Case 25

Interstitial Fibrosis: Restrictive Lung Disease

Simone Paciocco, a 42-year-old wife and mother of two teenagers, was diagnosed 3 years ago with diffuse interstitial pulmonary fibrosis. As much as possible, Simone has tried to continue her normal activities, which include working as an assistant manager at a bank. However, keeping up with the demands of day-to-day life has become increasingly difficult. Simone tires easily and can no longer climb a flight of stairs without becoming extremely short of breath. She is being closely followed by her physician, a pulmonologist.

Tables 3-9 and 3-10 show the information obtained at a recent physical examination.

<table>
<thead>
<tr>
<th>TABLE 3-9</th>
<th>Simone’s Arterial Blood Gases at Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{aO_2}$ (arterial $P_{O_2}$)</td>
<td>76 mm Hg (normal, 100 mm Hg)</td>
</tr>
<tr>
<td>$P_{aCO_2}$ (arterial $P_{CO_2}$)</td>
<td>37 mm Hg (normal, 40 mm Hg)</td>
</tr>
<tr>
<td>% saturation</td>
<td>97% (normal, 95%-100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3-10</th>
<th>Results of Simone’s Pulmonary Function Tests at Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung capacity</td>
<td>Decreased</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>Decreased</td>
</tr>
<tr>
<td>Residual volume</td>
<td>Decreased</td>
</tr>
<tr>
<td>$D_{lco}$</td>
<td>Decreased</td>
</tr>
<tr>
<td>$FEV_1/FVC$</td>
<td>Increased</td>
</tr>
</tbody>
</table>

$D_{lco}$, lung diffusing capacity; $FEV_1$, volume expired in the first second of forced expiration; $FVC$, forced vital capacity.

After these results were obtained at rest, Simone was asked to exercise on a stair climber. After only 2 minutes, she became extremely fatigued and had to discontinue the test. The arterial blood gas measurements were repeated, with the following results (Table 3-11).

<table>
<thead>
<tr>
<th>TABLE 3-11</th>
<th>Simone’s Arterial Blood Gases During Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{aCO_2}$ (arterial $P_{O_2}$)</td>
<td>62 mm Hg (normal, 100 mm Hg)</td>
</tr>
<tr>
<td>$P_{aCO_2}$ (arterial $P_{CO_2}$)</td>
<td>36 mm Hg (normal, 40 mm Hg)</td>
</tr>
<tr>
<td>% saturation</td>
<td>90%</td>
</tr>
</tbody>
</table>

QUESTIONS

1. Diffuse interstitial fibrosis is a restrictive pulmonary disease characterized by decreased compliance of lung tissues. Use this information to explain Simone’s decreased total lung capacity, decreased functional residual capacity (FRC), and decreased residual volume at rest. Why was there an increase in her $FEV_1/FVC$ (fraction of the forced vital capacity (FVC) expired in the first second of expiration)?
2. Lung diffusing capacity (DL) is measured with carbon monoxide. Why CO? What is the meaning of Simone's decreased DL<sub>CO</sub>?

3. In addition to changes in lung compliance, diffuse interstitial fibrosis is also characterized by thickening of alveolar membranes. Use this information to explain Simone's decreased arterial P<sub>O<sub>2</sub></sub> (Pa<sub>O<sub>2</sub></sub>) at rest.

4. Use Figure 3–10 to explain why O<sub>2</sub> exchange between alveolar gas and pulmonary capillary blood in healthy people is considered a "perfusion-limited" process. In fibrosis, why does O<sub>2</sub> exchange convert to a "diffusion-limited" process? How does this conversion affect Pa<sub>O<sub>2</sub></sub>?

