

# STUDIES IN MAN OF THE VOLUME OF THE RESPIRATORY DEAD SPACE AND THE COMPOSITION OF THE ALVEOLAR GAS<sup>1</sup>

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Interest is currently focussed on the analysis of the factors influencing the exchange of oxygen and carbon dioxide between the blood and gas phases of the lung under a variety of experimental conditions. To this end, respiratory equations have been developed which include as unknowns either the volume of the respiratory dead space or the composition of alveolar gas. A new indirect method for determination of these two essential factors has been recently described by Pappenheimer, Fishman, and Borrero (1) and studied in anesthetized dogs and also in a few normal subjects. This method, hereafter referred to as the "iso-saturation method," makes possible the graphic solution of the Bohr formula for both the volume of the respiratory dead space and for the composition of alveolar gas; it entails the measurement of the composition of expired air over a wide range of tidal volumes, while respiratory gas tensions in the blood leaving the lungs are maintained constant during controlled hypoxemia.

The purpose of this paper is to extend the observations made on normal man with the iso-saturation method, and to explore its applicability to subjects with abnormal pulmonary function.

## Principle of the "Iso-Saturation Method"

In order to facilitate the presentation of the results, the method, previously described in detail by Pappenheimer, Fishman, and Borrero (1), is briefly reviewed.

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The expired breath may be considered to derive from two sources: 1. A respiratory dead space, where inspired gas (corrected to BTPS) has not exchanged oxygen and carbon dioxide with the blood and thus retains its identity; and 2. an alveolar space, which contains inspired gas modified by exchanges of oxygen and carbon dioxide (at BTPS) with blood. The volume and composition of this alveolar component of the expired breath is determined by the respective volumes of the total ventilation and of the respiratory dead space, and by the relative contributions and ventilation-perfusion ratios of the gas exchanging areas of the lungs.

These considerations are the basis for the Bohr formula:

$$V_{D_x} = \frac{(P_{E_x} - P_{A_x})}{(P_{I_x} - P_{A_x})} \cdot V_T \quad (1)$$

where

$V_T$  = tidal volume  
 $V_{D_x}$  = volume containing respiratory dead space gas  
 $V_{A_x}$  = volume containing alveolar gas =  $V_T - V_{D_x}$   
 $P_{I_x}$ ,  $P_{A_x}$ ,  $P_{E_x}$  = the partial pressures of the gas in inspired, alveolar and expired gas, respectively; all volumes are expressed at body temperature, pressure, saturated with water vapor (BTPS),

and by substitution and rearrangement, using oxygen ( $O_2$ ) as the test gas

$$\frac{V_{D_{O_2}}}{V_T} = \frac{P_{E_{O_2}} - P_{A_{O_2}}}{P_{I_{O_2}} - P_{A_{O_2}}} \quad (2)$$

If the alveolar, as well as the inspired, gas mixture could be maintained constant despite variation in tidal volume, equation (2) then would be

come (1, 2)

$$\frac{V_{D_{O_2}}}{V_T} = K \cdot P_{E_{O_2}} - K_1 \quad (3)$$

where,

$$K = \frac{1}{P_{I_{O_2}} - P_{A_{O_2}}} \quad \text{and} \quad K_1 = K \cdot P_{A_{O_2}}.$$

Similar considerations apply to the use of carbon dioxide ( $CO_2$ ) as gas  $x$ .

*The respiratory dead space.* It is apparent that in equation (3), the volume of the dead space has become a function of the tidal volume and expired gas composition. It was indicated in the original report (1) that graphic solution of the Bohr formula with constant inspired and alveolar gas permitted evaluation of two experimental possibilities:

1.  $V_{D_{O_2}}$  varies proportionally as  $V_T$  so that  $\frac{V_{D_{O_2}}}{V_T}$  is constant and  $\therefore P_{E_{O_2}}$  remains constant as  $V_T$  varies.

2.  $V_{D_{O_2}}$  is constant and independent of  $V_T$ , so that  $P_{E_{O_2}}$  varies linearly as  $\frac{1}{V_T}$ .

The two possibilities are illustrated in Figure 1A. These possibilities were experimentally tested in the previous study (1) and it was shown, under the conditions of the experiments, that  $V_{D_{O_2}} = K$ . Consequently, progressive decrease in tidal volume until  $V_T = V_{D_x}$  (where  $x$  is either oxygen or carbon dioxide) makes  $P_{E_x} = P_{I_x}$ , and numerical values for  $V_{D_x}$  may be obtained by extrapolation. This is illustrated for  $V_{D_{O_2}}$  in Figure 1B, and compared with  $V_{D_{CO_2}}$  in Figure 1D.

*Alveolar gas tension.* When  $\frac{1}{V_T} = 0$ ,  $P_{A_x} = P_{E_x}$  and a numerical solution for  $P_{A_x}$  can be obtained by extrapolation. Figure 1C illustrates the use of this method to obtain  $P_{A_{O_2}}$  and Figure 1D includes the determination of  $P_{A_{CO_2}}$ .

The application of the iso-saturation method to the solution of equation (3) depends on the use of arterial blood as an index to constant mean alveolar gas composition. Earlier experiments (1) with inspired gas mixtures low in oxygen content, have demonstrated that with controlled respiratory frequency and over a wide range of tidal volume, a stable degree of arterial hypoxemia

