Small Airway Disease in Asthma: Pathophysiology and Assessment

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Small Airways
How are they defined?

- Anatomically by lack of cartilage in airway wall
- Physiologically by size of catheter used to measure “peripheral airway” resistance
- Distal, peripheral or small airways probably reflect generations 7-19 with diameters of 0.5-2mm (terminal bronchioles, respiratory bronchioles and alveolar ducts)

Small Airways in Asthma

- Distal, peripheral or small airways probably reflect generations 7-19 with diameters of 0.5-2mm (terminal bronchioles, respiratory bronchioles and alveolar ducts)
- Physiologically this probably reflects the transition point from turbulent to laminar flow
  - For a given small airway generation the cross sectional area is larger than for a large airway generation. If flow is the same through both generations, linear velocity should be less for small airways. Reynolds number predicts laminar flow with low laminar velocity.

Airway & Alveolar Tissue Eosinophils

- Kraft et al. AJRCCM; 1996;154:1505

% Overnight Fall in FEV1 vs. Tissue Eosinophils

- Hamid et al. JACI 1997;100:44

Immunohistochemical Markers in the Large & Small Airways

- Mercedes et al. JACI 1997;100:44
Alveolar Tissue CD4 Correlates with the FEV1

$ r = -0.25 $  
$ p = 0.34 $ (Spearman)

$ r = -0.77 $  
$ p = 0.0014 $ (Spearman)

Is There Distal Lung Remodeling?

Small Airway Wall Thickness Increased in Cases of Both Fatal and Non-fatal Asthma

Small Airway Remodeling

Remodeling features of the central and peripheral airways

Pattern of inflammatory cells also differs by lung region

Different distribution of inflammatory cells: Mast cells

Histologic Section* of Intrapulmonary Bronchi Normal Subject Without Asthma

Histologic Section* of Intrapulmonary Bronchi Fatal Asthma

Measurement of Peripheral Airways Resistance: Wedged Bronchoscopic Technique

Peripheral Airway Resistance Is Significantly Increased in Patients with Asthma

12/7/2012
Peripheral Resistance (Rp)

- Control
- Non-Nocturnal Asthma
- Nocturnal Asthma

<table>
<thead>
<tr>
<th>Rp (cmH2O/ml/min)</th>
<th>4 AM</th>
<th>4 PM</th>
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<tbody>
<tr>
<td>Control</td>
<td>*</td>
<td>+</td>
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<tr>
<td>Non-Nocturnal</td>
<td></td>
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<td>Nocturnal Asthma</td>
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* † p = < 0.0001

Kraft M, et al. 2001; 163:1551

Small Airways in Asthma

- How are they assessed?
  - Impulse oscillometry
  - Multiple breath nitrogen washout
  - Imaging
  - Inflammatory markers (systemic, expectorated, alveolar FeNO)
  - FEF25-75%
  - Airtrapping (RV, IC, SBN2 for CV/CC)
  - Aerosol bolus dispersion

The Small Airways: Role in Recurrent Exacerbations in Severe Asthma

- Unstable asthma
- Stable asthma

<table>
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<tr>
<th>Percent Predicted</th>
<th>Unstable asthma</th>
<th>Stable asthma</th>
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<tr>
<td>FEV1, TLC, FRC, RV, RV/TLC, dN2, CV, CC/TLC</td>
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p = .02
p = .03


IOS

Clinical: Impulse Oscillometry

- 38 ICS naïve asthma patients with mild-to-moderate disease treated with either Qvar (400 mcg/day, n=26) or CFC BDP (800 mcg/day, n=12) for 12 weeks in open label fashion
- Yamaguchi et al Pul Pharm Ther 2009 (e-pub)
Imaging as a Possible Modality to Measure Small Airway function

CT & Alveolar Nitric Oxide and Small Airways

- 16 mild-to-moderate asthma (FEV1 62–120%)
- 5 weeks' treatment placebo or 320 mg ciclesonide daily
- Assessed: mean FeF 25-75%, % fall in FVC at provocative dose of AMP and MCh, expiratory lung volume on CT after MCh challenge, single-breath nitrogen closing volume and alveolar exhaled nitric oxide (eNO).

Cohen et al. Eur R J 2008;31:1213

CT & Alveolar Nitric Oxide and Small Airways

Cohen et al. Eur R J 2008;31:1213
ICS Therapy: Small vs Large Particles?

- Practical significance
  - Increased total lung deposition with more peripheral lung deposition and less oropharyngeal deposition
- Biologic significance
  - More effective topical anti-inflammatory effect both centrally and peripherally
- Clinical significance
  - To be discussed at follow up pro/con

Conclusions

- The distal lung appears to contribute to asthma pathogenesis and has physiologic consequences
- There are data to suggest that remodeling also occurs in the distal lung
- Should the distal lung be considered a therapeutic target