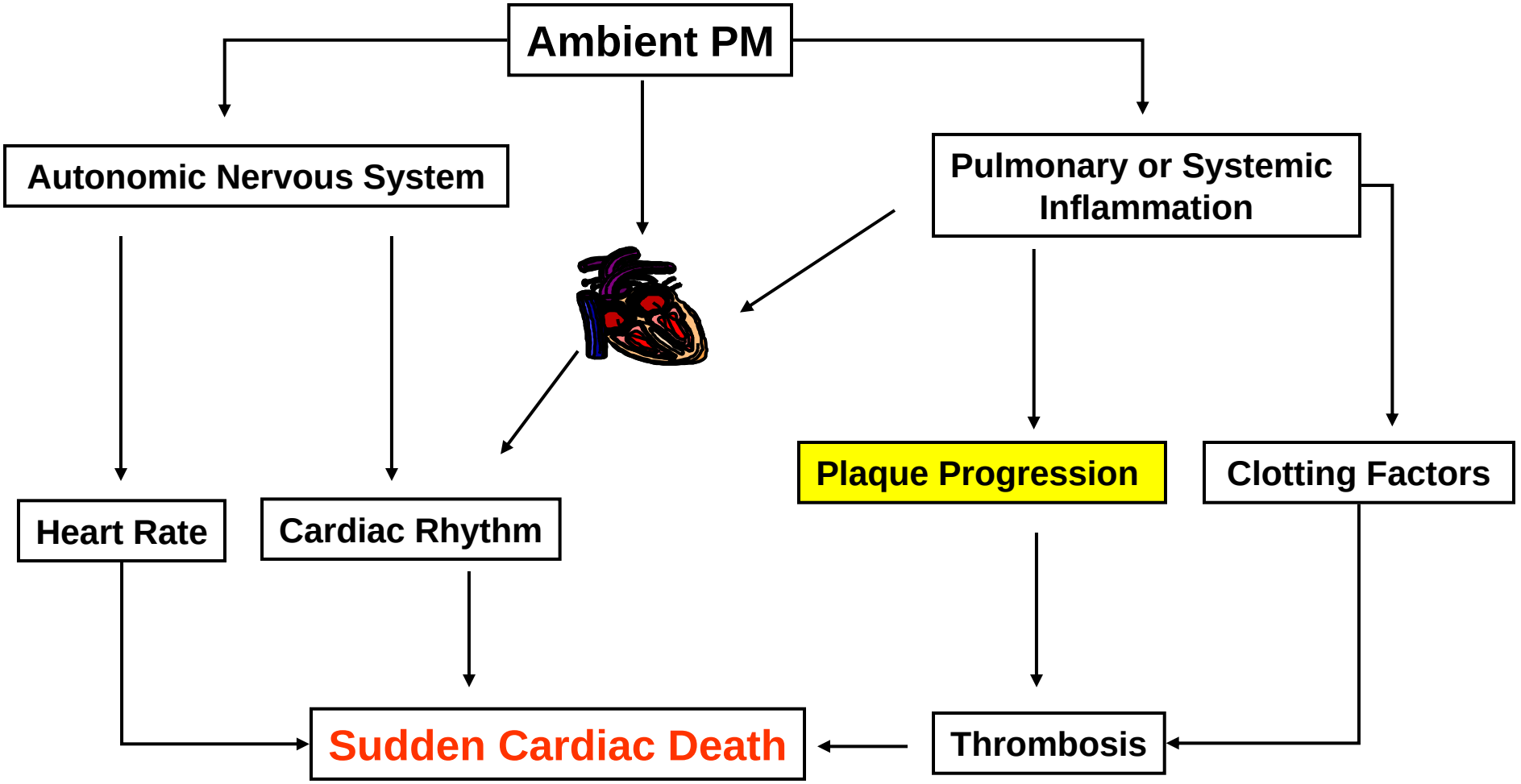
Humans exposed to CAPS have changes in several blood factors which could potentially lead to a more pro-thrombogenic environment.

The net changes in these factors could potentially lead to an environment conducive to the formation of blood clots.



