

US EPA ARCHIVE DOCUMENT

Mechanisms of Atherosclerosis in Air Pollution Exposure

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Acute Exposure to CAPS Results in Alterations in Vasomotor Tone in Humans

Brook RD, Brook JR, Urch B, Vincent R,, Silverman F, Rajagopalan S. Inhalation of Fine Particulate Air Pollution and Ozone Causes Acute Arterial Vasoconstriction in Healthy Adults. *Circulation*. 2002;105:1534-1536.

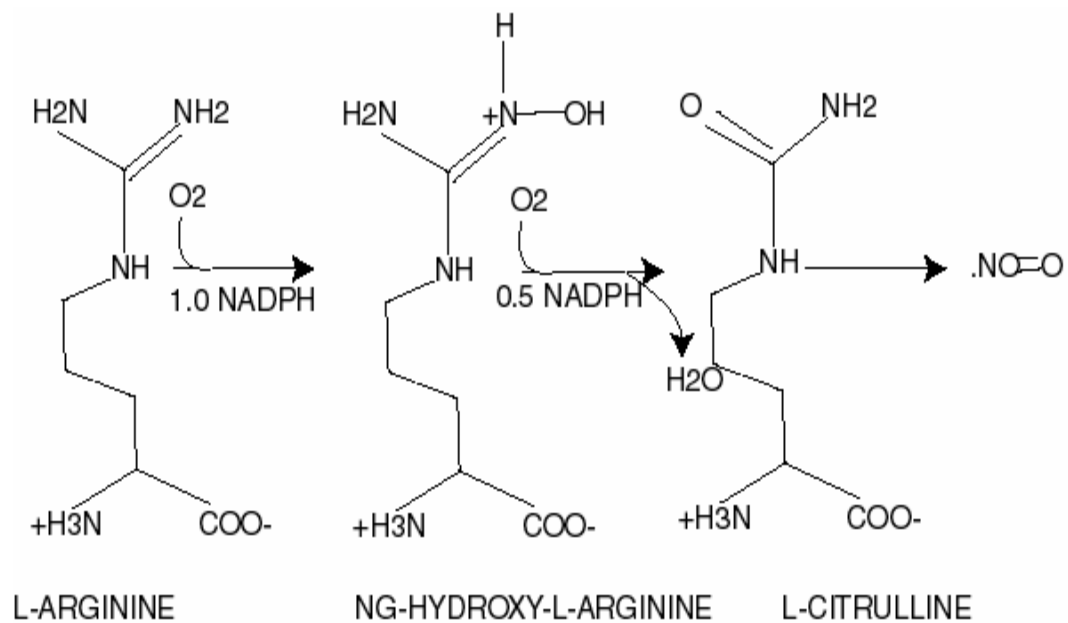
Limitations of Current Models to Study Effects of Airborne Pollution

- Variability of the recovery of the particles from the filter or bag houses.
- Uncertainty if components retrieved reflects the original particles.
- Usage of higher concentrations than encountered in a real world setting.
- Routes of installation (such as intra-tracheal route) that are not equivalent to inhalation.
- Usage of exposure systems that do not provide particles that may be of relevance in cardiovascular risk - fine ($PM_{2.5}$) and ultrafine ($PM_{0.1}$) particles.

