ON THE DETERMINATION OF THE PHYSIOLOGICALLY
EFFECTIVE PRESSURES OF OXYGEN AND CARBON
DIOXIDE IN ALVEOLAR AIR

From the Naval School of Aviation Medicine U. S. Naval Air Station, Pensacola, Florida

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Although studies of the composition of alveolar air have been invaluable to
the advance of respiratory physiology a precise definition of alveolar gas pressures
and the accurate sampling of alveolar air have proved elusive goals (1). Owing
to the cyclic nature of the ventilatory process the partial pressures of O2 and
CO2 in the alveoli are changing continually (time factor) (9), and, owing to
inequalities in intrapulmonary ventilation and circulation, the partial pressures
in different parts of the lungs may differ significantly (space factor) (10, 15).
Therefore, the concept that a single value represents the partial pressure of an
alveolar gas requires the assumption that the spot sample of alveolar air be
representative with respect to both time and space.

There are cogent reasons for believing that the two principal methods for
sampling alveolar air (the single complete expiration method of Haldane and
Priestley and the fractional sampling technic of Sonne and Nielsen) do not
guarantee that the sample always is, in fact, representative. Neither method
insures that the sample contains proportional contributions of alveolar air from
all portions of the lung (space error), nor that the sample obtained has not lost
O2 and gained CO2 during the brief period of stasis within the alveoli (time error).
For example, the partial pressures of O2 and CO2 in samples of alveolar air
obtained by the Haldane-Priestley technic vary with respect to the timing of
the expiratory effort (end-inspiration or end-expiration) (5, 6). And again,
fractional sampling of the alveolar air by the Sonne-Nielsen technic has yielded
evidence that successive samples of alveolar air taken at different stages during
expiration vary appreciably with respect to gaseous composition (14).

Despite these limitations many fundamental contributions to an understanding
of respiratory mechanisms have come from studies of the composition of alveolar
air at rest (4, 7). However, during even moderate exercise the rate of evolution
of CO2 into and the escape of O2 out of the alveoli may be increased tenfold or
more so that the slight delay necessary to expel the alveolar sample is sufficient
to permit radical changes to develop. This failure of the direct sampling technics
to provide reliable data during exercise has led us to measure alveolar gas
pressures by an indirect method now to be described.

The indirect measurement of alveolar gas pressures. Indirectly determined
alveolar CO2 and O2 pressures are calculated from the arterial pCO2 and the

1 The opinions or assertions contained herein are the private ones of the writers and are
not to be construed as official or reflecting the views of the Navy Department or the naval
service at large.

2 Present address: the Johns Hopkins Hospital, Baltimore, Md.
pCO₂ and pO₂ of the inspired and expired air. The significance of these calculated alveolar pressures depends on the interrelations of the various factors entering into the calculation and will be considered below in detail. We may state at this point, however, that the goal of the indirect method is to determine the physiologically effective partial pressures of CO₂ and O₂ in the alveoli. The effective alveolar pressures may be defined precisely as those pressures which, if present continually and uniformly in all functioning alveoli, would permit the exchange of CO₂ and O₂ between the alveoli and the blood, during a series of ventilatory cycles, in amounts exactly equal to the gas exchange as measured from analyses of the inspired and expired air.

In order to discuss certain differences between ideal direct and indirect samples we shall present first our concept of an ideal direct sample, as furnished by the most frequently used technic, the Haldane-Priestley. In this technic a complete forcible expiration is performed which ideally would squeeze all of the alveolar air from the lung. If this goal were attained the ideal direct sample would contain contributions from each alveolus in proportion to the volume of air which it contained. By contrast, the indirect method is based, in the case of oxygen, upon the concept that in an ideal alveolar sample the contribution of each alveolus is in proportion to its ventilation. There probably would be slight differences between what we shall call the average (direct) values and the effective (indirect) values, even under ideal conditions, due primarily to inequalities in the ventilation-perfusion ratio in different parts of the lungs.

**Estimation of effective alveolar pCO₂.** The estimation of effective alveolar pCO₂ is based on the assumption that effective alveolar pCO₂ equals arterial pCO₂ (3). The arterial pCO₂ is thus considered to equal the mean of the entire range of alveolar CO₂ pressures existing in different parts of the lung and at different moments in the ventilatory cycle. The validity of this assumption depends on the magnitude of two unfavorable factors: a, the tendency of the arterial pO₂ to be higher than alveolar pO₂ because of the resistance offered by the "pulmonary membrane"; and b, the tendency of the peripheral arterial pCO₂ to exceed alveolar pCO₂ owing to the admixture of venous blood with a higher CO₂ tension. The sources of such venous admixture might be 1, blood which has passed through inadequately ventilated alveoli; 2, the bronchial circulation; 3, the anterior cardiac and Thebesian veins of the left heart, and 4, such venous-to-arterial shunts as may exist within the lesser circulation.

