Pathophysiolog and Clinical Effects of Chronic Hypoxia

David J Pierson MD FAARC

Introduction
Mechanisms of Tissue Hypoxia
Physiologic Responses to Hypoxia
  Respiratory System
  Cardiovascular System
  Central Nervous System
  Adaptation to Altitude
Symptoms and Signs of Hypoxia
Chronic Mountain Sickness
Hypoxia during Sleep
Chronic Hypoxia in Chronic Obstructive Pulmonary Disease
  Pathogenesis of Cor Pulmonale in Chronic Obstructive Pulmonary Disease
  Clinical Manifestations of Hypoxia and Cor Pulmonale in Chronic Obstructive Pulmonary Disease
  Effects of Hypoxemia on Mortality in Chronic Obstructive Pulmonary Disease
Summary

[Respir Care 2000;45(1):39–51] Key words: hypoxia, hypoxemia, desaturation, respiratory system, clinical effects, altitude, chronic obstructive pulmonary disease, cor pulmonale, oxygen therapy, mortality.

Introduction

No aspects of respiratory care receive more attention in both education and clinical practice than assessing whether the body is getting enough oxygen and providing more oxygen when it is not. Several years ago a Respiratory Care Journal conference focused on problems with oxygenation in the critically ill patient. For that conference I reviewed the pathophysiology and clinical effects of an acute deficiency of oxygen. To lay the physiologic groundwork for this conference on long-term oxygen therapy (LTOT), this article addresses the pathophysiologic and clinical effects of chronic oxygen deficiency in patients with pulmonary disease. After clarifying the terminology used to describe impaired oxygenation in the clinical setting, it discusses the basic physiologic mechanisms of tissue hypoxia, the effects of oxygen deficiency on the various organ systems of the body, and the clinical manifestations of chronic hypoxia in different contexts. Pertinent to the context of this conference, the last section focuses in some detail on the effects of chronic hypoxia in patients with chronic obstructive pulmonary disease (COPD).

Although clinicians use the terms hypoxia and hypoxemia every day, the majority of textbooks of physiology, respiratory care, and pulmonary medicine do not give explicit definitions for them. Dictionaries define them, but they vary somewhat in how they do this (Table 1). Although the wording is a bit different, all three of the commonly used dictionaries in the table state that hypoxia is a decrease in tissue oxygen supply below normal levels. Stedman’s Medical Dictionary also lists several subtypes of hypoxia, which include the following terms relevant to this article:
Table 1. Definitions of Hypoxia-Related Terms from Three Dictionaries

<table>
<thead>
<tr>
<th>Term</th>
<th>Webster’s³</th>
<th>Dorland’s⁴</th>
<th>Stedman’s⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>A deficiency in the amount of oxygen that reaches the tissues of the body</td>
<td>Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of tissue by blood</td>
<td>Decrease below normal levels of oxygen in inspired gases, arterial blood, or tissue, short of anoxia</td>
</tr>
<tr>
<td>Anoxia</td>
<td>An abnormally low amount of oxygen in the body tissues</td>
<td>A total lack of oxygen; often used interchangeably with hypoxia to mean a reduced supply of oxygen to the tissues</td>
<td>Absence or almost complete absence of oxygen from inspired gases, arterial blood, or tissues; to be differentiated from hypoxia</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>Inadequate oxygenation of the blood</td>
<td>Deficient oxygenation of the blood: hypoxia</td>
<td>Subnormal oxygen of arterial blood, short of anoxia</td>
</tr>
</tbody>
</table>

- Anemic hypoxia: hypoxia due to a decreased concentration of functional hemoglobin or a reduced number of red blood cells, as seen in anemia and hemorrhage;
- Hypoxic hypoxia: hypoxia resulting from a defective mechanism of oxygenation in the lungs, as caused by a low tension of oxygen, abnormal pulmonary function, airway obstruction, or a right-to-left shunt in the heart;
- Ischemic hypoxia: tissue hypoxia characterized by tissue oligemia and caused by arteriolar obstruction or vasoconstriction;
- Oxygen affinity hypoxia: hypoxia due to reduced ability of hemoglobin to release oxygen;
- Stagnant hypoxia: tissue hypoxia characterized by intravascular stasis due to impairment of venous outflow or decreased arterial inflow.

The definition of anoxia varies somewhat more than that of hypoxia in the sources commonly available to clinicians. The former term generally refers to a more severe state of oxygen deficiency and generally carries an implication of irreversible damage, as in anoxic encephalopathy following cardiac arrest. As shown in Table 1, the greatest variation of all in the context of this article is encountered in definitions for the term hypoxemia. In Dorland’s Illustrated Medical Dictionary™ hypoxemia is a synonym for hypoxia. However, all three sources say that hypoxemia refers to deficient oxygen in the blood. Stedman’s,⁵ but not the others, indicates that hypoxemia refers specifically to arterial blood.

None of the dictionaries cited, nor any of the textbooks I could find in preparing this article, define hypoxemia in the setting of the abnormal oxygenation we encounter clinically. That is, none of them say that it means “less oxygen than would be present in a normal person’s blood under the same circumstances.” For clinical purposes I will therefore use hypoxemia to mean a decreased oxygen tension (P\(_{O_2}\)) in the blood below the normal range. Thus, the term should not be used when P\(_{O_2}\) is in the normal range, even if pulmonary gas exchange is markedly deranged or there is one of the other subtypes of hypoxia defined above.

