Pathophysiology of COPD

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Objectives

• What do we mean by “COPD”? 
• Who gets COPD? 
• Effects of Cigarette Smoke?  
  – Anatomic/Pathologic changes  
  – Functional abnormalities 
• Clinical Syndromes 
• Therapeutic Approaches
DEFINITIONS
COPD: Progressive airflow limitation that is not fully reversible

- **Emphysema**: Lung tissue destruction & air space enlargement
- **Chronic Bronchitis**: Productive cough for at least 3 months in 2 successive years

Normal  Emphysema
Obstructive Lung Diseases

- Smoking-Related ("COPD")
  - Emphysema
  - Chronic Bronchitis
- Asthma (Reversible airways obstruction)
- Bronchiectatic Lung Diseases
  - Cystic Fibrosis
- Small Airway Diseases
  - Obliterative Bronchiolitis (OB)
  - Bronchiolitis Obliterans/Organizing Pneumonia (BOOP)
Overlap of Obstructive Lung Diseases
COPD: Scope of the Problem

- 15 million Americans w/COPD
- 4\textsuperscript{th} leading cause of adult death (rising)
- WHO predicts \uparrow COPD
  - 12\textsuperscript{th} \rightarrow 5\textsuperscript{th} prevalence
  - 6\textsuperscript{th} \rightarrow 3\textsuperscript{rd} mortality
- 30 Billion $$ annual healthcare costs
- Are future COPD cases preventable?
  - Yes! 50 million active US cigarette smokers
RISK FACTORS
Cigarettes & Lung Function

• Normal yearly FEV1 decline (15-30 ml/yr)
• The Lung Health Study showed that FEV1 declines 2-5x faster in a subset of smokers
• Not all smokers get COPD
  – 15% of American smokers
  – 5% of Taiwanese smokers
Genetics as a Risk Factor

- A1AT deficiency
  - A1AT made in liver (nl level 200 mg/dl)
  - Function: Inhibits elastin breakdown
  - Phenotype M = normal (PiMM)
  - Phenotype Z = ↓ solubility/transport from liver
  - PiZZ = 30 mg/dl in serum
  - PiMZ = 50-60 mg/dl in serum
  - Accounts for only 1% COPD in the US
Risk Factors: Genetics

Areas where genes may play a role:

• Elastase-AntiElastase balance
• Xenobiotic metabolism
• Inflammation
• Mucociliary clearance
Environmental Factors

• “Dutch” Hypothesis
  – Airways hyperreactivity → “fixed” obstruction
  – ↑ airways hyperreactivity in relatives of emphysema pts

• Toxic exposures
  – 2nd hand smoke
  – Industrial pollution
    • Sulfur dioxide
    • Cadmium
    • Particulates

• Recurrent/Childhood Infections
MECHANISMS OF DISEASE
Elastase – AntiElastase Theory

- Instill elastases in animal lungs \(\rightarrow\) emphysema
- Desmosine (elastin breakdown product) in urine of emphysema patients
- Alpha1-Antitrypsin (A1AT): known anti-elastase
- A1AT deficiency tips balance = Emphysema
COPD in 2003: Evolving Concepts

MMP = Matrix Metalloproteinase
COPD: Experimental Model

Exposure of normal mice to smoke results in enlargement of airspaces consistent with emphysema.
MMP-12 (MME) deficient mice have markedly reduced “recruited” alveolar macrophages
Elastase – AntiElastase Balance

Cigarette Smoke
Pollution
Infection
Inflammation

Neutrophil elastase
Proteinase 3
Cathepsins
Matrix metalloproteinases (1, 2, 9, 12)
Others

Increase

Decrease

α₁-Antitrypsin
Secretory leukoprotease inhibitor
Elafin
Tissue inhibitors of matrix metalloproteinases

A1AT deficiency
Smokers w/other deficiencies
After the smoke clears….the fire rages on

- Inflammation
- Oxidative stress
- ?Viral infection
ANATOMIC CHANGES & FUNCTIONAL CONSEQUENCES
Effects of Smoke: Anatomy

• **Alveoli/Parenchyma**
  - Inflammatory cell recruitment
  - Tissue destruction

• **Bronchioles**
  - Narrowing, fibrosis, inflammation
  - **Resistance** = $1/\text{radius}^4$ so small ↓ in size, ↑↑ resistance

• **Bronchi**
  - Mucus glands: ↑ size, ↑ number, ↑ mucus secretion
  - Thickening of airway walls
  - Ciliary dysfunction w/ ↓ mucus clearance
Functional Consequences: Parenchyma

- ↓ Elastic recoil
- ↓ Driving pressure to expel air
- ↑ Airway collapse
- ↑ Lung Volumes
  - ↑ RV, FRC, & TLC

Normal
Emphysema
Functional Consequences

Loss of structural supports

compliance
Functional Consequences: Airways

- ↑ Resistance
- ↑ Reactivity
- ↑ Air Trapping
- ↑ Lung Volumes
  - ↑ RV
  - ↑ FRC
  - TLC =
CLINICAL PRESENTATIONS
Dyspnea: “an uncomfortable sensation of breathing”

<table>
<thead>
<tr>
<th>Sensation</th>
<th>Congestive Heart Failure</th>
<th>Interstitial Lung Disease</th>
<th>Asthma Disease</th>
<th>Neuromuscular and Chest-Wall Disease</th>
<th>Pregnancy Disease</th>
<th>Pulmonary Vascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid breathing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Incomplete exhalation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Shallow breathing</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Increased work or effort</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Feeling of suffocation</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air hunger</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Chest tightness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy breathing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Adapted from Simon et al. and Elliott et al.*
Causes of Dyspnea in COPD

