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Oxygen Saturation of 75%, but No Symptoms!

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History

At the age of 30, a young father noticed a low oxygen saturation while playing with the finger pulse oximeter of his child awaiting surgery. Since he was completely asymptomatic, he did not seek medical attention. At the age of 51, he was referred to the outpatient clinic of our pulmonary department after detection of a severe nocturnal "hypoxemia". Previous evaluation for obstructive sleep apnea by nocturnal respiratory polygraphy because of snoring revealed a significantly decreased average oxygen saturation (SpO_2 71%). The former smoker (25 pack-years) was known for allergic/seasonal bronchial asthma with occasional use of an inhaled short-acting β-2-selective adrenergic agonist (terbutalin) preceding physical activity. He denied having respiratory symptoms like dyspnea, cough, thoracic pain, or infections, and did not experience a decline of his physical performance.

The patient presented to our outpatient clinic with a significantly decreased peripheral O_2 saturation of 76–82% while breathing ambient air, which was measured by different pulse oximeters (Fig. 1). SpO_2 rose only to 86% while breathing 7 L/min supplemental oxygen via nasal cannula. Other vital signs were normal (blood pressure 124/68 mm Hg, heart rate 86 beats/min, respiratory rate 16/min) and the patient showed no signs of respiratory distress. Physical examination revealed normal breath sounds without any signs of heart failure. Skin coloration was inconspicuous. Pulmonary function tests showed normal lung volumes without restriction (TLC 6.06 L,

Fig. 1. 51-year-old asymptomatic male. Patient with unremarkable appearance (no cyanosis, no jaundice). Low SpO_2 (73%/79%) measured with two different pulse oximeters.

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Table 1. Results of pulse oximetry, arterial blood gas analysis and further laboratory analyses

	Results	Normal range
Pulse oximetry		
SpO_2	76–82%	>92%
Arterial blood gas analysis		
SaO_2	89%	93–98%
paO_2	10.9 kPa (82 mm Hg)	9.5–13.9 kPa (71–104 mm Hg)
p50	5.3 kPa (40 mm Hg)	3.2–3.7 kPa (24–28 mm Hg)
$paCO_2$	5.1 kPa (38 mm Hg)	4.7–6.1 kPa (35–46 mm Hg)
pH	7.45	7.35–7.45
Standard bicarbonate	26 mmol/L	18–29 mmol/L
Further analysis		
Hemoglobin	138 g/L	135–168 g/L
Reticulocytes	2.2%, 107×10^9/L	0.8–2.2%, $40–100 \times 10^9$/L
MCHC	318 g/L	320–360 g/L
MCV	89 fl	80–98 fl
MCH	28 pg	27–33 pg
LDH	183 U/L	<480 U/L
Bilirubin	11 μmol/L	<17 μmol/L
Haptoglobin	0.44 g/L	0.3–2 g/L
Erythropoietin	24.8 mU/mL	4.3–29.0 mU/mL

89% predicted) or airway obstruction (FEV_1/FVC 75%, FEV_1 3.16 L, 89% predicted), but signs of small airway disease (MEF50 66% predicted). The diffusing capacity was above normal range (DLCO 126% predicted). Spiroergometry confirmed a normal cardiopulmonary performance (VO_2max 23.5 mL/min/kg, 95% predicted) with a mildly diminished oxygen pulse (19.6 mL, 76% predicted), decreased slope and early plateau. Arterial blood gas analysis measured an oxygen saturation (SaO_2) of 89%, paO_2 10.9 kPa (82 mm Hg) and p50 5.3 kPa (40 mm Hg). Table 1 lists the laboratory results.

What is your diagnosis?

Diagnosis: Hemoglobinopathy Cheverly

Due to the discrepancy between invasively and noninvasively measured SO_2, evaluation for an abnormal hemoglobin was performed. Conventional hemoglobin electrophoresis (alkaline cellulose acetate) was normal. Alpha-2 hemoglobin [3.2% (normal range 1.8–3.2%)] and fetal hemoglobin [0.5% (normal range <1.5%)] were not increased. High-pressure liquid chromatography showed a small peak at 4.52 min (Fig. 2) leading to the suspicion of Hb Constant Spring, the most common non-deletional α-thalassemia [1]. However, performing Sanger sequencing of the α-globin gene cluster, neither Hb Constant Spring nor any other point mutation could be detected.

The oxygen saturation curve assessed by spectrophotometer (Fig. 3) confirmed the elevated p50 (4.4 kPa/32.7 mm Hg), which indicates a reduced oxygen affinity of the hemoglobin. Finally, by sequencing the β-globin gene (Fig. 4), a heterozygous mutation c.137 T>C, previously described as hemoglobin Cheverly, was detected.

