Responses to Fresh Aerosols in Sensitive Subjects

Mechanisms of Particle-Induced Cardiac Ischemia

EOHSI

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UMDNJ ROBERT WOOD JOHNSON MEDICAL SCHOOL
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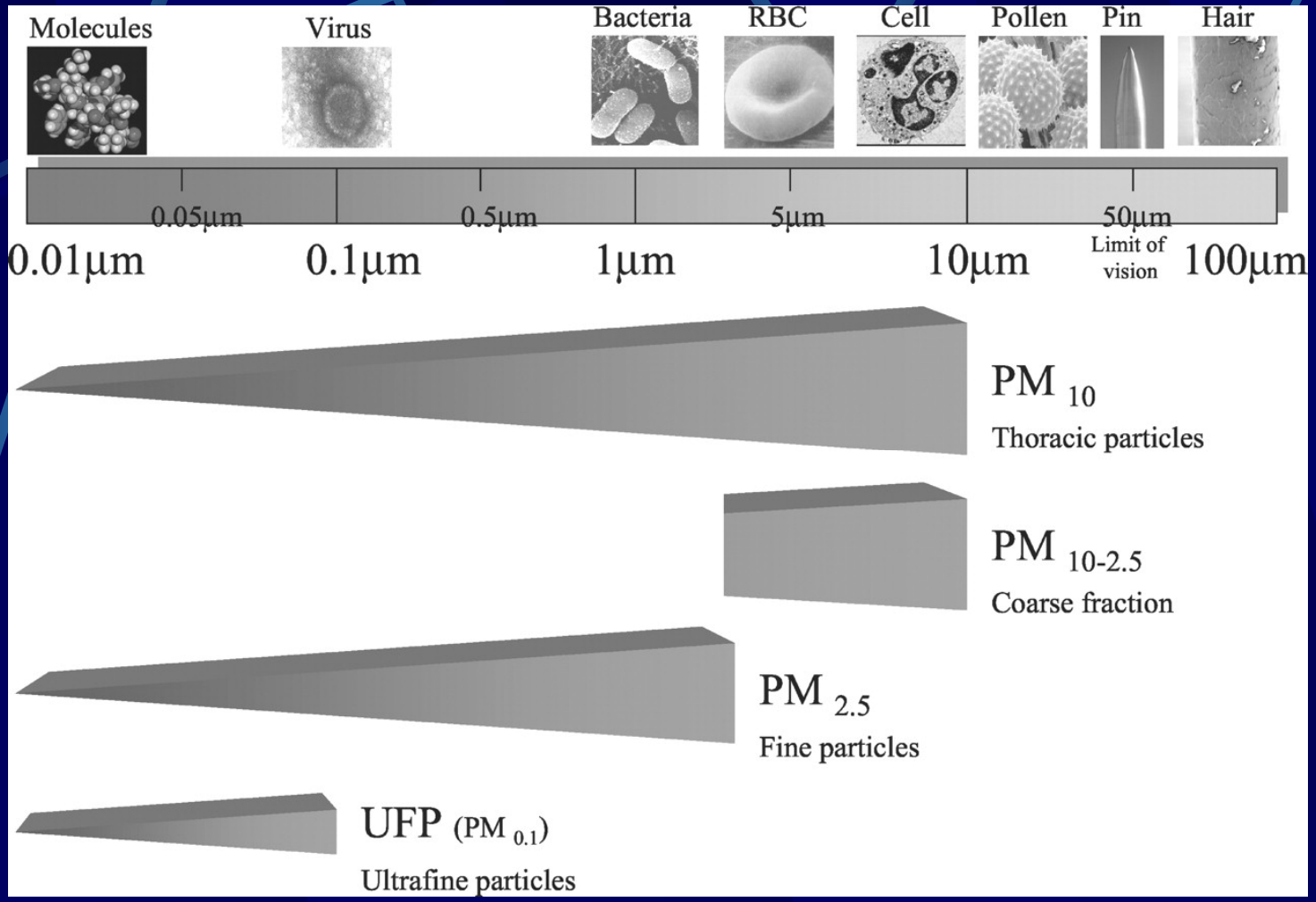


Brook et al. Air Pollution and Cardiovascular Disease. Circulation 109(21):2655-2671.

