CLINICAL VIGNETTE

Hemoglobin Hammersmith as a Cause of Spurious Pulse Oximetry Measurements

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Introduction

Pulse oximetry is a simple noninvasive method used to estimate arterial blood oxygen saturation based on the difference in light absorbance of oxyhemoglobin and deoxyhemoglobin at red 660 nm and near-infrared 940 nm wavelengths.[1] Pulse oximetry is used extensively in both outpatient and inpatient settings and frequently recorded as the fifth vital sign. Beyond its application in the operating room, the pulse oximeter is widely used for monitoring during patient transport, drug or anesthesia administration, and home oxygen therapy.[2] Its universal usage is incumbent upon awareness of its limitations, especially as it applies to certain patient populations.

Medical personnel frequently possess a minimal understanding of how pulse oximetry works and are unaware of its limitations. Of note, asymptomatic patients with certain hemoglobinpathies, such as unstable hemoglobin disorders, may present with falsely low pulse oximetry readings. Physicians should be aware of the discrepancies between pulse oximetry measurements (SpO2) and true arterial oxygen content (SaO2) and consider unstable hemoglobinopathies when presented with these findings. This paper presents basic information on pulse oximetry's functions and limitations and the importance to consider hemoglobin variants in the differential diagnosis when encountering asymptomatic patients with low SpO2. The case highlights the marked discrepancy between SpO2 and SaO2 and the impact of certain hemoglobinopathies, especially unstable hemoglobin.

Patient History

A 40-year-old Chinese female with chronic congenital hemolytic anemia secondary to hemoglobin Hammersmith was seen in hematology for regular follow-up. She first presented at 9 months age with hepatosplenomegaly, jaundice, and hemolytic anemia. Evaluation in Taiwan revealed a hemoglobin of 8.0 g/dl, hematocrit of 25.5%, and reticulocyte count of 55.6%.[3] The impression was that the patient had thalassemia, though no definite diagnosis was made.

The patient was then evaluated at a Children's Hospital and given folic acid supplement and remained stable for two years, when a marked increase in spleen size was noted. She was reevaluated at another Children's Hospital with hepatosplenomegaly and a hemoglobin of 6.9 g/dl., indirect hyperbilirubinemia and left ventricular hypertrophy with mild T-wave abnormalities.

A diagnosis of hemoglobin Hammersmith was established when the patient was 4 years old. The variant was identified through fingerprints of amino-ethylated globin chains from hemolysate precipitates. The abnormality was isolated to the β-chain, in which a new βT-5 peptide was found below its normal position. Comparison of amino acids and peptide mapping revealed that the β42 phenylalanine residue in the abnormal chain was replaced by serine, indicating that the abnormal hemoglobin is Hb Hammersmith. Identification of the variant was re-confirmed by high-performance liquid chromatography of the globin chains and analysis of the tryptic peptides.[3]

She underwent splenectomy and her hemoglobin level has since remained stable rarely required transfusions.

The patient had been seen multiple times at hematology clinic with extremely low SpO2, even though she was asymptomatic. During a recent inpatient cardiac evaluation, her SpO2 measured 54%, but spectrophotometry confirmed her oxygen saturation to be at least 90%. At the time of her latest clinic visit. The patient was in her usual state of health with a temperature of 36.4 degrees Celsius, pulse rate of 63, blood pressure of 120/79 and SpO2 52%. She was alert and showed no signs of respiratory distress. She was noted to be jaundiced with holosystolic murmur on a cardiac exam. The remainder of her physical was unremarkable.

