

## Ambient Pollution and Blood Pressure in Cardiac Rehabilitation Patients

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**Background**—Multiple studies have demonstrated a consistent association between ambient particulate air pollution and increased risk of hospital admissions and deaths for cardiovascular causes. We investigated the associations between fine particulate pollution (PM<sub>2.5</sub>) and blood pressure during 631 repeated visits for cardiac rehabilitation in 62 Boston residents with cardiovascular disease.

**Methods and Results**—Blood pressure, cardiac risk factor, and exercise data were abstracted from records of rehabilitation visits between 1999 and 2001. We applied mixed-effect models, controlling for body mass index, age, gender, number of visits, hour of day, and weather variables. For an increase from the 10th to the 90th percentile in mean PM<sub>2.5</sub> level during the 5 days before the visit (10.5 µg/m<sup>3</sup>), there was a 2.8-mm Hg (95% CI, 0.1 to 5.5) increase in resting systolic, a 2.7-mm Hg (95% CI, 1.2 to 4.3) increase in resting diastolic, and a 2.7-mm Hg (95% CI, 1.0 to 4.5) increase in resting mean arterial blood pressure. The mean PM<sub>2.5</sub> level during the 2 preceding days (13.9 µg/m<sup>3</sup>) was associated with a 7.0-mm Hg (95% CI, 2.3 to 12.1) increase in diastolic and a 4.7-mm Hg (95% CI, 0.5 to 9.1) increase in mean arterial blood pressure during exercise in persons with resting heart rate ≥70 bpm, but it was not associated with an increase in blood pressure during exercise in persons with heart rate <70 bpm.

**Conclusions**—In patients with preexisting cardiac disease, particle pollution may contribute to increased risk of cardiac morbidity and mortality through short-term increases in systemic arterial vascular narrowing, as manifested by increased peripheral blood pressure. (*Circulation*. 2004;110:2184-2189.)

**Key Words:** air pollution ■ blood pressure ■ cardiovascular diseases ■ environmental exposure ■ epidemiology

Both elevated blood pressure (BP) and ambient particle exposure are associated with increased risk of cardiovascular morbidity and mortality.<sup>1-5</sup> However, whether particle exposure increases the risk of acute cardiovascular events in part through elevating BP is not known. Inhalation of both fine-particulate air pollution and ozone was associated with brachial artery vasoconstriction in a chamber study of healthy adults.<sup>6</sup> A repeated-measures study of 30 patients with chronic obstructive pulmonary disease<sup>7</sup> in Los Angeles, Calif, and a survey of a general population of adults in Germany<sup>8</sup> found that higher levels of particulate air pollution were associated with higher resting BP. We assessed the effects of particulate air pollution on systolic BP (SBP), diastolic BP (DBP), and mean arterial BP (MAP) in a vulnerable population of 62 outpatients with cardiac disease evaluated repeatedly at rest and during exercise in a cardiac rehabilitation program.

### Methods

#### Health Data

With Human Subjects approval, baseline and repeated-measures cardiac rehabilitation data were extracted at a Boston hospital for all

residents of greater Boston (within route 495) who started the program between May and December 1999 and completed it by January 2001. The study included 62 subjects with 631 visits. On entry, a staff member measured height and weight and administered a questionnaire/record assessment of the patient with regard to diagnoses on entry, exercise tolerance test (ETT) results, current medications, and cardiac risk factors (eg, hypertension, diabetes, smoking status, alcohol use, exercise, stress, lipid profile, and family history). For patients without ischemia, the target heart rates for aerobic conditioning were determined by the heart rate reserve method.<sup>9</sup> If the ETT was positive for ischemia, a target heart rate was set at 10 bpm below the onset of angina symptoms and/or 10 bpm below the ischemic threshold (indicated by onset of ST-segment depression ≥1-mm on ECG during ETT).<sup>9</sup> Target treadmill speeds were set to achieve 50% to 80% of the patient's VO<sub>2</sub>max estimated from ETT data and measured as units of metabolic equivalents.<sup>9</sup> For submaximal walking speeds on the treadmill, actual workload or VO<sub>2</sub> was estimated in metabolic equivalents according to the American College of Sports Medicine.<sup>9</sup>