Particles and MI

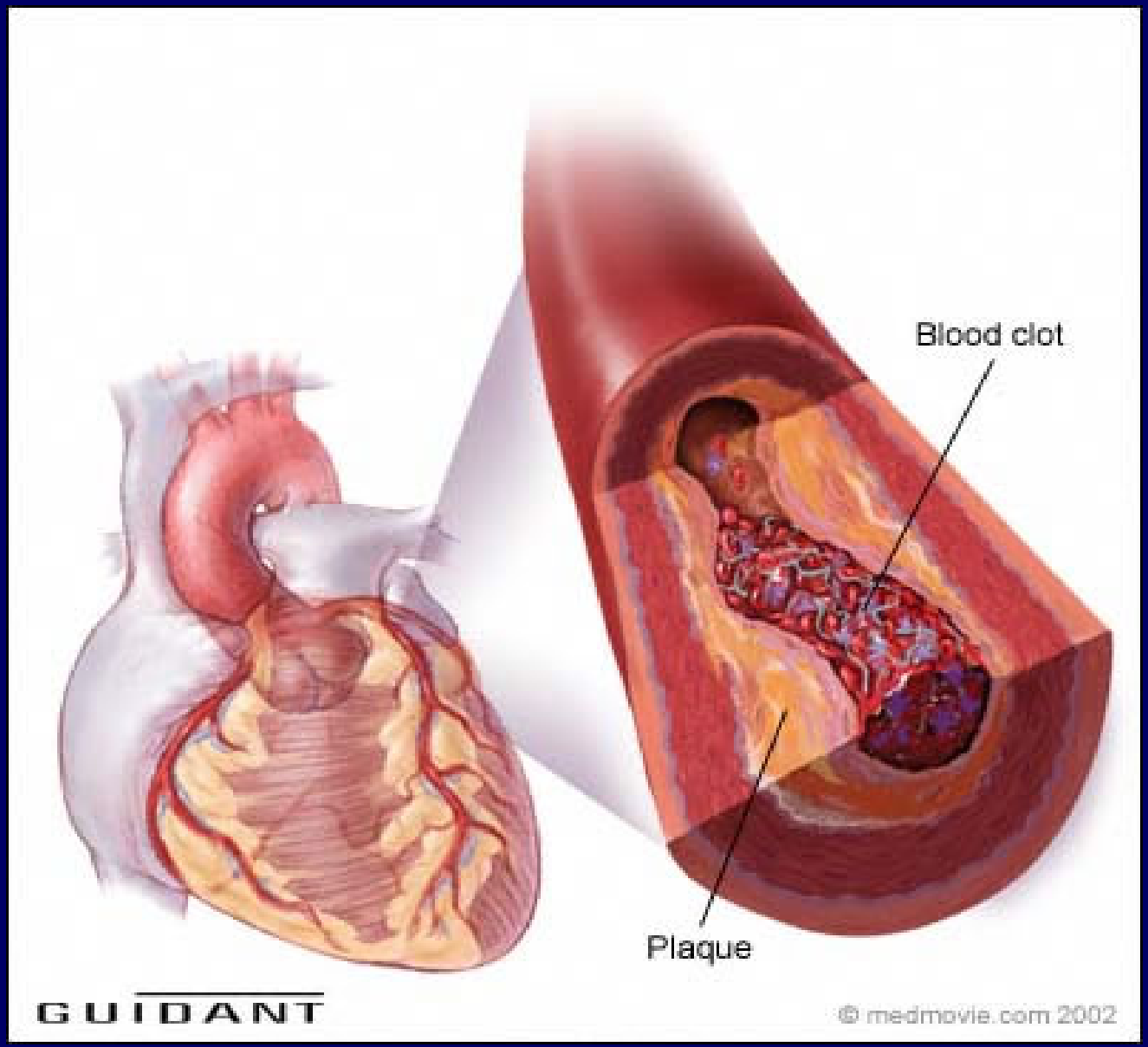
- MI risk increased 50% for 25 mcg/m3 PM2.5 elevations in 2 hours preceding onset of symptoms. [1]
- UF particles increase thrombosis within one hour of intratracheal instillation by platelet activation.[2]
- These effects occur too quickly for lung inflammation to manifest and explain

1.Peters et al, Increased Particulate Air Pollution and the Triggering of Myocardial Infarction. Circulation 103:2810 2815 (2001).

