

**THE MEASUREMENT OF THE OXYGEN CONTENT  
OF THE MIXED VENOUS BLOOD, AND OF THE  
VOLUME OF BLOOD CIRCULATING PER MINUTE.  
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THE measurement of the oxygen in the mixed venous blood is of interest, since it forms the basis of the "Coefficient of Utilisation" (Krogh) and also because the deficit in oxygen between the venous blood and the arterial blood can be used as the basis of a method for the measurement of the minute volume. This principle was introduced by Fick in 1870 and has been used since by a great number of workers. The previous work will be found fully discussed in a paper by Liljestrand and Lindhard (1). In animals the composition of the mixed venous blood can be obtained by direct analysis, but in man it must be inferred from the alveolar air, which must in some way be brought into equilibrium with the venous blood. The application of the principle of Fick has been rendered more difficult as knowledge has advanced, for the work of Christiansen, Douglas and Haldane (2) has shown that the oxygen determinations are only correct if both the oxygen and carbonic acid in the alveolar air are in equilibrium with the venous blood. They have devised methods for the accomplishment of this, which have formed the subject of a demonstration to the Physiological Society.

The present research was undertaken in the hope that some more simple method might be forthcoming which would measure the oxygen content in the venous blood with sufficient accuracy for many purposes. The sources of error divide themselves into two main categories: (1) the technical errors contingent on inaccuracies in gas analysis and the production of some artificial equilibrium between the oxygen in the lung and that in the blood, (2) the physiological errors due to some upset of the circulation by the artificial process of respiration imposed by the experiment. In devising the present method we regarded errors of the latter type as the more serious because they are so elusive. If it were possible to make the assumption that the composition of the general venous blood were constant the problem would be relatively simple, but

this assumption cannot safely be made, even when the body is not doing muscular work. In order therefore to get rid of the physiological errors as much as possible, we laid down certain conditions which our method should fulfil: (1) that the respiration should only be interrupted for five to seven seconds, the time necessary to transfer the mouth from any form of respiration apparatus to that in which the alveolar air is estimated and (2) that the estimation should be made in a single observation which would give the composition of the venous blood in the body at a given moment of time.

By breathing nitrogen in a way to be described presently an equilibrium may be produced between the mixed venous blood and the alveolar air in the lung. The partial pressure of oxygen in the alveolar air is then a measure of the partial pressure of oxygen in the mixed venous blood of the lung capillaries at the moment. This blood differs from the normal mixed venous blood inasmuch as it is depleted to some extent of carbonic acid. On this account the oxygen pressure is too low. By the application of an empirical correction an approximation to the proper oxygen pressure can be obtained which is as close to the correct value as other collateral errors would in any case admit of.

The method of respiration is as follows: a bag fitted with a tap and valves, as described by Douglas, is filled with nitrogen. The valves and tap are so disposed that the subject of the experiment can inspire at will either from the external air or the bag, but his expired air must in either case go into the outer atmosphere. He then goes through the following processes: (1) he clips his nose, (2) breathes through the valves, inspiring atmospheric air till he is satisfied that he is breathing normally, (3) makes a rather deep expiration, (4) turns the tap so that the next inspiration comes from the bag, (5) takes a rather deep inspiration from the bag and then breathes normally for several respirations (four or five according to the rate of respiration), (6) turns the tap on the bag so as to shut it. (7) With his mouth closed and taking no further inspiration he turns to a Haldane gas analysis apparatus which is in readiness, fitted with an alveolar air tube and takes a sample of his alveolar air. (Process (7) should take about six seconds.) The person who is conducting the experiment takes the time with a stop-watch between operations (4) and (6). This is known as the "interval of nitrogen respiration." Our convention is not to include in it the time taken over operation (7). The actual time therefore occupied in the establishment of the equilibrium is about six seconds longer than the "interval of nitrogen respiration."

Evidence that equilibrium is established between the air in the lung and the blood in its capillaries.

