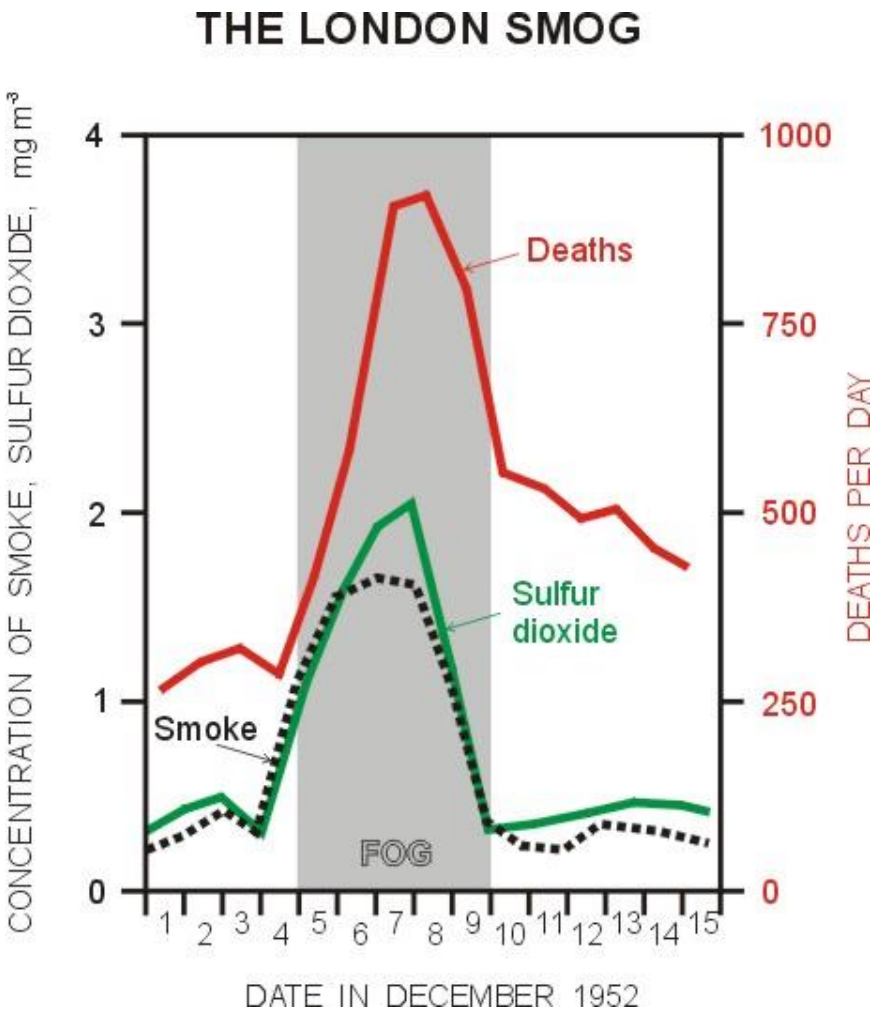
Frontiers in Air Quality

Advances in Air Quality Toxicology

Heart and Lungs – Victims of Polluted Air

Anders Blomberg, MD, PhD
Professor, Consultant Physician
Dept. of Public Health and Clinical Medicine
Umeå University

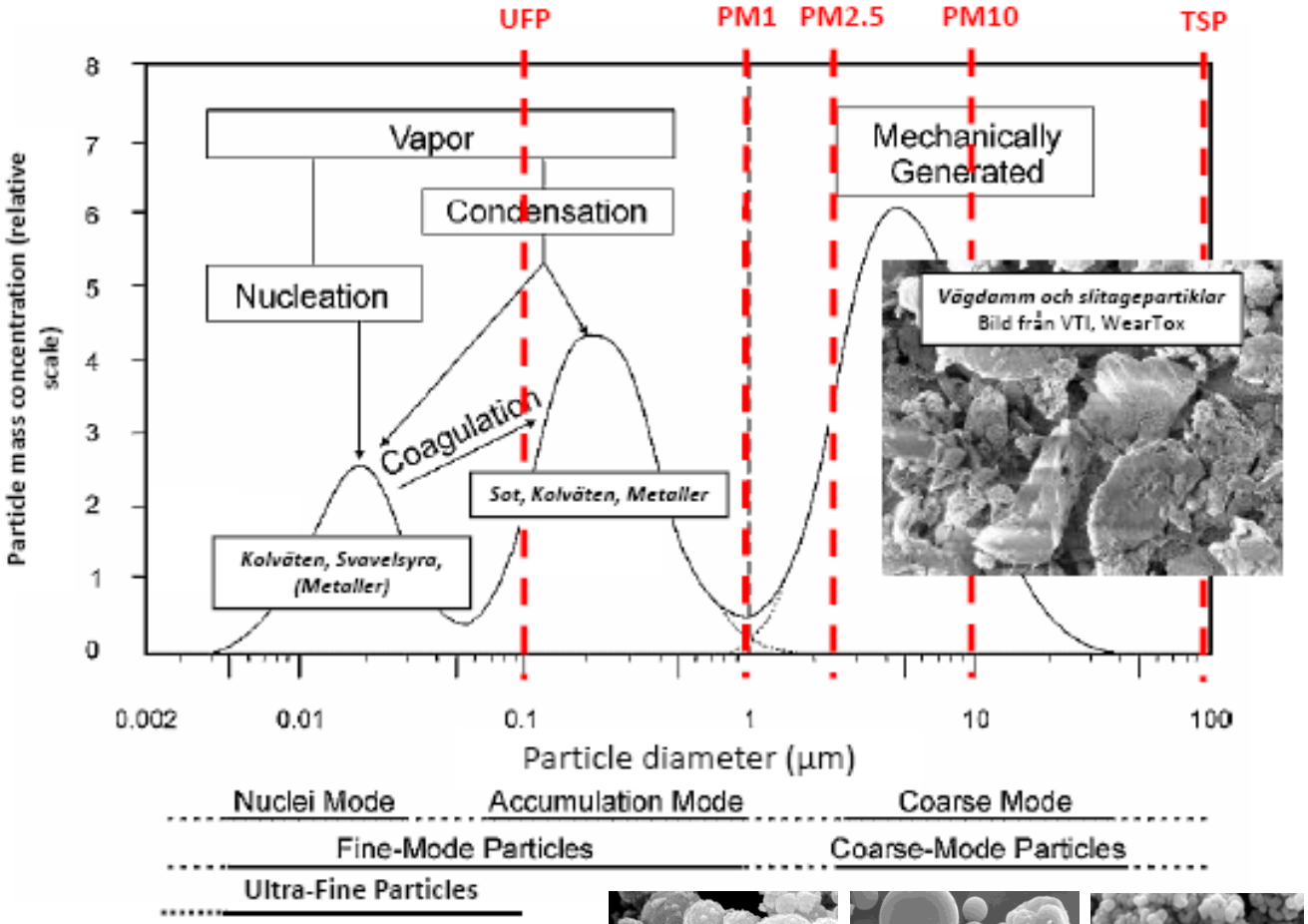
How did it start?

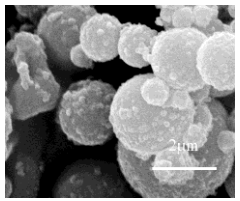


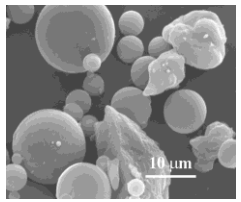
Combustion-derived particulate matter air pollution

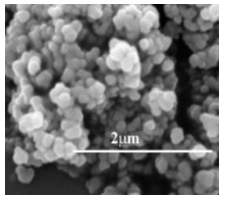
- Diesel exhaust
  - Petro diesel
  - Biodiesel
- Wood smoke/biomass burning

