Urinary 8-Isoprostane and 8-OHdG Concentrations in Boilermakers With Welding Exposure

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Objective: *To investigate the association of exposure to fine particulate matter ($PM_{2.5}$) with DNA damage and oxidative stress in boilermakers exposed to welding fumes.* ***Methods:*** *Forty-one workers were monitored over 24 hours during which baseline, postshift, bedtime, and next morning measurements were collected. Twenty-two workers participated as controls.* ***Results:*** *Linear regression was used to model pairwise change in u-8-isoprostane and u-8-OHdG: pre- to postshift, preshift to bedtime, postshift to bedtime, and postshift to next morning. In the models, pre- to postshift change in 8-OHdG was statistically significant, whereas postshift to bedtime change in 8-isoprostane showed an unexpected inverse relationship with $PM_{2.5}$.* ***Conclusions:*** *Acute welding exposure is associated with a postshift blunting of systemic inflammation in chronically exposed boilermakers, as measured by 8-isoprostane. The level of oxidative DNA damage as measured by 8-OHdG is less clear.* (J Occup Environ Med. *2008;50:182–189*)

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Oxidative stress and oxidative DNA damage have been the focus of much research attempting to understand the pathogenesis of morbidity and mortality related to coronary artery disease,[1] diabetes mellitus,[2] and obesity.[3] Correlates of oxidative stress have also been used to understand occupational illness, particularly among welders.[4–9] The process of welding generates high levels of metal fume containing primarily fine and ultrafine particles.[10] Welding fumes are known to cause a variety of health effects[11] including metal fume fever,[12] occupational asthma, industrial bronchitis, and pneumonia.[6,13–14] Epidemiologic studies have also shown associations with increased rates of cancer in welders.[15,16]

8-iso-prostaglandin $F_{2\alpha}$ (8-isoprostane) has been used widely in research as a biomarker of oxidative stress, formed by the oxidative metabolism of arachidonic acid. It is thought to be a stable and reliable marker of oxidative stress without diurnal variation.[17] Disease states such as type 2 diabetes mellitus,[2] obesity,[3] coronary heart disease,[1] asthma,[18–20] and acute respiratory distress syndrome[21] have all been studied using 8-isoprostane as a potential pathophysiologic or risk marker. The use of 8-isoprostane in occupational research has been much more limited, however. One of the few studies has been Han et al's investigation of oxidative stress and free-radical activity in asymptomatic shipyard welders.[4] This group was investigating the potential etiology of the wide variety of welding-induced health problems. They found elevated serum 8-isoprostane levels in the male welders as compared with male office workers, even when controlling for age and smoking status.

Excreted in urine as a DNA repair product, 8-hydroxy-2′-deoxyguanosine (8-OHdG) is a biomarker of oxidative DNA damage and repair, and is therefore a potential marker of carcinogenicity as well as oxidative stress.[22] It has been shown that smokers can excrete up to 50% more urinary 8-OHdG (u-8-OHdG) at baseline than nonsmokers,[22,23] and that environmental tobacco smoke can also induce production in u-8-OHdG in vitro.[24] Furthermore, Mizoue et al have shown an inverse relationship between body mass index (BMI) and u-8-OHdG in smoking Japanese workers.[25] Compared with 8-isoprostane, 8-OHdG has been used more extensively in occupational research, although results have been mixed. One study of boilermakers during a boiler overhaul showed increased u-8-OHdG levels postshift when adjusting for smoking and age.[9] The primary exposures in this study were metal fume and fine particulate matter (PM) from welding, as well as residual oil fly ash. In a similar study from the same boiler overhaul, it was shown that the excretion of u-8-OHdG was influenced heavily by smoking status and the specific metal components of the metal fume.[8] In this study, however, nonsmokers had higher levels of u-8-OHdG excretion at baseline, in contrast to previous literature cited above. In other studies, ambient air pollution appeared to increase u-8-OHdG excretion in urban bus drivers,[26] but polyaromatic hydrocarbons in diesel exhaust appeared to have no relationship with u-8-OHdG levels.[27]

In this study, we hypothesized that the acute welding exposure induces a local and systemic inflammatory response, and this response might be elucidated by cross-shift measurements of urinary 8-OHdG and 8-isoprostane. Using a cohort of boilermakers performing welding, we assessed the change over time in urinary biomarkers by taking samples at preshift (baseline), postshift, bedtime, and the next morning. These four time points should allow a more complete picture of the inflammatory response than pre- and postshift values used in other studies.