![Figure 3–10 O<sub>2</sub> diffusion along the length of the pulmonary capillary in healthy people and patients with fibrosis. Pa<sub>O<sub>2</sub></sub>, partial pressure of oxygen in alveolar gas; Pa<sub>0<sub>2</sub></sub>, partial pressure of oxygen in arterial blood.](image)

5. What was the total O<sub>2</sub> content of Simone's blood while she was at rest? Assume that the O<sub>2</sub>-binding capacity of her blood was 1.34 mL O<sub>2</sub>/g hemoglobin, her hemoglobin concentration was 15 g/dL, and the solubility of O<sub>2</sub> in blood is 0.003 mL O<sub>2</sub>/100 mL blood/mm Hg.

6. While exercising on the stair climber, Simone's Pa<sub>O<sub>2</sub></sub> decreased even further, to 62 mm Hg. Propose a mechanism for this further decrease in Pa<sub>O<sub>2</sub></sub>.

7. Why did the percent saturation of hemoglobin in Simone's blood decrease (from 97% to 90%) when she exercised? How did the decrease in percent saturation affect Simone's exercise tolerance?

8. Simone was hypoxemic (i.e., she had a decreased Pa<sub>O<sub>2</sub></sub>). However, she was not hypercapnic (i.e., she did not have CO<sub>2</sub> retention or an increased Pa<sub>CO<sub>2</sub></sub>). In fact, at 37 mm Hg, her Pa<sub>CO<sub>2</sub></sub> was slightly lower than normal. Simone clearly has a problem with O<sub>2</sub> exchange, but she doesn't seem to have a problem with CO<sub>2</sub> exchange. How can hypoxemia occur in the absence of hypercapnia?
ANSWERS AND EXPLANATIONS

1. Simone had decreased total lung capacity, decreased FRC, and decreased residual volume. In explaining these findings, it is important to understand that restrictive pulmonary diseases (e.g., interstitial fibrosis) are associated with decreased compliance of lung tissues. Because the lungs are stiff and noncompliant, greater changes in pulmonary pressures and greater effort are needed to expand the lungs during inspiration. As a result, all lung volumes and capacities are compromised (or decreased).

Simone's FEV1/FVC (the fraction expired in the first second of forced expiration) was increased, however. This finding may be surprising. Recall, however, that the airways are normally held open by elastic forces in lung tissues. The greater the elastance of the lung tissues, the greater the elastic forces that tether the airways open. Thus, in fibrosis and other restrictive diseases in which compliance is decreased and elastance is increased, the airways are more dilated than normal. (In fibrotic lungs, the dilated airways, surrounded by scar tissue, have a characteristic honeycomb appearance.) The increased airway diameter results in decreased resistance to airflow, which is evidenced by an increased FEV1/FVC. Although FVC (like the other lung volumes and capacities) is decreased, the fraction expired in the first second actually can be increased.

2. DL is measured with CO as follows. In the single-breath method, a subject maximally inspires air containing CO, holds his breath for 10 seconds, and then expires. The amount of CO that is transferred from alveolar gas into pulmonary capillary blood is measured to assess the diffusion characteristics of the alveolar-pulmonary capillary barrier.

Why use CO? Why not use some other gas? CO is used because it is diffusion-limited (i.e., its transfer from alveolar gas into pulmonary capillary blood depends solely on the diffusion process). To understand this point, recall two important principles concerning the diffusion of gases: (1) The partial pressure of a gas in solution depends on the concentration of free, unbound gas. (2) The diffusion of gas is driven by a difference in partial pressure. In the single-breath method, the partial pressure of CO in alveolar gas is very high and the partial pressure of CO in pulmonary capillary blood is initially zero. (Normally, we have no CO in our blood.) Thus, the partial pressure gradient across the alveolar-pulmonary capillary barrier is initially very high. The gradient remains high, even after CO begins to diffuse from alveolar gas into the blood, because CO binds avidly to hemoglobin in the blood, forming carboxyhemoglobin. Binding of CO to hemoglobin keeps both the free, unbound CO concentration and the partial pressure of CO in the blood low. Thus, the driving force for CO diffusion is maintained along the length of the pulmonary capillary. Consequently (because the driving force for CO diffusion never dissipates), the amount of CO that is transferred from alveolar gas into pulmonary capillary blood depends solely on the diffusion characteristics of the alveolar-pulmonary barrier (e.g., its thickness).

