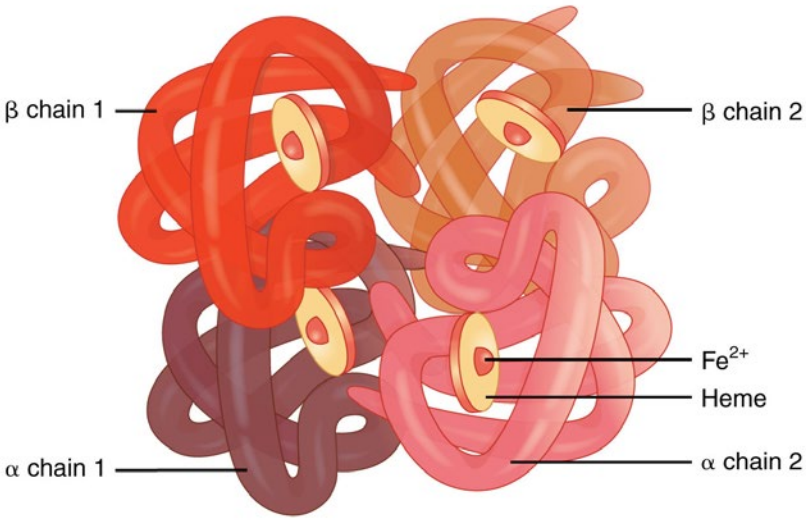
SWISS SOCIETY OF NEONATOLOGY

Persistently low oxygen saturation in a neonate – there is more than meets the eye

May 2018



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Title figure:
Hemoglobin molecule

A neonate presenting with low oxygen saturations is considered an emergency, as the cause may be a serious respiratory or cardiac condition. However, there is a broad list of differential diagnoses causing a low oxygen saturation. Here, we present one rare but important cause in a male neonate with persistently low oxygen saturations.

This male infant was born at 41 0/7 weeks to a healthy 24-year-old G1/P1 by normal vaginal delivery. The antenatal history was unremarkable. Rupture of membranes had occurred nine hours before delivery and meconium-stained amniotic fluid had been noted. The infant adapted well with Apgar scores of 8, 8 and 10 at 1, 5 and 10 minutes, respectively. Arterial and venous umbilical cord pH values were 7.28 and 7.38. The infant's birth weight was 3570 g (P75 – 90).

One hour after delivery, the infant developed symptoms of respiratory distress with nasal flaring, intercostal retractions and an SpO_2 of 86%. Based on the clinical presentation, which included discrete petechiae, slightly cyanotic extremities and a capillary refill time of 2 – 3 seconds, neonatal infection was suspected and empirical intravenous antibiotic therapy was initiated with amoxicillin and gentamicin. Therapy was stopped after six days when inflammatory markers and blood cultures remained negative.

Initial polycythemia was treated with a single bolus of normal saline. Nasal CPAP and supplemental oxygen were given for five days; CPAP could then be stopped and respiratory support continued with high flow nasal cannula oxygen. There was a persistent oxygen requirement with an FiO_2 of up to 0.45 to maintain oxygen saturations > 90%. Chest X-rays and echocardiography on day one and seven of life showed no relevant pathology.

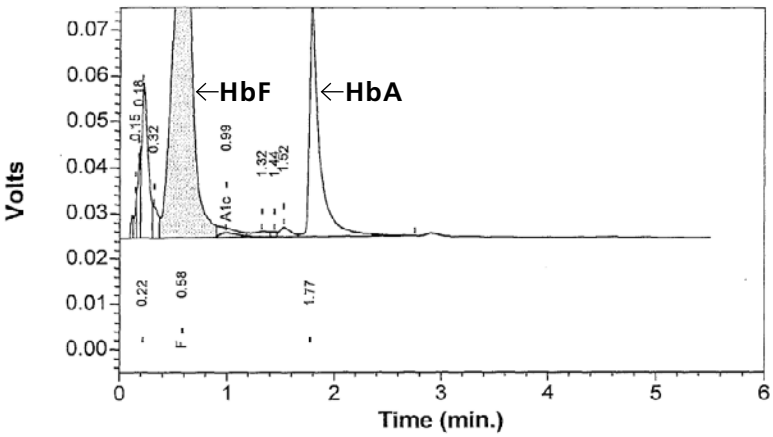

Fig. 1

High performance liquid chromatography showed no abnormal bands. The largest peak belongs to hemoglobin F (HbF), the second largest to hemoglobin A (HbA).

