Acute Changes in Vascular Function Among Welders Exposed to Metal-Rich Particulate Matter

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Background: Although welding fume exposure is associated with adverse cardiovascular outcomes, the mechanisms remain unclear. To investigate the role of vascular function, we assessed levels of the augmentation index (a correlate of arterial stiffness) after short-term exposure to welding-derived fine particulate matter ($PM_{2.5}$).

Methods: In a panel study, we monitored 26 male welders over 24 hours on a welding day (n = 25), a nonwelding day (n = 15), or both (n = 14). Augmentation index (expressed as a percent) was obtained in the morning before exposure (baseline) and after exposure in the afternoon and the following morning. Personal $PM_{2.5}$ exposure was measured over 6 hours of welding or an equivalent nonwelding period. We used linear mixed models adjusting for baseline augmentation index, smoking, age, and time to evaluate the effects of welding (binary) and $PM_{2.5}$ (continuous) on augmentation index levels. We also assessed modification by welding exposure the day before monitoring (binary).

Results: Welding was associated with a 2.8% increase in afternoon augmentation index (95% confidence interval = −1.4 to 7.0) and a 2.4% decrease (−6.9 to 2.2) in next-morning augmentation index. Additional exposure the day prior to monitoring was associated with a greater afternoon increase (5.1%; 0.8 to 9.5). Using $PM_{2.5}$ concentration, a positive association was observed in the afternoon and an inverse association the next morning; results differed by previous day's welding status after excluding outliers.

Conclusions: Subsequent to welding fume exposure, there is an increase in afternoon augmentation index and a decrease in next-morning augmentation index, with greater changes after consecutive days of exposure. These results suggest that exposure to the $PM_{2.5}$ component of welding fume elicits acute adverse vascular responses.

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Welding fume is a complex mixture containing metal-rich airborne particulate matter (PM), generated when heated metal vaporizes and condenses in air. Exposure includes high concentrations of respirable particles with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$). Although the pulmonary health effects of welding fume exposures are well-known,[1] there is growing concern for the cardiovascular health effects. Several mortality studies report increased risk of death from ischemic heart disease among welders.[2–4] In addition, the prevalence of myocardial infarction and other cardiovascular events and symptoms are increased in welders.[5] The underlying mechanisms responsible for these cardiovascular effects are largely unclear; however, a role for vascular function may be involved.[6,7] Several studies have demonstrated vasoconstriction and increases in blood pressure after short-term exposure to ambient PM.[8–12] Vascular changes may be mediated by direct action of PM on lung receptors[13] or via inflammatory pathways.[14]

In observational studies, vasoconstriction has been measured by vasoreactivity and brachial artery diameter.[8,9] These measurements are not feasible in workplace studies where practical restrictions warrant the use of simpler techniques. One component of vascular function that is easily measured with a portable device is the aortic augmentation index, a measure of wave reflections that relates to central aortic pulse pressure, and is a correlate of arterial stiffness.[15] It is derived from reflective properties of the arterial bed and is measured reproducibly[16,17] by the noninvasive technique of pulse wave analysis. Increased augmentation index is associated with advancing age, hypertension, diabetes, and hypercholesterolemia.[18–20] The measurement is also a strong and independent marker of established coronary artery disease[21] and correlates with risk of coronary artery disease development.[22] Acute increases in the augmentation index are observed in individuals after exposure to first- and second-hand cigarette smoking.[23,24] However, the relation between the augmentation index and metal-rich occupational particulate exposures has not been studied.

We conducted a panel study to investigate the relationship between short-term exposure to metal-rich $PM_{2.5}$ and the augmentation index over a 24-hour period in a group of welders on either or both a welding and a nonwelding day. The augmentation index was evaluated with respect to weld-

ing exposure status and personal $PM_{2.5}$ exposure concentrations. The effect of additional welding exposure on the day before monitoring was also examined.

METHODS

Study Population and Design

The study population consisted of male boilermaker construction workers recruited among members of a local union. Boilermakers are regularly exposed to welding fumes and are responsible for building, installing, maintaining, and repairing industrial power-generating boilers. Twenty-seven men participated, although one was excluded from the analysis because of arrhythmia, which prevented accurate pulse wave readings, giving a total of 26 participants. The Institutional Review Board of the Harvard School of Public Health approved the study protocol and informed written consent was obtained from each individual prior to participation.