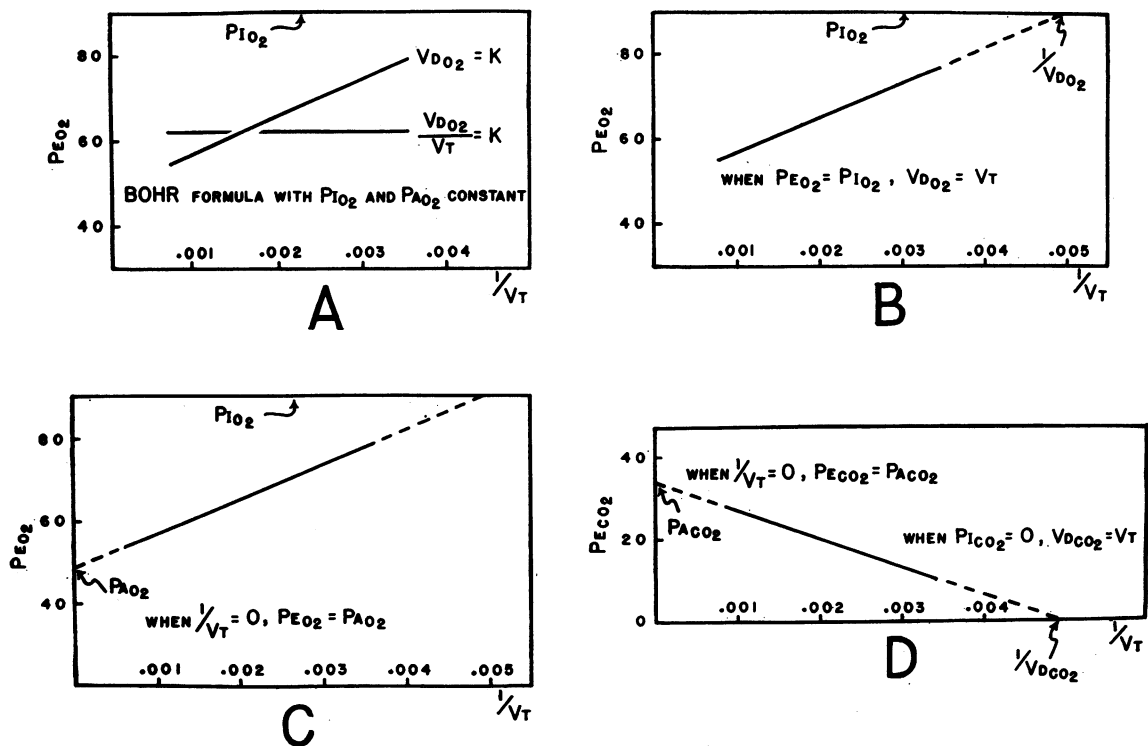


FIG. 1. GRAPHIC SOLUTION OF THE BOHR FORMULA FOR THE DETERMINATION OF  $V_{D_{O_2}}$ ,  $V_{D_{CO_2}}$ ,  $P_{A_{O_2}}$ ,  $P_{A_{CO_2}}$  (SEE TEXT)

can be achieved, employing an oximeter as a null-point indicator of arterial per cent  $\text{HbO}_2$  saturation. Furthermore, under these conditions, the linear alignment of the experimental points relating the composition of expired air to the reciprocal of the tidal volume, implies constancy of mean alveolar gas composition, and, therefore, of the A-a gradient.

#### METHODS

All experiments were done with the subject comfortably seated. In each experiment, successive points were obtained, at different respiratory frequencies. Frequency of respiration ranged from 8 to 88 per minute and was fixed for each experimental point by synchronization of breathing with a metronome; the depth of ventilation was regulated voluntarily so to maintain a constant per cent  $\text{HbO}_2$  in arterial blood as controlled by oximetry, thus insuring minimal fluctuations in  $\text{PaO}_2$ .

In some instances, a mild degree of exercise was used in order to achieve larger tidal volumes. This was done by means of a stationary bicycle ergometer, allowing sufficient time (approximately 15 minutes) for a steady state of respiration and of circulation to be reached.

A Millikan oximeter (single channel with compensated circuit, C.M.R. Model 13) was used throughout these experiments as a nullpoint instrument. This device permitted the subject to adjust his ventilation so as to return to the same per cent  $\text{HbO}_2$  mark on the galvanometer dial during successive experiments. The exact saturation corresponding to this mark was determined by arterial blood sampling and determination of its oxygen content and oxygen capacity with the Van Slyke-Neill apparatus.

In subjects free of pulmonary disease the oximeter scale was set at 100 after approximately 5 minutes of breathing 100 per cent oxygen, whereas in patients with pulmonary disease, the per cent  $\text{HbO}_2$  in arterial blood was determined directly by gas analysis, and the oximeter scale set accordingly. The instrument was checked for drift or instability at the end of each determination, and a deviation of greater than 2 per cent from the initial "ear thickness" or "saturation" readings caused the experiment to be discarded. An appropriate inspired mixture of oxygen in nitrogen was chosen in order to reduce the per cent  $\text{HbO}_2$  saturation in arterial blood to a range of 70 to 80 per cent. Whereas a 10 to 12 per cent oxygen mixture was needed to accomplish this comfortably in normal subjects, higher inspired oxygen mixtures were required in one of the subjects with pulmonary disease. The inspired mixture was made available through a demand valve as the subject breathed in time with a metronome, adjusting his tidal volume to reach the indicated saturation. Approximately 10 to 15 minutes after stabilization at the indicated galvanometer reading, three washouts of the spirometer with expired gas were completed, and a two-minute sample was collected for measurement of tidal volume and analysis. Repeated measurements of ventila-

tion, oxygen intake, and respiratory exchange ratio obtained between 10 to 15 minutes after stabilization of the galvanometer reading, suggested that a steady state of ventilation, circulation, and gas exchange had been reached.

Arterial blood samples were drawn during the gas collection period through an indwelling brachial arterial needle, previously placed following novocaine anesthesia.  $\text{PaO}_2$  and  $\text{PaCO}_2$  were determined directly and indirectly, in duplicate, according to methods previously described (3, 4). The results by both methods were required to check within 2 mm. Hg, for inclusion in the study. The partial pressures of oxygen and carbon dioxide in expired and inspired gases were calculated from the results of gas analysis using the 0.5 ml. micro-Scholander analyzer. With data thus obtained, the A-a gradients and oxygen diffusing capacity ( $\text{DL}_{\text{O}_2}$ ) of the lungs were calculated. For the latter calculation, made only in normal subjects, (a) the oxygen uptake figure was the average of multiple measurements; (b) the mean oxygen pressure gradient between the alveolar gas and the capillary blood was determined by a modification of Bohr's graphic integration method previously described (5), assuming that the mixed venous-capillary blood per cent  $\text{HbO}_2$  difference was 25 per cent and that, at the level of hypoxia employed, the venous admixture component of the A-a gradient was negligible. Obviously these assumptions can only apply to the normal subject.

#### Subjects for study

Eight normal subjects and three patients with abnormal pulmonary function were investigated. The pertinent vital statistics appear in Table I. The three patients selected had not on previous studies shown significant physiologic variation from day to day. They represent three distinct types of pulmonary dysfunction: 1. Non-obstructive emphysema; 2. overdistension of a normal lung following pneumonectomy; and 3. alveolar-capillary

TABLE I  
Vital statistics of eleven subjects studied

Subject	Age	Sex	Height	Body surface area		Vital capacity	Diagnosis
				cm.	m <sup>2</sup>	ml.	
A. P. F.	33	m	183	2.08	5130	Normal	
P. S.	30	m	185	2.20	4740	Normal	
W. B.	32	m	180	1.99	5560	Normal	
S. R.	38	m	174	1.84	4450	Normal	
M. B.	29	m	180	2.05	5400	Normal	
L. D.	28	f	168	1.63	4300	Normal	
G. J.	36	m	182	2.00	6560	Normal	
R. Mc.	30	m	175	1.90	4860	Normal	
G. W.	67	m	169	1.70	3040	Non-obstructive pulmonary emphysema	
G. B.	49	m	180	1.84	2315	1 month post right pneumonectomy	
E. H.	19	m	175	1.68	2860	Diffuse pulmonary granulomatosis	

TABLE II

Summary of physiologic measurements in the three patients with various types of pulmonary insufficiency

Measurement	Normal	G. W.	G. B.	E. H.
Lung volumes in per cent of predicted value				
Vital capacity	100	73	105*	55
Total capacity	100	113	104*	61
Residual air	100	254	145*	83
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	25	55	33	27
Maximum breathing capacity in per cent of predicted value	100	71	42	100
Alveolar N <sub>2</sub> per cent after 7 min. pure oxygen breathing	2.5	2.17	1.08	1.58
Ventilation in L./min./sq.m.b.s.†				
Rest	3.1	5.46	—	6.50
1 min. standard exercise	10.7	12.10	—	19.70
Arterial blood % HbO <sub>2</sub> ‡				
Rest	96	95	96	92
1 min. recovery, post-exercise	96	95	—	75
Arterial blood Carbon dioxide pressure, at rest, in mm. Hg‡	38	42	—	39

\* Compared to predicted values for normal lung.

