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Exposure to Ambient Fine Particulate Matter and Primary Cardiac Arrest among Persons With and Without Clinically Recognized Heart Disease

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The authors studied the association between incidence of primary cardiac arrest and daily measures of fine particulate matter (≤2.5 μm) using a case-crossover study of 1,206 Washington State out-of-hospital cardiac arrests (1985–1994) among persons with (n = 774) and without (n = 432) clinically recognized heart disease. The authors compared particulate matter levels on the day of the cardiac event and the 2 days preceding the event with levels from matched reference days. The estimated relative risk for a 13.8-μg/m^3 increase in fine particulate matter (nephelometry: 0.54×10^{-1} km^{-1} bsp) on the day prior to cardiac arrest was 0.94 (95% confidence interval: 0.88, 1.02). Pollutant levels measured on the same day as the event and on the 2 days preceding the event demonstrated similar results. No increased risk was found among all cases with preexisting cardiac disease (odds ratio = 0.97, 95% confidence interval: 0.89, 1.07); however, an unexpected association appeared between current smokers with preexisting heart disease and increased particulate matter levels 2 days prior to the event (odds ratio = 1.29, 95% confidence interval: 1.06, 1.55). This association was not present in the 0- or 1-day lag analyses or in persons with other diseases. There was no consistent association between increased levels of fine particulate matter and risk of primary cardiac arrest.

air pollutants; air pollution; heart arrest; heart diseases; environmental exposure

Abbreviations: CI, confidence interval; $PM_{1.0}$, particulate matter ≤1.0 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤10 μm in aerodynamic diameter.

Primary cardiac arrest represents a significant public health problem in developed countries, accounting for an estimated 250,000–300,000 events annually (1–5). In addition, an improvement in mortality from acute myocardial infarction in conjunction with an aging population has resulted in an epidemiologic cohort at increased risk for primary cardiac arrest (5). Although major advances have occurred in our understanding of the more proximate cellular and molecular influences that contribute to the overall incidence of primary cardiac arrest (6–12), gaps remain in our understanding of the triggering factors responsible for primary cardiac arrest in both apparently healthy persons and those with established cardiac diseases.

Large epidemiologic studies have suggested that increased levels of air pollutants such as fine particulate matter (particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$)) and nitrogen dioxide are associated with an increased incidence of myocardial infarction (13–15), uncompensated congestive heart failure (15, 16), cardiac arrhythmias (17), and total cardiac mortality in susceptible populations (15, 17–20).

One study that was limited to persons without previously identified heart disease did not find an association between primary cardiac arrest and particulate matter levels (21). To further evaluate the potential for particulate matter to trigger primary cardiac arrest, we studied primary cardiac arrest occurring in a different population that included persons with clinically documented heart disease. We hypothesized that an increase in fine particulate matter on the same day as or 1 day preceding an event would be associated with an elevated risk of primary cardiac arrest among persons with

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preexisting cardiac disease. Moreover, we postulated that persons with recently documented uncompensated congestive heart failure or increasing numbers of angina episodes would be at greater risk.

MATERIALS AND METHODS

Overview

We linked population-based surveillance data on out-of-hospital primary cardiac arrest occurring between 1985 and 1994 (n = 1,542) among members of a large health maintenance organization in western Washington State (the Group Health Cooperative of Puget Sound) with central-site air pollution monitoring data on particulate matter ≤1.0 μm in aerodynamic diameter ($PM_{1.0}$), particulate matter ≤10 μm in aerodynamic diameter (PM_{10}), carbon monoxide, and sulfur dioxide. These data were further enhanced by data on two meteorologic variables: daily averages of relative humidity and temperature at Seattle-Tacoma International Airport (obtained from the National Oceanic and Atmospheric Administration). To control for bias, we employed a case-crossover design that compared each event date with a set of referent exposure dates falling on the same day of the week during the same month as the case event (21–24). The study protocol was approved by the institutional review boards of the Group Health Cooperative and the University of Washington.

Study population

The study population was derived from members of the Group Health Cooperative of Puget Sound, a health maintenance organization that serves approximately 350,000 enrollees in western Washington State, who experienced an episode of out-of-hospital primary cardiac arrest in western Washington between 1985 and 1994. We defined primary cardiac arrest as a sudden pulseless condition in the absence of a noncardiac condition as the cause of cardiac arrest. We reviewed ambulatory care medical records for each potential case to exclude cases with a noncardiac cause of cardiac arrest. Furthermore, we reviewed medical examiner reports, autopsy reports, and emergency medical service incident reports, when available, for all cases with a history of depression, psychosis, and seizure to confirm the absence of evidence of suicide, drug overdose, or status epilepticus as a cause of out-of-hospital arrest. Cases were identified from two sources: emergency medical service databases from Seattle and King County (Washington) and, for those not covered by the paramedic system, the Group Health Cooperative death record.