The study was conducted over 5 weekends in the winter of 2006 at a welding school. Participants were monitored over 24 hours on a high-exposure welding day or a low-exposure nonwelding day or both. For those who participated on both days, the order of exposure differed across participants, with some first monitored when welding, and others first monitored when not welding. The 2 days were separated by at least 1 week. $PM_{2.5}$ exposure was measured throughout the course of the 6-hour welding shift, or equivalent nonwelding period. Augmentation index was measured at baseline in the morning before work started, immediately postshift in the afternoon, and the following morning.

Exposure and Assessment

The school consisted of one large room outfitted with 10 workstations, each with local exhaust ventilation. On a welding day, participants were monitored while receiving instruction and practicing manual metal arc welding, tungsten inert gas welding, and metal inert gas welding. The most common type of welding performed was manual metal arc welding on mild and stainless steel. Adjacent to the welding room was a break room where nonwelding participants were monitored while doing office or bookwork.

To measure personal $PM_{2.5}$ exposure, gravimetric particle samplers were placed within the workers' breathing zone. Samples were collected onto a 37 mm polytetrafluoroethylene membrane filter (Gelman Laboratories, Ann Arbor, MI) using a KTL cyclone (GK2.05SH, BGI Incorporated, Waltham, MA) with a 50% aerodynamic diameter cutpoint of 2.5 μm, used in line with a personal pump drawing 3.5 L/min of air. The filters were weighed before and after sampling on a MT5 microbalance (Mettler-Toledo Incorporated, Columbus, OH) after equilibrating for a minimum of 24 hours in a temperature and humidity controlled room. The $PM_{2.5}$ mass concentration was calculated by dividing the mass collected on the filter by the sampled air volume. To account for differences in sampling times, $PM_{2.5}$ concentrations were standardized to 8-hour time weighted averages. One $PM_{2.5}$ concentration was assigned for each worker for each 24-hour sampling period.

Workers were monitored during on an off-season of boilermaker work (winter); however, some worked or practiced welding the day before monitoring. To account for previous day's welding fume exposure in the analyses, information on days since last welded was collected.

Augmentation Index Determination

Measurements were performed in a temperature-controlled room with a SphygmoCor Px Pulse Wave Analysis System Model SCOR-Px (Atcor Medical Pty Ltd., Sydney, Australia). All data were collected directly into laptop computers installed with the system software (Version 7.1) by 2 trained study technicians. All attempts were made to use the same technician and system for the same participant throughout the study. Calibration of peripheral pressure recordings was performed with the average of 3 brachial systolic and diastolic blood pressure readings obtained with an automated blood pressure machine before each augmentation index measurement.

Participants were seated comfortably with both feet planted on the ground and with the dominant arm extended onto a flat surface, ensuring that the bend at the elbow was at heart level. After 5 minutes of rest, a high-fidelity micronanometer was used to flatten the radial artery with gentle pressure. Ten seconds of sequential pulse pressure waveforms were recorded during each reading. The waveforms were transformed into a corresponding central aortic waveform via a validated transfer function. The systolic part of the central aortic waveform is characterized by a 1st peak caused by left ventricular ejection and a 2nd peak caused by wave reflection.[22] The difference between the peaks reflects the degree to which the central aortic pressure is augmented by wave reflection. The augmentation index (AIx) is defined as the augmented pressure divided by the pulse pressure and expressed as a percentage $\left[\text{AIx}\ (\%) = \frac{AP}{PP} * 100\%\right]$. Larger values of the index indicate increased wave reflection (ie, earlier return of the reflected wave).[25]

Augmentation index values were normalized for a heart rate of 75 bpm because augmentation index is influenced by heart rate in a linear and inverse fashion.[26] Ejection duration shortens with an increase in heart rate, so that the reflected wave arrives later in the cardiac cycle relative to the incident wave, causing the height of the second systolic peak to be lowered, thereby reducing augmentation of central systolic pressure and the augmentation index.[26] The pulse wave analysis device simultaneously measures heart rate and the system software provides a heart rate-adjusted augmentation index in addition to a nonadjusted value.

