# Equivalent Air Altitude and the Alveolar Gas Equation

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**INTRODUCTION:** It is expedient to use normobaric hypoxia (NH) as a surrogate for hypobaric hypoxia (HH) for training and research. The approach matches inspired oxygen partial pressure ($P_IO_2$) at the desired altitude to that at site pressure ($P_B$) by reducing the inspired fraction of oxygen ($F_IO_2$) to <0.21 using the equation: $P_IO_2 = (P_B - 47) \times F_IO_2$, where 47 mmHg is the vapor pressure of water at 37°C. The investigator then has at site pressure the equivalent $P_IO_2$ as at altitude, i.e., the NH exposure is at an "equivalent air altitude." Some accepted as fact identical signs and symptoms of hypoxia for both conditions. However, those that derived the alveolar air equation showed that the coupled alveolar oxygen ($P_AO_2$) and carbon dioxide partial pressures ($P_ACO_2$) for NH and HH are not identical when $P_IO_2$ is equivalent. They attribute the difference in alveolar gas composition under equivalent $P_IO_2$ to a nitrogen dilution effect or, more generally, to the respiratory exchange effect. Those that use NH as a convenient surrogate for HH must concede that physiological responses to NH cannot be identical to the responses to HH given only equivalent hypoxic $P_IO_2$.

**KEYWORDS:** normobaric hypoxia, hypobaric hypoxia, nitrogen dilution effect, respiratory exchange effect, alveolar oxygen, alveolar carbon dioxide.

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Giants of environmental physiology once roamed the Earth.[4] Unfortunately, an important implication from the alveolar gas equation (AGE) about equivalent air altitude (EAA) from the giants who derived the AGE has been lost to history. But their insight can be resurrected. The derivation of the AGE evolved through time. Documentation is left to a science historian, but in 1946 Fenn, Rahn, and Otis[6] derived the equivalent of Eq. 1 and called it the alveolar air equation.

$$P_AO_2 = (P_B - 47) \times F_IO_2 - P_ACO_2 \times \left[F_IO_2 + \left((1 - F_IO_2)/RER\right)\right], \quad \text{Eq.1}$$

where the unit of pressure is mmHg, $F_IO_2$ is the dry-gas fraction of oxygen in breathing gas, $P_B$ is ambient pressure, 47 mmHg is water vapor partial pressure at 37°C, RER is respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$, as $ml \cdot min^{-1}{}_{(STPD)}$), and $P_AO_2$ and $P_ACO_2$ are alveolar partial pressure for oxygen and carbon dioxide, respectively. Note that $1 - F_IO_2$ is the dry-gas fraction of nitrogen ($F_IN_2$) and this relationship brings $F_IN_2$ into focus as a contributor to $P_AO_2$.

With the aid of their 1946 $O_2$-$CO_2$ diagram, Fenn et al.[6] explored various theoretical applications of the AGE, particularly hypobaric hypoxia (HH) and the integrated physiological responses to acute and chronic exposures. They surmised from the AGE that combinations of $F_IO_2$ and $P_B$ that resulted in the same hypoxic inspired partial pressure of oxygen ($P_IO_2$) as breathing air at altitude would not produce the same $P_AO_2$ as at altitude. This important conclusion was lost to history. The precision of the AGE in this regard was replaced with the utilitarian EAA concept.

The EAA is that altitude on air where the hypoxic $P_IO_2$ is equivalent to the $P_IO_2$ of the alternative condition in question, where $P_IO_2 = (P_B - 47) \times F_IO_2$. Notice that $P_B$, $PH_2O$, and $F_IO_2$ are the first three terms in the AGE. It became expedient for some to equate hypoxic $P_IO_2$ when $F_IO_2 \neq 0.21$ to the $P_IO_2$ associated with ascent on air, the EAA for their condition, and then accept that all responses to hypoxia in their condition would be equivalent to those observed at that altitude. The allure of this approach is clear, as physiological responses to HH were well described, even in the early 1950s. It was easier to conduct training or normobaric hypoxia (NH) research at sea level ($P_B = 760$ mmHg, $F_IO_2 < 0.21$) at a particular hypoxic $P_IO_2$

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without the expense of operating an altitude chamber or traveling to high altitude to achieve the same $P_IO_2$. The precise but complex AGE became secondary to the utilitarian EAA concept and then that concept was accepted as fact. NH easily became a surrogate for HH. The work done in the 1940s and 1950s on "equivalent altitudes" based on the AGE was largely forgotten.

