A CONCEPT OF MEAN ALVEOLAR AIR AND THE VENTILATION-BLOODFLOW RELATIONSHIPS DURING PULMONARY GAS EXCHANGE

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IN THE past many different methods have been employed for the direct sampling of alveolar air. A sound criticism of the validity of the technique has usually been futile since one was at loss to define or determine mean alveolar composition. The ease with which alveolar air composition can be altered by the slightest change in ventilation is very impressive and makes one aware of the possibility of unequal ventilation in various parts of the lung and the consequential regional variability of gas concentration. The concept of unequal bloodflow to the various alveoli has received less attention, although this factor is equally important in altering the gas composition.

It is the purpose of this paper 1) to define the alveolar air composition in terms of alveolar ventilation and pulmonary bloodflow which allow one to define a concept of mean alveolar gas composition; 2) to discuss a method for the direct sampling of mean alveolar air; 3) to compare this with the Haldane technique of sampling alveolar air; 4) to predict on the basis of the ventilation-bloodflow equations the effect of unequal ventilation and bloodflow upon the alveolar-arterial oxygen gradient.

A Concept of Mean Alveolar Air. The alveolar air equation and the alveolar ventilation equation have given us a theoretically precise definition of the relation of the alveolar-gas concentrations and the ventilation (1). When this equation is combined with the Fick equation, it allows one to express the alveolar gas concentration in terms of bloodflow and ventilation (2).

Let:

- \( F \) = bloodflow in liters/min.
- \( V_a \) = alveolar ventilation in liters/min. R.T.P.S.
- \( (A-V)O_2 \) = arterial-venous oxygen difference in ml/l.
- \( X_0 \) = oxygen intake in ml/min. S.T.P.
- \( Q \) = respiratory quotient
- \( PC \) = partial pressure of CO\textsubscript{2} in alveolar air.

Then the bloodflow according to the equation of Fick is

\[
X_0 = F(A-V)O_2 \tag{1}
\]

and the alveolar ventilation according to Fenn et al. (1) is

\[
X_0 = \frac{V_a \times PC}{.864Q} \tag{2}
\]

Combining the equations and eliminating \( X_0 \) we have

\[
pC = \frac{F}{V_a} (A-V)O_2 (.864Q) \tag{3}
\]
The \( pO_2 \) can be calculated for equation 3 from the alveolar air equation if the R.Q. is known. Since \( V_a \) and F appear as a ratio, the equation becomes independent of metabolic rate. The \( pCO_2, pO_2 \) and R.Q., therefore, become a function of the \( V_a/F \) for any given inspired gas tension and mixed venous blood gas tension (see below).

The solution of this equation for a given steady state is most easily accomplished by a graphic method. If one assumes a specific \( pO_2 \) and \( pCO_2 \) tension of the mixed venous blood entering the lung as well as an inspired oxygen tension, then one can graphically, with the aid of the Henderson nomogram for blood and the Penn diagram (1) for gas R.Q., determine all the simultaneous \( pO_2 \) and \( pCO_2 \) tensions which satisfy equation 3.

This is done in the following manner. Various gas R.Q. lines are plotted radiating from the inspired \( O_2 \) tension, I, on the Fenn \( O_2 - CO_2 \) diagram (fig. 1). The point describing the \( O_2 \) and \( CO_2 \) CONTENT VOL %

![Diagram](http://ajplegacy.physiology.org/)

Fig. 1. THE CURVE (SOLID LINE) represents all the possible simultaneous \( O_2 \) and \( CO_2 \) tensions which could theoretically exist in the pulmonary capillaries and the alveolar air when the mixed venous blood has the composition \( V \), and the inspired gas tension has the composition I. The solid diagonals represent various iso-gas R.Q. lines and the dotted lines the iso-oxygen content. Each point on this curve is the product of a certain ventilation-bloodflow ratio, \( V_a/F \), which simultaneously determines the respiratory quotient, Q, at which the blood and alveoli are exchanging.

