COPD Update: 2017

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You see a new patient for shortness of breath. He is a former smoker (50 pack years) and has had progressive DOE, such that he has some trouble keeping up with people his own age walking on level ground. In the office, spirometry shows an FEV1/FVC of 0.55 and an FEV1 of 60% of predicted. Room air oxygen saturation is 94% at rest and while walking. What is the diagnosis? Why is he dyspneic without significant oxygen desaturation?

Presentation Outline

- Diagnosis/pathophysiology/pathogenesis
- Management of stable COPD
  - Pharmacologic treatment
  - COPD as a systemic disease
  - Oxygen therapy
- Management of exacerbations
- Surgical management

Definition of Disease

- COPD, a common preventable and treatable disease, is characterized by persistent symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by noxious particles or gases.

Global Initiative for Chronic Obstructive Lung Disease: "GOLD" guidelines 2017 update. (Vogelmeier et al)

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COPD: major diagnostic criteria

- Symptoms: dyspnea on exertion, cough
- Exposure
  - Cigarette smoking: generally > 20 pack years
- Air-flow obstruction
  - Reduced ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC < 0.70)

COPD Epidemiology

- 6.3% of US adults have COPD (CDC 2011)
- Leading cause of mortality
  - In US: 3rd leading cause
  - Worldwide: projected to be 3rd in 2020
- Annual cost in US
  - 29.5 billion direct
  - 20.4 billion indirect

Lung disease in smokers with normal spirometry

- Clinical significance of symptoms in smokers with normal pulmonary function (NEJM 2016)
  - High prevalence of symptoms, chest CT airways disease and "COPD" treatment among current/former smokers with normal spirometry
- Clinical and radiologic disease in smokers with normal spirometry (JAMA 2015)
  - High prevalence of symptoms, chest CT emphysema among current former smokers with normal spirometry
  - "35 million smokers in US with unrecognized disease"

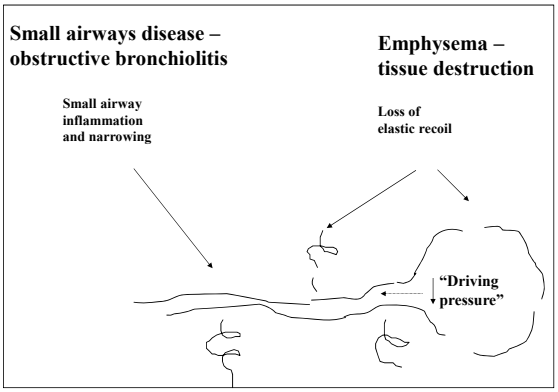
Among current or former smokers <u>without</u> airflow obstruction (and not meeting criteria for COPD):

- Evidence of emphysema or air-trapping on chest CT
  - 15% at age 50
  - 50% age > 75

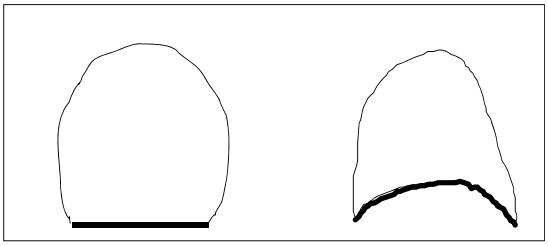
High prevalence of HRCT abnormalities in subjects with normal spirometry, Regan et al. JAMA 2015

COPD: pulmonary pathophysiology

- Expiratory air-flow limitation
- Ventilation-perfusion mismatch
- Hyperinflation



Hyperinflation and respiratory muscle weakness

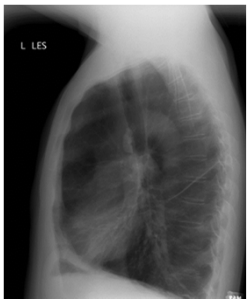


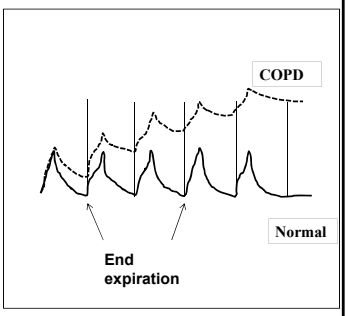
Shorter muscle length - less actin, myosin overlap

