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Ischemic and Thrombotic Effects of Dilute Diesel-Exhaust Inhalation in Men with Coronary Heart Disease

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ABSTRACT

BACKGROUND

Exposure to air pollution from traffic is associated with adverse cardiovascular events. The mechanisms for this association are unknown. We conducted a controlled exposure to dilute diesel exhaust in patients with stable coronary heart disease to determine the direct effect of air pollution on myocardial, vascular, and fibrinolytic function.

METHODS

In a double-blind, randomized, crossover study, 20 men with prior myocardial infarction were exposed, in two separate sessions, to dilute diesel exhaust (300 μ g per cubic meter) or filtered air for 1 hour during periods of rest and moderate exercise in a controlled-exposure facility. During the exposure, myocardial ischemia was quantified by ST-segment analysis using continuous 12-lead electrocardiography. Six hours after exposure, vasomotor and fibrinolytic function were assessed by means of intraarterial agonist infusions.

RESULTS

During both exposure sessions, the heart rate increased with exercise ($P < 0.001$); the increase was similar during exposure to diesel exhaust and exposure to filtered air ($P = 0.67$). Exercise-induced ST-segment depression was present in all patients, but there was a greater increase in the ischemic burden during exposure to diesel exhaust (-22 ± 4 vs. -8 ± 6 millivolt seconds, $P < 0.001$). Exposure to diesel exhaust did not aggravate preexisting vasomotor dysfunction, but it did reduce the acute release of endothelial tissue plasminogen activator ($P = 0.009$; 35% decrease in the area under the curve).

CONCLUSIONS

Brief exposure to dilute diesel exhaust promotes myocardial ischemia and inhibits endogenous fibrinolytic capacity in men with stable coronary heart disease. Our findings point to ischemic and thrombotic mechanisms that may explain in part the observation that exposure to combustion-derived air pollution is associated with adverse cardiovascular events. (ClinicalTrials.gov number, NCT00437138.)

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THE WORLD HEALTH ORGANIZATION (WHO) estimates that air pollution is responsible for 800,000 premature deaths worldwide each year.¹ Short-term exposure to air pollution has been associated with increases in cardiovascular morbidity and mortality, with deaths due to ischemia, arrhythmia, and heart failure.² In a large cohort study from the United States, Miller et al. recently reported that long-term exposure to air pollution increases the risk of death from cardiovascular disease by 76%.³ These associations are strongest for fine particulate air pollutants (particulate matter of less than 2.5 μm in aerodynamic diameter [$\text{PM}_{2.5}$]), of which the combustion-derived nanoparticulate in diesel exhaust is an important component.⁴ Substantial improvements in air quality have occurred in the developed world over the past 50 years, yet the association between $\text{PM}_{2.5}$ and mortality has no apparent threshold and is evident below current air-quality standards.⁵

Preclinical models of exposure to particulate air pollution demonstrate accelerated atherosclerotic plaque development⁶ and increased *in vitro*⁷ and *in vivo*⁸ platelet aggregation. Epidemiologic and observational clinical studies suggest that exposure to air pollution may worsen symptoms of angina,⁹ exacerbate exercise-induced myocardial ischemia,^{10,11} and trigger acute myocardial infarction.^{12,13} These clinical findings are limited by imprecision in the measurement of pollution exposure, the effect of potential confounding environmental and social factors, and the lack of mechanistic data.¹⁴ Controlled exposures to air pollutants can help address these shortcomings by providing a precisely defined exposure in a regulated environment that facilitates investigation with validated biomarkers and surrogate measures of cardiovascular health. Using a carefully characterized exposure system, we have previously shown that exposure to dilute diesel exhaust in healthy volunteers causes lung inflammation,¹⁵ depletion of airway antioxidant defenses,¹⁶ and impairment of vascular and fibrinolytic function.¹⁷

To our knowledge, there have been no controlled exposures in patients with coronary heart disease, an important population that may be particularly susceptible to the adverse cardiovascular effects of air pollution. We assessed the effect of inhalation of dilute diesel exhaust on myocardial, vascular, and fibrinolytic function in a population of patients with stable coronary heart disease.

METHODS

SUBJECTS

Twenty men with stable coronary artery disease participated in this study, which was performed with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and with the written informed consent of all participants.

