Case 23

Asthma: Obstructive Lung Disease

Ralph Grundy was a 43-year-old lineman for a Midwestern power company. He was married and the father of four children who were 24, 22, 21, and 18 years of age. Ralph had a history of asthma since childhood. His asthma attacks, which were characterized by wheezing and shortness of breath, were often precipitated by high pollen levels and cold weather. He used an inhaled bronchodilator (albuterol, a β2-adrenergic agonist) to treat the attacks. At the time of his death, Ralph had been trying desperately to get "inside" work. His asthma attacks were becoming more frequent and more severe, and he had been taken to the emergency room five times in the past year.

Three days before his death, Ralph had an upper respiratory infection, with nasal and chest congestion and a fever of 101.8°F. He was exhausted from "just trying to breathe," and the bronchodilator inhaler wasn't working. On the third day of the illness, Ralph's oldest son took him to the emergency room of the local community hospital. He had inspiratory and expiratory wheezes and was in severe respiratory distress. Table 3-4 shows the information obtained when he arrived at the emergency room at 4 p.m.

<table>
<thead>
<tr>
<th>Table 3-4</th>
<th>Ralph's Respiratory Values at 4 p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>30 breaths/min (normal, 12-15)</td>
</tr>
<tr>
<td>FiO2 (fractional concentration of O2)</td>
<td>0.21 (room air)</td>
</tr>
<tr>
<td>pH</td>
<td>7.48 (normal, 7.4)</td>
</tr>
<tr>
<td>PaO2 (arterial P02)</td>
<td>55 mm Hg (normal, 100 mm Hg)</td>
</tr>
<tr>
<td>PaCO2 (arterial Pco2)</td>
<td>32 mm Hg (normal, 40 mm Hg)</td>
</tr>
</tbody>
</table>

The emergency room staff treated Ralph with an inhaled bronchodilator and had him breathe 50% O2 (FiO2, 0.5). At 6 p.m., his condition had not improved; in fact, it had worsened, and Ralph was obtunded (sleepy and inattentive). Before proceeding with more aggressive treatment (e.g., anti-inflammatory drugs and intubation), the emergency room staff obtained a second set of measurements (Table 3-5).

<table>
<thead>
<tr>
<th>Table 3-5</th>
<th>Ralph's Respiratory Values at 6 p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>8 breaths/min</td>
</tr>
<tr>
<td>FiO2 (fractional concentration of O2)</td>
<td>0.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.02 (normal, 7.4)</td>
</tr>
<tr>
<td>PaO2 (arterial P02)</td>
<td>45 mm Hg (normal, 100 mm Hg)</td>
</tr>
<tr>
<td>PaCO2 (arterial Pco2)</td>
<td>80 mm Hg (normal, 40 mm Hg)</td>
</tr>
</tbody>
</table>

Ralph died before aggressive treatment could be initiated. At autopsy, his airways were almost totally occluded by mucus plugs.
QUESTIONS

1. Asthma is an obstructive disease in which the airways narrow, increasing the resistance to airflow into and out of the lungs. What are the relationships between airflow, resistance, and airway diameter? Use equations to support your answers.

2. Figure 3-6 shows the results of pulmonary function tests performed on Ralph during an asthma attack the previous year. For the test, Ralph first took a normal tidal breath, then a maximal inspiration, followed by maximal expiration. The test was repeated after he inhaled a bronchodilator, a β₂-adrenergic agonist.

![Figure 3-6](image)

**Figure 3-6** Lung volumes during forced expiration during an asthma attack and during treatment with an inhaled bronchodilator.

What was Ralph’s tidal volume? What was his forced vital capacity (FVC) during the asthma attack and after treatment with the bronchodilator? What was his FEV₁ (volume expired in the first second of forced expiration) during the attack and after bronchodilator treatment? What was Ralph’s FEV₁/FVC during the attack and after treatment? What is the significance of the changes in FVC, FEV₁, and FEV₁/FVC that were produced by the bronchodilator?

3. What effect did Ralph’s asthma have on residual volume and functional residual capacity (FRC)?

4. Why was Ralph exhausted from “just trying to breathe”? How does obstructive lung disease increase the work of breathing?

5. Why was Ralph’s arterial $P_{O_2}$ ($P_{aO_2}$) decreased at 4 P.M.? (Hint: Consider how changes in the ventilation-perfusion ($V/Q$) ratio might alter $P_{aO_2}$.)

6. What is an A–a gradient, and what is its significance? What was Ralph’s A–a gradient at 4 P.M.? (Assume that his respiratory quotient was 0.8.)
7. Why was Ralph hyperventilating at 4 P.M.? Why was his arterial $P_{CO_2}$ ($P_{a\,CO_2}$) decreased (compared with normal)? What acid–base abnormality did he have at 4 P.M.?