† Sq.m.b.s. = square meter of body surface area.

‡ While breathing 21 per cent oxygen.

block associated with diffuse granulomatosis of the lung. The results of pulmonary function studies on each of the three patients are presented in Table II.

## RESULTS

The results in the eight normal subjects and in the three patients will be considered separately. All measurements made at rest and data calculated therefrom, are summarized in Table III, including the volume of the respiratory dead space and the composition of alveolar gas obtained by extrapolation.

### Normal Subjects

The results confirm those previously reported (1) and are illustrated for two subjects in Figures 2, 3, and 4. These figures are representative of those obtained in all the subjects, and demonstrate that the experimental points cluster around a sloping straight line with a minimum of scatter, and therefore make possible the extrapolations which

are necessary to define the volume of the respiratory dead space ( $V_{D_{O_2}}$  and  $V_{D_{CO_2}}$ ) and the alveolar gas composition ( $P_{AO_2}$ ) and ( $P_{ACO_2}$ ).

The points obtained during mild exercise in two subjects are indicated by separate symbols in the figures and fall on the same straight line as those obtained at rest. In a few experiments performed during more strenuous exercise, the points fell above the line. They were invariably associated with a higher respiratory exchange ratio ( $R_E$ ) than recorded in Table III. Since either a change in A-a gradient, or failure to achieve the steady state, may account for these observations, and since a fixed A-a gradient and maintenance of a steady state are prerequisite for the application of the method, these few points are not illustrated in the figures.

### Volume of the respiratory dead space

The main findings concerning the volume of the respiratory dead space were as follows: (a) The sloping straight line indicates (equation (3), Figures 1 and 2), that  $V_D$  is constant despite variation in  $V_T$ ; (b) the addition of a measured external dead space increases the calculated  $V_D$  by an amount equivalent to the water capacity of the added tube. As seen in Figure 4,  $V_{D_{O_2}}$  and  $V_{D_{CO_2}}$  increase by 156 ml., and 150 ml., respectively, after addition of an external  $V_D$  of 150 ml. As seen in the same figure, the application of a tight abdominal binder to change the midposition of the chest, did not alter significantly either the  $V_{D_{O_2}}$  or the  $V_{D_{CO_2}}$ ; similar observations were made in subject P. S.; (c) the  $V_D$  is fixed and is not influenced by variations in the composition of the low oxygen mixture which is used to maintain iso-saturation (Figure 3); when the same type of experiments are done by a trained subject, without anoxia or oximeter control, using room air as the inspired gas mixture, and voluntary adjustment of tidal volume to achieve comfortable ventilation at a given frequency, a considerable scatter of experimental points is observed (Figure 5). This scatter was anticipated since the subject maintained his arterial per cent HbO<sub>2</sub> in the upper, flat, part of the oxyhemoglobin dissociation curve, where slight changes in per cent HbO<sub>2</sub> may be associated with marked changes in  $P_{AO_2}$ ; (e) during all the experimental variations described above,  $V_{D_{O_2}}$  and  $V_{D_{CO_2}}$  remained approximately equal.

TABLE III  
Summary of physiologic measurements (columns 1-9) and calculated data (columns 10-17) obtained by the "iso-saturation method" in eight normal subjects and in three patients with abnormal pulmonary functions \*

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Subject	No. of experimental points	F <sub>IO<sub>2</sub></sub>	V̇O <sub>2</sub>	RE	Arterial				V <sub>D</sub> O <sub>2</sub>	V <sub>D</sub> CO <sub>2</sub>	P <sub>AO<sub>2</sub></sub>	P <sub>ACO<sub>2</sub></sub>	P <sub>AO<sub>2</sub></sub> -P <sub>ACO<sub>2</sub></sub>	P <sub>ACO<sub>2</sub></sub> -P <sub>ACO<sub>2</sub></sub>	R <sub>A</sub>	D <sub>L</sub> O <sub>2</sub>
					O <sub>2</sub> Sat.	pH	P <sub>AO<sub>2</sub></sub>	P <sub>ACO<sub>2</sub></sub>								
A. P. F.	11	.118	325±30	.98±.03	80	7.45	45	35	161	161	52	33	7	+2	1.00	24
P. S.	13	.109	275±25	.95±.04	80	7.47	41	33	171	166	47	31	6	+2	1.00	20
W. B.	9	.109	348±30	1.10±.02	78	7.49	39	34	163	169	50	30	11	+4	1.09	19
S. R.	6	.109	250±10	.99±.02	79	7.49	41	33	152	147	45	32	4	+1	.96	25
M. B.	8	.101	308±25	.96±.03	77	7.52	38	29	147	147	42	31	4	-2	.96	32
L. D.	6	.101	200±20	1.05±.05	82	7.52	44	26	93	86	47	26	3	0	1.00	18
G. J.	10	.101	305±30	.99±.03	83	7.59	40	23	199	215	45	29	5	-6	1.08	28
R. Mc.	8	.101	300±15	.95±.02	79	7.50	39	31	145	147	43	28	4	+3	.98	33
G. W.	6	.119	220±17	.93±.05	80	7.50	40	32	190	187	58	29	18	+3	1.03	—
	7	.101	244±29	1.02±.04	70	7.56	28	30	204	195	46	27	18	+3	1.03	—
G. B.	21	.118	271±20	.90±.10	80	7.50	40	32	160	157	51	28	11	+4	.81	—
E. H.	22	.159	316±17	.89±.02	83	7.47	47	32	191	189	82	29	35	+3	.91	—

\* F<sub>IO<sub>2</sub></sub> = Fraction of oxygen in inspired gas.

V̇O<sub>2</sub> = Oxygen consumption at rest in ml. per min. in (STPD).

RE = Average respiratory exchange ratio calculated from analyses of expired gas.

Art. O<sub>2</sub> Sat. = Per cent oxyhemoglobin in arterial blood.

P<sub>AO<sub>2</sub></sub> = The average pressure of oxygen in arterial blood in mm. Hg.

P<sub>ACO<sub>2</sub></sub> = The average pressure of carbon dioxide in arterial blood in mm. Hg.

