**Alveolar Gas Equation**

The alveolar gas equation for calculating $\text{PAO}_2$ is essential to understanding any $\text{PaO}_2$ value and in assessing if the lungs are properly transferring oxygen into the blood. Is a $\text{PaO}_2$ of 28 mm Hg abnormal? How about 55 mm Hg? 95 mm Hg? To clinically interpret $\text{PaO}_2$ one has to also know the patient's $\text{PaCO}_2$, $\text{FIO}_2$ (fraction of inspired oxygen) and the $P_B$ (barometric pressure), all components of the equation for $\text{PAO}_2$:

$$\text{PAO}_2 = \frac{1-\text{FIO}_2}{\text{R}} \left( \text{FIO}_2 (P_B - \text{P}_{\text{H}_2\text{O}}) - \text{PACO}_2 \left[ \text{FIO}_2 + \frac{\text{PACO}_2}{\text{R}} \right] \right)$$

Despite this undisputed physiologic fact physicians sometimes make clinical decisions based on $\text{PaO}_2$ alone, without reference to the calculated $\text{PAO}_2$. The abbreviated equation below is useful for clinical purposes; in this version alveolar $\text{PO}_2$ equals inspired $\text{PO}_2$ ($\text{PIO}_2$) minus arterial $\text{PCO}_2$ x 1.2, assuming the $\text{R}$ value is 0.8 (and assuming identical values for arterial and alveolar $\text{PCO}_2$). Water vapor pressure in the airways is dependent only on body temperature and is 47 mm Hg at normal body temperature (37 degrees C).

$$\text{PAO}_2 = \text{FIO}_2 (P_B - 47) - 1.2(\text{PaCO}_2)$$

Ambient $\text{FIO}_2$ is the same at all altitudes, 0.21. It is usually not necessary to measure $P_B$ if you know its approximate average value where the blood was drawn (e.g. sea level 760 mm Hg; Cleveland 747 mm Hg; Denver 640 mm Hg). In the abbreviated equation $\text{PaCO}_2$ is multiplied by 1.2, a factor based on assumed respiratory quotient ($\text{CO}_2$ excretion over $\text{O}_2$ uptake in the lungs) of 0.8; this factor becomes 1.0 when the $\text{FIO}_2$ is 1.0. The following comments are meant to show how the alveolar gas equation can be clinically helpful without the need for anything more than mental calculation.

a) If $\text{PIO}_2$ is held constant and $\text{PaCO}_2$ increases, $\text{PAO}_2$ and $\text{PaO}_2$ will always decrease. Since $\text{PAO}_2$ is a calculation based on known (or assumed) factors, its change is predictable. $\text{PaO}_2$, by contrast, is a measurement whose theoretical maximum value is defined by $\text{PAO}_2$ but whose lower limit is determined by ventilation-perfusion ($\text{V-Q}$) imbalance, pulmonary diffusing capacity and oxygen content of blood entering the pulmonary artery (mixed venous blood). In particular, the greater the imbalance of ventilation-perfusion ratios the more $\text{PaO}_2$ tends to differ from the calculated $\text{PAO}_2$. (The difference between $\text{PAO}_2$ and $\text{PaO}_2$ is commonly referred to as the 'A-a gradient.' However, 'gradient' is a misnomer since the difference is not due to any diffusion gradient, but instead to $\text{V-Q}$ imbalance and/or right to left shunting of blood past ventilating alveoli. Hence 'A-a $\text{O}_2$ difference' is the more appropriate term.)

b) The alveolar-arterial $\text{PO}_2$ difference, notated $\text{P(A-a)O}_2$, varies normally with age and $\text{FIO}_2$. Up to middle age, breathing ambient air, normal $\text{P(A-a)O}_2$ ranges between 5 and 20 mm Hg. Breathing an $\text{FIO}_2$ of 1.0 the normal $\text{P(A-a)O}_2$ ranges up to about 110 mm Hg. If $\text{P(A-a)O}_2$ is increased above normal there is a defect of gas transfer within the lungs; this defect is almost always due to $\text{V-Q}$ imbalance.
A 27-year-old young woman came to the emergency room complaining of pleuritic chest pain of several hours duration. She was not a smoker but gave a history of using birth control pills. Her chest x-ray and physical exam were normal except for splinting with deep inspirations. Arterial blood gas showed pH 7.45, PaCO$_2$ 31 mm Hg, HCO$_3$ - 21 mEq/L, PaO$_2$ 83 mm Hg (breathing ambient air; PB 747 mm Hg). She was presumptively diagnosed as having pleurodynia and discharged with pain medication.