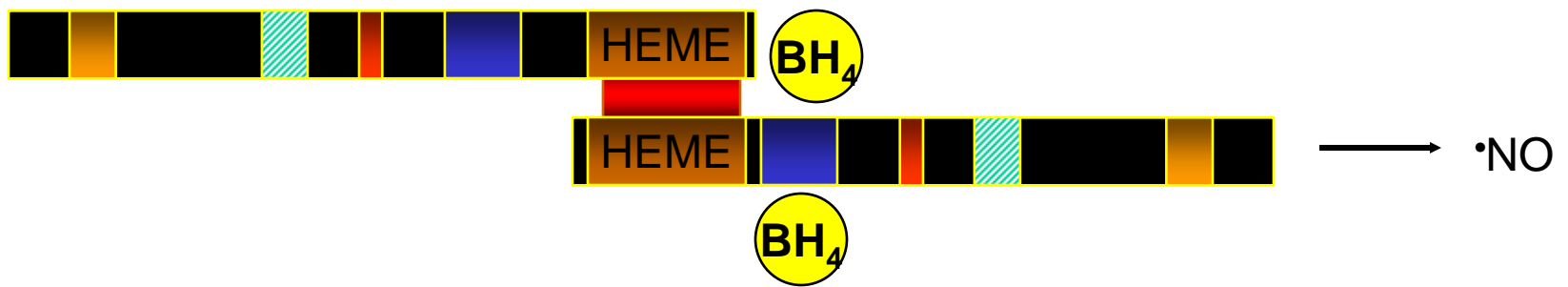
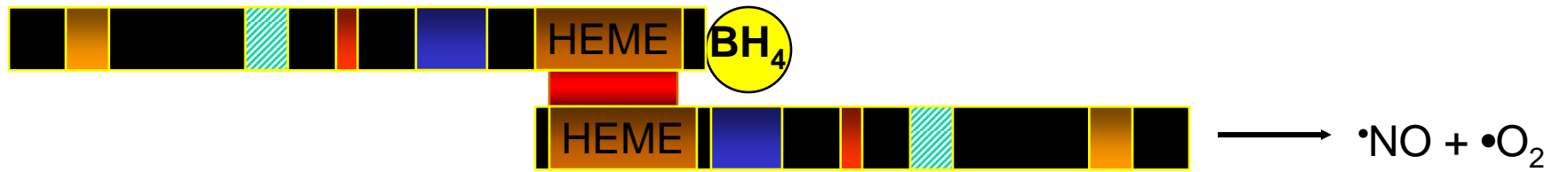
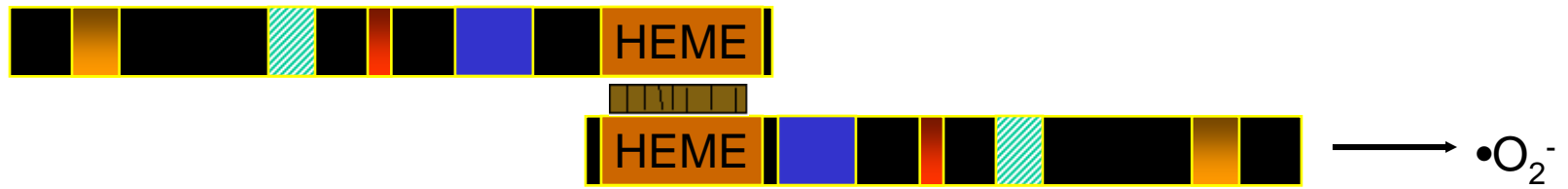
Rationale for Chronic Exposure Studies-Relevance to Atherogenesis

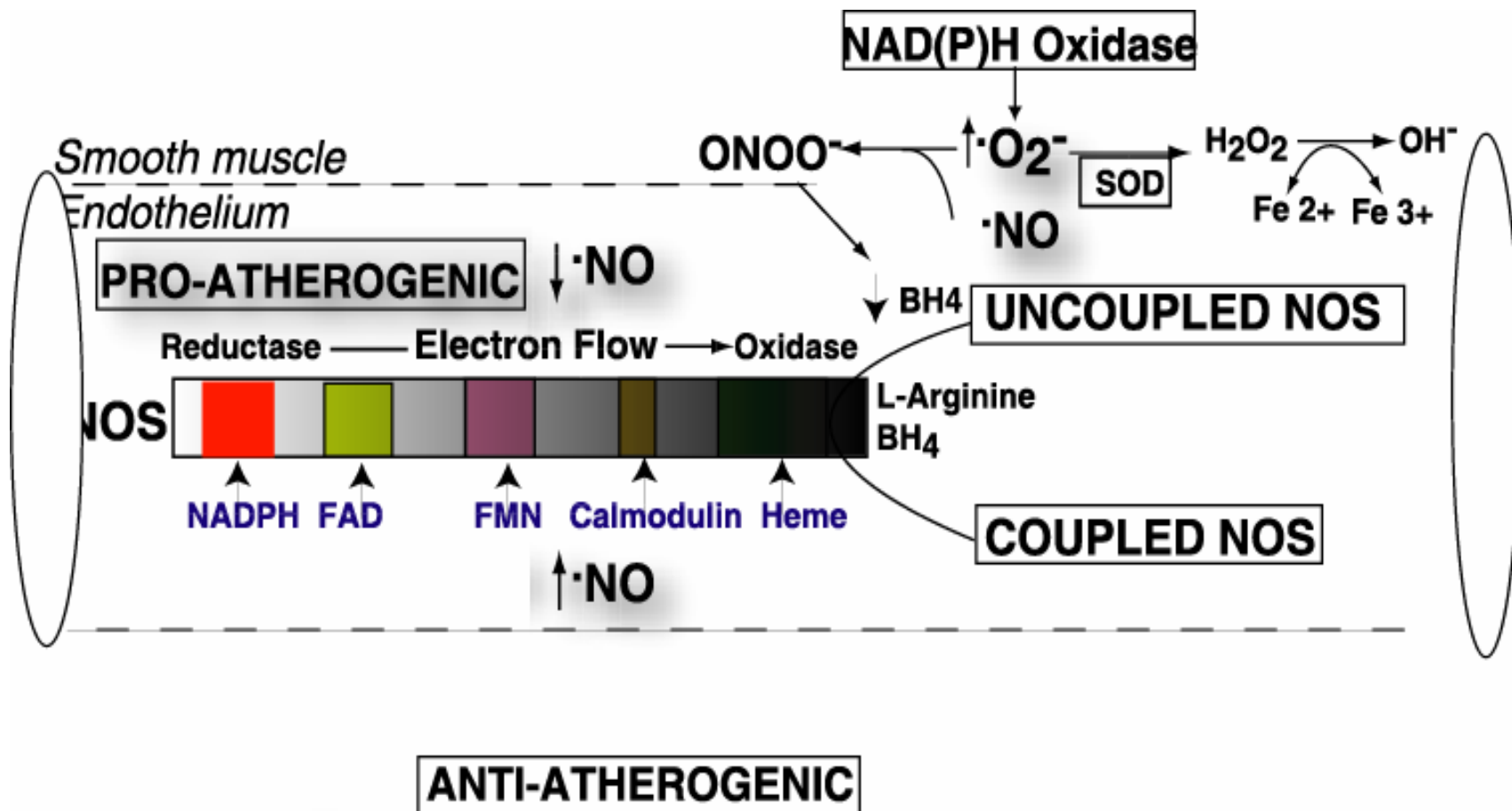
- Risk factors such as hypertension, hyperlipidemia, diabetes are characterized by progressive impairment in vessel wall function through cumulative exposure to the risk factor-acute responses often not predictive of chronic effect
- The presence of potent endogenous defense mechanisms localized to the vessel wall may delay the onset of abnormalities
- The vasculature not the first point of contact