V<sub>D</sub>O<sub>2</sub>, V<sub>D</sub>CO<sub>2</sub> = Dead space volumes for oxygen and carbon dioxide determined graphically in ml. at BTSPS.

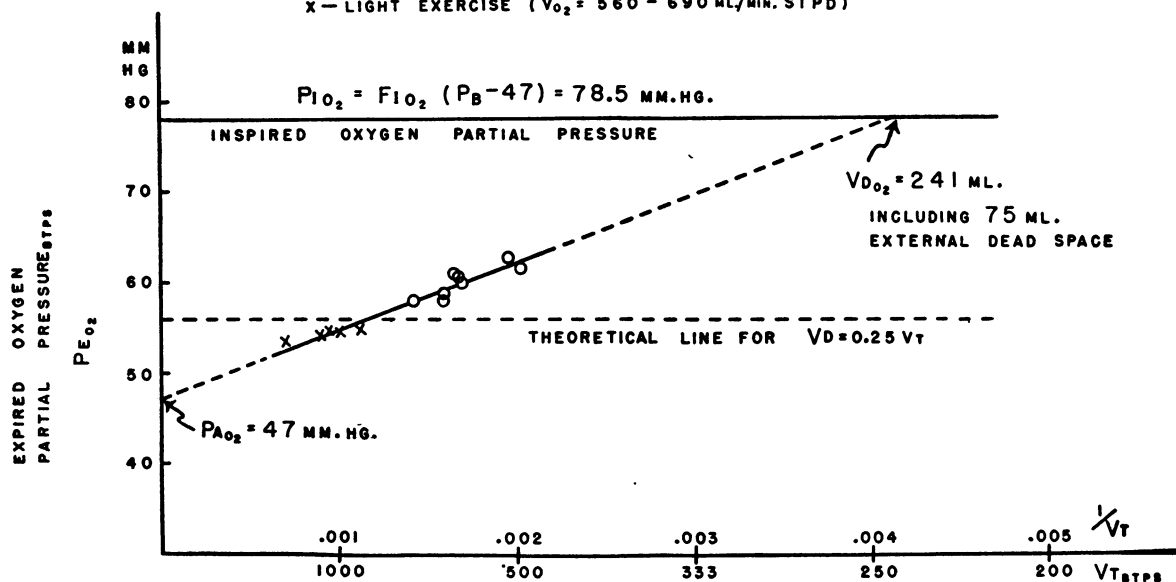
P<sub>AO<sub>2</sub></sub>, P<sub>ACO<sub>2</sub></sub> = Alveolar oxygen and carbon dioxide pressures determined graphically in mm. Hg.

R<sub>A</sub> = Average alveolar exchange ratio calculated from P<sub>AO<sub>2</sub></sub> and P<sub>ACO<sub>2</sub></sub> determined graphically.

D<sub>L</sub>O<sub>2</sub> = Diffusing capacity of the lung, in the resting subject, calculated by the Bohr graphic integration method expressed in ml. per min. per unit mean pressure difference between alveolar and capillary oxygen tension.

DETERMINATION OF DEAD SPACE FOR OXYGEN ( $V_{D_{O_2}}$ )  
AND  
ALVEOLAR OXYGEN PARTIAL PRESSURE ( $P_{A_{O_2}}$ )

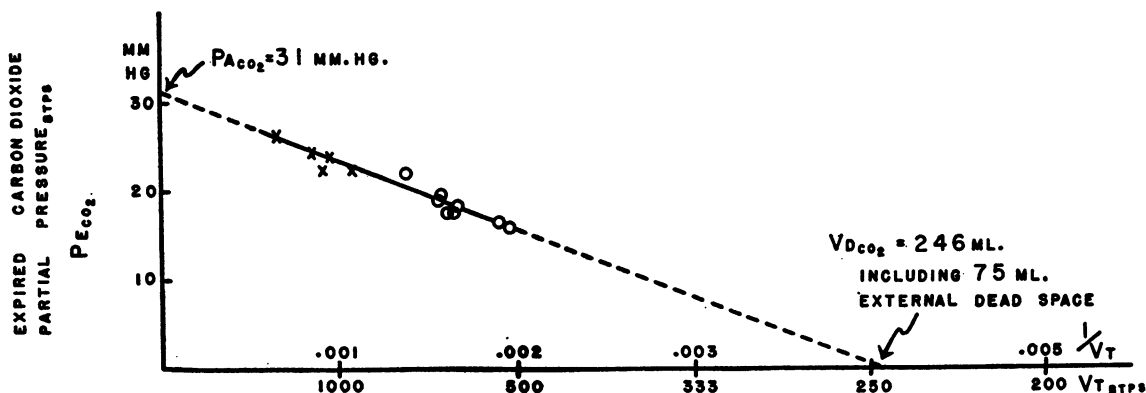
SUBJECT: P.S. OXIMETER,  $HbO_2 = 80 \pm 2\%$   
O—REST ( $\dot{V}_{O_2} = 275 \pm 35$  ML/MIN. STPD)  
X—LIGHT EXERCISE ( $\dot{V}_{O_2} = 560 - 690$  ML/MIN. STPD)



A

DETERMINATION OF DEAD SPACE FOR CARBON DIOXIDE ( $V_{D_{CO_2}}$ )  
AND  
ALVEOLAR CARBON DIOXIDE PARTIAL PRESSURE ( $P_{A_{CO_2}}$ )

SUBJECT: P.S. OXIMETER  $HbO_2 = 80 \pm 2\%$



B

FIGS. 2 A AND B. ILLUSTRATIONS OF THE APPLICATION OF THE ISO-SATURATION METHOD IN A NORMAL SUBJECT  
Note that the experimental points fall on a sloping straight line.