Different air pollution sources – different sizes









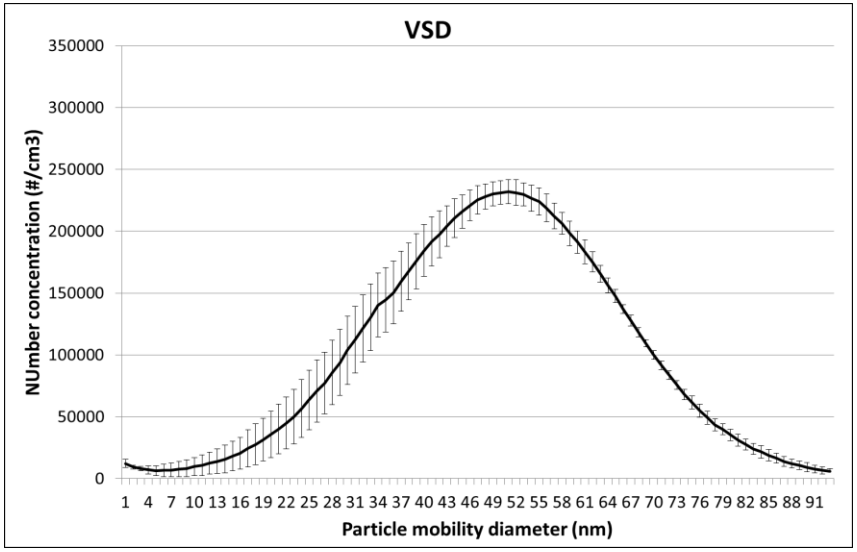
Coarse <10 µm

Fine <2.5 µm

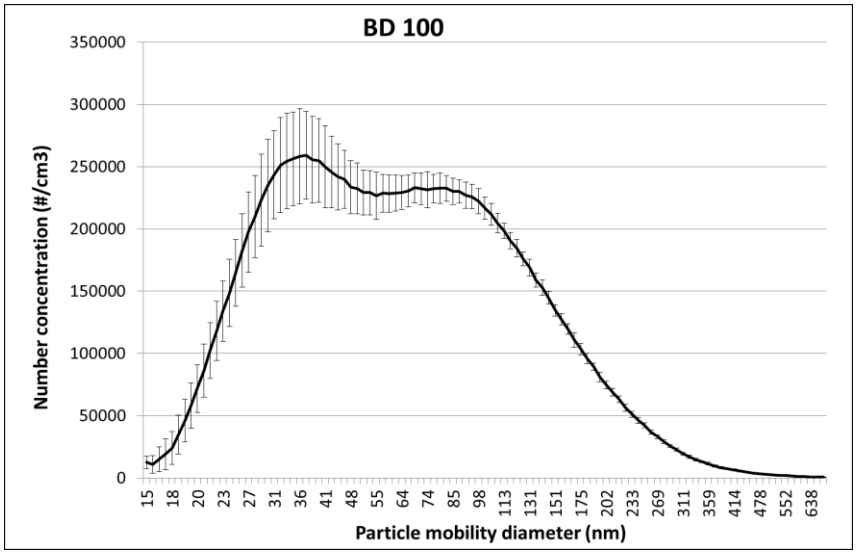
Ultrafine <0.1 µm

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 ⇄ air pollutant

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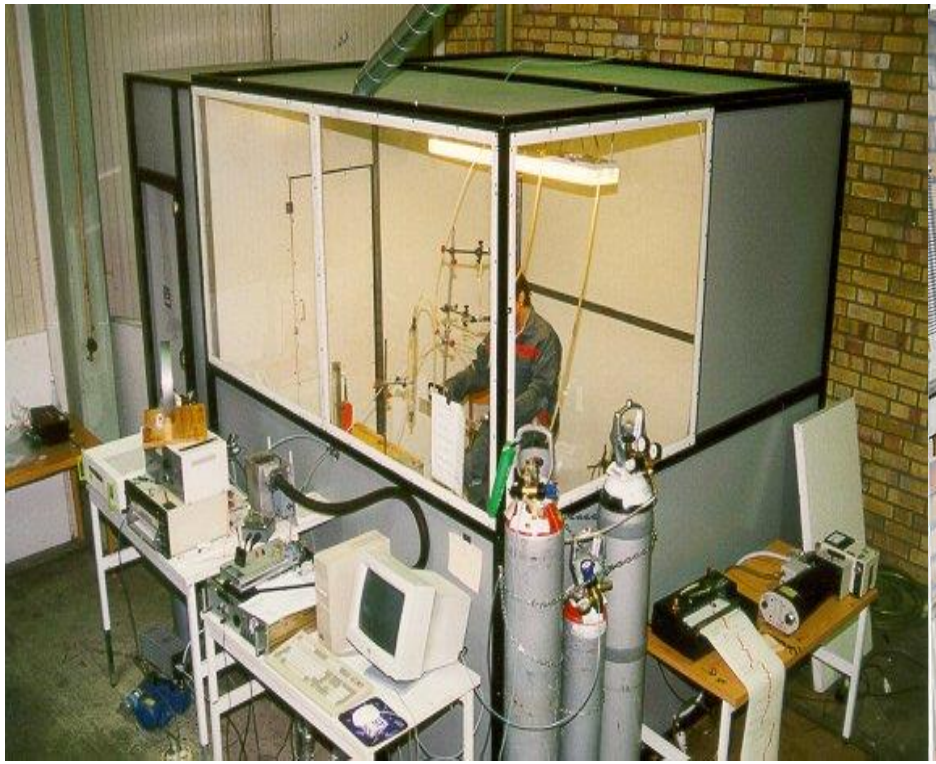
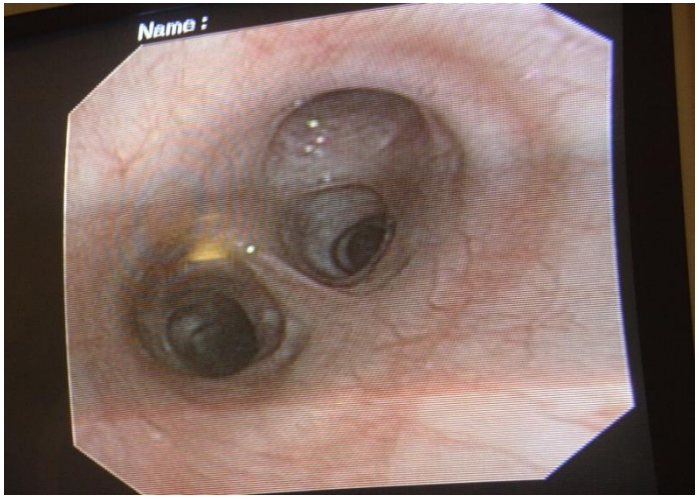
Exposure Setup

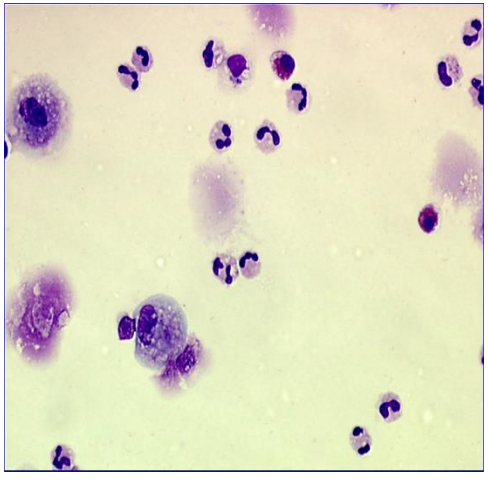
Diesel exhaust used as a model of PM pollution

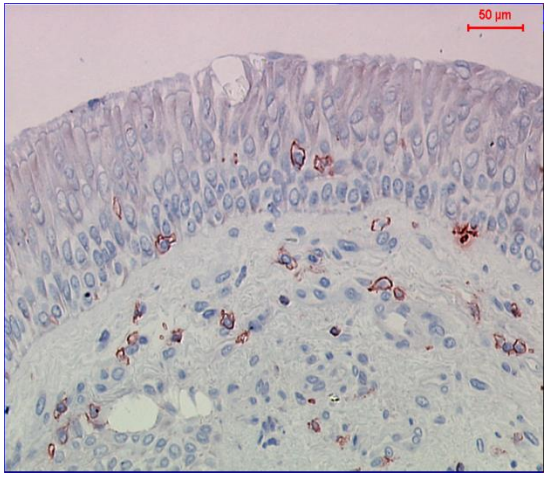
Exposure to diesel exhaust and filtered air for 1-2 hours on two separate occasions

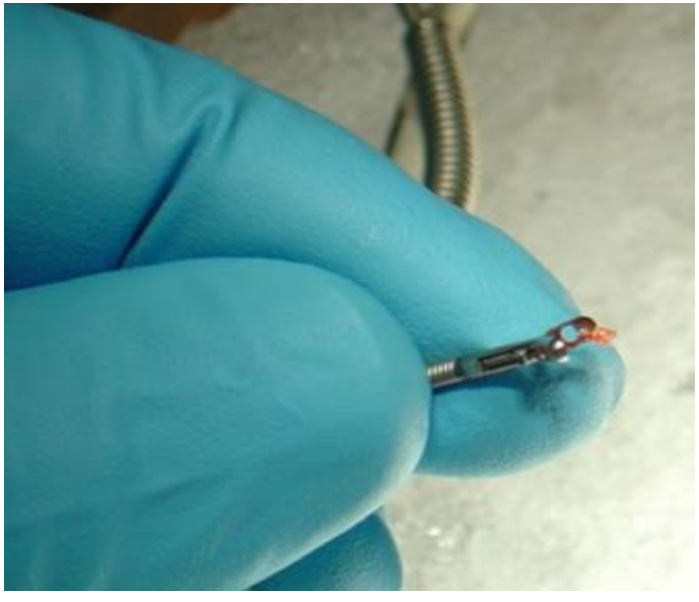


Bronchoscopy



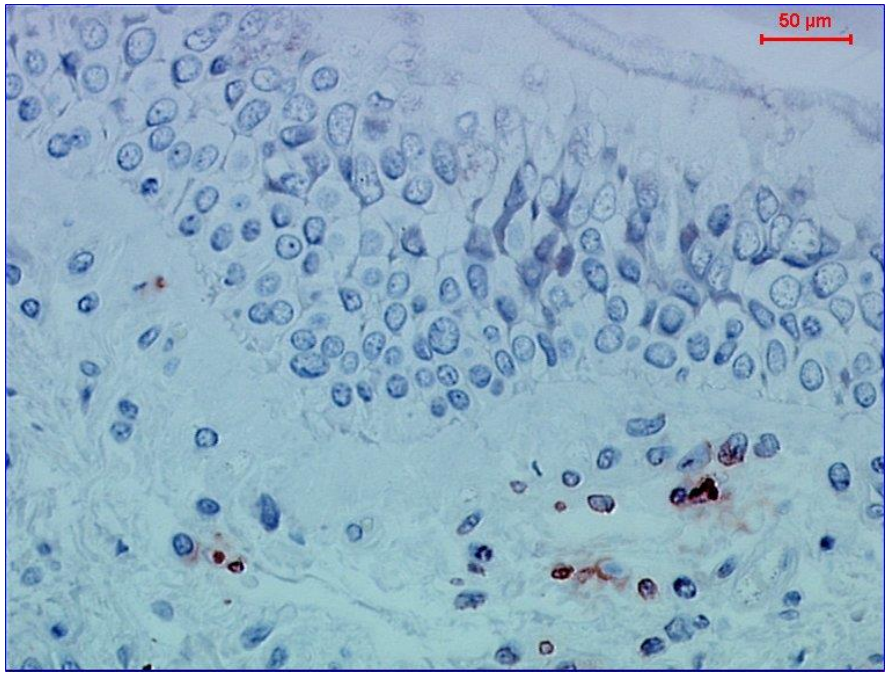




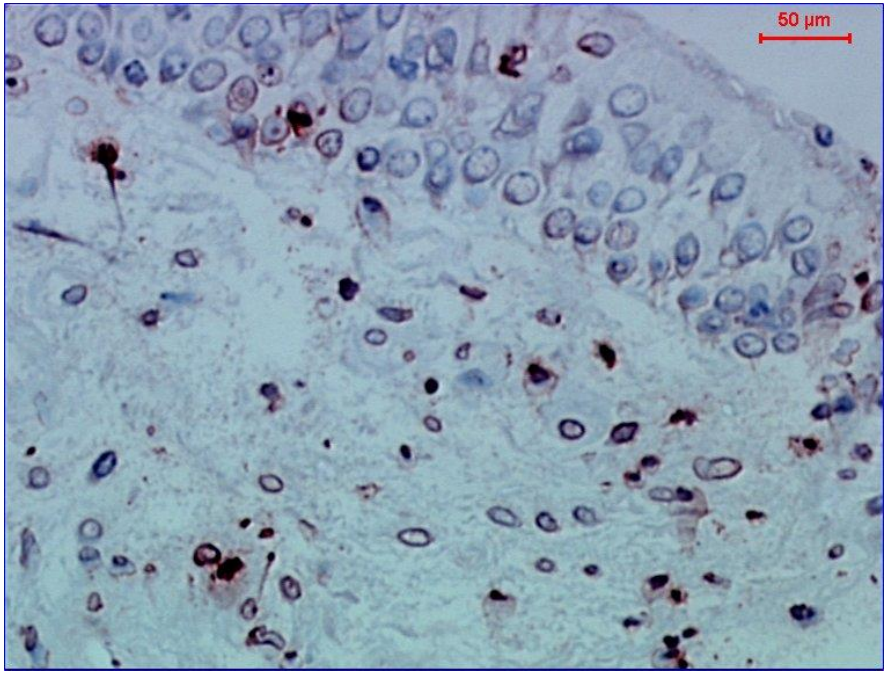


Exposure to diesel exhaust in healthy volunteers - *biopsies*

Filtered air



Diesel exhaust



Neutrophils

Salvi *et al* AJRCCM 1999

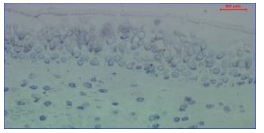
Airway effects by diesel exposure in healthy humans

MAPKs

- p38

Transcription factors

- AP-1, NFκB

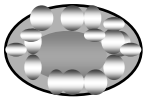


Cytokines

- IL-8, IL-13, GRO-α

Adhesion molecules

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



Inflammatory cells

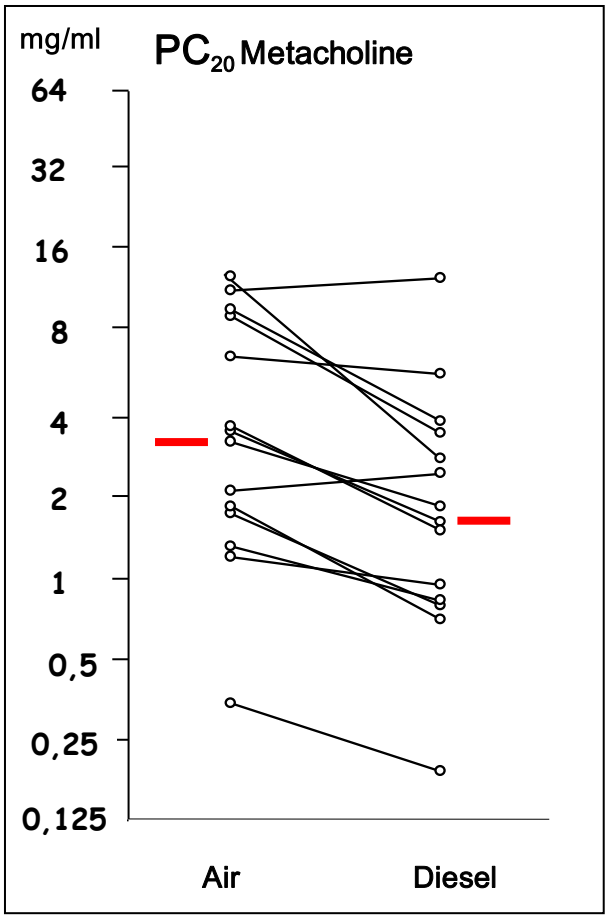
- Neutrophils, mast cells, lymphocytes

Diesel exhaust –
PM concentrations 100 vs. 300 µg/m^3

- Slower development of airway inflammation at a lower concentration
- Events occuring at 6 hours after 300 µg/m^3 can be found 18 hours after 100 µg/m^3

