Pseudohypoxemia in a Patient With Chronic Lymphocytic Leukemia

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Introduction

Arterial blood gas analysis is one of the most common tests performed on patients in ICUs to measure Pa_{O_2} as a means to determine adequate gas exchange. However, the Pa_{O_2} in an arterial blood sample can be impacted by metabolically active cells, including either white blood cells or platelets. We present a patient who had severe defects in measured Pa_{O_2} related to chronic lymphocytic leukemia.

Case Summary

A 75-year-old man was transferred to our hospital for hypoxic respiratory failure requiring intubation after presenting with a 2 day history of progressive dyspnea and orthopnea. His past medical history was notable for chronic lymphocytic leukemia, prostate cancer, hypertension, and an abdominal aortic aneurysm repair. The patient was initially admitted to an outside hospital with an acute myocardial infarction supported by a positive troponin I, reduced left ventricular ejection fraction on echocardiogram, and anuric renal failure. He required intubation and mechanical ventilation for severe hypoxemia and was transferred to our hospital.

He had no known drug allergies. His home medications included metoprolol, furosemide, lisinopril, and aspirin. He had no history of tobacco, ethanol, or illicit drug use. On arrival to our ICU the patient had a blood pressure of 105/55 mm Hg, heart rate of 102 beats/min, temperature of 36.6°C, and Spo_2 100% on F_{IO_2} of 0.60. The patient was intubated and sedated. His exam was notable for clear breath sounds, normal heart sounds, and no jugular venous distention. No pitting edema or clubbing was identified. He had minimal urine output.

His laboratory data revealed an elevated pro-brain natriuretic peptide of 46,525 pg/mL (normal < 850), creatine kinase-myocardial band of 6 ng/mL (normal < 10), and an elevated troponin T of 0.22 ng/mL (normal < 0.1). Electrocardiogram revealed sinus tachycardia, low voltage, and non-specific T wave changes. The complete blood count demonstrated a hemoglobin of 7.0 g/dL, platelet count of 73,000/μL, and white-blood-cell count of 572,000/μL, consistent with the patient's diagnosis of chronic lymphocytic leukemia. A basic metabolic profile was notable for an elevated blood urea nitrogen of 51 mg/dL and creatinine of 2.2 mg/dL. Lactate dehydrogenase was elevated to 769 U/L (100–200), and uric acid and phosphorus levels were normal. An arterial blood gas analysis obtained on F_{IO_2} of 0.60 showed a pH of 7.28, Pa_{CO_2} of 51 mm Hg, and a Pa_{O_2} of 41 mm Hg, which increased to Pa_{O_2} of 68 mm Hg on an F_{IO_2} of 1.0. A chest radiograph showed mild pulmonary edema. An echocardiogram showed new global left ventricular dysfunction, with an ejection fraction of 25%, normal right ventricle, and mild mitral regurgitation. Mixed venous oxygen saturation was 59%.

Cardiogenic shock with secondary acute renal failure was the initial diagnosis, given his history of progressive dyspnea and orthopnea, recent elevated troponin, new severely reduced left ventricular dysfunction, and evidence of poor tissue perfusion with low mixed venous oxygen saturation and poor urine output. The patient did not initially respond to intravenous diuretics, and required dialysis for volume removal, with resolution of his pulmonary edema. His hemodynamics improved and urine output normalized; however, the patient remained profoundly hypoxemic, as assessed by arterial blood gas analysis on mechanical ventilation. The patient continued to require F_{IO_2} of 0.60, with Spo_2 of 100%, with a discordant Pa_{O_2} of 48–72 mm Hg. Because of a concern of leukostasis contributing to possible ventilation-perfusion mismatch and hypoxemia, leukopheresis was initiated.

