Blood Pressure Response to Controlled Diesel Exhaust Exposure in Human Subjects

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Abstract—Exposure to traffic-related air pollution is associated with risk of cardiovascular disease and mortality. We examined whether exposure to diesel exhaust increased blood pressure (BP) in human subjects. We analyzed data from 45 nonsmoking subjects, 18 to 49 years of age in double-blinded, crossover exposure studies, randomized to order. Each subject was exposed to diesel exhaust, maintained at 200 $\mu g/m^3$ of fine particulate matter, and filtered air for 120 minutes on days separated by ≥ 2 weeks. We measured BP pre-exposure, at 30-minute intervals during exposure, and 3, 5, 7, and 24 hours from exposure initiation and analyzed changes from pre-exposure values. Compared with filtered air, systolic BP increased at all of the points measured during and after diesel exhaust exposure; the mean effect peaked between 30 and 60 minutes after exposure initiation (3.8 mm Hg [95% CI: −0.4 to 8.0 mm Hg] and 5.1 mm Hg [95% CI: 0.7–9.5 mm Hg], respectively). Sex and metabolic syndrome did not modify this effect. Combining readings between 30 and 90 minutes, diesel exhaust exposure resulted in a 4.4-mm Hg increase in systolic BP, adjusted for participant characteristics and exposure perception (95% CI: 1.1–7.7 mm Hg; $P=0.0009$). There was no significant effect on heart rate or diastolic pressure. Diesel exhaust inhalation was associated with a rapid, measurable increase in systolic but not diastolic BP in young nonsmokers, independent of perception of exposure. This controlled trial in humans confirms findings from observational studies. The effect may be important on a population basis given the worldwide prevalence of exposure to traffic-related air pollution. (***Hypertension***. 2012;59:943-948.) ● Online Data Supplement

Key Words: air pollution ■ diesel exhaust ■ cardiovascular ■ blood pressure ■ autonomic nervous system

The relationship between exposure to air pollution, specifically combustion-generated and traffic-related fine particulate matter ($PM_{2.5}$), and increased risk for cardiovascular disease is increasingly consistent and well supported. Population-based effects have been observed based on increased short-term (eg, hourly or daily) and long-term (eg, annual average) exposure levels. The physiological pathway(s) through which exposure induces such effects remains uncertain. Experimental research suggests that the process might involve several pathways, including a shift in autonomic balance, systemic inflammatory response mechanisms, and prolonged endothelial dysfunction.[1]

Because diesel exhaust (DE) is the dominant source of urban $PM_{2.5}$,[2] we use DE inhalation as a model for traffic-based $PM_{2.5}$ exposure. Based on the hypothesis that alterations in blood pressure (BP) are a mode of action through which inhaled pollutants can increase both acute and chronic risk of cardiovascular events, we examined the systemic BP response in volunteers exposed to both DE and filtered air (FA) in an experimental setting.

Materials and Methods

A total of 49 adult subjects participated in 4 exposure studies conducted at the University of Washington DISCOVER Center on Cardiovascular Disease and Traffic-Related Air Pollution. Experiments used the same protocol and equipment, and data were pooled for analysis.

Subjects were nonsmokers, not regularly exposed to secondhand smoke, and not taking antihypertensive medication. Thirty-two volunteers were defined as healthy, with no history or evidence of hypertension, asthma, diabetes mellitus, hypercholesterolemia, cardiovascular illness, or other chronic medical condition, based on questionnaire, spirometry, fasting glucose and lipid panel, and ECG. Additional qualifications included body mass index <30 kg/m², fasting blood sugar (glucose) <126 mg/dL, and BP <130/85 mm Hg. Seventeen subjects were adults with metabolic syndrome disease (MeS), defined as meeting 3 of the following conditions: (1) waist circumference ≥102 cm in males and ≥88 cm in females; (2) triglycerides ≥150 mg/dL; (3) high-density lipoprotein cholesterol <40 mg/dL in males and <50 mg/dL in females; (4) systolic BP (SBP) ≥130 mm Hg or diastolic BP (DBP) ≥85 mm Hg; or (5) fasting glucose ≥100 mg/dL. Age, sex, race/ethnicity, smoking, and medication use were self-reported. Urinary cotinine was measured in samples collected at the first visit to confirm nonsmoking status using the CAS-COT kit (Innovacon, Inc, San Diego, CA). We

excluded self-reported smokers or participants with cotinine >200 ng/mL. One volunteer was excused from participating in the study based on cotinine screening, and 3 were excluded from data analysis after completing all of the exposures.

