

# Altitude, the Ratio of PaO<sub>2</sub> to Fraction of Inspired Oxygen, and Shunt: Impact on the Assessment of Acute Lung Injury

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The ratio of PaO<sub>2</sub> to the fraction of inspired oxygen (PaO<sub>2</sub>/FIO<sub>2</sub>) is commonly used to determine the severity of acute lung injury and acute respiratory distress syndrome (ARDS). The research presented here used computational models of the lung to analyze the effect of altitude on the PaO<sub>2</sub>/FIO<sub>2</sub> ratio and pulmonary shunt.

At a given shunt, the PaO<sub>2</sub>/FIO<sub>2</sub> ratio is lower at higher altitudes. Therefore, when evaluating for ARDS based on a PaO<sub>2</sub>/FIO<sub>2</sub> ratio of <200 mm Hg, patients residing at high altitudes will have less shunt and, presumably, less severe lung injury than patients at sea level.

This should be taken into consideration when comparing patients from different altitudes. Shunt should more often be measured directly or be estimated assuming a constant arteriovenous oxygen content difference.

**Key words:** Shunt. Oxygenation index. Ratio PaO<sub>2</sub> to fraction of inspired oxygen (FIO<sub>2</sub>), PaO<sub>2</sub>/FIO<sub>2</sub>. Acute respiratory distress syndrome (ARDS). Altitude.

La altitud modifica la relación entre la PaO<sub>2</sub>/FiO<sub>2</sub> y el cortocircuito: impacto en la valoración de la lesión pulmonar aguda

El cociente presión arterial de oxígeno/fracción inspiratoria de oxígeno (PaO<sub>2</sub>/FiO<sub>2</sub>) se utiliza comúnmente para definir el grado de lesión pulmonar y el síndrome de insuficiencia respiratoria progresiva del adulto. En el presente trabajo se analizan las modificaciones que experimenta el índice con la altura sobre el nivel del mar y con los cortocircuitos en modelos computacionales de pulmón.

El cociente PaO<sub>2</sub>/FiO<sub>2</sub> disminuye con la altura sobre el nivel del mar al mismo cortocircuito. Por lo tanto, los pacientes que residen a alturas considerables sobre el nivel del mar tienen un cortocircuito menor y presumiblemente un grado de daño pulmonar menor que los residentes al nivel del mar en el momento de cumplir el criterio de síndrome de insuficiencia respiratoria progresiva del adulto con un cociente PaO<sub>2</sub>/FiO<sub>2</sub> de 200 Torr.

Esta variación debe tomarse en cuenta para la comparación de pacientes cuando provienen de alturas diferentes e indica que se ha de utilizar más frecuentemente la medición directa del cortocircuito o bien el cortocircuito calculado, asumiendo una diferencia arteriovenosa del contenido de oxígeno constante.

**Palabras clave:** Cortocircuito. Índices de oxigenación. PaO<sub>2</sub>/FiO<sub>2</sub>. Síndrome de insuficiencia respiratoria progresiva del adulto (SIR-PA). Altitud.

## Introduction

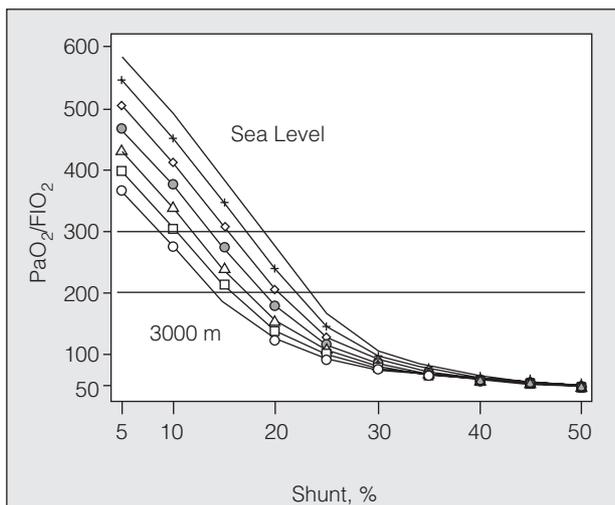
In patients with acute respiratory distress syndrome (ARDS), the primary physiological mechanism of hypoxemia is shunt. Shunt is precisely measured using the Berggren equation based on simultaneous arterial blood and mixed venous blood samples drawn with a pulmonary artery catheter while the patient is ventilated with pure oxygen. However, this measurement is rarely performed and is not generally available. Shunt is more