For example, **Table I** shows five conditions that result in the same hypoxic $P_IO_2$ of 80 mmHg. Condition 1 is an ascent to 4572 m (15,000 ft) while breathing air. All others are from breathing a mixture where $F_IO_2 \neq 0.21$, so $F_IN_2$ varies above and below 0.79 (argon in air included as $N_2$), including the extreme case where $F_IN_2 = 0$ during an ascent on 100% $O_2$ to 12,802 m (42,000 ft). Many today would expect physiological responses for conditions 2 through 5 to be equivalent to those for condition 1. The very real possibility of decompression sickness in some of these exposures is ignored in this discussion about hypoxia.

Fenn et al. in 1946[6] and Rahn and Fenn in 1956[7] explored the implications of the AGE under conditions other than ascent on air, like conditions 2 through 5 in Table I. **Table II** shows calculations from the AGE for a moment frozen in time during an otherwise dynamic response to hypoxia. A central nervous system (CNS)-mediated hypoxia-induced increase in minute ventilation ($\dot{V}_E$) reduces body stores of $CO_2$ and so reduces $P_ACO_2$ and temporarily increases RER to 1.3 in all but condition 5 (described later). The ratio of alveolar ventilation rate ($\dot{V}_A$, $l_{(BTPS)}$/min) to $CO_2$ production rate ($\dot{V}CO_2$, ml · $min^{-1}{}_{(STPD)}$) is not explicit in the AGE, but ultimately sets the $P_AO_2$-$P_ACO_2$ point. The number of arrows implies the trend in direction and magnitude for $\dot{V}_A/\dot{V}CO_2$ abstracted from various literature sources.

Notice that any a priori expectation of similar $P_AO_2$ outcomes for identical $P_IO_2$ is not warranted. $P_AO_2$ from conditions 2 through 5 do not match the $P_AO_2$ from condition 1 under column 6, even if $P_ACO_2$ is constant at 30 mmHg under column 7. There is no equivalency across these conditions, except for the $P_IO_2$. Also notice that, with RER of 1.3, all $P_AN_2$ are less than their corresponding $P_IN_2$ in Table I. Reality is more complex than just described, as RER is not constant; it changes as $\dot{V}_A/\dot{V}CO_2$ changes through feedback with the CNS. The differences in $P_AO_2$ given equivalent $P_IO_2$ are attributed to a "$N_2$ dilution effect" of the alveolar gas.

The impressive decrease in $P_AO_2$ when 100% oxygen is breathed (like condition 5) compared to ascent on air (like condition 1) based on the AGE was a stimulus for Rahn and Otis[8] to test this theoretical result. They exposed mice to altitude ascent on either air or 100% oxygen. Their results and conclusion can be more easily understood by consulting background information from Rahn and Fenn.[7] No other arrangement of words improves on their original description.

**Table I.** Selected Conditions for $P_IO_2$ of 80 mmHg.

| CONDITION | $P_B$ (mmHg) | $F_IO_2$ | $F_IN_2$ | $P_IO_2$ (mmHg) | $P_IN_2$ (mmHg) |
|---|---|---|---|---|---|
| 1. Ascent with air | 428 | 0.210 | 0.790 | 80.0 | 301.0 |
| 2. Normobaric hypoxia | 760 | 0.112 | 0.888 | 80.0 | 633.1 |
| 3. Hyperbaric hypoxia | 1520 | 0.054 | 0.946 | 80.0 | 1393.4 |
| 4. Ascent with enriched $O_2$ | 347 | 0.266 | 0.734 | 80.0 | 220.2 |
| 5. Ascent with 100% $O_2$ | 127 | 1.00 | 0.000 | 80.0 | 0 |