tensions of the mixed venous blood, \( V \), is likewise located on the diagram. A straitedge connecting the venous \( O_2 \) and \( CO_2 \) tensions of \( V \) on the blood nomogram is then pivoted on its point of intersection with a chosen blood R.Q. point until the \( pCO_2 \) and \( pO_2 \) values correspond to identical values on the diagonal of figure 1 representing the same R.Q. At these tensions only, can blood and alveolar gases exchange at the same R.Q. Similar points can be found for various other R.Q.'s which yield a curve (fig. 1) denoting all the possible combinations of \( CO_2 \) and \( O_2 \) tensions which could exist under these conditions. Since the original development of this procedure (2) Riley (3) has (personal communication) proposed quite independently a similar solution. Essentially, he plots all the possible \( O_2 \) and \( CO_2 \) tensions for a given blood R.Q. coming from a given venous point and shows where they intersect the gas R.Q. line. This procedure has much merit for it affords a more graphic visualization of blood and gas exchange on the \( O_2-CO_2 \) diagram.

It follows from the equation that any point along this curve is the result of a particular alveolar ventilation to bloodflow ratio, \( V_a/F \). To determine this ratio from equation 3 the (A-V) oxygen difference must be known in addition to the \( pCO_2 \) and Q. This can be obtained from the isopleths of arterial \( O_2 \) content that have been added to the figure 1. Thus, between the venous point, V, where the ventilation is \( \infty \), and the other end of the curve I, where the bloodflow is \( \infty \), an infinite number of \( V_a/F \) ratios can theoretically exist in the various alveoli. In the alveoli where normally the maximal exchange occurs, at an R.Q. of .8, the \( V_a/F \) ratio in this particular example is 1.0.
We have now defined for this specific example all the possible simultaneous \( O_2 \) and \( CO_2 \) tensions which could exist in any part of the lung as well as in the pulmonary capillary blood if we assume that the terminal diffusion gradient across the alveolar membrane is for practical purposes negligible. The next object is to determine the mean alveolar gas concentration. This is done easily, if the R.Q. is known. Thus, if we choose in our example an R.Q. of .8 then the intersection of this gas R.Q. line with the curve of Figure 1 determines the only point at which blood can exchange at this particular R.Q. This is at a \( pCO_2 \) and \( pO_2 \) of 40 and 100 mm Hg respectively and assumes that all blood in all the alveoli is exchanging at this particular R.Q. Of course, it is very probable that this is not normally the case and that alveoli exchange individually at various R.Q.'s and that only the mean of all of them result in an R.Q. of .8. As will be discussed below, a normally distributed population of \( Va/F \) values will not appreciably affect the predicted alveolar value, but only change the arterial \( pO_2 \).

The validity of the theoretical alveolar air curve (Fig. 1) should be experimentally demonstrable if one could alter the \( Va/F \) ratio without changing the steady state and the venous tension, \( V \). The closest approach to such a test can be accomplished by analysis of the alveolar air composition after breath holding and hyperventilation when this is done at various intervals up to one circulation time (20 sec.). It might be assumed that the venous tension will remain constant during this period. Such experiments have been previously described (4), and are here compared with the theoretical curve (Fig. 2). Although a discrepancy is apparent, probably due to altered \( CO_2 \) output, cardiac output and partial recirculation, a general agreement is rather striking and lends support to the theoretical conclusions regarding the possible combinations of \( CO_2 \) and \( O_2 \) which could exist simultaneously in the alveoli. It has always been an impressive fact that the simultaneous gas tensions could be altered only along a very narrow and predictable pathway no matter by what method the steady state was altered (5).

**Sampling of Mean Alveolar Air.** It has been shown above that the mean alveolar air can be theoretically defined provided 3 facts are known: 1) the venous gas tensions, 2) the inspired gas tensions and 3) the R.Q. (It also presupposes that there exists no terminal alveolar membrane gradient.) The question now arises how close these values for the theoretical mean alveolar air can be approached by direct methods which do not involve the sampling of mixed venous blood.

Riley et al. (6) have approached this problem by collecting and analyzing the arterial blood for the \( CO_2 \) tension. Since such a sample represents a mixture of practically all the blood that has passed through the pulmonary capillaries, it must represent the mean arterial \( pCO_2 \) tension and is for all practical purposes in equilibrium with the alveolar \( pCO_2 \). (It is shown that a considerable venous admixture has a negligible effect upon the mean arterial \( pCO_2 \) tension. Furthermore, it is shown below that a normal probability distribution of \( Va/F \) among the alveoli, likewise has a negligible effect.)

