

Ultrafine Particle Deposition and Clearance in the Healthy and Obstructed Lung

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Abstract

Numerous epidemiological studies have shown associations between exposure to particulate air pollution and acute increases in morbidity and mortality, particularly in persons with chronic obstructive pulmonary disease. The dosimetry of ultrafine particles in the human lung is poorly characterized. We studied the deposition and clearance of an ultrafine technetium-99m labeled aerosol in 10 patients with chronic obstructive pulmonary disease and 9 healthy subjects. Particle retention was followed for 2 hours post-inhalation and again at 24 hours by gamma scintigraphy. Central-to-peripheral ratios indexed airway deposition. Particle accumulation in the liver was examined by quantifying activity below the right lung. The dose rate for an aerosol exposure of 10 $\mu\text{g}/\text{m}^3$ was calculated. Patients had a significantly greater dose rate than healthy subjects (2.9 ± 1.0 vs. 1.9 ± 0.4 $\mu\text{g}/\text{hr}$, $p=0.02$). Central-to-peripheral ratios were slightly greater in patients than healthy subjects (1.11 ± 0.10 vs. 1.01 ± 0.11 , $p=0.05$). Clearance did not statistically differ between health and disease. On average, 24-hour retention was $85 \pm 8\%$ (corrected for isotope dissolution). No accumulation in the liver's vicinity was observed. Data suggest that relative to healthy subjects, patients with moderate-to-severe airways obstruction receive an increased dose from ultrafine particle exposure.

Introduction

A fair amount of data on the deposition of ultrafine particles in healthy volunteers is available. However, ultrafine deposition data for the diseased lung are limited to five chronic obstructive pulmonary disease (COPD) patients and three restrictive lung disease patients studied by Anderson and colleagues. Data for ultrafine particle clearance from the human lung are far more limited. The purpose of our study was to characterize the deposition and clearance of a technetium-99m-labeled ultrafine aerosol in patients with COPD and healthy age-matched volunteers.

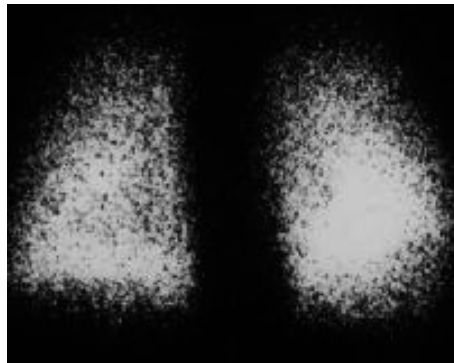
Conclusions

We have found that patients with moderate to severe COPD have an increased Dose of 54% relative to healthy subjects. Some of this increased deposition occurs in the airways, although most likely occurs in the parenchymal lung. Given that these patients have heterogeneous ventilation within their lungs, they may receive a tissue dose to the parenchymal lung that is many times that occurring in the healthy lung. We found no evidence of the rapid pulmonary clearance of these insoluble, carbon ultrafine particles into the circulation. The increased tissue dose received by COPD patients may contribute to systemic effects as a result of an exacerbation of their airway inflammation and cytokine release into circulation, but not the rapid movement of significant number of insoluble particles into the circulation.

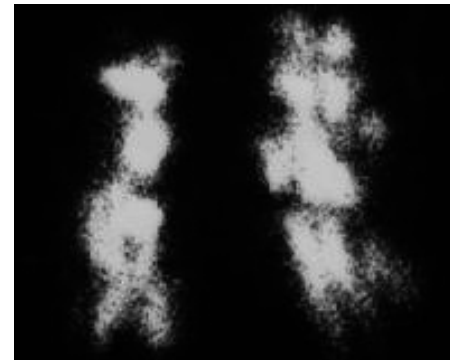
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Healthy



Severe Obstruction

0.2 μm aggregates composed of 7-23 nm primary particles

Burch et al. *J Nucl Med.* 27: 842-846, 1986

Background

Exposure to ambient particulate matter is associated with increased morbidity/mortality in respiratory/ cardiovascular disease.

Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. Respiratory effects are associated with the number of ultrafine particles. *Am J Respir Crit Care Med* 1997;155:1376–1383.

Toxicity of ultrafine particles is greater than fine particles composed of same material.

Ferin J, Oberdorster G, Penny DP. Pulmonary retention of ultrafine and fine particle in rats. *Am J Respir Cell Mol Biol* 1992;6:535–542.

Rapid translocation of ultrafine particles into the blood?

Nemmar A, Hoet PHM, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, Vanbilloen H, Mortelmans L, Nemery B. Passage of inhaled particles into the blood circulation in humans. *Circulation* 2002;105:411–414.

Subjects

	FEV ₁ %pred	Raw cm-H ₂ O / lps	DI _{CO} %pred	PIII SBN ₂ %N ₂ / L
Healthy (n=9)	104 ± 16	1.26 ± 0.42	112 ± 9	1.85 ± 0.82
COPD (n=10)*	54 ± 20	2.52 ± 0.91	72 ± 23	8.88 ± 5.26

* significantly different from healthy, p<0.01

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COPD (n=10)*	54 ± 20	2.52 ± 0.91	72 ± 23	8.88 ± 5.26
Bronchitic (n=7)*¶	64 ± 13	2.16 ± 0.63	84 ± 13	5.69 ± 2.60
Emphysemic (n=3)*	31 ± 9	3.36 ± 1.04	43 ± 5	15.3 ± 1.5

* significantly different from healthy, p<0.01

¶ significantly different from emphysemic, p≤0.05

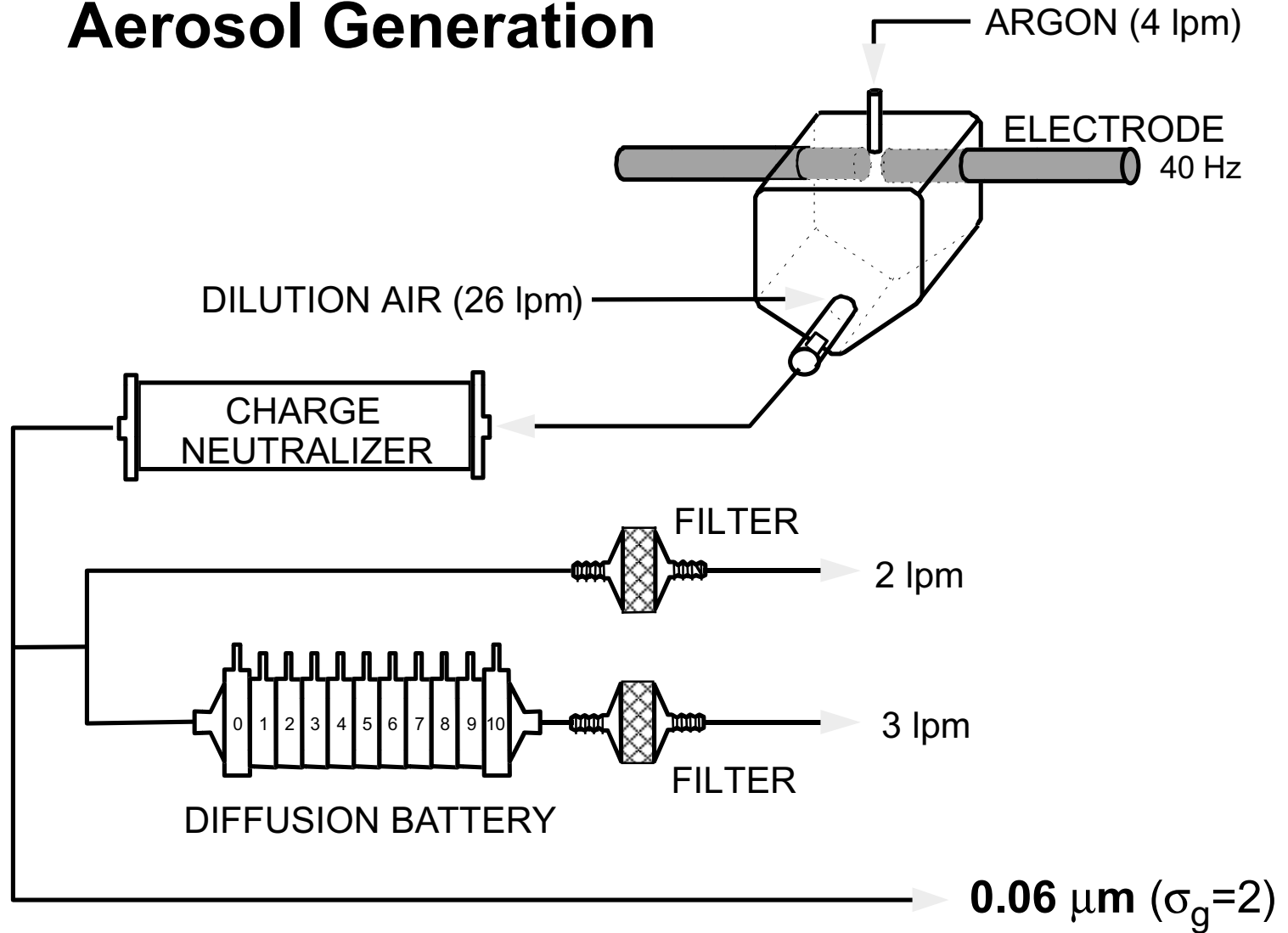
Protocol

Ultrafine Aerosol Inhalation (carbon-Tc-99m)

