Pulse Oximetry and Factors Associated With Hemoglobin Oxygen Desaturation in Children With Sickle Cell Disease

By Wayne R. Rackoff, Nanette Kunkel, Jeffrey H. Silber, Toshio Asakura, and Kwaku Ohene-Frempong

The observation of low transcutaneous arterial oxygen saturation (SaO₂) in otherwise well sickle cell patients has lead to questions about the interpretation of pulse oximetry values in these patients. We undertook a prospective study of children with sickle cell disease to (1) determine the prevalence of, and factors associated with, low transcutaneous SaO₂ in clinically well patients, (2) develop an algorithm for the use of pulse oximetry in acutely ill patients, and (3) assess the accuracy of pulse oximetry in these patients. Eighty-six clinically well children with hemoglobin (Hb) SS had a lower mean transcutaneous SaO₂ than 22 Hb SC patients and 10 control subjects (95.6% vs 99.1% vs 99.0%, respectively; \( P < .001 \)). In Hb SS patients, a history of acute chest syndrome and age greater than 5 years were associated with lower transcutaneous SaO₂ (mean 93.8% for those with a history of acute chest syndrome vs 97.8% for those without a history of acute chest syndrome, and 94.0% for patients > 5 years old vs 97.2% for those ≤5 years old; \( P < .001 \)). These associations were not seen in Hb SC patients. During acute illness, Hb SS patients with acute chest syndrome had transcutaneous SaO₂ values that were less than 96% and at least 3 points lower than measurements made when they were well. A nomogram was designed to aid in the interpretation of transcutaneous SaO₂ in acutely ill Hb SS patients when a comparison value is not available. The accuracy of pulse oximetry was shown by the correlation between SaO₂ measured by pulse oximetry and calculated by using the patient’s oxygen dissociation curve and PaO₂ \( (r = .97) \). This study provides evidence that Hb oxygen desaturation is not a universal finding among children with sickle cell disease and identifies factors associated with Hb oxygen desaturation. We conclude that pulse oximetry may be useful to assess whether progressive pulmonary dysfunction begins at an early age in Hb SS patients, and to assess acutely ill patients for the presence of hypoxemia associated with acute chest syndrome.

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MATERIALS AND METHODS

Study population. Patients with Hb SS or Hb SC who were ≤18 years of age were eligible for study. This study was approved by the Institutional Review Board of The Children’s Hospital of Philadelphia. At the time of enrollment in the study, informed consent was obtained from the patient’s parents and, when appropriate, the patient. Specimens were obtained only at the time of clinically indicated venipuncture or arterial sampling.

Patients were enrolled at the time of routine hematologic or emergency department visits at The Children’s Hospital of Philadelphia between January 15, and September 15, 1991. Twenty-seven percent of Hb SS and 23% of Hb SC patients enrolled in the Comprehensive Sickle Cell Center at The Children’s Hospital of Philadelphia were enrolled in this part of the study. The ratio of Hb SS to Hb SC patients enrolled in the study was not significantly different from the patient population of the center \( (P = .66) \). Patients’ resting pulse oximetry values and medical history, including major complications of sickle cell disease, were recorded. During the first 3 months of the study, patients who were due for their yearly laboratory evaluation had an additional 0.5 to 1.0 mL of venous blood drawn for determination of the oxygen dissociation curve and 2,3-diphosphoglycerate level. Patients without a history of hemoglobinopathy, anemia, or pulmonary disease were recruited to serve as control subjects for these studies.

Patients were also enrolled in the emergency department at the time of visits for acute illness. A medical history, including the presence of respiratory signs and symptoms and pain, and laboratory data were recorded by the examining physician on a standard form. Oxygen dissociation curves were measured in a subset of Hb patients.
SS patients. Arterial blood gases were measured at the discretion of the examining physician.

