'Ideal' Alveolar Air and the Analysis of Ventilation-Perfusion Relationships in the Lungs

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THE ANALYSIS OF BLOOD-GAS RELATIONSHIPS in the lungs is handicapped by ambiguity regarding the concept of alveolar air (1). It is well known that patients suffering from pulmonary diseases may have alveolar air which varies in composition in different parts of the lungs (2, 3), yet there has been no adequate way of defining the composition of alveolar air under such circumstances. Furthermore, the relationships between alveolar ventilation and alveolar perfusion with blood, which are primary factors in determining the composition of the alveolar air, have been dealt with only in general terms. The purpose of this paper is to discuss a specific definition of alveolar air which is applicable to both normal and pathological conditions, and, with the help of this concept, to outline a system of analysis of ventilation-perfusion relationships in health and disease.

SCHEMATIC REPRESENTATION OF VENTILATION, PERFUSION AND GAS EXCHANGE

The cyclic nature of the ventilatory process tends to obscure certain fundamental relationships between alveolar air and the blood in the alveolar capillaries. Let us therefore consider a schematic representation of ventilation, perfusion and gas exchange in which these processes are conceived of as continuous (fig. 1). Inspired air and mixed venous blood pass into the alveoli where they approach equilibrium with respect to partial pressures of oxygen and carbon dioxide by diffusion of gases across the pulmonary membrane. The blood leaving the alveolar capillaries is modified slightly by the admixture of a small amount of venous blood which can be thought of as a shunt. The alveolar air leaving the alveolar spaces is modified by the admixture of dead space air, which has the composition of inspired air and may also be thought of as a shunt.

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FUNDAMENTAL RELATIONSHIPS BETWEEN RESPIRATORY GASES IN THE BLOOD AND IN THE ALVEOLAR AIR

The quantity of carbon dioxide added to the alveolar air is the same as the quantity given up by the blood, and the quantity of oxygen given up by the alveolar air is the same as that added to the blood. Hence:

\[ V_a \times (AL - I) \text{ in } \% CO_2 = P \times (V - C) \text{ in vol. } \% CO_2 \]

\( \text{CO}_2 \text{ added to alveolar air } = \text{CO}_2 \text{ given up by blood.} \quad (1) \)

\[ V_a \times (I^2 - AL) \text{ in } \% O_2 = P \times (C - V) \text{ in vol. } \% O_2 \]

\( \text{O}_2 \text{ given up by alveolar air } = \text{O}_2 \text{ taken up by blood.} \quad (2) \)

Fig. 1. SCHEMATIC REPRESENTATION of ventilation, perfusion and gas exchange. \( I = \) in-
spired air; \( AL = \) alveolar air; \( E = \) expired air; \( V = \) mixed venous blood; \( C = \) blood leaving the
alveolar capillaries; \( AR = \) mixed arterial blood; \( V_t = \) total ventilation; \( V_a = \) alveolar ventilation,
i.e. alveolar air flow; \( P = \) perfusion with blood, i.e. alveolar capillary flow; C.O. = cardiac output.

The ratio of alveolar ventilation to alveolar perfusion with blood may be expressed as a rearrangement of equations (1) and (2):

\[ \frac{V_a}{P} = \frac{(C - V) \text{ in vol. } \% O_2}{(I^2 - AL) \text{ in } \% O_2} - \frac{(V - C) \text{ in vol. } \% CO_2}{(AL - I) \text{ in } \% CO_2}. \quad (3) \]

where

\[ I_s = \text{insp. } \% O_2 + \frac{\text{alv. } \% CO_2 \times \text{insp. } \% O_2 \times (1 - R.Q.)}{\text{insp. } \% O_2 \times R.Q.}. \]

Inspired air \( \% O_2 \) is corrected in this way in order to take into account the difference in volume between inspired air and alveolar air. The first half of equation (4) then becomes equivalent to equation (12) below, when \( I \) in \( \% CO_2 \) = 0.
The ratio of carbon dioxide exchange to oxygen exchange, i.e. the respiratory quotient (R.Q.), may be expressed as another rearrangement of equations (1) and (2):

\[
R.Q. = \frac{(AL - I) \text{ in } \% \text{CO}_2}{(I_C - AL) \text{ in } \% \text{CO}_2} - \frac{(V - C) \text{ in vol. } \% \text{CO}_2}{(C - V) \text{ in vol. } \% \text{O}_2}.
\]

Gas R.Q.  
Blood R.Q.

CONCEPT OF 'IDEAL' ALVEOLAR AIR

The fundamental equations provide a means of defining precisely what the composition of the alveolar air and the blood leaving the alveolar capillaries would be if these values were homogeneous throughout the lungs and if perfect equilibrium were reached between the blood and gas phases. This statement is based upon the following considerations.

If the subject is in a steady state, the composition of the inspired air entering the alveoli and of the mixed venous blood entering the alveolar capillaries is constant throughout all parts of the lungs and can be determined by direct sampling and analysis. On the other hand, the composition of the alveolar air and of the blood leaving the alveolar capillaries is variable, depending upon ventilation-perfusion relationships as indicated by equation (3). Each different value for alveolar air and alveolar capillary blood is associated with a different value for R.Q., as indicated by equation (4). At the specific R.Q. which applies to the lung as a whole, there is only one value of alveolar and capillary p\text{CO}_2 and of alveolar and capillary p\text{O}_2 which satisfies both the gas R.Q. and the blood R.Q. equations. This one value, which we shall call the 'ideal' value, is therefore the only value which could exist homogeneously throughout all parts of the lungs and still be compatible with the quantitative aspects of gas exchange which actually exist in a given subject.3

DETERMINATION OF 'IDEAL' ALVEOLAR AIR

The mathematical derivation of the 'ideal' alveolar point requires that the blood and gas R.Q. equations both be expressed in terms of partial pressure since it is only in these terms that the identity between alveolar air and the blood leaving the alveolar capillaries exists. Because of the difficulty in changing units in the case of the blood R.Q. equation, the derivation is more easily presented graphically.4

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3 Essentially this same concept has been arrived at independently by H. Rahn (personal communication).

