



Frontiers in Air Quality

Advances in Air Quality Toxicology

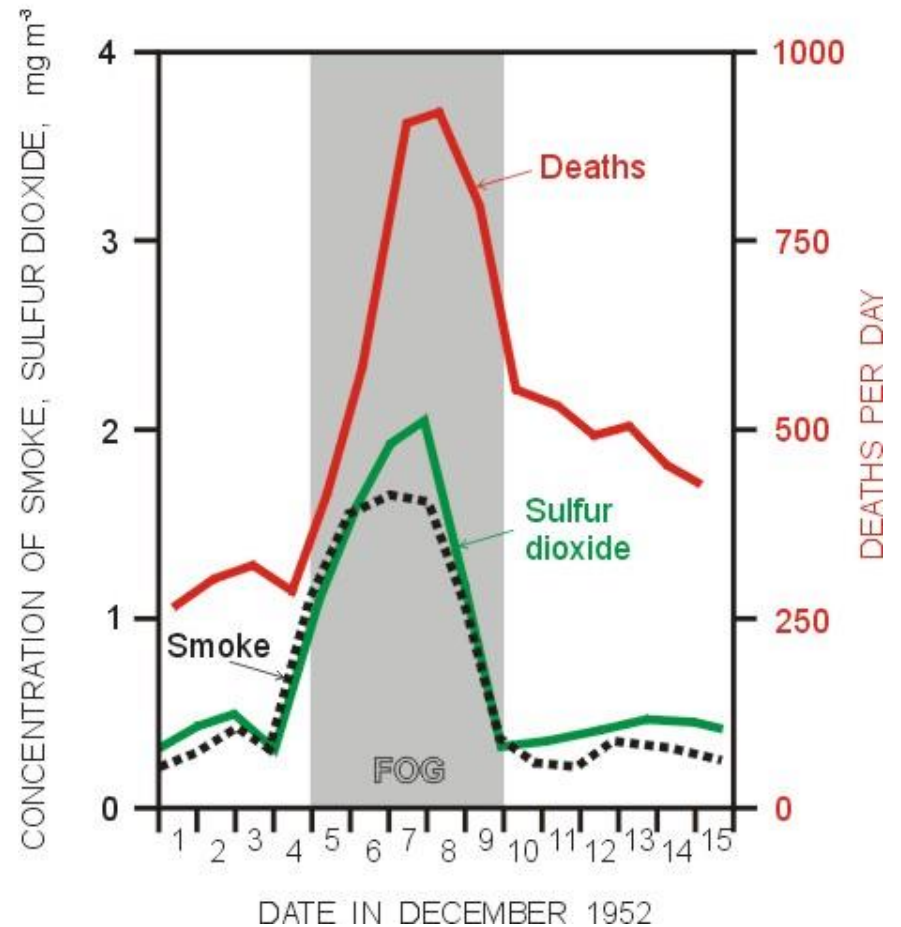
Heart and Lungs – Victims of Polluted Air

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Umeå University

How did it start?



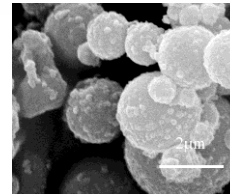
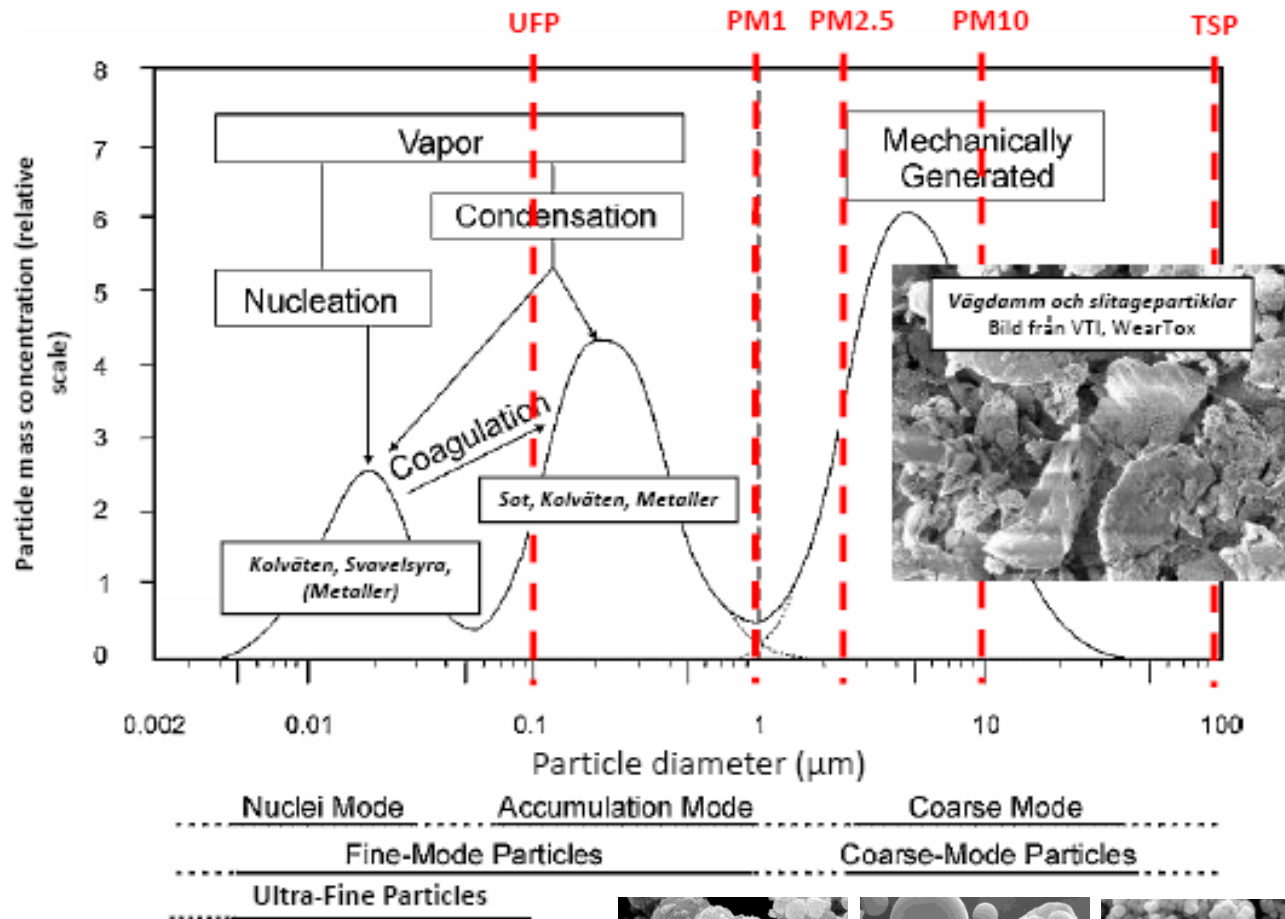
THE LONDON SMOG



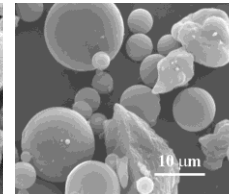
Combustion-derived particulate matter air pollution

- Diesel exhaust
 - Petro diesel
 - Biodiesel
- Wood smoke/biomass burning

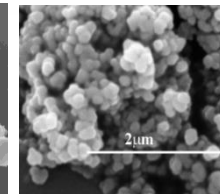
Different air pollution sources – different sizes



