Overview of Obstructive Diseases of the Lung, Lung Physiology and Imaging Modalities

Jann Mortensen

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Disposition

Obstructive disease
- Definition
- Epidemiology
- Mechanisms
- Natural history
- Treatment
- Diagnosis

Physiology
- Dynamic spirometry
- Lung volumes
- Transfer factor
- Reversibility

Imaging
- Chest X-ray
- CT
- Nuclear medicine
  - V/Q
  - MCC
  - PET
Change in mortality
USA 1965 - 1998

Compared to 1965

-59%
-64%
-35%
+163%
-7%

1965-1998
Ischemic heart disease
Stroke
Other cardiovascular dis.
COPD
Other reasons

www.copdgold.com
Chronic obstructive disease

Chronic bronchitis

Emphysema

Obstruction
FEV₁ / FVC < 70 %

Asthma
Obstruction is measured with Spirometry

Obstruction: \( \frac{FEV_1}{FVC} < 70\% \)

\[ FEV_1 = \text{Forced expiratory volume in the 1 second} \]
\[ FVC = \text{Forced vital capacity} \]
COPD and asthma definitions

**Asthma**
- *Chronic bronchitis*
- *Emphysema*
- *Productive Cough*
  - Most days
  - >3 months
  - >2 yrs
  - ie. Based on symptoms
- *Asthma*
  - *Reversible airways-obstruction*
  - ie. based on objective measures

**Emphysema**
- *Destruction of alveolar walls, resulting in permanent enlargement of airspaces and loss of lung elasticity*
  - ie. Based on pathoanatomy
COPD and asthma

Destruction of alveolar walls, resulting in permanent enlargement of airspaces (and loss of lung Elasticity)

Emphysema

Normal

Emphysema

Normal
Asthma & COPD

Onset: Early/Childhood

Asthma
- Eosinophils
- Airway hyperresponsiveness
- Bronchodilator response
- Steroid response
- Symptoms episodic
  Night/early morning

COPD
- Neutrophils
- *No airway hyperresponsiveness
- *No bronchodilator response
- *No steroid response
- Symptoms progressive
  *No < 15%

Ca. 10% have both

Onset: mid-life
Smoking history
Pathological airway changes

Normal airway

Constricted airway in asthma and COPD

- Inflammation
- Epithelium
- Basement membrane
- Smooth muscle
- Mucus plug
- Mucus glands hypertrophy
Airway generations and regional localisation?

Chronic bronchitis  Emphysema  Asthma

Figure 1.4. Idealization of the human airways according to Weibel. Note that the first 16 generations (2) make up the conducting airways and the last 7 the respiratory zone (or the transitional and respiratory zone). BR: bronchus; RL: bronchiole; TBL: terminal bronchiole; RBL: respiratory bronchiole; AD: alveolar duct; AS: alveolar sac. (From Weibel, E. R. Morphometry of the Human Lung. Berlin: Springer-Verlag, 1963, p. 111.)
Definition of asthma

• A chronic inflammatory disorder of the airway

• Infiltration of mast cells, eosinophils and lymphocytes

• Recurrent episodes of wheezing, coughing and shortness of breath

• Widespread, variable and often reversible airflow limitation

• Airway hyperresponsiveness

Global Initiative for Asthma (GINA). WHO/NHLBI, 1995
‘Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation, that is not fully reversible.

The airflow limitation is generally both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.’

This definition does not use the terms chronic bronchitis and emphysema, and excludes asthma (reversible airflow limitation)
What causes COPD

Including passive smoking
Other causes:
Occupational dust and chemicals
Indoor air pollution to cooking and heating
Outdoor air pollution
Respiratory infections in early childhood increase risk in adulthood
CELLULAR MECHANISMS OF COPD

Cigarette smoke

Alveolar macrophage

MCP-1

Neutrophil chemotactic factors
Cytokines (IL-8)
Mediators (LTB₄)

Neutrophil

PROTEASE INHIBITORS

PROTEASES

Neutrophil elastase
Cathepsins
Matrix metalloproteinases

Alveolar wall destruction (Emphysema)

Mucus hypersecretion (Chronic bronchitis)
Natural history: Effect of smoking on annual decline in lung function

FEV₁ (% of value at age 25)

Age (years)

Never smoked or not susceptible to smoke

Stopped at 45

Stopped at 65

20%

Smoked regularly and susceptible to its effects

Disability

Death

Adapted from Fletcher & Peto. Br Med J 1977
Smoking cessation improves decline in FEV$_1$

The Lung Health Study

- 5.887 with mild to moderate COPD
- Multicenter RCT
- Initial improvement & slower decline in FEV$_1$
- Anthonisen et al, JAMA 1994
Natural history of COPD

- Dyspnea
- Deconditioning
- Disability
- Systemic disease
- Hypoxemia
- Death

FEV₁ in % pred.

