Cardiovascular Effects of Urban and Rural Coarse Particulate Matter in African American and White Adults

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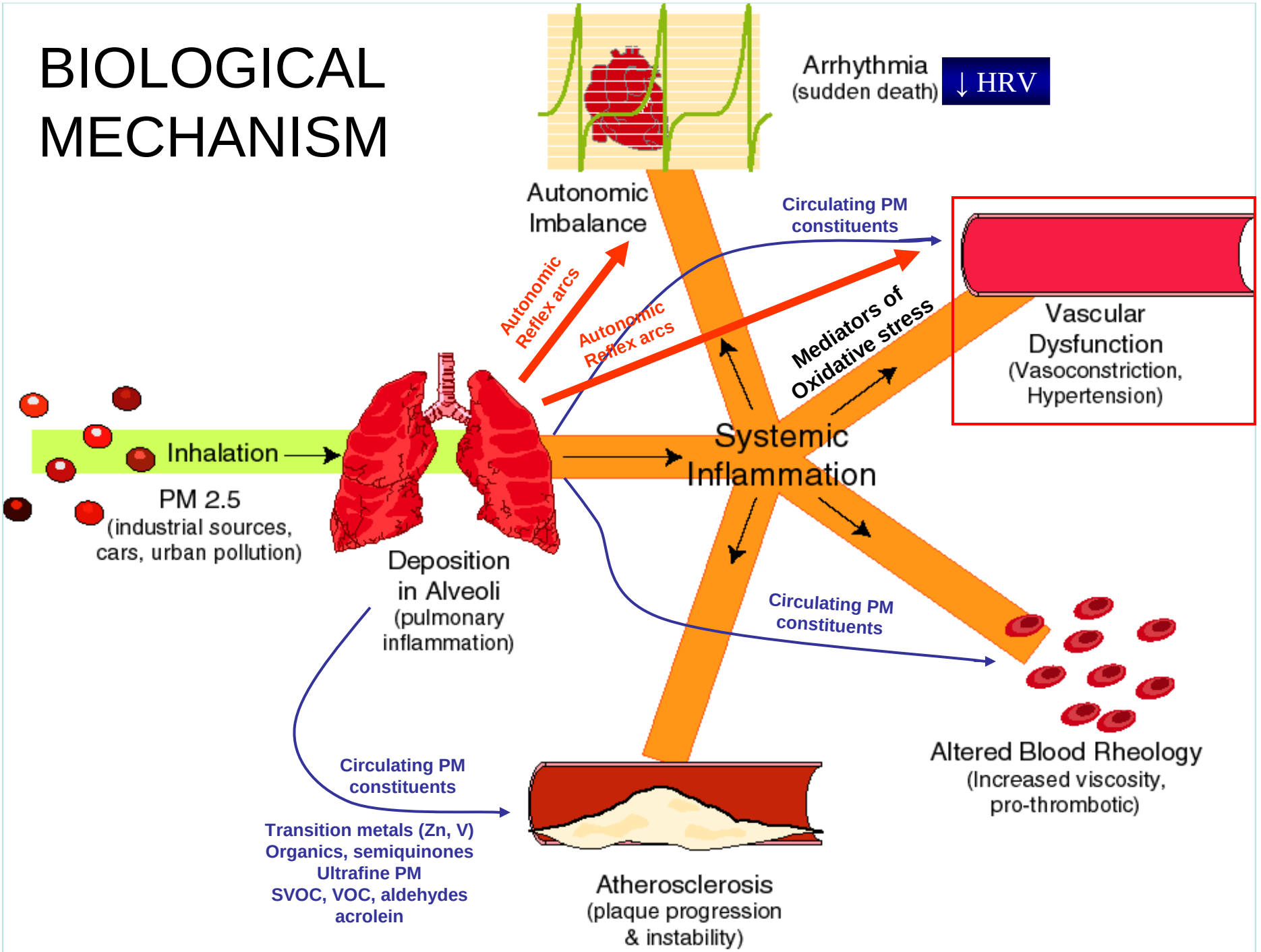
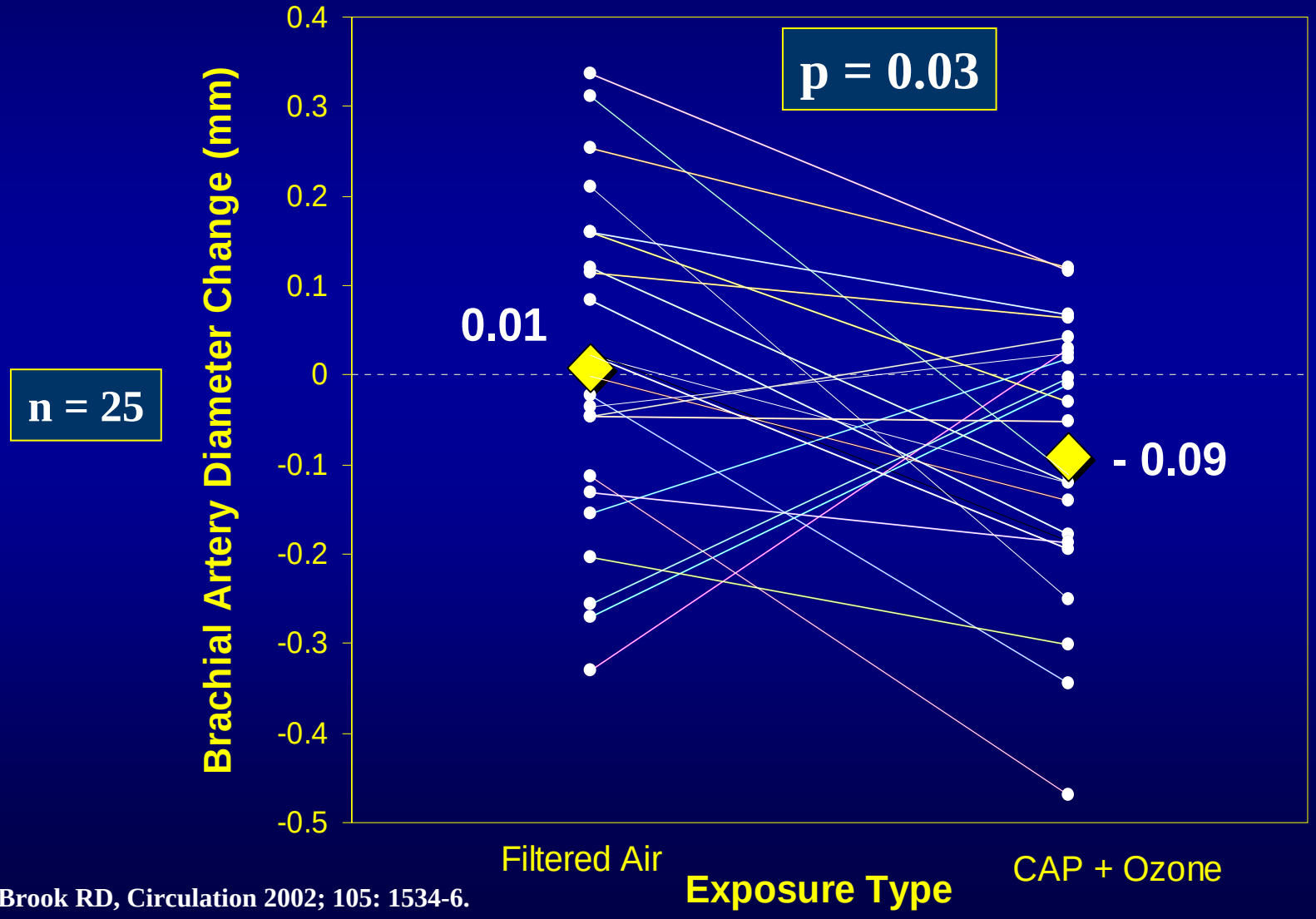
BIOLOGICAL MECHANISM