Coarse
<10 μm



Fine
<2.5 μm

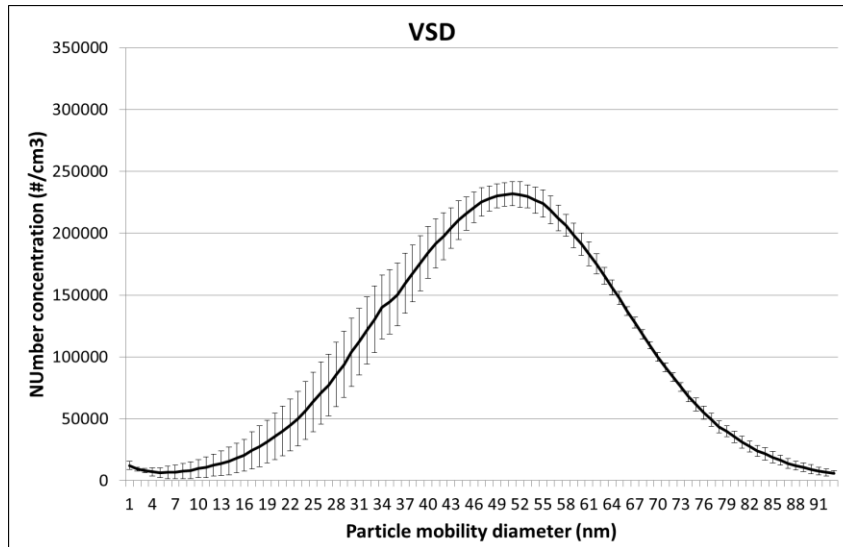


Ultrafine
<0.1 μm

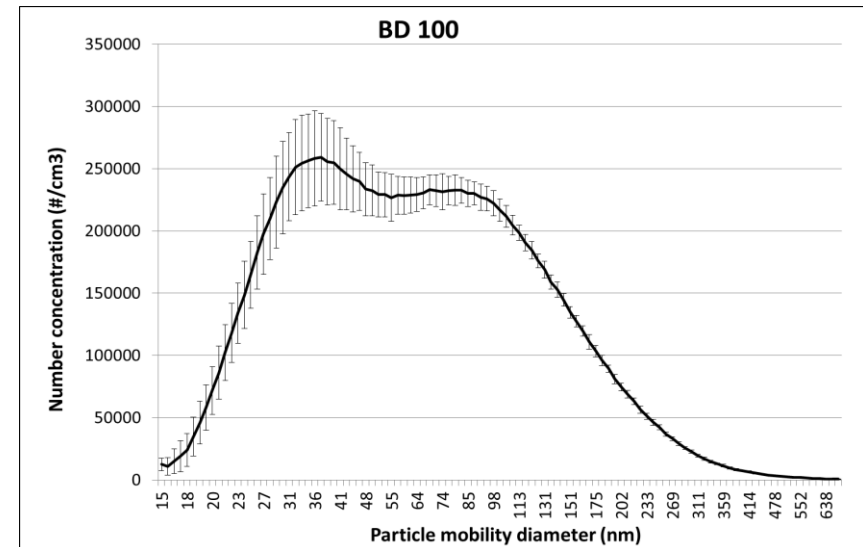
Particle sizes

Petro diesel vs. Biodiesel RME100

Petro diesel



Biodiesel



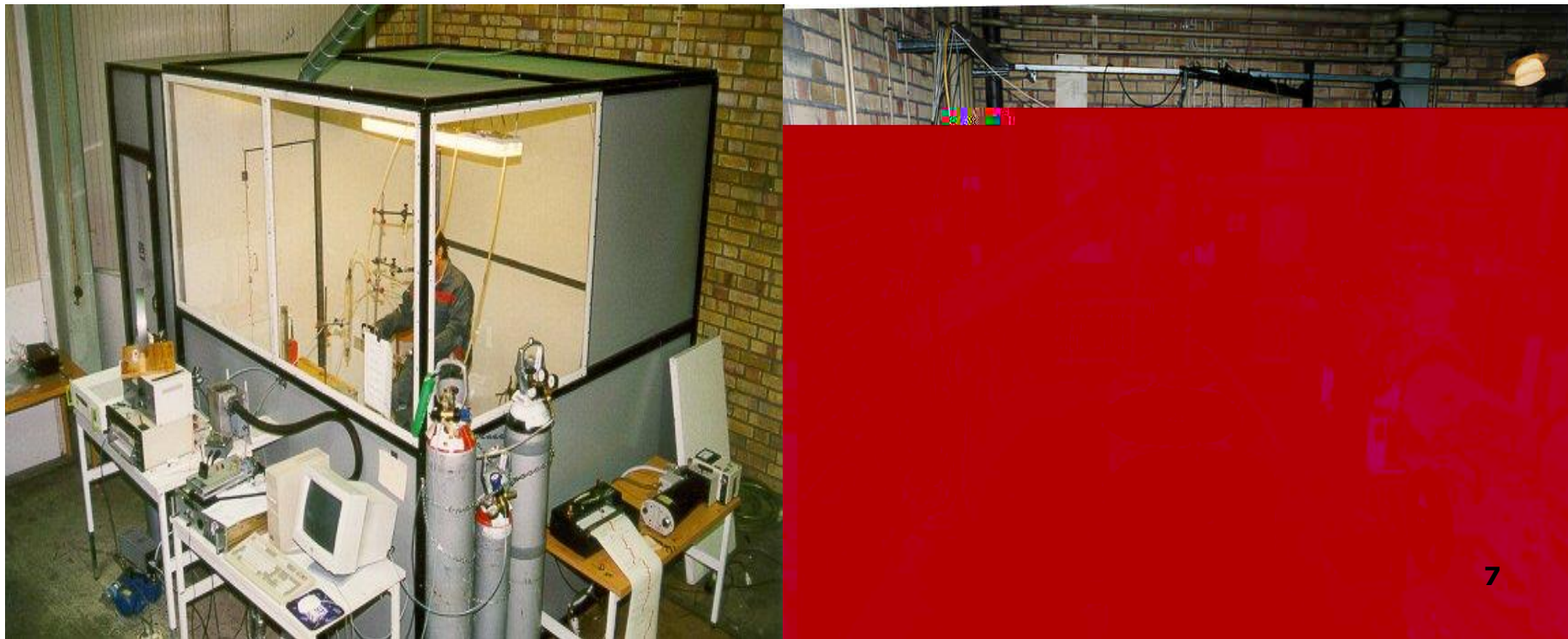
Human exposure chamber studies

- Selected populations
 - ◆ Healthy, allergy, asthma, COPD, elderly
- Exposure situation mimicking real life
 - ◆ Traffic situations, work places
- Controlled exposure concentrations
- Predetermined workload/ventilation rate
- Randomised sequence
 - ◆ Filtered air $\rightleftharpoons$ air pollutant

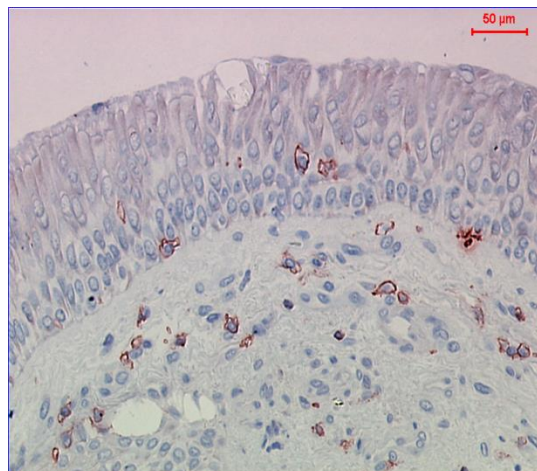
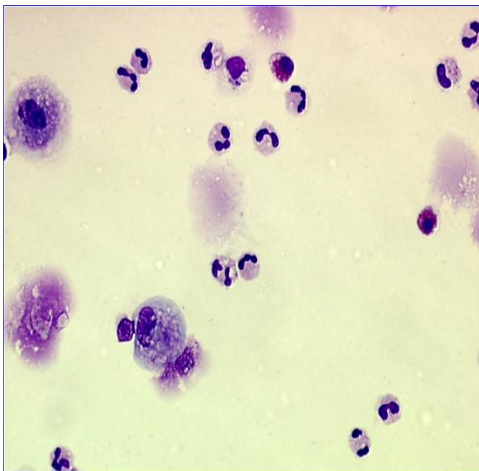
Exposure Setup

Diesel exhaust used as a model of PM pollution

Exposure to diesel exhaust and filtered air for 1-2 hours on two separate occasions

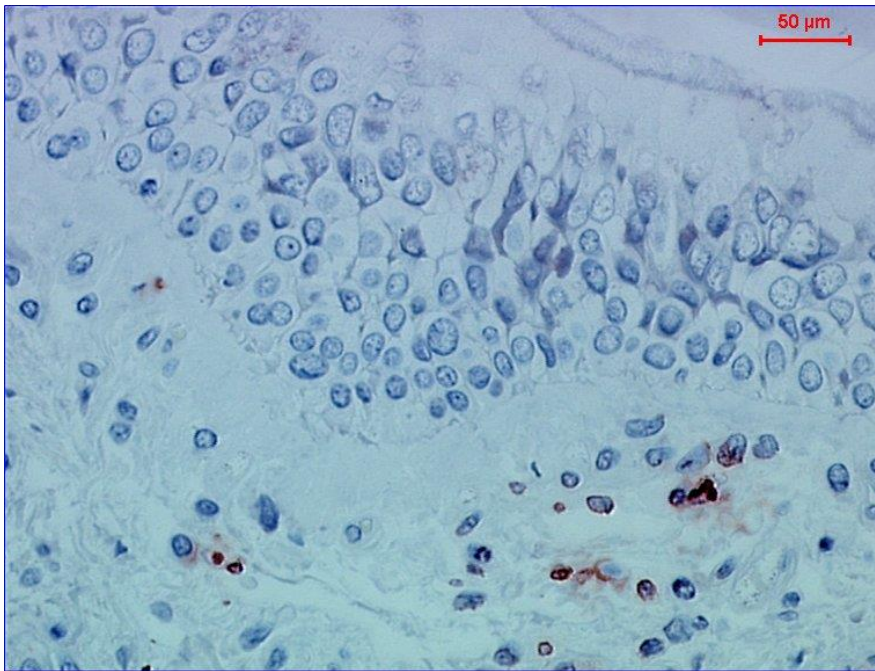


Bronchoscopy

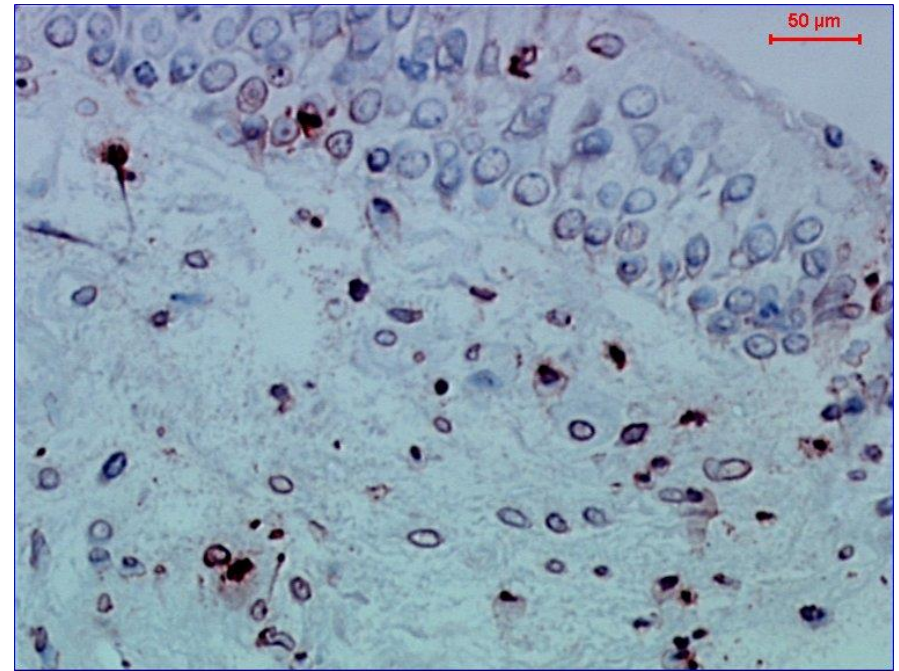


Exposure to diesel exhaust in healthy volunteers - *biopsies*

Filtered air



Diesel exhaust



Neutrophils

Salvi *et al* AJRCCM 1999

Airway effects by diesel exposure in healthy humans

MAPKs

- p38

Transcription factors

- AP-1, NF κ B

Cytokines

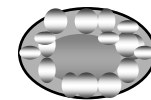
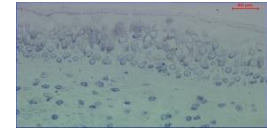
- IL-8, IL-13, GRO- α

Adhesion molecules

- ICAM-1, VCAM-1, LFA-1

Inflammatory cells

- Neutrophils, mast cells, lymphocytes



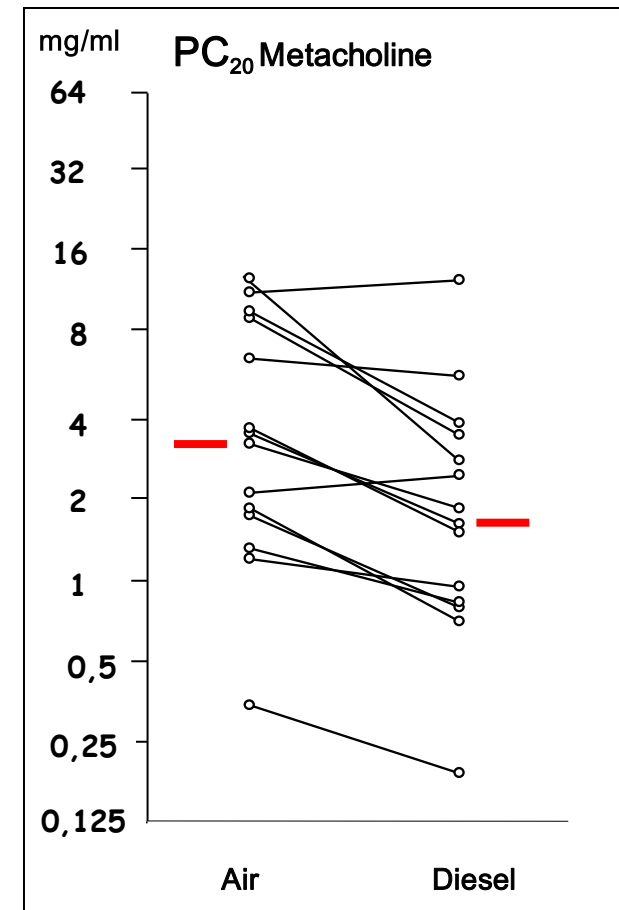
Diesel exhaust – PM concentrations 100 vs. 300 $\mu\text{g}/\text{m}^3$

- Slower development of airway inflammation at a lower concentration
- Events occurring at 6 hours after 300 $\mu\text{g}/\text{m}^3$ can be found 18 hours after 100 $\mu\text{g}/\text{m}^3$

Diesel exhaust increases airway hyperresponsiveness in asthmatics..