All the men had proven coronary heart disease, with a previous myocardial infarction (>6 months before enrollment) treated by primary angioplasty and stenting, and were receiving standard secondary preventive therapy. Men with angina pectoris (Canadian Cardiovascular Society class ≥ 2), a history of arrhythmia, diabetes mellitus, uncontrolled hypertension, or renal or hepatic failure, as well as those with unstable coronary disease (acute coronary syndrome or symptoms of instability 3 months before enrollment), were excluded. All eligible volunteers were invited to a prestudy screening for exercise stress testing; subjects who were unable to achieve stage 2 of the Bruce protocol or who had marked changes on an electrocardiogram (left bundle-branch block, early ST-segment depression >2 mm) and those in whom hypotension developed were excluded. Current smokers and men with asthma, substantial occupational exposure to air pollution, or an intercurrent illness were also excluded from the study.

STUDY DESIGN

Using a randomized, double-blind, crossover study design, we evaluated the subjects in two 8 a.m. sessions at least 2 weeks apart. In each session, the subjects were exposed to controlled amounts of dilute diesel exhaust or filtered air. Each subject was exposed for 1 hour in an exposure chamber, as previously described.¹⁵ During each exposure, the subjects performed two 15-minute periods of exercise on a bicycle ergometer separated by two 15-minute periods of rest. For each subject, the ergometer workload was calibrated to achieve a ventilation of 15 liters per minute per square meter of body-surface area to ensure a similar exposure on both occasions. The workload was constant for both exposures and was equivalent to stage 2 of the Bruce protocol (range, 110 to 150 watts; 5 to 7 metabolic equivalents). All subjects were fitted with 12-lead Holter electrocardiographic monitors (Medical Lifecard 12 Digital Holter Recorder, Del Mar Reynolds). In accordance with

previous exposure studies in healthy volunteers, vascular assessments were made 6 to 8 hours after exposure to diesel exhaust or filtered air.¹⁷

DIESEL-EXHAUST EXPOSURE

The diesel exhaust was generated from an idling Volvo diesel engine (Volvo TD45, 4.5 liters, 4 cylinders, 680 rpm) from low-sulfur gas-oil E10 (Preem), as described previously.¹⁵ More than 90% of the exhaust was shunted away, and the remainder diluted with filtered air heated to 20°C (relative humidity approximately 50%) before being fed into a whole-body exposure chamber (3.0 m by 3.0 m by 2.4 m) at a steady-state concentration.

The chamber was monitored continuously for pollutants, with exposures standardized with the use of nitrogen oxide concentrations to deliver a particulate matter concentration of 300 μg per cubic meter (median particle diameter, 54 nm; range, 20 to 120). There was little variation between exposures in the mean (\pm SE) number of particles ($1.26\pm 0.01\times 10^6$ particles per cubic centimeter) or in the concentrations of nitrogen oxide (4.45 ± 0.02 ppm), nitrogen dioxide (1.01 ± 0.01 ppm), nitric oxide (3.45 ± 0.03 ppm), carbon monoxide (2.9 ± 0.1 ppm), and total hydrocarbon (2.8 ± 0.1 ppm). The predominant polycyclic aromatic hydrocarbons (approximately 90% of the total) were phenanthrene, fluorene, 2-methylfluorene, dibenzothiophene, and different methyl-substituted phenanthrenes. Only a minor fraction of polycyclic aromatic hydrocarbons (3.5%) was associated with particulate matter: 0.04% total particulate matter and 0.06% particulate-matter organic fraction. The concentration of particulate matter of less than 10 μm in aerodynamic diameter (PM_{10}) in the exposure chamber exceeded the WHO air-quality standard of 50 μg per cubic meter by a factor of 6, and the nitrogen dioxide concentration exceeded the WHO standard of 0.105 ppm by a factor of 10.¹⁸

VASCULAR STUDY

All subjects underwent brachial-artery cannulation with a 27-standard wire-gauge steel needle. After a 30-minute baseline saline infusion, subjects were given infusions of acetylcholine at rates of 5, 10, and 20 μg per minute (endothelium-dependent vasodilator, Clinalfa), bradykinin at rates of 100, 300, and 1000 pmol per minute (endothelium-dependent vasodilator that releases tissue plasminogen activator [t-PA], Clinalfa), and sodium nitroprusside at rates of 2, 4, and 8 μg per minute

