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Accessibility
Particulate Air Pollution, Oxidative Stress Genes, and Heart Rate Variability in an Elderly Cohort

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BACKGROUND AND OBJECTIVES: We have previously shown that reduced defenses against oxidative stress due to glutathione S-transferase M1 (GSTM1) deletion modify the effects of PM2.5 (fine-particle air pollution of < 2.5 µm in aerodynamic diameter) on heart rate variability (HRV) in a cross-sectional analysis of the Normative Aging Study, an elderly cohort. We have extended this to include a longitudinal analysis with more subjects and examination of the GT short tandem repeat polymorphism in the heme oxygenase-1 (HMOX-1) promoter.

METHODS: HRV measurements were taken on 539 subjects. Linear mixed effects models were fit for the logarithm of HRV metrics—including standard deviation of normal-to-normal intervals (SDNN), high frequency (HF), and low frequency (LF)—and PM2.5 concentrations in the 48 hr preceding HRV measurement, controlling for confounders and a random subject effect.

RESULTS: PM2.5 was significantly associated with SDNN (p = 0.04) and HF (p = 0.03) in all subjects. There was no association in subjects with GSTM1, whereas there was a significant association with SDNN, HF, and LF in subjects with the deletion. Similarly, there was no association with any HRV measure in subjects with the short repeat variant of HMOX-1, and significant associations in subjects with any long repeat. We found a significant three-way interaction of PM2.5 with GSTM1 and HMOX-1 determining SDNN (p = 0.008), HF (p = 0.01) and LF (p = 0.04). In subjects with the GSTM1 deletion and the HMOX-1 long repeat, SDNN decreased by 13% [95% confidence interval (CI), −21% to −4%], HF decreased by 28% (95% CI, −43% to −9%), and LF decreased by 20% (95% CI, −35% to −3%) per 10 µg/m³ increase in PM.

CONCLUSIONS: Oxidative stress is an important pathway for the autonomic effects of particles.

missing potential confounding variables or HMOX-1 data. Among the remaining 539 subjects, GSTM1 data were available for 476 subjects, who had one (n = 314) or two (n = 162) HRV measurements. In subjects with multiple HRV measurements, the time interval between measurements was approxi-
mately 3 years. This study was conducted in compliance with all applicable regulations (including institutional review board approval). All subjects gave written informed consent prior to the study.

**HRV measurement.** HRV was measured at rest during normal breathing for 7 min using a two-channel (five-lead) ECG monitor (Trillium 3000; Forest Medical, East Syracuse, NY) while the subject was seated. Standard deviation of normal-to-normal intervals (SDNN), high frequency (HF) (0.15–0.4 Hz), and low frequency (LF) (0.04–0.15 Hz) were computed with a fast Fourier transform using software (Trillium 3000 PC Companion Software; Forest Medical) complying with established guidelines (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). In the analysis, we used the 4 consecutive minutes of ECG reading that included the lowest number of artifacts.

**Air pollution and weather data.** Continuous PM2.5 was measured at a stationary monitoring site on the roof of Countway Library of Harvard University in downtown Boston using a Tapered Element Oscillating Microbalance (TEOM; Model 1400A, Rupprecht & Patashnick Co., East Greenbush, NY). Meteorologic data was obtained from the Boston airport weather station. The 48-hr moving average of PM2.5 before each HRV measurement was used as the exposure index, as this exposure period has shown the strongest association in previous studies (Park et al. 2005).