Decreased zone of apposition

Emphysema Normal

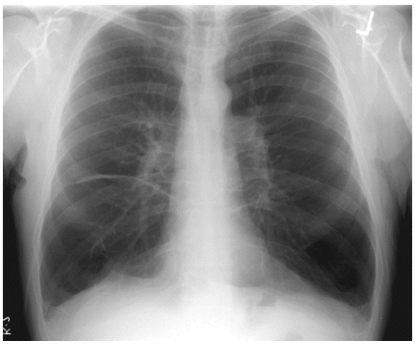
Dynamic hyperinflation in COPD



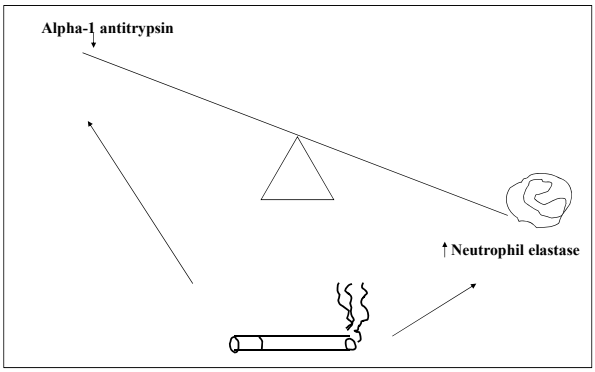


COPD Pathogenesis

54 y.o. non-smoker with severe air-flow obstruction



Protease – Antiprotease hypothesis of emphysema pathogenesis

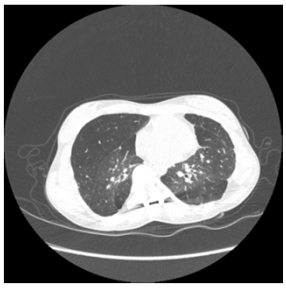


COPD pathogenesis

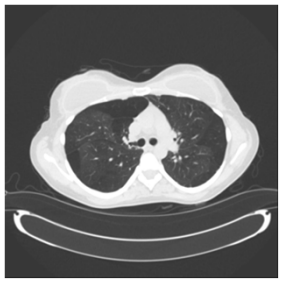
- Processes
  - Inflammation
  - Apoptosis
  - Senescence
  - Inadequate repair
  - Remodeling
- Mediators
  - IL-1B, TNF-a, TGF-B, IL-6, VEGF, MMP-9, MMP-12, CXCL8, oxidants
- Cells
  - Macrophages, neutrophils, lymphocytes, airway smooth muscle, airway epithelium

Risk factors, other than smoking, for COPD development

- Biomass fuel exposure
  - Wood, animal dung, crops, coal for indoor heating and cooking
- Occupational exposures (e.g. dust)
- HIV-infection
- Childhood respiratory disease



24 y.o. female never smoker with severe air-flow obstruction



34 y.o. female never smoker with severe air-flow obstruction

Bronchopulmonary dysplasia

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1. Inhaled corticosteroid (ICS)
2. Inhaled corticosteroid/long acting beta agonist combination (ICS/LABA)
3. Long acting muscarinic antagonist (LAMA)
4. Whatever the insurance company tells you to do…

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COPD Assessment

- "GOLD" Categories based on:
  - Severity of spirometric abnormality
  - Symptoms
  - Future risk of exacerbations
- Other assessment considerations
  - CXR
  - Pulse oximetry; consider ABG if ≤ 92%
  - Alpha-1 anti-trypsin if age < 45 or strong family history

GOLD COPD "phenotyping" based on degree of air-flow obstruction

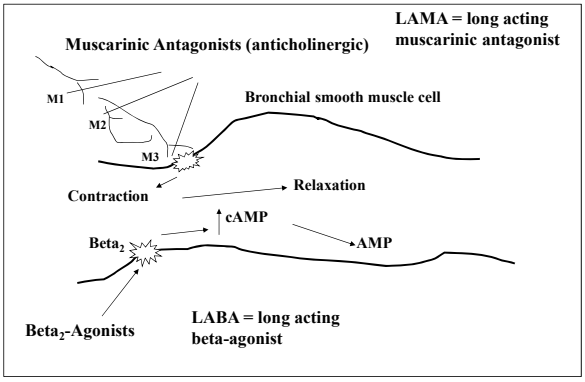
FEV1/FVC less than 0.7

- GOLD 1 FEV1 ≥ 80% predicted
- GOLD 2 50% ≤ FEV1 > 80%
- GOLD 3 30% ≤ FEV1 > 50%
- GOLD 4 FEV1 < 30% predicted

