Why Are Small Airways Important In Asthma?

“Physiology Of Small Airways Disease”

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

Workgroep Inhalatie Technologie, Jun 1999.
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
Pathophysiologic Changes in the Small Airways of Asthma Patients

Transbronchial Biopsies

1. Lumen occlusion
2. Subepithelial fibrosis
3. Increase in smooth muscle mass
4. Inflammatory infiltrate

Immunostaining of eosinophils in small airway with major basic protein (in red)

1. Shows large number of eosinophils around the small airway

Structural alterations in small airways have been implicated as an underlying reason for increased asthma severity and AHR..... Difficult to control asthma.

Differences In ECM Composition In Small Airways Between Fatal Asthma And Controls

Dolhnikoff et al, JACI 2009; 123:1090-1097
Is There Differential Inflammation in Proximal and More Distal Airways?

• Some studies suggest that the cellular infiltrate increases toward the periphery, but others show similar or decreased infiltration
  – May reflect heterogeneity of asthma as well as the different methods used in the studies.

• The amount of collagen is lower in the small airways, but the smooth muscle presence is similar.
  – May contribute to an increased collapsibility and increased hyperresponsiveness of small airways.

van den Berge et al, *Chest* 2011;139;412-423
Are the Outer and Inner Walls Different in Small Airways?

- There are indications that the outer wall is more inflamed than the inner wall, and that peribronchiolar regions are also involved in the inflammatory process.
  - The latter may contribute to an uncoupling of small airways and surrounding lung parenchyma and thus increase collapsibility of small airways.

van den Berge et al, *Chest* 2011;139;412-423
Small Airway (<2 mm) Principles

- 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

Source: Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)
Small Airway (<2 mm) Principles

- 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
  – total pulmonary resistance is not significantly increased or marginally so
  – frequency dependence of compliance or resistance is present

Source: Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)
Function Of Tracheobronchial Tree As Reflected By Physiologic Measures

Source: *Journal of Allergy and Clinical Immunology* 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)
Assessment Of Air Trapping As A Result Of Small Airways Closure

Lung function tests

<table>
<thead>
<tr>
<th>Normal</th>
<th>Air trapping</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>FVC↓</td>
</tr>
<tr>
<td>RV</td>
<td>RV↑</td>
</tr>
</tbody>
</table>

Imaging (HRCT)

Contoli et al. Allergy 2010; 65: 141–151
FEV1

- 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

Contoli et al Allergy 2010; 65: 141–151
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 lung biopsies obtained through bronchoscopy

Contoli et al Allergy 2010; 65: 141–151
Small Airways Dysfunction Defined by a Reduction in FEF\textsubscript{25\%-75\%}

- May be better measure of small airways function than FEV\textsubscript{1}, particularly in children, but controversial
- Decreases following exercise without changes to FEV\textsubscript{1}
- Useful measure with methacholine challenge tests

Impaired Lung Function with Loss of Reversibility in Severe Asthma

% predicted FEF 25-75

Non-Asthmatics

Mild/Moderate Asthma

Severe Asthma

P<0.01

P<0.01

P<0.005

P<0.001

ns

= Pre-b’dilator

= Post b’dilator
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
Impact of Small Airways on Resistance Measures

<table>
<thead>
<tr>
<th>Resistance Measure</th>
<th>Normal</th>
<th>Peripheral Airway Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Airways</td>
<td>0.9</td>
<td>0.9 cmH$_2$O L$^{-1}$ s$^{-1}$</td>
</tr>
<tr>
<td>Peripheral Airways</td>
<td>0.1</td>
<td>0.2 cmH$_2$O L$^{-1}$ s$^{-1}$</td>
</tr>
<tr>
<td>Total Airways</td>
<td>1.0</td>
<td>1.1 cmH$_2$O L$^{-1}$ s$^{-1}$</td>
</tr>
</tbody>
</table>
Increased Peripheral Airway Resistance in Patients With Asthma

Increased Peripheral Resistance in Patients With Asthma

Distal lung dysfunction at night in patients with asthma


*P<.05 between the groups at 4:00 PM.
†P<.05 between the groups at 4:00 AM.
Positive Correlation Between Peripheral Resistance and Residual Volume: Evidence for Air Trapping


Mean $Rp$ (cmH$_2$O/ml/min)

<table>
<thead>
<tr>
<th>Time</th>
<th>RV (L)</th>
<th>$r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:00 AM</td>
<td>4.0</td>
<td>0.59</td>
<td>0.03</td>
</tr>
<tr>
<td>4:00 PM</td>
<td>4.0</td>
<td>0.71</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Increased Small Airways Resistance in Asthma with Loss of Reversibility in Severe Asthma
• 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.