**HMOX-1 and GSTM1 genotyping.** The HMOX-1 locus (UniGene Hs.301961; UniGene 2007a) was amplified at exons 4 and 5 by polymerase chain reaction (PCR) as previously described to differentiate between the null polymorphism and the presence of one or more copies of the gene (Schwartz et al. 2005b). The HMOX-1 (UniGene Hs.517581; UniGene 2007b) microsatellite (GT)n length assay was designed per Yamada and coworkers (Yamada et al. 2000). Briefly, the HMOX-1 locus was amplified by PCR at the 5' promoter flanking region containing (GT)n repeats with primers as described by Yamada, and the sizes of the PCR products were analyzed with a laser-based automated DNA sequencer (AB 3100; Applied Biosystems, Foster City, CA). Although the exact cutoff for HMOX-1 mod-
ulation is still unknown, constructs with lengths of > 25 repeats showed reduced HMOX-1 basal promoter activity and decreased transcriptional upregulation in response to various stimuli like H2O2 compared with lengths < 25 repeats (Chen et al. 2002; Yamada et al. 2000). In the analysis of the data, we used the 25-repeat cutoff to categorize the study subjects in two categories (25 (GT)n repeats in both alleles or ≥ 25 (GT)n repeats in at least one allele) based on the HMOX-1 microsatellite length.

**Statistical analysis.** HRV measurements were log10-transformed to improve normality. The following potential confounders were chosen a priori and included in the analysis: age, body mass index (BMI), mean arterial pressure, fasting blood glucose, cigarette smoking (never/former/current), alcohol consumption (≥ 2 drinks a day, yes/no), use of beta-blockers, calcium channel blockers, acetylcholinesterase (ACE) inhibitors, room temperature, season, smoking status, and the presence of HMOX-1 and GSTM1 microsatellite length.
and 48-hr moving average of outdoor apparent temperature. Potential nonlinearity between apparent temperature and HRV was accounted for using a linear and quadratic term.

Because our data included repeated measures of HRV for many participants, our data may lack independence. To deal with this, we fit a mixed effects model (PROC MIXED in SAS version 9.0; SAS Institute Inc., Cary, NC). We assumed:

\[ Y_{it} = b_0 + u_i + b_1X_{it} + \cdots + b_kX_{it} + \beta \text{Pollutant} + e_{it}, \tag{1} \]

where \( Y_{it} \) is the logarithm of HRV in subject \( i \) at time \( t \), \( b_0 \) is the overall intercept, and \( u_i \) is the separate random intercept for subject \( i \). In the above, \( X_{it} \) are the covariates measured at each of the visits in which the HRV measurements were taken. This captures the correlation among measurements within the same subject.

**Results**

Table 1 shows the levels and distribution of the variables used in this study, overall, and for the different combinations of GSTM1 genotype and HMOX1 microsatellite repeat length. The study participants were all male, with average age of 72.8 years (SD = 6.6 years) at the first HRV measurement. No differences among the subpopulations defined by the combinations of GSTM1 genotype [wild-type or null] and HMOX1 microsatellite repeat length (< 25 [GT]n repeats in both alleles or ≥ 25 [GT]n repeats in at least one allele) were found in age, BMI, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, fasting blood glucose, total cholesterol, high-density lipoproteins (HDL), triglyceride, smoking status, alcohol intake (≥ 2 drinks/day), history of coronary heart disease (CHD), diabetes, hypertension, or stroke, and use of beta-blockers, calcium channel blockers, or ACE inhibitors (Table 1). The two genes were not associated with each other (\( p > 0.67 \)).

Table 2 shows the results of the analyses for the association of PM2.5 with changes in HRV for the entire population (model 1), by GSTM1 genotype (model 2), and by HMOX1 microsatellite (GT)n repeat length (model 3).

For the entire population, we found that a 10 µg/m³ increase in PM2.5 in the 48 hr before the HRV measurement was associated with a 6.8% decrease in SDNN (95% confidence interval, CI), \((-12.9 \text{ to } -0.2; p = 0.0434)\) and with a 17.3% decrease in HF (95% CI, \(-30.0 \text{ to } -2.3; p = 0.026)\). PM2.5 concentrations were also negatively associated with LF (estimated change = \(-11.2\%, \text{ 95\% CI, } -22.8 \text{ to } -2.2\), but the result was not statistically significant (\( p = 0.10 \)).