Pulse oximetry. All patients were studied using one of two pulse oximeters (Model N-200; Nellcor, Hayward, CA). The appropriate sensor was placed on the right index finger of older patients or the right big toe of infants. The transcutaneous SaO$_2$ was recorded when a steady pulse and oxygen saturation read-out were obtained. The pulse oximeters in the emergency department and clinic were compared using 26 normal adult volunteers; no pair of values was greater than 1 point different.

Oxygen dissociation curve, 2,3-diphosphoglycerate, and Hb F. Oxygen dissociation curves were measured at 37°C and pH 7.40 by the continuous dual-spectrophotometric technique previously described by Asakura. Specimens were preserved in EDTA, and kept on ice until they were tested; oxygen dissociation curve measurements were made within 8 hours of specimen collection. Quantitative 2,3-diphosphoglycerate levels were measured using the method of Rose and Leibowitz. Hb F levels were determined by the alkali denaturation method.

Statistical analysis. Independent samples and paired t-tests were used to compare the means of continuous, normally distributed variables. All statistical tests were two-tailed. Means with Hb SC or control subjects (Table 1). All Hb SC patients had transcutaneous SaO$_2$ values that were in the normal range (96% to 100%), whereas 44.2% of Hb SS patients had transcutaneous SaO$_2$ values lower than 96%.

In the Hb SS patients, a past history of acute chest syndrome and age greater than 5 years were associated with lower mean transcutaneous SaO$_2$ values (Table 1). These associations were not seen in clinically well Hb SC patients (Table 1). In multivariate regression analysis, both a history of acute chest syndrome and older age were associated with lower transcutaneous SaO$_2$ in Hb SS patients ($P < .01$ for both coefficients). The effect of a history of acute chest syndrome was significant despite long intervals since the last episode (median, 10 months).

The effect of Hb F level was examined for 52 of the 86 Hb SS patients on whom data were obtained at study entry. As expected, Hb F levels were significantly higher in those ≤5 years old (mean, 18.1% ± 12.7%; n = 24) than in patients older than 5 years (mean, 7.6% ± 6.5%; n = 8; $P < .001$). The Hb F levels of patients with a history of acute chest syndrome (mean, 9.9% ± 8.4%; n = 30) were significantly lower than those without a history of acute chest syndrome (mean, 15.8% ± 13.4%; n = 22; $P = .008$). The effects of age, acute chest syndrome history, and Hb F level on transcutaneous SaO$_2$ were examined in a multivariate regression analysis; a history of acute chest syndrome was associated with lower transcutaneous SaO$_2$ ($P = .007$), lower Hb F levels were associated with lower transcutaneous SaO$_2$ ($P = .012$), and the effect of age on transcutaneous SaO$_2$ was not significant ($P = .459$) when Hb F level was included in the model.

Oxygen dissociation curves were measured in 32 of the 86 clinically well Hb SS patients, 12 of the 22 clinically well Hb SC patients, and 10 control subjects. As shown in Fig 1, the curves for Hb SS patients were right-shifted when compared with those of Hb SC patients and control subjects (compared at PO$_2$ equal to 70, 80, and 90 mm Hg; $P < .001$). As a result of this shift, lower Hb oxygen saturation values represent higher PaO$_2$ values than would be predicted by a normal oxygen dissociation curve. Although the curves of Hb SC patients are right-shifted when compared with those of control subjects, the difference is not significant. This is despite the fact that the mean 2,3-diphosphoglycerate level for Hb SC patients was significantly higher than that of control subjects (5,634.2 ± 844.0 nmol/mL red blood cells [RBC] vs 4,370 ± 392.1 nmol/mL RBC; $P < .05$) and similar to Hb SS patients (5,789.0 ± 703.3 nmol/mL RBC).