The resistance of the pulmonary membrane to the escape of CO₂ may be dismissed as an insignificant factor because of the rapid diffusion of CO₂ through tissues, estimated by Krogh to be 30 times as great as that of O₂ (11). The amount of admixture of non-arterialised blood arising from the various sources listed above (factor b) may be estimated by expressing the joint effect as though there had been added a certain volume of mixed venous blood to completely arterialised blood. For example, let us consider the extreme situation where each 80 parts of fully arterialised blood will have 20 parts of mixed venous blood added to them (from the above sources) before they are ejected into the peripheral arterial tree (2). What change in pCO₂ will result? If a mixture is made of
bloods of the following composition in the given proportions we can calculate by means of the Henderson-Hasselbalch equation what the characteristics of the resulting mixture will be:

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<tbody>
<tr>
<td>Arterial</td>
<td>80</td>
<td>38</td>
<td>7.400</td>
<td>53.6</td>
</tr>
<tr>
<td>Venous</td>
<td>20</td>
<td>45</td>
<td>7.371</td>
<td>59.4</td>
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</tbody>
</table>

The CO₂ content of the mixture is calculated thus: 

\[(0.8 \times 53.6) + (0.2 \times 59.4) = 54.7 \text{ vols. per cent}
\]

which, at a pH of 7.394, will exert a pCO₂ of 39.5 mm Hg. Therefore, the addition of 1 part of venous blood to 4 parts of arterial blood will raise the pCO₂ of the peripheral arterial blood only 1.5 mm Hg. As will be seen below an error of 1.5 mm Hg in determining the effective alveolar pCO₂ will introduce an error in the estimation of alveolar pO₂ which will not exceed 2 mm Hg.

It need hardly be emphasized that the presence of a congenital cardiac anomaly which deflects enormous quantities of venous blood directly into the arterial tree will introduce a larger divergence of arterial from alveolar pCO₂.

**Estimation of effective alveolar pO₂.** Because a significant tension gradient may exist between alveolar air and arterial blood (3), it cannot be assumed, as in the case of CO₂, that the effective alveolar pO₂ and the arterial pO₂ are equal. However, given a known value for effective alveolar pCO₂ and a known relationship between the effective alveolar pCO₂ and pO₂ one could calculate the effective alveolar pO₂.

What then is the relationship between the effective alveolar pCO₂ and pO₂, i.e., the effective alveolar RQ? Let us consider first the expired air, which is a mixture of alveolar air and dead space air. The RQ of the expired air is determined solely by the alveolar component since the dead space air is merely a diluent (1,8). Furthermore, the alveolar component of the expired air contains contributions from each alveolus in proportion to its ventilation. Accordingly, the alveolar component of the expired air is the effective alveolar air, and the expired air RQ is the effective alveolar RQ.³ The required relationship between effective alveolar pCO₂ and pO₂ is thus provided by the expired air RQ.

The effective alveolar pO₂ can be calculated then from determinations of the arterial pCO₂ and the RQ of the expired air without sampling the alveolar air directly. The equation for the calculation is derived from the accepted alveolar equation as follows:

\[
\text{alveolar RQ} = \frac{\text{alveolar pCO₂}}{\text{tracheal pO₂} \times \left(\frac{\% \text{ expired N}_2}{\% \text{ inspired N}_2}\right)^6 - \text{alveolar pO₂}}
\]  

³Ferguson and Dugal recently showed that for normal resting subjects during anoxia (when the time factor is much reduced) the alveolar RQ determined from the direct sample closely approximated the expired air RQ, indicating that under these conditions the average and the effective alveolar pressures are very nearly identical (6).

⁴37°C., saturated, ambient pressure.

⁵The tracheal pO₂, when multiplied by this ratio, is expressed in terms of expired air.
effective alveolar RQ = \\
\[
\frac{\text{effective alveolar } pCO_2}{\text{tracheal } pO_2 \times \left( \frac{\% \text{ expired } N_2}{\% \text{ inspired } N_2} \right) - \text{effective alveolar } pO_2}
\]  
(1a)

\[
\text{effective alveolar } pCO_2 = \text{arterial } pCO_2
\]  
(2)

\[
\text{effective alveolar } RQ = \text{expired air } RQ
\]  
(3)

Substituting (2) and (3) in equation (1a):

\[
\text{expired air } RQ = \\
\frac{\text{arterial } pCO_2}{\text{tracheal } pO_2 \times \left( \frac{\% \text{ expired } N_2}{\% \text{ inspired } N_2} \right) - \text{effective alveolar } pO_2}
\]  
(4)

and transposing:

\[
\text{effective alveolar } pO_2 = \\
\text{tracheal } pO_2 \times \left( \frac{\% \text{ expired } N_2}{\% \text{ inspired } N_2} \right) - \frac{\text{arterial } pCO_2}{\text{expired air } RQ}
\]  
(4a)