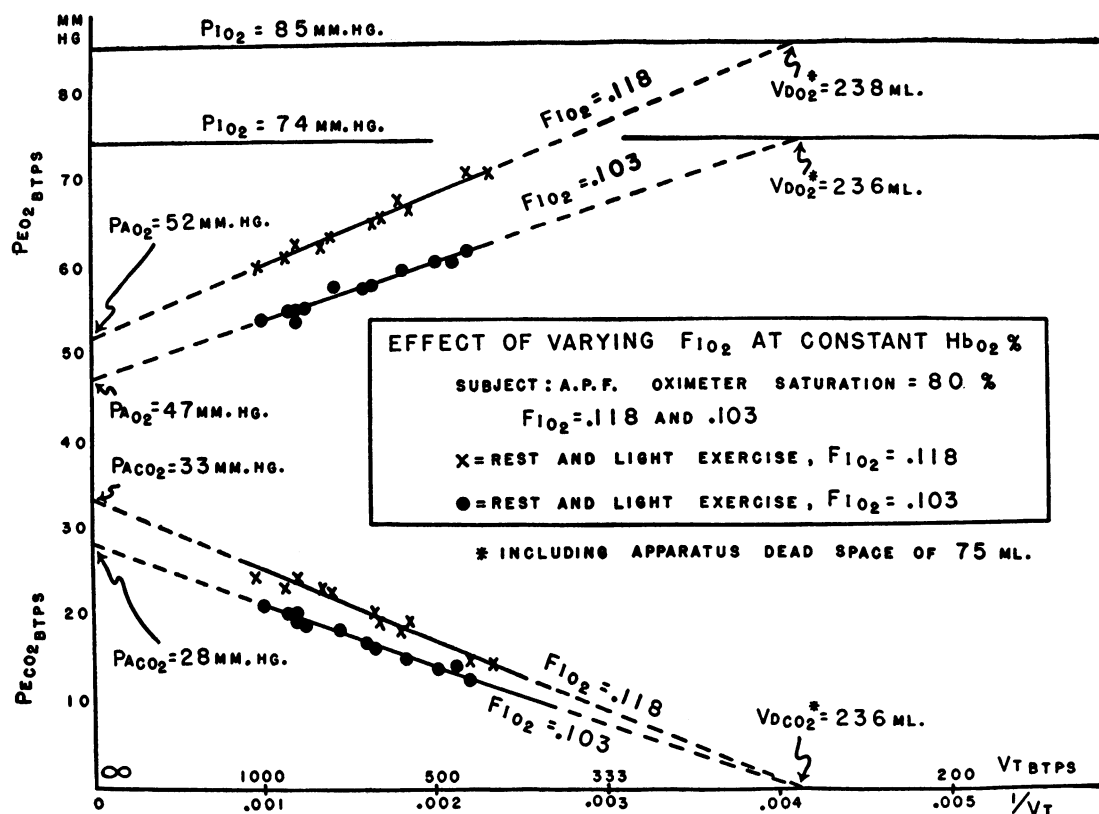


FIG. 3. APPLICATION OF THE ISO-SATURATION METHOD IN A NORMAL SUBJECT—EFFECT OF VARYING INSPIRED GAS MIXTURE

Note that  $V_{DO_2}$  and  $V_{DCO_2}$  remain constant and equal, and that  $PAO_2$  and  $PACO_2$  vary.

### Alveolar gas composition

The extrapolated values of  $PAO_2$  and  $PACO_2$  obtained under the conditions of these experiments ranged, respectively, from 42 to 55 mm. Hg, and from 26 to 33 mm. Hg. These variations are in part related to the different degrees of hyperventilation required to maintain approximately the same level of per cent  $HbO_2$  saturation. This effect is well illustrated in Figure 3, where two different inspired gas mixtures were used to maintain the same per cent  $HbO_2$ . It can also be seen in Table III, that the exchange ratio of alveolar gas (RA) obtained by extrapolation corresponds closely to the expired gas exchange ratio (RE).

### Alveolar-arterial $O_2$ and $CO_2$ gradients and oxygen diffusing capacity of the lungs

The values for alveolar tensions ( $PAO_2$  and  $PACO_2$ ) obtained by extrapolation were used in conjunction with blood gas tensions ( $Pao_2$  and

$Paco_2$ ) obtained by analyses of the arterial blood, to determine in normal subjects the A-a gradient for oxygen and  $CO_2$ , and to calculate the oxygen diffusing capacity of the lung ( $DLO_2$ ). As seen in Table III: (a) the  $O_2$  A-a gradient ranged between 3 and 11 mm. Hg, with an average of 6 mm. Hg; (b) the  $CO_2$  A-a gradient varied from -6 to +4 mm. Hg, with an average of 0.5 mm. Hg; and (c) the  $DLO_2$  at rest ranged from 18 to 33 with an average of 22 ml. per min. per mm. Hg.

### Patients with Pulmonary Dysfunction

The results in these three patients demonstrate that the experimental points fall, as in the normal subjects, along a sloping straight line with a minimum of scatter. This is illustrated in Figures 6 and 7.

### Volume of respiratory dead space

In the three patients,  $V_{DO_2}$  and  $V_{DCO_2}$  were equal, and not influenced by mild exercise, by vari-

ation in the arterial per cent  $\text{HbO}_2$ , or by addition of an external dead space. Two subjects, G. W. and E. H., of relatively small size (Table I) had relatively large dead space volumes. The third subject, G. B., with a (overdistended) single lung, had a  $V_D$  equal to 160 ml.

#### Alveolar gas composition

In the patient G. W., with non-obstructive emphysema, and in G. B., with a single, overdistended lung, the  $\text{PAO}_2$  and  $\text{PACO}_2$  were not significantly different from those observed in normals with similar oxygen mixtures. In E. H., with diffuse granulomatosis of the lung, the composition of the gas mixture required to maintain 80 per cent saturation was higher, and therefore, comparison of the alveolar  $\text{PAO}_2$  with the normal subject is not possible.

#### Alveolar-arterial $\text{O}_2$ pressure gradient

The A-a gradients in patient G. W., determined in two distinct series of experiments at two levels of arterial per cent  $\text{HbO}_2$  saturation (80 per cent and 70 per cent, respectively) were 18 mm. Hg (Table III). This is a much larger figure than seen in any of the normal subjects.

In the patient E. H., with diffuse granulomatosis, the A-a gradient reached the high value of 35 mm. Hg. It is of particular interest that in the same subject, using the Riley-Cournand method of analysis and a 16 per cent oxygen mixture which resulted in a similar lowering of the arterial per cent  $\text{HbO}_2$ , a value of 29 mm. Hg was obtained. In subject G. B. with one remaining lung, the A-a gradient was within the normal range.

The oxygen diffusing capacity was not calculated in the two subjects with the large A-a gradi-