commonly assessed based on a series of oxygenation indices that do not require a pulmonary artery blood sample: the ratio of PaO<sub>2</sub> to the fraction of inspired oxygen (PaO<sub>2</sub>/FIO<sub>2</sub>), the ratio of PaO<sub>2</sub> to alveolar oxygen pressure (PaO<sub>2</sub>/PAO<sub>2</sub>), the arterial-alveolar oxygen tension gradient of the PaO<sub>2</sub> (P[A-a]O<sub>2</sub>), and the ratio of P[A-a]O<sub>2</sub> to PaO<sub>2</sub>.<sup>1-10</sup>

In 1994, the American-European Consensus Conference on ARDS issued definitions that have been accepted by many clinicians and researchers.<sup>11,12</sup> The recommendations cover radiographic, gasometric, and clinical categories, including use of the PaO<sub>2</sub>/FIO<sub>2</sub> ratio.<sup>11,12</sup> An acute lung injury is defined by a PaO<sub>2</sub>/FIO<sub>2</sub> ratio of equal to or less than 300 mm Hg and ARDS is defined by a ratio of less than or equal to 200 mm Hg.<sup>11,12</sup> However, in addition to known PaO<sub>2</sub>/FIO<sub>2</sub> ratio

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Manuscript received December 2, 2003. Accepted for publication March 9, 2004.



**Figure 1.** Relation between the ratio of PaO<sub>2</sub> to fraction of inspired oxygen ratio (PaO<sub>2</sub>/FIO<sub>2</sub>) in mm Hg and arteriovenous shunt (horizontal axis), in function of altitude. The highest curve corresponds to sea level and the lowest one corresponds to an altitude of 3000 m. The curves between them show the relations at altitude increments of 500 m. At the highest altitude, the PaO<sub>2</sub>/FIO<sub>2</sub> ratio is less than the shunt. The PaO<sub>2</sub>/FIO<sub>2</sub> ratios of 300 and 200 (horizontal lines) correspond to the gas exchange levels associated with lung injury and acute respiratory distress syndrome, respectively. Shunt sizes vary with altitude.

miscalculations as a result of varying FIO<sub>2</sub>,<sup>1-10,13,14</sup> inaccuracies can result from changes in altitude. Since a large percentage of the world's population resides at altitudes considerably above sea level,<sup>15,16</sup> it is important to determine the impact of altitude on oxygenation indices. In the present study, the impact of altitude on oxygenation indices is analyzed through computational models of gas exchange—in particular, the PaO<sub>2</sub>/FIO<sub>2</sub> ratio.

## Method

In the present study, the PaO<sub>2</sub>/FIO<sub>2</sub> indices were estimated at different values of shunt and altitude based on data provided by 2 mathematical models of pulmonary gas exchange: the West model<sup>17</sup> and the oxygen status algorithm (OSA) designed by Siggaard-Andersen and Siggaard-Andersen.<sup>8</sup> The West model requires knowing oxygen consumption, carbon dioxide production, hemoglobin level, hematocrit, barometric pressure, FiO<sub>2</sub>, base excess, pressure at 50% saturation, fraction of inspired carbon dioxide, cardiac output, alveolar ventilation, shunt, and degree of change in the pulmonary ventilation-perfusion relationship.<sup>17</sup> With this data, the West model calculates the gasometric concentrations of arterial and venous blood through successive iterations. The OSA was designed mainly to calculate gas exchange variables, after inputting values for arterial blood gases, including hemoglobin saturation. The OSA program does not use cardiac output values, but rather assumes an arteriovenous oxygen content difference (C[a-v]O<sub>2</sub>) of 5.15 mL/dL. Nor does it use changes in the ventilation-perfusion relationship or calculate the venous admixture. Percentages of carboxyhemoglobin, methemoglobin, and fetal hemoglobin in blood are also required, as is 2,3-diphosphoglycerate (2,3-DPG) content. Both models use a FIO<sub>2</sub> of 1.0, which

