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An Educational Case for Applying the Alveolar-Arterial Gradient in Hypoxemia: An Underutilized and Underappreciated Clinical Tool

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LEARNING OBJECTIVES

1. Recognize the 5 mechanisms of hypoxemia.
2. Calculate an Alveolar-arterial gradient using the alveolar gas equation.
3. Apply the Alveolar-arterial gradient in a clinical setting to narrow the differential for hypoxemia.

INTRODUCTION

The Alveolar-arterial gradient, commonly known as the A-a gradient, measures the difference in the oxygen concentration in the alveoli and the arteries across the capillary membrane in the lung. In an ideal system, the A-a gradient would be zero because there would be perfect equilibrium as oxygen diffuses and equalizes across the alveolar and arterial sides of the capillary membrane. However, there is a physiologic A-a gradient because of the differences in perfusion and ventilation in the apical and basilar regions of the lungs. Because this relationship exists, the changes in the A-a gradient have clinical utility in guiding the differential diagnosis of hypoxemia.

The A-a gradient is calculated from the equation[1]:

$$\text{A-a Gradient} = PAO_2 - PaO_2$$

PAO_2 is the partial pressure of oxygen in the alveoli, and PaO2 is the partial pressure of oxygen in the artery. The partial pressure of oxygen in the alveoli can be calculated from the alveolar gas equation[1]:

$$PAO_2 = (P_{atm} - P_{H2O})\, FiO_2 - PaCO_2/RQ$$

PaO_2 = measured directly from an arterial blood gas (ABG).

P_{atm} is the atmospheric pressure, which at sea level is estimated at 760 mmHg. The P_{H2O} is the partial pressure of water, estimated at approximately 47 mmHg. FiO_2 is the fraction of inspired oxygen. An arterial blood gas (ABG) measures $PaCO_2$, the partial pressure of carbon dioxide in alveoli, which is around 40 to 45 mmHg in normal physiological conditions. RQ is the respiratory quotient, estimated at 0.8.

The expected, "normal", physiologic A-a gradient also changes based on age and can be estimated from the equation1:

$$\text{A-a gradient} = (\text{Age} + 10) / 4$$

In this case, we describe the clinical benefit and practical application of the A-a gradient and alveolar gas equation in elucidating the etiology of hypoxemia. It is a fast, effective, inexpensive tool that can provide great diagnostic utility and save patients from more invasive or costly tests.

CASE PRESENTATION

The patient is a 63-year-old man with a past medical history of a cerebrovascular accident, coronary artery disease with myocardial infarction, alcohol use disorder, hypertension, anxiety, and chronic pain.

The patient was admitted to a hospital medicine service with altered mental status and acute hypoxemic and hypercapnic respiratory failure. The altered mental status was due to alcohol withdrawal and polysubstance use (opioids, benzodiazepines). The respiratory failure was believed to be due to aspiration pneumonia. The patient's outpatient medications were notable for alprazolam 1 mg three times daily and oxycodone 30 mg three times daily, which were continued this admission. With treatment of his alcohol withdrawal and pneumonia, his mental status returned to baseline. However, the patient continued to have persistent hypercapnia and hypoxemia of an unclear etiology. He

had computed tomography angiography imaging that demonstrated no pulmonary embolism but did show atelectasis bilaterally. He was transferred to the Pulmonary service for further workup, with anticipation that he would need more invasive testing such as bronchoscopy and concern that further worsening could lead to intubation and mechanical ventilation.

After transfer to the Pulmonary service, several blood gases were obtained:

An ABG was drawn while the patient was awake on 3 liters of oxygen by nasal cannula with a normal respiratory rate:

pH 7.31, $PaCO_2$ 80 mmHg, PaO_2 58 mmHg

PAO_2 = (760 - 47) X 0.32 - 80/0.8 = 128.8

PaO_2 from ABG = 58

A-a gradient = 128.8 - 58 = 70.8

Expected physiologic A-a gradient for his age = (63 + 10) / 4 = 18

An ABG was drawn overnight while the patient was on bilevel positive airway pressure (BIPAP) at 32% FiO2:

pH 7.33, $PaCO_2$ 61 mmHg, PaO_2 128 mmHg

PAO_2 = (760 - 47) X 0.32 – 61/0.8 = 151.91

PaO2 from ABG = 128

A-a gradient = 139.4 – 128 = 23.9

DISCUSSION

What does hypoxemia with a high A-a gradient signify?