2. Nemmar et al Diesel Exhaust Particles in Lung Acutely Enhance Experimental Peripheral Thrombosis. Circulation 107:1202-1208 (2003).

Current Knowledge

- MI's are felt to be due to inflammatory mechanisms
- UF and Fine particles provoke alveolar inflammation leading to increased blood coagulability over hours to days
- Measured as increases in viscosity, fibrinogen, Factor VII, plasminogen activator inhibitor, CRP, WBC, and platelet activation


Blood clot
Plaque
GUIDANT
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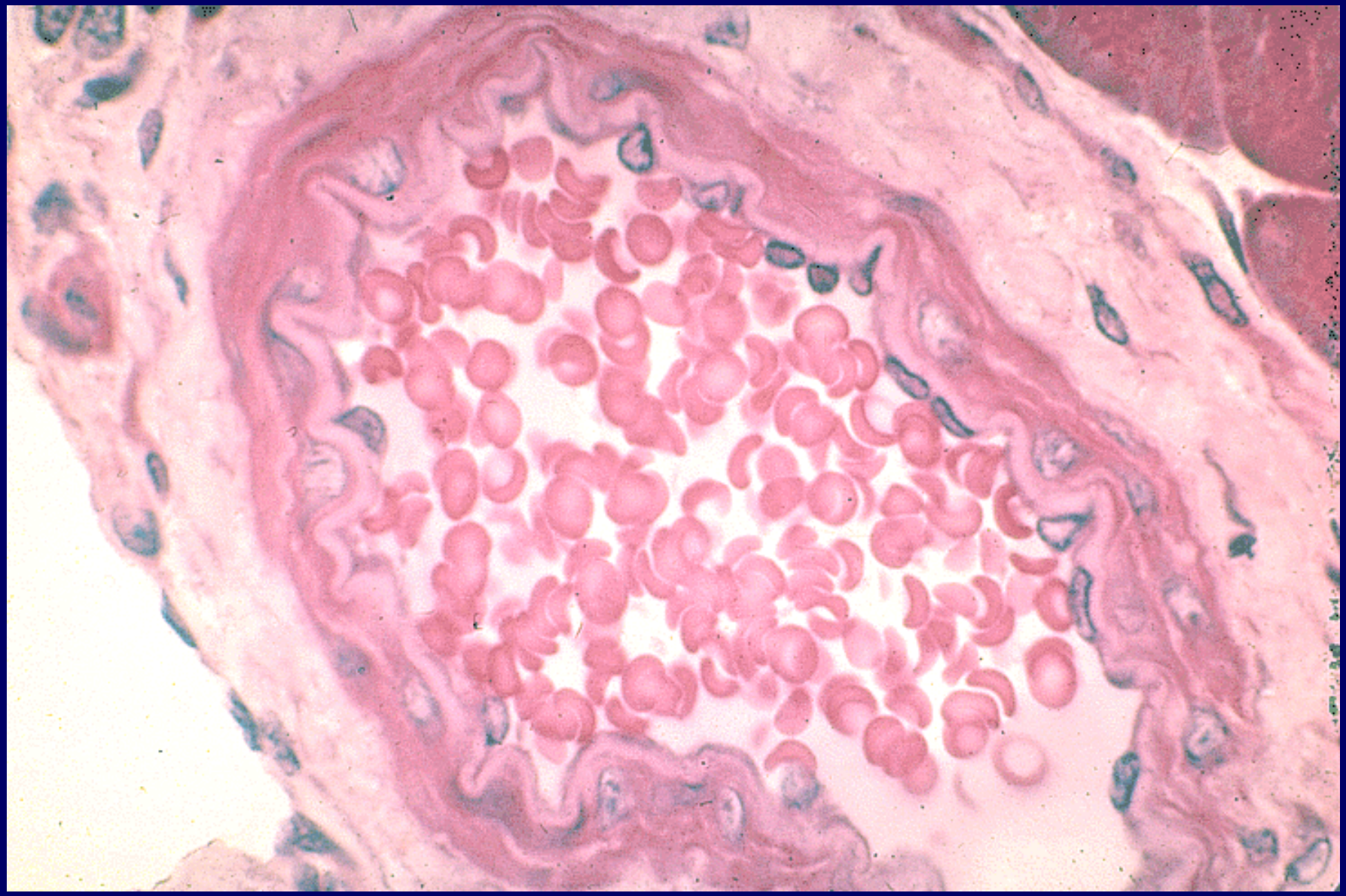


