Seeing is Believing: New Imaging Physics to Transform Asthma Patient Outcomes

Grace Parraga PhD
Robarts Research Institute,
Department of Medical Biophysics, Department of Medicine,
Graduate Program in Biomedical Engineering,
Western University London CANADA

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Pulmonary MRI: Structure & Function

- Conventional MRI measures the environment of protons in tissue
- No ionizing radiation
- Inhaled $^3\text{He}/^{129}\text{Xe}/^{19}\text{F}$ functional MRI
- 2400km airways
- ~15 breaths/min
- ~450 breaths/this talk!
- ~1B breaths/lifetime
- 300M alveoli d=300nm
Breathing: When things go wrong

4.3 MILLION people die each year from exposure to Indoor Air Pollution

3 BILLION people around the world cook every meal over an open fire

50% of premature deaths among children are caused by Indoor Air Pollution

World Health Organization

Indoor Air Pollution

50%
The Burden of Lung Disease: Asthma

- **Most common** chronic childhood disease¹
- **Single largest** cause of hospitalization of Canadian kids³
- **Single largest** cause of school absence & 3rd leading cause of work loss⁴ ~2M Ontarians ~ 25% children

<table>
<thead>
<tr>
<th>Ontario Total Health Care Costs</th>
<th>2011</th>
<th>2041</th>
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<tbody>
<tr>
<td>Lung Cancer</td>
<td>$293.9 million</td>
<td>$33.5 billion</td>
</tr>
<tr>
<td>Asthma</td>
<td>$1.8 billion</td>
<td>$100 billion</td>
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<tr>
<td>COPD</td>
<td>$3.9 billion</td>
<td>$311 billion</td>
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Diseased Airways and Airspaces

Progressive Airflow Limitation

Parenchyma
Healthy
Disease

Airways
Healthy
Disease

Can imaging biomarkers help?

- Provide sensitive, specific, precise & accurate measurements that can be used to:
  - Directly measure disease pathologies
  - Quantify Tx response / Discover & develop new Tx
  - Phenotype patients for personalized treatment
  - Guide treatment decisions
  - Predict & improve patient outcomes
Hyperpolarized Inhaled Gas Pulmonary MRI

Advantages
→ Functional information
→ Objective and independent of patient effort
→ High temporal & spatial resolution
→ FAST, 7-15s image acquisition!!!
→ No ionizing radiation = safe for serial & longitudinal evaluation

Canadian Centres
→ 2004: Robarts Research Institute, Western University
→ 2011: Thunder Bay Regional Research Institute, Lakehead University
→ 2013: SickKids, University of Toronto
→ 2018: St. Joseph’s Healthcare Hamilton, McMaster University
129Xe and 3He MRI: Requirements/Challenges

**Requirements…**
- Coils, polarizer, gas, expertise

**Challenges…**
- Relatively expensive ($200/dose)
- Current access to methods are limited
- Regulatory approval needed (& underway)
- Divergent, disruptive (why bother: FEV₁ is OK)
- Validation still required
- Image processing pipelines still required
- Driven by Physics, Engineering? Respirology? Radiology?
Conventional Pulmonary $^1$H MRI

Conventional $^1$H MRI

Measures environment of protons → lung structure

Low signal due to high gas density
Hyperpolarized Gas MRI Acquisition Fundamentals
This is what Asthma looks like: MRI & CT

Healthy

26 y/o F; FEV$_1$=102$\%_{\text{pred}}$

Asthma

44 y/o F; FEV$_1$=95$\%_{\text{pred}}$
Can we Quantify and Automate Ventilation Defect Measurements?
Quantitative MRI Biomarkers of Lung Ventilation

Co-Registration

Segmentation

Ventilation Defect Percent (VDP) = \frac{VDV}{TCV}

TCV = Thoracic Cavity Volume
VDV = Ventilation Defect Volume

Mathew et. al. Acad Radiol. 2008
Kirby M et al. Acad Radiol 2011
Functional MRI Biomarker Development

Extending Semi-Automatic Ventilation Defect Analysis for Hyperpolarized 129Xe Ventilation MRI

Automated Segmentation & Registration: 2017

Spatial Fuzzy C-Means Thresholding for Lung Ventilation Hyperpolarized MRI

Paul J.C. Hughes, MEng, Felix C. Hughes, Alberto Biancardi, PhD, Helen Marsden

Globally optimal co-segmentation of three-dimensional pulmonary 1H and hyperpolarized 3He MRI with spatial consistence prior

Fumin Guo, Jing Yuan, Martin Rajchl, Sarah Svenningsen, Dante PI Capaldi, Khadija Sheikh, Aaron Fenster, Grace Parraga
MRI of Asthma: What we discovered

MRI ventilation defects worsen in response to different triggers and respond to Tx

1. Costella S et al. Respirology 2012.; Samee; DeLange; DeLange; Altes
MRI of Asthma: What we discovered

Temporally & spatially persistent & some intermittent not homogeneous, not stochastic, not diffuse

Potential treatment targets?

Day 1

Day 14

MRI of Asthma: What we collectively discovered

- Temporal and spatially persistent/intermittent abnormalities
- Sensitive to treatment
- Reflect airway remodeling, inflammation
- Correlate with indices of disease severity
- Worsen after triggers and bronchoconstriction

But....

Can MRI predict outcomes that matter to patients?
Asthma control & symptoms
Worse asthma control (↑ACQ)

Worse VDP

Worse quality-of-life (↓AQLQ)

ACQ ≤ 2 (n=7)

ACQ > 2 (n=9)

Can we use MRI function to Guide Therapy Decisions?
Personalized Treatment: Targeting Inflammation

Inflammation Not Controlled

Pre-BD

Post-BD

Inflammation Controlled

Benralizumab (Anti-IL5Rα)

Post-BD

VDP=19%

FEV₁=67%_{pred}, ACQ=2.3

VDP=10%

FEV₁=76%_{pred}, ACQ=2.3

VDP=3%

FEV₁=84%_{pred}, ACQ=0.4

BD non-responsive, anti-IL5Rα responsive

Nair, Svenningsen and Parraga Unpublished data
Personalized Treatment: Image-guided Bronchial Thermoplasty

ACQ=1.6
PC$_{20}$=0.05mg/mL
SABA= 4 puffs/day

Inflammation Controlled
Baseline
Post-MCh

Bronchial Thermoplasty (BT)
Baseline
Post-MCh

Post-BT
ACQ=0.0
PC$_{20}$=1.50mg/mL
SABA= 1-2 puffs/14 days

Nair, McCormack, Cox, Svenningsen and Parraga Unpublished data
Translation: Image-Guided Interventions

Now approved for image-guided Biopsy to confirm and validate MRI findings
Relationship of Ventilation & Airway Abnormalities

Target Airway: LB3
Pathway to Target: Trachea – LMB – LUL – SDB – LB3

Ventilation
VDP_{LB3} = 40 %

Airway Morphometry
W_{A_{LB3}} = 63 %
L_{A_{LB3}} = 18 \text{ mm}^2
London Lung Imaging Research Team

[Image showing a group of individuals wearing shirts with lung images and various logos from research institutions]
Impact?