Using this definition, a patient with an arterial P\(_{O_2}\) (P\(_{aO_2}\)) of 100 mm Hg is not hypoxemic. This would be true even if to achieve that P\(_{aO_2}\) the patient had to breathe a high fraction of inspired oxygen (F\(_{O_2}\)), or if the hemoglobin concentration (and thus the blood’s total oxygen content) were greatly reduced. Finally, in the absence of consistency in the cited references, since a reduced P\(_{O_2}\) may be as important clinically in mixed venous blood as it is in the arterial blood, whether the blood in question is venous or arterial should be specified when referring to hypoxemia.

This article is ultimately about hypoxia at the tissue level. Directly measuring tissue oxygenation is not feasible in most clinical circumstances, however, and either P\(_{aO_2}\) or arterial oxyhemoglobin saturation (S\(_{aO_2}\)) is usually measured. Nonetheless, it is important to remember that it is the adequacy of tissue oxygen supply, not necessarily the values of P\(_{aO_2}\) or S\(_{aO_2}\), that determines whether the patient’s life or organ function is threatened.

Mechanisms of Tissue Hypoxia

Figure 1⁶ emphasizes the interconnectedness of the components of tissue oxygenation. Oxygen enters the body via the lungs, is transported to the tissues via the blood, and is consumed by the intracellular “respiratory engine” to provide the energy for metabolism. A defect at any point in the system—lungs, heart, blood, or tissues—can disrupt normal oxygenation and cause tissue damage or death of the organism.

In clinical practice a deficiency of oxygen in the arterial blood is commonly defined in relation to the oxyhemoglobin dissociation curve (Fig. 2).⁷ Because of the sigmoid shape of the relationship between P\(_{aO_2}\) and S\(_{aO_2}\), concern about arterial hypoxemia increases when P\(_{aO_2}\) is in the area of the “elbow” of the curve (at approximately 60-70 mm Hg), below which S\(_{aO_2}\) decreases more rapidly with further decrements in P\(_{aO_2}\). Clinical concern intensifies as P\(_{aO_2}\) falls below 50-60 mm Hg and S\(_{aO_2}\) diminishes even more rapidly, and hypoxic acute respiratory failure is generally considered to be present when P\(_{aO_2}\) is below 50 mm Hg.⁷ However, although hypoxemia is probably the most common cause of life-threatening tissue hypoxia, this definition is too narrow.²
Pathophysiology and Clinical Effects of Chronic Hypoxia

Tissue hypoxia may result from an abnormality anywhere in the system, and its prevention or correction is the ultimate goal of supplemental oxygen therapy. Oxygen tensions in the diagram are inspired (P_i), alveolar (P_A), arterial (P_a), and venous (P_v). ADP = adenosine diphosphate. ATP = adenosine triphosphate. (Adapted from Reference 6, with permission.)

Fig. 1. Pathway for oxygen from outside air to ultimate consumption within the mitochondria of cells. Tissue hypoxia may result from an abnormality anywhere in the system, and its prevention or correction is the ultimate goal of supplemental oxygen therapy. Oxygen tensions in the diagram are inspired (P_i), alveolar (P_A), arterial (P_a), and venous (P_v). ADP = adenosine diphosphate. ATP = adenosine triphosphate. (Adapted from Reference 6, with permission.)

Fig. 2. Relationship of arterial oxygen tension (P_aO_2, horizontal axis) to oxyhemoglobin saturation (S_aO_2, left vertical axis) and arterial oxygen content (C_aO_2, right vertical axis) in the clinically relevant P_aO_2 range (0-100 mm Hg) as well as at a P_aO_2 of 600 mm Hg. The amount of oxygen dissolved in plasma is unimportant in most clinical settings, virtually all of it being bound to hemoglobin. The values for C_aO_2 assume a normal blood hemoglobin concentration of 15 g/dL. (From Reference 7, with permission.)

Fig. 3. Relationship of arterial oxygen tension to oxyhemoglobin saturation and arterial oxygen content.

Potential role of mechanisms other than hypoxemia (that is, a low P_aO_2). For example, life-threatening anemic hypoxia may be present in the face of a normal P_aO_2. In Figure 2 the right vertical axis shows the arterial oxygen content (C_aO_2) corresponding to the S_aO_2, associated with a given P_aO_2 in a person with a normal blood hemoglobin concentration of 15 g/dL. Clinicians may assume that a normal P_aO_2 means that tissue oxygenation is normal, but such is not necessarily the case. This is because, except under hyperbaric conditions, for clinical purposes C_aO_2 is as high as it can get once the hemoglobin is fully saturated. With hemoglobin concentrations less than normal, C_aO_2 must also be proportionally reduced. Figure 3 shows what the C_aO_2 curve looks like when the hemoglobin concentration varies. Even in the absence of hypoxemia, with S_aO_2 100%, C_aO_2 can only be about two thirds of normal with a hemoglobin concentration of 10 g/dL, and much less than that with more severe anemia.

Systemic oxygen delivery is the product of C_aO_2 and cardiac output. Even when C_aO_2 is normal, tissue oxygenation may be inadequate if cardiac function is impaired. The latter is commonly encountered both in the intensive care unit (as with cardiac failure or the application of excessive positive end-expiratory pressure*) and in the ambulatory care setting (as with chronic congestive heart failure). Reference to Figure 1 and Table 2 shows that impaired tissue oxygen utilization can also be a cause of oxygenation failure, even when systemic oxygen delivery is adequate. However, this mechanism is seldom encountered in the setting of chronic lung disease.

