Chronic Obstructive Pulmonary Disease

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Education is at the heart of patient care.
Disclosures

• I have no relationships with commercial entities.
• I receive support from the NIH for my research on dyspnea.
Goals and Objectives

• To describe recent insights into the epidemiology and pathology of COPD
• To incorporate knowledge about COPD phenotypes into decision-making about treatment options
• To delineate the key elements of the physiology of airflow obstruction in emphysema and the implications of these principles for clinical practice
• To detail the essential elements in the evaluation of patients with COPD and to highlight common pitfalls in the assessment of these patients
• To outline therapeutic advances in the treatment of COPD
COPD – Definition includes:

- Chronic airflow obstruction
- Range of pathologic changes in the lung (abnormal inflammatory response to noxious particles or gases)
- Extra-pulmonary effects
- The obstruction is progressive
- May have elements of airways reactivity, i.e., the obstruction may be partially reversible
- “Preventable and treatable.”
COPD – Definitions: old phenotypes

- **Chronic bronchitis**: productive cough for 3 months in each of 2 consecutive years
- **Emphysema**: abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls, and without evidence of fibrosis
- **Other**: bronchiectasis, airway reactivity
COPD Phenotypes are Growing

• Airway vs Emphysema
  ✓ Hersh et al., COPD 2007;4:331
  91 patients early onset, severe COPD (FEV1 < 40% pred): emphysema predominant, lower FEV1, less bronchospasm

• Range of phenotypes
  ✓ Friedlander et al., COPD 2007;4:355
    “Frequent exacerbater,” pulmonary cachectic, rapid decliner, airways hyperresponsive, impaired exercise tolerance
  ✓ Jankowich and Rounds, Chest 2012;141:222 (review)
    Combined pulmonary fibrosis and emphysema syndrome; spiro may be normal, but CT with extensive emphysema
Emphysema Increases Mortality

251 pts stable COPD followed for 8 yrs. Multivariate analysis: amount of emphysema (LAA = low attenuation areas) on CT, best association with mortality. *Chest* 138:635, 2010
Frequent Exacerbator

2138 pts-ECLIPSE study (Eval of COPD Longitudinally to Identify Predictive Surrogate End points). Exacerbation freq in 3 yrs. Multivariate analysis.

COPD - Epidemiology

• 2011: 6.5% of adults in US diagnosed with COPD
• 2010: 10.3 million office visits, 1.5 million ED visits and 699,000 hospital discharges (Chest 144:284, 2013)
• Chronic bronchitis vs emphysema - clinical vs radiographic diagnosis (e.g., 79% of COPD with emphysema on CT; degree of emphysema may predict mortality – Chest 141:1216, 2012)
• Healthcare costs in 2010 - $32.1 billion (Chest 2015;147:31-45)
**GOLD Classification**

Global Initiative for Chronic Obstructive Lung Disease

*Am J Resp Crit Care Med 176; 532-555, 2007*

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV₁/FVC</th>
<th>FEV₁/FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: mild</td>
<td>&gt; 0.70</td>
<td>≥ 80% predicted</td>
</tr>
<tr>
<td>II: moderate</td>
<td>≤ 0.70</td>
<td>≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>III: severe</td>
<td>≤ 0.70</td>
<td>≤ 50% predicted</td>
</tr>
<tr>
<td>IV: very severe</td>
<td>&lt; 0.70</td>
<td>FEV₁ &lt; 30% predicted or FEV₁ &lt; 50% predicted plus chronic respiratory failure*</td>
</tr>
</tbody>
</table>

* Respiratory failure: arterial partial pressure of oxygen (PaO₂) < 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO₂ (PaCO₂) > 6.7 kPa (50 mm Hg) while breathing air at sea level.*
Should People be Screened for COPD with Spiro?