Table 1. Baseline Characteristics of the 20 Subjects with Coronary Heart Disease.*

Characteristic	Value
Age (yr)	60 \pm 1
Smoking history (no. of subjects)	
Nonsmoker	12
Former smoker	8
Current smoker	0
Hypertension (no. of subjects)	8
Height (cm)	173 \pm 6
Weight (kg)	79 \pm 3
Body-mass index	27 \pm 1
Time since index infarction (mo)	35 \pm 4
Coronary angiographic findings	
No. of diseased vessels	
1	13
2	6
3	1
Culprit lesion (no. of subjects)	
Left anterior descending coronary artery	14
Circumflex coronary artery	4
Right coronary artery	2
Cholesterol (mg/dl)	
Total	173 \pm 6
LDL	100 \pm 8
HDL	48 \pm 2
Triglycerides (mg/dl)	128 \pm 23
Fasting glucose (mg/dl)	102 \pm 6
Medications (no. of subjects)	
Aspirin	20
Statin	18
Beta-blocker	15
ACE inhibitor or angiotensin-receptor blocker†	4

* Plus–minus values are means \pm SE. The body-mass index is the weight in kilograms divided by the square of the height in meters. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and ACE angiotensin-converting enzyme. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

† ACE inhibitor therapy was withdrawn 7 days before each vascular study. All other regular medications were continued throughout the study.

(endothelium-independent vasodilator, David Bull Laboratories); each infusion was given for 6 minutes. Infusions of the three vasodilators were separated by 20-minute saline infusions and given in a randomized order. Therapy with angiotensin-converting-enzyme inhibitors was withdrawn

Table 2. Effect of Exercise on Heart Rate and ST Segment in the 20 Subjects during Exposures to Filtered Air and Diesel Exhaust.*

Characteristic	Filtered Air	Diesel Exhaust	P Value†
Exercise phase 1			
Heart rate — bpm			
Baseline	63±2	61±2	0.24
Maximum	87±3	86±3	0.67
Maximum ST-segment change (μV)			
Lead II	-28±13	-56±10	0.03
Lead V ₂	-28±10	-41±12	0.18
Lead V ₅	-14±8	-33±9	0.04
Change in ischemic burden (mVsec)			
Lead II	-11±5	-23±4	0.004
Lead V ₂	-13±5	-21±6	0.04
Lead V ₅	-4±3	-12±4	0.01
Exercise phase 2			
Heart rate (bpm)			
Baseline	67±2	65±2	0.35
Maximum	91±3	87±3	0.12
Maximum ST-segment change (μV)			
Lead II	-17±15	-49±12	0.006
Lead V ₂	-18±12	-41±13	0.04
Lead V ₅	-7±9	-28±10	0.02
Change in ischemic burden (mVsec)			
Lead II	-8±6	-22±4	0.0007
Lead V ₂	-11±5	-20±6	0.02
Lead V ₅	-2±3	-12±5	0.006

* Plus-minus values are means ±SE; mVsec denotes millivolt seconds.

† P values were calculated with Student's t-test.

7 days before each vascular study, because it augments bradykinin-induced release of endothelial t-PA.¹⁹ All other medications were continued throughout the study.

Forearm blood flow was measured in both arms by venous occlusion plethysmography with the use of mercury-in-Silastic strain gauges, as described previously.²⁰ Heart rate and blood pressure in the noninfused arm were monitored at intervals throughout each study while the subject was in the supine position, with the use of a semi-automated, noninvasive oscillometric sphygmomanometer.

FIBRINOLYTIC AND INFLAMMATORY MARKERS

Blood (10 ml) was withdrawn into acidified buffered citrate (Stabilyte tubes, Biopool International)

for t-PA assays and into citrate (BD Vacutainer) for plasminogen activator inhibitor type 1 (PAI-1) assays. Plasma t-PA and PAI-1 antigen concentrations were determined by means of enzyme-linked immunosorbent assays (TintElize t-PA, Biopool EIA; Coaliza PAI-1; and Chromogenix AB). Serum C-reactive protein concentrations were measured with an immunonephelometric assay (BN II nephelometer, Dade Behring).