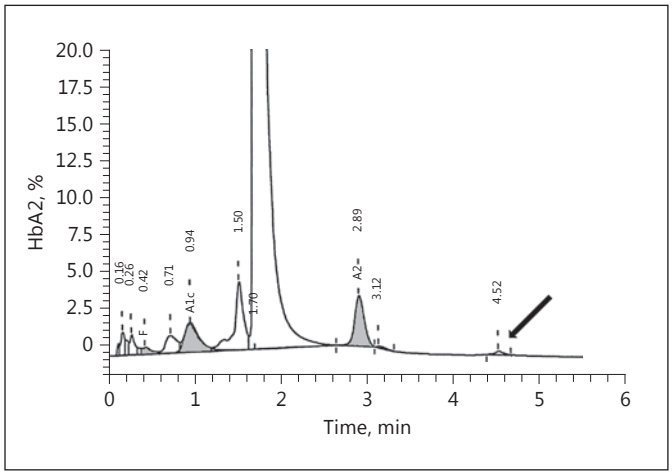

Fig. 2. Cation-exchange high-pressure liquid chromatogram of the patient's blood sample showing an abnormal peak after 4.52 min retention time (arrow).

Discussion

Impairment in gas exchange or ventilation/perfusion mismatches are the most common causes of low SpO_2 in daily routine in pulmonary medicine. Potential sources of error in pulse oximetry are poor peripheral perfusion, skin pigmentation, nail polish, motion artefacts and interfering ambient light. Although anemia does not change the ratio of oxyhemoglobin to deoxyhemoglobin, severe anemia can cause underestimation of SpO_2, especially in hypoxemic subjects, mainly because pulse oximeters are calibrated on healthy subjects without anemia [2, 3]. In general, small amounts of COHb and MetHb are not detected by pulse oximetry and lead to overestimation of SpO_2, if present [4]. Variant hemoglobins are rare causes of falsely low pulse oximetry readings and are usually taken into consideration only after extensive assessment for respiratory and cardiac diseases, exclusion of MetHb, SulfHb, COHb, and other factors disturbing the performance of pulse oximeters [5].

The true SaO_2 is measured by arterial blood gas analysis (applying more than 100 wavelengths). Discordant SaO_2 and SpO_2 values (defined as >5% difference) occur in some variant hemoglobins, with underestimation of the true SaO_2 because these hemoglobins have unusual absorption spectra for which the two wave pulse oximeters are not designed [6]. If SaO_2 and SpO_2 are concordantly low (<5% difference), focus should be on the amount of oxygen dissolved in arterial blood (paO_2). Physiologically, the oxygen saturation increases in an S-shaped curve as paO_2 rises. This curve can shift to the right with increase in temperature, lower pH (acidity) and higher concentrations of CO_2 or 2,3-bisphosphoglycerate [7]. An increased p50 indicates a shift of the curve to the right and towards lower oxygen affinity, which enables the hemoglobin to unload more oxygen in the peripheral tissues. Therefore, at normal paO_2, the tissue oxygenation of hemoglobin Cheverly is not affected, despite a lowered SaO_2.

Hemoglobinopathies are common hereditary diseases and more than 1,000 mutations of the globin chains are described. The quantitative thalassemia syndromes are the most frequent mutations and prevalence can be as high as 95% in certain populations. Most of the qualitative hemoglobinopathies have frequencies below 1% and can be associated with various or even no clinical manifestations [8]. In 1982 and 1983, an elderly Italian male with cyanotic heart disease [9] and an anemic female in Baltimore [10] were the first patients described with the Cheverly variant hemoglobin. In a German observational study, over a period of four decades, only 9 patients within hemoglobin Cheverly have been found [11]. A point mutation in the β-globin gene (single base modification) with replacement of thymidin by cytosin (c.137 T>C) and consecutive replacement of the amino acid phenylalanine by serine (p.45 Phe>Ser) weakens the heme-globin inter-