Materials and Methods

Study Design

The study was a short-term prospective study of boilermakers performing welding.

Study Population

The Institutional Review Board of the Harvard School of Public Health (Boston, MA) approved the study. Written consent was obtained from each subject. The study population was 41 men and consisted of a mix of current boilermakers, apprentice boilermakers, and some retirees. Subjects were recruited from union rolls. Participants were monitored over several weekends during two separate study periods in January and February 2004 and 2006.

Work Description

Welding was performed at the apprentice school within the union hall of the Boilermakers Local 29 in Quincy, MA, where the participants used their usual work practices while welding in booths throughout the day. Subjects arrived on Saturday morning around 7:30 AM, and after preshift health monitoring was performed, they welded for approximately 6 hours including a 30- to 60-minute lunch break. All participants were performing stick welding with mild steel.

Control Population

Boilermakers participating as welders in the study were also recruited to serve as controls on another weekend. On those control weekends, they also arrived at the union hall on Saturday at 7:30 AM and underwent identical testing as the welders throughout the study period. They remained, however, in the union hall proper during the study period, separated from the apprentice school where welding was taking place. All controls also participated in a welding weekend, but not all welders participated in a control weekend.

Urine Collection

All participants completed a self-administered modified American Thoracic Society questionnaire with specific data collected on medical history, respiratory symptoms, smoking history, and work exposure history. Spot urine samples were collected from each subject preshift (baseline), postshift, bedtime, and the next morning thus covering a 24-hour period and leading to a maximum of four urine samples for each individual. All urine samples were dipped on-site for semiquantitative urinalysis. Spot urinary creatinine was measured for each sample (PathLab Inc., Portsmouth, NH).

Blood Collection

A fasting blood sample was drawn on both mornings of the study period (preshift and next morning) and was analyzed for fasting cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides. The lipid profile from the first morning (preshift) was used for analyses unless the triglyceride level was at least 100 mg/dL greater than the next morning sample. In such cases, the first morning's sample was presumed to be nonfasting, and the second morning's results were used instead.

Spirometry

Micro Plus handheld turbine spirometers (Micro Medical Ltd., Kent, UK) were used to measure forced expiratory capacity in the first second (FEV_1), forced vital capacity (FVC), and peak expiratory flow on participants at baseline before the simulated work shift. Before the measurements were taken, all participants were weighed on a portable scale, and their height was measured with shoes off. For one subject, self-reported weight of 375 pounds was used (based on a recent doctor's visit) because the scale could not read beyond approximately 300 pounds. The same equipment was used in 2004 and 2006. Percent predicted values of FEV_1 and FVC were then calculated for each subject using the Knudsen equations.[28]

Particulate Exposure Assessment

Personal breathing zone measurements were taken across the shift period. The exposure time was calculated using the "on" and "off" times logged from when the monitor was attached to the participant and turned on, and then when the monitor was turned off postshift. Integrated gravimetric samples were collected by using KTL cyclones (GK2.05 SH cyclones, BGI Inc., Waltham, MA) with an aerodynamic diameter cut point of 2.5 μm. The cyclones were used in-line with pumps drawing 3.5 L/min of air. An average flow rate was calculated by recording the actual flow rate at the beginning and end of the sampling period, and dividing by two. The sampled air volume was calculated by multiplying the sampling time by the average flow rate. The PM was collected using 37-mm polytetrafluoroethylene membrane filters in the cyclones. Filters were first conditioned in a temperature- and humidity-controlled room for 24 hours before as well as 48 hours after the study period. After the prestudy conditioning, the filters were weighed using an MT5 microbalance (Mettler-Toledo, Inc., Columbus, OH). A detailed weighing protocol was used which included daily calibration of the balance, periodic weighing of standards, and a minimum of two weight determinations per sample. The mass collected on the filter was calculated as the difference between the pre- and postsampling filter weights. The gravimetric $PM_{2.5}$ mass concentration was then calculated by dividing the mass collected on the filter by the sampled air volume. The gravimetric measurements were used for the current analyses.