8. What was Ralph’s A–a gradient at 6 P.M.? (Assume that his respiratory quotient remained at 0.8.) What is the significance of the change in A–a gradient that occurred between 4 P.M. and 6 P.M.?

9. Why was Ralph’s $P_{a\,CO_2}$ increased at 6 P.M.? What acid–base abnormality did he have at that time? Why was he obtunded?
1. Airway resistance is inversely correlated with airway diameter or radius. As the radius of an airway increases, resistance to airflow decreases, according to Poiseuille's law:

\[ R = \frac{8 \eta l}{\pi r^4} \]

where

- \( R \) = resistance of the airway
- \( \eta \) = viscosity of inspired air
- \( l \) = length of the airway
- \( r \) = radius of the airway

This relationship, which is especially powerful because of the fourth-power dependence on radius, should be familiar from cardiovascular physiology.

Airflow is inversely proportional to airway resistance, according to the now familiar relationship between flow, pressure, and resistance:

\[ Q = \frac{\Delta P}{R} \]

where

- \( Q \) = airflow (L/min)
- \( \Delta P \) = pressure difference (mm Hg or cm H₂O)
- \( R \) = airway resistance (cm H₂O/L per sec)

Thus, airflow (Q) is directly proportional to the pressure difference (\( \Delta P \)) between the inlet and the outlet of the airway (e.g., between the mouth and the alveoli) and inversely proportional to the resistance of the airway (R). The pressure difference is the driving force for airflow; resistance is the impediment to airflow.

By combining the relationships for airway radius, resistance, and airflow, we conclude that the larger the radius of the airway, the smaller the resistance and the higher the airflow. Conversely, the smaller the radius, the larger the resistance and the lower the airflow.

Note that, although the resistance of a single airway is inversely correlated with its radius, the medium-sized bronchi are actually the site of highest airway resistance in the intact respiratory system (even though it seems that the smallest airways should have the highest resistance). This apparent discrepancy is explained by the parallel arrangement of the small airways. When resistances are arranged in parallel, the total resistance is lower than the individual resistances.

2. Tidal volume is the volume inspired and expired during normal breathing. Forced vital capacity (FVC) is the volume that can be forcibly expired after a maximal inspiration. FEV₁ is the volume expired in the first second of the forced expiration. FEV₁/FVC is the fraction of FVC expired in the first second. In healthy people, FEV₁/FVC is approximately 0.8 (or 80%); in other words, normally, most of the vital capacity is expired in the first second of forced expiration (Table 3-6).

<table>
<thead>
<tr>
<th>Table 3-6</th>
<th>Ralph's Lung Volumes and Capacities During an Asthma Attack and During Treatment With a Bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During Asthma Attack</strong></td>
<td><strong>During Bronchodilator Treatment</strong></td>
</tr>
<tr>
<td>Tidal volume</td>
<td>0.5 L</td>
</tr>
<tr>
<td>FVC</td>
<td>2.5 L</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.2 L</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*FVC*, forced vital capacity; *FEV₁*, volume expired in the first second of forced expiration.
Ralph had asthma, an obstructive disease that is characterized by inflammation and narrowing of the airways. This narrowing (i.e., decreased airway radius) led to increased resistance and decreased airflow, as discussed in the previous question. Ralph's wheezes were the sounds produced when he expired forcibly through these narrowed airways.

In asthma, the airways are narrowed for three major reasons: (1) hyperresponsiveness of bronchial smooth muscle to a variety of stimuli, which causes bronchospasm and bronchoconstriction during an attack; (2) thickening and edema of the bronchial walls secondary to inflammation; and (3) increased production of bronchial mucus that obstructs the airways. The first mechanism (bronchoconstriction) can be reversed by administering bronchodilator drugs, such as $\beta_2$-adrenergic agonists (e.g., albuterol).

Increases in airway resistance, such as those seen in asthma, lead to decreases in all expiratory parameters, including FVC, FEV$_1$, and FEV$_1$/FVC. The higher the airway resistance, the more difficult it is to expire air from the lungs. Airway resistance is especially increased during forced expiration, when intrapleural pressure becomes positive and tends to compress, or even close, the airways (Figure 3-7). Therefore, FVC decreases during an asthma attack because the airways close prematurely during expiration. One result of this premature closure of the airways is that air that should have been expired remains in the lungs (air trapping).

The inhaled bronchodilator relaxed Ralph's airways, increasing their radii and decreasing their resistance to airflow. The decrease in airway resistance improved Ralph's expiratory functions, as evidenced by the increased FEV$_1$ and FEV$_1$/FVC. Also, because his airways did not close prematurely, his FVC was increased.