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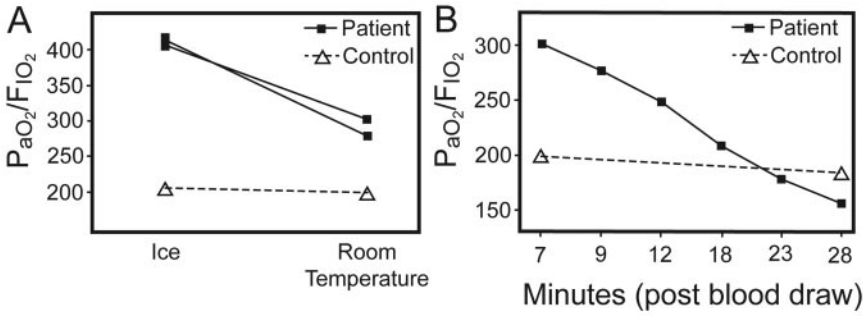

Fig. 1. Arterial blood gas measurement of oxygen tension. Arterial samples were drawn from our patient and from a control subject on and FIO_2 of 1.0. A: Samples immediately placed on ice versus kept at room temperature, and PaO_2 measured after 5 minutes (2 samples from our patient). B: Serial PaO_2 measurements at 2–5 min intervals on an arterial sample drawn and maintained at room temperature.

Suspicions were raised for pseudohypoxemia, because the SpO_2 readings did not correlate with the PaO_2. To specifically test for hypermetabolic activity and increased oxygen consumption related to leukocytosis, we first ran simultaneous arterial samples when our patient was on an FIO_2 of 1.0, at room temperature and on ice to slow metabolic activity of the leukocytes (Fig. 1A). We observed dramatically improved PaO_2 from samples preserved on ice. Next, we obtained an arterial sample on an FIO_2 of 1.0 and analyzed PaO_2 over time, when compared to that of a control patient (see Fig. 1B). We observed a rapid rate of decline in PaO_2 in our patient with leukocytosis, when compared to a control arterial sample.

After confirming our suspicion of pseudohypoxemia, this patient was weaned to an FIO_2 of 0.30 and remained with SpO_2 of 98–100%, without evidence of low tissue perfusion. He was liberated from the ventilator successfully the same day. He was subsequently begun on systemic chemotherapy for his chronic lymphocytic leukemia.

Discussion

Pseudohypoxemia secondary to leukocytosis was first described in 1979 and was coined "leukocyte larceny."[1,2] This phenomenon is believed to be secondary to a high number of metabolically active white blood cells with an elevated consumption of the dissolved oxygen in arterial blood samples.[3,4] It is recognized that both leukocytes and platelets account for the majority of the oxygen consumption in whole blood once removed from the body. The rate of oxygen consumption by white blood cells is typically clinically unimportant in the majority of patients with normal blood counts.[5] Spuriously low PaO_2 measurements are more common either when the white-blood-cell count exceeds 50,000/μL, or with severe thrombocytosis.

Patients with leukemia and hyperleukocytosis are at high risk for many causes of severe hypoxemia, including infection, pulmonary embolism, pulmonary leukostasis, leukemic infiltration, opportunistic neoplasms, hemorrhage, and drug-related toxicities[6]; therefore, a thorough workup is required to rule out alternative causes of hypoxemia. Inconsistencies between the SpO_2 and PaO_2 measurements help to rule out these causes of hypoxemia (Fig. 2). In this scenario only a few possible diagnoses remain, including methemoglobinemia and pseudohypoxemia. To differentiate these causes, compare the PaO_2 to the SpO_2. In methemoglobinemia the PaO_2 will be normal and the SpO_2 will be falsely low. Pseudohypoxemia will present with normal SpO_2 and falsely low PaO_2. In contrast, carbon monoxide poisoning will present with a normal PaO_2 and SpO_2. Discordant values between PaO_2 and SpO_2 should be thoroughly investigated.