The NOS Catalyzed Reaction

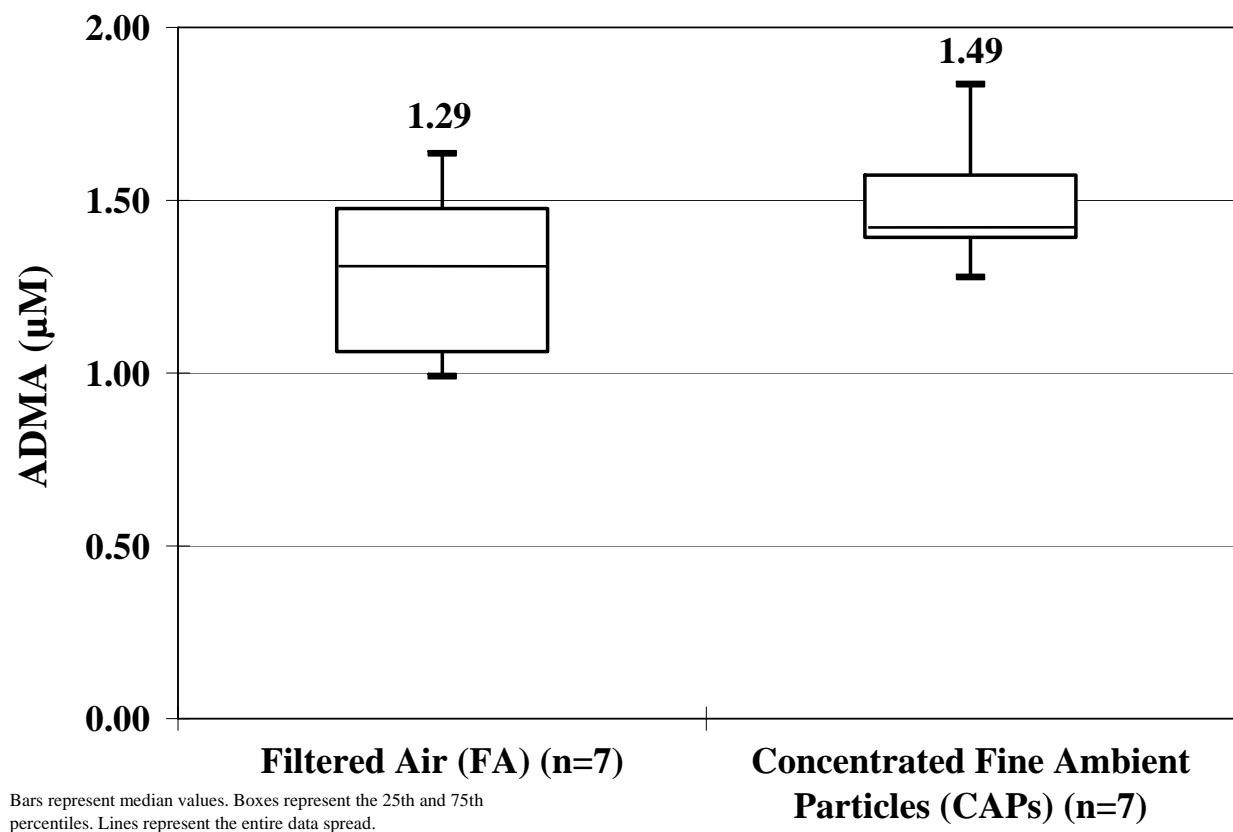


NOS: Role of BH₄



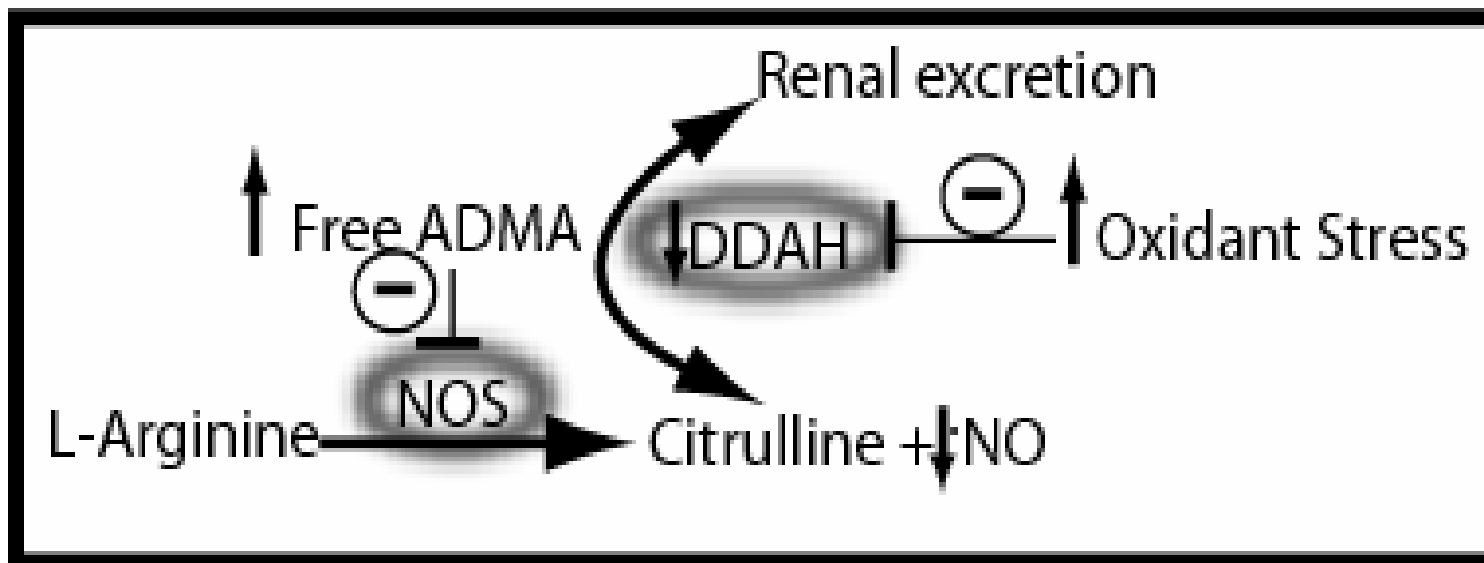


CAPS Increases ADMA Levels



Dvonch JT, Brook RD, Keeler GJ, Rajagopalan S et al. Effects of concentrated fine ambient particles on rat plasma levels of asymmetric dimethylarginine. *Inhal Toxicol.* 2004 Jun;16(6-7):473-80.