On the basis of the theoretical discussion above, this mean arterial \( pCO_2 \) value should be identical with the mean alveolar \( CO_2 \) tension. (This theoretical mean tension has been designated as ‘ideal’ tension by Riley (3)). Thus, substituting mean alveolar \( CO_2 \) for mean arterial \( pCO_2 \) and determining the respiratory quotient from the expired air, Riley is able to calculate the mean alveolar \( pO_2 \) from the alveolar air equation. This method is theoretically entirely sound for obtaining the mean alveolar composition but offers practical difficulties since it requires an arterial puncture and considerable skill in the determination of arterial \( pCO_2 \). Furthermore, any single determination of arterial \( pCO_2 \) by the method of Riley et al. (6) can only be read with an accuracy of \pm 3 mm. \( pCO_2 \).
On the other hand, methods of obtaining alveolar air directly offer many practical advantages and it is our purpose to ascertain how closely these methods approach the theoretical concept of mean alveolar air. In the past there have been essentially 2 methods of sampling alveolar air. In the original method (Haldane) all the expiratory reserve was forced out of the lung and the last part analyzed, while others have sampled from the last part of each normal tidal volume. These 2 methods do not yield identical results and the difference can probably be best appreciated when the time course of CO₂ concentration is recorded for each individual breath on a fast infrared CO₂ analyzer recently described by Fowler (7) from this laboratory (fig. 3). It can be seen that after the deadspace is washed out with a normal tidal expiration, the CO₂ concentration rises quickly and tends to plateau off. With a forced expiration (Haldane), however, the alveolar CO₂ keeps on rising. This curve is typical of some 15 healthy individuals who have been recorded by this method.

Fig. 2. THEORETICAL ALVEOLAR AIR COMPOSITION CURVE (solid line) compared with directly obtained samples (dashed line) when the Va/F ratio of the normal alveolar air (open circle) is altered by breath holding or hyperventilation. (see text).

With the Haldane technique part 'X' is sampled. In a method described by us recently (5, 8), part 'Y' is sampled. In this example the CO₂ difference between these 2 points is approximately 3 mm. Hg.

Sampling the last part of each normal tidal has several advantages, for it averages the last 10–15 cc. of each tidal volume expired during normal breathing and, furthermore, it does not require trained subjects for delivering a properly timed, forced expiration. In addition to the automatic sampling the continuous analysis is extremely convenient. In order to determine the reliability of these samples as representing mean alveolar air, tests were performed comparing the alveolar pCO₂ with the arterial pCO₂.

The CO₂ comparisons were carried out by Miss Suskind in this laboratory (unpublished). While the alveolar air was analyzed continuously by the method referred to above, blood samples were taken from the radial artery in the human subjects and the femoral artery in the dogs. This approach allowed for simultaneous sampling of these 2 components. Nine experiments were carried out on man and 80 were done on dogs under nembutal or pentothal narcosis. The mean difference
for all experiments between the alveolar pCO\(_2\) and the arterial pCO\(_2\) was 0.78 mm. Hg, standard error of the mean 0.58. (In our hands we find that on the average the pCO\(_2\) determination of the blood differs from the equilibrating test gas mixture by less than .3 mm. Hg with a standard deviation of 2.5.) These observations would suggest that the alveolar pCO\(_2\) obtained by this method of sampling from the last fraction of each tidal volume is in very close agreement with the arterial pCO\(_2\). Therefore, this value, as pointed out above, represents the mean alveolar pCO\(_2\) unless an appreciable terminal membrane gradient exists, which is unlikely (6).

In the continuous method of alveolar air analysis the pO\(_2\) is simultaneously analyzed and must, therefore, represent the mean alveolar pO\(_2\) provided that the alveolar air R.Q. is identical to the expired air R.Q., the latter representing the classical standard.

