Personal exposure to specific volatile organic compounds and acute changes in lung function and heart rate variability among urban cyclists

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A B S T R A C T

Background: Few studies have examined the acute cardiorespiratory effects of specific volatile organic compound (VOC) exposures from traffic pollution.

Methods: A cross-over study was conducted among 42 healthy adults during summer 2010 in Ottawa, Canada. Participants cycled for 1-h along high and low-traffic routes and VOC exposures were determined along each route. Lung function, exhaled nitric oxide, and heart rate variability were monitored before cycling and 1–4 h after the start of cycling. Bayesian hierarchical models were used to examine the relationship between 26 VOCs and acute changes in clinical outcomes adjusted for potential confounding factors.

Results: Each inter-quartile range (IQR) increase in propane/butane exposure was associated with a 2.0 millisecond (ms) (95% CI: 0.65, 3.2) increase in SDNN (standard deviation of normal-to-normal intervals), a 24 ms2 (95% CI: 0.6, 41) increase in LF (low frequency power), and a 65 ms2 (95% CI: 11, 118) increase in HF (high frequency power) in the hours following cycling. IQR increases in ethane and isoprene were associated with a 5.8 ms (95% CI: −9.8, −1.7) decrease in SDNN and a 24 ms2 (95% CI: −44, −7.9) decrease in HF, respectively. IQR increases in benzene exposure were associated with a 1.7 ppb (95% CI: 1.1, 2.3) increase in exhaled nitric oxide and each IQR increase in 3-methylhexane exposure was associated with a 102 mL (95% CI: −157, −47) decrease in forced expiratory volume in 1-s.

Conclusions: Exposure to traffic-related VOCs may contribute to acute changes in lung function, inflammation, or heart rate variability.

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1. Introduction

Existing evidence suggests that traffic-related air pollution may contribute to cardiorespiratory morbidity. Indeed, time spent in traffic has been associated with increased risks of asthma (McConnell et al., 2010), decreased survival after stroke (Maheswaran et al., 2010), increased hospitalizations for cardiovascular causes (Zanobetti et al., 2009), and increased mortality (Maynard et al., 2007; Brook et al., 2010). More recently, ultrafine particles (UFP) have emerged as potentially important traffic-related air pollutants as they are produced in large numbers by vehicle emissions and may have an important impact on physiological measures of cardiovascular health including heart rate variability (HRV) (Chan et al., 2004), ST-segment depression (Pekkanen et al., 2002), and endothelial function (Lucking et al., 2001). However, studies of the acute cardiorespiratory effects of other traffic-related air pollutants including specific volatile organic compounds (VOCs) that are produced during fuel combustion or through evaporative emissions are relatively scarce.

Tsai et al. (2010) examined the association between outdoor levels of six specific VOCs and cardiovascular mortality in Taiwan and noted increased risks for propane, iso-butane, and benzene. In addition, occupational VOC exposures have been associated with decreased HRV (Ma et al., 2010) and others have reported associations between ambient organic carbon levels and altered HRV in elderly patients with cardiovascular disease (Chuang et al., 2007; Schneider et al., 2010). Recently, we examined the impact of total VOC exposures on cardiorespiratory outcomes among healthy urban cyclists but did not identify important associations (Weichenthal et al., 2011). However, we did not examine specific...
VOCs, and as a result we may have missed potentially important relationships if some but not all VOCs were associated with acute changes in HRV and/or respiratory function. With respect to HRV, inverse associations are of particular interest as decreased HRV has been associated with increased risks of cardiovascular morbidity (Dekker et al., 1997; Liao et al., 1997; Tsuji et al., 1996). Therefore, to address limitations of our previous analysis, here we examine associations between a number of specific VOCs and acute changes in HRV, exhaled nitric oxide (NO), and lung function in the same population of urban cyclists.

2. Materials and methods

Detailed descriptions of the study design, participant characteristics, clinical measures, and exposure monitoring methods are provided elsewhere (Weichenthal et al., 2011). Briefly, during the summer of 2010, 42 healthy non-smoking adults cycled for approximately 1 h along high and low-traffic routes on two separate occasions. All cycling took place on weekdays between 1130 h and 1230 h and individual routes were separated by at least 5 days. Cycling routes were approximately 10 km in length. The high-traffic route was located on busy roadways in the downtown core of Ottawa, Canada, whereas the low-traffic route travelled along a bicycle path away from traffic along the Ottawa River. Participants were predominantly male (67%), Caucasian (93%), and ranged in age from 19–58 years. The study was approved by the Health Canada Research Ethics Board.