Before exercise, a technician administered a questionnaire about the patient's present clinical status, medication compliance, and symptom status and measured resting heart rate. Readings of resting SBP and DBP were taken in the supported left arm of the seated

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subject with a mercury-column sphygmomanometer with cuff-size adjustment based on arm circumference. Readings were recorded to the nearest even number. The patient was monitored during the session on ECG telemetry with a modified lead II configuration. The program session consisted of treadmill (walking or jogging), cycle ergometry, or weight training exercise and concluded with a 5- to 10-minute rhythmic cool-down, followed by stretching and a relaxation period. Treadmill exercise consisted of a 5-minute warm-up period, 23 minutes of cardiovascular conditioning at the target heart rate and prescribed intensity, and 2 minutes of cool-down walking. Treadmill speed, incline, heart rate, and rating of perceived exertion were recorded every 5 minutes. Exercise BP was recorded toward the end of the 23 minutes of aerobic conditioning intensity, before cool-down, with the patient in standing position.

### Air Pollution and Weather

Hourly measurements of particulate air pollution (PM<sub>2.5</sub>; particulate air matter with aerodynamic diameter <2.5 μm) were obtained from an ambient monitor site operated on the rooftop of a local facility <1 km from the hospital. Because of effective hospital filtering of outdoor particles and lack of indoor sources, PM<sub>2.5</sub> levels indoors were very low or below detectable limits (results not shown).

Hourly mean temperature, dew-point temperature, and barometric pressure from the National Weather Service at Logan Airport in East Boston were extracted from climatic records (Earth-Info, Inc).

### Statistical Analysis

We examined whether pollution influences between-visit (within-person) BP, adjusting for specific fixed and varying personal, meteorological, and temporal characteristics. All models examining resting or exercise BP as outcomes included random effects for subjects; fixed effects for body mass index (BMI), sex, age, and indicator variables for hour of day; and smooth functions for temperature, dew-point temperature, and visit number to take into account any long-term trend. Visits for all modes of exercise were included in models assessing resting BP as an outcome. When analyzing maximum BP and maximum heart rate as outcomes, we included only visits in which treadmill exercise was performed and controlled for maximum workload. We used natural spline smoothing functions in which predictor variables had previously been demonstrated to have nonlinear relationships with health outcomes.<sup>10</sup> The BP outcome variables were log-transformed to normalize data. We used mixed-effect models to obtain specific estimates for measured covariates and to examine interactions between time-varying or time-invariant covariates and PM<sub>2.5</sub>.<sup>11</sup>

To evaluate the cumulative effects of exposure, we examined the averages of PM<sub>2.5</sub> 24 to 120 hours before to the rehabilitation session as predictors of BP. The moving averages were computed if 75% of the data were present. Effects were estimated for an increase in pollution exposure from the 10th to the 90th percentile in mean PM<sub>2.5</sub> level. Effects are expressed either as mean change (mm Hg) or as percent change in BP.

### Results

The age range of the 62 patients was wide (39 to 90 years); 47% were <60 years and 81% were <70 years of age (Table 1). Fifty-eight (94%) had documented coronary artery disease (myocardial infarction, CABG surgery, angina pectoris, coronary angioplasty, positive ETT, abnormal coronary angiogram). Of those without documented coronary artery disease, 1 had congestive heart failure, 1 had atrial arrhythmias and deconditioning, 1 had cerebrovascular disease (stroke) and aortic valve replacement with left bundle-branch block, and 1 had myocarditis/pericarditis with mitral regurgitation. Results of analyses did not change significantly when the subject with 33 visits was omitted. The interquartile range of number of visits per subject was between 6 and 13.

TABLE 1. Participant Characteristics (n=62)

Age, y	61 (39–90)
Gender	
Male	45 (73)
Female	17 (27)
Coronary artery disease*	58 (94)
Congestive heart failure	3 (5)
Hypertension	31 (50)
Diabetes	13 (21)
Medication use	
β-Blocker	51 (82.0)
Calcium channel blocker	12 (19.4)
ACE inhibitors	32 (52)
Cigarette smoking	
Never	18 (29)
Former	34 (55)
Current	6 (10)
Visits†	8 (3–33)
BMI, † kg/m <sup>2</sup>	26.7 (16.8–48.5)
Exercise mode‡	
Treadmill	525 (83.2)
Walking	419 (66.4)
Jogging	106 (16.8)
Bicycle	39 (6.2)
Other	65 (10.3)
Maximum work load (METS)‡	3.7 (1–9.9)

Values are median (range) or n (%). METS indicates metabolic equivalents.