To test the possible discrepancy between these, the alveolar R.Q. was determined by continuous alveolar air analysis and compared with R.Q. values from the collected expired air. The expired air was analyzed by the same automatic meters as well as by Haldane gas analyses in 27 experiments on 7 different subjects. The average values are presented in table 1 and show no significant difference between the expired air and the simultaneous alveolar air R.Q. These results would suggest that this method of sampling yields an R.Q. which is in agreement with expired air R.Q. values. Thus, we may draw the conclusion that the alveolar air sampled continuously from the end of normal tidal expirations, yields a value which must be very close to the theoretical mean alveolar pO\(_2\) and pCO\(_2\).

The other method (Haldane) for sampling alveolar air must also be discussed. This method analyzes the last part of the forced expiration. When this method is compared with samples taken by the previous method (8) one finds on the average a 2 mm. higher CO\(_2\) and a 5 mm. lower pO\(_2\) for the Haldane technique. This is not surprising when we look at figure 2 and also consider that this forced expiration usually lasts 2–3 seconds beyond the time taken for a normal expiration (end-expiratory sample). Similar differences were obtained by Riley et al. (6) who compared the alveolar CO\(_2\) obtained by the Haldane technique (end-inspiratory samples) with the arterial pCO\(_2\). They observed on the average a 4.4 mm. Hg higher value in the alveolar sample taken at rest.
It should be pointed out that the subjective impression of the time it takes to expire completely may be quite misleading, unless a simultaneous air velocity record is obtained. It is during the last phase of expiration that the CO₂ in many subjects rises rather steeply due to the smaller lung volume which is still exchanging with the blood. Actually, tests have shown (unpublished) that during this prolonged expiration, the oxygen uptake remains normal, but the CO₂ output is reduced. The net result is that not only must the CO₂ rise above and the O₂ fall below the average value existing at the end of a normal tidal, but the ratio between oxygen uptake and CO₂ output is altered, producing an abnormally low R.Q. These changes become exaggerated when larger intervals than 2–3 seconds are used for the forced expiration or when the breath is held (4).

Table 1 B shows the alveolar R.Q. differences obtained by the 2 methods of sampling. These experiments were done on 10 subjects and were reported elsewhere (8). But in view of the values cited in table 1 A, they assume new interest since they show the Haldane method to deviate from the expired air R.Q. and by an average value of .03 R.Q. units. This would support the contention that a forced expiration is actually equivalent to breath holding which brings about similar changes in O₂, CO₂ and R.Q. of alveolar air (4).

The O₂ and CO₂ Dead Space. The discrepancy between the tidal air samples and forced expiration samples, furthermore, explains the difference which has been noted by others between the dead space calculated from the oxygen values and CO₂ values. Theoretically, it can be shown that this dead space must be the same as long as the R.Q. of the expired and alveolar air are the same. The reason for the observed difference of a larger oxygen dead space is very probably that the alveolar samples were always obtained by the Haldane technique. Figure 4 shows the average expired air, E, and the alveolar air, A, values obtained in 27 experiments in which the alveolar CO₂, O₂ and R.Q. values were 38.1, 102 and .829 and the expired CO₂, O₂ and R.Q. were 27.8, 114 and .828 respectively. The Bohr formula, deadspace tidal volume

\[ \frac{A-E}{\Delta} \]

can be represented graphically in figure 4 for the O₂ as well as the CO₂ values. The ratio \( \frac{A-E}{\Delta} \) must be equal for both sides of the quadrangle as long as both A and E are on the same diagonal or R.Q. line.
If one assumes on the basis of the former experiments (6) that a Haldane sample had been delivered instead, the alveolar air values would have been located at point A-\textsuperscript{1} in figure 4. During the delivery of the sample, the concentration of point A would change and move up on the breath holding curve, B.H. (4).

The actual values cited above yield with the average tidal volume of 648 cc. (B.T.P.S.) an O\textsubscript{2} and CO\textsubscript{2} deadspace of 176 cc. If we subtract a 35 cc. apparatus deadspace from this figure, we obtain a personal deadspace (breathing through the nose) of 140 cc. Had Haldane samples been used instead, the personal deadspace would have been 164 cc. for CO\textsubscript{2} and 188 cc. for O\textsubscript{2}. On the basis of the foregoing discussion it would appear that the deadspace values derived from Haldane samples are probably too large, particularly for the O\textsubscript{2} deadspace.

