Case report

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

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ABSTRACT

Asymptomatic patients with hemoglobin (Hb) variants can be detected by low oxygen levels in pulse oximetry (SpO₂).

Depending on the type of Hb variant, low SpO₂ values are either falsely low, with corresponding normal arterial oxygen saturation (SaO₂), or truly low, with low SaO₂ values, as observed in Hb variants with low oxygen binding affinity. In this context, attention must be paid to the method of determining SaO₂.

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 (SpO₂), while a few produce symptoms of varying severity or low SpO₂ 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 SpO₂ and SaO₂ 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.

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E-mail address: alfom100@hhu.de (A. Fomenko).
2. Case presentation

A 61-year-old female patient presented to our hospital for evaluation of a low SpO₂ discovered 4 months ago prior to a meniscal surgery. Preoperatively, SpO₂ 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/m².

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 (VO₂max), ventilatory anaerobic threshold 76% of predicted VO₂ peak (VAT), 121% of predicted workload and an 109% of predicted oxygen pulse (VO₂/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 SpO₂.

3. Discussion

According to the diagnostic algorithm proposed by Verhovsek et al. for unexpectedly low SpO₂ values, a low SpO₂ 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 SpO₂ and CO-oximetrically measured SaO₂ are helpful in such cases, as this allows to correctly classify discordant and concordant saturations. While discordant saturations indicate Hb variants with variable

### Table 1

| Parameter                  | Test results | Normal range          |
|----------------------------|--------------|-----------------------|
| Blood gas analysis         |              |                       |
| SaO₂                       | 94%          | 94-98%                |
| PaO₂                       | 75mmHg       | 71-104mmHg            |
| PCO₂                       | 41mmHg       | 35-45mmHg             |
| pH                         | 7.4          | 7.35-7.45             |
| HCO₃⁻                      | 26mmol/L     | 21-26mmol/L           |
| Pulse oximetry (SpO₂)      | 79%          | 95-100%               |
| Complete blood count       |              |                       |
| Hemoglobin                 | 12.7g/dl     | 12-15 g/dl            |
| Hematocrit                 | 37.6%        | 33-43%                |
| Erythrocytes               | 4.2/µl       | 4.3-5.9/µl            |
| MCV                        | 90.5fl       | 76-100 fl             |
| MCH                         | 30.6gpl      | 27-33gpl              |
| MCHC                        | 33.8g/dl     | 33.3-37g/dl           |
| Leucocytes                 | 7.7/µl       | 3.2-9.8/µl            |
| Thrombocytes               | 286/µl       | 130-400/µl            |

### Table 2

| Parameter            | Rest | VAT | Peak | Pred | Pred% |
|----------------------|------|-----|------|------|-------|
| Time (min)           | 0:41 | 10:40 | 19:18 |      |       |
| RER                  | 0.87 | 0.89 | 1.13 |      |       |
| VO₂ (ml/min)         | 297  | 1114 | 1608 | 1457 | 110   |
| VO₂ (%)              | 0    | 70  | 113  |      |       |
| VO₂/kg (ml/min/kg)   | 3.6  | 16  | 19.4 | 17.6 | 110   |
| VE (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   |      |       |
| VO₂/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 VE = ventilation; VO₂ = oxygen uptake; VO₂/HR = oxygen pulse; VO₂R = oxygen uptake reserve.
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 $\text{SpO}_2$ 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 ($\text{SpO}_2$) do not necessarily reflect true arterial oxygen saturation ($\text{SaO}_2$) \[6\].

In such instances, blood-gas analyzers with integrated CO-oximeters can overcome these limitations and provide reliable $\text{SaO}_2$ results. $\text{SaO}_2$ 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 $\text{SaO}_2$ measurement in the presence of Hb variants.

In contrast, blood gas analyzers which rely on empirical equation for $\text{SaO}_2$ determination calculate $\text{SaO}_2$ from measured $\text{PaO}_2$ and assume that factors affecting the oxygen-haemoglobin dissociation curve, such as Hb variants, are normal \[8\].

Hb variants demonstrating low $\text{SpO}_2$ values are most commonly erroneously low compared to $\text{SaO}_2$ 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 $\text{SpO}_2$ and measured $\text{SaO}_2$ by cooximetry \[2\].

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Fig. 1. Nine panel plot demonstrating no cardiopulmonary limitation.