\*Diagnosis of myocardial infarction, CABG surgery, angina pectoris, coronary artery angioplasty, positive ETT, or abnormal coronary angiogram at entry.

†Calculated from repeated-measures observations.

‡Based on data from 521 repeated measures with treadmill exercise only.

Outcome measures, along with relevant pollution measures, are shown in Table 2. Median resting BP was 120/70 mm Hg, with a median heart rate of 64 bpm. PM<sub>2.5</sub> was relatively low, with 10% to 90% ranges varying from 10.4 μg/m<sup>3</sup> for the 120-hour average to 19.6 μg/m<sup>3</sup> for the 1-hour average measurements.

We present the relation of PM<sub>2.5</sub> to BP expressed as percent change in Figures 1 and 2 and as mean change in Table 3. Resting BP increased with increasing PM<sub>2.5</sub>, averaged over the preceding 48 to 120 hours (5 days before testing), with the largest and most significant associations at 120 hours (Figure 1 and Table 3). For an increase from the 10th to the 90th percentile in mean PM<sub>2.5</sub> level during the 120 hours before the visit (10.4 μg/m<sup>3</sup>), we found a 2.23% (95% CI, 0.04 to 4.45) increase in resting SBP, a 4.06% (95% CI, 1.8 to 6.4) increase in resting DBP, and a 3.2% (95% CI, 1.2 to 5.2) increase in resting MAP. These percent changes are equivalent to 2.7-, 2.8-, and 2.8-mm Hg differences in SBP, DBP, and MAP, respectively (Table 3). Results for resting BP were essentially the same when fixed-effects modeling was used. Our findings are robust and not dependent on the choice of a single averaging period.

**TABLE 2. Distribution of the Health Outcomes, Air Pollution, and Weather Variables\***

	Mean	Percentile			
		10th	50th	90th	90th–10th
BP, mm Hg					
Resting SBP	121.9	100.0	120.0	148.6	...
Maximum SBP	139.8	115.0	140.0	164.9	...
Resting DBP	70.1	60.0	70.0	80.0	...
Maximum DBP	71.6	60.0	70.0	80.0	...
Resting MAP	87.3	73.3	86.7	102.7	...
Maximum MAP	94.5	80.0	94.7	108.0	...
Heart rate, bpm					
Resting	67.0	52.0	64.0	87.0	...
Maximum	96.8	75.0	95.0	122.0	...
PM <sub>2.5</sub> , μg/m <sup>3</sup>					
Same hour	10.9	2.9	8.5	22.5	19.6
24-h Average	10.2	4.2	8.8	17.6	13.4
48-h Average	10.3	5.1	9.4	19.1	13.9
72-h Average	10.7	5.5	9.4	17.6	12.1
96-h Average	10.9	5.9	9.6	16.7	10.7
120-h Average	11.0	6.4	9.5	16.8	10.4
Sulfur dioxide, ppm					
Same hour	0.007	0.002	0.006	0.014	0.012
120-h Average	0.005	0.003	0.004	0.009	0.006
Ozone, ppm					
Same hour	0.020	0.006	0.018	0.035	0.029
120-h Average	0.024	0.015	0.022	0.036	0.021
Black carbon, μg/m <sup>3</sup>					
Same hour	1.386	0.560	1.290	2.410	1.850
120-h Average	0.964	0.656	0.960	1.213	0.557
Carbon monoxide, ppm					
Same hour	0.813	0.482	0.758	1.226	0.744
120-h Average	0.664	0.488	0.651	0.863	0.376
Nitrogen dioxide, ppm					
Same hour	0.024	0.013	0.022	0.035	0.022
120-h Average	0.022	0.017	0.021	0.027	0.010
Dew-point temperature, °C	8.2	−6.1	10.6	18.9	...
Temperature, °C	14.2	2.2	15.6	24.4	...

