This lecture will only be presented if time permits after COPD or Rhinitis lecture. It will be covered on the exam only if it is presented in class.

Learning objectives. At the end of this presentation, the learner should be able to:

1. Describe the pathophysiology and clinical presentation of the following forms of drug induced pulmonary disorders:
   a. Apnea
   b. Bronchospasm
   c. Pulmonary edema
   d. Pulmonary hypertension
   e. Pneumonitis
   f. Pulmonary eosinophilia
   g. Pulmonary fibrosis
   h. Lupus syndrome
   i. Pseudolymphoma
   j. Granulomatous reactions
   k. Pneumothorax

2. Given a case history, be able to recognize which of the above named drug induced pulmonary disorders is being described and which of the drugs the patient is taking is the most likely causative agent.

3. Given a patient with drug induced apnea, be able to identify the most likely causative agent(s) and which of the following mechanisms is the most likely cause of the apnea:
   a. CNS or respiratory tract depression
   b. Neuromuscular blockade
   c. Respiratory muscle myopathy

4. Explain why a bronchodilator (or other inhaled drug) given as a metered dose inhaler or a dry powdered inhaler may cause bronchospasm.

5. Recognize a case of drug induced anaphylaxis presenting as bronchospasm

6. Describe the clinical presentation of aspirin induced bronchospasm and which patients may be at greater risk for developing this type of reaction.

7. Explain the pharmacologic basis for ibuprofen (or another non-steroidal anti-inflammatory drug) induced bronchospasm in a patient with a similar reaction to aspirin.

8. Describe the clinical presentation of ACE inhibitor induced cough and the proposed mechanism of this disorder.

9. Recognize a patient with ACE inhibitor induced cough and be able to recommend alternative treatment strategies. (It is presumed that the student recognizes the names of the most commonly prescribed ACE inhibitors).
10. Provide two possible explanations as to the cause of opioid induced pulmonary edema and risk factors that predispose to this reaction.

11. Name three drugs or drug categories associated with drug induced pulmonary hypertension.

12. Provide a mechanism of action for anorexic induced pulmonary hypertension

13. Identify clinical factors that help to differentiate nitrofurantoin induced pulmonary eosinophilia (acute pneumonitis) from pneumonia.

14. Name three other drugs besides nitrofurantoin that have been identified as causing drug-induced pneumonitis.

15. Explain how high dose oxygen is a risk factor for developing pulmonary fibrosis

16. Identify the antiarrhythmic drug that is most commonly implicated in causing pulmonary fibrosis and dosing regimens of this drug that increase the risk of developing fibrosis.

17. Name six factors that increase the risk of developing pulmonary fibrosis when taking cytotoxic drug.

18. Given a case study of a patient taking cytotoxic drugs, recognize which of the drugs taken by the patient poses the greatest risk of inducing pulmonary fibrosis and which of the patient factors listed in objective 17 are present in the patient.

19. State the cumulative dose of bleomycin that is considered the upper limit of acceptable dosing to reduce the risk of developing pulmonary fibrosis.

20. Describe how a patient may administer methylphenidate (Ritalin) that would increase the risk of developing a granulomatous lung reaction.

21. Describe how a patient may administer heroin that would increase the risk of developing pneumothorax.

Reading and Recommended Readings/ Bibliography


Lecture outline:

See separate PowerPoint slide set
1. Exercise 1. Take a deep breath (inspiration) and hold it for two seconds. You are now at **full inspiratory capacity** and you have 6-8 liters of air in your lung. Let the air out slowly (expiration) to a relaxed state.

2. Exercise 2. Repeat exercise 1. As you breathe in, pay attention to the movement of your chest and the rate (how fast) that air is flowing into your lung at the beginning, middle, and end of taking the full breath.

As you move your diaphragm downward and expand ancillary chest muscles, the size of your chest cavity increases, creating negative pressure in your chest. Since air outside your mouth has higher pressure than within the chest cavity and your lungs, air flows down into the lungs.

The rate of inspiratory flow starts slow, but reaches the maximal rate of flow very quickly. As the lungs fill with air, the resistance to airflow increases due to pressure equalization between the outside and within the lungs. Also, the lungs have stretched to full capacity, further increasing resistance to inward airflow. The inspiratory flow rate will be slowed if the airway lumen is narrowed by obstruction or if airflow is turbulent due to bronchospasm, airway edema, bronchial wall thickening, or mucous in the airway lumen.

On relaxed (non-forceful) expiration, the action of chest wall muscles and diaphragm reduces the size of the chest cavity and increases intra-pulmonary pressure to move air back out to the atmosphere. It may take more force to move the air out if the airway lumen is narrowed or obstructed. In other words, flow rates may be slowed.

3. Exercise 3. Again take a full deep breath to full inspiratory capacity. This time **slowly** blow the air out as fully as you can. Keep blowing until no more air comes out. This should take 5-10 seconds. If you measured the total **volume** of air that is exhaled (5-6 liters), you will have a measure of **vital capacity**. (Volume of air expired from full inspiration to full expiration.) There is still air left in your lungs (residual volume) and in your airways (dead air space). You can never fully blow all the air out of your lung. If you did, your lungs might collapse. However, a strong blow to the back or fall to the ground can forcefully cause excess air to be knocked out of the lungs (getting the “wind knocked out of you”), a very uncomfortable feeling of inability to catch your breath.

4. Exercise 4. Again take a deep breath to full inspiratory capacity. This time blow the air out as **fast and fully** as you can. Keep blowing until no more air comes out. This should take about 4-5 seconds if you do not have airway disease. It will take longer if you have airway obstruction due to asthma, chronic bronchitis or emphysema.

