

# Mast Cell Mediated Cardiac Effects of Particulate Matter

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# Hypothesis:

Particulate matter mediated activation of cardiac mast cells results in matrix metalloproteinase (MMP) activation and accelerated myocardial remodeling, thereby further impairing cardiac function and leading to an increased incidence of adverse cardiovascular events.

# Mast Cell Mediated Myocardial Remodeling

- Cardiac mast cell-mediated activation of gelatinase and alteration of ventricular diastolic function.

**Chancey et al. *Am J Physiology* 282: H2152-H2158, 2002.**

- Cause and effect relationship between myocardial mast cell number and matrix metalloproteinase activity.

**Brower et al. *Am J Physiology* 283: H518-H525, 2002.**

# Link Between Mast Cells, Particulate Matter Exposure and Cardiovascular Disease

Canines as sentinel species for assessing chronic exposures to air pollutants: part 2. Cardiac pathology.

**Calderon-Garciduenas et al. Toxicol. Sci. 61(2):356-67, 2001.**

- **Cardiac Mast Cell Degranulation Noted**

# Particulate Matter Exposure and Pulmonary Mast Cell Activation

Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers.

**Salvi et al. Am J Respir Crit Care Med. 159:702-9, 1999.**

- **Histamine Release and Increase in Mast Cell Number**

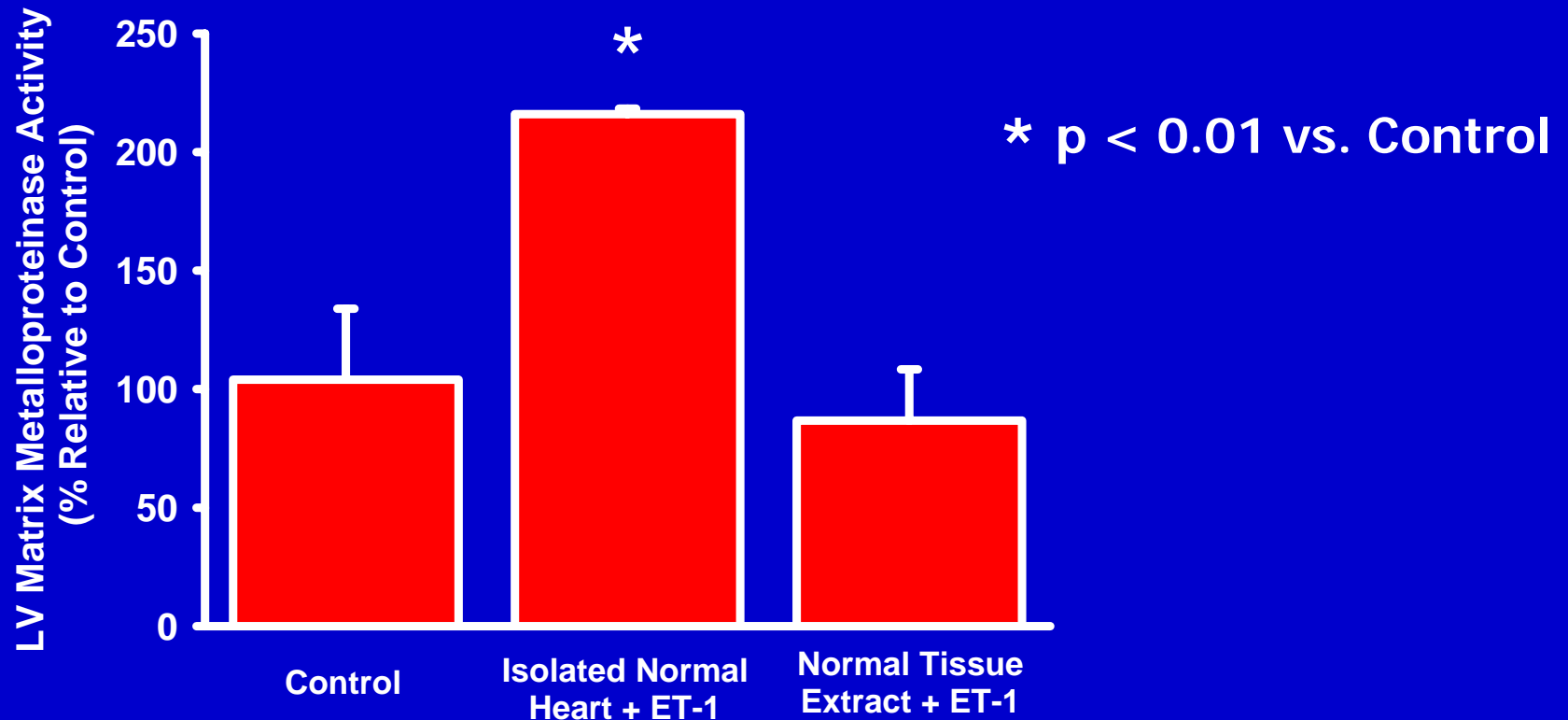
# Particulate Matter Mediated Increase in Endothelin

