ASTHMA AND COPD ARE THEY A SPECTRUM OF SAME DISEASE?

PATHOPHYSIOLOGY

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COPD=chronic obstructive pulmonary disease.

The Dutch Hypothesis

- Various forms of airway obstruction are different expressions of a single disease
  - Chronic nonspecific lung disease (CNSLD)
- Host and environmental factors play a role in pathogenesis
  - Host factors: atopy and AHR
    - Other endogenous factors: sex and age
  - Exogenous factors: allergens, viral infections, smoking (pollutants)
- Diffuse airway obstruction = common pathophysiologic characteristic

The British Hypothesis

- Asthma and COPD are distinct entities caused by different mechanisms
  - Differences in inflammation
  - Airway remodeling vs alveolar remodeling
  - Epidemiology
What Is Asthma? What Is COPD?

<table>
<thead>
<tr>
<th>Asthma¹</th>
<th>COPD²</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A <strong>chronic inflammatory disorder</strong> of the airways in which many cells and factors play a role</td>
<td>• A preventable and treatable disease</td>
</tr>
<tr>
<td>• Inflammation results in</td>
<td>• Associated with significant <strong>extrapulmonary effects</strong> and important <strong>comorbid conditions</strong></td>
</tr>
<tr>
<td>– <strong>Recurrent symptoms</strong></td>
<td>• Characterized by airflow limitation that is</td>
</tr>
<tr>
<td>– Variable <strong>airflow obstruction</strong> that is mostly reversible</td>
<td>– <strong>Not fully reversible</strong></td>
</tr>
<tr>
<td>– Increase in existing <strong>bronchial hyperresponsiveness</strong></td>
<td>– <strong>Usually progressive</strong></td>
</tr>
<tr>
<td></td>
<td>– Associated with an <strong>abnormal inflammatory response</strong> to noxious particles or gases</td>
</tr>
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</table>

Interactions Between Asthma and COPD

Genetic susceptibility

Environmental factors
(Allergy, infection, smoking, air pollution)

Bronchial Inflammation
Bronchial Hyperresponsiveness

Asthma

COPD
Genetic Associations that Suggest a Common Origin in COPD & Asthma

- IgE
- BHR
- Rate of FEV1 decline
- Airway thickness

IL-13  ADAM33

Inflammatory Cascade Differs Between Asthma and COPD

**Asthma**
- Allergens
- Epithelial Cells
- Mast Cell
- CD4+ Cell (Th2)
- Eosinophils
- Bronchoconstriction and airway hyperresponsiveness
- Eotaxin, IL-4, IL-5, IL-13

**COPD**
- Cigarette Smoke
- Epithelial Cells
- Alveolar macrophage
- CD8+ cell (Tc1)
- Neutrophils
- Small airway fibrosis and alveolar destruction
- TNF-α, IL-8, IL-1β, IL-6

**Airflow Limitation**
- Reversible
- Not Fully Reversible

IL = interleukin; TNF = tumor necrosis factor.
Pathophysiological Changes in Asthma and COPD
Contrasting Histopathology of Asthma and COPD

Asthma

- Inflammation
- Airway Smooth Muscle
- Basement Membrane
- Fibrosis
- Alveolar Disruption

COPD

Structural Changes in Asthma and COPD

- **Asthma**
- **COPD**
- **Emphysema**
Inflammatory Phenotypes in Asthma vs. COPD

**Asthma**
- Eosinophils and mast cells
- Neutrophils (severe)
- CD 4+ T\textsubscript{H}2 cells
- LTC4, D4, E4
- Cytokines
  - IL 4, IL 5, IL 13
  - RANTES, eotaxins, MCP-1

**COPD**
- Macrophages and neutrophils
- Eosinophils (exacerbations)
- CD 8+ T cells,
- LTB4, Interferon γ
- Cytokines
  - IL 8, IL-1
  - TNF-α

Mauad T, Dolhnikoff M. Curr Opin Pulm Med 2008; 14: 31 - 38
Site of Airway Obstruction in Asthma and COPD:
Asthma in Medium Sized Airways, COPD in the Small Airways
However,

- Asthma is often a progressive process with a partially reversible component that can involve small peripheral airways.
- CT scans demonstrating increased airway wall thickness like COPD:
  - Volume of lung in density range c/w emphysema: 5% in mild and 23% severe asthmatics.

Sciurba FC Chest 2004:126:17S
Inflammation- Similarities

1. Alveolar inflammation demonstrated in asthma *
2. Severe asthma- BAL with neutrophils **
3. COPD: tissues eosinophils during exacerbations
   - Pts with eosinophils have better response to steroids ***

* Kraft M. Am J Respir Crit Care Med 1996:154:1505
**Wenzel S Am J Respir Crit Care Med:1999:160:1001
***Chanez P Am J Respir Crit Care Med 1997:155:1529
Pathophysiology of Asthma

- Inflammation in asthma is characterized by eosinophils, CD4+ T-lymphocytes, macrophages and mast cells
- Prominent pathological features of asthma include:
  - airway hyperresponsiveness
  - episodic bronchospasm in the large airways
  - vasodilation and angiogenesis
- Severe asthma can be classified into two subtypes: eosinophil (+) and eosinophil (-)
- Neutrophils are found in severe, corticosteroid-dependent asthma
Pathophysiology of COPD