Interestingly, there was a significant discrepancy between the transcutaneous SpO_2 of 88 – 89% and an arterial PaO_2 of 225 mmHg when oxygen was added. At this point, the possibility of a hemoglobinopathy was considered, and the infant was transferred to a tertiary hospital for further investigation. Hemoglobin electrophoresis and hemoglobin chromatography were performed (Fig. 1). On electrophoresis, abnormal bands were detected. Since there was no evidence for a pulmonary or cardiac cause, the presence of an abnormal hemoglobin with decreased oxygen affinity was suspected. Repeated arterial blood gas analyses supported this hypothesis (Table 1).

Parameters [normal range]	Ambient air	FiO2 0.3
pH [7.35 – 7.45]	7.45	7.44
pCO_2 [27 – 43 mmHg]	37 mmHg	39 mmHg
bicarbonate [17.2 – 23.6 mmol/l]	25.3 mmol/l	25.9 mmol/l
base excess [-7.0 to + 0.2 mmol/l]	1.6 mmol/l	2.1 mmol/l
paO_2 [65 – 80 mmHg]	85 mmHg	167 mmHg
SaO_2 [93 – 98%]	79%	87%
SpO_2	80%	85%
hemoglobin [135 – 168 g/l]	156 g/l	151 g/l
lactate [0.5 – 1.67 mmol/l]	1.1 mmol/l	1.3 mmol/l

Table 1. Results of two arterial blood gas analyses: paO_2 (partial pressure of oxygen, arterial blood sample), SaO_2 (oxygen saturation, arterial blood sample), and SpO_2 (transcutaneous oxygen saturation) were simultaneously measured in room air and after one hour with supplemental oxygen (FiO_2 0.3).

Since the infant showed no clinical symptoms apart from discrete intermittent cyanosis of the lips, supplemental oxygen therapy was stopped and the infant was discharged on the 23rd day of life without monitoring.

When hemoglobin electrophoresis and chromatography of both parents were normal, DNA-sequencing of the γ-globin gene was performed and revealed a mutation in the hemoglobin F, previously described as Hb-F Sarajevo (Fig. 2). Hb-F Sarajevo shows a mutation on the $^{G}\gamma$-gene with an A to C transversion at position HBG2:c.308 causing a change from asparagine to threonine (1, 2).

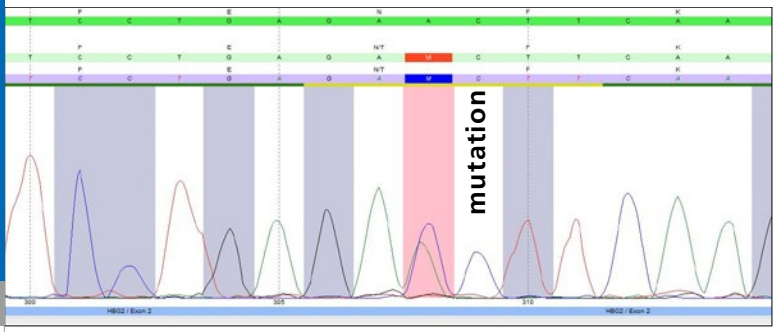

Fig. 2

DNA-sequencing shows the typical mutation for Hb-F Sarajevo on the $^{G}\gamma$-gene *with an A to C transversion at position HBG2:c.308 causing a change from asparagine to threonine (1, 2): instead of the expected green signal for adenine (A), a blue signal is detected standing for cytosine (C); The letter M indicates a mutation.*

This case demonstrates the importance of including hemoglobinopathies in the differential diagnosis of a patient presenting with low oxygen saturations.

The arterial partial pressure of oxygen (paO_2) describes the concentration of dissolved oxygen in arterial blood. SaO_2 is the oxygen saturation in the arterial blood; it is defined as the ratio of oxygenated hemoglobin concentration divided by the total hemoglobin concentration. SaO_2 and paO_2 can both be measured in a sample of arterial blood. Oxygenation can also be estimated noninvasively by pulse oximetry, which measures peripheral arterial oxygen saturation (SpO_2), a surrogate marker for SaO_2. SpO_2 is estimated by initial calibration of the signal measured by photoplethysmography and simultaneous measurements of SaO_2. It has an accuracy with a standard deviation of ± 2% (3). SaO_2 and paO_2 are related through the oxyhemoglobin dissociation curve (4).

Hemoglobinopathies are hereditary disorders of globin chain synthesis. They can be divided into quantitative disorders (thalassemias) with a deficient synthesis of normal hemoglobin, or qualitative disorders, characterized by the presence of structural variants of hemoglobin. As hemoglobinopathies are a very heterogeneous group of disorders, the manifesting clinical symptoms differ widely. Structural changes in the hemoglobin protein can cause instability of the

protein, leading to lysis and anemia, or change oxygen affinity. The new hemoglobin can also show a different absorption spectrum for light absorbance leading to spuriously low SpO_2 measurements (5).