Elevation of Serum Endothelins and Cardiotoxicity Induced by Particulate Matter (PM(2.5)) in Rats with Acute Myocardial Infarction.

**Kang et al. *Cardiovasc. Toxicol.* 2:253-262, 2002.**

- Total serum endothelin concentrations were significantly elevated in both myocardial infarct and sham-operated control rats following PM exposure.

# Endothelin-1 Mediated MMP Activation

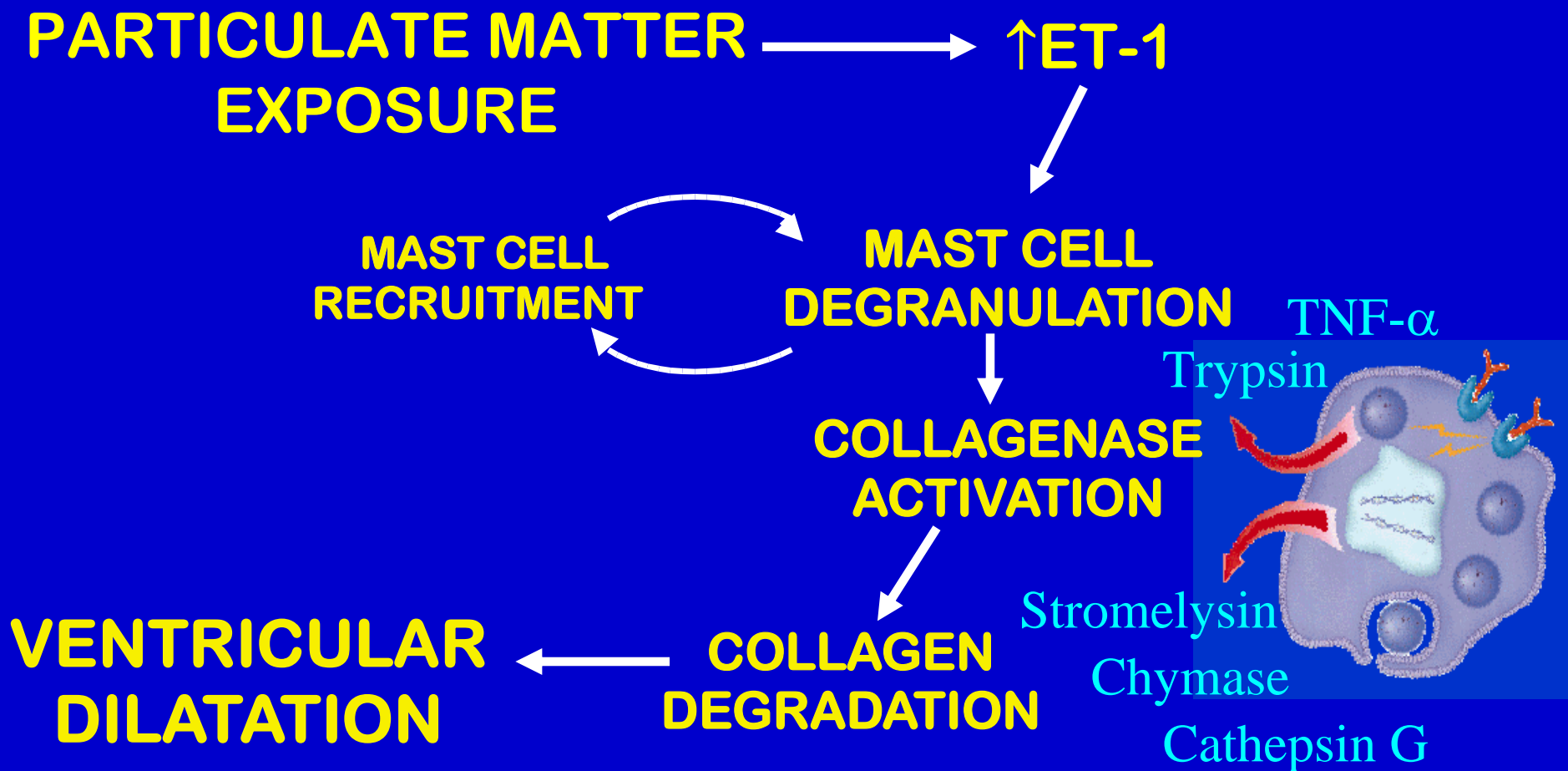


## Collagen Volume Fraction

Control	0.99% $\pm$ 0.04
ET-1 Treated	0.69% $\pm$ 0.09*

Murray et al.  
Am J Physiol 2004.

# Particulate Matter: Mast Cell - MMP Hypothesis





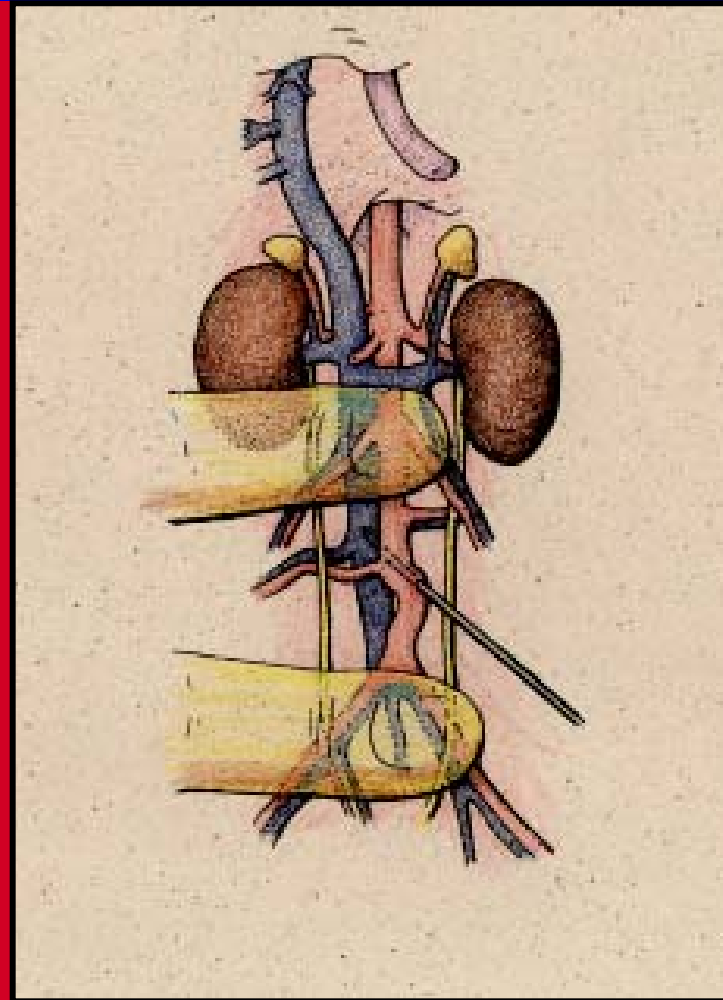
# Specific Aims

To determine:

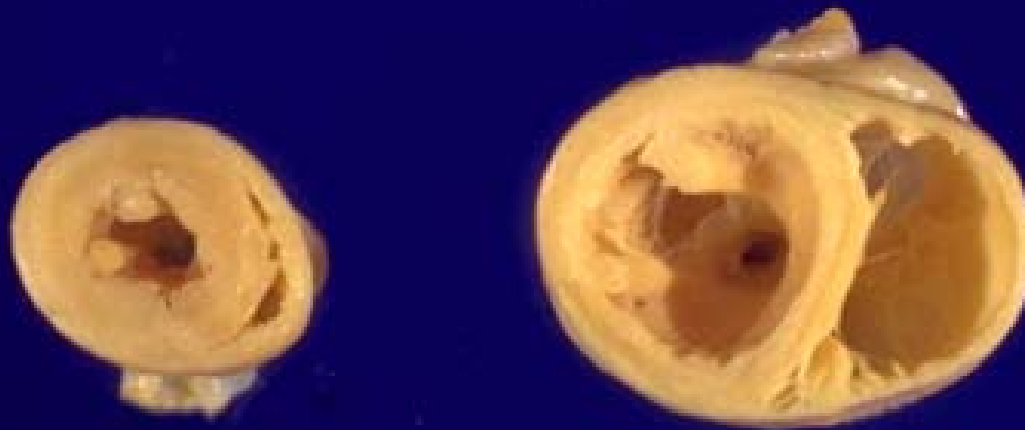
- 1) the causal relationship between acute diesel PM exposure, mast cell activation, and exacerbation of CHF with a resultant increase in morbidity and mortality
- 2) the mechanisms by which subchronic diesel PM exposure accelerates cardiac remodeling and the development of CHF.

# Infrarenal A-V Fistula

Aortocaval Fistula  
Opened Between  
Aorta and Vena  
Cava Using an 18  
Gauge Needle

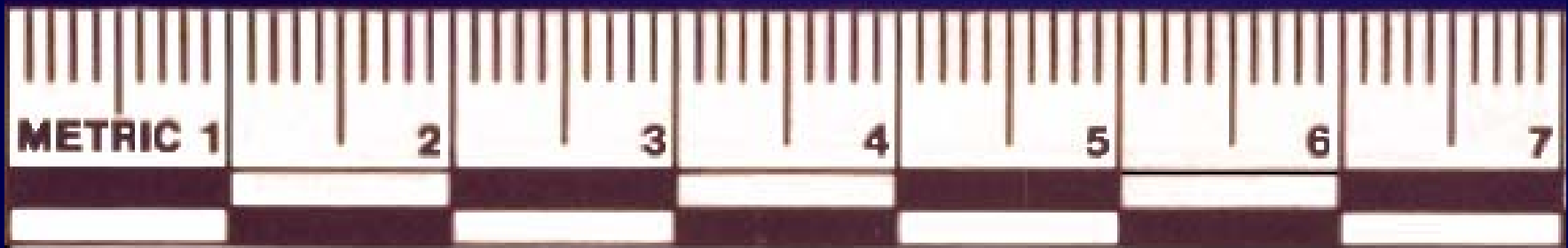


# Cardiac Remodeling Post-Fistula



Normal

Heart Failure



Brower et al. Am J Physiol 280: H674-H683, 2001.