Discussion

Pulse Oximetry: Pulse oximetry measurements are based on the differential absorption of red and near-infrared light (IR) light by oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb). O_2Hb absorbs greater amounts of near-IR light and lesser amounts of red light than HHb, consistent with the brighter red appearance of O_2Hb compared to that of HHb. Pulse oximeters take advantage of this differential absorption by transmitting red 660 nm and near-IR 940 nm light through the finger. The relative amount of absorbed red and near-IR light is then used to calculate the portion of Hb bound to oxygen.[1]

The pulse oximeter can detect arterial blood oxygen content because of pulsatile fluctuations in the amount of red and IR light absorption during the cardiac cycle. Arterial blood volume increases during systole and decreases during diastole, while venous and capillary blood volumes remain relatively consistent. The light that is emitted by the pulse oximeter creates

signals with a stable "direct current" (DC) component and a pulsatile "alternating current" (AC) component. The absorption amplitude of emitted light is then used to calculate the Red:IR Modulation ratio (R):

$$R = \frac{\frac{A_{red,AC}}{A_{red,DC}}}{\frac{A_{IR,AC}}{A_{IR,DC}}}$$

where A = absorbance. In summary, R is a ratio of pulsatile and non-pulsatile components of red light and IR absorbance. R is used to determine SpO2 using a curve calibrated to measurements collected from healthy volunteers, ranging from 70% to 100%.[1] Consequently, SpO2 < 70% are unreliable measurements, though it is unlikely that differences in values below this threshold would significantly change clinical decision-making.

Inaccurate SpO2 measurements in pulse oximetry: Because the Red:IR Modulation ratio is calculated based on a sample of healthy volunteers, there exist inherent limitations to the accuracy of pulse oximetry measurements. Inaccurate measurements can generally be separated into three categories: falsely normal or elevated SpO2, falsely low SpO2, or conditions that could result in either falsely low or high SpO2. Table 1 summarizes the common causes of an inaccurate SpO2 reading.

Falsely normal or elevated SpO2: Carbon monoxide poisoning and sickle cell anemia vaso-occlusive crises are two common causes of falsely normal or high oximetry readings, Carbon monoxide poisoning can cause inaccurate oximetry readings because COHb absorbs red light similarly to O2Hb and absorbs little infrared light, making it difficult for the oximeter to differentiate between COHb and O2Hb.[1] The utility of pulse oximetry in monitoring the oxygen levels of a patient with sickle cell anemia has also been debated. In a vaso-occlusive crisis, pulse oximeters have been found to overestimate fractional O2Hb (*F*O2Hb) content and underestimate SaO2. These differences in measurement are posited to become more significant in vaso-occlusive crises,[1] prompting physicians to be cognizant of these discrepancies when detecting hypoxia in sickle cell patients.

Falsely low or high SpO2: Physicians should consider methemoglobinemia on their differential diagnosis when encountering a patient who appears cyanotic. Methemoglobin absorbs light similarly to HHb, and patients can appear cyanotic as a result. Furthermore, because methemoglobin absorbs red and infrared light equally well, R can approach 1, which equivocates to a SpO2 of 80-85%. Patients with high levels of methemoglobin will have a SpO2 approaching 85%, leading to either an over- or underestimation of true oxygen saturation depending on their state of hypoxemia. Sulfhemoglobin affects SpO2 similarly, though the clinical consequences of sulfhemoglobinemia are milder than that of methemoglobinemia.

Finally, there has been debate on how sepsis and septic shock affect SpO2 readings. SpO2 and SaO2 readings of 80 patients with septic shock show that in those with low systemic vascular resistance, SpO2 underestimated SaO2. These findings have been supported by further human studies. In contrast, a retrospective review of 88 patients with severe sepsis found that SpO2 overestimated SaO2, suggesting that multiple variables are at play, making it difficult to predict how SpO2 will be affected in septic patients.

Falsely low SpO2: Many conditions, can be responsible for falsely low SpO2. Hemoglobinopathies, a common cause of spurious hypoxemia, will be discussed in a later section. Other causes such as venous pulsations from an oximeter that is attached too tightly or dark fingernail polish can both impact pulse oximetry readings.[1] Excessive movement from tremor or convulsions can cause SpO2 readings to dip to below 50%, though improvements to pulse oximeter algorithms may reduce the significance of these problems.[3] Intravenous dyes can also impact the accuracy of readings. For example, methylene blue, used for the treatment of methemoglobinemia, has a red absorption spectrum very similar to that of HHb, resulting in readings that suggest low oxygen saturation. Indocyanine green and indigo carmine pigments can also cause falsely low SpO2, though they only cause minor decreases in SpO2 as they do not greatly absorb red light.