Additional GOLD "COPD phenotyping" – based on exacerbation risk and symptoms

- C , D = Increased Risk of Exacerbations
  - 2 or more exacerbations in the previous year (or 1 requiring hospitalization)
- B, D = Increased Breathlessness/Dyspnea
  - Walk slower than a similar age person on level ground (MRC stage 2)
  - COPD Assessment Test score ≥ 10
    - Evaluates: mucus production, chest tightness, dyspnea, ADLs, sleep, energy

Bronchodilator therapy in COPD



Long-acting bronchodilators for COPD

- **LAMA**
  - **Tiotropium**
    - ***Spiriva***
  - **Aclidinium**
    - ***Tudorza***
  - **Umeclidinium**
    - ***Incruse***
- **LABA**
  - **Salmeterol**
    - ***Serevent***
  - **Formoterol**
    - ***Foradil***
  - **Olodaterol**
    - ***Striverdi***

Combination inhalers for COPD

- **LAMA/LABA**
  - **Umeclidinium/Vilanterol**
    - ***Anoro***
  - **Tiotropium/Olodaterol**
    - ***Stiolto***
  - **Glycopyrrolate/Formoterol**
    - ***Bevespi***
  - **Glycopyrrolate/indacaterol**
    - ***Utibro***
- **ICS/LABA**
  - **Fluticasone/Salmeterol**
    - ***Advair***
  - **Budesonide/Formoterol**
    - ***Symbicort***
  - **Mometasone/Formoterol**
    - ***Dulera***
  - **Fluticasone/Vilanterol**
    - ***Breo***

Drug therapy considerations based on exacerbation risk

- **If increased risk of exacerbation (GOLD C,D) the regimen should contain a LAMA or ICS**
- **ICS therapy in COPD should be given in a combination inhaler ICS/LABA**
- **If no increased risk of exacerbations ICS is generally not first line**
- **LAMA/LABA combination may be optimal for exacerbation prevention**

LAMA/LABA vs ICS/LABA for COPD (Wedzicha et al, NEJM 2016)

- **3200 COPD patients with at least one exacerbation in the previous year randomized to LAMA/LABA (Utibro) vs ICS/LABA (Advair)**
- **Prevention of exacerbations was superior in the LAMA/LABA**

First-line treatment recommendations according to COPD category

- **Group "A" – minimal symptoms and low exacerbation risk**
  - **Any bronchodilator**
- **Group "B" – significant symptoms but low exacerbation risk**
  - **LAMA or LABA**
- **Group "C" – minimal symptoms but increased exacerbation risk**
  - **LAMA**
- **Group "D" – significant symptoms and increased exacerbation risk**

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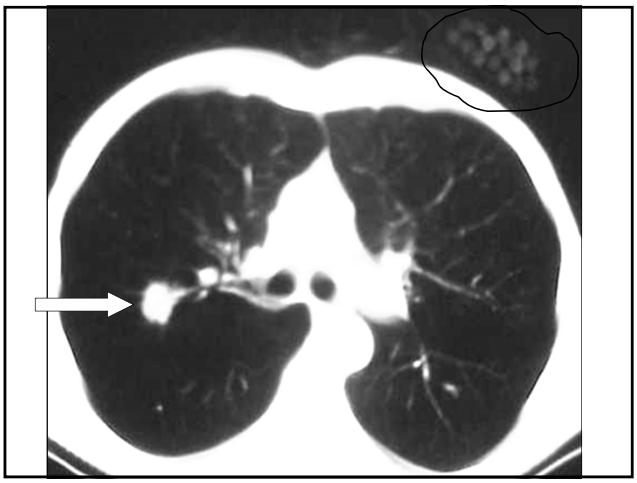

Presentation Outline

- **Diagnosis/pathophysiology/pathogenesis**
- **Management of stable COPD**
  - **Pharmacologic treatment**
  - **COPD as a systemic disease**
  - **Oxygen therapy**
- **Management of exacerbations**
- **Surgical management**

Your patient does well with LAMA therapy for quite some time. Now, 10 years after his initial presentation he notes gradually increasing DOE, such that he trouble walking 100 yards without stopping. He had one exacerbation in the last year – 2 months ago and has had considerably more trouble after that. In the office, spirometry shows an FEV1/FVC of 0.49 and an FEV1 of 51% of predicted. Room air oxygen saturation is 93%. What treatment addition is expected to have the greatest effect of alleviating his DOE?

