Physiology of Asthma and Involvement of Small Airways

Charles G. Irvin Ph.D.
Professor of Medicine, Pulmonary Medicine
Director, Vermont Lung Center
University of Vermont

Pathophysiology of asthma - common wisdom

Asthma is:

- Airway inflammation
- Airflow limitation
  - Small airways
- Reversibility
  - Remodeling
- Periodicity of airflow limitation
- Airways hyper-responsiveness
Airflow limitation/obstruction

- Spirometry
  - FEV₁; FVC
- Flow volume loops
- Other measures:
  - Sgaw
  - Forced oscillations
  - Peak flow
  - Lung volumes

Forced expiratory maneuver

Subject takes in a full breath to total lung volume and then exhales maximally into the spirometer

The FVC maneuver

- Phase 1: Deep inhalation
- Phase 2: Maximal exhalation
- Phase 3: Keep blowing for 6 seconds

#1 DEEP inhalation
#2 BLAST out
#3 Keep blowing for 6 seconds
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Spirometry

- FEV₁: After a maximal inspiration, the volume of air that can be forcefully expelled in one second.
- Effort dependent.
- High degree of reproducibility.
- Reported as percent predicted.
- Objective clinical tool to assess the severity of airway obstructive disease.
- Predictive of asthma exacerbations.
- Predictive of death due to all causes.
Uses of spirometry in asthma

- Confirm asthma
- Classify asthma severity
- Early recognition of exacerbations - “asthma control”
- Monitor medication effectiveness

The flow-volume loop

The flow-volume loop (2)
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

The flow-volume loop (3)

Extrathoracic obstruction

Vocal chord dysfunction

Flow

Volume

Cross sectional variance for FEV₁ and FVC

<table>
<thead>
<tr>
<th>Factor</th>
<th>% of variance up to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>30%</td>
</tr>
<tr>
<td>Age</td>
<td>8%</td>
</tr>
<tr>
<td>Height</td>
<td>20%</td>
</tr>
<tr>
<td>Weight</td>
<td>2%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>12%</td>
</tr>
<tr>
<td>Technical</td>
<td>3-10%</td>
</tr>
<tr>
<td>Unexplained</td>
<td>30%</td>
</tr>
</tbody>
</table>

Adapted from ATS Am Rev Respir Dis 144: 1202; 1991

Spirometry is age, race and gender dependent

Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Spirometry

<table>
<thead>
<tr>
<th>%pred FEV₁</th>
<th>Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>near LLN</td>
<td>Borderline*</td>
</tr>
<tr>
<td>60%-LLN</td>
<td>Mild</td>
</tr>
<tr>
<td>50-59%</td>
<td>Moderate</td>
</tr>
<tr>
<td>35-49%</td>
<td>Severe</td>
</tr>
<tr>
<td>&lt;35%</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

These cut-off points are arbitrary.

The FEV₁/FVC falls with age:
60 world-wide spirometry studies

Accelerated decline in lung function in asthma

The New England Journal of Medicine

A 13-YEAR FOLLOWUP STUDY OF VENTILATORY FUNCTION IN ADULTS WITH ASTHMA

The screen versions of these slides have full details of copyright and acknowledgements.
Accelerated decline in lung function in asthma (2)

In the Busselton Health Study, Asthma and its Treatment, T. Hungenberg, F. Hungenberg, J. J. Irvin, and J. J. Irvin, The effects of asthma and its treatment on lung function in adults, the decline in lung function is similar to that observed in the general population. Among asthmatics, the decline in lung function is relatively similar to that observed in the general population. Among smokers, the decline in lung function is accelerated.

Classifying asthma severity and initiating treatment in youths ≥12 years of age and adults

EIB = exercise-induced bronchospasm; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity


Levels of asthma control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (all of the following)</th>
<th>Partly controlled (any present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (2 or less/week)</td>
<td>More than twice/week</td>
<td>3 or more features of partly controlled asthma present in any week</td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Nighttime symptoms: awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for rescue &quot;reliever&quot; treatment</td>
<td>None (2 or less/week)</td>
<td>More than twice/week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV1)</td>
<td>Normal</td>
<td>&lt;80% predicted or personal best (if known) on any day</td>
<td></td>
</tr>
<tr>
<td>Exacerbation</td>
<td>None</td>
<td>One or more/year</td>
<td>1 or more/any week</td>
</tr>
</tbody>
</table>
The heterogeneous airways

- Parallel
- Axial
- Temporal

What is a SMALL airway?

