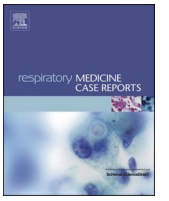
Respiratory Medicine Case Reports 38 (2022) 101681

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case report

Hemoglobin Rothschild – Unimpaired physical performance and oxygen uptake – A case report with literature review

Alexey Fomenko [a,b,*], Thomas Kolokowski [b], Detlev Heyse [b], Polina Petkova [d], Malak Hassan [d], Kaweh Rezazadegan [d], Niklas Walther [c], Dominic Dellweg [e]

[a] Institute for Virology, Universitätsklinikum Freiburg, Germany
[b] Department for Pulmonary Medicine, Intensive Care Medicine and Sleep Medicine, Fachkrankenhaus Kloster Grafschaft GmbH, Germany
[c] Charité Research Organisation, Charité, University Medicine Berlin, Germany
[d] Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany
[e] Department for Internal Medicine, Pulmonary Medicine and Gastroenterology, Pius-Hospital Oldenburg, Germany

ARTICLE INFO

Keywords:
Hb variant
Hb Rothschild
VO_2 max
Oxygen gap
Pulse oximetry
CO-oximetry

ABSTRACT

Asymptomatic patients with hemoglobin (Hb) variants can be detected by low oxygen levels in pulse oximetry (SpO_2).

Depending on the type of Hb variant, low SpO_2 values are either falsely low, with corresponding normal arterial oxygen saturation (SaO_2), or truly low, with low SaO_2 values, as observed in Hb variants with low oxygen binding affinity. In this context, attention must be paid to the method of determining SaO_2.

Low oxygen affinity Hb variants such as Hb Rothschild (HbR) might compensate for low oxygen loading in the lung through unloading more oxygen in peripheral tissues. This is the first case report to illustrate that maximal oxygen uptake and the workload are unimpaired in HbR variant patients.

1. Introduction

Hemoglobin variants are mutants of adult hemoglobin (HbA) due to mutations in globin chain genes.

Over 1000 Hb variants have been described, most of which are clinically inapparent and have normal oxygen saturation measurements by pulse oximetry (SpO_2), while a few produce symptoms of varying severity or low SpO_2 readings [1,2].

Point mutation in β-globin gene of Hb Rothschild (HbR) causes a substitution of tryptophane to arginine (β37(C3)Trp → Arg) that results in a unique oxygen binding affinity, as physico-chemical studies demonstrated [3,4]. It was shown that HbR in the fully deoxygenated state has a higher oxygen affinity than the (deoxygenated) T state of HbA. In the oxygenated state however, HbR dissociates into αβ-dimers that have lower affinity. These phenomena explain the simultaneous high and low oxygen affinity, whereas the predominance of dimers explains the overall low binding affinity [4,5].

While reduced SpO_2 and SaO_2 values in HbR have been previously described [2,6], the effects on physical performance and oxygen uptake of HbR patients have not yet been described to the best of our knowledge.

Additionally, to characterize clinical features of HbR patients we performed a literature review.

* Corresponding author. Institute for Virology, Universitätsklinikum Freiburg, Hermann-Herder-Straße 11, 79104, Freiburg im Breisgau, Germany.
E-mail address: alfom100@hhu.de (A. Fomenko).

https://doi.org/10.1016/j.rmcr.2022.101681
Received 25 November 2020; Received in revised form 13 May 2022; Accepted 28 May 2022
Available online 3 June 2022

Table 1
Blood gas analysis, pulse oximetry and complete blood count.

Parameter	Test results	Normal range
Blood gas analysis		
SaO_2	94%	94–98%
PaO_2	75mmHg	71–104mmHg
PCO_2	41mmHg	35–45mmHg
pH	7.4	7.35–7.45
HCO_3	26mmol/L	21–26mmol/L
Pulse oximetry (SpO_2)	79%	95–100%
Complete blood count		
Hemoglobin	12.7g/dl	12–15 g/dl
Hematocrit	37.6%	33–43%
Erythrocytes	4.2/pl	4.3–5.9/pl
MCV	90.5fl	76-100 fl
MCH	30.6pg	27–33pg
MCHC	33.8g/dl	33–37 g/dl
Leucocytes	7.7/nl	3.2–9.8/nl
Thrombocytes	286/nl	130-400/nl

Table 2
Selected exercise parameters. Notice: deviation of HRR (%) and $\dot{V}O_2$R (%).

