*Case Reports*

# Low Oxygen Affinity Variant Haemoglobin in an elderly woman presenting with low oxygen saturation

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## Abstract

*An asymptomatic 81-year-old woman was referred by her general practitioner regarding a pulse-oximetry oxygen saturation (SpO2) of 74%. An arterial blood gas analysis (ABG) on air showed PaO2 12.9 kPa, oxygen saturation 80%, with normal pH, PaCO2, methaemoglobin and carboxyhaemoglobin levels. After a normal chest x-ray, tinzaparin was administered empirically for possible occult pulmonary embolus. This diagnosis was subsequently excluded with an unremarkable computed tomography pulmonary angiogram (CTPA). She was further investigated as an out patient. DNA globin-gene analysis identified a variant haemoglobin revealed to be haemoglobin Saint Mande (HbSM). Following reassurance regarding the benign nature of her condition, she has remained well.*

## Keywords

*Variant haemoglobin, low oxygen affinity haemoglobin, haemoglobinopathy, hypoxia.*

## Key Points

- Low oxygen affinity haemoglobins should be considered in an asymptomatic patient with discordantly low SpO2 when there is no cardio-pulmonary explanation.
- Further investigative tests include high performance liquid chromatography (HLPC), and/or haemoglobin electrophoresis. Definitive diagnosis is with globin DNA sequencing to establish the mutation.
- Early and accurate diagnosis of variant haemoglobin will facilitate genetic counselling, avoid medical over-evaluation and alleviate patient and family concern.
- Medical diagnosis cards can be useful for patients with low oxygen affinity haemoglobins, for example, in preventing disproportionate medical concern at emergency departments.

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## Case History

An 81-year-old woman was referred by her GP as finger probe oximetry had revealed a SpO2 of 74%. She described mild shortness of breath on climbing hills, consistent with her age. Her past medical history was of treated hypertension and childhood septicaemia. She denied any allergies and over-the-counter medication use. There was no significant family history. She had never smoked and did not consume alcohol. She was fully independent and lived with her husband with no known heating appliance related issues at home.

On examination, she was comfortable at rest. She was afebrile with a regular pulse of 80 per minute, respiratory rate of 18 per minute, and a finger probe SpO2 80% on room air. There was mild central cyanosis. Respiratory examination was normal. Her venous pressure was normal, with no evidence of deep vein thrombosis. Heart sounds were normal, and there was no hepato-splenomegaly or lymphadenopathy.

Eight litres of oxygen was administered in the emergency department and ABG demonstrated PaO2 22.6kPa [normal range: 11 - 13 kPa] with oxygen saturation 94%. The partial pressure of CO2, pH and bicarbonate were normal. A repeat ABG on room air showed PaO2 12.9 kPa, oxygen saturation of 80%, and normal methaemoglobin and carboxyhaemoglobin. Chest x-ray was normal. She had a mild normocytic anaemia; haemoglobin (Hb) 115 g/L [normal range: 115 – 165 g/L].

Although her d-dimer level was normal, occult pulmonary embolism was still considered as a diagnosis to explain her hypoxia. However a CTPA revealed no evidence of pulmonary embolism (PE) to a sub-segmental level, and normal lung parenchyma. With no evidence of cardiorespiratory pathology, the differential of haemoglobinopathy was raised. Outpatient haematology review was arranged.

At review 6 weeks later she remained well. She reported that people had commented on the blue appearance of her lips over many years but she had not sought medical advice. Clinical assessment was again normal except for similarly low SpO2. An echocardiogram showed no evidence of shunt or other cardiac pathology. Globin electrophoresis by

HPLC had identified an abnormal band in the Hb A2 region quantified at 38.8% (Figure. 1). Hb F was <1% and there was no Hb H detected. There was no family history of haemoglobin disease. She had 2 daughters who were both well and who had never experienced cyanotic episodes. Indeed, finger probe SpO2 of one the accompanying daughters in clinic was 98%.

The clinical picture and investigation was indicative of congenital low oxygen affinity variant haemoglobin. Consent was obtained to undergo globin-gene analysis. This demonstrated a mutation in exon 2 of the beta-globin gene at codon 102 (AAC:Asn > TAC:Tyr). This mutation was confirmed to be HbSM. She was reassured and has remained well.

## Discussion

This case describes an asymptomatic elderly woman who was found to have incidental low SpO2 on finger probe pulse oximetry. Investigations eventually led to diagnosis of a benign variant haemoglobin requiring no medical intervention. With pulse oximetry increasingly forming part of the GP toolkit, physician recognition of associated 'low oxygen saturation' referrals are of importance. The team managing her care eventually suspected the possibility of variant haemoglobin through three considerations: a) patient was symptom-free; b) no cardio-pulmonary disease was found and c) discordant values between SpO2 and PaO2.