Our final analysis included 1,206 case days and 4,094 referent exposure days among these case individuals. Case patients were excluded if they lived outside of King County or South Snohomish County, because we did not think that the air pollution data represented exposures for persons residing outside of this geographic area. The personal-level clinical data were abstracted from the ambulatory care medical records; therefore, cases were included in the analysis only if they had received care at the Group Health Cooperative within 12 months of the primary cardiac arrest event.

Medical record review

We determined clinical characteristics from the ambulatory care medical review. Information obtained regarding each patient's medical history included the following: physician diagnosis of myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, congestive heart failure, cardiomyopathy, arrhythmias, valvular heart disease, stroke, hypertension, peripheral vascular disease, diabetes mellitus, hypercholesterolemia, chronic obstructive pulmonary disease, and asthma. The record review also provided information on the severity of prior cardiac and lung disease. Information gathered on demographic and risk factors included age, race, gender, blood pressure, heart rate, cigarette smoking, and alcohol use. Smoking was categorized as current smoking, ever smoking, or never smoking. It was further quantified in number of pack-years, and daily consumption was quantified as number of cigarettes smoked per day. The pharmacy record detailed use of cardiac medication, including beta blockers, calcium channel blockers, diuretics, and angiotensin-converting enzyme inhibitors. We also obtained a copy of the results of the most recent 12-lead electrocardiogram taken prior to the index date.

Exposure assessment

The primary exposure metric was 24-hour average particulate matter, as measured by nephelometry from three King County monitoring sites (Lake Forest Park, Duwamish, and Kent). We performed analyses of the association between particulate matter and primary cardiac arrest using 0-day through 2-day lags. Prior studies of the induction of myocardial infarction and cardiac arrhythmia by air pollutants have found associations at lags ranging from 1 hour to 48 hours (17, 18, 20). To allow for comparability with other studies, we converted the nephelometric measure of particulate matter to an equivalent $PM_{2.5}$ measure (25). In King County, nephelometry data correlate well with gravimetric particle measurements in the 0.1–1.4 $\mu g/m^3$ aerodynamic range. They are also highly correlated with $PM_{2.5}$ levels (Pearson's r^2 = 0.85) (26). To adjust for the effects of copollutants, we included 24-hour average measures of sulfur dioxide from the Duwamish site and 24-hour averaged measures of carbon monoxide averaged over four sites in King County. The number of PM_{10} observations was too small for use in multivariate analyses.

Statistical methods

The data were analyzed using the statistical packages SAS (version 8.0; SAS Institute, Inc., Cary, North Carolina) and SPSS (version 10; SPSS, Inc., Chicago, Illinois). We performed simple descriptive analyses including summary statistics and graphic plots of the exposure and demographic data. Levels of correlation between covariates were assessed using Pearson's correlation coefficient and simple linear regression of covariates.

Case-crossover index and referent days were selected on the basis of previous methodological work (23). Air pollu-

tion exposures occurring on index days were compared with exposures that occurred on all referent days in the same time stratum as the index date. There were 840 time strata in our study. These were defined as all observations made on a single day of the week during one month and year. This time-stratified referent selection scheme minimizes bias due to nonstationarity of air pollution time-series data (22–24).

We then performed conditional logistic regression analysis to obtain estimates of odds ratios and 95 percent confidence intervals. The primary outcome was incident primary cardiac arrest, and the primary exposure variable was exposure to fine particulate matter, defined as the interquartile increase in 24-hour average light scattering as measured by nephelometry. In secondary analyses, we evaluated day-of-event and 2-day lags, as well as other pollutant variables (PM_{10}, carbon monoxide, sulfur dioxide). Lagged analyses used time strata defined by the lagged index date. Relative humidity and temperature were included as confounding variables and were entered as both linear and quadratic terms in the conditional logistic regression models. We performed stratified analyses to assess effect modification of the association between primary cardiac arrest and particulate matter. We considered age, gender, race, smoking status, preexisting disease (chronic obstructive pulmonary disease or heart disease), alcohol use, and activity level. To assess potentiation of effect by known risk modifiers for primary cardiac arrest, we performed further subanalyses among persons with preexisting heart disease, assessing the effects of smoking and medication use. Smoking status was categorized as current smoking versus not smoking at the last clinic visit prior to the event (never smoker or ex-smoker). To determine whether severity or type of heart disease influenced the association between primary cardiac arrest and particulate matter level, we used separate models to consider all forms of heart disease as a single variable or covariates of subtypes of heart disease (ischemic heart disease, congestive heart failure, supraventricular tachycardia, bradycardia). Supraventricular tachycardia is represented by cases with atrial fibrillation (n = 45), paroxysmal supraventricular tachycardia (n = 14), or paroxysmal atrial tachycardia (n = 9) but without established coronary artery disease, cardiomyopathy, or congestive heart failure. Moreover, to better define susceptible subpopulations, we performed analyses that stratified the data by severity of ischemic heart disease (unstable angina at the last clinic visit prior to primary cardiac arrest) and severity of congestive heart failure.