  - US Preventative Services Task Force
  - Meta analysis - could you prevent COPD exacerbations? Reduce morbidity and mortality? Enhance smoking cessation?
  - Screen 833 pts to prevent 1 COPD exacerbation
  - *No data to suggest decrease M&M*
  - *No data to support enhanced smoking cessation*

- Note: FEV1/FVC ratio declines with normal aging
- Controversy about “small lungs” in growth and development
COPD Mortality

• Fourth leading cause of death in US (125,000 deaths in year 2007 – CDC data); expected to be third leading cause of death globally by 2030.

• By 2020, number of women dying > men (studies suggest women may be more susceptible to cigs: Silverman et al. AJRCCM 2000;162:2152)

• Only disease among top 10 in which mortality is increasing.
COPD - Causes of Death

pulm>cardiovasc>cancer  NEJM 356;851854, 2007
COPD - Risk Factors

- Cigarettes - active and passive smoking (*30-50% of current/former smokers have airflow obstruction*)
- Airways reactivity: “Dutch Hypothesis” – common links between COPD and asthma
- Genetic susceptibility
  - alpha 1 anti - trypsin deficiency
  - Other genes may explain variability in risk with smoking
- Bacterial, viral infections; cig smoke reduces immune response – interferon, IL-1 (*Chest 143:196, 2013*)
- Air pollution and occupational exposures
Dutch Hypothesis

• First proposed in 1961
• Three principles
  – Various forms of COPD have overlapping features
  – One form of obstructive lung disease (asthma) may evolve into another (COPD)
  – Development of obstructive lung disease result of combination of:
    1) inflammation and airway reactivity
    2) genetic predisposition
    3) environmental factors
A teaching hospital of Harvard Medical School

Asthma-COPD Overlap Syndrome (ACOS)

Estimated present in 15-45% of people with obstructive lung disease

NEJM 2015;373:1241
Asthma COPD Overlap Syndrome

NEJM 2015;373:1241
Asthma COPD Overlap Syndrome

- As many as 60% of patients with COPD may have bronchial hyper-reactivity
- Non-smokers with asthma have been found with
  - Decreased elastic recoil, i.e., ↑ compliance
  - Centrilobular emphysema

*Chest* 2015;148:313
Demographics of ACOS Patients

• Younger (age 60.6 vs. 65.9)
• African-American (26.8% vs 14.4%)
• Higher BMI (29.6 vs. 25.1)
• Current smokers (50.9% vs. 20.7%)

COPD – rate of decline in lung function

Large cohort studies. Baseline FEV1 less than 80% predicted; slow rate of decline. Possible childhood risk factors (maternal smoking, resp. infections, asthma)

*NEJM 2015:373;111*
Risk Factors - Genes

- Alpha 1 anti-trypsin
- 30-50% of lung function may be determined by genetics; susceptibility to COPD likely *polygenic*. Family studies: Siblings of COPD patients increased risk

  Am J Respir Crit Care Med 164:1419, 2001

- Genes activated by smoking may *lead to disease* (Chest 133:1344, 2008) OR may be *protective* (protective genes in promoter region MMP12 associated with higher FEV1, reduced risk of COPD - New Engl J Med 361:2599, 2009)
Genetics and Disease Insights

• COPDGene Study
  – Analysis of 2500 people of African and European ancestry; multivariate logistic regression modeling
  – African-Americans more likely to have early onset disease
    
    Am J Respir Crit Care Med 2011;184:414-420

• Genetics and COPD phenotypes
  – 12,031 subjects
  – Five loci identified with emphysema related phenotypes, one with airway, two with gas trapping
    
    Am J Respir Crit Care Med 2015;192:559-569
Smoking → Inflammation

- Inflammation - increased neutrophils in mucosa; increased CD-8 cells in subepithelium.
  