If you measured the total **volume** of air exhaled (5-8 liters), you will have a measure of **forced vital capacity (FVC)**. This may be slightly higher than vital capacity because of the forcefulness of the upward movement of the diaphragm and contraction of chest wall muscles.

Repeat this step, this time paying attention to the rate of air movement out of the lungs at the beginning, middle, and end of expiration. As with inspiration, there is almost an immediate
rise to the peak expiratory flow rate (PEFR, peak flow rate) and then a slowing of flow rate as the lungs empty and the airways actually start to collapse from pressure change. The flow rate is zero at the end of expiration. As might be expected, narrowed or obstructed airways will likely produce a slower flow rate. Patients with asthma might be able to eventually blow out almost the same amount of air (forced vital capacity), but it might take several seconds longer to get the air out.

Since airflow is very rapid to start, it is not surprising that the greatest amount of air is expired during the first one second of the forced expiratory exercise. The amount of air in liters expired in the first second is called the forced expiratory volume in one second (FEV₁.) Under normal conditions, a volume of air equal to approximately 80% of vital capacity is expired in the first second. The remaining 20% is expelled over 2-4 seconds.

In patients with obstructed airways, the rate of flow (peak expiratory flow rate) and the FEV₁ are generally both reduced. FVC may be decreased or normal.

FEV₁ is a more reliable and consistent indicator of airway obstruction than PEFR, but the results of the two tests generally move in the same direction. In some patients there may be a direct proportionality between FEV₁ and PEFR, in other patients they may trend in the same direction, but not necessarily in the same magnitude of change.

5. Quantifying results of pulmonary function tests (PFTs)

Tables are available to determine predicted normal values for both FEV₁ and PEFR. Gender, age, and height are the variables used to estimate normal values for both tests. These normals are population means. Any given individual, even without asthma or COPD, may be 1-2 standard deviations above or below the predicted normal.

When performing these tests, the measurement is repeated three times at each testing time. The highest observed value of the three is the result to be reported, not the mean.

Trends over time are more important than test results on any one day or time of day. There is fluctuation throughout the day and over days and weeks. By performing the test at the same time of day for 1-2 weeks, one can generally determine their own personal best value. When determining the personal best, the testing should be done before any immediate acting bronchodilators (e.g., albuterol) are given.

Performing the tests 10-20 minutes after a dose of bronchodilator provides an indication of the capacity of the bronchioles to dilate (reversibility). If post bronchodilator values are consistently higher than baseline results, it may indicate that the underlying disease is not well controlled and that over time (e.g., after antiinflammatory therapy), the baseline values (and thus the desired personal best) might have to be adjusted upward. Of course if bronchodilators create no change, either the person is already at their personal best or they have poor bronchial tone that is not responsive to bronchodilators (non-reversible airway disease; e.g., COPD, chronic bronchitis, emphysema).

The equations used to express pulmonary function tests are the same for both FEV₁ and PEFR.

Percent of predicted = (observed value/ predicted normal) x 100
Percent of personal best = \((\text{observed value/personal best}) \times 100\)

Percent of change = \((\text{post albuterol value – pre albuterol value})/ \text{pre albuterol value} \times 100\)

\text{Percent of change} = (\% \text{ predicted after albuterol - } \% \text{ predicted pre albuterol}) / \% \text{ predicted pre albuterol} \times 100

6. Reversibility. Determining \textbf{clinical relevance} of reversibility

A greater than 15 to 20\% \textbf{increase (percent of change)} in FEV\textsubscript{1} or PEFR after a bronchodilator is often considered an indication of reversibility. However, consider the following in determining clinical relevance:

If the baseline value is very high (e.g., a person with asthma is well controlled and near their personal best), then the post bronchodilator value may change very little. It is mathematically more difficult to obtain a large percent increase when the starting value is already high. In this case, we need to know the person’s response when the baseline function is lower (e.g., during a worsening of their asthma).

If the baseline value is very low (e.g., in severe or chronic disease), it is mathematically easy to obtain a higher percentage change, even if the absolute change is small. For this reason, an \textbf{absolute change of 0.2 L or less of FEV\textsubscript{1} may not be considered clinically significant.}

Even if the percentage change appears low, if the patient feels that they obtained relief from their respiratory distress, the response may be considered clinically relevant.

The results from a single testing time (best of three attempts) may not predict the cumulative effects of long-term therapy. This again argues for daily monitoring to look for upward or downward trends in baseline (pre-bronchodilator) pulmonary function. Even if daily calendars are not available, it is helpful to repeat the tests weekly or monthly during times of instability to look for trends. Don’t forget, however, that this may be misleading if the pulmonary function varies throughout the day or upon exposure to specific triggers (e.g., a pet).

When looking \textbf{for trends over time, it is best to compare pre-bronchodilator results} to get the best view of the underlying disease control.

Patients with chronic bronchitis or emphysema generally do not have reversible airway disease unless they also have an “asthmatic component.” In these patients, it is helpful to assess response to both a beta agonist (albuterol) and an anticholinergic (ipratropium). The majority of COPD patients do not have significant reversibility with either drug. Some will show reversibility with one drug, drug but not the other. A few have reversibility with both drugs. Caution: since they often have low baseline pulmonary function, they may get a relatively high percentage change in FEV\textsubscript{1} after a bronchodilator, but the absolute change is still below 0.2 L.

During acute exacerbations, patients with COPD often show much greater response to bronchodilators and should be treated the same as a patient with an acute exacerbation of asthma.