The quality control of the pressure waveforms is based on the homogeneity and height of the recorded waves. The software provides a quality control index for each reading

obtained. We attempted to obtain recordings of optimal quality by accepting readings with an index ≥90. The average of 3 within-session augmentation index values with an index ≥90 was calculated for each observation. Readings were recorded until the 3 measures of desired quality were obtained. However, due to time constraints, we were not able to obtain the optimal number of readings for every participant; 15% of 114 augmentation index observations were based on one measurement with an index ≥90 and 8% were based on averaging readings with an index ≥80. Repeatability was assessed by calculating the standard deviation (SD) of the within-session measurements for each participant at each time point using a one way analysis of variance.[27] The overall within-session SD was 3.4%, comparable to previously reported values.[25,28] A plot of the within-session SD versus the mean augmentation index for each observation showed no trend between variability and the mean augmentation index level.

Collection of Additional Covariates

Additional information on demographics, medication usage, and medical, smoking, and occupational history were obtained from self-administered modified American Thoracic Society questionnaires.[29] Information on first- and second-hand smoke exposure and caffeine and alcohol consumption during the monitoring period was recorded on time activity sheets, as in previous studies of this population.[30] However, we observed that few individuals accurately completed the section on second-hand smoke, and thus these data were not used. Information on respirator use during monitoring was also recorded.

Data Analysis

We estimated mean levels and standard errors of the augmentation index at baseline, afternoon, and the next morning by exposure status the day before monitoring and the day of monitoring, using linear mixed effects models that accounted for the correlation of repeated measurements within persons. The mean levels were adjusted for age and smoking status within 4 hours of each measurement (binary).

Linear mixed effects models were also used to determine the effect of welding exposure (binary) and work-shift $PM_{2.5}$ exposure (continuous) on afternoon and next-morning augmentation index levels. In these models, baseline was used as a predictor because exposure occurred after the baseline measurement. An autoregressive covariance matrix was chosen as the working covariance structure because it minimized Akaike's information criterion. Age and smoking within the last 4 hours of each afternoon and next morning measurement (binary) were controlled for in the model. The augmentation index exhibits a strong circadian variation, with a decrease from morning to afternoon and an increase back to baseline values in the morning,[25,31] and so we included an indictor for time (next morning versus afternoon). The effects of exposure and smoking on the augmentation index were allowed to vary by time, using interaction terms with time. Caffeine and alcohol consumption (predictors of short-term changes in the index that are potentially correlated with particulate exposure) were considered as covariates in the models to adjust for possible confounding. Inclusion of these variables, however, did not alter the regression coefficients for exposure and so were dropped from the final analyses to maintain parsimony of the models. Regression coefficients and 95% confidence intervals (CIs) for both the afternoon and the next-morning augmentation index levels were estimated from the model. The general form of the model was:

$$Y_{ij} = \beta_0 + \beta_1 bl_{ij} + \beta_2 weld_{ij} + \beta_3 time_{ij} + \beta_4 (weld_{ij} * time_{ij}) + \beta_5 smoke_{ij} + \beta_6 (smoke_{ij} * time_{ij}) + \beta_7 age_i + e_{ij}$$

where bl = baseline augmentation index level; weld = 1 for welded and 0 otherwise; time = 1 for the next morning and 0 for afternoon; smoke = 1 for smoked within the last 4 hours and 0 otherwise; and age was a continuous variable centered at the mean. A similar model was used to investigate the relationship with $PM_{2.5}$ concentration.

Additional models accounted for the potential effects of welding exposure the day before monitoring by using indicator variables to reflect welding exposure over the 2 days (ie, exposed the day prior to monitoring only, exposed the day of monitoring only or exposed both days, with the reference being unexposed on both days). In the $PM_{2.5}$ model, an indictor for exposure the day prior to monitoring was included, as well as its interaction with $PM_{2.5}$.

Residual plots and the distribution of the error terms were assessed to check the normality of the residuals and fit of the model. For the $PM_{2.5}$ models, effect estimates excluding outliers defined as observations with a Studentized residual ≤ -2 or ≥ 2 were also obtained.