  *Maestrelli P. Am J Respir Crit Care Med 2001*

- LVH more common in COPD pts (even with normal O2 levels) without hx of hypertension c/w controls
  
  *Anderson et al. Chest 143:91, 2013*

- Oxidative stress from reactive oxygen species → carbonyl stress (oxidative damage to tissue leads to reactive organic molecules that modify proteins non-enzymatically)
  
  *Kirkham and Barnes, Chest 144:266, 2013*

- Data feeds controversy about steroids and anti-oxidants
Presence of IL-17A in Lung Tissue and Severity of Disease

*Am J Respir Crit Care Med 2016:193:1092-1100*

**Figure 5.** Presence of IL-17A as measured by immunoreactivity in lung tissue from never-smokers, smokers without chronic obstructive pulmonary disease (COPD), GOLD (Global Initiative for Chronic Obstructive Lung Disease) I-II COPD, and GOLD III-IV COPD. There was significantly more IL-17A immunoreactivity in GOLD III-IV lung tissue than in that of never-smokers and smokers without COPD (*P < 0.05).*
COPD - A Systemic Disease?

• Framingham Heart Study *Chest 2008;133:19-25*
  ✓ Associations found with systemic inflammatory biomarkers and impaired airway function: CD40 ligand, IL-6, P-selectin, myeloperoxidase, CRP

• CRP and survival *Chest 2008;133:1336*
  ✓ Patients with moderate to severe COPD: CRP *not* associated with survival compared with other clinical tools (BODE index, FEV1, 6 minute walk distance, etc.)

• Statins and mortality COPD *Am J Cardiol 2008;102:192*
  ✓ Observational study; statins used for cardiovascular disease; patients with COPD had decreased mortality c/w those not on statins
Muscle Dysfunction in COPD

Am J Respir Crit Care Med 2015;191:616
COPD Physiology

• Loss of elastic recoil
• Airways obstruction - the ‘equal pressure point’
• Hyperinflation
• AutoPEEP
Lung Parenchyma supports Airways
Schwartzstein RM, Parker MJ, Respiratory Physiology 2005
Hyperinflation

• Shortening of muscles leads to a mechanical disadvantage in the attempt to generate negative intra-pleural pressure
• Contributes to the development of ventilatory muscle fatigue
• May stimulate chest wall receptors contributing to dyspnea
Auto-PEEP

- Persistence of positive pressure in the airways at the end of exhalation
- Associated with hyperinflation
- Results in an additional burden during inspiration - a ‘threshold inspiratory load’
AutoPEEP

- AutoPEEP accompanies expiratory flow limitation
- Heterogeneous lung units with variable time constants (TC=R X C)
- Contributes to work of breathing, dyspnea

Marini, AJRCCM 2011;184:756
Dyspnea: More than you thought...

- Basic physiology of dyspnea is complex - many factors contribute to respiratory discomfort
- The qualities of respiratory discomfort vary and may provide insight into the etiology of the dyspnea
- Level of dyspnea more closely correlated with 5-year survival than FEV1 *(Chest 121:1434, 2002)*
- Daily physical activity is independent predictor for mortality and hospitalization due to exacerbation *(Chest 142:338, 2012; and Thorax 67:117, 2012)*
Descriptors of Dyspnea

- My breath does not go in all the way
- My breathing requires effort
- I feel that I am smothering
- I feel a hunger for more air
- My breathing is heavy
- I can not take a deep breath
- I feel out of breath
- My chest feels tight
- My breathing requires more work
- I feel that I am suffocating
- I feel that my breath stops
- I am gasping for breath
- My chest is constricted
- My breathing is rapid
- My breathing is shallow
- I feel that I am breathing more
- I can not get enough air
- My breath does not go out all the way
Physiology of Dyspnea

- ‘Tightness, constriction’ - bronchospasm
- ‘Urge to breathe, air hunger’ - increased respiratory drive: e.g., CO₂, severe asthma, CHF
- ‘Effort of work of breathing’ - increased mechanical impedance
- ‘Unsatisfied inspiratory effort’ - hyperinflation
- ‘Heavy breathing, breathing more’ - deconditioning
COPD and Dyspnea

• *Work or effort* of breathing the dominant sensations; *air hunger*, *inability to get a deep breath* or sense of 'unsatisfying breath' may be prominent in more severe disease.

