


CASE REPORT

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# A long-lasting low oxygen saturation hiding Titusville hemoglobin diagnosis in a premature 14-month-old child – case report

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## Abstract

**Background** There are some clinical conditions that can impact the accuracy of  $\text{SpO}_2$  measurements, leading to an incorrect diagnosis of hypoxemia. Low oxygen affinity hemoglobinopathy can present with low  $\text{SpO}_2$  and discordance with  $\text{PaO}_2$  and general clinical conditions.

**Case Presentation** We report the case of a 14-month-old male, born extremely premature, with severe bronchopulmonary dysplasia (BPD). He required continuous high-flow nasal cannula (HFNC) oxygen therapy and was hospitalized due to a viral respiratory infection causing dyspnea and desaturation. Once the child clinically recovered, all attempts to wean him off oxygen resulted in rapid drops in  $\text{SpO}_2$ . This occurred despite the absence of increased work of breathing, cyanosis, or abnormal  $\text{PaO}_2$ .

**Conclusions** Severe BPD and recurrent respiratory issues could have per se justified the persistently low  $\text{SpO}_2$ . Incongruence between low  $\text{SpO}_2$  values, normal  $\text{PaO}_2$  levels and good clinical condition, once the child was recovered, raised suspicion of low oxygen affinity hemoglobin (Hb) variants. Abnormal Hb peak detected through high-performance liquid chromatography allowed rare diagnosis of Hb Titusville, confirmed by molecular analysis. In conclusion, the case matched a rare low oxygen affinity hemoglobinopathy (Hb Titusville), highlighting its relevance in unexplained hypoxemia. Diagnosis challenges necessitate a systematic approach to prevent misinterpretations.

**Keywords** Hypoxemia, Hb Titusville, Oxygen therapy, Hemoglobinopathy, Bronchopulmonary dysplasia

## Background

Oxygen saturation measurement by pulse oximeter ( $\text{SpO}_2$ ) is a non invasive, indirect method to estimate the level of oxygenated hemoglobin (Hb). Pulse oximetry has become a common practice in many clinical contexts, including the Intensive Care setting, given the good correlation with the arterial partial pressure of oxygen ( $\text{PaO}_2$ ), an invasive measurement of the actual arterial oxygen content. However, there could be some clinical conditions that can impact the accuracy of  $\text{SpO}_2$  measurements, leading to an incorrect diagnosis of hypoxemia. Hemoglobins with low oxygen affinity are a rare

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group of variant Hb, which shift the oxygen-Hb dissociation curve to the right and can present with low  $\text{spO}_2$  and discordance with normal  $\text{PaO}_2$ . A concurrent respiratory disease, as well as bronchopulmonary dysplasia of the preterm, might make it difficult to reach a clinical suspicion.

### Case presentation

A 14-month-old male, born extremely premature (26 weeks gestation), presenting severe bronchopulmonary dysplasia (BPD) that still required continuous high-flow nasal canula (HFNC) oxygen therapy ( $\text{FiO}_2$  0.30) at his age, was hospitalized for dyspnea, desaturation ( $\text{spO}_2$  86% in HFNC,  $\text{FiO}_2$  0.30) and insufficient response to increased amount of oxygen ( $\text{spO}_2$  93% in HFNC,  $\text{FiO}_2$  0.45). His medical history was remarkable for recurrent respiratory exacerbations, which frequently led to hospitalization and transient increase in oxygen level administered.