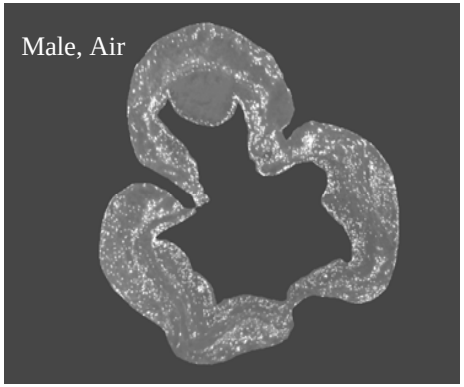
Devlin et al, 2004

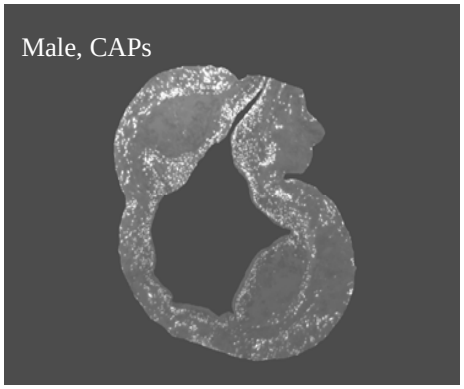
Potential Effects of PM on the Cardiovascular System

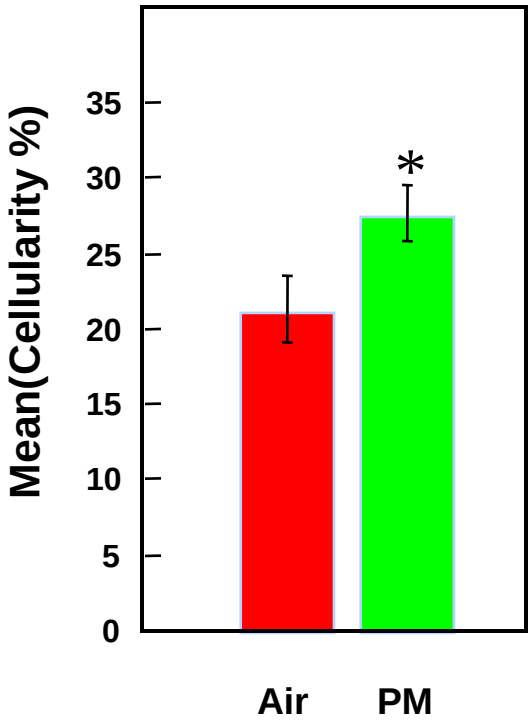


PM Increases Arterial Plaque Thickness

Subchronic exposure of ApoE-/-LDLr-/- double knockout mice to CAPS for 6h/day, 5d/week, for 6 months (average of 110 μg/m³) increases plaque cellularity.