allows precise shunt assessment with arterial and mixed venous blood samples. When the patient has a lower FIO<sub>2</sub>, the shunt is overestimated by alterations in the ventilation-perfusion relationship and diffusion limitations when present. In addition, the PaO<sub>2</sub>/FIO<sub>2</sub> ratio and other simplified oxygenation indices previously mentioned vary with FIO<sub>2</sub> and, therefore, variations resulting from changes in altitude are difficult to distinguish—the problem that has led to the present study. The barometric pressure was estimated based on the altitude<sup>19</sup>; PaCO<sub>2</sub> was also estimated based on altitude, to reflect values for acclimated subjects.<sup>16</sup> All calculations assumed a hemoglobin concentration of 15 g/dL, a hematocrit of 45, a pH of 7.4 (an appropriate alkaline excess for hemoglobin), PaCO<sub>2</sub>, and a 50% saturation of 26.9 mm Hg. In addition, the West model assumes an oxygen consumption of 300 mL/min and a carbon dioxide production of 240 mL/min (respiratory exchange ratio of 0.8). The OSA used a 2,3-DPG concentration of 5.3 mmol/L and concentrations of carboxyhemoglobin, fetal hemoglobin, and methemoglobin of 0.5% each. The total cardiac output values (6 L/min), hemoglobin, and 50% saturation level remained constant at varying altitudes and shunt sizes. The cardiac output of acclimated subjects tended to remain constant with changes in altitude.<sup>20</sup>

The computational models of the programs differ, but both use iteration to adjust the values. If a slightly unbalanced ventilation-perfusion ratio is input into the West program and a C(a-v)O<sub>2</sub> similar to that assumed by the OSA model is generated (5.15 mL/dL) the estimated arterial blood concentrations would be very similar to those that would be estimated by the OSA program if normal concentrations of 2,3-DPG and abnormal hemoglobin levels were input. In addition, the relationship between the oxygenation indices and altitude can be clearly defined in both models.

The arterial blood composition and the PaO<sub>2</sub>/FIO<sub>2</sub> ratio were estimated with increasing shunts from 1% to 50% of cardiac output and varying altitudes from sea level to 3000 m. Estimated shunt behavior in relation to altitude was determined by using a C(a-v)O<sub>2</sub> of 3.5 mL/dL recommended for critically ill patients.<sup>1</sup>

The shunt formula was as follows:

$$\text{Estimated shunt} = (\text{CcO}_2 - \text{CaO}_2) / (\text{Cc} - 2 - \text{Ca} = 2) + 3.5$$

where CcO<sub>2</sub> is the end-capillary oxygen concentration and CaO<sub>2</sub> is the arterial oxygen concentration.