..despite treatment with inhaled corticosteroids



Exposure to diesel exhaust

Healthy vs. Asthmatics (6 h)

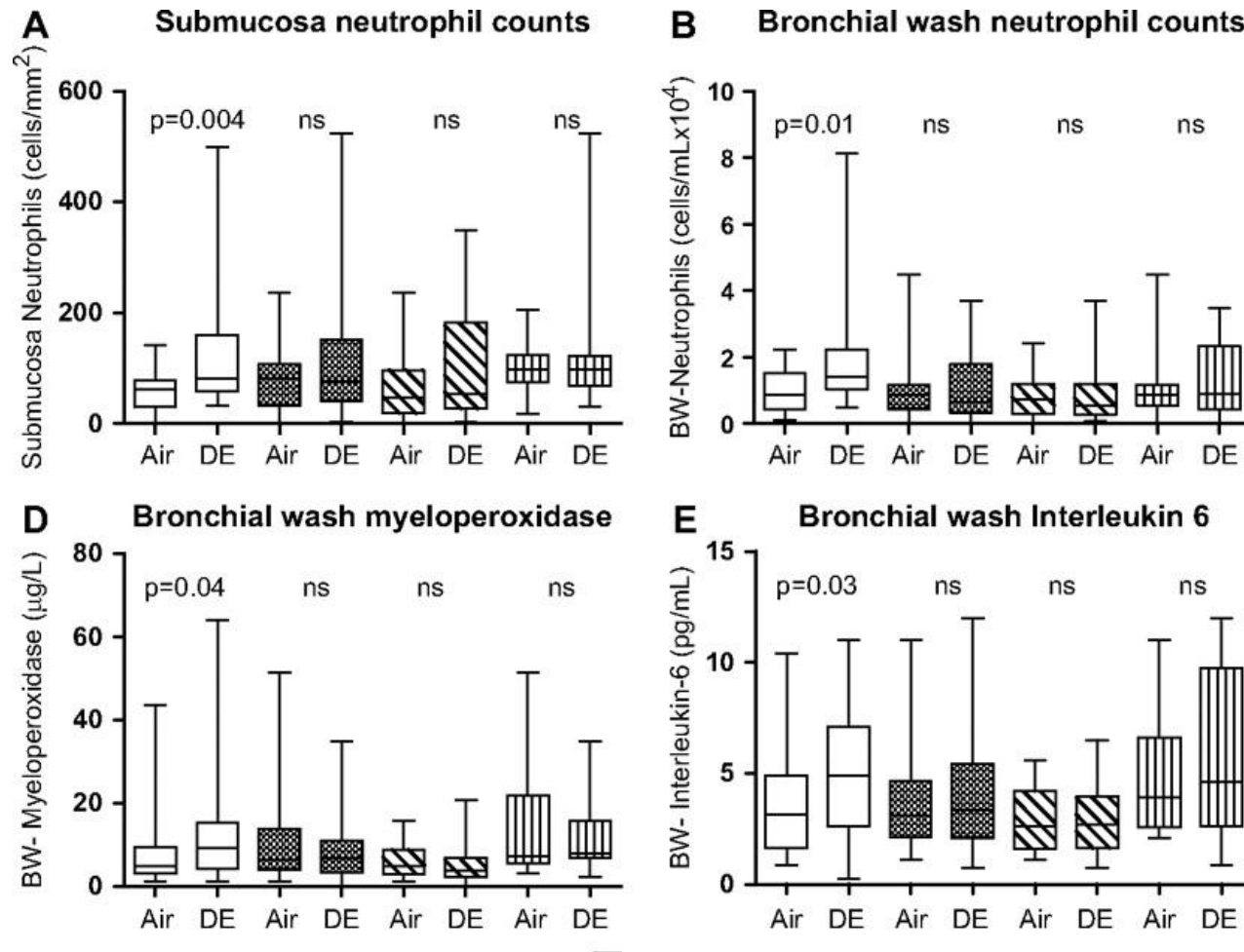
		Healthy	Asthmatics
Cells		↑ (PMN), Ly	
Cytokines	BAL	↑ IL-6, IL-8	
	biopsies		↑ IL-10
Adhesion molecules		↑ P-selectin VCAM-1	
Lung function		↑ R_{AW}	↑ R_{AW}

Do asthmatics react more/worse at a later time point after diesel exhaust exposure or in another way?

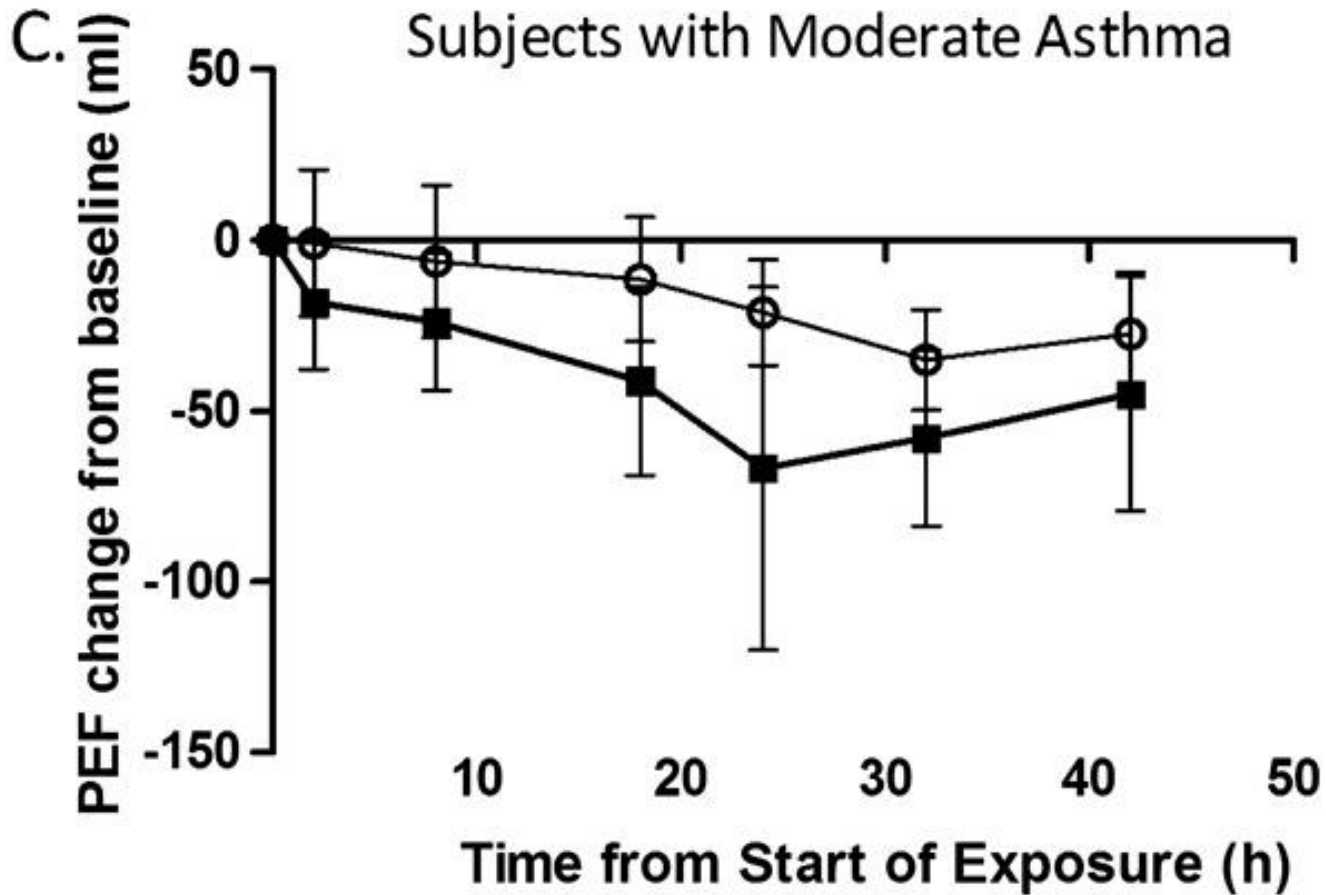
13

Stenfors *et al.* ERJ 2004

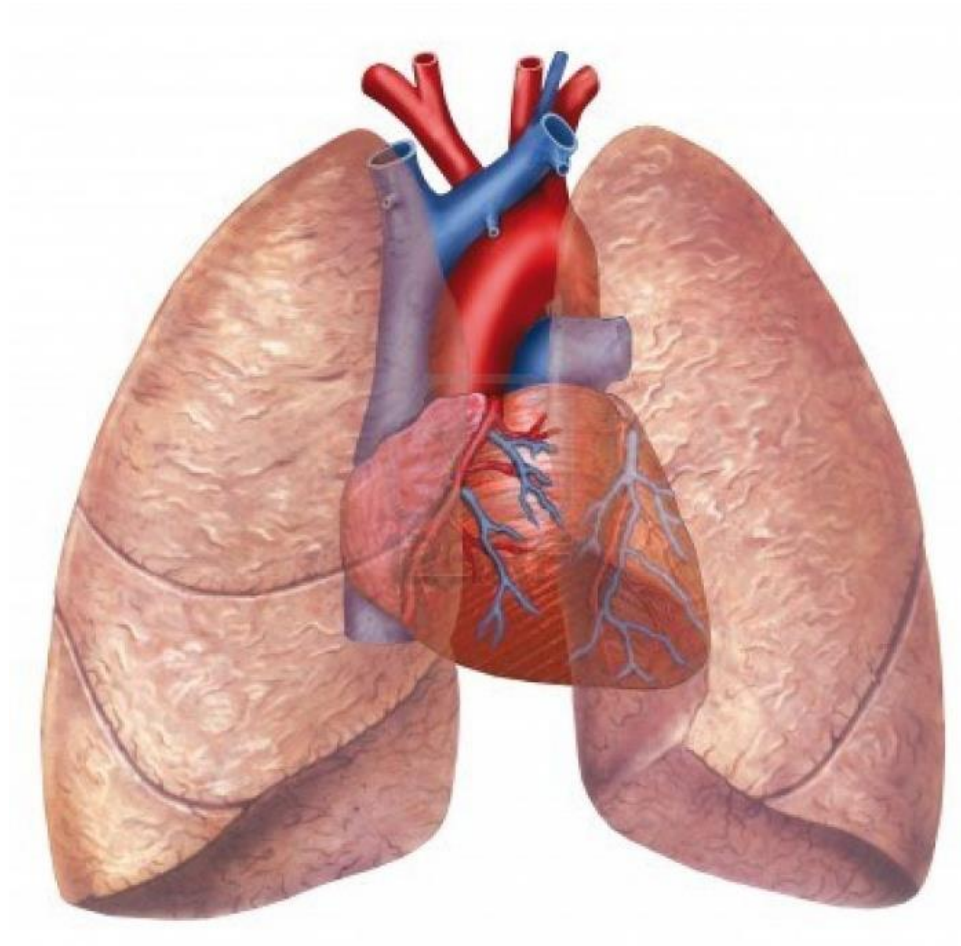
Diesel exhaust - asthmatics



PEF-responses in asthma



From lungs to heart.....