Endothelial Function and ASCVD

- Endothelial dysfunction precedes plaque formation and may **acutely** promote abnormal reactions between vessel walls, platelets & WBC
- Can be assessed **noninvasively** by USG: brachial artery reactivity (flow mediated dilation) following ischemia
- Acutely responds to ascorbic acid, tea, ETS, or 150mcg/m3 PM2.5 + 120ppb ozone

Endothelial Susceptibility

- Low concentrations of NO are important to endothelial function; also inhibit platelet aggregation
- Variant eNOS (Glu298Asp) variably increases risk of ASCVD; +/- decreases FMD
- 10% homozygous prevalence in UK and Italy

Hypothesis

- The acute increase in risk of cardiac events following inhalation of ultrafine and fine particles is mediated by **a rapid and direct passage of the particles** from the lung into the blood, leading immediately to **platelet activation and endothelial dysfunction**.

- Individuals with **genetically increased** risk for ASCVD and endothelial dysfunction will be more sensitive to the effects of ultrafine and fine particles on the endothelium.

Specific Aims

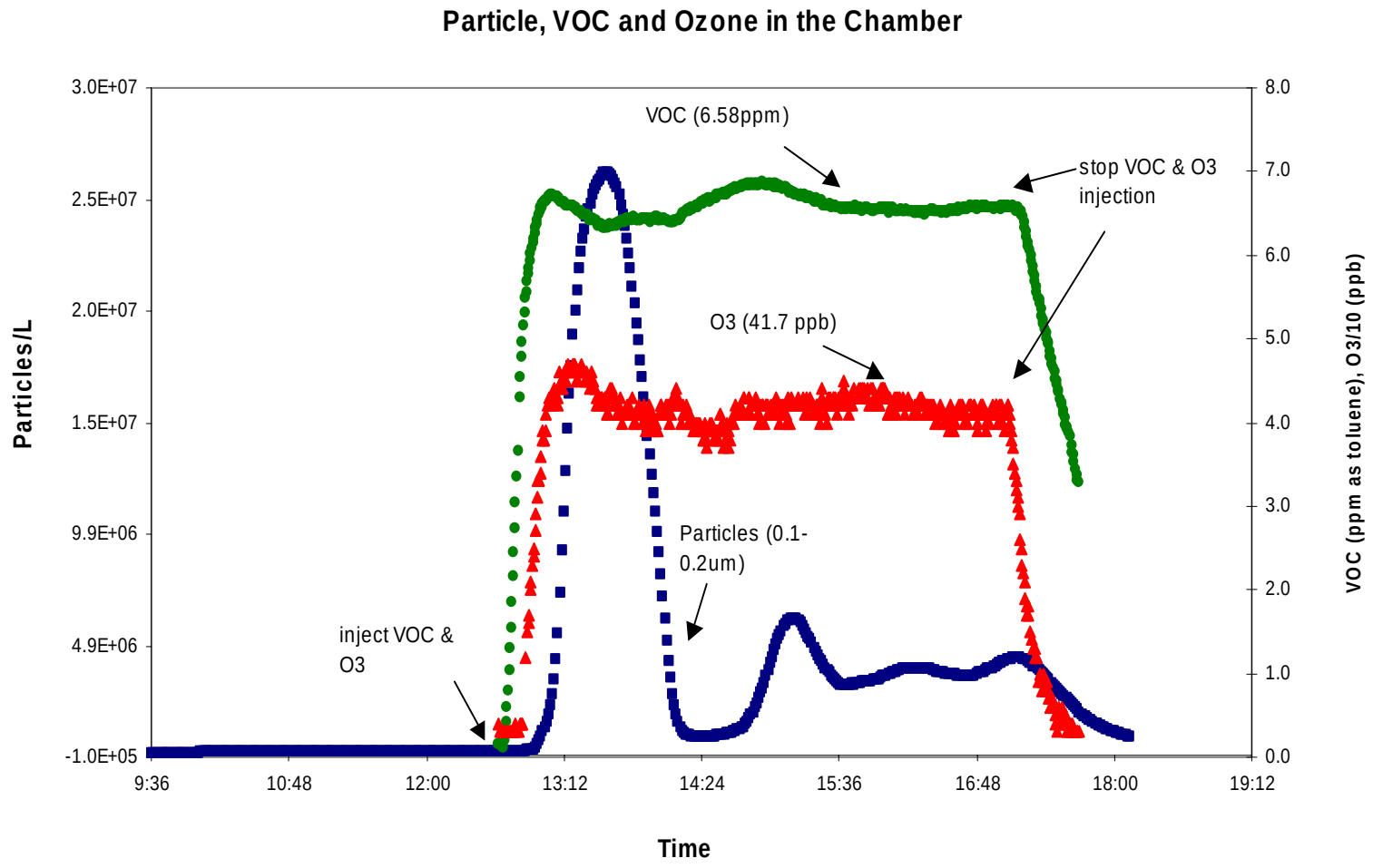
- Determine if exposure of 50 healthy, young, non-smoking volunteers for two hours to **freshly generated aerosols** will lead to abnormalities in endothelial, platelet and cardiac function that are **independent of pulmonary inflammation**

