

Blood oxygenation and spurious hypoxemia

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One of the principal utilities of arterial blood gas (ABG) analysis is to help assess blood oxygenation status. The two ABG parameters used for this assessment are $pO_2(a)$ (partial pressure of oxygen in arterial blood) and $sO_2(a)$ (% of total hemoglobin that is saturated with oxygen).

In health $pO_2(a)$ is maintained within the range 10.6-13.3 kPa (80-100 mmHg) and hypoxemia (reduced blood oxygen) is diagnosed if $pO_2(a)$ is less than 10.6 kPa (80 mmHg). The purpose of this article is to highlight the spurious severe hypoxemia that occurs in patients with particularly high white-cell count or high platelet count. In these patients there is a marked discrepancy between measured (*in vitro*) $pO_2(a)$ and true (*in vivo*) $pO_2(a)$.

The article will address the supposed mechanism that gives rise to spurious hypoxemia and the ways in which it can be identified. Some representative case histories will be presented which serve to show that failure to recognize spurious hypoxemia can lead to needless investigation and inappropriate intervention, including assisted ventilation.

The article begins with a brief overview of the significance of $pO_2(a)$ and $sO_2(a)$ for assessment of blood oxygenation.

Approx. reference intervals:

$pO_2(a)$ on room air	10.6-13.3 kPa (80-100 mmHg)
$sO_2(a)$ on room air	96-98 %
White-cell count	4.0-11.0 × 10 ⁹ /L (4.0-11 × 10 ³ /μL)
Platelet count	150-400 × 10 ⁹ /L (150-400 × 10 ³ /μL)

Blood oxygenation

All cells require a continuous supply of oxygen and one of the principal life-preserving functions of blood is delivery of oxygen present in inspired air from lungs to tissue cells. An adequate supply of oxygen to tissues depends then on adequate oxygenation of blood.

Oxygen is carried in blood in two forms. Most (around 98 %) is carried bound to hemoglobin, but a very small amount is dissolved in blood plasma. It is this

very small amount of dissolved unbound oxygen that determines $pO_2(a)$. Although $pO_2(a)$ reflects only a very small portion of the total oxygen in arterial blood, it is the major determinant of the amount of oxygen carried by hemoglobin (% hemoglobin saturation, $sO_2(a)$) and therefore the total amount of oxygen carried by blood.

The relationship between partial pressure of oxygen in blood (pO_2) and hemoglobin oxygen saturation (sO_2), described by the oxygen dissociation curve (Fig. 1), determines that when $pO_2(a)$ is within the normal range (10-12 kPa), hemoglobin is almost maximally saturated ($sO_2(a) > 97\%$).

Providing that blood contains a normal amount of hemoglobin, $sO_2(a) 97\%$ indicates adequate oxygenation.

However, if $pO_2(a)$ is reduced to say less than 8.0 kPa, hemoglobin binds significantly less oxygen ($sO_2(a) < 90\%$) and, irrespective of hemoglobin concentration, blood is not well oxygenated. It is evident from examination of the linear portion of the oxygen dissociation curve that only a slight reduction in $pO_2(a)$ below 8 kPa is associated with a precipitous fall in $sO_2(a)$ and therefore a marked reduction in the oxygen content of blood. Respiratory failure is defined by a $pO_2(a)$ of less than 8 kPa (<60 mmHg).