This young woman's PaO$_2$ was initially judged 'normal' and so an abnormality in oxygen transfer was missed. The calculated PIO$_2$ and PAO$_2$ were 147 mm Hg and 110 mm Hg, respectively. Her P(A-a)O$_2$ was elevated at 27 mm Hg (110 minus 83), indicating a state of V-Q imbalance, and therefore some parenchymal lung disease or abnormality. Indeed, she returned the next day with similar complaints, at which time a lung scan showed defects interpreted as high probability for pulmonary embolism.

c) Because of several assumptions in clinical use of the alveolar gas equation, precision in calculating PAO$_2$ is not achievable. Fortunately an estimate of P(A-a) O$_2$ is usually sufficient for clinical purposes. In Case 3, for example, the fact that the patient was hyperventilating and PaO$_2$ was only 83 mm Hg indicates an elevated P(A-a)O$_2$ and therefore a defect in gas exchange. The alveolar gas equation shows that with hyperventilation PaO$_2$ should go up; PaO$_2$ should be much higher than 83 mm Hg in a hyperventilating 27-year-old patient. Similarly, a patient breathing 40% oxygen whose PaO$_2$ and PaCO$_2$ are normal for room air (e.g., PaO$_2$ 90 mm Hg, PaCO$_2$ 40 mm Hg) has an elevated P(A-a)O$_2$ and therefore a defect in gas exchange; with this FIO$_2$, PAO$_2$ should be over 200 mm Hg and PaO$_2$ well over 100 mm Hg. These observations require nothing more than knowledge of the alveolar gas equation and simple mental calculation.

d) Since oxygen enters the pulmonary capillary blood by passive diffusion, it follows that in a steady state the alveolar PO$_2$ must always be higher than the arterial PO$_2$. This fact is useful to spot 'garbage' blood gas data, a not infrequent problem. For example, a PaO$_2$ of 150 mm Hg in a patient breathing 'room air' at sea level (FIO$_2$ = .21) must represent some kind of error, since at all conceivable PaCO$_2$ values the P(A-a)O$_2$ would have a negative value; even with extreme hyperventilation (PaCO$_2$ 10 mm Hg) the alveolar PO$_2$ would be no higher than 140 mm Hg. A moment's reflection will reveal several possible explanations for the apparently negative alveolar-arterial PO$_2$ difference: the patient was in fact breathing supplemental oxygen during or just prior to the sample drawing; an air bubble in the arterial sample syringe; a quality control or reporting error from the lab; a transcription error - someone wrote down the wrong number; etc.

What about the oxygen values mentioned at the beginning of this section? A PaO$_2$ of 28 mm Hg would be normal on the summit of Mt. Everest for a climber breathing ambient air. At the summit barometric pressure is 253 mm Hg, which provides a PIO$_2$ of only 43 mm Hg (Table I).
TABLE I. Gas Pressures at Various Altitudes*

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>ALT.</th>
<th>P_B</th>
<th>FIO₂</th>
<th>PIO₂</th>
<th>PaCO₂</th>
<th>PAO₂</th>
<th>PaO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea Level</td>
<td>0</td>
<td>760</td>
<td>.21</td>
<td>150</td>
<td>40</td>
<td>102</td>
<td>95</td>
</tr>
<tr>
<td>Cleveland</td>
<td>500</td>
<td>747</td>
<td>.21</td>
<td>147</td>
<td>40</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>Denver</td>
<td>5280</td>
<td>640</td>
<td>.21</td>
<td>125</td>
<td>34</td>
<td>84</td>
<td>77</td>
</tr>
<tr>
<td>*Pikes's Peak</td>
<td>14114</td>
<td>450</td>
<td>.21</td>
<td>85</td>
<td>30</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>*Mt. Everest</td>
<td>29028</td>
<td>253</td>
<td>.21</td>
<td>43</td>
<td>7.5</td>
<td>35</td>
<td>28</td>
</tr>
</tbody>
</table>

*All pressures in mm Hg; Pike’s Peak and Mt. Everest data from summits.

ALT. = altitude in feet
P_B = barometric pressure
FIO₂ = fraction of inspired oxygen
PIO₂ = pressure of inspired oxygen in the trachea
PaCO₂ = arterial PCO₂, assumed to = alveolar PCO₂
PAO₂ = alveolar PO₂, PAO₂ is calculated using an assumed R value of 0.8 except for the summit of Mt. Everest, where 0.85 is used.
PaO₂ = arterial PO₂, assuming a P(A-a)O₂ of 7 mm Hg at each altitude; each PaO₂ value is normal for its respective altitude.