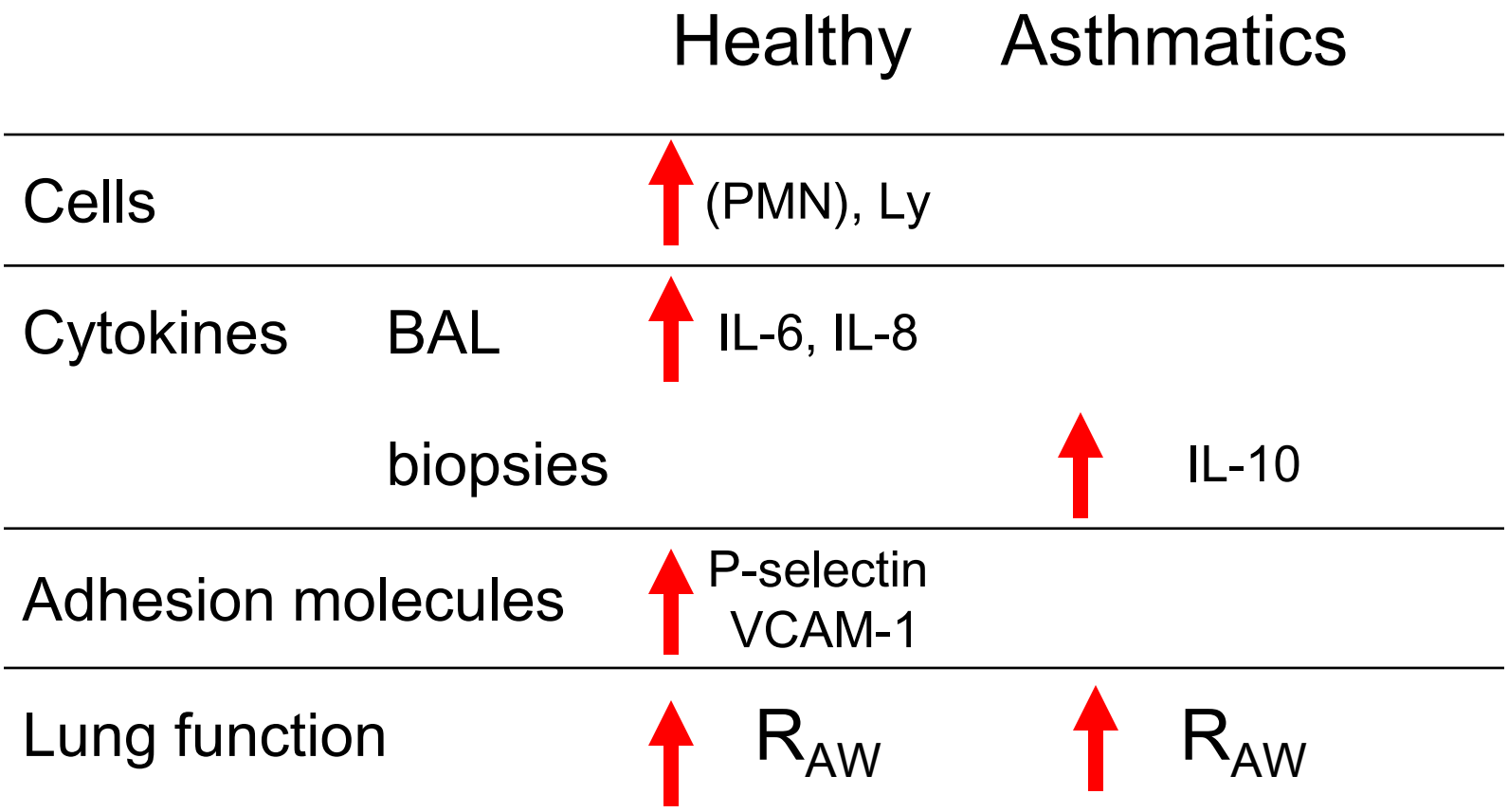
Diesel exhaust increases airway hyperresponsiveness in asthmatics..

..despite treatment with inhaled corticosteroids



Nordenhäll *et al,* ERJ 2001

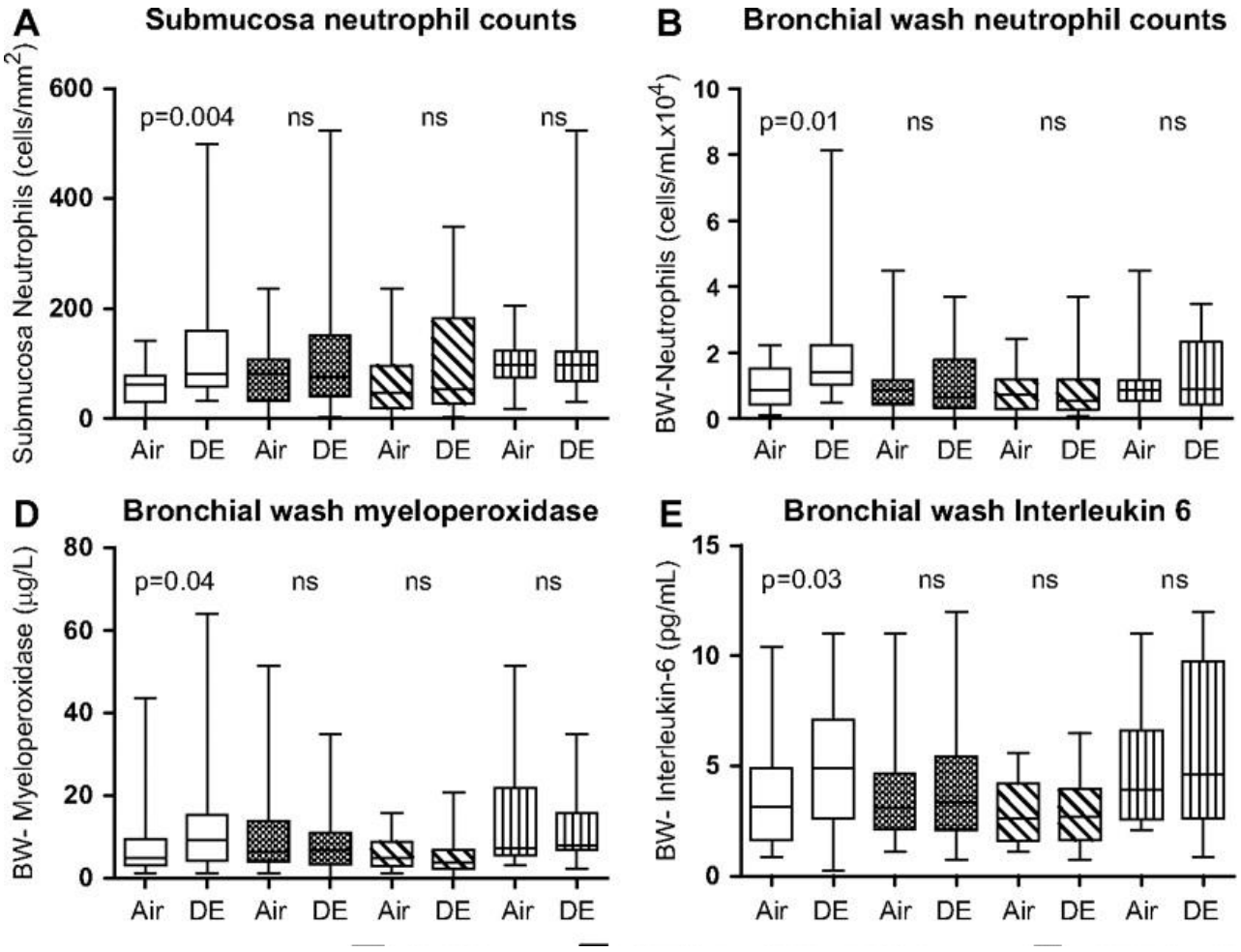
Exposure to diesel exhaust Healthy vs. Asthmatics *(6 h)*