- 60 nm ($\sigma_g=2$) aggregates,
primary particles 22 nm ($\sigma_g=1.2$)
- Natural breath pattern (measured previously
by RespiTrace)
- Retention followed for 2 hours by gamma camera
- Retention scan at 24 hours

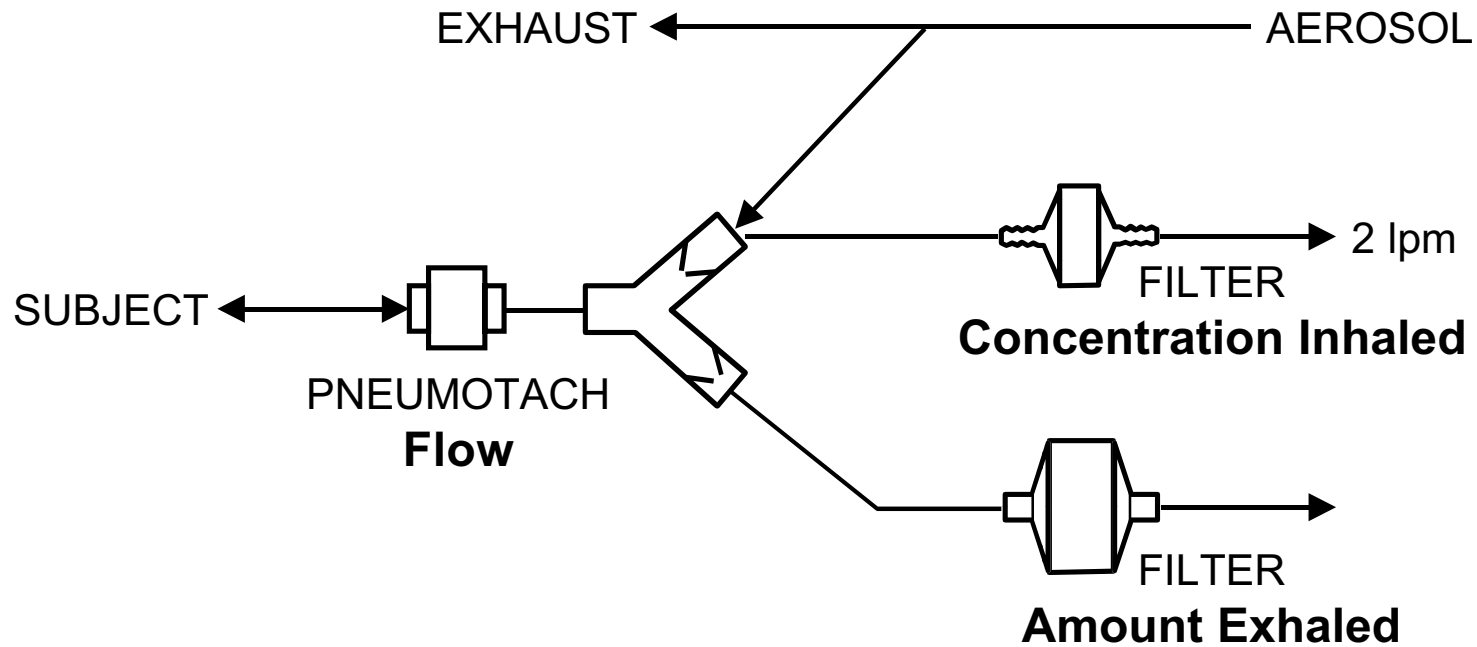
Multi-breath gas equilibrium & washout (Xe-133)

Aerosol Generation



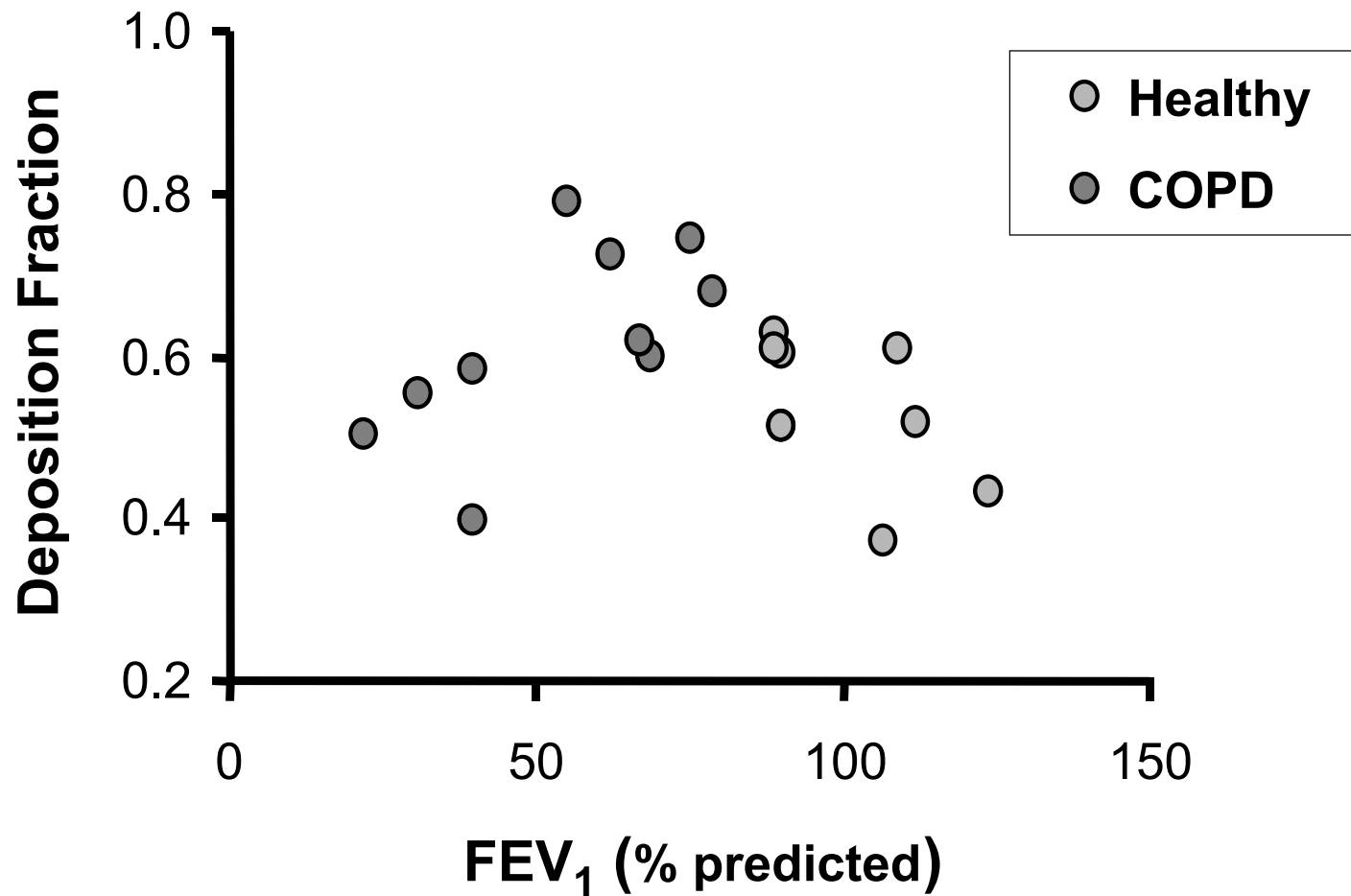
Brown et al. *Aerosol Sci. Technol.* 32(4): 325-337, 2000