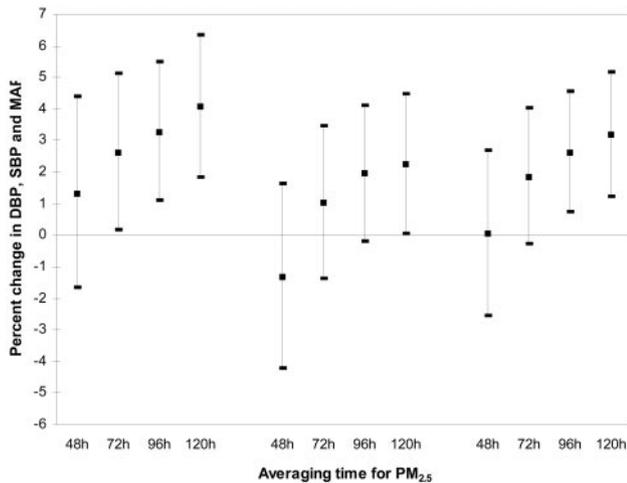
\*Summary statistics based on 631 study observations between May 1, 1999, and January 5, 2001.

In single-pollutant models adjusting for all other nonpollutant factors but excluding PM<sub>2.5</sub>, higher resting DBP was significantly associated with 120-hour averages (but not shorter averages) of sulfur dioxide (3.9% increase; 95% CI, 0.3 to 7.6), ozone (2.7% increase; 95% CI, 0.02 to 5.4), and black carbon (9.4% increase; 95% CI, 1.1 to 18.4) but not with carbon monoxide or nitrogen dioxide. However, only PM<sub>2.5</sub> remained associated with elevated DBP in multiple-pollutant models (results not shown).

In unstratified models, there was a trend toward increasing exercise DBP with increasing PM<sub>2.5</sub>, but results did not reach statistical significance. No associations were found between particle levels and either exercise SBP or MAP.

#### Effect Modification by Resting Heart Rate $\geq 70$ bpm

PM<sub>2.5</sub> did not influence exercise BP when subjects had a resting heart rate  $< 70$  bpm (Figure 2 and Table 3). However, for subjects with a resting heart rate  $\geq 70$  bpm, an increase (10th to 90th percentile) in PM<sub>2.5</sub> in the previous 48 to 120 hours was associated with increased BP during exercise, with the maximum effect at 48 hours before testing. A 13.9-μg/m<sup>3</sup> (10th to 90th percentile) increase in 48-hour PM<sub>2.5</sub> for this averaging period was associated with a 9.9% (95% CI, 2.99 to 17.2) increase (Figure 2) or a 6.95-mm Hg mean increase in exercise DBP (Table 3) ( $P=0.03$  for interaction between PM<sub>2.5</sub> and heart rate). When other medications or cardiac risk factors were included in the model, the results did not change.



**Figure 1.** Percent increase in resting BP (DBP, SBP, and MAP) for increase (10th to 90th percentile) in average PM<sub>2.5</sub> for previous 48, 72, 96, and 120 hours. Results are from mixed-effects models adjusting for BMI, age, gender, visit, hour of day, and temperature variables.

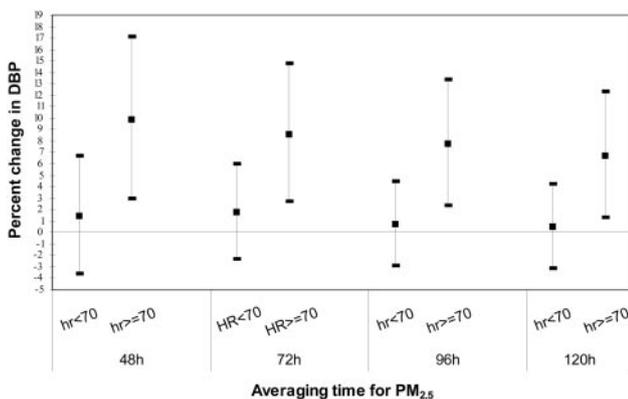
Similar but somewhat weaker effect modification was seen for exercise MAP ( $P=0.11$ ) but not for exercise SBP ( $P=0.8$ ). A 13.9- $\mu\text{g}/\text{m}^3$  increase in 48-hour mean PM<sub>2.5</sub> was associated with a 4.6% (95% CI, 0.1 to 9.4) increase or a 4.3-mm Hg increase in exercise MAP in those with a resting heart rate  $\geq 70$  bpm (Table 3). Resting heart rate did not modify the relation of pollution to resting BP.