RESULTS

Over the 10 years of the study, the annual incidence of primary cardiac arrest was 121 events per year (range, 99–144 events/year). The case population predominantly comprised older (median age, 69 years) White males (table 1). Furthermore, 69 percent of the persons who experienced myocardial infarction had preexisting cardiac disease, and 27.5 percent were current smokers at the time of primary cardiac arrest.

Summary of exposure results

Table 2 summarizes the distribution of daily mean values for air pollution and temperature variables in our study. The

TABLE 1. Demographic and clinical characteristics of patients with primary cardiac arrest in a Washington State health maintenance organization, 1985–1994*

Variable	No. of participants	%
Sex		
Male	859	71.2
Female	347	28.8
Race		
Black	80	6.6
White	1,039	86.2
Asian	18	1.5
Hispanic	2	0.2
Native American	4	0.3
Missing data	54	4.5
Other	9	0.7
Smoking status		
No smoking within 1 year of primary cardiac arrest	819	67.9
Current smoking	332	27.5
Missing data	55	4.6
Hypertension		
No	652	54.1
Yes	554	45.9
Diabetes mellitus		
No	970	80.4
Yes	235	19.5
Family history of myocardial infarction or primary cardiac arrest		
No	487	40.4
Yes	477	39.6
Missing data	242	20.0
Heart disease†		
No	432	35.8
Yes	774	64.2
Coronary artery disease‡		
No	906	75.1
Yes	300	24.9
Ischemic heart disease at last clinic visit		
No	1,072	88.9
Yes	133	11.0
Congestive heart failure		
No	833	69.1
Yes	373	30.9
Severe congestive heart failure§ (NYHA¶ class II–IV)		
No	1,107	91.8
Yes	81	6.7
Missing data	18	1.5

* The median age of the subjects was 69 years (range, 19–79).

† The heart disease category comprised persons with ischemic heart disease, congestive heart failure, arrhythmic heart disease, and valvular heart disease.

‡ Categories of heart disease were not mutually exclusive; therefore, cases may be represented in more than one category.

§ Determined at the most recent clinic visit prior to out-of-hospital primary cardiac arrest.

¶ NYHA, New York Heart Association.

TABLE 2. Descriptive data on air pollutant and temperature variables for the day of a primary cardiac event, 1 day prior to the event, and 2 days prior to the event, Washington State, 1985–1994

Variable	Lag time (days)	Minimum	Percentile cutpoint				Maximum	Mean	IQR*
			25%	50%	75%	90%			
Nephelometry ($\times 10^{-1}$ km^{-1} bsp)	0	0.05	0.31	0.48	0.85	1.50	5.99	0.71	0.54
	1	0.05	0.32	0.49	0.86	1.46	5.99	0.70	0.54
	2	0.05	0.31	0.48	0.87	1.46	5.99	0.70	0.56
PM_{10}*,† (μg/m^3)	0	7.38	17.97	24.83	35.13	45.60	89.83	28.05	17.16
	1	7.38	18.25	24.93	34.76	46.15	89.83	27.97	16.51
	2	7.38	18.13	24.78	35.39	47.25	89.83	28.40	17.26
Sulfur dioxide (ppm*)	0	0.00	0.0049	0.0076	0.010	0.014	0.03	0.0080	0.0055
	1	0.00	0.0048	0.0075	0.010	0.014	0.05	0.0080	0.0055
	2	0.00	0.0050	0.0070	0.010	0.014	0.05	0.0080	0.0050
Carbon monoxide (ppm)	0	0.52	1.30	1.71	2.28	3.01	7.56	1.90	0.98
	1	0.52	1.30	1.75	2.32	3.01	7.21	1.92	1.02
	2	0.52	1.32	1.77	2.33	3.01	7.56	1.93	1.02
Temperature‡ (°F)	1	15	45	52	61	66	81	52.40	16
Relative humidity‡ (%)	1	21.50	59	69.25	78.13	85.5	100	68.26	19.13

* IQR, interquartile range; PM_{10}, particulate matter ≤10 μm in aerodynamic diameter; ppm, parts per million.

† The total number of observations for PM_{10} was significantly lower than that for other pollutant measures because of the lack of routine monitoring of this pollutant prior to 1990.