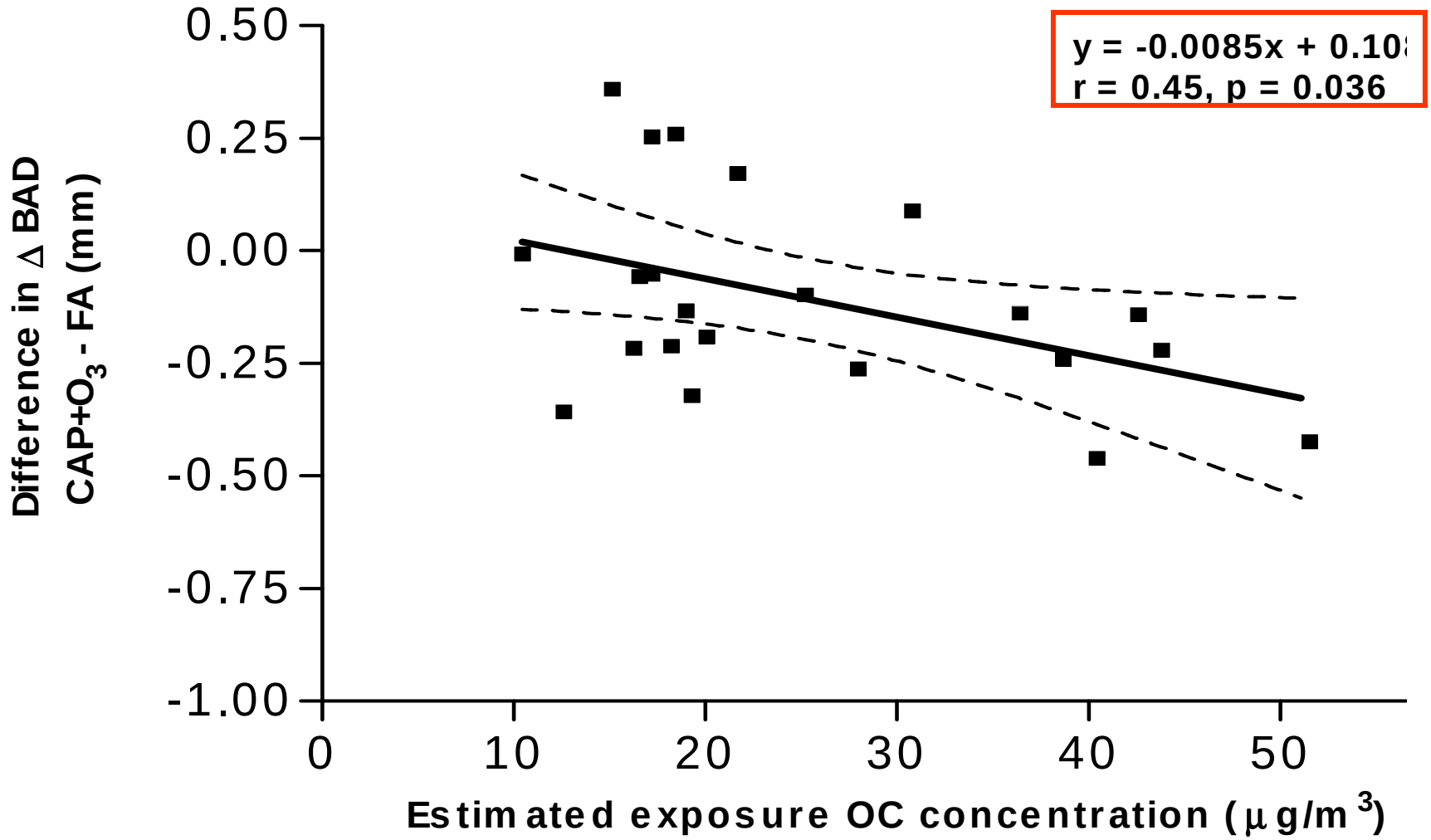
Brachial Artery Diameter Changes in Response to Air Pollution versus Filtered Air



Brook RD, Circulation 2002; 105: 1534-6.