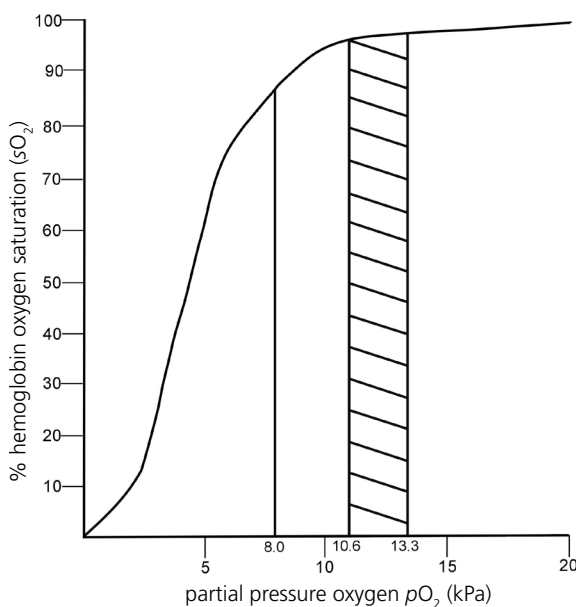


Fig. 1: Oxygen dissociation curve

Although adequate oxygenation of blood cannot be guaranteed if $pO_2(a)$ or $sO_2(a)$ are within their respective reference ranges (there are other considerations, including hemoglobin concentration and presence of dyshemoglobins) [1], reduced $pO_2(a)$ and $sO_2(a)$ always indicate inadequate blood oxygenation, i.e. hypoxemia.

The more severe the hypoxemia, the greater is the risk of hypoxia (insufficient oxygen to support aerobic metabolism in tissue cells) and consequent cell dysfunction and, ultimately, organ failure.

Causes of reduced $pO_2(a)$ (hypoxemia)

Oxygen in inspired air diffuses from the alveoli of the lungs to the blood due to the pO_2 gradient across the alveolar membrane. Maintenance of normal $pO_2(a)$ depends on:

- adequate partial pressure of oxygen in inspired air ($pO_2(l)$)
- normal alveolar ventilation (and therefore normal respiratory rate)
- adequate blood perfusion of the alveoli
- match between alveolar ventilation and perfusion (normal V/Q)

Consideration of these four factors allows some understanding of the many causes of reduced $pO_2(a)$ (hypoxemia).

At high altitude the attendant low barometric pressure determines that $pO_2(l)$ is reduced. Despite normal respiratory and cardiac function, $pO_2(a)$ is thus reduced at high altitude.

Reduced global alveolar ventilation is the cause of the reduced $pO_2(a)$ that occurs when the respiratory center in the brain is damaged by disease or injury, or depressed by drugs.

Neuromuscular damage affecting the lungs, for example in Guillian Barre syndrome, likewise reduces global alveolar ventilation, leading to reduced $pO_2(a)$. A local mismatch between alveolar ventilation and

alveolar perfusion causes the reduced $pO_2(a)$ that occurs in respiratory infection (pneumonia), chronic obstructive airways disease and pulmonary edema.

The alveoli are well perfused but some alveoli are damaged/congested, thereby reducing local ventilation. Inadequate local alveolar perfusion due to thrombus formation accounts for the hypoxemia that occurs in those suffering pulmonary embolus.

Of particular significance for this article is the hypoxemia and associated respiratory failure that can complicate the course of leukemia and other hematological malignancies.

The etiology of respiratory failure in the context of hematological malignancy varies [2, 3] and may be due to infection (pneumonia) consequent on the reduced immunity that the disease and its treatment provokes, or have a non-infectious cause.

Those with extremely high white-cell counts, for example, are at high risk of a syndrome called leukostasis in which white cells aggregate in the microvasculature, inducing endothelium-mediated damage to organs, predominantly the brain and lungs [4].

Respiratory failure is a common consequence of leukostasis. Whether the result of infection or a non-infectious cause such as leukostasis, respiratory failure is a not uncommon complication of hematological malignant disease. For this reason many patients suffering leukemia or related hematological malignant disease may be submitted for arterial blood gas analysis and measurement of $pO_2(a)$.

The finding of reduced $pO_2(a)$ in these patients particularly, must be interpreted with care. It may reflect the true $pO_2(a)$ of arterial blood, allowing a correct diagnosis of hypoxemia and, if sufficiently reduced, respiratory failure. However, it may alternatively be falsely low in which case the correct diagnosis is spurious hypoxemia or pseudohypoxemia.

In vitro metabolism - the cause of spurious hypoxemia

Spurious hypoxemia arises due to the continuing metabolism of the blood cells after blood has been sampled (i.e. *in vitro* metabolism). Like all living tissues blood cells continue to metabolize glucose in vitro and this metabolism is associated with consumption of oxygen and production of carbon dioxide.