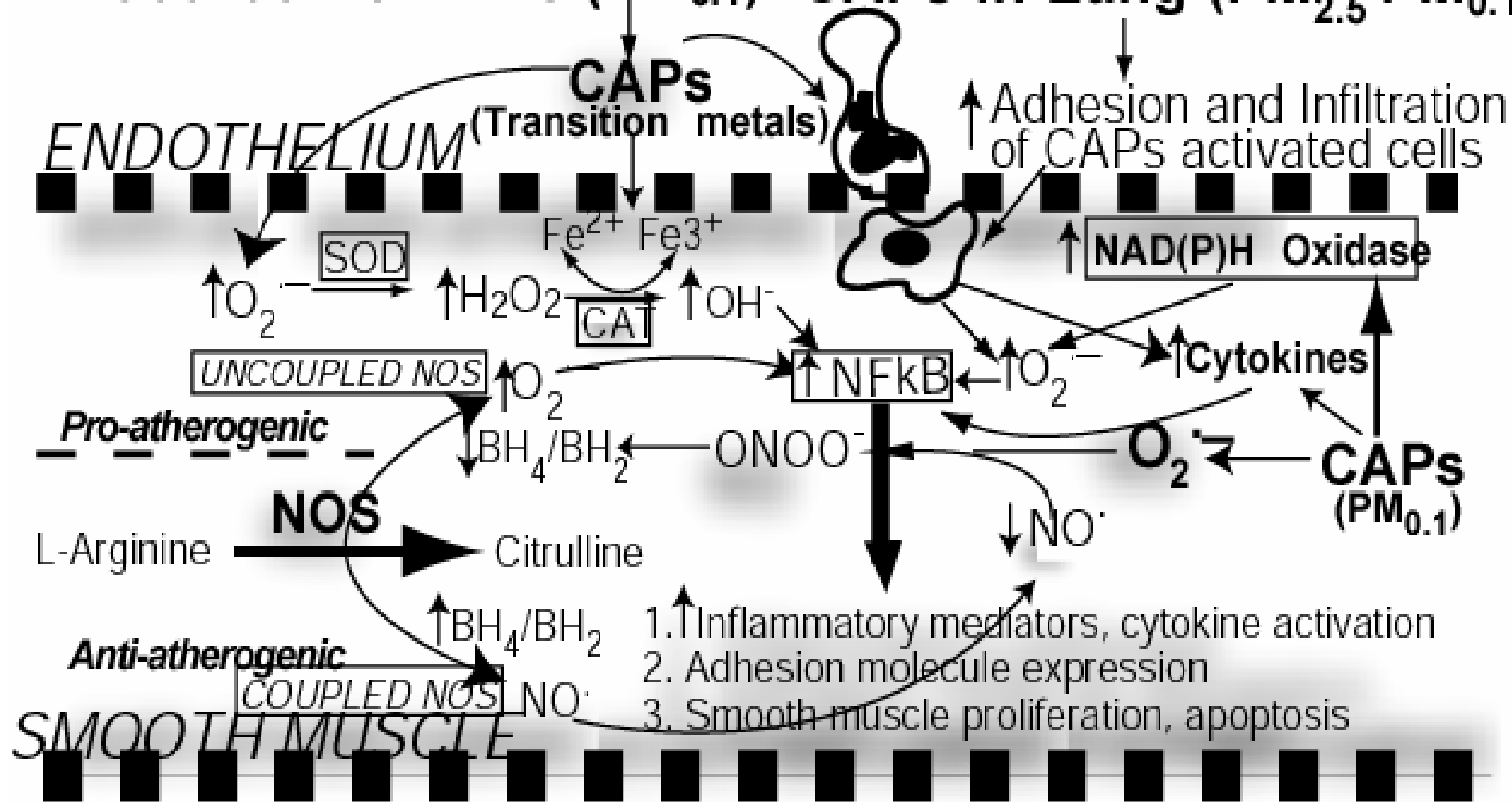
ADMA and NOS Function

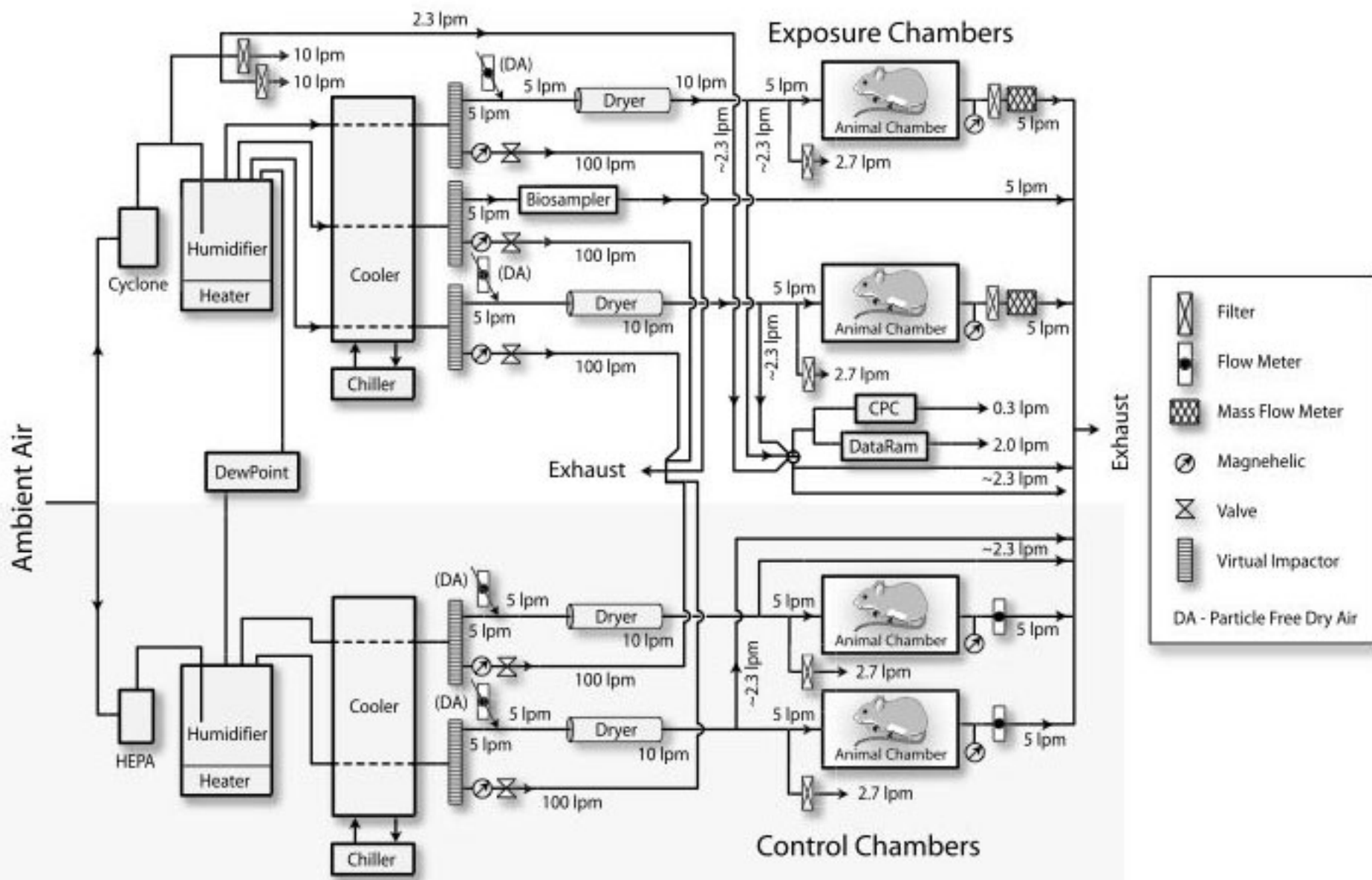


