

Chronic Obstructive Pulmonary Disease

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I. Introduction

A. Definitions

1. The term "COPD" is limited to chronic bronchitis and emphysema, which is a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.
2. Chronic bronchitis: presence of chronic productive cough for 3 months in each of two successive years (with other causes of chronic cough eliminated).
3. Emphysema: abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by the destruction of the alveolar walls and without obvious fibrosis.

B. Epidemiology

1. 14 million individuals in the US have COPD (12.5 million with chronic bronchitis, 1.65 million with emphysema).
2. The prevalence has risen 30% in women in the last 20 years.
3. It is the fourth leading cause of death in US.

II. Etiology and Physiology

A. Risk Factors

1. Smoking
 - a. Greatest risk factor for COPD - accounts for 80-90% of the risk.
 - b. Number of cigarettes each day and duration of smoking are both important (duration relatively more important for risk of lung cancer).
 - c. Pipe and cigar smokers are at intermediate risk for COPD (between cigarette smokers and nonsmokers).
 - d. Passive smoking is associated with an increased risk of airway

hyperreactivity; it is unclear whether there is also a risk for developing COPD.

2. Airways reactivity - presence of airways reactivity in patients with COPD may increase the rate of decline in lung function.
3. Alpha 1 anti-trypsin deficiency (AAT) deficiency accounts for 1% of cases of COPD.
 - a. AAT is produced in the liver and found in lungs. It inhibits neutrophil elastase. Coded on chromosome 14.
 - b. Threshold protective level - 35% of normal levels (above 80 mg/dL averts significant lung disease).
 - c. Patients with severe deficiency may develop symptoms in late 40s or early 50s. Lung disease is accelerated by smoking.
 - d. Patients develop emphysema with predilection for lung bases.
4. Other: air pollution and occupational exposure probably play a relatively small role in US today.

B. Pathology of COPD

1. Enlargement of bronchial mucus glands with increased numbers of Goblet cells. Mononuclear inflammatory process in bronchioles. Smooth muscle hypertrophy in terminal bronchioles.
2. Three pathologic types of emphysema
 - a. Centriacinar: process begins in the respiratory bronchioles and spreads peripherally. Most common type of emphysema resulting from cigarette smoking. Tends to involve upper portions of the lung.
 - b. Panacinar: the entire alveolus is involved. Type of emphysema seen in homozygous AAT. Involves lower regions of lung.
 - c. Distal Acinar: preferentially involves distal airway structures, alveolar ducts, and sacs. Associated with apical bullae and spontaneous pneumothorax.

C. Physiology of Airflow Obstruction

1. Loss of elastic recoil:

Destruction of lung tissues leads to more compliant lung. The airways lose the "tethering" effect of the surrounding lung tissue making them more susceptible to collapse during exhalation. More of the expiratory curve is "flow limited," i.e., more effort by the patient does not produce greater expiratory flows.

2. Equal pressure point:

Tendency of airways to collapse as a result of loss of elastic recoil. With positive intrathoracic pressure during exhalation, the equal pressure point (the point where the pressure outside the airway and inside the airway are equal) moves toward more distal (and more compressible) airways. Greater tendency to airways collapse which limits airflow regardless of the expiratory "effort." Patients with emphysema spend much of their expiratory cycle on the "effort independent" portion of the expiratory curve.

3. Hyperinflation:

With early collapse of airways, air is trapped and the patient breathes at higher lung volumes. This places the respiratory muscles at a relatively inefficient position on their length-tension curve leading to greater use of accessory muscles and more difficulty generating negative intrapleural pressures.

4. AutoPEEP:

Given expiratory flow limitation through much of the expiratory cycle, expiratory time is increased. Patients may be forced to initiate the next inspiration before function residual capacity (FRC) is reached. Thus, there is still positive pressure in the airways at the end of expiration (PEEP). To generate negative pressure for the next breath, the patient must overcome this PEEP before any inspiratory flow occurs. This poses what has been termed an "inspiratory threshold load" on the system and increases the work of breathing.