Exposures were double-blind, crossover, and randomized to order, with sessions separated by a minimum 2-week washout period to eliminate carryover effects. All of the exposures and assessments were conducted following the same daily schedule to limit variation between sessions. Women were only exposed during the first 2 weeks of a menstrual cycle, and pregnancy was ruled out by a urine pregnancy test before each exposure. Subjects were instructed to fast for a minimum of 8 hours before the exposure session. Baseline BP and vital signs were taken shortly after subject arrival, at approximately 7:30 AM.

Each subject was exposed on separate days to each condition, DE or FA, for 120 minutes. Each 120-minute exposure began at approximately 8:30 AM. Resting BP and heart rate (HR) measurements were taken during exposure (at 5, 30, 60, 90, and 110 minutes from exposure start) and 3, 5, 7, and 24 hours after exposure, using an automated digital oscillometric monitor (Welch-Allyn Atlas 300 or 52000; Welch-Allyn, Skaneateles Falls, NY; Omron HEM-705CP; Omron, Vernon Hills, IL), with cuff placed on the left upper arm. Subjects were resting and seated during the exposure period and postexposure. For each participant, a consistent position and measurement device were used for all of the measurements, with a single measurement taken at each time point. After exposure, subjects rested at the Clinical Research Center at the University of Washington Medical Center until release, ≥8 hours after exposure start. Each subject received an identical defined composition meal between the 3- and 5-hour postexposure measurements. Most subjects left the Clinical Research Center 8 hours after exposure commencement and returned for follow-up measurements ≈24 hours after exposure. Ten subjects with MeS participated in a more closely monitored protocol and remained at the Clinical Research Center overnight and through the next day follow-up period.[3]

All of the researchers, nurses, and technicians participating in the study were blinded to exposure type, with the exception of the exposure engineer. To evaluate blinding adequacy, subjects were asked during exposure to estimate the level of DE in the chamber (as high, medium, or none). We considered this perception of exposure in our analysis. The University of Washington Human Subjects Division approved subject consent forms and the study protocol.

Exposure System

As described previously,[4] DE was generated using a 2002 model turbocharged direct-injection 5.9-L Cummins B-series engine in a 100-kW generator set, running at steady state before subject arrival (6BT5.9G6; Cummins, Inc, Columbus, IN). Load was maintained at 75% of rated capacity, using a load-adjusting load bank (Simplex, Springfield, IL), No. 2 undyed on-highway low sulfur diesel fuel and Valvoline 15W-40 crankcase oil. Emission dilution was completed in 2 phases, with final $PM_{2.5}$ concentration maintained at 200 $\mu g/m^3$ in the breathing zone (average: 205.4 $\mu g/m^3$; SD: 5.4 $\mu g/m^3$). To ensure that exposure levels are stable, $PM_{2.5}$ concentrations were assessed in real-time using a tapered element oscillating microbalance (1400a $PM_{2.5}$; Rupprecht and Patashnick Co, Albany, NY) and adjusted continuously with a feedback control system based on nephelometry measurements. The 116-m^3 exposure room was maintained at a temperature of 20°C to 21°C with 50% relative humidity. Based on multistage impactor-collected samples, the facility's DE particle mass median diameter was 0.080 μm. Typical particle count per cubic centimeter for our exposure scenario was 2.8×10^3 for FA and 5.3×10^4 for DE exposures, based on 1-minute averages. Nephelometers positioned within the room are used to confirm spatial uniformity of particle concentrations. For DE exposures, average concentrations of nitrogen dioxide were 35 ppb (≈1.5% of total nitrogen oxide). Concentrations of carbon monoxide averaged 0.30 ppm for FA and 0.80 ppm for DE. FA was ambient air passed through a carbon matrix filter and HEPA filter (99.99% efficient) and was used to dilute the exhaust in DE exposures. (In some experiments, there were additional sessions at different exposure

levels or with additional treatments in conjunction with DE and FA; those sessions were excluded from the analysis).