In additional sensitivity analyses, 2 individuals using ACE inhibitors and beta-blockers were excluded because these drugs may alter pulse wave characteristics.[32] Analyses were also performed using the augmentation index values not adjusted for heart rate to determine the effect of such adjustment. Further, we evaluated the effect of using augmentation index values with a quality index ≥80 in separate models. Analyses were performed with SAS v.9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Study Population and Exposure Characteristics

A description of the study population is presented in Table 1. Among the 26 participants, 25 were monitored on a welding day, 15 were monitored on a nonwelding day, and 14 were monitored on both days. Workers who participated on both days were comparable to those who participated on 1 day with respect to age, smoking status, years as a boilermaker, lipids, baseline augmentation index, blood pressure, and heart rate (data not shown). A total of 40 exposure

TABLE 1. Characteristics of Male Welders in the Study Population (n = 26)

White; no. (%)	24 (92)
Current smokers; no. (%)	10 (39)
Age in years; mean ± SD (range)	41.2 ± 11.7 (24 to 64)
Years as a boilermaker; median (range)	5 (<1 to 38)
Cardiovascular history; no. (%)	
Hypertension	5 (19)
Myocardial infarction	1 (4)
BMI (kg/m^2); mean ± SD	30.8 ± 7.5
Heart rate (bpm); mean ± SD	73.0 ± 9.9
Systolic blood pressure (mm Hg); mean ± SD	131 ± 14.6
Diastolic blood pressure (mm Hg); mean ± SD	82.4 ± 13.2
Lipid levels (mg/dL); mean ± SD (range)	
Total cholesterol	202 ± 49.2 (124 to 377)
HDL cholesterol	49.4 ± 13.9 (24 to 91.5)
LDL cholesterol	120 ± 39.1 (62.5 to 249)
Triglycerides	164 ± 77.4 (53 to 372)
Current medication usage; no. (%)	
ACE inhibitor	2 (8)
Angiotensin II inhibitor	1 (4)
Beta-blocker	2 (8)
Diuretic	2 (8)
Statin	3 (12)
Baseline augmentation index (%); mean ± SD (range)	
Nonweld day	13.9 ± 13.2 (−11.0 to 33.0)
Weld day	13.6 ± 13.1 (−14.7 to 38.0)

HDL indicates high density lipoprotein; LDL, low density lipoprotein.

TABLE 2. Exposure Characteristics of Welders in the Study Population by Type of Monitoring Day

	Nonwelding Day (n = 15)	Welding Day (n = 25)
Sampling time (h); mean ± SD	7.20 ± 1.26	6.52 ± 1.49
$PM_{2.5}$ (8-h TWA, mg/m^3); median (range)	0.05 (0.01 to 0.19)	0.39 (0.03 to 2.62)
Welded the day before; no. (%)	5 (33)	8 (32)

samples and 114 augmentation index measurements were collected (40 baseline, 40 afternoon, and 34 next morning).

Exposure characteristics are presented in Table 2. The overall median $PM_{2.5}$ concentration was 0.21 mg/m^3, with an interquartile range of 0.05 to 0.51 mg/m^3. None of the workers wore respirators during the study period. Characterization of the $PM_{2.5}$ samples using x-ray fluorescence showed substantial metal contents in all samples, particularly iron and manganese (data not presented), indicating that on a nonwelding day individuals were exposed to low levels of welding fumes from the welding room.

Augmentation Index Levels at Baseline, Afternoon, and Next Morning

The mean augmentation index levels, expressed in units of percent, were consistently higher in the morning (at baseline and the next morning) and lower in the afternoon across exposure conditions (Fig. 1). For participants unexposed, the day before and the day of monitoring (the reference group), the variation in augmentation index levels throughout the day represented natural circadian variation (A). Exposure the day before monitoring resulted in baseline levels that were approximately 25% lower than when there was no exposure the day before (C & D versus A & B). Welding resulted in higher afternoon augmentation index levels, regardless of whether or not exposure occurred the day before monitoring (B & D). In addition, next-morning augmentation index levels were relatively lower after welding exposure, although exposure over both days resulted in the lowest next-morning augmentation index level. The variation of augmentation index levels throughout the 24-hour period was noticeably attenuated with exposure over 2 days.