Low oxygen saturation is most frequently caused by cardio-respiratory pathology. Differential diagnoses include ventilation/perfusion mismatch from pulmonary vascular disease including PE, pneumonia, obstructive airway diseases, interstitial lung disease and congestive cardiac failure, and right to left shunt from cardiac disease. However, in the absence of any cardio-respiratory cause, it is important to consider congenital haemoglobinopathy as a possible explanation for low oxygen saturation resulting from a low affinity haemoglobin. The latter includes HbSM, which presents with low oxygen saturation but other ABG parameters such as oxygen partial pressure remain normal.[1-6] Other causes of low SaO2 with otherwise normal ABG parameters include poor peripheral perfusion diminishing the pulsatile wave form, poor contact from coloured fingernail polish, acquired and hereditary methaemoglobinaemia (Table 1).[11] Methaemoglobinaemia, a toxin-related

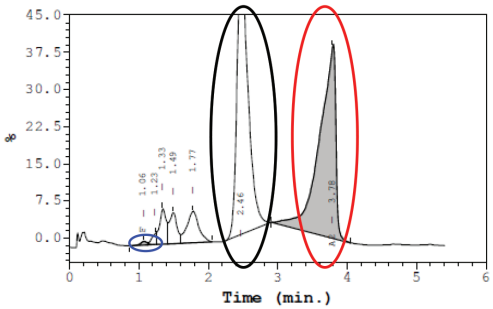
| Peak Name | Calibrated Area % | Area % | Retention Time (min) | Peak Area |
|---|---|---|---|---|
| F | 0.5 | --- | 1.06 | 6873 |
| Unknown | --- | 0.9 | 1.23 | 15894 |
| P2 | --- | 3.3 | 1.33 | 60767 |
| Unknown | --- | 3.3 | 1.49 | 62142 |
| P3 | --- | 5.4 | 1.77 | 99662 |
| Ao | --- | 42.7 | 2.46 | 794992 |
| A2 | 38.8* | --- | 3.78 | 822091 |

Total Area: 1,862,420

**F Concentration = 0.5 %**
**A2 Concentration =38.8*%**

*Values outside of expected ranges

Analysis comments:




Area circled with colour blue represents percentage amount of haemoglobin F.
Area circled with colour black represents percentage amount of haemoglobin Ao.
Area circled with colour red represents an abnormal haemoglobin occupying the haemoglobin A2 position.

**Figure 1.** Haemoglobin electrophoresis report for case.

**Table 1.** Causes of spuriously low oxygen saturation readings.

| *Causes of spuriously low SpO2* |
|---|
| • Equipment failure<br>a. Faulty pulse oximeter<br>b. Faulty arterial blood gas machine |
| • Fingernail polish & excessive movement |
| • Intravenous pigmented dyes |
| • Venous pulsations |
| • Congenital haemoglobinopathies |
| • Methaemoglobinemia (inherited & acquired) |
| • Sulfhaemoglobinemia |
| • Sepsis & septic shock (can also falsely elevate SpO2) |

Table adapted from *Chan et al.* 2013.

cause of low oxygen saturation, forms an important part of the differential diagnosis. Like low oxygen affinity haemoglobins, methaemoglobinaemia can also cause cyanosis.[1] However, methaemoglobin can be readily differentiated from low oxygen affinity haemoglobins. Exposing blood to pure oxygen will cause methaemoglobin to turn chocolate brown whilst low oxygen affinity haemoglobins will turn bright red reflecting fully oxygenated blood.[3, 7] Carbon monoxide poisoning is another important toxin related effect but rather causes a normal or falsely elevated finger probe SpO2.[11]

Low oxygen affinity haemoglobins have an oxygen-haemoglobin dissociation curve physiologically shifted to the right of normal (Figure 2).[3] Therefore, the point on the curve to which Hb is half-saturated with oxygen is higher than normal (increased p50). Although these haemoglobins run lower arterial oxygen saturations for a given partial pressure compared to normal, oxygen delivery to tissues is preserved or even enhanced meaning that there is no need for medical intervention above simple advice and reassurance.