Chan et al., 2004

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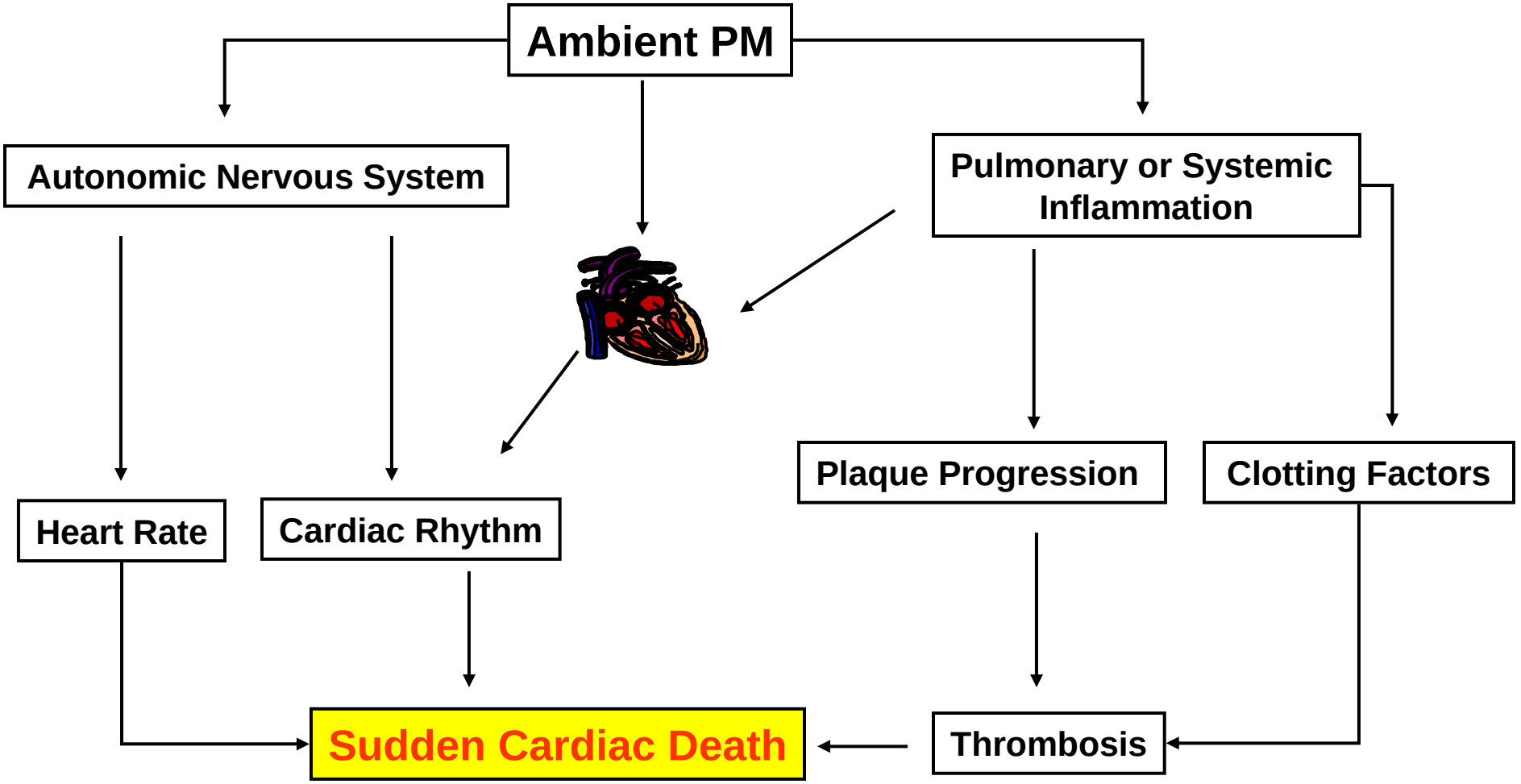
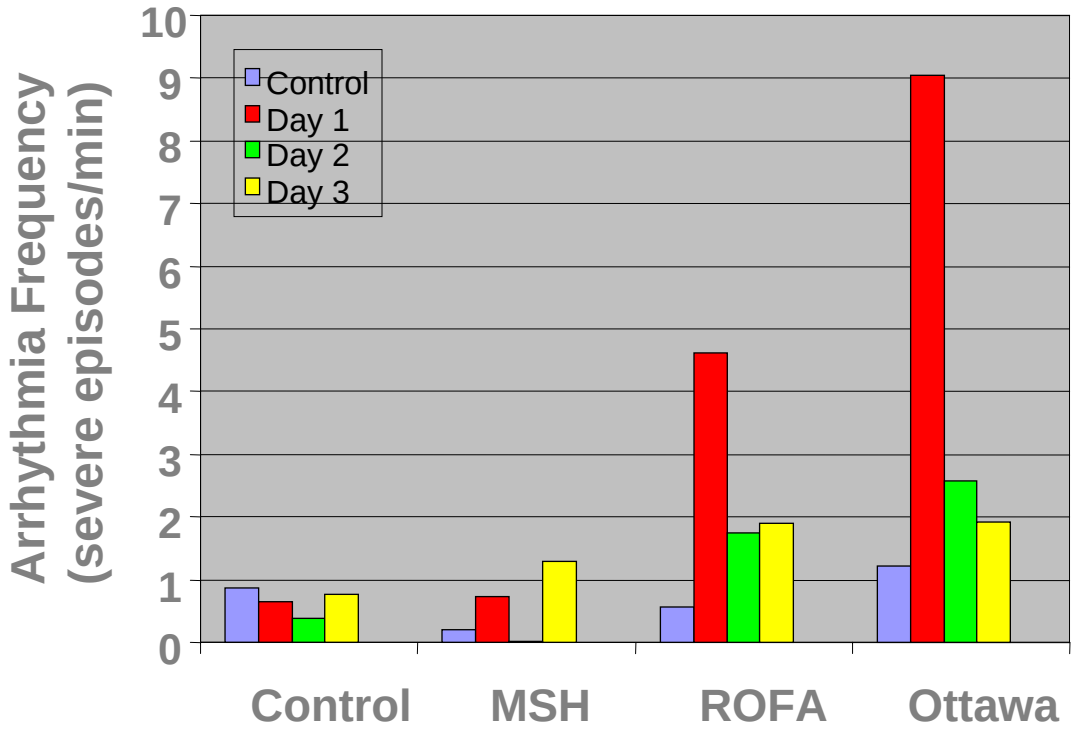
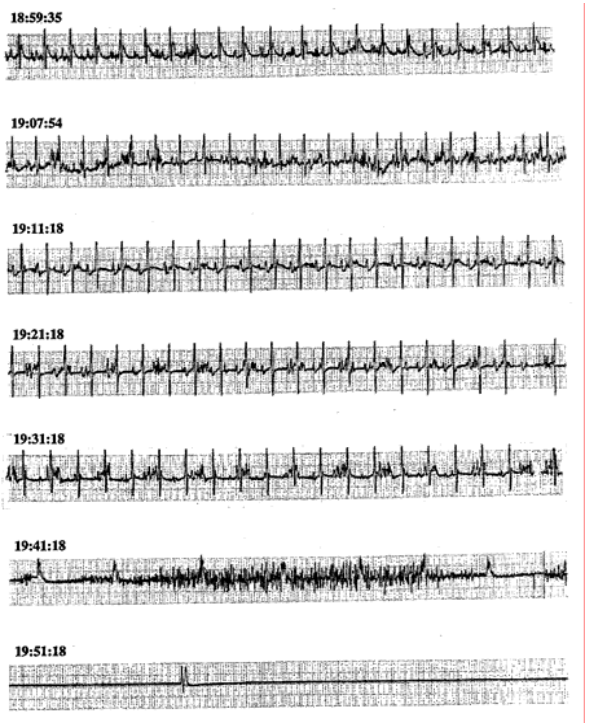