Welding Fume Exposure and the Augmentation Index

In the models considering welding exposure status on the day of monitoring only, crude and adjusted results were comparable (Table 3). In the fully adjusted model, the afternoon level of augmentation index was increased on a welding

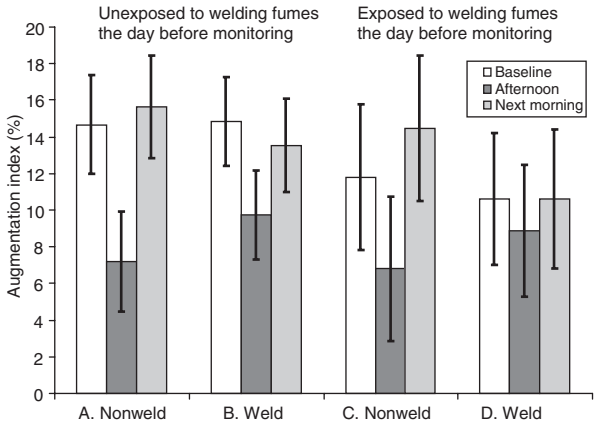

FIGURE 1. Augmentation index by exposure status the day before and the day of 24-hour monitoring, at baseline, afternoon, and the next morning (mean indicated by shaded box; standard error, by vertical lines). Under condition A, the changes in the augmentation index over time are representative of circadian variation. Under conditions B and D, the afternoon augmentation index was higher after exposure to welding fume. Under conditions C and D, baseline values were lower after exposure to welding fumes the day before monitoring, in comparison to baseline values under conditions A and B. Under D, where exposure to welding fumes occurred 2 days in a row, the least variation in the augmentation index throughout the day occurred. All values were adjusted for age and smoking status using a linear mixed effects model for repeated measures.

day compared with a nonwelding day (β = 3.0; CI = −1.2 to 7.1) (Table 3, Section I). In contrast, levels were lower the morning following a welding day versus a nonwelding day (−2.5; −7.0 to 2.0).

Taking into account welding exposure the day before monitoring, there was a greater increase in afternoon augmentation index levels after exposure to welding fume both days (5.5; 1.1–10.0) (Table 3, Section II). The next-morning level decreased 1.5% (−7.2 to 4.2) after exposure both days.

The effects of smoking in the 4 hours before augmentation index measurement were qualitatively consistent and, in general, comparable in magnitude with the effects of welding exposure both in the afternoon and the next morning.

$PM_{2.5}$ Concentrations and the Augmentation Index

Without regard for welding exposure the day before monitoring, an interquartile range change in $PM_{2.5}$ was associated with an increase in the afternoon augmentation index of 1.0% (−0.3 to 2.4) and a next morning decrease of 1.17% (−3.1 to 0.7) (Table 4, Section I). Accounting for welding exposure the day before monitoring, positive effect estimates were consistently observed in the afternoon and negative effect estimates were consistently observed the next morning. There was no indication of a differential effect of $PM_{2.5}$ by previous day's welding exposure status (Table 4, Section II) until exclusion of 4 outliers. A larger effect of $PM_{2.5}$ concentration on the afternoon augmentation index level was observed with exposure to welding fumes the day before versus none (3.5; 0.9 to 5.3 versus 0.2; −1.0 to 1.3). In addition, there was a smaller association between $PM_{2.5}$ and next-morning augmentation index with exposure to welding fumes the day before versus none (−2.7; −4.4 to −1.0 versus −5.8; −8.7 to −2.8).

Sensitivity Analyses

Exclusion of the 2 individuals on ACE inhibitors and β-blockers (one of whom also had an outlying observation in the $PM_{2.5}$ models) resulted in slightly smaller regression parameters for the effect of $PM_{2.5}$ on afternoon augmentation index levels, but did not alter the parameters for the next morning levels (Table 5). Analyses using augmentation index values that were not adjusted for heart rate resulted in smaller effect estimates and wide CIs that included 0. Using all augmentation index values with a quality index ≥80 also resulted in substantially smaller regression coefficients for $PM_{2.5}$ and wide CIs that included 0.