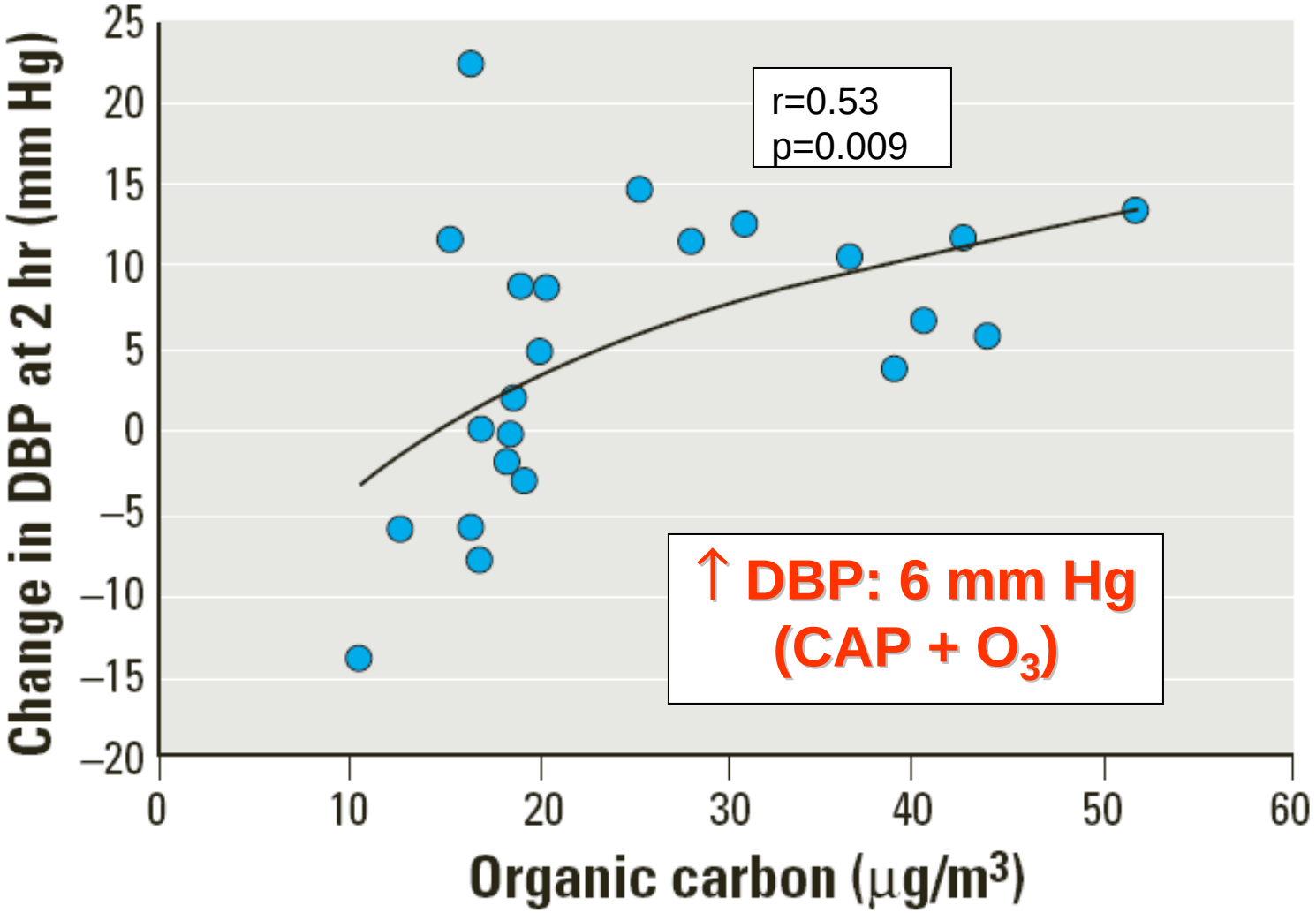
Relative Contributations of $PM_{2.5}$ Chemical Constituents to Acute Arterial Vasoconstriction in Humans

Mean vasoconstriction = 0.09 mm



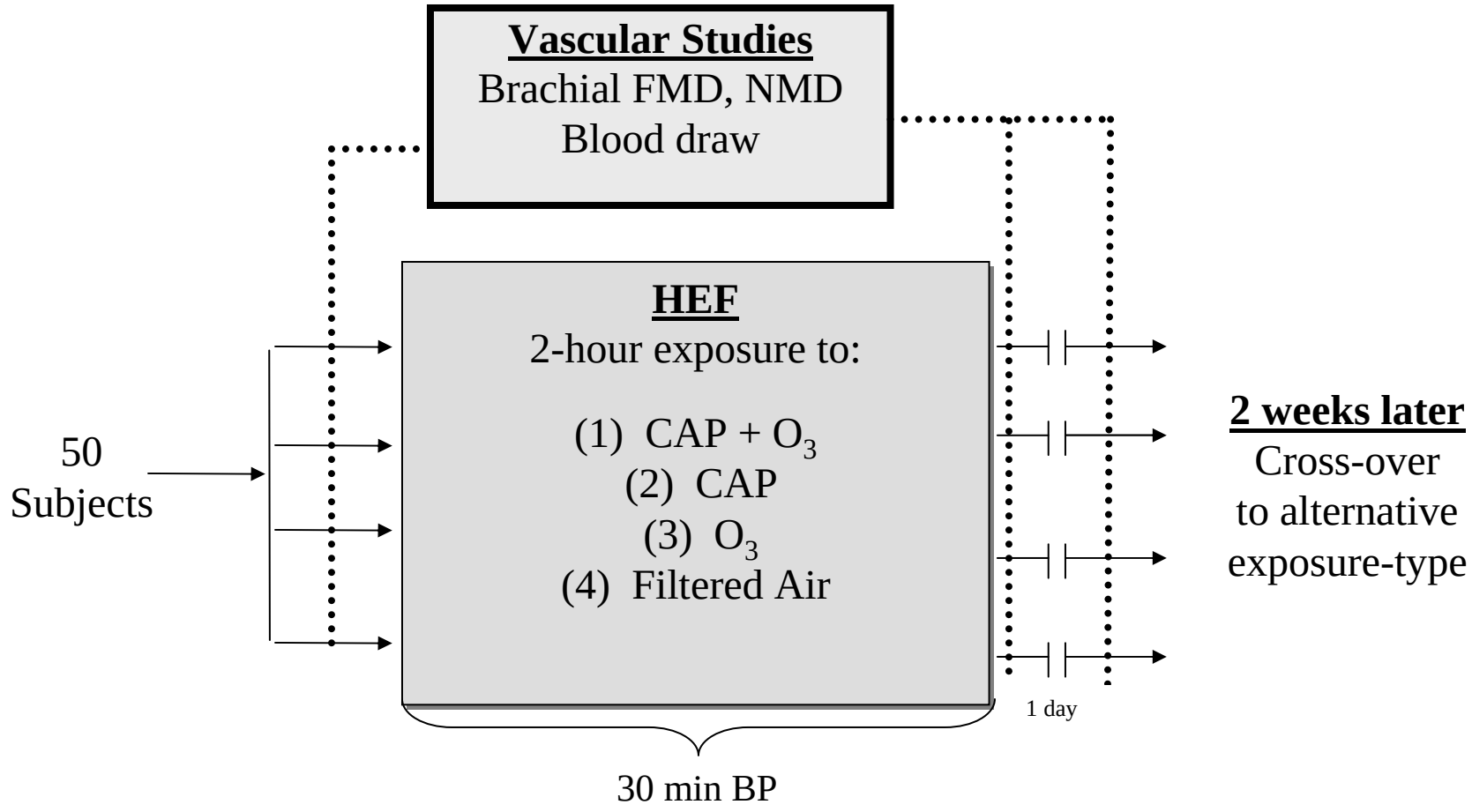
Urch B, Inhalation Toxicology 2004; 16: 345-52