Notice: $\text{VO}_2\text{max}$ 110% of predicted (Panel 3), workload 121% of predicted (Panel 1) notes: $\text{EqO}_2$ and $\text{EqCO}_2$ = ventilatory equivalent of oxygen and carbon dioxide; $\text{HR}$ = heart rate; $\text{RER}$ = respiratory exchange ratio; $V_E$ = ventilation; $V_{CO}_2$ = carbon dioxide production; $\dot{V}O_2$ = oxygen uptake; $\dot{V}O_2/\text{HR}$ = oxygen pulse; $V_{O}_2 R$ = oxygen uptake reserve; $V_{Tex}$ = tidal volume (expiratory), PET$O_2$ and PET$CO_2$ = end-tidal pressure of oxygen and carbon dioxide.

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A. Fomenko et al.
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 SpO₂ and SaO₂ 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 PaO₂ 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 PaO₂ results will show incorrectly normal SaO₂ values are normal [9].

When SaO₂ results are evaluated in suspected Hb variants, attention should be paid to the method on which the SaO₂ determination is based. This is particularly evident in low oxygen affinity Hb variants with low SpO₂. In this Hb variants, due to normal PaO₂ values blood gas analyzers which calculate SaO₂ based on PaO₂ will show incorrectly normal SaO₂ results. Whereas CO-oximetry-based SaO₂ measurement would result in a correctly low SaO₂, thus providing concordant low SpO₂ and SaO₂ 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 SaO₂ results.

This explains why discordant SpO₂ and SaO₂ 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 SaO₂.

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 O₂ 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 (VO₂max 110% of predicted), normal workload (121% of predicted) and oxygen pulse (VO₂/HR 109% of predicted).

Cardiorespiratory reserve was preserved at VO₂max, suggesting a cardiorespiratory economization possibly due to HbR oxygen transport capacity. Accordingly, a deviation of % VO₂R 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 O₂ 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 Rothschild". 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

### Table 3

| Author                      | Year | Case no. | Age in years (gender) | Ancestry of the patient | Symptoms                                      | Hb (g/dl) | HbR (%) | SpO₂ (%) | SaO₂ (%) | PaO₂ (mmHg) | Family history                                                                 |
|-----------------------------|------|----------|-----------------------|-------------------------|------------------------------------------------|-----------|---------|-----------|-----------|---------------|--------------------------------------------------------------------------------|
| Danish et al.               | 1982 | 1        | 33 (f)                | Germany                 | fatigue                                        | 11.5      | 38      | NA        | NA        | NA            | Child of case no. 3                                                             |
| (14)                        |      | 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)                                               |
| Brunet et al.               | 2003 | 4        | 27 (f)                | USA                     | no                                             | 12.8      | −50     | NA        | NA        | NA            | Negative                                                                         |
| (6)                         |      | 5        | 53 (f)                | Korea                   | no                                             | normal    | 40.3    | 83        | 86        | 94            | Positive (2 children)                                                            |
| Hladik et al.               | 2008 | 6        | 5 (m)                 | Italy                   | no                                             | 11.4      | 39.5    | 81        | NA        | 47            | Probably positive (as SpO₂ in mother, maternal grandfather, maternal uncle)   |
| (15)                        |      |          |                       |                         |                                                |           |         |           |           |               |                                                                                  |
| Ali et al.                  | 2017 | 7        | 27 (f)                | Netherlands             | episode of cyanosis during chest infection in pregnancy | 11.5      | 38.1    | 81        | NA        | 95            | Probably positive (as SpO₂ and cyanosis during chest infection of brother, and low SpO₂ in father) |
| (16)                        |      |          |                       |                         |                                                |           |         |           |           |               |                                                                                  |
| Gonzalez et al.             | 2019 | 8        | 53 (m)                | Spain                   | no                                             | normal    | 35      | 76        | 76        | 41            | Probably (SpO₂ low in sister and 2 nephews)                                    |
| (17)                        |      |          |                       |                         |                                                |           |         |           |           |               |                                                                                  |

Notes: Hb = hemoglobin concentration, Hb R = Proportion of Hb R, NA = not available.
in another case [14,16]. While a child with HbR did not show cyanosis during a pneumonia. Fatigue was reported in two cases.

The occasional mild anemia in HbR can be explained by compensatory decrease in erythropoiesis due to the increased oxygen 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 SpO₂ 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 SaO₂ or PaO₂ in conjunction with the trend of SpO₂ might be more valuable than absolute SpO₂ values in HbR variant.

4. Conclusions

Low SpO₂ 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 SpO₂ values SaO₂ results should be evaluated, with preference being given to cooximetric SaO₂ 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), a001858.
[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 hemoglobin: 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, 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. Izmizaki, 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 (C3) 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>C] through high index of suspicion on abnormal pulse oximetry, Hemoglobin 41 (2) (2017) 137–139.
[17] L.M. Gonzalez García, J.M. Hernández Pérez, M. Tapia Torres, P. Ropero Gradilla, Hemoglobin Rothschild: a rare case 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.