Human rhinovirus was detected in the nasopharyngeal aspirate and his blood count showed Hb 11.3 g/dl, white blood cells  $17,900 \times 10^9/\text{L}$ , and C-reactive protein 2.63 mg/dl. The child was successfully treated with nebulized albuterol, intravenous steroids and increased oxygen supplementation ( $\text{FiO}_2$  up to 0.45). On day 5 he fully recovered (no pathologic sounds on auscultation, respiratory rate 32 breaths/min, pulse 115 bpm, blood pressure 97/53 mmHg) and  $\text{spO}_2$  returned to pre-exacerbation levels (95% on HFNC,  $\text{FiO}_2$  0.30). However, attempts of oxygen weaning always led to a rapid drop to  $\text{spO}_2$  of 85–88%, though without increased work of breathing, pulse rate or cyanosis. A contrast-enhanced chest CT scan detected the presence of consolidations with aerial bronchogram in the paravertebral portions of the lower lobes (Fig. 1); echocardiographic assessment resulted normal, and the arterial blood gas (ABG) on room air revealed respiratory alkalosis (pH 7.54,  $\text{PaCO}_2$  26 mmHg,  $\text{PaO}_2$  114 mmHg,  $\text{HCO}_3$  25.8 mmol/L).  $\text{SpO}_2$  monitoring, conducted over three separate nights with different respiratory supports (HFNC, CPAP, and BiPAP, respectively) on oxygen supplementation, showed a mean  $\text{SpO}_2$  value of 92%, regardless of the airway pressure used (Fig. 2). Nocturnal transcutaneous carbon dioxide monitoring ( $\text{tCO}_2$ ) was normal (mean value: 38 mmHg, maximum value: 43 mmHg). Incongruence between low  $\text{spO}_2$  values, normal ABG  $\text{PaO}_2$  levels and an overall good clinical condition has raised the suspicion of low oxygen affinity variant Hb.

### Discussion and conclusion

Hypoxemia is defined as a reduction of oxygen tension in the arterial blood. The main underlying mechanisms of hypoxemia are mostly related to ventilation/perfusion (V/Q) mismatch, right-to-left shunt, diffusion

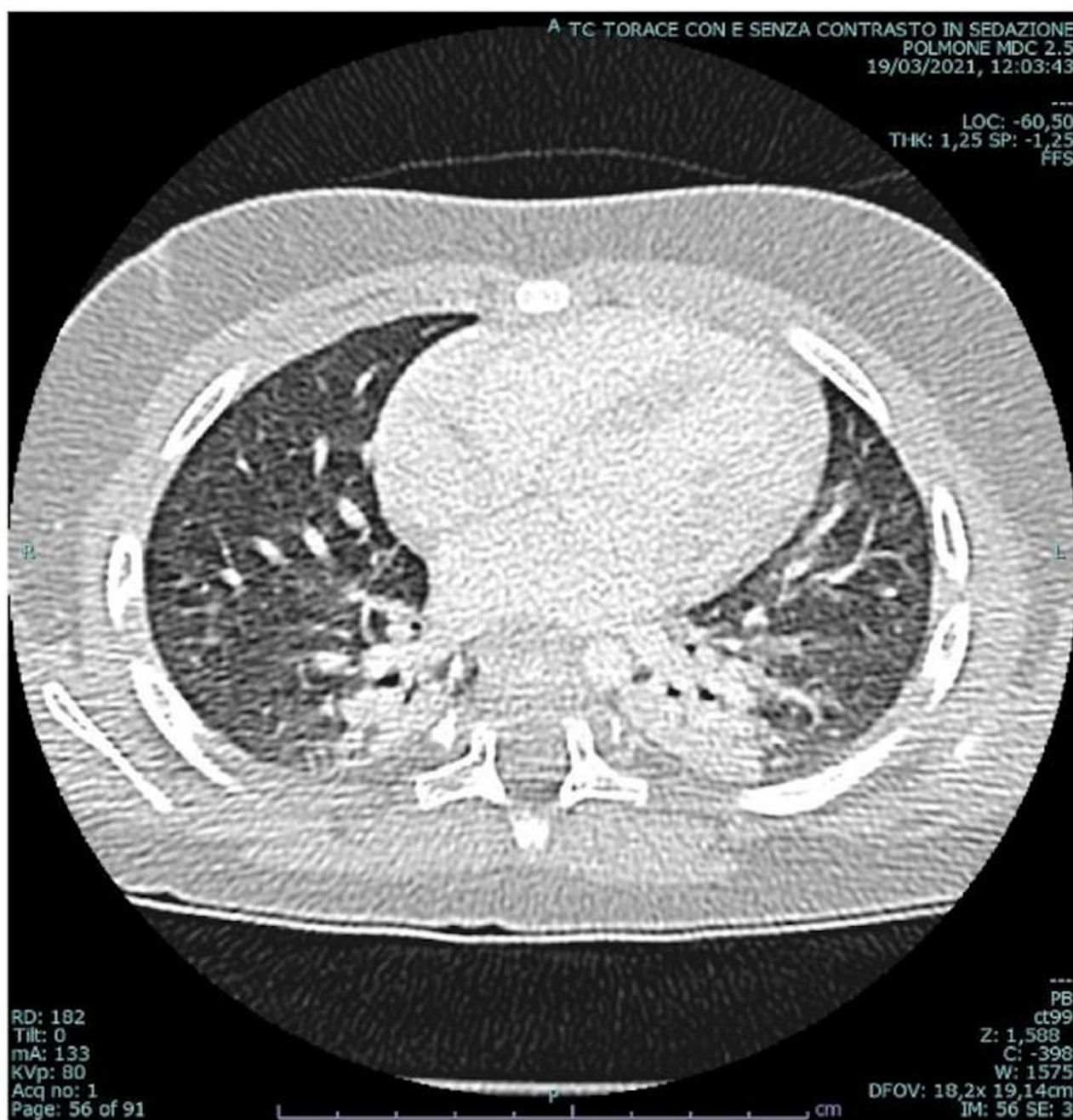
impairment or hypoventilation [1]. The CT scan revealed lung atelectasis with low ventilation/perfusion (V/Q) ratios, which could have contributed to hypoxemia without  $\text{CO}_2$  retention. In such cases, ventilatory support with positive end-expiratory pressure (CPAP or BiPAP) typically improves alveolar recruitment [2] and increases  $\text{SpO}_2$ . However, we did not observe any improvement in  $\text{SpO}_2$  with these interventions.