1. **LABA**
2. **ICS/LABA**
3. **Theophylline**
4. **Pulmonary rehabilitation**

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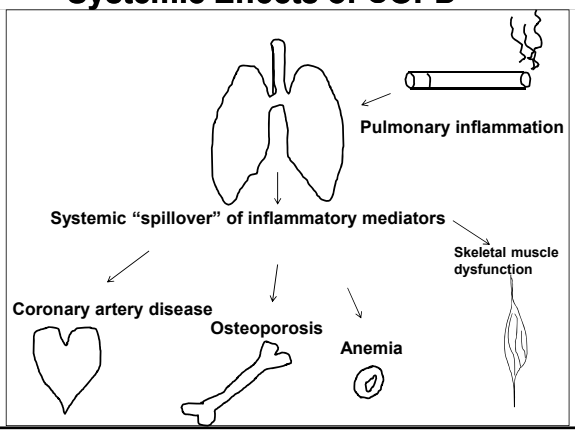
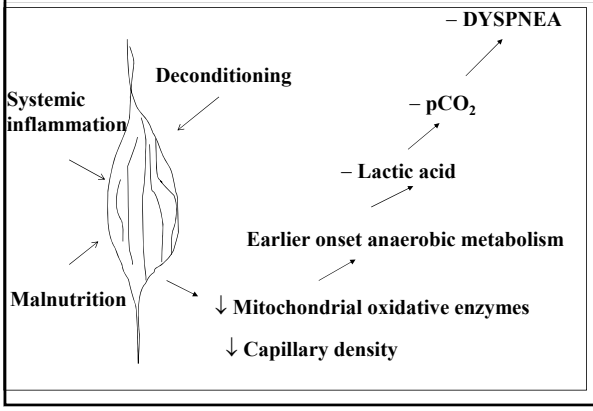
Systemic Effects of COPD

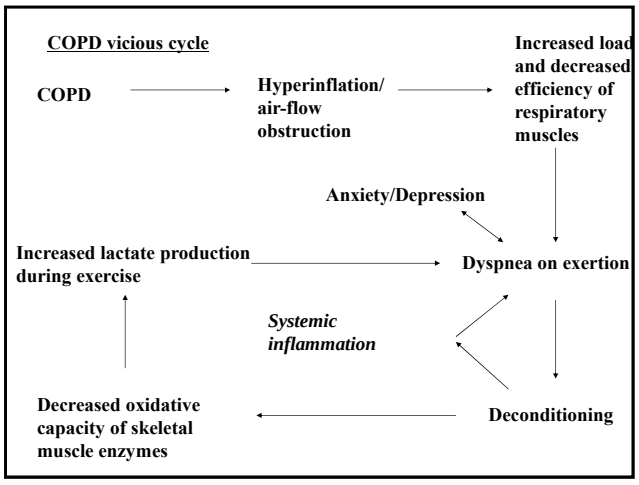


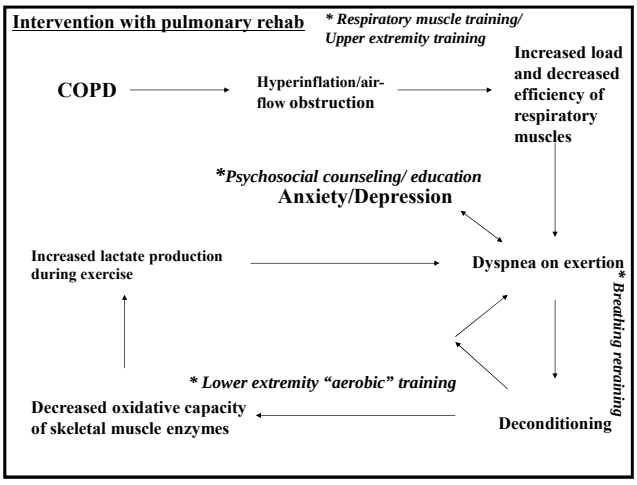
Decreased muscle oxidative capacity in COPD