While it is important to remember the additional mechanisms for tissue hypoxia discussed above, arterial hypoxa-
emia is the most common cause encountered in the long-term setting. Table 3 lists the four physiologic mechanisms of chronic arterial hypoxemia and provides clinical examples of each mechanism. Diffusion impairment is a fifth possible mechanism, although it occurs mainly during exercise at very high altitude and is not a significant contributor to hypoxemia as seen in patients with COPD. A reduction in the inspired \( P_{\text{O}_2} \), as encountered at high altitude produces hypoxemia despite the normal function of all the components of respiration. In primary lung disease, hypoxemia is the result of one or more of the three remaining processes in the table-alveolar hypoventilation, ventilation-perfusion ratio \((V/Q)\) mismatching, and right-to-left shunting.

The most common mechanism for hypoxemia in patients with chronic pulmonary disease is mismatching of ventilation and perfusion, or, more accurately, an increase in low-\( V/Q \) regions in the lung. Patients with COPD also often have a component of alveolar hypoventilation resulting from reduced carbon dioxide elimination in relation to its production by the body, and determined by the presence of hypercapnia. Chronic hypoxemia due to right-to-left intrapulmonary shunting is rarely encountered, and this mechanism is generally not a significant contributor to hypoxemia in patients with COPD. That the latter is so is fortunate for both patient and clinician with respect to LTOT, because it means that hypoxemia in COPD is relatively easy to correct, as discussed below.

Knowing the mechanism or mechanisms of hypoxemia in a given patient is important in diagnosis, because different diseases produce hypoxemia in different ways and also in therapy, as hypoxemia caused by the different mechanisms responds differently to administration of supplemental oxygen and to other measures. To determine the mechanism or mechanisms of hypoxemia in a given patient, it is first necessary to estimate the alveolar-to-arterial \( P_{\text{O}_2} \) difference \([P(\text{A-a)}_{\text{O}_2}]\), commonly called the A-a gradient. Alveolar \( P_{\text{O}_2} (P_{\text{A-O}_2}) \) must first be determined using the alveolar gas equation:

\[
P_{\text{A-O}_2} = P_{\text{I-O}_2} - P_{\text{a-CO}_2}/R
\]

wherein \( P_{\text{a-CO}_2} \) is the arterial carbon dioxide tension and \( R \) is the respiratory quotient. In this equation, the \( P_{\text{I-O}_2} \) is calculated from barometric pressure \( (P_B) \), the partial pressure of water vapor \( (P_{H_2O}) \) at body temperature, and the \( F_{\text{I-O}_2} \):

\[
P_{\text{I-O}_2} = (P_B - P_{H_2O}) \times F_{\text{I-O}_2}
\]

When breathing air at sea level, \( P_{\text{I-O}_2} \) is: \((760 - 47 \text{ mm Hg}) \times 0.21\), or approximately 150 mm Hg. The respiratory quotient \( (R) \), the overall ratio of CO produced to \( O_2 \) consumed by the body, is about 0.8 for persons eating a usual North American mixed diet, and this assumed value is used in calculating \( P_{\text{A-O}_2} \). Thus, if the patient’s \( P_{\text{a-CO}_2} \) is 40 mm Hg:

\[
P_{\text{A-O}_2} = 150\text{mmHg} - 40\text{mmHg}/0.8 = 100\text{mmHg}
\]
Mechanisms of Chronic Arterial Hypoxemia

Practical Distinction Among the Main Mechanisms of Hypoxemia

Table 3. Mechanisms of Chronic Arterial Hypoxemia

<table>
<thead>
<tr>
<th>Physiologic Mechanism</th>
<th>Clinical Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low inspired Po,&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Chronic mountain sickness</td>
</tr>
<tr>
<td>Alveolar hypoventilation</td>
<td>COPD with hypercapnia, Obesity hypoventilation syndrome</td>
</tr>
<tr>
<td>Ventilation-perfusion mismatching</td>
<td>COPD, Pulmonary fibrosis, Most other chronic pulmonary diseases</td>
</tr>
<tr>
<td>Right-to-left shunting</td>
<td>Arteriovenous malformation, Hepatopulmonary syndrome</td>
</tr>
</tbody>
</table>

P<sub>O</sub><sub>2</sub> = oxygen tension. COPD = chronic obstructive pulmonary disease.

Table 4. Practical Distinction Among the Main Mechanisms of Hypoxemia

<table>
<thead>
<tr>
<th>Physiologic Mechanism</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar hypoventilation</td>
<td>Hypercapnia, Normal P&lt;sub&gt;A-a&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Ventilation-perfusion mismatching</td>
<td>Increased P&lt;sub&gt;A-a&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;, Good response to supplemental O&lt;sub&gt;2&lt;/sub&gt;, High F&lt;sub&gt;O&lt;/sub&gt;2, not required</td>
</tr>
<tr>
<td>Right-to-left shunting</td>
<td>Increased P&lt;sub&gt;A-a&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;, Poor response to supplemental O&lt;sub&gt;2&lt;/sub&gt;, High F&lt;sub&gt;O&lt;/sub&gt;2, or PEEP may be required to correct hypoxemia</td>
</tr>
</tbody>
</table>

P<sub>A-a</sub>O<sub>2</sub> = alveolar-arterial oxygen gradient, F<sub>O</sub>2 = fraction of inspired oxygen. PEEP = positive end-expiratory pressure.

Table 4

If this patient’s P<sub>a</sub>O<sub>2</sub> were 85 mm Hg, P<sub>A-a</sub>O<sub>2</sub> would thus be 100 – 85 or 15 mm Hg. A P<sub>A-a</sub>O<sub>2</sub> value of less than about 20 mm Hg can be considered normal for clinical purposes, and a value greater than about 30 mm Hg is distinctly abnormal.

