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**

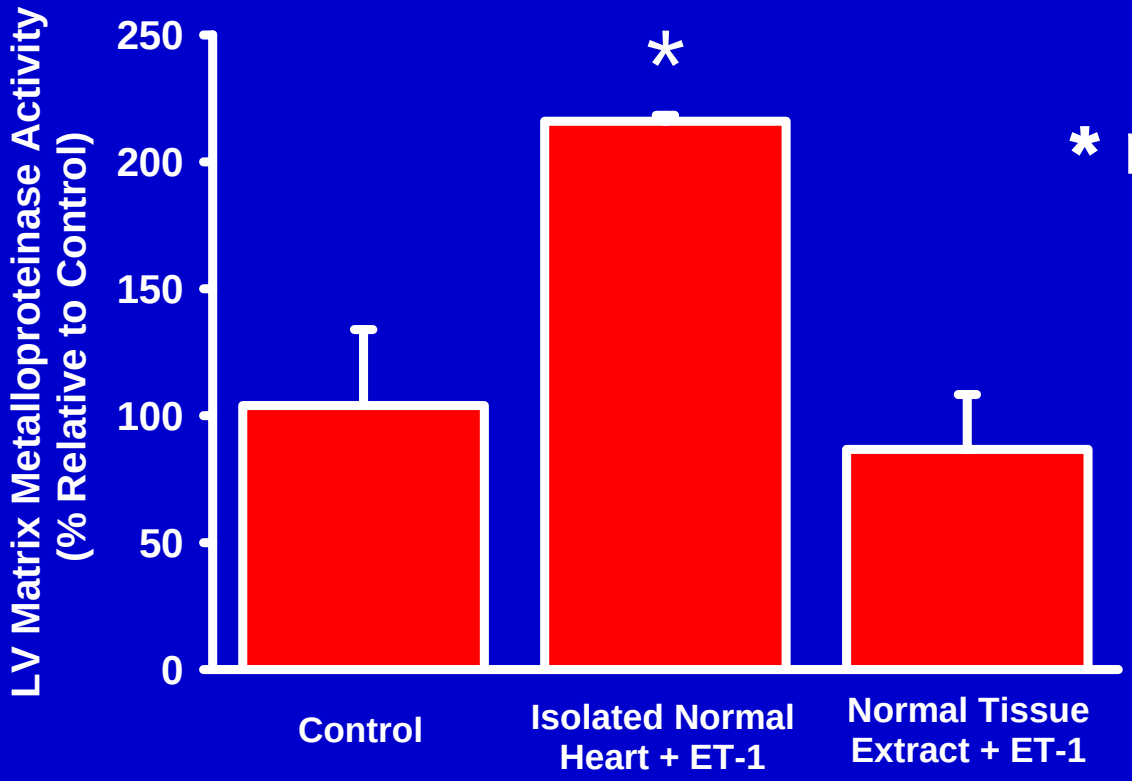
Particulate Matter Mediated Increase in Endothelin

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



* p < 0.01 vs. Control

Collagen Volume Fraction

Control	0.99% ± 0.04
ET-1 Treated	0.69% ± 0.09*

Murray et al.
Am J Physiol 2004.

