Particle toxicity and pollutant gas/particle interactions in a rat model of acute myocardial infarction

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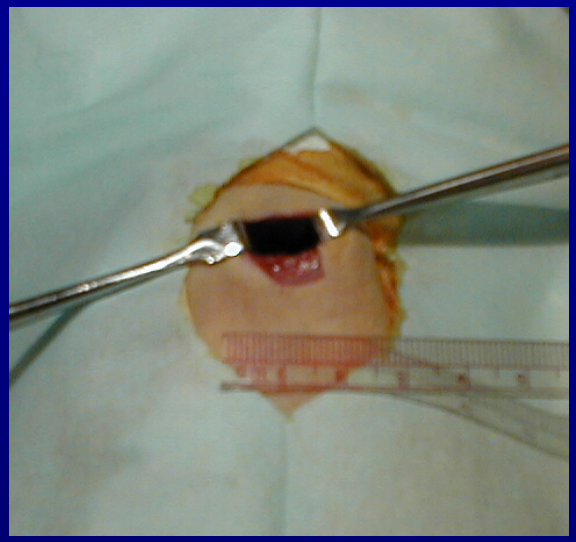
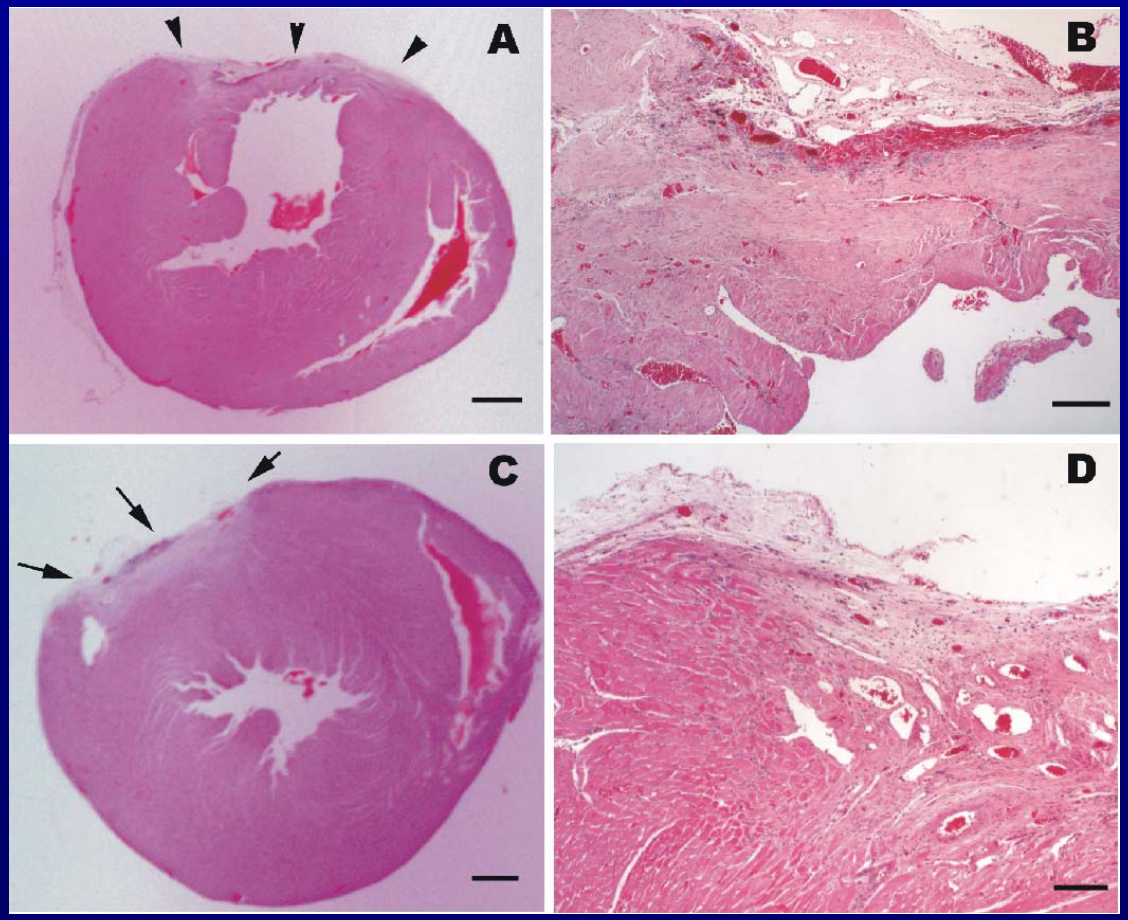
Rat Model of Acute MI

- Perform left thoracotomy to expose heart.
- Cauterize left main coronary artery to induce MI.
- Close chest.



