

Pulse Oximetry Is a Poor Predictor of Hypoxemia in Stable Children With Sickle Cell Disease

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Objective: To evaluate the accuracy of the pulse oximeter to detect hypoxemia in patients with sickle cell disease in an ambulatory care setting.

Study Design: Simultaneous measurements of PaO₂, arterial oxygen saturation by co-oximetry (criterion standard), and pulse oximetry were performed in 21 children with sickle cell disease during 22 outpatient visits. The bias and precision of the pulse oximeter compared with measured arterial oxygen saturation by co-oximetry were determined. The sensitivity, specificity, and positive and negative predictive values of the pulse oximeter to detect hypoxemia (PaO₂ <70 mm Hg) were also calculated.

Results: The mean difference between pulse oximetry and measured oxygen saturation (bias) was 5.0% and the SD (precision) was 5.3. Twenty-one patients had a PaO₂ greater than 70 mm Hg; 7 of these (33%) were predicted to be hypoxic by pulse oximetry with values less than 93%, for a specificity to detect normoxia of 67%.

Conclusion: Making treatment decisions based on pulse oximetry data alone in patients with sickle cell disease who are not acutely ill may be inappropriate.

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LUNG DISEASE in individuals with sickle hemoglobin is responsible for significant morbidity and mortality.¹ Acute chest syndrome (ACS), characterized by fever and new infiltrates on chest radiograph, is the second most common cause of hospitalization in patients with sickle cell disease and causes 25% of deaths. Repeated episodes of ACS are associated with development of chronic lung disease, with progressive hypoxemia and decreased survival.¹ Alternatively, hypoxemia may predispose to development of ACS.

Difficulties exist, however, in the evaluation of hypoxemia in patients with sickle cell anemia. Before the widespread adoption of pulse oximetry, PaO₂ by blood gas monitoring had been the standard for evaluating hypoxemia. The criterion standard for measuring arterial oxygen saturation (SaO₂) is analysis of an arterial blood sample by co-oximetry, which measures fractional SaO₂ (oxyhemoglobin as a proportion of total hemoglobin, including nonfunctional hemoglobins such as carboxyhemoglobin and methemoglobin). Although the co-oximeter was the criterion standard used to validate pulse oximeter

devices in healthy populations, it is infrequently used clinically. In most clinical situations, oxygen saturation is not directly measured from an arterial blood sample but is calculated using a normal oxyhemoglobin dissociation curve from the PaO₂.

Pulse oximetry is a convenient, in vivo, noninvasive technique for measuring oxygen saturation. It combines the principles of spectrophotometry with those of photoelectric plethysmography to determine the oxygen saturation of hemoglobin.² Oxygen saturation is determined by the ratio of oxyhemoglobin to the sum of oxyhemoglobin and reduced hemoglobin. Pulse oximeters perform optical measurements at only 2 wavelengths of light to discriminate oxygenated and deoxygenated hemoglobin. Carboxyhemoglobin and methemoglobin also absorb light at the wavelengths measured by the pulse oximeter and, if abundant, can affect the accuracy of the pulse oximeter.² These devices were calibrated using healthy volunteers with insignificant amounts of dysfunctional hemoglobins.³

Pulse oximetry is widely used to assess arterial oxygenation. It provides a useful estimate of hypoxia, in which oxygen

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PATIENTS AND METHODS

Twenty-one patients with documented sickle cell hemoglobinopathy (Hb SS only) were evaluated during routine outpatient visits (N = 22) to the Pediatric Hematology or Pulmonary clinics at Johns Hopkins Hospital, Baltimore, Md, an inner-city university teaching hospital, between March 1, 1992, and April 30, 1998. Patients were clinically well at the time of the study. Their ages ranged from 3 to 18 years (mean, 10.9 years); 9 were girls and 12 were boys. No patient was receiving long-term transfusion therapy. All measurements were made while the patient was breathing room air.