There are five mechanisms of hypoxemia: Ventilation and perfusion mismatch, right-to-left shunt, diffusion impairment, hypoventilation, and a low inspired partial pressure of oxygen (PO_2). The patient has an A-a gradient of 70.8, which is far greater than 18, the physiologic A-a gradient expected for his age. An elevated A-a gradient already narrows our differential for hypoxemia because it is only consistent with a ventilation and perfusion mismatch, right-to-left shunt, and diffusion impairment.[2]

Ventilation and perfusion (V/Q) mismatch is the most common etiology of hypoxemia, with many potential causes.[3] A low V/Q ratio suggests that perfused lung is not ventilated appropriately. Causes include pulmonary edema, pneumonia, atelectasis, asthma, COPD, bronchiectasis, and acute respiratory distress syndrome. As more alveolar units are lost or cannot be ventilated, the ventilation decreases more significantly than the perfusion, and the shunt physiology worsens. The lungs will attempt to compensate by vasoconstricting areas of poor ventilation and vasodilating areas with good ventilation to find a more balanced V/Q ratio. High V/Q ratios suggest that ventilation is greater in proportion than perfusion, for example, in pulmonary embolism. This process leads to dead space in which ventilated lung does not perform the appropriate gas exchange. Notably, hypoxemia due to V/Q mismatch improves readily with supplemental oxygen.[4]

The two other mechanisms of hypoxemia with an elevated A-a gradient are a right-to-left shunt and diffusion impairment. A right-to-left shunt is caused by a patent foramen ovale, pulmonary arteriovenous fistulas, or any intrapulmonary shunt. An intrapulmonary shunt can occur when ventilation is significantly lost in a well-perfused lung region. Diffusion impairment occurs when oxygen transport across the alveolar wall is delayed. This happens due to decreased alveolar surface area for diffusion or fibrosis of the barrier. Notable causes of diffusion impairment include emphysema and interstitial lung disease. While this may not often cause significant resting hypoxemia, it can lead to profound desaturations in severe cases due to increased cardiac output leading to short transit time of red blood cells across alveolar capillaries. Clinically, in a right-to-left shunt, the hypoxemia does not respond to supplemental oxygen. In diffusion impairment, supplemental oxygen does improve hypoxemia.

A large A-a gradient rules out two etiologies of hypoxemia. A low inspired PO_2 is a mechanism of hypoxemia with a normal A-a gradient. Common causes of this would be the high altitude and scuba diving. Hypoventilation is another etiology of hypoxemia with a normal A-a gradient. It can be caused by decreased respiratory drive, chest wall rigidity, neuromuscular weakness, upper airway obstruction, and obstructive lung disease.[5]

What etiology of hypoxemia does our patient have?

Our patient has a high A-a gradient, which, as defined above, narrows our differential to V/Q mismatch, right-to-left shunt, and diffusion impairment. Now we can use our history and other diagnostic tests to narrow the etiologies further. An echocardiogram with a bubble study ruled out a right-to-left shunt. Because the agitated saline bubbles did not reach the left side of the heart, we know there was no intracardiac or intrapulmonary shunt. A diffusion restriction etiology such as ILD or emphysema was inconsistent with the history and his computed tomography (CT) imaging.

The differential for V/Q mismatch has a wide array of causes, as we described. In this case, the patient still had significant hypoxemia despite treating his pneumonia with appropriate antibiotics. The patient was transferred with the anticipation that he may have an atypical infection or require a more specialized and invasive workup, such as bronchoscopy or high-resolution CT imaging.

The two A-a gradients and alveolar gas equations we presented were crucial factors in elucidating the diagnosis and guiding our management. The two blood gases were drawn within a 24-hour period, with the first blood gas drawn while the patient was resting on 3L oxygen, and in the second scenario, the patient was resting while on BIPAP with 3L oxygen. The A-a gradient was significantly elevated to 70.8 in the first setting, and in the second, the A-a gradient was nearly normalized at 23.9.