‡ The 0-day lag and 2-day lag measures for temperature and relative humidity closely approximated 1-day lag measures; therefore, those results are not shown.

pollutant levels did not vary significantly between lag days. Analyses of correlation between pollutants revealed that the light-scattering measure of particulate matter was highly correlated with both carbon monoxide (Pearson's $r = 0.82$) and gravimetric PM_{10} (Pearson's $r = 0.76$). The mean level of fine particulate matter, for the days studied, did not vary significantly over the duration of study (data not shown). The calculated equivalent measure for the interquartile range increase in $PM_{2.5}$ was 13.8 μg/m^3 (3).

Associations between particulate matter and copollutants and risk of primary cardiac arrest

In univariate analyses of air pollutant effects on risk of primary cardiac arrest, interquartile increases in the individual pollutants (particulate matter, carbon monoxide, sulfur dioxide) were not associated with primary cardiac arrest after adjustment for relative humidity and temperature (table 3). Stratification of cases by race, gender, age (>55 years vs. ≤55 years), smoking status, alcohol use, and activity level did not modify the association between fine particulate matter and primary cardiac arrest (table 4).

The results of analyses stratified by disease category are shown in table 5. These analyses did not find an association between an increase in particulate matter on the day of the event or during the preceding 2 days and primary cardiac arrest among persons with preexisting heart disease or pulmonary disease. Persons with recent ischemic heart disease or severe congestive heart failure did not have greater risk of a primary cardiac arrest event with elevated

TABLE 3. Risk of primary cardiac arrest for an interquartile-range increase in air pollutant levels measured on the day of the event, 1 day prior to the event, and 2 days prior to the event, Washington State, 1985–1994*

Variable	Increment (IQR†)	Day of event		1 day prior to event		2 days prior to event	
		OR†	95% CI†	OR	95% CI	OR	95% CI
Nephelometry‡	0.541×10^{-1} km^{-1} bsp	0.94	0.88, 1.01	0.94	0.88, 1.02	1.00	0.93, 1.08
PM_{10}†	16.51 μg/m^3	1.05	0.87, 1.27	0.91	0.75, 1.11	1.03	0.82, 1.28
Sulfur dioxide	0.0055 ppm†	0.95	0.86, 1.04	1.01	0.92, 1.10	0.93	0.86, 1.01
Carbon monoxide	1.02 ppm	0.95	0.85, 1.05	0.97	0.87, 1.08	0.99	0.89,1.11

* Analyses of the association between primary cardiac arrest and the pollutant included adjustment for relative humidity and temperature.

† IQR, interquartile range; OR, odds ratio; CI, confidence interval; PM_{10}, particulate matter ≤10 μm in aerodynamic diameter; ppm, parts per million.

‡ The interquartile-range increase in the nephelometry measure was equivalent to a 13.8-μg/m^3 increase in particulate matter ≤2.5 μm in aerodynamic diameter.

TABLE 4. Odds ratios for primary cardiac arrest related to a 13.8-μg/m³ increase in fine particulate matter (particulate matter ≤2.5 μm in aerodynamic diameter), by subject characteristics, Washington State, 1985–1994

Variable	No. of events	Day of event		1 day prior to event		2 days prior to event	
		OR*	95% CI*	OR	95% CI	OR	95% CI
Age (years)							
≤55	142	0.95	0.76, 1.18	0.89	0.71, 1.12	0.95	0.75, 1.20
>55	1,063	0.94	0.88, 1.02	0.95	0.88, 1.03	1.01	0.93, 1.10
Sex							
Male	859	0.95	0.87, 1.03	0.96	0.88, 1.04	1.01	0.93, 1.10
Female	347	0.93	0.82, 1.06	0.92	0.80, 1.07	0.98	0.83, 1.15
Race							
White	1,039	0.93	0.86, 1.01	0.95	0.88, 1.03	1.03	0.95, 1.12
Non-White	104	1.09	0.88, 1.36	0.96	0.75, 1.22	0.88	0.68, 1.14
Smoking status							
Current smoker	332	1.05	0.92, 1.19	0.98	0.86, 1.12	1.06	0.92, 1.22
Nonsmoker	819	0.93	0.85, 1.01	0.93	0.85, 1.02	0.97	0.89, 1.07
Alcohol drinking†							
Drinker	142	1.13	0.92, 1.39	1.15	0.94, 1.41	1.16	0.92, 1.45
Nondrinker	864	0.94	0.86, 1.03	0.93	0.85, 1.02	1.00	0.92, 1.10
Activity level							
Unrestricted	1,104	0.96	0.89, 1.03	0.96	0.89, 1.04	1.01	0.93, 1.10
Limited	49	0.82	0.56, 1.20	0.70	0.45, 1.09	0.97	0.65, 1.43

* OR, odds ratio; CI, confidence interval.

† A drinker was defined as someone who consumed more than two alcoholic drinks per day. A nondrinker was defined as someone who consumed 0–2 drinks per day.