Each study day ran from approximately 1030 h to 1530 h. Once at the study site, participants were fit with digital Holter monitors (See Light Extend; GE Medical Systems Information Technologies Inc., Milwaukee, WI, USA) and completed questionnaires to collect demographic information as well as medical history. Baseline HRV, exhaled nitric oxide (Niox Mino, Aerocrine, New Providence, NJ, USA), and lung function measurements (reported here as forced expiratory volume in 1 s (FEV₁)) (KoKo Legend spirometers, nSpire Health, Longmont, CO, US) were collected prior to cycling and follow-up measurements were collected immediately after cycling and every hour for the next 3 h (i.e., 1–4 h after the start of cycling). Time domain (SDNN, standard deviation of normal-to-normal intervals; RMSSD, root mean square of successive differences in adjacent NN intervals; pNN50, percentage of adjacent NN intervals differing by more than 50 ms) and frequency domain (LF, low-frequency power; HF, high-frequency power; LF/HF, the ratio of LF to HF) measures of HRV were based on the last 5 min of each segment of the study day. Average heart rate was also determined for each 1-h segment of the study day. Electrocardiogram data were analyzed by expert technicians at the Arthritis Monitoring Center in Ottawa using a GE Medical Systems Information Technology workstation (MARS version 7.2). Beat annotations were automatically assigned by the software and were verified and reviewed by technicians; only normal sinus beats were used in the analysis. HRV and exhaled NO measures were collected before spirometry procedures.

2.1. Exposure monitoring

Mean VOC exposures were determined along each route using 1-l SUMMA canisters placed in panniers located on technicians’ bicycles travelling directly in 2.1. Exposure monitoring

exhaled NO measures were collected before spirometry procedures. Review of the data collected revealed a number of occasions with missing data. For these occasions, we chose the closest available reading and included it in the analysis. CO was included in the analyses as the majority of these compounds displayed at least some variation between the high and low-traffic routes. Mean personal exposure to UFPs (TSI Model 3007, TSI, St. Paul, MN, USA), PM₂.₅ (TSI Dust Trak, TSI, St. Paul, MN, USA), black carbon (MicroAeth Model AE51, Magee Scientific, Berkeley, CA, USA), and CO (Langan Enhanced CO Monitor Model T15n, Langan Products, San Francisco, CA, USA) were determined using direct reading instruments mounted in panniers on participants’ bicycles. Mean personal exposure to UFPs was available in our previous report (Weichenthal et al., 2011).

In total, 38 participants completed both the high and low-traffic routes whereas two participants completed only the low-traffic route and one participant completed only the high-traffic route. Baseline health outcome data were comparable to other studies of healthy adults as previously described (Weichenthal et al., 2011) and the VOC exposure database was complete for all cycling routes. In general, VOC exposure levels were higher along the high-traffic route relative to the low-traffic route for the majority of the compounds monitored; these values are listed in Table 1 along with inter-quartile range (IQR) values for both routes combined. However, for some compounds (e.g., Freons, carbon tetrachloride, chloromethane) there was little difference between routes and exposures likely reflect general background concentrations. In addition, several VOCs were strongly correlated (r > 0.80) and as a result 9 VOCs were dropped from statistical analysis. In general, decisions on which VOCs to drop were based on ambient concentrations and known toxicities (e.g., benzene) but in some cases there were no clear reasons to favour one compound over the others and one was selected at random. These compounds, along with those with which they were highly correlated are listed in Table 2. All other VOCs were retained for analyses. Correlations between VOCs and other air pollutants included in statistical models (NO₂, PM₂.₅, O₃, UFPs) were low (r < 0.3). Descriptive data for other traffic-related air pollutants are available in our previous report (Weichenthal et al., 2011).

3.1. VOCs and exhaled NO

Model coefficients describing relationships between VOC exposures and changes from baseline in exhaled NO are listed in Table 3. Benzene and Freon 12 were positively associated with exhaled NO whereas inverse associations were observed for chloromethane, dichloromethane, ethane, Freon 113, and isoprene. The directions of observed associations were generally consistent between single and multiple-VOC models with the exception of Freon 12 which was inversely associated with exhaled NO in the single-VOC model and positively associated with exhaled NO in the multiple-VOC model. In all cases, however, the magnitudes of associations between specific VOCs and exhaled NO were small (i.e., < 2 ppb change per IQR increase in exposure).

3.2. VOCs and lung function (FEV₁)

Several VOCs were inversely associated with FEV₁ with the strongest association observed for 3-methylhexane (Table 4).
Inverse relationships were also observed between FEV1 and chloromethane, carbon tetrachloride, Freon 113, Freon 12, 1, 4-dichlorobenzene, and isoprene in single-VOC models but the magnitudes of these relationships decreased in multiple-VOC models because correlations among these variables made it difficult to separate out their individual effects in a multivariate model. In the case of 1, 4-dichlorobenzene and isoprene, positive associations were observed with FEV1 in multiple-VOC models.