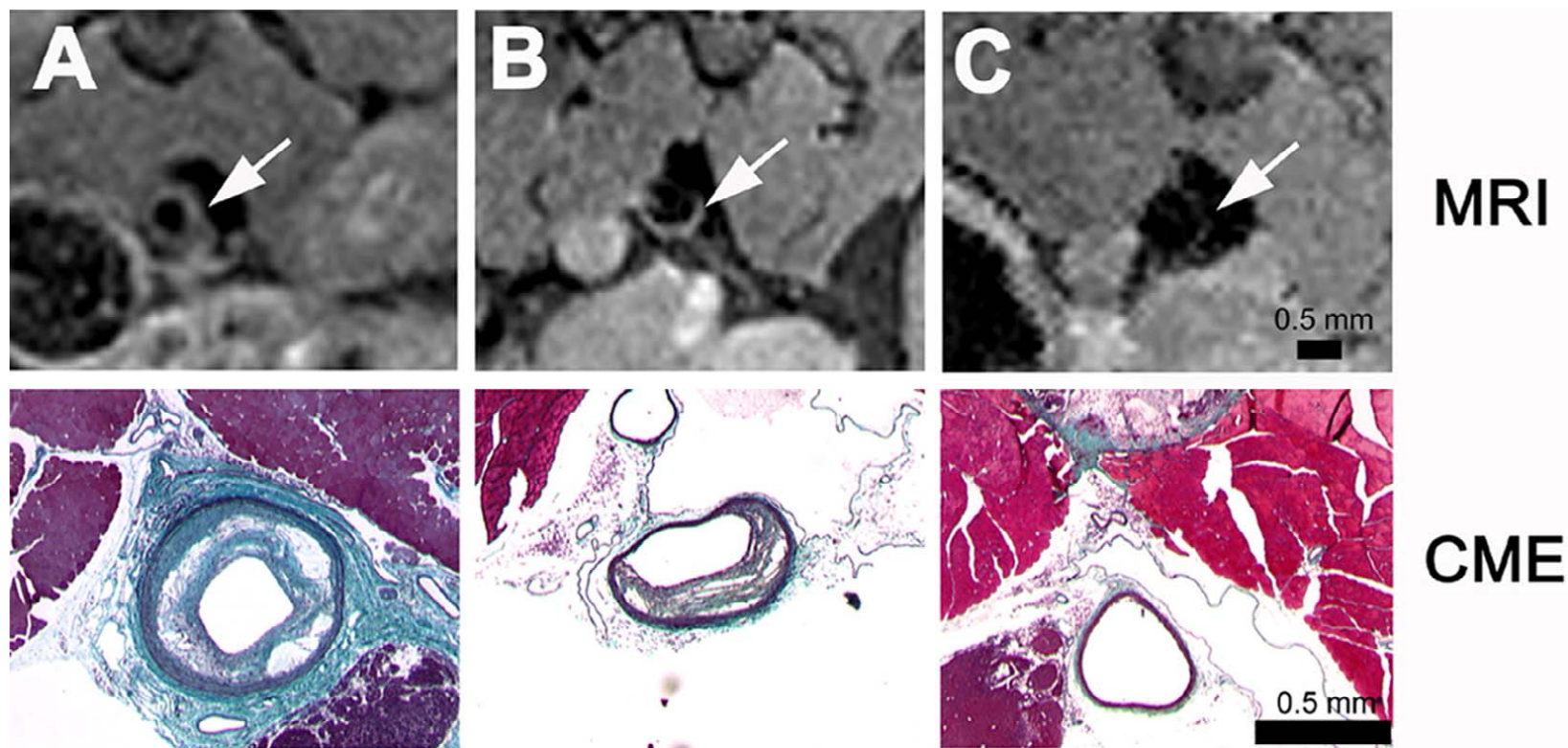
Hypothesis

- *Vascular ROS Production and ↓ •NO: An Effect of PM_{2.5} and PM_{0.1} ?*