Oxygen saturations by pulse oximetry (SpO_2) were recorded by one of us (K.C.) using a Criticare 504-US pulse oximeter (Criticare, Waukesha, Wis) after at least 2 minutes of stable SpO_2 determined in the presence of a regular pulsatile photoplethysmography signal apparent on the visual display of the oximeter. Arterial blood samples were drawn in sterile fashion by the same skilled investigator (K.C.). Blood samples were transported on ice to a blood gas analyzer with a built-in co-oximeter (Radiometer ABL 520; Westlake, Ohio), and arterial oxygen saturation and blood gas analyses were performed within 10 minutes; SaO_2 , pH, $PaCO_2$, and PaO_2 values were recorded.

For each patient, we computed the difference between SpO_2 and SaO_2 and reported the frequency of distribution of these differences, the bias (mean difference between SpO_2 and SaO_2), and the precision (SD).

We also plotted SpO_2 with PaO_2 for each individual to determine the ability of pulse oximetry to detect hypoxemia. Low oxygen saturation was defined as less than 93% because this would predict a PaO_2 less than 70 mm Hg based on a normal oxyhemoglobin curve. We chose this value because hypoxemia with a PaO_2 less than 70 mm Hg has been associated with significant chronic lung disease and is associated with development of right ventricular hypertrophy in patients with sickle hemoglobin. To evaluate the accuracy of the pulse oximeter to detect hypoxemia, we determined the sensitivity (the percentage of patients with an $SpO_2 < 93\%$ and a $PaO_2 < 70$ mm Hg of all patients with a $PaO_2 < 70$ mm Hg), specificity (the percentage of patients with an $SpO_2 > 93\%$ and a $PaO_2 > 70$ mm Hg of all patients with a $PaO_2 > 70$ mm Hg), positive predictive value (the percentage of patients with a $PaO_2 < 70$ mm Hg of all patients with an $SpO_2 < 93\%$), and negative predictive value (the percentage of patients with a $PaO_2 > 70$ mm Hg of all patients with an $SpO_2 > 93\%$).

saturations of less than 93% predict a PaO_2 less than 70 mm Hg. The pulse oximeter has been validated in various cohorts of patients with presumably "normal" hemoglobins, such as neonates, and in patients with cyanotic heart disease.⁴ However, its validity in patients with hemoglobinopathies has not been evaluated, to our knowledge. The PaO_2 at which the oxygen saturation is 50% (P50) is 26.5 mm Hg in individuals with normal hemo-

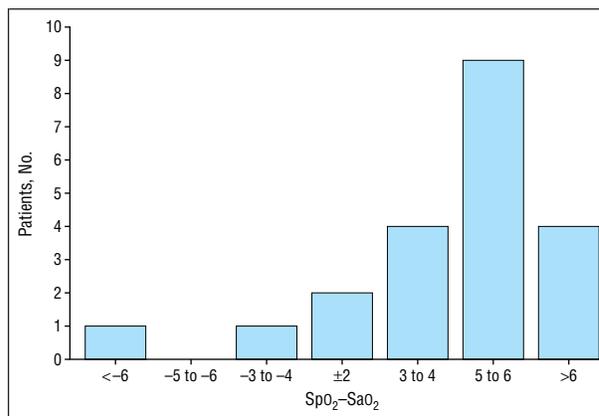


Figure 1. Frequency of distribution of the difference between oxygen saturations by pulse oximetry (SpO_2) and measured by co-oximetry (arterial oxygen saturation [aO_2]) in individual patients with sickle cell disease. The expected bias (mean difference between SpO_2 and SaO_2) of the pulse oximeter in healthy populations is 2%, and the expected precision (SD) of the pulse oximeter is 2. Thirteen of 22 SpO_2 measurements were 2 SDs or more than SaO_2 measurements. The bias for this study of outpatients with sickle hemoglobin is 5.0%, and precision is 5.3.

globin. The oxygen dissociation curves of patients with sickle cell disease tend to be right shifted.⁵ The presence of sickle cell anemia increases the P50 to 35 to 50 mm Hg.⁶ Therefore, in patients with sickle cell anemia, a measurement of oxygen saturation is not predictive of the same PaO_2 values as in patients with normal oxyhemoglobin dissociation. This discrepancy seems to have been overlooked in previous studies of pulse oximetry in patients with sickle cell disease. This raises the following question: Is pulse oximetry an appropriate tool to define hypoxemia in this population?