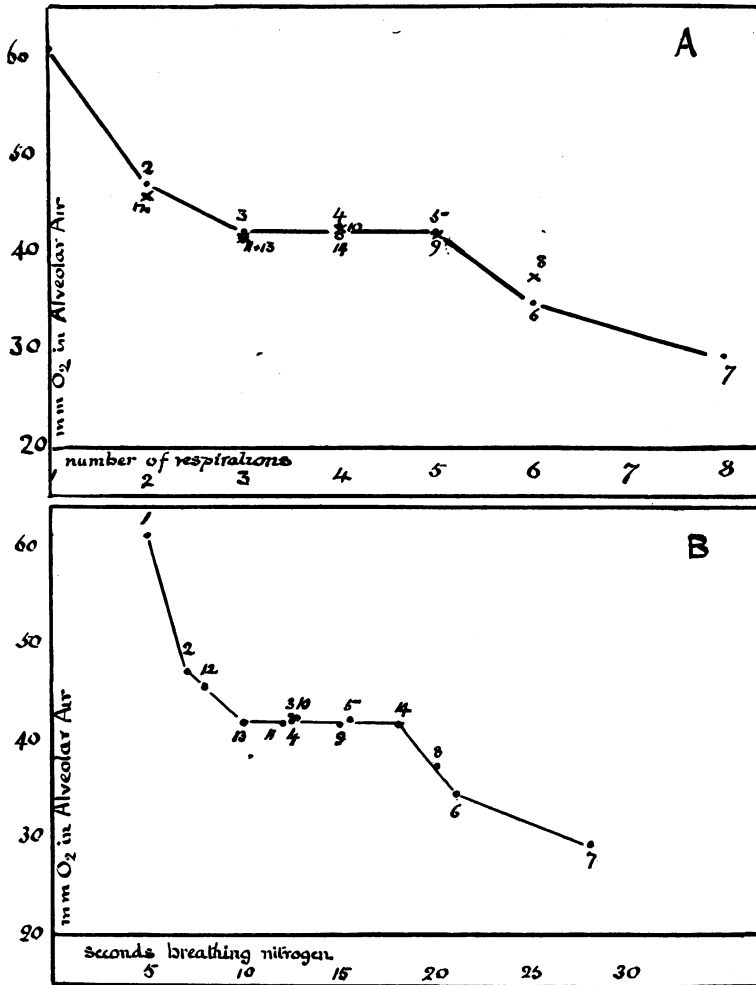


Fig. 1. A. ordinate = alveolar oxygen pressure.  
 abscissa = number of respirations in the interval of nitrogen respiration (hereafter referred to as I.N.R.).

B. ordinate as in A.  
 abscissa = duration in seconds of I.N.R.

Numerals attached to the points indicate the order in sequence in which the determinations were made. The two graphs represent the same set of determinations.

(a) The first point we would urge is that within considerable limits the composition of the alveolar air is independent of either the length

of the "interval of nitrogen respiration" or of the number of respirations included in it. The results plotted graphically in the figure illustrate this point.

In Fig. 1 *A* and *B* are plotted out the results of successive observations during the course of a morning. Commencing with the smallest number of respirations and the shortest I.N.R. the oxygen pressure in the alveolar air falls until in test 3 it is 42 mm.; further increase of the number of respirations or of the extension of the I.N.R. does not influence the partial pressure of oxygen in the alveolar air until in test 6 the I.N.R. reaches 21 seconds. With longer intervals (test 7) the oxygen pressure falls still lower, presumably because the I.N.R. is now so long that the blood which already traversed the lung at the commencement of the I.N.R. returns once more to it before the close, and not having been oxygenated at the commencement of its circuit of the body is abnormally venous at the close. Passing from test 7 the I.N.R. was shortened progressively until when it fell below 20 seconds the oxygen pressure returned to 42 mm., and remained at that figure (within half a mm.) till the I.N.R. was cut down to four to eight seconds; the oxygen pressure in the alveolar air then rose to 45, but again returned to 42 in tests 13 and 14 in which the I.N.R. was 10 and 18 seconds respectively.