Parameter	Rest	VAT	Peak	Pred	Pred%
Time (min)	0:41	10:40	19:18		
RER	0.87	0.89	1.13		
$\dot{V}O_2$ (ml/min)	297	1114	1608	1457	110
$\dot{V}O_2$ R (%)	0	70	113		
$\dot{V}O_2/kg$ (ml/min/kg)	3.6	16	19.4	17.6	110
V_E (L/min)	10	32	59	75	79
Workload (W)	0	53	97	80	121
HR (1/min)	75	109	150	159	94
HRR (%)	0	40	89		
$\dot{V}O_2/HR$ (ml)	4	12	10.7	9.8	109

Notes: HR = heart rate; HRR = heart rate reserve; RER = respiratory exchange ratio; VAT = ventilatory anaerobic threshold V_E = ventilation; $\dot{V}O_2$ = oxygen uptake; $\dot{V}O_2/HR$ = oxygen pulse; $\dot{V}O_2$R = oxygen uptake reserve.

2. Case presentation

A 61-year-old female patient presented to our hospital for evaluation of a low SpO_2 discovered 4 months ago prior to a meniscal surgery. Preoperatively, SpO_2 was measured at 78% and the surgery was postponed.

She denied dyspnea, orthopnea, fever, cough, chest pain or exposure to any medications. Apart from a medial meniscus tear, her medical and family history was unremarkable. She has a 15 pack year history of smoking and lives a sedentary lifestyle, BMI was 29.4kg/m^2.

Vital signs were obtained: blood pressure: 110/70mmHg, respiratory rate 15/min, heart rate 67/min, temperature: 36.8°C, oxygen saturation 79%. Cardiopulmonary examination was normal and there was no clubbing nor cyanosis. Chest X-ray, pulmonary function tests and cardiac stress test were all reportedly normal.

Laboratory tests and blood gas analysis results, as well as pulse oximetry readings are listed in Table 1.

Cardiopulmonary exercise testing (CPET) close to maximal exertion was carried out using cycle ergometry and ramp protocol of 5 Watts per minute. The patient stopped the test due to general fatigue. Referring to Table 2 and Fig. 1 she achieved 110% of predicted maximal oxygen uptake (VO_2max), ventilatory anaerobic threshold 76% of predicted VO_2 peak (VAT), 121% of predicted workload and an 109% of predicted oxygen pulse ($\dot{V}O_2$/HR).

On a detailed query, the patient revealed that she was diagnosed with Hb Rothschild 30 years ago after a hospitalization related to childbirth. Since she was otherwise healthy, she did not seek medical attention until she suffered a meniscal injury and the subsequent preoperative evaluation revealed the low SpO_2.

3. Discussion

According to the diagnostic algorithm proposed by Verhovsek et al. for unexpectedly low SpO_2 values, a low SpO_2 warrants an investigation for cardiorespiratory diseases [2]. Following the clinical examination blood gas analysis with CO-oximetry should be considered as an initial test. The assessment of SpO_2 and CO-oximetrically measured SaO_2 are helpful in such cases, as this allows to correctly classify dicordant and concordant saturations. While discordant saturations indicate Hb variants with variable