Falsely normal or elevated SpO_2	**Falsely low SpO_2**	**Falsely low or high SpO_2**
• Carbon monoxide poisoning • Sickle cell anemia vaso-occlusive crises	• Venous pulsations • Excessive movement (e.g. convulsions, tremor) • Intravenous pigmented dyes • Inherited abnormal hemoglobin • Dark fingernail polish • Severe anemia (with concomitant hypoxemia)	• Methemoglobinemia • Sulfhemoglobinemia • Poor probe positioning • Sepsis, septic shock

Table 1. Common causes of spurious SpO_2 measurements.[4]

Oximeter Error in Hemoglobinopathies: Hemoglobinopathies, which have an overall incidence of 7% in the world, can affect the hemoglobin molecule's ability to efficiently carry oxygen, resulting in an abnormal oxygen affinity curve.[5] Though many variants have normal matching SpO2 and SaO2 readings, it is

not infrequent for hemo-globinopathies to present with aberrant scenarios, including 1) high SpO2 and low SaO2, 2) low SpO2 and SaO2, and 3) low SpO2 and normal SaO2, as seen in our patient. These differences in oximetry readings and oxygen saturation have even raised the possibility of using pulse oximetry in screening for hemoglobinopathies in certain populations.

Many variant hemoglobinopathies that cause abnormal SpO2 readings have already been identified, several of which are unstable variants.[4] Unstable hemoglobinopathies are caused by a substitution or deletion of an amino acid from the hemoglobin molecule. Over 200 variants have been identified and are inherited in an autosomal dominant inheritance pattern.[4] Unstable hemoglobinopathies typically are associated with spurious pulse oximetry readings.

Hemoglobin Hammersmith is one such unstable hemoglobinopathy caused by a substitution of Phe → Ser at the 42nd position on the beta chain, causing hemolytic Heinz body anemia.[6] Typical manifestations of this hemoglobin variant include neonatal hyperbilirubinemia and progressive hepatosplenomegaly, jaundice, and bilirubinuria. Hemoglobin Hammersmith has also been associated with spuriously low O_2 saturation as determined by pulse oximetry. Of note, all documented cases have had low SpO2 with normal SaO2. Lang et al describe a female patient with Hb Hamm whose SpO2 during an operation measured 45% on room air and 60% on 100% oxygen ventilation; arterial blood gas analysis revealed a PaO2 of 418mmHg.[7] Tuohy et al describe a pair of African-American twins diagnosed with Hb Hamm with low SpO2.[8] Furthermore, two other unstable hemoglobin variants, hemoglobin Cheverly and hemoglobin Koln, have been associated with falsely low measurements.[8,9] These variants may have been registered by the pulse oximeter as deoxyhemoglobin, contributing to low values.

Conclusion

Pulse oximeters, while generally useful in estimating oxygen saturation in patients, have limited applicability in many situations. An inaccurate interpretation of spurious results could lead to errant clinical decision-making and unnecessary patient anxiety. Because of its ubiquitous use, physicians should be aware of these limitations and the differential diagnoses, when managing patients with low pulse oximetry measurements. They should consider alternative methods such as arterial blood gas analysis to confirm oximeter readings. Our case was chosen to illustrate a common cause of spurious oximetry readings, that of hemoglobinopathies and especially patients with unstable hemoglobin. The marked discrepancy between SpO2 and SaO2 in this patient highlights the complexities in interpreting oximeter readings in everyday use. Finally, a spuriously low SpO2 measurement should encourage physicians to consider hemoglobinopathies on their list of differential diagnoses.

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