The PM2.5-HRV association was modified by GSTM1 genotype, with PM2.5 concentrations negatively associated with SDNN, HF, and LF in GSTM1-null subjects, whereas no association between PM2.5 and HRV was found in GSTM1–wild-type carriers. In subjects with the GSTM1-null deletion, a 10-µg/m³ increase in PM2.5 was associated with a 10.5% decrease in SDNN (95% CI, \(-18.2 \text{ to } -2.2; p = 0.015)\), a 24.2% decrease in HF (95% CI, \(-39.2 \text{ to } -5.5; p = 0.014)\), and a 17.0% decrease in LF (95% CI, \(-31.0 \text{ to } -2.0; p = 0.048)\). In GSTM1–wild-type subjects, the estimated decreases in HRV for a 10-µg/m³ increase in PM2.5 were 2.0% (95% CI, \(-39.2 \text{ to } -8.5; p = 0.0073)\) and with a 20.1% decrease in LF (95% CI, \(-34.5 \text{ to } -2.7; p = 0.0261)\). GSTM1 genotypes and HMOX1 microsatellite repeat lengths had a marginally significant (\( p = 0.059)\) when the SDNN component of HRV was considered but was not significant for HF (\( p = 0.14)\) and LF (\( p = 0.11\)).

We further evaluated the interrelationship between PM2.5, GSTM1, and HMOX1 by estimating the effect of PM2.5 on HRV within each combination of the GSTM1 genotypes and HMOX1 microsatellite repeat length categories (Table 3). These results indicate a clear trend of increasingly negative coefficients as we move across gene categories. In carriers of both the GSTM1-null deletion and at least one allele with ≥ 25 HMOX1 microsatellite (GT)n repeats, PM2.5 was negatively associated with all three HRV outcomes, whereas no significant association was found in subjects with any other combinations. In subjects carrying the GSTM1-null deletion and at least one allele with ≥ 25 HMOX1 microsatellite (GT)n repeats, a 10-µg/m³ increase in PM2.5 in the 48 hr before the HRV measurement was associated with a 12.7% decrease in SDNN (95% CI, \(-20.6 \text{ to } -3.9; p = 0.0059)\), a 27.8% decrease in HF (95% CI, \(-43.0 \text{ to } -8.5; p = 0.0073)\), and a 20.1% decrease in LF (95% CI, \(-34.5 \text{ to } -2.7; p = 0.0261)\). GSTM1 genotypes and HMOX1 microsatellite repeat lengths had a marginally significant (\( p = 0.059)\) when the SDNN component of HRV was considered but was not significant for HF (\( p = 0.14)\) and LF (\( p = 0.11\)).

**Table 2.** Adjusted percent change (95% CI) of heart rate variability (HRV) for each 10 µg/m³ of PM2.5 in the 48 hr before the measurement, by HMOX1 microsatellite repeat length or GSTM1 polymorphism.

<table>
<thead>
<tr>
<th>HRV measurement²</th>
<th>GSTM1 Effect by GSTM1</th>
<th>GSTM1 null</th>
<th>PM2.5 Effect by HMOX1</th>
<th>PM2.5 Effect by HMOX1 Microsatellite Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>log₁₀ SDNN</td>
<td>–6.8%</td>
<td>–2.0%</td>
<td>–0.5%</td>
<td>7.4%</td>
</tr>
<tr>
<td>(–12.9 to –0.2)</td>
<td>(–13.1 to 8.3)</td>
<td>(–18.2 to –2.2)</td>
<td>(–30.0 to –2.0; p = 0.0150)</td>
<td>(–8.7 to 26.2)</td>
</tr>
<tr>
<td>p = 0.0436</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.3991</td>
</tr>
<tr>
<td>log₁₀ HF</td>
<td>–17.3%</td>
<td>–4.0%</td>
<td>–24.2%</td>
<td>8.9%</td>
</tr>
<tr>
<td>(–30.0 to –2.3)</td>
<td>(–24.8 to 22.6)</td>
<td>(–39.2 to –5.5)</td>
<td>(–7.1 to 62.8)</td>
<td>(–32.9 to –5.0)</td>
</tr>
<tr>
<td>p = 0.0263</td>
<td>p = 0.0742</td>
<td>p = 0.0139</td>
<td>p = 0.6759</td>
<td>p = 0.0115</td>
</tr>
<tr>
<td>log₁₀ LF</td>
<td>–11.2%</td>
<td>–0.6%</td>
<td>–17.0%</td>
<td>14.0%</td>
</tr>
<tr>
<td>(–22.8 to 2.2)</td>
<td>(–19.0 to 22.0)</td>
<td>(–31.0 to –0.2)</td>
<td>(–18.6 to 59.5)</td>
<td>(–25.7 to –0.5)</td>
</tr>
<tr>
<td>p = 0.0986</td>
<td>p = 0.9545</td>
<td>p = 0.0478</td>
<td>p = 0.4465</td>
<td></td>
</tr>
</tbody>
</table>