Particulate Matter:
Mast Cell - MMP Hypothesis

PARTICULATE MATTER EXPOSURE → ↑ET-1

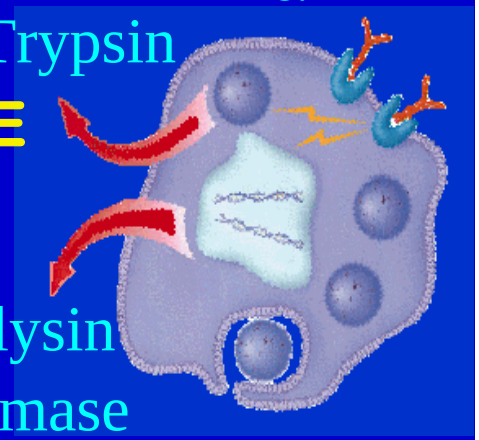
↑ET-1 → MAST CELL DEGRANULATION

MAST CELL DEGRANULATION ⇄ MAST CELL RECRUITMENT

MAST CELL DEGRANULATION → COLLAGENASE ACTIVATION

COLLAGENASE ACTIVATION → COLLAGEN DEGRADATION

COLLAGEN DEGRADATION → VENTRICULAR DILATATION



Specific Aims

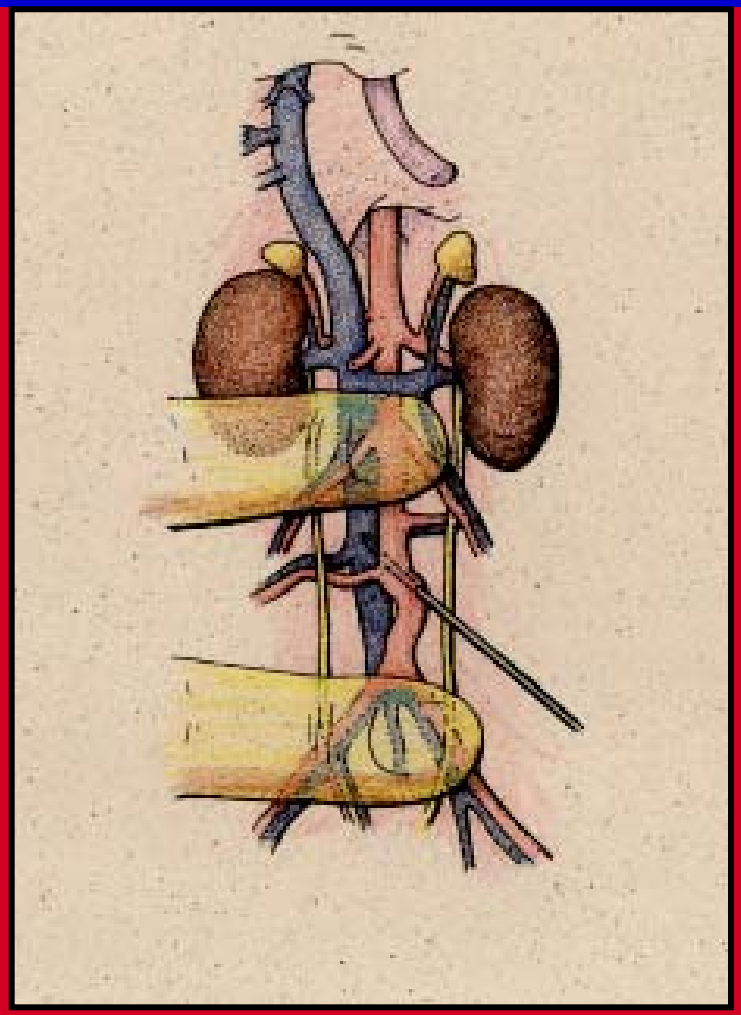
To determine:

- **1) the causal relationship between acute diesel PM exposure, mast cell activation, and exacerbation of CHF with a resultant increase in morbidity and mortality**