Bothering exacerbations
Hospital admission
Pulmonary hypertension

Age
Can steroids modify development of COPD?

Copenhagen City Lung Study:

No effect of budesonide on $\overline{\text{FEV}}_1$ in early COPD

EUROSCOPE:

- No effect of budesonide on $\overline{\text{FEV}}_1$ in mild COPD
- Initial improvement of $\text{FEV}_1$
Can steroids modify development of COPD?

ISOLDE

• No effect of fluticasone on $\text{EFV}_1$ in moderate/severe COPD

• 25% reduction in no. of exacerbations by fluticasone

• Improved “health status” (SGRQ)

751 patients, parallel design, 3 yr, 1000 ug fluticasone or placebo

Conclusion on inhaled steroids:
1. Do not change the decline of $\text{EFV}_1$ but
2. Improve the rate of exacerbations in severe COPD
Guidelines for management of COPD

- Smoking cessation
- Influenza vaccination
- Exercise where possible
- Bronchodilator treatment
- Inhaled steroids
- Pulmonary rehabilitation
- Long-term oxygen therapy
- Lung volume reduction Surgery
- Transplantation
Diagnosis: Consider COPD

SYMPTOMS
- Cough
- Sputum
- Dyspnea

RISK FACTORS
- Tobacco
- Occupational exposure
- Air pollution

SPIROMETRI
Spirometry

Reference values:
Age, sex, height, ethnic group
Flow rate =
driving elastic Pressure / Airway resistance

Asthma
COPD
Emphysema

Increase in Airway resistance
Low elastic recoil

Graph showing:
- FEV1
- FVC
- Forventet
- FEV1/FVC < 70%
Reversibility: spirometric (FEV$_1$) tracings

Each FEV$_1$ curve represents the highest of three repeat measurements. Global Initiative for Asthma (GINA). WHO/NHLBI, 1995
Establish the diagnosis of COPD

- History
- Physical examination

- **Lung function tests**
  - Spirometry
  - Lung volumes
  - Carbon monoxide diffusing capacity
  - Arterial blood gases

- Imaging
(slow) Spirometry: Static lung volumes
Body plethysmography = Bodybox

\[ P \times V = (P + \Delta P) \times (V - \Delta V) \]
\[ V_{FRC} = \frac{\Delta V_{\text{box}}}{\Delta P_{\text{mouth}}} \times (P_{\text{FRC}} - P_{\text{H2O}}) \]

\[ \Delta P_{\text{box}} \sim \Delta V \]

\( \Delta P_{\text{box}} \sim \Delta V \) from calibration with pumped air
\[ V_{FRC} = \frac{\Delta V_{box}}{\Delta P_{mouth}} \times (P_{FRC} - P_{H2O}) \]

\[ \Delta P_{box} \sim \Delta V \]

\[ \Delta P_{box} \sim \Delta V \text{ from calibration with pumped air} \]
Typical Static volumes
Patophysiology

- Progressive airways obstruction ->
  - hyperinflation, increased work of breathing, dyspnea

- Impaired gas exchange
  - loss of alveoli/airways obstruction -> disturbed perfusion/ventilation
  - hypoxemia and hypercapnia, and eventually acidosis
Carbon monoxide diffusing capacity
(mm mol/min/Kpa)

= Transfer faktor
Diffusion of gas is proportional with:

- The membrane’s area (↑)
- Thickness (↓)

and the difference in concentration over the membrane.
Single breath

1) simple
2) rapid
3) reproducible 5% (10%)

A *rapid* inspiratory vital capacity (from RV to TLC) is taken from a reservoir bag. The breath is held (automatically, against a closed shutter) for approximately 10 seconds at maximal inspiration, before a *rapid* and complete exhalation is made. The first 750 ml are discarded as contaminated with anatomic dead space gas, the next 500 ml are collected in a bag as an alveolar sample for analysis of CO and He.