Total Particle Deposition

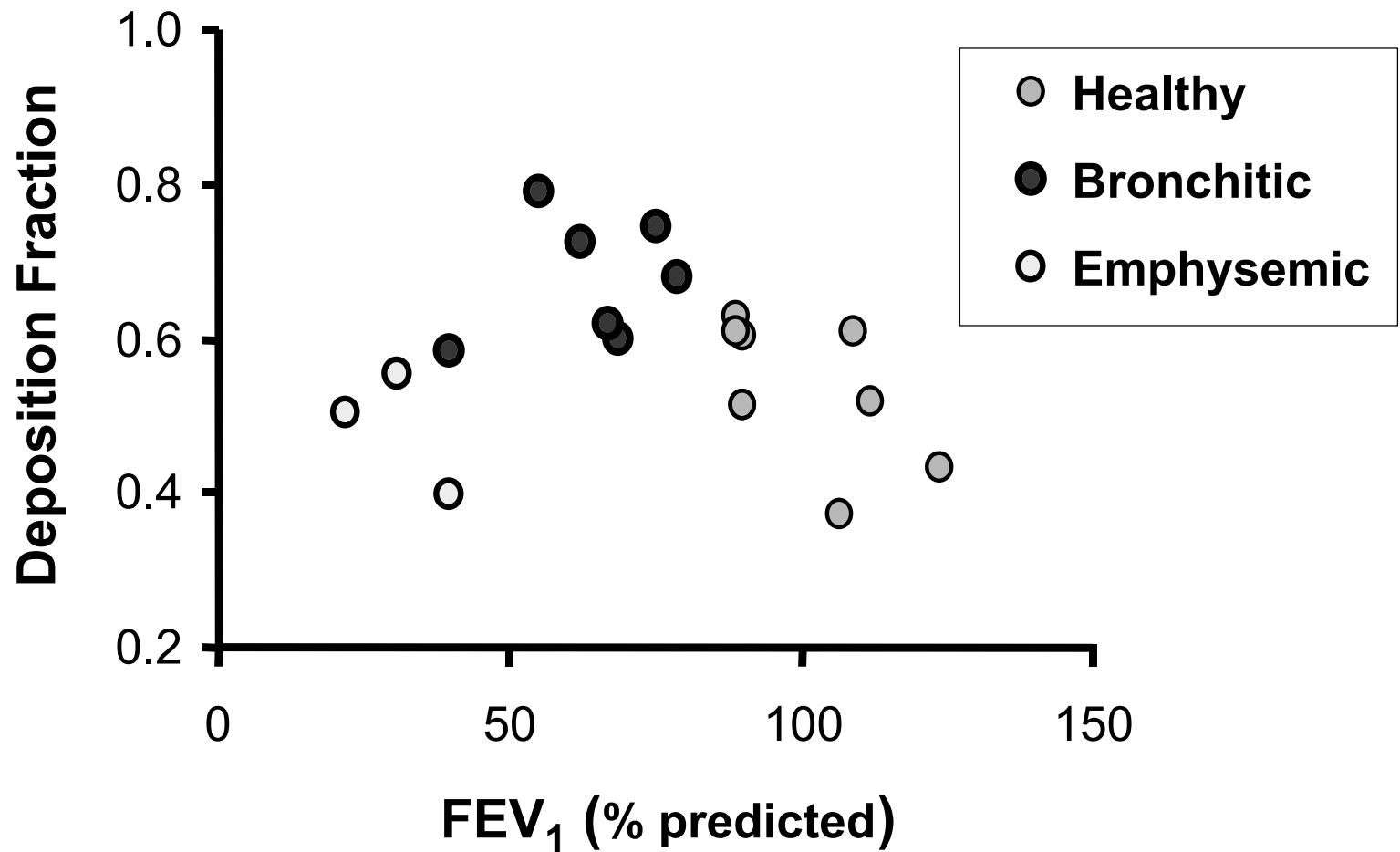


$$\text{Deposition Fraction (DF)} = \frac{(\text{Activity}_{\text{in}} - \text{Activity}_{\text{out}})}{\text{Activity}_{\text{in}}}$$