# Particulate Matter Exposure

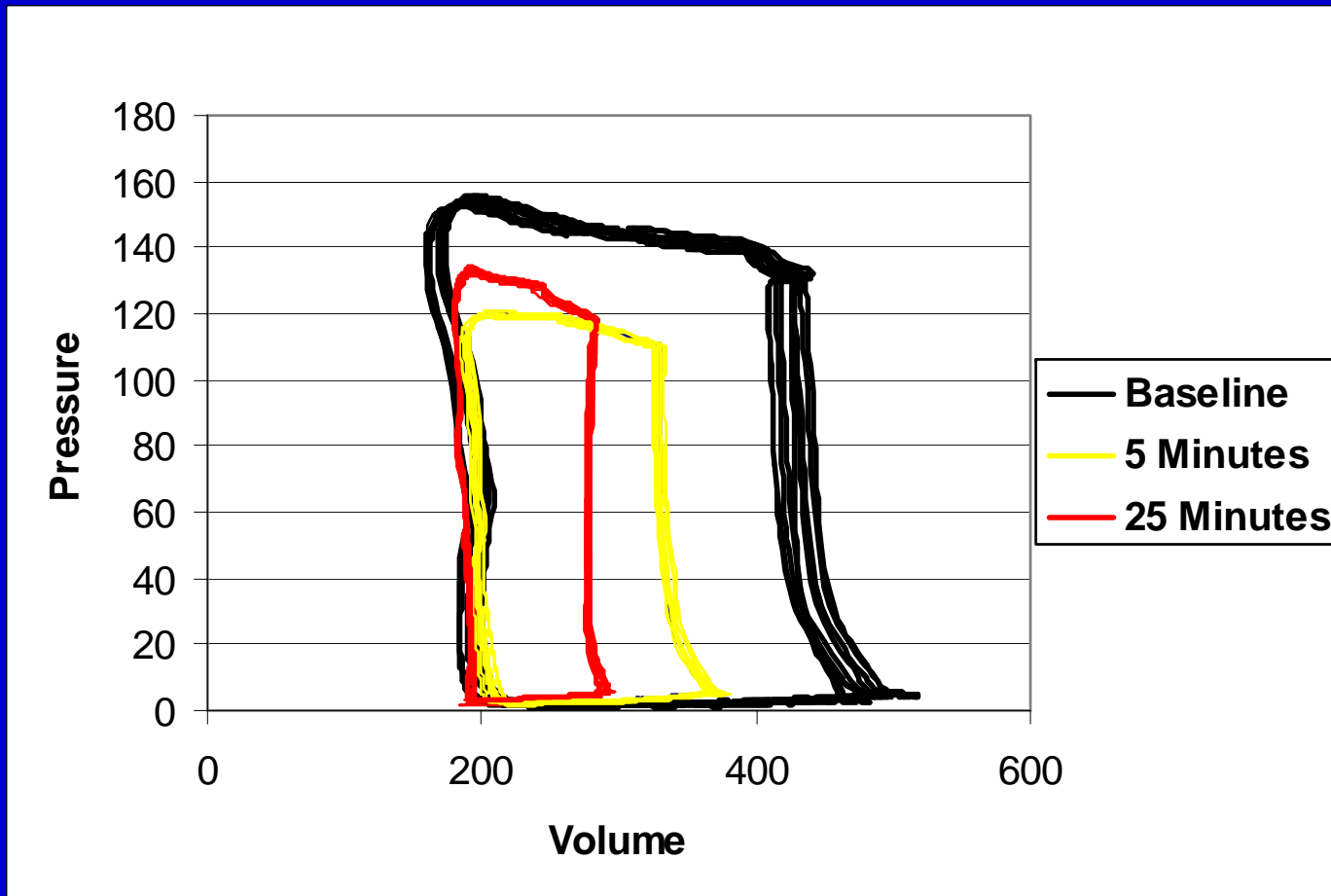
## Nebulization

- SRM 2975 DEP (NIST)
  - 4.5 mg / 20 ml 0.9% Saline
  - Nebulized delivery at 3.0-3.5 l/min O<sub>2</sub>
  - One 30 min exposure per day