The significance of this continued *in vitro* metabolism for the accuracy of blood gas analysis was first quantified in the early 1960s [5, 6].

This work determined that measured $pO_2(a)$ is affected by a number of factors including: the temperature at which the blood is stored; the time interval between collection and measurement; and the number of oxygen-consuming blood cells (white cells, platelets and reticulocytes) contained in the sample.

Mature erythrocytes contribute little to the total *in vitro* oxygen consumption because these cells lack mitochondria and metabolize glucose by anaerobic glycolysis. The rate of *in vitro* oxygen consumption was found to be proportional to white-blood-cell count, platelet count and reticulocyte count.

These and related findings provided the rationale for the development of the now familiar protocol for processing arterial blood samples prior to analysis.

To minimize the effect of *in vitro* oxygen consumption and thereby ensure that the measured $pO_2(a)$ most accurately reflects *in vivo* $pO_2(a)$, samples must be analyzed immediately, or at least within 30 minutes.

Storage of specimens in iced water also reduces *in vitro* metabolism, although caution in the use of this strategy is recommended if the blood is sampled to plastic syringes.

These routine precautions are not sufficient to prevent significant *in vitro* oxygen consumption if the sample contains an extremely high number of white cells or platelets, and it is in the context of hyperleucocytosis

(white-blood-cell count $> 100 \times 10^9/L$) or extreme thrombocytosis (platelet count $> 2000 \times 10^9/L$) that spurious hypoxemia occurs.

These extreme blood counts are only really encountered in patients suffering leukemia and other hematological malignant disease so that the problem of spurious hypoxemia is confined to this patient group. Since immature leukemic (blast) cells consume more oxygen than normal white cells, it is not only the number of white cells but also their immaturity that contribute to spurious hypoxemia in leukemic patients.

Demonstrating the link between hyperleucocytosis and spurious hypoxemia

Spurious hypoxemia was first described in 1979 [7, 8] by physicians who noted that some patients suffering leukemia or thrombocytosis had reduced $pO_2(a)$, despite no clinical evidence of disease that might compromise blood oxygenation, or symptoms of reduced oxygenation.

These patients all had an extremely high white-cell count or platelet count, and $pO_2(a)$ spontaneously reverted to normal when the white-cell count or platelet count was reduced by chemotherapy.

An early study of two such patients by Fox *et al* [9] confirmed and quantified the link between hyperleucocytosis and spurious hypoxemia that clinical observation suggested. The first patient was a 27-year-old male with chronic myeloid leukemia.

At the time of the study, 18 months after diagnosis, his white-blood-cell count was $276 \times 10^9/L$. His measured $pO_2(a)$ when breathing room air was 4.0 kPa (30 mmHg). Despite this evidence of life-threatening hypoxemia he had no pulmonary symptoms, and nothing abnormal was detected on chest X-ray film.

The second patient was a 74-year-old male with chronic lymphocytic leukemia. His white-blood-cell count was $360 \times 10^9/L$. He, too, had no pulmonary symptoms and a clear chest film, but his measured $pO_2(a)$ was

7.0 kPa (53 mmHg), indicating marked hypoxemia and respiratory failure.

For the study, arterial blood from each patient and a healthy control was tonometered with a gas mixture containing 20.6 % oxygen (partial pressure of the order 20 kPa or 150 mmHg).

After 30 minutes, equilibration blood was withdrawn from the tonometer to a glass syringe and $pO_2(a)$ measured immediately, and at intervals during the following hour, to monitor the *in vitro* decay in $pO_2(a)$. During this measuring hour blood was stored in the syringe under anaerobic conditions at room temperature (22 °C).

This procedure was repeated on four separate occasions over a 7-day period, during which the patients' white-cell count decreased in response to therapy.