Adapted from: Weibel ER. Morphometry of the Human Lung. 1963

The screen versions of these slides have full details of copyright and acknowledgements
Narrowing of parallel airways

\[ R = \frac{\rho l}{\pi r^4} \]

Obstruction of parallel airways

So obstruction is better than narrowing!

\[ R_s = \frac{P_{br} - P_{pl}}{V} \]

Pleural surface (Ppl)

Retrograde Catheter
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Peripheral airway resistance

Rp
(cm H2O/ml/min)

Flow (ml/min)

Kraft et al., AJRCCM 163: 1551; 2001

4 AM

4 PM

Control
Non-nocturnal asthma
Nocturnal asthma

* p = < 0.0001
† p = 0.0001

The screen versions of these slides have full details of copyright and acknowledgements
Physiology of Asthma and Involvement of Small Airways

Charles G. Irvin Ph.D.

**Lung volumes**

In normal asthma, lung volumes change as follows:
- **RV**: Normal
- **TLC**: Normal
- **FEV1**: Normal
- **VC**: Normal
- **FRC**: Normal

As asthma severity increases:
- **RV**: Increases
- **TLC**: Increases
- **FEV1**: Decreases
- **VC**: Decreases
- **FRC**: Increases

**Hyperinflation defends the FEV1**

Increasing asthma severity leads to hyperinflation, which helps to maintain the FEV1.

**Am chest tightness correlates with RV**

The correlation between BL-RV and am chest tightness is as follows:
- **BL-RV on placebo**: $r = 0.20$, $p = 0.41$
- **BL-RV on montelukast**: $r = 0.55$, $p = 0.04$
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Closing volume/capacity

Unstable asthma
Stable asthma

FEV₁, TLC, FRC, RV, RV/TLC, ERV, CV/CVC, CC/TLC

A: Normal
B: Methacholine/Exercise challenge
C: Effect of salbutamol on hypoventilation areas

MRI + hyperpolarized 3He

Wagers, Jaffe and Irvin In Allergy: Principles & Practices 2004

MRI + hyperpolarized 3He

Samee et al., J Allergy Clinical Immunol 2003
Enhanced lung deposition with smaller particle size

<table>
<thead>
<tr>
<th>Drug</th>
<th>MMAD (mm)</th>
<th>Oral</th>
<th>Lung</th>
<th>Exhaled</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP HFA</td>
<td>1.1</td>
<td>29%</td>
<td>55%</td>
<td>14%</td>
</tr>
<tr>
<td>BDP CFC</td>
<td>3.5</td>
<td>94%</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Enhanced lung deposition with smaller particle size

Enhanced lung deposition with smaller particle size

Effect of particle size on FEV₁

Asthma is:

- Airway Inflammation
- Airflow limitation
  - Small airways
- Reversibility
  - Remodeling
- Periodicity of airflow limitation
- Airways hyper-responsiveness
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Significant bronchodilator response

<table>
<thead>
<tr>
<th>Society</th>
<th>FVC (%)</th>
<th>FEV₁ (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP 1974</td>
<td>15-25</td>
<td>15-25</td>
<td>% baseline and 2 of 3 efforts</td>
</tr>
<tr>
<td>ITIS 1984</td>
<td>15</td>
<td>12</td>
<td>% baseline</td>
</tr>
<tr>
<td>ATS 1991</td>
<td>12</td>
<td>12</td>
<td>% baseline and 200ml</td>
</tr>
<tr>
<td>ATS/ERS 2005</td>
<td>12</td>
<td>12</td>
<td>% baseline and 200ml</td>
</tr>
</tbody>
</table>

Airways hyper-responsiveness correlates with bronchodilator responsiveness

Adapted from Ryan et al., Thorax 37: 423 1982
Physiology of Asthma
and Involvement of Small Airways
Charles G. Irvin Ph.D.