It will be apparent that for the purpose of constructing the equations above the effective alveolar pCO$_2$ and the effective alveolar pO$_2$ are not derived in an entirely parallel manner. The use of the arterial pCO$_2$ as a measure of the effective alveolar pCO$_2$ weights the contribution of each alveolus in proportion to its perfusion with blood, while the use of the expired air RQ for the calculation of the effective alveolar pO$_2$ weights the contribution of each alveolus in proportion to its ventilation. As shown above, however, even as gross a distortion of the ventilation-perfusion ratio as a 20 per cent venous-to-arterial shunt will lead to a minimal change in the determined value of alveolar pCO$_2$. For practical purposes, then, the indirectly determined alveolar pCO$_2$ may be considered to be effective in the same sense that the indirect alveolar pO$_2$ is effective.

The errors introduced into the calculation of effective alveolar pO$_2$ as a result of technical errors in the analysis of the respired gases will be less than 0.5 mm. Hg. The only source of significant error is the determination of the arterial pCO$_2$. This error rarely exceeds ± 3 mm. Hg and it will affect the calculated alveolar pO$_2$ accordingly: if the RQ is 1.0 the error in effective alveolar pO$_2$ will be equal and opposite to the error in arterial pCO$_2$; the maximum error will occur when the RQ is low but will not exceed 4 mm. Hg.

Methods. Experimental determination of effective alveolar pressures. In order to estimate the effective alveolar pressures, the following determinations were made on five male subjects during 31 experiments:

1. The pCO$_2$ of the arterial blood. The sample was withdrawn at a slow, steady rate for a period of one minute through an indwelling needle introduced earlier into the brachial artery through an area of local anesthesia. The pCO$_2$ was determined by the bubble method of Riley, Proemmel and Franke (13).
2. The \( CO_2 \) and \( O_2 \) pressures of the expired air. The expired air was collected by standard technics in a Douglas bag for a period of one minute. The collection period for expired air began 5 to 10 seconds before the sampling of arterial blood was begun and was ended a similar brief period before the arterial sampling was completed. Gas analyses were performed in the Haldane-Henderson apparatus. These determinations furnished the data for calculating the expired air RQ.

3. The \( CO_2 \) and \( O_2 \) pressures of the inspired air.

The effective alveolar \( pO_2 \) was calculated by substituting these determined values in equation 4a.

Comparison of effective alveolar pressures with the pressures in Haldane-Priestley samples of alveolar air. The direct samples of alveolar air were obtained by the Boothby modification of the Haldane-Priestley technic (a sharp deep expiration at the end of a normal inspiration) (4) after the conclusion of the minute period during which the arterial blood and the expired air were collected. The subjects were trained carefully until consistent samples of alveolar air were obtained repeatedly. The experiments at rest were performed with the subject either lying supine or standing quietly but without any standardized period of rest. The exercise experiments were performed on a motor-driven treadmill inclined 5 degrees (8.8 per cent grade) moving at 4.8 Km./hr. (3 m.p.h.). The exercise was continued for 5 to 8 minutes, or until the minute ventilation had become constant, before samples were obtained. This grade of work required an oxygen consumption which averaged 1.5 l./m. Experiments were performed while subjects were breathing room air or oxygen-nitrogen mixtures designed to produce moderate anoxia.

RESULTS. The comparative data obtained from 31 experiments are presented in table 1. The differences at rest between effective alveolar pressures and Haldane-Priestley alveolar pressures are, in general, not great. During exercise, however, the accumulation of \( CO_2 \) and the depletion of \( O_2 \) in the direct alveolar samples was so large that the direct samples yielded values which differed widely from the effective pressures determined by the indirect method.

DISCUSSION. The indirect method for determining alveolar \( CO_2 \) and \( O_2 \) pressures was developed primarily to circumvent difficulties in the direct methods which are related to the space and time factors. By using the \( pCO_2 \) of the arterial blood as a measure of effective alveolar \( pCO_2 \), the blood becomes a physiological integrator of the \( CO_2 \) pressures existing in all parts of the lung which are perfused, and errors resulting from the space factor thus are minimised. Likewise, the arterial blood integrates the normal variations in alveolar \( pCO_2 \) which occur from moment to moment during the ventilatory cycle, and errors resulting from the time factor are eliminated. The arterial blood can be used in this manner in the case of \( CO_2 \) because the blood in the alveolar capillary reaches virtual gaseous equilibrium with the alveolar air.