Simone's DLCO was decreased because interstitial fibrosis is associated with thickening of the alveolar walls. This thickening increases the diffusion distance for gases such as CO and O2 and decreases the total amount of gas that can be transferred across the alveolar wall.

3. At rest, Simone's PaO2 was 76 mm Hg, which is lower than the normal value (100 mm Hg). Before we discuss why Simone's PaO2 was decreased, let's consider how the value of 100 mm Hg is achieved in healthy people. Equilibration of O2 occurs across the alveolar-pulmonary capillary barrier as follows. O2 diffuses readily from alveolar gas into pulmonary capillary blood, driven by its partial pressure gradient, until the PaO2 of the blood equals that of alveolar gas (approximately 100 mm Hg). Thus, the normal equilibration process results in a PaO2 of 100 mm Hg.

In Simone's case, however, perfect equilibration of O2 was impossible: thickening of the alveolar walls impaired O2 diffusion (as detected in a decreased DLCO), and PaO2 could not become equal to alveolar P02 (PA02).

4. Figure 3-10 shows the relationship between arterial P02 (PA02) and distance, or length, along the pulmonary capillary. For reference, alveolar P02 (PA02) is represented by the dashed horizontal line at 100 mm Hg.
The curve for healthy people (normal) shows how O₂ equilibrates across the alveolar-pulmonary capillary barrier, as described in Question 3. Mixed venous blood enters the pulmonary capillary with a P₀₂ of 40 mm Hg. At the beginning of the capillary, there is a large partial pressure gradient for O₂ diffusion because the P₀₂ of alveolar gas is much higher than that of mixed venous blood. O₂ readily diffuses down this partial pressure gradient, from alveolar gas into the pulmonary capillary blood. Initially, as O₂ enters the capillary, it binds to hemoglobin, which keeps the capillary P₀₂ low and maintains the partial pressure gradient for O₂ diffusion. However, after all of the binding sites on hemoglobin are occupied, the P₁₀₂ of the blood rapidly increases and becomes equal to the Pₐ₀₂. This equilibration point occurs approximately one-third of the distance along the capillary. From that point on, no further net diffusion of O₂ can occur because there is no longer a partial pressure gradient, or driving force. Blood leaves the capillary and becomes systemic arterial blood with a Pₐ₀₂ equal to 100 mm Hg. In healthy people, this process is described as perfusion-limited because equilibration of O₂ occurs early along the length of the pulmonary capillary. The only way to increase the amount of O₂ transferred into the blood is to provide more blood flow, or perfusion.

In patients with fibrosis, let's presume (for the sake of discussion) that mixed venous blood enters the pulmonary capillary at the same P₀₂ as in healthy people (40 mm Hg). Thus, the driving force for O₂ diffusion is initially identical to that of healthy people. However, in fibrotic lungs, O₂ diffusion is severely impaired because of thickening of the alveolar walls. As a result, the rate of O₂ diffusion is much lower than in normal lungs. Although P₀₂ gradually increases along the length of the capillary, O₂ never equilibrates. The blood that leaves the pulmonary capillary (to become systemic arterial blood) has a much lower P₀₂ than alveolar gas (in Simone's case, 76 mm Hg). Thus, in fibrosis, O₂ exchange becomes diffusion-limited. The partial pressure gradient for O₂ is maintained along the entire length of the pulmonary capillary, and equilibration never occurs. (For purposes of discussion, mixed venous blood was shown entering the pulmonary capillary with a normal P₀₂ of 40 mm Hg. However, because the disease process decreases Pₐ₀₂, it is expected that venous P₀₂ would eventually be decreased as well. This simplification does not detract from the major point of the question.)