Tools for investigating cardiovascular events of air pollution in humans *in-vivo*

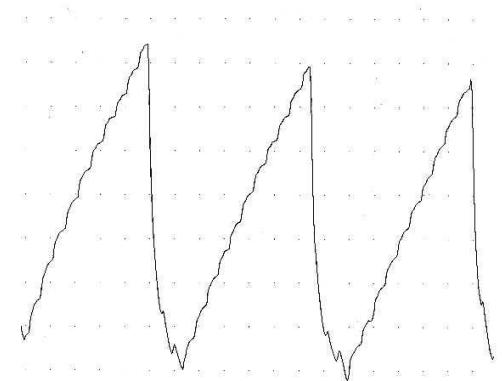
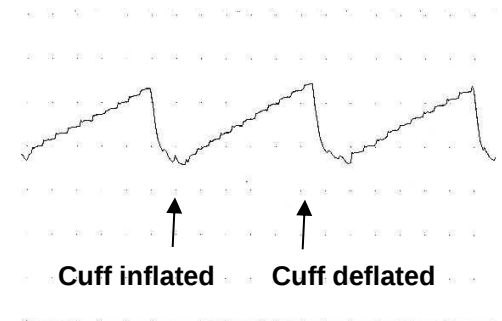
- Forearm plethysmography
- *Ex-vivo* model of thrombosis
- Coagulation markers
- Arterial stiffness
- Blood pressure
- Heart rate and rhythm

Measuring endothelial function

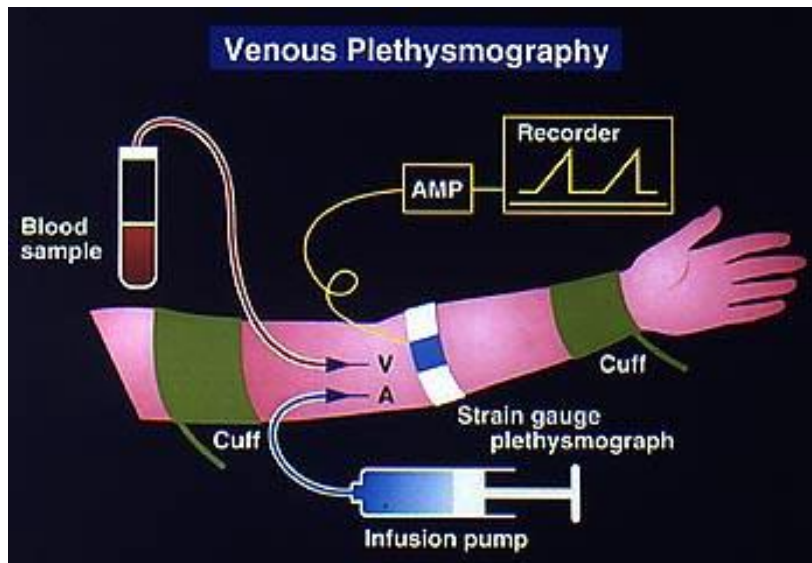


VENOUS OCCLUSION PLETHYSMOGRAPHY

Non-infused

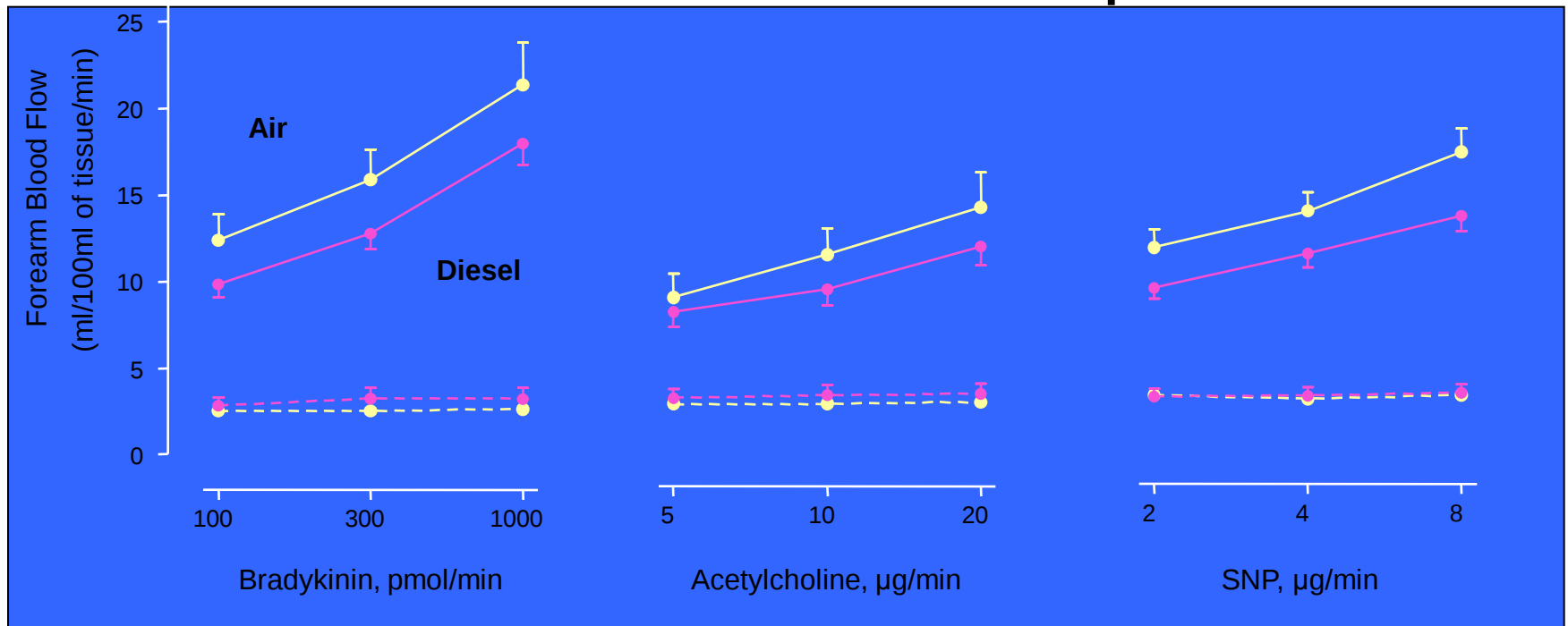


Infused arm



BILATERAL VENOUS SAMPLING 18

Decreased forearm blood flow 6 hours after diesel exhaust exposure

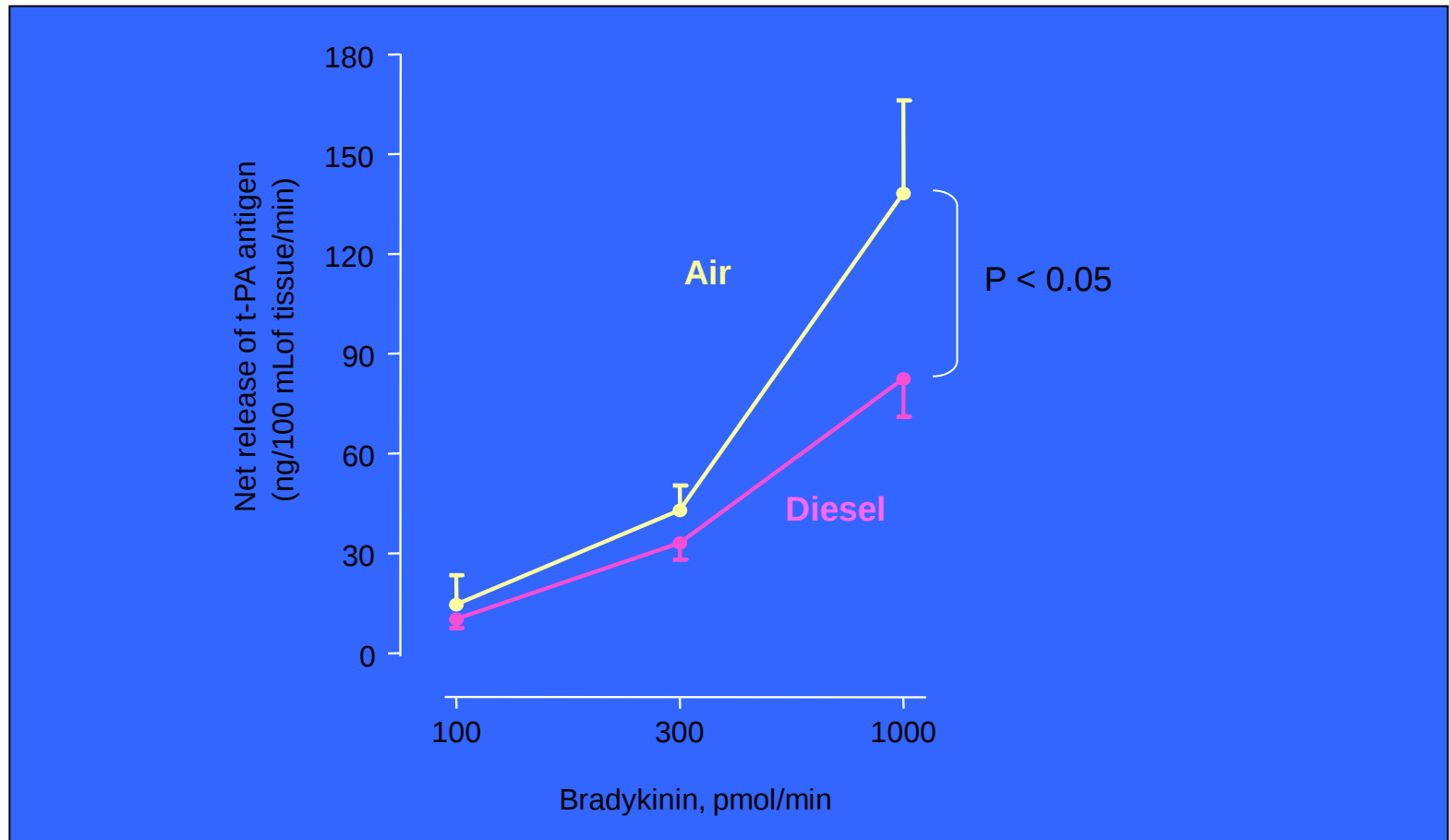


Infused (solid line) and non-infused (dashed line) FBF following diesel exhaust (●) and air (●) during bradykinin ($P=0.006$), acetylcholine ($P=0.07$) and sodium nitroprusside ($P=0.0002$).

