Published in final edited form as:

Occup Environ Med. 2011 July ; 68(7): 474–478. doi:10.1136/oem.2010.055681.

Cardiac Autonomic Dysfunction from Occupational Exposure to Polycyclic Aromatic Hydrocarbons

Mi-Sun Lee, PhD, MPH, Shannon Magari, ScD, MS, MPH, and David C. Christiani, MD, MPH, MS*

Environmental and Occupational Medicine and Epidemiology Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA

Abstract

Objectives—Polycyclic aromatic hydrocarbons (PAHs) exposures have been associated with cardiopulmonary mortality and cardiovascular events. This study investigated the association between a biological marker of PAHs exposure, assessed by urinary 1-hydroxypyrene (1-OHP), and heart rate variability (HRV) in an occupational cohort of boilermakers.

Methods—Continuous 24-hour monitoring of the ambulatory electrocardiogram (ECG) and pre and post shift urinary 1-OHP were repeated over extended periods of the work week. Mixed effects models were fit for the 5-minute standard deviation of normal-to-normal intervals (SDNN) in relation to urinary 1-OHP levels pre and post workshift on the day they wore the monitor, controlling for potential confounders.

Results—We found a significant decrease in 5-min SDNN during work of –13.6% (95% confidence interval, –17.2% to –9.8%) for every standard deviation (0.53 microgram/gram [$\mu\text{g/g}$] creatinine) increase in the next-morning pre-shift 1-OHP levels. The magnitude of reduction in 5-min SDNN were largest during the late night period after work and increased with every standard deviation (0.46 $\mu\text{g/g}$ creatinine) increase in post-shift 1-OHP levels.

Conclusion—This is the first report providing evidence that occupational exposure to PAHs is associated with altered cardiac autonomic function. Acute exposure to PAHs may be an important predictor of cardiovascular disease risk in the work environment.

Keywords

heart rate variability; cardiac autonomic function; polycyclic aromatic hydrocarbons

INTRODUCTION

Cardiac autonomic dysfunction, mainly noted by reductions in heart rate variability (HRV), in relation to environmental toxic pollutants has been reported previously. Specifically, fine particulate matter [particles with a mean aerodynamic diameter less than 2.5 micrometers

*Reprint Requests and Correspondence: David C. Christiani, MD, MPH, MS, Environmental and Occupational Medicine and Epidemiology Program, Department of Environmental Health, Harvard School of Public Health, 665 Huntington Ave, Building I Room 1401, Boston, MA, 02115, Tel. 617-432-3323, Fax. 617-432-3441, dchris@hsph.harvard.edu.

Competing Interests

The authors declare that they have no competing interests.

Licence to BMJ Publishing Group Limited for Publication

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in Occupational and Environmental Medicine editions and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence <http://oem.bmjournals.com/misc/fora/licenceform.shtml>

(μm) ($\text{PM}_{2.5}$)]^{1–5} and airborne heavy metals⁶ are known to play a role in reductions in HRV parameters, implying their potential contributions to the global burden of cardiovascular disease (CVD).

Polycyclic aromatic hydrocarbons (PAHs) are considered human carcinogens⁷, and are encountered in a wide range of occupational settings such as the pyrolysis of fossil fuels, coal and coke production and iron and steel foundries, as well as in the ambient environment in air pollution and cigarette smoke. To assess the internal dose of PAHs exposure, urinary 1-OHP, a metabolite of pyrene, has been used widely as a relevant marker of ambient PAHs exposure in various occupational^{8–10} and non-occupational settings¹¹. While the carcinogenic potential of PAHs exposure in terms of increased risk of lung cancer¹² and cardiopulmonary mortality¹³ have been documented, very little is known about their adverse effects on the cardiovascular system. Recent research has shown that occupational exposure to PAHs is associated with an elevated risk of ischemic heart disease¹⁴ and mortality from CVD compared with the general population¹⁵. Experimental studies have demonstrated elevated blood pressure and heart rate¹⁶, development of arteriosclerosis¹⁷, impaired neurobehavioral activity¹⁸, and damage in neural cell¹⁹ with exposure to PAHs.

To date, no epidemiologic studies have examined the potential link between PAHs exposure and cardiac autonomic responses, specifically long-term HRV extended over two 24-hour periods. This study aimed to provide information on the effect of PAHs exposure, assessed by analyzing the association of repeat urine samples analyzed for 1-OHP, on HRV parameters among a cohort of boilermakers exposed to the combustion products contained in an oil fired boiler.