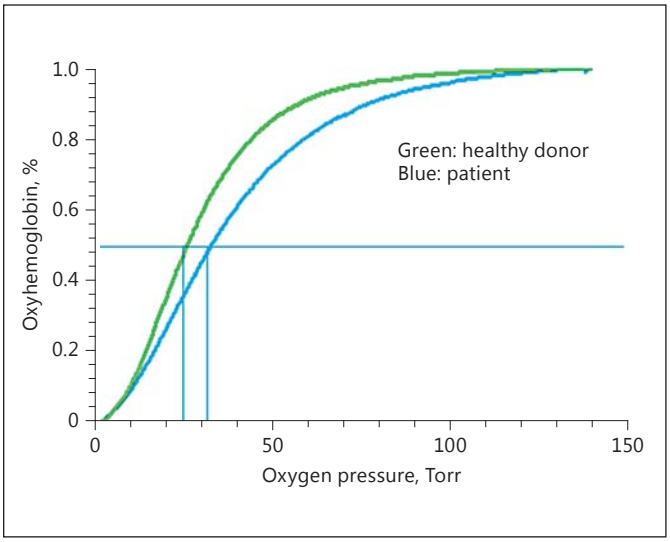

Fig. 3. Oxygen dissociation curves of normal (healthy donor, green) and low oxygen affinity (patient, blue) hemoglobin measured by dual wavelength spectrophotometer (HemoAnalyzer®, TCS Medical Products, USA). As the p50 value increases (blue curve), the oxygen affinity of hemoglobin decreases (right shift) compared to the healthy donor (green curve).

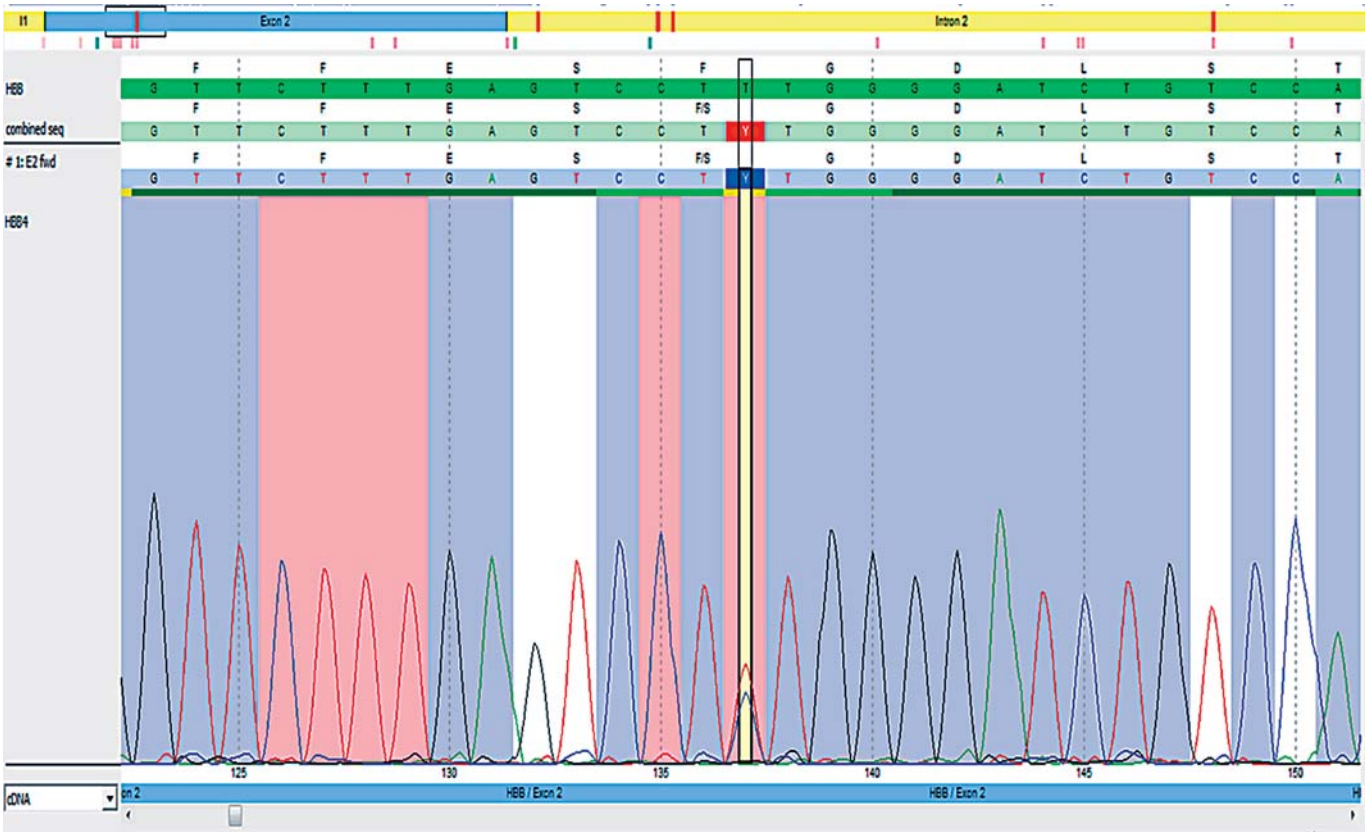

Fig. 4. Sanger sequencing of the β-globin gene cluster. This cutout of the β-globin gene Sanger sequencing of the index patient illustrates the detected base substitution (T>C, indicated by Y) at position codon 137 (highlighted with a box). The reference sequence (HBB) is shown at the top and the four DNA bases (T, C, A, G) are represented by different colors. Further, the location of the mutation in the β-globin gene cluster is illustrated by the boxes above the sequences showing part of intron 1 and 2 as well as exon 2, where the described mutation is indicated with a red bar.