Gene-Environment Interactions

To further understand potential mechanisms, we also examined whether response to DE varied by a common nucleotide variant (A1166C and rs5186) in the angiotensin II type 1 receptor gene, a component of the renin-angiotensin system intricately involved in BP regulation.[5,6] The analysis, conducted on this one single nucleotide polymorphism selected on an a priori basis, can be found in the online-only Data Supplement.

Statistical Analysis

Statistical analysis was performed using Stata 10.0 statistical software (Stata Corp, College Station, TX) and R (www.r-project.org). Descriptive analyses, paired t tests, nonparametric median tests were used in initial analyses, with the χ^2 test used for categorical variables. BP at each time point was first baseline corrected by subtracting the same session's pre-exposure BP (time $[t] = -60$ minutes), giving change in BP measured at each recorded interval. The baseline-corrected value for the FA session was then compared with the analogous value in the DE session for a time-specific, participant-specific measure of DE effect. To estimate the effect at specific time points (and for ease of incorporation into multivariate modeling), the BP difference-in-differences (DD) was calculated for each participant i and time point t in minutes ($t=0$ is the initiation of the exposure period):

$$DD_{i,t} \equiv y_{i,t}^{(DE)} - y_{i,(-60)}^{(DE)} - [y_{i,t}^{(FA)} - y_{i,(-60)}^{(FA)}]$$

in which y represents the BP measurement. At each time point, DD values from all 45 of the participants were used for a raw estimate of the mean DE effect, with significance evaluated via a 1-sample t test against the null hypothesis of no effect.

To pool data from different time points and allow for evaluation of potential confounders and the considerable individual variability in BP, SBP readings were analyzed in a hierarchical regression model. The DE effect was modeled as the interaction between exposure and an indicator function for midexposure measurements (30–90 minutes) and a second for postexposure readings (180 minutes to the next day), each contrasted with the pre-exposure measurement. The model was adjusted for sex, MeS, angiotensin II type 1 receptor genotype, perception of exposure, and an indicator for the participant's first session exposure type. Subgroup sizes were not sufficient to examine effect modification for these variables, which, in our specification, is equivalent to a 3-way interaction. The model was fit via linear mixed effects in the R language "lme4" package and allowed for an estimation of the mean effect while accounting for random variations in session-specific individual baselines. Seven subjects were excluded from the regression analysis, because of missing angiotensin II type 1 receptor genotype or missing or incompatible exposure-perception data.

Results

Subject characteristics are summarized in the Table. All of the baseline characteristics of healthy and MeS subjects were significantly different, with the exception of sex and race/ethnicity. One MeS subject was excluded based on data collection difficulties attributed to body dimension, permitting complete data analysis for 45 participants.

Mean effect of exposure on SBP is shown in Figure 1A and effect attributable to DE in Figure 1B. In both healthy and MeS subjects, SBP increase (change from session baseline) with DE exposure was greater than that with exposure to FA (Figure 1A). The largest effects were 30 and 60 minutes after DE exposure commenced (3.8 mm Hg [95% CI: −0.4 to 8.0], $P=0.08$; 5.1 mm Hg [95% CI: 0.7–9.5], $P=0.02$, respectively). Increases in SBP persisted after termination of DE

Table.   Characteristics of Study Participants

Characteristic	Healthy	Metabolic
No.	31	14
Male, n (%)	22 (71)	8 (57)
Age, y	28±8.6	39±7.3
White, n (%)	24 (77)	10 (71)
Body mass index	23±2.1	39±6.9
SBP, mm Hg	112±16.1	130±14.5
DBP, mm Hg	67±10.6	77±8.3
Heart rate, bpm	64±9.6	77±8.5
Total cholesterol, mg/dL	158±30.1	197±33.7
LDL	96±23.6	126±31.4
HDL	48±11.3	37±5.0
Triglycerides	73±42.0	182±118
Glucose, mg/dL	90±5.1	98±9.3

All of the values reported are mean±SD unless otherwise noted. Differences between healthy and metabolic syndrome subjects were statistically significant, with the exception of race and sex. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein. DBP and triglyceride $P\leq0.01$; all others $P\leq0.001$.

exposure, with mean differences ranging from 2.0 to 3.5 mm Hg over baseline through the following morning, ≈24 hours later.

To further investigate the strength of evidence for a DE effect, we developed the hierarchical regression model described in the Methods section. The midexposure differential DE effect (30–90 minutes, pooled) was estimated as +4.4 mm Hg (95% CI: 1.1–7.7; $P=0.0009$). Effect estimates for subgroups are reported in the online-only Data Supplement.