3. Ralph's asthma was associated with increased airway resistance, which compromised his expiratory functions. As a result, air that should have been expired remained in the lungs, increasing his residual volume and his functional residual capacity (FRC). Recall that FRC is the resting, or equilibrium, position of the lungs (i.e., the volume in the lungs between breaths). Because Ralph's FRC was increased, his normal "tidal" breathing had to occur at higher lung volumes.

4. The work of breathing is determined by how much pressure change is required to move air into and out of the lungs. In obstructive lung diseases, such as asthma, the work of breathing is increased for two reasons. (1) A person with asthma breathes at higher lung volumes (because
of the higher FRC), as discussed earlier. During inspiration, a person with asthma must lower intrathoracic pressure more than a healthy person to bring air into the lungs; thus, more work is required during inspiration. (2) During expiration, because airway resistance is increased, higher pressures must be created to force air out of the lungs; this greater expiratory effort requires the use of accessory muscles. (In healthy people, expiration is passive and does not require the assistance of accessory muscles.) Increased work of breathing is reflected in higher rates of $O_2$ consumption and $CO_2$ production.

5. Recall the ventilation-perfusion ($\dot{V}/\dot{Q}$) relationship in the lungs. Ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) are normally matched such that ventilated alveoli lie in close proximity to perfused capillaries. This $V/Q$ matching (i.e., $V/Q = 1.0$) allows $O_2$ exchange to proceed normally (as shown in the upper portion of Figure 3-8). $O_2$ diffuses from alveolar gas into pulmonary capillary blood until alveolar $P_{O_2}$ and pulmonary capillary $P_{O_2}$ are equal (normally 100 mm Hg).

![Figure 3-8](image_url)  
**Figure 3-8** Effect of airway obstruction on ventilation-perfusion ($\dot{V}/\dot{Q}$) ratio and $O_2$ exchange. $P_{O_2}$, partial pressure of oxygen.
Ralph’s arterial \( P_{O_2} (P_{A_{O_2}}) \) was decreased (hypoxemia) because he had a V/Q defect (or mismatch). Bronchoconstriction and obstruction of some airways prevented adequate ventilation of some regions of his lungs. In these unventilated regions, fresh air, with its supply of \( O_2 \), did not reach the alveoli for gas exchange. Therefore, the pulmonary capillary blood that perfused these unventilated alveoli was not oxygenated. As shown in the lower portion of Figure 3–8, the \( P_{O_2} \) of the blood in these capillaries remained the same as that of mixed venous blood. This portion of the pulmonary blood flow is called a shunt because the blood flow bypasses ventilated alveoli and is not oxygenated. Ralph’s pulmonary venous blood (which becomes systemic arterial blood) was a mixture of blood from well-ventilated and poorly ventilated regions of the lungs; therefore, his systemic arterial blood had a \( P_{O_2} \) of less than 100 mm Hg.

6. The A–a gradient is the difference between alveolar \( P_{O_2} \) (\( P_{A_{O_2}} \), or “A”) and arterial \( P_{O_2} \) (\( P_{A_{O_2}} \), or “a”). The A–a gradient tells us whether \( O_2 \) is equilibrating normally between alveolar gas and pulmonary capillary blood. For example, the normal A–a gradient is close to zero because \( O_2 \) equilibrates almost perfectly: \( P_{A_{O_2}} \) and \( P_{A_{O_2}} \) are equal, or nearly equal. However, if a V/Q defect (or mismatch) occurs, then \( P_{A_{O_2}} \) is less than \( P_{A_{O_2}} \) and the A–a gradient is larger than zero. The greater the disturbance in \( O_2 \) exchange, the larger the A–a gradient.

The A–a gradient is determined by measuring "a" (the \( P_{O_2} \) of arterial blood, or \( P_{A_{O_2}} \)) and calculating "A" (the \( P_{O_2} \) of alveolar gas, or \( P_{A_{O_2}} \)) with the alveolar gas equation (described in Case 20). Therefore, at 4 P.M.:

\[
\text{"a"} = 55 \text{ mm Hg}
\]

\[
\text{"A"} = P_{A_{O_2}} - P_{A_{CO_2}} \frac{P_{A_{CO_2}}}{R}
\]

\[
= (PB - P_{H_2}O) \times F_{O_2} - P_{A_{CO_2}} \frac{P_{A_{CO_2}}}{R}
\]

\[
= (760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 0.21 - \frac{32 \text{ mm Hg}}{0.8}
\]

\[
= 150 \text{ mm Hg} - \frac{32 \text{ mm Hg}}{0.8}
\]

\[
= 110 \text{ mm Hg}
\]

A–a = 110 mm Hg - 55 mm Hg

\[
= 55 \text{ mm Hg}
\]

Compared with a healthy person, whose A–a gradient is close to zero, Ralph’s A–a gradient was greatly increased. In other words, \( O_2 \) could not equilibrate between alveolar gas and pulmonary capillary blood because of Ralph’s V/Q defect (specifically, a decreased V/Q ratio).