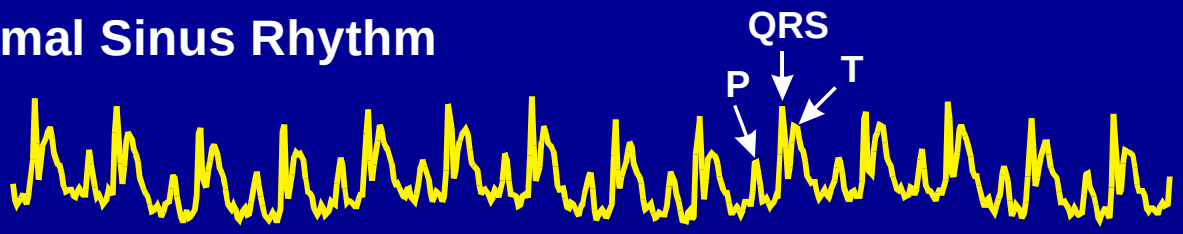
Surgical Outcomes



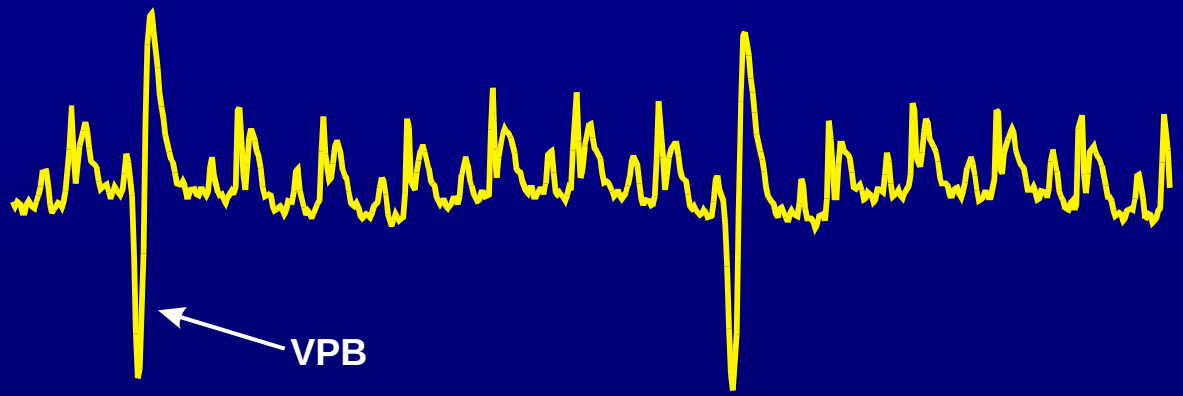
Wellenius et al. , 2004

Sample ECG

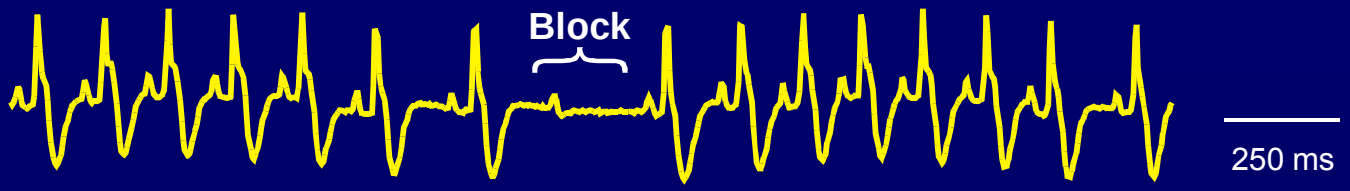
Normal Sinus Rhythm



Ventricular Premature Beats

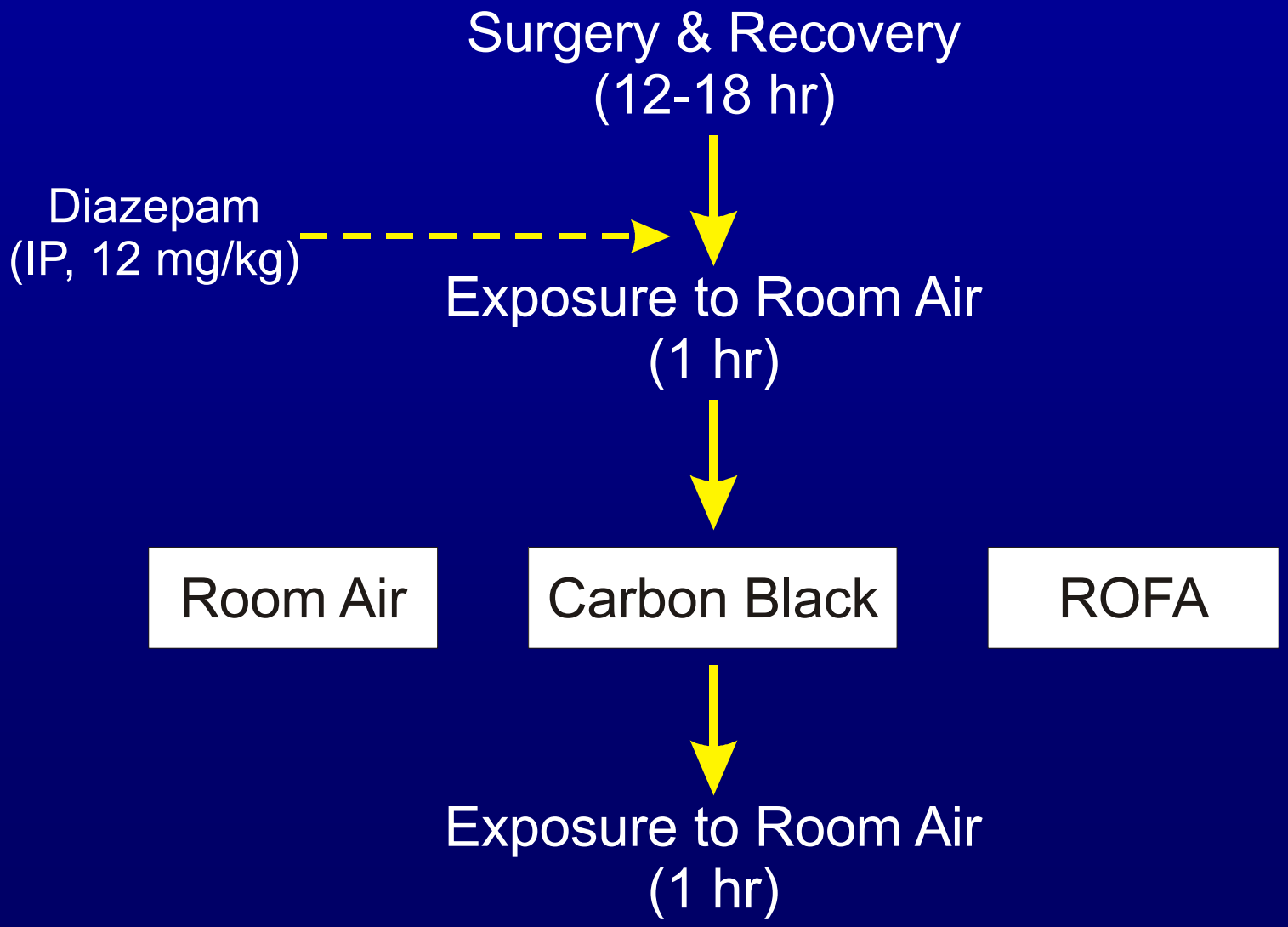