(*b*) Evidence of another character was furnished by subject S., who in addition to being able to produce data similar in character to those plotted in Fig. 1, could inhale so great a volume of nitrogen at a single breath that with short I.N.R.'s he had a lower oxygen pressure in his alveolar air than with longer ones. Thus according to the quantity of nitrogen which he inspired in the first deep respiration he could approach the horizontal portion of the curve which relates the alveolar oxygen pressure to I.N.R. either from below or above—but in either case the ultimate result was the same. Indeed by simply taking one deep breath of nitrogen and holding the breath for a sufficient time he could obtain the same result (cp. Fig. 2 *A*).

In this figure dots represent determinations of the oxygen in the alveolar air produced by the procedure described above, whilst the crosses were determinations after a different procedure, namely: A maximal expiration was made, then a maximal inspiration of nitrogen—the breath was held for a length of time expressed along the abscissa at the end of which time the alveolar air was taken and analysed. The ultimate identity in position of the plateaux on the two curves, one approached from above, the other approached from below, seems to leave no doubt that in each case when the plateau was reached, the alveolar

air and the blood in the lung capillaries were in equilibrium and therefore that the partial pressure of oxygen in the alveolar air was the measure of that in the blood.

*Correspondence between the partial pressure of oxygen of the alveoli, and that of mixed venous blood.*

In making the analyses of the alveolar air, the partial pressure of  $\text{CO}_2$  was estimated in every case, as well as that of oxygen. In the plateau region the carbonic acid pressure was very regularly about

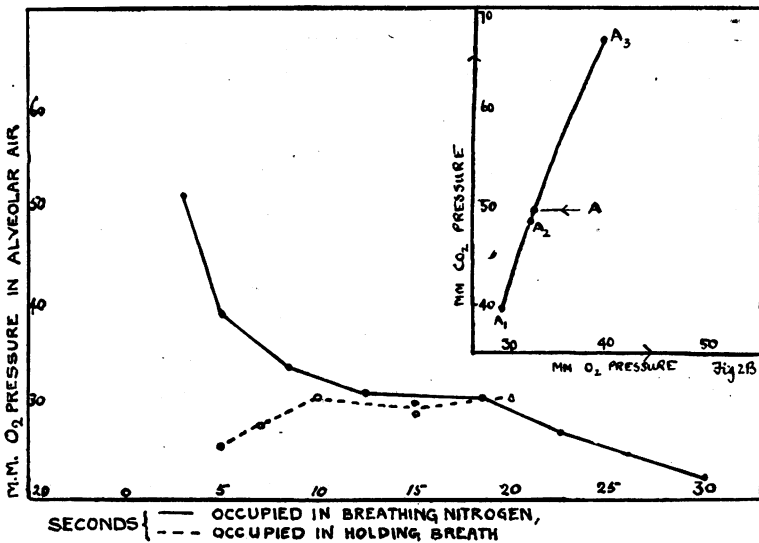


Fig. 2 A and B (inset).

40 mm.—a value which corresponds to that for normal alveolar air, but not that for normal mixed venous blood. Clearly then the  $\text{CO}_2$  pressure is below what it should be and therefore the  $\text{CO}_2$  pressure in the lung capillaries is below what it should be; but if that is so, it follows that there is an error in the oxygen pressure, for if the  $\text{CO}_2$  pressure be raised, the oxygen pressure in the venous blood will be raised, and therefore an equilibrium will be struck with a higher pressure of oxygen in the alveolar air. The error involved was investigated on Shoji. Four determinations were made with no  $\text{CO}_2$  in the inspired air, a fifth with about 5 p.c.  $\text{CO}_2$ , a sixth with a further addition of  $\text{CO}_2$ . The oxygen and  $\text{CO}_2$  in the alveolar air were as follows:

TABLE I.