Urinary 8-OHdG Testing

U-8-OHdG levels were determined using a competitive enzyme-linked immunoassay performed by Genox Corporation (Baltimore, MD). Briefly, 50-μL urine samples along with standards were mixed with 50 μL of anti-8-OHdG monoclonal antibody and then treated with 8-OHdG protein conjugate. The samples were allowed to react for 1 hour at 37°C. After washing, an enzyme-labeled secondary antibody was added and allowed to react for 1 hour at 37°C. After a second washing stage, 100 μL of the chromatic substrate (3,3′,5,5′)-tetramethlbenzidene was added and allowed to react at room temperature for 15 minutes. The optical density of the resulting yellow color was then measured at 490 nm. Quality control (QC) was conducted using pooled urine samples randomly intermixed with study samples. The measured QC values were averaged and compared with the established QC value with acceptable values predetermined as the mean ± 2 SD. For each study sample, duplicate or triplicate measurements were performed, and any sample with a coefficient of variation (%) ≥20% was retested. The limit of detection (LOD) for 8-OHdG is 0.64 ng/mL. For results below the LOD, the LOD/2 (or 0.32) was used in analyses. The concentration of u-8-OHdG was adjusted to the urinary concentration of creatinine (ng 8-OHdG/mg creatinine) to control for variations in dilution of urine. As these were spot samples, no correction was made for volume of urine collected.

Urinary 8-Isoprostane Testing

U-8-isoprostane levels were determined using a competitive enzyme-linked immunoassay performed by Genox Corporation. Briefly, a polyclonal antibody to 8-isoprostane is used to bind 8-isoprostane in the sample. After simultaneous incubation at room temperature, samples were washed, and substrate was added. After a short additional incubation, the enzymatic reaction was stopped with a stop solution, and the optical density of the yellow color generated was read at 405 nm. Pooled urine samples were used for QC, intermixed at random with study samples. The QC values were averaged and compared with established values. Acceptable QC values were predetermined as the mean ± 2 SD. Duplicate or triplicate measurements were performed on each study sample, and any sample with a coefficient of variation (%) ≥20% was retested. As with u-8-OHdG, values were adjusted for spot urine creatinine to control for variations in dilution of urine.

Statistical Analysis

Linear regression was used to investigate the association of changes in u-8-OHdG and u-8-isoprostane among the entire study population (welders and controls) with the following potential explanatory variables: $PM_{2.5}$, age, BMI, smoking status (current or noncurrent), self-reported total years as a smoker, years as a boilermaker (self-reported, and verified by union records), baseline lung function, and duration of the welding shift. Analysis was carried out using SAS v9.1 (SAS Institute, Inc., Cary, NC). Because outcome variables did not meet criteria for normality by examining the skewness, kurtosis, and the Shapiro-Wilk diagnostic, Wilcoxon tests were used in unadjusted analyses. Except for current smoking status, which was considered as a dichotomous variable, all other variables were considered as continuous. Linear regression models were used to investigate the potential influential covariates as predictors of the change in u-8-OHdG or u-8-isoprostane from one time point to another, therefore creating models for each biomarker of 1) preshift to postshift change, 2) preshift to bedtime change, 3) postshift to bedtime change, and 4) postshift to next morning change. Both backward and stepwise elimination methods were used to select the statistically significant covariates, and the significant models and significant covariates were the same with both methods. $PM_{2.5}$ and dichotomous smoking status were forced into all models. With welders and controls considered together in the models, $PM_{2.5}$ served as the exposure measurement for welding status. Formal statistical significance was defined a priori as $P \leq 0.05$, but $P = 0.1$ was used to determine covariates' inclusion in the models. Modeling also included an investigation of confounding and effect modification.