Blood Pressure Responses to Concentrated Ambient $PM_{2.5}$ (CAP) versus Filtered Air



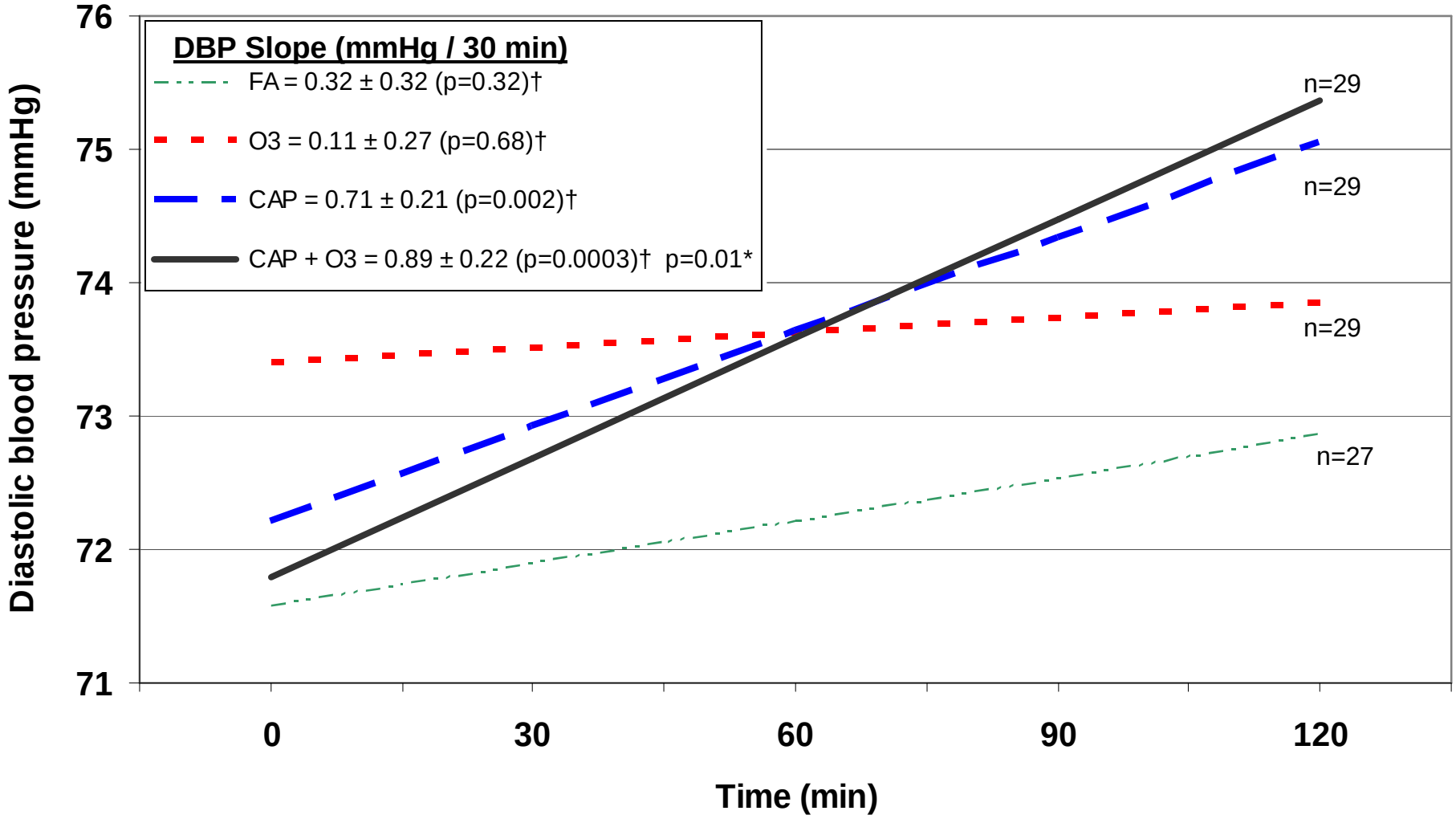
Urch B, Environ Health Perspectives 2005; 113: 1052-55.

Cardiovascular Linkage between Endothelial dysfunction ANd AIR pollution (CLEANAIR Toronto)



CAP, concentrated ambient fine particles (150 μg/m^3); O_3, ozone (120 ppb)

Diastolic Blood Pressure Changes during Exposures in Toronto



† vs slope = 0

* For "CAP effect" = slopes of [CAP + (CAP+O3)] vs [O3 + FA]

