A 11-year-old African American male with sickle cell disease (SCD) was referred for evaluation of suspected sleep apnea. Nocturnal symptoms included restlessness, diaphoresis, snoring, kicking, and increased work of breathing. The family reported occasional excessive daytime sleepiness and napping after school. The patient had a history of vaso-occlusive crisis episodes requiring transfusion. Medications at the time of the study included methylphenidate (Metadate), hydroxyurea, penicillin V potassium (Pen VK), and folic acid.

Physical examination: Bilaterally enlarged tonsils

Laboratory study: Hematocrit 26%

Summary of sleep study results: Apnea-hypopnea index: 14.2 events per hour with 2 obstructive apneas, 2 central apneas, 87 hypopneas, and a minimum arterial oxygen saturation (SaO₂) of 84%. The 30-second tracing shown in Figure 1 was typical for non-rapid eye movement sleep (Figure 1).

Question: What is the explanation for the low SaO₂ during apparently stable breathing?

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The arterial oxygen saturation (SaO₂) is measured noninvasively by pulse oximetry (SpO₂) to detect arterial oxygen desaturation and hypoxemia. The SaO₂ is usually defined as the amount of oxyhemoglobin (O₂Hb) divided by the sum of the O₂Hb and the deoxygenated or reduced hemoglobin (RHb).

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\text{SaO}_2 \% = \frac{\text{O}_2\text{Hb}}{\text{O}_2\text{Hb} + \text{RHb}} \quad \text{(Equation 1)}
\]

At normal arterial oxygen levels, only a small amount of oxygen is dissolved in the blood and most of the oxygen-carrying capacity depends on the amount of hemoglobin bound to oxygen. However, determining the oxygen-carrying capacity of hemoglobin is complicated by the fact that both carboxyhemoglobin (COHb) and methemoglobin (MetHb) are forms of circulating hemoglobin that do not bind oxygen. The true fraction of hemoglobin bound to oxygen (FOHb) then depends on the fraction (%) of carboxyhemoglobin (FCOHb) and methemoglobin (FMetHb) as well as the fraction of reduced hemoglobin (FRHb).

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\text{FOHb} + \text{FRHb} + \text{FCOHb} + \text{FMetHb} = 100\% \quad \text{(Equation 2)}
\]

For example, if the FOHb = 85%, FCOHb = 8%, FMetHb = 1%, then the FRHb is 6%. Using these numbers, the SaO₂ equals 85 × 100/(85 + 6) or 93%, which is considerably higher than an FOHb of 85%. The FOHb and the amount of hemoglobin are the main determinants of the oxygen-carrying capacity of the blood. The difference between the SaO₂ and the FOHb is primarily determined by the amount of COHb and MetHb. The FOHb is sometimes called the fractional saturation, and the SaO₂ the functional or effective saturation.

The above 4 fractions of hemoglobin can be accurately measured by co-oximeters that measure the absorption of 4 or more wavelengths of electromagnetic radiation by a sample of arterial blood. This is possible because the 4 forms of hemoglobin differ in their absorption for the different wavelengths of radiation. In contrast, pulse oximetry uses only 2 wavelengths, 660 nm (red) and 940 nm (infrared) to measure the O₂Hb and RHb. The absorption of radiation at 660 nm is much greater with RHb than with O₂Hb, whereas O₂Hb absorbs more radiation at 940 nm (Figure 2A). Pulse oximetry is based on the empiric observation that the ratio (R) of absorbance at the 2 wavelengths is related to the oxygen saturation (Figure 2B). This relationship (calibration curve) is determined experimentally by determining R at varying oxygen saturations. To specifically determine the absorbance of arterial blood, the AC (pulse added absorbance) at each wavelength is divided by the DC (background absorbance) to account for the effect of the absorption of the radiation by venous blood and tissue. Carboxyhemoglobin has about the same absorbance at 660 as oxyhemoglobin and, if present, increases the measured SpO₂ value. In normal individuals, FCOHb is 2% or less but can be 8% or more in cigarette smokers. Patients with SCD often have FCOHb values of 4% or more due to production of carbon dioxide from chronic hemolysis. Based on a canine experiment, it has been estimated that a pulse oximeter sees COHb as 90% O₂Hb and 10% RHb. For example, from the following values (FOHb = 85%, COHb = 4%, MetHb = 0%, RHb = 11%), one can estimate the SpO₂ as 88.6% (85 + .9 × 4). This is essentially the same as the SaO₂ computed from equation 1 for these values. As noted below, SpO₂ measurements in patients with SCD who have carboxyhemoglobinemia often show fairly good agreement with the SaO₂ but overestimate the FOHb.