### Main Effects of Subjects' Characteristics

Higher BMI was associated with higher resting and exercise DBP, SBP, and MAP. For an interquartile BMI difference of 8.4 kg/m<sup>2</sup>, we estimated a 8.2-mm Hg (95% CI, 2.9 to 13.6) increase in resting SBP and a 13-mm Hg (95% CI, 6.9 to 19.1) increase in exercise SBP for multivariate models including 48-hour PM<sub>2.5</sub> and covariates listed in Methods. Older age was significantly associated with elevated SPB but not DBP or MAP.

### Discussion

We found that in patients with cardiovascular disease, particulate pollution may lead to increased resting BP and, in



**Figure 2.** Percent increase in exercise DBP for increase (10th to 90th percentile) in average PM<sub>2.5</sub> for previous 48, 72, 96, and 120 hours. Results are from mixed-effects models adjusting for BMI, age, gender, visit, hour of day, and temperature variables.

patients with elevated heart rate, to increased BP during exercise. BP control is an important factor in reducing cardiac morbidity and mortality in the post-coronary event period.<sup>1,12</sup> Our finding of a 2.2-mm Hg increase in resting SBP per 10.4  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> is comparable in magnitude to the SBP effects in the general population survey of 2607 individuals 25 to 64 years of age in an Augsburg, Germany, study<sup>8</sup> and to the finding of a Los Angeles, Calif, study of subjects with severe chronic obstructive pulmonary disease observed daily for 4 days.<sup>7</sup> Comparisons can be only approximate, however, because neither of those studies had data on effects of respirable particles (PM<sub>2.5</sub>) and neither investigated pollution effects on BP in patients with preexisting cardiac disease undergoing an exercise program. Our study also found consistent effects on DBP and SBP. Further evidence that particle pollution can influence macrovascular diameter and tone is found in a recently reported randomized, double-blind, crossover chamber study<sup>6</sup> demonstrating that short-term inhalation of both fine-particulate air pollution and ozone was associated with brachial artery narrowing.

The modest increases in pollution-associated BP could reflect a systemic, including coronary artery, increase in tone, with its adverse implications for the potential for plaque rupture or cardiac ischemia.<sup>15,16</sup> Potential mechanisms for the particle effects on increased vascular tone include an increase in systemic inflammation and consequent vascular endothelial perturbation by direct mechanisms or via oxidative stress pathways.<sup>17</sup> Human and animal studies<sup>18</sup> support the role of particles in increasing systemic inflammation, with pollution-related increases in plasma viscosity,<sup>19</sup> C-reactive protein,<sup>20</sup> plasma fibrinogen,<sup>21</sup> and white blood cell counts.<sup>21,22</sup>

The longer cumulative particle effects, occurring over 48 to 120 hours, suggest that the mechanism of action of pollution on BP may involve systemic inflammation and subsequent endothelial dysfunction rather than more immediate effects of autonomic dysfunction.

In cardiac patients, resting heart rate  $\geq 70$  bpm often suggests greater sympathetic tone, which may increase cardiac work. We hypothesized that those with resting heart rate  $< 70$  bpm and thus with less sympathetic/more vagal stimuli would have less effect of pollution on BP during exercise. Resting heart rate of  $< 70$  bpm can result from effective  $\beta$ -blocker use to reduce excessive sympathomimetic influences and cardiac workload, cardiac fitness (a larger cardiac output for a given heart rate), or in some instances, conduction abnormalities. When patients were on  $\beta$ -blockers, 22% had a resting heart rate  $\geq 70$  bpm without evidence of being effectively  $\beta$ -blocked. Being on  $\beta$ -blockers did not protect against the effect of pollution on BP when resting heart rate was  $\geq 70$  bpm (results not shown). Heart rate  $< 70$  bpm may have been a primary source of protection against exercise-related pollution effects or may have been a characteristic of individuals who were less susceptible to pollution because they had cardiac disease that was milder or controlled better.