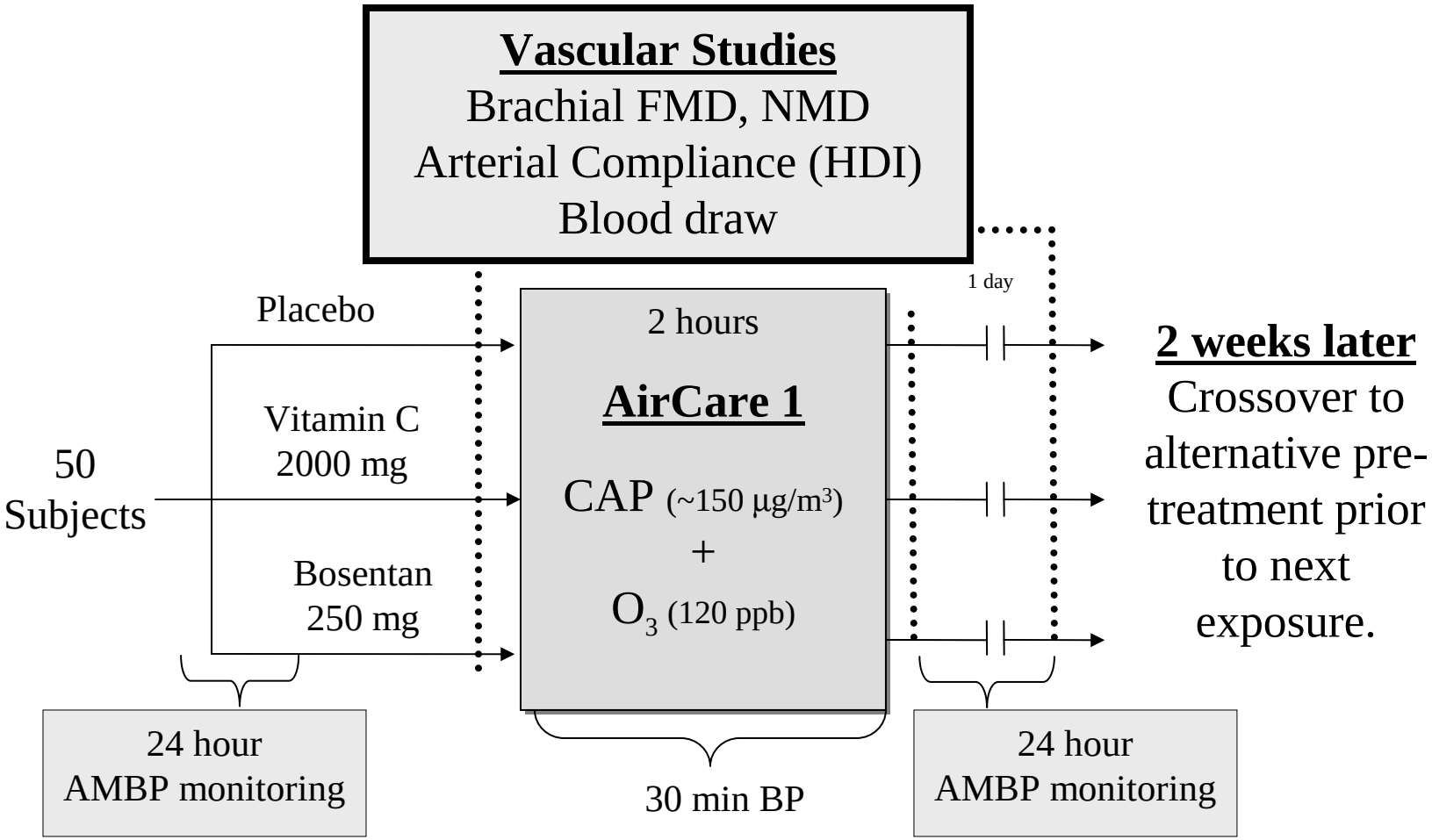
FA (filter air); O3 (ozone); CAP (concentrated ambient fine particulate matter); DBP (diastolic blood pressure)

Endothelial Function Changes in Toronto Exposures

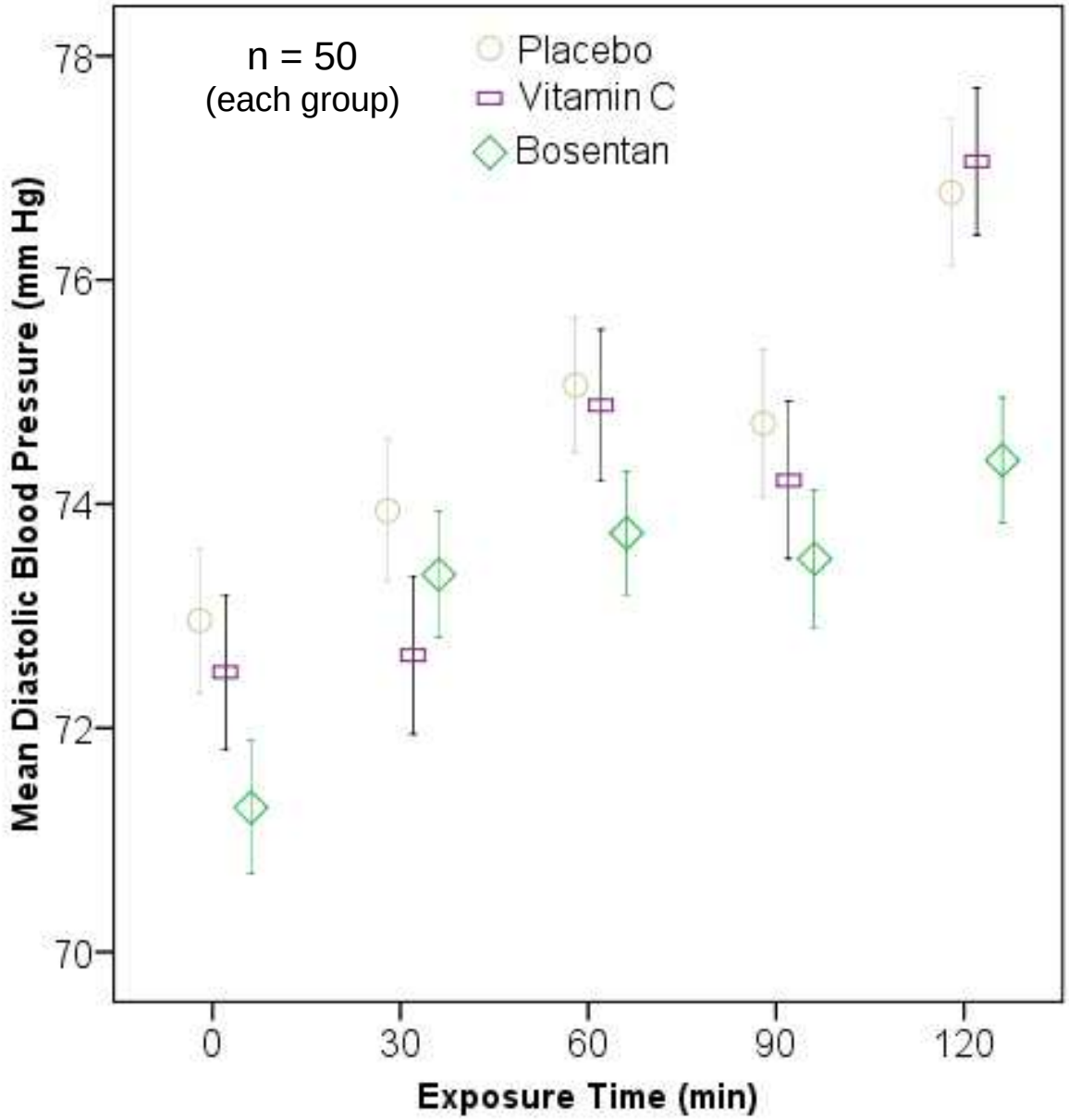
24 post – pre-exposure FMD changes

- FA: 2.7 ± 9.0% (n=30) p=0.11
- O3: -0.9 ± 7.5% (n=29) p=0.50
- CAP: -2.9 ± 6.2% (n=28) p=0.02
- CAP+O3: -2.3 ± 6.4% (n=28) p=0.07

Cardiovascular Linkage between Endothelial dysfunction ANd AIR pollution (CLEANAIR Ann Arbor)