The results relating to the first patient (Fig. 2) demonstrate clearly that the rate of $pO_2(a)$ *in vitro* decay was significantly higher than the control but reduced towards normal as the white-cell count was reduced from $276 \times 10^9/L$ to $55 \times 10^9/L$. Of great significance was the finding that the rate of decay is greatest during the first 2 minutes after sampling.

For blood with a white-cell count of $276 \times 10^9/L$, $pO_2(a)$ was found to fall by a staggering 9.6 kPa (72 mmHg) during the first 2 minutes after removal from the tonometer.

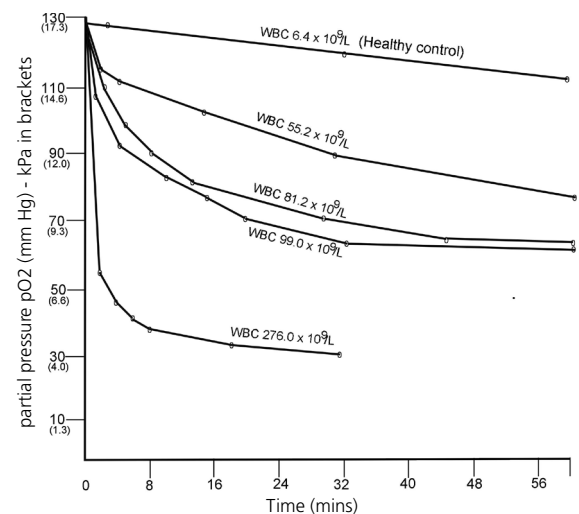


Fig. 2: Effect of white blood count (WBC) on rate of *in vitro* pO_2 decay for blood stored at room temperature (see text for explanation).

The group demonstrated that *in vitro* decay in $pO_2(a)$ could be entirely eliminated by addition of potassium cyanide (0.5 mg/1 mL blood) to the blood, prior to tonometry, providing evidence that cellular respiration (oxygen consumption) was responsible for the observed *in vitro* $pO_2(a)$ decay.

In a separate experiment, the effect of lowering the temperature was tested by storing blood on ice during the measuring hour. This blunted, but did not eliminate *in vitro* $pO_2(a)$ decay; a finding that confirms that placing arterial blood samples on ice does not entirely eliminate spurious hypoxemia [10, 11] as some have suggested [8].

This blunted response can be accounted for by the observation that the rate of $pO_2(a)$ decay is greatest in the minutes immediately after sampling, during the time that temperature equilibration with iced water is occurring.

Identifying spurious hypoxemia

A number of strategies have been proposed for identifying spurious hypoxemia. These have included the use of an intra-arterial continuous blood gas monitoring device [12]; addition of sodium cyanide or sodium fluoride to arterial blood prior to blood gas analysis [9, 13] and the use of arterial plasma rather than arterial blood to measure $pO_2(a)$ [14].

The simplest and most widely used strategy is to employ pulse oximetry [11, 15, 16]. Pulse oximetry provides an alternative to arterial blood gas analysis for assessing blood oxygenation that depends on non-invasive measurement of capillary oxygen saturation.

Oxygen saturation as measured by pulse oximetry (SpO_2) approximates closely to $sO_2(a)$. In cases of spurious hypoxemia, because $pO_2(a)$ is falsely low, the calculated value for $sO_2(a)$, generated simultaneously during arterial blood gas analysis, is also falsely low.

However, $sO_2(a)$, as measured by pulse oximetry (SpO_2) accurately reflects *in vivo* $sO_2(a)$. Thus spurious

hypoxemia is characterized by a disparity between SpO_2 (normal) and $pO_2(a)$ and $sO_2(a)$ (both markedly reduced).

Of course it is entirely conceivable that the conditions that give rise to spurious hypoxemia (extreme hyperleucocytosis/thrombocytosis) may be present in a patient who also has a problem that compromises gas exchange, and therefore an actual reduction in $pO_2(a)$. In other words, spurious hypoxemia and true hypoxemia can co-exist.

In such cases SpO_2 will be reduced but $pO_2(a)$ and $sO_2(a)$ will be reduced to a much greater extent; the marked disparity between SpO_2 and $pO_2(a)/sO_2(a)$ will still be evident.