Atrioventricular Block



Wellenius et al. , 2002

Experimental Design



Change in VPB Frequency During Exposures as Compared to Room Air

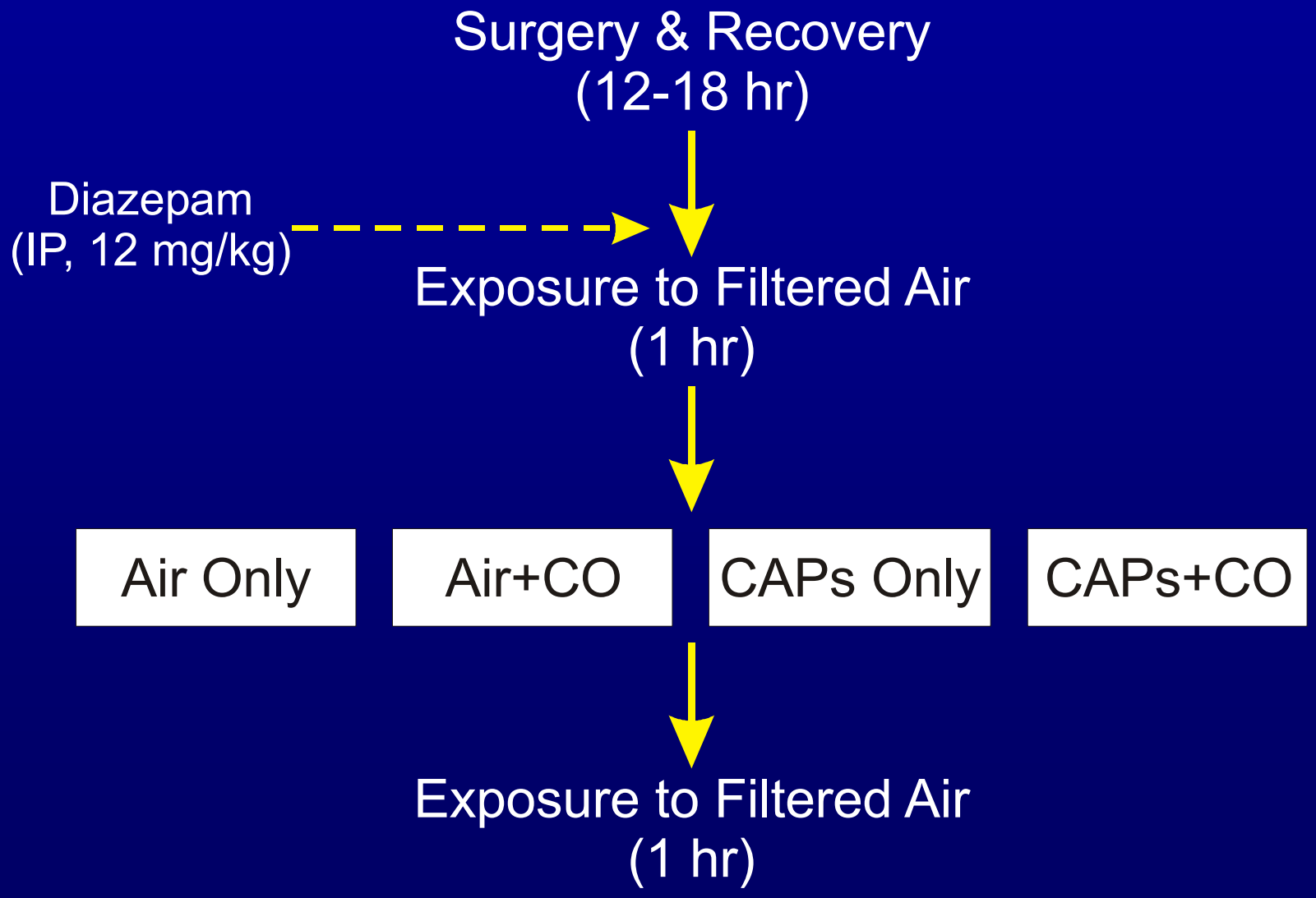
Exposure	% Δ	95% CI	p
ROFA	↑ 566.7%	185.4, 1457.2	<0.0001
Carbon Black	↓ 52.3	-90.6, 140.5	0.37

Wellenius et al. , 2002

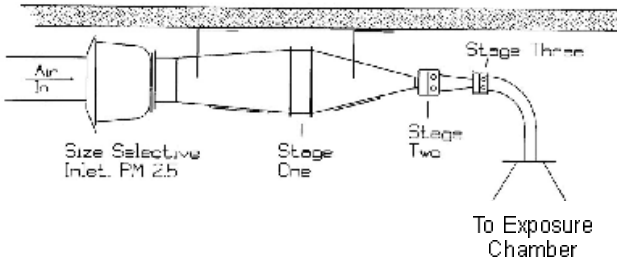
Study Hypotheses

1. Exposure to CAPs will increase arrhythmia incidence
2. Exposure to low levels of CO will increase arrhythmia incidence
3. Exposure to a combination of CAPs and CO will synergistically increase arrhythmia incidence

