Air Pollution Exposure and Interstitial Lung Disease

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Financial Interest Disclosure
Kerri Johannson

• Travel Support from Intermune (2013)
Outline

• Air pollution overview
• Health effects (focus: respiratory disease)

Air pollution exposure associated with acute exacerbations of idiopathic pulmonary fibrosis - results from a recent study

• Potential Mechanisms in ILD
• Application to your ILD patient
• The Exposome
Fresh Air: Historical Panacea

- *The Canada Lancet*
- >100 articles discussing ‘fresh air’ (1872-1900)
- Constitutional weakness, psychological ailments, physical deformities

“A student, undergoing his examination, was asked what was the action of disinfectant. He replied: “They smell so badly that the people open the windows, and fresh air gets in.”

http://niche-canada.org/2014/02/10/fresh-air-in-even-the-dustiest-of-sources/
Air Pollution

US Environmental Protection Agency’s Criteria Pollutants

- Particulate matter (<10um, <2.5um, <1um)
- Ground level (atmospheric) ozone (O$_3$)
- Nitrogen oxides (NO$_x$, NO$_2$)
- Sulfur oxides (SO$_x$, SO$_2$)
- Carbon monoxide (CO)
- Lead (Pb)
Adverse Health Outcomes

- Outpatient medical visits\(^1\)
- Hospitalizations\(^2\)
- Acute coronary syndromes\(^3\)
- Cardiovascular death\(^4\)
- All-cause mortality\(^5\)

\(^1\)Bell et al. Am J Respir Crit Care Med Vol 179. pp 1115-1120, 2009
\(^3\)Dockery et al. NEJM 1993 329;24:1753-1760.
Respiratory disease

- Impaired lung function and growth\textsuperscript{1}
- Asthma\textsuperscript{2}
- COPD\textsuperscript{3}
- Bronchiolitis obliterans syndrome post lung transplant\textsuperscript{4}
- Lung cancer\textsuperscript{5}

Acute Respiratory Events

• Respiratory hospitalizations\(^1\)
• Asthma exacerbations\(^2\)
• COPD exacerbations\(^3\)
• Early life pulmonary infections\(^4\)
• Cystic fibrosis pulmonary exacerbations\(^5\)

Environmental Interstitial Diseases

- Asbestosis
- Pneumoconioses
- Chronic beryllium disease
- Hypersensitivity pneumonitis
- Smoking-related ILDs
- Idiopathic Pulmonary Fibrosis (IPF)?
Acute Exacerbation of Idiopathic Pulmonary Fibrosis Associated with Air Pollution Exposure

Idiopathic Pulmonary Fibrosis

Etiologies of Acute Respiratory Worsening

- AE - 55.2%
- Infection - 31.3%
- Pneumothorax - 5.5%
- CHF - 3.1%
- Uncertain - 3.1%
- PTE - 1.2%
- AEP - 0.6%

Acute exacerbations of IPF

Definition:

- Worsening of dyspnea within 30 days
- New pulmonary opacities on HRCT Chest
- Exclusion of known causes of clinical deterioration (infection, PE, CHF, pneumothorax)

High mortality

Clinically meaningful outcome

Hypothesis

Increased exposure to air pollution leads to an increased risk of acute exacerbation of IPF

Study Design

Retrospective case control with risk-set sampling
Study Cohort

Initial Cohort
n=505

Excluded (n=69)
Baseline data n=22
Exposure data n=47

Analysis Cohort
n=436

AE-IPF
n=75

No AE-IPF
n=361
Air Pollution Exposure

• Jan 1, 2001 - Dec 31, 2010
• Fixed tele-monitoring systems (TMS)
• Hourly levels of PM$_{10}$, O$_3$, NO$_2$, SO$_2$, CO
• Geocoded address, assigned to nearest TMS
• Mean, maximum, exceedances above standards
• 42-day period preceding diagnosis of AE-IPF
Statistical Analysis

1) Cox proportional hazard models for incidence of AE-IPF
   • Adjusted for FVC % predicted, smoking status