- **Decreased citrate synthase in vastus lateralis of COPD patients (Maltais, Thorax 2000)**
  - **Key mitochondrial oxidative enzyme**
  - **Levels correlate with functional class**
  - **Improvement in citrate synthase following exercise training**
- **Marked attenuation of lactate production in COPD patients following pulmonary rehab (Casaburi, Am Rev Respir Dis 1991)**

Skeletal muscle dysfunction and COPD







Ischemic heart disease in COPD

- Ischemic heart disease increased in COPD
  - Shared risk factors
  - Shared inflammatory pathways
- Myocardial injury overlooked in COPD (Respir Med 2008)
- In general, treatment of IHD should be similar to guidelines for the non-COPD population

Beta-blockers in COPD: change in attitude timeline

1983
"It has been established that no beta-blocker is entirely safe in patients with chronic obstructive lung disease."
J Cardiovasc Pharm.

2005
"…cardioselective beta-blockers should not be routinely withheld from patients with COPD."
Cochrane Review

2011
"β blockers may reduce mortality and COPD exacerbations …, independently of overt cardiovascular disease and cardiac drugs"
BMJ

2016
βLOCK COPD: placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate of COPD exacerbations.
Federally funded multi-center trial

Your patient with COPD, hospitalized with an acute exacerbation is ready for discharge. At rest on room air her O2 saturation is 94%. Walking around the nurses station several times she is not short of breath, but her O2 sat drops to 86%. As part of her discharge planning you should arrange the following outpatient therapy:

1. **Supplemental oxygen 2 liters/min at rest, sleep and with exertion**
2. **Supplemental oxygen 2 liters/min with exertion only**
3. **Supplemental oxygen 2 liters/min with exertion and while sleeping**
4. **Discharge without oxygen; follow-up in 2 weeks**

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Supplemental oxygen in COPD

- Improves mortality in patients with severe resting hypoxemia (pO2 ≤ 55 mmHg)
  - Medical Research Council Trial (Lancet 1981)
    - Patients randomized to oxygen 24/7 vs no oxygen
    - Improved survival in oxygen 24/7 group
  - Nocturnal Oxygen Treatment Trial (Ann Intern Med 1980)
    - Patients randomized to oxygen 24/7 vs oxygen during sleep
    - Improved survival in oxygen 24/7 group

NOTT and MRC oxygen trials

- Key points
  - Major eligibility: PaO2 ≤ 55mmHg (~ SaO2 ≤ 88%)
    - With edema, pulmonary HTN, polycythemia: pO2 56-59 (sat 89%)
  - Patients in a stable state, at rest. Hypoxemia confirmed with repeat ABG within 3 weeks
  - 290 total patients

Supplemental oxygen in COPD

- Unanswered questions
  - Is supplemental oxygen helpful in patients with nocturnal desaturation only?
  - Is supplemental oxygen helpful in patients with desaturation during exertion only?
  - Is supplemental oxygen helpful in patients with moderate resting hypoxemia?
    - e.g. O2 sats 89-93%

Supplemental O2 in US

- ~ 1.4 million users
- ~ 2.8 billion dollars/year
- Cost increasing by 12-13%
- ~75% of Medicare's outpatient costs for COPD

Long Term Oxygen Treatment Trial (LOTT)

- Patients randomized to supplemental O2 or no O2
- Outcomes tracked: mortality, hospitalizations, quality of life
- Eligibility
  - ✓ COPD – FEV1/FVC < 70%; FEV1 ≤ 65% of predicted
  - ✓ Age > 40
  - ✓ Resting O2 sat 89-93% or
  - ✓ O2 sat 80 – 89% with exertion

CMS

NIH National Heart, Lung, and Blood Institute

A randomized trial of long-term oxygen for COPD with moderate desaturation (New Engl J Med 2016)