TABLE 5. Odds ratios for primary cardiac arrest related to a 13.8-μg/m³ increase in fine particulate matter (particulate matter ≤2.5 μm in aerodynamic diameter), by disease state and day of exposure measure, Washington State, 1985–1994

Disease state*	Day of event		1 day prior to event		2 days prior to event	
	OR†	95% CI†	OR	95% CI	OR	95% CI
All cases (*n* = 1,206)	0.94	0.88, 1.01	0.94	0.88, 1.02	1.00	0.93, 1.08
Heart disease‡ (*n* = 774)	0.95	0.87, 1.04	0.97	0.89, 1.07	1.06	0.96, 1.16
Ischemic heart disease (*n* = 300)	0.91	0.80, 1.04	0.97	0.84, 1.11	1.09	0.95, 1.26
Active angina (*n* = 133)	0.98	0.81, 1.20	1.07	0.88, 1.31	1.08	0.89, 1.32
Congestive heart failure (*n* = 373)	0.91	0.80, 1.03	0.99	0.87, 1.13	1.11	0.97, 1.26
Supraventricular tachycardia§ (*n* = 68)	1.41	0.97, 2.04	1.55	1.07, 2.25	1.23	0.84, 1.82
Bradycardia¶ (*n* = 44)	0.97	0.64, 1.46	1.29	0.85, 1.96	1.30	0.84, 2.01
Respiratory disease						
Asthma (*n* = 110)	1.01	0.80, 1.27	0.92	0.71, 1.19	0.93	0.71, 1.22
COPD† (*n* = 248)	1.00	0.86, 1.17	1.04	0.88, 1.23	1.08	0.92, 1.28

* Disease state as determined at the most recent clinic visit prior to the out-of-hospital primary cardiac arrest.

† OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

‡ Categories of heart disease were not mutually exclusive; therefore, cases may be represented in more than one category. Because of small numbers, persons without coronary artery disease, cardiomyopathy, or congestive heart failure with antecedent ventricular arrhythmia (*n* = 4) or valvular heart disease (*n* = 17) are not presented separately in this table.

§ Supraventricular tachycardia represents paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, or paroxysmal atrial tachycardia without antecedent history of coronary artery disease or congestive heart failure.

¶ Bradycardia was defined as a heart rate of less than 50 beats per minute without prior diagnosis of myocardial infarction, ischemic heart disease, or congestive heart failure. Bradycardia was noted either in the medical record or on an electrocardiogram prior to the primary cardiac arrest event. Only eight persons with this diagnosis had pacemakers at the time of the event.

TABLE 6. Odds ratios for primary cardiac arrest related to a 13.8-μg/m³ increase in fine particulate matter (particulate matter ≤2.5 μm in aerodynamic diameter) among persons with prior recognized heart disease, by smoking status, Washington State, 1985–1994

Disease state and smoking status*	Day of event		1 day prior to event		2 days prior to event	
	OR†	95% CI†	OR	95% CI	OR	95% CI
All heart disease						
Current smoker (*n* = 177)‡	1.08	0.92, 1.26	1.06	0.89, 1.26	1.29	1.06, 1.55
Nonsmoker (*n* = 576)	0.91	0.82, 1.02	0.94	0.84, 1.05	0.99	0.88, 1.11
Type of heart disease						
Ischemic heart disease						
Current smoker (*n* = 67)	1.06	0.84, 1.34	0.99	0.75, 1.30	1.39	1.04, 1.86
Nonsmoker (*n* = 223)	0.86	0.73, 1.02	0.93	0.78, 1.11	0.99	0.83, 1.18
Active angina						
Current smoker (*n* = 31)	1.28	0.88, 1.86	1.26	0.79, 2.01	1.57	0.99, 2.48
Nonsmoker (*n* = 96)	0.87	0.68, 1.12	0.93	0.72, 1.21	0.91	0.70, 1.17
Congestive heart failure						
Current smoker (*n* = 72)	1.00	0.79, 1.28	1.03	0.78, 1.35	1.46	1.10, 1.96
Nonsmoker (*n* = 290)	0.88	0.76, 1.03	0.96	0.82, 1.12	0.99	0.84, 1.17
Supraventricular tachycardia						
Current smoker (*n* = 15)	12.80	1.05, 156.57	2.56	0.82, 7.99	1.15	0.46, 2.86
Nonsmoker (*n* = 52)	1.19	0.74, 1.90	1.35	0.87, 2.10	1.15	0.73, 1.82
Bradycardia						
Current smoker (*n* = 8)	0.84	0.14, 4.95	0.42	0.03, 5.34	0.51	0.05, 5.79
Nonsmoker (*n* = 36)	0.99	0.63, 1.55	1.42	0.90, 2.24	1.39	0.88, 2.20

* The nonsmoker category included former smokers and never smokers.
† OR, odds ratio; CI, confidence interval.
‡ *n* = number of cases.

exposure to particulate matter. Moreover, none of the following factors influenced the association between particulate matter and primary cardiac arrest among all persons with heart disease: preexisting hypertension, diabetes, hypercholesterolemia, current medication use (beta blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, beta agonists), baseline heart rate greater than 90 beats/minute (vs. <90 beats/minute) at the last clinic visit, controlled blood pressure versus uncontrolled blood pressure (systolic blood pressure >160 mmHg vs. <160 mmHg) at the last clinic visit, and family history of cardiac disease (data not shown).