• COPD is a disease characterized by inflammation in:
  – airways
  – systemic circulation

• COPD is a systemic disease that can cause weight loss and muscle weakness

• Prominent pathological features of COPD include:
  – mucus hypersecretion
  – small airway fibrosis
  – alveolar destruction
  – extrapulmonary effects
Pulmonary Function

• Classically
  – Asthma reversible airway obstruction
  – COPD partially reversible

Boulet L Can Respir J 1998:5:270
Fabbri LM Am J Respir Crit Care Med 2003:167:418
## Spirometry Is Essential in Both Asthma and COPD

**Asthma**
- Necessary to establish a diagnosis\(^1\)
- Low FEV\(_1\) is strongly predictive of risk for exacerbations\(^1,2\)
- Important in assessing control\(^1\)

**COPD**
- Essential for diagnosis\(^3\)
- Used to determine severity, which is linked to
  - Treatment decisions
  - Prognosis

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Acute Bronchodilator Response Does not Differentiate Between Asthma and COPD: Changes in Responder Classification After Albuterol and Ipatropium Bromide

Numbers in circles refer to the total classified as positive responders at that visit and those in squares are the nonresponders on the same occasion.

* Reversible defined as ≥ 12% and 200-mL increase in FEV₁ following 4 puffs (360 mcg) of albuterol.

## Physiologic Differences Between Asthma and COPD

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<thead>
<tr>
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<th>COPD</th>
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<tbody>
<tr>
<td><strong>Elastic recoil</strong></td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Diffusion capacity (DL_{CO})</strong></td>
<td>Normal or Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Lung volume</strong></td>
<td>Normal</td>
<td>Hyperinflation</td>
</tr>
<tr>
<td><strong>Bronchodilator response</strong></td>
<td>Flow-dominant</td>
<td>Volume-dominant</td>
</tr>
</tbody>
</table>

Sciurba FC. *Chest.* 2004;126:117S-124S.
Lung Volumes

• Nonreversible COPD pts 83% had improvement in lung volumes
  – Those with most severe disease > improvement

• Asthma study 15% reversibility in lung volumes not FEV-1

O’Donnel C Eur Respir J 2001:18:914
Smith HR Chest 1992:101:1577
Airway Hyperresponsiveness

- Positive Methacholine occurs in nearly all asthmatics, < 5% normals
- 63% of men and 87% of women with COPD show AHR with < 25 mg/ml of metacholine
  - Lower PFT’S associated with >AHR, decline in lung function and mortality
  - Smoking cessation has positive effect on AHR and improves FEV1 greater in those with AHR

Natural History of Asthma

FEV1/Ht³ (L/m³)

- Normal
- Asthma
- Smokers with Asthma

Age (Yrs.)

Peat JK. Eur J Respir Dis. 1987
Natural History of COPD

Mannino DM. *Chest.* 2002;121:121S-126S.

Fletcher and Peto, 1977
Physiologic Differences

Asthma
- Normal DLCO
- Normal lung volume
- Normal elastic recoil
- Flow dominant BD response

COPD
- Abnormal DLCO
- Hyperinflation
- Decreased elastic recoil
- Volume dominant BD response

Sciurba FC, CHEST 2004;117S-124S
### Asthma Imitates Mild/Moderate COPD With Increasing Age

<table>
<thead>
<tr>
<th>Asthma in young age</th>
<th>Asthma in old age</th>
</tr>
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<tbody>
<tr>
<td>±80% extrinsic</td>
<td>Mainly intrinsic</td>
</tr>
<tr>
<td>Often normal FEV₁</td>
<td>Often reduced FEV₁(60% of patients)</td>
</tr>
<tr>
<td>Often reversible obstruction</td>
<td>Often less reversible obstruction</td>
</tr>
<tr>
<td>Remission likely (60%–70% patients)</td>
<td>Remission unlikely (20% patients)</td>
</tr>
</tbody>
</table>

Systemic Consequences of COPD

- Weight loss with decreased fat-free mass
- Muscle wasting and weakness
- Cardiac co-morbidity
- Other systemic effects:
  - osteoporosis
  - anemia
  - depression
Similarities Between Asthma and COPD Pathophysiology

- Airway obstruction and hyperresponsiveness underly pathophysiology
- Inflammation plays a key role for both
- Complex interaction between genetic predisposition and the environment, may have common susceptibility genes
- Associated with progressive loss of lung function
- Heterogeneous (variable) natural history & clinical course
- The presence or absence of reversibility of FEV1 does not distinguish COPD from asthma
Progressive airflow obstruction

Most patients have increased bronchial responsiveness

Usually intermittent airflow obstruction but sometimes has a less reversible obstruction

High levels of bronchial responsiveness

Cellular inflammation including neutrophils, macrophages, eosinophils and mast cells may occur in exacerbations

Cellular inflammation with eosinophils, mast cells, T lymphocytes, in severe disease neutrophils

Broad inflammatory mediator responses

Airway remodeling (epithelial injury and fibrosis)

Cytokine, chemokine, protease responses

Emphysema (lung destruction) frequent

Systemic consequences

Differences Between Asthma and COPD

**Pathophysiology**

**Asthma**

**COPD**