5. Airways reactivity:

1/3 of patients will have evidence of reversible airways obstruction after a single dose of a bronchodilator. Up to 2/3 of patients will

demonstrate improved lung function with repeated testing.

6. Natural history:

Under normal conditions, lung function decreases by approximately 25-30 mL/year. Rate of decline is steeper in smokers and, with greater number of cigarettes there is a greater rate of decline. Once an individual stops smoking, however, the rate of decline returns toward that of a nonsmoker. Patients with chronic bronchitis who stop smoking may have improvement in cough and sputum as well as oxygenation.

After an acute respiratory infection, there may a decline in lung function and oxygenation, which does not return back to previous baseline for 30-90 days.

Mortality: with FEV1 < 0.75 L, the mortality rate at one year is 30%, and at ten years is 95%. However, some patients "beat the odds" for quite a while.

III. Assessment of the Patient with COPD

A. History:

Smoking history, presence of acute changes in symptoms suggestive of airways reactivity or myocardial ischemia, quantification of exercise capability (patients often make subtle changes in lifestyle to compensate for increasing shortness of breath and tell you that they don't have much dyspnea), frequency of and precipitating factors for acute decompensations, evidence of right heart failure, quality of their shortness of breath.

Most patients whose exercise capability is reduced by emphysema will describe "increased effort and work of breathing" while those who have bronchospasm may describe a sense of "chest tightness," and those who are limited by deconditioning will note "huffing and puffing" or "heavy breathing."

B. Physical examination:

1. Assessment of severity of airways obstruction: use of accessory muscles, supraclavicular and intercostal retractions, pulsus paradoxus
2. Assessment of hyperinflation: AP diameter, Hoover's sign (inward motion of lower lateral rib cage on inflation, which is indicative of a flat diaphragm), hyperresonance on percussion
3. Assessment of right ventricular function: right sided S3; elevated jugular venous pressure, enlarged liver, peripheral edema

C. Laboratory evaluation

1. CBC: Polycythemia may be indication of chronic hypoxemia or nocturnal desaturation. Elevated WBC during acute respiratory insufficiency may be an indication of bacterial infection.
2. Pulmonary function tests:
Spirometry to assess severity of obstruction.

Lung volumes to determine presence of air trapping (the helium dilution technique may underestimate lung volumes in the presence of severe bullous emphysema; may need to use body plethysmography).

Diffusing capacity to assess degree of destruction of alveolar capillary surface area. May provide clue that patient will desaturate with activity. Patients with low DLCO are more likely to desaturate.

Flow-volume loop to help distinguish emphysema from asthma. In asthmatic, the flows are reduced at all lung volumes; in emphysema there is expiratory coring indicative of collapse of airways or unequal emptying of different parts of the lung variably affected by the emphysema.

3. Chest x-ray; computerized tomography

CXR: presence of hyperinflation (retrosternal clear space, flat diaphragm, AP diameter); localization of bullous disease to distinguish classical emphysema (upper zones) from alpha-1-anti-trypsin deficiency (basilar disease).

CT scan is not utilized on routine basis. It is more sensitive at assessing the degree of bullous disease than chest x-ray; necessary if contemplating volume reduction surgery/bullectomy (need to assess whether bullous disease is homogeneous or heterogeneous and status of remaining lung).

4. Oximetry: Determine whether patient is hypoxemic at rest and with exercise. Necessary for justifying supplemental oxygen (or can use arterial blood gas, but ABG does not lend itself to exercise assessment).

IV. Management Issues

A. Smoking cessation

1. **Addiction:** Nicotine is the primary agent responsible for the addiction of smoking. Cotinine, a metabolite of nicotine, can be measured in the urine and can be used to confirm smoking or exposure to second hand smoke. Withdrawal symptoms include anxiety, irritability, difficulty concentrating, anger, fatigue, depression, and sleep disruption. Symptoms occur primarily during the first week after cessation of smoking.
2. **Approaches to smoking cessation:** For most patients, quitting "cold turkey" is more successful than gradual withdrawal. If patient does not truly want to quit, any program is likely to fail. Continued abstinence at 6 months to 7 years as low as 27%. Strong social supports are important. The patient should be informed that while much of the damage done by cigarettes may be irreversible, the rate of progression of disease can still be impacted by smoking cessation (and risk of non-pulmonary disease, eg, MI, stroke, cancer, can be modified).