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

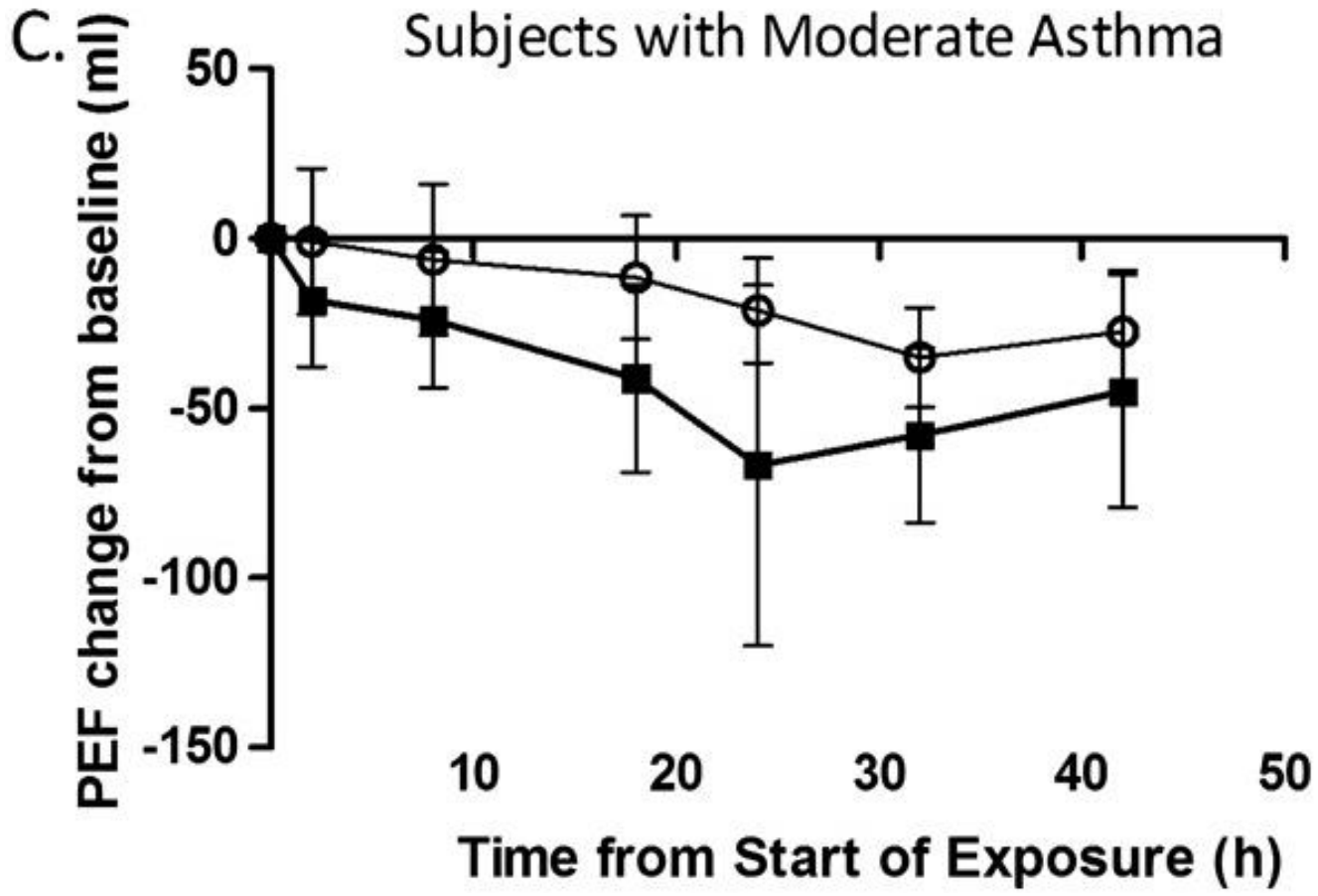
Stenfors *et al.* ERJ 2004

Diesel exhaust - asthmatics

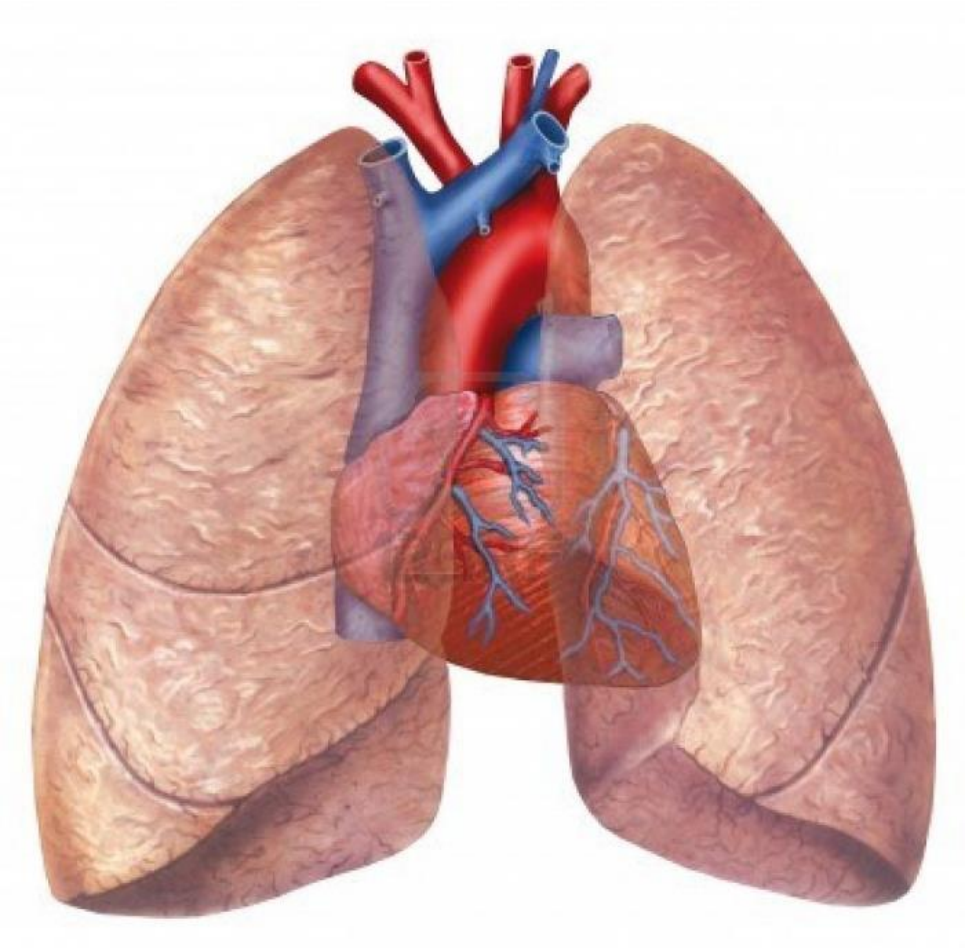


Behndig A F *et al.* Thorax 2011

PEF-responses in asthma



From lungs to heart……



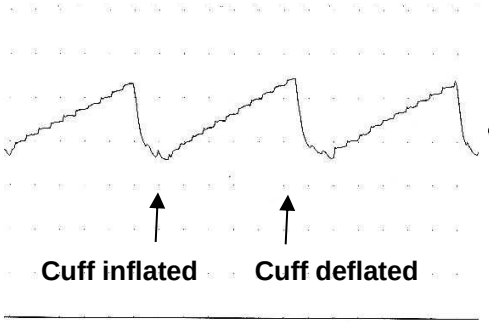
Tools for investigating cardiovascular events of air pollution in humans *in-vivo*

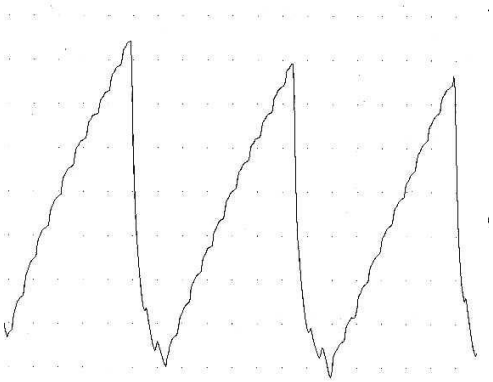
- Forearm plethysmography
- *Ex-vivo* model of thrombosis
- Coagulation markers
- Arterial stiffness
- Blood pressure
- Heart rate and rhythm