A retrospective review⁷ of simultaneous pulse oximetry and arterial blood gas analysis data obtained from patients with sickle cell disease in the emergency department suggested that the pulse oximeter did not predict hypoxemia well. Because of the possibility that illnesses causing emergency department visits might have affected these measurements, we decided to evaluate prospectively the accuracy of the pulse oximeter to detect hypoxemia in patients with sickle hemoglobinopathies at baseline during outpatient visits. Treatment might be considered for these patients to prevent long-term complications of chronic hypoxemia.

RESULTS

In this study of patients with sickle cell disease, the bias was 5.0% and the precision was 5.3. The difference between SpO_2 and SaO_2 was greater than 4% in 13 of 22 measurements > 2 SD of the expected precision of 2%.^{4,8} (Figure 1). Only 1 SpO_2 measurement was more than 4% lower than the SaO_2 .

Twenty-one patients with 22 outpatient visits were normoxic by $PaO_2 (> 70$ mm Hg) (Figure 2). The reference oxyhemoglobin curve is presented for comparison. The oxyhemoglobin curve is shifted to the right in many patients with sickle cell disease, and there is wide variability. Only 14 measurements were predicted to be normoxic by pulse oximetry, so specificity of pulse oximetry was only 67% (95% confidence interval, 45%-86%). Because the incidence of hypoxia by blood gas analysis

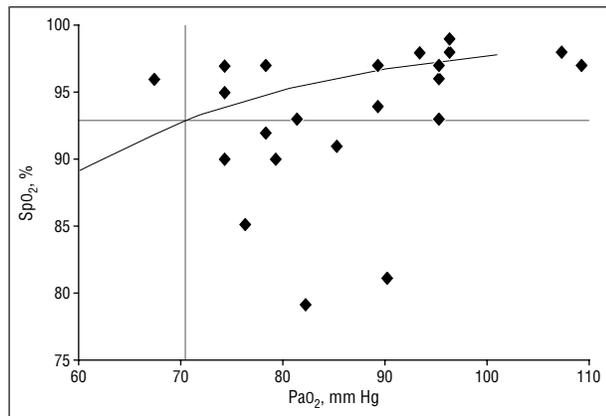


Figure 2. Plot of simultaneous oxygen saturation by pulse oximetry (SpO_2) and PaO_2 in individuals with sickle cell disease. The curve depicts the normal oxyhemoglobin relation (the PaO_2 at which the oxygen saturation is 50% = 26.5 mm Hg) defining the expected PaO_2 for a given oxygen saturation. The cross bars depict the ability of pulse oximetry to identify hypoxemia if defined by an SpO_2 less than 93% and a PaO_2 less than 70 mm Hg. The negative predictive value of a pulse oximetry reading greater than 93% was 94% (95% confidence interval, 70%-99%).

was so low, inferences about the sensitivity of the pulse oximeter to detect hypoxia and positive predictive value could not be made. The negative predictive value of a pulse oximetry reading of 93% or higher was 94% (95% confidence interval, 70%-99%). Because the prevalence of a PaO_2 less than 70 mm Hg was only 4%, the negative predictive value should be interpreted with caution.

COMMENT

Pulse oximetry in clinically stable patients with sickle cell disease evaluated in an outpatient setting had poor specificity in detecting hypoxemia. Many more patients would have been considered hypoxic based on pulse oximetry measurements alone than were actually hypoxic enough to require intervention. Pulse oximeters have been validated in healthy, nonsmoking individuals³ and have an expected bias of 2% (mean difference between SpO_2 and SaO_2) and precision (SD) of 2.^{4,8} Pulse oximetry measurements in patients with sickle cell anemia in this study had a bias of 5.0% and precision (SD) of 5.3.