- 738 patients randomized - oxygen vs no oxygen (1:1)
- No difference in time to death or first hospitalization
- No difference in any secondary outcome
  - COPD exacerbations
  - Quality of life
  - Lung function
  - 6 minute walk distance

CMS

NIH National Heart, Lung, and Blood Institute

Recommendations for supplemental oxygen in COPD:

- 24/7 oxygen for patients with severe hypoxemia at rest
  - PaO2 ≤ 55mmHg (~ SaO2 ≤ 88%)
    - With edema, pulmonary HTN, polycythemia: pO2 56-59 (sat 89%)
- Individualized approach in patients with oxygen desaturation only during exercise (O2 sat 80-88%)
  - Therapeutic trial in dyspneic patients who are interested

Management of stable COPD

- Take home points
  - Goals of therapy: improve quality of life, decrease symptoms, decrease acute exacerbations
  - Bronchodilators central to symptomatic management – alleviation of hyperinflation key
  - Patients with 2 or more acute exacerbations (or 1 requiring hospitalization) should be treated with LAMA and/or ICS containing regimen
  - Strongly consider pulmonary rehabilitation in patients short of breath despite pharmacologic management
  - Supplemental oxygen improves survival in patients with severe resting hypoxemia.

Presentation Outline

- Background and pathophysiology
- Management of stable COPD
- Management of exacerbations
- Surgical management

Your 66 y.o. patient with severe COPD presents with increased cough productive of discolored sputum following a "cold". He also has increased dyspnea and chest tightness. On exam he is in no acute distress and vital signs are stable. There is increased wheezing on chest exam and the rest of the exam is unchanged. Room air pulse oximetry is 90% and a CXR in the office shows no infiltrates. You should:

- A. Begin oral antibiotics and prednisone as an outpatient.
- B. Send the patient to the ER for ABG's
- C. Send the patient to the ER to rule out myocardial infarction
- D. Begin oral prednisone, but defer antibiotics
- E. Begin antibiotics, but defer prednisone

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Acute exacerbation of COPD (AECOPD)

- Acute worsening of respiratory symptoms resulting in additional therapy
- Most common causes: infection of tracheobronchial tree and air-pollution; no cause can be found in ~1/3 of cases
- Outpatient treatment
  - Inhaled albuterol with/without ipratropium
  - Prednisone 40mg daily for 5 days
  - Antibiotics if increased dyspnea and increased sputum volume or purulence

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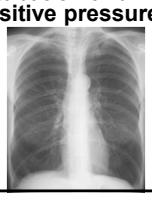
Your patient with severe COPD presents to the ED with increased cough, and SOB after developing a URI. On exam he is afebrile, pulse 112, RR – 24, BP – 120/80. He is alert but using his accessory muscles to breathe. ABG's on 2 liters show: pH – 7.31, pO2 – 61, PCO2 – 49, HCO3 – 26. Which of the following intervention is associated with improved survival in this setting?

a) Prednisone 40 mg daily for 5 days
b) Levofloxacin 500 mg daily for 7 days
c) Endotracheal intubation and mechanical ventilation
d) Non-invasive positive pressure ventilation (NIPPV)



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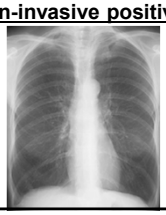

Trends in In-Hosptial Outcomes in AECOP Lima et al, COPD 2015

- Over 3 million AECOPD hospitalizations analyzed between 2006-2009
- All-cause hospital mortality declined from 5.1 to 4.2%
- Main predictors of survival: NIPPV use

Acute exacerbation of COPD (AECOPD)

- Inpatient management
  - Titrate oxygen to keep O2 sats 88-92%
  - Inhaled albuterol with/without ipratropium
  - Prednisone 40 mg daily for 5 days
  - Antibiotics
    - if increased dyspnea and increased sputum volume or purulence
    - Mechanical ventilation
  - Non-invasive ventilation as initial approach in those with respiratory acidosis

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Prevention of COPD exacerbations

- Smoking cessation, avoidance of environmental exposures
- Inhaled corticosteroids
- Inhaled long-acting bronchodilators
- Rofumilast
- Azithromycin
- Pulmonary rehab