The different physiologic mechanisms of hypoxemia can be distinguished clinically using the patient’s initial arterial blood gas results and the response to administration of supplemental oxygen (Table 4). If the patient is hypercapnic, alveolar ventilation is present by definition. In the presence of a normal P<sub>A-a</sub>O<sub>2</sub>, alveolar hypoventilation produces a fall in P<sub>a</sub>O<sub>2</sub> that is roughly equivalent to the increase in P<sub>a</sub>CO<sub>2</sub>. The body consumes a greater quantity of O<sub>2</sub> than the CO<sub>2</sub> it produces, by the relationship R. This is illustrated in Figure 4,7 which shows that P<sub>a</sub>O<sub>2</sub> and P<sub>a</sub>CO<sub>2</sub> change in opposite directions, assuming an unchanging P<sub>S</sub>O<sub>2</sub>, and R = 0.8. An increase in P<sub>a</sub>CO<sub>2</sub> of 20 mm Hg will be associated with a fall in P<sub>a</sub>O<sub>2</sub> of about 25 mm Hg in an otherwise normal individual. Equivalent changes in the opposite direction occur with hyperventilation.

As shown in Table 4, alveolar hypoventilation (along with a low inspired P<sub>O</sub><sub>2</sub>, not shown) causes hypoxemia without increasing P<sub>A-a</sub>O<sub>2</sub>. Both V/Q mismatching and right-to-left shunting increase P<sub>A-a</sub>O<sub>2</sub>, but they can be distinguished for practical purposes by the response of P<sub>a</sub>O<sub>2</sub> to the administration of low-flow supplemental oxygen. If supplemental oxygen restores the P<sub>a</sub>O<sub>2</sub> to the normal range or substantially increases it, V/Q can be assumed to be the cause, while persistent hypoxemia implies the presence of very low V/Q areas, if not actual shunt.

The clinical importance of this distinction is that high F<sub>O</sub>2, positive end-expiratory pressure, or other measures may be required if the hypoxemia is caused by shunt, while V/Q mismatch causes hypoxemia that can easily be corrected. If both hypercapnia and an increased P<sub>A-a</sub>O<sub>2</sub> are present, then both alveolar ventilation and V/Q mismatching are contributing to the hypoxemia.

Physiologic Responses to Hypoxia

JBS Haldane is said to have remarked that a lack of oxygen not only stops the machine but also wrecks the machinery. The correctness of this observation is manifestly apparent with acute, severe hypoxia as encountered in cardiopulmonary arrest or severe hypoxic acute respiratory failure. However, in the context of this review the destructive effect of hypoxia on the machinery of the body is less dramatic and most often encountered in the form of altered function rather than structural damage.

In the 1960s it was shown that a P<sub>O</sub><sub>2</sub> of at least 18 mm Hg is necessary to sustain mitochondrial function, and to generate adenosine triphosphate, which is essential for all major cellular biochemical functions. Cellular hypoxia may be defined as a state in which convective or diffusive oxygen transport fails to meet the tissue demand for oxygen and when the rate of adenosine triphosphate synthesis becomes limited by the oxygen supply. Decreases in ox-
Table 5. Physiologic Responses to Hypoxia

<table>
<thead>
<tr>
<th>System</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Increased ventilation</td>
</tr>
<tr>
<td></td>
<td>Respiratory alkalosis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Pulmonary vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Decreased maximum oxygen consumption</td>
</tr>
<tr>
<td></td>
<td>Decreased myocardial contractility</td>
</tr>
</tbody>
</table>

Fig. 5. General relationship between arterial oxygen tension (PaO₂) and hypoxic ventilatory drive. As PaO₂ falls below about 65 mm Hg in most normal individuals, hypoxic drive progressively increases its stimulus to breathe. The vertical axis depicts the intensity of the hypoxic stimulus, whether the individual is capable of increasing minute ventilation or prevented from doing so by airway obstruction or other disease process. (From Reference 12, with permission.)

Table 5 summarizes the normal responses of the respiratory and cardiovascular systems to hypoxia. In most instances these responses are compensatory and serve to prevent organ dysfunction or tissue damage that would otherwise occur. Differences among normal individuals in the presence and vigor of these responses probably account for much of the variation in clinical presentation observed in patients with chronic hypoxia caused by pulmonary disease.

Respiratory System

The main respiratory response to hypoxia is an increase in hypoxic ventilatory drive, which in normal individuals results in increased ventilation (Fig. 5).12-14 This response is to PaO₂, not to SaO₂ or CaO₂, and is mediated by the peripheral arterial chemoreceptors, located in the carotid bodies.13 At sea level, ventilation is driven primarily by CO₂ and by input from stretch receptors in the chest wall, so that only about 10% of the minute ventilation can be accounted for by hypoxic ventilatory drive. Regardless of whether ventilation or central drive is measured, the hypoxic response is curvilinear, unlike the linear response to hypercapnia. The vigor of the response, and thus the position and slope of the curve in Figure 5, is affected by PaCO₂. Hypercapnia displaces the curve upward and to the right, whereas hypocapnia has the opposite effect.

Hypoxic ventilatory drive is diminished in a small proportion (less than 5%) of the normal population, and also in many highly successful athletes and after prolonged residence at high altitude. It declines with normal aging. It is also blunted in congenital cyanotic heart disease, in myxedema and severe hypothyroidism, in certain types of autonomic nervous system dysfunction, and with the chronic use of narcotics. Patients who have undergone carotid body resection, a now-abandoned procedure once performed as treatment for dyspnea in emphysema, also have blunted hypoxic ventilatory drive.

The increased ventilation associated with hypoxia is perceived as dyspnea by many individuals. Available evidence suggests that dyspnea in this context may also result in part from a direct stimulus of breathlessness,15 although this appears highly variable among individuals. As with chronic hyperventilation in other settings, the normal response to prolonged hypoxia leads to compensatory metabolic acidosis produced by increased renal bicarbonate loss.