## Results

The estimated arterial oxygen concentrations and PaO<sub>2</sub>/FIO<sub>2</sub> ratios produced by the West and OSA models were equivalent. Shunt size increased as PaO<sub>2</sub>/FIO<sub>2</sub> decreased, but the values estimated for altitudes between 0 and 3000 m differed (Figure 1). For a given shunt, the PaO<sub>2</sub>/FIO<sub>2</sub> ratio decreased as altitude increased, although the curves converged as large shunt values were reached. The complex curvilinear relationship between shunt and the PaO<sub>2</sub>/FIO<sub>2</sub> ratio is also evident. Figure 2 shows that the PaO<sub>2</sub>/FIO<sub>2</sub> ratio decreases in relation to altitude with no change in shunt or FIO<sub>2</sub> and that the impact of altitude decreases as shunt increases. Oxygenation indices dependent on PaO<sub>2</sub> (PaO<sub>2</sub>/PAO<sub>2</sub>, PaO<sub>2</sub>/PiO<sub>2</sub>, P(A-a)O<sub>2</sub>, and P(A-a)O<sub>2</sub>/PaO<sub>2</sub>) also have curvilinear relationships with shunt and altitude,

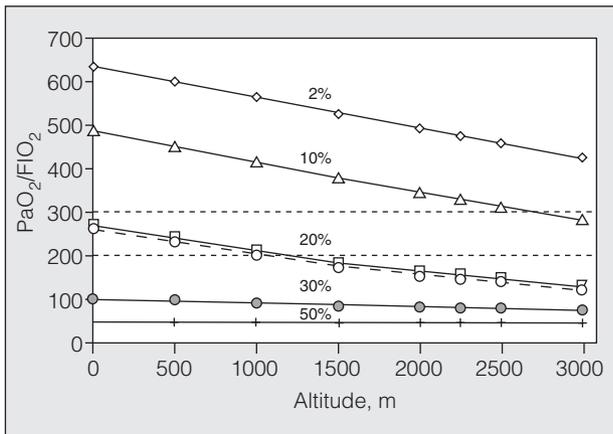


Figure 2. Relation between the ratio of PaO<sub>2</sub> to fraction of inspired oxygen (PaO<sub>2</sub>/FIO<sub>2</sub>) in mm Hg and altitude in meters (horizontal axis), in function of varying shunt values (lines). The PaO<sub>2</sub>/FIO<sub>2</sub> ratio diminishes at higher altitudes, but the impact of altitude on large shunts is not significant. Two lines are visible for a shunt of 20%; the continuous line was obtained using the oxygen status algorithm and the dashed line (- -) was obtained using the West algorithm. A single arteriovenous oxygen content difference of 5.15 mL/dL was used to exemplify the equivalence of the calculations.

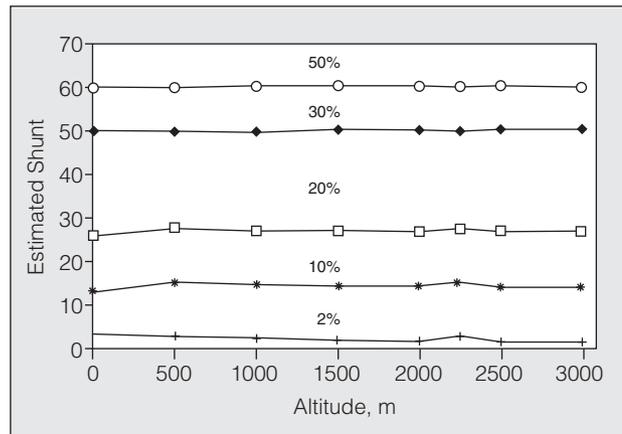


Figure 3. Relation between the percentage of estimated shunt (vertical axis) and altitude in meters (horizontal axis), in function of actual shunt values (lines). The arteriovenous oxygen content difference used in calculation was 3.5 mL/dL. Bias can be observed in the estimated shunt, but it does not change with altitude. The bias depends on the margin of error in the estimation of the actual arteriovenous oxygen content difference (5.15 mL/dL) and it can be negative or positive.

changing in varying degrees with large and small shunts. In contrast, Figure 3 shows that estimated shunt does not change significantly with altitude, although a systematic error is produced resulting from error in estimating the true C(a-v)O<sub>2</sub>.