Ascent on 100% oxygen is simpler to understand than ascent on air. When breathing 100% oxygen at high altitude, the hypoxic $P_IO_2$ is reduced in the alveoli by only the "addition of $CO_2$, which will either displace an equal amount of $O_2$ or take the place of $O_2$ that has been removed by the blood stream."[7] A requirement to satisfy Dalton's Law of Partial Pressures is that the sum of all partial pressures equals $P_B$: $P_AO_2 + P_ACO_2 = P_IO_2 = (P_B - 47)$, so $P_AO_2 = P_IO_2 - P_ACO_2$. The $P_AO_2$-$P_ACO_2$ point depends only on $\dot{V}_A/\dot{V}CO_2$, and "the rate of $O_2$ consumption itself does not affect the $P_AO_2$-$P_ACO_2$ point because, however many molecules of $O_2$ are taken out of the alveoli air by the blood, an equal number is free to flow in from the trachea to maintain equality of pressure."[7] For the case of breathing 100% oxygen, the $O_2$-$CO_2$ diagram has only one diagonal for each altitude evaluated and the origin of each diagonal is at $P_IO_2$. All $P_AO_2$-$P_ACO_2$ points lie on a diagonal of the $O_2$-$CO_2$ diagram having slope $= -1$, so $P_ACO_2 = -1 \times P_AO_2 + P_IO_2$. Again, all $P_AO_2$-$P_ACO_2$ points on this diagonal are set by $\dot{V}_A/\dot{V}CO_2$.

In contrast, for air breathing there is for each $P_IO_2$ a family of radiating diagonals. The diagonal for RER $= 1$ on this $O_2$-$CO_2$ diagram is where every mol of oxygen taken out of the alveoli is replaced by an equal mol of $CO_2$ added to the alveoli. In most cases the resting metabolic respiratory quotient (and therefore the matching RER) is $< 1$: the volume of gas inhaled is greater than the volume of gas exhaled. This is manifested under steady-state conditions as a slightly higher expired $F_EN_2$ than inspired $F_IN_2$. As stated in Rahn and Fenn,[7] "The difference in these volumes ($O_2 - CO_2$) represents the additional inspired gas which flows in without corresponding volume change of the lungs. When, conversely, the $CO_2$ output exceeds the $O_2$ intake, then the volume exhaled exceeds the volume inhaled and the difference represents extra alveolar gas exhaled without corresponding movement of the chest and lungs. If now air is inhaled in place of pure $O_2$, and if RER $< 1$, this difference between the exchanging $O_2$ and $CO_2$ volumes is replaced not by pure $O_2$ but by 79% $N_2$ and 21% $O_2$. This results in an increase in $P_AN_2$, (above $P_IN_2$), a decrease in $P_AO_2$, and no change in $P_ACO_2$ and thus displaces the alveolar point to the left of the RER $= 1$ line. The lower the RER, the greater the dilution of alveolar $O_2$ by $N_2$ and the farther the alveolar point is shifted to the left. (Furthermore, for a given RER $< 1$, the greater the $F_IN_2$ in the inspired air, the further the alveolar point is shifted to the left). Conversely, if RER $> 1$, the amount of inspired air taken in is less than the actual volume change of the chest and lungs, so each ml of $CO_2$ liberated in excess of the $O_2$ consumed actually displaces (or prevents the intake of) 0.79 ml of $N_2$ into the alveoli. Thus $P_AN_2$ is decreased below the $P_IN_2$, $P_AO_2$ is increased and the alveolar point moves to the right of the RER $= 1$ line." (See $P_IN_2$ in Table I and $P_AN_2$ in Table II). Further quoting from Rahn and Fenn,[7] "Again, the higher the RER and the greater the $F_IN_2$, the greater the diminution of $P_AN_2$ and the further the alveolar point is displaced to the right. In this whole description $P_ACO_2$ was considered as constant so that the remainder