DISCUSSION

On average, welding increased the afternoon augmentation index and decreased the next-morning index. When exposures before study participation were accounted

TABLE 3. Association Between Welding (Yes/No) and Augmentation Index Level (%) in the Afternoon and the Next Morning* (n = 74)

	Crude Models		Adjusted Models†	
	Afternoon % (95% CI)	Next Morning % (95% CI)	Afternoon % (95% CI)	Next Morning % (95% CI)
Exposure status day of monitoring				
Weld verses nonweld	2.7 (−1.5 to 6.8)	−2.5 (−7.2 to 2.2)	3.0 (−1.2 to 7.1)‡	−2.5 (−7.0 to 2.0)
Smoked cigarettes within last 4 h (yes/no)	—	—	2.6 (−0.7 to 6.0)	−1.3 (−7.0 to 4.4)
Exposure status over 2 d§				
Exposed day before monitoring only	1.7 (−7.9 to 10.6)	1.3 (−6.1 to 8.7)	2.2 (−7.2 to 11.5)	0.9 (−5.6 to 7.3)
Exposed day of monitoring only	2.2 (−3.0 to 7.3)	−2.4 (−8.5 to 3.8)	2.8 (−2.2 to 7.8)	−2.4 (−8.3 to 3.5)
Exposed both days	5.2 (1.4 to 9.0)	−0.8 (−6.0 to 4.4)	5.5 (1.1 to 10.0)¶	−1.5 (−7.2 to 4.2)
Smoked cigarettes within last 4 h (yes/no)	—	—	3.2 (−0.2 to 6.6)	−1.4 (−6.8 to 4.1)

*All models adjusted for time and for welding by time interaction.
†Models additionally adjusted for age, smoking, and smoking by time interaction.
‡Weld by time interaction P = 0.06.
§Reference category is unexposed both days.
¶Weld by time interaction P = 0.03.

TABLE 4. Association Between an IQR Change in Work-Shift $PM_{2.5}$ and Augmentation Index Level (%) in the Afternoon and the Next Morning* (n = 74)

	Crude Models		Adjusted Models†		Adjusted Models Excluding Outliers‡	
	Afternoon % (95% CI)	Next Morning % (95% CI)	Afternoon % (95% CI)	Next Morning % (95% CI)	Afternoon % (95% CI)	Next Morning % (95% CI)
Not accounting for previous exposure						
$PM_{2.5}$	0.9 (−0.5 to 2.3)	−1.1 (−3.1 to 0.9)	1.0 (−0.3 to 2.4)	−1.2 (−3.1 to 0.7)	1.0 (−0.2 to 2.2)	−2.7 (−4.7 to −0.8)
Smoked cigarettes within last 4 h (yes/no)	—	—	3.1 (−0.2 to 6.3)	−1.3 (−6.6 to 4.1)	3.3 (0.3 to 6.4)	1.6 (−2.0 to 5.2)
Accounting for exposure day before						
$PM_{2.5}$ (did not weld the day before)	0.8 (−0.4 to 2.0)	−1.4 (−3.8 to 9.7)	1.0 (−0.1 to 2.1)	−1.2 (−3.4 to 1.0)	0.2 (−1.0 to 1.3)§¶	−5.8 (−8.8 to −2.8)
$PM_{2.5}$ (welded the day before)	1.1 (−1.4 to 3.5)	−1.2 (−3.6 to 1.2)	1.0 (−1.6 to 3.6)	−1.2 (−3.4 to 1.0)	3.5 (1.2 to 5.6)	−2.7 (−4.4 to −1.0)
Smoked cigarettes within last 4 h (yes/no)	—	—	3.2 (−0.03 to 6.5)	−1.4 (−6.2 to 3.4)	3.4 (0.3 to 6.5)	−0.1 (−3.5 to 3.4)

IQR = 0.46 mg/m^3.
*All models adjusted for time and for $PM_{2.5}$ by time interaction.
†Models additionally adjusted for age, smoking, and smoking by time interaction.
‡In adjusted models excluding outliers, n = 69 for model that does not account for previous exposures and n = 70 for model that does account for previous exposures.
§$PM_{2.5}$ by time interaction $P < 0.0001$.
¶$PM_{2.5}$ by welded-the-day-before interaction $P = 0.006$.