METHODS

Study Population

A repeated measures short-term prospective study on a cohort of boilermakers was established in 1998. The study population consisted of 40 male boilermakers working at a union welding school and a power plant during the overhaul of an oil-fired boiler⁴ in eastern Massachusetts. These boilermakers are exposed to PAHs from several sources including first and second hand tobacco smoke and uniquely, ROFA (residual oil fly ash) during boiler repair work⁹. Participants responded to a self-administered questionnaire on demographic and medical history (e.g., respiratory and cardiac systems) and completed PAHs biomonitoring (pre-shift/post-shift urine samples) and ECG monitoring over two 24 hour periods. The study protocol was approved by the Institutional Review Board of the Harvard School of Public Health. Written informed consent was obtained from all participants.

Urinary 1-OHP and Cotinine and Creatinine Analysis

We collected spot urine samples in sterile sample cups at the start (pre-shift) and end (post-shift) of each workshift, for up to 5 consecutive work days with the maximum number of 10 urine samples from each subject. Out of 253 urine samples collected, 139 pre-shift and 112 post-shift, 2 were excluded in the analyses due to missing data on the time of sample collection. All urine samples were aliquotted and frozen at -20°C until laboratory analysis. The urinary 1-OHP was analyzed using reverse-phase high-performance liquid chromatography (HPLC) with fluorescence detection (FD). The analytic procedure has been described previously^{9, 20}. Briefly, 10 mL of urine from each sample was adjusted to pH 5.0 with acetic acid and acetate buffer (LabChem Inc, Pittsburgh, PA), and hydrolyzed enzymatically with β -glucuronidase/arylsulfatase (Sigma, St Louis, MO). The mixture was incubated overnight at 37°C in a shaking water bath. The extraction of the PAH metabolite was done by a solid-phase extraction (SPE) cartridge packed with C-18 reverse phase liquid

chromatographic material (Sep-Pak C18 cartridge, Millipore, Waters, Milford, MA, USA). The 1-OHP measurement was made using an Agilent 1100 HPLC modular system consisting of 4-solvent gradient pump system (G1311A), an autosampler (G1313A), vacuum degassing unit (G1322A) and a fluorescence detector (G1321A) with excitation wavelength of 240 nm and emission wavelength of 390 nm. The 1-OHP was determined using a 250–4 Merck LiChrospher® PAH column (Agilent Technologies, Palo Alto, CA). The limit of detection (LOD) for the assay was 0.034 ng/mL. Urinary cotinine analysis was performed at ESA Laboratories (Chelmsford, MA, USA). Cotinine was determined by reverse-phase HPLC combined with UV spectrophotometry detection⁹. Urinary creatinine, measured by the Jaffe reaction, was used to calibrate each sample. The concentrations of 1-OHP and cotinine were calculated as µg/g creatinine, respectively.

HRV Measurement

We used HRV and HR as measures of autonomic cardiac response to PAHs exposure. The electrocardiogram (ECG) of each individual was measured continuously for 24-hour using a five-lead ECG Holter monitor, Dynacord 3-Channel Model 423 (Raytel Cardiac Services, Windsor, CT). A detailed description for the ECG monitoring protocol has been provided previously⁴. Briefly, separate electrodes were placed at participant's skin, if needed, the area was shaved for proper adhesion and the leads were periodically checked by study staff. Each 24-hour recording was sent to Raytel Cardiac Services for processing and analysis using a StrataScan 563 (DelMar Avionics, Irvine, CA) and then screened to correct data artifacts. Only beats with an RR interval between 0.6 and 1.5 milliseconds (msec) and an RR ratio of 0.8 to 1.2 were included in HRV analysis. A trained professional with no exposure information performed all analyses and edited all normal or abnormal findings based on standard criteria. The SD of normal-to-normal intervals (SDNN, in milliseconds) as a time-domain HRV measure and the mean heart rate (HR, in beats per minute) were calculated in 5-minute segments for the entire recording.