Physiologically, in our patient, BIPAP had a great effect on keeping the alveoli ventilated and maximizing alveolar recruitment. Because this intervention alone was able to resolve the A-a gradient and impressively improve oxygenation, our differential was thus further narrowed to processes that filled or collapsed alveoli, such as pulmonary edema and atelectasis. On our physical exam, the patient examined as hypovolemic yet had rales in the bases. He was also often sedentary and lying in bed with poor posture. Thus, atelectasis was highest on our differential.

We implemented a plan for the patient to frequently walk the halls, increase the use of the incentive spirometer, and improve the management of his secretions with nebulizers and chest physiotherapy. With these non-invasive and practical measures, the patient's oxygen requirement and hypoxemia resolved within the next two days, and he was discharged home on room air. He was able to avoid unnecessary further antibiotics, imaging, and bronchoscopy.

Why was the patient hypercapnic, and how does that impact the A-a gradient and alveolar gas equation?

While atelectasis may explain the patient's hypoxemia, it does not explain the degree of hypercapnia. The patient's PaCO2 levels were in the 60-80 mmHg range, and he had elevated serum bicarbonate suggesting that he chronically retains CO_2. In a patient without prior lung disease, chronic hypercapnia would be very unusual. However, his medication history is notable for a combination of prescribed opiates, benzodiazepines, and recreational alcohol. His opiate and benzodiazepine regimen was continued inpatient, leading to continued hypercapnia and likely worsening his severe atelectasis.

After transfer to the Pulmonary service, the opiates and benzodiazepines were weaned, the patient's respiratory drive improved significantly, and his hypercapnia resolved. Notably, hypoventilation and subsequent hypercapnia will lead to hypoxemia, and it is a mechanism of hypoxemia with a normal A-a gradient. Within an alveolus, if the partial pressure of any one gas increases, then the partial pressure of the other gases must decrease. The partial pressure of oxygen in the alveolus (PAO_2) can be significantly reduced if the partial pressure of carbon dioxide is high.

As a reminder, the A-a gradient and alveolar gas equation are:

$$\text{A-a Gradient} = PAO_2 - PaO_2$$

$$PAO_2 = (P_{atm} - P_{H2O})\, FiO_2 - \mathbf{PaCO_2}/RQ$$

PaO_2 is measured from an ABG

Using the alveolar gas equation, you can see that a higher $PaCO_2$ leads to a lower PAO_2, and thus the gradient between PAO_2 and PaO_2 will be smaller and trend toward normal. In our case, the patient's degree of atelectasis was severe enough that the A-a gradient remained elevated despite the hypercapnia.[1]

TAKE HOME POINTS

- The alveolar gas equation can help you narrow your mechanisms of hypoxemia. An elevated A-a gradient is consistent with a ventilation and perfusion mismatch, right-to-left shunt, and diffusion impairment. A normal A-a gradient suggests hypoventilation or a low inspired PO_2.
- Supplemental oxygen will improve oxygenation in V/Q mismatch, hypoventilation, and diffusion impairment. It will not improve oxygenation in hypoxemia due to right-to-left shunt.
- Hypercapnia affects your alveolar gas equation by reducing the A-a gradient because it decreases the PAO_2.
- In our calculations, there is an assumption for the FiO_2 depending on the oxygen delivery device. For example, a patient on oxygen via a nasal cannula will also be breathing ambient air with 21% FiO_2 through the mouth and thus the fraction of inspired oxygen can be lower than what would be estimated by the liters per minute of oxygen going through

the nasal cannula. FiO_2 is more precisely controlled with certain devices such as venturi masks, non-rebreathers, continuous positive airway pressure and non-invasive ventilation machines with face masks.

- Calculating the Alveolar gas equation is fast, cost-effective, and minimally invasive. It provides a wealth of information that can guide your management. Our patient avoided further invasive testing, radiation exposure, and medical costs because our alveolar gas equations, arterial blood gases, and A-a gradient calculations provided a clear explanation of our patient's hypoxemia and hypercapnia.

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