DATA ANALYSIS

Electrocardiographic recordings were analyzed with the use of the Medical Pathfinder Digital 700 Series Analysis System (Del Mar Reynolds). ST-segment deviation was calculated by comparing the ST segment during each 15-minute exercise test with the average ST segment for the 15-minute period immediately before the start of the exposure. The ST-segment amplitude was determined at the J point plus 80 msec. The ischemic burden during each exercise test was calculated as the product of the change in ST-segment amplitude and the duration of exercise. Leads II, V₂, and V₅ were selected a priori for ST-segment analysis to reflect separate regions of myocardium. The maximum ST-segment depression and ischemic burden were determined for these leads individually and as a composite.

Plethysmographic data and net t-PA release were determined as described previously.^{20,21}

STATISTICAL ANALYSIS

Continuous variables are reported as means ±SE. Analysis of variance with repeated measures and a two-tailed Student's t-test were performed as appropriate with the use of GraphPad Prism software. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Subjects were all middle-aged men with predominantly single-vessel coronary artery disease (Table 1). They reported no symptoms of angina and had no major arrhythmias during exposure or in the subsequent 24 hours.

MYOCARDIAL ISCHEMIA

The heart rate increased with exercise during exposures to diesel exhaust and filtered air (P<0.001 for both comparisons with the baseline rates; P=0.67 for the comparison of rates during exposure to diesel exhaust and during exposure to filtered

air) (Table 2). Myocardial ischemia was detected during exercise in all subjects, with greater maximum ST-segment depression during exposure to diesel exhaust than during exposure to filtered air (Table 2 and Fig. 1A and 1B) ($P < 0.05$). The ischemic burden induced by exercise was greater during exposure to diesel exhaust (Fig. 1C).

VASOMOTOR FUNCTION

There were no significant differences in resting heart rate, blood pressure, or baseline blood flow in the noninfused forearm between or during the two study visits. Although there was a dose-dependent increase in blood flow with each vasodilator ($P < 0.001$ for all comparisons), neither endothelium-dependent nor endothelium-independent vasodilatation was affected by inhalation of diesel exhaust (Fig. 2). Comparison of these data with the findings in a contemporary reference population of healthy male volunteers (mean age, 53 ± 4 years) showed impaired vasodilatation in response to acetylcholine ($P = 0.02$) but not to sodium nitroprusside (Fig. 2).

FIBRINOLYTIC AND INFLAMMATORY MARKERS

There were no significant differences in basal plasma concentrations of t-PA (10.5 ± 1.0 and 9.5 ± 1.0 ng per milliliter, respectively) or its endogenous inhibitor, PAI-1 (18.8 ± 3.0 and 17.0 ± 2.0 ng per milliliter, respectively), 6 hours after exposure to either diesel exhaust or filtered air. Likewise, leukocyte, neutrophil, and platelet counts and serum C-reactive protein concentrations were not altered at 6 or 24 hours by exposure to diesel exhaust or filtered air. Bradykinin caused a dose-dependent increase in plasma t-PA concentrations (data not shown) and net t-PA release (Fig. 3) in the infused arm ($P < 0.001$ for both comparisons) that was suppressed after exposure to diesel exhaust ($P = 0.009$; 35% decrease in the area under the curve).

DISCUSSION

We have demonstrated that transient exposure to dilute diesel exhaust, at concentrations occurring in urban road traffic, exacerbates exercise-induced myocardial ischemia and impairs endogenous fibrinolytic capacity in men with coronary heart disease. These findings provide a plausible explanation for the epidemiologic observation that exposure to air pollution is associated with adverse cardiovascular events.