The estimated shunts for different PaO<sub>2</sub>/FIO<sub>2</sub> values and altitudes are presented in the Table. For example, when the PaO<sub>2</sub>/FIO<sub>2</sub> ratio is 300—the cutoff indicative of acute lung injury at 100% oxygen—a shunt that is 19% at sea level would be 11.5% in Mexico City and 9.5% at 3000 m. This indicates that the PaO<sub>2</sub>/FIO<sub>2</sub> ratio will identify patients with less severe lung injuries at higher altitudes than at sea level. It should be noted that the calculations in the Table were based on a FIO<sub>2</sub> of 1.0 and the results will change considerably with modifications to the FIO<sub>2</sub>. For example, if a measurement were made at sea level with a FIO<sub>2</sub> of 0.5

TABLE  
Shunt for Varying PaO<sub>2</sub>/FIO<sub>2</sub> Ratios and Altitudes\*

| Altitude, m | Barometric Pressure | PaCO <sub>2</sub> | PaO <sub>2</sub> /FIO <sub>2</sub> |        |        |
|-------------|---------------------|-------------------|------------------------------------|--------|--------|
|             |                     |                   | 200, %                             | 250, % | 300, % |
| 0           | 760                 | 40                | 23                                 | 21.5   | 19     |
| 500         | 718                 | 36.8              | 21                                 | 19     | 17     |
| 1000        | 678                 | 35.4              | 20                                 | 18     | 16     |
| 1500        | 641                 | 34.2              | 19                                 | 16.5   | 14     |
| 2000        | 604                 | 33.0              | 18                                 | 15     | 13     |
| 2240        | 585                 | 32.4              | 17.5                               | 14.5   | 11.5   |
| 2500        | 570                 | 31.8              | 16.5                               | 14     | 11     |
| 3000        | 537                 | 30.6              | 15                                 | 12     | 9.5    |

\*FIO<sub>2</sub> indicates the fraction of inspired oxygen. The barometric pressure was calculated based on altitude. Estimated PaCO<sub>2</sub> data are given for acclimated subjects. Calculations were based on an assumed FIO<sub>2</sub> of 1.0, hemoglobin of 15.0 g/dL, methemoglobin of 26.8 mm Hg, temperature of 37°C, respiratory ratio of 0.86, and pH of 7.40. Calculations were derived using the oxygen status algorithm assuming an arteriovenous oxygen content difference of 5.15 mL/dL.

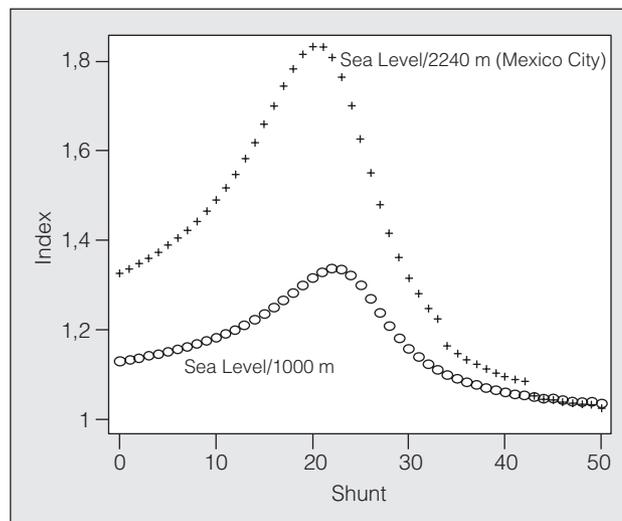


Figure 4. Plot of the index expressing the relation between the ratio of PaO<sub>2</sub> to the fraction of inspired oxygen (PaO<sub>2</sub>/FIO<sub>2</sub>) at sea level and the same ratio at the altitude of Mexico City (upper curve), and between the PaO<sub>2</sub>/FIO<sub>2</sub> ratio at sea level and at 1000 m (lower curve) on the vertical axis and the degree of shunt on the horizontal axis. As can be observed, the index varies widely in relation to both altitude and degree of shunt. For this reason, estimating shunt based on PaO<sub>2</sub>/FIO<sub>2</sub> and altitude is complex.

and a PaO<sub>2</sub>/FIO<sub>2</sub> of 300, the shunt would be 12.5%, whereas it would be 19% with a FIO<sub>2</sub> of 1.0. However, even with varying FIO<sub>2</sub> values, the PaO<sub>2</sub>/FIO<sub>2</sub> changed with the altitude.