Experimental Design

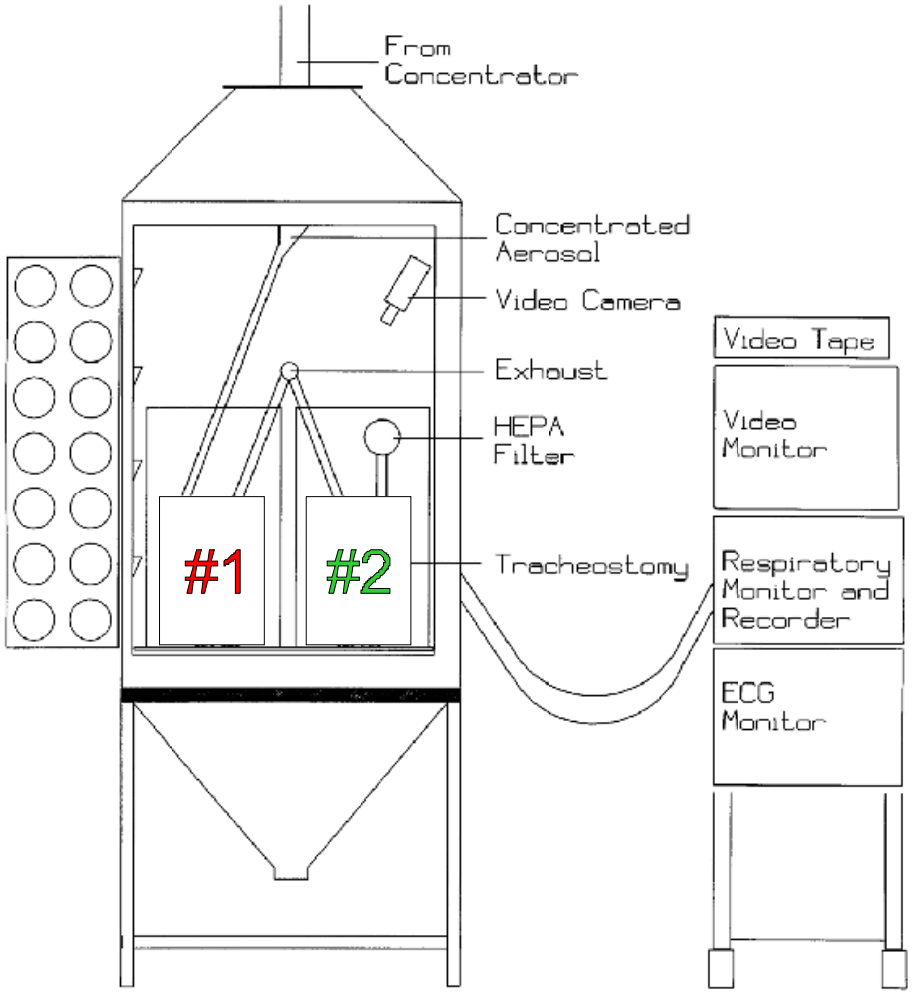


Harvard Ambient Particle Concentrator



CAPs:

- $PM_{2.5}$
- Concentration is ~30x ambient
- Composition is same as ambient



Exposure Characterization

Sampling Airstream	Sample Type	Parameter	Analytic Method
Ambient Air Particles	Integrated	Mass Concentration	Gravimetric Analysis
		Sulfate	Ion Chromatography
		Ammonium	Ion Chromatography
		Particle Size Distribution	Gravimetric Analysis
	Continuous	Carbon Monoxide	Non-Dispersive Infrared