PM Causes Fatal Arrhythmias in Animals

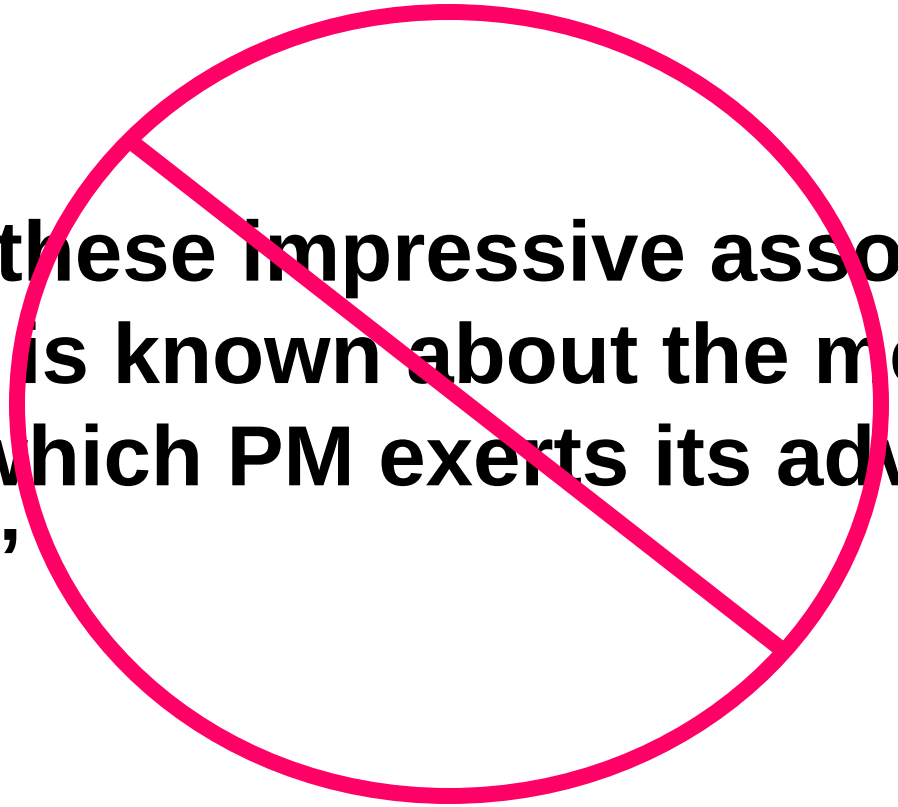
Rats were treated with PM from various sources and arrhythmias measured for 3 days after exposure