Whilst recommending the use of pulse oximetry to identify spurious hypoxemia Lele A *et al* [16] rightly caution that SpO_2 can be falsely raised (thereby masking true hypoxemia) if the blood contains an abnormally high concentration of dyshemoglobins (carboxyhemoglobin, COHb; methemoglobin, MetHb).

In addition, severe metabolic alkalosis or hypothermia shifts the oxygen dissociation curve to the right so that $sO_2(a)$ (and therefore SpO_2) will be higher for any given $pO_2(a)$. They provide a useful algorithm (Fig. 3) for the investigation of suspected spurious hypoxemia that takes account of these limitations of pulse oximetry.

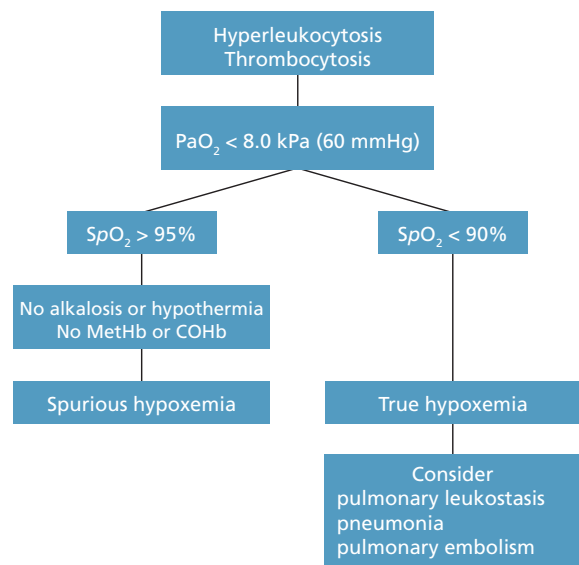


Fig. 3: Diagnostic approach to hypoxemia in patients with hyperleukocytosis or thrombocytosis (ref 16)

Illustrative case histories

Case 1 - Spurious hypoxemia leads to unnecessary intervention

This case [17] concerns a 34-year-old woman with acute lymphoblastic leukemia (ALL) who was admitted to hospital 10 months after diagnosis because she had become short of breath during the previous 10 days.

The breathlessness had been accompanied by sore throat, productive cough and fatigue. Respiratory rate was increased (36/min).

Full blood count on admission revealed anemia (Hb 6.9 g/L) and hyperleukocytosis (white-cell-count $191 \times 10^9/L$, 77 % lymphoblasts). Chest X-ray was normal. A diagnosis of bronchitis was made and intravenous antibiotics were prescribed, eliciting improvement.

On the second day, however, she again complained of cough and breathlessness and this, despite no change on physical examination, no cyanosis and a second normal chest X-ray, provoked a request for arterial blood gas analysis.

This revealed a $pO_2(a)$ of 4.4 kPa (33 mmHg) and a calculated $sO_2(a)$ of 78.7 %. This evidence of severe hypoxemia accompanying dyspnea prompted major intervention. The patient was intubated and placed on a mechanical ventilator.

However, spurious hypoxemia was emerging as a possible explanation for the apparent disconnect between the documented severe hypoxemia and the patient's relatively mild clinical presentation. Later on the same day she was weaned off the respirator, extubated and treated with oxygen (10 L/min) via a mask.

During oxygen therapy $pO_2(a)$ (6.3 kPa) and $sO_2(a)$ (79.8 %) remained unaccountably low.

Eventually a diagnosis of spurious hypoxemia, secondary to hyperleukocytosis, was made when pulse oximetry revealed a marked disparity between SpO_2 (94 %) and

$pO_2(a)$ (4.4 and 6.3 kPa) and $sO_2(a)$ (78.7 and 79.8 %). A third blood gas sample was taken whilst the patient was still receiving oxygen, but on this occasion the sample was immediately iced and analyzed to minimize in vitro $pO_2(a)$ decay. $pO_2(a)$ of this sample was 26.3 kPa (197 mmHg) and $sO_2(a)$ 100 %.

