CASE 18

A 36-year-old woman presents to her primary care physician with complaints of shortness of breath, arthritic pain, and multiple skin lesions. The patient is short of breath on examination with a slightly low pulse oximetry reading, consistent with mild hypoxemia. She has multiple skin lesions, and a biopsy reveals noncaseating granulomas consistent with sarcoidosis. Chest x-ray findings revealing hilar adenopathy are also suggestive of sarcoidosis. The physician explains to the patient that he likely has a restrictive disease process, and recommends formal pulmonary function testing.

◆ What parameters are measured in a pulmonary function test?

◆ What changes in pulmonary function would be consistent with a restrictive disease?

◆ How would a restrictive lung process lead to hypoxemia?

◆ What changes in pulmonary function might be observed in this patient?
ANSWERS TO CASE 18: GAS EXCHANGE

Summary: A 36-year-old woman with sarcoidosis has both skin and lung involvement. Her physician explains that sarcoidosis is a restrictive lung disease.

◆ **Parameters measured in a pulmonary function test:** Changes in the volume of inspired air versus time. Lung capacities and airflow rates can be measured. Figure 15-1 in Case 15 shows a spirometry measurement.

◆ **Pulmonary function consistent with restrictive disease:** Decreased vital capacity and decreased functional residual capacity (FRC) or resting lung volume. Conditions that restrict lung expansion are neuromuscular conditions, problems with the chest wall, pleural disease, and decreased lung compliance. Depending on the nature of the restrictive disease, there may be little or no change in rates of airflow.

◆ **How restrictive lung processes cause hypoxemia:** Thickening of alveolar membrane, which increases the diffusion distance.

◆ **Changes in pulmonary function with sarcoidosis:** Decreased lung compliance ($\Delta$volume/$\Delta$pressure), increased lung elastic recoil, decreased resting lung volume (FRC), decreased vital capacity. Gas exchange will be affected:

- N$_2$O gas exchange: perfusion-limited exchange
- CO gas exchange: diffusion-limited exchange

**CLINICAL CORRELATION**

Both restrictive and obstructive lung diseases can affect gas exchange in the lung. Examples of restrictive diseases are sarcoidosis, connective-tissue disorders, interstitial pneumonia, environmental exposure, and pulmonary vascular disease. Restrictive diseases result in poor gas exchange because of a thickening of the alveolar membrane that results in restriction of oxygen diffusion with increased diffusion distance. Obstructive diseases include emphysema, chronic bronchitis, and asthma. Obstructive disorders result in poor gas exchange because of decreased surface area for diffusion of gases. These two pulmonary problems can often be distinguished from each other by pulmonary function tests, but the clinical presentation is the most important method of diagnosis.
APPRAOCH TO GAS EXCHANGE PHYSIOLOGY

Objectives

1. List lung volumes and lung capacities.
2. Define lung compliance and elastic recoil.
3. Explain how measurements of lung volumes and gas flow rates can be used to distinguish between obstructive and restrictive lung diseases.
4. Discuss alveolar gas exchange and factors that determine the rate of O₂ diffusion.

Definitions

Obstructive disease: Disorders that cause an increase in the airway resistance to flow such as narrowing of the passages due to inflammation or compression.

Restrictive disease: Disorders that impair or increase the work necessary for lung expansion.

DISCUSSION

Pulmonary function tests are used to identify and distinguish obstructive from restrictive lung diseases. The mechanical factors that contribute to lung function fall into the following categories:

1. Resistance to airflow through the airways.
2. Elastic recoil of the lungs.
3. Elastic recoil of the chest wall.

An easy way to remember the distinction is to realize that obstructive diseases manifest themselves as increased resistance to airflow and restrictive diseases manifest themselves as restriction of lung expansion. Pulmonary function tests measure the velocity of airflow and lung volumes. These parameters provide an accurate assessment of lung disease.