Our data demonstrated a slight increase in risk of primary cardiac arrest from an increase in exposure to fine particulate matter 1 day before the event for persons with a history of supraventricular tachycardia (odds ratio = 1.55, 95 percent confidence interval (CI): 1.07, 2.25) (table 5). This estimated odds ratio was higher in the subset of cases with preexisting supraventricular tachycardia who were current smokers at the time of the event for the exposures measured on the same day and 1 day prior to the event, but not for the particulate matter exposures measured 2 days prior to primary cardiac arrest (table 6).

Stratification of persons with preexisting heart disease by smoking status did not alter the null association between primary cardiac arrest and particulate matter on the day of the event or the preceding day. However, similar analyses with particulate matter measured 2 days prior to the event suggested consistent associations between an increase in particulate matter and primary cardiac arrest among current smokers with heart disease (odds ratio = 1.29, 95 percent CI: 1.06, 1.55). Further stratification by type of heart disease found that both active smokers with ischemic heart disease (odds ratio = 1.39, 95 percent CI: 1.04, 1.86) and active smokers with congestive heart failure (odds ratio = 1.46, 95 percent CI: 1.10, 1.96) were at increased risk of primary cardiac arrest from elevated particulate matter levels 2 days prior to the event (table 6).

Medication use did not change the absence of association between lagged 0- to 2-day fine particulate matter levels and primary cardiac arrest among all cases with heart disease (data not shown). However, smokers with heart disease who were not using any cardiac medication had an increased risk of primary cardiac arrest from an increase in fine particulate matter 2 days prior to the event as compared with those using these medications. Persons not using an angiotensin-converting enzyme inhibitor (*n* = 136) had an odds ratio of 1.39 (95 percent CI: 1.12, 1.72), as compared with an odds ratio of 0.97 (95 percent CI: 0.60, 1.54) among those using angiotensin-converting enzyme inhibitors (*n* = 26). Those not on calcium channel blockers (*n* = 136) had an odds ratio of 1.31 (95 percent CI: 1.07, 1.61), as compared with an odds

ratio of 1.17 (95 percent CI: 0.65, 2.09) among those taking calcium channel blockers ($n = 26$). Persons who were not on diuretics ($n = 70$) had an odds ratio of 1.46 (95 percent CI: 1.05, 2.03), as compared with an odds ratio of 1.19 (95 percent CI: 0.94, 1.51) among those taking diuretics ($n = 92$). In contrast, this same pattern of association was not found for use of beta blockers and beta agonists.

We repeated the detailed single-pollutant analyses with carbon monoxide as the exposure. In these models, in which data were stratified by disease status and primary cardiac arrest risk factors, we did not find an association between increased carbon monoxide levels and primary cardiac arrest (data not shown).

DISCUSSION

Despite consistent epidemiologic evidence that elevated levels of particulate matter are associated with an increased risk of cardiac morbidity and mortality in susceptible populations, this study did not demonstrate a consistent association between an increase in exposure to fine particulate matter and primary cardiac arrest among persons with and without prior cardiac disease.

Our study was designed to discern an association between primary cardiac arrest and increased particulate matter levels in a new case series that included persons with and without preexisting cardiac and lung disease. A previous study by Levy et al. (21) had not found such an effect among cases without prior clinically recognized heart or lung disease. Our analysis found the suggestion of an effect among persons with prior heart disease and not lung disease, but the effect appeared to be limited to current smokers and to increases in fine particulate matter 2 days prior to the event. These stratum-specific findings were not expected and may be a result of multiple comparisons. However, it is possible that current smokers with preexisting cardiac disease are particularly susceptible to the effects of particulate matter air pollution.

It is difficult to posit an additive effect of particulate matter among current smokers, since they would be exposed to an order-of-magnitude-greater level of particulate matter from smoking than from outdoor air. However, cigarette smoking may enhance the sensitivity of persons with heart disease to the proarrhythmic effects of particulate matter. Epidemiologic studies have demonstrated that current smoking status is associated with elevated risk of primary cardiac arrest among persons with and without heart disease (27). Potentiation of the proarrhythmic effect could also be explained by cigarette smoke-induced increases in platelet aggregation (28, 29), nicotine-associated increases in catecholamine levels and decreases in heart-rate variability (30), and free-radical amplification of pulmonary inflammation (29, 30).