3.3. VOCs and heart rate variability

Model coefficients describing the relationships between VOC exposures and changes in baseline HRV are listed in Tables 5 and 6. Ethane and propane were each associated with changes in SDNN with a positive association for propane. Isoprene and isobutane were both inversely associated with pNN50 in single-VOC models but the magnitude of these associations decreased in multiple-VOC models. A small inverse association was also observed between trichloroethane and pNN50 for propane. Isoprene and isobutane were both inversely associated with LF whereas isoprene was found to be inversely associated with HF. In general, inversely associated and positively associated VOCs retained for analysis in both single and multiple-VOC models, but in several cases the magnitudes of these associations decreased in multiple-VOC models.

4. Discussion

To our knowledge this is the first study to evaluate the impact of specific VOC exposures on acute changes in cardiorespiratory outcomes among urban cyclists. Total VOC exposures were not strongly associated with acute changes in HRV measures. For frequency domain measures of HRV, evidence of a positive association was observed between propane and HF and LF whereas isoprene was inversely associated with HF. In general, the directions of observed associations were consistent between single and multiple-VOC models but in several cases the magnitude of associations decreased in multiple-VOC models.

<table>
<thead>
<tr>
<th>VOC</th>
<th>Change/IQR (95% CI)</th>
<th>VOC</th>
<th>Change/IQR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>0.92 (0.17, 1.7)</td>
<td>Benzoic acid</td>
<td>0.23 (-0.04, 0.49)</td>
</tr>
<tr>
<td>Chloromethane</td>
<td>-1.08 (-1.13, -1.03)</td>
<td>Chlorinated hydrocarbon</td>
<td>-0.08 (-0.13, -0.03)</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>-1.0 (-1.0, -1.0)</td>
<td>Chloroform</td>
<td>-0.03 (-0.08, -0.02)</td>
</tr>
<tr>
<td>Ethane</td>
<td>-2.1 (-2.3, -1.9)</td>
<td>Cyclopropane</td>
<td>-0.09 (-0.14, -0.04)</td>
</tr>
<tr>
<td>Freon 11</td>
<td>-1.1 (-2.1, -1.0)</td>
<td>Cyclohexane</td>
<td>-0.01 (-0.06, 0.04)</td>
</tr>
<tr>
<td>Freon 12</td>
<td>-0.71 (-1.3, -0.17)</td>
<td>Cyclopentane</td>
<td>-0.03 (-0.08, -0.02)</td>
</tr>
<tr>
<td>Isoprene</td>
<td>-0.46 (-0.89, -0.028)</td>
<td>Cyclohexanol</td>
<td>-0.01 (-0.06, 0.04)</td>
</tr>
</tbody>
</table>

VOCs retained for analysis were not strongly associated with acute changes in time domain measures of HRV. For frequency domain measures of HRV, evidence of a positive association was observed between propane and HF and LF whereas isoprene was inversely associated with HF. In general, the directions of observed associations were consistent between single and multiple-VOC models but in several cases the magnitude of associations decreased in multiple-VOC models. A small inverse association was also observed between trichloroethane and pNN50 for propane. Isoprene and isobutane were both inversely associated with LF whereas isoprene was inversely associated with HF. In general, inversely associated and positively associated VOCs retained for analysis in both single and multiple-VOC models, but in several cases the magnitudes of these associations decreased in multiple-VOC models.

Likewise, dichloromethane was associated with increased LF:HF in single-VOC models but not in multiple-VOC models.
compounds were highly correlated and thus we could not separate associations may have occurred by chance. In addition, several many compounds were evaluated for each outcome and some evaluating the potential health effects of these compounds. Furthermore, the direction of these associations often differed between compounds suggesting that it may not be appropriate to lump all VOCs together as “total VOCs” when evaluating the potential health effects of these compounds.

Nevertheless, caution is required in interpreting our results as many compounds were evaluated for each outcome and some associations may have occurred by chance. In addition, several compounds were highly correlated and thus we could not separate their individual effects. For example, all compounds listed as eliminated from further analysis because of high correlations with included compounds (Table 2) may have effects on the outcomes, and some effects changed between univariate and multivariate models, emphasizing the difficulties of estimating separate effects.

Table 4
Model estimates for VOCs and changes in baseline FEV1 (mL).