4 The mathematical demonstration that there is a unique solution to the blood and gas R.Q. equations when the subject is in a steady state is complicated by the necessity for using equations for the CO\text{2} and O\text{2} dissociation curves of blood. However, under the guidance of Dr. Domingo Gomez, the following steps have been outlined:

Equation (4) may be divided into the gas and blood R.Q. equations, respectively. The change
The graphic determination of 'ideal' alveolar air is based in part upon the work of Fenn, Rahn and Otis (4). These authors showed that when pCO₂ and pO₂ were used as coordinates, different R.Q.'s could be plotted as straight lines radiating from a point representing moist inspired air. It can be seen from equation (4) that the slope of the R.Q. lines is determined by the ratio \( \frac{(AL - I)}{\text{pCO}_2} \) and \( \frac{(I - AL)}{\text{pO}_2} \). In figure 2 several R.Q. lines have been plotted using a normal value for moist inspired air at body temperature and pressure (pO₂ = 150 mm. Hg; pCO₂ = 0).

The consideration of alveolar ventilation and alveolar perfusion as parallel phenomena led to the realization that data regarding blood in the alveolar capillaries can be plotted in a manner similar to the alveolar air. When the second half of equation (4) is used it is found that if vol. %CO₂ and vol. %O₂ are chosen as coordinates, then lines representing different blood R.Q.'s may be drawn. These lines radiate from the mixed venous blood point (V) and have a slope which is determined by the ratio \( \frac{(V - C)}{\text{vol. %CO}_2} \). In figure 3 several blood R.Q. lines are plotted, using values for the composition of mixed venous blood which were obtained by cardiac catheterization in a normal subject (O₂ content = 13.2 vol. %; CO₂ content = 54.1 vol.%).

The normal individual under consideration had an R.Q. of 0.8. Thus, of units in equation (5) is permissible because the relationship between percentage and partial pressure is linear in the gas phase.

\[
(\frac{AL}{I}) \text{ in pCO}_2 = \text{R.Q.} \times (\frac{I - AL}{\text{pO}_2})
\]

Equation (6) must now be expressed in terms of partial pressure in order that the identity between alveolar and capillary tensions may be used in solving for alveolar pCO₂ and alveolar pO₂. The following symbols will be used:

For the gas phase,

\[
\begin{align*}
AL \text{ in pCO}_2 &= \text{pCO}_2^{\text{AL}} \\
I \text{ in pCO}_2 &= \text{pCO}_2^{I}
\end{align*}
\]

For the blood phase, in general,

\[
\begin{align*}
\text{vol. %CO}_2 &= f(pCO_2) \\
\text{vol. %O}_2 &= F(pO_2)
\end{align*}
\]

where \( f \) and \( F \) are 2 different functions describing the CO₂ and O₂ dissociation curves, respectively. Specifically,

\[
\begin{align*}
V \text{ in vol. %CO}_2 &= f(pCO_2v) \\
V \text{ in vol. %O}_2 &= F(pO_2v) \\
C \text{ in vol. %CO}_2 &= f(pCO_2c) \\
C \text{ in vol. %O}_2 &= F(pO_2c)
\end{align*}
\]

Equations (5) and (6) may then be expressed as follows:

\[
\begin{align*}
pCO_2^{\text{AL}} - pCO_2^{I} &= \text{R.Q.} \times (pO_2^{\text{AL}} - pO_2^{I}) \\
f(pCO_2v) - f(pCO_2c) &= \text{R.Q.} \times F(pO_2v) - F(pO_2c)
\end{align*}
\]

Since complete equilibrium is assumed between the alveolar air and the blood leaving the alveolar capillaries,

\[
pCO_2^{\text{AL}} = pCO_2^{AL} \text{ and } pO_2^{\text{AL}} = pO_2^{AL}
\]

Substituting these values in (8) we have the system:

\[
\begin{align*}
pCO_2^{\text{AL}} - pCO_2^{I} &= \text{R.Q.} \times (pO_2^{AL} - pO_2^{I}) \\
f(pCO_2v) - f(pCO_2c) &= \text{R.Q.} \times F(pO_2^{AL}) - F(pO_2v)
\end{align*}
\]

When pCO₂v, pO₂v, pCO₂c, pO₂c and R.Q. are known, the system (9) contains only 2 unknowns, pCO₂AL and pO₂AL, and may therefore be solved. There may be more than one solution for the two unknowns, but one and only one is possible in physical terms.
From figure 2, the composition of his mixed alveolar air was defined by some point along the line corresponding to R.Q. = 0.8, and from figure 3 the composition of the mixed blood leaving the alveolar capillaries was defined by some point along the line on this graph corresponding to R.Q. = 0.8. In figure 4, the blood R.Q. line has been replotted on the alveolar air diagram by converting from volumes per cent to partial pressure by reference to the appropriate blood-gas dissociation curves. The relationship between volumes per cent and partial pressure is not linear for either carbon dioxide or oxygen, so the blood R.Q. line in figure 4 is curved. The intersection of the two R.Q. lines...
(fig. 4, X) is the point at which the blood and gas leaving the alveoli have the same pCO₂ and pO₂ at the R.Q. of the body as a whole. The point of intersection is thus the 'ideal' alveolar point. In figure 5 the blood R.Q. line has been plotted in terms of blood gas content, and X, transposed from figure 4, shows the respiratory gas content of 'ideal' capillary blood in equilibrium with ‘ideal’ alveolar air. Details of the construction of figures 4 and 5 are shown in the Appendix.