7. Ralph was hyperventilating at 4 P.M. because hypoxemia stimulated peripheral chemoreceptors located in the carotid bodies. This stimulation led to an increased breathing rate (hyperventilation). At 4 P.M., Ralph’s arterial \( P_{CO_2} \) (\( P_{A_{CO_2}} \)) was decreased secondary to the hyperventilation. (Recall that \( P_{A_{CO_2}} \) is inversely correlated with alveolar ventilation.) This decrease in \( P_{A_{CO_2}} \) caused an acid–base disorder called respiratory alkalosis. The pH of arterial blood is determined by the ratio of \( HCO_3^- \) to \( CO_2 \), as described by the Henderson-Hasselbalch equation:

\[
pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2}}
\]

where

\[
pH = -\log_{10} [H^+]
\]

6.1 = pK of the \( HCO_3^-/CO_2 \) buffer

\( HCO_3^- \) = \( HCO_3^- \) concentration of arterial blood

\( P_{CO_2} \) = \( P_{CO_2} \) of arterial blood

The decrease in \( P_{CO_2} \) (secondary to hyperventilation) decreased the denominator of the Henderson-Hasselbalch equation and, consequently, increased the pH of Ralph’s arterial blood (i.e., respiratory alkalosis).
8. At 6 P.M., Ralph's A–a gradient was as follows (note that $F_{O_2}$ was increased from 0.21 to 0.5, or 50%):

\[ a = 45 \text{ mm Hg} \]

\[ A = P_{L_2} - \frac{P_{ACO_2}}{R} \]
\[ = (760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 0.5 - \frac{80 \text{ mm Hg}}{0.8} \]
\[ = 357 \text{ mm Hg} - 100 \text{ mm Hg} \]
\[ = 257 \text{ mm Hg} \]

\[ A-a = 257 \text{ mm Hg} - 45 \text{ mm Hg} \]
\[ = 212 \text{ mm Hg} \]

Ralph's A–a gradient had increased further at 6 P.M. Increasing $F_{O_2}$ to 0.5 caused Ralph's alveolar $P_{O_2}$ ("A") to increase from 110 mm Hg to 257 mm Hg. However, this change did not improve Ralph's blood oxygenation. In fact, at 6 P.M., his arterial $P_{O_2}$ ("a") had decreased further, to 45 mm Hg. The fact that Ralph's A–a gradient widened (or increased) suggests that even more regions of his lungs were receiving inadequate ventilation; as a result, the V/Q defect was even greater.

9. At 6 P.M., Ralph's $P_{ACO_2}$ was 80 mm Hg. This value was significantly elevated compared with both the normal value of 40 mm Hg and Ralph's value at 4 P.M. (which was lower than normal). We have already discussed why Ralph's $P_{ACO_2}$ was reduced at 4 P.M. (i.e., he was hyperventilating secondary to hypoxemia). The dramatic increase in Ralph's arterial $P_{CO_2}$ between 4 P.M. and 6 P.M. reflects significant worsening of his condition. Undoubtedly, Ralph's airways had become more obstructed (a suspicion that was confirmed at autopsy), his work of breathing was further increased, he was hypoventilating, and he could not eliminate the CO$_2$ that his body produced. Retention of CO$_2$ elevated his $P_{ACO_2}$ and caused respiratory acidosis, as predicted by the Henderson-Hasselbalch equation:

\[ pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2}} \]

The increase in $P_{CO_2}$ (in the denominator) caused his arterial pH to decrease to 7.01 (respiratory acidosis). Ralph was obtunded as a result of the narcotic effect of high $P_{CO_2}$.
Key topics

- A—a gradient
- $\beta_2$-Adrenergic agonists
- Airflow, pressure, resistance relationship
- Airway resistance
- Albuterol
- Asthma
- Bronchoconstriction
- Bronchodilator drugs
- FEV$_1$
- FEV$_1$/FVC
- Forced expiratory volume (FEV)
- Forced vital capacity (FVC)
- Functional residual capacity (FRC)
- Hyperventilation
- Hypoventilation
- Hypoxemia
- Obstructive pulmonary disease
- Peripheral chemoreceptors
- Poiseuille’s law
- Respiratory acidosis
- Respiratory alkalosis
- Tidal volume
- Ventilation–perfusion (V/Q) defect, or mismatch
- V/Q ratio