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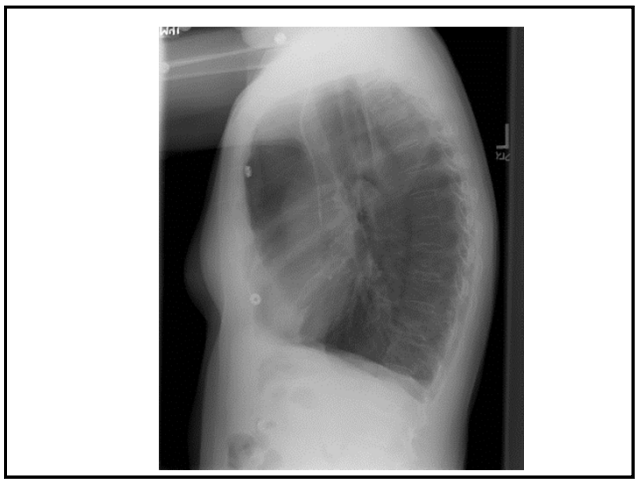
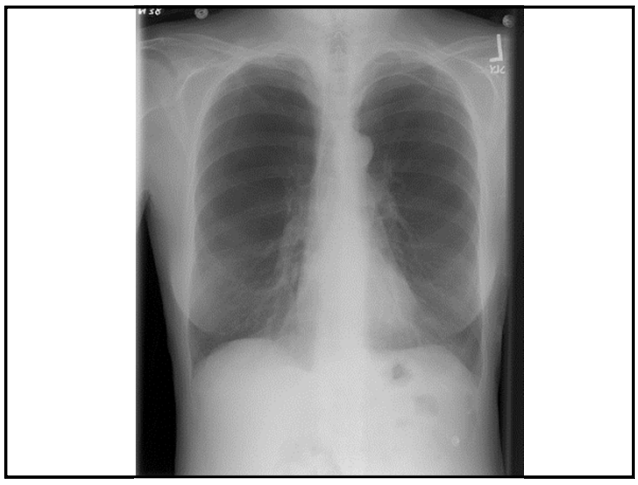
Case

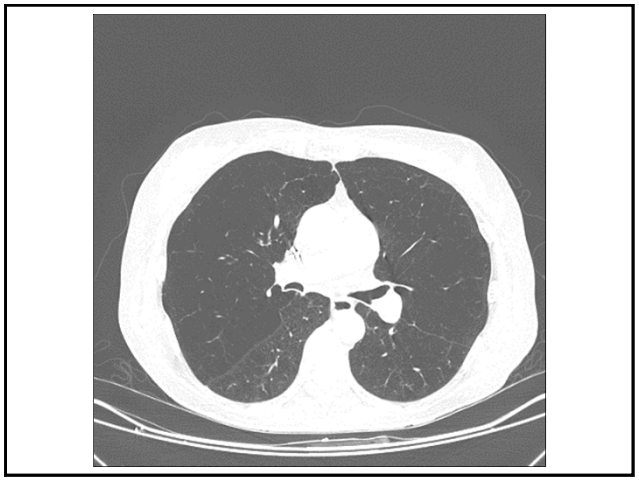
- 62 y.o. female; presents in a wheelchair; dyspneic getting dressed
- Long history of emphysema
- 40 pack year smoking history
  - No longer smoking

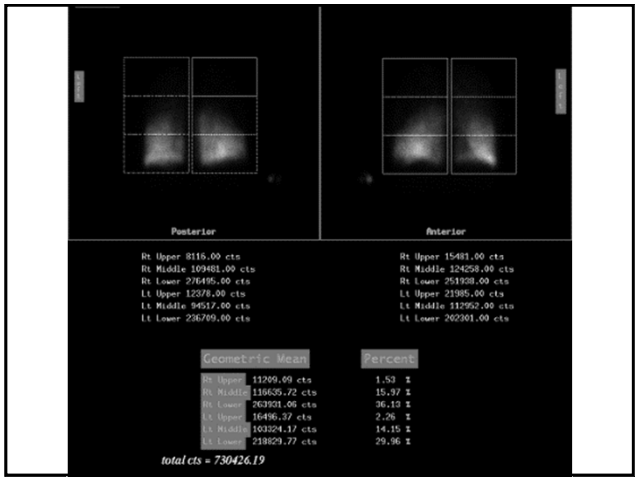
Pulmonary diagnostic studies August 2004