• Hyperinflation and auto-PEEP may be playing key physiologic roles.
Pulmonary Function Tests

- **Spirometry** - may be more consistent in COPD than are peak flows
- **Lung volumes** - air trapping, hyperinflation; beware of impact of bullous disease on helium dilution measurements of lung volumes
- **Diffusing capacity** - predictive of desaturation
- **Flow volume loop** - may help distinguish “pure” emphysema and asthma
# PFT’s in COPD

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre</th>
<th>%Pre</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FVC (L)</td>
<td>2.25</td>
<td>46</td>
<td>4.80</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>0.62</td>
<td>18</td>
<td>3.38</td>
</tr>
<tr>
<td>FEF25-75% (L/S)</td>
<td>0.27</td>
<td>8</td>
<td>3.19</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>27</td>
<td>38</td>
<td>70</td>
</tr>
<tr>
<td><strong>Lung Volumes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC (L)</td>
<td>9.90</td>
<td>134</td>
<td>7.22</td>
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<tr>
<td>FRC (L)</td>
<td>7.90</td>
<td>193</td>
<td>4.07</td>
</tr>
<tr>
<td>RV (L)</td>
<td>3.51</td>
<td>252</td>
<td>2.43</td>
</tr>
<tr>
<td>VC (L)</td>
<td>6.12</td>
<td>73</td>
<td>4.80</td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.73</td>
<td>54</td>
<td>3.15</td>
</tr>
<tr>
<td>ERV (L)</td>
<td>1.78</td>
<td>107</td>
<td>1.65</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>64</td>
<td>189</td>
<td>34</td>
</tr>
<tr>
<td>He Equlil, (MIN)</td>
<td>5.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diffusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dsb ml/min/mmHg</td>
<td>8.11</td>
<td>29</td>
<td>27.23</td>
</tr>
<tr>
<td>VA(sb) (L)</td>
<td>5.73</td>
<td>79</td>
<td>7.22</td>
</tr>
<tr>
<td>Hb (gm/100ml)</td>
<td>11.50</td>
<td></td>
<td>27.23</td>
</tr>
</tbody>
</table>
Flow-volume Curve in COPD
Oximetry

• Assess oxygenation at rest
• Desaturation on exercise (correlate with low diffusing capacity PFT’s)
• Consider nocturnal oximetry if evidence of right heart failure or polycythemia
• Increasing data on role of pulmonary hypertension as factor in decreased exercise capacity
It’s Never Too Late To Stop Smoking

Schwartzstein RM

Smokers lose one decade of life expectancy; stop by age 40, reduces risk by 90%
NEJM 368:4, 2013
Smoking Cessation - Varenicline

Review article: smoking cessation – Chest 137:428, 2010

![Graph showing the effect of varenicline on the reinforcing effects of smoking.]

**Figure 1.** The effect of varenicline on the reinforcing effects of smoking.
Smoking Cessation: Multi-pronged Approach

- Behavioral (telephone and group counseling) and pharmacotherapy interventions combined best results

  - Behavioral interventions (phone, counseling, etc.) plus pharmacotherapy 1.76 odds ratio of success compared to usual care
  - Nicotine replacement, buprprion and varenicline all effective (varenicline most effective)
  - 2 studies looked at electronic cigarettes – no significant effect for smoking cessation
Electronic Cigarettes

*NEJM* 2016;375:1372-1381

- Battery operated, nicotine delivery devices; produce vapor with nicotine and propylene glycol or glycerol
- Only 14% quit smoking with e-Cigs in randomized trial
- 1/3 of users have never smoked cigarettes; vapor may contain formaldehyde and other carcinogens
- Nicotine may be “gateway drug;” associated with other drug abuse (*NEJM* 2014;371:932); particular problem for adolescents susceptible to addiction (*Ann Int Med* 2015;163:59-60)
Bronchodilators in COPD

*Inspiration or Expiration?*

- **Taube et al. AJRCCM 162:216, 2000**
  - Beta agonists: $\Delta FIV1$ (inspiratory flow!) best predictor of decreased dyspnea; $\Delta IC$ also better than $FEV1$.