Cardiovascular System

The most characteristic and important cardiovascular response to hypoxia is pulmonary vasoconstriction, which
reduces the caliber of pulmonary vessels and raises vascular resistance in a region of low alveolar $P_{O_2}$. Hypoxic pulmonary vasoconstriction (HPV), first described a half century ago by Euler and Liljestrand, serves to maintain $V/Q$ matching in a localized area of airway obstruction or infiltration (Fig. 6), but has a deleterious overall effect when alveolar hypoxia is widespread throughout the lung, as in chronic mountain sickness or COPD. Occurring primarily at the precapillary level and involving small muscular arteries and arterioles, and augmented by acidosis, HPV causes pulmonary hypertension and is a primary factor in the pathogenesis of cor pulmonale, as will be discussed later. The pulmonary vascular response to hypoxia occurs in two phases. The first is the acute hypoxic vasoconstrictor response described above. When the hypoxia is prolonged for at least several weeks, a second phase consisting of vascular remodeling begins.

A variety of substances counteract HPV. In addition to inhalational anesthetics, these substances include prosta-cyclin and inhaled nitric oxide. Both of the latter agents have been used, at least experimentally, to treat chronic pulmonary hypertension.

Severe hypoxia has a direct deleterious effect on cardiac function. Myocardial contractility and maximum output are diminished during conditions of reduced oxygen supply. While maximum oxygen consumption is reduced in chronic hypoxia, cardiac output remains normal at rest, owing primarily to an increased red blood cell mass.

Central Nervous System

Representing only 2-3% of an adult’s body mass, the brain receives 20% of the cardiac output and accounts for about one fourth of overall resting oxygen consumption. The brain is one of the most oxygen-sensitive organs of the body, and it is not surprising that neurologic dysfunction is a prominent manifestation of hypoxia. As discussed by Wedzicha elsewhere in this issue, neuropsychiatric manifestations of chronic hypoxia can be a major source of morbidity in patients with COPD.

Cerebral vascular resistance is prominently affected by acute hypoxia, and increases when $P_{O_2}$ falls below 50-60 mm Hg. However, with continued hypoxia, adaptation occurs, and overall cerebral blood flow in hypoxemic patients with COPD is normal. The brain is very sensitive to changes in perfusion, and effects of hypoxia on the brain are more likely to be due to decreased perfusion than to hypoxemia.

Adaptation to Altitude.

At high altitude $F_{O_2}$ remains the same, but $P_{O_2}$ decreases as barometric pressure falls. In comparison with its value of about 150 mm Hg at sea level, $P_{O_2}$ is approxi-
A natural experiment has been carried out in Tibet since that country was assimilated politically into China 50 years ago. A number of physiologic studies have been carried out in Lhasa (altitude 3,658 m) comparing the native Tibetans with Han (Chinese) residents, the latter having lived at altitude for only a few years. These studies show that, compared with healthy Han residents of Lhasa, native Tibetans have increased resting ventilation, increased hypoxic ventilatory response, larger vital capacity, and lower resting Paco2 and PA-aO2. Tibetans also have less electrocardiographic evidence of right ventricular hypertrophy than do their Han counterparts. From the results of these studies it can be concluded that the Tibetans are better adapted to life at altitude than are the Han, perhaps indicating evolutionary adaptation to chronic hypoxia over many generations.

**Symptoms and Signs of Hypoxia**

The symptoms and signs of hypoxia (Table 7) are non-specific and similar to those of heart failure and several other conditions. Although many patients with hypoxia are dyspneic, this is highly variable, and the clinical manifestations tend to be neurological and cardiovascular rather than respiratory. Similarly, although cyanosis is supposed to be present whenever there is more than 5 g/dL of deoxygenated hemoglobin, this sign varies enough from patient to patient and among different observers to be of little clinical value in detecting hypoxemia. These observations emphasize the importance of the objective measurement of oxygenation in both diagnosis and treatment of hypoxia.

**Chronic Mountain Sickness**

Chronic mountain sickness is a disorder affecting many long-term residents of altitudes above 9,000 feet. It is similar in some ways to what is seen in COPD patients with chronic hypoxemia, although it does not involve airflow obstruction and has several features not generally observed in COPD. As mentioned above, it occurs commonly in the Rockies and the Andes, but is uncommon among natives of the Himalayas and the Tibetan Plateau. Symptoms of chronic mountain sickness include lethargy, mental slowness, and decreased exercise capacity. Affected individuals are plethoric and usually have conjunctival injection and peripheral edema. Laboratory evaluation shows more severe hypoxemia and higher PaCO2 than observed in others at the same altitude, along with erythrocytosis that may be profound, with hematocrit values of 75% or more. The disorder is believed to result from maladaptation to high altitude, with relative hypoventilation, pulmonary hypertension, and cor pulmonale. It becomes more common with increasing age, and is more commonly seen in men than in women before menopause. Treatment aims to relieve hypoxemia and blood hyperviscosity. Ideally, affected individuals should move permanently to a lower altitude, but this may not be an option for socioeconomic reasons. Similarly, LTOT is seldom available in the remote regions where chronic mountain sickness is prevalent. Staged phlebotomy is performed to maintain the hematocrit closer to the level expected for the altitude at which the patient lives.