Concentrated Air Particles	Integrated	Mass Concentration	Gravimetric Analysis
		Sulfate	Ion Chromatography
		Elemental/Organic Carbon	Thermal/Optical Reflectance
		Trace Metals	X-Ray Fluorescence
		Endotoxins	KLARE Limulus Ameobocyte Assay
	Continuous	Non-Volatile Fine Mass Concentration	Tapered Element Oscillating Microbalance
		Black Carbon	Aethalometer
		Particle Number Concentration	Condensation Particle Counter

Godleski et al. *HEI* 2000

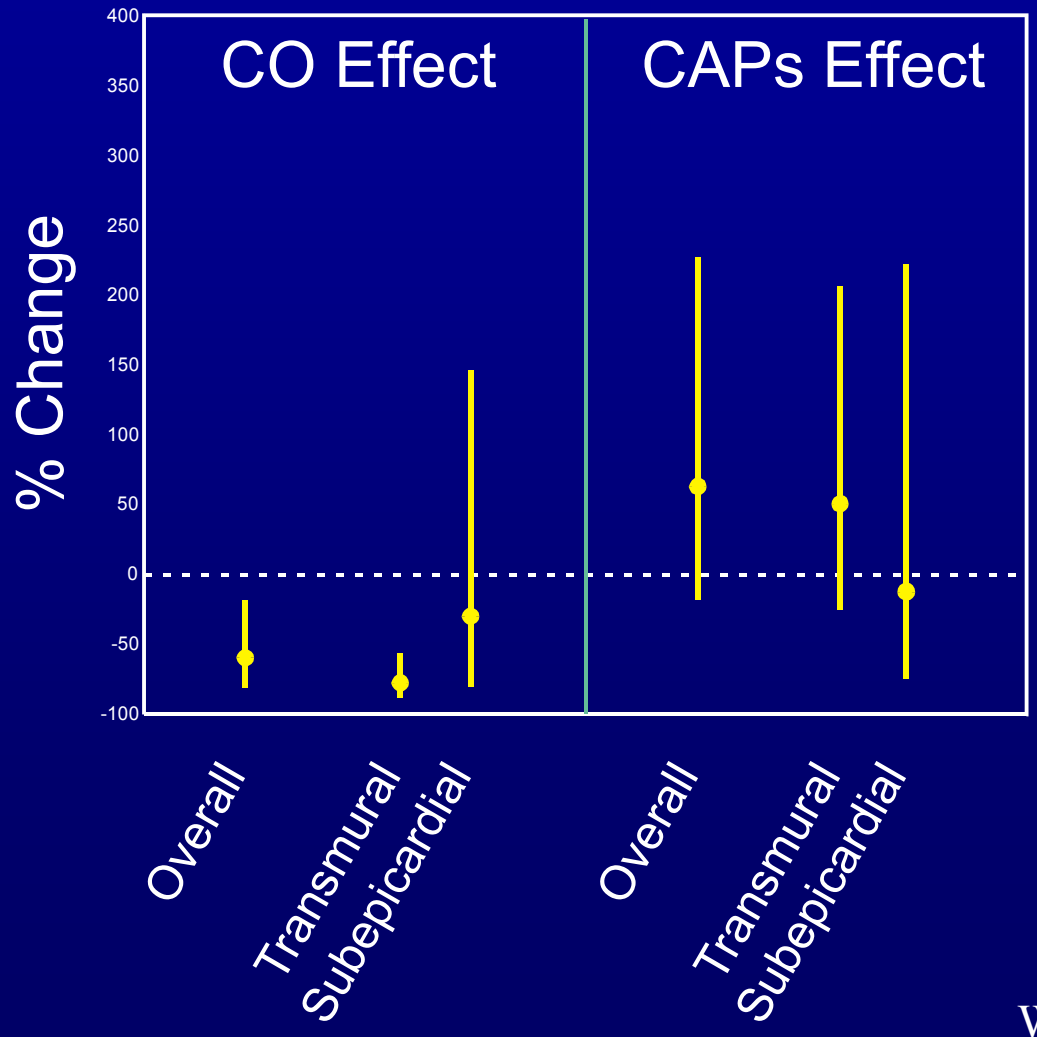
Change in VPB Frequency During CAPs and CO Exposures as Compared to Filtered Air