Pharmacologic interventions: Nicotine replacement can reduce symptoms of withdrawal and facilitate smoking cessation as part of a complete program. No clear advantage of nicotine gum vs. patch. Bupropion (antidepressant) has been shown to reduce withdrawal symptoms.

B. Immunizations

Patients should receive pneumococcal vaccine and annual influenza vaccine.

C. Bronchodilators

1. **Beta agonists**

Bronchodilation and symptomatic relief may be evident despite relatively small changes in FEV1. Patients with moderate to severe COPD may be operating at the point on their FEV1/dyspnea curve where a small change in lung function will translate into a significant improvement in symptoms.

Beta agonists should be used on an "as needed" basis if possible, although there is no evidence that regular use of beta agonists is harmful (a recent randomized, double-blind, placebo controlled study of beta agonists in mild asthma has documented safety of regular use in that patient group - *N Eng J Med*, 335:841, 1996).

Recent evidence suggests a possible role for longer acting agents, (eg, salmeterol). It should be considered in particular if patient

appears to have nocturnal bronchospasm.

2. Anti-cholinergics

Studies suggest that these agents may be more effective in COPD than are beta agonists and they have fewer side effects. The most common error is to use at too low a dose. They can be given 4-6 puffs tid-qid. Onset of action slower than beta agonists.

3. Theophylline

This drug probably has utility in patients with significant side effects from high dose beta agonists (allowing the use of two drugs below their toxic levels) as well as in patients with nocturnal symptoms. It enhances muscle function and may have some anti-inflammatory effect.

4. Steroids

20-30% of patients with COPD will improve lung function if given a trial of steroids. A simple pre-and post-bronchodilator spirometry is not sufficiently sensitive to predict who will or will not respond to steroids. One approach is to give 40 mg of Prednisone orally qd for 2 weeks as a trial to determine if the airway's obstruction is reversible. Since many patients get a non-specific euphoria and increase in energy, it is important to document pulmonary function before and during administration of steroids to convince yourself that there is objective evidence that they have made a difference. If patients have an increase in FEV1, the oral steroid should be tapered and an inhaled steroid initiated in an effort to sustain the benefit.

Consider a steroid trial in patients who have moderate to severe functional limitation.

D. Oxygen therapy

Long-term oxygen therapy improves survival in hypoxemic patients with COPD. Improved pulmonary hemodynamics plays a role. Oxygen administration reverses hypoxic pulmonary vasoconstriction, reduces pulmonary artery pressure and right ventricular work, and improves cardiac output and oxygen delivery to the tissues.

Assessment of need for oxygen therapy can be accomplished with an arterial blood gas or pulse oximeter. Patients must demonstrate $pAO_2 < 55$ or oxygen saturation $< 88\%$ (or PAO_2 of 55-60, O_2 sat of 89% with signs of tissue hypoxia such as cor pulmonale, polycythemia, right ventricular failure, or impaired mental status). In patients with marginal values at rest or patients with polycythemia, one should also assess oximetry during exercise and consider nocturnal testing (especially if polycythemia or right

ventricular failure is present). Oxygen supplementation during exercise reduces dyspnea, pulmonary hemodynamics are improved, and exercise capability increases.

While nasal prongs are most common way to deliver supplemental oxygen, one should consider a transtracheal catheter in young individuals who are concerned about the cosmetic impact of nasal prongs, and in patients who wish their portable O₂ containers to last for longer periods before being refilled (one can achieve the same results using lower flow rates with transtracheal as compared to nasal prong oxygen).

Patients must be cautioned not to smoke when using supplemental oxygen.