2) Mortality and cumulative exposure
   • Adjusted for age, sex, FVC % predicted
## Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Exacerbation (n=75)</th>
<th>No Acute Exacerbation (n=361)</th>
<th>P-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>63.7 (8.4)</td>
<td>62.8 (7.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>17 (23)</td>
<td>74 (20)</td>
<td>0.67</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>26 (35)</td>
<td>89 (25)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>32 (43)</td>
<td>177 (49)</td>
<td>0.20</td>
</tr>
<tr>
<td>Current</td>
<td>17 (22)</td>
<td>95 (26)</td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity, % predicted</td>
<td>69.3 (17.7)</td>
<td>78.1 (17.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diffusion capacity for carbon monoxide, % predicted (subset)</td>
<td>62.5 (19.3) (n=58)</td>
<td>67.1 (19.2) (n=338)</td>
<td>0.11</td>
</tr>
<tr>
<td>Prednisone, n (%)</td>
<td>56 (74.7)</td>
<td>202 (56.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>GERD treatment (Proton pump inhibitor or H₂-antagonist), n (%)</td>
<td>57 (76.0)(^b)</td>
<td>192 (53.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Ozone and Nitrogen Dioxide Exposure and Risk of Acute Exacerbation

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>1.57 (1.09, 2.24)</td>
<td>.01</td>
</tr>
<tr>
<td>maximum</td>
<td>1.42 (1.11, 1.82)</td>
<td>.01</td>
</tr>
<tr>
<td>exceedances</td>
<td>1.51 (1.17, 1.94)</td>
<td>.002</td>
</tr>
<tr>
<td>NO2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>1.41 (1.04, 1.91)</td>
<td>.03</td>
</tr>
<tr>
<td>maximum</td>
<td>1.27 (1.01, 1.59)</td>
<td>.04</td>
</tr>
<tr>
<td>exceedances</td>
<td>1.20 (1.10, 1.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>1.22 (0.97, 1.55)</td>
<td>.09</td>
</tr>
<tr>
<td>maximum</td>
<td>1.07 (0.77, 1.47)</td>
<td>.7</td>
</tr>
<tr>
<td>PM10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>1.08 (0.77, 1.51)</td>
<td>.66</td>
</tr>
<tr>
<td>maximum</td>
<td>1.08 (0.76, 1.52)</td>
<td>.68</td>
</tr>
<tr>
<td>exceedances</td>
<td>1.06 (0.83, 1.36)</td>
<td>.62</td>
</tr>
<tr>
<td>SO2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>1.04 (0.73, 1.47)</td>
<td>.84</td>
</tr>
<tr>
<td>maximum</td>
<td>1.03 (0.81, 1.32)</td>
<td>.79</td>
</tr>
</tbody>
</table>
Sensitivity Analyses

- Differing exposure periods
- Cases within 15 km of nearest TMS
- Humidity and Temperature adjustment
- Differing standards (WHO, EPA, Korean)
- Two pollutant models (co-linearity)
Conclusions

- AE-IPF is associated with increased mean and maximum levels and number of exceedances above regulatory standards of O$_3$ and NO$_2$ in the 6 weeks preceding diagnosis
- No consistent relationships with PM$_{10}$, SO$_2$, CO
- No relationship with mortality
Limitations

- Retrospective
- Exposure estimates
- No smaller PM data
- Acute outcome
APPLE-IPF

- Air
- Pollution
- Prospective
- Longitudinal
- Evaluation
- patients with IPF
Study Overview

- IPF patients living in California
- Weekly spirometry, UCSD SOB, Likert score, medical status form
- Interpolated/land-use regression modeled exposure estimates
- Weekly and 9-month outcomes
Home Spirometric Monitoring
Potential Mechanisms

- Oxidative stress
- Cumulative injury to alveolar epithelium
- Concomitant airways disease
- Telomerase activity/telomere length
- Inflammation
Oxidative Stress

- Air pollution leads to oxidative stress\(^1\)
- Superoxide anion
- Hydroxyl radicals
- Effects attenuated by supplemental anti-oxidants\(^2\)
- IPF patients found to have reduced glutathione\(^3\)
- PANTHER single-arm results

Telomere Length

- IPF associated with shortened telomeres
- Air pollution $\rightarrow$ oxidative stress $\rightarrow$ shortened telomeres
- Short-term exposures $\rightarrow$ longer telomeres (upregulated via inflammatory mediation)
- Longer-term exposures $\rightarrow$ shortened telomeres

Local and Systemic Inflammation

- 23 healthy volunteers
- Randomized crossover study
- Controlled exposure to Air x 2 hours, then 0.3ppm O₃ x 2 hours with intermittent exercise
- Blood and lung function testing pre and post exposure
- BAL post exposure

Ozone-induced changes in markers of vascular inflammation.