In newborn infants, the largest fraction of hemoglobin (60 – 80% of total hemoglobin) is hemoglobin F. Hemoglobin F is composed of two α-globin and two γ-globin protein chains. The two γ-globin genes (HBG1 and HBG2), located on chromosome 11, define hemoglobin F. Fetal blood has a higher oxygen affinity than adult blood. Hemoglobin A, which represents the majority of adult hemoglobin, consists of two α-globin and two β-globin protein chains. Hemoglobin F is almost completely replaced by hemoglobin A by approximately 6 to 12 months of age (6). Therefore, anomalies of the α- and γ-globin chains may be apparent immediately after birth, whereas β-globin mutations manifest only after several months of life when hemoglobin F has been replaced by hemoglobin A (1, 7).

In recent years, many new hemoglobin variants have been discovered and characterized. In January 2017, the database of human hemoglobin variants and thalassemias contained 1709 hemoglobin variants; of these, 58 involved the $^{A}\gamma$-globin gene (HBG1) and 73 involved the $^{G}\gamma$-globin gene (HBG2) (8).

Hemoglobin variants with proven low oxygen affinity include Hb Venusberg, Hb Chico and Hb Basset. Low

oxygen affinity generally leads to a low oxygen saturation, peripheral cyanosis and anemia. Because of the low oxygen affinity, oxygen is easily delivered to the tissues. Thus, there is no hypoxic stimulation of erythropoietin production leading to anemia (7).

A systematic search for reports of low SpO_2 associated with hemoglobin variants revealed 21 hemoglobin variants. Three hemoglobin-variants showed a concordance of low SpO_2 and SaO_2 values (Hb Rothschild, Hb Canebiere, Hb Bassett). Eleven hemoglobin variants showed low SpO_2 and normal SaO_2 (e.g., Hb Lansing, Hb Titusville and Hb Bonn). Seven hemoglobin variants had a low SpO_2 and uncertain/unreported SaO_2 (e.g. Hb Sunshine Seth, Hb Louisville and Hb Chico). However, it remains difficult to explain these constellations of SpO_2 and SaO_2 values based on the underlying hemoglobin variant. In some hemoglobin variants, the SpO_2 values were interpreted as being spuriously low due to abnormal absorption spectra between 600 – 900 nm (5).

The SpO_2 is estimated by the ratio of light absorption in the red and infrared spectra. Deoxyhemoglobin shows a greater red light absorption (600 – 750 nm), oxyhemoglobin a greater absorption in the infrared spectrum (850 – 1000 nm). Currently available pulse oximeters contain two light emitting diodes at 660 and 940 nm wavelengths. From the ratio of light absorption, the percentage of oxyhemoglobin can be

estimated (4, 5, 7). In Hb Bonn, for example, a point mutation leads to an additional absorption maximum at 668 nm (7, 9). Thus, erroneous measurements of an increased proportion of deoxyhemoglobin result (5).

To the best of our knowledge, only two other cases with a low SpO_2 and Hb-F Sarajevo mutation have been described. The first case was published in 2012 by Zimmermann-Baer et al. in Switzerland (1), the second in 2016 by Lozar-Krivec et al. in Slovenia (2). Both infants were born at term and presented with low SpO_2 measurements of 74% and 72%, respectively. Cardiac and respiratory causes were excluded. In both cases, the parental gene carrier originated from the same geographic region (Bosnia). Interestingly, the parents of our patient also have Bosnian roots.

Because of the discrepancy between the PaO_2 and SaO_2, Lozar-Krivec et al. hypothesized a shift to the right of the oxygen-hemoglobin dissociation curve due to low oxygen affinity (1). However, the exact consequences on biochemical and functional properties remain unknown. The Hb Kansas variant shows the same mutation site but is located on the β-globin. This mutation leads to a stabilization of deoxyhemoglobin (also called T state) and, therefore, the steady state of oxy- and deoxyhemoglobin is shifted towards the deoxyhemoglobin state (Fig. 3). The same changes might explain the low SpO_2 and SaO_2 in the Hb-F Sarajevo variant (1, 10).