Individuals with HbSM typically have an arterial SaO2 of around 80% with normal PaO2.[1, 3] Due to the propensity of these haemoglobins to deoxygenate, cyanosis can occur. Furthermore,

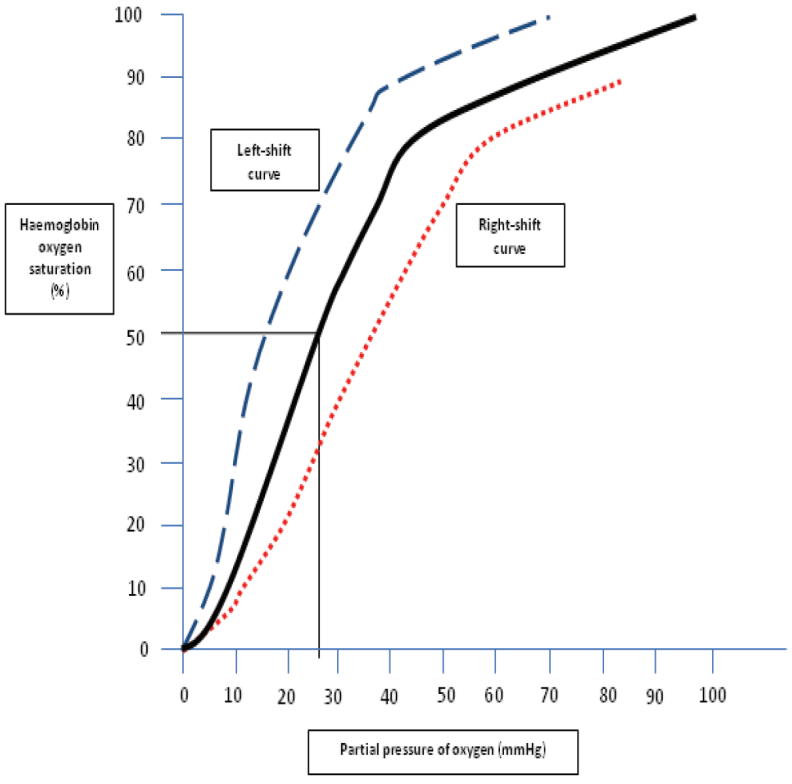



**Figure 2.** Oxygen-haemoglobin dissociation curve.

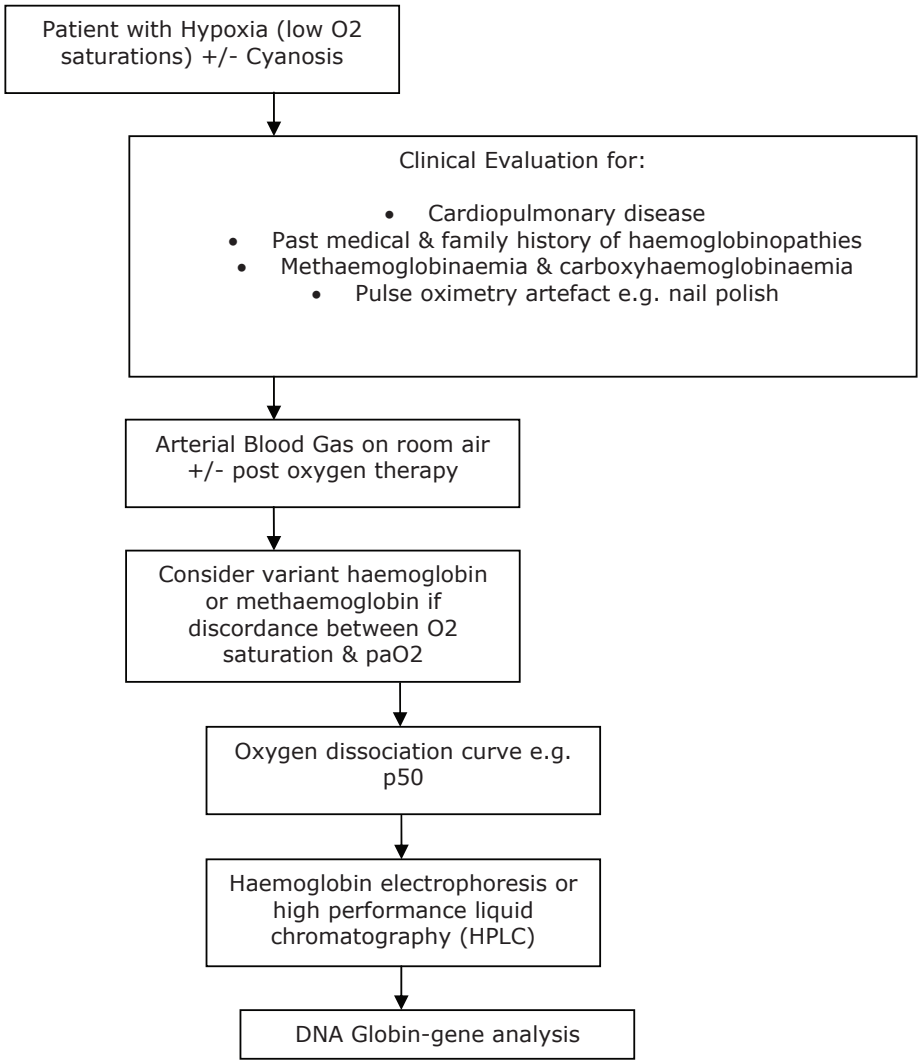



Figure adapted from Verhovsek et al. 2011.