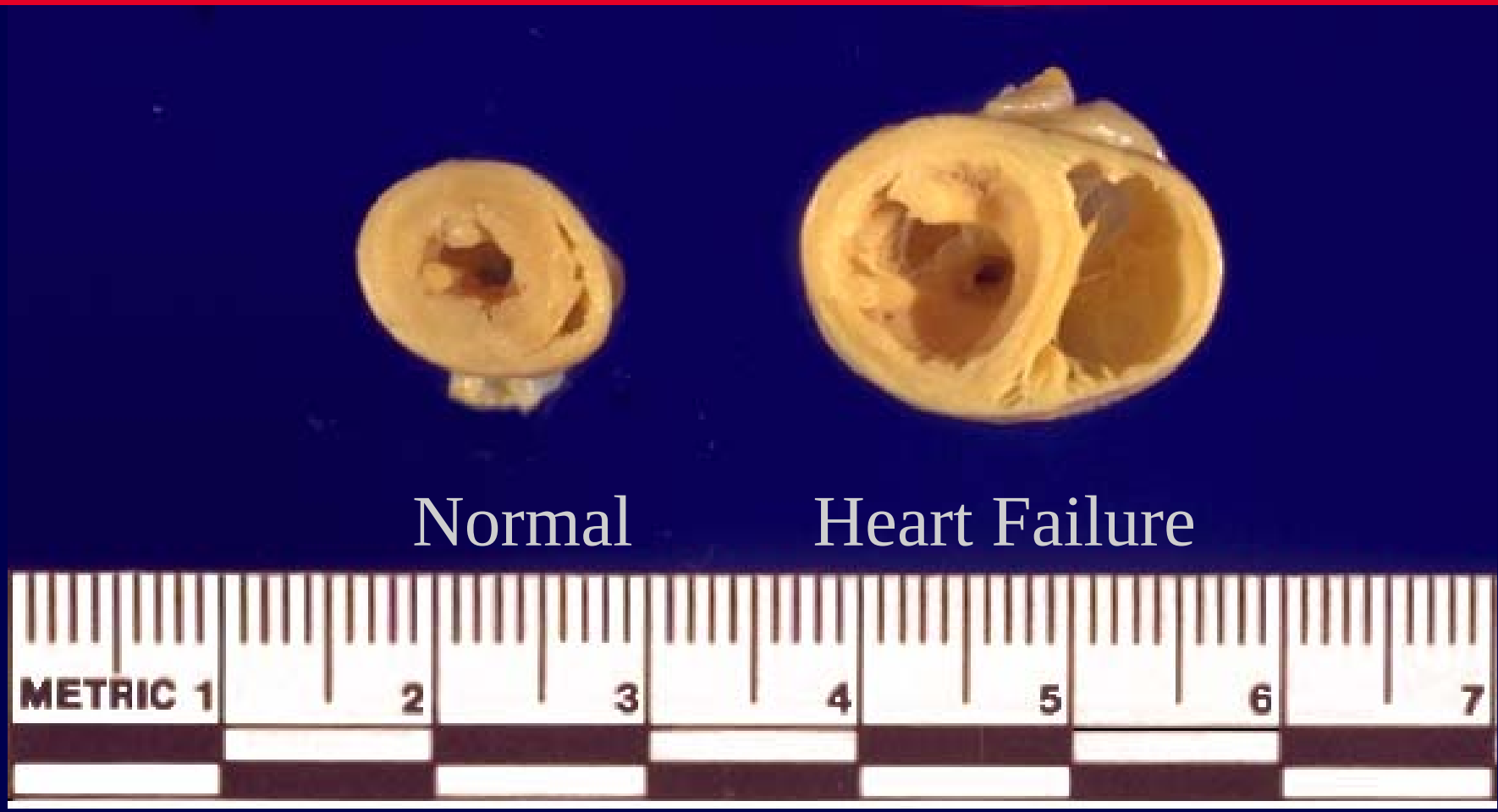
- **2) the mechanisms by which subchronic diesel PM exposure accelerates cardiac remodeling and the development of CHF.**