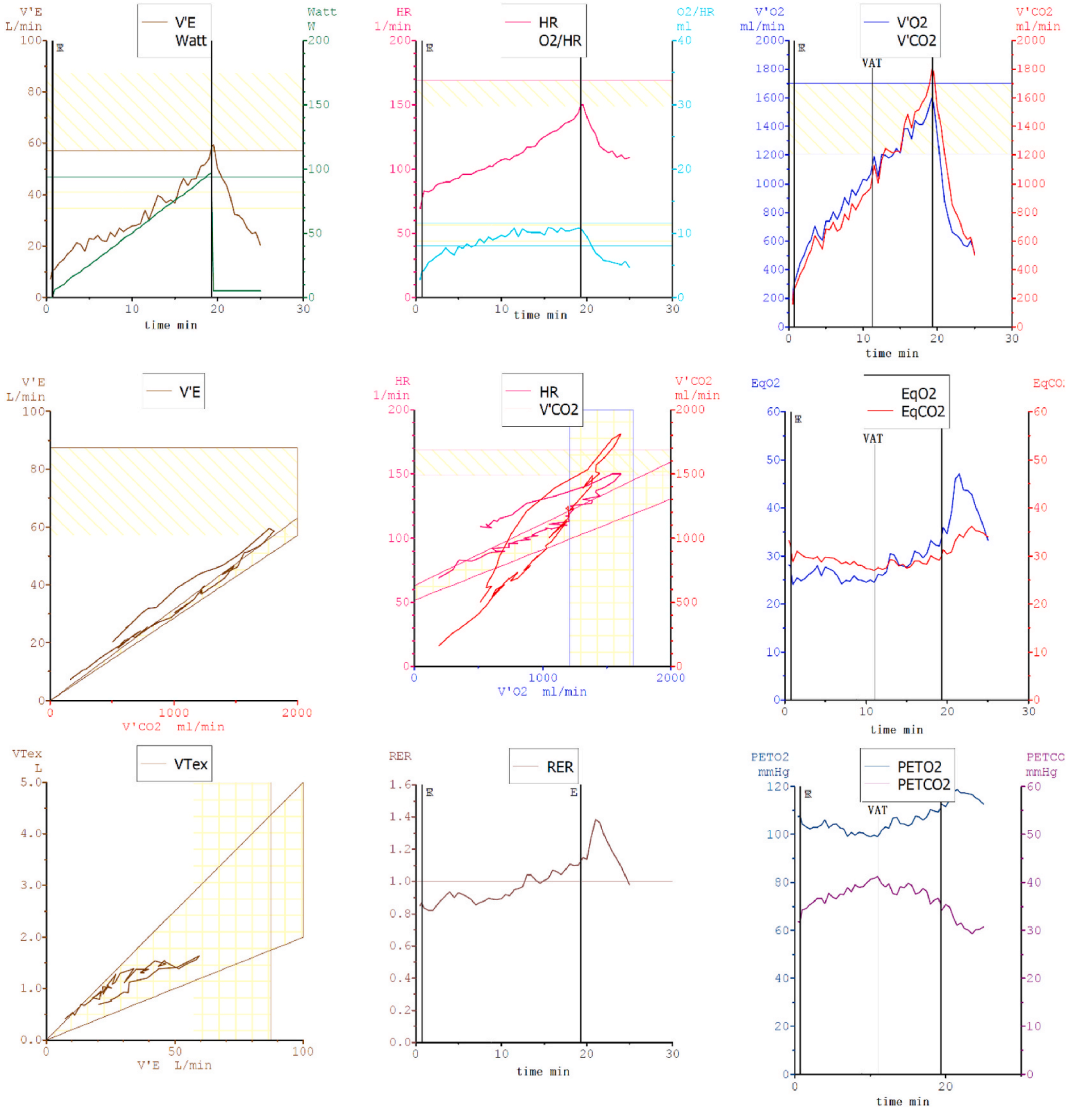


Fig. 1. Nine panel plot demonstrating no cardiopulmonary limitation.
Notice: $\dot{V}O_2$max 110% of predicted (Panel 3), workload 121% of predicted (Panel 1) notes: EqO_2 and $EqCO_2$ = ventilatory equivalent of oxygen and carbon dioxide; HR = heart rate; RER = respiratory exchange ratio; V'_E = ventilation; $\dot{V}CO_2$ = carbon dioxide production; $\dot{V}O_2$ = oxygen uptake; $\dot{V}O_2/HR$ = oxygen pulse; $\dot{V}O_2$ R = oxygen uptake reserve; VTex = tidal volume (expiratory), PETO2 and PETCO2 = end-tidal pressure of oxygen and carbon dioxide.

Hb-oxygen-affinity, concordant saturations indicate hypoxemia and thus either cardiopulmonary disease or low-affinity variants.

Over 1000 Hb variants have been described, most of which have normal SpO_2 values.