5. The total O₂ content of blood has two components: (1) free, dissolved O₂ and (2) O₂-hemoglobin. By now, you know that O₂-hemoglobin is by far the greater contributor to total O₂ content. However, to be thorough, let's calculate both dissolved and bound O₂ for Simone at rest, as described in Case 21.

\[
\text{Dissolved O}_2 = \text{P}_0\text{O}_2 \times \text{solubility} = 76 \text{ mm Hg} \times 0.003 \text{ mL O}_2/100 \text{ blood/mm Hg} = 0.23 \text{ mL O}_2/100 \text{ mL blood}
\]

\[
\text{O}_2-\text{hemoglobin} = \text{O}_2-\text{binding capacity} \times \% \text{ saturation} = (15 \text{ g/dL} \times 1.34 \text{ mL O}_2/\text{g hemoglobin}) \times 97\% = 20.1 \text{ mL O}_2/100 \text{ mL blood}
\]

\[
\text{Total O}_2 \text{ content} = \text{dissolved O}_2 + \text{O}_2-\text{hemoglobin} = 0.23 \text{ mL O}_2/100 \text{ mL blood} + 19.5 \text{ mL O}_2/100 \text{ mL blood} = 19.7 \text{ mL O}_2/100 \text{ mL blood}
\]

6. You were asked to suggest possible reasons why Simone's Pₐ₀₂ decreased further when she exercised. Worsening of hypoxemia during exercise is typical in pulmonary fibrosis. We know that thickening of the alveolar walls compromises O₂ diffusion and lowered Simone's Pₐ₀₂ at rest. But why should O₂ exchange worsen during exercise? Perhaps, based on the discussions of the importance of ventilation-perfusion (V/Q) matching in this chapter, you wondered whether exercise might induce a V/Q defect in fibrosis. Good thinking!

During exercise, we expect both ventilation and perfusion (cardiac output) to increase to meet the body's greater demand for O₂. However, in fibrosis, these increases in ventilation and cardiac
output are limited, and because of the limitations, hypoxemia worsens with exercise. Because of the restrictive nature of fibrosis, it is difficult for patients to increase their tidal volume as a mechanism for increasing ventilation; instead, they tend to increase breathing rate. This rapid, shallow breathing increases dead space ventilation. Increasing dead space causes a \( V/Q \) defect and worsens hypoxemia. Also in fibrosis, there are associated increases in pulmonary vascular resistance, which increase afterload on the heart and limit the increase in cardiac output. The limited increase in cardiac output and tissue blood flow results in increased tissue extraction of \( O_2 \), which decreases venous \( P_{O_2} \). Thus, when patients with fibrosis exercise, the mixed venous blood entering the lungs has a \( P_{O_2} \) that is lower than at rest. This lower "starting point," coupled with the diffusion defect already discussed, causes arterial blood to have an even lower \( P_{O_2} \) during exercise than at rest.

7. Simone's percent saturation was further decreased during exercise because her \( P_{A_2} \), was further decreased. The \( O_2 \)-hemoglobin curve (discussed in Case 21) describes the relationship between percent \( O_2 \) saturation of hemoglobin and \( P_{O_2} \) (see Figure 3-4). At a \( P_{O_2} \) of 100 mm Hg, hemoglobin is 100% saturated (four \( O_2 \) molecules per hemoglobin molecule). At a \( P_{O_2} \) of 76 mm Hg (Simone at rest), hemoglobin is approximately 97% saturated. At a \( P_{O_2} \) of 62 mm Hg (Simone during exercise), hemoglobin is approximately 90% saturated.

Because her percent saturation was decreased, the total \( O_2 \) content of Simone's blood was lower during exercise than at rest. How did this change affect \( O_2 \) delivery to the tissues? \( O_2 \) delivery is the product of blood flow (cardiac output) and \( O_2 \) content of the blood. Although Simone's cardiac output was undoubtedly increased during exercise (but less than in a healthy person), her \( O_2 \) content was decreased because the amount of \( O_2 \) bound to hemoglobin was decreased. Given the increased \( O_2 \) requirement of the body during exercise, it is not surprising that \( O_2 \) delivery to the tissues was insufficient to meet the demand (i.e., Simone's exercise tolerance was very poor).