If the climber maintained PaCO₂ at 40 mm Hg his PAO₂ would be minus 5 mm Hg, a value wholly incompatible with life! Ability to oxygenate blood at this altitude without supplemental oxygen is made possible (in large part) by extreme hyperventilation. On one expedition to the summit, 10 minutes after supplemental oxygen was removed a climber's end-tidal PCO₂ (equivalent to PACO₂) was measured at 7.5 mm Hg; assuming an R value of 0.85, the PAO₂ was only 35 mm Hg. Based on a theoretical alveolar-arterial PO₂ difference of 7 mm Hg, the climber's PaO₂ at the summit was estimated at 28 mm Hg - very low but 'normal' under the circumstances. A PaO₂ of 55 mm Hg would likewise be normal at Pike's Peak, Colorado, assuming a PaCO₂ of 30 mm Hg from modest hyperventilation and a P(A-a)O₂ of 7 mm Hg (Table V). On the other hand, a PaO₂ of 95 mm Hg would represent a serious abnormality in anyone breathing 100% oxygen near sea level, as under these conditions PaO₂ should be over 500 mm Hg. In summary, to properly interpret PaO₂ one needs to have some appreciation of the alveolar PO₂, which requires knowing (at least approximately) the barometric pressure, FIO₂ and PaCO₂.

4. Oxygen Content Equation

All physicians know that hemoglobin carries oxygen and that anemia can lead to severe hypoxemia. Making the necessary connection between PaO₂ and O₂ content requires knowledge of the oxygen content equation.

\[
\text{CaO}_2 = (\text{SaO}_2 \times \text{Hb} \times 1.34) + .003(\text{PaO}_2)
\]

How much glucose is in the blood if the glucose level is 80 mm Hg? This question makes no sense, of course, because glucose is not a gas and therefore exerts no pressure in solution; any question regarding 'how much' is answered by determining its content, which in the case of glucose is usually reported as mg/dl blood. Oxygen is a gas and its molecules do exert a pressure but, like glucose, oxygen also has a finite content in the blood, in units of ml O₂/dl blood. To remain viable tissues require a certain amount of oxygen per minute, a need met by a requisite oxygen content, not oxygen pressure. (Patients can and do live with very low PaO₂ values, as long as their oxygen content and cardiac output are adequate.) The oxygen carrying capacity of one gram of hemoglobin is 1.34 ml. With a hemoglobin content of 15
grams/dl blood and a normal hemoglobin oxygen saturation (SaO2) of 98%, arterial blood has a hemoglobin-bound oxygen content of 15 x .98 x 1.34 = 19.7 ml O2/dl blood. An additional small quantity of O2 is carried dissolved in plasma: .003 ml O2/dl plasma/mm Hg PaO2, or .3 ml O2/dl plasma when PaO2 is 100 mm Hg. Since normal CaO2 is 16-22 ml O2/dl blood, the amount contributed by dissolved (unbound) oxygen is very small, only about 1.4% to 1.9% of the total. Given normal pulmonary gas exchange (i.e., a normal respiratory system), factors that lower oxygen content - such as anemia, carbon monoxide poisoning, methemoglobinemia, shifts of the oxygen dissociation curve - do not affect PaO2. PaO2 is a measurement of pressure exerted by uncombined oxygen molecules dissolved in plasma; once oxygen molecules chemically bind to hemoglobin they no longer exert any pressure.

PaO2 affects oxygen content by determining, along with other factors such as pH and temperature, the oxygen saturation of hemoglobin (SaO2). The familiar O2-dissociation curve can be plotted as SaO2 vs. PaO2 and as PaO2 vs. oxygen content (Figure 3). For the latter plot the hemoglobin concentration must be stipulated. When hemoglobin content is adequate, patients can have a reduced PaO2 (defect in gas transfer) and still have sufficient oxygen content for the tissues (e.g., hemoglobin 15 grams%, PaO2 55 mm Hg, SaO2 88%, CaO2 17.8 ml O2/dl blood). Conversely, patients can have a normal PaO2 and be profoundly hypoxemic by virtue of a reduced CaO2. This paradox - normal PaO2 and hypoxemia - generally occurs one of two ways: 1) anemia, or 2) altered affinity of hemoglobin for binding oxygen. A common misconception is that anemia affects PaO2 and/or SaO2; if the respiratory system is normal, anemia affects neither value. (In the presence of a right to left intrapulmonary shunt anemia can lower PaO2 by lowering the mixed venous oxygen content; when mixed venous blood shunted past the lungs mixes with oxygenated blood leaving the pulmonary capillaries, lowering the resulting PaO2.25 With a normal respiratory system mixed venous blood is fully oxygenated - as much as allowed by the alveolar PO2 - as it passes through the pulmonary capillaries.)