For some Hb variants, however, the reliability of pulse oximetry is limited as its function is based on light absorption by oxyhemoglobin and deoxyhemoglobin of the adult hemoglobin (HbA) [7]. Therefore, pulse oximetry measurement is invalid in the presence of Hb variants whose absorption spectra differ from those of HbA, and oxygen saturation measurements by pulse oximetry (SpO_2) do not necessarily reflect true arterial oxygen saturation (SaO_2) [6].

In such instances, blood-gas analyzers with integrated CO-oximeters can overcome these limitations and provide reliable SaO_2 results. SaO_2 measurement by CO-oximetry is based on a spectrophotometric method where different wavelengths of light are emitted to directly measure the concentrations of oxyhemoglobin, deoxyhemoglobin and dyshemoglobins rendering this method accurate for SaO_2 measurement in the presence of Hb variants.

In contrast, blood gas analyzers which rely on empirical equation for SaO_2 determination calculate SaO_2 from measured PaO_2 and assume that factors affecting the oxygen-haemoglobin dissociation curve, such as Hb variants, are normal [8].

Hb variants demonstrating low SpO_2 values are most commonly erroneously low compared to SaO_2 due to altered absorption spectra. This phenomenon is called oxygen (saturation) gap and is considered as discordance of greater than or equal to 5% between SpO_2 and measured SaO_2 by cooximetry [2].

Table 3
Literature review of hemoglobin Rotschild cases.

Author (Year)	Case no.	Age in years (gender)	Ancestry of the patient	Symptoms	Hb (g/dl)	HbR (%)	SpO_2 (%)	SaO_2 (%)	PaO_2 (mmHg)	Family history
Danish et al. (1982) [14]	1	33 (f)	Germany	fatigue	11.5	38	NA	NA	NA	Child of case no. 3
	2	23 (m)	Germany	no	13.5	37	NA	NA	NA	Child of case no. 3
	3	55 (f)	Germany	fatigue	13.6	38	NA	NA	NA	Positive (children: case no. 1&2)
	4	27 (f)	USA	no	12.8	~50	NA	NA	NA	negative
Bruns et al. (2003) [6]	5	53 (f)	Korea	no	normal	40.3	83	86	94	Positive (2 children)
Hladik et al. (2008) [15]	6	5 (m)	Italy	no	11.4	39.5	81	NA	47	Probably positive (as SpO_2 in mother, maternal grandfather, maternal uncle)
Alli et al. (2017) [16]	7	27 (f)	Netherlands	episode of cyanosis during chest infection in pregnancy	11.5	38.1	81	NA	95	Probably positive (as SpO_2 and cynosis during chest infection of brother, and low SpO_2 in father)
Gonzalez Garcia et al. (2019) [17]	8	53 (m)	Spain	no	normal	35	76	76	41	Probably (SpO_2 low in sister and 2 nephews)

Notes: Hb = hemoglobin concentration, Hb R = Proportion of Hb R, NA = not available.

It is not possible to correlate between the oxygen gap phenomenon and the affinity property of a Hb variant, since the phenomenon could be caused by Hb variants with normal, high and low oxygen affinity [2].

Whereas concordant low SpO_2 and SaO_2 readings are produced by Hb variants with low affinity [2,9]. In Hb variant, this constellation indicates true but most commonly clinically asymptomatic hypoxemia, since oxygen unloading in peripheral tissues is increased and therefore no signs of tissue hypoxemia occur, so PaO_2 values are normal [9].

When SaO_2 results are evaluated in suspected Hb variants, attention should be paid to the method on which the SaO_2 determination is based. This is particularly evident in low oxygen affinity Hb variants with low SpO_2. In this Hb variants, due to normal PaO_2 values blood gas analyzers which calculate SaO_2 based on PaO_2 will show incorrectly normal SaO_2 results. Whereas CO-oximetry-based SaO_2 measurement would result in a correctly low SaO_2, thus providing concordant low SpO_2 and SaO_2 results, thereby indicating a low affinity variant. This provides a first guess for the Hb affinity, which would otherwise not be possible based on calculated SaO_2 results.

This explains why discordant SpO_2 and SaO_2 results were obtained in our patient, even though the HbR variant is a known variant with low oxygen affinity and concordant low saturation values, as our hospital operates with blood gas analyzers that calculate SaO_2.