Experiment	...	...	(1)	(2)	(3)	(4)	(5)	(6)	Mean of (1), (2), (3), (4)
Pressure of gases in	{	O <sub>2</sub>	27.8	27.2	29.8	30.4	32.2	39.6	29.0
alveolar air in mm.		CO <sub>2</sub>	39.2	37.1	39.8	41.2	48.2	67.7	39.3

From the known data of Shoji's blood, the line which represents the relation of CO<sub>2</sub> pressure to 1/K in the equation  $F/100 = \frac{Kx^n}{1+Kx^n}$  at all pressures of CO<sub>2</sub> between 0 and 80 mm. is  $1/K = 75.7 \times p \text{ CO}_2 + 600$ .

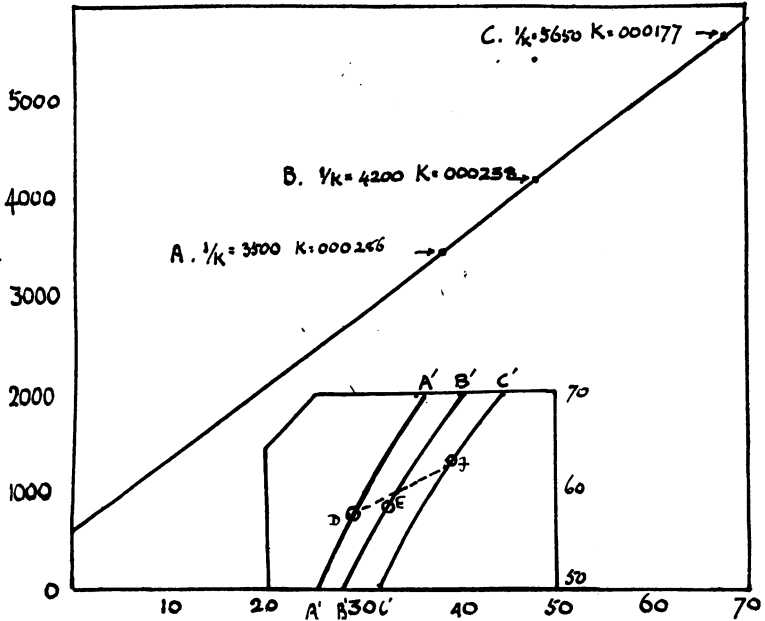


Fig. 3.

From this line set off on paper, as in Fig. 3, the values of 1/K, and consequently those of log K for CO<sub>2</sub> pressures involved, are as follows:

Exps.	CO <sub>2</sub>	log K	Fig.
1-4	39.3	4.4564	A
5	48.2	4.3766	B
6	67.7	4.248	C

From these values of log K the corresponding dissociation curves AA', BB', CC' may be drawn, the portions involved being shown in the inset of Fig. 3. On these curves the observed oxygen readings are set off as follows.

Oxygen pressure	Curve	Percentage saturation of blood with oxygen
29	AA'	56.4
32	BB'	58.4
37	CC'	63.7

A line joining these points gives the percentage saturation of the blood, whatever be the  $\text{CO}_2$  pressure in the alveolar air sample, between 38 and 68 mm., and which therefore embraces the  $\text{CO}_2$  pressure of the mixed venous blood. If this line were quite horizontal, one could take any  $\text{CO}_2$  pressure, draw the proper curve belonging to it and read off the percentage saturation of the mixed venous blood. As the line is not quite horizontal a slight correction must be introduced. The  $\text{CO}_2$  pressure of the mixed venous blood was determined in Shoji's case by the method given by Christiansen, Douglas and Haldane(2). It was 49.5 mm. The proper curve for this pressure is scarcely distinguishable from  $BB'$ . The line  $DE$  crosses  $BB'$  at 58.4 p.c. saturation and is therefore a point 2 p.c. above the point  $D$  on the line  $AA'$  which was the uncorrected point as found by our method. The actual percentage saturation of Shoji's mixed venous blood may be obtained by adding 2 p.c. to the figure obtained by our method. A similar series of experiments on Barcroft's blood gives a correction of 3 p.c. to be added to the observed percentage saturation. Probably if the error is taken as 2.5 p.c. a result will be obtained which is commensurate with the general accuracy of the experiments.