**Hypoxia during Sleep**

Although the subject of hypoxia during sleep is beyond the scope of this review, this phenomenon affects millions of people and has assumed increasing importance in recent years. There is considerable overlap between COPD and sleep-disordered breathing. The separate problem of nocturnal oxygen desaturation in patients who are not hy-
Pathophysiology and Clinical Effects of Chronic Hypoxia

Fig. 7. Pathogenesis of cor pulmonale in chronic obstructive pulmonary disease. Long-term oxygen therapy attempts to reverse this process by eliminating alveolar hypoxia, the primary stimulus to increased pulmonary vascular resistance (PVR). However, as indicated in the diagram, the increased PVR is multifactorial, and only a partial reduction in pulmonary arterial pressures is achieved.

Pulmonary Hypertension

Increased Right Ventricular Afterload

Right Ventricular Hypertrophy

Right Ventricular Failure

Cor Pulmonale

Pathogenesis of Cor Pulmonale in Chronic Obstructive Pulmonary Disease

The term cor pulmonale refers to alterations in the structure and function of the right ventricle due to disease of the lungs rather than of the heart per se. More specifically, as defined by an expert committee of the World Health Organization, cor pulmonale is “hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart, as in congenital heart disease.”55 The term cor pulmonale applies to patients who show evidence of structural change in the right ventricle, whether or not they have overt right-sided heart failure. However, it should not be used as a synonym for right heart failure, nor in patients with pulmonary hypertension who show no evidence of right ventricular hypertrophy.56

The pathophysiology of cor pulmonale in COPD, reviewed in a classic paper by Fishman,57 has been revisited more recently in a comprehensive review by MacNee.56,58 The factors involved in its pathogenesis are depicted in Figure 7.59 Alveolar hypoxia triggers HPV and its attendant increase in pulmonary vascular resistance. If the hypoxia is prolonged, the increased right ventricular afterload produced by the chronically elevated pulmonary artery pressure results in hypertrophy of the right ventricle. Eventually, if the process continues, overt right-sided heart failure ensues, with peripheral edema, hepatic congestion, and other signs of increased blood volume and elevated central venous pressure.

As suggested in the figure, the pathogenesis is not so straightforward as implied by the preceding description. Hypoxemia exerts an effect on the pulmonary vasculature separate from alveolar hypoxia, as does acidosis. Reduction in pulmonary capillary surface area caused by emphysema also contributes to the increased pulmonary vascular resistance. In addition, when present, erythrocytosis may further augment the pulmonary hypertension.

Clinical Manifestations of Hypoxia and Cor Pulmonale in Chronic Obstructive Pulmonary Disease

Just as the symptoms and signs of hypoxia are variable among individuals, the clinical manifestations of chronic hypoxia and cor pulmonale in patients with COPD show considerable variation. How dyspneic COPD patients with chronic hypoxemia are depends a lot on the severity of their airflow obstruction, but may also be a function of their underlying hypoxic ventilatory drive. The relationship between \( P_{aO_2} \) and the urge to breathe, as depicted in Figure 5, varies among normal individuals, as mentioned previously, with some small fraction of the population having markedly blunted hypoxic chemosensitivity. For individuals with COPD and normal or heightened underlying hypoxic drive, the development of hypoxemia would be expected to increase the severity of their dyspnea. Such individuals might seek to avoid hypoxemia by increasing ventilation insofar as they were capable of doing so. These patients would remain normoxic until very late in the course of their disease, but would be very dyspneic. On the other hand, it may be surmised that, for those individuals with naturally blunted hypoxic drives who develop COPD, hypoxemia might not stimulate additional breathlessness. Not being distressed by the development of chronic hypoxemia (with its attendant cyanosis), such individuals might develop cor pulmonale earlier than their normoxic, more dyspneic counterparts. These two extremes in clinical presentation—the “pink puffer” (also known as “Type A” COPD) and the “blue bloater” (“Type B”) (Fig. 8)—are atypical, but are consistent with present understanding of pathophysiology and illustrate the spectrum of clinical presentation in patients with chronic hypoxemia complicating COPD.
Pathophysiology and Clinical Effects of Chronic Hypoxia

Fig. 8. Two patients with severe chronic obstructive pulmonary disease and comparable degrees of airflow obstruction, who illustrate two clinical extremes of the syndrome believed to be determined at least in part by how they respond to hypoxia. The “blue bloater” on the left has longstanding severe chronic hypoxemia and cor pulmonale but little dyspnea, whereas the “pink puffer” on the right maintains relatively normal oxygenation in the face of severe dyspnea. (From Reference 60, with permission.)

Effects of Hypoxemia on Mortality in Chronic Obstructive Pulmonary Disease

Evidence for the effects of chronic hypoxia on mortality and morbidity in COPD is largely indirect. Early studies of the natural history of severe COPD\(^6\)-\(^8\) did not examine the separate influences of hypoxia, the severity of airflow obstruction, and other factors. However, by examining the findings of several large-scale studies some useful conclusions may be drawn about the impact of chronic hypoxia as a factor separate from other prognosticators.

Among patients with COPD, the more severe the pulmonary hypertension the worse the prognosis.\(^6\),\(^8\) Figure 9 shows that 5-year survival among COPD patients with mean pulmonary artery pressures less than 25 mm Hg when initially examined is not very different from that expected for persons of the same age. However, the prognosis worsens progressively with increasing mean pulmonary arterial pressure, and few patients with initial values exceeding 45 mm Hg survive 5 years. The data in Figure 9\(^6\) do not take the severity of airflow obstruction into account, and no doubt those individuals who fared best also tended to have less severe disease. As previously discussed, hypoxia is also not the only factor contributing to pulmonary hypertension in these patients, and LTOT does not restore pulmonary arterial pressures to normal.\(^6\)-\(^6\) However, the data in the figure provide strong evidence for an important impact of the magnitude of pulmonary hypertension on survival in patients with COPD.