Our study has several limitations related to study design and interpretation of study results. Although lower BP generally confers lower cardiovascular risk, among patients with preexisting cardiovascular disease, very low BP may represent a low-flow state with poor cardiac output. In one study,

**TABLE 3. Mean (95% CI) Change\* in DBP, SBP, and MAP in Association With 48-, 96-, and 120-Hour Averages of PM<sub>2.5</sub>**

	Mean (95% CI) PM <sub>2.5</sub>			n
	48-h Average	96-h Average	120-h Average	
Resting BP, mm Hg†				
DBP	0.92 (−1.15–3.05)	2.27 (0.76–3.80)	2.82 (1.26–4.41)	583
SBP	−1.60 (−5.06–1.97)	2.36 (−0.21–4.97)	2.68 (0.04–5.38)	583
MAP	0.04 (−2.19–2.33)	2.27 (0.64–3.93)	2.76 (1.07–4.48)	583
Maximum BP, mm Hg‡				
DBP				459
HR <70 bpm	1.01 (−2.54–4.75)	0.51 (−2.04–3.14)	0.33 (−2.24–3.00)	
HR ≥70 bpm	6.95 (2.11–12.11)	5.46 (1.69–9.43)	4.72 (0.92–8.72)	
SBP				459
HR <70 bpm	−0.15 (−5.06–4.94)	0.78 (−2.70–4.35)	1.13 (−2.53–4.89)	
HR ≥70 bpm	0.74 (−5.54–7.33)	1.59 (−3.37–6.74)	0.91 (−4.25–6.28)	
MAP				459
HR <70 bpm	0.41 (−2.84–3.78)	0.66 (−1.68–3.05)	0.47 (−1.88–2.89)	
HR ≥70 bpm	4.32 (0.04–8.79)	3.56 (0.20–7.04)	3.10 (−0.30–6.62)	

HR indicates heart rate.

\*Mean change computed as  $\exp[\beta \times (10\% - 90\% \text{ PM}_{2.5}) - 1] \times \text{geometric mean of outcome}$ .

†Mixed-effects models controlling for BMI, age, gender, smooth functions of hour of day, temperature, dew-point temperature, and visit number.

‡Mixed-effects models controlling for BMI, age, gender, smooth functions of hour of day, temperature, dew-point temperature, maximum workload, visit number, indicator for resting heart rate < or ≥70 bpm, and an interaction term between resting heart rate and PM<sub>2.5</sub>.

very low DBP was associated with a higher risk of a subsequent cardiac event but also with a lower risk of stroke.<sup>23</sup> Lowering BP may increase risk if it results in reflex sympathomimetic stimulation and tachycardia or orthostatic hypotension in the elderly.<sup>12</sup> The clinical benefit of BP reduction in post-myocardial infarction patients varies by medication and is a function of the other cardiophysiological effects of those medications.<sup>12,24</sup>

We had significantly more power (n=631) to evaluate the effects of time-varying environmental factors on within-person changes in BP than to evaluate effects of time-invariant covariates (n=62) on between-person BP. Although we had excellent measures of certain cardiac risk factors (BMI, age, sex), we had incomplete information on other factors (eg, lipids). However, it is unlikely that there is influential residual confounding related to fixed patient characteristics. Our primary analyses used random-effects models, enabling us to define primary effects and interactions with air pollution of well-measured subject characteristics, the individual effects of which could not be evaluated in a fixed-effects model. Fixed-effects models have the advantage of adjusting for both measured and unmeasured time-invariant characteristics of the individual but the disadvantage of not providing estimates for specific measured time-invariant subject characteristics.<sup>25</sup> To evaluate the sensitivity of our air pollution results to the choice of model, for resting BP, we repeated analyses using fixed-effects models and obtained results very similar in size and precision to those from the random-effects models (results not shown). Although we had stationary measures of ambient air pollution, we were limited by the absence of personal exposure measurements.

Although this limitation may affect the variability of our observed risk estimates, recent studies show that the consequence of using ambient particle measures to estimate exposure is likely to be a modest underestimation of pollution effects.<sup>26</sup> Furthermore, results from several exposure studies have consistently shown that ambient concentrations are good surrogates of personal exposures to PM<sub>2.5</sub>, particularly for eastern US cities such as metropolitan Boston and for particles of ambient origin.<sup>27</sup>

This Boston study suggests that changes in PM<sub>2.5</sub> lead to within-person increases in resting and exercise BP among vulnerable patients with cardiovascular disease. The particle-related changes in peripheral BP may be manifestations of more widespread short-term systemic changes in vascular tone/diameter and may partially explain the association of pollution with increased risk of acute cardiac events in patients with preexisting cardiac disease.

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