**Table II.** Equivalent Hypoxic $P_IO_2$ and $P_AO_2$.

| CONDITION | $P_IO_2$ (mmHg) | $P_ACO_2$ (mmHg) | $\dot{V}_A/\dot{V}CO_2$ | RER | $P_AO_2$ (mmHg) | $P_AO_2$ @ $P_ACO_2$ OF 30 mmHg | $P_AN_2$ (mmHg) |
|---|---|---|---|---|---|---|---|
| 1 | 80.0 | 30 | ↑↑ | 1.30 | 55.4 | 55.4 | 295.6 |
| 2 | 80.0 | 29 | ↑↑↑ | 1.30 | 56.9 | 56.1 | 627.1 |
| 3 | 80.0 | 28 | ↑↑↑↑ | 1.30 | 58.1 | 56.5 | 1386.9 |
| 4 | 80.0 | 31 | ↑ | 1.30 | 54.2 | 55.1 | 214.8 |
| 5 | 80.0 | 30 | ↑↑ | 1.00 | 50.0 | 50.0 | 0 |

For the $\dot{V}_A/\dot{V}CO_2$ column, the number of arrows implies the trend in direction and magnitude abstracted from various literature sources.

of the available pressure must be divided between the $P_AO_2$ and the $P_AN_2$."

Mice breathing air at a lower $P_IO_2$ [at about 10,058 m (33,000 ft), a $P_IO_2$ of 32 mmHg] remained conscious for the same amount of time as those breathing 100% oxygen at a higher $P_IO_2$ [at about 15,240 m (50,000 ft), a $P_IO_2$ of 40 mmHg]. This seemingly contrary observation is predicted from the AGE. The conclusion was that with RER $>>$ 1 during the air exposure, the $P_AO_2$-$P_ACO_2$ point was similar to the $P_AO_2$-$P_ACO_2$ point when breathing 100% oxygen. Recall that breathing 100% oxygen restricts all $P_AO_2$-$P_ACO_2$ points to a single diagonal of slope $= -1$ with, in this case, a $P_IO_2$ intercept of 40 mmHg. Mice on air at a lower $P_IO_2$ had a hypoxic response (time to loss of consciousness) equivalent to that of mice on 100% oxygen at higher $P_IO_2$, because the $P_AO_2$-$P_ACO_2$ point was similar for both exposures. The $P_AO_2$-$P_ACO_2$ point in the two exposures is a better expression of hypoxic dose than $P_IO_2$ to correlate with the same physiological response, the time to loss of consciousness. But the $P_AO_2$-$P_ACO_2$ point is still insufficient as hypoxic dose because the $P_AO_2$-$P_ACO_2$ points are in flux, similar for the two exposures only in an instant of time. It is conceptually better to consider hypoxic dose to be the integrated $P_AO_2$-$P_ACO_2$ response. Then one can consider two exposures to have equivalent hypoxic physiological responses when the integrated $P_AO_2$-$P_ACO_2$ responses are similar.

At equivalent hypoxic $P_IO_2$, the advantage or disadvantage of breathing air instead of 100% oxygen is a function of RER, and also applies to other comparisons where $F_IN_2 \neq 0.79$. The advantage of hypoxic air over hypoxic 100% oxygen, as quantified with the AGE, was attributed to the transitory $N_2$ dilution effect or, more generally, the respiratory exchange effect. The magnitude and direction of the effect changes as RER changes as an integrated response to hypoxia to reestablish homeostasis.

After extensive theoretical analysis, Fenn, Rahn, and Otis[6] concluded, "This illustrates convincingly the possible fallacies involved in the common expedient of simulating high altitude conditions by low oxygen mixtures." After further consideration and consolidation of empirical evidence, Rahn and Fenn[7] said in their Introduction, "Our present graphical approach to respiratory problems originated in an effort to arrive at a precise definition of equivalent altitudes. This seems to be at first a simple practical problem, but it turned out to have unexpected theoretical complications." On the basis of a specific analysis in Section 6.4, titled "Equivalent Altitudes," Rahn and Fenn[7] concluded, "This example illustrates the difficult problem of trying to define what is meant by equivalent altitudes. It is evidently not enough to equate the inspired $O_2$ tensions; and a low $O_2$ percentage at sea level is by no means identical to the same inspired $Po_2$ breathing pure $O_2$ at altitude."