Changes in DBP were not associated with DE and did not vary widely between FA and DE exposures (Figure 2). Baseline-corrected HR was higher on average with DE than with FA exposure; however, the effect was not significant, and no trend was apparent (Figure 3). Regression analysis revealed similar trends for DBP and HR: both were elevated during the exposure session, regardless of arm assignment; however, unlike SBP, the differential midexposure DE effect between arms was not significant for either end point. Participants correctly identified the exposure in 61% of exposure sessions, although only 34% correctly identified the exposure for both sessions, and 53% chose the same exposure level at both sessions.

Discussion

The systolic BP increase that we detected during and after experimental DE inhalation supports earlier observational research linking air pollution, especially traffic-related air pollution, with increased BP. This evidence provides insight into the key sequences underlying the acute effects of pollution-related risk for cardiovascular events. Our findings in healthy and MeS subjects suggest that the hemodynamic response to DE is rapid, moderately sustained, not related to perception of exposure, and limited to SBP.

Previous controlled human inhalation studies on air pollutants have produced somewhat inconsistent results in terms of BP outcomes, which may be attributed to methodological

differences. Controlled exposures to concentrated ambient particles (CAPs) and ozone have been associated with acute arterial vasoconstriction and increased DBP (3–6 mm Hg) but small or no increases in SBP.[7,8] In a 2-city study, Brook et al[7] found both SBP and DBP increased with exposure to urban-sourced CAPs (likely rich in traffic-related pollutants) but only DBP increased with exposure to CAPs sourced from a suburban/rural setting. CAPs studies are often challenged by inconsistent exposure composition and concentrations, which can complicate physiological interpretation, unlike our DE exposures.

Congruent with our findings, Mills et al[9] reported a nonsignificant increase in SBP and DBP (8 and 6 mm Hg, respectively) in young men 2 hours after controlled exposure to 300 $\mu g/m^3$ of DE. In a study of healthy adults completing a 2-hour walk along a Beijing roadway, Langrish et al[10] found that exposure to ambient $PM_{2.5}$ (86–140 $\mu g/m^3$) amplified exercise-induced increases in SBP; on average, SBP was 7 mm Hg lower when the participants wore PM-reducing masks. It is important to note that the BP measurements reported in both studies were taken only after, and not during, the exposure. Our results indicate that the most significant BP response to DE occurs more rapidly, within the first hour of exposure. The recording of this response during inhalation and, hence, the ability to more accurately describe the time course of effects, constitutes a major strength of this study.

Physiological responses in animal models have been inconsistent, appearing to vary based on exposure method, species, and genotype/phenotype. $PM_{2.5}$ inhalation exposures, likely most germane to the human response to air pollutants, have been shown to synergistically enhance SBP and mean arterial pressure in both rats and mice when combined with infusion of angiotensin II.[11,12] Possibly indicative of a $PM_{2.5}$-renin-angiotensin system interaction, a separate study reported significant increases in plasma angiotensin II concentrations in rats after short-term inhalation of $PM_{2.5}$.[13]

Epidemiological research has reported the most consistent associations between short-term $PM_{2.5}$ exposures and SBP increase. A study of 347 adults in 3 Detroit, Michigan, neighborhoods found consistent and linear escalations in SBP associated with each 10-$\mu g/m^3$ rise in ambient $PM_{2.5}$, with an overall average 3.2-mm Hg increase; among those not on antihypertensives living within the most polluted community, the corresponding increase reached 10.3 mm Hg.[14] Delfino et al[15] reported similar increases in both SBP (mean: 8.2 mm Hg) and DBP (mean: 5.8 mm Hg) associated with a 5.2-$\mu g/m^3$ increase in ambient organic carbon, a combustion-generated component of $PM_{2.5}$. Our results provide needed experimental confirmation to these and other observations by demonstrating in a well-controlled study that DE inhalation alone can increase SBP in young adults.