- **O’Donnell et al. Eur Respir J. 18:914, 2002**
  - Post salbutamol, 83% of patients improved lung volume measurements, i.e., less hyperinflation, in absence of $\Delta FEV1$

- **Celli et al. Chest 124:1743, 2003**
  - Tiotropium increased IC more than FEV1
Goals of Therapy in COPD?

- FEV1 – severity
- Change in FEV1—progression
- Exacerbations – activity
- Quality of life, symptoms – Impact on patient
- Future: biomarkers; disease activity

Am J Resp Crit Care Med 2016;194:541-549
Goals of Therapy in COPD - History

Am J Resp Crit Care Med 2016;194:541-549
Salmeterol vs. Tiotropium

- 1 year study, 7376 patients with COPD
- Randomized, double-blind
- Tiotropium increased time to first exacerbation (187 vs. 145 days) with 17% reduction in risk of exacerbation *(note): absolute number of exacerbations not included in the study; fewer than half of the patients had an exacerbation during the year)*

*NEJM 2011;164:1093*
LABA + LAMA vs. LABA + ICS

*NEJM 2016;374:2222-2234*

- Indacaterol + Glycopyrronium vs Salmeterol + Fluticasone
- 11% reduction in annual rate of COPD exacerbation
- Absolute rate reduction: 4.03 to 3.59
Fluticasone + Vilanterol

*NEJM* 2016;375:1253-1260

- Community study with GPs in the UK; open label study
- Intervention vs. “usual care”
- Significantly lower rate of “moderate to severe” exacerbations with intervention
- Time to event analysis → no difference.
- Absolute difference in rates: 1.90/year (control) vs. 1.74/year (intervention)
Corticosteroids

- Approximately 1/3 of patients will respond to steroids with improved lung function
- Cannot predict which patients will respond based on pre and post bronchodilator challenge with beta agonist
- Small changes in FEV1 may make big changes in dyspnea
- Consider two week trial of moderate doses of Prednisone - document PFT’s
Inhaled Steroids reduce *COPD exacerbations*

Meta-analysis (11 studies, 8164 pts); modest benefit of ICS in preventing COPD exacerbations, primarily in pts with FEV1<50% predicted *Chest 137:318, 2010*
Inhaled Steroids and Pneumonia

*Lancet 374:668, 2009*
- Pooled data from 7 studies (7,042 pts)
- Budesonide +/- formoterol vs placebo or formoterol
- 6 months follow-up
- No increase in pneumonia risk

No change in mortality in either study

*Chest 136:1029, 2009*
- Systematic review (12,446 pts)
- LABA/ICS vs LABA alone
- Combo had better FEV1, fewer moderate exacerbations
- Increased risk of pneumonia
Pneumonia and Mortality in COPD

- Limits of studies of pneumonia in COPD and ICS
  - Risk of bias
  - Lack of systematic ascertainment of pneumonia; dependence on adverse risk reporting
  - Retrospective, observational study designs

- No evidence of increased mortality

- Possible “double-effect” – an adverse effect plus an unexplained mitigating effect; ICS may improve mortality

Am J Respir Crit Care Med 2015;191:141-148
Inhaled Steroids and Pneumonia

• Cochrane Database Systematic Review 2014
  – Randomized controlled studies; at least 12 weeks duration
  – Budesonide or Fluticasone vs. placebo with/without LABA
  – ICS increased non-fatal serious adverse pneumonia events, i.e., require hospital admission
  – No difference in overall mortality rates
ICS Reduces Mortality after Pneumonia