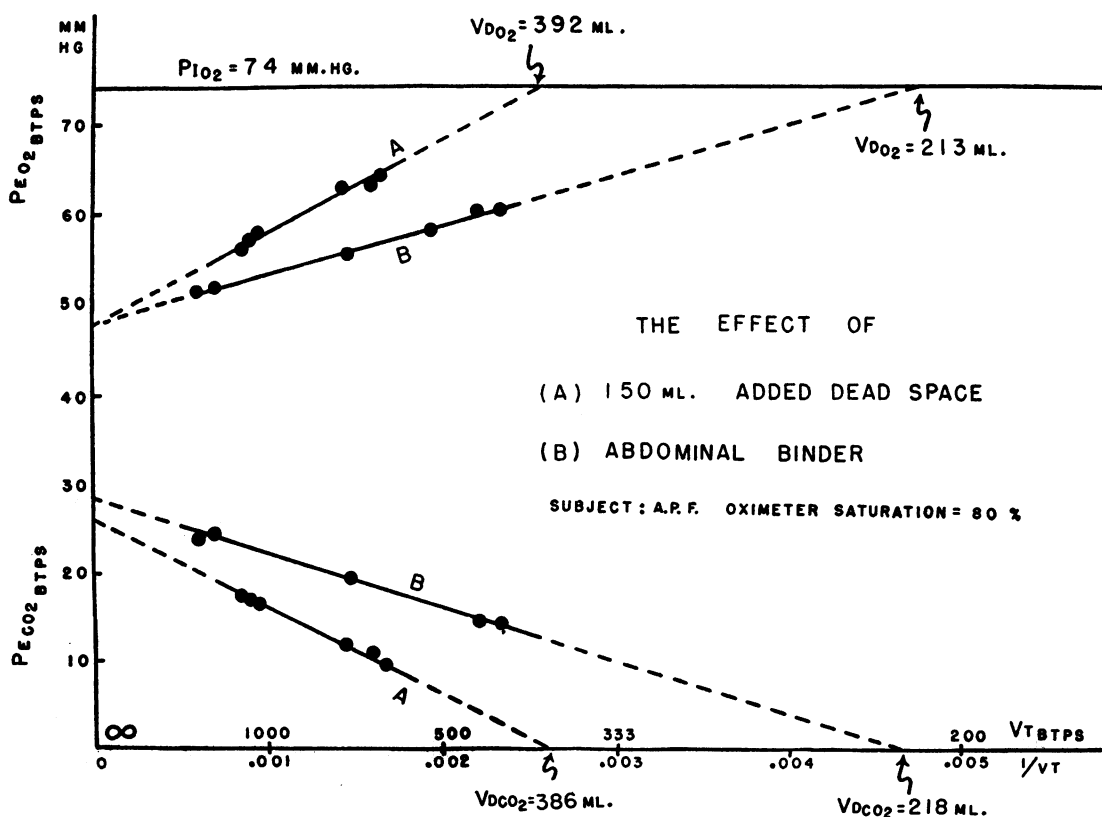


FIG. 4. APPLICATION OF THE ISO-SATURATION METHOD IN A NORMAL SUBJECT

Note that (a) addition of a measured additional dead space causes a corresponding increase in the measured  $V_D$  (see Figure 3), and (b) that change in the mid-position of the lung by an abdominal binder causes only a slight decrease in  $V_D$ .

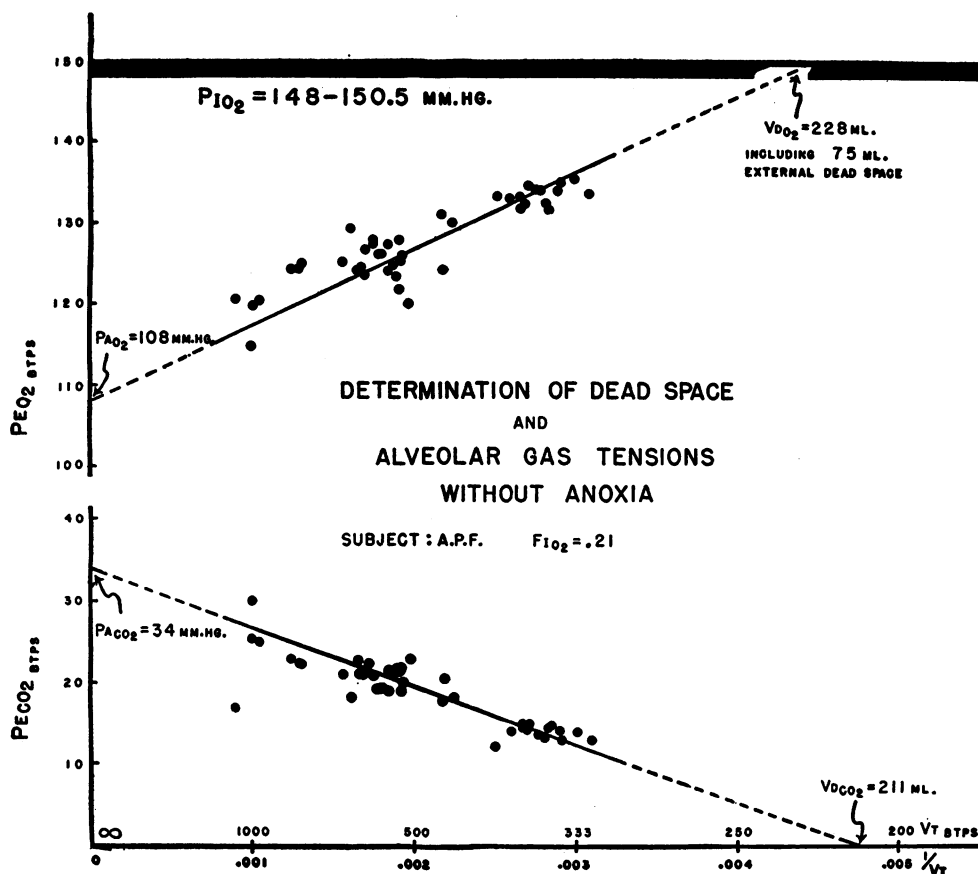


FIG. 5. APPLICATION OF THE ISO-SATURATION METHOD IN A NORMAL SUBJECT  
Note that without anoxia there is a considerable scatter of the experimental points.

ents, since in the presence of pulmonary disease, despite significant arterial per cent  $\text{HbO}_2$  unsaturation, the specific contribution of venous admixture to the A-a gradient cannot be ascertained. In the subject with one single lung, it was calculated to be 13, a figure below the range observed in normals.

#### DISCUSSION

##### *Respiratory dead space*

The results described above confirm those of the earlier study with the iso-saturation method (1) and indicate that the volume of the respiratory dead space ( $V_D$ ) remains constant despite wide variation in tidal volume ( $V_T$ ) and that this constancy is maintained during a wide variety of experimental conditions, including change in the composition of inspired gas and the addition of

external dead space. The data furthermore indicate that  $V_{D_{O_2}}$  is equal to  $V_{D_{CO_2}}$ , and that, therefore, in the steady state,  $R_A = R_E$ .