Exposures	% Δ	95% CI	p
CAPs	↑64.2%	-17.7, 227.6	0.16
CO	↓60.4%	-80.7, -18.8	0.012
CAPs/CO*	↓35.0%	-53.6, 246.6	ns

*: In a model assuming no interaction between CAPs and CO

Wellenius et al. , 2004

Effects on Arrhythmia Frequency



Wellenius et al. , 2004

Key Findings

- Animal model for studying arrhythmias is available
- Frequency ventricular arrhythmias
  - Significantly increased by ROFA
  - Tendency towards increase by CAPs
  - Significantly decreased by CO
  - No interaction was observed between the effects of CAPs and CO.

Magnitude of Effect by Exposure

Exposure	% Δ	95% CI	p
ROFA	↑ 566.7%	185.4, 1457.2	<0.0001
CAPs	↑ 64.2%	-17.7, 227.6	0.16
CO	↓ 60.4%	-80.7, -18.8	0.012

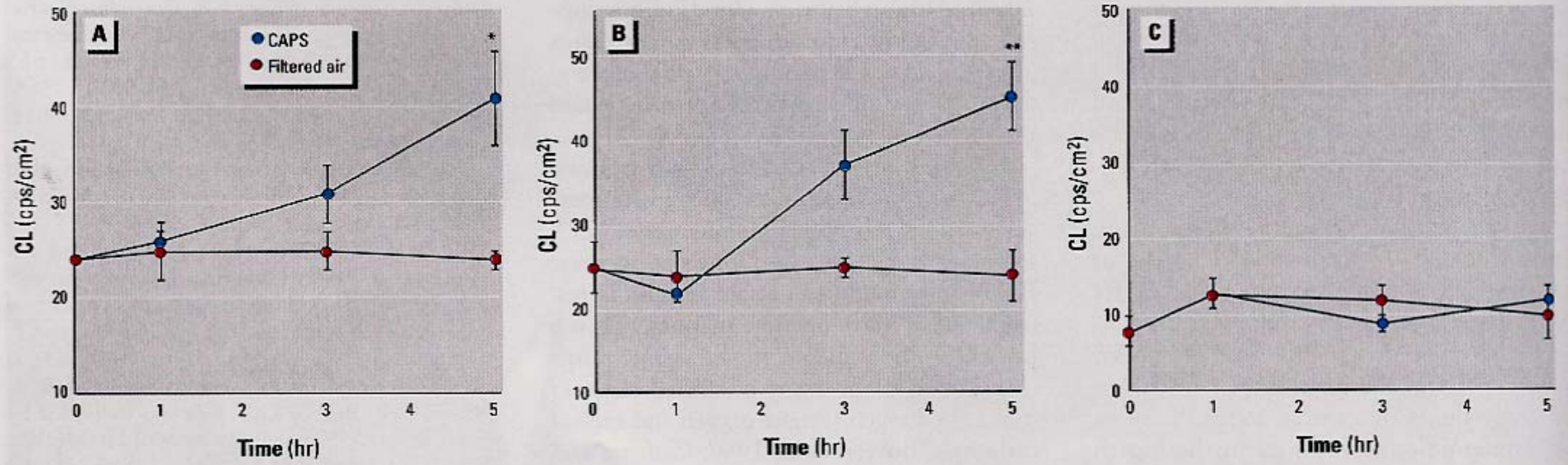
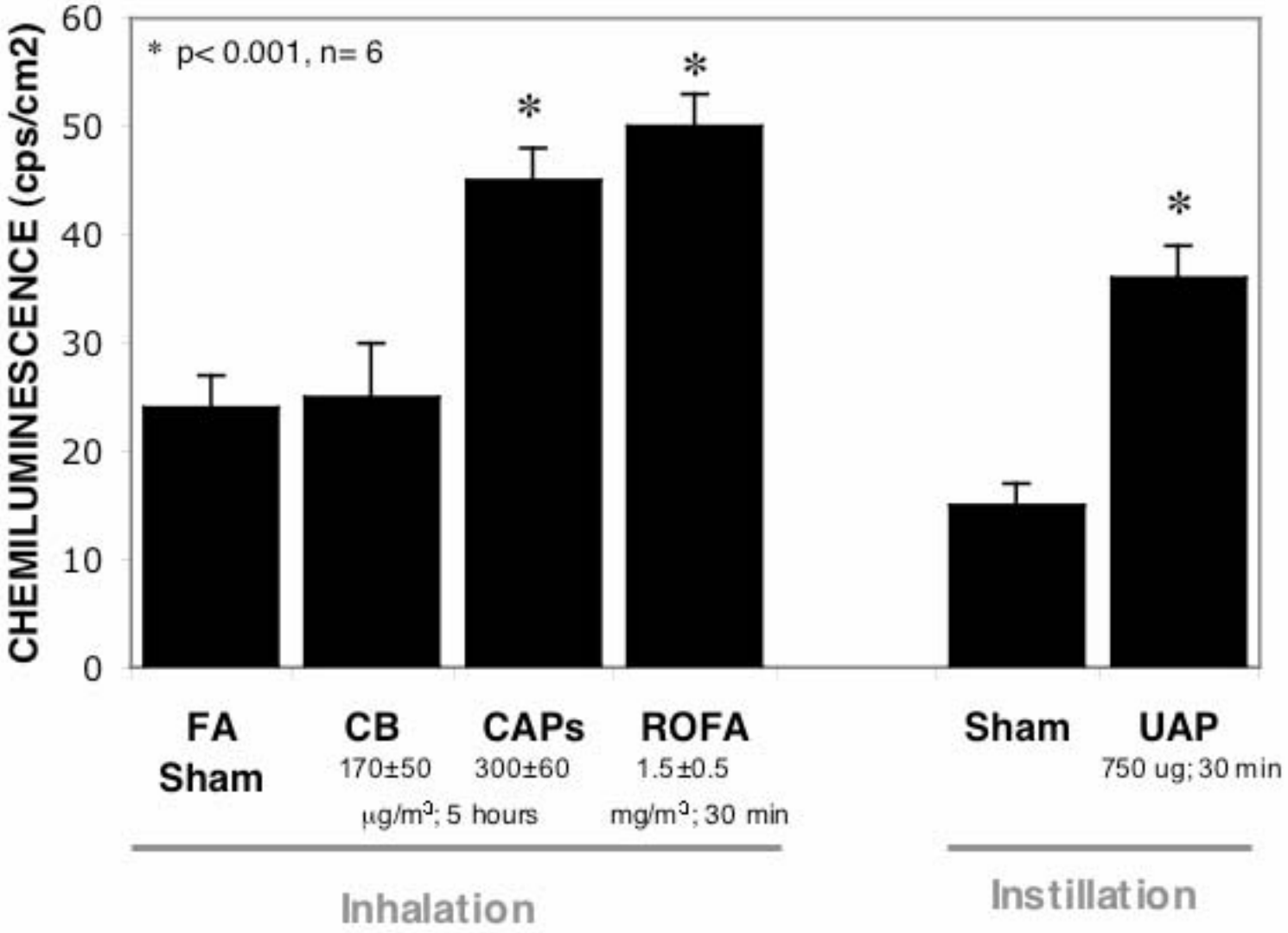


Figure 1. Time course of increase of *in situ* CL from the lung (*A*), heart (*B*), and liver (*C*) of rats exposed to CAPs (average mass concentration, 300 ± 60 μg/m³) or filtered air for 1, 3, and 5 hr. See "Materials and Methods" for details. Each point represents the mean ± SEM ($n = 10$ determinations). Compared with their sham controls or with time 0, $^{*}p < 0.001$ and $^{**}p < 0.005$.