Results

Study Population and Demographics

Table 1 summarizes major subject characteristics. In 2004, 23 boilermakers participated; in 2006, 27 boilermakers participated. Eight boilermakers participated in both years. Of these 42 participants, 23 boilermakers also participated in a control weekend. One participant from 2006 had to be excluded for active treatment of stage IV lung cancer; this participant had completed both an exposure and a control weekend. Thus in total, 41 exposure (welding) weekends and 22 control weekends were analyzed. Age ranged from 24 to 62, and years as a boilermaker ranged from 0 (two new apprentices) to 33. The cohort was relatively obese with a mean BMI of 30.5. Overall, 35% participants were active smokers. Among the welding group, 34% were active smokers; among the control group, 36% were active smokers. This difference was not statistically significant. The welding and control groups did not differ in any demographics or baseline characteristics except for $PM_{2.5}$ exposure ($P < 0.0001$), as would be expected. The mean gravimetric $PM_{2.5}$ in the welding group was 0.82 mg/m^3, and 0.05 mg/m^3 in the control group. Percent predicted FEV_1 at baseline trended toward significance, however, with $P = 0.08$. When comparing smokers with nonsmokers at baseline (Table 2), subjects varied significantly by BMI with smokers being leaner, but mean BMI in smokers still fell into overweight range at 28.1. Baseline u-8-OHdG was higher in smokers, trending toward significance with $P = 0.09$ (Table 3). No other covariates, including lipid profiles or $PM_{2.5}$, varied between smokers and nonsmokers.

Urinary 8-Isoprostane Analysis

In total, there were 63 urine samples tested for the pre- and postshift time points. Only 39 (62%) bedtime samples were successfully collected, and 48 (76%) next morning samples. In unadjusted analyses, mean u-8-isoprostane levels between welders

TABLE 1
Subject Characteristics

	Mean ± SD (Range)
Age (yr)	40 ± 10 (24–62)
BMI	31 ± 6 (21–55)
Total yr as a smoker	10 ± 10 (0–37)
Total yr as a boilermaker	10 ± 10 (0–33)
Fasting total cholesterol (mg/dL)	212 ± 49 (124–379)
FEV_1 predicted at baseline (%)	96 ± 13 (70–130)
FVC predicted at baseline (%)	99 ± 12 (78–128)
Duration of welding shift (hr)	6.1 ± 1.6 (2.6–8.7)

TABLE 2
Comparison of Baseline Characteristics of Welders vs Controls

	Welders (n = 41) Mean ± SD	Controls (n = 22) Mean ± SD	Wilcoxon P Value
Age (yr)	39.9 ± 9.7	40.1 ± 11.4	0.9
BMI	31.0 ± 6.6	29.7 ± 5.6	0.6
Current smoking status	—	—	0.9
Total yr as a smoker	9.5 ± 9.9	11.9 ± 10.6	0.4
Total yr as a boilermaker	9.4 ± 7.7	11.3 ± 11.4	0.5
Fasting total cholesterol (mg/dL)	218.0 ± 53.8	200.0 ± 36.4	0.2
FEV_1 predicted at baseline (%)	93.4 ± 11.7	99.5 ± 14.0	0.08
FVC predicted at baseline (%)	96.9 ± 11.6	101.9 ± 12.2	0.1
Duration of welding shift (hr)	6.0 ± 1.5	6.1 ± 1.7	0.9
$PM_{2.5}$ exposure (mg/m^3)	0.82 ± 0.65	0.05 ± 0.05	<0.0001