Obviously, however, the lower the hemoglobin content the lower the oxygen content. It is not unusual to see priority placed on improving a chronically hypoxemic patient's low PaO2 when a blood transfusion would be far more beneficial. Anemia can also confound the clinical suspicion of hypoxemia since anemic patients do not generally manifest cyanosis even when PaO2 is very low. Cyanosis requires a minimum quantity of de-oxygenated hemoglobin to be manifest - approximately 5 grams% in the capillaries.26,27 A patient whose hemoglobin content is 15 grams% would not generate this much reduced hemoglobin in the capillaries until the SaO2 reached 78% (PaO2 44 mm Hg); when hemoglobin is 9 grams% the threshold SaO2 for cyanosis is lowered to 65% (PaO2 34 mm Hg).27

Altered hemoglobin affinity may occur from shifts of the oxygen dissociation curve (e.g., acidosis, hyperthermia), from alteration of the oxidation state of iron in the hemoglobin (methemoglobinemia), or from carbon monoxide poisoning.

**CASE 4.**

A 54-year-old man came to the emergency room (ER) complaining of headaches and shortness of breath. On room air his PaO2 was 89 mm Hg, PaCO2 38 mm Hg, pH 7.43; hematocrit was 44%. SaO2 was not directly measured but instead calculated at 98% for this PaO2, based on a standard oxygen dissociation curve. After some improvement he was scheduled for a brain CAT scan two days later, and discharged from the ER. He was brought back to the ER the next evening, unconscious. Ambulance attendants alerted the ER physician to a possible faulty heater in the patient's house. This time carbon monoxide and SaO2 were measured along with routine arterial blood gases. The results: PaO2 79 mm Hg, PaCO2 31 mm Hg, pH 7.36, SaO2 53%, carboxyhemoglobin 46%.

This patient's true SaO2 would have been much lower than 98% had it been measured on the first ER visit instead of just calculated. The physician missed hypoxemia as a cause of headache and dyspnea because of the 'normal' calculated SaO2. Carbon monoxide by itself does not affect PaO2 but only SaO2 and O2 content. (Slight reduction in PaO2 on the patient's second visit was attributed to some basilar
atelectasis and resulting V-Q imbalance. Confusion about interpretation of oxygen saturation in the presence of excess CO is not unusual and even finds its way into peer-review literature.28

To know the oxygen content one needs to know the hemoglobin content and the SaO₂; both should be measured as part of each arterial blood gas test. As shown above, a calculated SaO₂ may be way off the mark and can be clinically misleading. This is true even without excess CO in the blood. One study of over 10000 arterial samples found wide variation in measured SaO₂ for a given PaO₂; for example, in the PaO₂ range of 56-64 mm Hg the measured SaO₂ ranged from 69.7 percent to 99.4 percent. 28

Finally, it should be noted that pulse oximeters are not reliable in the presence of dyshemoglobins - hemoglobins that cannot bind oxygen. The two major dyshemoglobins encountered in clinical practice are carboxyhemoglobin (COHb) and methemoglobin (Methb). Oximeters do not differentiate hemoglobin bound to carbon monoxide from hemoglobin bound to oxygen; the machines report the sum of both values as oxyhemoglobin.30-34

In contrast to blood co-oximeters, which utilize four wavelengths of light to separate out oxyhemoglobin from reduced hemoglobin, methemoglobin and carboxyhemoglobin, pulse oximeters utilize only two wavelengths of light 33-34. As a result, pulse oximeters measure COHb and part of any Methb along with oxyhemoglobin, and combine the three into a single reading, the SpO₂. (Methb absorbs both wavelengths of light emitted by pulse oximeters, so that SpO₂ is not affected as much by Methb as for a comparable level of COHb).

Thus a patient with 80% oxyhemoglobin and 15% carboxyhemoglobin would show a pulse oximetry oxygen saturation (SpO₂) of 95%, a value too high by 15%. For this reason pulse oximeters should be used cautiously (if at all) when there may be an elevated carbon monoxide level, for example in patients assessed in an emergency department. Note that excess carboxyhemoglobin is present in all cigarette and cigar smokers. A resting SpO₂ should be interpreted cautiously in any outpatient who has smoked within 24 hours. The half-life of CO breathing ambient air is about 6 hours, so 24 hours after smoking cessation the CO level should be normal, i.e., less than 2.5%. If there is concern about the true SaO₂, it should be measured on an arterial blood sample; alternatively, the percent COHb can be measured on a venous sample, and the value subtracted from the SpO₂.