- Determine if individuals with **genetically** increased risk for ASCVD and endothelial dysfunction exhibit **enhanced sensitivity** to freshly generated aerosols.

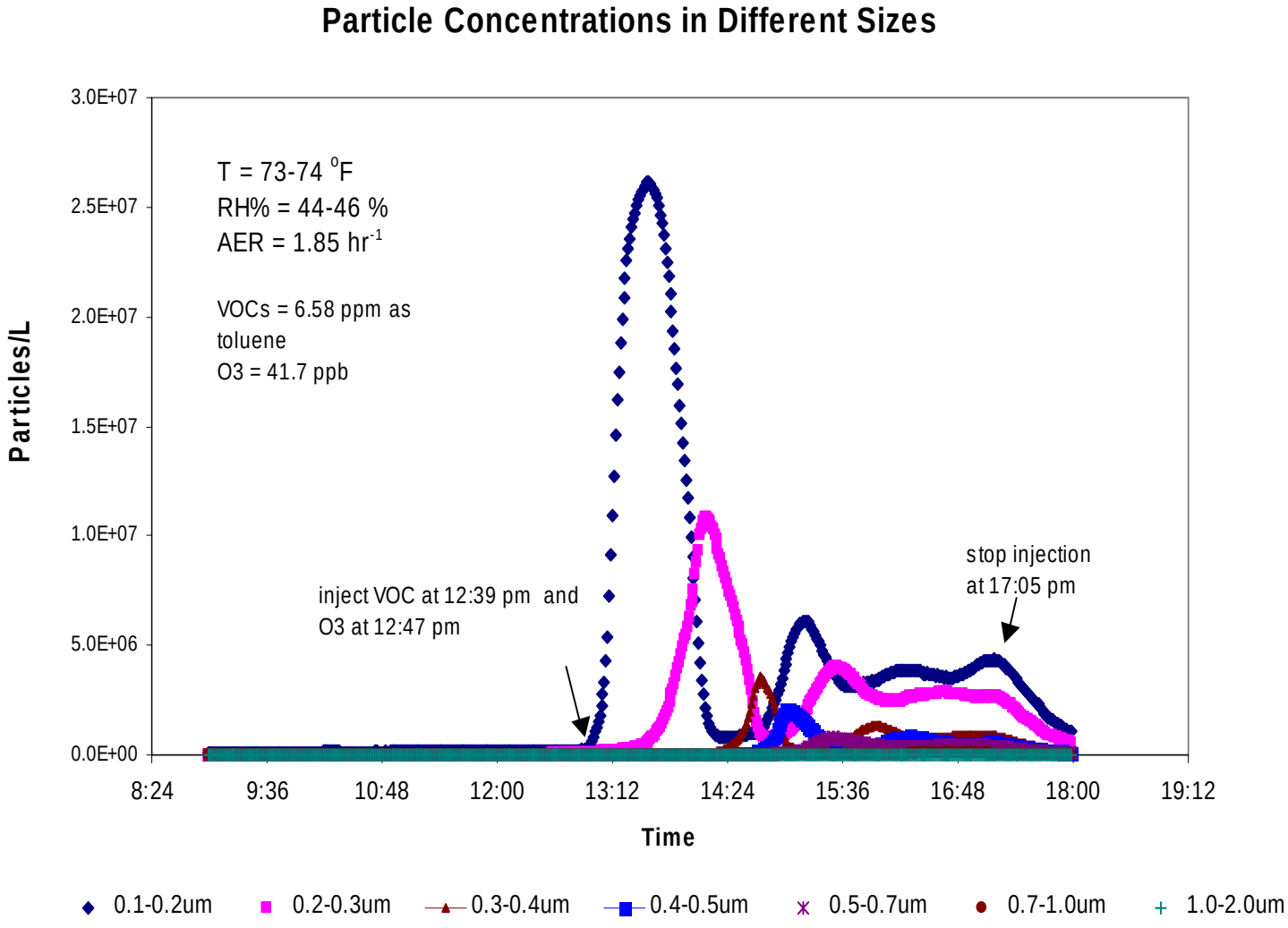
Two Different Fresh Fine and Ultrafine Aerosols