HbR variant has a complex and unique oxygen binding property with simultaneous high and low oxygen binding affinity depending on the conditions and an overall low oxygen binding curve. In the oxygenated R state, HbR dissociates into αβ-dimers, which have low oxygen affinity. While the deoxygenated T state of the Hb Rothschild has higher affinity for ligands than HbA [4,5,10].

The low oxygen affinity, owing to dissociation into dimers, impairs O_2 uptake in the lungs [3]. Increased oxygen delivery to the peripheral tissues has been described for other low affinity Hb variants [1], however, to potulate an analogy for HbR is difficult, as HbR has high affinity in the T-state. Thus, in attempt to translate this biochemical property into the oxygen transport physiology of the HbR variant, even a reduced oxygen transport capacity could be hypothesized.

However, our patient showed no signs of impairment of the oxygen carrying capacity in the CPET. We observed unimpaired maximal oxygen uptake ($\dot{V}O_2$max 110% of predicted), normal workload (121% of predicted) and oxygen pulse ($\dot{V}O_2/HR$ 109% of predicted).

Cardiorespiratory reserve was preserved at $\dot{V}\,O_2$max, suggesting a cardiorespiratory economization possibly due to HbR oxygen transport capacity. Accordingly, a deviation of % $\dot{V}O_2$R and %HRR could be determined, values which are normally closely correlated [11].

These observations are in line with animal studies on low affinity Hb variants which showed enhanced physical performance, increased tissue oxygenation and O_2 consumption [12], and increased left ventricular work [13].

To assess the clinical characteristics of reported hemoglobin Rothschild cases we performed a literature review in PubMed (MEDLINE), Web of Science and Google Scholar using the terms "hemoglobin Rothschild" or "Hb Rotschild". Furthermore, a manual search of the reference lists of all included publications was performed. Articles were included if symptoms of hemoglobin Rothschild patients were reported, whereas we excluded articles that focused exclusively on the physicochemical properties of the HbR molecule without reporting clinical findings. Table 3 summarizes the clinical characteristics of selected cases.

We identified 5 studies reporting on 8 cases. The first case report was published in 1982 by Danish et al. [14], while the remaining case reports were published after 2000 [6,15–17]. All but one of the patients were caucasian. Overall, the clinical presentation was mild at most. Mild anemia was present in one case, and cyanosis was reported in a pregnant HbR patient during a respiratory infection

in another case [14,16]. While a child with HbR did not show cyanosis during a pneumonia. Fatigue was reported in two cases.

The occassional mild anemia in HbR can be explained by compensatory decrease in erythropoiesis due to the increased oxgyen delivery to periphery [15,16] and has also been described in patients with other low affinity hemoglobin variants [9]. Whereas the explanations for fatigue and cyanosis in Hb Rothschild need further confirmation through future reports, as it might also reflect coincidence.

Pulse oximetry has been used to screen family members of an HbR patient in three articles [6,16,17]. In addition to early identification and counseling of the patient about the condition and low SpO_2 levels, an emergency card might avoid unnecessary investigations and anxiety in future medical care [18]. As far as intraoperative monitoring of HbR patient is concerned, focus on CO-oximetrically measured SaO_2 or PaO_2 in conjunction with the trend of SpO_2 might be more valuable than absolute SpO_2 values in HbR variant.

4. Conclusions

Low SpO_2 values in asymptomatic patients should raise high suspicion of Hb variant, as otherwise unnecessary diagnostic interventions could be the consequence.

In such cases, in addition to the reduced SpO_2 values SaO_2 results should be evaluated, with preference being given to cooximetric SaO_2 measurement.

The clinical implication regarding oxygen uptake and physical performance of patients with Hb variants can be evaluated by CPET. Our case report suggests that oxygen uptake and physical performance are unimpaired in HbR patients, despite the complex oxygen binding properties of this Hb variant.

Declaration of competing interest

The authors have no conflicts of interest to disclose regarding this case report and review.