Measuring endothelial function

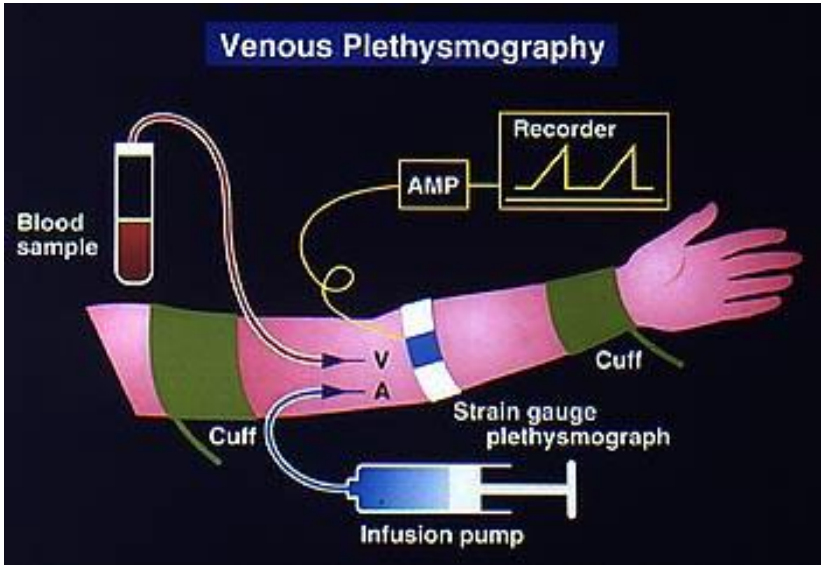
VENOUS OCCLUSION PLETHYSMOGRAPHY

Non-infused



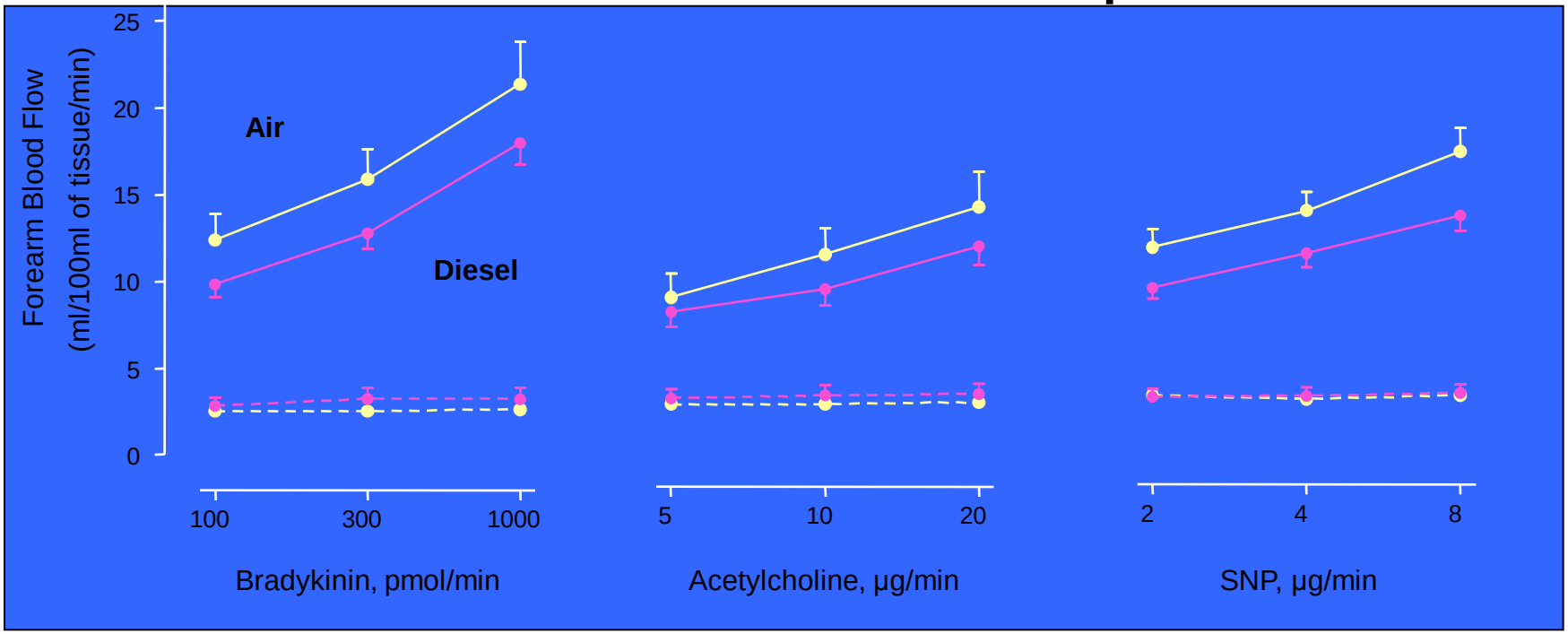


Infused arm



BILATERAL VENOUS SAMPLING

Decreased forearm blood flow 6 hours after diesel exhaust exposure



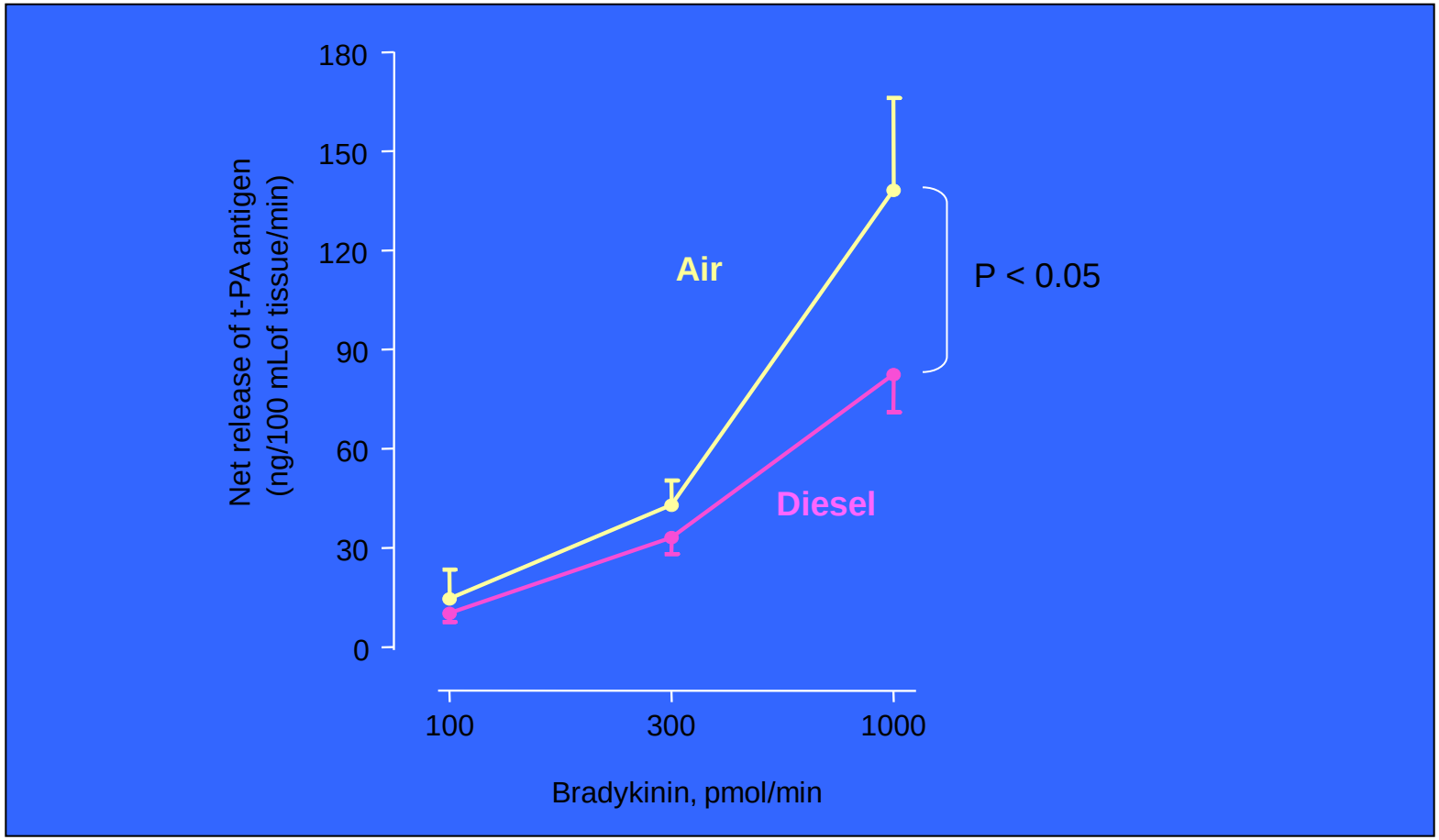
Infused (solid line) and non-infused (dashed line) FBF following diesel exhaust (●) and air (●) during bradykinin (P=0.006), acetylcholine (P=0.07) and sodium nitroprusside (P=0.0002).

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

Mills *et al.* Circulation 2005

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

Mills *et al.* Circulation 2005

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 13, 2007 VOL. 357 NO. 11

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.

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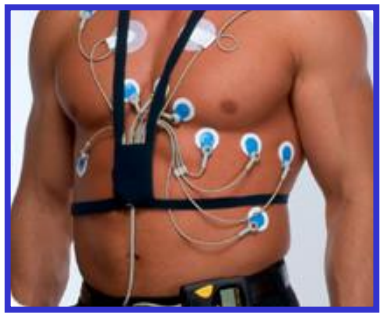
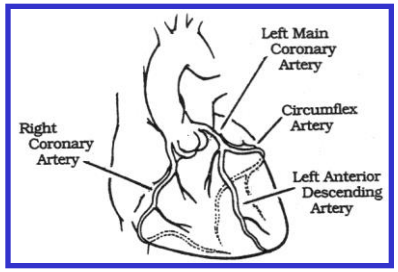
Effect of exposure to diesel exhaust in patients with stable coronary heart disease

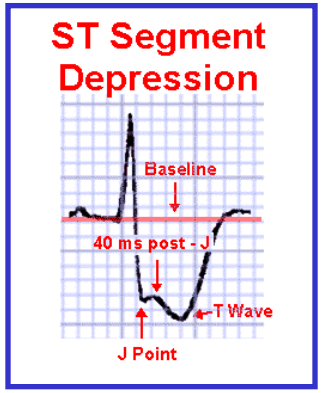
- 20 male patients
- Coronary heart disease successfully treated with PCI – stable disease
- No diabetes mellitus
- No congestive heart failure
- Normal maximal exercise test
- No symptoms
- Full ”protective” medication