Diastolic Blood Pressure Changes during CAP + O_3 Exposure (Ann Arbor)



Diastolic Blood Pressure

(slope: mmHg / 30 min ± SE)

Pretreatment

Placebo = 0.84 ± 0.29
p=0.002†

Bosentan = 0.63 ± 0.21
p=0.003†
p=0.60*

Vitamin C = 0.99 ± 0.33
p=0.003†
p=0.67*

†vs slope = 0
*vs placebo pre-treatment slope

Vascular Responses in CLEANAIR Study (Ann Arbor)

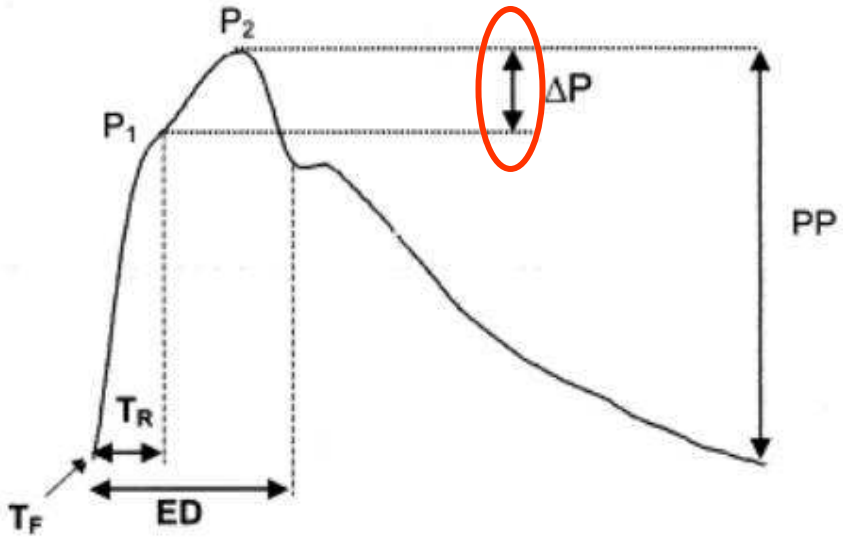
	Placebo Visit			Vitamin C Visit			Bosentan Visit		
	Pre-exposure	Post-Exposure	24 Hr Post-exposure	Pre-exposure	Post-Exposure	24 Hr Post-Exposure	Pre-exposure	Post-Exposure	24 Hr Post-Exposure
Endothelial Function									
BAD (mm)	3.7 ± 0.8	3.7 ± 0.7	3.7 ± 0.7	3.7 ± 0.7	3.7 ± 0.7	3.8 ± 0.7	3.7 ± 0.7	3.7 ± 0.7	3.7 ± 0.7
FMD (%)	5.6 ± 4.1	6.8 ± 5.9	6.6 ± 4.7	5.0 ± 5.9	5.6 ± 7.9	7.4 ± 5.5 ‡	6.4 ± 6.7	4.4 ± 8.4	6.3 ± 6.5
NMD (%)	17 ± 7	18 ± 8	18 ± 7	19 ± 8	19 ± 8	20 ± 7	21 ± 9	19 ± 7	19 ± 8
Hemodynamics									
Cardiac Output ($L \cdot min^{-1}$)	5.8 ± 0.9	5.6 ± 0.8	5.8 ± 0.9	5.9 ± 0.8	5.6 ± 0.8 ‡	5.9 ± 0.8	5.7 ± 0.8	5.7 ± 0.7	5.9 ± 0.9
SVR ($dynes \cdot sec \cdot cm^{-5}$)	1188 ± 314	1155 ± 261	1172 ± 333	1137 ± 170	1114 ± 169‡	1129 ± 335‡	1169 ± 248	1114 ± 169	1129 ± 335
C1 ($10 \cdot ml \cdot mm\ Hg^{-1}$)	19.0 ± 6.6	26.1 ± 38.1	19.0 ± 8.0	18.1 ± 7.2	19.9 ± 6.1	18.1 ± 5.4	18.1 ± 5.4	19.9 ± 6.1	18.1 ± 5.4
C2 ($100 \cdot ml \cdot mm\ Hg^{-1}$)	9.0 ± 2.7	10.8 ± 11.7	8.8 ± 3.2	9.4 ± 3.1	8.8 ± 2.6	9.1 ± 2.5	9.0 ± 2.7	8.8 ± 2.6	11.4 ± 14.9
Ambulatory Monitoring									
SBP (mm Hg)	117 ± 7	------	115 ± 7*	116 ± 7	------	113 ± 8*	116 ± 9	------	113 ± 8*
DBP (mm Hg)	69 ± 6	------	68 ± 5‡	68 ± 6	------	67 ± 6*	69 ± 7	------	66 ± 6*
HR ($beats \cdot min^{-1}$)	71 ± 9	------	71 ± 11	72 ± 7	------	72 ± 10	71 ± 9	------	74 ± 10*

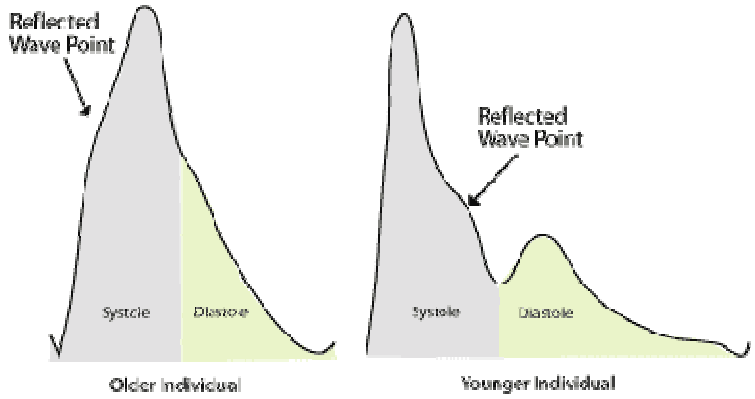
*p<0.001 versus pre-exposure value for same visit
†p<0.01 versus pre-exposure value for same visit
‡p<0.05 versus pre-exposure value for same visit

BAD (Brachial artery diameter); FMD (Flow-mediated dilatation); NMD (Nitroglycerin-mediated dilatation); CO (Cardiac output); SVR (Systemic vascular resistnace); C1 (Large artery compliance); C2 (Small artery compliance); SBP (Systolic blood pressure); DBP (Diastolic blood pressure); HR (Heart rate)

SECONDHAND SMOKE

Augmentation index @HR75 (AIx@75) = % of SBP due to augmentation pressure standardized for HR





Central aortic hemodynamics

Treatment	AIx@75 < 35 yrs old (n=13)	AIx@75 ≥ 35 yrs old (n=12)
placebo	-2.0 ± 9.9% (p=0.06)	+3.9 ± 4.3% (p=0.02)
atorvastatin	-	0.8 ± 5.5 % (p=0.66)

Coarse PM-CV

O***verall hypothesis***

Short-term exposure to coarse PM, from both rural and urban sources, promotes pro-vasoconstrictive vascular dysfunctions via biological pathways related to cardiovascular autonomic imbalance in African American and White subjects alike.