**Figure 3.** Algorithm towards evaluation of a low oxygen affinity haemoglobin.

ensuing from its properties in maintaining oxygen tissue delivery, a mild anaemia can be an accompanying clinical manifestation. The first patient described to have HbSM exhibited cyanosis of the lips and a haemoglobin concentration of 9.6g/dL.[1] However, low oxygen affinity haemoglobins do not always produce cyanosis and anaemia.

HbSM arises from a gene substitution mutation on the β-chain of haemoglobin.[1] This allows for molecular conformational alteration of regions affecting interaction of haemoglobin and oxygen such that haemoglobin has a predisposition towards the deoxygenated state.[3]

Investigative tests include performing an oxygen-dissociation curve (p50), HLPC, and/or Hb electrophoresis (Figure 3). Definitive diagnosis is by globin DNA sequencing to establish the mutation.

Diagnosis of low oxygen affinity haemoglobins is strikingly rare. A systematic review was performed for reports of low oxygen saturation and confirmed variant Hb between the years of 1950 to 2010.[2] During this period, 25 publications were found with data from 41 patients matching these criteria, with an age range from neonate to 63 years old.

Our case is made more unusual as this congenital diagnosis was identified in an octogenarian. Although asymptomatic, concern regarding her low SpO2 spurned a plethora of investigations and treatment including repeated ABG's, treatment dose anticoagulation and a CTPA despite normal d-dimer. Administering supplemental oxygen is also not without risk; worsening ventilation/perfusion mismatch, absorption atelectasis and coronary and

cerebral vasoconstriction have all been reported with hyperoxaemia caused by supplemental oxygen.[7,8,9]

Early recognition and diagnosis of low oxygen affinity haemoglobins allows for appropriate genetic counselling of patient and family. Secondly, medical over-evaluation and treatment can then be prevented; in this case an explanatory alert card was given to the patient for future medical encounters.

## Conflict of interest

Nothing to declare.

## References

1. Arous N, Braconnier F, Thillet J, *et al*. Hemoglobin Saint Mandé beta 102 (G4) asn replaced by tyr: a new low oxygen affinity variant. *FEBS Letters*. 1981; **126(1)**: 114–116.
2. Verhovsek M, Henderson M, Cox G, *et al*. Unexpectedly low oximetry measurements associated with variant hemoglobins: A systematic review. *American Journal of Hematology*. 2011; **85(11)**: 882–885.
3. Nagel RL. *Disorders of Hemoglobin Function and Stability*. In Steinberg MH. *et al*. Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical management. *2nd ed. Cambridge University Press*, 2009.
4. Kutlar F, Unguru Y, Dixon N, *et al*. Two New Hemoglobin Variants: Hb Tallahassee [α3(A1)Ser Tyr; HbA2: c. 11C>A] and Hb Madison-NC [β119 (GH2) Gly Ser; HBB: c. 358G>A]. *Hemoglobin*. 2014; **38(3)**: 207–210.
5. Bonaventura J. & Riggs A. Hemoglobin Kansas, a human haemoglobin with a neutral amino acid substitution and an abnormal oxygen equilibrium. *The Journal of Biological Chemistry*. 1968; **243**: 980.
6. Nagel RL, Lynfield J, Johnson J, *et al*. Hemoglobin Beth Israel. A mutant causing clinically apparent cyanosis. *New England Journal of Medicine*. 1976; **295**: 125.
7. Feller-Kopman D. & Schwartzstein R. The role of hypoventilation and ventilation perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine* 2001; **163**: 1755.
8. Downs JB. Has oxygen administration delayed appropriate respiratory care? Fallacies regarding oxygen therapy. *Respiratory Care* 2003; **48**: 611–20.
9. Thomson AJ, Webb DJ, Maxwell SR, *et al*. Oxygen therapy in acute medical care. *British Medical Journal* 2002; **324**: 1406–7.
10. Rehman HU. Methaemoglobinaemia. *Western Journal of Medicine*. 2001; **175(3)**: 193–196.
11. Chan ED, Chan MM, & Chan MM. Pulse oximetry: Understanding its basic principles facilitates appreciation of its limitations. *Respiratory Medicine* 2013; **107(6)**: 789–799.