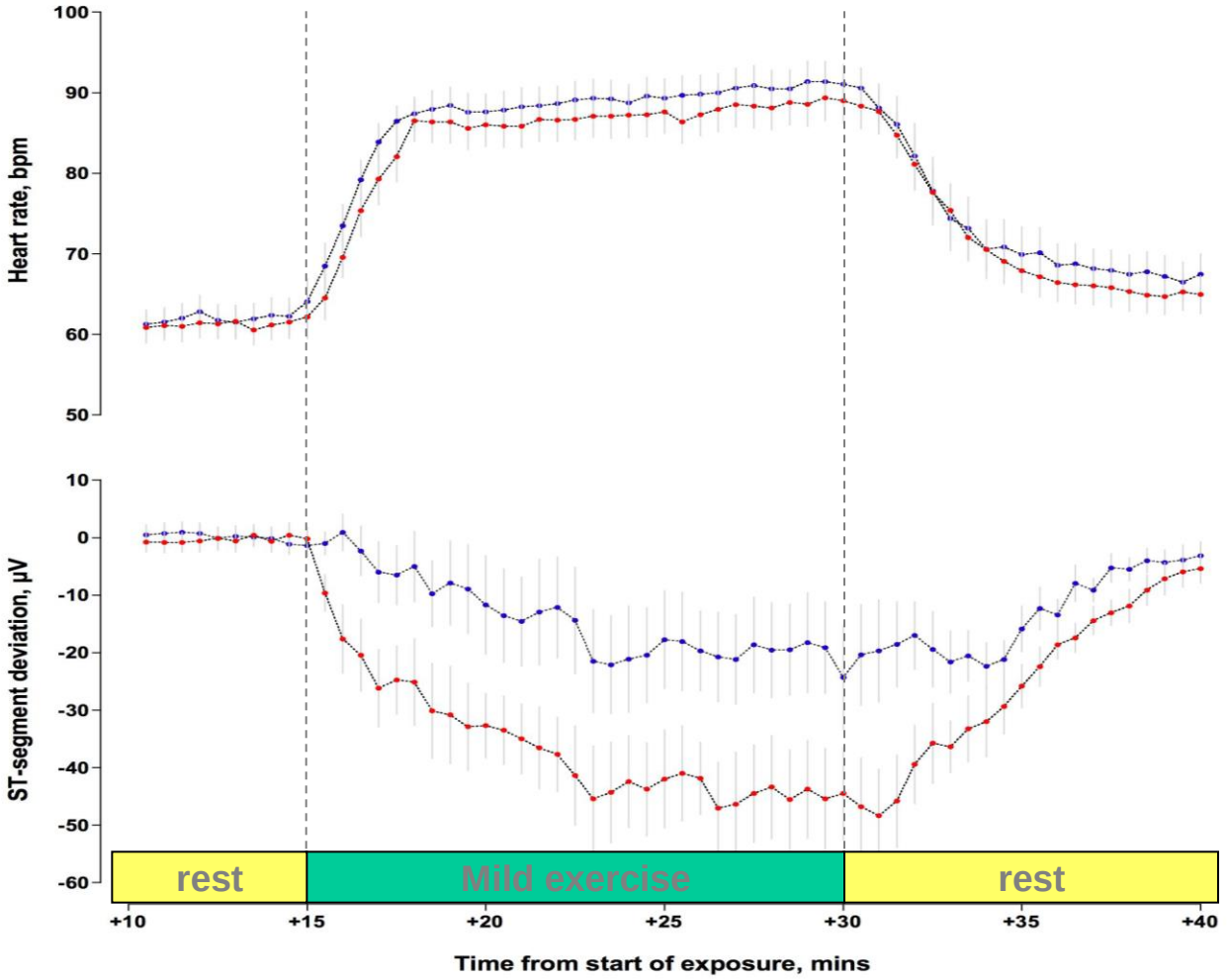
Mills *et al.* New Engl J Med 2007

Exercise-induced ischaemia

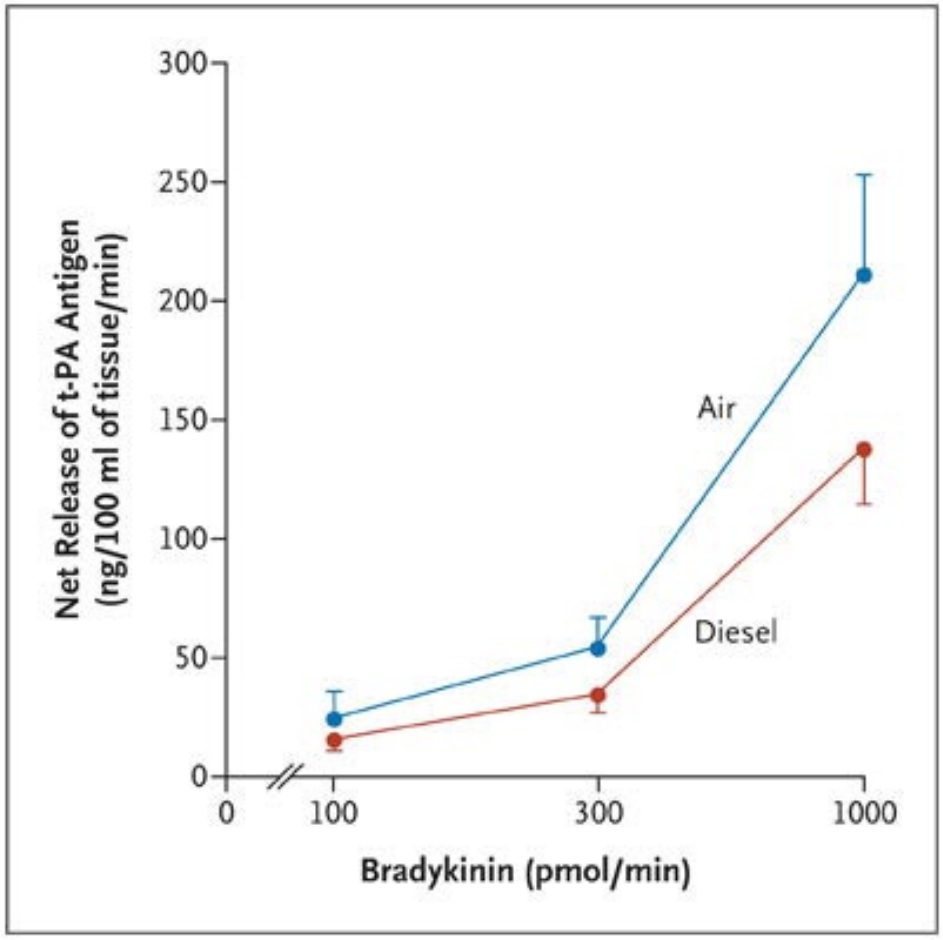








Impaired endogenous fibrinolysis

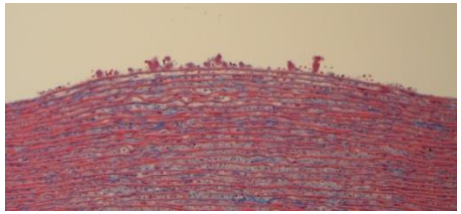


p=0.009

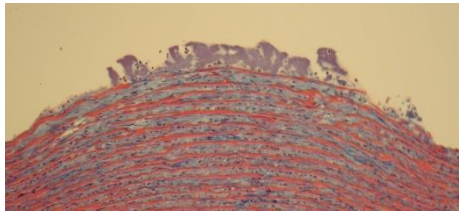
Mills *et al.*, New Engl J Med 2007

Thrombus formation *ex-vivo*

Air

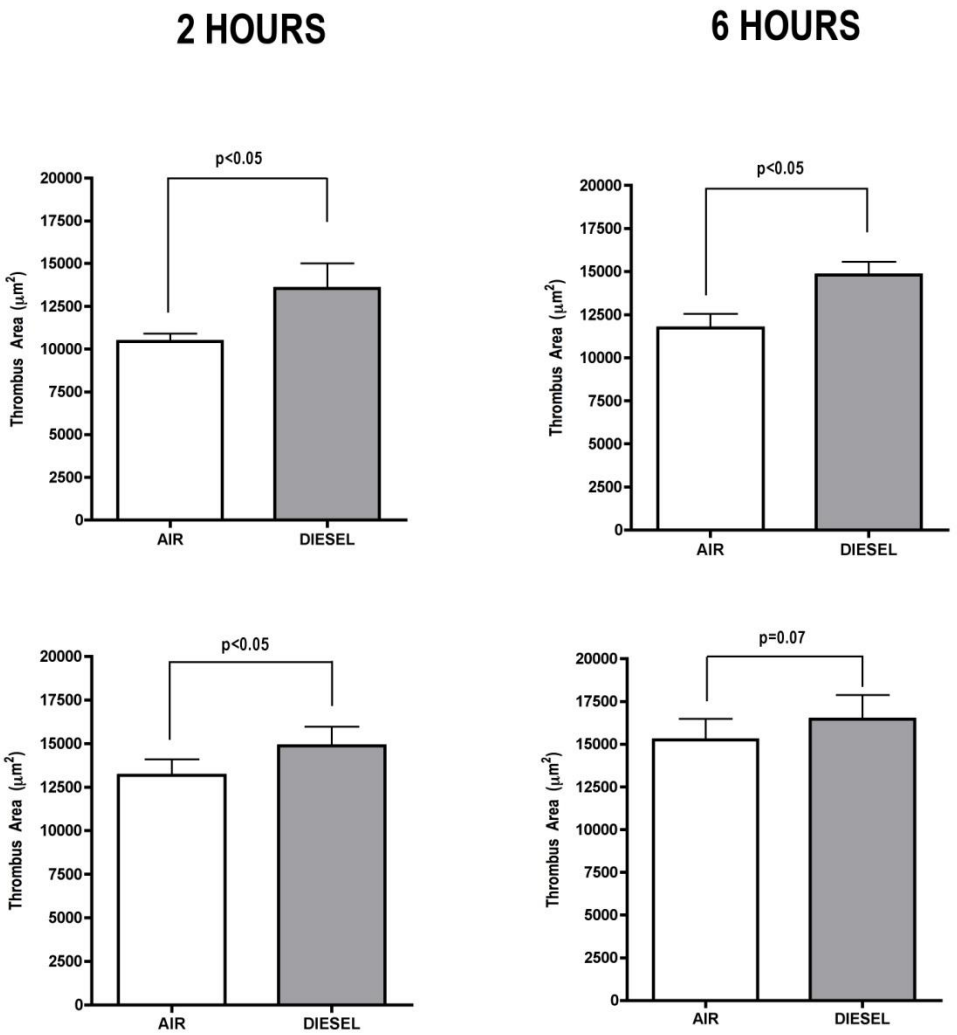


Diesel



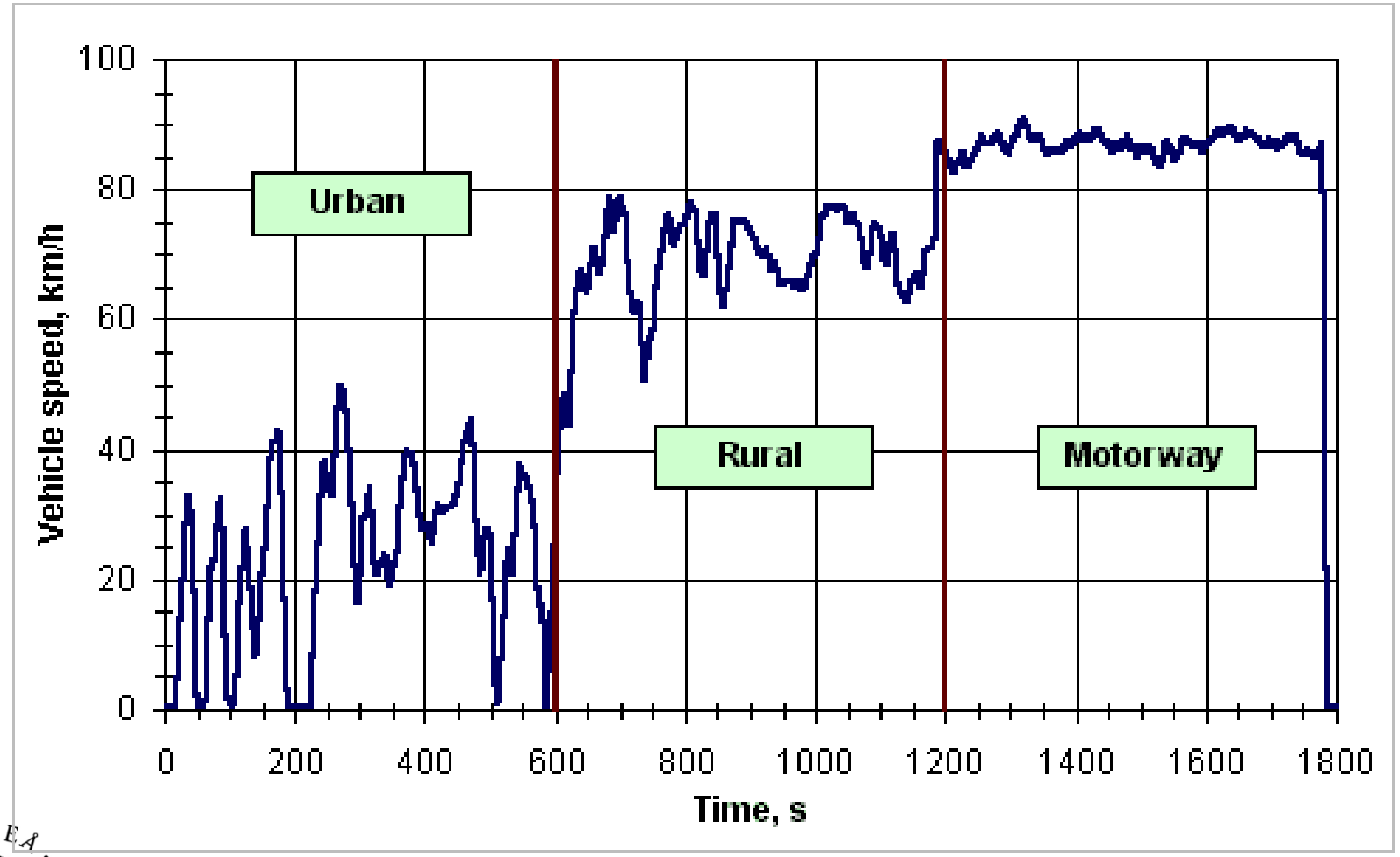
Low Shear Chamber

High Shear Chamber

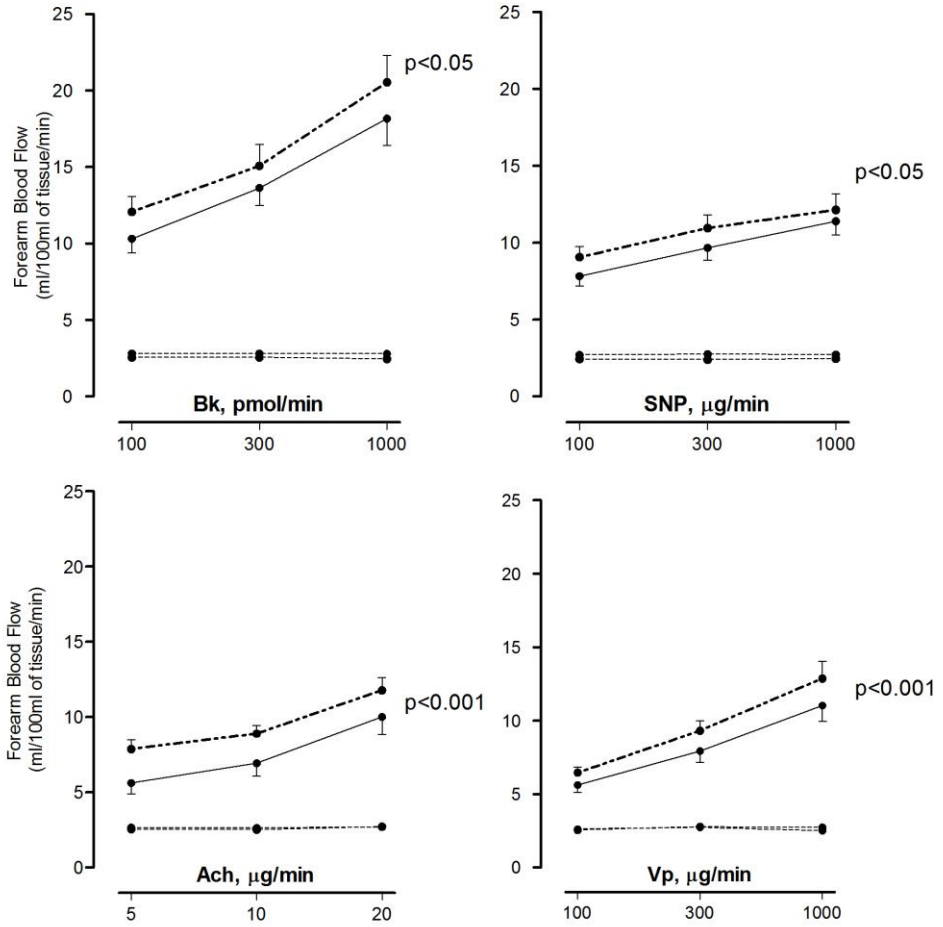


Lucking *et al*, Eur Heart J 2008

Idling v.s urban running cycle



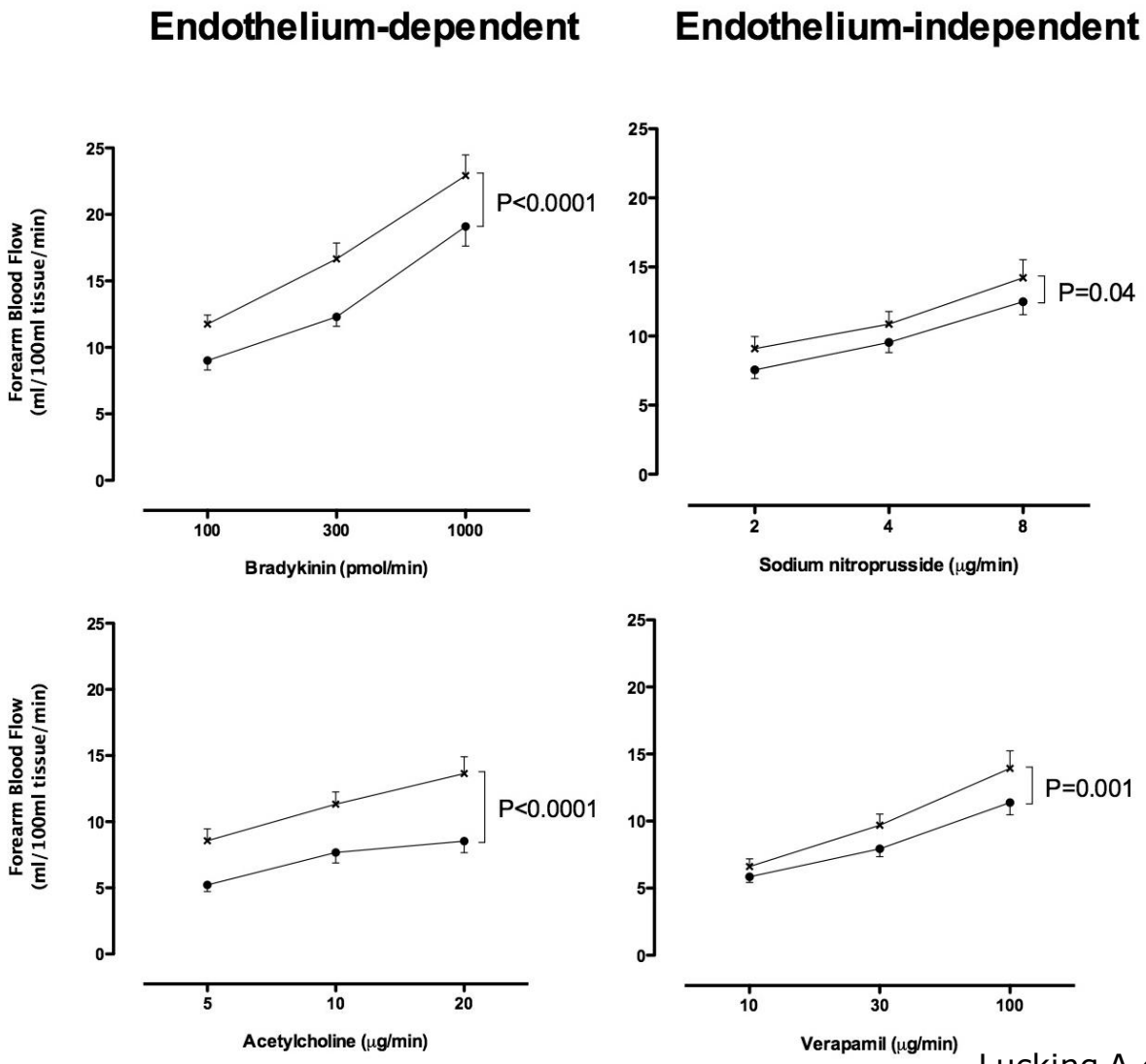
Vascular responses similar regardless of idling or city cycle