Coarse PM-CV Project Team

- **Principal Investigator:**
  Robert D. Brook
  Division of Cardiovascular Medicine, University of Michigan (UM)

  Co-investigators:
  - J. Timothy Dvonch, Gerald Keeler (School of Public Health, UM)
  - Niko Kaciroti (Biostatistics, UM)
  - Diane R. Gold (Harvard School of Public Health)

- Collaborators:
  - Bruce Urch, Jeffrey R. Brook, Frances Silverman
    Gage Occupational and Environmental Health Unit
    University of Toronto
    (Harvard EPA Center Project)

Coarse PM-CV

Specific Aim 1

To demonstrate that coarse CAP exposure causes acute vascular dysfunctions in 25 white and 25 AA subjects (n=50).

- Concentrated ambient coarse PM (CAP) [150-300 μg/m^3] for 2 hrs triggers vascular dysfunctions at each individual site (vs filtered air).

  primary outcomes: ↓ brachial artery diameter
  ↑ intra-exposure diastolic blood pressure (BP)
  secondary outcomes: ↓ FMD

- The vascular dysfunctions are mediated by CV autonomic balance

  ↓ HRV correlated and temporally related to vascular dysfunction.

- To further elucidate the extent of the CV impact of coarse PM exposure by incorporating novel CV outcomes
  - continuous intra-exposure BP/hemodynamics (Finometer)
  - central aortic hemodynamics, arterial compliance (sphygmoCor)
  - microvascular endothelial function (EndoPAT2000)

Coarse PM-CV

Specific Aim 2

To demonstrate that similar vascular dysfunctions occur in both races (Whites, AA) to both CAP sources (urban, rural).

- Vascular dysfunctions and autonomic imbalance occur in all subjects after all 3 different sources of CAP
  - Urban Toronto (Harvard EPA center)
  - Urban Detroit, and rural Southeast Michigan (Coarse STAR)
- Compare CV responses due to urban vs. rural CAP in Michigan
- Compare CV responses between AA vs. Whites in Michigan
- Candidate genetic SNP (glutathione-S-transferase M1 null)
  - subject and/or race susceptibility differences to CAP (from stored plasma)

Coarse PM-CV

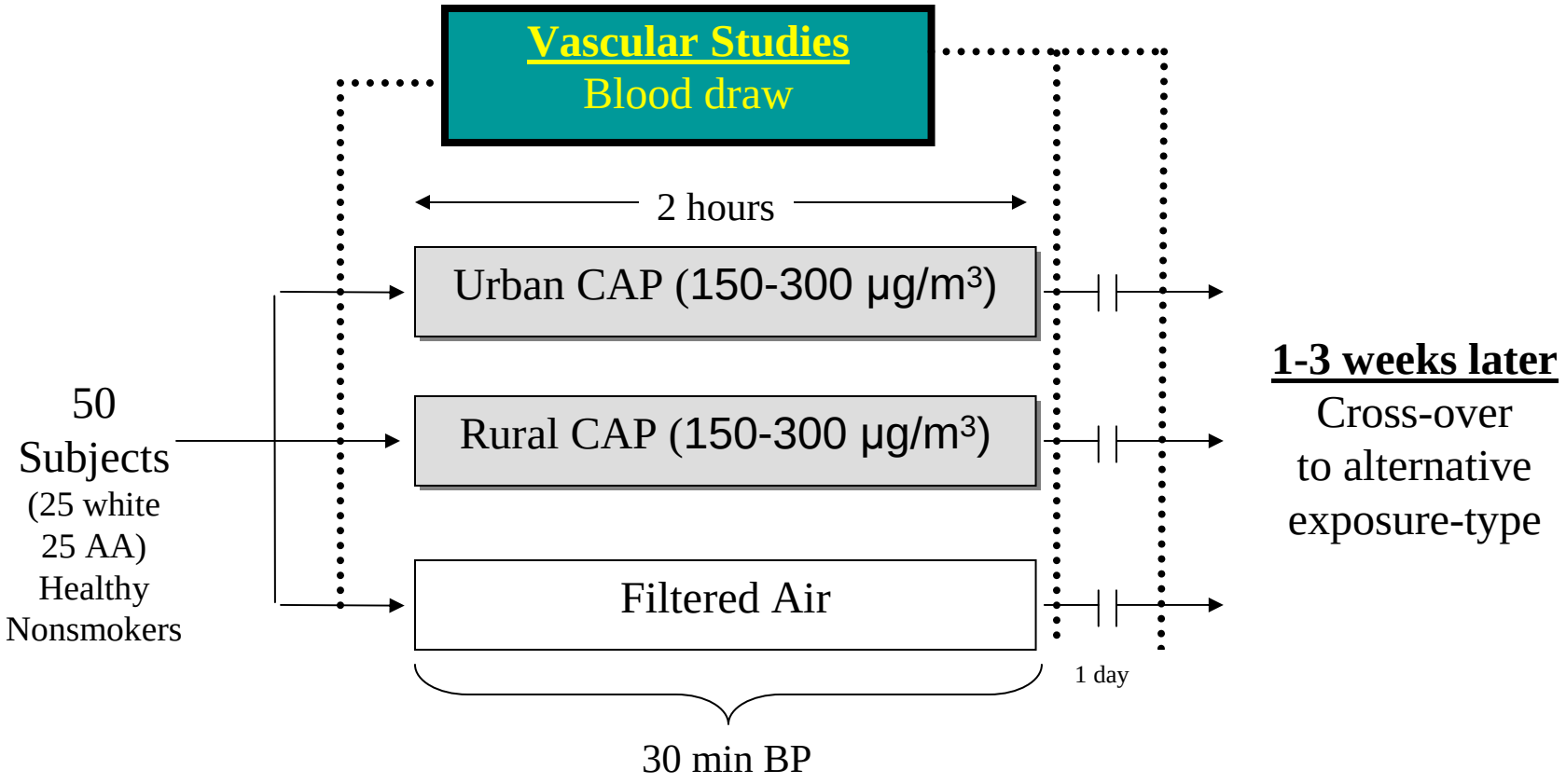
Specific Aim 3

To elucidate the CAP constituents and sources responsible for the CV responses.