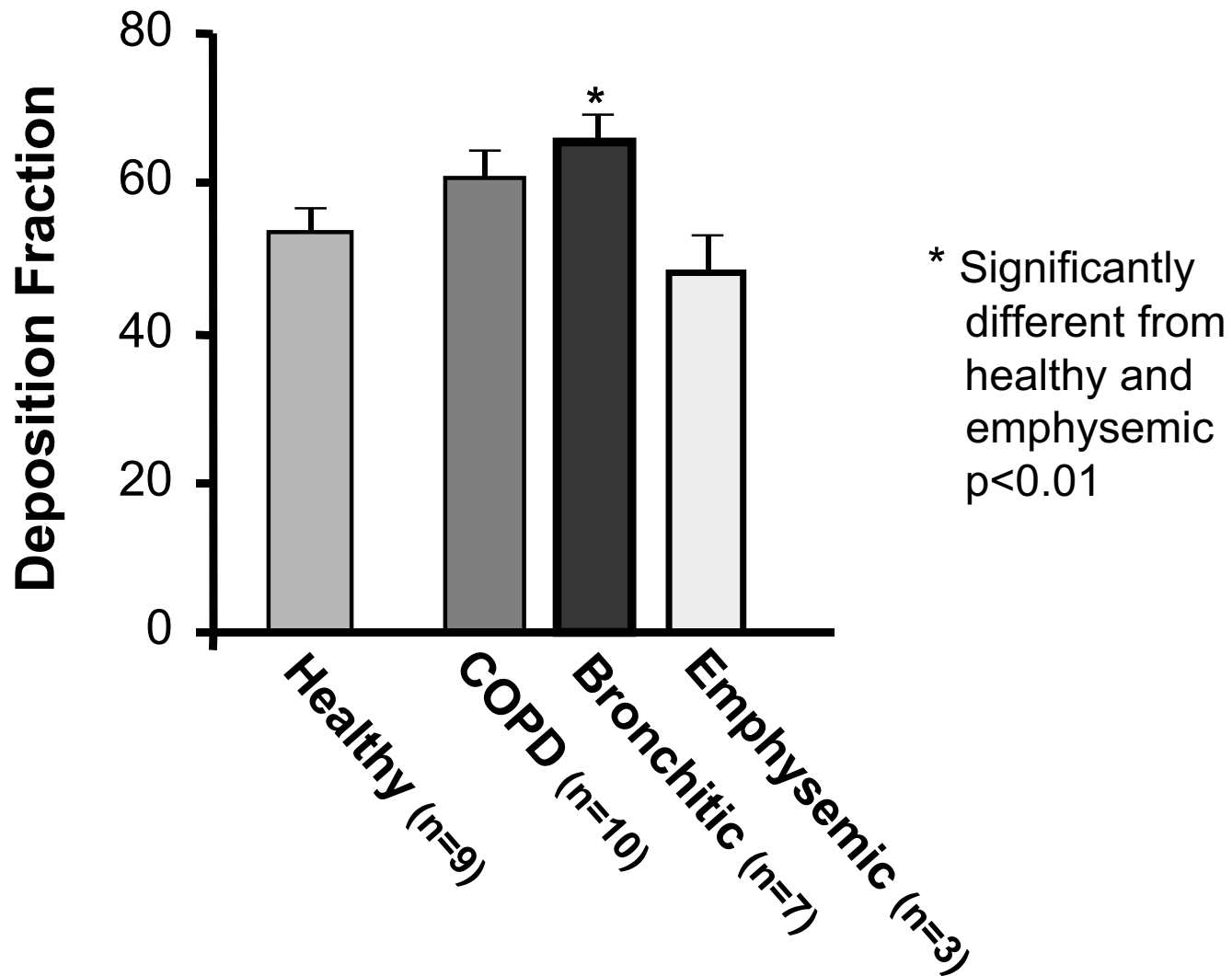
Deposition fraction vs. lung function



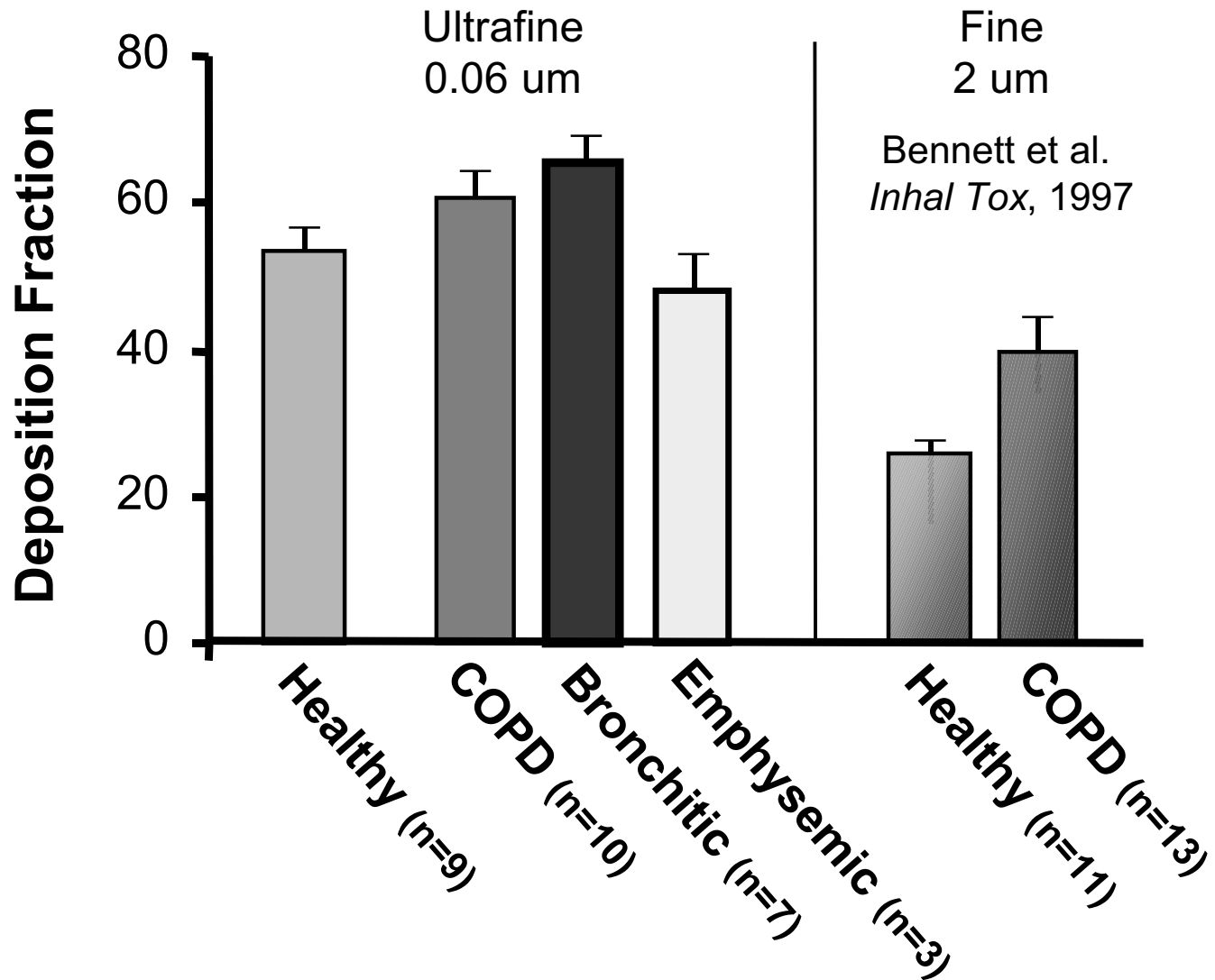
Deposition fraction vs. lung function



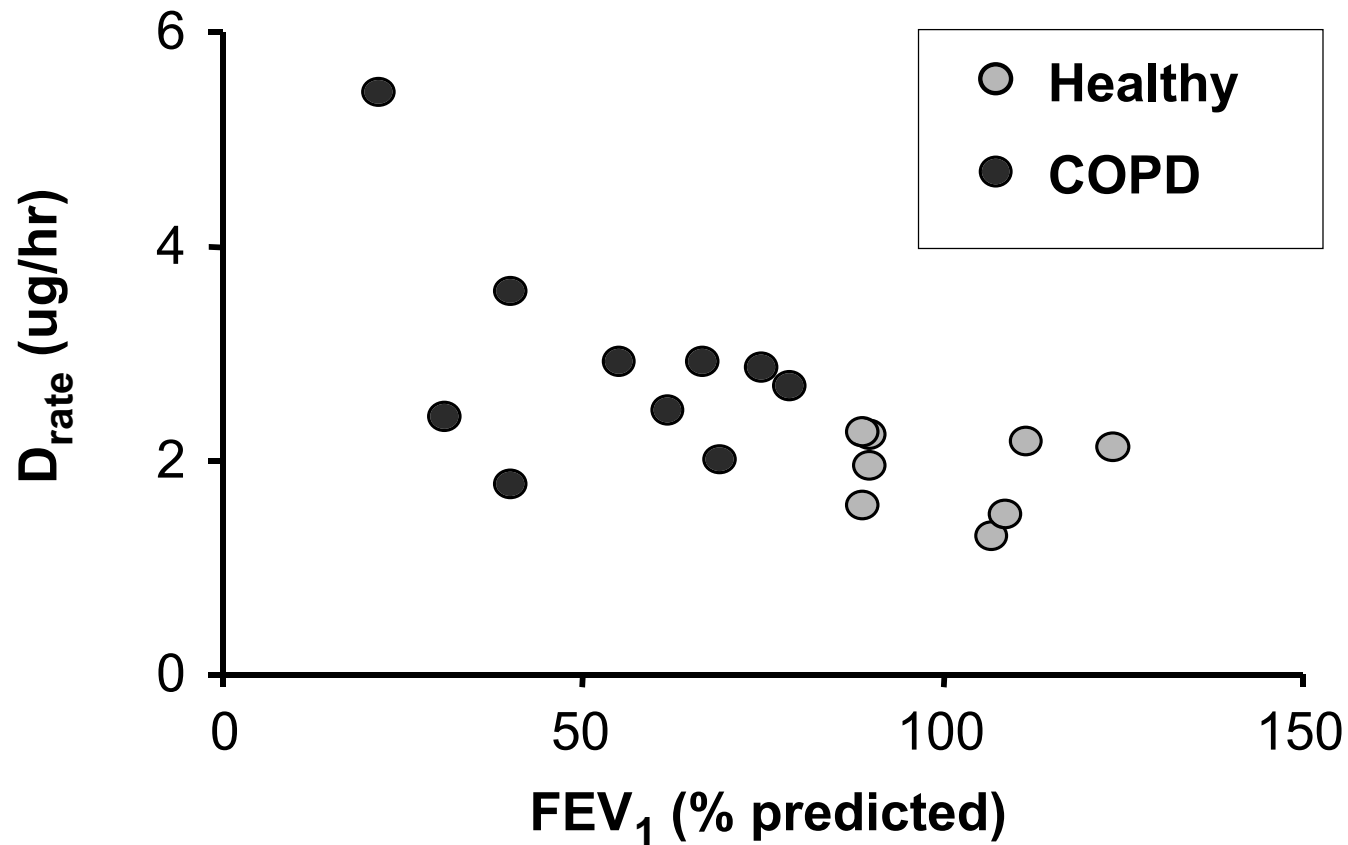
Total Particle Deposition



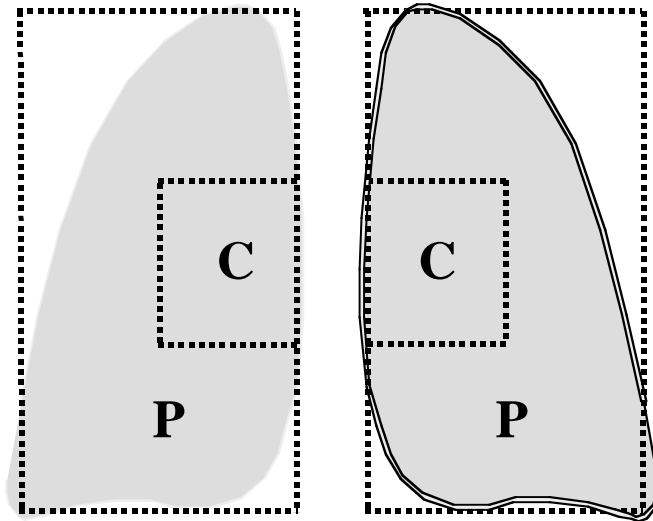
Total Particle Deposition



Deposition rate ($D_{rate} = DF \times Ve \times \text{aerosol conc (10\mu\text{g}/\text{m}^3)$)
increases with decreasing lung function



Regional Particle Deposition (C/P)