All models adjusted for age, BMI, mean arterial pressure, fasting blood glucose, cigarette smoking (never/former/current), alcohol consumption (two or more drinks a day, yes/no), use of beta-blockers, use of calcium channel blockers, use of ACE inhibitor, room temperature, season, and 48-hr moving average of outdoor apparent temperature.

²Standard deviation of SDNN, power in HF (0.15–0.4 Hz) and LF (0.04–0.15 Hz) computed using a fast Fourier transform algorithm.

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combined effect on the association between PM2.5 and HRV, as shown in Table 3 by the significant three-way interaction term between GSTM1, HMOX-1, and PM2.5 (coded as PM2.5 × a trend variable that is 1 for GSTM1 present and both short repeats, 2 for GSTM1 null and both short repeats, 2 for one long repeat and GSTM1 present, and 4 for GSTM1 null and at least one long repeat).

To test whether the effect modification by genotype was driven by a few individuals or represented a more general shifting of the distribution of PM2.5–HRV slopes, we refit our models adjusting for age, BMI, mean arterial pressure, fasting blood glucose, cigarette smoking (never/former/current), alcohol consumption (two or more drinks a day, yes/no), use of PM2.5 in the 48 hr before the measurement.

Effect modification of HMOX-1 microsatellite repeat length and GSTM1 combinations on the adjusted percent change (95% CI) of HRV for each 10 µg/m3 of PM2.5 in the 48 hr before the measurement.

Discussion

Our study, based on an elderly population in Boston, showed that functional genetic variations in GSTM1 and HMOX-1, both of which are related to defense against oxidative stress, modify the effects of PM2.5 on HRV. In the present work, we have extended our previous results examining the modification of the PM2.5–HRV association by GSTM1 (Schwartz et al. 2005b) to include other HRV outcomes and repeated measures on subjects, to show effect modification by HMOX-1, and to show a three-way interaction between the two genes and combustion particles.

This work is part of a series of studies seeking to examine the potential pathways by which particles affect HRV. Specifically, we are looking at oxidative stress and endothelial function as potential pathways to this outcome. We hypothesize that if a pathway is important in the effect of PM2.5 on HRV, then factors that modify that pathway, either genes or drugs, may modify the PM2.5 response. We are also looking at metal-processing pathways as an indirect test of the hypothesis that metals on the PM2.5 particles play an important role in the HRV response (Park et al. 2006).

In our previous work on the same population we showed that ambient PM2.5 concentrations averaged over the 48 hr before the examination were associated with a reduction HF, with negative, albeit nonsignificant, associations seen with SDNN and LF (Park et al. 2005). In the present work, based on longer follow-up and additional HRV measurements, we were also able to show a significant effect on SDNN, as well as a more pronounced, although still nonsignificant, negative association with LF.

As part of our examination of oxidative stress we have previously shown that particles had no effect on HRV in subjects with the functional GSTM1 polymorphism (GSTM1–wild-type) but had a substantially increased effect in those with the deletion (GSTM1-null) (Schwartz et al. 2005b). Similarly, we showed that statin use and obesity, which both modify ROS production, altered PM2.5 effects on HRV (Schwartz et al. 2005b), thus confirming the critical role of oxidative stress pathways. In this article, we extend these results by showing a three-way interaction with genetic modifiers of response to oxidative stress.