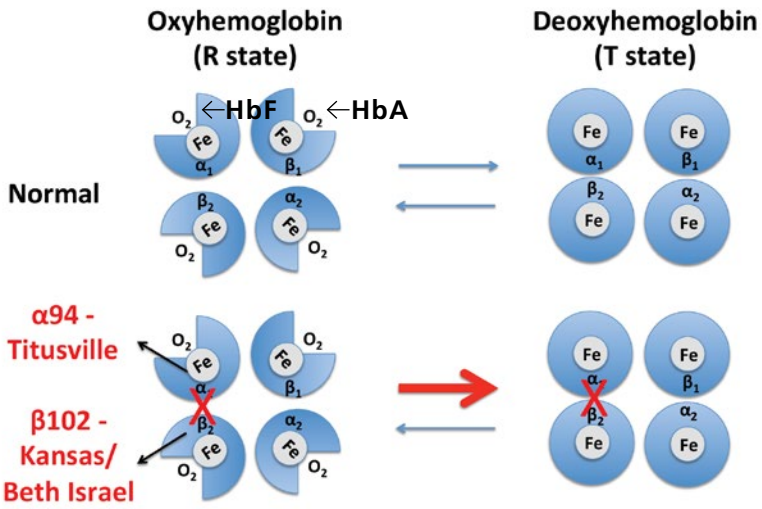

Fig. 3

Due to a mutation in the α_1- or β_2-globin, the normal interaction between these globins is disturbed. In the above represented mutations, a shift from the R to the T state is the consequence (from Steinberg et al., with the permission from Professor H. Tamary (10)).

We hypothesize that there is a decreased oxygen affinity of the hemoglobin in our patient with a right shift of the oxyhemoglobin dissociation curve (Fig. 4), resulting in low SpO_2 and normal (room air) or high (on supplemental oxygen) SaO_2 (Table 1). There were no signs of hemoglobin instability (no anemia, no cell lysis). A relevant change in the absorption spectra is unlikely as the values of SaO_2 and SpO_2 were comparable when measured simultaneously. However, SaO_2 and SpO_2 were both decreased under ambient air, whereas PaO_2 was normal, indicating decreased affinity. The normal lactate level under ambient air further supports our hypothesis: due to its decreased affinity, oxygen is readily released in the periphery preventing clinically relevant hypoxia. Finally, the increase in PaO_2 in an FiO_2 of 0.3 excludes relevant shunts (pulmonary or cardiac) as explanation for the low SpO_2.

At the age of 6 months, as expected for hemoglobinopathies affecting hemoglobin F, SpO_2 normalized in the infant presented in this case report. The same observation was reported by Zimmermann-Baer and by Lozar-Krivec (1, 2). Zimmermann-Baer et al stated that the initial low SpO_2 levels did not affect growth and psychomotor development of their patient (2).

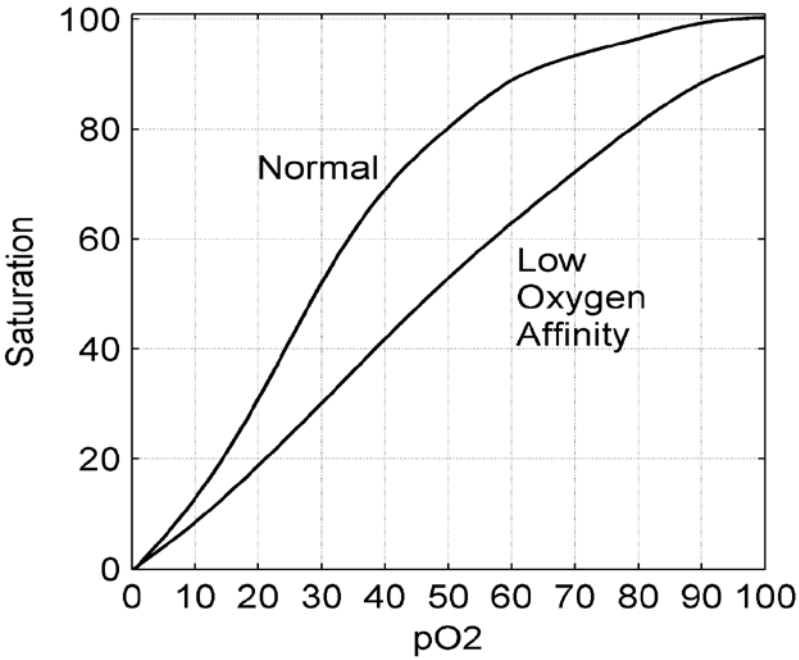

Fig. 4

Oxygenation dissociation curves: a right shift of the oxygen dissociation curve leads to a lower oxygen affinity. Therefore, a higher pO2 is necessary to reach the same oxygen saturation. However, due to the lower affinity oxygen is also more easily released in the periphery to the tissue (from Steinberg et al., with the permission from Professor H. Tamary (10)).

CONCLUSION

Hemoglobinopathies should be suspected in a clinically asymptomatic child with low SpO_2 measurements when underlying cardiac or pulmonary disorders have been excluded (5, 7). In hemoglobin variants, oximetry readings do not adequately reflect the oxygenation-carrying properties of arterial blood – abnormal hemoglobins can affect the oxyhemoglobin dissociation curve as well as the absorption spectra (4). Altered oxygen affinity due to an abnormal hemoglobin can lead to low SaO_2 and SpO_2 levels without relevant tissue hypoxia. Therefore, in these patients, SpO_2 is not necessarily a reliable marker for the oxygenation status of tissue (4).

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