More accurate measurements of oxygen tension can be achieved by minimizing delay in processing arterial samples and preserving samples on ice. Previous work demonstrates that delayed processing of samples results in reduction of PaO_2 in subjects with severe leukocytosis. Rapid cooling of arterial samples on ice will reduce the metabolic activity of the white blood cells, resulting in a decreased rate of decline in oxygen concentrations.[1,2] This method remains limited, as considerable oxygen consumption occurs during sample cooling and will continue at a higher rate than normal, despite the reduced metabolic activity.[7] Other proposed methods to more accurately measure the PaO_2 include either continuous arterial sampling or plasma sampling.[8,9] Potassium cyanide can be used to block white blood cell metabolic activity, which will inhibit leukocyte larceny of dissolved oxygen. Finally, the addition of sodium fluoride to the sample may prevent leukocytes uptake of glucose and oxygen.[2] These methods are technically challenging and are not widely available in a clinical setting. Pulse oximetry is thought to be the most reliable and clinically useful method to assess true oxygenation, and remains an invaluable tool to assist in the diagnosis of pseudohypoxemia.

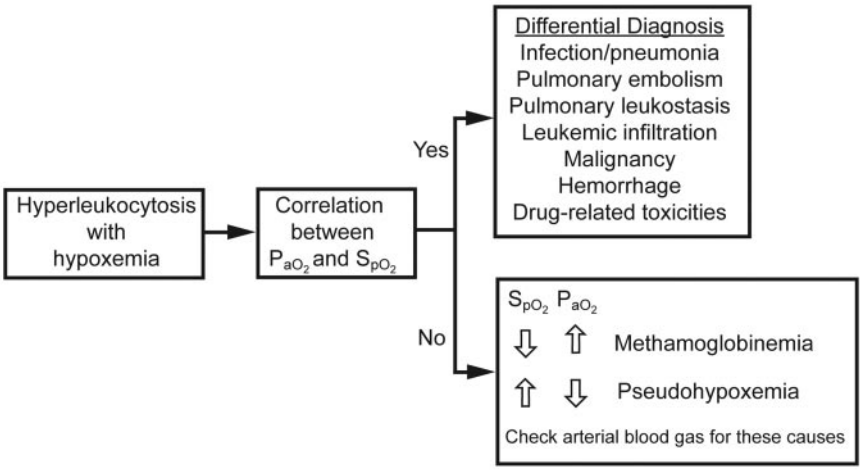

Fig. 2. Diagnostic approach for patients with either hyperleukocytosis or thrombocytosis with hypoxemia. Discordant measurements of Pao_2 and Spo_2 should be thoroughly investigated.

Our patient demonstrates that very high white-blood-cell counts falsely lower arterial blood gas measurements of oxygen tension. Astute clinicians should consider the diagnosis of pseudohypoxemia in the patient with white-blood-cell counts $> 50{,}000/\mu L$ or severe thrombocytosis, high Spo_2, very low Pao_2, and no alternative etiology of hypoxemia. Cooling (on ice) and rapid analysis of arterial samples may improve reliability of analysis of Pao_2. As observed in our patient, pulse oximetry in the context of clinical evidence supporting adequate tissue perfusion may prove the most reliable method to assess oxygenation in patients with leukocyte larceny. Early diagnosis of pseudohypoxemia could prevent unnecessary testing and prolonged mechanical ventilation.

Teaching Points

- Pseudohypoxemia is a phenomenon observed in patients with substantially elevated white blood cell and/or platelet counts.
- Clinicians should consider pseudohypoxemia in their differential diagnosis of patients with high Spo_2, very low Pao_2, and white-blood-cell counts $> 50{,}000/\mu L$ or severe thrombocytosis and no alternative etiology of hypoxemia.
- Cooling of arterial samples and rapid analysis may improve reliability of analysis of Pao_2 in patients with very high white-blood-cell counts.
- Pulse oximetry is the most reliable method to clinically assess oxygenation in patients with leukocyte larceny.

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