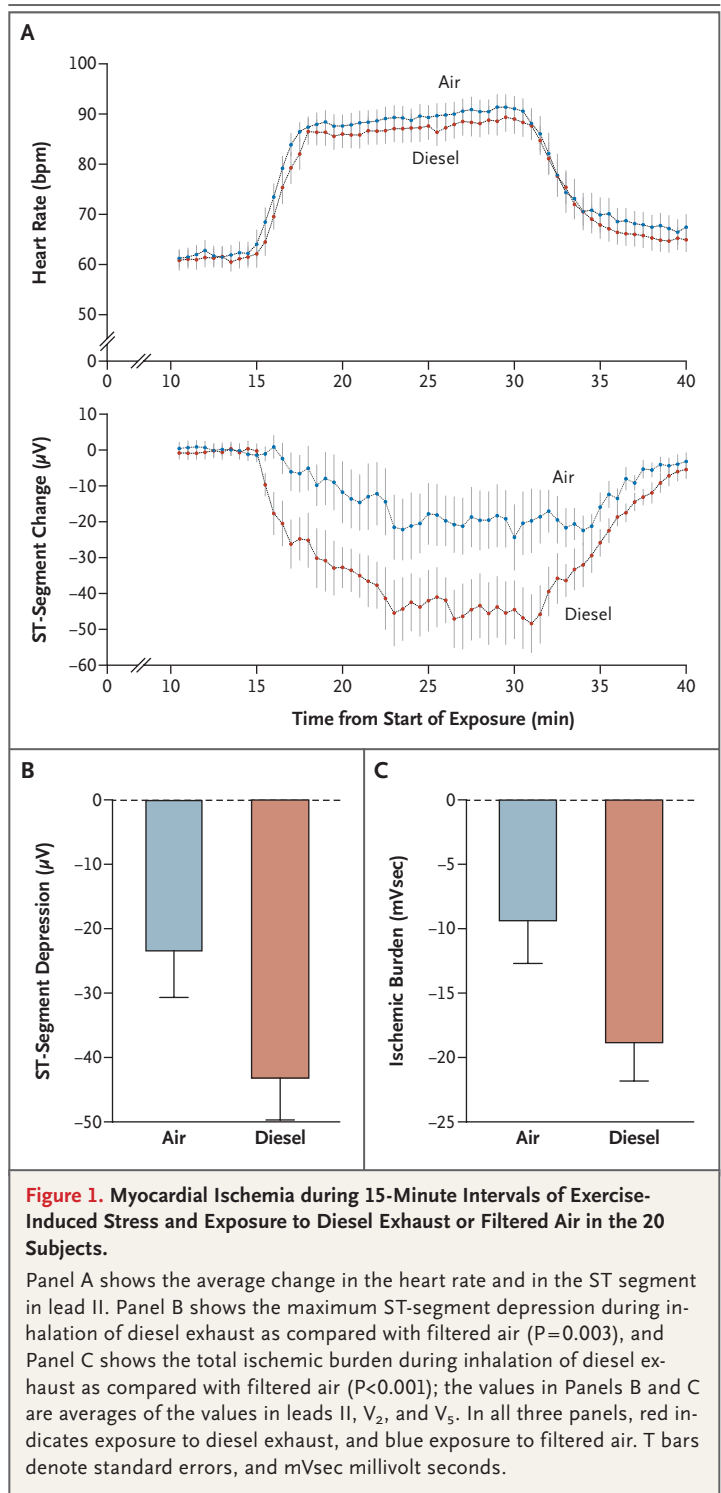


Figure 1. Myocardial Ischemia during 15-Minute Intervals of Exercise-Induced Stress and Exposure to Diesel Exhaust or Filtered Air in the 20 Subjects.

Panel A shows the average change in the heart rate and in the ST segment in lead II. Panel B shows the maximum ST-segment depression during inhalation of diesel exhaust as compared with filtered air ($P = 0.003$), and Panel C shows the total ischemic burden during inhalation of diesel exhaust as compared with filtered air ($P < 0.001$); the values in Panels B and C are averages of the values in leads II, V_2 , and V_5 . In all three panels, red indicates exposure to diesel exhaust, and blue exposure to filtered air. T bars denote standard errors, and mVsec millivolt seconds.

Concentrations of particulate matter can regularly reach levels of $300 \mu\text{g}$ per cubic meter in heavy traffic, in occupational settings, and in the world's largest cities.²² A major proportion of this

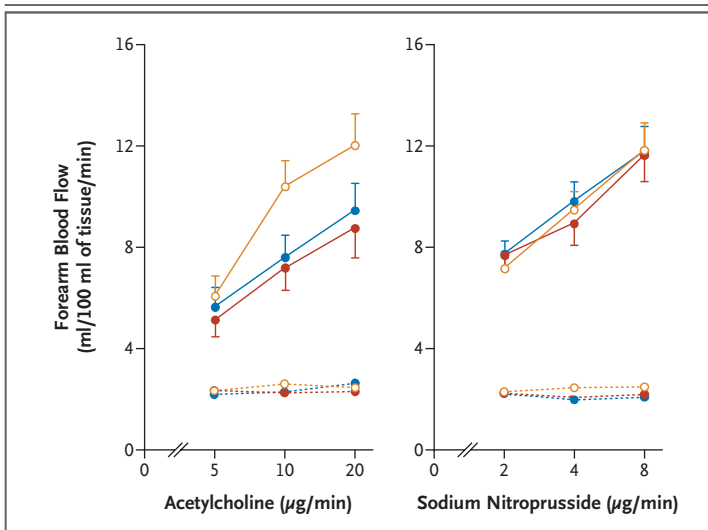


Figure 2. Forearm Blood Flow 6 to 8 Hours after Exposures to Diesel Exhaust and Filtered Air.