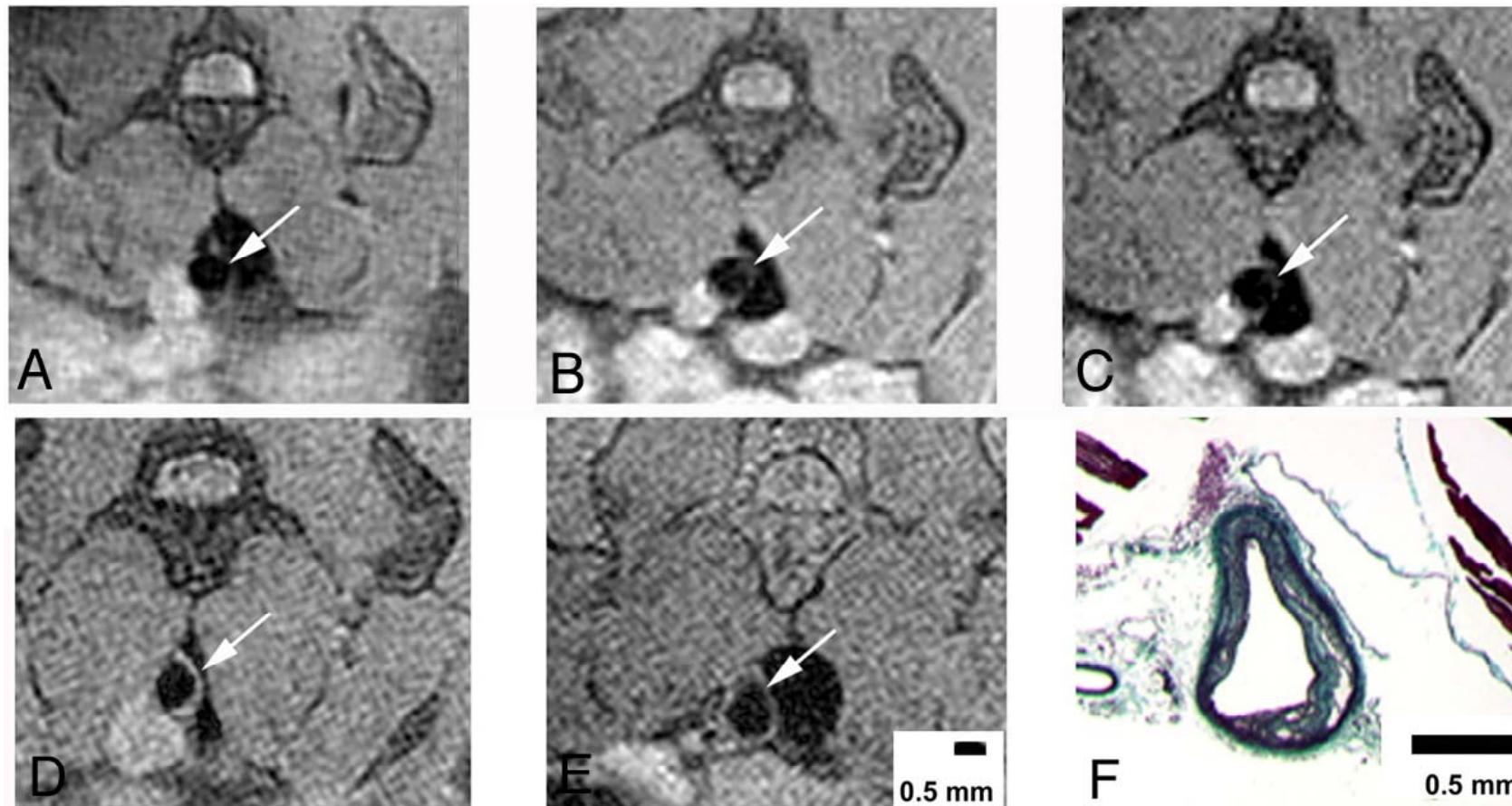
Blood-borne CAPs (PM_{0.1}) CAPs in Lung (PM_{2.5} PM_{0.1})