A lower Hb level is usually associated with a higher 2,3-diphosphoglycerate level and a more right-shifted oxygen dissociation curve. When the oxygen dissociation curve is

### Table 1. Transcutaneous SaO$_2$ Values in Clinically Well Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>All</th>
<th>ACS</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Values</td>
<td>No History</td>
<td>History</td>
</tr>
<tr>
<td>Hb SS</td>
<td>95.6 ± 3.8*</td>
<td>97.8 ± 2.3</td>
<td>93.8 ± 3.9†</td>
</tr>
<tr>
<td></td>
<td>(86)</td>
<td>(40)</td>
<td>(46)</td>
</tr>
<tr>
<td>Hb SC</td>
<td>99.1 ± 0.9</td>
<td>99.1 ± 1.0</td>
<td>99.1 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>(22)</td>
<td>(12)</td>
<td>(10)</td>
</tr>
<tr>
<td>Control</td>
<td>99.0 ± 0.8</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Values are mean transcutaneous SaO$_2$% ± 1 SD (n).

* Kruskal-Wallis test $P < .001$; Hb SS significantly different from Hb SC and control by Dunn procedure, $a = 0.05$.
† $P < .001$ for no history of ACS versus history of ACS and ≤5 years versus >5 years.
‡ $P = .459$.
right-shifted, the $P_{50}$ is higher and the Hb oxygen saturation at PO$_2$ equal to 70 mm Hg is lower. In Hb SC patients and in control subjects, lower Hb levels were associated with higher 2,3-diphosphoglycerate levels ($P < .001$), and higher 2,3-diphosphoglycerate levels resulted in higher $P_{50}$ measurements ($P = .046$) and lower Hb oxygen saturation at PO$_2$ equal to 70 mm Hg ($P = .043$). In Hb SS patients, 2,3-diphosphoglycerate did not appear to mediate the effect of anemia on the shape of the oxygen dissociation curve. Lower Hb levels were associated with higher $P_{50}$ measurements ($P < .001$) and lower Hb oxygen saturation at PO$_2$ equal to 70 mm Hg ($P < .001$). However, there was not a significant association between Hb level and 2,3-diphosphoglycerate level ($P = .573$) or between 2,3-diphosphoglycerate level and $P_{50}$ ($P = .214$) or the Hb oxygen saturation at PO$_2$ equal to 70 mm Hg ($P < .931$). Thus, the expected relationship between Hb level, 2,3-diphosphoglycerate level, and the shape of the Hb oxygen dissociation curve was seen in Hb SC patients and control subjects, but not in patients with Hb SS.

For the 32 Hb SS patients who had an oxygen dissociation curve measured when clinically well, mean transferreric SaO$_2$ values were 92.4% ± 3.0% for those with a history of acute chest syndrome ($n = 13$) and 97.3% ± 4.7% for those with no history of acute chest syndrome ($n = 19$). The lower transferreric SaO$_2$ values seen in Hb SS patients with a history of acute chest syndrome could represent normal PaO$_2$ values if these patients had more right-shifted oxygen dissociation curves than patients without a history of acute chest syndrome. However, the mean PaO$_2$ calculated from patients’ oxygen dissociation curves and transferreric SaO$_2$ values is significantly lower for patients with a history of acute chest syndrome (76.6 ± 11.4 mm Hg) than for those with no history of acute chest syndrome (90.7 ± 12.9 mm Hg; $P < .01$).

**Pulse oximetry in acutely ill patients.** Eight patients with Hb SC disease were studied in the emergency department at the time of visits for acute illness. One patient with acute chest syndrome presented with a transferreric SaO$_2$ of 88%. Hb SC patients seen for pain ($n = 5$) and fever ($n = 2$) had transferreric SaO$_2$ values in the normal range (range, 96% to 100%; mean, 97.6% ± 1.6%).

Fifty-five patients with Hb SS disease were studied in the emergency department at the time of visits for acute illness. Thirty-two of the 55 patients had pulse oximetry at both the time of acute illness and when clinically well. No patient whose transferreric SaO$_2$ was ≥96% or within 3 points of a measurement made when the patient was clinically well was diagnosed with acute chest syndrome, either in the emergency department or after admission to the hospital. Five of the 32 patients had transferreric SaO$_2$ values that were less than 96% and more than 3 points lower than their transferreric SaO$_2$ when clinically well. Two of these patients were diagnosed with acute chest syndrome in the emergency department, and a third patient had an emergency department diagnosis of vaso-occlusive pain, but developed acute chest syndrome during the subsequent hospital stay. A fourth patient, who had a history of asthma, was treated for bronchospasm and discharged. The fifth patient was admitted with fever and acute abdominal pain associated with a massive hair bezoar.