- Retrospective cohort study from VA population
- 15,768 pts with COPD, discharge dx of pneumonia
- Prior use of ICS independently assoc. with reduced mortality 90 days

**AJRCCM 184:312-316, 2011**
Inhaled Steroids and Risk of TB and Flu

*Chest 2014;145:1286*

- Systematic review; randomized, controlled trials – 25 for TB (shown in graph), 26 for influenza
- Higher risk for TB (but few events); no difference for flu
Corticosteroid + LABA vs LABA Alone

*Cochrane Database Systematic Review*
*2012;9:CD006829*

- Combination therapy
  - Reduced risk for exacerbation (relative risk reduction 24%)
  - No change in mortality
  - Higher risk for pneumonia; outweighed by reduced exacerbation risk
  - Improved quality of life

- Excluded patients on anti-cholinergics
Drugs Slow Decline in FEV1?

- **Celli et al., AJRCCM 2008;178:332**
  -- 5300 pts; 3 yr follow-up
  -- Double-blind, placebo
  -- RX: placebo = 55 ml/yr
    salmeterol = 42 ml/yr
    salmeterol + flutic = 39 ml
  -- Drugs significantly different from placebo, not from each other

- **Tashkin et al., NEJM 2008;359:1543**
  -- 5993 pts
  -- Double-blind, placebo
  -- RX: placebo vs tiotropium in addition to regular therapy
  -- No difference FEV1
  -- Tio group reduced exacerbations, hospital, resp failure
Withdrawal of Inhaled Steroids Decreases PFTs

NEJM 2014;371:1285

- 2485 pts, hx of COPD exacerbation; tio + salmeterol + ICS
- Randomly assigned to stop ICS over 12 weeks
- No diff in exacerbations but greater decline in FEV1 with stop in ICS
Prophylactic Antibiotics and COPD Exacerbations

• Cochrane Review 2013
• Seven RCTs; studies involved macrolides either continuous or intermittent; duration 3 to 36 months
• Results: number of patients experiencing exacerbations reduced from 69 to 54%; statistically but not clinically significant ↑QOL
• No major problems with resistant organisms
COPD Readmissions

• 26 million admits
• 3.5% COPD
• 20.2% readmit in 30 days; only half due to resp illness
• Dual medicare – medicaid higher risk

Chest 2015;147:1219
# Oxygen Therapy - Indications

*Chest 138:179, 2010*

<table>
<thead>
<tr>
<th>Continuous oxygen use</th>
<th>Intermittent oxygen use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting PaO₂ ≤ 55 mm Hg</td>
<td>Desaturation (SpO₂ ≤ 88%) with activity</td>
</tr>
<tr>
<td>Resting PaO₂ of 56-50 mm Hg with any one of the following:</td>
<td>Desaturation (SpO₂ ≤ 88%) at night</td>
</tr>
<tr>
<td>Dependent edema</td>
<td></td>
</tr>
<tr>
<td>P pulmonale on the electrocardiogram (P wave exceeding 3 mm in standard lead II, III, or aVF)</td>
<td></td>
</tr>
<tr>
<td>Polycythemia (hematocrit, &gt; 56%)</td>
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</table>

SpO₂ = oxygen saturation by pulse oximetry.

*aReimbursed by the Centers for Medicare & Medicaid Services.*
Oxygen and Mortality

- **COT** – continuous oxygen therapy (24 hrs/day)
- **MRC** – Medical Research Council (15 hrs/day)
- **NOT** – nocturnal oxygen trial

*Chest 138:179, 2010*
Roflumilast – Phosphodiesterase 4 Inhibitor

- Anti-inflammatory agent
- 2 placebo-controlled, multi-center trial; note: inhaled steroids stopped
- 3091 pts, over age 40, FEV1 < 50% predicted
- Roflumilast 500 mcg/day
- Exacerbations reduced 1.37 to 1.14 (p<0.003)
- FEV1 increased 48 ml