E. Exercise/pulmonary rehabilitation

1. **Deconditioning:** Many patients with COPD and exertional dyspnea fall into a cycle of reduced activity, deconditioning, more dyspnea, further reductions in activity, more severe deconditioning, etc. This usually occurs slowly over months to years. Studies have demonstrated that many of these patients have greatly reduced aerobic capacity, low anaerobic threshold, and peripheral muscle and cardiovascular deconditioning. These factors can be improved with an exercise program. It is important to ask the patient whether he, at the time exercise must be stopped, is limited by "fatigue," "leg discomfort," or "shortness of breath." If dyspnea is the culprit, one should then inquire about the quality of the sensation. Patients limited by deconditioning respond to exercise programs (minimum of 3-4 times/week) with improved functional capability. Both lower extremity and upper extremity exercise have shown to be beneficial.

Exercise training may have additional benefit of enhancing clearance of lung secretions.

2. **Inspiratory Muscle Training:** Experimental studies have demonstrated that dyspnea correlates with the ratio of inspiratory pressure achieved on each breath to the maximal inspiratory pressure possible for that patient. Thus, increasing the maximal inspiratory pressure (MIP) by strengthening ventilatory muscles would alleviate dyspnea. Clinical studies have been equivocal. Training is recommended for patients with clearly reduced MIP, i.e., <50 cmH₂O utilizing a training device that insures a minimal inspiratory effort on each breath (threshold trainer) since one study has demonstrated that without such a device, patients will prefer to hypoventilate rather than work hard to breathe in.
3. **Desensitization to Dyspnea:** Much of what is accomplished in rehabilitation programs results from desensitization to the discomfort associated with obstructive airways disease. Patients given education and social support learn to tolerate the symptom. They feel more "in control" and avoid the deterioration in

functional status that accompanies not only the breathlessness but the anxiety that often results. Much of the breathing retraining techniques that are taught (e.g., pursed lips breathing, diaphragmatic breathing) may work in part by giving the patient coping strategies for dealing with his discomfort.

F. Volume reduction surgery

1. Two basic physiologic principles behind the surgery: (A) the chest is hyperinflated which places the muscles of inspiration at a mechanical disadvantage; (B) large bullae compress relatively normal areas of lung. Removal of region of lung that consists primarily of large bullae will reduce the size of the thorax, lengthen the diaphragm, and allow greater ventilation of relatively normal lung.
2. Preliminary data indicate a positive response to surgery with improved gas exchange, lung function, and exercise capacity. The procedure is palliative - the underlying lung disease continues to progress and, in some cases, the surgery may hasten deterioration. Patients with heterogeneous disease (i.e., some regions of lung with severe emphysema, other areas with relatively normal lung) do better than those with homogeneous disease.

G. Lung transplantation:

Single-lung transplants have proven successful. Procedure remains limited by lack of donor organs, cost, and complications associated with immunosuppressive therapy. Survival for single lung transplants: 67% at 1 year, 57% at 2 years, and 47% at 4 years. Results somewhat better in recent years.

V. Acute Respiratory Insufficiency - identify the cause. COPD "exacerbation" is an overused term that conveys little information about the acute problem.

A. Risk factors

1. Airway reactivity: Patients with significant airways reactivity are at risk for developing acute on chronic respiratory insufficiency when exposed to stimuli that trigger bronchospasm (eg, allergens, heat and humidity, cold air, pollutants, cigarette smoke, etc).
2. Infections: Patients with COPD, particularly if history of chronic bronchitis, have impaired airway clearance. COPD increases the incidence of acute respiratory infections, including acute bronchitis and pneumonia.
3. Congestive heart failure: Frequent comorbid condition in patients with COPD. Failure may be difficult to diagnose in acutely ill individual -

classical rales may not be present, CXR may not demonstrate vascular redistribution and interstitial edema. CHF must always be considered in patient with acute or subacute deterioration in symptoms.