- Diesel Exhaust
- 200 mcg/m3
- Secondary Organics
- 200mcg/m3

RESULTS:


Particle, VOC and Ozone in the Chamber
Particles/L
VOC (ppm as toluene), O3/10 (ppb)
Time
3.0E+07
2.5E+07
2.0E+07
1.5E+07
9.9E+06
4.9E+06
-1.0E+05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
9:36
10:48
12:00
13:12
14:24
15:36
16:48
18:00
19:12
VOC (6.58ppm)
stop VOC & O3 injection
O3 (41.7 ppb)
Particles (0.1-0.2um)
inject VOC & O3

RESULTS:


Particle Concentrations in Different Sizes
T = 73-74 °F
RH% = 44-46 %
AER = 1.85 hr-1
VOCs = 6.58 ppm as toluene
O3 = 41.7 ppb
inject VOC at 12:39 pm and O3 at 12:47 pm
stop injection at 17:05 pm
Particles/L
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
8:24
9:36
10:48
12:00
13:12
14:24
15:36
16:48
18:00
19:12
Time
0.1-0.2um
0.2-0.3um
0.3-0.4um
0.4-0.5um
0.5-0.7um
0.7-1.0um
1.0-2.0um

Two Different Subject Groups

- Healthy, Young, Random Volunteers
- Independent of Cardiac Risk Factors

- Healthy, Young, Volunteers
- Carrying 2 Alleles for endothelial Nitric Oxide Synthase (eNOS) Single Nucleotide Polymorphism (SNP)