Statistical Analysis

Dependent variables, 5-min HR and 5-min SDNN, were $\log_{10}$ transformed to improve normality and stabilize the variance. Potential confounders such as age, cotinine levels, at-work (or not), day of week, and heart rate, were identified *a priori* and included in the multivariate analysis. In general, urinary 1-OHP represents relatively recent exposures, generally within a few hours or days before urine collection, but does not sufficiently reflect the exposure at the time point of urine collection. Therefore, we investigated the association of worktime and nighttime HRV with creatinine-adjusted 1-OHP measurements analyzed in pre-shift and post-shift urine on the day the monitor was worn using mixed effects models. In general, their work period is from 0800 to 1430 hours (6 hours) and night period is from 0000 to 0600 hours (6 hours). We used 6-hour time windows for HRV and HR, derived from the continuous 5-min data, to estimate the effective time course of action of the 1-OHP levels throughout a 24 hour period. A random effect for each subject and fixed covariates such as age, urinary cotinine levels, and HR were treated as continuous variables and work (yes/no) and day of week as a dichotomous variable in the models. We estimated the percent change in the 6-hour time window of SDNN and HR for one standard deviation increase in creatinine-adjusted 1-OHP levels in pre and post-shift as $[10^{(\beta \times SD)} - 1] \times 100\%$, with 95% confidence intervals (CI) $\{10^{[SD \times (\beta \pm 1.96 \times SE)]} - 1\} \times 100\%$, where β and SE are the estimated regression coefficient and its standard error. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Table 1 summarizes the demographic and exposure characteristics and HRV measurements of the subjects. The study population consisted of 40, mostly Caucasian (92.5%) males, with an average age of 38.2 years (SD 12.7). The mean 5-min HR and 5-min SDNN were 83.3 beats per minute (SD 9.4) and 58.9 msec (SD 19.8), respectively. The geometric mean (GM) of creatinine adjusted 1-OHP concentration for the overall (pre and post-shift) urine samples was 0.26 $\mu\text{g/g}$ creatinine. When stratified by workshift, the means were 0.25 $\mu\text{g/g}$ creatinine for the pre-shift samples and 0.27 $\mu\text{g/g}$ creatinine for the post-shift samples.

We examined mixed effects regression models for the adjusted percent change in SDNN and HR during work time and night time, associated with creatinine-adjusted 1-OHP levels in the pre and post-shift urine sample (Table 2). During the work periods, SDNN significantly declined by 13.6% (95% CI, -17.2% to -9.8%, $P < 0.0001$) for every SD (0.54 $\mu\text{g/g}$ creatinine) increase in creatinine-adjusted pre-shift 1-OHP level on the next morning and by 10.1% (95% CI, -13.2% to -6.9%, $P < 0.0001$) for every SD (0.46 $\mu\text{g/g}$ creatinine) increase in creatinine-adjusted post-shift 1-OHP level after controlling for potential confounders. There was no significant association between HR and pre-shift 1-OHP level but an inverse association was found with the post-shift 1-OHP level. During the sleep periods, SDNN significantly declined by 10.0% (95% CI, -15.0% to -4.7%, $P = 0.0003$) and HR increased by 4.8% (95% CI, 3.1% to 6.6%, $P < 0.0001$) for every SD increase in creatinine-adjusted pre-shift 1-OHP level on the next day. We observed the most pronounced decline in SDNN during the night after the monitored work period, 18.9% (95% CI, -23.1% to -14.4%, $P < 0.0001$), and an increase in HR of 10.3% (95% CI, 8.9% to 11.7%, $P < 0.0001$) for one SD increase in creatinine-adjusted post-shift 1-OHP level.

Figure 1 presents the estimated percent changes in 6 hour time window of SDNN and HR with creatinine-normalized 1-OHP levels in the pre and post-shift urine. The 48-hour monitoring period, including a work interval and sleeping interval was depicted for capturing the time course of action of the biological PAHs exposure. For instance, the 6-hour time window of SDNN at 0800 hours and at 1400 hours means the SDNN data from 0500 to 1100 hours and 1100 to 1700 hours, respectively. After adjusting for potential covariates, a significant reduction in SDNN was found throughout the work time (1000 to 1400), and then gradually increased until going to sleep. In addition, the most pronounced depression in SDNN was during sleep periods, reaching a nadir during 0400 to 0500 hours and then steadily recovering until returning to work the next day. We also observed an increase in HR during the late night, reaching a zenith during the sleep period at 0400 to 0500 hours with a decrease after waking.