Studies have attempted to correlate numerous anatomic, spirometric, imaging, and functional measurements with survival in COPD patients. Of these, the forced expiratory volume in the first second (FEV\(_1\)) remains the best single assessment of functional impairment and predictor of survival.\(^6\),\(^6\) Burrows\(^6\) performed a long-term follow-up study on 200 patients with COPD and showed a clear separation into survival groups according to initial FEV\(_1\), (Fig. 10). Half of all patients with initial FEV\(_1\) values exceeding 1.25 L were alive 10 years after starting the study, while 75% of those with initial FEV\(_1\) values less than 750 mL were dead within 5 years.\(^6\)

Chronic hypoxia increases mortality regardless of the severity of airflow obstruction.\(^6\),\(^6\) Thus, each of the curves in Figure 10 is shifted downward by the presence of chronic stable hypoxemia. The Nocturnal Oxygen Therapy Trial (NOTT)\(^7\) and British Medical Research Council (MRC) multicenter study of LTOT\(^7\) demonstrated that LTOT improved survival in patients with COPD and chronic stable hypoxemia. In the NOTT, patients who used oxygen only at night had a significantly poorer survival over the three...
years of the study than patients assigned to continuous oxygen use.\textsuperscript{70} Using data from the NOTT study and also the results of the Intermittent Positive Pressure Breathing Trial (IPPB),\textsuperscript{72} Anthonisen et al were able to demonstrate the downward shift of the survival curve due to chronic hypoxia for a given degree of airflow obstruction.\textsuperscript{68,69} Patients included in the IPPB study had COPD but had to be normoxemic as a criterion for inclusion. Anthonisen et al matched patients in the IPPB study, the nocturnal-only oxygen arm of the NOTT, and the continuous oxygen arm of the NOTT for degree of airflow obstruction as measured by FEV\textsubscript{1}. They found that survival was the same for the IPPB patients and the continuous-oxygen NOTT patients, and better than for the nocturnal-oxygen NOTT patients (Fig. 11).\textsuperscript{68} Thus, COPD patients with the same severity of disease as measured by FEV\textsubscript{1} had worse survival if they were hypoxemic and the hypoxemia was relieved only about half the time, whereas chronic hypoxemia did not worsen survival if oxygen was used most of the time.

The MRC and NOTT studies show that, with respect to survival, for COPD patients with stable chronic hypoxemia, some oxygen every day is better than none, but more oxygen is better yet. Survival in the MRC oxygen group and in the NOTT nocturnal-only group was approximately the same (and better than in the MRC no-oxygen group), but survival in the NOTT continuous-oxygen group was substantially better than in either of them. The NOTT included measurements of actual oxygen use by the patients, and showed that the continuous-oxygen patients actually used their oxygen on average only about 18 h/d. Based on the dose-response relationship inferred from combining the results of the two studies, it may be hypothesized that true 24 h/d use would increase survival even more.
evidence in support of this hypothesis, but it provides a rationale for encouraging patients who qualify for LTOT to use their oxygen as much of the time as possible.

Summary

Hypoxia exists when there is a reduced amount of oxygen in the tissues of the body. Hypoxemia refers to a reduction in $P_{O_2}$ below the normal range, regardless of whether gas exchange is impaired in the lung. $C_aO_2$ is adequate, or tissue hypoxia exists. There are several potential physiologic mechanisms for hypoxemia, but in patients with COPD the predominant one is $V/Q$ mismatching, with or without alveolar hypventilation, as indicated by $P_{aCO_2}$. Hypoxemia caused by $V/Q$ mismatching as seen in COPD is relatively easy to correct, so that only comparatively small amounts of supplemental oxygen (less than 3 L/min for the majority of patients) are required for LTOT. Although hypoxemia normally stimulates ventilation and produces dyspnea, these phenomena and the other symptoms and signs of hypoxia are sufficiently variable in patients with COPD as to be of limited value in patient assessment.

Chronic alveolar hypoxia is the main factor leading to development of cor pulmonale-right ventricular hypertrophy with or without overt right ventricular failure in patients with COPD. Pulmonary hypertension adversely affects survival in COPD, to an extent that parallels the degree to which resting mean pulmonary artery pressure is elevated. Although the severity of airflow obstruction as measured by FEV$_1$ is the best correlate with overall prognosis in patients with COPD, chronic hypoxemia increases mortality and morbidity for any severity of disease. Large-scale studies of LTOT in patients with COPD have demonstrated a dose-response relationship between daily hours of oxygen use and survival. There is reason to believe that continuous, 24-hours-per-day oxygen use in appropriately selected patients would produce a survival benefit even greater than that shown in the NOTT and MRC studies.

REFERENCES


Discussion

Petty: David, it’s a fact that FEV, is a good prognostic indicator, and it’s the better prognostic indicator if made age-specific. That is, at what age your FEV, is abnormal, and is it reversible? And that becomes the indicator for early identification and intervention. That’s the reason why we have such a passion today for the National Lung Health Education program, because our real challenge now is to deal with early stages of disease, and I have a pin for most of you called...
"The Second Breath of Life." The first breath of life, of course, is the baby’s breath that allows the child to live in the first place, and the second breath of life is your spirogram during adulthood that tells how long you’re probably going to live.

O’Donohue: Dave, in your definition of hypoxemia as decreased oxygen in the blood, would you consider someone who is anemic to be hypoxic since they have decreased oxygen in the blood, or is it strictly the Po2?

Pierson: Dorland’s, from which I took that (and I surveyed a number of other dictionaries as well), gives us a number of different kinds of hypoxia. There’s anemic hypoxia, stagnant hypoxia, hypoxic hypoxia, histotoxic hypoxia, and one or two others, and they would describe anemic hypoxia as that due to insufficient delivery of oxygen by virtue of not enough.