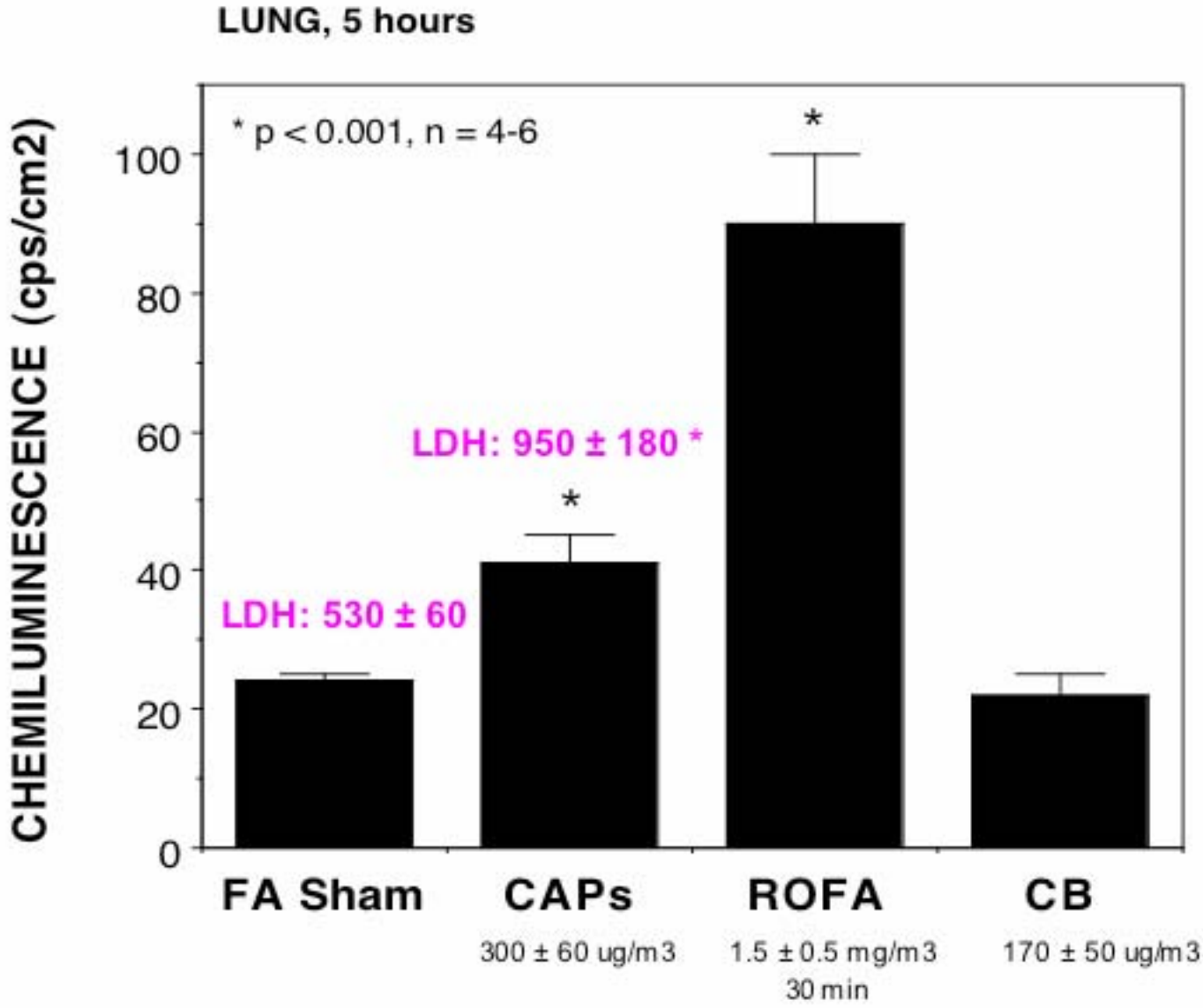
Gurgueira SA, et al. Rapid Increases in the Steady-State Concentration of Reactive Oxygen Species in the Lungs and Heart after Particulate Air Pollution Inhalation. Environ. Health Perspect. 110:749-755 (2002)

PM exposure increases the steady-state concentration of oxidants in the heart



Gurgueira et al, *EHP* 2002; Rhoden et al, in preparation 2004

CAPs inhalation increases the steady-state concentration of oxidants in the lung.



Summary

- Particle / Gaseous pollutant effects can be disentangled in laboratory studies.
- Particles and environmentally relevant levels of CO have opposite effects on arrhythmias in a model of acute MI.
- Similar exposure protocols yield similar results in measurements of *in vivo* chemiluminescence in the heart and arrhythmias in the MI studies.
- ROFA has greater toxicity than CAPs.