BPD is the most common complication of prematurity, characterized by a multifactorial disruption of alveolar and vascular development and subsequent chronic sequelae. Approximately one-quarter of extremely preterm BPD infants are discharged with supplemental oxygen to minimize lung injury and promote growth and neurodevelopment [3]. Long-term oxygen therapy may be required for variable duration, the median age of oxygen weaning ranging from 10 to 15 months [4]. Therefore, the requirement of a full-day and continuous oxygen supplementation in a 14-month-old, well grown child, clinically asymptomatic once recovered from the rhinovirus infection seemed quite unusual.

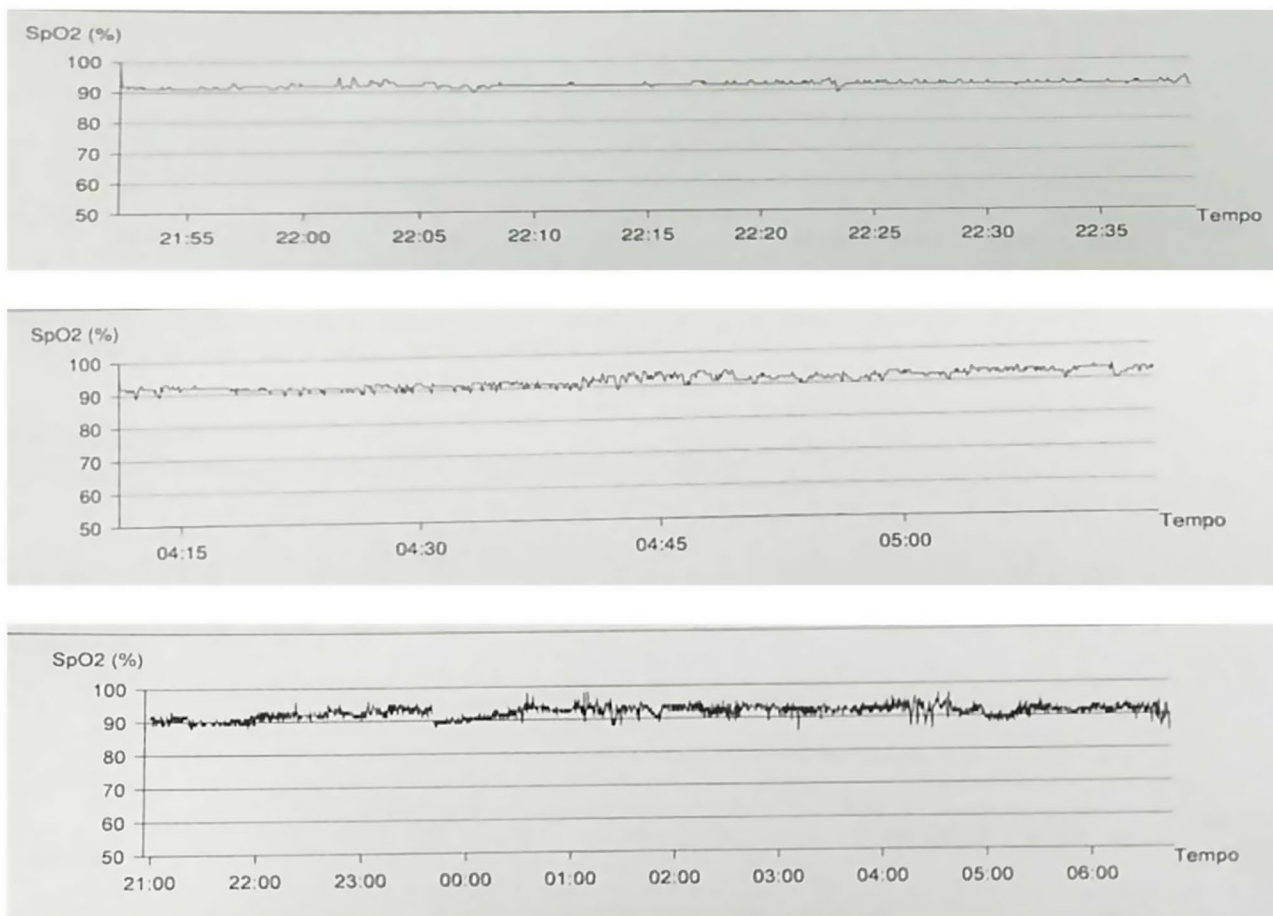
Finally, the normality of echocardiographic findings and the physiological range of nocturnal  $\text{tCO}_2$ , allowed to reasonably rule out cardiovascular alterations, diffusion impairment and hypoventilation.

$\text{SpO}_2$  detected by pulse oximetry measures the ratio between oxygenated and deoxygenated Hb, while  $\text{PaO}_2$  provides the partial pressure of oxygen dissolved in the arterial blood. In physiological conditions there is an optimal correlation between  $\text{SpO}_2$  and  $\text{PaO}_2$ , and a decrease in  $\text{SpO}_2$  is a reliable sign of hypoxemia. Mutations in the Hb  $\alpha$  and/or  $\beta$  chains can alter the oxygen-carrying affinity of hemoglobin. In low-affinity Hb variants, the sigmoidal oxygen-Hb dissociation curve shifts to the right. This reduces the binding of oxygen to Hb but enhances oxygen release at higher partial pressures, improving cellular oxygen availability [5]. In this condition,  $\text{spO}_2$  may be significantly lower than  $\text{PaO}_2$ , and  $\text{P}_{50}$ , a blood gas parameter which represents the oxygen tension at 50% saturation and measures Hb-oxygen affinity, is increased [6]. Unfortunately,  $\text{P}_{50}$  was not routinely calculated by blood gas analyzers and this incomplete information may have contributed to the initial misinterpretation of the ABG results. In addition, respiratory alkalosis was another indirect sign of normal gas exchange in the lungs, as the low levels of carbon dioxide detected were likely related to a relative hyperventilation due to an unnecessary respiratory support.