The patient, who presumably at no time during her hospital stay had actually suffered significant reduction in blood oxygenation, soon recovered from her upper-respiratory-tract infection and was discharged home.

Clearly, mechanical ventilation and oxygen therapy had been administered inappropriately in this case because spurious hypoxemia had gone unrecognized.

Case 2 – Spurious hypoxemia in a patient with normal white-cell count

This case [18] concerns a 72-year-old lady who presented first with complaint of fatigue. Blood count revealed raised hemoglobin, Hb (18.7 g/dL) and hematocrit, Hct (56 %), normal white-cell count ($8.3 \times 10^9/L$) and very high platelet count ($2,168 \times 10^9/L$).

Further blood testing to investigate apparent polycythemia (raised Hb Hct) revealed increased red-cell mass and reduced erythropoietin. Examination of a bone-marrow biopsy found abnormalities consistent with a diagnosis of polycythemia vera, a myeloproliferative (malignant) disease. This diagnosis is entirely consistent with initial blood test results.

Arterial blood gas analysis at this time revealed evidence of marked hypoxemia and respiratory failure ($pO_2(a)$ 6.2 kPa, 47 mmHg; and $sO_2(a)$ 74 %).

Intensive investigation followed to explain this finding. It was supposed that the hypoxemia was genuine and might be the cause of polycythemia (secondary erythrocytosis).

This series of investigations included chest radiography, computed tomography scan of chest, pulmonary function tests, transthoracic bubble-contrast

echocardiography and $p50$ testing for possible high-affinity hemoglobinopathy.

None of this testing revealed any abnormality, and 3 months after initial presentation the patient was referred to a tertiary medical facility for investigation of unexplained marked hypoxemia.

Here initial evaluation included pulse oximetry. The patient's SpO_2 was 98 %, indicating normal blood oxygenation. Simultaneously collected blood gases, however, indicated, as before, severe hypoxemia ($pO_2(a)$ 5.3 kPa, 40 mmHg; $sO_2(a)$ 73 %).

The disparity between pulse oximetry and blood gas results suggested spurious hypoxemia due to extreme thrombocytosis (platelet count at this time was $2,425 \times 10^9/L$). To test this hypothesis, blood gases were repeated, but on this occasion KCN (1 mM final concentration) was added to the sample to eliminate in vitro oxygen consumption.

Results from this adulterated sample were entirely normal ($pO_2(a)$ 12.5 kPa, 94 mmHg; and $sO_2(a)$ 98 %) and consistent with SpO_2 (98 %) recorded during blood sampling. This confirmed spurious hypoxemia.

Treatment for polycythemia vera was immediately instituted and over the following weeks and months hematocrit and platelet counts reduced towards normal as the patient's condition improved.

At 20 months after initiation of treatment, platelet count was $721 \times 10^9/L$ and blood gases on a sample collected conventionally (i.e. without KCN) at this time returned a normal $pO_2(a)$ (11.1 kPa, 84 mmHg) and $sO_2(a)$ (97 %) result.

This case history demonstrates that spurious hypoxemia can occur in patients with normal white-cell count if platelet count is very high. It also serves to remind that, if not recognized, spurious hypoxemia can lead to needless investigation and delay in appropriate treatment.

Summary

Spurious hypoxemia is a disparity between measured and actual $pO_2(a)$ due to in vitro consumption of oxygen by blood cells (white cells and platelets).

Spurious hypoxemia occurs in those with very high white-cell count ($>100 \times 10^9/L$ or very high platelet count ($>1500 \times 10^9/L$). Such extreme blood counts are confined to those with hematological malignant disease.

Failure to identify spurious hypoxemia can lead to needless investigation and inappropriate intervention, including mechanical ventilation.

Pulse oximetry provides a simple, reliable way of identifying spurious hypoxemia and the means of monitoring blood oxygenation in those with spurious hypoxemia.

Spurious hypoxemia represents just one of many ways in which hematological conditions give rise to factitious biochemical measurements. The wider topic is the subject of a recent comprehensive review [19].

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