The time course of exposure-related effects has been challenging for population-based investigations. Most studies average pollutant concentrations over 24-hour periods; however, actual ambient conditions often include transient spikes in pollutant levels. Peters et al[16] found that risk of onset of myocardial infarction increased 2.6- to 3.9-fold within 1 hour of exposure to urban traffic, suggesting a more acute response
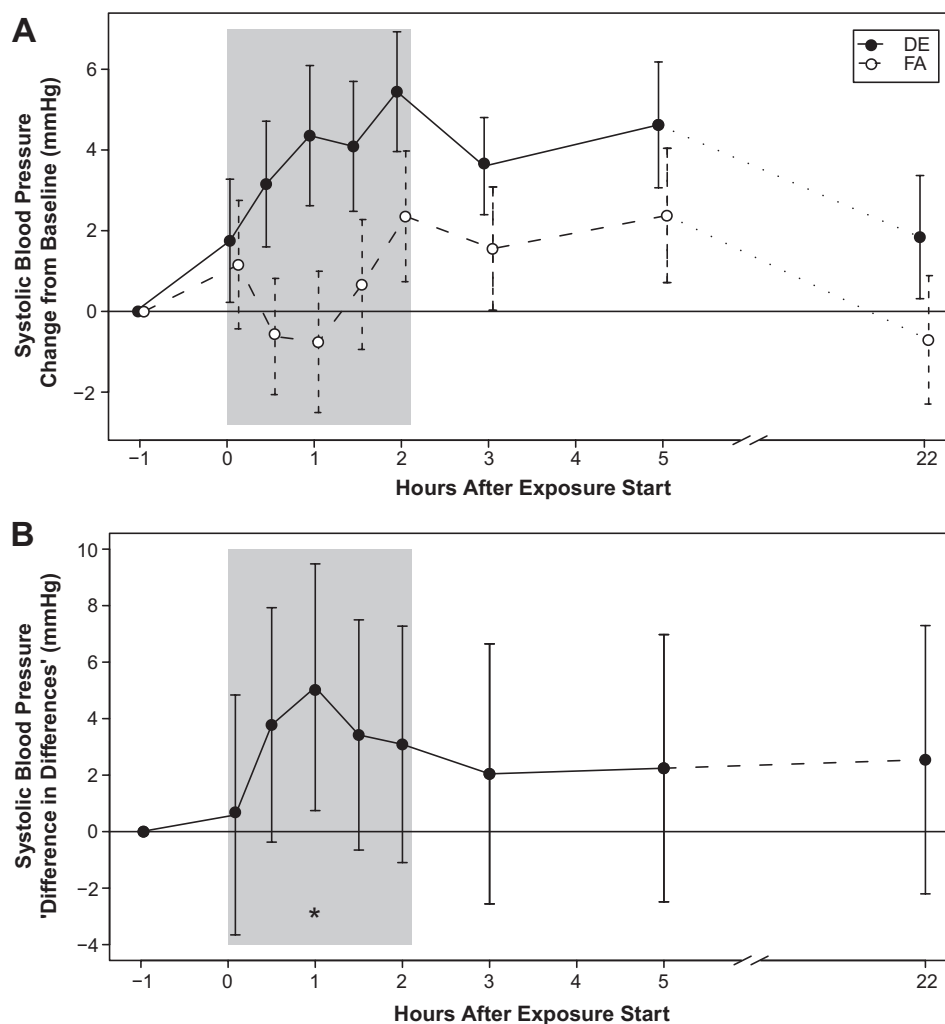
Figure 1. A, Mean change in systolic blood pressure (SBP) from baseline. Mean difference between SBP at each time point and SBP pre-exposure for diesel exhaust (DE ●) and filtered air (FA ○). Error bars represent 95% CIs for the mean. The shaded area is the exposure period. **B**, Mean diesel exhaust effect on SBP. Mean difference between change (from pre-exposure) in SBP with DE exposure and change in SBP with FA exposure: a measure of the DE effect on SBP. The mean effect is positive at all of the time points, with peak difference (5.1 mm Hg [95% CI: 0.7–9.5]; $P=0.02$) occurring ≈60 minutes after exposure start. Error bars represent 95% CIs for the paired t test.

than might be predicted with longer-term modeling. Although we detected DE-related changes in SBP up to 1 day after exposure, peak increases occurred only 30 to 60 minutes from commencement of DE inhalation. This rapid change is a novel finding, supporting the hypothesis that acute exposure to $PM_{2.5}$ induces dysregulation of the autonomic nervous system.[17]