O’Donohue: Hypoxia is the term to which I am referring, not hypoxemic.

Pierson: Hypoxemia. Here I’ve not been able to find unanimous agreement. For example, Stedman’s Medical Dictionary says hypoxemia is deficient oxygen in the arterial blood, whereas Dorland’s doesn’t specify the condition of the blood. I have always used the definition that hypoxemia means that your Po2 is abnormally low. So, if I’m breathing 100% oxygen, and I have acute respiratory distress syndrome (ARDS) and am on a ventilator, and my Po2 is 80, I am not hypoxemic. Likewise, if my hemoglobin is only 5, I may have an oxygen content that’s only a third of normal, but I’m not hypoxemic by that convention. But I think that it’s difficult to find a universally-agreed-upon identification. Does that agree with your concept, Walter?

O’Donohue: Yes, absolutely. I have always personally used the term to mean a decreased Po2. Patients with severe anemia have decreased oxygen content, but I have never referred to them as being hypoxicemic.

Pierson: It would be a shame if we couldn’t at least agree on the ABC’s for our discussion for these next two and a half days.

O’Donohue: But in both cases they have decreased oxygen in the blood.

Stoller: David, I thought it was a wonderful talk. At the risk of being a splitter, I just want to comment on your use of the hepatopulmonary syndrome as an example of right-to-left shunt, and lumping it with arteriovenous malformation. Regarding your self-acknowledged 20-year-old slide about the 5 mechanisms of hypoxemia (eg, V/Q mismatch and so on), some authors have suggested that the hepato-pulmonary syndrome represents an unusual admixture of diffusion impairment and right-to-left shunt, such that some authors have actually added a sixth cause of hypoxemia called diffusion-perfusion impairment. In the hepatopulmonary syndrome, there is dilatation of the capillaries causing the unusual circumstances in which blood is passing very quickly through dilated capillaries. This creates an impediment to diffusion of oxygen to the very center of the stream, which partially corrects with supplemental oxygen, albeit incompletely.\(^1,2\) So, at the risk of being a nitpicker about that issue, we should mention diffusion-perfusion impairment as another physiologic cause of hypoxemia, to make the list complete.

REFERENCES

McCoy: I’ve got a practical sort of question for you, about the fact that long-term oxygen therapy is mostly delivered in the home setting. The people who manage the reimbursement for home oxygen therapy seem to not understand the question of the effects of hypoxemia, and come back with a “So what?” It seems that most of the research shows that survival is the “So what?” answer. To a payer, as bad as it sounds, “So what?” with someone not surviving costs less. One of the things they need to understand is what the cost and consequences are of some-
one who is not treated correctly for their disease with regard to hospitalization, doctor’s visits, medication, other modalities, and just exactly what is involved in that process so that they can better understand the “So what?”

Pierson: I think that’s an excellent observation, and in my discussion of the clinical effects, if you will, of chronic hypoxia, I should include the effects on the person, the effects on the family, and the effects on the health care system, because, in fact, chronic hypoxia extracts an enormous cost. This gets back to something Tom was saying about plopping those medical records down on the desk of the state health administrator. I think that’s a very well-made point.

Zielinski: David, you mentioned that you had no time to develop in detail as many items as you talked about. May I add some data on adaptation of Tibetans, who are the only population, I think, who adapted very well to the conditions of living at high altitude. It was found that Tibetans do not react to hypoxia with pulmonary vasoconstriction. Of course, it is very difficult to perform pulmonary catheterization in those people. Five young Tibetans—lifelong residents of Lhasa—agreed to have pulmonary artery catheterization with hemodynamic measurements taken at rest, breathing hypoxic mixture, and on exercise. At rest, pulmonary arterial pressure was perfectly normal (15 ± 1 mm Hg). Pulmonary vascular resistance was also normal. Breathing hypoxic mixture lowering their $P_{aO_2}$ 36 ± 2 mm Hg only slightly increased pulmonary vascular resistance. These data suggest that Tibetans lost hypoxic pulmonary vasoconstriction and remodeling common to lowlanders and residents of the Andes in South America. Also in China there is the High Altitude Medical Research Institute. Professor Tianyi Wu, director of the institute, had an opportunity to catheterize 3 or 4 healthy Tibetans. They also had normal pulmonary arterial pressure despite living at altitude of some 4,000 meters (personal communication). In a study comparing working capacity at high altitude of trained lowlanders and Sherpas, the latter showed superior work capacity. This was attributable to (1) economy of ventilation with preservation of normal blood pH, (2) a very high lung diffusing capacity for oxygen, and (3) a high cardiac output relative to work intensity. Lifelong Tibetan residents of Lhasa (3,658 m) had higher hypoxic ventilatory response and minute ventilation than acclimatized Han Chinese coming from lowlands.

REFERENCES


Spratt:* A question on the treatment of nocturnal hypoxemia. I believe right now the American Thoracic Society standards for chronic obstructive pulmonary disease suggest treatment only if you have signs and symptoms of cor pulmonale. From Fletcher’s work and from what we know from obstructive sleep apnea patients developing pulmonary hypertension, a part of the pulmonary hypertension is going to be irreversible. Are we waiting too late to treat those people if we’re waiting for signs and symptoms of cor pulmonale, and is there a way we can predict those patients who are more likely to develop those long-term problems so we can treat them earlier?

REFERENCES


Pierson: We thought that was such an important question that we devoted an entire presentation to it. Walter’s going to give that presentation, and I look forward to the answers to those questions.

---

*Greg Spratt, Rotech Medical Corporation, Kirksville, Missouri.