DISCUSSION

To our knowledge, there have been no other studies exploring the temporal relationship between occupational PAHs exposure and changes in cardiac autonomic function, as measured by long-term time domain HRV parameters, and with repeated biomonitoring measurements at specific time points. The present study demonstrates that biological PAHs exposure provokes an imbalance in cardiac autonomic control, as indicated by reductions in SDNN, and stimulating sympathetic nerve activity, as indexed by HR increases. More specifically, significant reductions in SDNN and increases in HR during the late night in association with pre-and postshift 1-OHP levels were found. Our results also provide the effective time course of action of the effects of 1-OHP levels on the time window of SDNN. Specifically, SDNN in relation to pre and postshift 1-OHP levels began to decline during work and markedly dropped during their sleep time and reached a nadir approximately 4 hours before returning to work.

To date, there is no evidence of an inverse association between occupational PAHs exposure and long-duration HRV declines. Most studies have focused on the effects of ambient particulate exposures^{1–5} and their components of transition metals⁶ on HRV. Therefore, our findings may not be directly comparable with other studies of ambient exposure. However, toxicological studies and epidemiologic investigations regarding other CVD outcomes with PAH-exposed occupations support our results, including elevated blood pressure and heart rate in rats¹⁶ and increased mortality from fatal ischemic heart disease¹⁴ and risk of cerebrovascular disease and arteriosclerosis²¹ in human studies.

Although the underlying pathophysiologic mechanism remains unclear, direct neurocardiac toxicity of PAHs exposure on the cardiovascular system, blood, and lung receptors and indirect effects mediated through oxidative stress pathways may be related²². PAHs are released into the environment in both gaseous compounds and particulate matter. Direct cardiac effects may occur because PAHs are lipophilic, and inhaled PAHs are retained in the respiratory tract²³. Some PAHs such as a Benzo[a]pyrene (B[a]P) can bypass the blood-brain barrier, mainly the cerebral capillaries, which restrict the passage of toxic chemicals into the central nervous system (CNS), and thereby gain direct access to the CNS²⁴. Additionally, B[a]P could reach the CNS indirectly via the olfactory nerve²⁵, and accumulate in the cerebellum²⁶ which may involve cardiovascular modulation²⁷. Rats exposed to PAHs evinced acute neurotoxicity such as neuromuscular defects, autonomic dysfunction, and delayed responses to sensorimotor stimuli^{18, 28, 29}. In addition, direct activation of pulmonary neural reflex arcs or alterations in cardiac ion channel may be potential mechanisms²². These effects can explain the acute (within several hours) cardiovascular responses such as increased incidence of myocardial infarction³⁰. Less acute (between a few hours to days) and chronic indirect effects may occur via oxidative stress pathways, which can lead to autonomic cardiac imbalance as an increase in sympathetic and a reduction in parasympathetic tone²². PAHs may affect autonomic cardiac dysfunction indirectly by promoting reactive oxygen species (ROS) by inducing xenobiotic metabolizing enzymes (XMEs) such as the cytochrome P450 (CYP) family that plays a central role in the onset, progression and prognosis of CVDs³¹ through an arylhydrocarbon receptor (AhR)-dependent manner^{32, 33}. The CYP families have been identified in cardiovascular tissue including heart, endothelial cells and smooth muscle of blood vessels³¹. Further support that PAHs exposure are associated with oxidative DNA damage³⁴, assessed by 8-Hydroxy-2'-deoxyguanosine (8-OHdG), and induction of lipid peroxidation³⁵, as measured by malondialdehyde (MDA), comes from studies of cooking oil fume exposed workers. Increased oxidative stress is responsible for activation of apoptosis in cardiac cells in the heart³⁶.

We found the 6-hour time windows of nighttime HRV and HR were associated with 1-OHP. The larger declines in HRV with 1-OHP levels were seen at late night (0000 to 0600) as compared to day time. The observed declines in nighttime HRV may be attributable to several possible explanations. First, according to previous investigations among boilermakers, HRV late at night may better capture the time course of biological response that occurs within the lag between exposure and outcomes of less than 24-hr². Second, the night period, mainly dominated by sleep, is generally free from potential confounders such as physical activity². Third, in general, urinary 1-OHP represents the recent cumulative exposures within several hours to days due to its short half-life. The half-lives of 1-OHP in earlier studies of workplace inhalation of PAHs varied between 6 to 35 h³⁷, 16 and 20 h³⁸, 6.1 h³⁹ and 9.8 h⁴⁰. Considering its short half-life and potential direct mechanism of action, PAHs exposure may lead to adverse cardiac autonomic outcomes on the same day, especially during the night time after work.

