Small Airways Disease

“Respiratory Function In Small Airways And Asthma”

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Relevant Questions On Small Airway Involvement In Asthma

- How can ‘small airway disease’ be defined?
- What is the link between small airway abnormalities and clinical presentation in asthma?
- When does small airway involvement become relevant in the natural history of the disease?
- Is it possible to reverse small airway abnormalities with pharmacological treatment?

Contoli et al Allergy 2010; 65: 141–151

Disease Process in Asthma is Located in All Parts of Bronchial Tree Including Small Airways and Alveoli

- Pathophysiologic Changes in the Small Airways of Asthma Patients
  - Lumen occlusion
  - Subepithelial fibrosis
  - Increase in smooth muscle mass
  - Inflammatory infiltrate
  - Immunostaining of eosinophils in small airway with major basic protein (in red)
  - Shows large number of eosinophils around the small airway


Small Airway (<2 mm) Principals

- Account for less than 10% of total airflow resistance
- Nerves generally do not penetrate that deep into the small airways
- Do not have cartilaginous support
- Surfactant is important to their patency
- Without parenchymal airway independence, activation of small airway smooth muscle leads to uninhibited small airway narrowing

Small Airway (<2 mm) Principals

- Estimated to be 24,000 small airways and bronchioles
- Thousands could be narrowed or totally obstructed without significant loss of lung function
- Most important mechanism to preserve airway function in small airways appears to be their sheer number

Source: Journal of Allergy and Clinical Immunology 2009; 124:S72–S77 (DOI:10.1016/j.jaci.2009.08.048)
**Definition of Small Airway Obstruction**

- Dysfunction that involves only small airways can be defined as a situation when:
  - static lung compliance is unaltered
  - resistance is not significantly increased or marginally so
  - frequency dependence of compliance or resistance is present

**Function Of Tracheobronchial Tree As Reflected By Physiologic Measures**

\[ \text{FEV1/FVC} \]

- Does not provide comprehensive evaluation of the whole bronchial tree
- Does reflect cross-sectional area of the lung
- Highly related to FVC in asthma because of an increase in RV caused by airway closure
  - FEV1/FVC ratio appears to measure central airway remodeling
- Does not properly reflect small airway abnormalities

**FEV1**

- May be better measure of small airways function than FEV1, particularly in children, but controversial
- Decreases following exercise without changes to FEV1

**Small Airways Dysfunction Defined by a Reduction in FEF_{25\%-75\%}**

- Useless measure with methacholine challenge tests

**Assessment Of Air Trapping As A Result Of Small Airways Closure**

**FEF25-75**

- Pros:
  - Noninvasive
  - Easy to perform
  - Related to air trapping by CT scan
- Cons:
  - Serial measures are highly variable
  - Influenced by large airway obstruction and volume changes
    - Often normal when FEV1/FVC > 75%
  - Did not correlate with small airway inflammation as determined by bronchoscopic lung biopsies

**Source:** Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)

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**Contoli et al. Allergy 2010; 65: 141-151**
Impaired Lung Function with Loss of Reversibility in Severe Asthma

Residual Volume and FVC
- Both are:
  - Noninvasive
  - Easy to perform
  - Reproducible
- RV has shown a closer relationship with changes in peripheral resistance, indicating it could correlate with small airway functions
- FVC improvements have been observed after treatment with extrafine formulations when compared with non-extrafine treatments:
  - Suggesting greater reduction in air trapping, which reflects small airway obstruction

Increased Peripheral Airway Resistance in Patients With Asthma

Positive Correlation Between Peripheral Resistance and Residual Volume: Evidence for Air Trapping

Increased Peripheral Resistance in Patients With Asthma

Impact of Small Airways on Resistance Measures

*P < 0.05 between the groups at 4:00 PM.
†P < 0.05 between the groups at 4:00 AM.
**Increased Small Airways Resistance in Asthma with Loss of Reversibility in Severe Asthma**

Graph showing the percentage of predicted resistance (R0) for normal, mild/moderate, and severe asthma groups. The graph indicates significant differences between pre- and post-bronchodilator conditions, with p-values of <0.005 and <0.001 for mild/moderate and severe asthma, respectively.

**IOS Methodology**

- Measures the relationship between pressure waves applied externally to the respiratory system and resulting respiratory airflow.
- Brief pulses of pressure generated by a loudspeaker instantaneously moving back and forth, superimposed on the subject's spontaneous breathing.

**Principles of Forced Oscillation**

- Airway resistance can be measured with IOS.
- Small airway obstruction is associated with an increase in resistance predominantly at lower frequencies (frequency-dependence resistance).
- Simple and fairly reproducible measure.
- Time consuming: 30 min.
- Correlates with FEF 25-75%.
- More sensitive than FEV1 for measuring physiological effects of bronchodilators.

**IOS Clinical Relevance**

- Peripheral airway function as evaluated by IOS [R5–R20 (the fall in resistance from 5 to 20 Hz) and X5 (reactance at 5 Hz)], in addition to the proximal airway index (R20), significantly correlated with:
  - Health status
  - Dyspnea
  - Disease control.
- Multiple regression analyses revealed that peripheral airway function significantly contributes to these, independently of the proximal airway index.
- In contrast, FEV1 did not significantly contribute to health status or dyspnea.