Our reasons for believing that the experiments so far described with this correction, do give us a true measurement of the oxygen content of the mixed venous blood are strengthened, when we try to form a more concrete picture of what is happening in the lung, during the six-second interval in which the breath is held. During the whole of this period, mixed venous blood enters the pulmonary capillaries, charged with  $\text{O}_2$  and  $\text{CO}_2$ , at certain definite partial pressures, and unless the latter are the same as the partial pressures of the corresponding gases in the alveoli at the beginning of the interval, diffusion exchange will take place until the partial pressure of  $\text{O}_2$  and  $\text{CO}_2$  in the alveoli are equal respectively to the partial pressure of  $\text{O}_2$  and  $\text{CO}_2$  in the mixed venous blood entering the capillary. Actually unless the composition of air breathed from the Douglas bag is carefully adjusted, six seconds will not be long enough to allow true equilibrium to be reached. For instance when pure  $\text{N}_2$  is breathed from the bag, the alveolar sample as averaged from Exps. 1-4 of Table I only show  $p \text{O}_2$  (partial pressure of oxygen) = 29 mm., and  $p \text{CO}_2$  = 39.3 mm. If we could examine the condition of the blood at different points along a pulmonary capillary at the instant at which the alveolar sample was taken, we ought to find that  $p \text{O}_2$  and  $p \text{CO}_2$  gradually changed as we proceeded from the point where blood enters the capillary until we reached a certain point  $A_1$ , at which they equal 29

and 39.3 mm. respectively. At points of the capillary between  $A_1$  and the point where the blood leaves,  $p O_2$  and  $p CO_2$  should be the same as at  $A_1$ . Similarly when  $N_2$  containing 5 p.c.  $CO_2$  is breathed, as in Exp. (5) of Table I, we ought, at the instant the six-second interval ends, to be able to find a point  $A_2$  in the pulmonary capillary at which  $p O_2$  of the blood = 32.2 mm., and  $p CO_2 = 48.2$  mm. beyond which point  $p O_2$  and  $p CO_2$  are constant.  $A_2$  lies nearer than  $A_1$  to the point at which blood enters the capillary. Finally in Exp. (6), where  $N_2$  containing a higher percentage of  $CO_2$  was breathed, the corresponding point  $A_3$  contains blood at higher  $p O_2$  and  $p CO_2$  than the mixed venous blood entering the capillary. The true  $p O_2$  and  $p CO_2$  of the mixed venous blood must therefore lie between the values corresponding to points  $A_2, A_3$ . If we plot  $p CO_2$  against  $p O_2$  for the three points  $A_1, A_2, A_3$  as in Fig. 2 *B*, it is seen that  $A_1, A_2, A_3$  lie not very far apart upon what is practically a straight line. It seems legitimate then to presume that the point  $A$ , which indicates  $p O_2$  and  $p CO_2$  of the mixed venous blood, also lies on the line  $A_1, A_2, A_3$ . The true  $p CO_2$  for the mixed venous blood is measured with sufficient accuracy by the method of Christiansen, Douglas and Haldane(2), the point  $A$  on the line  $A_1, A_2, A_3$  corresponding to this ordinate is observed, and the abscissa of  $A$  gives the true  $p O_2$  for the mixed venous blood. Actually for the mixed venous blood we find that  $p CO_2 = 49.5$  mm.,  $p O_2 = 32.6$  mm., and the percentage saturation calculated from Hill's equation = 58.5.