Without a baseline transferreric SaO$_2$ value for comparison, the evaluation of acutely ill Hb SS patients is difficult; the variability in oxygen dissociation curves means that a wide range of transferreric SaO$_2$ values may represent acceptable PaO$_2$ (Fig 1). Therefore, we used data from oxygen dissociation curves to construct a nomogram that relates Hb level when clinically well and transferreric SaO$_2$ when acutely ill to the chance that a patient has a PaO$_2$ greater than 70 mm Hg. Hb level when clinically well was used as a control variable because of the significant relationship between Hb level and Hb oxygen saturation at PO$_2$ equal to 70 mm Hg (see regression model below), and because it is relatively stable and is usually available to the clinician in the emergency department. The threshold PaO$_2$ value of 70 mm Hg was chosen because exchange transfusion is advocated for patients with acute chest syndrome and PaO$_2$ less than 70 mm Hg while the patient is breathing supplemental oxygen.

The Hb oxygen saturation that corresponded to a PO$_2$ of 70 mm Hg was recorded from the oxygen dissociation curves of 32 clinically well Hb SS patients in this study, 10 Hb SS patients seen in the emergency department during this study, and 33 clinically well Hb SS patients studied previously in the same laboratory. Mean Hb oxygen saturation values at PO$_2$ equal to 70 mm Hg were not significantly different among the three groups. Univariate regression analysis yielded the following results: (Hb oxygen saturation at PO$_2$ at 70 mm Hg) = 84.2 + (1.0 × Hb level); $r^2 = .181$; $P$
Pulse Oximetry in Sickle Cell Disease

< .001. The upper 95% confidence interval of the regression line was plotted as a threshold above which there is relative certainty that the measured Hb oxygen saturation represents a PaO₂ of greater than 70 mm Hg for a given Hb level (Fig 2).

To gain insight into the clinical utility of the nomogram, we used it to classify the 55 Hb SS patients studied at the time of visits to the emergency department for acute illness into those likely to have PaO₂ greater than 70 mm Hg and those in whom a lower PaO₂ was more likely. The occurrence of acute chest syndrome during that emergency department visit or the subsequent hospital admission was then examined. One of 40 patients whose transcutaneous SaO₂ was above the line, in the area in which PaO₂ greater than 70 mm Hg is likely, developed acute chest syndrome after admission to the hospital. Fifteen of 55 patients in our sample had transcutaneous SaO₂ values below the line. Of these 15, 4 were diagnosed with acute chest syndrome in the emergency department (transcutaneous SaO₂ range, 81% to 88%), 3 were admitted for fever or pain and developed acute chest syndrome while in the hospital, and 1 had a history of asthma and was treated for bronchospasm in the emergency department. For our sample, having a transcutaneous SaO₂ value above the line, in the area in which PaO₂ greater than 70 mm Hg is likely, developed acute chest syndrome in the emergency department or developing it during a subsequent hospital admission. The positive predictive value, the probability of having acute chest syndrome with a transcutaneous SaO₂ value below the line, was 47%.

Accuracy of pulse oximetry. Nine arterial blood gas measurements were made in 7 acutely ill Hb SS patients. These patients also had oxygen dissociation curve measurements from simultaneously drawn specimens, and transcutaneous SaO₂ measured by pulse oximetry just before arterial puncture. For each patient, the Hb oxygen saturation was calculated using measured PaO₂ and the patient’s oxygen dissociation curve. There was close agreement between the measured transcutaneous and calculated SaO₂ values (r = .972; n = 9). In the one case when the measured PaO₂ was less than 50 mm Hg, the transcutaneous SaO₂ value (66%) was significantly lower than would be predicted from the PaO₂ and oxygen dissociation curve (76%).