TABLE 5. Association Between an IQR Change in Work-Shift $PM_{2.5}$ and Augmentation Index Level (%) in the Afternoon and the Next Morning in Sensitivity Analyses* (n = 74)

	Excluding 2 Individuals on ACE Inhibitors and β-Blockers†		Models Based on AIx Values With an Operator Index ≥80%		Models Using AIx Values Not Adjusted for Heart Rate	
	Afternoon % (95% CI)	Next Morning % (95% CI)	Afternoon % (95% CI)	Next Morning % (95% CI)	Afternoon % (95% CI)	Next Morning % (95% CI)
Not accounting for previous exposure						
$PM_{2.5}$	0.7 (−0.4 to 1.9)	−1.1 (−3.1 to 0.8)	0.9 (−0.4 to 2.2)	−0.8 (−2.4 to 0.7)	0.9 (−0.6 to 2.4)	−1.2 (−3.2 to 0.9)
Smoked cigarettes within last 4 h (yes vs. no)	2.1 (−0.9 to 5.2)	−0.8 (−6.2 to 4.5)	2.0 (−1.4 to 5.4)	−0.9 (−4.7 to 2.9)	1.6 (−3.4 to 6.7)	−1.4 (−8.1 to 5.3)
Accounting for exposure day before						
$PM_{2.5}$ (did not weld the day before)	0.7 (−0.3 to 1.7)	−1.2 (−3.4 to 1.2)	1.0 (−0.3 to 2.2)	−0.8 (−2.5 to 1.0)	1.2 (−0.3 to 2.5)	−1.0 (−3.1 to 1.0)
$PM_{2.5}$ (welded the day before)	0.8 (−1.7 to 3.3)	−1.1 (−3.2 to 1.0)	0.7 (−2.0 to 3.4)	−1.0 (−3.2 to 1.3)	0.04 (−3.4 to 3.5)	−2.1 (−4.9 to 0.8)
Smoked cigarettes within last 4 h (yes vs. no)	2.3 (−0.7 to 5.3)	−1.0 (−5.9 to 3.9)	2.1 (−1.2 to 5.4)	−1.1 (−4.5 to 2.3)	1.7 (−3.8 to 7.1)	−1.7 (−7.2 to 3.8)

IQR = 0.46 mg/m^3.
*All models adjusted for time, $PM_{2.5}$ by time interaction, age, smoking, and smoking by time interaction.
†n = 70.
AIx indicates augmentation index.

for in the models, participants exposed to welding fume for at least 2 days in a row showed the greatest increase in the afternoon augmentation index and the smallest decrease in the next-morning index. A positive linear relationship was observed between the afternoon augmentation index and $PM_{2.5}$ among those who had welded the day before, after excluding outlying observations, providing further evidence that the welding fume exposure was responsible for the observed effects. Strong inverse exposure response relationships were also observed with the next-morning augmentation index and $PM_{2.5}$ after the exclusion of outliers. A smaller $PM_{2.5}$ effect observed the next morning for those who had welded the day before monitoring was consistent with the smaller change in the next-morning augmentation index observed with welding exposure over 2 days.

These changes resulted in a blunting of the afternoon decrease in the augmentation index observed with normal circadian variation and an attenuated increase in the anticipated rise in the index back to baseline values the following

morning. Exposure over 2 days in a row resulted in the least variability in the index throughout the course of the day. Results from crude analysis of crossover participants supported these findings (data not presented).

Although this is the first study to investigate the augmentation index in response to occupational PM exposures, previous studies have investigated other components of vascular function with ambient PM, providing evidence of acute vascular effects. In a study of controlled human exposures to concentrated ambient particles and ozone, acute arterial vasoconstriction measured by brachial artery diameter occurred immediately after 2 hours of exposure,[8] indicating an ability of particulate matter to elicit a rapid vascular response. Over a longer duration of exposure, an association between endothelium-independent vasoconstriction measured by flow-mediated dilation and 24-hour $PM_{2.5}$ was reported among adults with diabetes.[9] Vascular responses have also been demonstrated in animal studies, where short-term exposure to concentrated ambient particles and urban ambient particles induced vasoconstriction of pulmonary arteries in both healthy and compromised rats.[11,12] An association between elevated blood pressure and $PM_{2.5}$ exposure in the 2 preceding days among individuals undergoing cardiac rehabilitation further suggests an effect on vascular function.[10]

The responses in the augmentation index observed immediately after exposure and the next morning in this study indicate that there are both immediate and delayed (or prolonged) effects. These responses may reflect a continued response under the same mechanism or multiple mechanisms. Recovery back to baseline appeared to occur after a day of no exposure, as indicated by the small effect estimate the next morning only for those who welded the day before monitoring.