Exposure to dilute diesel exhaust for one hour impairs endothelium dependent and independent vasomotor function



Endogenous fibrinolysis – tissue plasminogen activator (t-PA) release at 6 hours



**Area under the curve for t-PA release was reduced
by 33% following diesel exhaust exposure**

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Ischemic and Thrombotic Effects of Dilute Diesel-Exhaust Inhalation in Men with Coronary Heart Disease

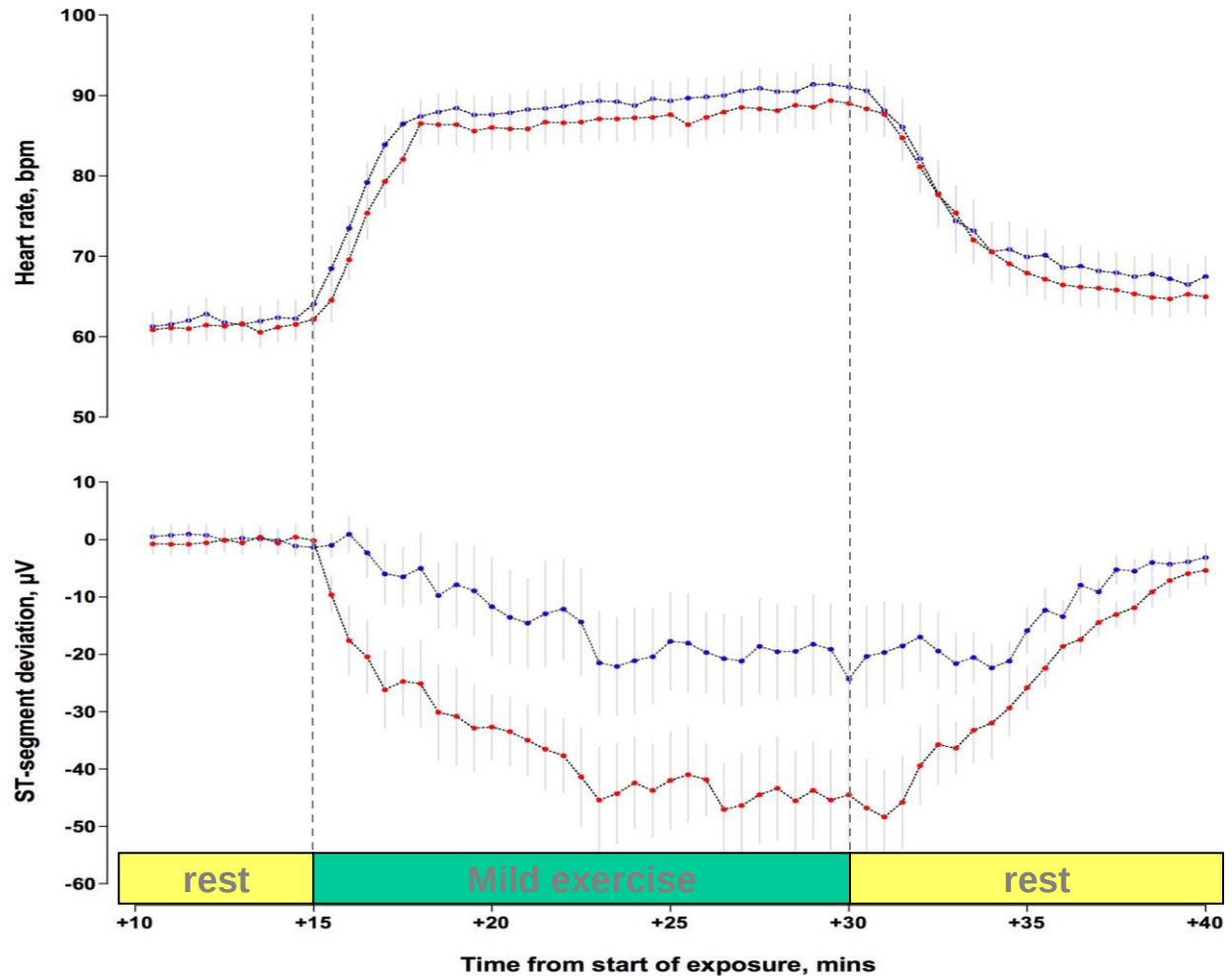
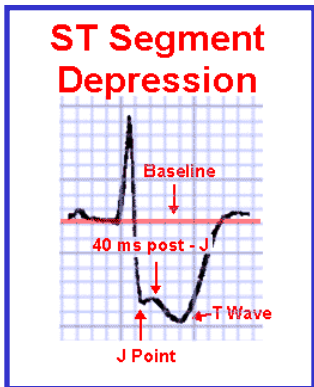
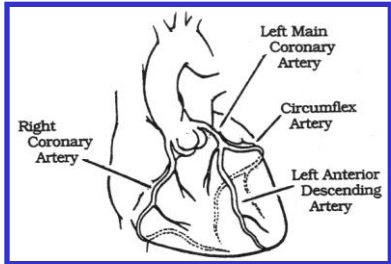
Nicholas L. Mills, M.D., Håkan Törnqvist, M.D., Manuel C. Gonzalez, M.D., Elen Vink, B.Sc.,
Simon D. Robinson, M.D., Stefan Söderberg, M.D., Ph.D., Nicholas A. Boon, M.D., Ken Donaldson, Ph.D.,
Thomas Sandström, M.D., Ph.D., Anders Blomberg, M.D., Ph.D., and David E. Newby, M.D., Ph.D.



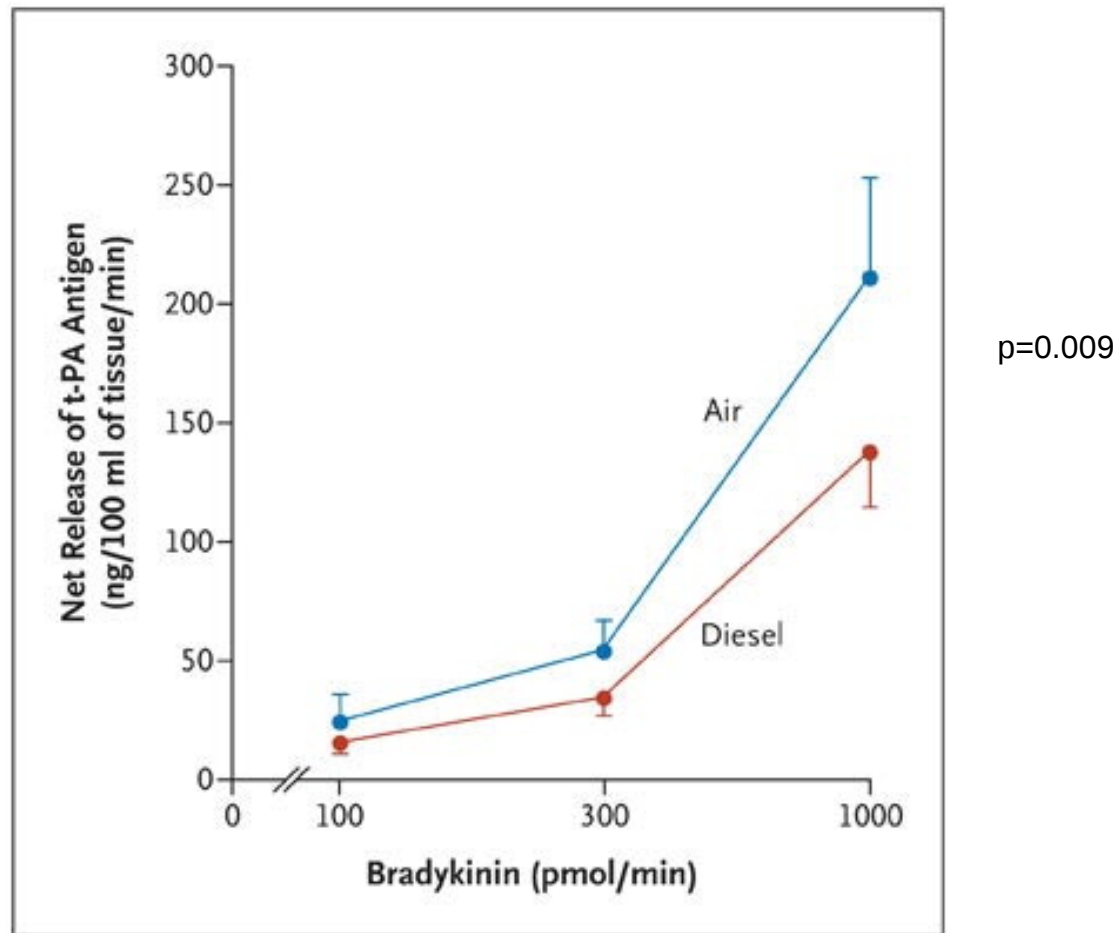
Effect of exposure to diesel exhaust in patients with stable coronary heart disease

- 20 male patients
- Coronary heart disease successfully treated with PCI – stable disease
- No diabetes mellitus
- No congestive heart failure
- Normal maximal exercise test
- No symptoms
- Full “protective” medication