The correction factor used to estimate the PaO<sub>2</sub>/FIO<sub>2</sub> ratio at sea level based on measurements at a higher altitude was difficult to establish (Figure 4). For shunts of 20%, the PaO<sub>2</sub>/FIO<sub>2</sub> ratio would be nearly double at the altitude of Mexico City in comparison with the ratio at sea level.

## Discussion

The advantage of the PaO<sub>2</sub>/FIO<sub>2</sub> ratio is clearly that it is easy to use, but its disadvantage is that it behaves differently at varying altitudes and values of FIO<sub>2</sub>. In particular, changes occurring with altitude mean that it is unreliable for comparing patients diagnosed with ARDS or acute lung injury using international criteria. In order to determine the effects of altitude on shunt size, it will undoubtedly be important to verify empirically the results we have found using computational lung models in which the gas exchange parameters that change in severely ill patients have been held constant in order to bring altitude-related variation to the forefront. It is important to mention that other simplified oxygenation indices such as PaO<sub>2</sub>/PiO<sub>2</sub>, PaO<sub>2</sub>/PAO<sub>2</sub> and P(A-a)O<sub>2</sub> are similarly influenced by changes in the FIO<sub>2</sub>.<sup>1-10,13,14</sup> Although the data is not presented here, they are effected by altitude and their use does not resolve the problem of the unreliability of the PaO<sub>2</sub>/FIO<sub>2</sub> ratio. The estimated shunt, on the other hand, is resistant to change of altitude. However, the estimation of shunt is a less reliable strategy to use for patients with respiratory insufficiency given that cardiac output and metabolic rate are often affected by disease, therapeutic management, and vasoactive drugs. Previous studies have looked at simplified oxygenation indices in detail have led to the conclusion that they are of questionable reliability,<sup>1-10,13,14</sup> although estimated shunt is the one that best correlates with measured shunt.<sup>1,2,6,9</sup>

The evaluation of lung injury and ARDS using the international definitions based on the PaO<sub>2</sub>/FIO<sub>2</sub> ratio results in fewer diagnoses of shunt (and lung injuries) in residents at high altitudes than residents at sea level. This problem implies that direct shunt measurement should be used more frequently with patients suffering hypoxemia and would be required when comparing subjects that reside at different altitudes. It is important to note that even in patients with a pulmonary catheter in place, the practice of measuring shunt while the patient is ventilated with pure oxygen has decreased because of the time it requires and because poorly ventilated alveolar units may collapse under high oxygen concentrations, and, therefore, worsen the shunt.<sup>11</sup> This problem is not present with multiple inert gas measurements,<sup>21</sup> but are not applicable in daily clinical practice. The Berggren method, which admits use of a FIO<sub>2</sub> that is less than 1.0 in ventilated patients, overestimates the actual shunt in patients with poorly ventilated pulmonary areas as a result of venous admixture. As the FIO<sub>2</sub> increases, the degree of overestimation decreases—producing yet an additional source of measurement variation. Despite this, traditional shunt measurement using the Berggren method is considered the standard technique because it is widely available, representative, and sufficiently stable.<sup>4,6,10,13</sup>

In patients who have not undergone direct shunt measurement, the effects of altitude can be adjusted for

by calculating shunt assuming a constant arteriovenous oxygen difference. However, this measurement will not be accurate if the arteriovenous difference is erroneous.

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