Roflumilast reduced frequency of exacerbations in freq exacerbator phenotype. Wedzicha et al. *Chest 143:1302, 2013*
Roflumilast + ICS and Exacerbations

- Severe to very severe COPD pts.; 2 or more exacerbations in prior year randomized to Roflumilast vs placebo
- Small ↑ FVC
- No change in overall exacerbation rate; sig. fall in rate if >3 exacerbations
COPD and Prognosis

The “BODE” Index

• Multidimensional grading system that incorporates respiratory and systemic expressions of COPD
  ✓ Body-mass index (B)
  ✓ Airflow obstruction (O)
  ✓ Dyspnea (D)
  ✓ Exercise capacity (E)

• Higher BODE score → greater risk of hospitalization and death

  Ong et al. Chest 128:3810, 2005
Nutrition and COPD

- Body weight has independent effect on survival
- Threshold value of 25 kg/m$^2$ below which mortality risk increased
- Possible role of systemic inflammation; not malnutrition per se. Increased markers of catabolism, e.g., IL-6
  

- In underweight patient, unclear weight gain enhances survival

- Vit D in pts with low levels may reduce exacerbations
  
Exercise

“What do you mean you’re out of breath? I haven’t switched it on yet!”
Pulmonary Rehabilitation

- Importance of deconditioning as a limiting factor in many patients with COPD;
- Mechanism of effect probably varies with patient:
  1) reconditioning; 2) more efficient use of breathing muscles; 3) strengthening of breathing muscles; 4) desensitization to dyspnea
- Up to 14% of pts with COPD stop exercising due to leg discomfort (FEV1 44% pred.) Chest 144:491, 2013
- Patients reporting “moderate or vigorous physical activity” each week, significant reduction in readmit rate after exacerbation
  Ann Am Thor Soc 11:695; 2014
Pulmonary Rehab

- Ries et al., Ann Int Med 1995
  
  A) Increased treadmill endurance
  B) Decreased dyspnea
  C) Decreased muscle fatigue

-- Effects lasted for 12 months of follow-up
Pulmonary Rehab - Efficacy

*Cochrane Database; systematic review 2015;February 23*

- 65 RCT’s reviewed; 3822 participants
- Mean FEV1 39% predicted
- Statistically significant improvement in QOL outcomes
- Significant increase in 6 MWT distance
Volume Reduction Surgery

- Physiologic principles: A) reduce the hyperinflation of the chest; B) allow more normal portions of the lung to expand and receive greater ventilation / perfusion
- Appear to be fewer complications with thoracoscopic vs median sternotomy approach
- Improvement in QOL measures, eg., physical and social functioning, vitality (*Chest* 115:383, 1999)
LVRS - Predictors of Success

  - National Emphysema Treatment Trial
  - 1218 patients, severe emphysema, 6-10 weeks of pulmonary rehab → randomization med/surg
  - Total group
    - No difference in mortality (despite increase in early mortality in surgery group)
    - At 24 months, exercise improved by 10 watts in 15% of surgery group, 3% of med group (p<0.001)
  - Cost $190,000 per quality-adjusted life-year gained at 3 years
NETT Study
Subgroup Analysis

• Predominantly Upper Lobe Emphysema and Low Exercise Capacity
  – Mortality lower in surgery vs medical therapy (p=0.005)

• Non-upper Lobe Emphysema and High Exercise Capacity
  – Mortality higher in surgery than medical group (p=0.02)
Endobronchial Valves and Coils

Endo valve vs standard care; randomized
• 12 month follow-up
• 4.3% ↑ FEV1
• Complications and exacerbations up with valves
• ? Suboptimal med RX

Endo coils compress emphysematous lung
• 315 pts; bilateral coils
• ↑ 6 MWD (10m vs loss of 7.6 m)
• Improved QOL measures
• Complications 34.8% vs 19.1% in control