Takeda et al, Respiration 2010;80:120
Nitrogen Washout Tests

- Can distinguish between ventilation inhomogeneity originating in peripheral vs. more proximal conducting airways
- Good reproducibility and sensitivity

I. Pure O$_2$ exhaled from upper airway

II. Rapid rise in N$_2$ which is anatomical deadspace

III. Alveolar gas normally plateaus & slope is measure of inequality of ventilation

IV. CV believed to be due to closure of the small airways in the lowest part of the lung
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

van den Berge et al, Chest 2011;139;412-423
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”.
Patients with unstable asthma have increased CVs and CCs compared with stable patients, suggesting air trapping or obstruction.


TLC=total lung capacity; FRC=functional residual capacity; dN=nitrogen washout slope; VC=vital capacity.
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
HRCT Assessments In Small Bronchi (1-5 Mm) Of 5 Lung Levels

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

J. Kosciuch et al, J Physiol Pharmacol, 2009
## Relations Between Airway Wall Thickness Or Lumen Dimension And Lung Function In Asthma

<table>
<thead>
<tr>
<th></th>
<th>WA</th>
<th>WA/BSA</th>
<th>WA%</th>
<th>WT</th>
<th>BWT</th>
<th>AL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-bronchodilator RV (%pred)</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>r=0.72, P&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>r=0.72, P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Post-bronchodilator FEV$_1$ (L)</td>
<td>NS</td>
<td>NS</td>
<td>r=-0.5, P=0.1</td>
<td>NS</td>
<td>r=-0.53, P=0.1</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td></td>
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<tr>
<td>Post-bronchodilator FEV$_1$ (%pred)</td>
<td>NS</td>
<td>NS</td>
<td></td>
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<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
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<tr>
<td>PC$_{20}$ (mg/ml)</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
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<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-bronchodilator Raw (cmH$_2$O/l/s)</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
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</tr>
</tbody>
</table>

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

Contoli et al. Allergy 2010; 65: 141–151
Do Small Airway Changes Correlate With Lung Function?

- 1 study in nocturnal asthma demonstrated that higher numbers of eosinophils in 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
  - different asthma populations have been investigated
  - number of studies is small
  - different techniques have been applied

van den Berge et al, *Chest 2011;139;412-423*
• Findings associated with distal lung disease:
  – Increased RV
  – Decreased FVC
  – Normal FEV1/FVC ratio

Source: Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)
The Role of Treating the Small Airways in Asthma

• Poorly controlled inflammation in small airways may contribute to asthma exacerbations, air trapping, lung function decline, and irreversible structural changes.

• Is it possible to reverse small airway abnormalities and improve physiologic measures?

Increased Pulmonary Deposition With Small Particle BDP

Proof Of Treatment: ICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HFA-BDP (1.1 µm)</th>
<th>CFC-FP (3.8 µm)</th>
<th>p</th>
<th>p (BvsF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV (L)</td>
<td>Pre</td>
<td>Post</td>
<td>p</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>.51</td>
<td>.44</td>
<td>.57</td>
<td>.76</td>
</tr>
<tr>
<td>CV/VC</td>
<td>18</td>
<td>14.2</td>
<td>(.02)</td>
<td>15.8</td>
</tr>
<tr>
<td>RV%</td>
<td>196</td>
<td>184</td>
<td>(.05)</td>
<td>205</td>
</tr>
<tr>
<td>FEV₁ Post Br Dil</td>
<td>67.6</td>
<td>71.9</td>
<td>(.02)</td>
<td>66.4</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (post)</td>
<td>42.5</td>
<td>51</td>
<td>(.002)</td>
<td>36.6</td>
</tr>
</tbody>
</table>

Proof Of Treatment: Montelukast

Improvement in symptoms (wheeze and chest tightness) correlated with improvements in RV ($P<0.05$)

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 long-term patient outcomes improve.
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