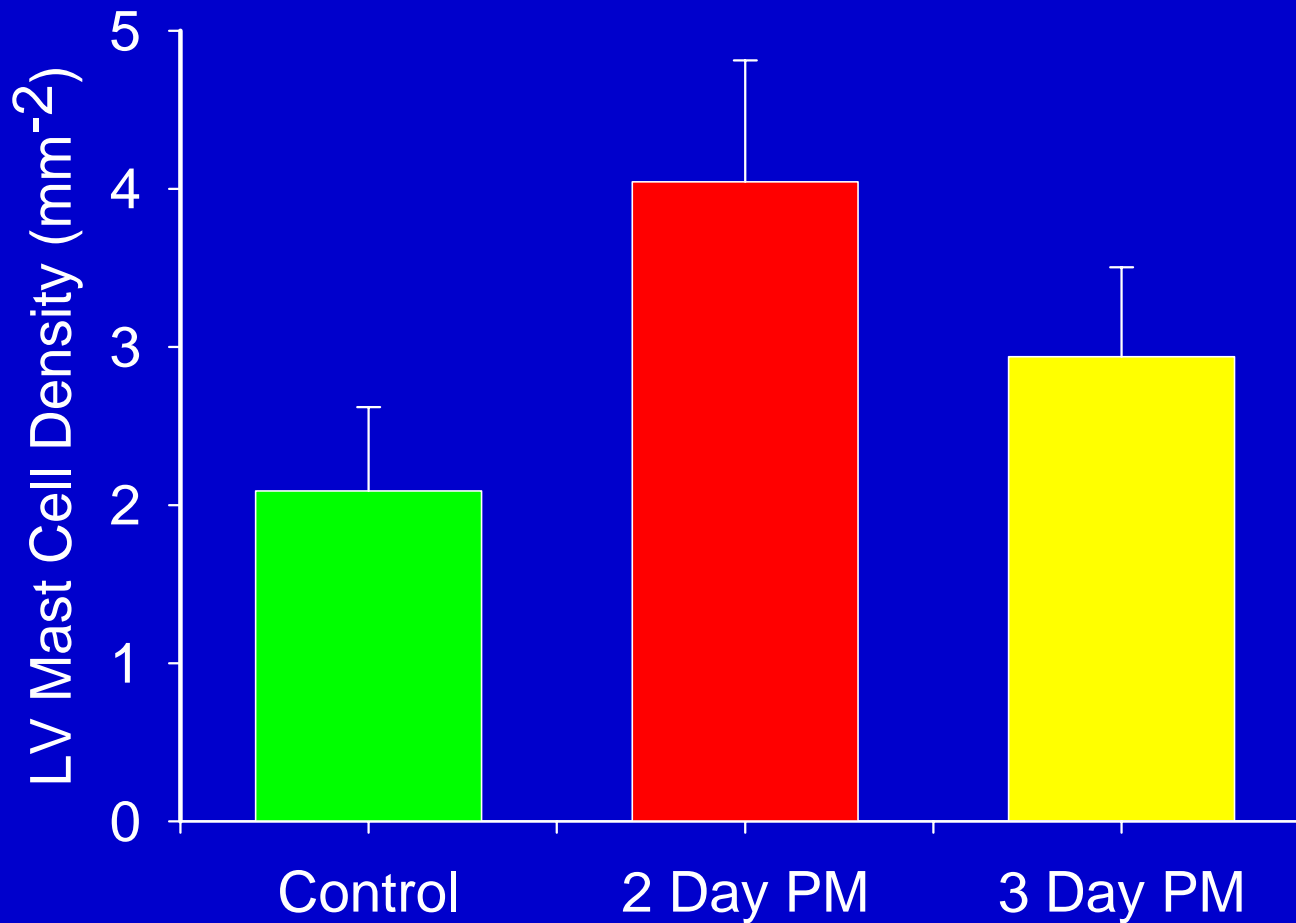
## Diesel Exhaust Emissions

- Lovelace Respiratory Research Institute

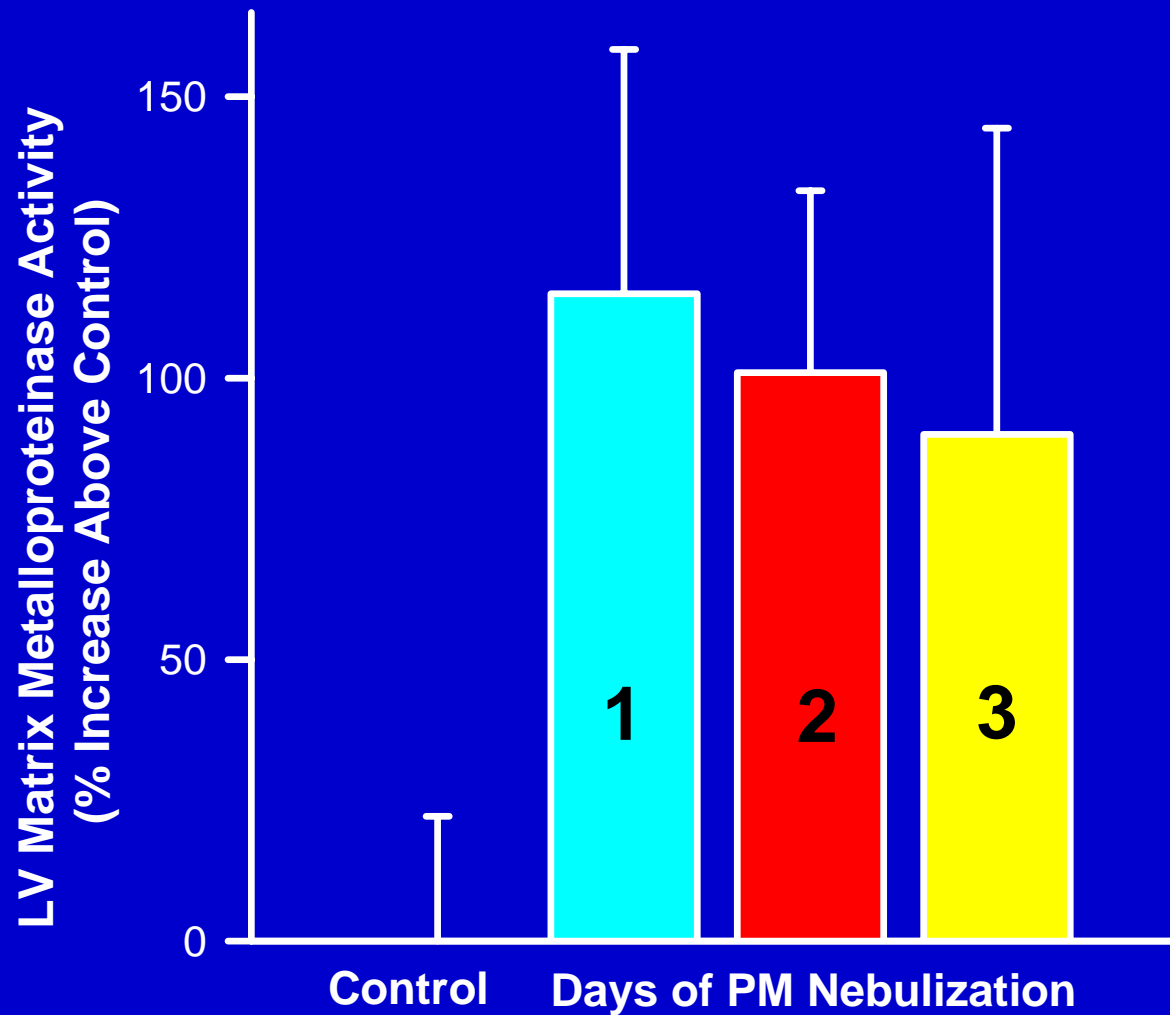
# PM Mediated Depression in Cardiac Function of Normal Hearts



# PM Mediated Mast Cell Response



# PM Mediated MMP Activation



# Ongoing Collaborations

## **Auburn University**

- Jason Gardner
- Joseph Janicki

## **Lovelace Respiratory Research Institute**

- Matt Campen
- Joe Mauderly
- Jake McDonald

## **University of Arkansas for Medical Sciences**

- Martin Hauer-Jensen

## **University of Alabama - Birmingham**

- Lou Dell'Italia
- Susan Oparil

## **University of South Carolina**

- Tom Borg
- Wayne Carver