Controlled Environmental Facility at EOHSI

Outcomes

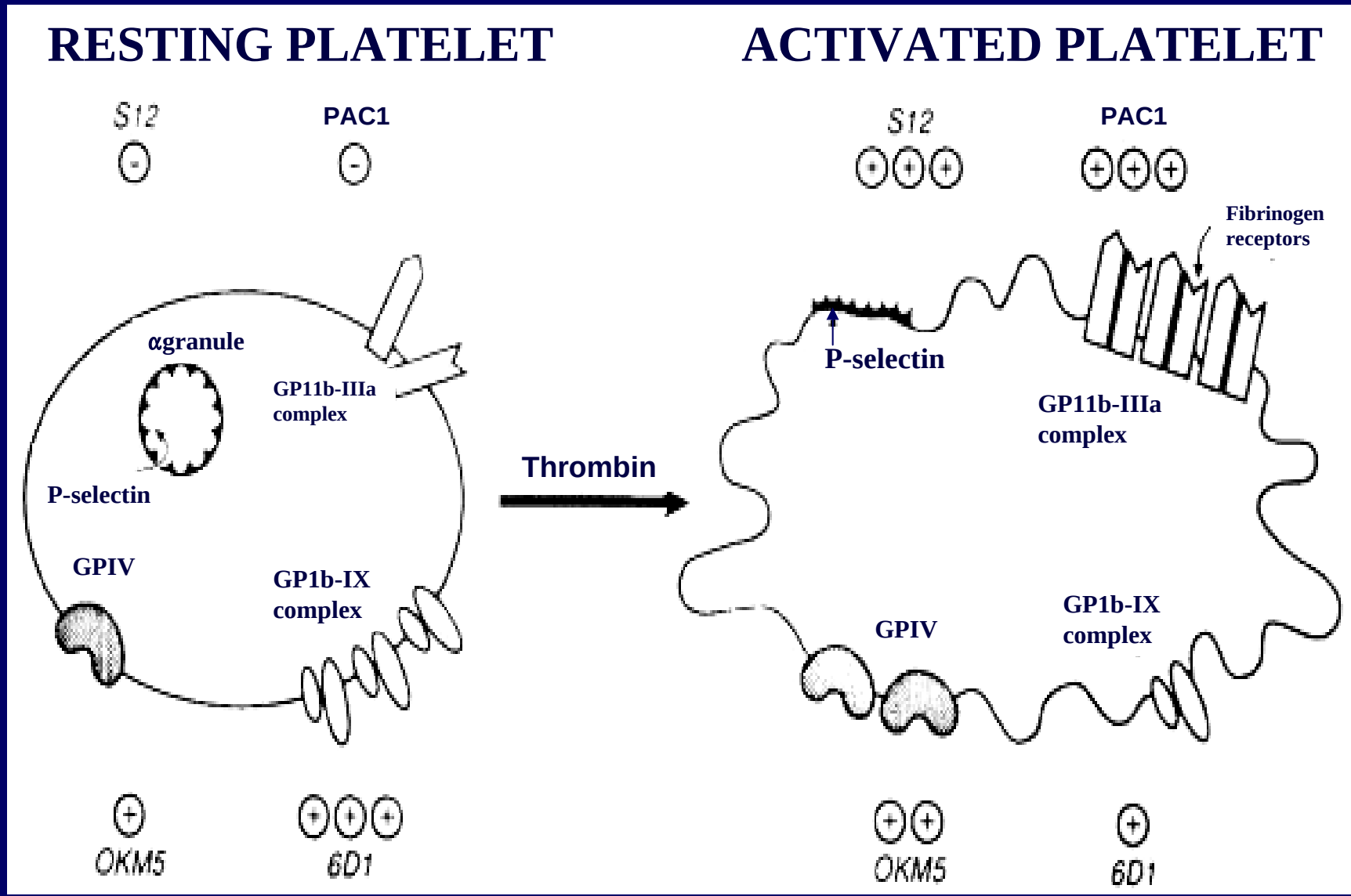
- ***IMMEDIATELY (2h)****
- Platelet Activation
- Vascular Reactivity Dec
- Pulmonary / Systemic Inflammation
  - Induced Sputum (inc WBC, IL-1, IL-6, TNF-a)
  - Blood (inc WBC, IL-1, IL-6, TNF-a)

  Spirometry

- ***DELAYED (6h)***
- Platelet Activation
- Pulmonary / Systemic Inflammation
  - Induced Sputum (inc WBC, IL-1, IL-6, TNF-a)
  - Blood (inc WBC, IL-1, IL-6, TNF-a)

  Spirometry

* Underline indicates an expected result


RESTING PLATELET
ACTIVATED PLATELET
S12
PAC1
αgranule
GP11b-IIIa complex
P-selectin
GPIV
GP1b-IX complex
Thrombin
Fibrinogen receptors
OKM5
6D1

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