<table>
<thead>
<tr>
<th>VOC</th>
<th>Change/IQR (95% CI)a</th>
<th>Change/IQR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>–37 (–87, 12)</td>
<td>35 (–39, 110)</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>–87 (–133, –42)</td>
<td>–8.3 (–59, 43)</td>
</tr>
<tr>
<td>Chloromethane</td>
<td>–112 (–159, –65)</td>
<td>–51 (–105, 28)</td>
</tr>
<tr>
<td>1,4-dichlorobenzene</td>
<td>–52 (–94, –9.7)</td>
<td>3.9 (0.93, 6.9)</td>
</tr>
<tr>
<td>Freon 113</td>
<td>–92 (–155, –33)</td>
<td>–62 (–125, 23)</td>
</tr>
<tr>
<td>Freon 12</td>
<td>–44 (–80, –7.8)</td>
<td>–2.7 (–23, 18)</td>
</tr>
<tr>
<td>Isobutane</td>
<td>–14 (–34, 4.9)</td>
<td>31 (1.5, 61)</td>
</tr>
<tr>
<td>Isoprene</td>
<td>–28 (–57, –0.71)</td>
<td>9.6 (8.9, 9.4)</td>
</tr>
<tr>
<td>3-methylhexane</td>
<td>–38 (–75, –0.77)</td>
<td>–102 (–157, –47)</td>
</tr>
<tr>
<td>Propane</td>
<td>57 (0.37, 117)</td>
<td>11 (–35, 25)</td>
</tr>
<tr>
<td>Trichloroethene</td>
<td>30 (–0.62, 61)</td>
<td>0.36 (–6.8, 7.6)</td>
</tr>
</tbody>
</table>

a Single-VOC model.
b Multiple-VOC model including all VOCs listed in the table. All models are adjusted for duration of cycling, relative humidity and ambient temperature during cycling, average heart rate during cycling, and mean levels of black carbon, NO2, O3, PM2.5, and UFPs during cycling.

Table 5
Model estimates for VOCs and changes in baseline SDNN, RMSSD, and pNN50.

<table>
<thead>
<tr>
<th>Heart rate variability</th>
<th>VOC</th>
<th>Change/IQR (95% CI)a</th>
<th>Change/IQR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN (ms)</td>
<td>Dichloromethane</td>
<td>5.4 (0.082, 11)</td>
<td>0.59 (–0.23, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Ethane</td>
<td>–7.7 (–16, 0.80)</td>
<td>–5.8 (–9.8, –1.7)</td>
</tr>
<tr>
<td></td>
<td>Propane</td>
<td>8.3 (1.9, 15)</td>
<td>2.0 (0.65, 3.3)</td>
</tr>
<tr>
<td></td>
<td>m, p-xylene</td>
<td>0.83 (–0.10, 1.8)</td>
<td>0.45 (–0.44, 1.3)</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>Isobutane</td>
<td>–0.59 (–1.4, 0.21)</td>
<td>–0.023 (–0.78, 0.75)</td>
</tr>
<tr>
<td></td>
<td>Isoprene</td>
<td>–1.2 (–2.4, 0.012)</td>
<td>–0.14 (–0.63, 0.34)</td>
</tr>
<tr>
<td></td>
<td>Freon 113</td>
<td>–1.8 (–3.8, 0.13)</td>
<td>–1.2 (–3.2, 0.86)</td>
</tr>
<tr>
<td></td>
<td>Isobutane</td>
<td>–0.61 (–1.2, 0.095)</td>
<td>0.071 (–0.62, 0.74)</td>
</tr>
<tr>
<td></td>
<td>Isoprene</td>
<td>–1.5 (–2.4, –0.60)</td>
<td>–0.20 (–0.68, 0.29)</td>
</tr>
<tr>
<td></td>
<td>Trichloroethene</td>
<td>–0.76 (–1.7, 0.19)</td>
<td>–0.28 (–0.53, –0.036)</td>
</tr>
</tbody>
</table>

a Single-VOC model.
b Multiple-VOC model including all VOCs listed in the table. All models are adjusted for duration of cycling, relative humidity and ambient temperature during cycling, average heart rate during cycling, and mean levels of black carbon, NO2, O3, PM2.5, and UFPs during cycling.

when a group of variables are highly correlated. This limitation is largely owing to the nature of the problem, and very large (likely infeasible) sample sizes would be needed to begin to untangle these effects. On the other hand, correlations between VOCs and other air pollutants (NO2, PM2.5, O3, UFPs) were weaker and therefore less problematic.