The augmentation index is often used as a surrogate measure of arterial stiffness; however, recent expert consensus states that the index should not be confused as a measure of arterial stiffness itself,[33] but may be more accurately considered as representing the effects of arterial stiffening.[15] Wave reflections are affected primarily by vascular elasticity, peripheral resistance, and the duration of cardiac systole.[34] Stiffer arteries (less elastic and with greater resistance) cause the transmission velocity of forward and reflected waves to increase, causing the reflected wave to arrive earlier in the central aorta. Therefore, augmentation results from early reflection of the waveform as aortic and arterial stiffness increase. Because short-term changes in arterial stiffness are influenced by changes in the functional components of the arterial wall (such as the vasoconstrictor tone exerted by its smooth muscle cells and endothelial function[35]), the more immediate response in the augmentation index observed in the afternoon may be explained by the action of $PM_{2.5}$ on sympathetic nervous innervation of vascular smooth muscle cells, thereby increasing vasoconstrictor tone. Immediate acute effects of passive smoking have also been hypothesized to be attributable to sympathetic nervous system activation[24] from the particle components of cigarette smoke.[35,36] The response observed the next morning may be explained by reductions in vascular-endothelium mediated vasodilators or, alternatively, increases in vascular-endothelium mediated vasoconstrictors related to inflammation. This is supported by a previous study, where particle-related increases in markers of systemic inflammation were observed the morning following exposure to welding fumes.[37]

We attempted to collect detailed information on exposure to first- and second-hand smoke during monitoring, although residual and uncontrolled confounding was likely. Confounding by gaseous copollutants, such as ozone and nitrogen dioxide, are of usual concern in particulate air pollution studies, although this was unlikely in the present study since previously obtained measurements among this cohort during welding were low and uncorrelated with PM.[38] In general, these gaseous concentrations are low in manual metal arc welding under a variety of operating conditions.[39]

In addition, effects of other factors of work besides our exposures of interest on augmentation index were not explored. Importantly, though, we were able to control for some potential effects of physical and mental stresses possibly related to work and the augmentation index by considering heart rate to be a surrogate measure. Our analysis using nonheart rate adjusted augmentation index yielded smaller effect estimates, indicating control of some of the potentially confounding effects of mental and physical stress. Notably, heart rate may be an intermediate between PM exposure and augmentation index, as PM exposures have been associated with increased heart rate.[40] However, larger effect estimates would have been observed in the nonadjusted analysis if controlling for heart rate had blocked some of the effects.

Our study was also limited by the small sample size and the occurrence of exposures before monitoring. Ideally all workers would have had an adequate washout period before monitoring. Despite this limitation that reduced statistical power, we were able to make observations about the effects of exposure over the course of more than 24 hours. However, the lack of detailed information on welding fume exposures incurred the day before monitoring is a limitation in the interpretation of our findings. The increase in the afternoon augmentation index and the decrease in the next-morning augmentation index, with resultant flattening of the circadian variation with consecutive days of welding fume exposure, should be further investigated by monitoring workers over longer durations and under a variety of recorded working conditions. Future studies should also evaluate the roles of specific metal components and smaller particle sizes (ie, ultrafine particles), as these may be particularly toxic.

The generalizability of our findings to other welders or groups exposed to PM is uncertain because of differing exposure patterns, exposure intensities, and particulate matter

composition. In addition, our small sample size may present another limitation in the generalizability of our findings to other welders. However, we found that baseline values for our participants who were unexposed the day before monitoring had values comparable to other healthy volunteers,[22,28] and the variation in augmentation index levels for those unexposed both days was similar to that observed in a study of men and women of comparable age to our study group.[31]

In summary, we observed acute changes in the augmentation index after exposure to welding fume that were related to the level of $PM_{2.5}$. However, the clinical consequences of acute changes in the augmentation index and alterations in its circadian variation are unclear. In a compromised vasculature and in the presence of a vulnerable plaque, it is reasonable to expect that an acute change in the augmentation index corresponding to vasoconstriction may lead to increased susceptibility to disruption of a vulnerable plaque and therefore increased risk of myocardial infarction. Ascertaining whether repeated and prolonged acute changes in the augmentation index in healthy individuals leads to compromised cardiovascular conditions will require further research. Nonetheless, our results support the possibility that alterations in vascular function occur subsequent to metal-rich PM exposure.

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