By this method, the  $V_D$  in the normal male subjects averaged 164 ml., with a range from 145 ml. to 215 ml., and in the normal female subject studied (L. D.) was 90 ml. These values correspond well with those recently described by other investigators using different methods. Thus, Fowler (6) used continuous, rapid analysis of the expired breath for nitrogen to identify completion of dead space wash-out and calculated an average "physiological"  $V_D$  of 156 ml. in males and 104 ml. in females. DuBois, Fowler, Soffer, and Fenn (7) determined "sequential" alveolar carbon dioxide values by continuous analysis of the expired breath and obtained by substitution in the Bohr formula an average "physiological"  $V_D$  of 177 ml. in normal males. Hatch, Cook, and Palm (8) ap-

THE DETERMINATION OF  $V_D$  AND  $P_A$   
 EFFECT OF VARYING ARTERIAL  $HbO_2\%$  AND EXTERNAL  $V_D$   
 SUBJECT: S.W. AGE: 57 DIAG: EMPHYSEMA, NON OBSTRUCTIVE

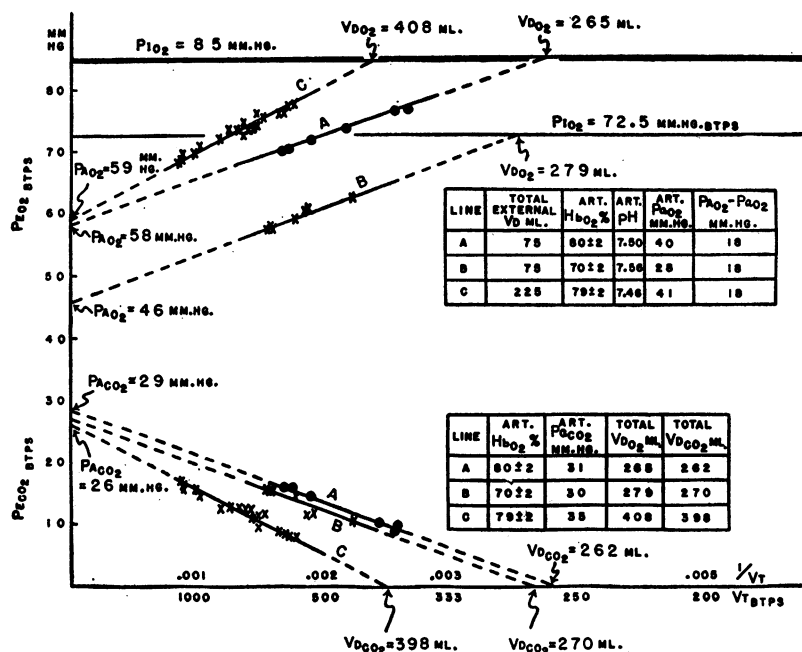


FIG. 6. APPLICATION OF THE ISO-SATURATION METHOD IN A PATIENT WITH NON-OBSTRUCTIVE EMPHYSEMA UNDER A VARIETY OF EXPERIMENTAL CONDITIONS, INCLUDING VARIATIONS IN DEGREE OF ANOXIA AND ADDITION OF AN EXTERNAL DEAD SPACE

Note that alignment of experimental points and the results confirm observations made in normal subjects.

plied fractional analysis of the expired breath to an experimental method somewhat similar in principle to the iso-saturation method, and concluded that the average "anatomic"  $V_D$  in normal male subjects was 130 ml.

Despite the designation "anatomic" or "physiological," these volumes for  $V_D$  are closely similar. This is readily understood from a brief consideration of the Bohr formula, where  $V_D$  emerges as a function of the value and the method used for  $P_A$ . In normal resting subjects, a variety of methods yield the same  $P_A$ ; in the presence of pulmonary disease, or during deviation from the resting state, discrepancies may be anticipated, the degree of difference depending on the method of sampling. Thus, the iso-saturation method, based on graphic solution of the Bohr formula, defines a well-ventilated, non-perfused space where no measurable

gas exchange occurs, and in which the inspired gas mixture retains its initial composition. In normal subjects this space must closely approximate the volume of the conducting airway, the anatomic  $V_D$ .

In contrast, the  $V_D$  determined by substituting  $P_{aCO_2}$  for  $P_{ACO_2}$  in the alveolar gas equation, as done in the Riley-Cournand method of analysis of ventilation-perfusion relationships, (4) includes not only this space, defined by its inspired gas composition rather than anatomic boundary, but also a fraction of the alveolar volume which is well ventilated, but poorly perfused.<sup>8</sup> In our series of

<sup>8</sup> This latter volume may be schematically represented by subdividing the total alveolar volume ( $V_{AT}$ ) of known composition ( $P_{Ax}$ ) into two virtual volumes with the following arbitrary composition: virtual volume 1 ( $V_{A1}$ ), containing "effective" alveolar gas ( $P_{A1}^0$ ) (5) and vir-