Our study suggests that PAHs exposure plays a critical role in alterations in cardiac autonomic function as measured by HRV in a healthy cohort of boilermaker construction workers. Although the relatively small sample size may limit the generalizability of this study, the link between decreased SDNN and biological PAHs exposure could be captured by the repeated measurements over 2 days. Noteworthy is that the declines in HRV were most distinct during the sleep period compared to worktime, implying evidence of acute cardiac toxicity of PAHs exposure.

Acknowledgments

The authors would like to thank Drs. Sutatpa Mukherjee, Jee-Young Kim, and Ema G. Rodrigues for their help in primary data collection and analyses, and Drs. Ki-Do Eum and Shona Fang for their comments in the data analysis.

Funding

This work was supported by National Institutes of Health grants R01ES9860 and ES000002.

Abbreviations

PAHs	polycyclic aromatic hydrocarbons
1-OHP	1-hydroxypyrene
ECG	ambulatory electrocardiogram
SDNN	standard deviation of normal-to-normal intervals
CVD	cardiovascular disease
HRV	heart rate variability
HR	heart rate

References

1. Baccarelli A, Cassano PA, Litonjua A, et al. Cardiac autonomic dysfunction: effects from particulate air pollution and protection by dietary methyl nutrients and metabolic polymorphisms. *Circulation*. 2008; 117:1802–9. [PubMed: 18378616]
2. Cavallari JM, Eisen EA, Chen JC, et al. Night heart rate variability and particulate exposures among boilermaker construction workers. *Environ Health Perspect*. 2007; 115:1046–51. [PubMed: 17637921]
3. Fang SC, Eisen EA, Cavallari JM, et al. Acute changes in vascular function among welders exposed to metal-rich particulate matter. *Epidemiology*. 2008; 19:217–25. [PubMed: 18300696]
4. Magari SR, Hauser R, Schwartz J, et al. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. *Circulation*. 2001; 104:986–91. [PubMed: 11524390]
5. Park SK, O'Neill MS, Vokonas PS, et al. Effects of air pollution on heart rate variability: the VA normative aging study. *Environ Health Perspect*. 2005; 113:304–9. [PubMed: 15743719]
6. Cavallari JM, Eisen EA, Fang SC, et al. PM2.5 metal exposures and nocturnal heart rate variability: a panel study of boilermaker construction workers. *Environ Health*. 2008; 7:36. [PubMed: 18613971]
7. IARC. Overall evaluations of carcinogenicity. Lyon (France): IARC; 1987. Vol Supplement No. 7
8. Mukherjee S, Rodrigues E, Aeschliman DB, et al. Urinary metal and polycyclic aromatic hydrocarbon biomarkers in boilermakers exposed to metal fume and residual oil fly ash. *Am J Ind Med*. 2005; 47:484–93. [PubMed: 15898092]
9. Mukherjee S, Rodrigues E, Weker R, et al. 1-hydroxypyrene as a biomarker of occupational exposure to polycyclic aromatic hydrocarbons (PAH) in boilermakers. *J Occup Environ Med*. 2002; 44:1119–25. [PubMed: 12500453]