Inference about the arterial oxygen pressure (PaO₂) based on the SaO₂ requires a knowledge of the factors that can affect the oxyhemoglobin dissociation curve (Figure 3). The oxyhemoglobin dissociation curve is shifted to the right with increases in body temperature, PaCO₂, 2,3DPG (a product of glycolysis), or H⁺ ion concentration (acidemia). The opposite changes in the factors shift the curve to the left. CO can not only bind a portion of the Hb (preventing oxygen binding) but can shift the oxyhemoglobin dissociation curve of the remaining Hb to the left. Variant
hemoglobins can shift the position of the curve to the left or right from that associated with normal hemoglobin (Hb A). In dilute solution, sickle hemoglobin (HbS) has similar affinity for oxygen as hemoglobin A. (They differ by only a single peptide.) However, at the higher hemoglobin concentration present in red cells, deoxygenated sickle hemoglobin forms polymers that have a low affinity for oxygen. The net effect is a rightward shift in the oxyhemoglobin dissociation curve for Hb S (Figure 3). The position of the oxyhemoglobin dissociation curve is often defined by the P50, which is the PO2 corresponding to an SaO2 of 50%. For Hb A, the P50 is 26 mm Hg but is 42 to 56 mm Hg in patients with SCD. This means that, for a given SaO2, the PaO2 is higher in patients with SCD than would be expected based on the normal oxyhemoglobin dissociation curve. The amount of right shift varies considerably between patients with SCD and can be influenced by transfusion with blood (Hb A).

Given the similar structures of Hb A and Hb S, one might expect similar absorption at the wavelengths of electromagnetic radiation used for oximetry. A number of studies have assessed the ability of pulse oximetry (SpO2) to estimate the SaO2 and to detect hypoxemia in patients with SCD. In general, the SpO2 exceeds the FO2Hb but is fairly close to the SaO2. Craft and coworkers found that the SpO2 exceeded the FO2Hb by a mean of approximately 7%. Ortiz et al studied 22 patients with SCD admitted with a vaso-occlusive episode. The mean SpO2 exceeded the FO2Hb (90.4% vs 87.1%) but approximated the SaO2 (91.5%). In this study, the COHb was 3.8%, and the P50 was 35 mm Hg. Blaisdell et al found that 33% of a group of patients with SCD who were predicted to be hypoxemic with SpO2 measurements less than 93% actually had PaO2 values greater than 70 mm Hg. Bromberg and coworkers studied 9 patients with SCD with SpO2 values ranging from 75% to 90%, and none had an arterial PO2 less than 70 mm Hg.

In the current patient, an arterial blood gas was obtained at the end of the study while the patient was awake and breathing room air. The values were a pH of 7.44, a PaCO2 of 37 mm Hg, a PaO2 of 90 mmHg, and a HCO3 of 25.3 mMol/L. The SpO2 measurement at same time was 92%. Co-oximetry was not performed on the sample, but prior measurements had shown FCOHb and FMetHb values of 4% and 1%, respectively. Given the high PO2 corresponding to an SpO2 of 92%, one can conclude that the low SpO2 in Figure 1 was not due to hypoxemia but, rather, to the patient’s abnormal hemoglobin.

CLINICAL PEARLS

1. The SpO2 is often greater than the oxygenated fraction of hemoglobin as measured by a co-oximeter in patients with SCD (primarily due to elevated carboxyhemoglobin).
2. The oxyhemoglobin dissociation curve for hemoglobin S is shifted to the right, compared to hemoglobin A. Therefore, a given SaO2 corresponds to a higher PaO2 than would be predicted based on Hgb A.
3. Lower-than-normal SpO2 values during sleep in patients with SCD may not represent hypoxemia. If clinically indicated, an arterial blood gas can be obtained for precise determination of the arterial PO2.
4. In patients with significant amounts of carboxyhemoglobinemia, to accurately determine the fraction of hemoglobin that is bound to oxygen use co-oximetry of a sample of arterial blood rather than pulse oximetry.

REFERENCES