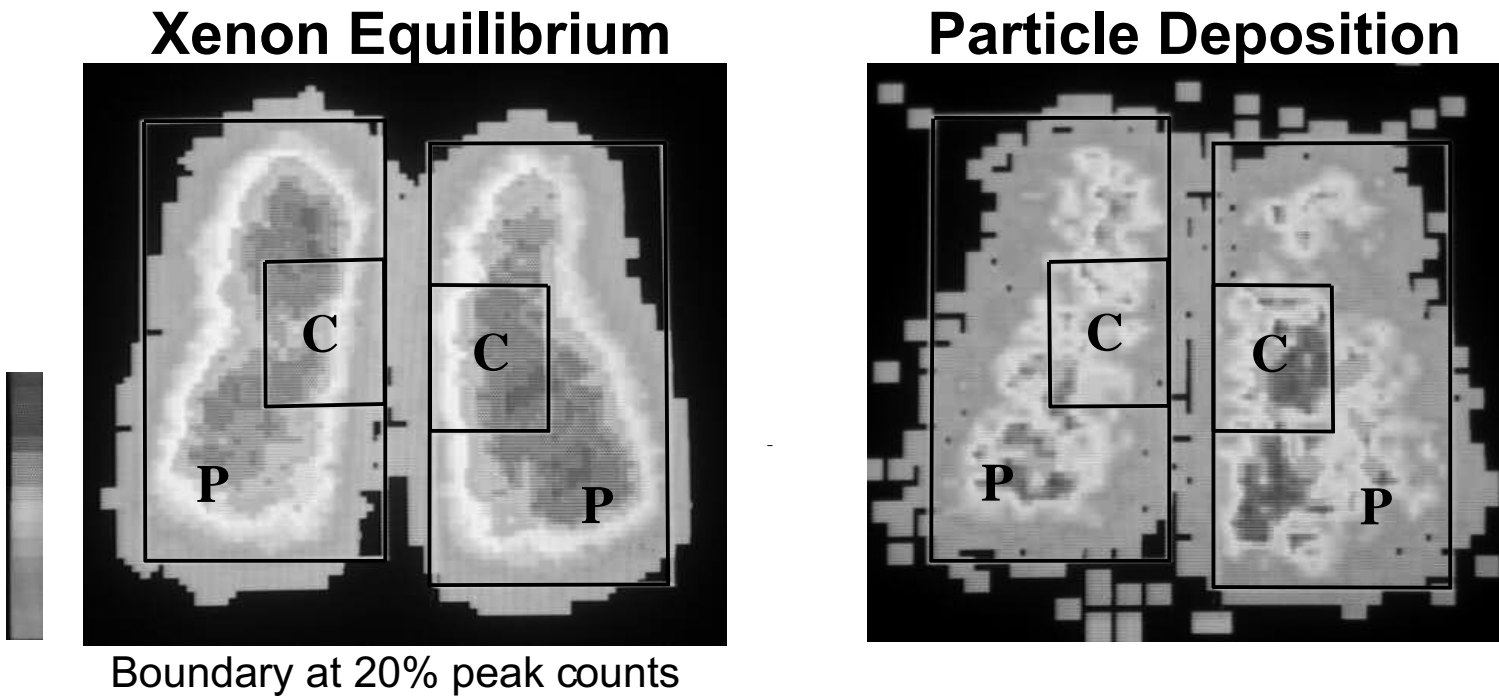
Lungs boundary at 20% peak xenon equilibrium counts.

C - central region
P - peripheral region

C/P Ratio

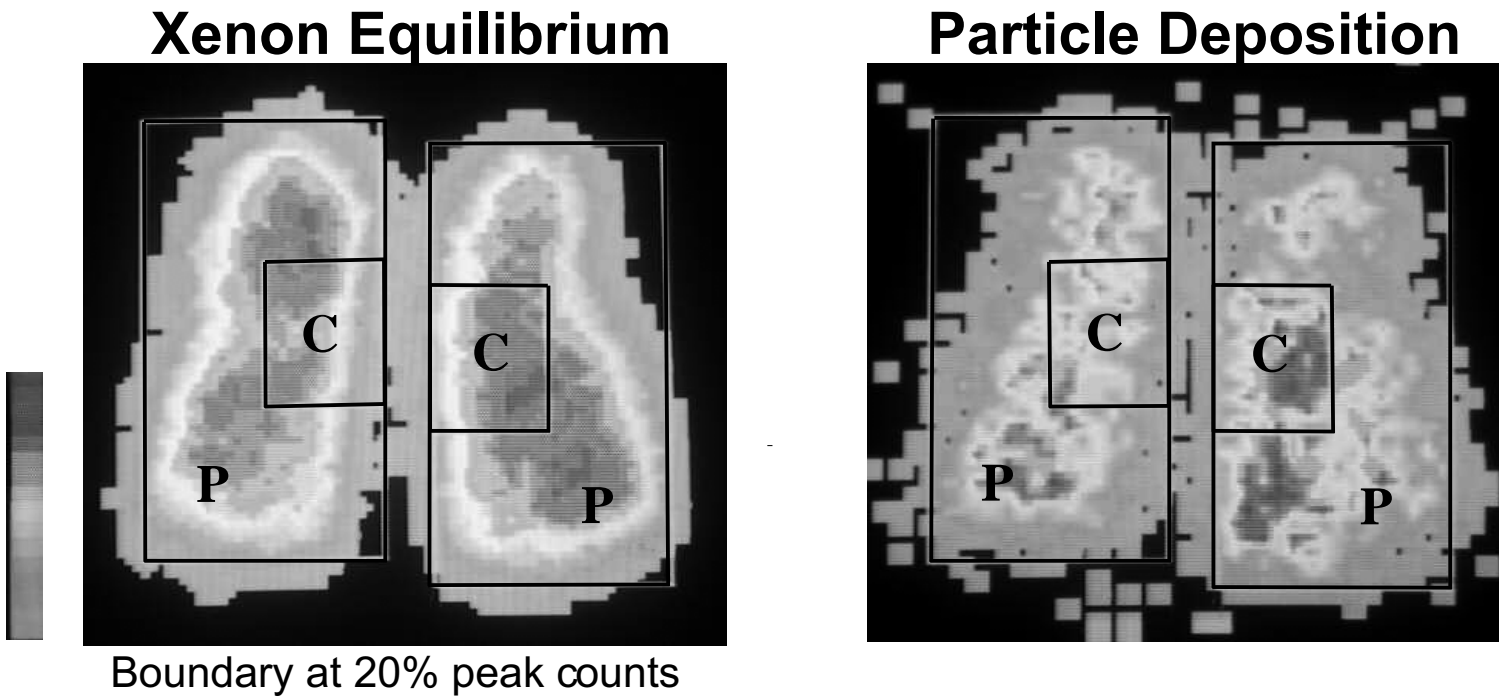
Deposition in C / P regions
Volume of C / P regions

Regional Particle Deposition (C/P)



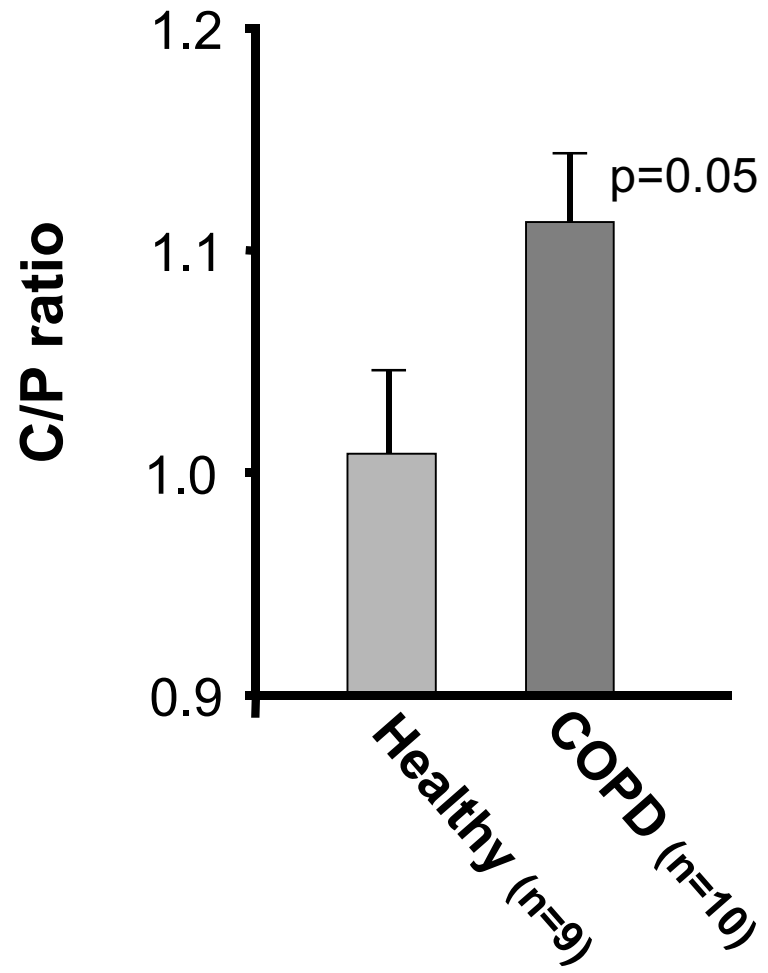
61 year old female, 31% predicted FEV₁

Regional Particle Deposition (C/P)