Values for infused (solid lines) and noninfused (dashed lines) forearm blood flow are shown for 17 subjects after exposure to diesel exhaust (red) and after exposure to filtered air (blue), as well as for a reference population of matched healthy controls (orange), during intrabrachial infusion of acetylcholine or sodium nitroprusside. $P < 0.001$ for dose response to both drugs in the infused arm. Among the 17 subjects, $P = 0.54$ for exposure to diesel exhaust versus filtered air during infusion of acetylcholine, and $P = 0.56$ during infusion of sodium nitroprusside. For the comparison of the subjects with healthy controls, $P = 0.02$ during acetylcholine infusion, and $P = 0.72$ during sodium nitroprusside infusion.

mass is attributable to combustion-derived nanoparticles from traffic, ranging from 20% at remote monitoring sites²³ to 70% in a road tunnel.²⁴ Exposure to 300 µg of particulate matter per cubic meter for 1 hour increases a person's average exposure over a 24-hour period by only 12 µg per cubic meter. Changes of this magnitude occur on a daily basis, even in the least polluted cities, and are associated with increases in the rate of death from cardiorespiratory disorders.²⁵ Our model is therefore highly relevant, in terms of both the composition and the magnitude of exposure, to the assessment of short-term health effects in men.

Given potential safety concerns, we recruited patients who had stable and symptomatically well-controlled coronary heart disease, with good exercise tolerance on formal stress testing. The study participants were closely monitored throughout the exposure and reported no adverse effects. Despite similar changes in the heart rate during exposure to diesel exhaust and to filtered air, we documented asymptomatic myocardial ischemia that was increased by a factor of up to three after

inhalation of diesel exhaust. This reproducible effect was present despite extensive use of maintenance beta-blocker therapy in patients without limiting angina. Thus, we have established that inhalation of diesel exhaust has an immediate, proischemic effect, and we believe this provides an important mechanism for the observed increase in myocardial infarction in the hour after exposure to traffic.¹³

Small areas of denudation and thrombus deposition are common findings on the surface of atheromatous plaques and are usually subclinical. Rosenberg and Aird have postulated that vascular-bed-specific defects in hemostasis exist and that propagation of coronary thrombosis is critically dependent on the local fibrinolytic balance.²⁶ The magnitude and rapidity of t-PA release from the vascular endothelium regulate the generation of plasmin and thus determine the efficacy of endogenous fibrinolysis.

We have previously reported impaired t-PA release in healthy volunteers 6 hours after inhalation of diesel exhaust, although this effect was not seen 2 hours after exposure.¹⁷ We have now confirmed similar reductions in acute t-PA release 6 hours after inhalation of diesel exhaust in patients with coronary heart disease. This delayed effect on endogenous fibrinolysis cannot explain our findings of immediate myocardial ischemia but is consistent with the observations of Peters and colleagues, who reported a second peak in the incidence of myocardial infarction 5 to 6 hours after exposure to traffic.¹³ Preclinical thrombotic models also lend support to our findings. Nemmar and colleagues reported that in a hamster model, instillation of diesel-exhaust particulate into the lungs increases venous and arterial thrombus formation at sites of vascular injury.²⁷ Taken together, these findings indicate an important thrombotic effect of diesel-exhaust inhalation that may promote coronary thrombosis.

Although we found important adverse effects of diesel exhaust on vascular fibrinolytic function, we did not detect an effect on vasomotor function. However, vasomotor function was assessed 6 hours after exposure and 5 hours after we documented an increase in the ischemic burden. We have previously demonstrated that exposure to diesel exhaust impairs vasomotor function in healthy volunteers.¹⁷ This effect was most marked at 2 hours but was still present 6 hours after exposure. Therefore, we cannot exclude the possibil-

ity of a detrimental vasomotor effect in patients at an earlier point in time.