References

[1] C.S. Thom, C.F. Dickson, D.A. Gell, M.J. Weiss, Hemoglobin variants: biochemical properties and clinical correlates, Cold Spring Harb. Perspect. Med. 3 (3) (2013), a011858.
[2] M. Verhovsek, M.P. Henderson, G. Cox, H.Y. Luo, M.H. Steinberg, D.H. Chui, Unexpectedly low pulse oximetry measurements associated with variant hemoglobins: a systematic review, Am. J. Hematol. 85 (11) (2010) 882–885.
[3] G. Gacon, O. Belkhodja, H. Wajcman, D. Labie, A. Najman, Structural and functional studies of Hb Rothschild beta (C3) Trp replaced by Arg. A new variant of the alpha1beta2 contact, FEBS Lett. 82 (2) (1977) 243–246.
[4] V.S. Sharma, G.L. Newton, H.M. Ranney, F. Ahmed, J.W. Harris, E.H. Danish, Hemoglobin Rothschild (beta 37(C3)Trp replaced by Arg): a high/low affinity hemoglobin mutant, J. Mol. Biol. 144 (3) (1980) 267–280.
[5] R.I. Handin, E. Samuel, Stossel, P. Thomas, BLOOD, Principles & Practice of Hematology, second ed., Lippincott, Williams & Wilkins, 2003, p. 1623.
[6] C.M. Bruns, L.A. Thet, R.D. Woodson, J. Schultz, K.M. Hla, Hemoglobinopathy case finding by pulse oximetry, Am. J. Hematol. 74 (2) (2003) 142–143.
[7] E.D. Chan, M.M. Chan, M.M. Chan, Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations, Respir. Med. 107 (6) (2013) 789–799.
[8] H.W. Breuer, H. Groeben, J. Breuer, H. Worth, Oxygen saturation calculation procedures: a critical analysis of six equations for the determination of oxygen saturation, Intensive Care Med. 15 (6) (1989) 385–389.
[9] J. Yudin, M. Verhovsek, How we diagnose and manage altered oxygen affinity hemoglobin variants, Am. J. Hematol. 94 (5) (2019) 597–603.
[10] C.S. Craik, I. Vallette, S. Beychok, M. Waks, Refolding defects in hemoglobin Rothschild, J. Biol. Chem. 255 (13) (1980) 6219–6223.
[11] D.P. Swain, J.A. Parrott, A.R. Bennett, J.D. Branch, E.A. Dowling, Validation of a new method for estimating VO2max based on VO2 reserve, Med. Sci. Sports Exerc. 36 (8) (2004) 1421–1426.
[12] T. Shirasawa, M. Izumizaki, Y. Suzuki, A. Ishihara, T. Shimizu, M. Tamaki, et al., Oxygen affinity of hemoglobin regulates O2 consumption, metabolism, and physical activity, J. Biol. Chem. 278 (7) (2003) 5035–5043.
[13] G. Berlin, K.E. Challoner, R.D. Woodson, Low-O(2) affinity erythrocytes improve performance of ischemic myocardium, J. Appl. Physiol. 92 (3) (2002) 1267–1276.
[14] E.H. Danish, J.W. Harris, F. Ahmed, H. Anderson, Hb Rothschild (beta 37 (C2) Trp leads to Arg): clinical studies, Hemoglobin 6 (1) (1982) 51–55.
[15] A. Hladik, K. LynShue, Dyshemoglobinemias and pulse oximetry: a therapeutic challenge, J. Pediatr. Hematol. Oncol. 30 (11) (2008).
[16] N.A. Alli, P. Wessels, N. Rampersad, B.E. Clark, S.L. Thein, Detection of Hb Rothschild HBB: c.[112t>A or 112T>C], through high index of suspicion on abnormal pulse oximetry, Hemoglobin 41 (2) (2017) 137–139.
[17] L.M. González García, J.M. Hernández Pérez, M. Tapia Torres, P. Ropero Gradilla, Hemoglobin Rothschild: a rare cause of low arterial oxygen saturation, Arch. Bronconeumol. 55 (12) (2019) 657–659.
[18] S. Guler, S. Brunner-Agten, S. Bartenstein, H.U. Bettschen, T. Geiser, P. Keller, et al., Oxygen saturation of 75% but No Symptoms!, Respiration 92 (6) (2016) 420–424.