**Effect of Unequal Ventilation and Bloodflow upon the Alveolar-Arterial Gradient.** In the foregoing discussion the concept of the theoretical mean alveolar gas concentration was based upon the assumption that all alveoli exchanged at the same R.Q. However, there is much evidence that ventilation is not equal in various parts of the lung (for a recent review see Rauwerda (9)) and Wearn et al. (10) have shown that the bloodflow is not constant in the alveoli. Thus, to appraise the variations in gas concentrations that may exist from one alveolus to the next and what effect this would produce upon the mean alveolar gas composition as well as upon the mean arterial gas tension, the variation of bloodflow and alveolar ventilation must be considered. Since both exert their effect upon the gas tensions, it is convenient to con-
consider them simultaneously and to evaluate the effect of the variation of alveolar ventilation to bloodflow ratio, \( \frac{V_a}{F} \). From equation 3 we obtain by rearrangement:

\[
\frac{V_a}{F} = \frac{0.864 Q (A-V)O_2}{pC}
\]  

(4)

If we return to our original conditions of our example, figure 1, with a R.Q. equal to 0.8 then the mean alveolar \( pO_2 \) and \( pCO_2 \) must be 100 and 40 mm Hg respectively, provided all the blood in all the alveoli is exchanging at this R.Q. Furthermore, these particular tensions are brought about by a \( \frac{V_a}{F} \) ratio of 1.0.

Theoretically other \( \frac{V_a}{F} \) ratios can occur ranging from 0 at the venous point to \( \infty \) at the inspired gas tension. Therefore, we may assume that the distribution of

| A) Values which will be found at the various standards of deviation which are not apparent in fig.4 |
|------------------|------------------|------------------|
| \( \frac{V_a}{F} \) | -3               | -2               | -1               | MEAN | +1               | +2               | +3               |
| R.Q.             | 0.45             | 0.59             | 0.77             | 1.00 | 1.30             | 1.69             | 2.20             |

Table 2

B) Blood and alveolar values which would be obtained if all alveoli exchanged at a \( \frac{V_a}{F} \) ratio of 1.0, (A), are compared with the mixture which would result if the \( \frac{V_a}{F} \) ratio varied around the mean (B) (see text)

<table>
<thead>
<tr>
<th></th>
<th>O(_2) CONTENT</th>
<th>CO(_2) CONTENT</th>
<th>ALV. ( pO_2 )</th>
<th>ALV. ( pCO_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A ..................</td>
<td>19.65</td>
<td>48.00</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>B ..................</td>
<td>19.55</td>
<td>47.90</td>
<td>99.4</td>
<td>39.7</td>
</tr>
<tr>
<td>Difference .......</td>
<td>0.10</td>
<td>0.10</td>
<td>0.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

the pulmonary bloodflow, \( F \), as well as the ventilation, \( V_a \), among the various alveoli is normal along a logarithmic scale. The distribution of the ratio \( \frac{V_a}{F} \) will then also be normal along a logarithmic scale. Returning to our example, we can say that not all alveoli have a \( \frac{V_a}{F} \) of 1.0 but that some have a larger and others a smaller ratio distributed along a normal logarithmic distribution curve with the mean of the log 1.0. A standard deviation equal to the log 1.3 is arbitrarily chosen.

Table 2 A lists the various \( \frac{V_a}{F} \) ratios and R.Q.'s which then will be found at 1, 2, and 3 standard deviations from the mean \( \frac{V_a}{F} \) of 1.0 and figure 5 shows how this distribution affects the \( O_2 \) and \( CO_2 \) content of the arterial blood and the \( pO_2 \) and \( pCO_2 \) of the alveolar air. The resulting mixtures which would result for each of the 4 entities are calculated (the sum of the values of each class interval multiplied by the frequency of its occurrence) and listed in table 2 B to be compared with the theoretical mean value which would be obtained if no variation of \( \frac{V_a}{F} \) had oc-