Barath *et al.* Part Fibre Toxicol, 2010

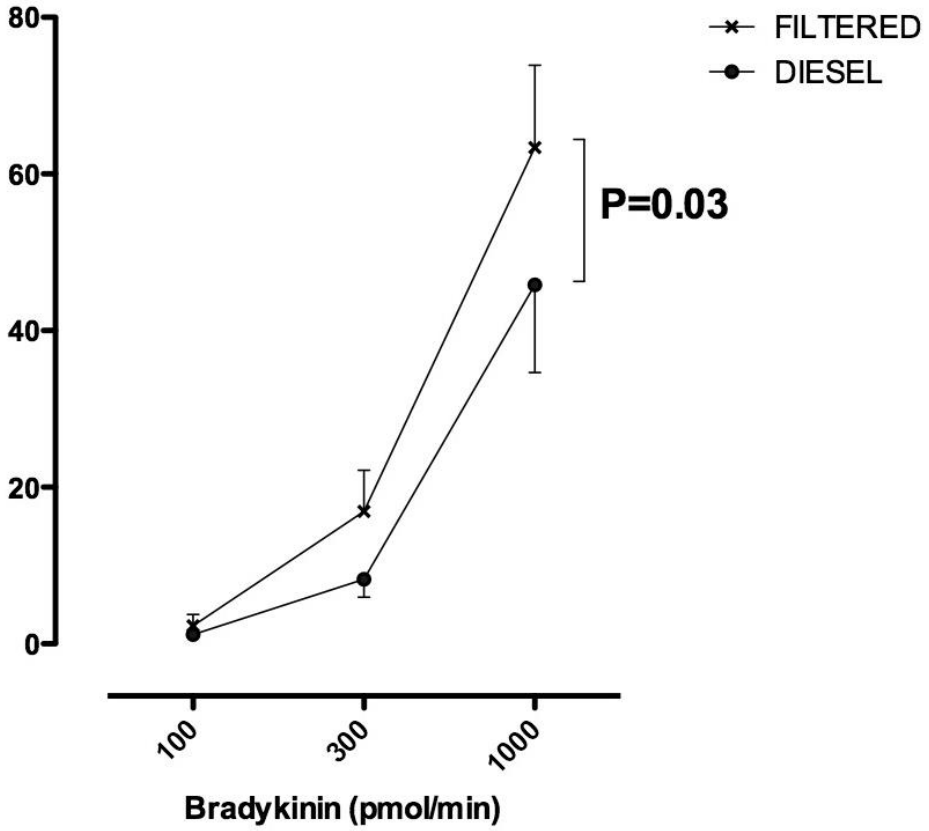
PARTICULATE TRAP-STUDY

DIESEL EXHAUST vs. FILTERED DIESEL EXHAUST



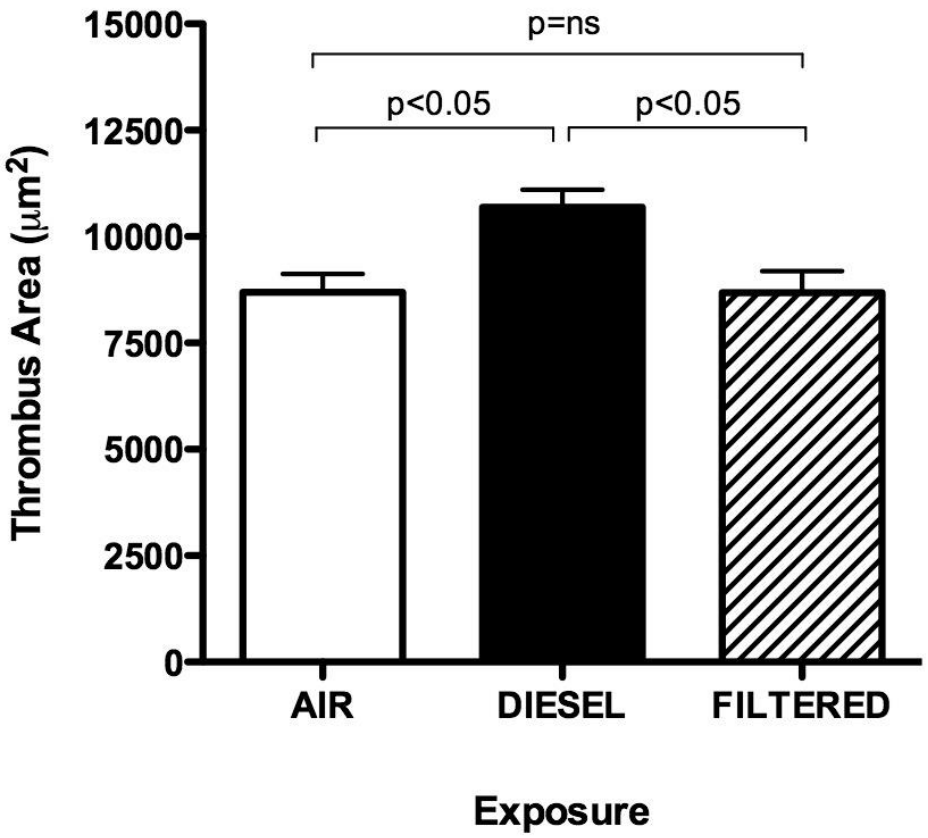
Lucking A *et al*, Circulation 2011

t-PA RELEASE



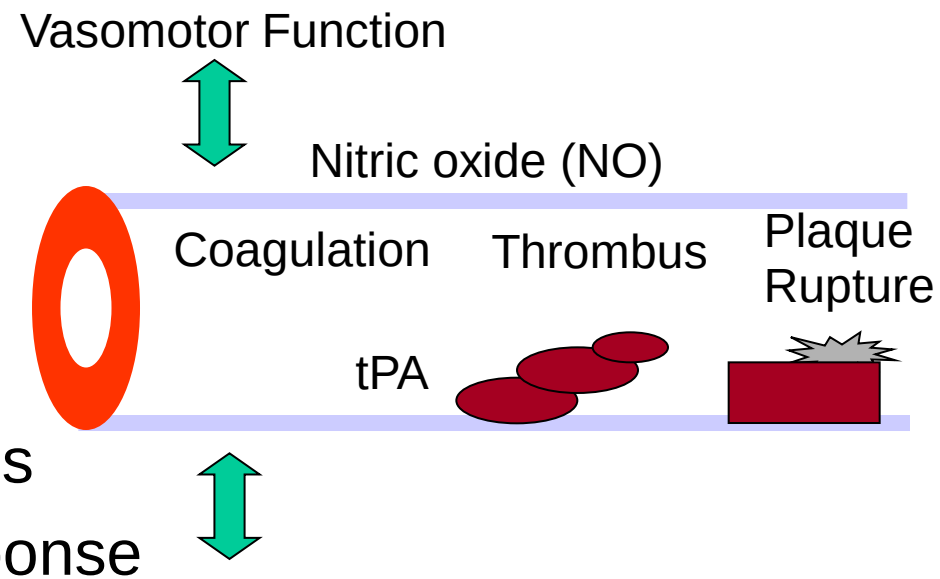
Lucking A *et al,* Circulation 2011

Reduced thrombus formation with filter

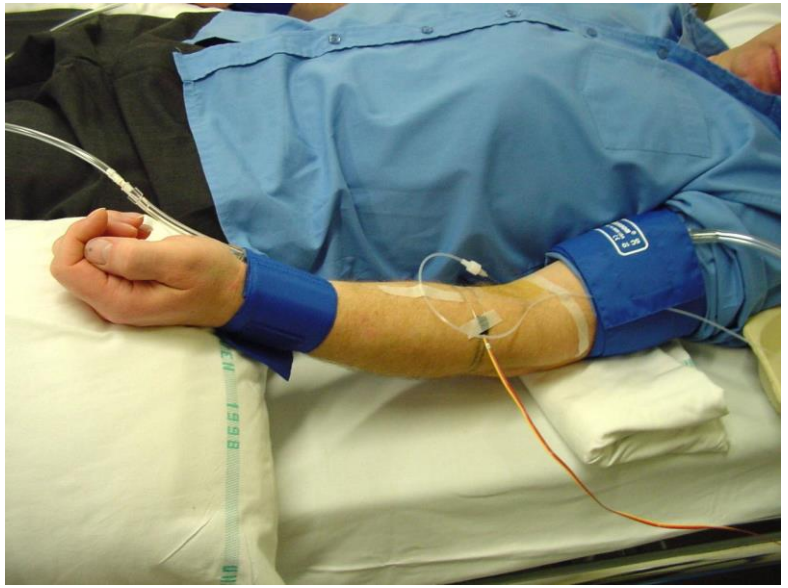


Lucking A *et al,* Circulation 2011

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

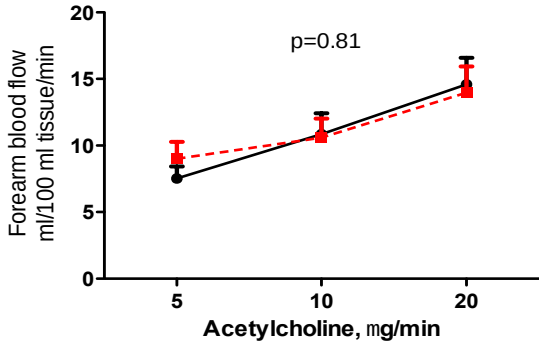
Three exposure studies in healthy human subjects with RME Biodiesel vs. petro diesel or filtered air

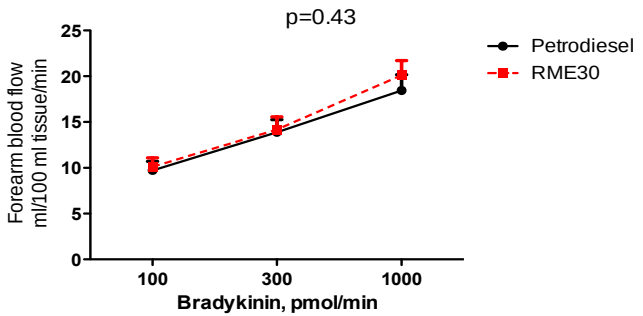
1 RME30 (30% biodiesel) vs. petro diesel
   - PM_1 300 μg/m^3 - *i.e. equal PM mass*
2 RME100 (100% biodiesel) vs. petro diesel
   - PM_1 300 μg/m^3 petro diesel vs. 165 μg/m^3 RME100, *i.e. equal engine load*
3 RME100 (100% biodiesel) vs. filtered air
   - PM_1 165 μg/m^3 RME100 vs. filtered air