ALTERNATIVE METHOD FOR APPROXIMATING ‘IDEAL’ ALVEOLAR AIR

A simpler method for determining the ‘ideal’ point is based on the fact that the arterial pCO₂ is essentially the same as the ‘ideal’ alveolar pCO₂. In figure 4 it can be seen that the blood R.Q. line, when plotted on the alveolar
air diagram, is very nearly horizontal in the region between the arterial blood point and the 'ideal' point. If it were truly horizontal, the arterial pCO₂ would exactly equal the 'ideal' alveolar pCO₂. In normal individuals and in patients with moderate impairment of pulmonary function the approach to equality is within 1 mm. Hg and is close enough to justify the statement that arterial pCO₂ is a good measure of 'ideal' alveolar pCO₂.

Alveolar pO₂ may be calculated from the arterial pCO₂ and the R.Q. This has been done by Rossier et al. (5), and independently by Riley, Lilienthal et al. (6). In effect this calculation determines the point on the gas R.Q. line where the pCO₂ is that of the arterial blood. In figure 4, for example, arterial pCO₂ = 42 mm. Hg; hence alveolar pCO₂ would be considered 42 mm. Hg and alveolar pO₂ would be calculated as 99.8 mm. Hg. This value for pO₂ is virtually identical to that of the 'ideal' point where pO₂ = 100 mm. Hg. The 'ideal' pCO₂ is 41.8 mm. Hg as compared to the arterial pCO₂ of 42 mm. Hg. It may thus be said that the calculated alveolar air values of Rossier et al. and of Riley and Lilienthal et al. are essentially the same as the 'ideal' alveolar air values except under special circumstances to be mentioned below.

The equation used by Rossier for calculating alveolar pO₂ is very similar to a rearrangement of equation (4), with the gas concentrations expressed as partial pressures and with arterial pCO₂ substituted for alveolar pCO₂:

$$\text{alv. pO}_2 = \frac{20.93 \times (B - 49.5)}{100} - \frac{\text{art. pCO}_2}{\text{R.Q.}}$$

(10)

Rossier makes no correction for the change in volume between inspired air and alveolar air, and a slightly higher value is subtracted for water vapor tension than is customary in this country.

Riley, Lilienthal, et al. formerly used a modified form of equation (10) in which there was a partial correction for the change in volume between inspired air and alveolar air:

$$\text{alv. pO}_2 = \frac{20.03 \times \exp \frac{\%N_2}{\text{insp. } \%N_2} (B - 47) - \frac{\text{art. pCO}_2}{\text{R.Q.}}}{100 \times \text{R.Q.}}$$

(11)

The theoretically correct equation, which has been derived by several authors (4, 7), is now being used in this laboratory.

$$\text{alv. pO}_2 = \text{insp. pO}_2 + \frac{\text{alv. pCO}_2 \times \text{insp. } \%O_2 \times (I - \text{R.Q.})}{100 \times \text{R.Q.}} - \frac{\text{alv. pCO}_2}{\text{R.Q.}}$$

(12)

When arterial pCO₂ is substituted for alveolar pCO₂, values for alveolar pO₂ are obtained which are within 2 mm. Hg of those obtained using equation (11).

VARIATIONS IN DIFFERENT PARTS OF THE LUNGS

Since the 'ideal' alveolar air is accurately definable in physiological terms it provides a point of reference from which to analyze deviations from the
ideal. In the following section variations in the composition of alveolar air in different parts of the lungs will be investigated by the same graphic methods which led to the definition of the 'ideal' point itself, i.e. the intersections of blood and gas R.Q. lines of equal magnitude.

Fig. 6. Curve through all points at which blood R.Q. = gas R.Q.

Fig. 7. Composition of blood leaving alveolar capillaries at all possible values of R.Q.

In figure 6 several blood and gas R.Q. lines are shown with a curve drawn through the points of intersection. Each point of intersection shows the respiratory gas tensions of the alveolar air and of the blood leaving the alveolar capillaries when a particular R.Q. obtains. The curve passes through the entire range of values for pCO₂ and pO₂, corresponding to all possible values for R.Q. In figure 7 the curve of figure 6 has been redrawn in terms of blood
gas content. It shows the composition of blood leaving the alveolar capillaries at all possible values of R.Q.

In figure 8 the curve of figure 6 has been copied and 3 ventilation-perfusion ratios indicated. Points on the curve which are close to the mixed venous blood point represent alveoli which are well perfused with blood, but poorly ventilated. The mixed venous blood point itself corresponds to blood passing through non-ventilated alveoli or to venous admixture. Points near to the inspired air point represent alveoli which are well ventilated but poorly perfused. The inspired air point corresponds to alveolar air from completely non-perfused alveoli. Air passing in and out of such alveoli is unaltered and therefore comparable to dead space air.

In figure 9 the reasons for a high R.Q. in association with a high ventilation-perfusion ratio are shown graphically. CO₂ and O₂ contents for the mixed venous blood entering the alveoli (V), for the mixed arterial blood from the entire lung (AR), and for capillary blood leaving well ventilated but poorly perfused alveoli (C) are shown. The ratio in terms of volumes per cent of the CO₂ V–AR difference to the O₂ AR–V difference is to be contrasted with the ratio of the CO₂ V–C difference to the O₂ C–V difference for the alveoli with a high ventilation-perfusion ratio. The R.Q. is much higher in the latter because the segment of curve between AR and C is very steep in the case of CO₂ and very flat in the case of O₂. The converse occurs when the ventilation-perfusion ratio is low, and the R.Q. of such areas falls below the over-all R.Q. of the lung as a whole.

The mixed blood leaving the alveolar capillaries is derived from alveoli with various R.Q.'s, and the mixed alveolar air also comes from alveoli with various R.Q.'s. Since in each case the R.Q. of the mixture is that of the body as a whole, the mixed blood leaving the alveolar capillaries (fig. 10, C) must
Fig. 9. **Physiological Oxygen and Carbon Dioxide Dissociation Curves** of blood plotted on the same scale. Ordinate = vol. %O₂ and vol. %CO₂ respectively; abscissa = pO₂ and pCO₂ respectively.

CO₂ dissociation curves = - - - fully oxygenated blood; - - - - fully reduced blood; V = mixed venous blood; AR = mixed arterial blood; C = blood leaving an alveolus which is well ventilated but poorly perfused.