B. Management

1. **Antibiotics:** Several studies have shown the benefit of using antibiotics in patients with COPD, especially if a history of chronic bronchitis or a change in the quality or quantity of sputum. If no evidence of pneumonia and patient does not appear "toxic," oral antibiotics are adequate.
2. **Bronchodilators:** Most physicians start with beta agonists which can be given every 30-60 minutes if patient is in moderate to severe respiratory distress. The drug can be given by metered dose inhaler with spacer or by nebulization. There is some evidence that addition of ipratropium gives greater bronchodilation than beta agonist alone without increased side effects.
3. **Theophylline:** Generally reserved for the most severe cases unresponsive to inhalational therapy and steroids. Potential toxicity is equivalent to the potential gain.
4. **Corticosteroids:** Used in patients with evidence of airways reactivity and previous bronchodilator response. If patient's history not well documented, steroids are generally used in cases of moderate to severe respiratory insufficiency.
5. **Oxygen therapy:** Therapy is guided by oxygen saturation. Oxygen saturation should be assessed with exercise prior to discharge. The patient may not return to baseline level of gas exchange for 4-6 weeks after acute decompensation, especially if an infection was present.

While administration of supplemental oxygen to patient with COPD and chronic hypercapnia may cause an increase in PaCO₂, evidence now repudiates the classical teaching that such patients will "stop breathing." Respiratory drive in these patients is supranormal due to combination of factors including dyspnea, stimulation of pulmonary and chest wall receptors, as well as deranged gas exchange. While administration of oxygen reduces the hypoxic drive to breathe, overall ventilatory drive remains above normal. Increased hypercapnia appears to be due to combination of (a) reduced ventilation, (b) change in V/Q mismatch, and (c) the Haldane effect, i.e., the shift in the carbon dioxide/Hgb dissociation curve to the right. Remember - hypoxia kills! Give adequate supplemental oxygen to get O₂ saturation to 90%. If this causes severe respiratory acidosis and acidemia, then the patient should be intubated and mechanically ventilated.

Venturi masks allow greater control of inspired concentration of oxygen than nasal prongs and other masks.

6. Noninvasive ventilatory support: Several studies suggest that use of BIPAP in patient with acute respiratory insufficiency due to COPD and superimposed process may obviate the need for intubation and mechanical ventilation.

Noninvasive ventilation cannot be used in patients with depressed mental status, excessive secretions, inability to protect their airway, apneas, or inability to cooperate with therapists.

CPAP in the chronic state may reduce chronic hypercapnia in some patients with COPD as well as alleviate exertional dyspnea. Many patients with COPD tolerate nasal masks poorly. It is still an experimental intervention.

CPAP has also been shown to benefit patients with congestive heart failure, probably in part by reducing afterload on the left ventricle. Data is less convincing for patients with pneumonia or asthma.

VI. Special Considerations

A. Acute respiratory failure and mechanical ventilation

1. Role of respiratory muscle fatigue: In the presence of paradoxical motion of the abdomen and increasing respiratory frequency with decreasing tidal volumes, muscle fatigue is probably contributing to the patient's decline. Institution of ventilatory support under these circumstances has been shown to "instantly" eliminate the EMG activity in the diaphragm. This finding is only demonstrated when the muscle is fatigued.
2. Ventilator settings: Most patients with COPD who develop respiratory failure are easily ventilated following intubation. Usually, the FIO₂ can be kept < 0.5. Patients usually do not fight the ventilator (in keeping with the thought that muscle fatigue is contributing to the respiratory failure), and peak pressures are not particularly high (reflecting the increased compliance of the lungs in emphysema). Assist control or IMV modes of ventilation are equally acceptable. Tidal volumes and frequency settings on the ventilator are determined primarily by the patient's size, the desired PaCO₂, and the presence of autoPEEP.
 - a. AutoPEEP: autoPEEP or intrinsic PEEP occurs when the patient has inadequate time to exhale; i.e., the next inspiration occurs while exhalation is in progress and there is

positive pressure in the airway at the moment of initiation of inspiration. If the ventilator frequency is too high, one may create autoPEEP by not allowing sufficient time for exhalation.