8. Although Simone has a problem with \( O_2 \) exchange and is hypoxemic (she has a decreased \( P_{A_2} \)), she does not seem to have a problem with \( CO_2 \) exchange. That is, she is not hypercapnic (she does not have \( CO_2 \) retention or an increased \( P_{A_{CO_2}} \)). In fact, both at rest and during exercise, Simone's \( P_{A_{CO_2}} \) was slightly lower than the normal value of 40 mm Hg. This pattern is common in patients with respiratory diseases: hypoxemia can occur without hypercapnia. But why?

Consider the sequence of events in Simone's lungs that created this pattern of arterial blood gases. The fibrotic disease affected some, but not all, regions of her lungs. The diseased regions had thickening of the alveolar walls and the diffusion barrier for \( O_2 \) and \( CO_2 \). The diffusion problem caused hypoxemia (decreased \( P_{A_2} \)) and may have brieﬂy caused hypercapnia (increased \( P_{A_{CO_2}} \)). However, because the central chemoreceptors are exquisitely sensitive to small changes in \( P_{A_{CO_2}} \), they responded to hypercapnia by increasing the ventilation rate. The increase in alveolar ventilation in healthy regions of the lungs eliminated excess \( CO_2 \) that was retained in unhealthy regions. In other words, by increasing alveolar ventilation, healthy regions of the lungs could compensate for unhealthy regions with respect to \( CO_2 \) exchange. As a result, Simone's \( P_{A_{CO_2}} \) returned to normal. Later in the course of her disease, hypercapnia may develop if she does not have enough healthy lung tissue to compensate for the unhealthy tissue, or if the work of breathing becomes so great that she cannot increase her alveolar ventilation sufficiently.

At this point, you may legitimately ask: If increased alveolar ventilation can rid the body of excess \( CO_2 \) that is retained by unhealthy regions of the lungs, why can't increased alveolar ventilation also correct the hypoxia? The answer lies in the characteristics of the \( O_2 \)-hemoglobin curve. Increased alveolar ventilation does little to increase the total \( O_2 \) content of blood in healthy regions of the lung because of the saturation properties of hemoglobin. Once hemoglobin is 100% saturated (i.e., four \( O_2 \) molecules per hemoglobin molecule), further \( O_2 \) diffusion increases the \( P_{O_2} \) of the pulmonary capillary blood until it equals the \( P_{O_2} \) of alveolar gas. Once equilibration occurs, there is no further diffusion of \( O_2 \). The \( O_2 \) added to this blood is mostly in the dissolved form, which adds little to total \( O_2 \) content. Furthermore, well-oxygenated blood from healthy regions of the lung is always mixing with, and being diluted by, poorly oxygenated blood from unhealthy regions. As a result, the \( P_{A_2} \) of the mixture (systemic arterial blood) will always be lower than normal.
Another question may arise from this discussion: Can the degree of hyperventilation be so great that the patient actually becomes hypocapnic (has decreased PaCO₂)? Absolutely! In fact, Simone’s PaCO₂ is slightly lower than normal. If PaO₂ is low enough to stimulate the peripheral chemoreceptors (i.e., < 60 mm Hg), hyperventilation occurs, even greater amounts of CO₂ are expired by healthy regions of the lung, and PaCO₂ falls below the normal value of 40 mm Hg.

In summary, it is not uncommon for a patient with lung disease to pass through three stages of abnormal arterial blood gases: (1) mild hypoxemia with normocapnia; (2) more severe hypoxemia (PaO₂ < 60 mm Hg) with hypocapnia, which results in respiratory alkalosis; and (3) severe hypoxemia with hypercapnia, which results in respiratory acidosis. At this point in her disease, Simone is somewhere between the first and the second stage.