**Nitrogen Washout Tests**

- Can distinguish between ventilation inhomogeneity originating in peripheral vs. more proximal conducting airways.
- Analysis of washout curve generated in single-breath or multiple-breath tests can provide information regarding distal lung abnormalities.
- Can determine closing volume.
- Good reproducibility and sensitivity.

**Closing Volume (CV) and Closing Capacity (CC)**

- CV = volume of gas in the lungs in excess of RV at the time when small airways close during maximal exhalation.
  - Normally increases with age and in obstructive airway disease.
  - Can be used to detect obstructive disease in high-risk patients before clinical signs appear.
- CC = CV + RV.
- Alterations in single-breath nitrogen washout CV correlated with:
  - Poor asthma control and recurrent exacerbations
  - Elevated alveolar NO in severe asthma.
**Difficult-to-Control Vs. Stable Asthma**

- There were no significant differences in lung function except increased closing volume and closing capacity in difficult to treat asthmatics.
  - “This is indicative of small airway pathology in these patients”
- “Delivery of anti-inflammatory medication to the small airways in this subgroup is of specific clinical relevance”.

AJRCCM 2000;161:1902-6

**High Resolution CT (HRCT)**

- Can only estimate wall thickness of bronchi > 2 mm in diameter.
- Air trapping and ventilation heterogeneity, which have been related to small airway closure, have been quantified using HRCT and correlated to functional parameters of small airway abnormalities.
- More severe asthma is associated with more severe air trapping indicating small airway disease.
- Problems:
  - Costly
  - Technically demanding
  - Hampered by exposure of patients to radiation.

Contoli et al Allergy 2010; 65: 141–151

**Proof Of Treatment: ICS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HFA-BDP (1.1 µm)</th>
<th>CFC-FP (3.8 µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV (L)</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>CV/VC</td>
<td>18</td>
<td>14.2</td>
</tr>
<tr>
<td>RV%</td>
<td>196</td>
<td>184</td>
</tr>
<tr>
<td>FEV1 Post Br Dil</td>
<td>67.6</td>
<td>71.9</td>
</tr>
<tr>
<td>FEF_{25-75} (post)</td>
<td>42.5</td>
<td>51</td>
</tr>
</tbody>
</table>


**HRCT Assessments In Small Bronchi (1-5 Mm) Of 5 Lung Levels**

D = airway external diameter  
L = airway luminal diameter  
WT = wall thickness  
AO = airway outer area  
AL = airway luminal area  
WA = airway wall area.

J. Kosciuch et al, J Physiol. Pharmacol, 2009

**Distal Lung Hyperreactivity**

- Important site of airway hyperreactivity (AHR).
- Reactivity of small airways in asthmatics is increased vs. normals to both nonspecific (Ach) and specific (Ag-mediated) stimuli.
  - Less responsive to bronchodilators
- Limitation: AHR has poor correlation to asthma severity and test is time consuming.
- Peripheral resistance was correlated to RV and RV is correlated to AHR. Thus airway closure could be the sole cause of AHR.

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**Relations Between Airway Wall Thickness Or Lumen Dimension And Lung Function In Asthma**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WA</th>
<th>WA/BSA</th>
<th>WA%</th>
<th>WT</th>
<th>BWT</th>
<th>A_W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-bronchodilator RV (%Pred)</td>
<td>NS</td>
<td>NS</td>
<td>0.72</td>
<td>0.05</td>
<td>0.72</td>
<td>0.48</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 (%L)</td>
<td>NS</td>
<td>NS</td>
<td>0.53</td>
<td>0.1</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 (%Pred)</td>
<td>NS</td>
<td>NS</td>
<td>0.75</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
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Is There A Simple Paradigm to Define Small Air Disease In Asthma?

- Dysfunction that involves only the small airways can be defined as a situation when:
  - Static lung compliance is unaltered
  - Resistance is not significantly increased or marginally so
  - Frequency dependence of compliance or resistance is present

- Findings associated with distal lung disease:
  - Increased RV
  - Decreased FVC
  - Normal FEV1/FVC ratio

Do Small Airway Changes Correlate With Lung Function?

- One study in nocturnal asthma demonstrated that higher numbers of eosinophils in the alveoli correlate with increased airway obstruction at night.

- Flunisolide-induced reduction in smooth muscle area in the small airway walls correlates with improved mid-expiratory flow rates.

- Small airway disease appears also to be present in milder asthma, because several studies showed a higher degree of air trapping on HRCT scan.

- Definitive conclusions are hard to draw because asthma is a heterogeneous disease and different asthma populations have been investigated, the number of studies is small, and different techniques have been applied to characterize aspects of inflammation and remodeling.

Summary

- Asthma is an inflammatory disease of large and small airways

- Well-controlled asthma is important to reduce the risk of exacerbation and improve quality of life

- Assessing and treating small airway disease may be important in achieving asthma control and better long-term outcomes

- Long-term studies with treatments aimed at small airways are needed to provide evidence that enduring patient outcomes improve