- b. Post-hypercapnic metabolic alkalosis: Patients with acute respirator failure may have an acute on chronic respiratory acidosis. When placing such a patient on the ventilator, one should aim for a PaCO₂ that approximates the patient's baseline state. If the ventilator is set with too high a minute ventilation, one will produce an alkalosis because the patient's kidneys have retained bicarbonate to compensate for the chronic hypercapnia. If this is not recognized quickly, the kidney will excrete bicarbonate and you may have difficulty weaning the patient from the ventilator.
3. Weaning: Assuming the patient has had an acute, reversible problem that has precipitated respiratory failure, one is almost always able to wean the patient from the ventilator. Attention must be paid to the patient's volume status (occult CHF is often a factor in preventing weaning), nutrition, judicious use of anxiolytics, and airways secretions.

Among a number of criteria for successful weaning, the respiratory frequency to tidal volume is now felt to be most predictive, $f/V_t < 100$ predicts successful spontaneous ventilation (note: tidal volume expressed in liters).

B. Surgery

1. Preoperative evaluation
 - a. Non-thoracic surgery: No level of lung function is an absolute contraindication to non-thoracic surgery. However, severe airways obstruction is associated with a higher rate of complications. The farther the procedure from the diaphragm, the lower the risk. In upper abdominal surgery, the mortality rate may be as high as 3-5% with morbid events occurring in as many as 80% of patients. If the procedure is elective, discontinuation of smoking for several weeks prior to surgery may result in diminution of secretions and improved gas exchange (ideally, stop cigarettes for 8 weeks prior to surgery). Baseline blood gases and spirometry should be obtained.

- b. Thoracic surgery: If contemplating removal of lung tissue in a patient with limited pulmonary reserve, it is important to not cause the patient to become a "respiratory cripple" or an individual who cannot be weaned from mechanical ventilation. Factors to consider include (a) the predicted postoperative FEV1, which should be > 0.8 L, (b) diffusing capacity > 40% predicted, and (c) PaCO₂ < 45 mm Hg. For patients facing a pneumonectomy, contraindications include an FEV 1 < 2 L and a diffusing capacity < 60% of predicted. Quantitative ventilation and perfusion scans may be helpful in predicting the impact of pulmonary resections on postoperative function.

In addition to measures of lung function as outlined above, there is evidence that a patient's functional status may also be a useful predictor of postoperative morbidity and mortality. Patients with a maximal oxygen consumption during an exercise test that is greater than 15 mL/kg/min have better outcomes.

2. Management: Maximize lung function preoperatively with bronchodilators (consider short course of steroids), good bronchopulmonary hygiene should be assured if excessive secretions, and exercise program should be initiated. Use of epidural anesthesia postoperatively has greatly facilitated airways clearance and early mobilization of patients, preventing additional complications.

C. Screening for lung cancer

1. Routine: Several large studies have demonstrated no survival benefit associated with routine radiologic screening for patients with COPD (PA and lateral CXR). Routine screening of sputum cytology is also not beneficial.
2. Hemoptysis: Hemoptysis in the presence of a normal CXR is associated with 5-10% incidence of malignancy on bronchoscopy. Risk increases with (a) age > 40; (b) history of cigarette smoking; and (c) duration of hemoptysis greater than 10 days. One or two episodes of hemoptysis in setting of acute respiratory infection and normal CXR generally does not warrant bronchoscopy. Hemoptysis in a smoker that occurs without evidence of infection and is repeated at a prolonged interval (i.e., more than 10 days) raises more suspicion.

D. Sleep Disorders

1. Patients with COPD have a higher prevalence of insomnia, excessive daytime sleepiness, and nightmares than the general population.

2. Many patients desaturate during REM sleep, and may be related to hypoventilation during sleep. Suspect in patients with borderline oxygen saturation at rest, polycythemia, and evidence of right ventricular failure. It is not yet clear whether treating isolated nocturnal desaturation has an impact on mortality.
3. Obstructive sleep apnea may coexist with COPD and some studies suggest the incidence of OSA in these patients is greater than would be expected based on the relative frequencies of the two conditions.

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