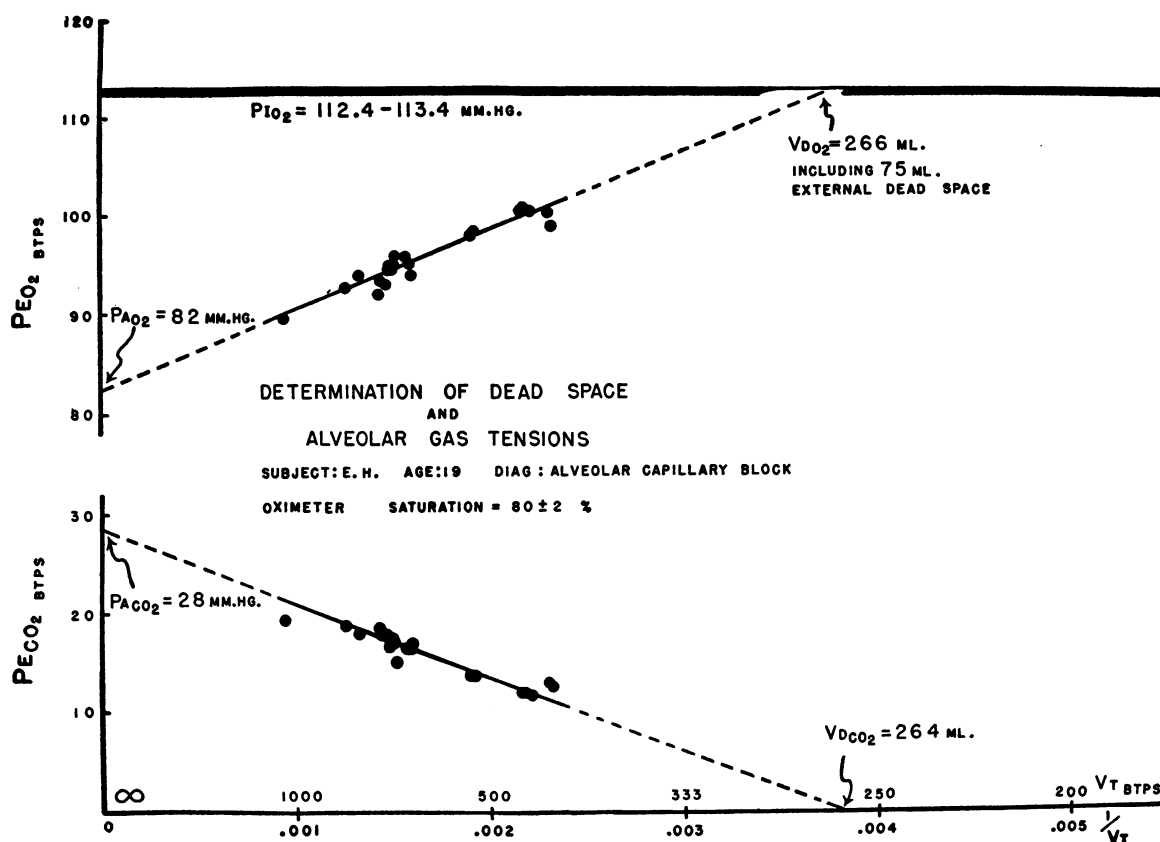


FIG. 7. APPLICATION OF THE ISO-SATURATION METHOD IN A PATIENT WITH DIFFUSE GRANULOMATOSIS OF THE LUNGS

seven normal male subjects, the mean and range of variation of  $V_D$  measured (a) by the iso-saturation method and (b) by substituting  $P_{aCO_2}$  for actual volume 2 ( $V_{A_2}$ ) with the same composition as inspired gas ( $P_{I_x}$ ). Therefore,  $V_{AT} \cdot P_{A_x} = V_{A_1} \cdot P_{A_x}^0 + V_{A_2} \cdot P_{I_x}$ . The "physiological" dead space of Riley and Cournand is the sum of the non-gas exchanging volume (defined by the iso-saturation method) + virtual volume 2 ( $V_{A_2}$ ). In normal subjects,  $V_{A_2}$  is very small, since there is little inhomogeneity of ventilation and perfusion.

In short, any method for determination of  $V_D$  based on the addition of a detector gas to the inspired gas mixture, measures a space closely approximating the anatomic  $V_D$ , plus an additional volume related to diffusion at the interface between anatomic  $V_D$  and alveolar gas; the iso-saturation method measures a similar volume. On the other hand, any method using a tracer gas which has undergone gas exchange, such as carbon dioxide, defines a  $V_D$  which is physiologically ineffective, and is influenced by the dynamics of alveolar ventilation and/or variations in ventilation-perfusion relationships.

This view has been previously expressed by Grosse-Brockhoff and Schoedel. Grosse-Brockhoff, F., and Schoedel, W., Der effective schädliche Raum. *Pflügers Arch.*, 1937, 238, 213.

$P_{aCO_2}$  in the Bohr equation, were almost identical. By the first method, the mean  $V_D$  equals 164 ml., with the range from 145 to 215 ml., as compared to  $V_D$  equal to 174 ml., with a range from 140 to 208 ml. by the second method. The  $V_D$  was also calculated by the two methods in the three patients, since it was anticipated that differences might appear. However, in the patient with non-obstructive emphysema, and in the patient with a single distended lung, the  $V_D$  were almost identical by both methods. In only one patient, with considerable impairment of gas exchange due to widespread granulomatosis of the lungs, was the discrepancy very significant. In this subject,  $V_D$  by the iso-saturation method measured 189 ml., and by the other method, 277 ml.

#### *The alveolar-arterial oxygen pressure gradient and diffusion constant of the lung*

The alveolar gas tension obtained by the iso-saturation method represents the alveolar component of expired gas (4). It differs from "ef-

fective" alveolar gas tension which is based on the use of arterial blood, because of contributions from well-ventilated, poorly perfused alveoli. In normal subjects, where there is little inhomogeneity of ventilation and perfusion, the differences between "effective" alveolar gas and the alveolar component of expired gas fall within the errors of the methods used for their determination.

The studies made by the iso-saturation method were all performed during anoxia. Consequently the calculated A-a gradient is a measure, in normals, of the failure of pulmonary capillary blood to reach equilibrium with alveolar oxygen tension. This gradient which averaged 6 mm. Hg with a range from 3 to 11 mm. Hg in normal subjects, compares well with the A-a gradient determined in normal subjects during anoxia by Lilienthal, Riley, Proemmel, and Franke (9).

The diffusion coefficient of the lung was calculated in the normal subjects using the A-a gradients and the Riley modification of the Bohr integration technique. The results were again similar to those calculated independently by the Riley-Cournand method of analysis. Similar calculations in the patients with pulmonary disease could not be done since no assumption as to the negligible effect of venous admixture on the A-a gradient during anoxia can be made.

#### *Clinical value of the iso-saturation method*

This method makes possible the determination of the volume of the respiratory dead (non-gas exchanging) space, the composition of alveolar gas and the A-a oxygen and carbon dioxide gradients during hypoxia, and the diffusion coefficient of the lungs in normal subjects and in patients with pulmonary dysfunction. However, the large number of experimental points needed for each determination, plus the high degree of cooperation required of the subject, and finally, the necessity of maintaining a steady state of circulation and respiration, limit the clinical utility of this method.

#### SUMMARY

1. The graphic solution of the Bohr formula according to the method described by Pappenheimer, Fishman, and Borrero (1) has been applied to the determination of the volume of the

respiratory dead (non-gas exchanging) space and the alveolar gas composition in eight normal subjects and in three patients with pulmonary disease.

2. The results confirm the previous observations on anesthetized dogs and normal human subjects, and indicate that this dead space ( $V_D$ ), remains constant over a wide range of tidal volumes and during a variety of experimental conditions. The average  $V_D$  in the seven male subjects was 164 ml.

3. An attempt has been made to identify the  $V_D$  measured by the iso-saturation method. This well-defined  $V_D$  containing inspired gas, must be distinguished from the virtual, "physiological"  $V_D$  calculated from blood gas tensions, which may vary during exercise and in pulmonary disease, due to changes in the dynamics of alveolar ventilation, and alveolar ventilation-perfusion relationships.

4. The alveolar gas compositions determined by this method were coupled with results of direct arterial blood gas analyses for the calculation of the alveolar-arterial (A-a) oxygen and carbon dioxide pressure gradients. In the normal subjects, the A-a oxygen and carbon dioxide gradients averaged 6 and 0.5 mm. Hg, respectively.

5. The A-a gradients were applied to the calculation of the oxygen diffusion capacity of the lungs in the normal subjects; the  $DL_{O_2}$ , at rest, was calculated to be 22 ml. per min. per mm. Hg.

6. The A-a gradient and  $V_D$  were similarly studied in three patients with three different types of pulmonary dysfunction. The A-a oxygen gradient and the  $V_D$  were considerably increased in one subject with diffuse pulmonary granulomatosis, but were within normal limits in one patient with chronic non-obstructive emphysema, and in another patient with a single distended lung. The results of the  $V_D$  measurements in the patient with diffuse pulmonary granulomatosis were used to emphasize the theoretical differences between the  $V_D$  measured by the iso-saturation method and the "physiological"  $V_D$ .

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ANNOUNCEMENTS OF MEETINGS

The 46th Annual Meeting of the American Society for Clinical Investigation will be held in Atlantic City, N. J., on Monday, May 3, 1954, with headquarters at the Chalfonte-Haddon Hall. The scientific session will begin at 9 a.m. at the Steel Pier Theater.

The annual meeting of the Association of American Physicians will be held at the Chalfonte-Haddon Hall on Tuesday, May 4, and Wednesday, May 5, 1954.