Conversely, some associations were consistent with existing evidence regarding the known toxicities of the compounds examined. For example, 3-methylhexane is a known respiratory irritant and thus its inverse association with FEV1 seems biologically plausible. Likewise, butane inhalation (abuse) is a known cause of coronary artery spasm and acute myocardial infarction in young adults and this effect depends in part on altered autonomic regulation of the heart (Menyar et al., 2005; Menyar, 2006). In this study, butane was highly correlated with propane and therefore the associations observed between propane and acute changes in heart rate variability (SDNN, LF, and HF) may be explained by butane. However, VOC exposure levels were generally low and few other studies have examined the reported associations; therefore, further evaluation is required to verify these findings. In particular, as cardiovascular morbidity is generally associated with decreased HRV the clinical implications of increased HRV require further evaluation. However, some evidence suggests that both increased and decreased HRV may be predictive of cardiovascular morbidity (de Bruyne et al., 1999).

Tsai and colleagues examined the association between ambient VOCs and daily counts of cardiovascular mortality in Taiwan between 2003 and 2006 (Tsai et al., 2010). Benzene, propane, and isobutane were each associated with increased risks of cardiovascular mortality at lag-0 day but correlations between these VOCs were high (r > 0.85) and thus it is not possible to attribute these effects to any single compound. Nevertheless, our finding of altered HRV in response to propane/butane is consistent with these results as impaired autonomic control of the heart is a known contributor to cardiovascular morbidity (Zareba et al., 2001). However, it is important to note that propane/butane was not associated with changes in LF:HF in the present study and thus did not appear to have an impact on the balance of sympathetic/parasympathetic modulation. Regardless, other
studies have also reported significant relationships between HRV and VOC exposures. In particular, Ma et al. (2010) noted decreased SDNN and RMSSD (Ma et al., 2010) with increased exposure to total VOCs whereas Mizukoshi et al. (2010) reported an inverse association between total VOCs and HF. In addition, Ma et al. (2010) also noted that the association between total VOCs and decreased SDNN and RMSSD was independent of PM2.5 with the strongest effects observed with 1–4 h moving averages. However, specific compounds were not examined in either of these two studies and further evaluation of the impacts of specific VOCs on HRV is warranted.

While only a small number of studies have examined the acute respiratory effects of ambient VOC exposures, some have observed positive associations between ambient VOCs and self-reported respiratory symptoms among asthmatic children (Delfino et al., 2003a; 2003b). In particular, Delfino et al. (2003a) reported increased respiratory symptoms with increasing outdoor levels of benzene, m,p-xylene, ethylbenzene, and tetrachloroethylene in Los Angeles, USA. In addition, exhaled breath concentrations (a marker of VOC exposure) of benzene were inversely associated with peak expiratory flow (Delfino et al. 2003b). Similarly, earlier studies reported significant associations between ambient benzene and hospital admissions for respiratory disease (Hagen et al., 2000), asthma exacerbation (Thompson et al., 2001) as well as childhood wheezing episodes (Buchdahl et al., 2000). In this study, we did not observe a strong association between personal exposure to benzene and lung function although benzene was associated with a small increase in exhaled NO. While this finding is not consistent with evidence discussed above, it may be explained in part by the inclusion of healthy young adults in this study as opposed to a more susceptible population such as asthmatics. Alternatively, exposures levels in Ottawa might have been below values likely to cause measureable decreases in lung function. The major strengths and limitations of this study are discussed in detail elsewhere (Weichenthal et al., 2011). For VOCs specifically, the use of personal exposure measures for multiple compounds is an important strength as other studies of ambient VOCs have generally relied on fixed site exposure measures that can result in significant exposure measurement error for compounds with high spatial variability (Suh and Zanobetti, 2010). In addition, the availability of detailed personal exposure data for other traffic-related air pollutants is an important advantage as it was possible to adjust for these factors in the analyses; however, personal exposure data was not available for NO2 and O3 and fixed site measures may not have completely controlled for personal exposures to these pollutants. Co-linearity between multiple VOCs was also an issue, and in some cases it was not possible to separate the independent effects of specific compounds. In general, however, VOC exposures among cyclists in Ottawa tended to be lower than in previous studies of cyclists’ exposures to VOCs (Bevan et al., 1991; van Wijnen et al., 1995) and findings should be replicated to increase confidence in the observed associations.

5. Conclusion

Twenty-six compounds were examined in this evaluation of the acute cardiorespiratory effects of VOC exposures in traffic. Evidence of possible associations were observed for a small number of compounds, and in particular, the association of propane/butane with acute changes in HRV is of interest as butane is a known cause of cardiovascular morbidity in cases of abuse. Future studies should aim to replicate this finding to verify whether or not low-level exposures may contribute to acute cardiovascular morbidity through altered autonomic modulation of the heart.

References