The interpretation of pulse oximetry data in patients with sickle cell anemia is problematic for several reasons. This instrument is often used as a surrogate for arterial measurements of PaO_2 . Pulse oximetry is reasonably accurate for this purpose in patients with normal oxygen dissociation curves. For example, an oxygen saturation of 95% predicts a PaO_2 of 80 mm Hg; an oxygen saturation of 93% predicts a PaO_2 of 70 mm Hg, and an oxygen saturation of 90% predicts a PaO_2 of 60 mm Hg. Clinical judgments are based on the assumption of a normal P50 of 26.5 mm Hg. Because patients with sickle hemoglobin can have significant right shift of the oxyhemoglobin curves, estimates of PaO_2 based on pulse oximetry can be grossly inaccurate. In this sample of children with sickle cell disease evaluated as outpatients, SpO_2 of less than 93% poorly predicted hypoxemia ($PaO_2 < 70$ mm Hg), suggesting that, if used as a marker for therapeutic intervention (ie, supplemental oxygen therapy or

tonsillectomy for suspected obstructive sleep apnea syndrome), patients with sickle cell disease may be overtreated.

Several studies have evaluated the accuracy of pulse oximetry in patients with sickle cell anemia. One of the first studied only 3 patients at the time of 4 hospitalizations.⁹ The authors concluded that pulse oximetry can be used to detect the degree of shift of an oxyhemoglobin curve for an individual with sickle hemoglobin, but they did not describe its use as a tool to detect hypoxemia (low PaO_2). Several investigators^{10,11} have compared pulse oximetry to calculated arterial oxygen saturations based on a normal P50 from a blood gas sample. Although investigators^{9,12} have concluded that SpO_2 accurately predicted oxygen saturations calculated from patients' oxygen dissociation curves derived from venous samples, they did not measure arterial oxygen saturations to determine the bias and precision of this device in patients with sickle hemoglobin. Failure to account for the right shift of the hemoglobin dissociation curve in sickle cell disease might have erroneously affected the interpretations of both of these studies.

Unlike co-oximeters, carboxyhemoglobin and methemoglobin also absorb light at the 2 wavelengths analyzed, but they cannot be readily distinguished from oxyhemoglobin and deoxyhemoglobin by pulse oximetry.¹³ This limitation is not problematic for most patients assessed by pulse oximetry; however, patients with sickle hemoglobin may have considerable amounts of carboxyhemoglobin and methemoglobin.¹⁴ When these hemoglobin species are abundant, the pulse oximeter might falsely overestimate arterial saturation. Consistent with our data, previous investigators^{14,15} have found that pulse oximetry tends to overestimate measured arterial saturations.

Several investigators have attempted to correlate pulse oximetry measurements with severity of disease.^{12,16,17} Rackoff et al¹² used pulse oximetry in a group of acutely ill patients with sickle cell disease in the emergency department to predict the probability of an ACS. Only 5 of 32 patients had an SpO_2 less than 96% and more than 3 points lower than their SpO_2 when well. The predictive value of a low SpO_2 and developing ACS was 47%. The predictive value of a low SpO_2 to detect hypoxemia ($PaO_2 < 70$ mm Hg) was not determined in this study. Patients may be referred for management of an evolving crisis and treated with transfusions and supplemental oxygen based on a diagnosis of "hypoxemia" made by pulse oximetry.

A review⁷ of the records of 19 patients with sickle cell disease who sought medical care in the emergency department from February 1, 1987, to January 31, 1991, examined the ability of pulse oximetry to predict PaO_2 . There were 93 simultaneous pulse oximetry (SpO_2) and PaO_2 data. An SpO_2 less than 95% as a predictor of a PaO_2 less than 80 mm Hg had a sensitivity of 80% and a specificity of 75%. The positive predictive value was 53%, and the negative predictive value was 91%. These data are consistent with our study of oximetry in patients with sickle cell disease in an outpatient setting. We suggest, based on our findings, that pulse oximetry is not a good predictor of hypoxemia in

patients with sickle cell disease when they are well, and it might not be useful in acute settings if the prevalence of hypoxemia is low.