The spectrophotometric technique used by pulse oximeters also makes their oxygen saturation reading less reliable in the presence of excess methemoglobin (methb). Methb reduces the SpO₂ linearly until a level of about 85%, at which point further increases in methb do not cause further lowering of SpO₂.35-37 A finding of unexpectedly low SpO₂ (e.g., 91% in a patient with normal cardiorespiratory system who is receiving nasal oxygen) should make one think of excess methb; in such cases an arterial blood sample should be obtained for direct measurement of SaO₂ and PaO₂.
TRUE-FALSE QUIZ
Lawrence Martin, M.D., FACP, FCCP

Directions: This quiz is designed to test your understanding of information in this paper. For each of the following five numbered statements or questions, there are five lettered responses (a-e), each of which may be true or false. Circle the correct or true responses. Answers immediately follow the quiz.

1. Normal range for PaCO$_2$ is 35-45 mm Hg. A change in PaCO$_2$ from normal to 28 mm Hg means the subject
   • a) is hyperventilating.
   • b) has excess alveolar ventilation for the amount of CO$_2$ production.
   • c) must have hypoxia, anxiety, and/or metabolic acidosis.
   • d) must be breathing faster than normal.
   • e) must have acute respiratory alkalosis.

2. The arterial PO$_2$ is predicted to be reduced to some extent from
   • a) anemia.
   • b) ventilation-perfusion (V-Q) imbalance with an increase in the number of low V- Q units.
   • c) increased PCO$_2$, while the subject is breathing room air.
   • d) carbon monoxide poisoning.
   • e) altitude.

3. To obtain a reasonable idea of the acid-base state of a patient’s blood, you would need to know the
   • a) pH and PaCO$_2$.
   • b) pH and PaO$_2$.
   • c) PaCO$_2$ and PaO$_2$.
   • d) PaCO$_2$ and HCO$_3$-
   • e) pH and SaO$_2$ (%saturation of hemoglobin with oxygen).

4. Arterial blood gas data (pH, PaCO$_2$, PaO$_2$, SaO$_2$) are related in some simple but important ways. Which of the following are valid relationships?
   • a) Alveolar PO$_2$ is related to PaCO$_2$ by the alveolar gas equation: as PaCO$_2$ goes up, alveolar PO$_2$ goes down.
   • b) PaO$_2$ is inversely related to blood pH: as pH goes up, PaO$_2$ goes down.
   • c) If PaCO$_2$ increases while HCO$_3$- remains unchanged, pH always goes down.
   • d) PaO$_2$ is related to SaO$_2$ on a linear scale (i.e., a straight-line relationship).
   • e) The SaO$_2$ is related to hemoglobin-bound arterial oxygen content on a linear scale (i.e., a straight-line relationship).

5. There are some "truisms" in terminology and physiology for proper blood gas interpretation. They include which of the following?
   • a) "Hyperventilation" and "hypoventilation" are clinical terms, and are not diagnosed by arterial blood gases.
   • b) The alveolar-arterial PO$_2$ difference increases with age and with increase in the fraction of inspired oxygen.
   • c) The arterial PO$_2$ cannot go above 100 mm Hg while breathing room air at sea level.
- d) A continuously negative alveolar-arterial PO\textsubscript{2} difference is incompatible with life.
- e) If arterial pH is normal, the patient cannot have a clinically significant acid-base disorder.

**ANSWERS**

1. a and b are true. The patient may have hyperventilation from many causes (including voluntary hyperventilation). The subject may be breathing deeper than normal, rather than faster. And the subject may be hyperventilating to compensate for metabolic acidosis, which would not be a respiratory alkalosis.

2. b, c and e are true; other responses are false. Anemia and carbon monoxide poisoning do not affect PaO\textsubscript{2} (except when there is a ventilation-perfusion imbalance and some right to left shunting).

3. a and d are true. You need to know two of the three Henderson-Hasselbalch equation variables to assess acid-base status.

4. a, c and e are true. PaO\textsubscript{2} and pH are not related in any formal way. The relationship of PaO\textsubscript{2} to SaO\textsubscript{2} is sigmoid-shaped, not straight line.

5. b and d are true. Hyperventilation and hypoventilation are specifically not defined by clinical or bedside criteria, but by changes in PaCO\textsubscript{2}. The PaO\textsubscript{2} can easily go above 100 mm Hg with hyperventilation and normal lungs. Arterial pH can be normal with two or more acid-base disorders occurring at the same time.

**REFERENCES**

22. Martin L. Abbreviating the alveolar gas equation. An argument for simplicity. Respir Care 1986;31:40-44.