R.Q. for lung as a whole = \( \frac{V - A}{C - V} \) in vol. %CO₂ = 54.1 - 39.5 = 0.8

\[ \text{R.Q. for hyperventilated alveoli} = \frac{V - C}{C - V} \text{ in vol. %CO}_2 = \frac{54.1 - 39.5}{2.9 - 0} = 5.0 \]

where

\[ \text{AL in %CO}_2 = \frac{\text{art. pCO}_2}{\text{B - 47}} \times 100 = \frac{42}{718} \times 100 = 5.85 \]

\[ \text{AL in %CO}_2 = \frac{\text{cap. pCO}_2}{\text{B - 47}} \times 100 = \frac{21}{718} \times 100 = 2.9 \]

The mixed capillary
blood is influenced more by alveoli lying to the left of the 'ideal' point than by
those lying to the right, since perfusion is large in proportion to ventilation
in these areas (low $V_a/P$ ratio). The mixed alveolar air is influenced more by
alveoli lying to the right of the 'ideal' point (high $V_a/P$ ratio) than by those
lying to the left, since ventilation is large in proportion to perfusion. Neither
the mixed capillary blood nor the mixed alveolar air can be determined accu-

rately, but approximate values are plotted in figure 10 for the sake of the theoretical discussion. In figure 11 the effect upon the mixed arterial blood of variations in ventilation–perfusion ratio is plotted in terms of volumes per cent.

QUANTITATIVE ESTIMATION OF VARIATIONS IN VENTILATION–PERFUSION RATIO

Quantitative estimation of variations in ventilation–perfusion ratio depends upon the magnitude of the difference between the ‘ideal’ alveolar air and the mixed alveolar air, and mixed capillary blood, respectively. If there were no such variations the partial pressures of the mixed alveolar air and the mixed alveolar capillary blood would be identical to each other and to the ‘ideal’ alveolar air. As shown above, however, ventilation of poorly perfused alveoli causes the composition of the mixed alveolar air to diverge from the ‘ideal’ along the gas R.Q. line in the direction of the inspired air. Perfusion of poorly ventilated alveoli causes the composition of the mixed capillary blood to diverge from the ‘ideal’ along the blood R.Q. line in the direction of the mixed venous blood. Although in each case these are the resultant effects of innumerable alveoli with different ventilation–perfusion ratios, it is nevertheless possible to describe the effect upon the mixed alveolar air as comparable to that which would result from the admixture of a certain proportion of inspired air to the ‘ideal’ alveolar air. The effect upon the mixed capillary blood can likewise be described as comparable to that which would result from the admixture of a certain proportion of mixed venous blood to ‘ideal’ capillary blood. It is therefore theoretically possible to quantitate the effects of variations in ventilation–perfusion ratio in terms of inspired air, or dead space air, admixture and venous admixture.

Unfortunately, since mixed alveolar air and mixed capillary blood cannot be determined with accuracy, the contributions to dead space admixture and venous admixture which result from variations in ventilation–perfusion ratio cannot be separated from the contributions resulting from anatomical dead space and true venous admixture. It is therefore necessary to measure the combined effects of both contributions and to expand the usual concepts of dead space and venous admixture. Dead space is considered to include not only the anatomical dead space but also a contribution from alveoli with a high ventilation–perfusion ratio. Venous admixture includes not only blood from the bronchial veins, Thébesian veins, shunts, etc., but also a contribution from alveoli with a low ventilation–perfusion ratio.

There are several corollaries to these concepts of dead space and venous admixture. The calculated alveolar ventilation, which is the difference between total ventilation and dead space ventilation, is reduced by the same amount that dead space ventilation is increased. The calculated alveolar
perfusion with blood is reduced by the amount by which venous admixture is increased. All alveoli are arbitrarily considered in 3 categories: those with an 'ideal' ventilation-perfusion ratio; those which are ventilated but not perfused; and those which are perfused but not ventilated.

**Dead Space.** The determination of dead space requires the following data: alveolar pCO₂, expired air pCO₂, inspired air pCO₂, tidal air volume and the volume of dead space in the apparatus. The Bohr equation may then be applied:

\[
\text{Dead space} = \frac{(X - E)}{(X - I)} \times \text{tidal air} - \text{dead space of apparatus}
\]

\[X = \text{'Ideal' alveolar pCO₂ = arterial pCO₂}. \quad (I_3)
\]

### Table 1. Ventilation-perfusion relationships in 8 normal male physicians

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>BAROMETRIC PRESSURE</th>
<th>'IDEAL' ALVEOLAR</th>
<th>ARTERIAL</th>
<th>ALVEOLAR-ARTERIAL GRADIENT</th>
<th>DEAD SPACE</th>
<th>VENOUS ADMIXTURE</th>
<th>CARDIAC OUTPUT</th>
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<tr>
<td></td>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
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<td>100</td>
<td>42</td>
<td>90</td>
<td>10</td>
<td>21</td>
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<td>96</td>
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<td>111</td>
<td>37</td>
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<td>110</td>
<td>36</td>
<td>99</td>
<td>11</td>
<td>29</td>
</tr>
</tbody>
</table>

Average: 38.6 103.7 38.6 94.6 9.1 10.0 4.2

Subjects at rest in the supine position. Ages ranged from 28 to 40 years.

This expression may be divided by the tidal air volume to determine the ratio of dead space to tidal air.