It is plausible that $PM_{2.5}$ interaction with nociceptive or noradrenergic receptors stimulates the sympathetic nervous system, either directly via vasoconstrictive effects of norepinephrine or indirectly via the renin-angiotensin system, raising circulating levels of the vasoconstrictor angiotensin II. In an earlier publication, we reported higher plasma concentrations of endothelin 1 with vasoconstriction after DE exposure; as discussed, endothelium-derived endothelin 1 synthesis might be a secondary response to autonomic nervous system activation via catecholamine stimulation or α-1 vascular smooth muscle receptors.[18] In addition to elevating BP, DE effects on endothelin 1 may further decrease blood flow

to the heart, contributing to cardiac events.[19] We did not find a significant increase in HR, as might be expected with β-adrenergic activation. We have also reported previously that we did not find evidence of changes in HR variability in this experimental setting.[18] This may suggest a vasoconstrictive α-adrenergic response without any corresponding β-adrenergic modulation of HR and vasodilation.[20]

Although SBP decreased after DE exposure termination, levels remained above baseline throughout the follow-up period, up to 24 hours postexposure. The pattern presented suggests a return to pre-exposure levels; however, we do not have data beyond our protocol's time frame to confirm this.

Unlike other controlled exposure studies, we did not see any change in DBP. This discrepancy may be because of dissimilarity in exposure pollutants. It is possible that distinct constituents induce particular physiological responses; most of the studies reporting DBP increase used CAP inhalation, CAP + ozone, or ambient air monitoring. A population-based study in Taiwan found that, whereas ambient particulate
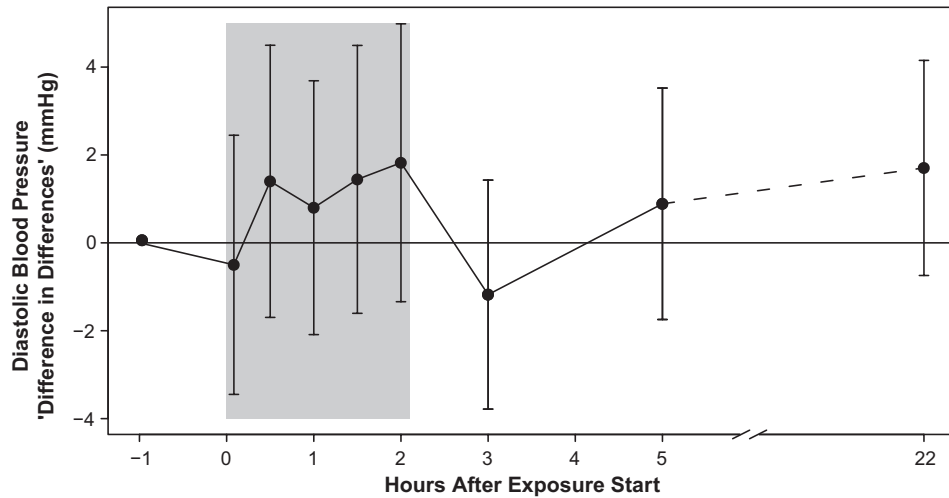
Figure 2. Mean diesel exhaust effect on diastolic blood pressure. Mean difference between change (from pre-exposure) in diastolic blood pressure with diesel exhaust exposure and with filtered air exposure. Error bars represent 95% CIs for the paired *t* test. The shaded area is the exposure period.

matter was related to increases in SBP, a rise in DBP was associated with elevated ozone levels.[21] Unfortunately, the wide variation in pollutant proportions and components of locally generated CAPs make it challenging to directly compare study results or to parse out from where discrepancies may stem.

Although our exposures cannot replicate the full mix and variability of actual pollutants in urban air, our DE facility allows for consistent exposures to standardized, replicable pollutant composition and concentration levels, providing a valid model for traffic-related air pollution. The crossover design and adjustment for pre-exposure BP enabled us to detect a pressure response to DE, accounting for interindividual and intraindividual variability. We cannot account for all of the activities and exposures that subjects may have had before exposure and between the 8- and 24-hour postexposure measurements for those participants who left the hospital. We have no reason to believe that such activities and exposure would be systematically different between days of DE exposure

or FA, and, hence, it is unlikely that these uncontrolled influences could bias results toward the results observed. The more sophisticated statistical modeling of our outcome also permitted us to consider a variety of potential confounding factors and to take account of within-individual correlations and the risk of multiple comparisons.