Exercise-induced ischaemia



Impaired endogenous fibrinolysis

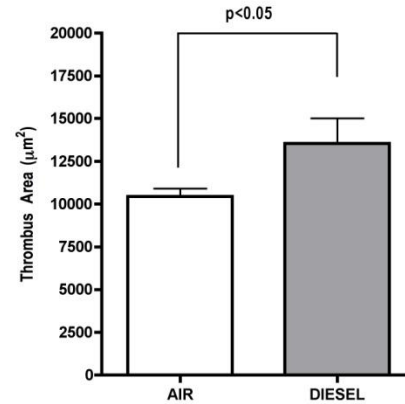


Thrombus formation *ex-vivo*

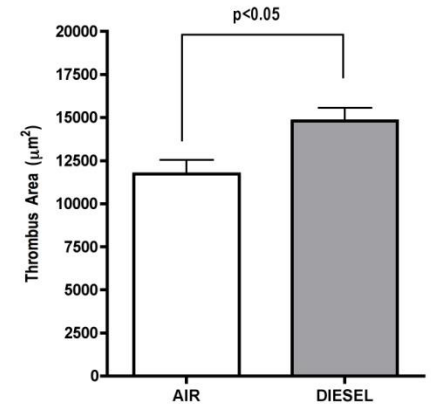


Low Shear
Chamber

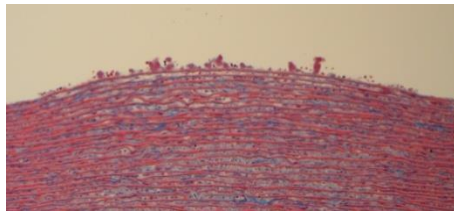
2 HOURS



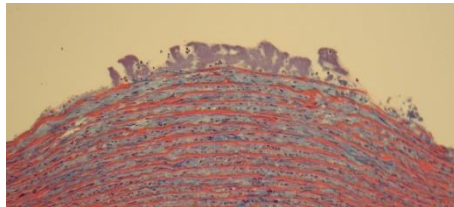
6 HOURS



Air

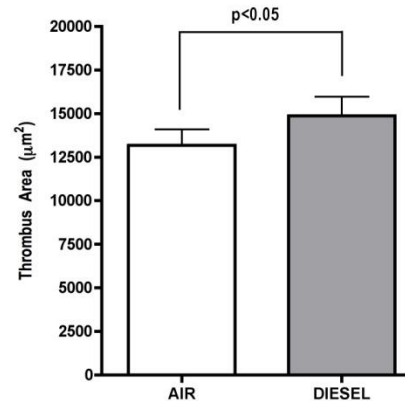


Diesel

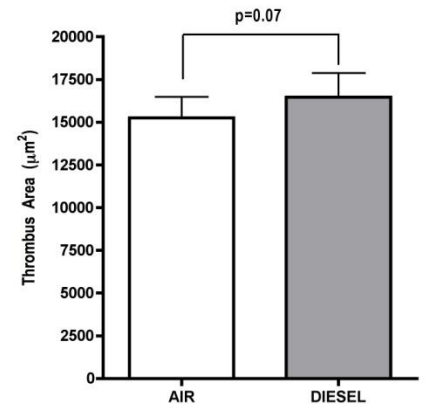


High Shear
Chamber

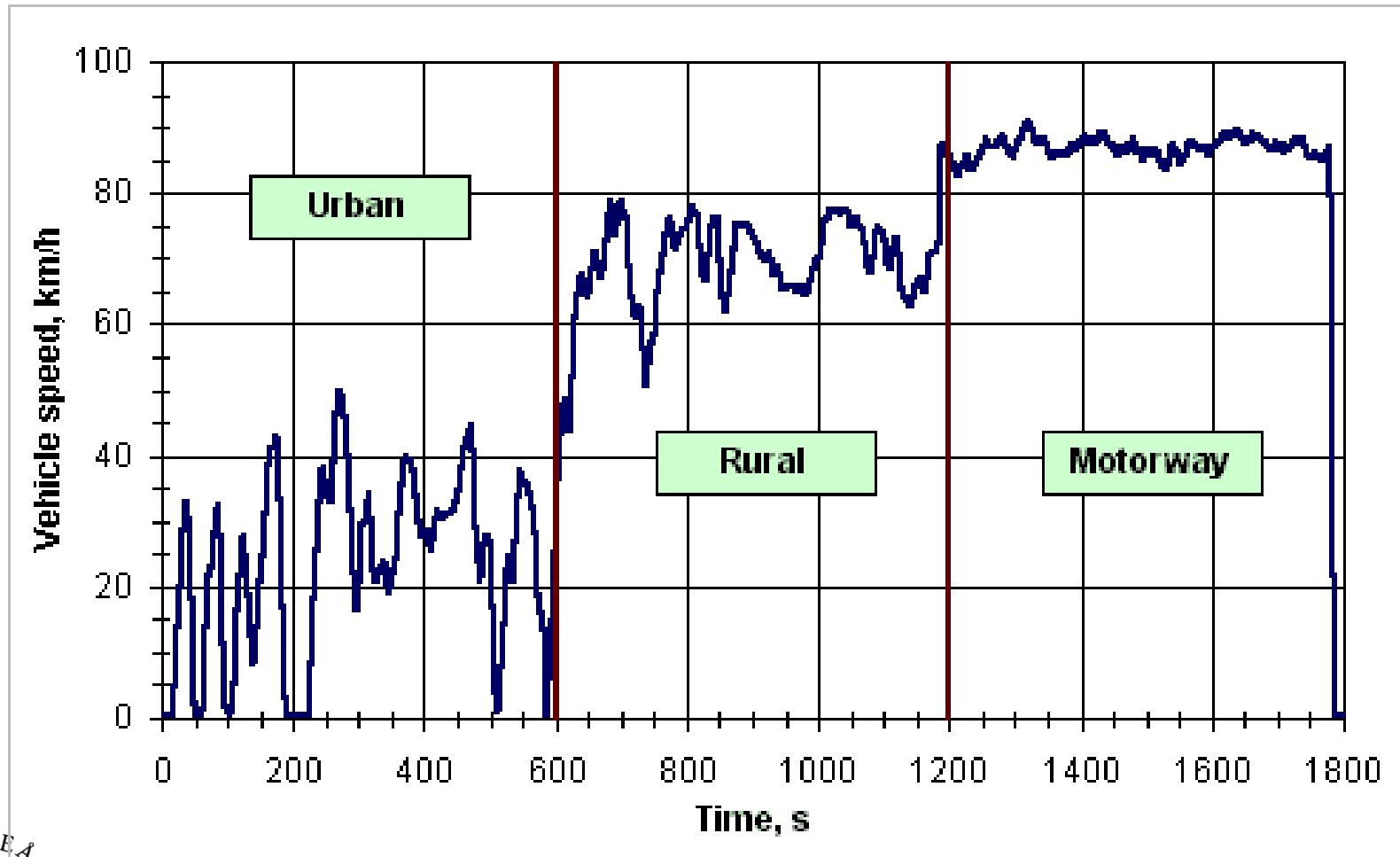
2 HOURS



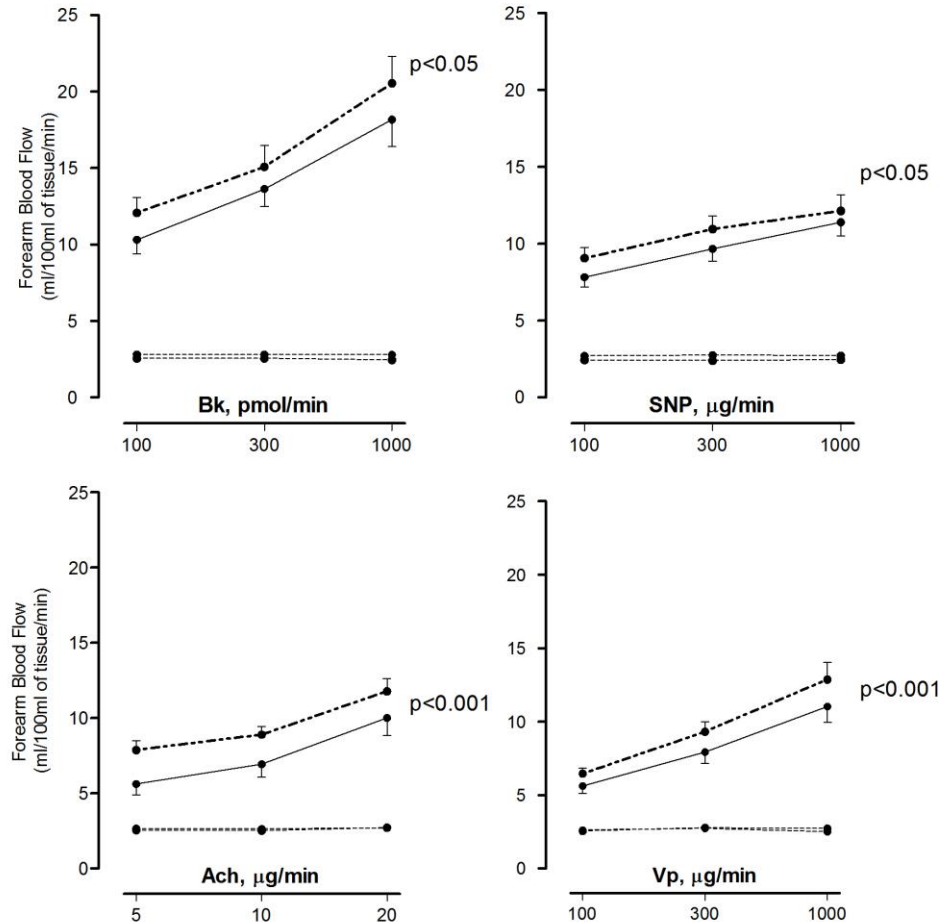
6 HOURS



Idling v.s urban running cycle



Vascular responses similar regardless of idling or city cycle

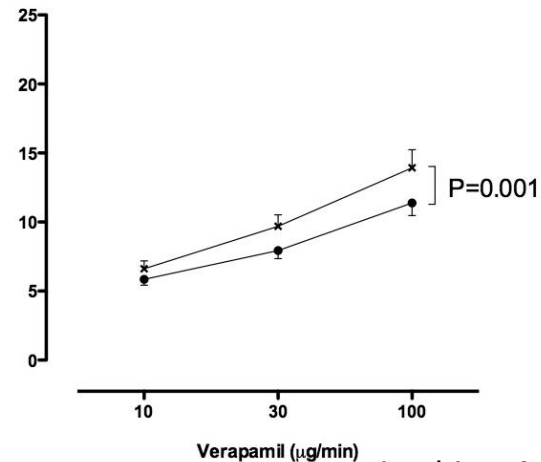
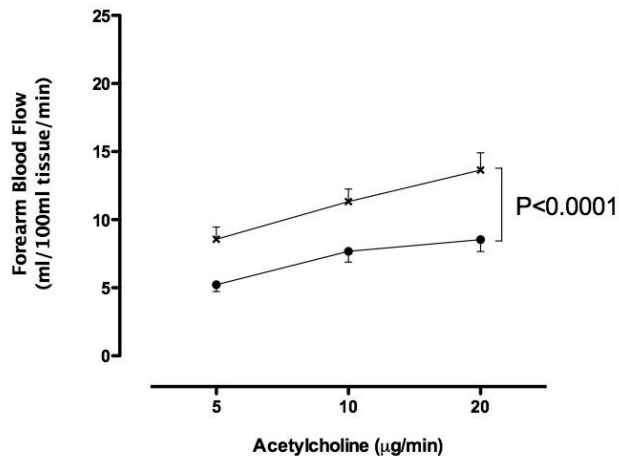
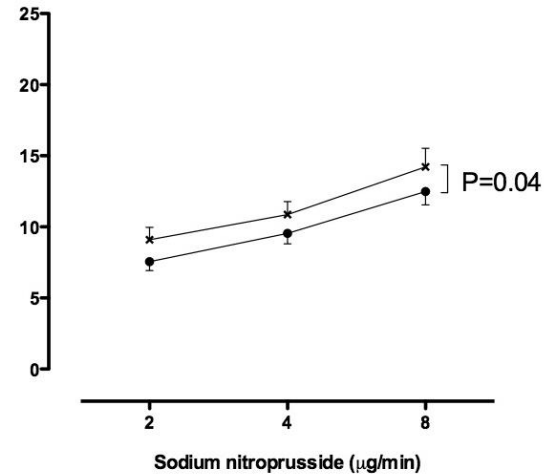
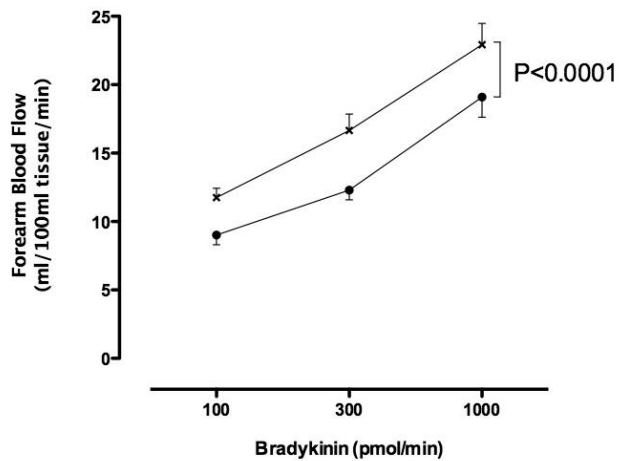