10. Wu MT, Huang SL, Ho CK, et al. Cytochrome P450 1A1 MspI polymorphism and urinary 1-hydroxypyrene concentrations in coke-oven workers. *Cancer Epidemiol Biomarkers Prev.* 1998; 7:823–9. [PubMed: 9752993]
11. Lee MS, Eum KD, Lee K, et al. Seasonal and regional contributors of 1-hydroxypyrene among children near a steel mill. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:96–101. [PubMed: 19124486]
12. Armstrong B, Hutchinson E, Unwin J, et al. Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: a review and meta-analysis. *Environ Health Perspect.* 2004; 112:970–8. [PubMed: 15198916]
13. Burstyn I, Boffetta P, Heederik D, et al. Mortality from obstructive lung diseases and exposure to polycyclic aromatic hydrocarbons among asphalt workers. *Am J Epidemiol.* 2003; 158:468–78. [PubMed: 12936902]
14. Burstyn I, Kromhout H, Partanen T, et al. Polycyclic aromatic hydrocarbons and fatal ischemic heart disease. *Epidemiology.* 2005; 16:744–50. [PubMed: 16222163]
15. Randem BG, Langard S, Kongerud J, et al. Mortality from non-malignant diseases among male Norwegian asphalt workers. *Am J Ind Med.* 2003; 43:96–103. [PubMed: 12494426]
16. Sasser LB, Lundstrom DL, Zangar RC, et al. Elevated blood pressure and heart rate in rats exposed to a coal-derived complex organic mixture. *J Appl Toxicol.* 1989; 9:47–52. [PubMed: 2538501]
17. Penn A, Snyder C. Arteriosclerotic plaque development is ‘promoted’ by polynuclear aromatic hydrocarbons. *Carcinogenesis.* 1988; 9:2185–9. [PubMed: 3142695]
18. Saunders CR, Ramesh A, Shockley DC. Modulation of neurotoxic behavior in F-344 rats by temporal disposition of benzo(a)pyrene. *Toxicol Lett.* 2002; 129:33–45. [PubMed: 11879972]
19. Tang Y, Donnelly KC, Tiffany-Castiglioni E, et al. Neurotoxicity of polycyclic aromatic hydrocarbons and simple chemical mixtures. *J Toxicol Environ Health A.* 2003; 66:919–40. [PubMed: 12825237]
20. Jongeneelen FJ, Anzion RB, Leijdekkers CM, et al. 1-hydroxypyrene in human urine after exposure to coal tar and a coal tar derived product. *Int Arch Occup Environ Health.* 1985; 57:47–55. [PubMed: 4077281]
21. Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. *Am J Ind Med.* 1988; 14:403–15. [PubMed: 3189356]
22. Brook RD, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation.* 2004; 109:2655–71. [PubMed: 15173049]
23. Gerde P, Muggenburg BA, Hoover MD, et al. Disposition of polycyclic aromatic hydrocarbons in the respiratory tract of the beagle dog. I. The alveolar region. *Toxicol Appl Pharmacol.* 1993; 121:313–8. [PubMed: 8346548]
24. Ramesh A, Inyang F, Hood DB, et al. Metabolism, bioavailability, and toxicokinetics of benzo(alpha)pyrene in F-344 rats following oral administration. *Exp Toxicol Pathol.* 2001; 53:275–90. [PubMed: 11665852]
25. Persson E, Larsson P, Tjalve H. Cellular activation and neuronal transport of intranasally instilled benzo(a)pyrene in the olfactory system of rats. *Toxicol Lett.* 2002; 133:211–9. [PubMed: 12119129]
26. Moir D, Viau A, Chu I, et al. Pharmacokinetics of benzo[a]pyrene in the rat. *J Toxicol Environ Health A.* 1998; 53:507–30. [PubMed: 9561966]
27. Zhu JN, Yung WH, Kwok-Chong Chow B, et al. The cerebellar-hypothalamic circuits: potential pathways underlying cerebellar involvement in somatic-visceral integration. *Brain Res Rev.* 2006; 52:93–106. [PubMed: 16497381]
28. Saunders CR, Shockley DC, Knuckles ME. Behavioral effects induced by acute exposure to benzo(a)pyrene in F-344 rats. *Neurotox Res.* 2001; 3:557–9. [PubMed: 15111245]
29. Saunders CR, Shockley DC, Knuckles ME. Fluoranthene-induced neurobehavioral toxicity in F-344 rats. *Int J Toxicol.* 2003; 22:263–76. [PubMed: 12933321]
30. Peters A, Dockery DW, Muller JE, et al. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation.* 2001; 103:2810–5. [PubMed: 11401937]