We did not find a gene-environment interaction with the angiotensin II type 1 receptor SNP selected a priori. Although subgroup sizes were not sufficient to evaluate effect modification, there was a suggestion of variation by sex, MeS, and perception. All of these subgroups exhibited a positive midexposure DE effect estimate, in accordance with our overall findings.

Subject blinding can be of concern in this research approach. Subjects correctly identified the exposure slightly better than expected by random chance; however, we did find blinding to be moderately effective; just slightly more than one third of participants correctly identified the exposure for both sessions, whereas nearly half selected the same exposure
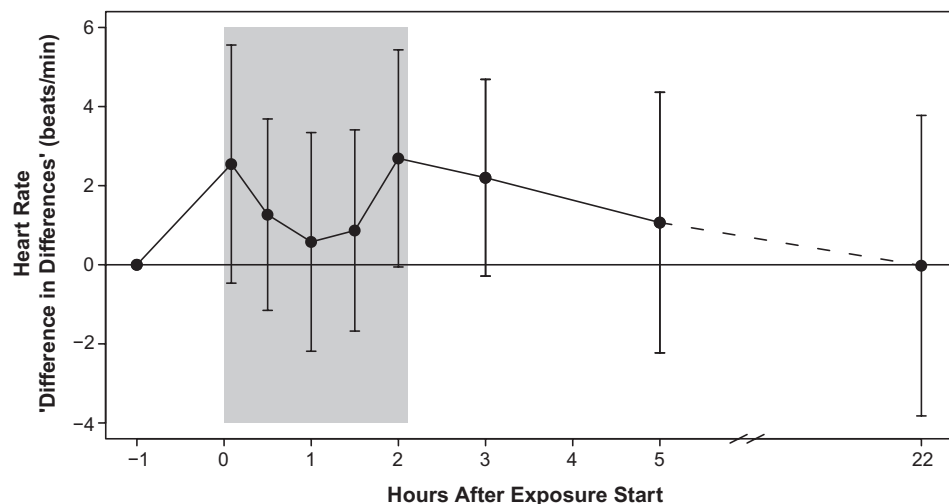

Figure 3. Mean diesel exhaust effect on heart rate. Mean difference between change (from pre-exposure) in heart rate with diesel exhaust exposure and with filtered air exposure. Error bars represent 95% CIs for the paired *t* test. The shaded area is the exposure period.

type in both DE and FA sessions. Because of concern that perception of exposure could influence the sympathetic response and BP, we adjusted for perception in our statistical modeling approach.

Our experimental model is specifically designed to reflect the effects of exposure to urban air pollution. Exposures to DE are rapidly increasing worldwide with greater urbanization and industrialization; mean 24-hour ambient and personal $PM_{2.5}$ levels in Beijing were found to be 128.5 and 102.5 $\mu g/m^3$, respectively, closer to our controlled exposure level than to recommended air quality standards.[22] Although $PM_{2.5}$ concentrations in most US cities are <35 $\mu g/m^3$ on average, transient spikes in pollutant levels and, therefore, exposure levels, are not uncommon. An acute rise in BP resulting from such an exposure has the potential to induce a variety of precursors to myocardial infarction, including atherosclerotic plaque disruption and myocardial ischemia. In this context, it is important to note that the findings we present reflect the mean SBP response to DE young, generally healthy subjects. Individual responses varied considerably, and our findings likely underrepresent the risk in susceptible populations.

This controlled study demonstrates that DE inhalation can increase BP in young adults. Transient effects detected during brief exposures may be important in conceptualizing how long-term exposures can induce proinflammatory, hypertrophic, and profibrotic phenomena, leading to clinical cardiovascular disease. The findings that we present may also help clarify how exposure to air pollutants can elevate risk for both acute and chronic cardiovascular outcomes.

Perspectives

DE inhalation can trigger a rapid and moderately sustained increase in SBP without accompanying changes in DBP or HR. Using a model of urban traffic-related air pollution exposure, our findings provide important insight into the timing associated with pollution-attributed vascular events. In isolation, the magnitude of the average DE effect on BP may not be clinically significant to an individual healthy adult; however, considering the prevalence of exposure and the growing base of susceptible individuals, pollutant-related effects on population risk of cardiovascular disease may be substantial.

Sources of Funding

Disclosures

None.

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