We had anticipated finding an association between same-day or prior-day elevated particulate matter levels and primary cardiac arrest. However, it is plausible that an elevated level of particulate matter 2 days prior to an event results in the induction of an inflammatory cascade in the lungs of susceptible persons that is followed by amplification of systemic proinflammatory cytokine levels and endothelial vasoconstrictors. This may lead to alterations in heart rate and blood pressure or amplification of the release of local inflammatory mediators and increased recruitment of T lymphocytes and monocytes with resultant plaque rupture and arrhythmia (4, 31–34). Interestingly, Peters et al. (17) found that 2-day lagged elevations in nitrogen dioxide and fine particulate matter levels were associated with increased automated implantable cardiac defibrillator firings.

The absence of a strong association between elevated particulate matter levels and primary cardiac arrest among persons with preexisting heart disease contrasts with studies performed in Massachusetts which demonstrated consistent associations between elevated particulate matter levels and cardiac events (14, 17). We speculate that these differences may be explained by the composition of particulate matter in the Seattle air shed or methodological differences in referent sampling between the case-crossover studies. The National Morbidity, Mortality, and Air Pollution Study found differences between cities for cardiac mortality and overall mortality due to particulate matter, with the greatest increase in cardiac mortality being observed in the northeastern United States (18–20). Although prior time-series studies in Seattle have documented an increase in respiratory disease exacerbations from increased levels of particulate matter, they failed to find an increase in cardiac morbidity or mortality. The Seattle air shed contains particulate matter that is relatively sparse in transition metals and sulfates (19). Recent in vivo data suggest that transition metals can catalyze an oxidative stress reaction in the lung, leading to inflammatory lung injury (33, 34) and increased arrhythmia (32, 34). Moreover, compositional analyses of ambient air in Quebec suggest that particulate matter with high sulfate fractions is more strongly associated with increased hospitalizations for cardiac and respiratory diseases (15, 35).

This study had several strengths. We were able to study the effect of fine particulate matter on the risk of out-of-hospital primary cardiac arrest in a large number of cases accumulated over a long period of time in an extensively characterized air shed. This was done with a well-characterized study population in a western US city with a long history of air monitoring. Moreover, our referent selection strategy was based on a sound theoretical foundation. This strategy has been shown to perform well in simulation studies (23). Last, studies of primary cardiac arrest contrast with studies that have examined the outcome of total cardiac mortality. The prevention of primary cardiac arrest in otherwise healthy vulnerable adults may lead to a dramatic savings in quality years of life (2–4).

However, our study had several limitations. First, this analysis utilized a 24-hour average measure of particulate matter that may have underestimated the effect of shorter peak exposures. For instance, Peters et al. (14) recently documented a relation between increased particulate matter levels and onset of myocardial infarction symptoms. Second, our analysis did not examine the potential proarrhythmic effects of elevated nitrogen dioxide levels because of the absence of available nitrogen dioxide exposure data over the period of study. Third, small numbers of persons using cardiac medications in our subgroup analyses may have led to an underestimation of the modulating effect of medica-

tions (e.g., beta blockers and sympathomimetics) on the association between particulate matter and primary cardiac arrest. Furthermore, the absence of a protective effect with use of beta blockers may have resulted from the indication for use, that is, worsening ischemic heart disease or prior myocardial infarction. Fourth, information on the use of statins, aspirin, and antioxidants, as well as recent lipoprotein level, was not readily available from the data set. Moreover, our analyses did not include information on socioeconomic status or educational level, both of which are known risk factors for primary cardiac arrest. Last, the proportion of cases with each preexisting cardiovascular disease reflected the population under study. It is possible that we may have found different overall results in a population containing a larger proportion of persons with advanced congestive heart failure or active angina.

In conclusion, the results of this study suggest that elevated levels of particulate matter are not consistently associated with out-of-hospital primary cardiac arrest among persons with preexisting heart or lung disease. A similar study carried out in an air shed with higher ambient levels of sulfates and metals would be of interest. To clarify recent research suggesting that very short-term elevations in particulate matter levels are associated with onset of myocardial infarction, further research is needed to examine the effect of short-term peak exposures (1-hour and 4-hour) on the risk of out-of-hospital primary cardiac arrest in populations with preexisting heart disease.