Infrarenal A-V Fistula

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



Cardiac Remodeling Post-Fistula



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

Particulate Matter Exposure

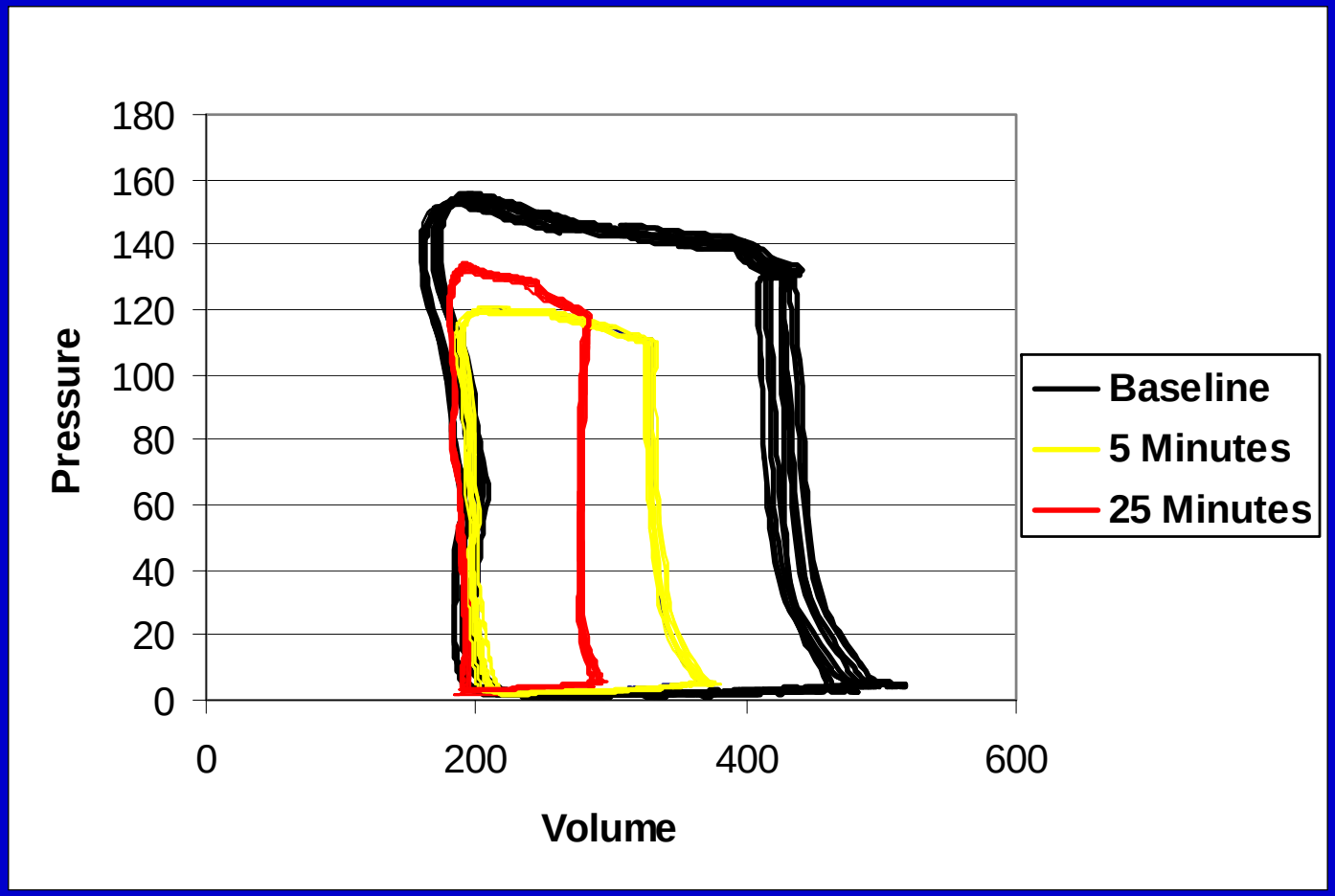
Nebulization

- SRM 2975 DEP (NIST)
  - 4.5 mg / 20 ml 0.9% Saline
  - Nebulized delivery at 3.0-3.5 l/min O2
  - One 30 min exposure per day