In order to use the calculated dead space as a means of estimating the physiological importance of alveoli in which the ventilation-perfusion ratio is higher than the 'ideal,' one must compare the patient's dead space to that of a normal individual. Normal values calculated in this way vary considerably in absolute terms but when expressed as the ratio of dead space to tidal air they become fairly constant. The ratio can be varied by altering the respiratory pattern, but when the individual responds to normal physiological drives the normal ratio of dead space to tidal air falls below 30 per cent at rest. During exercise the ratio either stays the same or falls. When the dead space volume exceeds 30 per cent of the tidal air volume it may be concluded that a significant proportion of alveoli have a ventilation-perfusion ratio which is higher than the 'ideal' (table 1).
The significance of the dead space value differs when different technics are used for making the determination. In a recent report by Fowler (8) "respiratory dead space was measured by simultaneous and continuous measurement of volume flow and N₂ content (Lilly-Hervey nitrogen meter) of gas expired following inhalation of 99.6 per cent O₂." Dead space values were said to be affected by: 1) anatomical volume of the bronchial tree; 2) gas diffusion between terminal bronchioles and alveolar spaces; and 3) uniformity of gas mixing throughout the lung. In Birath's method (9), which involves the intrapulmonary mixing of the inert gas hydrogen, the calculated value for dead space is also affected by the efficiency with which the gas is distributed throughout the lungs. Haldane's method (10), in which alveolar CO₂ is used, is affected by ventilation-perfusion relationships, but because of the technic used for sampling alveolar air the results are ambiguous during exercise or in patients with pulmonary disease. The introduction of the Sonne-Nielsen alveolar sampling technic (11) is an improvement but does not settle the question as to the representative nature of the alveolar sample. The use of arterial pCO₂ in the dead space determination eliminates ambiguity regarding the alveolar sample. The ratio of dead space to tidal air then becomes a value which can be used in the quantitative evaluation of areas of the lung having a high ventilation-perfusion ratio.

The relationship between dead space and tidal air can be visualized graphically, provided a correction is made for the effect of apparatus dead space upon the composition of the expired air. In figure 10, E₈ represents the composition which the expired air would have had if there had been no apparatus dead space. The ratio of dead space to tidal air corresponds to the ratio of X-E₈ to X-I.

The ratio of alveolar ventilation to total ventilation is i minus the ratio of dead space to tidal air. The minute volume of alveolar ventilation can be calculated either from this relationship or from the basic equation:

\[ \text{alveolar ventilation} = \frac{\text{CO}_2 \text{ output} \times 100}{\text{'ideal' alveolar } \%\text{CO}_2} \] (14)

Venous Admixture. The ratio of venous admixture to total blood flow, i.e. cardiac output, can be calculated in a manner analogous to the calculation of the dead space ratio:

\[ \frac{\text{V.A.}}{\text{C.O.}} = \frac{X - AR, \text{ in vol. } \%\text{O}_2}{X - V, \text{ in vol. } \%\text{O}_2} \] (15)

The term venous admixture is here used in the expanded sense and includes contributions of blood from poorly ventilated alveoli. The relationships described by equation (15) can be visualized in figure 11.

The calculation of venous admixture requires that the 'ideal' alveolar-
arterial \(O_2\) gradient be expressed in terms of volume per cent. Since the arterial blood normally falls on the upper flat portion of the oxygen dissociation curve, where a very small error in the oxygen content causes a significant error in \(pO_2\), it is preferable to use the directly determined arterial \(pO_2\) as the starting point in calculating venous admixture. The 'ideal' alveolar–arterial \(pO_2\) gradient can then be transposed into volumes per cent by reference to a standard oxyhemoglobin dissociation curve.

The ratio of alveolar perfusion with blood to total blood flow is \(1 - \text{ratio of venous admixture to total blood flow}\). Alveolar perfusion is readily calculated in absolute terms when the cardiac output is known.

When mixed venous blood is not known, 2 alternative procedures may be adopted. If the subject is in the resting state and is not in cardiac failure, an arterio–venous difference of 4.3 vols. per cent oxygen may be assumed (12) and the percentage of venous admixture calculated as above. The error in

\[
\text{TABLE 2. VENTILATION-PERFUSION RELATIONSHIPS IN 6 INDIVIDUALS WITH EMPHYSEMA}
\]

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>BAROMETRIC PRESSURE (mm. Hg)</th>
<th>'IDEAL' ALVEOLAR</th>
<th>ARTERIAL</th>
<th>ALVEOLAR-ARTERIAL GRADIENT</th>
<th>DEAD SPACE TIDAL AIR</th>
<th>VENOUS ADMIXTURE CARDIAC OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. F.</td>
<td>761</td>
<td>38</td>
<td>104</td>
<td>38</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>T. M.</td>
<td>754</td>
<td>49</td>
<td>89</td>
<td>49</td>
<td>19</td>
<td>48</td>
</tr>
<tr>
<td>L. L.</td>
<td>766</td>
<td>55</td>
<td>113</td>
<td>55</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>L. P.</td>
<td>766</td>
<td>55</td>
<td>79</td>
<td>55</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>H. W.</td>
<td>769</td>
<td>54</td>
<td>84</td>
<td>54</td>
<td>35</td>
<td>52</td>
</tr>
<tr>
<td>A. D.</td>
<td>762</td>
<td>56</td>
<td>81</td>
<td>56</td>
<td>37</td>
<td>35</td>
</tr>
</tbody>
</table>

Subjects at rest in the supine position. Corrections made when necessary for the effect of a diffusion gradient.

this procedure is ordinarily not great because the numerator in equation (15), which is not affected by the assumed value for mixed venous blood, is much more critical than the denominator.

The other alternative, when mixed venous blood is not known, is to estimate the amount of venous admixture on the basis of the 'ideal' alveolar–arterial \(pO_2\) gradient alone. When the subject is at rest and breathing room air, a gradient in excess of 12 mm. Hg may be considered abnormally large. This datum must be interpreted with discretion, however, since the significance of the 'ideal' alveolar–arterial \(pO_2\) gradient is affected both by the level of oxygenation of the arterial blood and by the arterio–venous difference.

**EXPERIMENTAL FINDINGS**

Average normal values of 'ideal' alveolar air have previously been reported under the name of 'effective' alveolar air (6), and the corresponding alveolar–arterial \(pO_2\) gradients were also presented (13). In table 1 a more
complete analysis of ventilation-perfusion relationships in 8 normal male physicians is presented. The average values are almost identical with those previously reported.