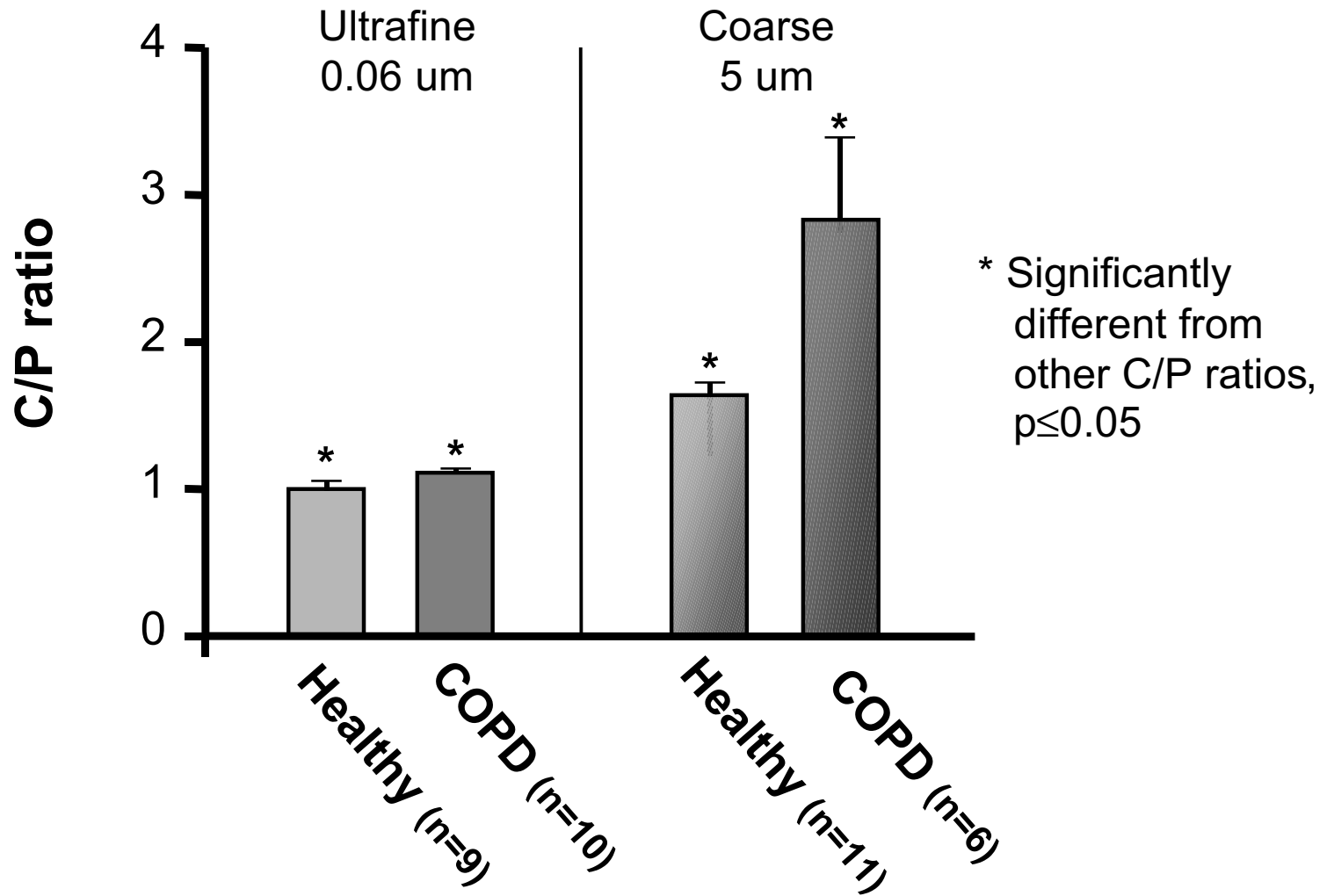


$$\mathbf{C/P\ Ratio} = \frac{\text{Deposition in C / P regions}}{\text{Volume of C / P regions}} = 1.17$$

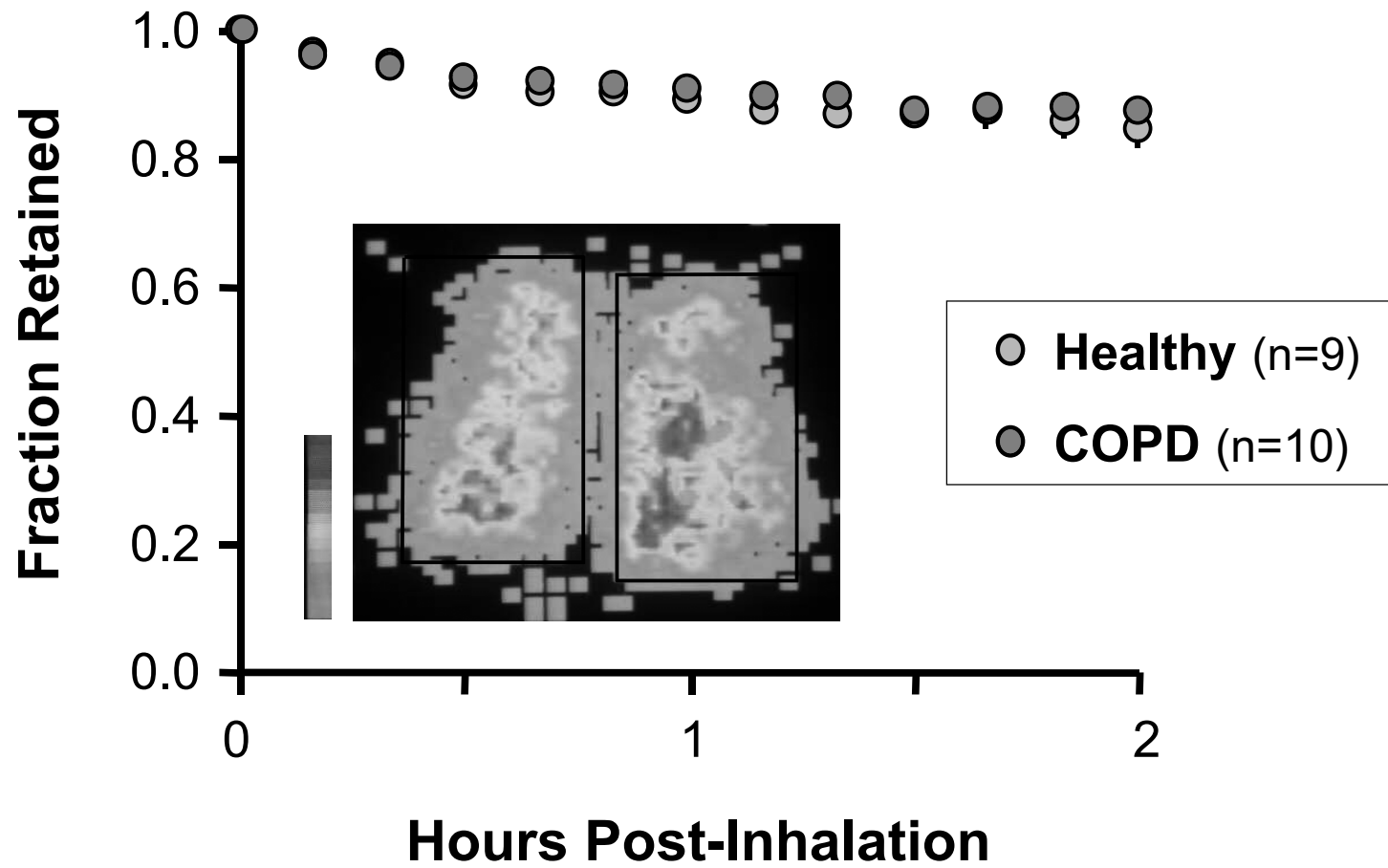
Regional Particle Deposition (C/P)



