Utility of Lung Clearance Index (LCI) as a Noninvasive Marker of Deployment Lung Disease

Silpa Krefft, M.D., M.P.H.
September 20, 2016
Disclosures

- Mountain and Plains Education and Research Center: Pilot Project Grant Funding (7/01/2014 – 6/30/2015)

- Sergeant Sullivan Center: support for Pilot Project Study: Utility of Lung Clearance Index as a Noninvasive Marker of Deployment Lung Disease
Over past 15 years, over 2.5 million people deployed to Iraq & Afghanistan.

Iraq:
• Operation Iraqi Freedom: March 2003 – 2009
• Operation New Dawn: 2010 – 2011
• Operation Inherent Resolve: 2014 - present

Afghanistan:
• Operation Enduring Freedom: 2001 - 2014
• Operation Freedom’s Sentinel: January 2015 – present
Deployment associated with complex and poorly characterized exposures

- Desert dust particulate matter
- Burn pit emissions
- Industrial fires and pollutants
- Cigarette smoke
- Vehicular diesel exhaust
- IED blasts
- Temperature/humidity extremes
- Microbial and allergenic agents
- Job-specific exposures (e.g. concrete work, solvents, welding fumes)
Little known about burn pit emissions

IOM Report: Long-term Health Consequences of Exposure to Burn Pits
[NRC, Natl Academies Press, 2011]
- Special focus on burn pit at Joint Base Balad (JBB)
- Highlights research gaps
- Suggests exposures may be more complex than burn pits only
- Recommends further exposure and health outcomes research with focus on longterm health effects
What may be in the air they breathe?

- **Enhanced Particulate Matter Survey**  
  [Engelbrecht, J Tox, 2009]
  - 15 locations (Iraq 6, Afghanistan 2)
  - All sites exceeded the Military Exposure Guideline of 15 ug/m3 for PM2.5
  - 3 main air pollutants:
    - Geological dust
    - Smoke from burn pits
    - Metals (Al, Cd, Pb in PM2.5 fraction)
Epidemiology: deployment lung disease

- Respiratory illnesses in deployed troops began surfacing in 2004.
  Helmer D, *JOEM*; 49, 2007

- A recent case series showed that a substantial number may be at risk for a lung disease called *constrictive bronchiolitis*.
  King M, *NEJM*; 365, 2011

- In one military study, 42% of deployers with no diagnosis despite comprehensive tests often including bronchoscopy.
  Morris MJ, *AJRCCM*; 190, 2014
Clinical Center for Deployment Lung Disease

Our Experience:

• 2009 – Calls about deployers returning from Afghanistan and Iraq with unexplained respiratory symptoms.

• February 2010 – Multidisciplinary Working Group convened and published white paper. Rose C, JOEM; 54, 2012

• Over past five years, received referrals at our Clinical Center on Deployment Lung Disease.
Case Series Hypotheses

• Patients who return from deployment to Iraq and Afghanistan are at risk for a spectrum of lung diseases including asthma and constrictive bronchiolitis.

• Risk for deployment-related lung disease is related to exposure (duration and frequency of deployment).
Case Series Methods

- **Inclusion criteria:**
  - Military deployers and civilian contractors with history of deployment to Iraq or Afghanistan (2001 – present)
  - Unexplained chest symptoms (decreased exercise tolerance, cough, dyspnea, chest tightness and wheezing)

- **Retrospective chart reviews**
  - Demographic characteristics
  - Deployment variables (frequency, duration)
  - Resting and exercise pulmonary function testing
  - Chest computed tomography (CT) – 9 radiologists, reviewed for small airways findings (i.e. bronchial wall thickening, mosaic attenuation/air trapping, centrilobular nodularity)
  - Surgical lung biopsy when available

- **Statistical methods:**
  - Descriptive statistics
  - T-test, Fisher’s test
Demographic Findings

Service branch: 66% (44/67) in Army

Median age (years): 38 (range 23-64)

Sex: 91% male

Reported smoking status:
• 52% never smokers (NS)
• 48% ever/current smokers
• Mean pack-years: 10.9
Results

Deployment Characteristics

- Mean deployment duration: 22 months (range: 4-120)
- Mean deployment frequency: 2 times (range: 1-5)
- Location:
  - 52% Iraq
  - 21% Afghanistan
  - 22% Both
  - 5% Other
Pulmonary Physiology

- 75% (50/67) with **normal spirometry** (defined as FEV1, FVC, and FEV1/FVC ≥ lower limit of normal (LLN)).