Sarcoidosis is a disease that causes inflammation in the tissues. It is characterized by noncaseating granulomas, and although it may occur in any tissue, the inflammation generally starts in the lungs or lymph nodes. In the present case, lung injury has occurred because of granule formation in the bronchioles and alveolar sacs and chronic inflammation resulting in scarring or formation of fibrotic tissue. Fibrosis in the lung tissue has a marked effect on the elasticity, or compliance, of the lung. Compliance is the change in volume of the lung for a given change in pressure. Physically, the lung volume is dependent on two factors: the elastic recoil of the lung to collapse on itself and the outward recoil of the chest wall. The interpleural pressure is the result of these two opposing forces.
**Lung volumes** are determined in a pulmonary function test by a spirometer (see Case 15). The patient breathes through a mouthpiece that is attached to an instrument which measures the volume of air that the patient is moving as a function of time. During normal quiet breathing, expansion of the chest wall reduces the interpleural pressure, causing an expansion of the lung volume. Relaxation of the inspiratory muscles allows a return of the chest wall and a decrease in lung volume. The volume is referred to as the **tidal volume** (TV). The amount of air that remains in the lungs at the end of normal, quiet expiration is referred to as the **FRC**, which for a normal individual is around 2300 mL. The FRC is an important and useful value in the evaluation of a lung disorder. Physiologically, the FRC is dependent on two factors: the **outward recoil of the chest wall** and the **elastic recoil of the lung**. Compliance is the inverse of the elasticity (compliance = Δvolume/Δpressure) of the lung tissue; therefore, the volume under these conditions will be dependent on and may be used as an estimate of lung compliance. A fibrotic lung compared with a normal lung is less compliant (higher elastic recoil); therefore, a given pressure change will cause a smaller change in volume and the FRC will be lower than normal. This can be contrasted to a high-compliance lung, which will undergo a larger volume change for a given pressure. Thus, a lower FRC would indicate a low-compliance (higher elastic recoil) lung consistent with a restrictive disease such as fibrosis. **Pulmonary fibrosis** is one of several causes of restrictive disease.

There are other mechanical factors that cause restrictive disease, such as **neuromuscular weakness of the respiratory muscles**, which can prevent full expansion of the chest. **Scoliosis** or malformations that interfere with chest movements or pneumothorax (air in the chest cavity) can prevent full expansion of the lungs. Rates of airflows may be affected in restrictive diseases, but usually can be identified on the basis of other factors. For example, with muscle weakness, the forced expiratory volume in the first second (FEV₁) is likely to be reduced simply as a result of the inability to exhale forcefully. In pulmonary fibrosis, the FEV₁ also may be reduced because of the reduced volume of air available; however, looking at the FEV₁/FVC (forced vital capacity) ratio can show a normal or elevated value in fibrosis.

**Obstructive diseases** usually can be distinguished by increased resistance to airflow. **Resistance to airflow** will occur under conditions in which there is a diminished diameter of the airway. For example, mucus reduces the airway diameter and increases airway resistance. Asthma causes active smooth muscle contraction with constriction of the airways. Another cause of airway constriction is dynamic compression of airways during expiration. Dynamic compression of airways is more pronounced in high-compliance tissues and is one of the major factors limiting pulmonary function in chronic obstructive pulmonary disease.

The diffusion of a gas through a barrier is described by the **Fick law of diffusion**, which states that the rate of diffusion of a gas through a barrier is dependent on the surface area of the barrier, the thickness of the barrier, the
\textbf{diffusion coefficient} of the gas, and the concentration gradient of the gas across the barrier. \textbf{Pulmonary gas exchange} is dependent on the \textit{surface area and thickness of the pulmonary capillary}, the \textit{partial pressure difference of the gas between the alveolar and blood compartments}, and the \textit{residence time of the blood in the alveolar capillary}. Thus, factors that affect the surface area or thickness of the pulmonary capillary can have a profound effect on the rate of diffusion of a gas between the two compartments.

Gases with different diffusion coefficients illustrate the limitations of gas transfer across the pulmonary capillary. \textbf{Nitrous oxide (N}_2\text{O)} diffuses very rapidly} and \textbf{equilibrates} across the pulmonary capillary in about \textbf{0.1 second}; beyond that point, there is no further net gas transport across the barrier. Since the residence time of blood in the capillary is about 0.75 second, \textbf{N}_2\text{O equilibrates fully} by the time the perfusing blood leaves the capillary. This is referred to as \textbf{perfusion-limited gas exchange}. In contrast, a gas such as \textbf{carbon monoxide binds avidly to hemoglobin} with a reaction time that is faster than the rate of diffusion across the capillary barrier. This means that the partial pressure of CO in the blood will be less than that in the alveolar compartment until the hemoglobin is saturated. The \textbf{residence time of blood in the capillary required for this to occur is more than 0.75 second}; thus, the partial pressure of CO in the blood leaving the capillary is lower than its alveolar concentration. This is referred to as \textbf{diffusion-limited gas exchange}.