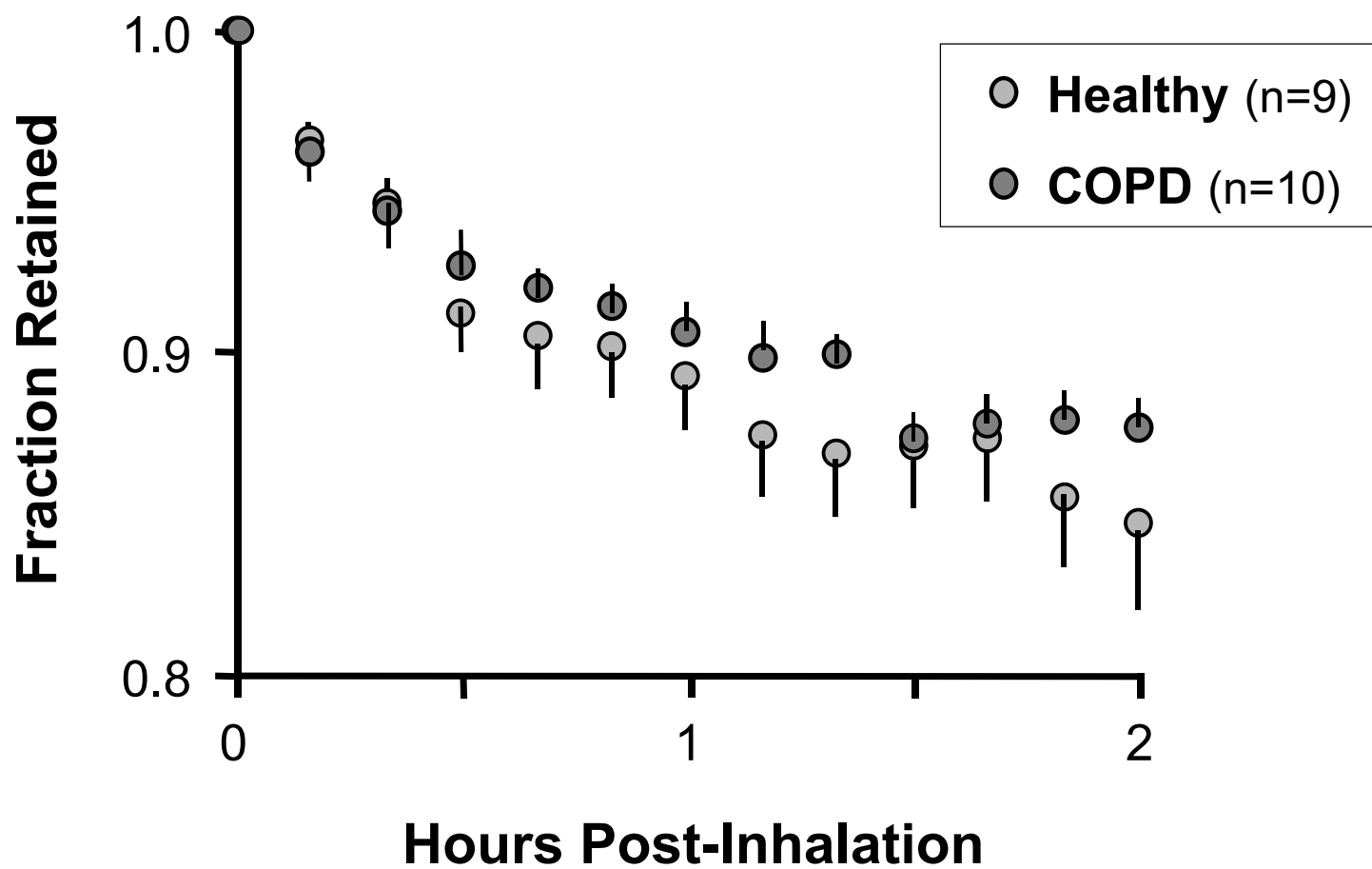
Regional Particle Deposition (C/P)