\[ ^2 \] Among the various kinds of distribution curves, this is probably the simplest form which could be assumed for the distribution of a ratio.
curred as originally assumed. It can be seen that from a practical standpoint none of the resulting mixtures differ from the theoretical mean with the exception of the O₂ content. Here we find that the arterialized blood leaving the lung capillaries has an O₂ content 0.1 volume per cent lower than if all the exchange had gone on at a Va/F of 1.0. The arterial blood leaving the capillaries is, therefore, represented by the open circle (fig. 5) and it can be seen that this is at an oxygen tension 8 mm. Hg lower than the mean alveolar O₂ tension. (Although the CO₂ content of the mixture also differs from the theoretical value by the same amount as the O₂ content, it affects the arterial pCO₂ by less than 0.2 mm. Hg.) It should be pointed out that the

mixed alveolar air as well as the mixed arterial blood points (table 2, B) no longer lie precisely on the blood R.Q. or gas R.Q. line of .8. This would suggest that the Va/F ratios are not symmetrically, but unequally distributed in such a manner that the mixed values still maintain an R.Q. of .8. However, the above example is a first approximation and the discrepancy in this case may be considered negligible.

When, under otherwise identical conditions, various other venous points are chosen, the pO₂ gradient is not appreciably altered. This means that a large or a small (A-V)pO₂ difference does not affect this gradient. On the other hand, if a larger deviation of Va/F than log. 1.3 is assumed, the pO₂ gradient can become appreciably larger. This may explain the greater alveolar-arterial oxygen gradient observed during exercise by Riley et al. (6). It should also be pointed out that an unequal distribution of Va/F ratios will result in increased O₂ gradients, particularly if a preponderance of alveoli have a Va/F ratio which is smaller than the theoretical mean.

Fig. 5. DISTRIBUTION OF THE PULMONARY blood gas values and alveolar gas values when a normal logarithmic distribution of Va/F is assumed around the mean value (solid circle). The resulting average mixture of the arterial blood will be altered only in respect to the oxygen content and arterial pO₂ (open circle). The resulting average mixture of alveolar gases remains essentially unchanged. Thus, the distribution of Va/F induces an alveolar-arterial pO₂ gradient of 8 mm. Hg (see text).
As discussed before, the standard deviation of this ratio was quite arbitrarily chosen and at present there is no way to ascertain the magnitude of this deviation nor whether the distribution of this Va/F ratio is distributed symmetrically or asymmetrically. On the other hand, with the above assumption we can say that in the normal lung this deviation is no greater than the one we assumed because the gradient of 8 mm. pO₂ obtained is of the same order of magnitude as that observed for the total gradient normally occurring (6). This gradient has so far been largely attributed to venous admixture arising from direct venous shunts, Thebesian and bronchial veins.

**SUMMARY**

An equation is derived which expresses the alveolar gas concentration in terms of the relative alveolar ventilation and pulmonary bloodflow. A graphical solution of this relationship is given which describes all the simultaneous O₂ and CO₂ concentrations which could theoretically exist for given mixed venous and inspired air tensions of these gases. Each of the possible alveolar air values, and therefore each R.Q., is determined by a definite ventilation to bloodflow ratio. If the R.Q. is known, the theoretical mean alveolar air composition can be defined by this equation.

This theoretical concept of mean alveolar air presupposes that the ventilation to bloodflow ratio is the same in all the alveoli. Since this is unlikely, a variation of this ratio along a normal distribution curve is assumed. The mean alveolar air mixture resulting from such a distribution does not differ appreciably from the theoretical mean. The resulting arterial blood mixture, however, yields a lower pO₂ tension, thus giving rise to an alveolar-arterial oxygen gradient.

Evidence is presented which indicates that the sampling of alveolar air from the last part of each normal expiration yields a value which is very close to the theoretical mean alveolar air composition, while the Haldane method of sampling yields CO₂ values which are slightly too high and R.Q. values which are slightly too low. The latter method is responsible for the difference in dead space volumes when they are calculated separately from the O₂ and CO₂ values. Theoretically, the volumes should be the same if the expired air R.Q. and alveolar air R.Q. are equal.

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