\textbf{Pulmonary capillary O}_2\text{ exchange} is \textbf{intermediate} between \textbf{N}_2\text{O} and \textbf{CO exchange}. The binding of O\textsubscript{2} to hemoglobin is slower than that of CO; however, its diffusion across the barrier allows it to reach equilibrium with the alveolar PO\textsubscript{2} in about 0.25 second. The higher arterial PO\textsubscript{2} increases the rate of O\textsubscript{2} binding to hemoglobin such that by the time the blood leaves the capillary, binding is complete. In other words, \textbf{O}_2\text{ transfer is normally perfusion limited}. As stated above, the rate of diffusion is dependent on the surface area of the barrier and the thickness of the barrier. Physiologically, conditions that alter either of these two properties can have serious impact on gas transfer from the lungs into the blood. These conditions can limit the rate sufficiently to the point that \textbf{O}_2\text{ transport becomes diffusion limited}, creating a significant alveolar–arterial O\textsubscript{2} gradient. In an individual with pulmonary fibrosis, as in the present case, there is a thickening of the alveolar-capillary barrier causing a reduction of O\textsubscript{2} exchange. Diffusion may also be reduced because of an accumulation of fluid in the alveolar-capillary membrane, increasing the barrier thickness. Alternatively, the effective surface area can be diminished because of tissue damage or destruction observed in emphysema. Any of these states will lead to decreased oxygenation of arterial blood.
COMPREHENSION QUESTIONS

[18.1] The lung function tests of a patient show a markedly reduced FEV$_1$ and an FRC of 4.2 L (normal 2.3 L). Which of the following is the most likely cause of the reduced FEV$_1$?

A. Weak expiratory muscles  
B. Small-diameter airways  
C. Pulmonary congestion  
D. Dynamic compression of airways  
E. Pulmonary fibrosis

[18.2] Mr Smith complains of shortness of breath and difficulty with moderate exercise. Pulmonary function tests indicate a reduced FRC, and his FEV$_1$ was 2.6 L (78%). His FVC was 3.1 L (70%). Which of the following is the most likely cause of Mr Smith’s problems?

A. Weak expiratory muscles  
B. Small-diameter airways  
C. Pulmonary congestion  
D. Dynamic compression of airways  
E. Pulmonary fibrosis

[18.3] A 36-year-old woman undergoes chemotherapy with bleomycin for an ovarian germ cell cancer. She develops mild pulmonary fibrosis secondary to the chemotherapy. Which of the following agents is most likely affected in its diffusion across the alveoli-pulmonary capillary barrier?

A. CO  
B. CO$_2$  
C. N$_2$O  
D. O$_2$

Answers

[18.1] D. The decrease in the FEV$_1$ indicates that there is a decrease in the rate of expiration. This is indicative of an obstructive disease; however, it also could result from weakened musculature, for example (restrictive). The FRC normally would be in the range of 2.3 L. In this individual the FRC is 4.2 L. The FRC can be used to estimate lung compliance ($\Delta V/\Delta P$), and a value this high suggests a high-compliance lung. High compliance is most consistent with dynamic compression of airways.
[18.2] **E.** Mr Smith has pulmonary fibrosis. The first indication is the reduced FRC, suggesting a decrease in lung compliance that would be consistent with a restrictive disease. Generally, changes in rates of change obtained in lung function tests are associated with obstructive disease. With Mr Smith, however, there is a decrease in the FEV₁. However, analysis of the FVC also shows a reduction and comparison to the FVC yields an FEV₁/FVC of 85%, which is normal. In patients such as Mr Smith, the FEV₁ is reduced, but not as a consequence of obstruction; simply, there is a smaller starting volume as a result of the fibrosis. The ratio FEV₁/FVC calculates to a normal value because there is a proportionate decrease in both of these parameters.

[18.3] **A.** Carbon monoxide binds avidly to hemoglobin and presents a remarkable “deep sink” for CO to enter the capillary network; therefore, it is considered diffusion limited. Thus, in pulmonary fibrosis, this gas is most likely to be affected. In contrast, nitrous oxide is perfusion dependent; carbon dioxide and oxygen are intermediate.

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**PHYSIOLOGY PEARLS**

- Obstructive diseases manifest themselves as increased resistance to airflow. Restrictive diseases manifest themselves as restriction of lung expansion.
- Pulmonary gas exchange is dependent on the surface area and thickness of the pulmonary capillary wall, the concentration gradient of the gas between the alveolar and blood compartments, and the residence time of blood in the pulmonary capillary.
- Diffusion limitation for O₂ can be corrected by increasing the O₂ concentration in inspired air.

**REFERENCES**


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