The oxygen affinity of sickle hemoglobin

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Abstract

The right-shifted oxyhemoglobin dissociation curve of sickle cell disease (SCD) has been thought to result in abnormally low arterial oxygen saturation (SO2), even when oxygen partial pressure (PO2) is normal. However, without polymer formation (minimal under normoxic conditions), HbS oxygen affinity is normal. We hypothesized that in SCD, in vivo SO2 is normal when PO2 is normal. We retrospectively examined 50 blood gas and COoximetry samples from SCD patients and from controls matched for pH, PO2, and carboxyhemoglobin. Control data fell close to the Severinghaus curve, as did non-hypoxemic (SO2 > 92.5%) SCD data. In contrast, hypoxemic (SO2 < 92.5%) SCD data fell well below the standard curve. Thus, although SCD patients’ oxygen affinity is low under hypoxic conditions, it is normal at normal arterial SO2. Therefore, a finding of abnormally low saturation demonstrates that PO2 is abnormally low. Given our previous finding that pulse oximetry faithfully reflects saturation in SCD, low pulse oximeter readings in SCD constitute reliable evidence of impaired gas exchange.

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1. Introduction

Many sickle cell disease (SCD) patients have abnormally high P50 (partial pressure of oxygen at 50% saturation) (Lonsdorfer et al., 1983). As a result, several investigators have suggested that pulse oximetry readings may be abnormally low in SCD, even when gas exchange is normal (Blaisdell et al., 2000; Comber and Lopez, 1996; Homi et al., 1997). If so, then a low pulse oximeter reading, e.g. 92%, may not necessarily indicate abnormal arterial oxygenation. However, in vitro, the oxygen affinity of HbS depends upon the severity of its polymerization; in the absence of polymer formation, sickle hemoglobin (HbS) has normal oxygen affinity (Fabry et al., 2001). Since HbS polymerization is a function of the severity of hypoxemia, oxygen affinity would be expected to be normal when arterial oxygenation is normal. We hypothesized that even among patients with right-shifted P50s, the oxygen affinity of hemoglobin remains normal at normal arterial PO2.

To test this hypothesis, we retrospectively reviewed data for PO2, pH, base excesses, and oxygen saturations (SO2) of SCD patients and controls matched for pH, PO2, and carboxyhemoglobin (COHb) to determine whether the hypoxic samples from SCD patients lie farther from the standard oxyhemoglobin dissociation curve (OHDC) than do the matched controls, and whether the well-oxygenated samples from SCD patients follow the standard OHDC.

2. Methods

Using Montefiore’s Clinical Looking Glass (a database derived from the Hospital’s clinical information system), we identified 50 patients with SCD (40 SS genotype, 6 SC genotype, and 4 SβThalassemia genotype) hospitalized between 1 January 2000 and 30 June 2007, and not transfused for at least 6 weeks, who had arterial blood gases and COoximetry performed on the same arterial or venous blood samples. We accepted samples with pH between 7.3 and 7.55, PCO2 between 20 and 65 mmHg, PO2 between 30 and 165 mmHg, and methemoglobin (metHb) less than 5%.

We confirmed the genotypes by reviewing the patients’ records. We tabulated the date, time, age, gender, pH, partial pressure of carbon dioxide (PCO2), base excess (BE), PO2, SO2, oxyhemoglobin concentration (O2Hb), carboxyhemoglobin concentration (COHb), and metHb. We also noted previous prescription of hydroxyurea. Once the SCD group was constructed, we assembled a control group of blood samples with arterial or venous blood gases and simultaneous COoximetry.
from non-SCD patients, matching for COHb within 1% point, PO₂ within 10 mmHg, and pH within 0.1 unit. Table 1 shows the characteristics of the two groups. The study was reviewed and approved by Montefiore’s Institutional Review Board for the Protection of Human Subjects.

For each sample with SO₂ ≤ 96.5%, we used the method of Severinghaus (1979) to calculate the expected PO₂, based on pH, BE, and SO₂ and calculated the right shift of the OHDC as the difference between the predicted and measured PO₂ (PO₂ cannot be accurately predicted for SO₂ > 96.5% (Severinghaus, 1979). For each sample, regardless of SO₂, we used the method of Severinghaus (1979) to calculate the expected SO₂, based on pH, PO₂, and base excess. We computed the difference between the predicted and measured saturations, a measure of the “downshift” of the OHDC for that sample. Right shift cannot be calculated at normal or high PO₂, where the OHDC is nearly flat, so we reasoned that the downshift would be a more meaningful estimate of any abnormality of oxygen affinity than right shift across the range of SO₂ we studied.

For samples with SO₂ < 92.5% (hypoxemic) and for samples with SO₂ > 92.5% (normoxemic), we compared the right- and downshifts among SCD and non-SCD groups, using Student’s t-test, accepting P<0.05 as evidence of statistical significance. We also performed simple and multiple regression analyses of SO₂, pH, PCO₂, COHb, and metHb (and genotype for the SCD patients) against the downshift for both SCD and control samples.

3. Results

Fig. 1 plots the control and SCD patients’ data in comparison to the Severinghaus curve. It is evident that the controls and the non-hypoxemic SCD patients’ data fall close to the standard curve, but that the hypoxemic SCD patients’ data fall well below. Neither the control group’s nor the non-hypoxemic SCD patients’ right- and downshifts among SCD and non-SCD groups, using Student’s t-test, accepting P<0.05 as evidence of statistical significance. We also performed simple and multiple regression analyses of SO₂, pH, PCO₂, COHb, and metHb (and genotype for the SCD patients) against the downshift for both SCD and control samples.

4. Discussion

We show that, although SCD patients do indeed have elevated P50s, indicating reduced hemoglobin oxygen affinity, at least under hypoxic conditions; they do not have abnormally low oxygen affinity at normal arterial partial pressures. By matching our control group for pH and COHb and by limiting the study to relatively low metHb, we demonstrated that none of these factors could be responsible for the different behavior of SCD and control OHDCs under hypoxic conditions. Examination of the data
from two previous smaller uncontrolled studies, conducted for other purposes, show similar shifts in the SCD patients’ OHDCs at low but not at normal PO2 (Ortiz et al., 1999; Fitzgerald and Johnson, 2001), but that fact was not commented upon. Thus, in SCD, when saturation is found to be abnormally low, it can be assumed that PO2 is also abnormally low. Given our previous finding that pulse oximetry faithfully reflects saturation in SCD (Ortiz et al., 1999), we conclude that a low pulse oximeter reading in SCD should not be discounted.

Our findings are compatible with the known behavior of sickle hemoglobin (HbS) in vitro. HbS polymerizes under hypoxic conditions, coming out of solution and producing the abnormal RBC deformability and bizarre shapes that are characteristic of the disease (Fabry et al., 2001). The polymer has much lower affinity for oxygen than does hemoglobin A or than does HbS when it is in solution. In fact, the P50 of nonpolymerized HbS is similar to that of HbA, and only when polymer forms is there a right shift (Fabry et al., 2001). The elevated 2,3 DPG (Bookchin and Lew, 1996) and the elevated HbF levels (Serjeant et al., 1996) of SCD are too small to effect more than a negligible shift of the OHDC to the right or left, respectively.

References