Although particle exposure has also been linked with activation of inflammatory pathways (Baccarelli et al. 2007b; Liao et al. 2004; Peters et al. 2001), alterations in blood coagulation (Baccarelli et al. 2007a; Liao et al. 2005), endothelial injury and dysfunction (Brook et al. 2002; Ikeda et al. 1998), and alterations in the autonomic control of the heart (Creason et al. 2001; Gold et al. 2000; Liao et al. 2004a), our findings suggest that genetic variations in oxidative stress pathways play a critical role in the cardiovascular effects of airborne particles.

Rodents exposed to concentrated urban particles evinced increased reactive oxygen species in both the lung and the heart (Gurgueira et al. 2002), an effect muted by preadministration of N-acetylcysteine, a glutathione precursor and potent antioxidant (Rhoden et al. 2004). Inhalation of particles produces oxidative stress directly or via acute pulmonary inflammation, thus causing a series of events, such as the production of proinflammatory mediators, an increase of extracellular calcium influx, and the disruption of nitric oxide regulation (Stone et al. 2000; Thomas et al. 2001), that may impair autonomic function and hence HRV. Diesel particles have also been shown to increase oxidative stress in endothelial tissue, inducing the production of HMOX-1 (Furuyama et al. 2006). The viability of cell cultures of microvascular endothelial cells was impaired by diesel particles with an accompanying large increase in induction of HMOX-1 (Hirano et al. 2003); this process was blunted by N-acetylcysteine. Woodsmoke particles have also been shown to deplete intracellular glutathione and upregulate HMOX-1 activity in

Table 3. Effect modification of HMOX-1 microsatellite repeat length and GSTM1 combinations on the adjusted percent change (95% CI) of HRV for each 10 µg/m3 of PM2.5 in the 48 hr before the measurement.

<table>
<thead>
<tr>
<th>HRV measurement</th>
<th>GSTM1 wild-type (no. of visits = 26a)</th>
<th>GSTM1 &lt; 25 repeatsb</th>
<th>GSTM1 ≥ 25 repeatsb and GSTM1 null (no. of visits = 309b)</th>
<th>GSTM1 ≥ 25 repeatsc and GSTM1 null (no. of visits = 303c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log10 SDNN</td>
<td>28.7% (12.0 to 88.2)</td>
<td>p = 0.1357</td>
<td>-2.7% (11.5 to 6.8)</td>
<td>p = 0.5620</td>
</tr>
<tr>
<td>Log10 HF</td>
<td>45.9% (25.3 to 75.3)</td>
<td>p = 0.4273</td>
<td>-5.2% (25.7 to 18.8)</td>
<td>p = 0.8153</td>
</tr>
<tr>
<td>Log10 LF</td>
<td>68.5% (23.0 to 270.4)</td>
<td>p = 0.1944</td>
<td>-2.9% (19.9 to 18.0)</td>
<td>p = 0.7722</td>
</tr>
</tbody>
</table>

All models adjusted for age, BMI, mean arterial pressure, fasting blood glucose, cigarette smoking (never/former/current), alcohol consumption (two or more drinks a day, yes/no), use of beta-blockers, use of calcium channel blockers, use of ACE inhibitor, room temperature, season, and 48-hr moving average of outdoor apparent temperature.

aStandard deviation of SDNN, power in HF (0.15–0.4 Hz) and LF (0.04–0.15 Hz) computed using a fast Fourier transform algorithm. bCarriers of < 25 microsatellite (GT) repeats in both alleles. cCarriers of ≥ 25 microsatellite (GT) repeats in at least one allele. dNumber of HRV measurements.

Figure 1. Kernel density plot of subject-specific random slopes for the association of PM2.5 level with SDNN, by GSTM1 genotype and HMOX-1 repeat length.
endothelial cells (Liu et al. 2005). Our results showing interactions of particles with GSTM1 deletion and microsatellite (GT)n repeat length in the gene coding for HMOX-1 are consistent with these laboratory findings that suggest a prominent role of ROS in particle toxicity.