What is the best index of a bronchodilator effect?

- 100 consecutive patients RAO
- All had airflow limitation
- 38% COPD; 62% asthma
- Volume plethysmograph
- BD
  - Metaproterenol 63%
  - Albuterol 23%
  - Isoproterenol 11%
- Improvement
  - FEV₁ ≥ 15%
  - FVC ≥ 15%
  - FEF 25-75 ≥ 20%
  - Sgaw ≥ 40%

What is the best index of a bronchodilator effect?

(2)

What is the best index of a bronchodilator effect?

(3)
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Bronchodilator response is airway opening

MRI + hyperpolarized 3He

A: Normal
B: Methacholine/Exercise challenge
C: Effect of salbutamol on hypoventilation areas

Assumption: fall in FEV₁ is due to remodeling

* Loss of lung function not correlated to thickness of basement membrane
Mechanisms of airway obstruction

Airway remodeling: friend or foe?

Asthma is:

- Airway Inflammation
- Airflow limitation
  - Small airways
- Reversibility
  - Remodeling
- Periodicity of airflow limitation
- Airways hyper-responsiveness
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

峰流率日记在哮喘

空气通气性超敏感性与PEF变异相关

哮喘：时域周期性

Frey et al., Nature 438 867, 2005

The screen versions of these slides have full details of copyright and acknowledgements
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Forced oscillations (FOT)

Que et al., J. Appl. Physiol. 91:1131, 2001

Freq. of event
Magnitude of Z

> 100,000 X increase!

Que et al., AJRCCM 161:161, 2000

The screen versions of these slides have full details of copyright and acknowledgements
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Asthma is:
- Airway Inflammation
- Airflow limitation
  - Small airways
- Reversibility
  - Remodeling
- Periodicity of airflow limitation
- Airways hyper-responsiveness

Airway hyper-responsiveness

Fig. 5. The relationship between log \( P_{O_2} \) and PEF, that occurred with the development of \( P_{O_2} = 60 \text{ mm Hg} \) and \( P_{O_2} = 40 \text{ mm Hg} \).
Physiology of Asthma
and Involvement of Small Airways
Charles G. Irvin Ph.D.

Why perform an airways challenge test?

- To confirm a diagnosis of asthma or EIB
- Rule out the diagnosis asthma
- To aid in defining or guiding treatment

Bronchial provocation tests

- Pharmacological ‘direct’
  - Methacholine
  - Histamine
- Physical ‘indirect’
  - Exercise
  - Eucapnic voluntary hyperpnea
  - Adenosine monophosphate
  - Hyperosmolar saline
  - Mannitol

Antigen-induced airway hyper-responsiveness

The screen versions of these slides have full details of copyright and acknowledgements
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Exercise induced bronchospasm

Inhibition of deep inspirations causes AHR in normal but not asthmatics
Summary

- Asthma is a syndrome that is characterized by pattern of physiological dysfunction that is highly variable
- FEV₁ (FVC) is the robust index most frequently used
- Small airway dysfunction characterizes asthma that is mild or in remission
Control of airway caliber & patency

- Smooth muscle
- Nerves
- Structure
- Volume

- Smooth muscle
- Luminal contents
  - Mucus
  - Liquid
  - Fibrin
  - Surfactant
- Sheer number

Summary (2)

- Bronchodilator responses are highly variable but reflect the underlying disease process

Heterogeneity of reversibility

- Asthma
- COPD

- Fully reversible
- Reversibility
- Fixed
Summary (3)

- Variability of airflow limitation is perhaps the best marker of asthma

The signal is the noise

Summary (4)

- Hyper-responsiveness is a sensitive but not specific aspect of the asthmatic lung and may provide a more objective basis for therapy
Physiology of Asthma and Involvement of Small Airways
Charles G. Irvin Ph.D.

Acknowledgements and dedication

• Colleagues
• Participants
• National Institutes of Health and American Lung Association

I would like to dedicate this lecture to:
Peter T. Macklem, OC, BA, MD, CM, DHC(Hon), FRCP, FRSC