TABLE 3
Comparison of Baseline Characteristics of Current Smokers vs Current Nonsmokers

	Smokers (n = 22) Mean ± SD	Nonsmokers (n = 41) Mean ± SD	Wilcoxon P Value
Age (yr)	37.2 ± 9.9	41.4 ± 10.2	0.1
BMI	28.1 ± 5.8	31.8 ± 6.2	0.02
Total yr as a boilermaker	7.0 ± 1.2	11.6 ± 11.4	0.1
Fasting total cholesterol (mg/dL)	206.5 ± 41.5	214.6 ± 52.7	0.6
FEV_1 predicted at baseline (%)	95.3 ± 11.4	95.6 ± 13.6	0.8
FVC predicted at baseline (%)	97.6 ± 10.0	99.2 ± 13.0	0.6
Duration of welding shift (hr)	6.2 ± 1.7	6.0 ± 1.5	0.7
Preshift u-8-isoprostane (pg/mg creatinine)	18.4 ± 11.6	14.9 ± 11.0	0.9
Preshift u-8-OHdG (ng/mg creat)	0.2 ± 0.07	0.1 ± 0.07	0.09
$PM_{2.5}$ exposure (mg/m^3)	0.67 ± 0.85	0.49 ± 0.49	0.8

and controls at each of the four monitoring times were not significantly different. When comparing pre- with postshift change, preshift to bedtime change, postshift to bedtime change, and postshift to next morning change, there were also no statistically significant differences between welders and controls.

In adjusted analyses, linear regression was used to compare these four periods of change (Table 4), as described earlier. Models for pre- to postshift change and preshift to bedtime change were not significant, although the pre- to postshift model trended toward significance with a P value of 0.09. Both the postshift to bedtime change and postshift to next morning change were significant. In the postshift to bedtime model ($P = 0.03$, $R^2 = 0.23$), $PM_{2.5}$ was the most significant covariate, and smoking status was not significant. Interestingly, however, $PM_{2.5}$ had an inverse relationship to u-8-isoprostane, as did smoking status. In the postshift to next morning model ($P = 0.003$, $R^2 = 0.38$), age, BMI, and baseline FVC percent predicted were all highly significant. The duration of the simulated work shift was also relatively significant, although $PM_{2.5}$ and smoking status were not. Again, $PM_{2.5}$ and smoking status showed an inverse relationship with u-8-isoprostane. When graphing the change over the 24-hour study period using the parameter estimates for $PM_{2.5}$ (Fig. 1), it appears that u-8-isoprostane initially rises over the shift, but then drops abruptly below baseline values to a bedtime nadir. It then returns to a baseline level by the following morning.

TABLE 4
Linear Regression Models of Change in Urinary 8-Isoprostane Across Time Points[a]

Model and Covariates	Parameter Estimate (SE)	P
Preshift to postshift change		0.09
$PM_{2.5}$	365.8 (214.8)	0.09
Current smoking status (no = 0, yes = 1)	227.8 (293.6)	0.4
Years as a boilermaker	28.5 (13.7)	0.04
Preshift to bedtime change		0.9
$PM_{2.5}$	29.5 (382.9)	0.9
Current smoking status	197.6 (521.1)	0.7
Postshift to bedtime change		0.03
$PM_{2.5}$	−585.6 (237.3)	0.03
Current smoking status	−38.0 (324.3)	0.9
Baseline FVC predicted (%)	−21.8 (11.9)	0.08
Postshift to next day change		0.003
$PM_{2.5}$	−372.8 (227.8)	0.1
Current smoking status	−349.0 (314.5)	0.3
Age	32.3 (13.4)	0.02
BMI	−74.9 (23.2)	0.003
Baseline FVC predicted (%)	−38.4 (13.6)	0.006
Duration of welding	3.4 (1.7)	0.05

[a]PM2.5 and current smoking status were forced into all models. Backward and stepwise elimination methods were used to select other possible covariates that included age, BMI, self-reported total year as a smoker, year as a boilermaker, baseline FEV_1 and FVC, and duration of welding. All participants (welders and controls) are included in the models.