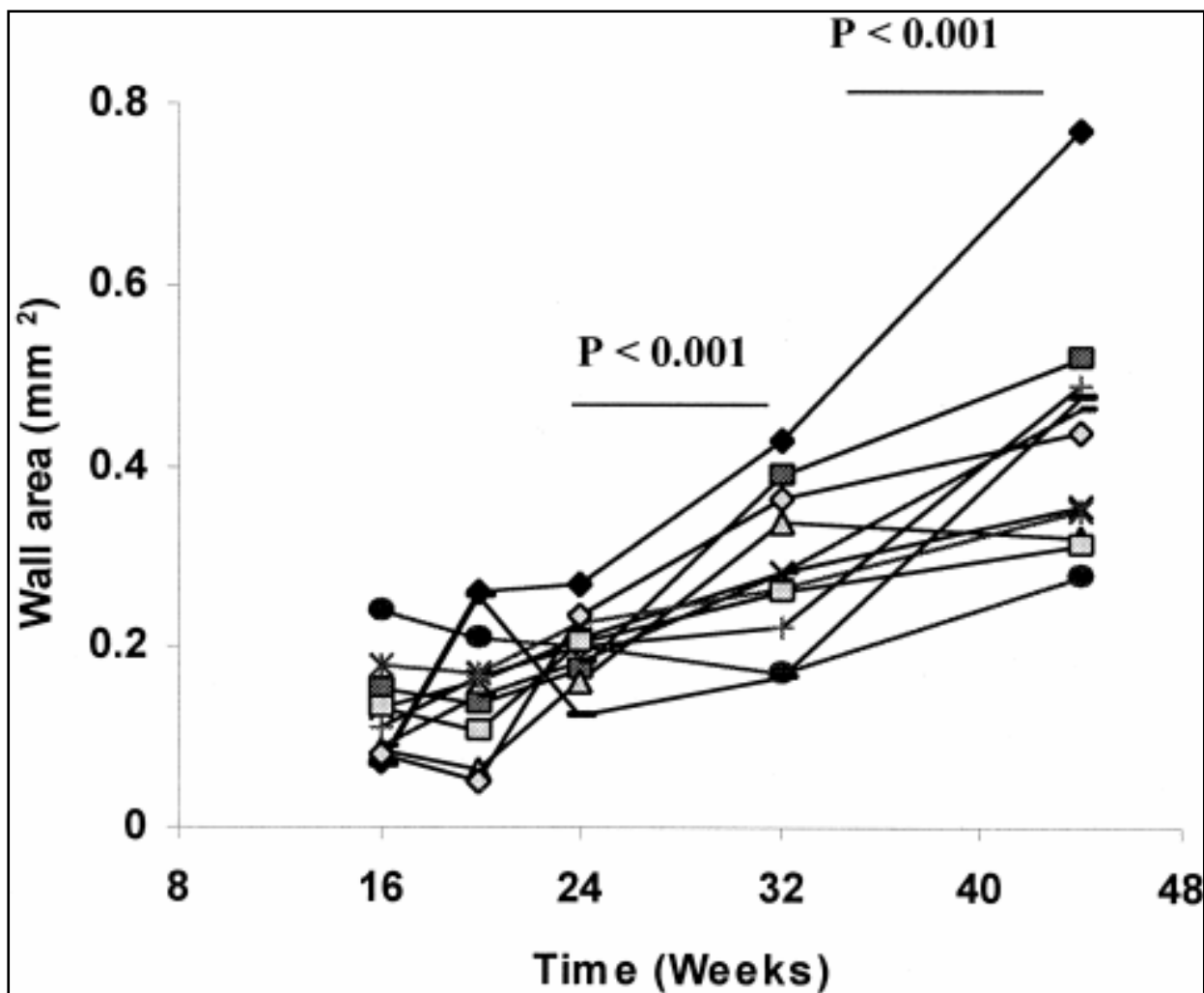




MRM (proton density weighted) and corresponding light photomicrographs (CME, combined Masson elastic stain) of transverse mouse aorta. (A) Concentric thickening in a aortic segment. (B) Rim of eccentric thickening is identified on the lateral and anterior aspects of the aorta. (C) normal, thin walled aorta.



PDW MRM images of abdominal aorta in Apo E^{-/-} mice. Normal aorta at 8 and 12 weeks (A-B). Mild thickening at 24 weeks (C). Eccentric plaque at 32 weeks (D). Marked concentric plaque by 44 weeks (E). Panel (F) shows good morphological agreement of histopathological section (CME-stained) corresponding to (E).



Aortic wall area as a function of time in a single Apo E^{-/-} mouse. Each set of symbols represents measurements from matched segments of aorta