DisCUSSION

Pulse oximetry is well studied as an alternative to the invasive monitoring of arterial oxygen saturation, but there are limited data on its use in patients with sickle cell disease. Weston Smith et al showed the accuracy of pulse oximetry in three patients with acute chest syndrome by using Hb oxygen saturation derived from the patient’s oxygen dissociation curve and measured PaO₂ to evaluate the transcutaneous SaO₂ value. Their report illustrated that pulse oximetry is accurate in patients with sickle cell disease when differences in patients’ oxygen dissociation curves are taken into account. Our data agree with and extend these findings. The arterial blood gas data, while limited, show that pulse oximetry is accurate in patients with Hb SS; there was close agreement between measured transcutaneous SaO₂ and Hb oxygen saturation calculated from a patient’s oxygen dissociation curve and PaO₂. In the 1 patient with severe hypoxemia, the agreement was not good. Increasing negative bias between transcutaneous SaO₂ and Hb oxygen saturation measured by blood oximetry at low saturation in anemic patients has been shown by Severinghaus and Koh. As the investigators point out, the error is protective, in that the degree of desaturation is overestimated by pulse oximetry.

Vichinsky et al have questioned the accuracy of pulse oximetry in patients with sickle cell disease. They reported wide variation between Hb oxygen saturation measured by pulse oximetry and blood oximetry in untransfused sickle cell patients. Increased levels of nonfunctional met-Hb and carboxy-Hb in untransfused patients with Hb SS may explain these findings. Pulse oximeters measure oxy-Hb as a percentage of functional Hb (oxy-Hb plus deoxy-Hb). Blood oximeters used in arterial blood gas laboratories measure oxy-Hb as a percentage of total Hb (fractional Hb oxygen saturation), including nonfunctional met-Hb and carboxy-Hb. If a sickle cell patient has a low Hb and increased met-Hb and carboxy-Hb because of hemolysis, blood oximetry will result in a lower Hb oxygen saturation value than pulse oximetry. For example, one of the Hb SS patients in our study had a transcutaneous SaO₂ of 85% measured by pulse oximetry, and met-Hb and carboxy-Hb levels of 5.0% and 4.7%, respectively; the patient had a fractional Hb oxygen saturation of 74% when measured in the blood gas laboratory. When the fractional Hb oxygen saturation value is adjusted to reflect oxy-Hb as proportion of functional Hb,
the resultant value is 82%, which is close to the value measured by pulse oximetry. The measured fractional Hb oxygen saturation is a useful check on the accuracy of pulse oximetry, but must be adjusted to reflect only functional Hb before a comparison is made. The comparison of measured transcutaneous SaO₂ and Hb oxygen saturation calculated from a patient’s oxygen dissociation curve and PaO₂ is the most appropriate check on the accuracy of pulse oximetry, because both methods are based on the measurement of oxy-Hb as a proportion of functional Hb.

The striking difference between Hb SC and Hb SS patients was an unexpected finding in this study. In contrast to Hb SS patients, all clinically well Hb SC patients had normal transcutaneous SaO₂. Also, the oxygen dissociation curves of Hb SC patients were significantly different from those of Hb SS patients, despite similar mean 2,3-diphosphoglycerate values for the two groups. In fact, the curves of Hb SC patients, while somewhat right-shifted, were not significantly different from those of control subjects. The expected relationship between Hb level, 2,3-diphosphoglycerate level, and the shape of the oxygen dissociation curve was seen in Hb SC patients and control subjects, but not in patients with Hb SS disease. Hb S must have an effect on Hb oxygen affinity that is different from the effect of 2,3-diphosphoglycerate. In this respect, our data agree with the findings of Seakins et al. who showed that the oxygen affinity of Hb SS blood is associated with intracellular Hb S concentration and not with 2,3-diphosphoglycerate content.