A limitation of the examples in Table II is that a snapshot of a dynamic process is not very informative. Physiological responses are coupled and in flux between the CNS and the respiratory system to set $\dot{V}_A$ and, therefore, the alveolar gas composition. A model (an integrated understanding) does not yet exist to show how variables from different conditions, but the same hypoxic $P_IO_2$, link the CNS to alveolar gas composition. The AGE is not enough in this regard. For example, subtle differences in the mechanics of breathing a gas at two different densities (at different $P_B$ in a comparison of NH and HH) result in different amounts of work of breathing ($\dot{V}O_2$ and $\dot{V}CO_2$) that in turn modify a changing RER. A common observation is that the increase in hypoxia-induced $\dot{V}_E$ is lower in HH than in NH. As a result, different distributions of hypoxic gas occur within the lung due to or as a consequence of subtle differences in pulmonary vascular vasoconstriction in response to the distribution of hypoxic ventilation. Potential differences in the ventilation-perfusion ratio ($\dot{V}_A/Q$) then establish arterial blood $P_aO_2$-$P_aCO_2$ that are not identical for equivalent $P_IO_2$ under different exposure conditions. $\dot{V}_A/Q$ is also modified by the distribution of pulmonary nitric oxide,[5] adding yet another layer of complexity as the ventilatory response to hypoxia evolves from acute to chronic exposure. Finally, an accurate application of the AGE requires equivalent inspired and expired volumes of $N_2$, i.e., $\dot{V}N_2 = \dot{V}_I \times F_IN_2 - \dot{V}_E \times F_EN_2 = 0$. This condition holds in maneuvers such as holding breath, hyperventilation, or exercise. But this condition is invalid when $P_B$ changes or $F_IO_2 \neq 0.21$, or some combination of both until a new $P_AN_2$ equilibrium is established. The $N_2$ partial pressure gradient between alveoli and tissue is different in magnitude and direction depending on the $P_IN_2$ in the breathing gas. This gradient is transient and the kinetics are different for NH versus HH. Nitrogen enters the tissues during NH, but exits during HH until a new dynamic equilibrium is established. All gases in the alveolar space must contribute a partial pressure that sums to ambient pressure during these conditions.

**Present**

Hypoxia research has suffered recently, particularly as a result of the assumption that NH is a surrogate for HH. Four reviews[1,3,9,10] and a pro-and-con debate[2] document much of the confusion about NH and HH with equivalent $P_IO_2$. Unfortunately, the critique of the EAA concept in the early 1950s based on the AGE was lost to many investigators. Current textbooks on aviation medicine and physiology do not adequately cover the limitations of the EAA concept. Current trends away from training in environmental physiology have left a generation of physiologists without an appreciation of how the AGE relates to

EAA, so this simple concept is accepted as fact. Therefore, many investigators incorrectly assume that equivalent physiological responses occur under equivalent hypoxic $P_IO_2$ "doses" for NH and HH exposures.

### Future

All that can be said with certainty is that two exposures with different $F_IO_2$ and $P_B$ that have the same $P_IO_2$ just have equivalent $P_IO_2$—that is it. It must not be assumed that other variables about the exposures are irrelevant to the outcome. At this time, it is unclear how the contributions of other variables ultimately influence $P_AO_2$-$P_ACO_2$, and then $P_aO_2$-$P_aCO_2$, and then cerebrospinal fluid $P_{CSF}O_2$-$P_{CSF}CO_2$, where the brain resides as the ultimate target organ for hypoxia. A task for the future is to quantify how all aspects of an experiment ultimately influence the $P_{CSF}O_2$-$P_{CSF}CO_2$ at the target organ to define the "true hypoxic dose" to associate with acute and chronic responses to hypoxia. Those drawn to this area for research or profit must concede that physiological responses to NH cannot be identical to the responses to HH given only equivalent hypoxic $P_IO_2$. We might quibble that physiological differences from NH and HH exposures are small when $P_IO_2$ is marginally hypoxic, but we can no longer assume they are identical. We must learn from the giants of the past to avoid confusion in the present and to keep our focus on problems to solve in the future. Finally, the astute reader will notice that nary a sentence was included about acid-base balance, hemoglobin, erythropoietin, or other aspects of blood chemistry in response to hypoxia, so clearly an integrated approach is needed.

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