The experimental finding that the \( pCO_2 \) of the Haldane-Priestley alveolar sample is higher than that of arterial blood sampled during the preceding minute probably results from the effect of the time factor which enters into alveolar sampling by the Haldane-Priestley technic; i.e., during the time required to give
### Table 1
Comparison of effective alveolar pressures (indirect) and Haldane-Priestley alveolar pressures (direct)

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>LABORATORY ALTITUDE: 9 FEET</th>
<th>BAROMETRIC PRESSURES: 765-775 MM. HG</th>
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<tr>
<td></td>
<td>Effective</td>
<td>H-P</td>
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<tr>
<td>Ki</td>
<td>39</td>
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<td>Ro</td>
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<td>42</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>42</td>
</tr>
</tbody>
</table>

**Average =**

**Rest**

+4.4 (-1 to +11) | -7.9 (0 to -17)

**Exercise**

| SUBJECT | ki | 43 | +11 | 108 | 89 | -19 |
|         | 41 | 48 | +7 | 63 | 54 | -9 |
|         | 37 | 44 | +7 | 57 | 43 | -14 |
| Ko      | 32 | 55 | +23 | 115 | 80 | -35 |
|         | 30 | 47 | +17 | 77 | 54 | -23 |
| Li      | 31 | 46 | +15 | 117 | 98 | -19 |
| Ri      | 35 | 44 | +9 | 111 | 99 | -12 |
|         | 27 | 40 | +13 | 73 | 55 | -18 |
|         | 29 | 40 | +11 | 66 | 50 | -16 |
| Ro      | 38 | 38 | +20 | 111 | 86 | -25 |

**Average =**

+12.7 (+7 to +23) | -18.5 (-9 to -35)

* Voluntary hyperventilation.

The alveolar sample, CO₂ continues to be given off from the blood so that the pCO₂ of the alveolar sample is higher than the average level during the relatively steady state before sampling. It is manifestly impossible, on the basis of the
diffusion theory, for the alveolar pCO2 to be in fact higher than the arterial pCO2. Error in the Haldane-Priestley sample due to the time factor is increased during exercise not because the time required to give the sample is prolonged but because the rate at which CO2 is discharged into the alveoli may be increased some ten times. The difference between directly and indirectly determined alveolar pCO2's varies from sample to sample and from subject to subject (table 1), owing in part to slight differences in the technic of giving the Haldane-Priestley sample. We should not expect, therefore, a constant high correlation between results by the two methods.

Experimentally, the pO2 of the Haldane Priestley sample is lower than the calculated effective alveolar pO2 because, during the time required to expel the Haldane-Priestley sample, the alveolar pO2 shifts from the tension normally prevailing toward that obtaining in the mixed venous blood.

It must be emphasized that the difference between the directly and indirectly determined alveolar pressures are due for the most part to the time factor and only in small part to the space factor. Errors in the Haldane-Priestley determinations due to the time factor appear to be significant at rest and very large during exercise and these errors cannot be corrected with accuracy because they are related to slight individual differences in the technic by which the subject gives the sample. These errors, we believe, are obviated by the indirect method.

The use of the expired air RQ in the indirect determination of effective alveolar pressures imposes certain limitations on the experimental application of the indirect method. The measurement of the expired air RQ requires the collection of expired air during a series of ventilatory cycles; if during this period the RQ is changing rapidly (e.g., the first few minutes of exercise or hyperventilation) the calculated effective alveolar pressures will represent a mean of the extremes rather than any instantaneous level. Likewise, if the ventilatory pattern is grossly irregular a similar situation obtains. However, in either instance the effective alveolar pCO2 and pO2 as determined are functionally significant values, provided that the periods for collection of the expired air and of the arterial blood are equal and coincident.

The advantages of the indirect method may be summarized as follows: a, the effective alveolar pressures represent a functional rather than a volumetric integration of the entire range of pressures existing throughout the lung (space factor); and b, the effective alveolar pressures are not derived from a spot sample expelled after a momentary delay but are derived from samples of arterial blood and expired air taken through several normal ventilatory cycles and are, therefore, representative of the mean physiological balance (time factor).

It would appear, then, that for investigations of the movement of O2 and CO2 and of the effect of alveolar gas pressures on arterial gas tensions (12), the effective (indirect) alveolar pressures are physiologically more significant than values obtained by presently available direct technics for sampling alveolar air.

**SUMMARY**

1. The limitations inherent in direct methods for sampling alveolar air become critical during experiments on exercising subjects.
2. An indirect method for calculating alveolar gas pressures has been devised which requires simply the determination of arterial pCO₂ and the pO₂ and pCO₂ of inspired and expired air.

3. A theoretical analysis indicates that alveolar gas pressures so determined represent the physiologically effective mean pressures and are not subject to errors introduced by "time" and "space" factors.

4. By this indirect method the effective alveolar pressures may be determined during exercise without encountering the difficulties inherent in the classical direct methods.

REFERENCES

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