NEJM 363;1233, 2010
JAMA 2016;315;2178
Lung Transplantation

• Single lung transplantation is successful despite the very compliant nature of the lung left behind
• Long wait for donor organ
• Survival still 50% at four years
COPD Summary

- COPD associated with varying phenotypes; role of inflammation leads to therapeutic strategies
- Elastic recoil key to physiology of emphysema
- Small changes in FEV1 and lung volumes may result in big changes in dyspnea; hyperinflation major consequence of obstruction
- Functional limit may not be from COPD; consider rehab
- Hypoxic patients need supplemental O₂
- Increasingly link treatment to phenotype, impact on patient
Additional Slides

The following slides address issues of COPD and acute respiratory failure, as well as several other topics. We do not have time to address these issues during the presentation, but I have provided the slides for your self-study.
Acute Respiratory Insufficiency (ARI)

• It’s not just an ‘exacerbation’ of COPD – Try to examine underlying problem - airway reactivity, infection, congestive heart failure
ARI - Therapy

- Antibiotics - several studies have demonstrated benefit of antibiotics in acute on chronic bronchitis; reduce in-hospital mortality and readmission rate (*Chest* 143:82, 2013)
- Bronchodilators: nebs vs MDI’s
- Corticosteroids
  - 2 studies suggest 10-14 days of therapy improved lung function and may reduce readmit rates for 6 months
  - Oral vs IV steroids - no clear diff. in outcomes, but IV group got larger doses and had longer hospital stay (*Daenen M et al. Eur Respir J* 19:928, 2002).
- Theophylline - reserved for severe cases or those with concerns about muscle fatigue?
ARI - Follow-up

112:120, 2002

- Population-based data: 25,000 pts in ED with asthma/COPD (Canada)
- Office visit within 30 days significantly reduced risk of ED readmit within the next 3 months

Red = no follow-up
Yellow = follow-up visit
ARI and Oxygen Therapy

• Hypoxia kills !!!
• Supplemental oxygen may cause an increase in PaCO$_2$, but it probably does not cause the patient to stop breathing
  – consider: Haldane effect and changes in V/Q matching in addition to a small drop in VE (Aubier et.al., ARRD, 1980)
• Drive to breathe remains above normal
Positive Pressure Ventilation
What can it achieve?

• Decrease load on ventilatory muscles
• Prevent alveolar collapse (with PEEP)
• Decrease venous return (important if component of CHF)
• Decrease afterload

✓ Brochard et al, *NEJM* 333:817, 1995 - NPPV led to decreased intubations, mortality & LOS in patients with COPD and ARI
✓ Meta-analysis confirms utility of NPPV for severe exacerbations only Ann Int Med 138:861, 2003
Other New (and Revisited) Therapies

Alpha 1 replacement therapy:

• NIH registry, patients enrolled 1989-1992
• Possible decrease in 5 year mortality
• Reduced rate of decline in lung function for those with FEV1 35-49% predicted
• Remains very expensive - incremental cost-effectiveness ratio for quality adjusted life year surpassed $100,000 in all treatment scenarios *Am J Respir Crit Care Med* 167:1387, 2003
• CT lung densitometry improved with therapy *Ann Amer Thorac Society* 2016;13:S370
COPD and Mechanical Ventilation

• Beware of creating autoPEEP - need adequate expiratory time, may need to increase inspiratory flow rate

• Beware post-hypercapnic metabolic alkalosis: remember, a high PaCO\(_2\) may be your friend when it’s time to wean the patient from the ventilator

\[ VA \propto \frac{VCO2}{PaCO2} \]
COPD and Surgery

- Non-thoracic surgery: no level of FEV1 is an absolute contraindication to surgery (note: COPD does not increase peri-operative mortality for AAA repair)
- Thoracic surgery: do not want to create a respiratory cripple; avoid if predicted post-op FEV1 < 0.8, DLCO < 40% pred., or hypercapnia
- Smoking cessation helps
- Exercise capacity may be best predictor - look for maximal oxygen consumption > 15 ml/kg/min