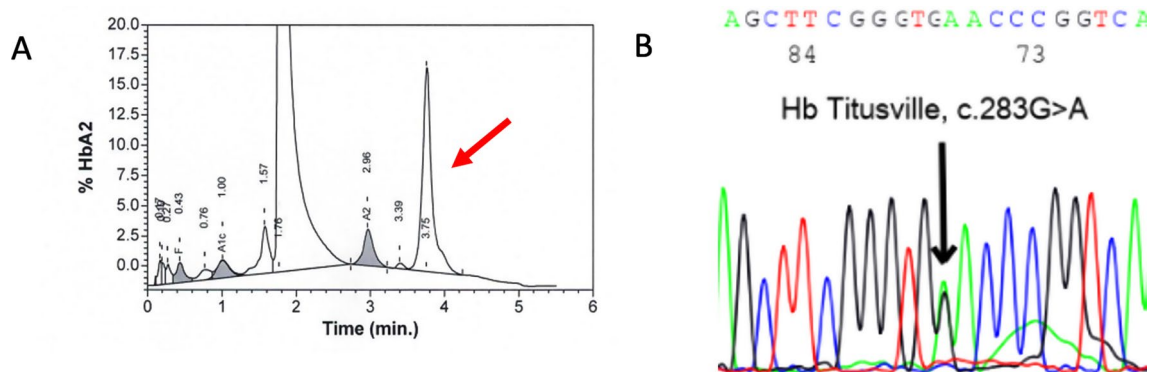
The final investigation included a high-performance liquid chromatography, which led to an abnormal Hb peak (15.9% Hb G Philadelphia?); further molecular analysis have, instead, detected a heterozygous mutation for c.283G > A in the HBA1 gene, consistent with Hb Titusville, a rare low-oxygen affinity Hb variant (Fig. 3).



**Fig. 1** High resolution CT bilateral consolidations in the apical segment of the lower lobes with air bronchogram



**Fig. 2** Nocturnal pulse oximetry measurement on oxygen supplementation (FIO<sub>2</sub> 0.30) through different respiratory supports. Top to bottom: High-flow nasal canula: 2 L/Kg; CPAP 8 cm H<sub>2</sub>O; Bipap: IPAP: 10 cm H<sub>2</sub>O, EPAP: 5 cm H<sub>2</sub>O



**Fig. 3** **A** High-performance liquid chromatographic showing an abnormal Hb peak (arrow). **B** Gene sequencing (electropherogram) showing codon 94 GAC > AAC mutation in alpha 1 gene

Moreover, the father of the child exhibited an asymptomatic spO<sub>2</sub> of 85% in room air and the Hb analysis of relatives documented the same mutation both in the patient's father and paternal uncle (all of Bangladeshi origin). Since its first description in 1975, Hb Titusville has only been reported in about 20 cases, often in the same family, among different ethnicities. Affected

individuals are mostly asymptomatic, except for eventual mild anemia and exertion dyspnea. This condition does not require any specific management for hypoxia and no long-term consequences are reported, not even in case of general anesthesia or major surgeries [7]. The diagnosis may however be challenging when dealing with comorbidities, as in this case; nevertheless a rational diagnostic

approach is crucial in order to avoid misdiagnoses and therapeutic mistakes.

#### Abbreviations

BPD	Bronchopulmonary Dysplasia
HFNC	High-Flow Nasal Cannula
FiO <sub>2</sub>	Fraction of Inspired Oxygen
spO <sub>2</sub>	Oxygen Saturation
Hb	Hemoglobin
ABG	Arterial Blood Gas
CT	Computed Tomography
CPAP	Continuous Positive Airway Pressure
BiPAP	Bilevel Positive Airway Pressure
PaCO <sub>2</sub>	Partial Pressure of Carbon Dioxide in Arterial Blood
PaO <sub>2</sub>	Partial Pressure of Oxygen in Arterial Blood
HCO <sub>3</sub>	Bicarbonate
tCO <sub>2</sub>	Transcutaneous Carbon Dioxide

#### Acknowledgements

We thank the patient's parents for providing permission to share the clinical information.

#### Author contributions

Study concept and design: MFP, CC, SG, YB. Acquisition of data: MFP, SG, MP, YB, ML, BM, AR.

#### Funding

Publication costs were funded by Grant Ricerca Corrente Italian Ministry of Health.

#### Data availability

The complete data reported in the current case report are available from the corresponding author on reasonable request.

#### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

#### Competing interests

The authors declare that they have no competing interests.

Received: 29 January 2024 / Accepted: 6 February 2025

Published online: 23 March 2025

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