Watkinson et al., 2000

Progress Made…



“Despite these impressive associations, very little is known about the mechan-isms by which PM exerts its adverse effects…”

Mechanistic Studies Have:

- **Defined several biologically plausible patho-physiological pathways by which PM can increase mortality and morbidity.**
- **Provided coherence to the epidemiology studies and extended their observations, thus strengthening the science in support of the PM standard.**

What Else Remains to Be Done?

My goal is simple. It is complete understanding of the universe, why it is as it is and why it exists at all." —

Stephen Hawking.

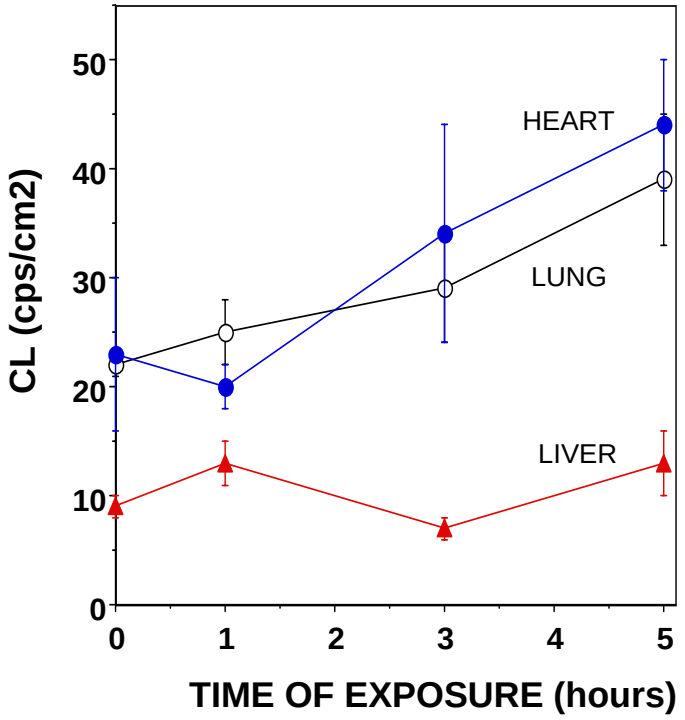
Key Areas of Uncertainty

- **Many of these studies have only recently been published and need to be replicated in other labs and species.**
- **It is not clear whether different PM components (or PM derived from different sources) exert their effects by the same or a series of different mechanisms.**
  - **additivity versus synergism**
- **It is not clear whether different mechanisms operate in different susceptible populations or in different organs.**
- **Most current mechanistic PM research has been at the organ or physiological level**
  - **very little known about how PM causes effects at the cellular or molecular level**

Does PM Cause Adverse Effects by Inducing Oxidative Stress?

Rats exposed to fine CAPS show chemiluminescence in the lung, heart, and liver.

This is an indication that PM can induce oxidative stress in critical organs.



Implications for:

protecting people from PM

Identifying potentially susceptible people

Gurgueira et al 2002