- *FEV_1 - 0.42 liters (17% of predicted)
- FVC – 0.91 liters (30% of predicted)
- Total lung capacity (TLC) – 8.01 liters (159% of predicted)
- Residual volume (RV) – 7.07 liters (352% of predicted)
- pO2 = 60 mmHg; pCO2 = 54 mmHg





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Anterior
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Rt Lower 276495.00 cts
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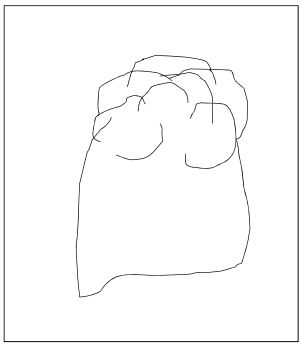
Lt Lower 236709.00 cts
Rt Upper 15481.00 cts
Rt Middle 124258.00 cts
Rt Lower 251938.00 cts
Lt Upper 21985.00 cts
Lt Middle 112952.00 cts
Lt Lower 202301.00 cts
Geometric Mean
Percent
Rt Upper 11269.09 cts 1.53 %
Rt Middle 116635.72 cts 15.97 %
Rt Lower 263931.06 cts 36.13 %
Lt Upper 16496.37 cts 2.26 %
Lt Middle 103324.17 cts 14.15 %
Lt Lower 218829.77 cts 29.96 %
total cts = 730426.19

Upper lobe predilection for emphysema:

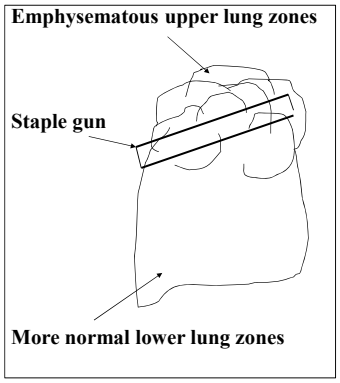


-Differences in inflammatory cell trafficking

-Differential accumulation of inhaled particulate matter, gases

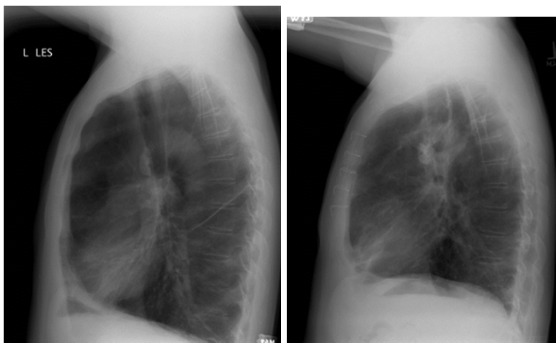
-Differences in oxidant stress

Lung volume reduction surgery (LVRS) for emphysema



Protocol: Median sternotomy or bilatateral video-assisted thoracoscopy. Target areas identified by CT scan and perfusion scan. ~30% of each lung removed by a stapling technique.

Post-op: Improved elastic recoil and V/Q matching in remaining lung. Decreased hyperinflation.



Case:Pre and post lung reduction

August 2004

- FEV_1 - 0.42 liters (17% of predicted)
- Residual volume (RV) – 7.07 liters (352% of predicted)
- Six-minute walk – 702 feet

June 2017

- FEV_1 - 0.51 liters (27% of predicted)
- Residual volume (RV) – 4.49 liters (209% of predicted)
- Six-minute walk – 1230 feet

Major selection criteria for LVRS

- Severe air-flow obstruction (FEV1 < 45% predicted)
- Hyperinflation/Air-trapping
- Upper lobe predominant disease
- No longer smoking

Lung transplant for COPD

- Consider referral
  - FEV1 < 25% pred
  - Room air pO2 < 60
  - pCO2 > 50 mmHg
  - BODE index of 5-6
  - Accelerated decline in FEV1
  - Not a candidate for LVRS

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Lung transplant for COPD

- Recommended listing criteria:
  - FEV1 < 15-20% of predicted
  - Three of more severe exacerbations in the preceding year
  - One severe exacerbation with acute hypercapnic respiratory failure
  - BODE index of > 7
  - Moderate-severe pulmonary hypertension

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