*Comparison with Christiansen, Douglas and Haldane's  
CO<sub>2</sub> method (2).*

An idea may be formed of the correctness of the method by a comparison between the oxygen lost from the blood, and that of the  $CO_2$  which it gains. In Shoji's blood, taking the percentage saturation of the mixed venous blood with oxygen as 58.5 p.c. and that of the arterial blood as 95 p.c., the difference is 36.5. The oxygen capacity of Shoji's blood was 20.7 c.c. per 100 c.c. of blood. Therefore 100 c.c. of blood took in  $\frac{36.5 \times 20.7}{100} = 7.55$  c.c. We determined the  $CO_2$  dissociation curve of Shoji's blood from which we obtained the following data. At a pressure of 39 mm.  $CO_2$ , his reduced blood contained 46.7 c.c. of  $CO_2$  per 100 of reduced blood. According to the data given by Christiansen, Douglas and Haldane, the fully oxidised blood should contain 5.5 c.c. less  $CO_2$  and arterial blood  $\frac{5.5 \times 95}{100}$  or 5.23 c.c. less than 46.7 c.c. The arterial



blood would therefore contain 41.5 c.c. By a similar calculation Shoji's mixed venous blood would contain  $\left(51.4 - \frac{6 \times 58.5}{100}\right) = 47.9$  c.c. The difference between the  $\text{CO}_2$  contents of the arterial and mixed venous blood would then be 6.4 c.c., which represents the  $\text{CO}_2$  given out by 100 c.c. of blood. When this figure is divided by that for the  $\text{O}_2$  taken in, namely, 7.5 c.c., a respiratory quotient of .850 is obtained. It seems, then, that the methods described by Haldane and his colleagues for the  $\text{CO}_2$  in the venous blood, and that described here for the  $\text{O}_2$ , give quite comparable results and that whichever is used as a basis for the calculation of the minute volume the result obtained would be nearly the same.

*Comparison with the  $\text{CO}_2$  method of Yandell Henderson.*

Yandell Henderson<sup>(3)</sup> has described a method for the determination of the minute volume on the basis of a determination of the  $\text{CO}_2$  in the mixed venous blood, which may be carried out in a few minutes. We made some determinations by Henderson's method and by our own with the following results:

Subject	$\text{O}_2$ given to 100 c.c. blood	$\text{CO}_2$ taken from 100 c.c. blood	Resp. quot. calculated	Resp. quot. observed	Minute volume	
					(1) Present method	(2) Henderson's
Redfield	4.7 c.c.	4.0 c.c.	.92	—	6.8 litres	6.65 litres
Barcroft	4.18	3.3	.8	.77		

Probably none of the above methods are very accurate, but for many purposes great accuracy is not required whilst a simple method is desirable. To obtain an ideal measurement of the blood flow there should be no change in the rate at which blood is driven round the body during the experiment. We have not accomplished this as satisfactorily as we could have wished. Clearly our initial respiration will tend to draw the blood which was in the veins to the heart. This, however, does not vitiate our result as the composition of the blood is that which it had when it left the capillaries. On the other hand, if the rate at which the blood passes through the systemic capillaries be altered, error will begin to appear when that blood begins to influence the composition of the air in the lung. In our experiments there is but one complete respiration of abnormal depth which will introduce a certain, but we believe, a trivial error. The final holding of the breath for six seconds does not affect the transit of any blood through the systemic capillaries which appears in the lung before the final expiration.

SUMMARY.

By the method of respiration described in the paper we believe that the coefficient of utilisation of oxygen from the blood may be measured within almost 10 p.c., from which the minute volume may be calculated to a corresponding degree of accuracy.

REFERENCES.

- (1) Liljestrand and Lindhard. *Journ. of Physiol.* 53, p. 420. 1920.
- (2) Christiansen, Douglas and Haldane. *Ibid.* 48, p. 244. 1914.
- (3) Yandell Henderson and Prince. *Journ. Biol. Chem.* 32, p. 325. 1917.