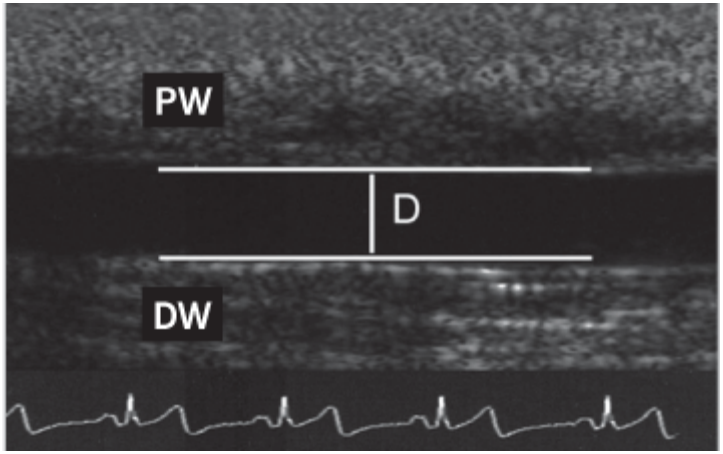
- **Detailed assessment of the differences in coarse PM composition, sources, and chemistry between the 3 experimental settings.**
- **Correlate CAP composition and sources with CV outcomes for insights into constituents responsible for triggering biological CV responses.**

Coarse PM-CV

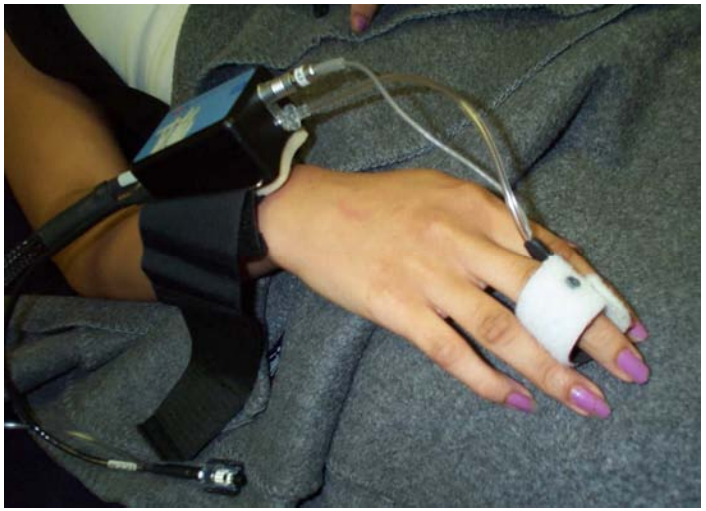
Study Protocol Design Outline



Method	Effect Assessed		Specific Parameter Measured
Vascular and hemodynamic responses (measured pre, post, and 23 hours post exposures)			
		Duration	
Ultrasound	Vascular tone	1 min	Brachial artery diameter (conduit artery tone). **PRIMARY OUTCOME #1 (specific aim 1A)**
Ultrasound	Microvascular arteriole tone	1 min	Brachial artery Doppler velocity and flow
Echocardio -graphy	Cardiac hemodynamics/performance Marker of cardiac SNS activity	10 mins	Cardiac output, stroke volume
SphygmoCor	Large arterial compliance Central aortic BP and hemodynamics	10 mins	Radial tonometer with computerized central aortic waveform analyses by transform function ***Novel exploratory secondary vascular endpoint***
Endo-PAT	MICROVASCULAR RESISTANCE ARTERY endothelial function (NON-DOMINANT ARM)	15 mins	Finger tonometer-determined microvascular endothelial-dependent flow responses ***Novel exploratory secondary vascular endpoint***
Ultrasound	CONDUIT endothelial and smooth muscle-dependent vascular function (DOMINANT ARM)	20 mins	Flow-mediated dilatation (FMD) (endothelial function) Nitroglycerin-mediated dilation (NMD) (smooth muscle)



CV outcome measurements to take place while subject is intra-chamber during exposure		
Brachial BP	BP, exposure times = 0,30,60,90,180 minutes	Systemic arterial BP **PRIMARY OUTCOME #2 (specific aim 1A)**
Finometer	BP, continuous during exposure	Continuous beat-to-beat BP and heart rate ***Complimentary secondary BP endpoint***
Holter ECG	CV autonomic balance (SNS / PSNS) Analyses performed at HSPH (as per project 3 of the Harvard EPA PM Center award).	Time and frequency domain heart rate variability Done before, during, and for 23 hrs post-exposures **PRIMARY OUTCOME #3 (specific aim 1A)**
Blood/urine biomarkers (measured through IV blood draw pre, post, and 21 hours post exposures		
Venous Plasma	Biomarkers of circulating systemic responses Measured by ELISA at HSPH (as per project 3 of the Harvard EPA PM Center award).	F_2 isoprostanes (oxidative stress) C-reactive protein (inflammation) Endothelin 1 (vasoconstrictor bioavailability) Glutathione-S-transferase M1 polymorphisms by PCR to test genetic sensitivity (stored blood)[58a]



Coarse PM-CV

Coarse PM characterization:

PM mass, carbon, ions and transition metals

Appropriate filers will collect 25-30 L/min CAP flow during each 2-hour long exposure.

Continuous estimated mass and number concentration light scattering insts and by direct mass recording Tapered Element Oscillating Micro-balance.

Teflon filters: gravimetric total mass.

Sulfate, nitrate, chloride, potassium, sodium and ammonium: ion chromatography.

Total organic and elemental carbon: thermal-optical-transmission analysis.

Inductively coupled plasma-mass spectrometry (ICP-MS): metals (e.g., Fe, Ni, Zn, Cu)

Gas chromatography mass spectrometry (GCMS) for selected semi-volatile and nonvolatile organics (e.g., PAHs, alkanes).

Source Apportionment:

PM characteristics will be quantified and categorized based on the trace element composition, size, and morphological characteristics.

Multivariate receptor modeling methods, Positive Matrix Factorization (PMF)

Associations between the health outcomes and the individual pollutants and CAP components as well as their likely sources

Coarse PM-CV Summary

Designed to specifically investigate:

- Acute CV responses to coarse PM
- Test if there are race differences in responses
- Test if there are location-determined response differences
- Investigate the sources and composition of PM responsible

QUESTIONS?