The upper limits of normal for subjects resting in the supine position breathing ambient air have been tentatively set at 12 or 13 mm Hg for alveolar-arterial pO_2 gradient, 30 per cent for the ratio of dead space to tidal air, and 7 per cent for the ratio of venous admixture to cardiac output.

In table 2 the findings in 6 individuals with various types and degrees of pulmonary emphysema are recorded. In the second case (T. M.) the inefficiency is largely ventilatory as indicated by a high ratio of dead space to tidal air (48%) and only a moderately high ratio of venous admixture to cardiac output (17.5%). In the last case (A. D.) the opposite situation obtains.

The ratio of effective tidal air to tidal air, or of effective alveolar ventilation to total ventilation, is, in percent, 100 minus the ratio of dead space to tidal air. The ratio of effective pulmonary blood flow to total pulmonary blood flow, or cardiac output, is 100 minus the ratio of venous admixture to cardiac output.

**DISCUSSION**

In a previous analysis of the alveolar-arterial gradient the theoretical necessity for the alveolar air and alveolar capillary blood to approach equilibrium more closely at high levels of oxygenation than at low levels was discussed (13). This phenomenon was suggested many years ago by Barcroft and has been elaborated upon by recent authors (14, 15). It is not to be inferred that the mean pO_2 gradient between alveolar air and alveolar capillary blood is necessarily different at different levels of oxygenation but simply that the final gradient as the blood leaves the alveolar capillary is different. This final gradient, which we shall call the diffusion gradient, differs because of the shape of the oxyhemoglobin dissociation curve. There are theoretical reasons for believing that the diffusion gradient is but a fraction of 1 mm Hg in normal resting individuals breathing room air at sea level (13, 15), while the gradient increases to as much as 9 mm Hg when the arterial oxygen saturation is reduced to 70 per cent by breathing a low oxygen gas mixture (13, 15).

In the analysis of venous admixture above it was assumed, as it has been throughout this paper, that no diffusion gradient existed, i.e. that perfect equilibrium was reached between the alveolar gases and the blood leaving the alveolar capillaries. This is a valid assumption, for practical purposes, in resting subjects whose arterial oxygen saturation is 96 per cent or higher during room air breathing. At such high levels of oxygenation, therefore, the pO_2 gradient between 'ideal' alveolar air and arterial blood is predominantly the resultant effect of venous admixture and perfusion of poorly ventilated alveoli. At an arterial oxygen saturation of 70 per cent not only does the diffusion
gradient increase, but the venous admixture gradient decreases. In normal individuals the venous admixture \( pO_2 \) gradient is believed on theoretical grounds to decrease to a fraction of 1 mm. Hg so that the total \( pO_2 \) gradient between ‘ideal’ alveolar air and arterial blood is predominantly the effect of failure to reach equilibrium, i.e. diffusion (13, 14, 15). Recent unpublished studies indicate that the ‘ideal’ alveolar-arterial \( pO_2 \) gradient can be quantitatively apportioned between diffusion (the membrane component) and venous admixture (the venous admixture component) provided the alveolar-arterial gradient is determined at two different levels of oxygenation, with the subject in the same metabolic state.

The \( pCO_2 \) gradient between alveolar air and the blood leaving the alveolar capillaries remains negligible at low levels of oxygenation. Thus, in the absence of a large shunt, the arterial \( pCO_2 \) remains a good measure of alveolar \( pCO_2 \), and the ‘ideal’ alveolar \( pO_2 \) can be calculated in the usual way using equation (12). The graphic method for determining ‘ideal’ alveolar \( pO_2 \) cannot be applied in the presence of a \( pO_2 \) diffusion gradient since this method is based upon the identity of alveolar \( pO_2 \) and the \( pO_2 \) of the blood leaving the individual alveolar capillaries. The graphic method therefore cannot be used during low oxygen breathing.

In the system of analysis of ventilation-perfusion relationships which has been presented it has been assumed that the blood R.Q., the alveolar air R.Q. and the expired air R.Q. are identical (1, 20, 21). A factor which would invalidate this assumption would be the exchange of significant quantities of oxygen or carbon dioxide through the walls of the larger airways. While some such exchange may possibly take place (16) it is undoubtedly small in amount and therefore not an important source of error. Another cause for discrepancy between the alveolar R.Q. and the expired air R.Q. would be anything causing an unsteady state, such as recent changes in activity or in the composition of the inspired air. Errors from such causes are minimized in practice by requiring the subject to maintain as constant a state as possible prior to and during the collection of samples. Exercise is performed on a stationary bicycle at a steady level for 7 minutes before sampling is begun, and subjects are required to breathe high or low oxygen mixtures for 10 minutes before sampling. These leveling off periods are not adequate to produce a completely steady state, but the consistency and reproducibility of results suggest that errors from this cause are not large. Strictly speaking, a steady state can never be achieved because of the cyclic nature of the ventilatory and circulatory processes. It is probable that moment to moment variations are responsible for some of the variations in ventilation-perfusion ratio for which there is evidence in normal individuals.

Rossier has pointed out that a large shunt may lead to a significant difference between arterial and alveolar \( pCO_2 \), and we have observed a difference
as great as 3 mm. Hg in patients with severe degrees of emphysema. Under these circumstances the 'ideal' alveolar pCO₂ can be accurately determined by the graphic method. On theoretical grounds it would seem that impaired diffusion across the alveolar membrane will not lead to a significant pCO₂ gradient until the pO₂ gradient has become so great as to be incompatible with life. Impaired diffusion of O₂ therefore does not invalidate the use of arterial pCO₂ as a measure of 'ideal' alveolar pCO₂.

There is no apparent reason why the 'ideal' alveolar air cannot be calculated by the graphic method even in the presence of congenital cardiac disease with large vascular shunts. One point and slope are all that is required to draw the blood and gas R.Q. lines, and in each case the R.Q., determined from the expired air, provides the slope. The arterial blood provides a point on the blood R.Q. line and inspired air provides a point on the gas R.Q. line. The point of intersection can be found graphically. Once the 'ideal' alveolar point is established, the ratio of dead space to tidal air can be calculated, providing evidence related to ventilation-perfusion relationships within the lungs in patients with congenital heart disease. The ratio of venous admixture to cardiac output will include the effects of both intrapulmonary shunt and right to left intracardiac shunts.