- ↑Airways resistance & ↓ Elastic Recoil
  - ↑work of breathing
  - ↑ventilatory drive
  - Hyperinflation w/diaphragm at mechanical disadvantage

- ↑ V/Q imbalance
  - ↑deadspace
  - ↓ ventilatory efficiency
  - ↑ $V_E$ proportional to metabolic rate
Clinical Manifestations

• Exertional Dyspnea
  – Limited ↑ ventilation in response to ↑ demand
  – Dynamic hyperinflation

• Cough & Phlegm
  – Stimulation of irritant receptors
  – Goblet cell hyperplasia
  – ↓ ciliary motility & function
  – Bacterial colonization of airways
Physical exam findings of COPD

- ↑ AP diameter
- Accessory muscle use
- Retractions
- Auscultatory findings
  - ↓ Air movement
  - ↑ Exhalation phase
  - Wheezes/rhonchi
- Peripheral wasting
- Clubbing
- Cyanosis
- Peripheral edema
Gas Exchange Abnormalities

• Hypoxemia
  • Non-uniformity of airways disease
  • Variability of ventilation
  • \textit{V/Q mismatch}

• Consequences of chronic hypoxemia
  • Hypoxic pulmonary (arteriolar) vasoconstriction
  • Pulmonary arterial hypertension
  • Right ventricular failure - Cor pulmonale
  • Secondary polycythemia
Gas Exchange: Hypercarbia

\[
\text{PaCO}_2 = \frac{k \text{VCO}_2}{V_A} = \frac{k \text{VCO}_2}{V_E \times (1-V_D/V_T)}
\]

- ↑ Work of breathing = ↑ Production
- Changes in central drive (↑RR, ↓TV)
  - Ineffective breathing pattern due to mechanics
  - Stimulation of irritant/J receptors in chronic bronchitics
- ↑ Dead space
COPD: Making the diagnosis

- **H & P**
- **PFTs**
- **CXR Findings**
  - Hyperinflation
  - Flattened diaphragms
  - ↑AP diameter
COPD: Making the diagnosis

- CT scan findings
  - Hyperinflation
  - Emphysema
  - Bullae
  - Pneumothorax
  - Airway collapse
  - Airway mucus
## Idealized Clinical Presentations

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pink Puffer</th>
<th>Blue Bloater</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>Emphysema</td>
<td>Chronic bronchitis</td>
</tr>
<tr>
<td>Symptom</td>
<td>Dyspnea</td>
<td>Cough/sputum</td>
</tr>
<tr>
<td>Appearance</td>
<td>Thin, wasted, not cyanotic</td>
<td>Obese, cyanotic</td>
</tr>
<tr>
<td>PO$_2$</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>PCO$_2$</td>
<td>Normal or ↓</td>
<td>Normal or ↑</td>
</tr>
<tr>
<td>Elastic Recoil</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>DLCO</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Normal</td>
<td>Often ↑</td>
</tr>
<tr>
<td>Cor Pulmonale</td>
<td>Infrequent</td>
<td>Common</td>
</tr>
</tbody>
</table>
THERAPY
First Line Therapy for COPD

SMOKING CESSATION!!

Data from Lung Health Study
Assisted Smoking Cessation

– Ask, Advise, Assist, Arrange
– Nicotine Replacement
  • Patch
  • Gum
  • Inhaled
– Bupropion (Wellbutrin SR® / Zyban®)
  • Noradrenergic antidepressant (9 week course)
  • 30% abstinent at 12 months c/w 15% placebo
Long-Term Oxygen Therapy

- \( \uparrow \) Survival
- \( \downarrow \) Pulm htn
- \( \uparrow \) Quality of life

- Pts: severe hypoxemia (PaO\(_2\) < 55 mmHg)
- 30\% US COPD costs
COPD Pharmacology

• Symptomatic relief w/small change in FEV$_1$
• No change in underlying pathology
  – Anticholinergic Bronchodilator
    • Muscarinic antagonist
    • Quaternary amine: Ipratropium (Atrovent®)
  – Sympathomimetic Bronchodilator ($\beta_2$-Agonists)
    • Short-Acting: Albuterol (Ventolin®, Proventil®)
    • Long-Acting: Salmeterol (Serevent®)
Bronchodilators: Site of Action

Epithelial Cells
Smooth Muscle
β₂-Receptor
Circulating Catecholamines
Submucosal Gland
Goblet Cell
Irritant Receptor
Blood Vessel
Vagus Nerve

Central Nervous System

1. 
2. 
3. 
4.

Sympathomimetics
Anticholinergics
Inhaled Corticosteroids: Controversy

- Limited data for chronic use
  - ISOLDE
  - EuroSCOP
  - Lung Health Study
- Pts w/“asthma overlap”
- Pro: ↓ severity AECOPD
- Con: ↑ PMN survival
Non-Medical Therapies

- Pulmonary Rehab
  - ↓ Dyspnea
  - ↑ Quality of life

- Non-Invasive Positive Pressure Ventilation
- Lung Volume Reduction Surgery
- Lung Transplantation
Summary

**RISK FACTORS**  ➔  **STRUCTURAL CHANGES**  ➔  **FUNCTIONAL CHANGES**  ➔  **SYMPTOMS**

- **Cigarette smoke**
- Susceptibility genes
- Latent adenoviral infections
- Childhood respiratory infections
- Environmental pollution
- Occupational pollution

- Proteolytic destruction of the lung parenchyma
- Airway inflammation and remodeling
- ↓ Expiratory flow
- Hyperinflation
- Mucus hypersecretion
- Dyspnea
- Expectoration
- Cough