Ozone-induced changes in lung function and pulmonary inflammation.

Application to your ILD patient

<table>
<thead>
<tr>
<th>Exposure History</th>
<th>Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Country of origin</td>
<td>• Air Quality Health Index</td>
</tr>
<tr>
<td>• Recent travel</td>
<td>• Personal protective equipment</td>
</tr>
<tr>
<td>• Current living environment</td>
<td>• HEPA filter</td>
</tr>
<tr>
<td>• Occupation</td>
<td>• Relocation</td>
</tr>
<tr>
<td>• Timing</td>
<td></td>
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</tbody>
</table>
Air Quality Health Index

1) Air quality index score in relation to health risk (1-10)

2) Level of health risk associated with index score (mild, moderate, high, very high)

3) Health messages targeted at general and ‘at-risk’ populations

4) Current hourly AQHI readings and maximum forecast values for today, tonight and tomorrow.

http://www.ec.gc.ca/cas-aqhi/default.asp?Lang=En
At-Risk Individuals

- Young, active children
- Elderly individuals
- People having existing respiratory or cardiovascular illnesses such as asthma, chronic obstructive pulmonary disease (COPD) or people with certain heart arrhythmias congestive heart failure, angina or previous heart attack
- People undertaking strenuous exertion outdoors, for example during sports or strenuous work.
The AQHI is calculated based on the relative risks of a combination of common air pollutants that is known to harm human health. These pollutants include:

- Ozone ($O_3$) at ground level,
- Particulate Matter ($PM_{2.5}/PM_{10}$) and
- Nitrogen Dioxide ($NO_2$).
The Exposome

• Complement the genome
• Proposed in context of cancer research

“Every exposure to which an individual is subjected from conception to death”

Wild, CP. International Journal of Epidemiology 2012;41:24-32
Figure 1 Three different domains of the exposome are presented diagrammatically with non-exhaustive examples for each of these domains.
### Table 1 Some examples of approaches and tools to measure the exposome

<table>
<thead>
<tr>
<th>Approach</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarkers (omics)</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>Genomics, transcriptomics, proteomics, metabolomics, epigenomics</td>
</tr>
<tr>
<td>Targeted</td>
<td>Adductomics, lipidomics, immunomics</td>
</tr>
<tr>
<td>Sensor technologies (including mobile phones)</td>
<td>Environmental pollutants, physical activity, stress, circadian rhythms, location [global positioning systems (GPS)]</td>
</tr>
<tr>
<td>Imaging (including mobile phones, video cameras)</td>
<td>Diet, environment, social interactions</td>
</tr>
<tr>
<td>Portable computerized devices (including palmtop computers)</td>
<td>Behaviour and experiences (ecological momentary assessment), stress, diet, physical activity</td>
</tr>
<tr>
<td>Improved conventional measurements (combined with environmental measures)</td>
<td>Job-exposure matrices; dietary recall (e.g. EPIC-Soft)</td>
</tr>
</tbody>
</table>
Conclusions

• Plausible relationship between air pollution exposure and ILD
• Epidemiologic and translational support
• Modifiable risk factor
• Warrants future study
Thanks

- Division of Respirology, University of Calgary, Calgary AB Canada
- University of California, San Francisco’s Interstitial Lung Disease Program
- Dr. Hal Collard, Dr. John Balmes, Dr. Eric Vittinghoff, Dr. Dong Soon Kim, Dr. Gil Kaplan, Dr. Kiyoung Lee, Dr. Wonjun Ji
- CHEST Foundation/Pulmonary Fibrosis Foundation