action and can cause instability of the affected β-globin chain. This can cause a mild hemolytic anemia in some of the cases. The low oxygen affinity of hemoglobin Cheverly causes the slightly decreased SaO_2 in the presence of a normal paO_2 measurement. In addition, the abnormal absorption spectrum of hemoglobin Cheverly explains the discordantly lower SpO_2 compared with SaO_2 [12, 13].

Conclusion and Clinical Implications

In rare cases, a variant hemoglobin can be the reason for falsely low SpO_2 readings and has to be considered in patients without any cardiopulmonary symptoms. Examination by electrophoresis and high-pressure liquid chromatography might not be sufficient to detect hemoglobinopathy, and sequencing of the globin genes might be necessary. Variant hemoglobins that have an abnormal absorption spectrum should be suspected if SpO_2 and SaO_2 are discordant. Low-affinity hemoglobin is present if p50 is elevated. In the case of hemoglobin Cheverly, both factors contribute to the abnormal constellation of decreased SaO_2 and SpO_2. Hemoglobin Cheverly is not expected to cause symptoms, but counselling of the affected individuals and equipping them with emergency cards can avoid unnecessary diagnostic and therapeutic procedures in case of routine medical interventions or medical emergencies, where the attending physician has to know about the inaccurate pulse oximeter reading. Further, we suggest a screening of family members simply by measuring SpO_2 with a pulse oximeter.

Key Words
Low oxygen saturation · Hemoglobinopathy · Hemoglobin Cheverly

References

1 Wisedpanichkij R, Jindadamrongwech S, Butthep P: Identification of Hb Constant Spring (HBA2:c.427T>C) by an Automated High Performance Liquid Chromatography Method. Hemoglobin 2015;39:190–195.
2 Chan ED, Chan MM, Chan MM: Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. Respir Med 2013;107:789–799.
3 Severinghaus JW, Koh SO: Effect of anemia on pulse oximeter accuracy at low saturation. J Clin Monit 1990;6:85–88.
4 Ralston AC, Webb RK, Runciman WB: Potential errors in pulse oximetry. I. Pulse oximeter evaluation. Anaesthesia 1991;46:202–206.
5 Zur B, Bagci S, Ludwig M, Stoffel-Wagner B: Oxygen saturation in pulse oximetry in hemoglobin anomalies. Klin Padiatr 2012;224:259–265.
6 Verhovsek M, Henderson MP, Cox G, Luo HY, Steinberg MH, Chui DH: Unexpectedly low pulse oximetry measurements associated with variant hemoglobins: a systematic review. Am J Hematol 2010;85:882–885.
7 Hamilton C, Steinlechner B, Gruber E, Simon P, Wollenek G: The oxygen dissociation curve: quantifying the shift. Perfusion 2004;19:141–144.
8 Hardison RC, Chui DH, Giardine B, Riemer C, Patrinos GP, Anagnou N, Miller W, Wajcman H: HbVar: a relational database of human hemoglobin variants and thalassemia mutations at the globin gene server. Hum Mutat 2002;19:225–233.
9 Sciarratta GV, Sansone G, Valbonesi M, Wilson JB, Lam H, Webber BB, Headlee ME, Huisman TH: Hb Cheverly or alpha 2 beta 2 45(CD4)Phe replaced by Ser in an elderly Italian male. Hemoglobin 1982;6:419–421.
10 Yeager AM, Zinkham WH, Jue DL, Winslow RM, Johnson MH, McGuffey JE, Moo-Penn WF: Hemoglobin Cheverly: an unstable hemoglobin associated with chronic mild anemia. Pediatr Res 1983;17:503507.
11 Kohne E, Kleihauer E: Hemoglobinopathies: a longitudinal study over four decades. Dtsch Arztebl Int 2010;107:65–71.
12 Hohl RJ, Sherburne AR, Feeley JE, Huisman TH, Burns CP: Low pulse oximeter-measured hemoglobin oxygen saturations with hemoglobin Cheverly. Am J Hematol 1998;59:181–184.
13 Yodfat UA, Vaida SJ: Unexpected falsely low pulse oximeter measurements in a child with hemoglobin Cheverly. Anesth Analg 2006;103:259–260.