PARTICULATE TRAP-STUDY

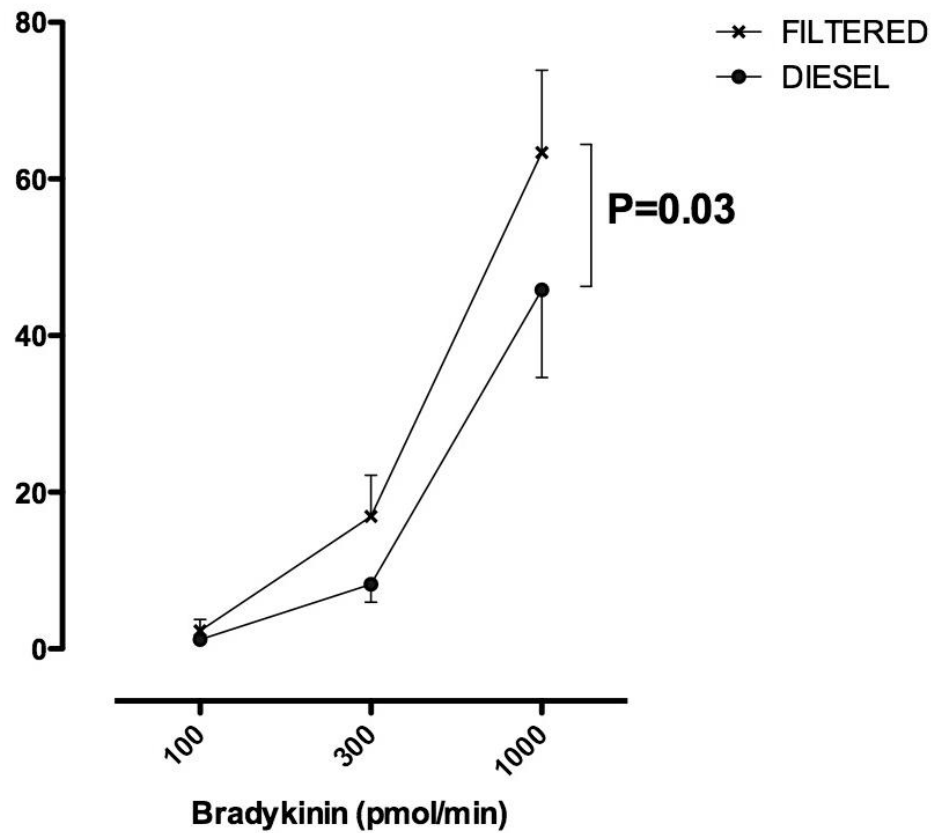
DIESEL EXHAUST vs. FILTERED DIESEL EXHAUST

Endothelium-dependent

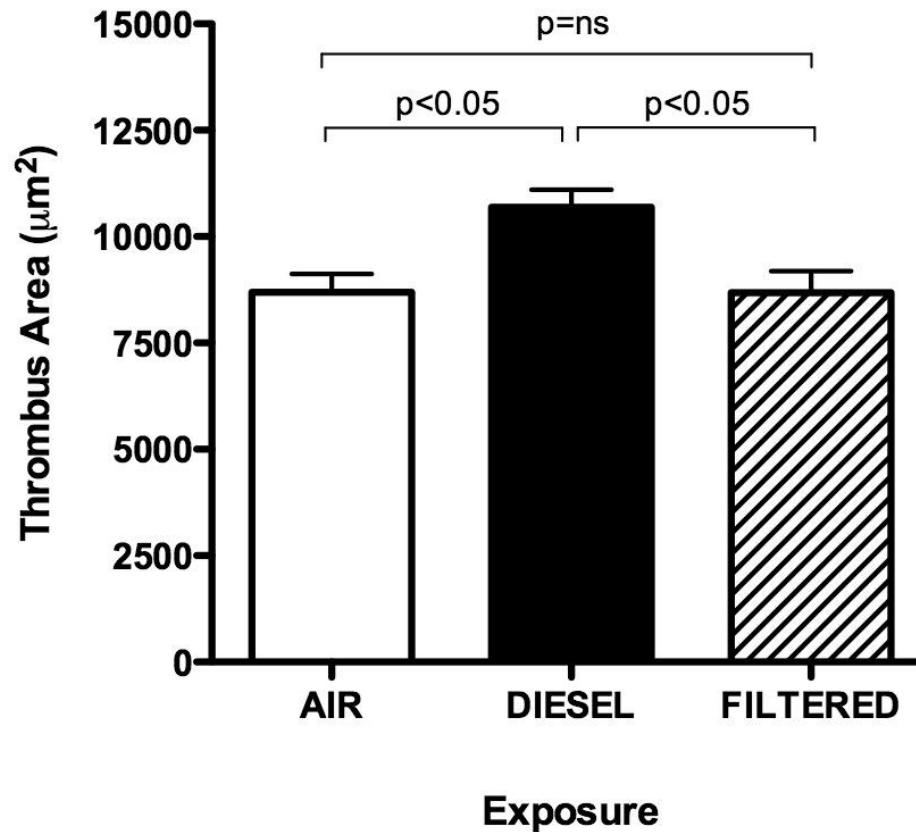
Endothelium-independent



t-PA RELEASE

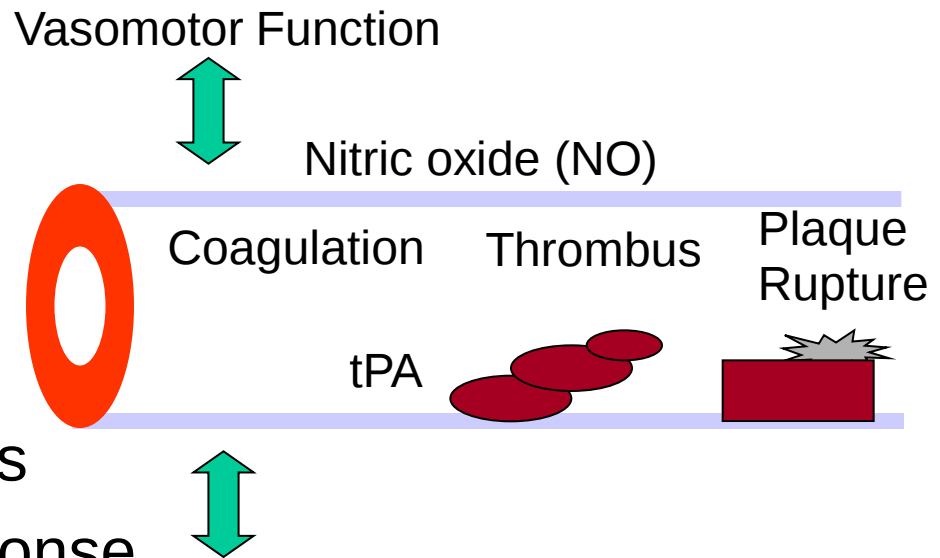


Reduced thrombus formation with filter



Vascular Effects of Diesel Exhaust – SUMMARY

- Arterial stiffness increases
- Reduced vasomotor response
- Reduced t-PA release
- Increased platelet adhesion
- Increased tendency for thrombus formation
- Mediated *through* the L-arginine-NO pathway
- Effects may be reduced by a particle trap



Biodiesel

RME - Rapeseed Methyl Ester

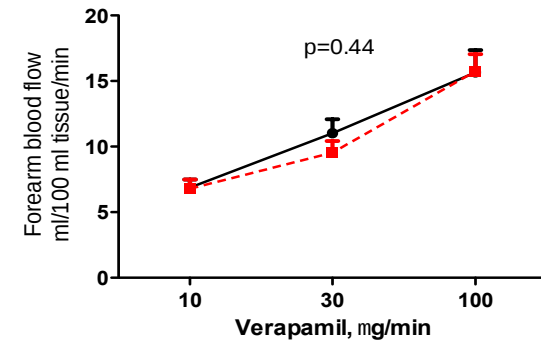
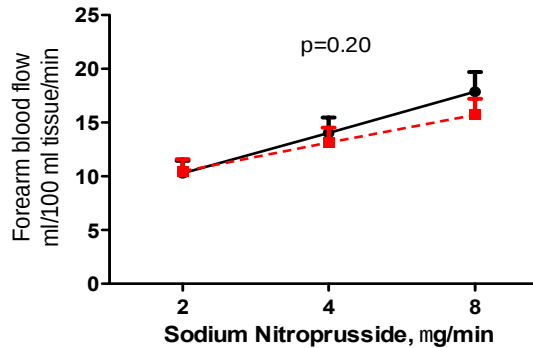
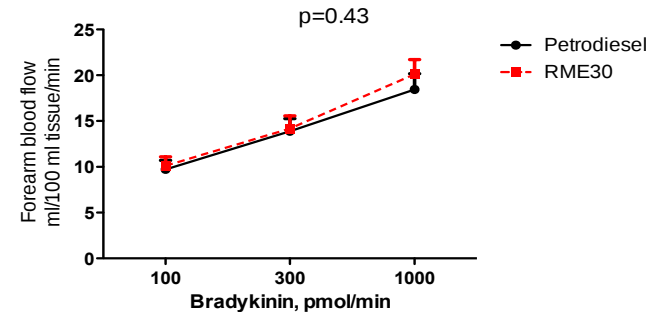
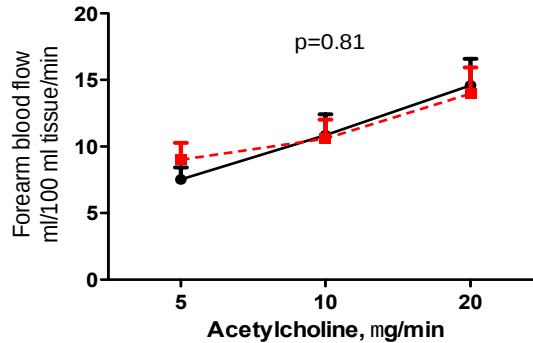
- 5-7% biodiesel included in diesel fuels in Sweden today - RME is the dominating addition
- 30 or 100% RME is used in some vehicles, due to lower price as well as being renewable
- RME may potentially be more widely used, as a 30% blend can be used without engine alternations or increased engine wear

Three exposure studies in healthy human subjects with RME Biodiesel vs. petro diesel or filtered air