*From Lung Function Tests, J.M.B. Hughes and N.B. Pride*
Inspiration of 0.3% CO og 10% He:

• • = CO conc. falls due to dilution + diffusion

• • = He conc. falls due to dilution only

Alveolus

Blood vessel

In:

Ex:

Conc.:
Diffusion capacity for CO is low if:

- Small area
  - Emphysema
  - Pulmonary fibrosis
- Thick membrane
  - Pulmonary fibrosis
- Ventilation / Perfusion disturbance
- Low Hemoglobin in capillaries (anemia, destruction of vascular tree)
Interpretation:
Ventilation and Diffusion Capacity

Irreversible obstructive lung function

- low FEV1/FVC, FVC, FEV1, and
- high RV, FRC, TLC

&

- Low diffusion ~ COPD with emphysema
- Normal diffusion ~ COPD without emphysema
Establishing the diagnosis of COPD

- Imaging
  - Chest X-ray
  - CT of chest
  - Nuclear medicine
    - V/Q
    - MCC
    - PET
1 choice: Chest x-ray

**Mild COPD:**
- Normal

**Advanced COPD:**
- Hyperinflation
- Flat diaphragm
- Vascular markings
- Thin heart shadow

- Complications
  - Infiltrates if pneumonia
  - Cor pulmonale

- Alternative diagnosis: nodules, pleural disease, interstitial disease
Computerised tomography

Superior to demonstrate (type, distribution and severity of) emphysema:

Findings:
- Low attenuation areas
- Bullae
- Attenuation and abnormal vascular tree

Monitoring:
- the progress through lung density measurements
Emphysema types demonstrated on CT:

- **Centriacinar**
  - Involves primarily the respiratory bronchiole.
  - The distal acinus or alveoli are unchanged.
  - Occurs more commonly in the upper lobes.
  - Most common type.
  - Seen in cigarette smokers.

- **Panacinar**
  - Involves entire respiratory acinus.
  - Commonly in the lower lobes.
  - 1/20 as rare as centriacinar emphysema.
  - In alpha 1 - antitrypsin deficiency.

- **Paraseptal**
  - The distal respiratory acinus, including alveolar duct and alveoli, is expanded.
  - Primarily adjacent to the pleura and connective tissue septa,
  - Especially in the upper lobes.
Monitoring the progress through lung density measurements

The gray area represent the relativ area (RA) of emphysematic lung, (threshold value of –910 HU)

A) RA 10%, 15\textsuperscript{th} percentile –894 HU

B) RA 31%, 15\textsuperscript{th} percentile –946 HU.
Computerised tomography

If complications are suspected:

- Lung cancer
- Pulmonary embolism
- Confirm alternative diagnosis
Single pulmonary nodule: Lung Cancer?

Positron emission Tomography (PET)

65 yrs female COPD, CT: 13 mm nodule in Right apex

18 F-flouro-deoxy-glucose (FDG)
FDG PET og CT

57 yr male COPD, 9 mm nodule

9 mm nodule

Diagnostics in single pulmonary nodules
(Nucl Med Comm 2004)
Major indications for PET in lung cancer

- "Diagnostical use" (Tumor)
  - indeterminate SPN on CT
    Relatively good evidence: class B

- Staging in NSCLC
  Good evidence: class A

Lancet Oncol 2001;2:659-66
Integrated PET-CT improves the diagnostic accuracy of the staging of NSCLC. N Engl J Med 2003; 348: 2500-7
Perfusion / Ventilation scintigraphy: Pulmonary embolism?
Emphysema: is LVRS possible?
LVRS in severe COPD

Before

After

Anterior/posterior projections

lg/jm
Special Genetic types of COPD: 
a1-antitrypsin deficiency emphysema

Homozygotic PiZZ, blood a1-antitrypsin test, 
1% of COPD cases, Early onset: 30–40 yrs

Panlobular:

a1-antitrypsin deficiency causes proteolytic damage of the lungs and emphysema
Special Genetic types of COPD: Primary ciliary dyskinesia

Homozygotic, Mucociliary function test; Rare: 1 in 15,000 subjects; Very early onset: from 0 yrs

Ultrastructural defects in cilia impairs mucus transport in the airways and results in infections and chronic sinusitis/otitis, bronchiectasis and (mild) COPD
Impaired mucociliary clearance in Primary Ciliary Dyskinesia

Markers

Stomach

start

1 h

2 h

24 h
Unresolved questions?

- Why do only 15-20% of smokers develop COPD?
- Why do some develop bronchitis and others emphysema?
- Are asthma and COPD different entities or interconnected?
- The patogenesis of COPD (genes and molecular biology)?
- How do we improve treatment?
- How do we identify pre-clinical (early) COPD?
  - PHIL?