Technical errors must be carefully minimized in the performance of the direct blood gas tension technic (17). It is helpful to calculate the arterial pCO₂ from the Henderson-Hasselbalch relationships in order to check the direct method. The arterial pO₂ determination can be compared with the oxygen saturation if the pH is known. The apparatus dead space, which includes the entire volume between the subject's mouth and both respiratory valves, must be reduced to a minimum and accurately measured in order to permit accurate physiological dead space determinations.

It has been observed consistently that the ratio of dead space to tidal air remains fairly constant in a given individual at rest, during moderate exercise, and during high and low oxygen breathing. This is true in both health and disease. The finding is constant enough to help in deciding whether an experiment is technically satisfactory. Furthermore, venous admixture and dead space are affected in opposite ways by an error in arterial pCO₂, so that inaccuracies may often be detected by examining these relationships.

One of the factors determining the magnitude of the venous admixture effect resulting from perfusion of poorly ventilated alveoli is the change in slope of the oxygen dissociation curve in the physiological range. When the subject breathes ambient air or air with a pO₂ in the vicinity of 150 mm. Hg, the blood in the alveolar capillaries covers a range of the oxygen dissociation curve which extends from the steepest portion to the very flat upper portion. This maximal change in slope provides conditions which cause blood from poorly ventilated alveoli to contribute maximally to the venous admixture.
If the same subject breathes a low oxygen mixture, the venous admixture effect resulting from perfusion of poorly ventilated alveoli is much reduced because the physiological range of the oxygen dissociation curve is limited to the steep portion where the change in slope is relatively slight. Finally, if the same subject breathes pure oxygen, the venous admixture effect from poorly ventilated areas is eliminated, in this case because the curve of intersections of the blood and gas R.Q. lines becomes a straight line. Under these conditions venous admixture measures only true shunt. Analysis of ventilation-perfusion relationships must be done where the resulting venous admixture effect is maximal and must therefore be done with the subject breathing ambient air or air in this general range.

Several methods have been proposed by which the distribution of the tidal air throughout the lungs can be evaluated (22, 23, 9, 24). The study of the ventilation-perfusion relationships differs from these in that the distribution of the tidal air is considered only in relation to the distribution of the alveolar capillary blood. If the distribution of the tidal air and the ventilation-perfusion relationships are evaluated independently it would seem possible to learn something about the distribution of alveolar capillary blood as an independent phenomenon. Furthermore, since the use of high concentrations of oxygen tends to reduce the apparent venous admixture resulting from perfusion of poorly ventilated alveoli, it may be possible to differentiate in part between true shunt and apparent venous admixture (25, 26). Such combinations of studies would lead to more precise understanding of ventilation and perfusion both as independent and as related phenomena.

**APPENDIX**

**DETERMINATION OF 'IDEAL' ALVEOLAR AIR**

The graphic determination of 'ideal' alveolar point requires the following data. For purposes of illustration values obtained on a normal subject will be used.

Subject: R. L. R.; barometric pressure: 765 mm. Hg

Blood:

<table>
<thead>
<tr>
<th>Arterial</th>
<th>Mixed venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCO₂</td>
<td>42 mm. Hg</td>
</tr>
<tr>
<td>pO₂</td>
<td>90 mm. Hg</td>
</tr>
<tr>
<td>CO₂ content</td>
<td>50.75 vol. %</td>
</tr>
<tr>
<td>O₂ content</td>
<td>17.1</td>
</tr>
<tr>
<td>Dissolved = .3</td>
<td>Dissolved = .1</td>
</tr>
<tr>
<td>Total = 17.4 vol. %</td>
<td>Total = 17.2</td>
</tr>
<tr>
<td>O₂ capacity</td>
<td>17.9</td>
</tr>
<tr>
<td>Dissolved = .5</td>
<td>Dissolved = .5</td>
</tr>
<tr>
<td>Total = 18.4 vol. %</td>
<td>Total = 18.5</td>
</tr>
<tr>
<td>O₂Hb saturation</td>
<td>95.5 %</td>
</tr>
</tbody>
</table>

Expired air:

<table>
<thead>
<tr>
<th>CO₂</th>
<th>4.05 %; 29.1 mm. Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂</td>
<td>16.10 %</td>
</tr>
</tbody>
</table>
N₂ .......................... 79.85 %
Ventilation .................. 6.18 l/min. BTPS; 5.14 l/min. STPD
Tidal air ..................... 672 ml/breath BTPS
Respiratory rate .............. 9.2 breaths/min.

Plotting gas R.Q. line, using pCO₂ and pO₂ as coordinates. The moist inspired air point is calculated from the equation

\[ \text{insp. } pO_2 = \frac{\text{B} - 47}{100} \]

A value for alveolar pCO₂, such as 40 mm. Hg, is assumed, and the corresponding value for alveolar pO₂ is calculated using equation (12). A straight line is drawn through the inspired air point

\[ (pO_2 = 150 \text{ mm. Hg}; pCO_2 = 0) \] and the assumed alveolar point

\[ (pCO_2 = 40 \text{ mm. Hg}; pO_2 = 102 \text{ mm. Hg}) \] (Figure 4, gas R.Q. line).

Plotting the blood R.Q. line, using vol. %CO₂ and O₂ as coordinates. The blood R.Q. line passes through both the mixed venous blood point and the arterial blood point. In subjects whose mixed venous blood and arterial blood have both been directly sampled, these two points can be plotted and a straight line drawn through them. However, since the R.Q. determines the slope of this line, one directly determined point and the R.Q. suffice for drawing the line. Ordinarily the arterial blood point is plotted as in figure 5;

\[ A - V \text{ difference} \]

\[ 4.0 = 5.0 \text{ vol. %} \]

\[ 0.8 = 10.2 \text{ mm. Hg} \]

A straight line through the assumed point (CO₂ = 54.75 vol. %; O₂ = 12.4 vol. %) and the arterial blood point is the blood R.Q. line. It passes through the mixed venous blood point, although the exact location of the latter will not be known unless it has been determined by other technics.