- 1 RME30 (30% biodiesel) vs. petro diesel
 - PM_{10} 300 $\mu g/m^3$ - *i.e. equal PM mass*
- 2 RME100 (100% biodiesel) vs. petro diesel
 - PM_{10} 300 $\mu g/m^3$ petro diesel vs. 165 $\mu g/m^3$ RME100, *i.e. equal engine load*
- 3 RME100 (100% biodiesel) vs. filtered air
 - PM_{10} 165 $\mu g/m^3$ RME100 vs. filtered air
 - Measurements of vascular effects 2-4 hours post exposure (studies 1-2)
 - Bronchoscopy with endobronchial biopsy and BW/BAL sampling 6 hours post exposure (study 3)

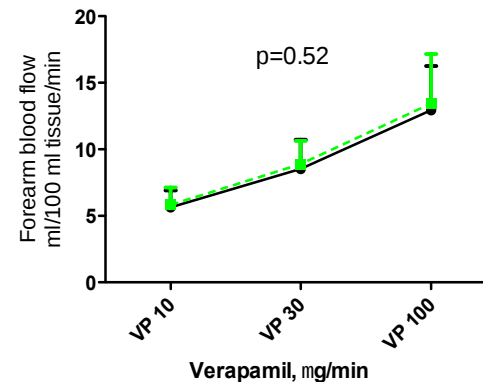
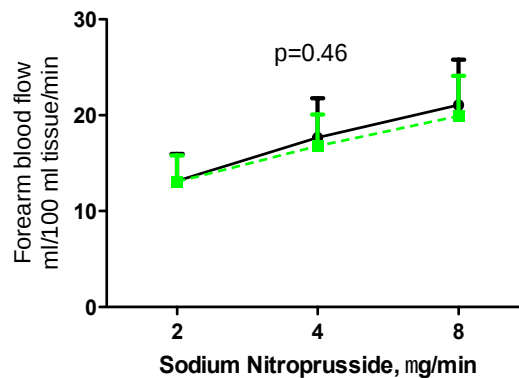
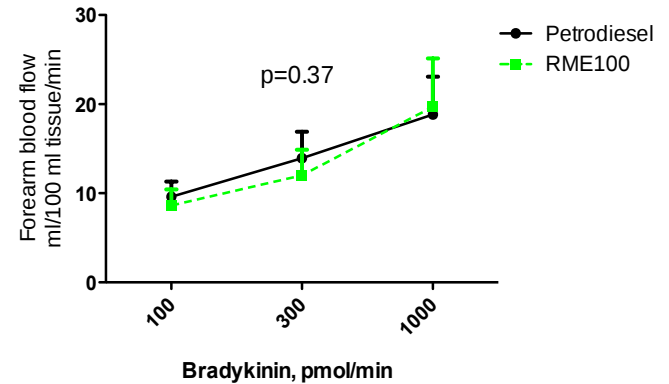
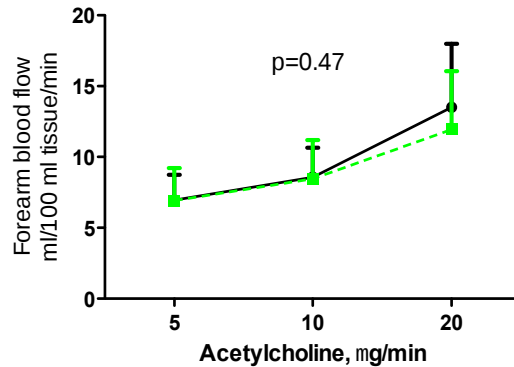
RME30 vs. petro diesel

Bilateral forearm plethysmography

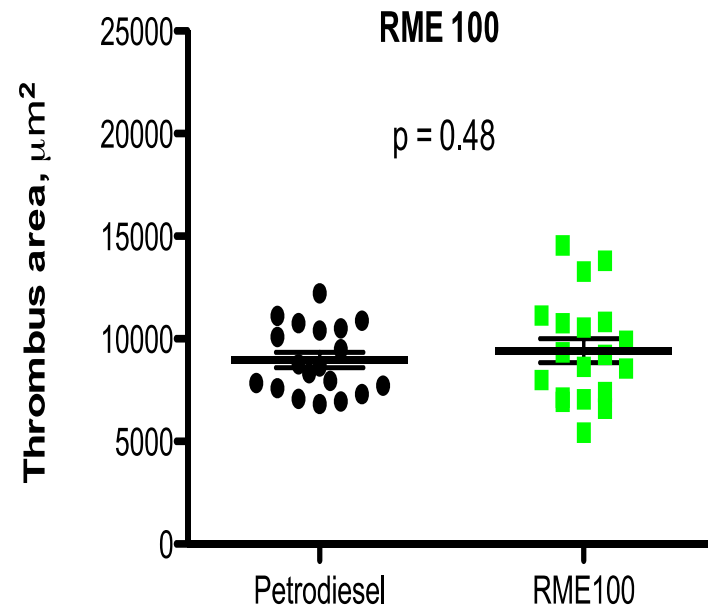
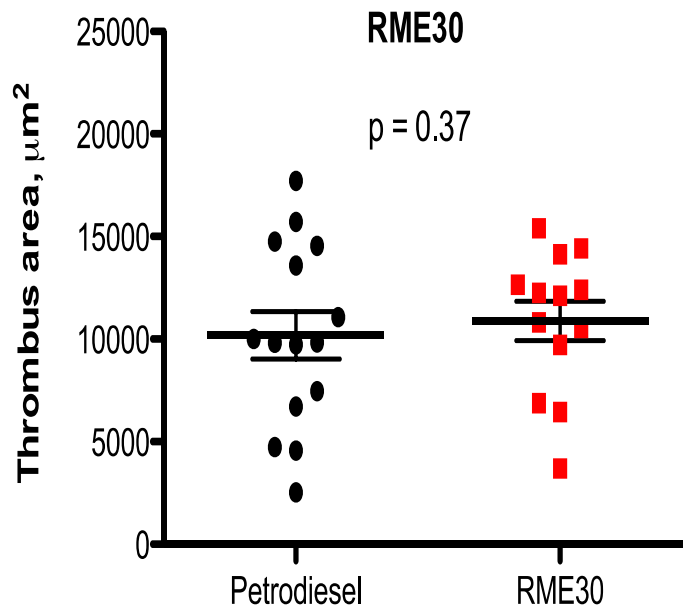


100% RME Biodiesel vs. petro diesel

Bilateral forearm plethysmography



No differences in thrombus formation

Unosson *et al*, manuscript

100% RME Biodiesel vs. filtered air

Bronchoscopy

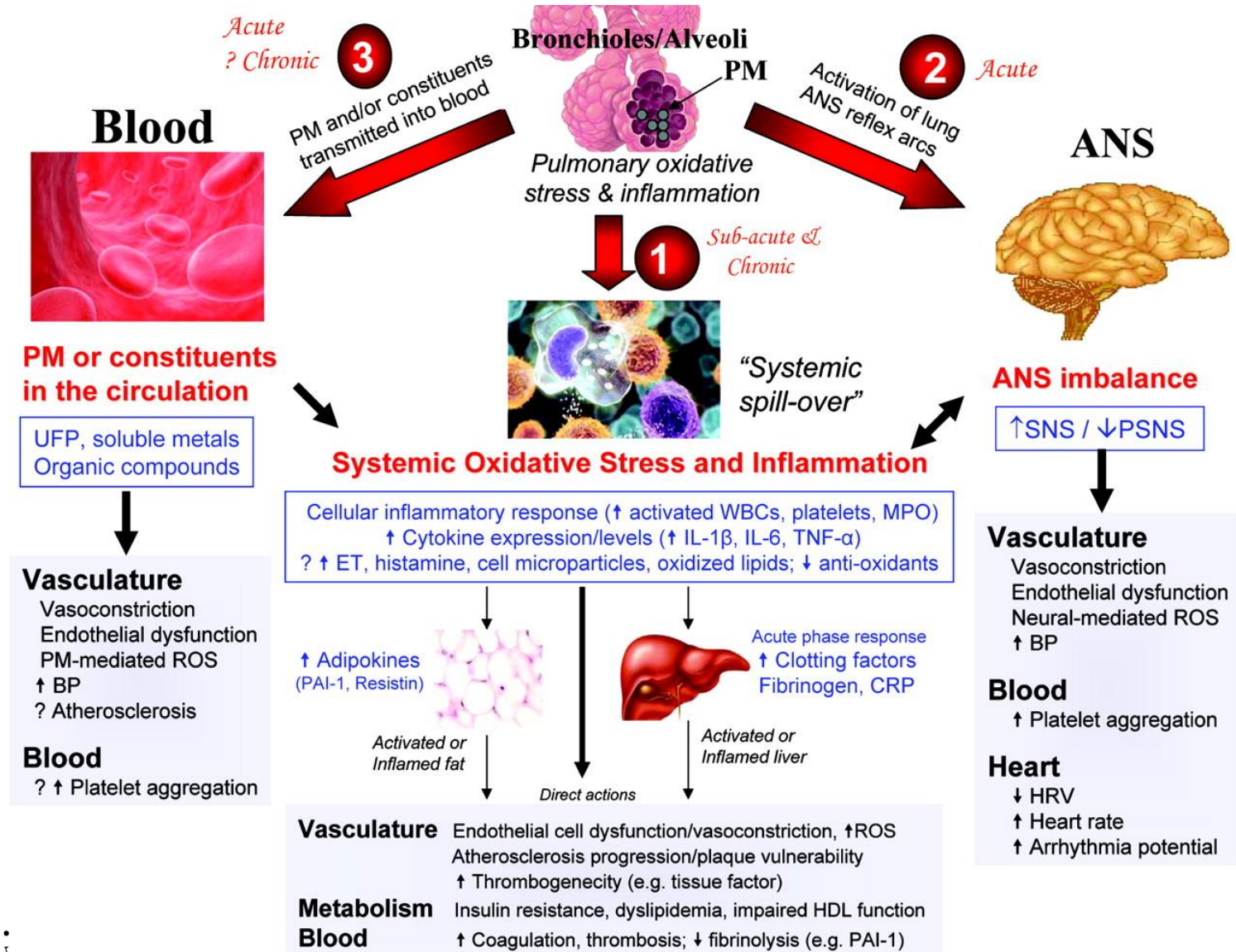
Bronchial Wash (BW)	Filtered air	Biodiesel	p-value
Macrophages	4.89 (3.40-7.32)	8.86 (3.19-12.28)	0.036
Neutrophils	0.93 (0.68-1.75)	1.80 (0.92-2.50)	0.008
Lymphocytes	0.25 (0.12-0.51)	0.41 (0.07-0.81)	0.233
Eosinophils	0.00 (0.00-0.00)	0.01 (0.00-0.02)	0.314

Values are given as medians (IQR). Wilcoxon signed ranks test.

Airway inflammatory responses similar as seen after exposure to petro diesel exhaust.

Biopsy data under progress.

Biological pathways linking PM exposure with CVDs



Brook, R. D. et al. Circulation 2010;121:2331-2378

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- Edinburgh, UK

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- Dr. Jeremy P Langrish Dr. Mark Miller

Dr. Andrew Lucking