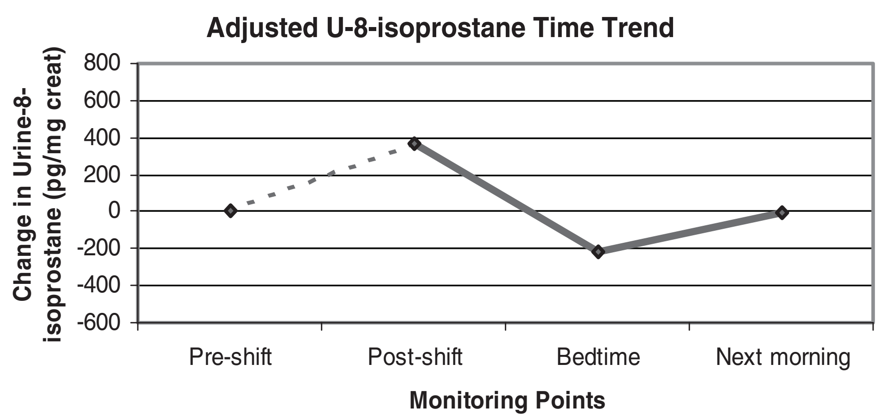

Fig. 1. Change in u-8-isoprostane over the study period for the whole population, expressed as parameter estimates for $PM_{2.5}$. Solid lines indicate significant changes. In the postshift to bedtime model, $PM_{2.5}$ is the main predictor of change in u-8-isoprostane. In the postshift to next morning model, the most significant predictors were age, BMI, and baseline FVC (Table 4).

Urinary 8-OHdG Analysis

In total, there were 63 urine samples tested for the pre- and postshift time points. Only 37 (59%) bedtime samples were successfully collected, and 48 (76%) next morning samples. In unadjusted analyses, mean u-8-OHdG levels between welders and controls at each of the four monitoring times were not significantly different. When comparing preshift with postshift change, welders had a significantly higher rise in u-8-OHdG excretion ($P = 0.03$). When comparing preshift with bedtime change, postshift to bedtime change, and postshift to next morning change, however, there were no statistically significant differences.

The only significant adjusted model was for pre- to postshift change ($P = 0.03$, $R^2 = 0.17$). No individual covariates in this model were significant to a $P = 0.05$ level; $PM_{2.5}$ and baseline FEV_1 percent predicted were significant at the 0.10 level, however. In this model, $PM_{2.5}$ has the expected direct relationship with u-8-OHdG excretion, although the other three nonsignificant models show the reverse (Table 5). Again, plotting the change over the 24-hour study period using the parameter estimates for $PM_{2.5}$ (Fig. 2), the shape of the curve is the same as for u-8-isoprostane, although only the first phase, showing a rise over the work shift, is statistically significant.

TABLE 5
Linear Regression Models of Change in Urinary 8-OHdG Across Time Points[a]

Model and Covariates	Parameter Estimate (SE)	P
Preshift to postshift change		0.03
$PM_{2.5}$	2.4 (1.4)	0.09
Current smoking status (no = 0, yes = 1)	3.0 (1.9)	0.1
Baseline FEV1% predicted	−0.1 (0.07)	0.06
Duration of work shift	0.02 (0.009)	0.1
Preshift to bedtime change		0.8
$PM_{2.5}$	−1.1 (3.2)	0.7
Current smoking status	2.6 (4.6)	0.6
Postshift to bedtime change		0.4
$PM_{2.5}$	−1.3 (3.4)	0.7
Current smoking status	−6.0 (4.9)	0.2
Postshift to next day change		0.2
$PM_{2.5}$	−3.5 (2.8)	0.2
Current smoking status	−2.8 (3.5)	0.4
Age	−0.3 (0.2)	0.08

[a]$PM_{2.5}$ and current smoking status were forced into all models. Backward and stepwise elimination methods were used to select other possible covariates that included age, BMI, self-reported total year as a smoker, year as a boilermaker, baseline FEV_1 and FVC, and duration of welding. All participants (welders and controls) are included in the models.