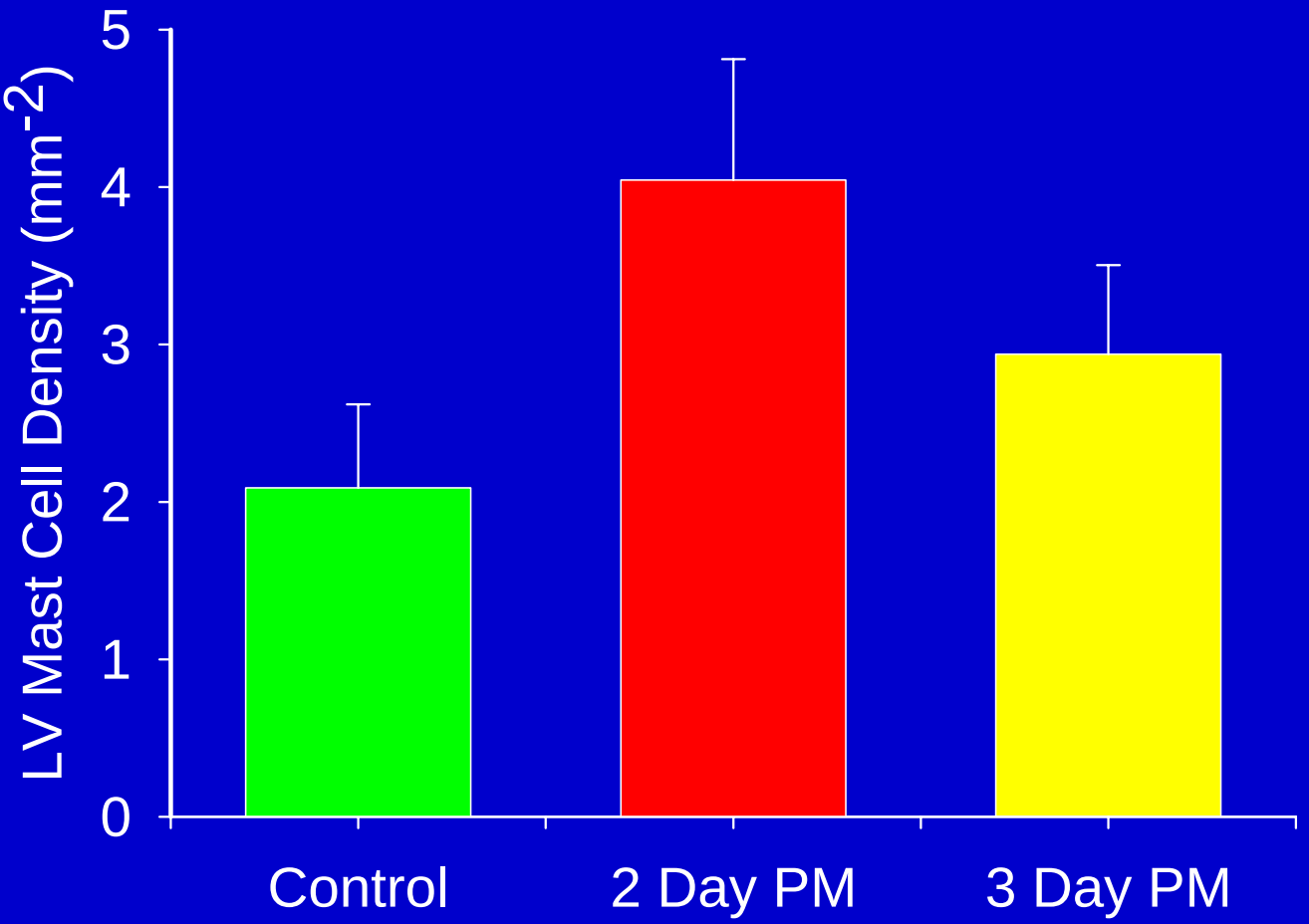
Diesel Exhaust Emissions

- Lovelace Respiratory Research Institute

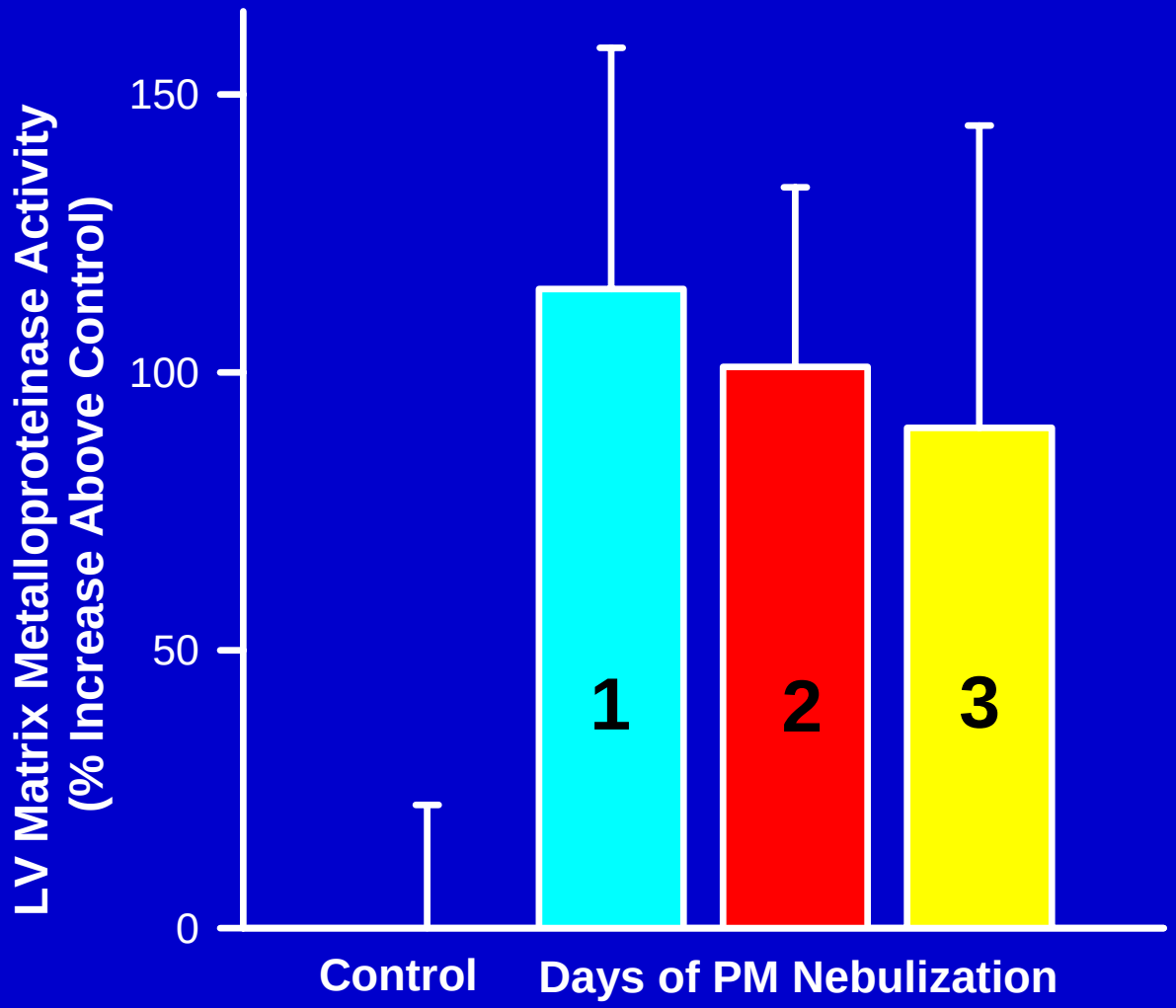
PM Mediated Depression in Cardiac Function of Normal Hearts



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