Patients with coronary heart disease are known to have impaired endothelial function,²⁸ and we confirm the presence of endothelial dysfunction in our patients. This may have hindered our ability to demonstrate a further impairment of vascular function after exposure to diesel exhaust. In addition, we performed our assessments while the subjects were taking medications that are known to influence endothelial vasomotor function.²⁹ Furthermore, Brook and colleagues reported that air pollution does not have an effect on endothelium-dependent vasodilatation.³⁰

We have identified two distinct and potentially synergistic adverse cardiovascular effects of air pollution in patients with coronary heart disease. These effects may contribute to the increased incidence of myocardial infarction after exposure to traffic. However, the precise mechanisms by which diesel-exhaust inhalation induces these ischemic and thrombotic effects have not been established in our study and will need to be determined in future work.

Our findings are consistent with epidemiologic studies showing associations between ambient particulate air pollution and increased myocardial ischemia during formal exercise testing.^{10,11} Myocardial ischemia occurs as a consequence of reduced myocardial oxygen supply, increased demand, or both. We hypothesize that oxidative stress and microvascular dysfunction in the resistance vessels of the myocardium may, in part, explain the adverse ischemic effects of exposure to dilute diesel exhaust. In vitro studies, animal models, and studies of exposures in humans have clearly established the oxidant and proinflammatory nature of combustion-derived particulate matter.³¹ Indeed, the pattern of vascular dysfunction in our previous studies suggested that oxidative stress and reduced nitric oxide availability may play a role in mediating the adverse vascular effects of diesel-exhaust inhalation.¹⁷

Diesel exhaust is a complex mixture of gases and particles, and from our findings, we cannot rule out a nonparticulate cause of the adverse cardiovascular effects. However, on the basis of epidemiologic studies,³² particulate matter is thought to be responsible for the majority of the adverse health effects of air pollution.³³ This view is supported by the recent observations of Miller and colleagues, who found that cardiovascular out-

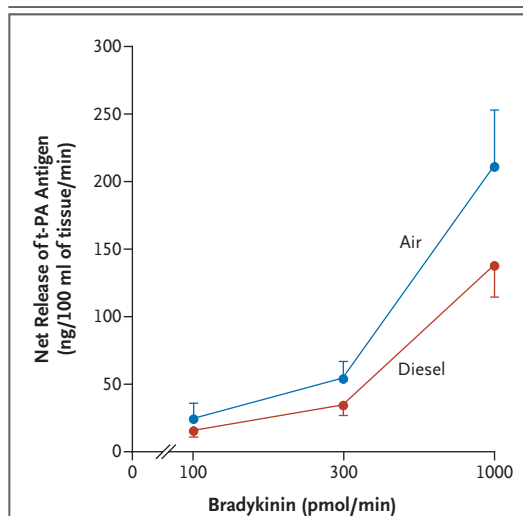


Figure 3. Release of Tissue Plasminogen Activator (t-PA) Antigen 6 to 8 Hours after Exposures to Diesel Exhaust and Filtered Air in 17 Subjects.

As compared with filtered air (blue), inhalation of diesel exhaust (red) reduced the net release of t-PA antigen (calculated as the product of forearm plasma flow and the difference in t-PA concentrations between the two arms) by 35% ($P=0.009$).

comes were strongly associated with long-term exposure to particulate matter but not with gaseous pollutants.³ Ambient nitrogen dioxide can be considered a surrogate for pollution from traffic, but it has little adverse effect in controlled-chamber studies, even at the exposure levels in our study.³⁴ We therefore suggest that the cardiovascular effects described here are mediated primarily by the particulates in diesel exhaust and not by its other components. This argues for the use of diesel-exhaust particle traps to limit the adverse health effects of traffic emissions. However, the causative role of particulates must first be definitively established, and the efficacy of particle traps confirmed.

Brief exposure to dilute diesel exhaust increases myocardial ischemia and impairs endogenous fibrinolytic capacity in men with stable coronary heart disease. Our findings suggest mechanisms for the observation that exposure to combustion-derived air pollution is associated with adverse cardiovascular events, including acute myocardial infarction. Environmental health policy interventions targeting reductions in urban air pollution should be considered in order to decrease the risk of adverse cardiovascular events.

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