31. Elbekai RH, El-Kadi AO. Cytochrome P450 enzymes: central players in cardiovascular health and disease. *Pharmacol Ther.* 2006; 112:564–87. [PubMed: 16824612]
32. Bin P, Leng S, Cheng J, et al. Association of aryl hydrocarbon receptor gene polymorphisms and urinary 1-hydroxypyrene in polycyclic aromatic hydrocarbon-exposed workers. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:1702–8. [PubMed: 18628420]
33. Korashy HM, El-Kadi AO. The role of aryl hydrocarbon receptor in the pathogenesis of cardiovascular diseases. *Drug Metab Rev.* 2006; 38:411–50. [PubMed: 16877260]
34. Pan CH, Chan CC, Wu KY. Effects on Chinese restaurant workers of exposure to cooking oil fumes: a cautionary note on urinary 8-hydroxy-2'-deoxyguanosine. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:3351–7. [PubMed: 19064550]
35. Pan CH, Chan CC, Huang YL, et al. Urinary 1-hydroxypyrene and malondialdehyde in male workers in Chinese restaurants. *Occup Environ Med.* 2008; 65:732–5. [PubMed: 18940956]
36. Cesselli D, Jakoniuk I, Barlucchi L, et al. Oxidative stress-mediated cardiac cell death is a major determinant of ventricular dysfunction and failure in dog dilated cardiomyopathy. *Circ Res.* 2001; 89:279–86. [PubMed: 11485979]
37. Jongeneelen FJ, van Leeuwen FE, Oosterink S, et al. Ambient and biological monitoring of cokeoven workers: determinants of the internal dose of polycyclic aromatic hydrocarbons. *Br J Ind Med.* 1990; 47:454–61. [PubMed: 2383514]
38. Buchet JP, Gennart JP, Mercado-Calderon F, et al. Evaluation of exposure to polycyclic aromatic hydrocarbons in a coke production and a graphite electrode manufacturing plant: assessment of urinary excretion of 1-hydroxypyrene as a biological indicator of exposure. *Br J Ind Med.* 1992; 49:761–8. [PubMed: 1463676]
39. Lafontaine M, Payan JP, Delsaut P, et al. Polycyclic aromatic hydrocarbon exposure in an artificial shooting target factory: assessment of 1-hydroxypyrene urinary excretion as a biological indicator of exposure. *Ann Occup Hyg.* 2000; 44:89–100. [PubMed: 10717260]
40. Brzeznicki S, Jakubowski M, Czerski B. Elimination of 1-hydroxypyrene after human volunteer exposure to polycyclic aromatic hydrocarbons. *Int Arch Occup Environ Health.* 1997; 70:257–60. [PubMed: 9342626]

Figure 1.

Percent change and 95% CIs in 6-hour time window in 5-min SDNN and 5-min HR associated per 1 SD ($0.53 \mu\text{g/g}$ creatinine) change in preshift 1-OHP levels and 1 SD ($0.46 \mu\text{g/g}$ creatinine) change in postshift 1-OHP levels using mixed-effects models adjusting for age, cotinine, working time or not (y/n), and day of week. SDNNs were additionally adjusted for HR. Error bars indicate 95% confidence intervals. Work time and night time indicate the periods during the day before preshift urine sampling. The star symbol-marked worktime represents the working daytime hours on the day of monitoring when postshift urines were sampled. The night time with the star symbol denotes the period after postshift urine sampling.

Table 1Demographic and exposure characteristics for study subjects ($n = 40$)

Characteristic	n (%) or Mean $\pm$ SD
Age (years)	38.2 $\pm$ 12.7
Race	
Caucasian	37 (92.5)
Black	2 (5.0)
Hispanic	1 (2.5)
5-min HR (bpm)	83.3 $\pm$ 9.4
5-min SDNN (msec)	58.9 $\pm$ 19.8
Cotinine (μ g/g creatinine) [†]	72.75 $\pm$ 7.74
1-OHP (μ g/g creatinine) [†]	0.26 $\pm$ 3.34
Preshift 1-OHP (μ g/g creatinine) [†]	0.25 $\pm$ 3.41
Postshift 1-OHP (μ g/g creatinine) [†]	0.27 $\pm$ 3.26

[†] GM $\pm$ GSD

Table 2

Estimated percent changes (95% CIs) in SDNN[†] and HR[‡] by work time and night periods with preshift and postshift 1-OHP (μg/g creatinine) levels using mixed-effects models

	Preshift 1-OHP (μg/g creatinine)	Post-shift 1-OHP (μg/g creatinine)
Worktime		
5-min SDNN [†]	-13.6 (-17.2 to -9.8) **	-10.1 (-13.2 to -6.9) **
5-min HR	-1.2 (-2.5 to 0.02)	-2.3 (-3.4 to -1.2) **
Night time		
5-min SDNN [†]	-10.0 (-15.0 to -4.7) **	-18.9 (-23.1 to -14.4) **
5-min HR	4.8 (3.1 to 6.6) **	10.3 (8.9 to 11.7) **

NOTE: Coefficients are expressed as percent change in SDNN and HR-associated per 1 SD (0.53 μg/g creatinine) change in preshift and 1 SD (0.46 μg/g creatinine) change in postshift 1-OHP levels adjusting for age (years), cotinine level (μg/g creatinine), working time or not (y/n), and day of week.

[†] Log₁₀-transformed value.

[‡] Additionally adjusted for HR.

* $P < 0.05$,

** $P < 0.00$