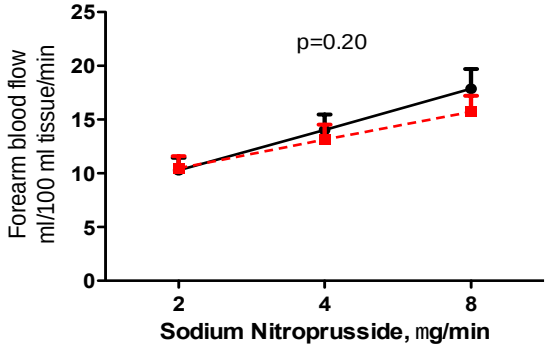
- Measurements of vascular effects 2-4 hours post exposure (studies 1-2)
- Bronchoscopy with endobronchial biopsy and BW/BAL sampling 6 hours post exposure (study 3)

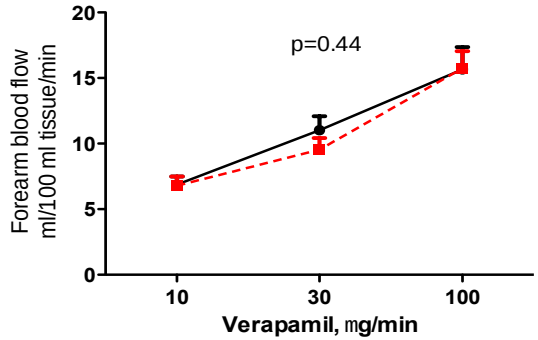
RME30 vs. petro diesel

Bilateral forearm plethysmography







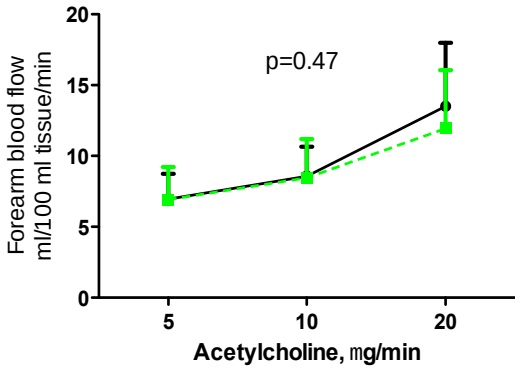


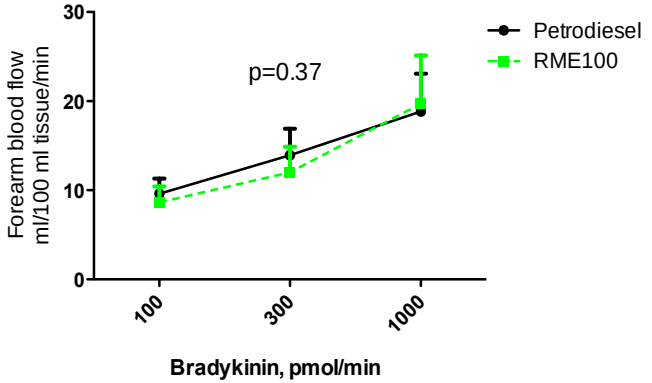
Similar vascular effects by RME30 and standard petro diesel

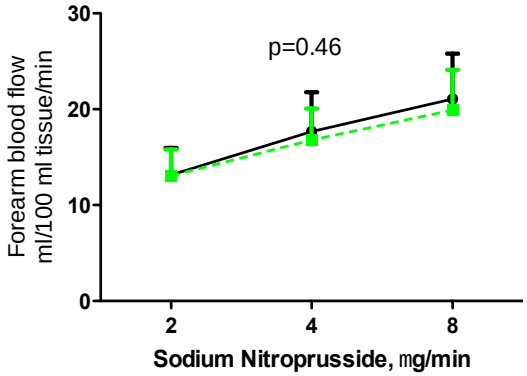
Unosson *et al*, manuscript

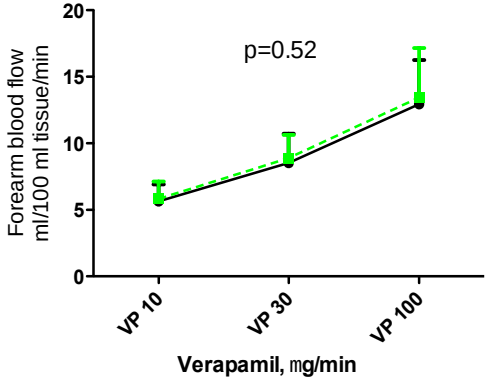
100% RME Biodiesel vs. petro diesel

Bilateral forearm plethysmography





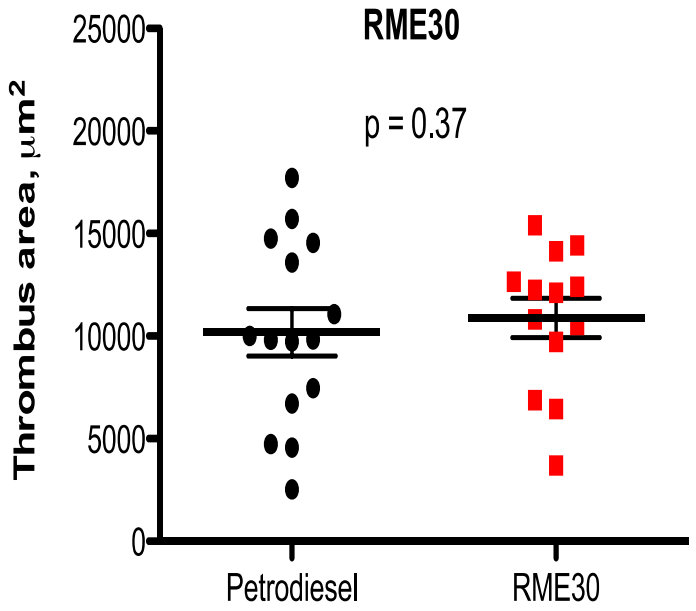


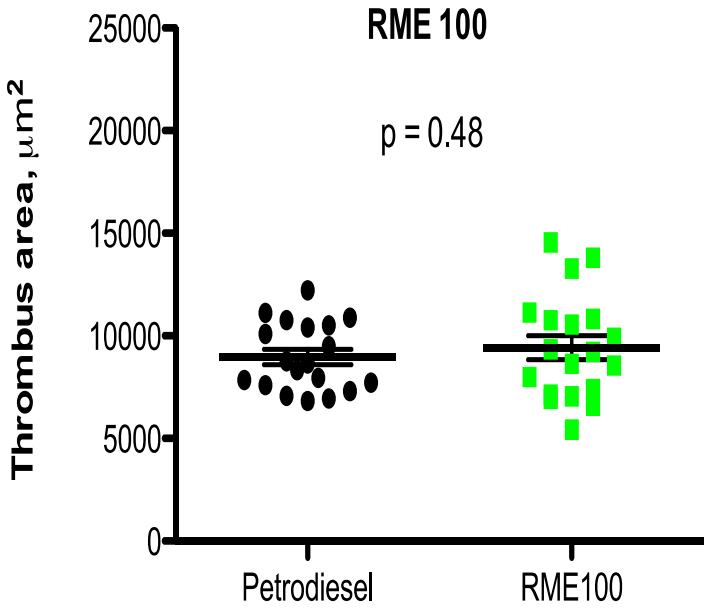


Similar vascular effects by RME100 and standard petro diesel

Unosson *et al,* manuscript

No differences in thrombus formation





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100% RME Biodiesel vs. filtered air

Bronchoscopy

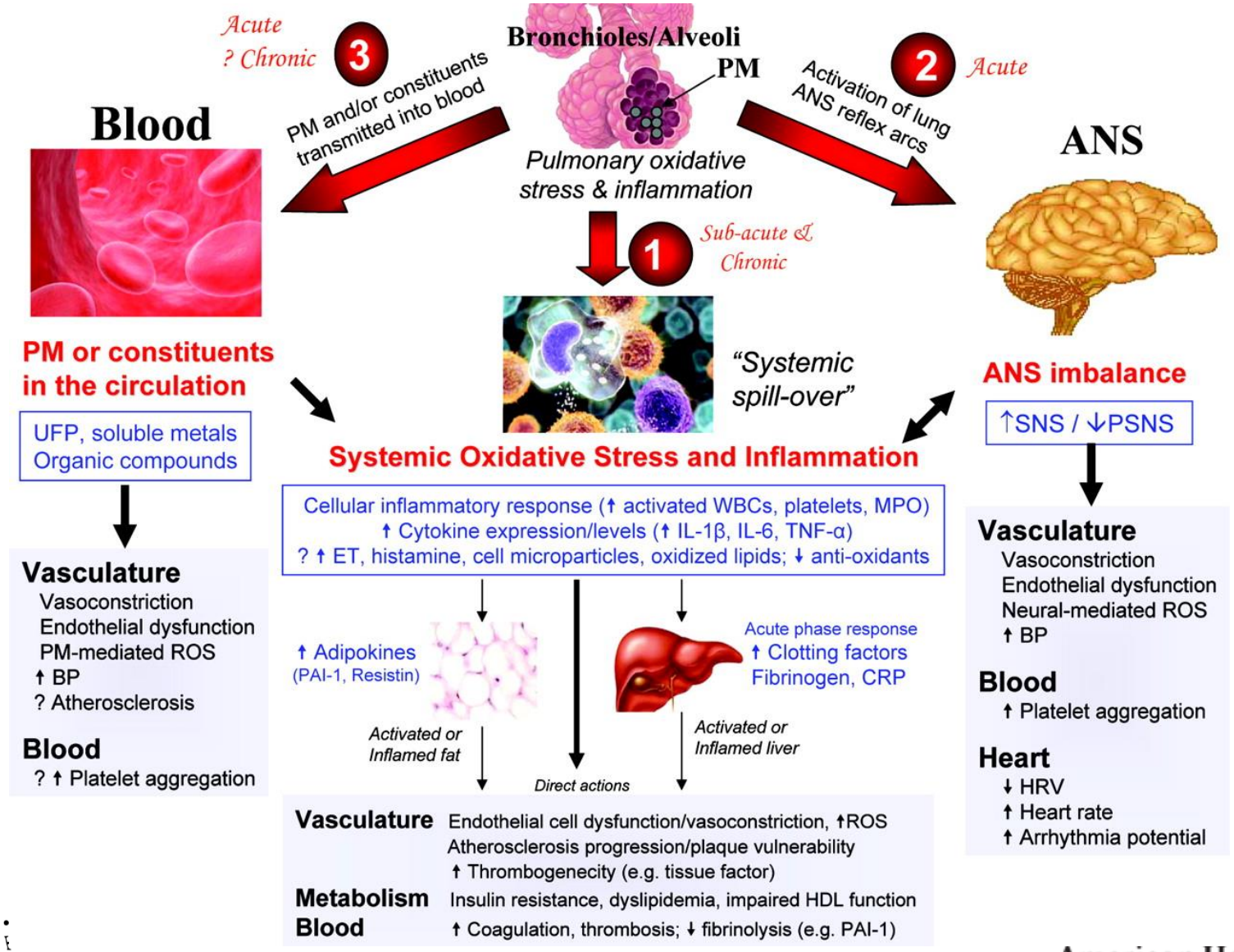
Bronchial Wash (BW)	Filtered air	Biodiesel	p-value
Macrophages	4.89 (3.40-7.32)	8.86 (3.19-12.28)	0.036
Neutrophils	0.93 (0.68-1.75)	1.80 (0.92-2.50)	0.008
Lymphocytes	0.25 (0.12-0.51)	0.41 (0.07-0.81)	0.233
Eosinophils	0.00 (0.00-0.00)	0.01 (0.00-0.02)	0.314

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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