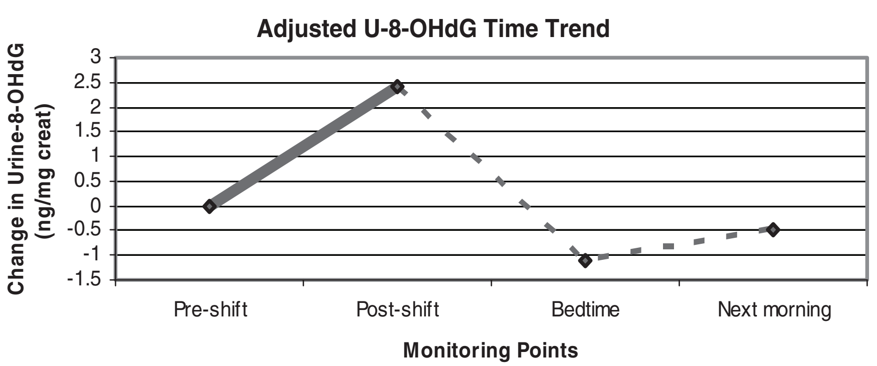

Fig. 2. Change in u-8-OHdG over the study period for the whole population, expressed as parameter estimates for $PM_{2.5}$. Solid lines indicate significant changes. In the preshift to postshift model, $PM_{2.5}$ and baseline FEV_1 are the most significant predictors of change in u-8-OHdG (Table 5).

Discussion

In this study, acute welding exposure was associated with a drop in u-8-isoprostane in the immediate postshift period, normalizing back to baseline by 24 hours from the start of the exposure. We hypothesize that this is evidence of a delayed blunting of the systemic inflammatory response. Measurement of u-8-OHdG showed a similar pattern, but models were less significant and explained less of the variability in biomarker measurements. Although the initial rise in u-8-isoprostane was expected, this change from preshift and postshift was not significant. The abrupt drop in the immediate postexposure period, from postshift to bedtime, was a significant and unexpected result. The recovery period appeared to occur between bedtime and the following morning. Although the drop in u-8-isoprostane was predicted by $PM_{2.5}$ exposure, the recovery period was not; instead, recovery was predicted by baseline characteristics such as age, BMI, FVC, as well as the duration of the exposure period.

The results in this study are unlikely to be affected by welding outside the study period. The study was conducted in January and February of the two study years, and most participants were not currently on a job because of the seasonal nature of work. Of the very few participants who were working, none had welded in the 2 days before the study period according to their self-report of last welding day.

Current smoking status was forced into all models as a likely confounder. Baseline values of u-8-isoprostane did not differ between smokers and nonsmokers, but u-8-OHdG excretion did trend toward significance. Because our welding and control groups had equal proportions of current smokers (34% and 36%, respectively), any differences in biomarkers that might be attributable to current smoking status should not affect the results either. We used total years of smoking as our continuous smoking metric because of missing data on intensity of exposure. This metric of duration only has been used in studies of diseases such as lung cancer, colon cancer, and Parkinson's disease.[29–33] In a study by Thurston et al, various smoking metrics were examined, and smoking duration did have a similar relationship to lung cancer risk as the pack-years metric more commonly used.[29]

This study did not characterize individual metal composition of the metal fume exposure because it is underpowered for such analysis. We restricted welding activities to stick welding with mild steel to keep the exposure as homogeneous as possible. Previous studies of a similar cohort done by our group have analyzed concurrent gases emitted during welding, namely nitrogen dioxide and ozone. The study by Liu et al in particular found that exposure was negligible.[34] Thus, we chose not to measure these gases in the current study.