Treatment of apparent hypoxemia based on pulse oximetry alone (when PaO₂ is actually >70 mm Hg) could be inappropriate, unnecessary, and even dangerous (suppression of erythropoiesis). If a child with sickle cell disease has an SpO₂ less than 93%, an arterial blood gas analysis is needed to validate the result before any therapeutic decisions are made to start supplemental oxygen therapy. Furthermore, there are no data to suggest that the relation between the oxygen saturation and PaO₂ (the P50) is static in an individual with sickle hemoglobin, so further studies of these relations when patients are well and acutely ill should be pursued. In addition, these data suggest that a normal SpO₂ might not require further evaluation. However, because numbers were small, this should be confirmed in larger and more diverse sickle cell populations. In summary, there are multiple sources of potential error in pulse oximetry when used in individuals with sickle hemoglobin, which should be considered when a patient is evaluated for hypoxemia. These data suggest that making treatment decisions based on pulse oximetry data alone in patients with sickle cell disease who are not acutely ill might be inappropriate; correlation of abnormal pulse oximetry values with arterial blood gas determination of PaO₂ and SaO₂ seems to be essential.

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REFERENCES

1. Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine (Baltimore)*. 1988;67:66-76.
2. Hay WWJ, Thilo E, Curlander JB. Pulse oximetry in neonatal medicine. *Clin Perinatol*. 1991;18:441-472.
3. Yelderman M, New WJ. Evaluation of pulse oximetry. *Anesthesiology*. 1983;59:349-352.
4. Poets CF, Southall DP. Noninvasive monitoring of oxygenation in infants and children: practical considerations and areas of concern. *Pediatrics*. 1994;93:737-746.
5. Becklake MR, Griffiths SB, McGregor M, Goldman HI, Schreve JP. Oxygen dissociation curves in sickle cell anemia and in subjects with the sickle cell trait. *J Clin Invest*. 1955;34:751-755.
6. Seakins M, Gibbs WN, Milner PF, Bertles JF. Erythrocyte Hb-S concentration: an important factor in the low oxygen affinity of blood in sickle cell anemia. *J Clin Invest*. 1973;52:422-432.
7. Goepf J, Murray C, Walker A, Simone E. Oxygen saturation by pulse oximetry in patients with sickle cell disease: lack of correlation with arterial blood gas measurements [abstract]. *Pediatr Emerg Care*. 1991;7:387.
8. Technology Subcommittee of the Working Group on Critical Care, Ontario Ministry of Health. Noninvasive blood gas monitoring: a review for use in the adult critical care unit. *CMAJ*. 1992;146:703-712.
9. Weston-Smith SG, Glass UH, Acharya J, Pearson TC. Pulse oximetry in sickle cell disease. *Clin Lab Haematol*. 1989;11:185-188.
10. Comber JT, Lopez BL. Evaluation of pulse oximetry in sickle cell anemia patients presenting to the emergency department in acute vaso-occlusive crisis. *Am J Emerg Med*. 1996;14:16-18.
11. Pianosi P, Charge TD, Esseltine DW, Coates AL. Pulse oximetry in sickle cell disease. *Arch Dis Child*. 1993;68:735-738.
12. Rackoff WR, Kunkel N, Silber JH, Asakura T, Ohene-Frempong K. Pulse oximetry and factors associated with hemoglobin oxygen desaturation in children with sickle cell disease. *Blood*. 1993;81:3422-3427.
13. Ralston AC, Webb RK, Runciman WB. Potential errors in pulse oximetry, III: effects of interferences, dyes, dyshaemoglobins and other pigments. *Anaesthesia*. 1991;46:291-295.
14. Craft JA, Alessandrini E, Kenney LB, et al. Comparison of oxygenation measurements in pediatric patients during sickle cell crises. *J Pediatr*. 1994;124:93-95.
15. Ortiz FO, Aldrich TK, Nagel RL, Benjamin LJ. Accuracy of pulse oximetry in sickle cell disease. *Am J Respir Crit Care Med*. 1999;159:447-451.
16. Samuels MP, Stebbens VA, Davies SC, Picton-Jones E, Southall DP. Sleep related upper airway obstruction and hypoxaemia in sickle cell disease. *Arch Dis Child*. 1992;67:925-929.
17. Brooks LJ, Koziol SM, Chiarucci KM, Berman BW. Does sleep-disordered breathing contribute to the clinical severity of sickle cell anemia? *J Pediatr Hematol Oncol*. 1996;18:135-139.