Pulmonary Clearance

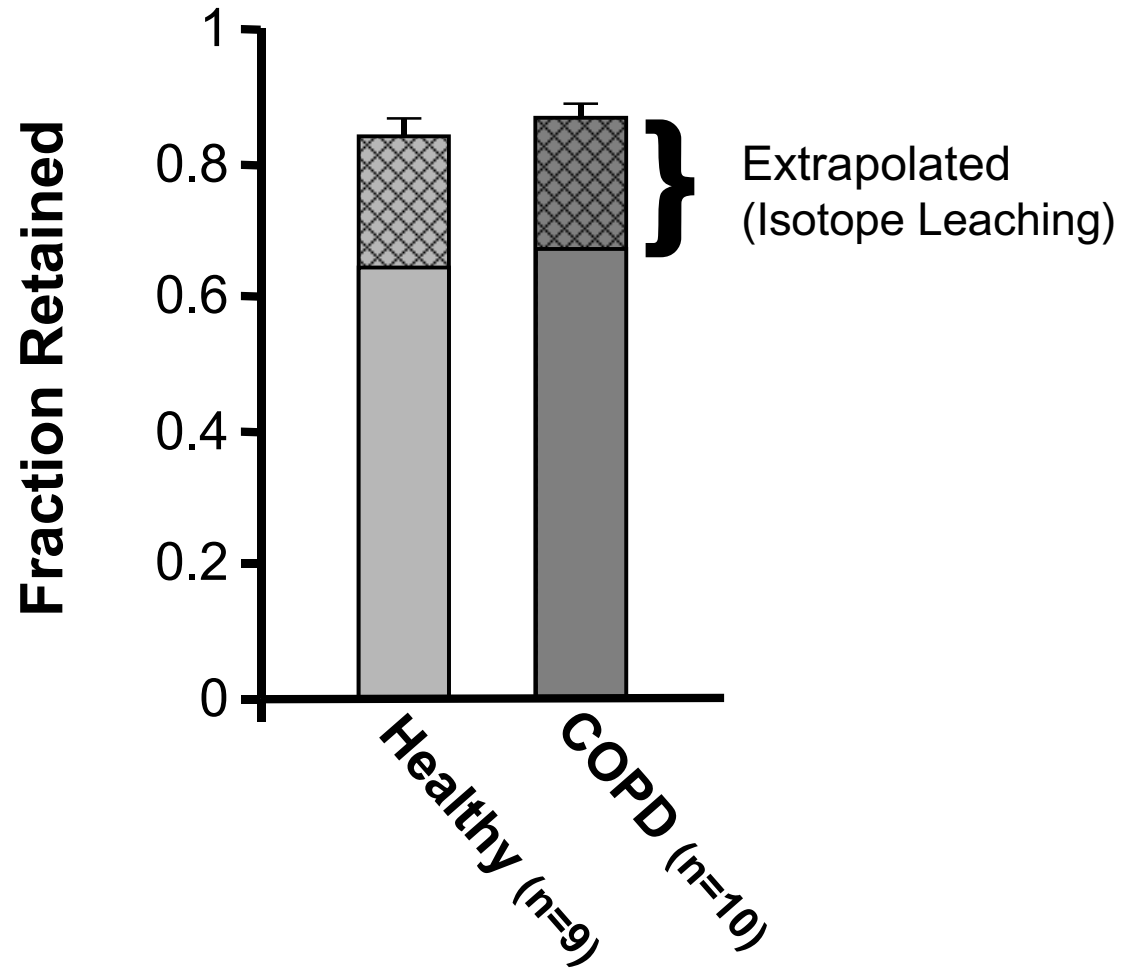


Pulmonary Clearance

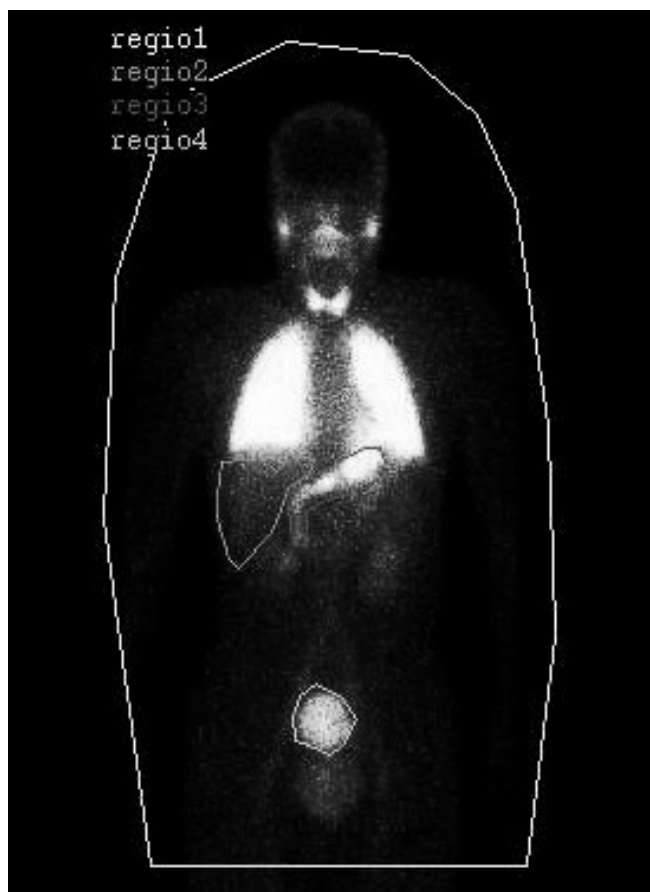


Pulmonary Clearance

24 hours post-inhalation

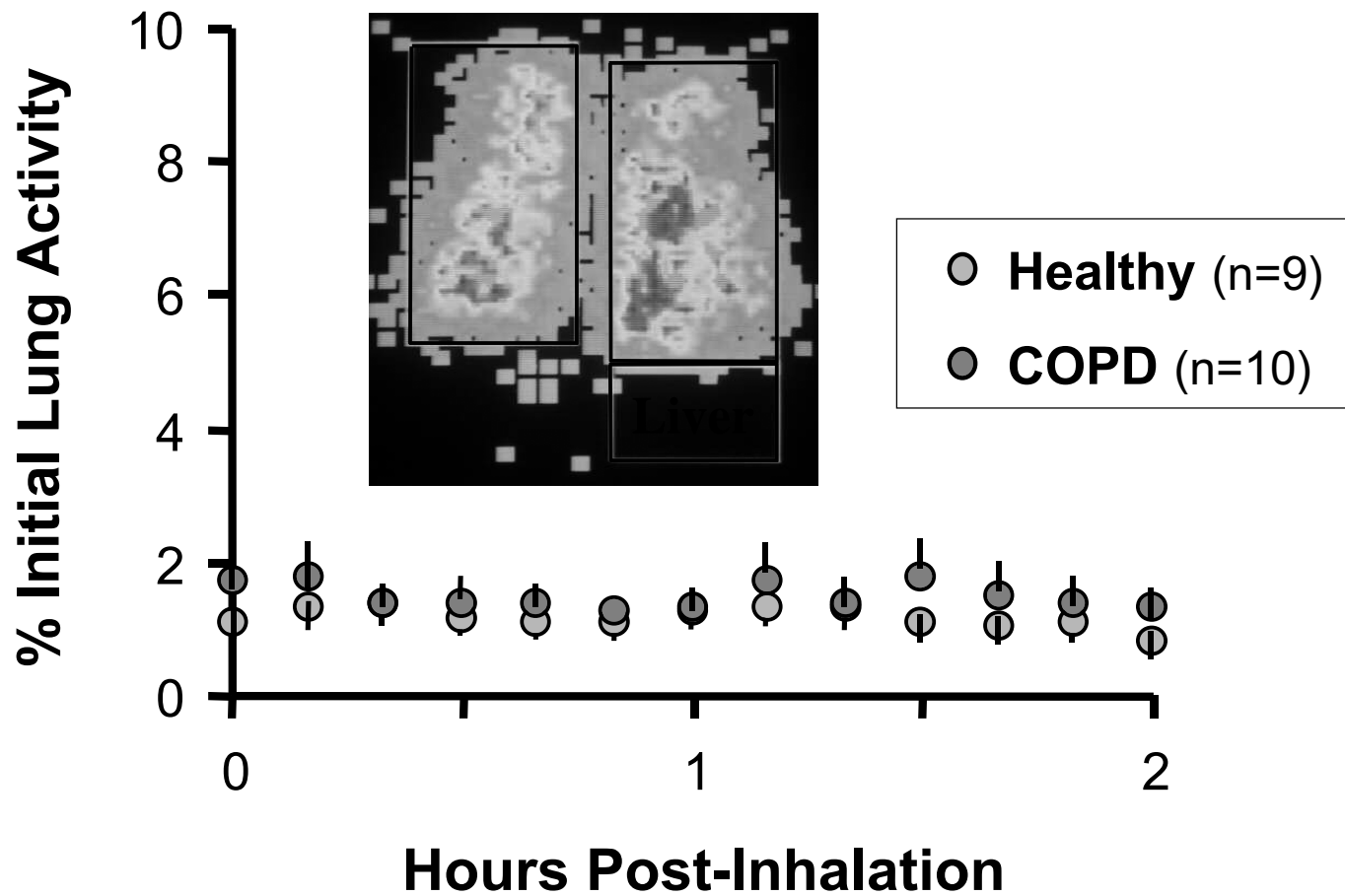


Passage of inhaled particles into the blood circulation in humans (*Nemmar et al, Circulation 105:411, 2002*)

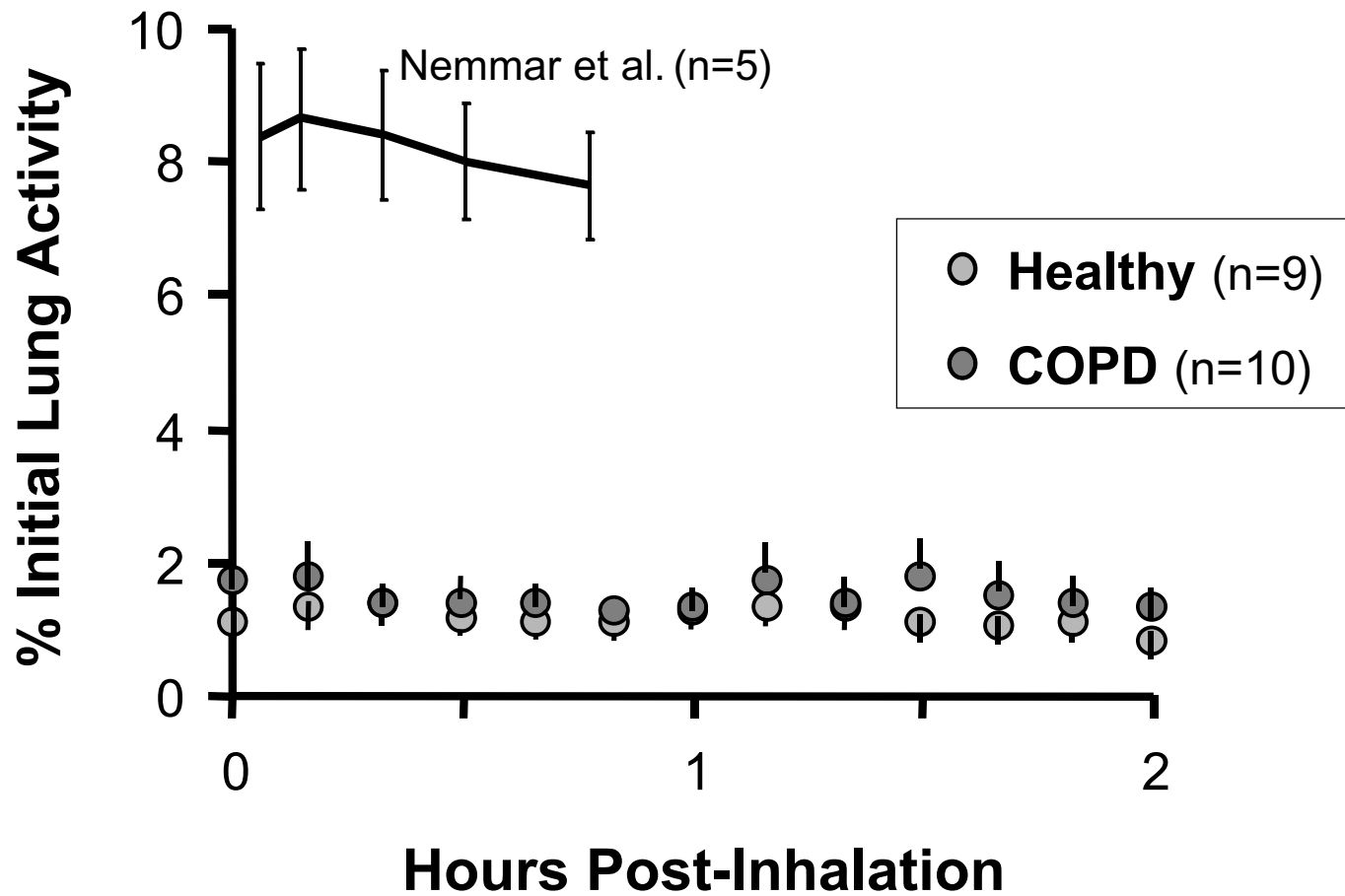


- Retention scan 60 minutes post ultrafine aerosol inhalation
- Rapid translocation into blood?
- 8% in liver (constant 5-45 min)
- 0.2 μm aggregates composed of 7-23 nm primary particles
- Lots of free isotope (i.e. isotope not bound to particles)
note: bladder, thyroid, blood

Translocation into Liver?



Translocation into Liver?



Summary

- Moderate airway obstruction (chronic bronchitis) increases UF deposition, while alveolar destruction (emphysema) decreases UF deposition
- COPD patients have 50% greater UF deposition rate at rest than healthy subjects
- Slight increase in UF deposition in large airways with obstruction, but much less than seen with coarse (5 μm) particles
- UF particle retention is similar in healthy vs. COPD
- No apparent translocation of UFs into the liver region for healthy or COPD