- 25% (13/64) **decreased DLCO** (<80% predicted).
  - Decreased DLCO is associated with increased duration (p=0.005) and frequency of deployment (p=0.003).

- 36% (16/44) had **positive bronchial challenges** consistent with airway hyperreactivity/asthma.

- 54% (36/67) with unexplained **low VO2 max % predicted** (<84% predicted) with few gas exchange, ventilatory, or cardiac abnormalities.
Results

Subtle Chest CT Abnormalities

- Chest CT abnormalities in bronchiolitis:
  - Bronchial wall thickening
  - Centrilobular nodularity
  - Mosaicism/air trapping (blue arrow)

- 88.7% (55/62) with air trapping, centrilobular nodularity, and airway wall thickening.
Indications for Surgical Lung Biopsy

- Unexplained and disabling chest symptoms.

- Other diagnostic tests (PFTs, exercise tolerance test, methacholine challenge, chest CT scan) are within normal limits or show only subtle, nonspecific abnormalities that do not clarify diagnosis.

- Empiric therapies (sustained inhaler treatment, steroid bursts), if tried, have been unsuccessful.

- Patient understands that the procedure is invasive, painful, associated with risk; and that findings may not inform therapy, affect symptoms or change outcomes.
Spectrum of Lung Histologic Abnormalities in 37 Deployers

3 patterns of lung disease:
- 65% emphysema/hyperinflation (15 of 24 NS)
- 51% bronchiolitis (12 of 19 NS)
- 49% granulomatous pneumonitis (9 of 18 NS)
Key Findings

- There were **no significant differences** based on smoking history (p=0.63 for Fisher’s test).

- Histopathologic findings of emphysema/hyperinflation, bronchiolitis, and granulomatous pneumonitis are significantly more likely in those with **increased duration** (p=0.0047) and **frequency** (p=0.003) of deployment.
Interim Summary

• Spectrum of histopathologic findings supports an *expanded case definition* of deployment-related lung disease:
  – Bronchiolitis
  – Emphysema
  – Granulomatous pneumonitis

• Confirms previous reports linking new-onset asthma and *bronchiolitis* to deployment.

• Deployment lung disease *unexplained by smoking status.*
Current Research Interests

• Focus on identifying noninvasive approaches to diagnosis
• Evaluate long-term lung function and respiratory health effects
• Explore pathogenesis and mechanisms of epithelial lung injury
• Treatment options (research-driven)
Lung Clearance Index (LCI) Testing
Study Rationale

• Given costs and risks associated with surgical lung biopsy, there is a critical need for a **noninvasive marker** of deployment lung disease (DLD).

• The most readily available and used lung function test, spirometry, has poor sensitivity in the detection of small airways disease.

• A test called **lung clearance index (LCI)** has shown promise as a noninvasive marker of small airways disease in early cystic fibrosis.
Introduction

Hypothesis

• We hypothesized that LCI scores would be higher in symptomatic deployers compared to controls (assuming an LCI score <7 is normal).

• We hypothesized that LCI would more sensitive than conventional lung function testing [pulmonary function testing (PFT) and cardiopulmonary exercise testing (CPET)].
Methods

Study design

We used a case-control design.

Eligibility and enrollment criteria:
• Age 18 years and older
• Smokers and never smokers
• Study enrollment period: February 1, 2015 – September 30, 2015
• Compared 21 healthy controls with no history of chronic lung disease and 20 symptomatic deployers
LCI testing

Study design

Methods:
• We reported the mean LCI score of 2 or 3 tests that met quality criteria (acceptability and reproducibility) based on previously published standards.