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REFERENCES

1. Spooner PM, Albert C, Benjamin EJ, et al. Sudden cardiac death, genes, and arrhythmogenesis: consideration of new population and mechanistic approaches from a National Heart, Lung, and Blood Institute workshop, part I. Circulation 2001; 103:2361–4.
2. Sotoodehnia N, Zivin A, Bardy GH, et al. Reducing mortality from sudden cardiac death in the community: lessons from epidemiology and clinical applications research. Cardiovasc Res 2001;50:197–209.
3. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J 2001;22:1374–450.
4. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998; 98:2334–51.
5. Myerburg RJ, Spooner PM. Opportunities for sudden death prevention: directions for new clinical and basic research. Cardiovasc Res 2001;50:177–85.
6. Ojio S, Takatsu H, Tanaka T, et al. Considerable time from the onset of plaque rupture and/or thrombi until the onset of acute myocardial infarction in humans: coronary angiographic findings within 1 week before the onset of infarction. Circulation 2000;102:2063–9.
7. Wu J, Zipes DP. Transmural reentry during acute global ischemia and reperfusion in canine ventricular muscle. Am J Physiol Heart Circ Physiol 2001;280:H2717–25.
8. Hayden MR, Tyagi SC. Arteriogenesis: angiogenesis within unstable atherosclerotic plaque—interactions with extracellular matrix. Curr Interv Cardiol Rep 2000;2:218–27.
9. Feng DL, Tofler GH. Diurnal physiologic processes and circadian variation of acute myocardial infarction. J Cardiovasc Risk 1995;2:494–8.
10. Domanski MJ, Zipes DP, Benditt DG, et al. Central clinical research issues in electrophysiology: report of the NASPE Committee. Pacing Clin Electrophysiol 2001;24:526–34.
11. Burke AP, Kolodgie FD, Farb A. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 2001;103:934–40.
12. Burke AP, Farb A, Malcom GT. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 1998;97:2110–16.
13. Schwartz J. Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 1999;10:17–22.
14. Peters A, Dockery DW, Muller JE, et al. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 2001;103:2810–15.
15. Goldberg MS, Bailar JC 3rd, Burnett RT, et al. Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. Res Rep Health Eff Inst 2000; Oct(97):7–113.
16. Kwon HJ, Cho SH, Nyberg F, et al. Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure. Epidemiology 2001;12:413–19.
17. Peters A, Liu E, Verrier RL, et al. Air pollution and incidence of cardiac arrhythmia. Epidemiology 2000;11:11–17.
18. Dockery DW, Pope CA 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753–9.
19. Samet JM, Zeger SL, Dominici F, et al. The National Morbidity, Mortality, and Air Pollution Study. Part II: morbidity and mortality from air pollution in the United States. Res Rep Health Eff Inst 2000;Jun(94):5–70.
20. Sarnat JA, Schwartz J, Suh HH. Fine particulate air pollution and mortality in 20 U.S. cities. N Engl J Med 2001;344:1253–4.
21. Levy D, Sheppard L, Checkoway H, et al. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 2001;12:193–9.
22. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133:144–53.
23. Levy D, Lumley T, Sheppard L, et al. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology 2001;12:186–92.
24. Lumley T, Levy D. Bias in the case-crossover design: implications for studies of air pollution. Environmetrics 2000;11:689–704.
25. Waggoner A, Weiss RE. Comparison of fine particle mass concentration and light scattering extinction in ambient aerosols. Atmos Environ 1980;14:623–6.
26. Sheppard L, Levy D, Norris G, et al. Effects of ambient air pollution on non-elderly asthma hospital admissions in Seattle, Washington, 1987–1994. Epidemiology 1999;10:23–30.
27. Peters RW, Brooks MM, Todd L, et al. Smoking cessation and arrhythmic death: the CAST experience. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. J Am Coll Cardiol

1995;26:1287–92.
28. Ludviksdottir D, Blondal T, Franzon M, et al. Effects of nicotine nasal spray on atherogenic and thrombogenic factors during smoking cessation. J Intern Med 1999;246:61–6.
29. Smith CJ, Fischer TH. Particulate and vapor phase constituents of cigarette mainstream smoke and risk of myocardial infarction. Atherosclerosis 2001;158:257–67.
30. Mehta MC, Jain AC, Mehta A, et al. Cardiac arrhythmias following intravenous nicotine: experimental study in dogs. J Cardiovasc Pharmacol Ther 1997;2:291–8.
31. Moreno PR, Falk E, Palacios IF, et al. Macrophage infiltration in acute coronary syndromes: implications for plaque rupture. Circulation 1994;90:775–8.
32. Godleski JJ, Verrier RL, Koutrakis P, et al. Mechanisms of morbidity and mortality from exposure to ambient air particles. Res Rep Health Eff Inst 2000;Feb(91):5–88.
33. Ghio AJ, Devlin RB. Inflammatory lung injury after bronchial instillation of air pollution particles. Am J Respir Crit Care Med 2001;164:704–8.
34. Costa DL, Dreher KL. Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. Environ Health Perspect 1997; 105(suppl 5):1053–60.
35. Anderson HR, Bremner SA, Atkinson RW, et al. Particulate matter and daily mortality and hospital admissions in the West Midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occup Environ Med 2001;58:504–10.