Despite the fact that children with Hb SC may suffer from severe episodes of acute chest syndrome, and that the Hb SC patients in this study had a similar rate of past acute chest syndrome, they differed from children with Hb SS with respect to the effect of a history of acute chest syndrome and age on transcutaneous SaO₂. In clinically well patients with Hb SS, a history of acute chest syndrome and older age are associated with significant arterial Hb oxygen desaturation, whereas no effect is seen in patients with Hb SC. Multivariate analysis suggests that older age represents decreasing Hb F levels in Hb SS patients, because the effect of age on transcutaneous SaO₂ is not significant when controlling for Hb F level. Cross-sectional studies of pulmonary function in children with sickle cell disease have not identified older age, a history of acute chest syndrome, or the SS phenotype as factors associated with worse pulmonary function studies. However, such studies were limited by the fact that pulmonary function testing with spirometry is not usually possible in children under 5 years of age, whereas the study of very young children is possible with pulse oximetry. Longitudinal studies of patients from birth are needed to define further the factors associated with the progressive pulmonary dysfunction suggested by our findings, and to determine whether Hb oxygen desaturation in childhood is associated with progressive pulmonary dysfunction later in life.

For clinicians caring for children with sickle cell disease, an important finding of this study is that pulse oximetry may be used to screen for hypoxemia in the acute setting if reasonable guidelines are followed. Our data show that children with Hb SC who have transcutaneous SaO₂ measurements less than 96% should be considered hypoxemic until proven otherwise, and that significant decreases from baseline transcutaneous SaO₂ are rarely associated with uncomplicated vaso-occlusive pain or fever. Comparison with a patient’s transcutaneous SaO₂ when clinically well appears to be the best means of identifying whether hypoxemia is present, because it obviates the need to make assumptions about the patient’s oxygen dissociation curve. For Hb SS patients, the nomogram shown in Fig 2 may be an alternative for predicting the hypoxemia associated with acute chest syndrome when a baseline transcutaneous SaO₂ value is not available. Additional prospective studies will be needed to validate our findings and define the best use of the nomogram.

We did not obtain serial measurements of transcutaneous SaO₂ on patients when they were clinically well. The fact that patients with uncomplicated pain and fever had transcutaneous SaO₂ measurements that were similar to measurements made when they were clinically well suggests that there is little day to day variation in SaO₂ in the absence of intervening acute chest syndrome or worsening chronic lung disease. Our current practice is to include the measurement of transcutaneous SaO₂ as part of the routine evaluation of patients with sickle cell disease. This practice will provide data on the consistency of transcutaneous SaO₂ measurements in patients with sickle cell disease and allows for comparison between transcutaneous SaO₂ values obtained when the patient is clinically well and those measured in the setting of acute illness.

This study is the most extensive study to date on the use of pulse oximetry to measure transcutaneous SaO₂ in children with sickle cell disease. Although only a small number of observations were made, the correlation between SaO₂ measured by pulse oximetry and calculated values was excellent. The differences between Hb SS and Hb SC patients and the identification of factors associated with Hb oxygen desaturation in children with Hb SS raises questions about the natural history of pulmonary dysfunction in patients with sickle cell disease. Longitudinal studies will be needed to confirm our findings and answer these questions. We conclude that pulse oximetry is useful in the clinical care of patients with sickle cell disease. Its routine use in the clinic may help us to understand better the natural history of pulmonary dysfunction in these patients; and, its appropriate use in the emergency department can aid in the evaluation of patients for hypoxemia associated with acute chest syndrome.

ACKNOWLEDGMENT

We thank the nurses and physicians of the Divisions of Hematology and Emergency Medicine at The Children’s Hospital of Philadelphia, especially Wendy Bulgarelli, RN, Renee Cecil, RN, and Jane Graves, LPN, for their help in patient recruitment and data collection. Michael Reilly, PhD, and Ko Uchida, MD, provided valuable assistance in performing oxygen dissociation curve and 2,3-diphosphoglycerate measurements. Alan Cohen, MD, provided valuable critical comments on the manuscript. Nellcor, Inc, kindly provided a pulse oximeter for use in this study.

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Pulse oximetry and factors associated with hemoglobin oxygen desaturation in children with sickle cell disease

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