Note: lower LCI score (typically less than 7) is associated with normal lung function.

Statistical Analysis:
• Descriptive statistics
• T-test and Fisher’s test for demographic data
• We compared mean LCI score between deployers and controls using analysis of variance (ANOVA) and adjusted it for smoking, age, and body mass index.
### Table 1. Demographics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 21)</th>
<th>Deployers (n = 20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years, range</strong></td>
<td>38.6 (26-62)</td>
<td>40.3 (25-59)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-- Male</td>
<td>95</td>
<td>95</td>
<td>1.00</td>
</tr>
<tr>
<td>-- Female</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-- Hispanic/Latino</td>
<td>5</td>
<td>25</td>
<td>0.09</td>
</tr>
<tr>
<td>-- Not Hispanic/Latino</td>
<td>95</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-- African-American or Black</td>
<td>5</td>
<td>5</td>
<td>1.00</td>
</tr>
<tr>
<td>-- White</td>
<td>90</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>-- More than one race</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-- Current smoker</td>
<td>14</td>
<td>5</td>
<td>0.33</td>
</tr>
<tr>
<td>-- Former smoker</td>
<td>10</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>-- Never smoker</td>
<td>76</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m2), range</strong></td>
<td>25.1 (21.0-42.8)</td>
<td>30.7 (23.5-39.7)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>
Figure 1. Distribution of LCI, Unadjusted ANOVA Analysis

* Note: c = controls, d = deployers
### Table 2. LCI Results

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 21)</th>
<th>Deployers (n = 20)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LCI, unadjusted (95% CI)</td>
<td>6.95 (6.62-7.28)</td>
<td>7.55 (7.21-7.89)</td>
<td>0.0146</td>
</tr>
<tr>
<td>Mean LCI, adjusted (95% CI)</td>
<td>7.39 (6.74-7.39)</td>
<td>7.63 (7.00-7.63)</td>
<td>0.1626</td>
</tr>
<tr>
<td>Percent LCI &gt; 7</td>
<td>48%</td>
<td>65%</td>
<td></td>
</tr>
</tbody>
</table>

* Note: p value of 0.0146 reported is unadjusted; p value of 0.1626 reflects ANOVA adjusted for covariates of age, smoking status, and BMI.
### Table 3. Percent of Symptomatic Deployers with Abnormal Clinical Testing (n = 20)

<table>
<thead>
<tr>
<th>Test</th>
<th>Percent with abnormal test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td></td>
</tr>
<tr>
<td>Residual volume (RV) of &gt;140% predicted</td>
<td>15</td>
</tr>
<tr>
<td>Diffusion capacity (DLCO) &lt;80% predicted</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td>CPET (VO2 max &lt;84% predicted)</td>
<td>40</td>
</tr>
<tr>
<td>LCI &gt;7</td>
<td>65</td>
</tr>
</tbody>
</table>

Pulmonary function tests
Conclusions

**Trend toward Higher LCI in Symptomatic Deployers**

- Trend toward higher LCI in symptomatic deployers, despite being limited by small numbers.

- BMI may account for some of the differences in LCI scores.

- LCI more sensitive than conventional lung function testing but requires further study with increased sample size.
These preliminary findings suggest that LCI may have a role in the early detection of small airways disease in deployers and others at risk for occupational bronchiolitis.

These data will be used to support further exploration of the use of LCI:

- larger population of military deployers with respiratory symptoms.
- early detection of small airways abnormalities in other chronic occupational lung diseases.
Acknowledgements

NJH Clinical Program on Deployment Lung Disease

– Cecile Rose, MD, MPH
– Bibi Gottschall, MD, MSPH
– Richard Meehan, MD
– Kalie Von Feldt, PA-C
– Catie Stroup (Research Coordinator)
– Caleb Richards, MD
– Jennifer Smith, PA-C, MSPAS
– Matt Strand, PhD (biostatistician)
Questions?