Transposing the blood R.Q. line to the alveolar air diagram. Transposition of the blood R.Q. line from the volumes per cent plot (fig. 5) to the partial pressure plot (fig. 4) requires that the physiological carbon dioxide and oxygen dissociation curves for the individual under consideration be constructed. Details of the methods for accomplishing this have been described elsewhere (18, 19), so only the steps involved will be mentioned here.

The physiological CO₂ dissociation curve is plotted on log log graph paper with vol. %CO₂ laid off along the vertical axis and pCO₂ along the horizontal (fig. 12). Knowledge of the mixed venous blood is not needed and the procedure will therefore be described as if this value were not known. The arterial blood point is plotted. The difference in CO₂ content between completely reduced and fully oxygenated blood is determined (6.2 vol.

![Fig. 12. Physiological carbon dioxide dissociation curve of K.L.K. plotted on log paper.](http://jap.physiology.org/)
and the CO₂ content of fully oxygenated blood calculated (50.5 vol. %CO₂ at pCO₂ = 42 mm. Hg), taking into account the oxygen unsaturation of the arterial blood. The CO₂ dissociation curve for fully oxygenated blood is drawn through this point, after determining the slope on the basis of the O₂Hb capacity. A dissociation curve for unsaturated blood is then drawn parallel to the curve for oxygenated blood. The carbon dioxide content corresponding to zero oxygen content is determined (64.9 vol. %), taking into consideration the R.Q. The point on the dissociation curve for unsaturated blood is found where the CO₂ content = 64.9. A straight line drawn through this point and the arterial blood point is the physiological CO₂ dissociation curve (fig. 12). It intersects the curve for fully oxygenated blood at pCO₂ = 41 mm. Hg. The physiological curve is discontinuous at this point, becoming the same as the fully oxygenated curve at pCO₂ values below 41 mm. Hg.

Fig. 13. PHYSIOLOGICAL oxygen dissociation curve of R.L.R. Standard curves from Handbook of Respiratory Data in Aviation Medicine.

To construct the physiological oxygen dissociation curve the arterial blood point is plotted on a standard oxygen dissociation curve (linear coordinates) on the basis of directly determined pO₂ and O₂Hb saturation values (fig. 13). Since the pH of mixed venous blood is 0.02 or 0.03 pH units lower than that of the arterial blood, the venous blood point is displaced about 2 mm. Hg to the right of the dissociation curve which passes through the arterial blood point. The physiological oxygen dissociation curve can be drawn with sufficient accuracy by eye between the arterial and mixed venous blood points, almost paralleling the standard curve for constant pH. This procedure is permissible because the effect of the difference in pH between arterial and mixed venous blood is small.

When the carbon dioxide and oxygen dissociation curves have been constructed, the necessary relationships are available for expressing the blood R.Q. line in terms of pCO₂.
and $pO_2$. In table 3 the data used in transposing this line from figure 5 to figure 4 are presented. Oxygen content values from figure 5 are first divided by the oxygen capacity and expressed as per cent saturation. Then the corresponding $pO_2$ values are read off from the physiological oxygen dissociation curve (fig. 13). Values of $CO_2$ content from figure 5 are expressed in terms of $pCO_2$ by reference to the physiological $CO_2$ dissociation curve (fig. 12). The $pO_2$ and $pCO_2$ values are plotted in figure 4. The ‘ideal’ point, identified by the intersection of the blood and gas R.Q. lines, has a $pCO_2$ of 41.8 mm. Hg and a $pO_2$ of 100 mm. Hg.

### Table 3. Subject R. L. R. (O$_2$Hb capacity = 17.9 vol. %)

<table>
<thead>
<tr>
<th>Carbon Dioxide</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>vol. %</td>
<td>mm. Hg</td>
</tr>
<tr>
<td>V = 54.1</td>
<td>46.5</td>
</tr>
<tr>
<td>53.4</td>
<td>45.5</td>
</tr>
<tr>
<td>51.9</td>
<td>43.4</td>
</tr>
<tr>
<td>AR = 50.75</td>
<td>42.0</td>
</tr>
<tr>
<td>X = 50.60</td>
<td>41.7</td>
</tr>
<tr>
<td>50.5</td>
<td>41.6</td>
</tr>
</tbody>
</table>

### SUMMARY

The partial pressure of oxygen in the alveolar air may vary widely in different parts of the lungs in patients with pulmonary disease. The composition which the alveolar air would have if it were homogeneous throughout the lungs can be determined precisely by solving the blood and gas R.Q. equations, assuming that there is equilibrium between the alveolar air and the blood leaving the alveolar capillaries. Alveolar air of the one and only composition which satisfies these equations is called the ‘ideal’ alveolar air.

Variations in the composition of alveolar air in different parts of the lungs occur primarily because of variations in ventilation-perfusion ratio. These relationships can be analyzed, using the ‘ideal’ alveolar air concept. Physiological dead space, when calculated using the ‘ideal’ alveolar air, includes a contribution from alveoli with a high ventilation-perfusion ratio. A ratio of dead space to tidal air in excess of 30 per cent indicates that a significant proportion of alveoli are well ventilated but poorly perfused. Venous admixture, when calculated using the ‘ideal’ value for blood leaving the alveolar capillaries, includes a contribution from alveoli with a low ventilation-perfusion ratio. A ratio of venous admixture to cardiac output in excess of 7 per cent indicates that a significant proportion of alveoli are well perfused but poorly ventilated. Analysis of ventilation-perfusion relationships must be done in the normal range of oxygenation, since breathing either a low oxygen mixture or a very high oxygen mixture minimizes the effects under consideration.
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