HMOX-1, the inducible heme oxygenase isoform, is expressed in multiple tissues, including vascular smooth muscle and endothelial cells (Exner et al. 2004). HMOX-1 expression has been shown to be upregulated in rat heart microvesSEL endothelial cells exposed to organic extracts of diesel exhaust particles (Furuyama et al. 2006), an effect that is likely to represent a response directed against ROS production (Morita 2005). Large individual differences in the ability to modulate the quantitative level of HMOX-1 activity in response to a given stimulus have been described, which correlate with differences in the length of a microsatellite (GT)n repeat in the 5’ flanking region of the HMOX-1 gene (Exner et al. 2004; Hirai et al. 2003; Yamada et al. 2000). The purine–pyrimidine alternating sequence in the (GT)n repeat has the potential to assume Z-DNA conformation, a left-handed double-helical structure that is thermodynamically unfavorable compared with B-DNA conformation (Rich et al. 1984) and has been described as negatively affecting transcriptional activity (Delic et al. 1991; Naylor and Clark 1990). Yamada and co-workers demonstrated by transient-transfection assay in cultured cell lines that the larger the number of (GT)n repeats in the HMOX-1 gene promoter, the lower is the HMOX-1 inducibility by ROS (Yamada et al. 2000).

In our study, HMOX-1 microsatellite (GT)n repeat length appeared to modulate the effects of PM2.5 on autonomic function, as measured by HRV variability. PM2.5 exhibited a negative correlation with SDNN, HF, and LF in individuals with ≥ 25 repeats, whereas no effect was seen in subjects with < 25 repeats. Furthermore, the strongest effects of PM2.5 were found in subjects that were lacking efficiency in antioxidant responses due to the combination of the GSTM1 deletion and ≥ 25 microsatellite (GT)n repeats in the HMOX-1 promoter. While the p-values for statistical interaction between PM2.5 and GSTM1 and between PM2.5 and HMOX-1 were not significant, the tests for the three-way interaction among PM2.5, GSTM1, and HMOX-1 were highly significant, confirming that the stronger effect modification of PM2.5 effects on HRV is seen when both genes are considered. The statistical modeling we used to fit the three-way interaction tested whether the size of PM2.5 effects in carriers of GSTM1 null and at least one long HMOX-1 repeat was 2 times larger than that observed in subjects carrying either GSTM1 null or one long HMOX-1 repeat. Thus, our data strongly suggest that particle exposure interacts with individual variations in the antioxidant response pathway to determine its effects on HRV.

A potential limitation of this study is that we used ambient PM2.5 concentrations from a single monitoring site as a surrogate for recent exposure to PM2.5. A recent study comparing ambient concentrations at this site with personal exposures in Boston has shown a high longitudinal correlation (Sarnat et al. 2005) between the two measurements; the study also reported that PM2.5 concentrations were spatially homogeneous over the Boston area. This suggests that our use of ambient concentrations is reasonable and the resulting exposure error is likely to be non-differential. In our analyses, we considered several potential confounding factors that may have influenced HRV measures, as we adjusted our models for age, BMI, mean arterial pressure, fasting blood glucose, cigarette smoking, alcohol consumption, room temperature, outdoor apparent temperature, season, and use of beta-blockers, calcium channel blockers, and ACE inhibitors. Therefore, chances that the observed associations reflected bias due to confounders are minimized.

Our results can be generalized only to an aged population that consists of older males who are almost all white. The effect on women and children as well as different ethnic groups should be addressed in future studies, particularly in relation to the exposure of different population groups to PM2.5 with varying geographic location, occupation, socioeconomic status, and behavioral characteristics. Other health outcomes including respiratory responses may also be affected by responses to ROS in an interaction with PM2.5 exposure. Our findings provide new information to guide research on the breadth of the effect of PM2.5 exposure.

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