The choice of analysis methodology was influenced by the unbalanced exposed and control groups as well as missing data for the bedtime and next morning urine samples, which made repeated measures analysis difficult. The bedtime sample relied on participants remembering to collect it, and remembering to bring it in on the next study day. This created more missing data than the next morning samples, which were only missing in the participants unable to return for the second study day. By using this pair-wise modeling approach, however, we may have underpowered our results. The linear regression method is also unable to account for correlation between measurements in the same subject the way that repeated measures methodology does. Still, our four-model approach made it possible to graph change over time, and to isolate factors influencing biomarker levels during various times in the 24-hour study period.

The inverse relationship between $PM_{2.5}$ and u-8-isoprostane in the roughly 8 hours after cessation of exposure may be the most intriguing finding in this study. There is very limited literature showing potential downregulation of inflammatory mechanisms in occupational groups, such as that shown in the current study. The literature that does exist, however, includes four studies in welders. In a study by Palmer et al, investigating the increased risk of pneumonia in welders, sputum interleukin-8 levels were decreased in welders versus matched controls from the same workplace who did not have welding fume exposure.[6] The authors hypothesized that this might point to a muted response of welders to inhaled PM. Furthermore, in the control population, serum matrix metalloproteinase-9 and immunoglobulin A levels were higher in smokers than nonsmokers; in the welders, however, this differential was not present. In other words, the welding exposure seemed to negate the protective benefit of being a nonsmoker. In a study by Fidan et al, investigators looked at oxidant-antioxidant status in welders from the automotive industry.[7] Controls were unexposed workers in the same industry. Welders in this study were found to have decreased total protein sulfhydryl groups, and decreased erythrocyte glutathione as compared with controls. Authors here hypothesized an impaired oxidative-antioxidative balance in the welders, and perhaps a decreased ability to cleanse oxygen radicals.

Finally, two studies from our own laboratory group have shown similar results. Firstly, Mukherjee et al. performed a study on boilermakers during a boiler overhaul, which involved exposure to metal fume and fine particulate as well as residual oil fly ash.[8] In the nonsmokers, u-8-OHdG levels were actually higher at the start of the study than in the smokers. These levels declined rapidly to those of the smokers, however, as the 5-day working week began. The authors hypothesized that there may be a downregulation in the ability to repair DNA among boilermakers. In the microarray study by Wang et al, preshift and postshift gene expressions were compared.[35] This study used a similar cohort of boilermakers and a similar work shift design as the current study. Interleukin-8 and other cytokines and receptor genes were transcriptionally downregulated in response to inhalation of metal fume and fine particulate.

One important aspect of this study's design that differs from much of the preexisting literature is that the control group participants are still career boilermakers with chronic welding exposures. This may influence the body's response to acute exposures, either as a protective mechanism from a constantly heightened state of oxidative stress and damage, or as a maladaptive phenomenon resulting from exposure-related dysfunction. In the case of u-8-OHdG, for instance, decreased levels could point to decreased DNA damage, or merely to decreased DNA repair activity. Several unanswered questions remain, including: 1) what is the mechanism of this inflammatory downregulation? 2) why is downregulation evident in welders but not other occupational groups? and 3) is this downregulation a protective or a maladaptive phenomenon? Further research is needed to elucidate the answers to these questions.

Conclusion

Acute welding exposure is associated with a postshift blunting in the systemic inflammatory response of chronically exposed boilermakers as measured by u-8-isoprostane. Recovery to baseline levels was predicted not by $PM_{2.5}$ or smoking status, but by the baseline characteristics of age, BMI, and baseline FVC percent predicted. The inverse relationship in the initial postshift period between u-8-isoprostane and $PM_{2.5}$ was unexpected. The mechanism of this phenomenon is unclear and should be the subject of further research. The magnitude of oxidative DNA damage as measured by u-8-OHdG is less clear from the current study, although the pattern of change over time appears to be similar to that of u-8-isoprostane.

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